

ELASTIC IMAGE REGISTRATION AND PATHOLOGY DETECTION

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I. Challenges in 3D Brain Imaging

The complexity of human brain structure mandates the use of engineering approaches drawn from computer vision, image analysis, computer graphics and artificial intelligence research fields to manipulate, analyze and communicate brain data. The rapid growth in brain imaging technologies has also been matched by an extraordinary increase in the number of investigations analyzing brain structure and function in clinical and research settings.

Image registration is central to many of the challenges in brain imaging today. Initially developed as an image processing subspecialty to geometrically transform one image to match another, registration now has a vast range of applications. In this chapter, we review the registration strategies currently used in medical imaging, with a particular focus on their ability to detect and measure differences. These include methods developed for automated image labeling and for pathology detection in individuals or groups. We show that these algorithms can serve as powerful tools to investigate how regional anatomy is altered in disease, and with age, gender, handedness and other clinical or genetic factors. Registration algorithms can encode patterns of anatomic variability in large human populations, and can use this information to create disease-specific, population-based brain atlases. They may also fuse information from multiple imaging devices to correlate different measures of brain structure and function. Finally, registration algorithms can even measure dynamic patterns of structural change during brain development, tumor growth, or degenerative disease processes (Toga et al., 1996; Thompson et al., 1999).

Pathology Detection. Normal anatomic complexity makes it difficult to design automated strategies that detect abnormal brain structure. Considerable research has focused on uncovering specific patterns of anatomic alterations in Alzheimer's Disease (AD) or other dementias (Friedland and Luxenberg, 1988), schizophrenia (Kikinis et al., 1994; Csernansky et al., 1998), epilepsy (Cook et al., 1994), attention deficit hyperactivity disorder (ADHD; Giedd et al., 1994), autism (Filipek et al., 1996; Courchesne, 1997), and cortical dysplasias (Sobire et al., 1995). At the same time, brain structure is so variable that group-specific patterns of anatomy and function are often obscured. Reports of structural differences in the brain linked to gender, IQ, and handedness are a topic of intense controversy, and it is even less clear how these factors affect disease-specific abnormalities (Thompson et al., 1999). The importance of these linkages has propelled registration to the forefront of brain imaging investigations. To distinguish abnormalities from normal variants, a realistically complex mathematical framework is required to encode information on anatomic variability in homogeneous populations (Grenander and Miller, 1998). As we shall see, elastic registration or *warping* algorithms offer substantial advantages for encoding patterns of anatomic variation and detecting pathology.

Analyzing Brain Data. One of the driving forces that made registration important in brain imaging was the need to perform brain to brain comparisons. Anatomic variations severely hamper the integration and

comparison of data across subjects and groups (Meltzer and Frost, 1994; Woods, 1996). Motivated by the need to standardize data across subjects, registration methods were developed to remove size and shape differences that distinguish one brain from another (Talairach and Tournoux, 1988). Transforming individual datasets into the shape of a single reference anatomy, or onto a 3D digital brain atlas, removes subject-specific shape variations, and allows subsequent comparison of brain function between individuals (Christensen *et al.*, 1993; Ashburner *et al.*, 1997). For similar reasons, *deformable brain atlases* are based on the idea that a digital brain atlas can be elastically deformed to fit a new subject's anatomy (Evans *et al.*, 1991; Gee *et al.*, 1993; Christensen *et al.*, 1993; Sandor and Leahy, 1995; Rizzo *et al.*, 1995; Toga and Thompson, 1997; Haller *et al.*, 1997). High-dimensional brain image registration, or *warping* algorithms (Christensen *et al.*, 1993; 1996; Collins *et al.*, 1994a; Thirion, 1995; Rabbitt *et al.*, 1995; Warfield *et al.*, 1995; Davatzikos, 1996; Thompson and Toga, 1996; Bro-Nielsen and Gramkow, 1996; Gee *et al.*, 1998; Grenander and Miller, 1998) will be discussed in detail in this chapter. These algorithms can transfer 3D maps of functional and vascular territories onto the scan of any subject, as well as information on tissue types, cytoarchitecture, histologic and neurochemical content (Mega *et al.*, 1997).

Measuring Anatomical Differences. As a valuable by-product, 3D warping algorithms also *quantify* local and global shape changes. The complex profiles of dilation and contraction required to warp an atlas onto the new subject's brain provide an index of the anatomical shape differences between that subject's brain and the atlas (Davatzikos *et al.*, 1996; Thompson *et al.*, 1997; Ashburner *et al.*, 1998). Differences in regional shape can be assessed by the displacement required to locally deform one brain volume into another, and can be further examined by applying vector and tensor field operators to the transformation field (Thompson and Toga, 1998; Thirion *et al.*, 1998). As a result, deformable atlases not only adapt to individual anatomy, but they offer a powerful strategy to analyze developmental, age-related or pathologic variations.

Population-Based Atlases. Pathology detection algorithms will be discussed later (Section 4). These invoke deformation fields that match one brain with a large number of others. The result is a *probabilistic brain atlas* that encodes patterns of anatomic variation in human populations, and incorporates algorithms to detect structural variants outside of the normal range (Mazziotta *et al.*, 1995; Thompson *et al.*, 1997).

Measuring Brain Changes. When applied to scans acquired over many months or years from a single subject, 3D warping algorithms can also calculate measures of local and global shape change over time (Toga *et al.*, 1996; Thompson and Toga, 1998; Thompson *et al.*, 1999). In many ways, static representations of brain structure are ill-suited to investigating dynamic processes of disease. With warping algorithms, 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 deformation field that matches one scan with the other. As a result, warping algorithms offer a powerful strategy to track temporal change and classify age-related, developmental or pathologic alterations in anatomy.

Hybrid Algorithms. The challenges created by cross-subject variations in brain structure prompted us to explore hybrid approaches for brain image registration and pathology detection. In these approaches, computer vision algorithms and statistical pattern recognition measures are integrated with anatomically-driven elastic transformations that encode complex shape differences in anatomy. As a result, objective criteria can be defined to identify how brain structure is altered by age, gender, handedness, disease, and other genetic or demographic factors (Thompson *et al.*, 1999). We begin with an overview of 2D and 3D image warping algorithms widely used in brain imaging, in the hope that hybrid algorithms will be developed in the future that capitalize on the merits of each approach.

II. Classification of Warping Algorithms

Model-Driven and Intensity-Driven Algorithms. A wide variety of 3D image warping algorithms have been designed to handle neuroanatomic data. *Model-driven* algorithms 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 parameterized and matched with their counterparts in the target scan, and their correspondences guide the volumetric transformation of one brain to another. In our own warping algorithms (Section 3; Thompson and Toga, 1996, 1998), higher-level structural information guides the mapping of one brain onto another, and a hierarchy of curve-to-curve and surface-to-surface mappings is set up, guaranteeing the biological validity of the resulting transform. The algorithms exploit anatomical information to match cortical regions, so that networks of sulci and gyri are individually matched. These strategies are discussed in Section 3.

Model-driven approaches contrast with *intensity-driven approaches*. Intensity-driven approaches aim to match regional intensity patterns in each scan based on mathematical or statistical criteria. Typically, they define a mathematical measure of intensity similarity between the deforming scan and the target. Measures of intensity similarity can include squared differences in pixel intensities (Christensen et al., 1993; Woods et al., 1993, 1998; Ashburner et al., 1997), regional correlation (Bajcsy and Kovacic, 1989; Collins et al., 1995), or mutual information (Kim et al., 1997). Mutual information has proved to be an excellent similarity measure for *cross-modality* registrations, since it assumes only that the *statistical dependence* of the voxel intensities is maximal when the images are geometrically aligned. The intensity similarity measure, combined with a measure of the structural integrity of the deforming scan, is optimized by adjusting parameters of the deformation field. Algorithms based on intensity patterns alone essentially by-pass information on the internal topology of the brain. Matching of neuroanatomic data in the absence of higher-level structural information presents an extremely difficult pattern recognition problem. Future hybrid approaches, based on a combination of model-based and densitometric criteria, are likely to benefit from the advantages of each strategy.

Intensity-Driven Approaches. A key insight, which spurred the development of intensity-based warping algorithms, was the connection of the image data with a physically deforming system in 3 dimensions (Broit, 1981). Physical continuum models (Fig. 1) consider the deforming image to be embedded in a 3-dimensional deformable medium, which can be either an elastic material or a viscous fluid. The medium is subjected to certain distributed internal forces, which reconfigure the medium and eventually lead the image 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.

Navier-Stokes Equilibrium Equations. 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:

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

Here \mathbf{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. Body forces, designed to match regions in each dataset with high intensity similarity, can be derived from the gradient of a local correlation function. In (Bajcsy and Kovacic, 1989), intensity neighborhoods to be

correlated in each scan were projected onto a truncated 3D Hermite polynomial basis to enhance the response of edge features and accelerate computation. More complex local operators can also be designed to identify candidates for regional matches in the target image (Amit, 1997). With proper boundary conditions the elasticity equilibrium equations can be solved numerically by finite difference, finite element, or spectral methods. If $\mathbf{U}: \mathbf{x} \rightarrow \mathbf{x} + \mathbf{u}(\mathbf{x})$, then $\mathbf{U}(\mathbf{R})$ is the final image, warped into register with the target scan. This elasticity-based warping scheme was introduced by Broit (1981). It was subsequently extended to a multiresolution/multigrid algorithm by Bajcsy and Kovacic (1989), and to a finite element implementation by Gee *et al.* (1993).

Viscous Fluid Approaches. More recently, Christensen *et al.* (1993, 1995, 1996) proposed a viscous-fluid based warping transform, motivated by capturing non-linear topological behavior and large image deformations. Designed to operate sequentially, this transform is actually a series of three algorithms which adjust successively finer features of the local anatomy until the transformed image matches the target scan. The optimal deformation field is defined as the one that maximizes a global intensity similarity function (defined on the deformed template and the target), while satisfying additional continuum-mechanical constraints that guarantee the topological integrity of the deformed template.

The transformation proposed by Christensen *et al.* (1996) is conducted in 3 successive stages. Stage 1 requires a sparse manual specification of the displacement field by isolating several corresponding landmarks in both 3D scans. The minimum energy configuration of the template compatible with this initial assignment is formalized as a Dirichlet problem (Joshi *et al.*, 1995). For a system of point landmarks, the associated Fredholm integral equation reduces to a linear system whose solution expresses the Stage 1 deformation field in terms of the self-adjoint linear operator describing the mechanics of the deforming system. A second step expresses the residual deformation in terms of an approximation series of eigenfunctions of the linear elastic operator. Basis coefficients are determined by gradient descent on a cost functional (2) that penalizes squared intensity mismatch between the deforming template $T(\mathbf{x}-\mathbf{u}(\mathbf{x},t))$ and target $S(\mathbf{x})$:

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

Finally, a third, *viscous* deformation stage allows large-distance non-linear fluid evolution of the neuroanatomic template. With the introduction of concepts such as deformation velocity and a Eulerian reference frame, the energetics of the deformed medium are hypothesized to be relaxed in a highly viscous fluid. The driving force, which deforms the anatomic template, is critical for successful registration. It is defined as the variation of the cost functional with respect to the displacement field:

$$\mathbf{F}(\mathbf{x}, \mathbf{u}(\mathbf{x}, t)) = -(T(\mathbf{x}-\mathbf{u}(\mathbf{x}, t)) - S(\mathbf{x})) \nabla T \Big|_{\mathbf{x}-\mathbf{u}(\mathbf{x}, t)} \quad (3)$$

$$\mu \nabla^2 \mathbf{v}(\mathbf{x}, t) + (\lambda + \mu) \nabla (\nabla^T \bullet \mathbf{v}(\mathbf{x}, t)) + \mathbf{F}(\mathbf{x}, \mathbf{u}(\mathbf{x}, t)) = \mathbf{0} \quad (4)$$

$$\partial \mathbf{u}(\mathbf{x}, t) / \partial t = \mathbf{v}(\mathbf{x}, t) - \nabla \mathbf{u}(\mathbf{x}, t) \mathbf{v}(\mathbf{x}, t) \quad (5)$$

The deformation velocity (4) is governed by the creeping flow momentum equation for a Newtonian fluid and the conventional displacement field in a Lagrangian reference system (5) is connected to a Eulerian velocity field by the relation of material differentiation. Experimental results were excellent (Christensen *et al.*, 1996).

