AN INTRODUCTION TO

BRAIN WARPING

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I. Overview and Preliminaries

The ability to measure and understand the rich complexity of brain structure and function often requires comparison against some index, standard or alternative representation. Indeed, the need to precisely locate the site of functional activation within an anatomic framework necessitates a comparison across image modalities or subjects. An anatomic framework may be in the form of a map to relate the name and location of structures within a coordinate system or a template with complete shape descriptions of structures. This requires a mechanism for placement of each sample into that coordinate system. Comparing images in different locations and orientations often with different geometries mandates some form transformation. In the simplest case, these transformations consist of repositioning one of the image sets relative to the other by translation and rotation. However, we are not concerned with the simple case (but translocations are included in all transformations regardless of how complex). Instead, the topic of this chapter (and book) deals with transformations of the geometry, namely warping, that effect the shape and form of brain image data. The geometric transformations considered warps include global scaling, affine transformations, linear, nonlinear and local deformations. Each of these transformations produces registered image sets that can be statistically and visually compared. Further, the transformations themselves contain considerable information regarding the regional similarity and difference between the data.

Warping is a subspecialty of image processing that deals with geometric transformation techniques (Wolberg, 1992). These transformations redefine the spatial relationship between points in an image(s). The degree of such transformations can range from simple repositioning to severe deformations. As noted above, for the purposes of multimodality and multisubject brain comparisons, warping is defined as those geometric transformations that alter the shape beyond transformations of simple repositioning. The extent of the warping is determined by the data source and the application. Similarly, the implementation (intensity-based or model-based) of the warping algorithm is dependent on the type of data and its resolution. For example, if anatomic or extrinsic landmarks are easily obtained, model-based algorithms may be employed. These require the identification of features in each data set. The location and number of these features are crucial to the goodness of fit. In other cases, intensity-based warping algorithms can maximize the cross correlation coefficients, or other similarity metrics, between datasets without the identification of features or landmarks. Later in this chapter, we will describe several algorithms for model-based and intensity-based warping.

The Importance of Warping

Several driving forces are responsible for the importance of warping. First, is the need to perform brain to brain comparisons. Considerable attention has focused on developing warping methods for removing size and shape differences that distinguish one brain from another. Interestingly, these efforts were initially motivated by the need to standardize data across subjects in the analysis of functional imaging data. The goal here has been the removal of anatomic variability (often considered artifact and the source of noise) to achieve better correspondence of functionally homologous brain regions across subjects. Even removal of the lowest order components of morphometric variability using only rigid-body rotations and linear scaling along prespecified axes (e.g., Talairach-type transformations) can be advantageous in analyzing functional imaging data, but higher order nonlinear models provide added benefit (Woods et al., 1998). Recently, the need to remove anatomic

differences in a given population has been recognized as a prerequisite for the development of brain atlases which improve upon those based on single individuals. Population-based atlases may provide a better fit for a given individual and may possess increased statistical power to detect subtle or distributed differences (Mazziotta et al., 1995; Thompson et al., 1997). However, in order to achieve the full potential of any population-based approach, appropriately applied warping algorithms are needed.

Structural anatomy, or some feature closely linked to structural anatomy, is generally the source of the information used to derive the warping transformation that removes these confounding differences in overall brain size and shape. The selection of these features is determined by their ease of identification and geometric stability in the population under study. To date, however, no study has systematically determined the contribution of large numbers of anatomic features relative to their ability to remove the overall size and shape differences in brain. The widespread acceptance of the Talairach (Talairach and Tournoux, 1988) system based upon anterior and posterior commissures and overall extrema is largely due to the lack of suitable substitutes.

Practically speaking, warping becomes very important for any template-based segmentation strategy. The ability to identify structures in the brain based upon *a priori* knowledge and a predefined map depends upon the assumption that the unlabeled brain and the template occupy the same space. Even relatively simple, but essential, operations such as skull/scalp stripping can be accomplished with a template strategy assuming acceptable warping results (Collins et al., 1995). Conversely, warping the results of individually segmented brains into a common space produces considerable information regarding the distribution of the morphological statistics for each structure so processed (Mazziotta et al., 1995). Probability maps of anatomic structures can be created from data such as these. Clearly, differently based warps based on different information will result in different probabilistic maps.

Later in this chapter a brief description of warping applications is presented. Several of these applications focus on the identification of differences between healthy and diseased populations, including patient populations with Alzheimer's Disease, schizophrenia and intracranial tumor growth. While some warping applications seek to compare, within modality, morphometric differences, others examine the relationship between *in vivo* and histologic data (Mega et al., 1997; see Figure 1). All of these however, depend on warping to compare the 3D geometry of individual brains with one another, with an atlas, or with a population. Warping can also provide information in 4D by describing the rate of geometric change (Toga et al., 1996; Thompson et al., 1998). Extensive morphological change occurs in the brains of developing or degenerating individuals. Depending on the warping strategy employed, information about the local rates of the change including regional dilation, contraction, shearing and other forces can be modeled.

Warping as a Source of Information

An indirect benefit of the progression of automated registration algorithms into increasingly higher orders of nonlinearity is that the transformation parameters used by the algorithms contain an increasingly detailed mathematical description of the morphometric differences between subjects. Ideally, each added nonlinear parameter should move additional anatomic variability out of the registered images and into the mathematical transformations as registration of homologous landmarks improves. Thus the amount of residual morphometric variability in the resampled images should decrease if the higher order transformations contain better descriptions of morphometric variability. With automated algorithms, this ideal should not be taken for granted, and validation requires demonstration that the residual variability of neuroanatomically identified landmarks is indeed improved. Once this has been demonstrated, it is appropriate to treat the transformations derived by the algorithm as legitimate sources of mathematical descriptors of morphometric variability.

Warping algorithms also create 3D maps of regional differences in anatomy between individuals or groups. These deformations can be analyzed in a statistical framework to investigate brain structure alterations in disease or

during brain development. The complex profiles of dilation and contraction required to warp a digital anatomic template, such as a brain atlas, onto a new subject's brain provide an index of the anatomical shape differences between that subject's brain and the atlas (Bookstein, 1989, 1997; Davatzikos *et al*., 1996b; Thompson and Toga, 1997; Subsol, 1998). Differences in regional shape can therefore be assessed by analyzing the deformation field which measures the local dilation or contraction required to deform one brain volume into another. As a result, warping approaches can be regarded as a **virtual sensor** (Gee et al., 1995) which produces signals and maps of these structural differences. When analyzed in a setting where normal variations are encoded, atlas deformation maps offer a framework for pathology detection (Thompson et al., 1997; Bookstein, 1997), identification of gender-specific anatomic patterns (Davatzikos, 1996b), and mapping of dynamic patterns of structural change in neurodevelopmental and degenerative disease processes (Toga et al., 1996; Thompson et al., 1998).

On the other side of the coin, many brain mapping investigators are not concerned with the information provided by the warp and, as noted above, even treat the process as a necessary inconvenience for brain to brain comparison. Certainly, the perceived mathematical complexity and arcane computer science contribute to such reactions. However, the danger is that warping algorithms can be considered 'black boxes', which can be trusted implicitly and used without attention to their underlying assumptions and inherent limitations. Nothing can be further from the truth. The application of warping algorithms is intimately intertwined with the biological question at hand, the source and quality of the data itself and a fundamental understanding of the imposed mathematical transmogrifications.

II. Origins - A Historical Perspective

The history of warping and its application to neuroimaging is relatively short but heavily influenced by a diverse group of specialties. Originating in engineering disciplines, warping is now a hybrid of mathematically, computationally and application based specialties. The ubiquitous inclusion of imaging has helped propel the previously exotic, sometimes peripheral subject of warping to a prominent place in medical imaging and brain mapping. It is interesting to note that some of the earliest work came from the remote sensing community in their quest to visualize and measure structures in (or from) outer space. Presently, some of the most exciting applications of warping occur in the field of brain mapping, where the goal is to visualize and measure structures of inner space.

Perhaps the birth of image warping can be traced to optical systems operating on analog image data (Wolberg, 1992), but the product of the warp was merely a visual deviation from the original. In spite of their light speed and utility in correcting acquisition error, these optical approaches provided neither sophisticated control nor statistical information. Digitally-based systems do.

Contributing Disciplines

The rapid and widespread influence of digital computer systems on most avenues of scientific discovery has probably had the most profound influence over imaging. Image processing, in addition to improving or altering the appearance or quality of the image, includes the process of geometric transformation. Military and space-related developments in this field were driven by the need to composite a single comprehensive view of an object from multiple images taken at different times, with different sensors and from different perspectives. This scenario is, in many ways, identical to the problems inherent in brain mapping, in view of the need to collect brain data from multiple subjects and imaging modalities.

Technological Advances

There have been several hardware and algorithmic contributions to the emergence and widespread application of brain warping. There also has been a push-pull relationship between technological requirements for warping algorithms and improved technology enabling more sophisticated approaches to warping. The advent of computer graphics (both software and hardware) created the potential for rapid and controllable strategies to warp surface geometries in 3D. The symbiotic progression of specialized computer architectures and algorithms also made possible the visualization of warps in a way that proved compelling even for Hollywood. Computational capabilities have increased with regard to processing speed (clock speed and parallelization), visualization and data input/output. Parallel computer architectures are increasingly essential for computationally demanding warps. While it is beyond the scope of this chapter to consider all the technological pros and cons of parallel computation strategies, the regular structure of image volumes and the organization of many warping algorithms can easily benefit from them (Christensen et al., 1996).

