A SURFACE-BASED TECHNIQUE FOR WARPING 3-DIMENSIONAL IMAGES OF THE BRAIN

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A Surface-Based Technique for Warping 3-Dimensional Images of the Brain

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ABSTRACT

We have devised, implemented and tested a fast, spatially accurate technique for calculating the high-dimensional deformation field relating the brain anatomies of an arbitrary pair of subjects. The resulting 3D deformation map can be used to quantify anatomic differences between subjects or within the same subject over time, and to transfer functional information between subjects or integrate that information on a single anatomic template. The new procedure is based on developmental processes responsible for variations in normal human anatomy, and is applicable to 3D brain images in general, regardless of modality. Hybrid surface models known as *Chen surfaces* (based on superquadrics and spherical harmonics) are used to efficiently initialize 3D active surfaces, and these then extract from both scans the developmentally fundamental surfaces of the ventricles and cortex. The construction of extremely complex surface deformation maps on the internal cortex is made easier by building a generic surface structure to model it. Connected systems of parametric meshes model several deep sulci whose trajectories represent critical functional boundaries. These sulci are sufficiently extended inside the brain to reflect subtle and distributed variations in neuroanatomy between subjects. The algorithm then calculates the high-dimensional volumetric warp (typically with 384^2x256x3 ≈ 0.1 billion degrees of freedom) deforming one 3D scan into structural correspondence with the other. Integral distortion functions are used to extend the deformation field required to elastically transform nested surfaces to their counterparts in the target scan. The algorithm's accuracy is tested, by warping 3D MRI volumes from normal subjects and Alzheimer's patients, and by warping full-color 1024^3 digital cryosection volumes of the human head onto MRI volumes. Applications are discussed, including the transfer of multi-subject 3D functional, vascular and histologic maps onto a single anatomic template, the mapping of 3D brain atlases onto the scans of new subjects, and the rapid detection, quantification and mapping of local shape changes in 3D medical images in disease, and during normal or abnormal growth and development.

Key Words: 3D image warping, brain mapping, surface and volume transformations, surface fitting, active contours, Chen Surfaces, spherical harmonic interpolation, geometric modeling.

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Introduction: The Elastic Warping Problem

Deep anatomical structures are often visualized and analyzed with the help of non-invasive medical imaging procedures. To aid in the identification of the imaged anatomic regions, a considerable amount of research has been directed towards the development of 3-dimensional *standardized atlases* of the human brain [1,2,3]. These provide an invariant reference system and the possibility of template matching, allowing anatomical structures in new scans to be identified and analyzed. Atlases also provide a precise quantitative framework for multi-modality brain mapping and serve as a guide in planning stereotaxic neurosurgical procedures.

Nevertheless, no two people's brains are the same, and this presents a challenge for any attempts to create standardized atlases. Even in the absence of any pathology, neural structures will vary between individuals not only in shape and size, but also in their orientations relative to each other [4]. Such normal variations have severely complicated the goals of comparing functional and anatomic data from many subjects, and of developing standardized atlases of the human brain.

In view of the complex structural variability between individuals, a fixed brain atlas will fail to serve as a faithful representation of the brains of new subjects. It would, however, be ideal if the atlas could be elastically deformed to fit a new image set from an incoming patient. *Deformable atlases* [5,6,7] not only account for the anatomical variations and idiosyncrasies of each individual patient, but they offer a powerful strategy for exploring and classifying age-related, developmental or pathologic variations in anatomy.

This paper advances a fast, spatially accurate, surface-based approach for the elastic warping of anatomical images, applicable to 3D image sets in general, regardless of modality. *Unlike previous techniques, the new method takes account of certain developmental processes which are responsible for the variations in neuroanatomy between normal individuals.* The new algorithms arose out of previous work in which new methods were developed for quantifying the variations in shape and location of cortical and subcortical brain structures [8,9]. In particular, connected systems of parametric meshes were used to model the internal interfaces of deep structures in a population of normal brains, and a probability space of random transformations, based on the theory of Gaussian random fields, was developed to reflect the observed variability in stereotaxic space of the connected system of anatomic surfaces [9,10,11]. A digital brain atlas, incorporating precise statistical information on the positional and geometric variability of important functional interfaces, was used to generate probability maps quantifying the severity of local structural variations in the anatomy of new subjects [10].

The new warping algorithm presented here uses a similar approach to model connected surface systems inside the brain, but it also calculates a 3D deformation field which can be used to non-linearly register one brain with another (or with a neuroanatomic atlas). The resultant deformation fields can subsequently be used to transfer physiologic data from different individuals to a single anatomic template, enabling functional data from different subjects to be compared and integrated.

The procedure calculates the volumetric warp of one brain image into the shape of another, by interpolating the deformation field required to elastically transform nested surfaces to their homologues, automatically extracted from the source and target data sets. The algorithm capitalizes on several existing methods for extracting surfaces from image volumes, and for modeling the surface dynamics of deformable biological tissue. The technique extends to the brain an existing high-fidelity surface estimation procedure which has already proved effective in modeling the dynamics of the heart. A similar algorithm for recovering 3D closed surfaces from noisy images has recently been successful in head and face modeling [11] and automated 3D image segmentation [12,13]. The algorithm specifies in detail the transformations mapping homologous surfaces from one 3D data set to another, and calculates the global warp of the tissue between them using a fast and spatially accurate interpolation scheme. In addition, a computationally fast algorithm for manipulating surfaces, previously described [14] and implemented in our laboratory, is extended to determine volume warps. It uses distance fields associated with the fundamental surfaces to evaluate *integral distortion functions*, which represent the induced effect of surface distortions on points in their vicinity. Since several of the inherent difficulties in current density-based warping approaches can be circumvented by the surface-based approach presented here, we begin by briefly examining the basic elements of current density-based strategies for elastic warping.