Convolution Filters. Linkage of continuum-mechanical models with a 3D intensity matching optimization problem results in an extremely computationally intensive algorithm. Registration of two 128^3 MR volumes took 9.5 and 13 hours for elastic and fluid transforms, respectively, on a 128×64 DECmpp1200Sx/Model 200 MASP (Massively Parallel Mesh-Connected Supercomputer). This spurred work to modify the algorithm for use on standard single-processor workstations (Thirion, 1995; Bro-Nielsen and Gramkow, 1996; Freeborough and Fox, 1998). Both elastic and fluid algorithms contain core systems of up to 0.1 billion simultaneous partial

differential equations (1,4), requiring many iterations of successive over-relaxation to find their solution. To avoid this need to pass a filter many times over the vector arrays, Bro-Nielsen and Gramkow (1996) developed a convolution filter to solve the system of partial differential equations in a single pass over the data. This speeds up the core step in the registration procedure by a factor of 1000. Since the behavior of the mechanical system is governed by the Navier-Stokes differential operator $L = \mu \nabla^2 + (\lambda + \mu) \nabla(\nabla^T \bullet)$, the eigenfunctions of this operator (Christensen et al., 1996) were used to derive a Green's function solution $\mathbf{u}^*(\mathbf{x}) = \mathbf{G}(\mathbf{x})$ to the impulse response equation $L\mathbf{u}^*(\mathbf{x}) = \delta(\mathbf{x} - \mathbf{x}_0)$. The solution to the full PDE $L\mathbf{u}(\mathbf{x}) = -\mathbf{F}(\mathbf{x})$ was approximated as a rapid filtering operation on the 3D arrays representing the components of the body force:

$$\mathbf{u}(\mathbf{x}) = -\int_{\Omega} \mathbf{G}(\mathbf{x} - \mathbf{r}) \cdot \mathbf{F}(\mathbf{r}) \, d\mathbf{r} = -(\mathbf{G} * \mathbf{F})(\mathbf{x}), \quad (6)$$

where \mathbf{G}^* represents convolution with the impulse response filter. As noted in (Gramkow and Bro-Nielsen, 1997), 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 derived above, 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). Variable viscosity fluids create a still more flexible registration model (Lester et al., 1999; $\lambda=0$, cf. equation (4)):

$$\mu \nabla^2 \mathbf{v}(\mathbf{x}, t) + \mu \nabla(\nabla^T \bullet \mathbf{v}(\mathbf{x}, t)) + (\partial \mu / \partial x_j) \nabla v_j(\mathbf{x}, t) + (\nabla \mu \bullet \nabla) \mathbf{v}(\mathbf{x}, t) + \mathbf{F}(\mathbf{x}, \mathbf{u}(\mathbf{x}, t)) = \mathbf{0} \quad (7)$$

In this model, a spatially-dependent viscosity field $\mu(\mathbf{x})$ controls the pliancy of the deforming image, slowing the deformation of some regions to enable others to register first. By combining a diffusion model with spatially-adaptive controls, this method shares some affinities with variable-conductance scale spaces, which have become a powerful approach for multi-scale feature detection in medical imaging (Ter Haar Romeny, 1994).

Multigrid and Coarse-to-Fine Optimization. Vast numbers of parameters are required to represent complex deformation fields. Optimal values for these parameters must therefore be searched, to find parameter sets that globally minimize the measure of mismatch between the warped image and target. In several robust systems for automated brain image segmentation and labeling, Dengler and Schmidt (1988), Bajcsy and Kovacic (1989), Collins et al. (1994, 1995), Gee et al. (1993, 1995) and Schormann et al. (1996) recover the optimal transformation in a hierarchical multi-scale fashion. Both template and target intensity data are smoothed with different sized Gaussian filters, and the registration is performed initially at coarse spatial scales, then finer ones. This accelerates computation and helps to avoid local minima of the mismatch measure. In an alternative approach, the deformation field is expressed as a steadily increasing sum of basis functions, whose coarse-scale parameters are estimated first and whose spatial frequency is increased as the algorithm progresses (Amit et al., 1991; Miller et al., 1993). The widely-used *Statistical Parametric Mapping* (Ashburner et al., 1997) and *Automated Image Registration* algorithms (Woods et al., 1998) take a similar coarse-to-fine approach. Increasingly complex warping fields are expressed in terms of a 3D cosine basis (SPM) or by using 3D polynomials of increasing order (AIR; polynomials also span the space of continuous deformation fields, by the Stone-Weierstrass theorem). Amit (1997) expresses 2D warping fields in terms of a wavelet basis. The small support of high-frequency wavelets allows local adjustments of the warping field in regions where the mismatch is large, without having to alter the field in other areas where the mismatch may already be small. In (Miller et al., 1993; cf. Amit et al., 1991), a stochastic algorithm generates the expansion coefficient set for the deformation field

$$\mathbf{u}(\mathbf{x}) = \sum_{i,j=1 \text{ to } d} \sum_{r=1,2} [2(i^2 + j^2)]^{-1/2} [\mu_{i,j,r} \mathbf{e}_{i,j,r}(\mathbf{x})] \quad (8)$$

in terms of an eigenbasis $\{\mathbf{e}_{i,j,r}\}$ for the linear elasticity operator. Stochastic gradient descent is used to find the optimal warping field parameters according to:

$$d\mu_{i,j,r}(t) = -(1/2) [\partial H(\mathbf{u}(t)) / \partial \mu_{i,j,r}] dt + dw_{i,j,r}(t). \quad (9)$$

Here $H(\mathbf{u}(t))$ is the combined measure of intensity mismatch and deformation severity, and $dw_{i,j,r}(t)$ is a Wiener process that allows provisional parameter estimates to jump out of local minima. At the expense of added computation time, stochastic sampling allows globally optimal image matches to be estimated.

Bayesian Registration Models. Bayesian statistical models provide a general framework for the presentation of deformable matching methods. Recently, they have also been applied to the brain image matching problem (Miller et al., 1993; Gee et al., 1993, 1995; Ashburner et al., 1997). In a Bayesian model, 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. In fact, all of the intensity-based approaches that combine an intensity mismatch term with a measure of deformation severity can be recast as an inference task in a Bayesian probabilistic framework. The Bayesian *maximum a-posteriori* (MAP) estimator solving the registration problem is the transformation $\hat{\mathbf{u}} = \text{argmin}_{\mathbf{u}} (D(\mathbf{u}) + E(\mathbf{u}))$ which minimizes a combined penalty due to the intensity mismatch $D(\mathbf{u})$ and the elastic potential energy $E(\mathbf{u})$ stored in the deformation field.

Model-Driven Algorithms. The extreme difficulty of matching brain data based on intensity criteria alone led to the development of algorithms driven by anatomical models, which can be extracted from each dataset prior to registration. Anatomic models provide an explicit geometry for individual structures in each scan. Model-driven algorithms can be classified by the type of features that drive them. These features include point, curve or surface models of anatomic structures. When parameterized consistently (see Section 3), mesh-based models of anatomic systems help guide the mapping of one brain to another. Anatomically-driven algorithms guarantee biological as well as computational validity, generating meaningful object-to-object correspondences, especially at the cortex.

Point-Based Matching. The simplest set of anatomic features which can guide the mapping of one brain to another is a set of point landmarks, identified manually (Bookstein, 1989) or automatically (Amit, 1997; Davis et al., 1997) in each dataset. A specification of correspondences at point landmarks can be extended to produce a deformation field for the full volume in a variety of ways, each consistent with the displacements assigned at the point landmarks. The ambiguity is resolved by requiring the deformation field to be the one that minimizes a specific *regularizing functional* (Tikhonov and Arsenin, 1977), which measures the roughness or irregularity of the deformation field, calculated from its spatial derivatives. Different regularizers measure smoothness in different ways, and have different ways of interpolating the deformation from the points into the full 3D volume. All regularizers penalize large values of the derivatives, creating warping functions that take on the values to be interpolated (displacements) at the specified points, but which do not vary erratically elsewhere. For producing 2D warping fields, *thin-plate splines* (Grimson, 1981; Bookstein, 1989) are functions which minimize the penalty:

$$J_{\text{thin-plate}}(\mathbf{u}) = \int_{\mathbf{R}^2} [(\partial_{11}\mathbf{u})^2 + 2(\partial_{12}\mathbf{u})^2 + (\partial_{22}\mathbf{u})^2] dx_1 dx_2 \quad (10)$$

where $\partial_{ij}\mathbf{u} = \partial^2\mathbf{u} / \partial x_i \partial x_j$. Other members of the family of multidimensional spline functions (Duchon, 1975; Meinguet, 1979; Wahba, 1990) have also been used for brain image warping. *Membrane splines* (Amit et al., 1991; Gee et al., 1993), *elastic body splines* (Miller et al., 1993; Davis et al., 1997), and *div-curl splines* (Suter, 1994) are warping functions which minimize the following measures of irregularity:

$$J_{\text{memb}}(\mathbf{u}) = \int [(\partial_1 u_1)^2 + (\partial_1 u_2)^2 + (\partial_2 u_1)^2 + (\partial_2 u_2)^2] dx_1 dx_2 \quad (11)$$

$$J_{\text{elas}}(\mathbf{u}) = \int \sum_{i=1 \text{ to } 2} \sum_{j=1 \text{ to } 2} [(\lambda/2)(\partial_i u_i)(\partial_j u_j) + (\mu/4)((\partial_i u_j) + (\partial_j u_i))^2] dx_1 dx_2 \quad (12)$$

$$J_{\text{div-curl}}(\mathbf{u}) = \int [\lambda \| \nabla \text{DIV} \mathbf{u} \|^2 + \mu \| \nabla \text{CURL} \mathbf{u} \|^2] dx_1 dx_2 \quad (13)$$

Just like the continuum-mechanical warps defined earlier, the warping fields generated by splines satisfy partial differential equations of the form $L\mathbf{u}(\mathbf{x}) = -\mathbf{F}(\mathbf{x})$, where $\mathbf{u}(\mathbf{x})$ is fixed at the specified points, $\mathbf{F}(\mathbf{x})$ plays the role of a body force term, and L is the biharmonic differential operator ∇^4 for the thin-plate spline, the Laplacian operator ∇^2 for the membrane spline, and the Cauchy-Navier operator $\mu \nabla^2 + (\lambda + \mu) \nabla(\nabla^T \bullet)$ for the elastic body spline (see Footnote 1).