Warping applications that are particularly demanding include nonlinear local deformations described in subsequent chapters, the use of large and/or highly sampled image volumes as well as the identification and extraction of features and characteristics of the data to be utilized in the warping algorithms themselves. From a computational standpoint, nonlinear models involving hundreds of parameters are increasingly practical for routine use in the analysis of functional imaging data, and algorithms are available for deriving these transformations in an automated fashion (Ashburner et al., 1997; Woods et al., 1998). Continued improvements in computer processing speed will enable the use of increasingly higher order nonlinear transformations in the future, and at some point, even highly nonlinear methods that currently require supercomputing resources (Christensen et al., 1996) are likely to become routinely practical.

III. Warping Strategies

Underlying Principles

Warping strategies can be divided into *intensity-driven* or *model-driven* approaches, depending on the types of features that drive the mapping of one brain onto the other. In *intensity-driven* approaches, a measure of intensity similarity is defined between the deforming scan and the target brain. Parameters of the deformation field are successively adjusted until the value of the similarity measure is maximized. Measures of similarity have included normalized cross-correlation (Bajcsy and Kovacic, 1989; Collins et al., 1994a, 1995), squared differences in pixel intensities (Christensen *et al*., 1993, 1995, 1996; Woods et al., 1998), measures based on optical flow models (Dengler and Schmidt, 1988), and mutual information metrics (Kim et al., 1997). Mutual information metrics measure the statistical dependency between intensity patterns in deforming scan and the target, making them suitable for cross-modality, as well as within-modality registrations.

In early warping models (Broit, 1981), normalized cross-correlation measures were defined between small spherical regions of the template and target, to identify candidate matches between the two scans. In (Bajcsy and Kovacic, 1989), intensity neighborhoods to be correlated in each scan were first projected onto a truncated 3D Hermite polynomial basis, enhancing the response of edge features and accelerating computation. More recent models have either used specialized templates to search for pre-defined intensity features in the target dataset (Amit, 1997), or have formulated the intensity matching problem in a Bayesian framework (Miller et al., 1993; Gee et al., 1993, 1995; Ashburner et al., 1997). In a Bayesian framework, statistical information on the imaging process (the *imaging* model) is combined with prior information on expected template deformations (the *prior* model) to make inferences about the parameters of the deformation field.

Model-driven algorithms differ from purely intensity-driven approaches. They first build explicit geometric models, representing separate, identifiable anatomic elements in each of the scans to be matched. These anatomical systems typically include functionally important surfaces (Szeliski and Lavallée, 1993; Downs et al., 1994; Moshfeghi et al., 1995; Thompson and Toga, 1996; Davatzikos, 1996), curves (Ge et al., 1995; Monga and

Benayoun, 1995; Subsol, 1995), and point landmarks (Bookstein, 1989; Amit et al., 1991). Anatomical elements are each parameterized and matched with their counterparts in the target scan, and their correspondences guide the volumetric transformation of one brain to the other. The use of higher-level structural information ensures that the mapping has biological as well as computational validity, and allows the patterns of deformation to be interpreted in terms of the underlying anatomy or physiology.

Several types of models have been used to guide warping algorithms. Automatically extracted *crest-lines* (Declerck *et al*., 1995; Subsol, 1998), defined using curvature-based criteria, follow salient anatomic features such as sulcal/ventricular curves and gyral crests, and can be matched in template and target datasets. The inherent parametric structure of these models allows additional geometric features (torsion, curvature and local Frenet frames) to be included in the matching criteria, to favor correct pairing of elements and guide internal correspondences (Kishon et al., 1991; Gourdon and Ayache, 1993; Khaneja et al., 1998). Curve-based sulcal models can be combined with intensity-based measures to assist in matching cortical regions (Collins *et al*., 1996). Approaches using sulcal lines or surfaces to drive a 3D volumetric warp are under active investigation in *Macaque* (Joshi *et al*., 1995) and human MR data (Declerck *et al*., 1995; Ge et al., 1995; Banerjee *et al*., 1995; Luo and Evans, 1995; Davatzikos, 1996; Thompson and Toga, 1996, 1998). Hybrid models, which incorporate the advantages of both model-driven and intensity-driven algorithms, are likely to capitalize on the merits of each approach.

Materials and Energy

Any successful warping transform for matching one brain with another must allow any segment of the template anatomy, however small, to dilate, contract, twist and even rotate, in order to accommodate fine anatomic variations. This warping is required to bring the template anatomy into structural correspondence with the target image at a very local level. As the complexity of the transform increases, the topology and connectivity of the deforming template have to be maintained under these complex reconfigurations. This is hard or simply impossible to achieve in traditional image warping manipulations (Christensen et al., 1995). Physical continuum models of the deformation address these difficulties by considering the deforming anatomic image to be embedded in a three-dimensional deformable medium, which can be either an elastic material or a viscous fluid (see Fig. 2). The medium is subjected to certain distributed internal forces, which reconfigure the medium to match the target. These forces can be based mathematically on the local intensity patterns in the datasets, with local forces designed to match image regions of similar intensity.

Continuum Mechanics. Several warping algorithms have been designed to deform brain data according to the laws of continuum mechanics, which describe the deformational behavior of real materials. In elastic media, the displacement field $\mathbf{u}(\mathbf{x})$ resulting from internal deformation forces $\mathbf{F}(\mathbf{x})$ (called '*body forces'*) obeys the Navier-Stokes equilibrium equations for linear elasticity:

$$\mu\nabla^2\mathbf{u} + (\lambda+\mu)\nabla(\nabla^T \bullet \mathbf{u}(\mathbf{x})) + \mathbf{F}(\mathbf{x}) = \mathbf{0},\ \forall \mathbf{x} \in R \qquad (1).$$

Here R is a discrete lattice representation of the scan to be transformed, $\nabla^T \bullet \mathbf{u}(\mathbf{x}) = \sum \partial u_j/\partial x_j$ is the cubical dilation of the medium, ∇^2 is the Laplacian operator, and Lamé's coefficients λ and μ refer to the elastic properties of the medium (see Fig. 2). Body forces, designed to match regions in each dataset with high intensity similarity, can be derived from the gradient of a local correlation function (Bajcsy and Kovacic, 1989), or by stochastic gradient descent on a cost functional which penalizes squared intensity mismatch between the deforming template $T(\mathbf{x}-\mathbf{u}(\mathbf{x},t))$ and target $S(\mathbf{x})$:

$$C(T(\mathbf{x}), S(\mathbf{x}), \mathbf{u}) = (1/2) \int_{\Omega} | T(\mathbf{x}-\mathbf{u}(\mathbf{x},t)) - S(\mathbf{x}) |^2 \, d\mathbf{x} \qquad (2).$$

Measures of squared intensity mismatch are typically more economical to compute than regional cross-correlation metrics or other matching criteria, and they have therefore been adopted by most groups working in the field (Miller et al., 1993; Christensen et al., 1996; Bro-Nielsen and Gramkow, 1996; Woods et al., 1998). With appropriate boundary conditions (Dirichlet or infinite) the elasticity equilibrium equations can be solved numerically by finite difference (Davatzikos, 1996), finite element (Gee et al., 1993, 1995), or spectral methods (Miller et al., 1993; Bro-Nielsen and Gramkow, 1996).

Recently, Christensen *et al*. (1993, 1995, 1996) proposed a deformable MRI-based atlas driven by a viscous-fluid based warping transform, which allows non-linear topological behavior and large image deformations, while satisfying continuum-mechanical constraints that guarantee the topological integrity of the deformed template (Christensen et al., 1996; Miller et al., 1998). The deformation velocity of the atlas is governed by the creeping flow momentum equation for a Newtonian fluid, and a series of three algorithms adjust successively finer features of the template anatomy until the transformed template matches the target scan in exquisite detail. A recent fast, 'demons-based' warping algorithm, Thirion (1995) calculates a flow velocity by regularizing the force field driving the template with a Gaussian filter. Since this filter may be regarded as a separable approximation to the continuum-mechanical filters which encode the response of a deformable medium to an impulse force, interest has focused on deriving additional separable (and therefore rapidly applied) filters to capture the deformational behavior of material continua in image registration (Gramkow, 1996).

Biological Constraints

Linkage of continuum-mechanical models with criteria for optimal intensity matching results in an extremely difficult pattern recognition problem. To guide the mapping of an atlas onto an individual scan, higher-level structural information can be invoked to guarantee the biological validity of the resulting transform (Thompson and Toga, 1996; Davatzikos, 1996a; Collins et al., 1996; Schormann et al., 1996). In one approach (Thompson and Toga, 1996) anatomic surfaces, curves and points are extracted and forced to match. The scheme involves the determination of several model surfaces (with a combination of automatic and manual methods), a warp between these surfaces, and the construction of a volumetric warp from the surface warp. Extremely complex surface deformation maps on the internal cortex are constructed by building a generic surface structure to model it. Connected systems of parametric meshes model primary sulci with deep trajectories. In advance, a high-resolution model of the external cortex is automatically extracted from both scans with an active surface algorithm (MacDonald *et al*., 1993). These models are subsequently re-parameterized to allow gyrus-by-gyrus matching of specific lobar and cortical regions (see Fig. 3). The ventricular system can also be partitioned into a system of connected surface elements, whose junctions match the boundaries of numerous cytoarchitectonic fields at the ventricular surface. Radial basis functions (Bookstein, 1989; Ruprecht and Müller, 1995; Thompson and Toga, 1996) or continuum-mechanical models (Davatzikos, 1996; Thompson and Toga, 1998) can be used to extend the deformation field required to elastically transform nested surfaces to their counterparts in the target scan. The compact representation of the high-dimensional deformation field provided by curve and surface-driven approaches allows rapid computation of the complex maps relating different brain architectures (Szeliski and Lavallée, 1993; Subsol, 1998). A summary of warping approaches which have been developed specifically for handling brain data is provided in Table 1.