I. Density-Based Approaches

Density-based approaches to elastic matching carry out local comparisons between an atlas and a target scan, before computing the optimal elastic transformation mapping one image volume onto the other. Such methods discard all information except small regional patterns in intensity, which are compared in both data sets. The information in the atlas, **A**, and the target scan, **P**, is conventionally stored in a 3D array, with a gray-scale intensity value $a_{ijk} \in \mathbf{A}$ and $p_{ijk} \in \mathbf{P}$ associated with each voxel position $\mathbf{a}_{ijk}$ and $\mathbf{p}_{ijk}$ in the atlas and target pattern (as the coordinates i, j, k take values in the range *1* to p, q and r respectively). The aim is to deform the intensity distribution in the atlas so that the result correlates well with that of the target pattern. Basically, the *similarity* S[T(**A**),**P**] is computed between all sorts of deformed versions of the atlas $\{T(\mathbf{A}) \mid T \in \mathbb{T}\}$ and the target pattern **P**, and the best map T* is defined as the one for which this similarity function is maximized.

To accommodate fine anatomic variations, all successful warping transforms need to be of extremely high spatial dimension [6]. This is because complex profiles of contraction or dilation of the atlas, at an extremely local level, are required to deform it into the shape of the target anatomy. To ensure that the topology and connectivity of the atlas are maintained under these complex transformations, the atlas image **A** is typically considered to be embedded in a 3D deformable medium with elastic [15,16,17] or viscous fluid [5,18] mechanics. This medium is subjected to certain distributed internal forces, causing it to become even more similar to **P**. For each 3D point **x** in the atlas, a local similarity function S(**x**,**x**+**u**) is defined, whose value is the normalized intensity correlation between a fixed-size neighborhood centered at **x** in the atlas, and a neighborhood of the same size centered at location **x**+**u** in the 3D target image. A local internal force **F**(**x**) drives the medium of the atlas into register with the target image. Its value at **x** is made proportional to the gradient vector of the local similarity function, causing the local similarity to increase. $\tilde{\mathbf{N}}$S is calculated at each **x** by assuming a second-order Taylor series approximation for S(**x**,**x**+**u**), in the neighborhood of a pre-computed local maximum of the function at S(**x**,**x**+**u***) [16].

The image is deformed until these external forces reach equilibrium with the internal restoring forces generated by the elasticity of the supporting material. The displacement field $\mathbf{x} \Rightarrow \mathbf{x}+\mathbf{u}$ at equilibrium is given by the set of Navier-Stokes equations for fixed **x**:

$$\mu \tilde{\mathbf{N}}^2 u_i(\mathbf{x}) + (\lambda+\mu)[\partial\theta/\partial x_i] + F_i(\mathbf{x}) = 0, \quad (i = 1, 2, 3), \quad (1)$$

where $\theta = \partial u_1/\partial x_1 + \partial u_2/\partial x_2 + \partial u_3/\partial x_3$ $\tilde{\mathbf{N}} \cdot \mathbf{u}(\mathbf{x})$ is the cubical dilation, where $\mathbf{F}(\mathbf{x})$ $(F_1, F_2, F_3)^T$ is the external force [namely $k.\tilde{\mathbf{N}}$S at each point **x** $(x_1, x_2, x_3)^T$ in the coordinate system before deformation], and where Lamé's elastic constants λ and μ refer to the elastic properties of the body. These 3 partial differential equations can be solved iteratively on a finite grid, and interpolated trilinearly to obtain a continuous displacement field **u**(**x**). If $\mathbf{U}: \mathbf{x} \Rightarrow \mathbf{x} + \mathbf{u}(\mathbf{x})$, then **U**(**A**) becomes the *final warped atlas*.

Serious shortcomings of these warping algorithms were revealed and explored by Christensen *et al.*, in [18,19]. Since the 1980s, linear models of the energetics of the deformed media included the *linearly elastic* [5,16,17], Laplacian [20,21] and biharmonic (or *thin-plate* [21,22,23]) models, all of which are limited by small deformation assumptions. The deformable media develop restoring forces proportional to the deformed distance, and result in a displacement field of artificially low magnitude, leaving the atlas incompletely warped onto the target scan. In [18], to overcome these limitations of the elastic model, the energetics of the medium was relaxed to obey *viscous fluid* mechanics, after an initial parametrically-defined solution to the elastic equilibrium equations was achieved with 100 iterations of a stochastic gradient search. The transformation was then refined by solving the viscous fluid differential equation:

$$\alpha\nabla^2\mathbf{v}(\mathbf{x},t)+\beta\nabla[\nabla^T\{\mathbf{v}(\mathbf{x},t)\}] = \mathbf{F}(\mathbf{x}), \qquad (2)$$

where $\mathbf{F}(\mathbf{x})$ is the driving force (per unit volume) which deforms the atlas into the shape of the target anatomy, and α and β are viscosity constants. This equation describes the instantaneous velocity of the deforming atlas at location $\mathbf{x}$ at time t. The velocity $\mathbf{v}(\mathbf{x},t)$ is related to the displacement field $\mathbf{u}(\mathbf{x},t)$ by the equation:

$$\mathbf{v}(\mathbf{x},t) = \{\partial\mathbf{u}(\mathbf{x},t)/\partial t\} + \mathbf{v}(\mathbf{x},t) \bullet\nabla\{\mathbf{u}(\mathbf{x},t)\}, \qquad (3)$$

and was solved at 500 time points to generate the final transformation. As the atlas deforms to match the target over time, the driving force goes to zero, which causes the velocity to go to zero and gives the final match.