Footnote 1: Note that spline-based warping functions can be defined either (1) as the variational minimizer of an irregularity measure or (2) as solutions to related PDEs. But, as pointed out by Arad (1995), strictly one looks for solutions to each problem in different function spaces (the Sobolev space $H^2(\Omega)$ for minimizing the regularizing integral - which is also known as a *Sobolev semi-norm* - and continuous function spaces such as $C(\Omega^c) \cap C^4(\Omega)$ for solving PDEs such as $\nabla^4 \mathbf{u}(\mathbf{x}) = \mathbf{0}$, $\mathbf{x} \in \Omega$).

Once a type of spline is chosen for warping, a formula can be used which specifies how to interpolate the displacement field from a set of points $\{\mathbf{x}_i\}$ to the surrounding 2D plane or 3D volume:

$$\mathbf{u}(\mathbf{x}) = p_{m-l}(\mathbf{x}) + \sum_i c_i G(\mathbf{x} - \mathbf{x}_i) \quad (14)$$

Here $p_{m-l}(\mathbf{x})$ is a polynomial of total degree $m-l$, where m is the order of derivative used in the regularizer, and G is a *radial basis function* or Green's function whose form depends on the type of spline being used (Joshi et al., 1995; Davis et al., 1997). The polynomial coefficients determine components of low-order data variations, such as a global rigid motion between the two brains, which are not penalized by the smoothness functional (Wolberg, 1990). The coefficients c_i in this formula are found by evaluating this equation at the points \mathbf{x}_i and solving the resulting linear system of equations. Various choices of radial basis functions $G(r)$, for $r = \|\mathbf{x} - \mathbf{x}_i\|$, are commonly used for medical image matching, and for multivariate data interpolation generally (Bookstein, 1989; Ruprecht and Müller, 1995; Thompson and Toga, 1996). Their behavior is also well-understood from their wide use in neural networks and pattern classifiers (Ripley, 1996). Choices of $r^2 \ln r$ and r correspond to the *thin-plate spline* in 2D and 3D, with r^3 for the *3D volume spline* (Davis et al., 1997), the 3×3 matrix $[\alpha r^2 \mathbf{I} - 3\mathbf{x}\mathbf{x}^T]r$ for the *3D elastic body spline* (Davis et al., 1997), and $(r^2 + c^2)^\alpha$ ($0 < \alpha < 1$) and $\ln(r^2 + c^2)^{1/2}$ ($c^2 \geq 1$) for *multiquadric* and *shifted-log* interpolants (Franke, 1979; Hardy, 1990; Ruprecht and Müller, 1995). Gaussian radial functions $G(r) = \exp(-r^2/2\sigma^2)$ belong to the same family, generating warping fields that minimize the following non-intuitive irregularity measure (Poggio and Girosi, 1990):

$$J_{\text{gauss}}(\mathbf{u}) = \sum_{n=0 \text{ to } \infty} (-1)^n (\sigma^{2n}/n! 2^n) \sum_i i_1 \dots i_n \int [\partial^n \mathbf{u}(\mathbf{x}) / \partial x_{i_1} \dots \partial x_{i_n}]^2 d\mathbf{x} \quad (15)$$

These Gaussian functions perform poorly unless σ is chosen carefully (Wolberg, 1990; Franke (1979) suggests using $\sigma = 1.008d/n$, where d is the diameter of the point set and n is the number of points). The best choice of radial basis functions depends on the objective. For modeling deformation of real biological tissue, elastic body splines out-perform thin-plate splines (Davis et al., 1997). Thin-plate splines, however, are advantageous in computing shape statistics (Bookstein, 1989). Use of radial basis functions in medical image registration algorithms has also been extended to neural network implementations (Davis et al., 1996).

Neural Network Approaches. Neural networks are widely used in pattern recognition and computational learning (Ripley, 1996), and provide ingenious solution for both landmark-driven and automated image matching. Two of the most common network types are multilayered perceptrons (MLPs) and radial basis function (RBF)

networks. RBF neural nets, in particular, use correspondences at known landmarks as a *training set* to learn a multivariate function mapping positions in the image (input) to the desired displacement field at that point (output). Intriguingly, the hidden units in the neural net are directly analogous to Green’s functions, or convolution filters, in the continuum-mechanical matching approach (Joshi et al., 1995; Bro-Nielsen and Gramkow, 1996). They are also directly analogous to Watson-Nadaraya *kernel estimators*, or Parzen windows, in non-parametric regression methods (Parzen, 1962; Fig. 2). As above, the k deformation field components are the output values of the neural net:

$$\mathbf{u}^k(\mathbf{x}) = \sum_{m=1 \text{ to } M} a_m \pi_m(\mathbf{x}) + \sum_{i=1 \text{ to } N} w_{ik} G_i(\mathbf{x}-\mathbf{x}_i) \quad (16)$$

Here the G_i are N separate hidden unit neurons with receptive fields centered at \mathbf{x}_i , $\sum a_m \pi_m$ is a polynomial whose terms are hidden units and whose coefficients a_m are also learned from the training set, and w_{ik} are synaptic weights (Fig. 2). The synaptic weights are determined by solving a linear system obtained by substituting the training data into this equation. If landmarks are available to constrain the mapping, the function centers \mathbf{x}_i may be initialized at the landmark positions, although fewer hidden units are desirable if the network output is to be accurate far from the landmarks. In a recent innovation (Davis et al., 1996), a 3D brain image matching neural net was developed that eliminates the need for landmark selection. Network weights (the coordinate transformation parameters) and the RBF center locations are successively tuned to optimize an intensity-based functional (normalized correlation) that measures the quality of the match. Hidden units were initially randomly placed across the image and the network was trained (i.e., the parameters of the warping field were determined) by evaluating the gradient of the normalized correlation with respect to the network parameters, and optimizing their values by gradient descent. Results matching 3D brain image pairs were impressive (Davis et al., 1996). For further discussion of the close relationship between continuum-mechanical PDEs, statistical regression and neural nets, see Ripley et al. (1996).

Curve-Based Approaches. When constructing a warping field for matching two brain images, greater anatomical accuracy can be achieved by using *curves* as anatomic driving features. In fact, many investigators of point-based landmark matching have included orientation attributes or directional information at landmarks to further constrain the transformation (Bookstein and Green, 1993; Mardia and Little, 1994). In 2D, matching of entire planar curved boundaries is ideal for correcting deformations in histologic tissue (Schormann et al., 1996; Mega et al., 1997; see Fig. 3). Approaches using sulcal lines 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). Curve-based sulcal models can be combined with intensity-based measures to assist in matching cortical regions (Collins et al., 1996).

Declerck et al. (1995) used *crest lines* to drive a volume transformation. Crest lines (Monga and Benayoun, 1995) are curved loci on a surface that satisfy the following geometric criterion: the largest principal curvature must be locally maximal in the associated principal direction. After an MR dataset is thresholded to segment the cortex and ventricles, crest lines on these surfaces are defined. They are matched with their counterparts in a target brain using (1) an iterative closest point algorithm, which finds candidate lines for matching, and (2) topological criteria to enforce one-to-one matching of curves and to ensure that their internal points are matched in a consistent, serial order. The 3D deformation field, expressed as a 3D tensor product of B-spline basis functions, is obtained by minimizing a regularizing term (as in point-based approaches) and a landmark mismatch term. This mismatch term limits the impact of spurious matches by tolerating some separation between curves that the algorithm decides to match.

Automated Matching. Identifying the subset of curved features which have a consistent topology across

subjects (and are therefore appropriate to match) is extremely challenging. The problem is, however, easier than in the general intensity-matching case, as the parametric forms of the curves have a differentiable structure. The inherent structure in the model allows additional geometric features (torsion, curvature and local Frenet frames) to be included in the matching function, to favor correct pairing (Kishon et al., 1991; Gourdon and Ayache, 1993). Sulcal curvature patterns are only weakly conserved across subjects, and even this consistency is restricted to specific anatomic regions (Ono et al., 1990; Thompson and Toga, 1997). Nevertheless, to help guide the automated matching of curves and surfaces in anatomic data, statistical priors have been defined, for different types of sulci, to describe their expected curvature (Khaneja et al., 1998; Manceaux-Demiau et al., 1998), torsion (Guéziec and Ayache, 1994; Khaneja et al., 1998) and stereotaxic position (Thompson et al., 1996, 1997, 1998). In an alternative approach based on Markov Random Fields, Mangin et al. (1994) extract a 3D skeletonized representation of deep sulci, parse it into an attributed relational graph of connected surface elements. They then define a syntactic energy on the space of associations between the surface elements and anatomic labels, from which estimates of correct labelings (and therefore correct matches across subjects) can be derived.

Surface-Based Approaches. Ultimately, accurate warping of brain data requires:

- (1) matching entire systems of anatomic *surface* boundaries, both external and internal, and
- (2) matching relevant curved and point landmarks, including ones within the surfaces being matched (e.g., primary sulci at the cortex, tissue type boundaries at the ventricular surface).

In our own model-driven warping algorithm (Thompson and Toga, 1996, 1997, 1998), systems of model surfaces are first extracted from each dataset, and used to guide the volumetric mapping. The model surfaces include many critical functional interfaces, as well as numerous cytoarchitectonic and lobar boundaries in 3 dimensions. Both the surfaces and the landmark curves within them are reconfigured and forced to match their counterparts in the target datasets exactly. We will discuss this approach in some detail.

Anatomical Models. Since much of the functional territory of the human cortex is buried in the cortical folds or *sulci*, a generic structure is built to model them (Fig. 4,5; Thompson and Toga, 1996), incorporating *a priori* topological and shape information about the deep sulcal pattern. The underlying data structure consists of a connected system of surface meshes, in which the individual meshes are parametric, and have the form of complex 3D sheets that divide and join at curved junctions to form a network of connected surfaces. Separate surfaces are used to model the deep internal trajectories of features such as the parieto-occipital sulcus, the anterior and posterior calcarine sulcus, the Sylvian fissure, and the cingulate, marginal and supracallosal sulci in both hemispheres. Additional major gyral and sulcal boundaries are represented by parameterized curves lying in the cortical surface. The ventricular system is modeled as a closed system of 14 connected surface elements whose junctions reflect cytoarchitectonic boundaries of the adjacent tissue (for details, see Thompson and Toga, 1998). Information on the meshes' spatial relations, including their surface topology (*closed* or *open*), anatomical names, mutual connections, directions of parameterization, and common 3D junctions and boundaries is stored in a hierarchical graph structure. This ensures the continuity of displacement vector fields defined at mesh junctions.

Parameterization. *Surface parameterization*, or imposition of an identical regular structure on anatomic surfaces from different subjects (Fig. 5), provides an explicit geometry that can be exploited to drive and constrain the correspondence maps which associate anatomic points in different subjects. Structures that can be extracted automatically in parametric form include the external cortical surface (discussed in Section 3, ventricular surfaces, and several deep sulcal surfaces. Recent success of sulcal extraction approaches based on deformable surfaces (Vaillant et al., 1997) led us to combine a 3D skeletonization algorithm with deformable curve and surface governing equations to automatically produce parameterized models of cingulate, parieto-

occipital, and calcarine sulci, without manual initialization (Zhou et al., 1999). Additional, manually-segmented surfaces can also be given a uniform rectilinear parameterization using algorithms described in (Thompson et al., 1996a,b), and used to drive the warping algorithm. Each resultant surface mesh is analogous in form to a uniform rectangular grid, drawn on a rubber sheet, which is subsequently stretched to match all data points. Association of points on each surface with the same mesh coordinate produces a dense correspondence vector field between surface points in different subjects. This procedure is carried out under very stringent conditions (*see Footnote 2*), which ensure that landmark curves and points known to the anatomist appear in corresponding locations in each parametric grid.