IV. Applications

Having surveyed several different approaches for warping brain data, some examples and applications will be described. Warping a brain to an atlas, warping one modality to another and warping multiple brains each have different objectives and different requirements of the underlying algorithms.

Normalization for Comparison and Analysis

The goal of understanding how brain structure and function vary in large human populations mandates the design of tools to integrate brain mapping data from multiple subjects and sources. Extreme variations in brain structure, especially in the gyral patterns of the human cortex, compound the difficulties of this task. Integrating and comparing data from multiple subjects and groups is hampered by the complexity of anatomic variations (Meltzer and Frost, 1994; Woods, 1996). Ideally, when analyzing functional imaging data, we would like to remove all morphological differences between individual brains before considering the distribution of functional information on the anatomic substrate. By spatially normalizing brain data from multiple subjects and sources, warping methods can transfer multi-subject 3D functional, vascular and histologic maps onto a single anatomic template (Fig. 4).

Coordinate Systems and Registration

Matching a Brain to an Atlas. In existing atlases, proportional scaling systems are typically employed to reference a given brain with an atlas brain (Talairach et al., 1967; Talairach and Tournoux, 1988). This requires individual data to be superimposed on the data in the atlas - in other words, to be transformed to match the space occupied by the atlas. In the Talairach stereotaxic system, piecewise affine transformations are applied to 12 rectangular regions of brain, defined by vectors from the anterior and posterior commissures to the extrema of the cortex. These transformations re-position the anterior commissure of the subject's scan at the origin of the 3D coordinate space, vertically align the interhemispheric plane, and horizontally orient the line connecting the two commissures. Each point in the incoming brain image, after it is 'warped' into the atlas space, is labeled by an (x,y,z) address referable to the atlas brain.

Although originally developed to help interpret brain stem and ventricular studies acquired using pneumoencephalography (Talairach et al., 1967), the Talairach stereotaxic system rapidly became an international standard for reporting functional activation sites in PET studies, allowing researchers to compare and contrast results from different laboratories (Fox et al., 1985, 1988; Friston et al., 1989, 1991). Despite difficulties in pooling data from highly variable cortical regions, the objectivity and wide use of Talairach coordinates greatly simplified the task of developing multi-modality atlases and reference systems for human brain data (Fox et al., 1994; Toga and Thompson, 1998). More complex warping approaches can be used to circumvent these limitations, by mapping data to a common template in a way which compensates for gross anatomic variations.

Digital Anatomic Templates. The success of any brain atlas depends on how well the anatomy of individual subjects match the representation of anatomy in the atlas. While stereotaxic methods provide a common coordinate system for pooling activation data and multi-subject comparisons, concern has been voiced over the anatomical template itself used by Talairach (Roland and Zilles, 1994). Based on *post mortem* sections of the brain of a 60 year-old female subject, which clearly did not reflect the *in vivo* anatomy of subjects in activation studies, the atlas plates were also compromised by having a variable slice separation (3 to 4 mm), and data from orthogonal planes were inconsistent. To address these limitations, the Montreal Neurological Institute (Evans et al., 1994) created a composite MRI dataset from 305 young normal subjects (239 males, 66 females; age: 23.4 +/- 4.1 years) whose scans were individually mapped into the Talairach system, intensity normalized, and averaged on a voxel-by-voxel basis (Evans et al., 1992). Although the resulting average brain (Fig. 5) has regions where individual structures are blurred out due to spatial variability in the population (Evans et al., 1992; 1994), the effect of anatomical variability in different brain areas is illustrated qualitatively by this average-intensity MRI dataset. The average intensity template is part of the widely-used *Statistical Parametric Mapping* package (SPM; Friston et al., 1995).

The availability of an average MRI dataset in the Talairach coordinate system spurred the development of automated methods to map new MRI and PET data into stereotaxic space. Automated image registration algorithms could be used to optimally align new MR data with the template by maximizing a measure of intensity

similarity, such as 3D cross-correlation (Collins et al., 1994a,1995), ratio image uniformity (Woods et al., 1993), or mutual information (Viola and Wells, 1995; Wells et al., 1997). Any alignment transformation defined for one modality, such as MRI, can be identically applied to another modality, such as PET, if a previous cross-modality intrasubject registration has been performed (Woods et al., 1993). For the first time then, PET data could be mapped into stereotaxic space via a correlated MR dataset (Woods et al., 1993; Evans et al, 1994). Registration algorithms therefore made it feasible to automatically map data from a variety of modalities into an atlas coordinate space based directly on the Talairach reference system.

Structure and Function

The fact that the Talairach atlas fails to adequately match individual scans stems partly from the fact that only linear transformations (rotation, scaling, translation) are prescribed by the Talairach system for adapting new scans to the atlas template. Numerous studies, in our laboratory and elsewhere, have determined how severe the inter-subject variations in anatomy are, even after transforming individual anatomic data into the Talairach stereotaxic system (Fig. 6). Extreme variations in cortical patterns are observed among normal subjects, and exacerbated in disease states by additional pathologic change. Caution is therefore necessary in using the Talairach stereotaxic system to support cross-subject and cross-group comparisons of cortically-derived events or functional maps. Warping methods provide significant advantages in further correcting for these structural differences. Without warping algorithms, subtraction of stereotaxic functional maps, especially in studies of disease states such as dementia, may lead to spurious results: maps of apparent significance may reflect differences which are anatomic, rather than functional, in character (Meltzer and Frost, 1994; Woods, 1996). These challenges have spurred the development of warping algorithms which execute rapidly on standard workstations (Collins et al., 1994; Ashburner et al., 1997; Woods et al., 1998), allowing analysis of functional differences in a context where anatomic differences are more completely factored out.

Atlases

Given the fact that there is neither a single representative brain nor a simple method to construct an ‘average’ anatomy or represent the complex variations around it, the construction of more flexible, widely-applicable brain atlases has become the focus of intense research (Mazziotta et al., 1995). *Deformable atlases*, which can be adapted to reflect the anatomy of new subjects, and *probabilistic atlases*, which retain information on population variability, are powerful new research tools with a range of clinical and research applications. These atlases can be used to guide knowledge-based image analysis algorithms (Zijdenbos and Dawant, 1994; Dinov et al., 1998), and can even support pathology detection in individual subjects or groups (Haller et al., 1997; Joshi et al., 1998; Thompson et al, 1997; Thompson and Toga, 1997; Joshi et al., 1998; Thirion et al., 1998).

Deformable Atlases

Brain atlasing research is based on the premise that accurate localization of brain structure and function in any modality is improved by correlation with higher resolution anatomic data placed in an appropriate spatial coordinate system. Atlases would be greatly improved if they could be *elastically* deformed to fit a new image set from an incoming subject. Warping transformations (including local dilations, contractions and shearing) can be used to adapt the shape of a digital atlas to reflect the anatomy of an individual subject, producing an *individualized* brain atlas. Pioneered by Bajcsy and colleagues at the University of Pennsylvania (Broit, 1981; Bajcsy and Kovacic, 1989; Gee *et al*., 1993, 1995), this approach was adopted by the Karolinska Brain Atlas Program (Seitz et al., 1990; Thurfjell et al., 1993; Ingvar et al., 1994), where warping transformations are applied to a digital cryosection atlas to adapt it to individual CT or MR data and co-registered functional scans.

Warping algorithms can be used to transfer all the information in a 3D digital brain atlas onto the scan of any given subject, while respecting the intricate patterns of structural variation in their anatomy. Such *deformable*

atlases (Seitz et al., 1990; Evans *et al.*, 1991; Miller et al., 1993; Gee *et al*., 1993; Christensen *et al*., 1993; Sandor and Leahy, 1995; Rizzo et al., 1995) can carry 3D maps of functional and vascular territories into the coordinate system of different subjects, as well as information on different tissue types and the boundaries of cytoarchitectonic fields and their neurochemical composition. Deformable atlas approaches offer a powerful means to transfer multi-modal brain maps between individuals and neuroanatomic atlases, respecting complex differences in the topography of the cortex and deep anatomic systems. When applied to atlases based on 3D digital cryosection images, warping algorithms produce flexible high-resolution templates of neuroanatomy which can be adapted to reflect the anatomy of individual subjects (Toga and Thompson, 1997; see also Chapter 19, Fig. 6).

Segmentation and Labeling

The potential of deformable atlases to transfer fine-scale structural information into brain scans of different subjects has greatly intensified research on template-driven segmentation (Dengler and Schmidt, 1988; Bajcsy and Kovacic, 1989; Collins et al., 1994a, 1995; Gee et al., 1993,1995; Haller et al., 1997).