Although the results of this complex technique are very spectacular [5,17-19], it is noted in [24] that the registration of two 128×128×148 volumes took 9 hours on a 64×64 MPP 12000Sx/model 200 MASPAR (Massively Parallel Machine) achieving an impressive 0.8 billion floating point operations per second (0.8 GigaFLOPS). Similarly, although computation time is not mentioned in [16], the method relies on correlation, which is known to be time-consuming, even in 2D [25]. In particular, having $\tilde{\mathbf{N}}S$ in the expression for the internal force $\mathbf{F}(\mathbf{x})$ is inevitable, but inconvenient computationally, especially when the correlation function S is so complex. This function contains integrals which are approximated by projection onto an orthonormal basis of functions of radial direction such as spherical harmonics, or (in [16]) onto the 3-dimensional Hermite functions $\psi_p(x_1)\psi_q(x_2)\psi_r(x_3)$, $(p, q, r \in \mathbb{N})$, where the ψ_i are Hermite polynomials $\psi_i(t)=[H_i(t).\exp(-t^2/2)]/[2^i.i!.\sqrt{\pi}]^{1/2}$, and $H_i(t)=(-1)^i\exp(t^2)[D_t^n\{\exp(-t^2)\}]$, for $t\in(-\infty,\infty)$. Finally, warping transformations based on continuum mechanics are determined only when the elasticity or viscosity coefficients are specified, and the selection of a pair of values for the visco-elastic parameters λ, μ, α, β is essentially arbitrary, in default of any biological information on what choice might be appropriate. The resultant need to optimize these additional parameters is expensive computationally, especially when a separate set of differential equations has to be derived and solved for each voxel.

In conclusion, several of the drawbacks and inherent difficulties with *density-based* elastic warping techniques can be circumvented by devising 3D *surface-based* approaches to the registration problem. These are considered next, and have many distinct advantages:

1. **Speed:** Compact representation of the 3D deformation field allows us to perform accurate high-dimensional warping in a reasonable amount of time (*c*. 30 minutes), on conventional UNIX workstations;

2. **Embryology:** Developmentally relevant surfaces can be isolated to constrain the warp, justifying the algorithm from an anatomic standpoint, and exploiting inherent biological information in the scans;

3. **Fidelity:** High spatial acuity of the warp is guaranteed at the surface interfaces used to constrain the warp, and these include many critical functional interfaces such as the ventricles and cortex, as well as numerous cytoarchitectonic and lobar boundaries in 3 dimensions.

II. Surface-Based Approaches

The overall scheme of the strategy adopted here is as follows: (i) choose relevant surfaces to model; (ii) model these surfaces; (iii) calculate the appropriate surface transformations; and (iv) calculate the global volume warp. The method capitalizes on two existing surface estimation techniques [13,26]. The technique pioneered in [26] has not previously been used to deal with neuroanatomical surfaces, although it has proven successful in modeling the dynamics of the left ventricular surface of the human heart. In the next section, we discuss our selection of surfaces in the brain which are important from a developmental point of view (namely, the cerebral cortex, and the portion of the ventricular system lateral to the *interventricular foramen of Monro* in each hemisphere). A separate warp is calculated for each hemisphere, since the two hemispheres develop independently, without interaction, and eventually become separated anatomically (except at the *corpus callosum*) by a midline interface of cerebrospinal fluid. It will therefore suffice to describe the warping strategy as it applies to a single hemisphere, say the left one, without loss of generality. The same procedure is subsequently applied to the other hemisphere. For each hemisphere, then, analytically-defined *Chen Surfaces* are fitted through anatomical landmarks to provide initial estimates of the biologically relevant surfaces in each image. These estimated surfaces are subsequently molded more precisely to the anatomical contours using a Euler-Lagrange evolution process [12]. In this method, each surface relaxes to a minimal energy state in a system of potentials associated with the image space. With these refined surfaces represented in analytical form, separate surface warps can be computed, mapping the lateral ventricles, cortex and an internal connected system of deep sulcal surfaces, from the atlas to the target scan. The transformation of the material between the fitted surfaces in the atlas is then calculated using weighted distortion functions and spherical harmonic interpolation.

III. The Search for Deformable Surfaces: An Embryologist's Suggestion

The first step in designing a surface-based warping strategy is to decide which surfaces to model. Any serious consideration of the spatial relations between the brain structures in the normal adult human should take into account their developmental history. Cortical neurogenesis is a highly stereotyped and well-understood process whose onset occurs around embryonic day 23 in humans.

The entire brain is generated by proliferation of the embryonic neural tube, which is basically a tubular sheath of cells surrounding a central fluid-filled cavity. The different rates of growth and proliferation of this sheath of cells produce on-going elastic deformations of its inner and outer surfaces. Once the fluid-filled precursors of the lateral ventricles

have protruded out, one on each side, the evolution of the cortical surfaces is constrained medially by an equal and opposing pressure due to the tissue of the other hemisphere. On each side, the evolution of the outer surface $\mathbb{O}$ is also constrained by the external pressure of the developing cranium, and this results in the complex folding and invagination of the cerebral cortex, whose final morphology is only loosely stereotyped across different individuals. The inner germinal surface $\mathbb{I}$ for each hemisphere becomes the respective lateral ventricle at maturity. The lateral ventricles are very readily discerned in magnetic resonance images, due to the drastic difference between the proton density and relaxation times of the ventricular system, which is filled with cerebrospinal fluid, and the tissue which surrounds it.