Footnote 2. For example, the calcarine sulcus (see Fig. 5(b)) is partitioned into two meshes (*CALCa* and *CALCp*). This ensures that the complex 3D curve forming their junction with the parieto-occipital sulcus is accurately mapped under both the surface displacement and 3D volumetric maps reconfiguring one anatomy into the shape of another. Fig. 5(b) illustrates this procedure, in a case where 3 surface meshes in one brain are matched with their counterparts in a target brain. A separate approach (discussed later, Section 3) is used to match systems of curves lying *within* a surface with their counterparts in a target brain.

Displacement Maps. For each surface mesh \mathbf{M}_i^p in a pair of scans \mathbf{A}_p and \mathbf{A}_q we define a 3D displacement field:

$$\mathbf{W}_i^{pq}[\mathbf{r}_i^p(u,v)] = \mathbf{r}_i^q(u,v) - \mathbf{r}_i^p(u,v) \quad (17)$$

carrying each surface point $\mathbf{r}_i^p(u,v)$ in \mathbf{A}_p into structural correspondence with $\mathbf{r}_i^q(u,v)$, the point in the target mesh parameterized by rectangular coordinates (u,v) . This family of high-resolution transformations, applied to individual meshes in a connected system deep inside the brain, elastically transforms elements of the surface system in one 3D image to their counterparts in the target scan.

3D Volume Transformation. As in approaches based on matching points and curves, the surface-based transformation can be extended to the full volume in a variety of ways. In one approach (Thompson and Toga, 1996), weighted linear combinations of radial functions, describing the influence of deforming surfaces on points in their vicinity, extend the surface-based deformation to the whole brain volume (see Fig. 6). For a general voxel \mathbf{x} in the scan \mathbf{A}_p to be transformed, we let $\delta_i^p(\mathbf{x})$ be the distance from \mathbf{x} to its nearest point(s) on each surface mesh \mathbf{M}_i^p , and let the scalars $\gamma_i^p(\mathbf{x}) \in [0,1]$ denote the weights $\{1/\delta_i^p(\mathbf{x})\} / \sum_{l=1 \text{ to } L} \{1/\delta_l^p(\mathbf{x})\}$. Then $\mathbf{W}^{pq}(\mathbf{x})$, the displacement vector which takes a general point \mathbf{x} in scan \mathbf{A}_p onto its counterpart in scan \mathbf{A}_q , is given by the linear combination of functions:

$$\mathbf{W}^{pq}(\mathbf{x}) = \sum_{l=1 \text{ to } L} \gamma_l^p(\mathbf{x}) \cdot \mathbf{D}_l^{pq}(\mathbf{np}_l^p(\mathbf{x})), \text{ for all } \mathbf{x} \in \mathbf{A}_p. \quad (18)$$

Here the \mathbf{D}_l^{pq} are distortion functions (Fig. 6) due to the deformation of surfaces close to \mathbf{x} , given by

$$\mathbf{D}_l^{pq}(\mathbf{x}) = \left\{ \int_{\mathbf{r} \in \mathbf{B}(\mathbf{x}; r_c)} w_l^p(\mathbf{x}, \delta_l^p(\mathbf{r})) \cdot \mathbf{W}_l^{pq}[\mathbf{np}_l^p(\mathbf{r})] d\mathbf{r} \right\} / \left\{ \int_{\mathbf{r} \in \mathbf{B}(\mathbf{x}; r_c)} w_l^p(\mathbf{x}, \delta_l^p(\mathbf{r})) d\mathbf{r} \right\}. \quad (19)$$

$\mathbf{W}_l^{pq}[\mathbf{np}_l^p(\mathbf{r})]$ is the (average) displacement vector assigned by the surface displacement maps to the nearest point(s) $\mathbf{np}_l^p(\mathbf{r})$ to \mathbf{r} on \mathbf{M}_l^p . R_c is a constant, and $\mathbf{B}(\mathbf{x}; r_c)$ is a sphere of radius $r_c = \min\{R_c, \min\{\delta_l^p(\mathbf{r})\}\}$. The w_l^p are additional weight functions defined as

$$w_l^p(\mathbf{x}, \delta_l^p(\mathbf{r})) = \exp(-\{d(\mathbf{np}_l^p(\mathbf{r}), \mathbf{x})/\delta_l^p(\mathbf{x})\}^2), \quad (20)$$

where $d(\mathbf{a}, \mathbf{b})$ represents the 3D distance between two points \mathbf{a} and \mathbf{b} . The Jacobian of the transformation field at each point \mathbf{x} is tracked during the computation, as recommended by Christensen *et al.* (1995). In rare cases where

the transformation is locally singular, the vector field computation is discretized in time, and the deformation field is reparameterized at successive time-steps, as suggested in (Christensen *et al.*, 1996). Intermediate surface blends $(1-t)\mathbf{r}_1^p(u,v)+t\mathbf{r}_1^q(u,v)$, ($t \in [0,1]$), are generated for every surface, and these surfaces are uniformly reparameterized at times $0 \leq t_m \leq t_{m+1} \leq 1$. The M warps mapping the full surface system and surrounding volume from one time-point to the next are concatenated to produce the final transformation. This incremental evolution of the transformation is visualized in a published video (Thompson and Toga, 1998). Recent extensions of the core algorithm to include continuum-mechanical, and other filter-based models of deformation (*cf.* Joshi, 1995; Davatzikos, 1996; Schiemann and Höhne, 1997; Gabrani and Tretiak, 1999) have yielded similar encouraging results. Experiments illustrating the performance of the algorithm on MRI data are shown in Fig. 7.

III. Cortical Pattern Matching

Cortical surfaces can be matched using a procedure which also matches large networks of gyral and sulcal landmarks with their counterparts in the target brain (Drury *et al.*, 1996; Davatzikos, 1996; Thompson and Toga, 1996, 1997; Van Essen *et al.*, 1997). Differences in the serial organization of cortical gyri prevent exact gyrus-by-gyrus matching of one cortex with another, but an important intermediate goal has been to match a comprehensive network of sulcal and gyral elements that are consistent in their incidence and topology across subjects. Elastic matching of primary cortical regions factors out a substantial component of confounding cortical variance in functional imaging studies, as it directly compensates for drastic variations in cortical patterns across subjects (Steinmetz *et al.*, 1990; Woods, 1996; Thompson *et al.*, 1997). Quantitative comparison of cortical models can also be based on the mapping which drives one cortex with another (Van Essen *et al.*, 1997; Thompson *et al.*, 1997). Because of its role in pathology detection algorithms (Section 4), we focus on this mapping in some detail.

Overview of Method. Our method (Thompson and Toga, 1996) is conceptually similar to that of (Davatzikos, 1996). 3D active surfaces (Fig. 8; Cohen and Cohen, 1992) 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 (Fig. 9). This vector flow field in parameter space indirectly specifies a correspondence field in 3D, which drives one cortical surface into the shape of another.

Algorithm Details. Several algorithms have been proposed to extract cortical surface models from 3D MR data (Sandor and Leahy, 1995; Davatzikos and Prince, 1996; Xu and Prince, 1996; Davatzikos, 1996; Sereno *et al.*, 1996). In one algorithm (MacDonald *et al.*, 1993, 1998), a spherical mesh surface is continuously deformed to match a target boundary defined by a threshold value in the continuous 3D MR image intensity field (Fig. 8). Evolution of the deformable surface is constrained by systems of partial differential equations. These equations have terms that attract the parametric model to regions with the pre-selected intensity value, while penalizing excessive local bending or stretching. If an initial estimate of the surface $v_0(s,r)$ is provided as a boundary condition (see Thompson and Toga, 1996, for details), the final position of the surface is given by the solution (as $t \rightarrow \infty$) of the Euler-Lagrange evolution equation:

$$\frac{\partial v}{\partial t} - \frac{\partial}{\partial s} (w_{10} \left| \frac{\partial v}{\partial s} \right|) - \frac{\partial}{\partial r} (w_{01} \left| \frac{\partial v}{\partial r} \right|) + 2 \frac{\partial^2}{\partial s \partial r} (w_{11} \left| \frac{\partial^2 v}{\partial s \partial r} \right|) + \frac{\partial^2}{\partial s^2} (w_{20} \left| \frac{\partial^2 v}{\partial s^2} \right|) + \frac{\partial^2}{\partial r^2} (w_{02} \left| \frac{\partial^2 v}{\partial r^2} \right|) = \mathbf{F}(v). \quad (21)$$

Here $\mathbf{F}(v)$ is the sum of the external forces applied to the surface, and the w_{ij} terms improve the regularity of the surface. The spherical parameterization of the deforming surface is maintained under the complex transformation, and the resulting model of the cortex consists of a high-resolution mesh of discrete triangular elements that tile the surface (Fig. 8).

Maps of the Cortical Parameter Space. Because the cortical model is obtained by deforming a spherical mesh, any point on the cortical surface (Fig. 9(a)) must map to exactly one point on the sphere (Fig. 9(b)), and *vice versa*. Each cortical surface is parameterized with an invertible mapping $D_p, D_q: (r,s) \rightarrow (x,y,z)$, so sulcal curves and landmarks in the folded brain surface can be reidentified in the spherical map (*cf.* Sereno et al., 1996 for a similar approach; Fig. 9(b)). To retain relevant 3D information, cortical surface point position vectors in 3D stereotaxic space are color-coded, to form an image of the parameter space in color image format [Fig. 9(b)/(c)]. To find good matches between cortical regions in different subjects [Fig. 9(a)/(d)], we first derive a spherical map for each respective surface model [Fig. 9(b)/(c)] and then perform the matching process in the spherical parametric space, Ω . The parameter shift function $\mathbf{u}(\mathbf{r}): \Omega \rightarrow \Omega$, is given by the solution $F_{pq}: \mathbf{r} \rightarrow \mathbf{r} + \mathbf{u}(\mathbf{r})$ to a curve-driven warp in the biperiodic parametric space $\Omega = [0, 2\pi) \times [0, \pi)$ of the external cortex (*cf.* Davatzikos, 1996; Drury et al., 1996; Van Essen et al., 1997; Fischl et al., 1999). This warp can be set up in a variety of ways. Spherical harmonic functions are an orthonormal basis on the sphere (they are eigenfunctions of the Laplacian operator), and can be used extend this curve-based deformation to the whole surrounding spherical map (Thompson and Toga, 1996). An alternative, mathematically more challenging approach is to use the regularization approach introduced earlier, with several modifications.