In these approaches, atlas deformations can carry pre-segmented digital anatomic models, defined in atlas space, into new patients' scans, automatically labeling their anatomy (Collins et al., 1995). Non-linear mapping of raster volumes or 3D geometric atlases onto individual datasets has been used to support automated brain structure labeling for hippocampal morphometry (Haller et al., 1997), analysis of subcortical structure volumes in schizophrenia (Iosifescu et al., 1997), estimation of structural variation in normal and diseased populations (Collins et al., 1994b; Thompson et al., 1997), and segmentation and classification of multiple sclerosis lesions (Warfield et al., 1995). Projection of digital anatomic models into PET data can also serve to define regions of interest for quantitative calculations of regional cerebral blood flow (Ingvar et al., 1994). These template-driven segmentations require extensive validation relative to more labor-intensive manual delineation of structures, but show considerable promise in medical imaging applications.

Probabilistic Atlases

A *deformable* brain atlas counteracts many of the limitations of a fixed atlas by using mathematically flexible transformations. Nevertheless, to realize the quantitative potential of digital atlases, data from single subjects must be extendable to populations (Mazziotta et al., 1995). Atlasing considerations suggest that a statistical confidence limit, rather than an absolute representation of neuroanatomy, may be more appropriate for representing particular subpopulations. Digital reference systems for brain data that retain quantitative information on structural and functional variation in human populations are known as **probabilistic atlases**.

Three major approaches currently exist for *probabilistic* atlas construction: *intensity-based*, *label-based*, and *deformation-based* approaches. These differ only in the attribute whose statistical distribution is modeled and analyzed. Initial approaches to population-based atlasing concentrated on generating 'average' representations of anatomy by intensity averaging of multiple MRI scans (Evans *et al*., 1992; Andreasen *et al*., 1994). A large number of MRI scans are each linearly transformed into stereotaxic space, intensity-normalized and averaged on a voxel-by-voxel basis, producing an average intensity MRI dataset. While cortical regions are largely blurred out due to anatomic variations not accounted for by a linear transformation, these templates can be used as targets for automated registration and mapping of MR and co-registered functional data into stereotaxic space (Evans et al., 1994). In *label-based* approaches, large ensembles of brain data are labeled, manually or automatically, and a probability map is constructed for each segmented structure, by determining the proportion of subjects assigned a given anatomic label at each voxel position in stereotaxic space (Evans *et al*., 1994; Paus *et al*., 1996). Statistical data on anatomic labels and tissue types normally found at given positions in stereotaxic space can be used to constrain the search space for significant activations in PET and SPECT imaging experiments (Dinov *et al*.,

1998; Mega *et al*., 1998), and provide a vital information source to guide mathematical algorithms which analyze neuroanatomic data in stereotaxic space.

Finally, *deformation-based* approaches directly build on the deformable atlas framework. By defining probability distributions on the space of deformation transformations applied to a prototypical anatomic template (Grenander, 1976; Amit et al., 1991; Grenander and Miller, 1994), statistical parameters of these distributions can be estimated from databased anatomic data to determine the magnitude and directional biases of anatomic variation (Thompson et al., 1996, 1997).

Random Vector Fields. In view of the clear clinical and research applications, mathematical methods are under active development to create probabilistic measures of anatomic variation which are capable of detecting pathology (Bookstein, 1989; 1997; Grenander and Miller, 1994; Thompson and Toga, 1997; Thirion et al., 1998). In our approach (Thompson and Toga, 1997), given a 3D MR image of a new subject, a warping algorithm (Thompson and Toga, 1996) calculates a set of high-dimensional volumetric maps, elastically deforming this scan into structural correspondence with other scans, selected one by one from an anatomic image database (see Fig. 7). Target scans are selected from subjects matched for age, handedness, gender, and other demographic factors (Thompson et al., 1997, 1998). The resulting family of volumetric warps provides empirical information on patterns of local anatomic variation. A probability space of random transformations, based on the theory of anisotropic Gaussian random fields (Thompson et al., 1997), is then used to encode the variations, including information on complex variations in gyral and sulcal topography from one individual to another. Confidence limits in stereotaxic space are determined, for points in the new subject's brain, enabling the creation of color-coded probability maps to highlight and quantify regional patterns of deformity in the anatomy of new subjects.

Pattern-Theoretic and Shape-Theoretic Approaches. In a related pattern-theoretic approach (Grenander and Miller, 1994), the deformational behavior of each subject's anatomy, driven into correspondence with other anatomies, is expressed as a system of partial differential equations, governed by a differential operator (such as the Laplacian ∇^2, or Cauchy-Navier operator $(\lambda+\mu)\nabla(\nabla\bullet) + \mu\nabla^2$) which controls the way in which one anatomy is deformed into the other. The properties of this operator can be used to make the deformation reflect the mechanical properties of deformable elastic or fluid media. Each deformation map is then expanded in terms of the eigenfunctions of the governing operator, and Gaussian probability measures are defined on the resulting sequences of expansion coefficients (Amit et al., 1991; Grenander and Miller, 1994).

Significant advantages can also be gained by analyzing deformation fields with Procrustes methods, developed for the statistical analysis of biological shape (Bookstein, 1989; 1997). Of particular relevance are methods used to define a mean shape in such a way that departures from this mean shape can be treated as a linear process. Linearization of the pathology detection problem, by constructing Riemannian shape manifolds and their associated tangent spaces, allows the use of conventional statistical procedures and linear decomposition of departures from the mean to characterize shape change. These approaches have been applied to detect structural anomalies in schizophrenia (DeQuardo et al., 1996; Bookstein, 1997).

Population Comparisons: Disease to Normal

Group-specific patterns of brain structure may go unnoticed in individual patients' scans due to extreme variations in anatomy between subjects. Population-based brain atlases, however, linked with appropriate warping algorithms, can incorporate extensive regional information on structural variability, and show great promise in identifying group trends and characteristics, especially in disease states.

Group-specific attributes are easier to identify if confounding factors, which contribute to patterns of normal anatomic variation, can be factored out. Structural image databases from twin monozygotic versus dizygotic

populations provide tremendous opportunities to investigate the relationship between genotype and phenotype, and more specifically, between genotype and disease. Striking similarities in brain structure for both mono- and dizygotic twins have been reported in studies of *corpus callosum* morphology (Oppenheim *et al*., 1989) and gyral patterning (Noga *et al*., 1996). These structural affinities can be exploited in clinical studies, since twins discordant for a specific disease-linked gene may be examined for regional structural differences in a context where effects of their shared genes are factored out (Goldberg *et al*., 1994; Noga *et al*., 1996).

Asymmetry Measures. In related work, Thirion et al. (1998) applied a warping algorithm to a range of subjects' scans, in each case matching each brain hemisphere with a reflected version of the opposite hemisphere. The resulting asymmetry fields were treated as observations from a spatially-parameterized random vector field, and deviations due to lesion growth or ventricular enlargement were detected using the theory developed in (Thompson et al., 1997; *see below*). A similar approach was used in (Thompson et al., 1998) to demonstrate that asymmetry of the posterior Sylvian fissure was significantly greater in subjects with Alzheimer's Disease than in elderly normal subjects matched for age, gender, educational level and handedness. Due to the asymmetrical progression of many degenerative disorders (Thompson et al., 1998), abnormal asymmetry may prove to be a sensitive index of pathology in individual subjects or groups. Analysis of variance in 3D deformation fields which match different subjects' anatomies, shows considerable promise in being able to differentiate intra-subject (between hemisphere), inter-subject, and inter-group contributions to brain variation in human populations (Fig. 6; Thompson et al., 1998).

Pathology Detection. In (Thompson et al., 1997), we developed an approach to detect structural abnormalities in individual subjects by constructing a reference image archive of high-resolution 3D brain scans from normal subjects, and constructing a family of volumetric warps to encode statistical properties and directional biases of local anatomical variation throughout the architecture of the brain (see Fig. 8). To identify differences in brain structure between two groups, we defined $\mathbf{W}_{ij}(\mathbf{x})$ as the deformation vector required to match the structure at position $\mathbf{x}$ in an atlas template with its counterpart in subject *i* of group *j*, and modeled the deformations as:

$$\mathbf{W}_{ij}(\mathbf{x}) = \boldsymbol{\mu}_j(\mathbf{x}) + \boldsymbol{\Sigma}(\mathbf{x})^{1/2}\boldsymbol{\varepsilon}_{ij}(\mathbf{x}),$$

where $\boldsymbol{\mu}_j(\mathbf{x})$ is the mean deformation for group *j*, and $\boldsymbol{\Sigma}(\mathbf{x})$ is a non-stationary, anisotropic covariance tensor field, which relaxes the confidence threshold for detecting abnormal structure in regions where normal variability is extreme, $\boldsymbol{\Sigma}(\mathbf{x})^{1/2}$ is the upper triangular Cholesky factor tensor field, and $\boldsymbol{\varepsilon}_{ij}(\mathbf{x})$ is a trivariate random vector field whose components are independent stationary Gaussian random fields. The global maximum of the random deformation field, or derived tensor fields (Thompson et al., 1998), can be used to test the hypothesis of no structural change in disease (Worsley, 1994a,b; Cao and Worsley, 1998). Similar multivariate linear models can be used to test for the effect of explanatory variables (e.g., age, gender, clinical test scores) on a set of deformation field images.