The lateral ventricles are useful landmarks for understanding the regional anatomy of the cerebral hemispheres. During development, the enormous proliferation of cells in the cerebral hemispheres forces the lateral ventricles and many other major structures in the brain into a characteristic C-shape [27]. This process is illustrated in Fig. 1. Since this proliferation causes different regions of the enclosed material to expand physically at different rates, the inner and outer limiting surfaces are continuously deformed until they become quite irregular. In later developmental stages, however, four stereotypical features on the lateral ventricles become distinct - the body, and the frontal, occipital and inferior horns (Fig. 2). In what follows, we will represent the mature geometry of the inner and outer developmental surfaces *in the left hemisphere* by $\mathbb{I}^*(\infty)$ and $\mathbb{O}^*(\infty)$. (The * indicates *closed* surfaces in 3D, while the ∞ suggests *convergence* to a mature morphology, for time-varying surfaces $\mathbb{I}^*(t)$ and $\mathbb{O}^*(t)$.) Exactly the same arguments may be applied to the cerebral cortex and lateral ventricle in the right hemisphere, which are modeled and warped independently, using the same algorithms. To be precise (and suppressing the '∞'), $\mathbb{I}^*$ will represent the mature geometry of the left lateral ventricle alone, considered as an autonomous system, notionally closed off from the third ventricle at the lateral tip of the *foramen of Monro*. $\mathbb{O}^*$ will represent the parenchyma of the cerebral cortex in the left hemisphere, closed off medially, at its midline interface with cerebrospinal fluid in the interhemispheric vault, the midline division in the human brain.

A useful first step in characterizing the neuroanatomical variations between two individuals might be to analyze the differences in the mature geometry of these two fundamental developmental surfaces. Any major surface variation, malformation or idiosyncrasy in an individual's $\mathbb{I}^*$ or $\mathbb{O}^*$, relative to the same surfaces in a standard 3D atlas, might fundamentally alter the spatial configuration and geometry of all the intervening structures relative to the atlas.

Although by no means the only source of anatomic variability between individuals, the instantaneous morphology of these two primary surfaces in each hemisphere over time will very largely govern the potential spatial relations and initial accretion points of newly-developing structures.

IV. Surface Fitting

(a). Initial Estimates: Fitting a Chen Surface through a set of Anatomical Landmarks

The warping technique proposed here requires the identification of the surfaces $\mathbb{I}^*$ and $\mathbb{O}^*$ in the atlas, and their counterparts in the target scan. It yields an explicit analytical form for each surface in its respective image space, with respect to a spherical coordinate system. Both the external cortical surface $\mathbb{O}^*$ and lateral ventricles $\mathbb{I}^*$ are extracted automatically from each scan using an extension of the widely-used Cohen and Cohen *active surface* method [12,28]. This method attracts an initial estimate of each surface to anatomic boundaries, or edges, in the surrounding 3D image, molding the initial surface accurately onto the local anatomical contours. The initial estimates required by this procedure are supplied in the form of a Chen surface construct, which is obtained by fitting an algebraically-defined surface through a set of manually-defined points. In [26], Chen *et al.* developed a powerful, hierarchical method for capturing the chief dynamic and deformational activity of the left ventricle of the human heart in the course of a cardiac cycle. We use a variant of this approach to fit two surfaces through manually-defined points on the surface of the lateral ventricles and on the cerebral cortex, respectively.

In magnetic resonance images, the large difference in relaxation parameters between neural tissue and cerebrospinal fluid makes it possible to isolate manually a large number of fiducial points on the convex hulls of our two fundamental surfaces. (A structure's *convex hull* is defined as the convex surface, with the smallest volume, containing the structure in question [29].) The convex hull is used, because it is regular enough to be easily characterized as a member of the family of surfaces designed by Chen *et al.*, and is sufficiently close to the actual ventricular surface for this surface to serve as a boundary condition in the Euler-Lagrange evolution equation. The surface of the ventricular system (Fig. 2) has a sufficiently stereotyped geometry for numerous points on its convex hull to be defined, *e.g.* the rostral tips of the frontal and temporal horns, as well as points along the *calcar avis*, the interface of the ventricular *atrium* (or *trigone*) with each wing of the ambient cistern, on the isthmus of the cingulate gyrus, and on the hippocampal fissures. Note that the exact location and distribution of these manually-defined points is not critical, since the surface fitted through them is only used as a rough initial estimate, which the active surface algorithm distorts towards the actual structure boundaries. Moreover, the points picked on the ventricles and external cortex in the two scans need not be homologous (*i.e.*, need not correspond anatomically), nor do they need to correspond to known functional landmarks. This is because these fiducials serve as a temporary estimate, and are not used in our final derivations of point-to-point mappings between surfaces.