Cortical Curvature. At first glance it seems that the previous approach, using ordinary differential operators to constrain the mapping, can be applied directly. For points $\mathbf{r}=(r,s)$ in the parameter space, a system of simultaneous partial differential equations can be written for $\mathbf{u}(\mathbf{r})$ using:

$$\begin{aligned} L(\mathbf{u}(\mathbf{r})) + \mathbf{F}(\mathbf{r}-\mathbf{u}(\mathbf{r})) &= \mathbf{0}, \quad \forall \mathbf{r} \in \Omega, \\ \mathbf{u}(\mathbf{r}) &= \mathbf{u}_0(\mathbf{r}), \quad \forall \mathbf{r} \in M_0 \cup M_1. \end{aligned} \quad (22)$$

Here M_0, M_1 are sets of points and (sulcal and gyral) curves where vectors $\mathbf{u}(\mathbf{r}) = \mathbf{u}_0(\mathbf{r})$ matching regions of one anatomy with their counterparts in the other are known, and L and F are 2D equivalents of the differential operators and body forces defined above. Unfortunately, the recovered solution $\mathbf{x} \rightarrow D_q(F_{pq}(D_p^{-1}(\mathbf{x})))$ will in general be prone to variations in the metric tensors $g_{jk}(\mathbf{r}_p)$ and $g_{jk}(\mathbf{r}_q)$ of the mappings D_p and D_q (Fig. 10). Since the cortex is not a *developable* surface (Davatzikos, 1996), it cannot be given a parameterization whose metric tensor is uniform. As in fluid dynamics or general relativity applications, the intrinsic curvature of the solution domain should be taken into account when computing flow vector fields in the cortical parameter space, and mapping one mesh surface onto another.

Covariant Formalism. To counteract this problem, we developed a *covariant formalism* (Thompson and Toga, 1998) which makes cortical mappings independent of how each cortical model is parameterized. Although spherical, or planar, maps involve different amounts of local dilation or contraction of the surface metric, this metric tensor field is stored and used later, to adjust the flow that describes the mapping of one cortex onto another. The result is a *covariant regularization* approach that makes it immaterial whether a spherical or planar map is used to perform calculations. Flows defined on the computational domain are adjusted for variations in the metric tensor of the mapping, and the results become independent of the underlying parameterization (i.e., spherical or planar).

The covariant approach was introduced by Einstein (1914) to allow the solution of physical field equations defined by elliptic operators on manifolds with intrinsic curvature. Similarly, the problem of deforming one cortex onto another involves solving a similar system of elliptic partial differential equations (Drury et al., 1996; Davatzikos, 1996; Thompson and Toga, 1998), defined on an intrinsically curved computational mesh (in the shape of the cortex). In the covariant formalism, the differential operators governing the mapping of one cortex to

another are adaptively modified to reflect changes in the underlying metric tensor of the surface parameterizations (Fig. 11).

Covariant Matching of Cortical Surfaces. Cortical surfaces are matched as follows. 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 (equation 19; Fig. 8; Thompson and Toga, 1996; Davatzikos, 1996). This procedure sets up an invertible parameterization of each surface in deformable spherical coordinates (Fig. 9), from which the metric tensors $g_{jk}(\mathbf{r}_p)$ and $g_{jk}(\mathbf{r}_q)$ of the mappings are computed. The solution to this PDE defines a Riemannian manifold (Bookstein, 1995). In contrast to prior approaches, this Riemannian manifold is then not flattened (as in Drury et al., 1996; Van Essen et al., 1997), but is used directly as a computational mesh on which a second PDE is defined (see Fig. 11). The second PDE matches sulcal networks from subject to subject. Dependencies between the metric tensors of the underlying surface parameterizations and the matching field itself are eliminated using generalized coordinates and Christoffel symbols (Thompson and Toga, 1998). In the PDE formulation, we replace L by the covariant differential operator L^{\ddagger} . In L^{\ddagger} , all L 's partial derivatives are replaced with covariant derivatives. These covariant derivatives are defined with respect to the metric tensor of the surface domain where calculations are performed.

Footnote 3. The covariant derivative of a (contravariant) vector field, $u^i(\mathbf{x})$, is defined as $u^i{}_{;k} = \partial u^i / \partial x^k + \Gamma^i{}_{jk} u^j$ (Schutz, 1990) where the $\Gamma^i{}_{jk}$ are *Christoffel symbols of the second kind*. This expression involves not only the rate of change of the vector field itself, as we move along the cortical model, but also the rate of change of the local basis, which itself varies due to the intrinsic curvature of the cortex (cf. Joshi et al., 1995b). On a surface with no intrinsic curvature, the extra terms (Christoffel symbols) vanish. The Christoffel symbols are expressed in terms of derivatives of components of the metric tensor $g_{jk}(\mathbf{x})$, which are calculated from the cortical model, with $\Gamma^i{}_{jk} = (1/2) g^{il} (\partial g_{lj} / \partial x^k + \partial g_{lk} / \partial x^j - \partial g_{jk} / \partial x^l)$. Scalar, vector and tensor quantities, in addition to the Christoffel symbols required to implement the diffusion operators on a curved manifold are evaluated by finite differences. These correction terms are then used in the solution of the Dirichlet problem for matching one cortex with another. A final complication is that different metric tensors $g_{jk}(\mathbf{r}_p)$ and $g_{jk}(\mathbf{r}_q)$ relate (1) the physical domain of the **input** data to the computation mesh (via mapping D_p^{-1}), and (2) the solution on the computation mesh to the **output** data domain (via mapping D_q). To address this problem (Fig. 9), the PDE $L^{\ddagger\ddagger} \mathbf{u}(\mathbf{r}_q) = -\mathbf{F}$ is solved first, to find a flow field $T_q: \mathbf{r} \rightarrow \mathbf{r} - \mathbf{u}(\mathbf{r})$ on the target spherical map with anatomically-driven boundary conditions $\mathbf{u}(\mathbf{r}_q) = \mathbf{u}_0(\mathbf{r}_q)$, $\forall \mathbf{r}_q \in M_0 \cup M_1$. Here $L^{\ddagger\ddagger}$ is the covariant adjustment of the differential operator L with respect to the tensor field $g_{jk}(\mathbf{r}_q)$ induced by D_q . Next, the PDE $L^{\ddagger} \mathbf{u}(\mathbf{r}_p) = -\mathbf{F}$ is solved, to find a reparameterization $T_p: \mathbf{r} \rightarrow \mathbf{r} - \mathbf{u}(\mathbf{r})$ of the initial spherical map with boundary conditions $\mathbf{u}(\mathbf{r}_p) = \mathbf{0}$, $\forall \mathbf{r}_p \in M_0 \cup M_1$. Here L^{\ddagger} is the covariant adjustment of L with respect to the tensor field $g_{jk}(\mathbf{r}_p)$ induced by D_p . The full cortical matching field (Fig. 12) is then defined as $\mathbf{x} \rightarrow D_q(F_{pq}(D_p^{-1}(\mathbf{x})))$ with $F_{pq} = (T_q)^{-1} \circ (T_p)^{-1}$.

Advantages. Using this method, surface matching can be driven by anatomically significant features, and the mappings are independent of the chosen parameterization for the surfaces being matched. High spatial accuracy of the match is guaranteed in regions of functional significance or structural complexity, such as sulcal curves and cortical landmarks (Fig. 11). Consequently, the transformation of one cortical surface model onto another is parameterized by one translation vector for each mesh point in the surface model, or $3 \times 65536 \approx 0.2$ million parameters (Fig. 12). This high-dimensional parameterization of the transformation is required to accommodate fine anatomical variations (cf. Christensen et al., 1995).

IV. Pathology Detection

Encoding Brain Variation. When applied to two different 3D brain scans, a non-linear registration or *warping* algorithm calculates a deformation map (Fig. 7,12) defining the spatial relationship between them. The deformation map describes the 3D patterns of anatomic differences. Several probabilistic approaches have been proposed for encoding variation based on deformation maps, both for brain image analysis (Amit et al., 1991; Grenander and Miller, 1994; Thompson and Toga, 1997; Thompson et al., 1997), and in the engineering literature on deformable templates (e.g., Zhong, 1997). By defining probability distributions on the space of deformation transformations applied to a prototypical 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. Encoding of local variation can then be used to assess the severity of structural variants outside of the normal range, which may be related to disease (Thompson et al., 1997).

Emerging Patterns. Cortical patterns are altered in schizophrenia (Kikinis et al., 1994), Alzheimer's Disease (Thompson et al., 1998) and a wide variety of developmental disorders. By using specialized strategies for group averaging of anatomy, specific features of anatomy emerge which are not observed in individual representations due to their considerable variability. Group-specific patterns of cortical organization or asymmetry can then be mapped out and visualized (Thompson et al., 1999; Narr et al., 1999).

In one study (Thompson et al., 1999), mappings that deform one cortex into gyral correspondence with another were used to create an *average* cortex for patients with mild to moderate Alzheimer's Disease (AD). Thirty-six gyral curves for 9 AD patients were transferred to the cortical parameter space (as in Fig. 9(b)), uniformly re-parameterized, and a set of 36 average gyral curves for the group was created by vector averaging of point locations on each curve. Each individual cortical pattern was then aligned with the average curve set using a spherical flow field (as in Fig. 9(c)). These 9 flow fields were then used to create an average cortex in 3D space, as follows. By carrying a code (that indexes 3D locations) along with the flow that aligns each individual with the average folding pattern (*cf.* Fig. 9(c)), information can then be recovered at a particular location in the average folding pattern, specifying the 3D cortical points that map to it in each subject. By ruling a regular grid over the warped coded map, and reading off 3D position values for each subject, cortical positions in any subject's *original* 3D anatomy can be recovered. This produces a new coordinate grid on a given subject's cortex, in which particular grid-points appear in the same location relative to the primary gyral pattern across all subjects (see Fischl et al., 1999, for a similar approach). By averaging these 3D positions across subjects, an average 3D cortical model was constructed for the group (Fig. 13). The resulting mapping is guaranteed to average together all points falling on the same cortical locations across the set of brains, and ensures that corresponding cortical features are averaged together.

Mapping Cortical Variability. By using the code to identify original cortical locations in 3D space, displacement maps can be recovered mapping each patient into gyrus-by-gyrus correspondence with the average cortex (Fig. 12). Anatomic variability can thus be defined at each point on the average mesh as the root mean square magnitude of the 3D displacement vectors, assigned to each point, in the surface maps from individual to average. This variability pattern is visualized as a color-coded map (Fig. 14). This map shows the anatomic variability, due to differences in gyral patterning, that remains after aligning MR data into the Talairach stereotaxic space, using the transforms prescribed in the atlas (Talairach and Tournoux, 1988).

Variability and Asymmetry. First, variability values rose sharply (Fig. 14) from 4-5 mm in primary motor cortex to localized peaks of maximum variability in posterior perisylvian zones and superior frontal association cortex (16-18 mm). Temporal lobe variability rose from 2-3 mm in the depths of the Sylvian fissure to 18 mm at the posterior limit of the inferior temporal sulcus in both brain hemispheres. Peak variability occurs in the vicinity of functional area MT (Watson et al., 1993), and extends into the posterior heteromodal association cortex of the parietal lobe (14-18 mm). Second, there is a marked anatomic asymmetry in posterior perisylvian cortex (Geschwind and Levitsky, 1968; up to 10 mm). This asymmetry is not clearly apparent individually, but appears clearly in the average representation. It also contrasts sharply with negligible asymmetry in frontal, parietal and occipital cortex (1-2 mm). Similar studies of deep sulcal cortex found this asymmetry to be greater in Alzheimer's patients than in controls matched for age, gender, handedness and educational level, corroborating earlier reports of an asymmetric progression of the disease (Thompson et al., 1998). The improved ability to localize asymmetry and encode its variability in a disease-specific atlas has encouraged us to develop a probabilistic atlas of the brain

in schizophrenia (Narr et al., 1999) where cortical organization and functional lateralization are also thought to be altered (Kikinis et al., 1994; cf. Csernansky et al., 1998).