Probabilistic atlases based on random deformation fields, and associated scalar fields derived using operators which emphasize specific deformational characteristics, have been used to assess gender-specific differences in the brain (Davatzikos, 1996; Cao and Worsley, 1998). Clinical applications include their use to detect structural abnormalities in neurodegenerative disorders such as Alzheimer's disease (see Chapter 19, Fig. 13; Thompson et al., 1997, 1998; Mega et al., 1998), and brain development (Thompson et al., 1998).

These algorithms are currently being tested by analyzing 3D MRI and high-resolution cryosection volumes from subjects with metastatic tumors (Thompson et al., 1997), schizophrenia (Moussai et al., 1998), neurodevelopmental disorders (Thompson et al., 1998) and Alzheimer's disease (Thompson et al., 1998), using a probabilistic atlas based on age-matched normal subjects imaged in each modality. In summary, probabilistic atlasing and high-dimensional volumetric warping techniques provide a basis to generate expert diagnostic

systems which retain quantitative information on inter-subject variations in brain architecture.

Alternative Geometries: Flat, Spherical

Cortical morphology is notoriously complex, and presents unique challenges in anatomic modeling investigations. In response to these challenges, much research has been devoted to developing cortical parameterization and flattening algorithms. These methods optimally transform maps of cortical features onto a simpler, non-convoluted surface such as a 2D plane (Van Essen and Maunsell, 1980; Carman et al., 1995; Schwartz and Merker, 1986; Drury et al., 1996), an ellipsoid (Dale and Sereno, 1993; Sereno et al., 1996) or a sphere (Davatzikos, 1996; Thompson et al., 1996, 1997, 1998; see Fig. 3).

Cortical parameterization offers substantial advantages for visualizing cortical topography, and provides potentially clearer interpretations of how architectonic fields and functional loci are related in the cortex (Van Essen et al., 1997). In the Visible Human Project (Spritzer, 1996), two (male and female) cadavers were cryoplaned and imaged at 1.0 mm intervals, and the entire bodies were also reconstructed via 5,000 post mortem CT and MRI images. The resulting digital datasets have served as the foundation for developing related atlases of regions of the cerebral cortex (Drury and Van Essen, 1997), based on flattening computational models of the cortical surface. The resulting templates serve as a structural framework upon which architectonic, functional, and electrophysiological data, can be compared and integrated. Parametric models of the cortex also make comparisons of cortical anatomy more tractable in disease states (Thompson et al., 1997) and even across species (Van Essen et al., 1997). They can also help overcome problems caused by wide cross-subject variations in cortical geometry, by supporting non-linear registration of cortically-derived functional data and histologic brain maps localized at the cortex (Thompson et al., 1996; Davatzikos, 1996; Mega et al., 1997).

Warping the Cerebral Cortex. Despite the advantages provided by transformations which simplify its geometry, the cortical surface presents significant challenges for all brain warping algorithms, which strive to match the anatomy of one subject's cortex with another. The need to make comparative measurements across subjects requires a surface-to-surface warp which not only matches overall cortical geometry, but also enforces point-to-point correspondence to a higher degree. Specialized approaches have been developed to match cortical regions, so that networks of sulci and gyri are individually matched. Differences in the serial organization of cortical gyri prevent exact gyrus-by-gyrus matching of one cortex with another. Some cortical areas are particularly subject to variations in the incidence and topology of accessory gyri, and one subject may have two or three gyri where one gyrus is found in another subject. This feature is especially notable in studies of paracingulate and temporo-parietal regions, in particular the *planum temporale* and posterior perisylvian areas which form a critical part of the language representation of the left hemisphere (Ono *et al*., 1990; Paus *et al*., 1996; Leonard, 1996). Since the assumption that brains are topologically equivalent breaks down once the functional units of the cortex are finely subdivided, an important intermediate goal has been to identify and match a comprehensive network of sulcal and gyral elements which are consistent in their incidence and topology across subjects (Ono et al., 1990; Rademacher et al., Thompson et al., 1996, 1997; Subsol, 1998).

In surface-based approaches, 3D deformable models (Cohen and Cohen, 1992; MacDonald et al., 1993; Davatzikos, 1996; Thompson and Toga, 1996; see Fig. 9) are used to automatically extract parametric representations of each subject's cortex, on which corresponding networks of anatomical curves are identified. The transformation relating these networks is expressed as a vector flow field in the parameter space of the cortex, which indirectly specifies a correspondence field in 3D driving one cortical surface into the shape of another (Drury et al., 1996; Davatzikos, 1996; Thompson and Toga, 1996; see Fig. 3, *panels 1 to 10*).

Because the surfaces being matched, by warping one to the other, have already been reparameterized or flattened, the effects of the first warping procedure (flattening) on the second (matching) need to be carefully evaluated. To

address this difficulty, a covariant regularization approach is introduced in (Thompson and Toga, 1998) to ensure that the cortical matching fields are not biased by differences in how surface models are flattened or parameterized. We first establish the cortical parameterization, in each subject, as the solution of a time-dependent partial differential equation (PDE) with a spherical computational mesh (Thompson and Toga, 1996; Davatzikos, 1996). This procedure sets up an invertible parameterization of each surface in deformable spherical coordinates, and allows direct computation of the metric tensors of the mappings. The solution to this PDE defines a Riemannian manifold (Bookstein, 1995) on which a second PDE is defined, to govern the matching of sulcal networks from subject to subject (Fig. 3, *panels 4 to 7*). The continuum-mechanical operator governing the mapping of one surface to another is replaced by its covariant counterpart (Thompson and Toga, 1998), in which correction terms (Christoffel symbols; *cf.* Einstein, 1914) compensate for fluctuations in the metric tensor of the flattening procedure. In view of their power to integrate cross-subject cortical data, parameterized or flattened representations of cortex show great promise in elucidating the functional organization of the cortex, and in investigating how these architectural patterns vary across individuals and species (Van Essen et al., 1997).

V. Visualization

Visualizing the results of a warp, specifically the mapping of one brain to another or to an atlas, can be in the form of displaying the correspondences between the image volumes or the deformation map itself. In addition to the statistical value of warping, the visual product can greatly enhance our ability to comprehend the relationship between image volumes. As the data itself consists of images, the ability to visualize it before, during and after any warping is essential. Once again the regularity of the data structure has certain advantages for visualization, just as it does for parallel warping algorithms. And just as warping algorithms can be implemented primarily based on intensity or model-based information, so too can visualization algorithms.

Visualization of neurobiological data enables us to create high quality images from combined datasets to gain insight into the structure and function of brain. These combined datasets can be a series of serial sections depicting anatomy or physiology, two or more modalities from the same subject or ultimately data from multiple modalities from multiple subjects. The techniques used to process this information into comprehensible displays also must provide access to the quantitative nature of the data. Morphometry and densitometry are necessary elements of useful visualization schemes. Because our ultimate objective requires the warping of brain datasets, we will incorporate those aspects of visualization that help synthesize new information from multiple sources as well as present it quantitatively.

Regardless of its source, organizing data into volumes can make visualization easier. A complete collection of brain slices can be reconstructed into a volume, whether it comes from tomographically or physically sectioned methods. Volume visualization has received considerable interest in recent years resulting in several publications entirely devoted to it. The interested reader should consult Friedhoff and Benzon (1989); Kaufman (1991); Robb (1985); Toga (1990); and Udupa and Herman (1991). Advanced topics in medical volume visualization can be found in Höhne et al. (1990) and Levoy et al. (1990).

Surfaces and Volumes

To visualize a volume dataset, two approaches can be used. The first, termed *volume rendering* (Drebin et al., 1988), projects volume primitives directly for shading and viewing. The second method, termed *surface rendering*, computes explicit geometric primitives (Herman and Liu, 1979; Toga et al., 1989) such as polygon meshes prior to the viewing and shading stages.

Representing the surface as explicit geometry is efficient when used with the conventional computer graphics approaches for shading and viewing. Further, it greatly reduces the necessary data storage and provides a data structure that can be measured. However, it requires the calculation of an intermediate surface representation.

Volume rendering, on the other hand, uses classification schemes to segment the data into components for inclusion (or exclusion) in a given view. Whereas surface rendering assumes that the data consists of surfaces that can be extracted and visualized, volume rendering does not assume any existing structure. Surface rendered models (by themselves) do not retain any information deep to the surface, while volume representations maintain the entire dataset allowing any part of the data to be viewed. Maintenance of the entire dataset also enables densitometric measurements. The utility of each approach is primarily dependent upon the type of data and the intent of the visualization. Numerous algorithms have been developed to take advantage of the relative strengths of each approach (Elvins, 1992; see Figure 10).

Both approaches are designed to communicate information about the datasets. Combining some of the characteristics of each can provide comprehensive and understandable displays that contain information suitable for morphometric and densitometric measurement. Warping multiple modalities and multiple subject datasets requires such a combined approach.