Fitting a Chen Surface through a General Set of Fiducials

The obvious limitations of such simple shape modeling primitives as spheres and cylinders suggest that the global shape of any convex surface might first be approximated using a *superquadric* surface [30]. Superquadrics are a parametrized family of shapes, widely used for shape representation in computer graphics, and capable of modeling a

large set of standard building blocks including not just spheres, cylinders and parallelepipeds, but also shapes in between. A superquadric surface is the spherical product of 2 superquadric curves and can be defined in vector form[1] [see *note 1*] as follows:

$$S(\varphi,\theta) = [x, y, z] = [a_x\cos^{\varepsilon_1}(\theta)\cos^{\varepsilon_2}(\varphi),\ a_y\cos^{\varepsilon_1}(\theta)\sin^{\varepsilon_2}(\varphi),\ a_z\sin^{\varepsilon_1}(\theta)];\ \varphi\in[-\pi,\pi],\ \theta\in[-\pi/2,\pi/2]; \quad (4)$$

$$i.e., [(x/a_x)^{2/\varepsilon_2} + (y/a_y)^{2/\varepsilon_2}]^{\varepsilon_2/\varepsilon_1} + (z/a_z)^{2/\varepsilon_1} = 1, \text{ or } (\ (x/a_x, y/a_y)\ _p, z/a_z)\ _q = 1, \quad (5)$$

where a_x, a_y, a_z denote the length of the superquadric along the x, y and z axes, and where $(.,.)_p$ and $(.,.)_q$ are the $2/\varepsilon_1$- and $2/\varepsilon_2$-norms on $\mathbb{R}^2$ respectively. Since the intrinsic axial symmetry of these superquadrics places a substantive limitation on what they can (as yet) model, we further extend the basic modeling repertoire to include *tapered* versions $\mathbf{t}(\mathbf{S})$ of all the surfaces $\mathbf{S}$ we have so far in our inventory of primitive shapes [*q.v.*, [26]]. Tapering of a superquadric about any one axis, say the z-axis, can be modeled in extreme generality by the deformation map $\mathbf{t}$: $(x,y,z)\rightarrow(f_x(z), f_y(z), z)$, where the tapering functions $f_x(z)$ and $f_y(z)$ are stipulated to be piecewise linear functions of z.

For each surface to be fitted, the centroid and distribution of the fiducials lying on it are used to generate a mutually orthogonal 3D coordinate system fixed to the biological surface. Relative to this new coordinate system, the positions of our fiducials are re-computed, and the best fitting superquadric is determined as follows. Among various optimization schemes for recovering superquadrics from data points, a common one is based on the *inside-outside* function, which for each point (x,y,z) in the neighborhood of a superquadric S is defined as:

$$f_S(x,y,z) = [\ (x/a_x)^{2/\varepsilon_2} + (y/a_y)^{2/\varepsilon_2}\ ]^{\varepsilon_2/\varepsilon_1} + (z/a_z)^{2/\varepsilon_1}. \quad (6)$$

As in [28], the superquadric chosen is the one for which the objective function $\mathbf{S}_{i=1\ to\ n}|f_S(x_i,y_i,z_i)-1|^2$ is minimized, where the summation is carried out over all n fiducial points, and where the function f_S depends on the superquadric under examination.

Because this superquadric is axially symmetrical, it fails to capture certain local furrows, grooves and other features in the real anatomical surface. Accordingly, an additional local surface estimation scheme is used, in which the residual distances of the data from the fitted superquadric surface are computed. Although these distances represent the deviations between the superquadric and the real surface only at certain (fiducial) points, a residual surface function $r_\varepsilon(\theta,\varphi)$ is calculated, representing the distance by which the superquadric is in error, in any radial direction. This residual surface can be arbitrarily closely approximated with a finite linear combination of *spherical harmonics*.[2] These spherical harmonics are then added to the basic superquadric to produce a composite function which very precisely replicates the local nuances of the real anatomical surface.

Given n fiducial points given in Cartesian coordinates as (x_i, y_i, z_i), *i=1 to n*, their spherical coordinates are

$$[\varphi_i, \theta_i, r_d(\varphi_i,\theta_i)] = [\tan^{-1}(y_i/x_i),\ \tan^{-1}(\{\sqrt{[x_i^2+y_i^2]}\}/z),\ \sqrt{[x_i^2+y_i^2+z_i^2]}];\ \varphi_i \in [-\pi,\pi],\ \theta_i \in [-\pi/2, \pi/2]; \quad (7)$$

On the fitted superquadric, the points $r_S(\varphi_i,\theta_i)$ in the same radial directions as those given above have Cartesian coordinates

$$S(\varphi_i,\theta_i) = [x, y, z]=$$

$$[f_x(\theta_i).a_x\cos^{\varepsilon 1}(\theta_i)\cos^{\varepsilon 2}(\varphi_i),\ f_y(\theta_i).a_y\cos^{\varepsilon 1}(\theta_i)\sin^{\varepsilon 2}(\varphi_i),\ a_z\sin^{\varepsilon 1}(\theta_i)];\ \varphi_i \in [-\pi,\pi],\ \theta_i \in [-\pi/2, \pi/2]. \quad (8)$$

and spherical coordinates

$$[\varphi_i, \theta_i, r_d(\varphi_i,\theta_i)] = [\varphi_i,\ \theta_i,\ \sqrt{[\{f_x(\theta_i).a_x\cos^{\varepsilon 1}(\theta i)\cos^{\varepsilon 2}(\varphi_i)\}^2 + \{f_y(\theta_i).a_y\cos^{\varepsilon 1}(\theta_i)\sin^{\varepsilon 2}(\varphi_i)\}^2 + \{a_z\sin^{\varepsilon 1}(\theta_i)\}^2]}], \quad (9)$$

where $f_x(\theta_i) = f_y(\theta_i) = k a_z\sin^{\varepsilon 1}(\theta_i)+1$. Consequently, the n points $r_\varepsilon(\varphi_i,\theta_i) = r_d(\varphi_i,\theta_i)-r_S(\varphi_i,\theta_i)$ can be used to fit our residual surface function $r_\varepsilon(\varphi,\theta)$, which is supposed to represent the distance by which the fitted superquadric is in error, in *any* radial direction. Now the radius $r(\varphi,\theta)$ of an arbitrary surface in a spherical coordinate system can be written as a linear sum of spherical harmonic basis functions:

$$r(\varphi,\theta) \approx \mathbf{S}_{n=1 \text{ to } N}\, \mathbf{S}_{m=0 \text{ to } n}\, [A_{nm}U_{nm}(\varphi,\theta)+B_{nm}V_{nm}(\varphi,\theta)]; \quad (10)$$