Comparing Registration Methods. Elastic registration approaches all produce two types of output: first, they *measure* anatomic variability by transforming brain data to match another brain, or a common digital template; second, by creating registered images, they can reduce the confounding effects of anatomic variation when comparing other types of brain data. The relative performance of different algorithms should therefore be compared. The availability of large numbers of digital anatomical models stored in population-based brain atlases (Thompson et al., 1999) presents opportunities to explore the strengths and limitations of different registration algorithms, and measure their accuracy quantitatively.

In a recent project to generate an Alzheimer's Disease brain atlas (Mega et al., 1997; Thompson et al., 1999; Woods et al., 1999), parametric surface meshes (Thompson et al., 1996) were created to model 84 structures per brain in 3D MRI scans of 9 Alzheimer's patients. The ability of different registration approaches to reduce anatomic variability was investigated. 3D patterns of residual structural variability were visualized after digitally mapping all structures from all subjects into several different coordinate systems, using the transformations described in the Talairach atlas (Talairach and Tournoux, 1988), as well as automated affine and polynomial transformations of increasing complexity (Woods et al., 1993, 1998). For all major anatomic systems (Fig. 15), automated affine registration reduced variability to a far greater degree than the Talairach system, with added benefit obtained by using higher-order polynomial mappings. As expected, the highest registration accuracy was achieved for brain structures with lowest complexity and topological variability across subjects (Fig. 15, *top row*). With increasing polynomial order, significantly better registration was observed across deep cortical sulci, and anatomical variation could be further reduced using model-driven algorithms that explicitly match gyral patterns.

Population-Based Brain Image Templates. Interestingly, the automated registration approaches were able to reduce anatomic variability to a slightly greater degree if a specially-prepared image template was used as a registration target (Woods et al., 1999; Thompson et al., 1999). Brain templates which have the mean global shape for a group of subjects can be created using Procrustes averaging (Bookstein et al., 1997) or transformation matrix averaging (Woods et al., 1998). Brain templates which have mean shape and intensity characteristics at a *local* level can also be generated. Recent methods have included Bayesian pattern theory and variational calculus (Haller et al., 1997; Grenander and Miller, 1998), variable diffusion generators (Thompson et al., 1999) or hierarchical registration of curves, surfaces and volumes to a set of mean anatomical models (Thompson and Toga, 1996, 1998).

Several approaches, many of them based on high-dimensional image transformations, are under active development to create average brain templates. Average templates have been made for the *Macaque* brain (Grenander and Miller, 1998), and for individual structures such as the *corpus callosum*, (Davatzikos, 1996; Gee et al., 1998), central sulcus (Manceaux-Demiau et al., 1998), cingulate and paracingulate sulci (Paus et al., 1996; Thompson et al., 1997), hippocampus (Haller et al., 1997; Joshi et al., 1998; Csernansky et al., 1998; Thompson et al., 1999) and for transformed representations of the human and *Macaque* cortex (Drury and Van Essen, 1997; Grenander and Miller, 1998; Thompson et al., 1999; Fischl et al., 1999). Under various metrics, incoming subjects deviate least from these mean brain templates in terms of both image intensity and anatomy (Fig. 16). Registration of new data to these templates therefore requires minimal image distortion, allows faster algorithm convergence, and may help to avoid non-global stationary points of the registration measure as the parameter space is searched for an optimal match. For these reasons, templates that reflect the mean geometry and intensity of a group are a topic of active research (Grenander and Miller, 1998; Thompson et al., 1999; Woods et al., 1999).

Random Tensor Field Models. Analysis of variance in 3D deformation fields that 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 (Thompson et al., 1998). In (Thompson et al., 1997), we developed an approach to detect structural abnormalities in individual subjects. Based on a reference image archive of brain scans from normal subjects, a family of volumetric warps was generated to encode statistical properties and directional biases of local anatomical variation throughout the brain (see Fig. 17). To identify differences in brain structure between two groups, or between a patient and the normal database the following steps were followed. After affine components of the deformation fields are factored out, 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:

$$\mathbf{W}_{ij}(\mathbf{x}) = \boldsymbol{\mu}_j(\mathbf{x}) + \boldsymbol{\Sigma}(\mathbf{x})^{1/2} \boldsymbol{\epsilon}_{ij}(\mathbf{x}). \quad (23)$$

Here $\boldsymbol{\mu}_j(\mathbf{x})$ 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 $\boldsymbol{\epsilon}_{ij}(\mathbf{x})$ is a trivariate random vector field whose components are independent stationary Gaussian random fields. Deviations from a mean deformation field based on normal subjects were modeled, for small N , as a Hotelling's T^2 -distributed random field, or as $N \rightarrow \infty$, as a χ^2 (chi-squared) distributed random field with 3 degrees of freedom, defined at nodes (u,v) in parametric mesh models of the anatomy of new subjects (Thompson et al., 1997). A T^2 or F statistic which indicates evidence of significant difference in deformations between two groups of subjects, or between a single subject and the normal database, can be calculated. By calculating these statistics at each lattice location in a 3D image, or across a parameterized 3D anatomical surface, a statistic image is formed. The global maximum of the random deformation field, or derived tensor fields (Thompson et al., 1998), can be used to identify the presence of structural change in disease (Worsley, 1994a,b; Cao and Worsley, 1998). Random field approaches, some of which are now widely used in packages for analyzing functional brain images (Friston et al., 1995), use the Euler characteristic (EC) of the excursion sets of a random field as an estimator of the number of local non-zero signal components, above a given threshold in a statistic image. They also use the expected value of the EC as an approximate p -value for the local maximum (Worsley, 1994a,b). This probability value allows a definitive statement of whether a statistically abnormal structural difference has been detected or not.

Probabilistic atlases based on random deformation fields have been used to assess gender-specific differences in the brain (Cao and Worsley, 1998), and to detect structural abnormalities induced by tumor growth (Thompson et al., 1997; Fig. 18), and in neurodegenerative disorders such as Alzheimer's disease (Fig. 19; Thompson et al., 1997, 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 (Ashburner et al., 1998; Gaser et al., 1998).

Abnormal Asymmetry. 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). Due to the asymmetrical progression of many degenerative disorders (Thompson et al., 1998), abnormal asymmetry may prove to be an additional, sensitive index of pathology in individual subjects or groups.

Shape Theory Approaches. Deformation fields expressing neuroanatomic differences have also been analyzed with Procrustes methods, developed for the statistical analysis of biological shape (Bookstein, 1989; 1997). In Procrustes methods, affine components of neuroanatomic difference are factored out by rotating and

scaling configurations of point landmarks in each subject into least-squares correspondence with a Procrustes mean shape. Residual deformations which reflect individual change or anatomic difference are then expressed in terms of an orthogonal system of principal deformations derived from the bending energy matrix of the operator which governs the deformation (Bookstein, 1997). A number of modes of variation, based on the eigenvectors of the covariance matrix of landmark positions, can be determined to describe the main factors by which the instance shapes tend to deform from the generic shape. 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 statistics 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).

Pattern-Theoretic Approaches. In a related approach based on pattern theory (Grenander and Miller, 1998), a spectral approach to representing anatomic variation is developed. This was the first approach to build on the framework of deformable atlases by representing variation in terms of probabilistic transformations applied to deformable neuroanatomic templates. Deformation maps expressing variations in normal anatomies are calculated, with a non-linear registration procedure based on continuum mechanics (Miller et al., 1993; Christensen et al., 1993). As noted in Section 2, the deformational behavior of each subject's anatomy, driven into correspondence with other anatomies, is expressed as a system of partial differential equations. The equations are 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, 1998). In Grenander's formalism, the distribution of the random deformation fields $\mathbf{u}(\mathbf{x})$ is assumed to satisfy the stochastic differential equation:

$$L(\mathbf{u}(\mathbf{x})) = \mathbf{e}(\mathbf{x}). \quad (24)$$

Here L is the operator governing the deformation and $\mathbf{e}(\mathbf{x})$ is a 3×1 random noise vector field, whose coefficients in L 's eigenbasis are zero-mean independent Gaussian variables with variances σ_k^2 . If the differential operator L has eigenbasis $\{\phi_k\}$ with eigenvalues $\{\lambda_k\}$, a probability density can be defined directly on the deformation field's expansion coefficients (z_1, \dots, z_n) . If

$$\mathbf{u}(\mathbf{x}) = \sum_k z_k \phi_k(\mathbf{x}) \quad (25)$$

then:

$$p(z_1, \dots, z_n) = \exp \left\{ -\frac{1}{2} \left(\sum_{k=1}^n \log \{ 2\pi\sigma_k^2 / \lambda_k^2 \} + \sum_{k=1}^n \{ |\lambda_k z_k|^2 / \sigma_k^2 \} \right) \right\} \quad (26)$$

Learning Information on Anatomic Variability. Essentially this spectral formulation is a model of anatomic variability. The parameters of this model are learned from an anatomic image database. Model parameters include the σ_k but even the eigenelements $\{\lambda_k, \phi_k\}$ can be learned, if L is treated as a parameterized operator, in much the same way as the Green's functions' parameters were learned in the neural net registration model discussed earlier. Once the model parameters are learned, every subject's anatomy can be represented by a feature vector (z_1, \dots, z_n) , whose elements are just the coefficients of the deformation field required to match their particular anatomy with a mean anatomical template (e.g., Fig. 16). The probability of abnormality in a new subject can therefore be estimated from (26).

Disease Classification and Subtyping.

A second opportunity arises if a *disease-specific atlas* is

available. This type of atlas represents a homogeneous group of patients matched for age, gender and relevant demographic factors (Thompson et al., 1999; Woods et al., 1999). If the parameters of anatomical variation are altered in disease, a pattern classifier can readily be constructed to classify new subjects according to their statistical distance from the diseased group mean relative to the normal group mean (Thompson et al., 1997; Joshi et al., 1998). From a validation standpoint, the operating characteristics of such a system can be investigated (i.e., false positives versus false negatives; Thompson et al., 1997; Joshi et al., 1998). Currently being tested as a framework for encoding anatomic variation, pattern-theoretic and other random tensor-based approaches build on the framework of deformable atlases and show considerable promise in the automated detection of pathology (Haller et al., 1997; Joshi et al., 1998).

Pathology Detection in Image Databases. Pattern recognition algorithms for automated identification of brain structures can benefit greatly from encoded information on anatomic variability. We recently developed a Bayesian approach to identify the *corpus callosum* in each image in an MRI database (Pitiot et al., 1999). The shape of a deformable curve (Fig. 20, *panel 7*) is progressively tuned to optimize a mathematical criterion measuring how likely it is that it has found the corpus callosum. The measure includes terms that reward contours based on their agreement with a diffused edge map (*panels 7-9*), their geometric regularity, and their statistical abnormality when compared with a distribution of normal shapes. By averaging contours derived from an image database, structural abnormalities associated with Alzheimer’s Disease and schizophrenia were identified (Fig. 20; Thompson et al., 1998; Narr et al., 1999). Automated parameterization of structures will accelerate the identification and analysis of disease-specific structural patterns.