Manipulation

Manipulating the location, orientation (and display primitives) of an image volume is, as noted in the beginning of this chapter, the simplest form of transformation. These translocations are often included with the more extreme transformations considered warping. Ignoring the issues of stereotaxy, multiple modality and multiple subject comparisons, certain locations and orientations are more illustrative than others. Similarly the display primitives and attributes of the display such as points, contours, wireframe meshes, solid modeling elements, Phong or Gouraud shading, opacity, color, etc. can greatly influence the viewer's comprehension of the material (Toga, 1990). Experimentation on the use of geometric transformations and variations of display primitives is often necessary to obtain the most satisfactory results.

Interactive manipulation of data is extremely useful in targeting specific loci or determining the similarity (or disparity) between two (or more) data sets. This is where the computational demand and requirement for specialized hardware dictate the capabilities. Computational speed and storage size limitations will determine the degree of interaction and type of data that can be manipulated in this way. But the usefulness of this approach in many settings is obvious.

Interactive visualization during the computation of a particular warp has many advantages. It allows the progress of the algorithm to be monitored, and provides insight as to the relationship between image volumes. To display the interim product of the algorithm, the visualization strategies are in competition with the computational resources utilized by the warping. Therefore, judicious use of complex visualization approaches is warranted.

Display

Visualizing measured quantities within a meaningful spatial framework is the intent of digital image display. Choosing the most appropriate method of presentation requires a diverse skill set that includes artistic, psychophysical and statistical considerations. Since the goal of display is to describe, summarize and in some instances interact with the data, great care is necessary in its design. An excellent treatise on this and related subjects was written by Tufte (1983, 1990). For our purposes we must use an image composition that conveys several important characteristics about the image volumes simultaneously. These include spatial, densitometric, correlative, and sometimes temporal information. The location and orientation of the data, and, in the case of surface models, the shape, size and relationship between substructures within the model, describe its spatial features. Textures mapped on the surface of structures can represent another modality such as a functional response, or can reflect the degree of similarity or difference between image volumes or models. The intensity or magnitude of a response is conveyed by the value of the pixel or voxel. These values can be transformed to represent a physiological measurement and/or pseudocolored to enhance their differences. Differences before

and after a warp can be displayed following an arithmetic operation such as image subtraction. Display of the relationship can be in the form of superpositioning multiple datasets, each with different color assignments (Mazziotta et al., 1991), texture mapping one modality upon another (Payne and Toga, 1990) or a statistical representation of the relationship between datasets (Toga et al., 1986).

The warping field itself can be displayed too. Several creative methods have been employed to display the resulting warping field relative to the image volume (Toga, 1994; Thompson and Toga, 1996). These can be in the form of vectors relative to a superimposed lattice, or as a colorized texture upon the surfaces of specific features (Fig. 11). Such displays immediately identify regional patterns relative to the underlying anatomy.

Changes over time are best displayed as animations (Toga and Payne, 1991; Thompson and Toga, 1997), but also can be visualized as a static image of rate of change. In these cases, the warping required to measure the change can also be used to create time-varying displays, especially if interpolations between time-points are required.

VI. Multidimensional Warping

Temporal Maps

One of the most promising applications of warping algorithms is their use as a *virtual sensor* (Gee et al., 1993), creating exquisitely detailed maps of anatomic differences. Maps of anatomical *change* can also be generated by warping scans acquired from the same subject over time (Thompson et al., 1998; Thirion et al., 1998). Despite their potential utility in clinical and research settings, detailed quantitative descriptors of local structural change, across time, have not been available.

Current structural brain imaging investigations focus on the analysis of 3-dimensional models of brain structure, derived from volumetric images acquired at a single time-point from each subject in the study. Based on these static anatomical models, computerized strategies are being developed which use warping to detect abnormal structure (Kikinis et al., 1994; DeQuardo et al., 1996; Bookstein, 1997; Thompson and Toga, 1997; Thompson et al., 1997; Haller et al., 1997; Thirion et al., 1998). In many ways, static representations of structure are ill-suited to determining the dynamic effects of disease. However, serial scanning of human subjects, when combined with a powerful set of warping and analysis algorithms, will enable disease and growth processes to be tracked in their full spatial and temporal complexity.

Serial scanning of human subjects (Fox et al., 1996; Freeborough et al., 1996; Thompson et al., 1998) or experimental animals (Jacobs and Fraser, 1994) in a dynamic state of disease or development offers the potential to create 4-dimensional models of brain structure. These models incorporate dynamic descriptors of how the brain changes during maturation or disease. For a range of patient populations, 4D models of the brain can be based on imaging and modeling its 3-dimensional structure at a sequence of time-points. In a changing morphology, warping algorithms enable one to model structural changes that occur over prolonged periods, such as developmental, aging or disease processes, as well as structural changes that occur more rapidly, as in recovery following trauma or tumor growth. A 4-dimensional approach is required to provide critical information on local patterns and rates of tissue growth, atrophy, shearing and dilation that occur in the dynamically changing architecture of the brain (Toga et al., 1996; Thompson et al., 1998).

Tracking Structural Change

Any comprehensive framework for modeling temporal change in 3-dimensional brain structure must draw upon methods for quantitating its material transformation between pairs of images acquired at successive time-points. The complexity of such a task is considerable, since it requires repeated acquisitions, averaging across subjects, and tracking homologous landmarks over a series of 3D scans. Modeling shape changes of a biological system

under deformation has been the subject of intense research, since the advent of high resolution medical imaging (Kambhamettu and Goldgof, 1992). Algorithms to recover, model and track structures in complex non-rigid motion have been used effectively in producing high-resolution surface animations of the beating heart (Chen et al., 1994), white blood cell motility (Bartels et al., 1992), and optical flow algorithms (Horn and Schunck, 1993; Denney and Prince, 1994). Warping algorithms are central to all of these approaches.

The warp is a 4D model. It specifies the displacement of every anatomic point in the brain across the disease or developmental stage spanned by the two images. As such, it permits complete morphometric quantitation of the dynamic effects of the underlying biological processes on the geometry of the brain and its substructures. It allows points, surfaces and curved anatomic interfaces to be matched up in a pair of image sets. As a result, changes in volumes, surface areas, orientations, distances and in metrical relations between substructures - as well as measures of dilation rates, contraction rates, and rates of shearing and divergence of the cellular architecture - may be computed locally, for all structures, directly from the warping field. Since the warping field assigns a displacement for every anatomic point across a time-step, curves, surfaces and volumes in an early image may be re-identified in a later one. This enables relative areas, lengths and volumes to be compared over time. Derivatives of these quantities with respect to time allow growth rates to be quantified locally for any structure; spatial derivatives of the warping field allow shearing and dilation to be measured locally, and compared for different substructures.

Early Approaches. A basic approach for detecting structural change in serial MRI scans of the same subject (and a pre-requisite for more sophisticated approaches) is based on rigidly registering one 3D scan with another, and constructing a map of the differences in MR signal intensities between the two scans (see Fig. 12). While this strategy is powerful in determining whether structural change has occurred in dementia (Fox et al., 1996; Freeborough et al., 1996), there are several clear advantages that warping algorithms can offer over rigid (or affine) registration. Without the use of warping algorithms to measure patterns of change:

(1) local information on anatomic change is unavailable, since rigid registration is used to overlay the scans;
(2) artifactual differences in signal intensity, radio-frequency drifts, and histogram differences can introduce errors in both the rigid registration and the resulting difference maps;
(3) maps of MR signal differences alone do not provide 3-dimensional measures of dilation, contraction or shearing of anatomic regions in the interval between the two scans.

Limitations with earlier approaches largely result from the use of rigid rather than non-linear registration, and use of the MR signal intensity as the source of information on structural change, rather than the tensor fields expressing local maps of 3-dimensional deformation and change. Tensor maps of neuroanatomic change (Fig. 13), characterized by a large number of parameters at each point in space, become available when temporal change is tracked using warping methods. These tensor maps can be computed in a variety of ways by non-linear registration and elastic matching algorithms (Woods et al., 1998; Toga, 1998; Thompson and Toga, 1998).

4D Atlases of Brain Development

Atlasing of developmental brain data presents unique challenges. The imposition of standardized coordinate systems is difficult, and their relationship to anatomic nomenclature is hard to define, when potentially drastic morphological differences exist among data sets. In Yoon et al. (1997), a photographic atlas of the human embryo was created, based on detailed observations *in utero* from the 4th to the 7th week after ovulation (Carnegie Stages 10-18). In Chong et al. (1997), 26 normal formalin-fixed fetal specimens with a gestational age of 9 to 24 weeks were examined with high-resolution MRI using a conventional clinical magnet and pulse sequences, and MR findings were correlated with histologic atlas data. Although templates of normal development helped to identify expected developmental features, it was noted that direct correlation of fetal MR images with anatomic atlases might result in a mistaken diagnosis of delayed development, because of a time lag in the detection of

structures on MR images.

Current atlases of fetal development (O'Rahilly and Müller, 1987; England, 1990) use collections of labeled data from multiple imaging modalities to characterize specific developmental stages. The first comprehensive MRI atlas of pediatric cranial anatomy (Salamon et al., 1990) incorporates 180 MRI scans acquired parallel to the orbito-meatal anatomical plane, and 360 explanatory diagrams depicting functional neuroanatomy from birth through 16 years of age. However, stereotaxic coordinate systems were not applied to the atlas data due to difficulties in using them to reference embryonic and pediatric data. In the spirit of the deformable atlas methods described earlier, extreme deformations could be imposed to fit all stages of development into a standardized atlas, but this would hardly meet the primary requirement of atlasing, which is to provide a natural coordinate framework in which to localize and classify structures present in developing brains. Alternatively, different atlases and coordinate systems for several discrete stages of development might be used. Numerous anatomic features, due to their emergence and disappearance during development, could be used to place individual brains into an appropriate atlas in the set. Warping approaches could then be applied to the atlas coordinate systems as a basis to compare and quantitate development (Toga et al., 1996; see Fig. 14).