A_{nm} and B_{nm} are real coefficients, while the functions[2] $U_{nm}(\varphi,\theta)$ and $V_{nm}(\varphi,\theta)$ are defined in a spherical coordinate system as

$$U_{nm}(\varphi,\theta)= \cos m\varphi\ P_{nm}(\cos\theta)$$
$$V_{nm}(\varphi,\theta)= \sin m\varphi\ P_{nm}(\cos\theta), \quad (11)$$

where $P_{nm}(.)$ is the associated Legendre function $P_{nm}(x)=(1-x^2)^{m/2}D_x^m P_n(x)$, with $P_n(x)=\{1/(2^n n!)\}.D_x^n(x^2-1)^n$.
The size of the coefficient set determines the fidelity with which the harmonic expansion can capture the local details of the biological surface, now conceived as a kind of fine tuning or modulation superposed on the fundamental superquadric originally fitted to the data. The residual surface $r_\varepsilon(\varphi,\theta) \approx \mathbf{S}_{i=1 \text{ to } M}\, \mathbf{a}_i B_i(\varphi,\theta)$ is interpolated using 25 basis functions $B_i(\varphi,\theta)$ and coefficients $\mathbf{a}_i$, the values of these coefficients being determined by minimizing the objective function $\varepsilon(\{\mathbf{a}_i\}_{i=1 \text{ to } M}) = \mathbf{S}_{j=1 \text{ to } n}\, [r_\varepsilon(\varphi_j,\theta_j)-\mathbf{S}_{i=1 \text{ to } M}\, \mathbf{a}_i B_i(\varphi_j,\theta_j)]^2$. Our final model of the global shape of the biological surface in question is now readily obtained by adding this interpolated residual surface to the superquadric fitted earlier, yielding $\mathbf{V}(\varphi,\theta) = r_s(\varphi,\theta)+r_\varepsilon(\varphi,\theta)$; $\varphi \in [-\pi,\pi]$, $\theta \in [-\pi/2, \pi/2]$. For convenience of expression, any surface fitted in this way though a convex set of fiducials will be termed a *Chen surface*. *Loosely speaking*, the surface is a superquadric with spherical harmonics modulated onto it.

By applying this surface-fitting procedure to our four sets of fiducials on the *convex hull* of $\mathbb{O}^*$ and $\mathbb{I}^*$, in both **A** and **P**, namely $\{f_i(\mathbf{A};\mathbb{O}^*)\}$, $\{f_j(\mathbf{A};\mathbb{I}^*)\}$, $\{f_i(\mathbf{P};\mathbb{O}^*)\}$, $\{f_j(\mathbf{P};\mathbb{I}^*)\}$, a pair of Chen surfaces is generated for a given hemisphere in each image, $\mathbb{C}\{f_i(\mathbf{A};\mathbb{O}^*)\}$, $\mathbb{C}\{f_j(\mathbf{A};\mathbb{I}^*)\}$, $\mathbb{C}\{f_i(\mathbf{P};\mathbb{O}^*)\}$ and $\mathbb{C}\{f_j(\mathbf{P};\mathbb{I}^*)\}$. These surfaces provide boundary conditions for

four independent sets of Euler-Lagrange evolution equations, which mold the estimated surfaces more faithfully onto the anatomical contours.

(b). Energy-Minimizing Surfaces in Systems of Potential Attractors: Molding Surfaces onto Anatomical Contours

Many methods for segmenting images into meaningful components are based on the fact that some biological parameter varies drastically at the interface between two different structures. If this parameter is represented in the image by the relative intensity of different pixels, we can search for edges between regions by thresholding on the value of a *gradient operator*, and deriving a *binary edge image*. Now imagine all the points in the edge image to be highly charged points in space, which would tend to attract any oppositely-charged surfaces in the vicinity towards them. Cohen's idea [12] is to imagine letting inflated, charged balloons deform through this system of attraction potentials, their surfaces being gradually distorted and stretched as they are sucked towards all the attractive edge points, finally coming to equilibrium (like soap bubbles in a wire mesh) when their surface energy is minimized.

Let Ω be the tile $[0,1] \times [0,1]$ in $\mathbb{R}^2$.