V. Conclusion

Registration algorithms, applied in a probabilistic framework, offer a new method to examine abnormal brain structure. Probability maps can be combined with anatomically-driven elastic transformations that associate homologous brain regions in an anatomic database. This provides the ability to perform morphometric comparisons and correlations in 3D between a given subject’s MR scan and a population database, or between population sub-groups stratified by clinical or demographic criteria.

Methods to compare probabilistic information on brain structure from different subpopulations are under rapid development. They include approaches based on random tensor fields (Thompson and Toga, 1997a,b, 1998; Thirion et al., 1998; Gaser et al., 1998; Cao and Worsley, 1998), singular value decomposition and ManCova (*multivariate analysis of covariance*; Ashburner et al., 1998), shape-theoretic approaches (Bookstein, 1997), stochastic differential equations (Christensen et al., 1993) and pattern theory (Grenander and Miller, 1998). The resulting probabilistic systems show promise for encoding patterns of anatomic variation in large image databases, for pathology detection in individuals and groups, and for determining effects on brain structure of age, gender, handedness and other demographic or genetic factors.

As well as disease-specific atlases reflecting brain structure in dementia and schizophrenia, research is underway to build *dynamic* brain atlases that retain probabilistic information on temporal rates of growth and regressive processes during brain development and degeneration. Refinement of these atlas systems to support dynamic and disease-specific data should generate an exciting framework to investigate variations in brain structure and function in large human populations.

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Table 1. Warping Algorithms for 3D Non-Linear Deformation of Brain Data.

Algorithm Type	Author	General Features
I. Intensity-Based		
A. Elastic	Broit	Connection developed between 3D image and a mechanical system
	Bajcsy/Kovacic	Multi-scale/Multi-resolution Approach; matching based on normalized cross-correlation in a 3D Hermite basis
	Dengler/Schmidt	‘Dynamic Pyramid’/optical flow approach; matching performed on the sign of pixels in a multi-resolution Laplacian pyramid; used for template-driven segmentation
	Miller/Christensen/Grenander	MASPAR (Massively Parallel) Implementation; Bayesian (probabilistic) pattern-theoretic framework; warp represented using eigenfunctions of elastic operator and solved in a stochastic PDE framework
	Gee	Bayesian (probabilistic) framework; uses finite elements; matches curvature and edge features as well as intensities and tissue classes
	Schormann/Zilles	Fast elastic matching for histologic applications
B. Hyperelastic	Rabbitt	Allows large deformation and temporal evolution of the anatomic template
C. Spline-Based	Meyer/Kim	Mutual information measures pattern similarity; allows cross-modality warping
D. Fluid	Christensen/Miller/Grenander	MASPAR (Massively Parallel) Implementation; allows large deformations; deformation velocity tracked in a Eulerian reference system; topology of the volumetric mapping investigated (related work by Freeborough, Lester)
	Bro-Nielsen/Gramkow	Fast filters used to implement continuum-mechanical deformations
E. Other	Collins	Maximizes normalized cross-correlation of intensity and edge features; used for automated image segmentation and labeling, and probabilistic atlas construction
	Thirion	Fast algorithm; ‘demon’-based diffusion method motivated by thermodynamics
	Woods	Automated Polynomial-Based Image Registration
	Ashburner/Friston	Bayesian (probabilistic) framework; represents warp using 3D trigonometric basis;
	Amit	part of <i>Statistical Parametric Mapping</i> package wavelet, and other, bases used to express deformation fields in a variational framework; graphical templates developed for automated feature detection
II. Model-Based		
Constraints:		
A. Points:	Bookstein	Thin-plate splines; used to investigate biological shape variation
	Davis	Landmarks used to drive 3D volume splines, elastic splines; neural network implementation
B. Curves:	Müller/Ruprecht	Explores 3D interpolation schemes and radial basis functions for warping
	Subsol/Declerck	Pre-extracted ‘crest-lines’ constrain the warp; used for automated atlas construction
C. Surfaces:	Ge; Banerjee; Collins	3D sulcal lines used for cortical surface matching
	Downs	Normalizes cortical convex hulls
	Terzopoulos	Snakes used for deformable curve and surface segmentation
	Szeliski/Lavallée	Warp rapidly computed on an adaptive octree-spline grid
	Davatzikos	Deformable surface models drive a 3D elastic registration; curvature maps used to constrain surface-to-surface matching (related work by Gabrani/Tretiak)
	Thompson/Toga	Connected systems of deep surface meshes and deformable surfaces used to drive the warp; tensor-based matching of cortical patterns for pathology detection; used to measure brain growth and to create disease-specific brain atlases
	Drury/Van Essen;	Cortical flattening and parameterization algorithms (related work by
	Dale/Sereno/Fischl	Schwartz/Merker, MacDonald/Evans)

	Miller/Drury/Van Essen	Matching of cortical flat maps
D. Other:	Joshi	Generalized Dirichlet problem formulated for point, curve, surface and volumetric matching

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Figure Legends

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Fig. 1. *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, $\mathbf{u}(\mathbf{x})$, 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. 2. *Automated Image Matching with Neural Networks*. Neural networks can be used to compute the deformation field required to warp one image into the shape of another. In one approach (Davis et al., 1997, (a)), each of the 3 deformation vector components, $\mathbf{u}^k(\mathbf{x})$, is the output of the neural net when the position in the image to be deformed, \mathbf{x} , is input to the net. In calculating the output, the numerical outputs of the hidden units (G_i, π_m) are weighted using synaptic weights, w_{ik} , different for each output component. If landmarks in both images are available to guide the mapping, the weights are found by solving a linear system. Otherwise, the weights can be tuned so that a measure of similarity between the deforming image and the target image is optimized. (b). When the number of landmarks driving the deformation mapping is very large (Thompson and Toga, 1998), a linear system can be set up, based on a model of linear elasticity, which is solved by successive over-relaxation methods. However, there is a strong mathematical connection between the Green's function (impulse response) of the deformation operator (b), hidden units in the neural net (a), and kernels used in non-parametric regression approaches (see main text). [*Acknowledgment: Diagram (a) is adapted from Davis et al., 1997*].

Fig. 3. *Curve-Driven Warping in a Histology Application*. Curve-driven warping algorithms can recover and compensate for patterns of tissue change which occur in *post mortem* histologic experiments. A brain section ((a), *left panel*), gridded to produce tissue elements for biochemical assays, is reconfigured ((a), *right*) into its original position in the cryosection blockface (Mega et al., 1997; algorithm from Thompson and Toga, 1996, modified to produce a 2D elastic warp). The complexity of the required deformation vector field in a small tissue region (*magnified vector map*, (b)) demonstrates that very flexible, high-dimensional transformations are essential (Thompson and Toga, 1996; Schormann et al., 1996). These data can also be projected, using additional warping algorithms, onto *in vivo* MRI and co-registered PET data from the same subject for digital correlation and analysis (Mega et al., 1997).

Fig. 4. *Connected Surface Systems used to drive the Warp*. Models of deep structures are used to guide the mapping of one brain to another (data from Thompson and Toga, 1996). Deep sulcal surfaces include: the anterior and posterior calcarine (CALCa/p), cingulate (CING), parieto-occipital (PAOC) and callosal (CALL) sulci and the Sylvian fissure (SYLV). Also shown are the superior and inferior surfaces of the rostral horn (VTSS/i) and inferior horn (VTIS/i) of the right lateral ventricle. Ventricles and deep sulci are represented by connected systems of rectangularly-parameterized surface meshes, while the external surface has a spherical parameterization which satisfies the discretized system of Euler-Lagrange equations used to extract it. Connections are introduced between elementary mesh surfaces at known tissue-type and cytoarchitectural field boundaries, and at complex anatomical junctions (such as the PAOC/CALCa/CALCp junction shown here). Color-coded profiles show the magnitude of the 3D deformation maps warping these surface components (in the right

hemisphere of a 3D T_1 -weighted SPGR MRI scan of an Alzheimer's patient) onto their counterparts in an identically-acquired scan from an age-matched normal subject.

Fig. 5. *Mesh Construction and Matching.* The derivation of a standard surface representation for each structure makes it easier to compare and analyze anatomical models from multiple subjects. An algorithm converts points (*dots*, top right panel) on an anatomical structure boundary into a parametric grid of uniformly spaced points in a regular rectangular mesh stretched over the surface (Thompson et al., 1996). Computation of anatomic differences between subjects requires transformation tools that deform connected systems of mesh-based surface models representing structures in one subject's anatomy, into correspondence with their counterparts in the anatomy of another subject. This mapping is computed as a surface-based displacement map (*right panel*), which deforms each surface locally into the shape of its counterpart. Maintenance of information on surface connectivity guarantees accurate mapping of curved junctions among surfaces, under both the surface-based and subsequent volumetric transformations. *Note:* Matching of surfaces with a *spherical* parameterization requires separate methods, which deal with the matching of curved internal landmarks (Section 3).

Fig. 6. *Volume Warp Calculation.* The volumetric transformation $\mathbf{W}_{pq}(\mathbf{x})$, of an arbitrary point \mathbf{x} in a scan, p , to its counterpart in another scan, q , is expressed as a weighted linear combination of distortion functions associated with each surface. Within a surface S_i , the relative contribution of each point in the projected patch $\{\mathbf{np}_i[\mathbf{B}(\mathbf{x};r_c)]\}$ to the elastic transformation at \mathbf{x} is given a relative weight w_i . The distortion at \mathbf{x} due to surface S_i is given by $\mathbf{D}_i^{pq}(\mathbf{x}) = \left\{ \int_{\mathbf{r} \in \mathbf{B}} w_i^p \mathbf{W}_i^{pq} d\mathbf{r} \right\} / \left\{ \int_{\mathbf{r} \in \mathbf{B}} w_i^p d\mathbf{r} \right\}$, where the \mathbf{W}_i^{pq} are the displacement maps defined on each surface (Fig. 4). The volume warp $\mathbf{W}_{pq}(\mathbf{x})$ is a weighted average (over i) of the $\mathbf{D}_i^{pq}(\mathbf{x})$, depending on the relative distance $\gamma_i(\mathbf{x})$ of \mathbf{x} from its near-points on each surface S_i . [Adapted from Thompson and Toga, 1996].

Fig. 7. *3D Image Warping Measures Patterns of Anatomic Differences.* T_1 -weighted MR sagittal brain slice images from (*left*, a) a normal elderly subject's scan, (b) a 'target' anatomy, from a patient with clinically-determined Alzheimer's disease; and (c) result of warping the reference anatomy into structural correspondence with the target. Note the precise non-linear registration of the cortical boundaries, the desired reconfiguration of the major sulci, and the contraction of the ventricular space and cerebellum. The complexity of the recovered deformation field is shown by applying the two in-slice components of the 3D volumetric transformation to a regular grid in the reference coordinate system. This visualization technique (d) highlights the especially large contraction in the cerebellar region, and the complexity of the warping field in the posterior frontal and cingulate areas, corresponding to subtle local variations in anatomy between the two subjects. To monitor the smooth transition to the surrounding anatomy of the deformation fields initially defined on the surface systems, the magnitude of the warping field is visualized (e) on models of the surface anatomy of the target brain, as well as on an orthogonal plane slicing through many of these surfaces at the same level as the anatomic sections. The warping field extends smoothly from the complex anatomic surfaces into the surrounding brain architecture, and severe deformations are highlighted in the pre-marginal cortex, ventricular and cerebellar areas.