In one experiment (Toga et al., 1996), warping approaches based on voxel-coding and distance fields (Payne and Toga, 1992; Zhou et al., 1998) were used to generate a dynamic map of brain development in the rat, based on high-resolution 3D image data and derived surface models of structure (Figure 14). Temporal interpolation between atlases in the set enabled the generation of additional anatomic templates, representing brains at any arbitrary stage of maturity in between those stages represented in the initial inventory.

Mapping Growth Patterns in 4 Dimensions

In our initial human studies (Thompson et al., 1998; Thompson and Toga, 1998), we developed several algorithms to create 4-dimensional quantitative maps of growth patterns in the developing human brain, based on time-series of high-resolution pediatric MRI scans. Deformation processes recovered by the warping algorithm were analyzed using vector field operators to produce a variety of tensor maps (Fig. 13). These maps were designed to reflect the magnitude and principal directions of dilation or contraction, the rate of strain, and the local curl, divergence and gradient of flow fields representing the growth processes recovered by the transformation.

In contrast to the near-zero maps of change recovered at short time intervals (2 weeks), tensor maps of growth spanning large time intervals (4 years) showed complex and heterogeneous patterns of change. In one subject scanned at ages 7, 9 and 11, comparative stability of lobar and thalamic anatomy, and negligible changes at the callosal midbody, were accompanied by pronounced focal growth at the callosal midbody, ventricular enlargement and loss of caudate tissue. To further characterize the growth process, derived properties of the deformation fields were examined, including local expansion, contraction or shearing effects recovered by the warping transformation. The Jacobian of the deformation field has been used as a local index of gender-specific shape differences in the corpus callosum (Davatzikos, 1996). Other local vector field operators, including the gradient and divergence ($\mathbf{\nabla u(x)}$, $\mathbf{\nabla^T \bullet u(x)}$; Thompson et al., 1998) and the specialized norm $\times$ divergence operator ($\|\mathbf{u(x)}\|.\mathbf{\nabla^T \bullet u(x)}$; Thirion and Calmon, 1997; Thirion et al., 1998) have been applied to deformation fields, in studies of brain development and multiple sclerosis lesion growth. Each of these operators is designed to emphasize different aspects of growth or pathologic processes.

Figure 13 shows the complex patterns of growth detected in a young normal subject during the 4-year period from 7 to 11 years of age. Despite minimal changes in overall cerebral volume, striking regional growth is detected at the *corpus callosum*, with peak values occurring throughout the posterior midbody (the same area

found to degenerate preferentially in our dementia studies (Thompson et al., 1998)). This pronounced pattern of growth contrasts with the near-zero maps of change observed over a 2-week interval (Fig. 13; *lower panel*).

Recovery and interpretation of maps of neuroanatomic change present considerable logistic and mathematical challenges. At the same time, they hold tremendous promise in representing, analyzing and understanding the extremely complex dynamic processes that affect regional anatomy in the healthy and diseased brain.

VII. Summary

The variety of warping approaches is equaled by their range of applications. There are classes of algorithms each suited to handling particular kinds of information, intensity patterns or anatomical features, for example. Within classes of warps, there are several mathematical strategies for achieving a solution. Furthermore, there is no obvious hierarchy with one better than another. Each has strengths and weaknesses, each may perform particularly well given certain kinds of data, and each often complements others in performance, application and strategy.

The results obtained using warping algorithms provide both a qualitative and statistical measure of brain image data. As we have seen, the warpings are by no means restricted to individual pairs, rather they are particularly well-suited to population and atlas-based transformations. The product of warping algorithms not only provides the ability to make comparisons, it also permits the generation of atlases and maps. The statistical product is often best accompanied by visualization. Incorporating interim displays and animating the spatial transformation has remarkable power for elucidating complex and significant morphological change. Finally, warping across modalities and with multiple dimensions has made possible the synthesis of comprehensive reference systems that fully describe brain structure and function within whole populations.

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Figure Legends

Fig. 1. *Warping Algorithms Integrate Multi-Modality Brain Data*. Histologic tissue sections, stained here to reveal neurofibrillary tangle density in a subject with Alzheimer's Disease, can be compared with functional imaging data acquired from the same subject *in vivo* (Mega et al., 1997). Images of stained tissue sections (*top left*) are elastically warped back into their original configuration in the cryosection blockface. An additional warp reconfigures the *post mortem* cryosection and histologic data back into their *in vivo* configuration, as imaged by pre-mortem MRI. All maps can then be correlated with PET data acquired *in vivo* from the same patient, which is aligned to the MR template using an additional cross-modality registration.

Fig. 2. *Continuum Mechanical Warping*. (a) The complex transformation required to reconfigure one brain into the shape of another can be determined using continuum-mechanical models, which describe how real physical materials deform. In this illustration, two line elements embedded in a linearly elastic 3D block (*lower left*) are slightly perturbed (*arrows*), and the goal is to find how the rest of the material deforms in response to this displacement. The Cauchy-Navier equations (shown in discrete form, *top*) are solved to determine the values of the displacement field vectors, **u(x),** throughout the 3D volume. (b)

Lamé Elasticity Coefficients. Different choices of elasticity coefficients, λ and μ, in the Cauchy-Navier equations (shown in continuous form, *top*) result in different deformations, even if the applied internal displacements are the same. In histologic applications where an elastic tissue deformation is estimated, values of the elasticity coefficients can be chosen which limit the amount of curl (*lower right*) in the deformation field. Stiffer material models (*top left*) may better reflect the deformational behavior of tissue during histologic staining procedures. *Note*: For visualization purposes, and to emphasize differences in deformation patterns, the magnitudes of the displacement vector fields shown in this figure have been multiplied by a factor of 10. The Cauchy-Navier equations, derived using an assumption of small displacements, are valid only when the magnitude of the deformation field is small.

Fig. 3. *Anatomically-Constrained Scheme for Matching of Cortical Regions.* Accurate detection and encoding of anatomic differences between subjects requires transformation tools which deform one cortical surface model (*panel 1*) into region-by-region correspondence with another (*10*). The computation of this mapping is conceptualized mathematically as a biologically-constrained elastic transformation, which deforms one cortical surface into the shape of another. The transformation is calculated in a very exact way, so that the sulcal patterns of each brain are brought into register. Elastic matching of cortical surfaces from different subjects is a multi-stage process (Thompson *et al*., 1997; Thompson and Toga, 1998). For computational reasons, the shape details of each cortical surface are encoded into a compact 5-dimensional data structure. Because the cortical model is a parameterized surface (*2*) arrived at by deformation of a spherical mesh (*see Fig. 6*), any cortical surface point must map to exactly one point on the sphere, and *vice versa*. The location on the sphere corresponding to a surface point defines the parameters of the point; curves on the brain surface, such as sulci, have exact counterparts on the globe coordinate grid (*4*). Each point on the sphere (*4*) is coded with a color value which uniquely represents its counterpart's location on the convoluted surface model (*3*) for that subject, in 3D stereotaxic space. Next, each octant of this sphere is flattened out onto a quadrant of a 2D plane (*5*). Sulcal curves and landmarks in the folded brain surface may be re-identified in this 2-dimensional 'flat map', because the flat map is just an alternative way of representing the brain surface. When flat maps are made from two different cortical surfaces (*5,6*), the respective sulci will be in different positions in each flat map, reflecting their different locations on the folded brain surface. A complex biologically-driven deformation algorithm (Thompson and Toga, 1996), corrected for metric tensor fluctuations in the underlying flat maps (Thompson and Toga, 1998), then drives systems of sulcal curves and cortical landmarks in one flat map (*5*) into exact correspondence with their counterparts in the target flat map, guiding the transformation of the adjacent regions. A covariant regularization approach is developed to compute the matching field (Thompson and Toga, 1998). The impact of the transformation is illustrated (*6*) by its effect on a regularly-spaced grid, ruled over the starting flat map, and passively carried along in the resultant deformation. Because the flat maps index cortical surface locations in 3D, the transformation of one flat map to another is recovered in 3D stereotaxic space as a displacement of points in one subject's cortex (*1*) onto their counterparts in the cortex of another subject (*10*). Consequently, the transformation of one cortical surface model onto another is calculated by applying the transformation of panels 1 through 5 in reverse (*6-10*). The full transformation (*1-10*) is parameterized by one translation vector for each mesh point in the surface model, or $3 \times 65536 \approx 0.2$ million parameters. This high-dimensional parameterization of the transformation is required to accommodate fine anatomical variations.