A surface v is defined by a mapping $v: \Omega \rightarrow \mathbb{R}^3$, *i.e.*, $(s,r) \rightarrow v(s,r) = (x(s,r), y(s,r), z(s,r))$, and the associated energy is given by the real-valued functional

$$E(v) = \int_\Omega \; w_{10} \left| \partial v/\partial s \right|^2 + w_{01} \left| \partial v/\partial r \right|^2 + 2w_{11} \left| \partial^2 v/\partial s \partial r \right|^2 + w_{20} \left| \partial^2 v/\partial s^2 \right|^2 + w_{02} \left| \partial^2 v/\partial r^2 \right|^2 \, ds dr + \int_\Omega P(v(s,r)) \, ds dr. \quad (12)$$

Here P is the potential produced at each point on the surface by the system of external attractors, and the other terms measure the smoothness of the fitted surface v. P is defined as $-\left| \tilde{\mathbf{N}} I \right|^2$, where I is the binary edge image convolved with a Gaussian of the form $\{-exp(-\boldsymbol{h}^2)\}$, where $\boldsymbol{h}$ is any point in our image space. The definition $P(v(s,r)) = -\left| \tilde{\mathbf{N}} I(v(s,r)) \right|^2$ is extended by trilinear interpolation from the image grid to the continuous domain. Its form ensures that our surface is maximally attracted by the minima of the potential, *i.e.*, by *edges*, which create local maxima in the gradient of the image intensity. The surface energy functional, defined on a class $\mathbb{V}$ of elastically deformed versions of v, is minimized when forces on the surface are in equilibrium. The final position of the surface is given by the solution[3] (as $t \rightarrow \infty$) of the Euler-Lagrange evolution equation:

$$\partial v/\partial t - \partial/\partial s(w_{10} \left| \partial v/\partial s \right|) - \partial/\partial r(w_{01} \left| \partial v/\partial r \right|) + 2\partial^2/\partial s \partial r(w_{11} \left| \partial^2 v/\partial s \partial r \right|)$$
$$+ \partial^2/\partial s^2(w_{20} \left| \partial^2 v/\partial s^2 \right|) + \partial^2/\partial r^2(w_{02} \left| \partial^2 v/\partial r^2 \right|) = \mathbf{F}_{total}(v), \quad (13)$$

Here $\mathbf{F}_{total}(v) = -\tilde{\mathbf{N}}\mathbf{P}(v) + \mathbf{F}_{balloon}(v)$ is the sum of the external forces applied to the surface, and $\mathbf{F}_{balloon}$ is a special additional force of the form $k_1.\mathbf{n}(s,r)$, where $\mathbf{n}(s,r)$ is the unit vector external and normal to v at $v(s,r)$, and k_1 is the force's amplitude [*q.v.* [28] for details]. This surface dynamics equation is seen as describing the deformation over

time of the surface of a balloon located in the same space as the image. This balloon first expands, but it is soon stopped by the strongly attractive forces of any potential minima it encounters, which are associated with edges in the image. The expanding surface can also pass by any noise points or weak edges it meets in the image, since these points first become singularities in the surface, before being removed by the regularization process as the surface progresses over a few iterations.

The initial estimate for the anatomical surface in question is supplied in analytical form as a *Chen surface*, which is subsequently molded more faithfully to the anatomical contours by using it as the boundary condition of the evolution procedure described above. In certain cases, where the gross anatomical asymmetry of the brain is not substantial, each equilibrium surface in the left hemisphere can be reflected in the interhemispheric plane to provide a boundary condition for the evolution process which extracts the homologous surface in the contralateral hemisphere. This change of variables surmounts the need to derive a second pair of Chen surfaces for the contralateral hemisphere, greatly accelerating the computational task of surface formation.

V. Mapping the Internal Cortex

For both the atlas and target images, the above algorithms use the positions of our fiducial points to compute an elaborate replication of the cortical and lateral ventricular surfaces in the left hemisphere of both the target anatomy and the atlas.

However, since much of the human cortex is buried deep in the cortical folds or *sulci*, connected systems of parametric meshes were also used to model the internal course of the following cortical structures in both hemispheres: the parieto-occipital sulcus, the anterior and posterior rami of the calcarine sulcus, the cingulate and marginal sulci, the supracallosal sulcus and the Sylvian fissure (Fig. 3). The internal surfaces of these major sulci were modeled in 3D as deep internal structures, using a multi-resolution parametric mesh approach [8-10]. As major functional interfaces in the brain, these primary sulci are easily identifiable in 3D brain images. As well as marking critical gyral and lobar boundaries, the chosen sulci penetrate deeply enough into the brain to form a natural partition of its cellular architecture. Consequently, their internal trajectories are sufficiently extended inside the brain to reflect subtle and distributed variations in neuroanatomy between individuals [9,10].

Interactive outlining of deep sulci in sagittally reformatted images resulted in a sampling of approximately 15000 points per sulcus, capturing the details of each sulcal surface at a very local level. Each sulcal surface was converted automatically into parametric mesh form as described in earlier work [9,10], using software developed in our laboratory. Briefly, a parametric grid of 100x150 uniformly spaced points, which act as nodes in a regular rectangular mesh, is stretched over the digitized surface (Fig. 4). Each resultant surface mesh is analogous in form to a regular rectangular grid, drawn on a rubber sheet, which is stretched to match all data points. This scheme provides a means for converting dense systems of points, sampled during outlining, into fully parametric surfaces which can be analyzed, visualized and compared geometrically and statistically. The mesh construction algorithm can be found in [10]. Finally, the equilibrium surfaces $v^{\infty}\{f_j(\mathbf{A};\mathbb{I}^*)\}$ and $v^{\infty}\{f_j(\mathbf{P};\mathbb{I}^*)\}$, representing the lateral ventricles in **A** and **P**, were each converted into a closed connected system of 4 parametric meshes representing the ventral and dorsal surface boundaries of the rostral and inferior horns, respectively (see Fig. 3).