Fig. 8. *Cortical Surface Extraction.* Prior to matching cortical surfaces across subjects, a high-resolution surface representation of the cortex is obtained with a semi-automatic 3D active surface extraction algorithm (MacDonald et al., 1993, 1998). 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 final model of the cortex (*lower left*) consists of a high-resolution mesh consisting of 100,000-150,000 discrete triangular elements that tile the surface (*lower right*).

Fig. 9. *Scheme to Match Cortical Regions with High-Dimensional Transformations and Color-Coded Spherical Maps.* High-resolution surface models of the cerebral cortex are extracted in parametric form, which produces a continuous, invertible one-to-one mapping between cortical surface points, (a), and their counterparts on a sphere. To find matches between cortical regions in different subjects [(a)/(d)], a Dirichlet problem is framed in the parametric space (Thompson and Toga, 1996, 1997, 1998; Davatzikos, 1996). Each point in the spherical map, (b), is color-coded at 16 bits per channel with

a color value which represents the location of its counterpart on the convoluted surface. When spherical maps are made from two different cortical surfaces, the respective sulci will be in different positions in each spherical map [(b),(c)], reflecting their different locations on the folded brain surface. Using a vector-valued flow field defined on the sphere (c), the system of sulcal curves in one spherical map is driven into exact correspondence with their counterparts in the target spherical map, guiding the transformation of the adjacent regions. The effect of the transformation is illustrated in (c) by its effect on a uniform grid, ruled over the starting spherical map and passively carried along in the resultant deformation. Complex non-linear flow is observed in superior temporal regions, as the superior temporal sulcus (STS) extends further posteriorly in the target brain, and the posterior upswing of the Sylvian fissure (SYLV) is more pronounced in the reference brain (a) than in the target (d). Outlines are also shown for the superior frontal sulcus (SFS) and central sulcus (CENT) which is less convoluted in the reference brain than in the target. Because the color-coded spherical maps index cortical surface locations in 3D, the transformation is recovered in 3D stereotaxic space as a displacement of points in one subject's cortex onto their counterparts in another subject (Fig. 12).

Fig. 10. *High-Dimensional Matching of Cortical Surfaces and Sulcal Networks.* Accurate and comprehensive matching of cortical surfaces requires more than the matching of overall cortical geometry. Connected systems of curved sulcal landmarks, distributed over the cortical surface, must also be driven into correspondence with their counterparts in each target brain. A cascade of mathematical mappings is required to achieve this. Active surface extraction of the cortex provides a continuous inverse mapping from the cortex of each subject to the spherical template used to extract it. Application of these inverse maps (D_p^{-1} , D_q^{-1}) to connected networks of curved sulci in each subject transforms the problem into one of computing an angular flow vector field F_{pq} , in spherical coordinates, which drives the network elements into register on the sphere (Thompson and Toga, 1996). To greatly accelerate computation of the overall mappings $D_q F_{pq} D_p^{-1}$, the forward mapping D_q , is pre-encoded via the mapping $I_q^{-1} K_q$ as a 3-channel floating point array (*shown in color*) defined on the co-domain of F_{pq} . The full mapping $D_q F_{pq} D_p^{-1}$ can be expressed as a displacement vector field that drives cortical points and regions in Brain P into precise structural registration with their counterparts in Brain Q.

Fig. 11. *Covariant Tensor Approach to Cortical Matching.* Current approaches for deforming one cortex into the shape of another typically simplify the problem by first representing cortical features on a 2D plane, sphere or ellipsoid, where the matching procedure (i.e. finding $\mathbf{u}(\mathbf{r}_2)$, above) is subsequently performed. Although these simple 2-parameter surfaces serve as proxies for the cortex, different amounts of local dilation and contraction ($g_{jk}(\mathbf{r})$) are required to transform the cortex into a simpler 2-parameter surface. These variations complicate the direct application of 2D regularization equations for matching their features. A covariant tensor approach is introduced to address this difficulty. The regularization operator L is replaced by its covariant form L^* , in which correction terms Γ_{jk}^i compensate for fluctuations in the metric tensor of the flattening procedure.

Fig. 12. *Matching an Individual's Cortex to the Average Cortex.* 3D variability patterns across the cortex are measured by driving individual cortical patterns into local correspondence with the average cortical model. (a) shows how the anatomy of one subject (*shown as a brown surface mesh*) deviates from the average cortex (*shown in white*), after affine alignment of the individual data. (b) shows the deformation vector field required to reconfigure the gyral pattern of the subject into the exact configuration of the average cortex. The transformation is shown as a flow field that takes the individual's anatomy onto the right hemisphere of the average cortex (*blue surface mesh*). The largest amount of deformation is required in the temporal and parietal cortex (*pink colors, large deformation*). Details of the 3D vector deformation field ((b), *inset*) show the local complexity of the mapping. (c). *Mapping a Patient into the Group Average Configuration.* Instead of matching just the cortex, this figure shows the complex transformation required to match 84 different surface models in a given patient, after affine alignment, into the configuration of an average surface set derived for the group (see Thompson et al., 1999, for details). The effects of several anatomic surfaces driving the transformation are indicated, including the cingulate sulcus (CING), hippocampal surface (HPCP), superior ventricular horn (VTS), parieto-occipital sulcus, and the anterior calcarine fissure (CALCa). This surface-based vector field is extended to a full volumetric transformation field (0.1 billion degrees of freedom) which reconfigures the anatomy of the patient into correspondence with the average configuration for the group. Storage of these mappings allows quantification of local anatomic variability.

Fig. 13. *Average Cortex in Alzheimer's Disease.* The average cortical surface for a group of subjects ($N=9$, Alzheimer's patents) is shown as a graphically rendered surface model. If sulcal position vectors are averaged without aligning the

intervening gyral patterns (*top*), sulcal features are not reinforced across subjects, and a smooth average cortex is produced. By matching gyral patterns across subjects before averaging, a crisper average cortex is produced (*bottom*). Sulcal features that consistently occur across all subjects appear in their average geometric configuration.

Fig. 14. *3D Cortical Variability in Talairach Stereotaxic Space*. (a) The profile of variability across the cortex is shown ($N=9$ Alzheimer's patients), after differences in brain orientation and size are removed by transforming individual data into Talairach stereotaxic space. The following views are shown: oblique frontal, frontal, right, left, top, bottom. Extreme variability in posterior perisylvian zones and superior frontal association cortex (16-18 mm; *red colors*) contrasts sharply with the comparative invariance of primary sensory, motor, and orbitofrontal cortex (2-5 mm, *blue colors*).

Fig. 15. *Comparing Different Registration Approaches*. The ability of different registration algorithms to reduce anatomic variability in a group of subjects ($N=9$, Alzheimer's patients) is shown here. Digital anatomic models for each subject were mapped into common coordinate spaces using the transformations specified in the Talairach atlas (*Tal*; Talairach and Tournoux, 1988), as well as automated affine (or first-order) and eighth-order polynomial mappings as implemented in the *Automated Image Registration* package (Woods et al., 1993, 1998, 1999). After applying each type of mapping to the models from all subjects, the residual variability of ventricular (*top row*) and deep cortical surfaces (*middle row*) and superficial sulci (*bottom row*), is shown as a color coded map across each structure. The color represents the 3D root mean square distance from individual models to an average model for each structure, where distance is measured to the near-point on the average mesh model (Thompson et al., 1999). As expected, polynomial transformations reduce variability more effectively than affine transformations, and both outperform the Talairach system. At the cortex, model-driven registration can be used to explicitly match gyral patterns, improving registration still further.

Fig. 16. *Average Brain Templates and 3D Cortical Variability*. Axial, sagittal and coronal images are shown from a variety of population-based brain image templates. For comparison purposes, (a) shows a widely-used average intensity dataset (ICBM305) based on 305 young normal subjects, created by the *International Consortium for Brain Mapping* (Evans et al., 1994); by contrast, templates (b) and (c) are average brain templates created from high-resolution 3D MRI scans of Alzheimer's Disease patients. (b) *Affine Brain Template*, constructed by averaging normalized MR intensities on a voxel-by-voxel basis data after automated affine registration; (c) *Continuum-Mechanical Brain Template*, based on intensity averaging after continuum-mechanical transformation. By using spatial transformations of increasing complexity, each patient's anatomy can increasingly be reconfigured into the average anatomical configuration for the group. After intensity correction and normalization, the reconfigured scans are then averaged on a pixel-by-pixel basis to produce a group image template with the average geometry and average image intensity for the group. Anatomical features are highly resolved, even at the cortex (c). Transformations of extremely high spatial dimension are required to match cortical features with sufficient accuracy to resolve them after scans are averaged together.

Fig. 17. *Pathology Detection with 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 anatomy 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 that correspond across a normal population (III). 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. 18. *Brain Distortions induced by Tumor Tissue: Probability Maps for Major Sulci in Both Hemispheres*. Color-coded probability maps (*right*) quantify the impact of two focal metastatic tumors (*illustrated in red*; see cryosection blockface, *left*) on the supracallosal, parieto-occipital, and anterior and posterior calcarine sulci in both brain hemispheres.

Fig. 19. *Pathology Detection in Alzheimer's Disease*. A color-coded probability map (a), shown on a 3D graphical surface model of an Alzheimer's patient's cortex, provides probability statements about the deviation of cortical regions from the norm. The inherent variability in normal cortical anatomy is encoded in the form of a surface-based probability field, known

as an anisotropic lattice process, or a random vector field (see Section 4). Adaptive to their biological context, these algorithms use contextual information on anatomic variations before assigning a probability value to each cortical point. The resulting map exhibits regions of severely depressed probability values ($p < 0.00001$), particularly in inferior frontal cortex. A probability map is also shown (b) for a normal control subject, age-matched to the AD patient and to subjects in the reference archive. 12.8% and 19.5% of the left and right inferior frontal cortex were severely abnormal ($p < 0.00001$) in the Alzheimer's patient, while only 0.21% and 0.37% of the same areas were indicated as abnormal in the control subject. The system is refined as the underlying database of subjects increases in size and content.

Fig. 20. *Automated Detection of Structures in Image Databases.* Here an algorithm is used to find the *corpus callosum* boundary (panel 9) in each image in an anatomic database ($N=104$; Pitiot et al., 1999). The output of an edge detector (panel 2) is run through a connectivity filter that suppresses the smallest connected sets of edge pixels. The filtered edge image is then diffused over time (panels 4-6) and a deformable curve (panel 7) is adapted to optimize a matching measure (panel 10). This measure penalizes curve shapes that are too bent or stretched, that fail to overlap the diffused edge image, or are unlikely based on a statistical distribution of normal corpus callosum shapes. Given an image database, algorithm parameters (such as the size of the connectivity filter; panel 11) can be tuned based on their overall performance on an image database. Their optimal values differ depending on how noisy the images are. Boundaries were averaged from patients with Alzheimer's Disease and from elderly controls matched for age, educational level, gender and handedness. Panel 12 shows a focal shape inflection in the Alzheimer's patients relative to normal elderly subjects of the same age, and a statistically significant tissue loss in the isthmus (the 2nd sector, when the structure is partitioned into fifths). The isthmus connects regions of temporo-parietal cortex that exhibit early neuronal loss and perfusion deficits in AD (Thompson et al., 1998).

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