Fig. 4. *Population-Based Multi-Modality Histologic Brain Atlas***.** The construction of a population-based histologic brain atlas requires extensive use of 2D and 3D warping algorithms (Schormann et al., 1996; Thompson et al., 1997; Mega et al., 1997, 1998). Here *post mortem* brain specimens from multiple human subjects are cryosectioned (*left, top row*). Serial anatomic sections are then treated using histologic staining procedures. Sections treated to reveal cellular composition using Nissl and Golgi stains can be interdigitated with other sections treated immunocytochemically or using *in situ* hybridization. Although maps of regional cellular and molecular content are derived from adjacent sections, complex deformations during staining procedures can compromise the spatial integrity of the maps. Images of stained sections can, however, be elastically warped back into their original configuration in the cryosection blockface, and, using a 3D warping algorithm, back into their *in vivo* configuration if *pre-mortem* anatomic scan data is available (Mega et al., 1997). Fusion of histologic atlas data from multiple subjects (*top right*) also requires 3D warping algorithms. By compensating for differences in gross anatomy between subjects, multi-subject data can be transferred to a single anatomic template for comparison and integration. Once gross structural variation is factored out, cytoarchitectonic variation with respect to gross anatomic landmarks can also be analyzed directly (Rademacher et al., 1993).

Fig. 5. *Mean MRI dataset based on 305 Normal Subjects*. Average neuroanatomic templates (Evans et al., 1994) can be used to localize functional activation data in stereotaxic space. Automated image registration and warping algorithms can also be used to align new MRI and co-registered functional data with this type of template, by maximizing a measure of intensity similarity, such as 3D cross-correlation (Collins et al., 1994a,1995), ratio image uniformity (Woods et al., 1992), or mutual

information (Viola et al., 1995; Wells et al., 1997).

Fig. 6. *Population-Based Maps of 3D Structural Variation and Asymmetry*. Statistics of 3D deformation maps can be computed to determine confidence limits on normal anatomic variation. 3D maps of anatomic variability and asymmetry are shown for 10 subjects with Alzheimer's Disease (AD; age: 71.9±10.9 yrs.), and 10 normal elderly subjects matched for age (72.9±5.6 yrs.), gender, handedness and educational level (Thompson et al., 1998). Normal Sylvian fissure asymmetries (right higher than left; $p<0.0005$), mapped for the first time in 3D, were significantly greater in AD than in controls ($p<0.0002$; *top panels*). In the 3D variability maps derived for each group (*lower panels*), the color encodes the root mean square magnitude of the displacement vectors required to map the surfaces from each of the ten patients' brains onto the average. Confidence limits on 3D cortical variation (*lower right panel*), exhibited severe increases in AD from 2-4 mm at the *corpus callosum* to a peak standard deviation of 19.6 mm at the posterior left Sylvian fissure.

Fig. 7. *Scheme for Constructing a Deformable Probabilistic Atlas.* A family of high-dimensional volumetric warps relating a new subject's scan to each normal scan in a brain image database is calculated (I-II, *above*), and then used to quantify local structural variations. Differences in cortical, ventricular, and deep sulcal topography are recorded in the form of vector field transformations in 3D stereotaxic space which drive both subcortical anatomy and the gyral/sulcal patterns of different subjects into register. The resulting family of warps encodes the distribution in stereotaxic space of anatomic points which correspond across a normal population (III), and their dispersion is used to determine the likelihood (IV) of local regions of the new subject's anatomy being in their actual configuration. Easily interpretable, color-coded topographic maps can then be created to highlight regional patterns of deformity in the anatomy of each new subject (Thompson et al., 1997). This approach quantifies abnormal structural patterns locally, and maps them in 3 dimensions.

Fig. 8. *Detection of a Series of Simulated Deformations of the Cortical Surface*. Color-coded probability maps are shown (*high probability: blue; low probability: red*) for a sequence of artificially-contracted cortical surface models. In this case, abnormalities are deliberately created and mathematically defined, and the nature and context of the deformations are systematically varied to determine the conditions which affect detection sensitivity. Probability maps are shown for cortical models contracted posteriorly by a total of: (a) 5mm; (b) 10mm; (c) 15mm; and (d) 20mm. Each map reflects the severity of the deformations exhibited by the contracted model, relative to the range of variations deliberately assigned to the reference set of cortical surfaces. Although no areas of cortical abnormality were indicated on the cortical surface model contracted by only 5 mm (a), when the contraction was increased to 20 mm (d), 26.2 % of the cortical surface exhibited probability values which were severely depressed ($p < 0.00001$). Note the severity of the effect in frontal areas, where the magnitude of the applied deformation was greatest. These experiments are designed to illustrate the graded response of the probability mapping algorithm, in assessing deformations of spatially-varying magnitude across the cortex.

Fig. 9. *Cortical Surface Extraction*. Specialized warping approaches can be developed for matching cortical surfaces in a very precise way, which guarantees that large networks of curved gyral and sulcal landmarks are individually matched (Thompson et al., 1997). The first step in this warping procedure is to obtain a high-resolution surface representation of the cortex. To do this, a semi-automatic 3D active surface extraction algorithm is used (MacDonald et al., 1993). In the course of the surface extraction, a spherical mesh surface (*top left*) is governed by a system of partial differential equations, which allow it to be continuously deformed to match a target boundary defined by a threshold value in the continuous 3D MR image intensity field. The algorithm operates in a multi-scale fashion, so that progressively finer surface detail is extracted at finer scale representations of the data. The initial surface, composed of 8192 polygons, is extracted rapidly, but expresses only the gross shape of the cortex (*top right*). After several finer scale steps, the data are sampled at 1.0 mm intervals resulting in a surface consisting of 100,000-150,000 polygons (*lower left*). The resulting model of the cortex consists of a high-resolution mesh of discrete triangular elements that tile the surface (*lower right*).

Fig. 10. *Combined Surface and Volume Rendering of Reconstructed Human Brain*. This figure illustrates the use of perspective and specific orientations to enhance the viewer's appreciation of depth and relative size of substructures. Different display primitives, including color and opacity, help distinguish among anatomic regions. The anatomic regions were interactively segmented using a contour-based system, and surface-rendered. A cut-plane was introduced to display densitometric information contained in the original histologic dataset. Thus this figure uses aspects of both approaches to volume visualization. A frontal-lateral view of the brain is used where the cortex is surface-rendered and Phong shaded, the ventricles are displayed as solid blue structures, the cerebellum is shown using yellow points, and the basal ganglia are

rendered solid red. The cut-plane is rendered based on an arbitrary color scale mapping of the original histologic imagery. The data comes from a single modality and a single *post mortem* cryoplaned specimen.

Fig. 11. *Nested Brain Surfaces after Registration into Standardized Talairach Stereotaxic Space*. 3D frontal views are shown of two normal subjects' brain surfaces, after digital transformation into Talairach stereotaxic space. One basis for comparison among cortical shapes is a deformation map, which represents the local transformation required to deform a high-resolution surface mesh, representing the cortical surface in one subject, onto a target surface from another individual. In particular, a network of lobar, sulcal, and cytoarchitectural landmarks are displaced into structural correspondence with their counterparts in a target brain. The resulting displacement map encodes regional differences in sulcal and gyral topography. Indicated here (*in color*) is the magnitude of the local displacement required to deform one cortical surface into correspondence with a target surface from another subject (*blue*). Differences in regional shape are assessed by computing the local displacements and deformation tensors required to transform one cortical surface into another, according to strict biological criteria.

Fig. 12. *Growth Patterns in the Developing Human Brain.* A young normal subject was scanned at the age of 7, and again four years later, aged 11, with the same protocol (data from Thompson et al., 1998). Scan histograms were matched, rigidly registered, and a voxel-by-voxel map of intensity differences (*left*) reveals global growth. In a control experiment, identical procedures were applied to two scans from a 7 year old subject acquired just two weeks apart, to detect possible artifactual change due to mechanical effects, and due to tissue hydration or CSF pressure differences in the young subject between the scans. These artifacts were minimal, as shown by the difference image, which, as expected, is largely noise. Rigid registration of the scans does not localize anatomic change, but is a precursor to more complex tensor models of structural change (see main text), which not only map local patterns of differences or change in 3 dimensions, but also allow calculations of rates of dilation, contraction, shearing, and torsion (Toga et al., 1996; Thompson et al., 1998).

Fig. 13. *Tensor Maps of Growth*. ((a), *top panel*:) A complex pattern of growth is detected in the *corpus callosum* of a young normal subject. This map illustrates structural change occurring in the 4-year period from 7 to 11 years of age. The effects of the transformation are shown on a regular grid ruled over the reference anatomy and passively carried along in the transformation which matches it with the target. Despite minimal changes in overall cerebral volume, callosal growth is dramatic, with peak values occurring throughout the posterior midbody. The pattern of growth contrasts with the near-zero maps of change observed between scans acquired over a 2-week interval ((a), *lower panel*). (b): Vector field operators help to emphasize patterns of contractions and dilations, emphasizing their regional character. Here, the color code shows values of the local Jacobian of the warping field, which indicates local volume loss or gain. Pronounced neuroanatomical growth is observed during the 4-year interval ((b), *top panel*). This contrasts sharply with the negligible change detected over a 2-week time-span ((b), *lower panel*).

Fig. 14. *Animation of Brain Development in the Rat*. This figure shows a developing rat brain, from *in utero* samples to neonate. An animation sequence was created to show timed growth patterns using an interpolant based on minimum distance fields. Surface models transformed over time provide 4-dimensional measures of structural change (Toga et al., 1996; Thompson et al., 1998).

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