VI. Surface Warp Calculation: Displacement Maps on the Extracted Surface Systems

This section describes the automatic construction of point-to-point surface maps describing the displacements needed to map individual surfaces in the atlas onto their counterparts in the target scan. In each hemisphere, the 6 meshes $\{M_i\}_{i=1to6}$ representing internal sulcal surfaces, as well as the 4 meshes $\{V_i\}_{i=1to4}$ jointly representing the lateral ventricles $\mathbb{I}^*$, were defined on a parametric grid of the same resolution (100x150). (The external cortex will be treated separately in a moment.) Consequently, the relationship between two ventricular components or between two sulci of the same type can be represented as a map which displaces one surface onto another, in a 3D coordinate space. This map is illustrated in Fig. 5. For each and every point on a surface mesh M_1, and every point on a similar mesh M_2, the two points were matched if they had the same grid location within their respective surfaces. For each such association, the discrepancy was computed as a 3D displacement vector between corresponding nodal points. Ultimately, this procedure yielded a full displacement map for every pair of surfaces of the same type.

As for the external cortex, let $v^{\infty}\{f_i(\mathbf{A};\mathbb{O}^*)\}$ and $v^{\infty}\{f_i(\mathbf{P};\mathbb{O}^*)\}$ be the equilibrium surfaces to which the Chen surfaces $\mathbb{C}\{f_i(\mathbf{A};\mathbb{O}^*)\}$ and $\mathbb{C}\{f_i(\mathbf{P};\mathbb{O}^*)\}$ converged, respectively. The displacement map transforming the external cortex of the atlas onto its counterpart in the target image is already partially determined (by the sulcal displacement maps) on a set of external curves $\{K_i\}_{i=1to4} = v^{\infty}\{f_i(\mathbf{A};\mathbb{O}^*)\} \cap \{M_i\}_{i=1to6}$ in each hemisphere of the atlas. These 8 superficial curves, in each image, where the sulcal surface meshes interface with the external cortical surface, represent lobar boundaries on the external surface of each brain. A new method was developed to interpolate the displacements already defined on these cortical landmark curves across the cortical surface of the atlas, so as to yield a continuous point-to-point transformation mapping one external cortex to the other.

Since $v^{\infty}\{f_i(\mathbf{A};\mathbb{O}^*)\}$ and $v^{\infty}\{f_i(\mathbf{P};\mathbb{O}^*)\}$ are given in spherical polar coordinates, it is "natural that the displacement fields [*i.e.*, in warping **A** onto **P**] are expressed as the longitudinal and latitudinal coordinates' variations for each point; these functions are in turn functions of spatial position, or functions of the longitudinal and latitudinal coordinates since the radial component of a given point is fixed by the constraint that the point is on the estimated surface." [26]. In other words, the surface warp mapping points on the surface $\mathbb{O}^*$ from the atlas to the target scan is completely determined by specifying the appropriate change in spherical angle occurring at each spherical angle in the atlas. The resultant surface transformation function $[\mathbf{D}\varphi,\mathbf{D}\theta](\varphi(\mathbf{k}_j),\theta(\mathbf{k}_j))$ is known at the nodal points $\mathbf{k}_j \in K_i$ on the superficial curves in the atlas, and can therefore be calculated elsewhere on the surface, as follows.

Let $\varphi(\mathbf{k}_j^*)=\varphi(\mathbf{k}_j)+\mathbf{D}\varphi(\varphi(\mathbf{k}_j),\theta(\mathbf{k}_j))$ and $\theta(\mathbf{k}_j^*)=\theta(\mathbf{k}_j)+\mathbf{D}\theta(\varphi(\mathbf{k}_j),\theta(\mathbf{k}_j))$, where $\mathbf{k}_j^*$ is the point in the target image onto which the nodal point $\mathbf{k}_j$ is mapped by the displacement map defined already on the sulci. Then the functions $\mathbf{D}\varphi(\varphi(\mathbf{a}),\theta(\mathbf{a}))$ and $\mathbf{D}\theta(\varphi(\mathbf{a}),\theta(\mathbf{a}))$ (for any point $\mathbf{a} \in v^{\infty}\{f_i(\mathbf{A};\mathbb{O}^*)\}$) both inject the unit sphere into the reals, and can therefore also be approximated by spherical harmonics, just as $r_\varepsilon(\varphi,\theta)$ was approximated earlier. In fact the vector function $[\mathbf{D}\varphi,\mathbf{D}\theta](\varphi(\mathbf{a}),\theta(\mathbf{a}))$ will be approximated by $[\mathbf{S}_{i=1 \text{ to } M}\, \boldsymbol{\lambda}_i B_i(\varphi,\theta), \mathbf{S}_{i=1 \text{ to } M}\, \boldsymbol{\mu}_i B_i(\varphi,\theta)]$, where the $\boldsymbol{\lambda}_i$, $\boldsymbol{\mu}_i$ minimize both

$$\varepsilon(\{\boldsymbol{\lambda}_i\}) = \mathbf{S}_{j=1 \text{ to } n}\,[\mathbf{D}\varphi(\varphi(\mathbf{k}_j),\theta(\mathbf{k}_j)) - \mathbf{S}_{i=1 \text{ to } M}\, \boldsymbol{\lambda}_i B_i(\varphi_j,\theta_j)]^2$$

$$\text{and } \varepsilon(\{\boldsymbol{\mu}_i\}) = \mathbf{S}_{j=1 \text{ to } n}\,[\mathbf{D}\varphi(\varphi(\mathbf{k}_j),\theta(\mathbf{k}_j)) - \mathbf{S}_{i=1 \text{ to } M}\, \boldsymbol{\mu}_i B_i(\varphi_j,\theta_j)]^2. \qquad (14)$$

The primary summations are carried out over all the j=1 to n nodes $\mathbf{k}_j$ in a given hemisphere of the atlas, as before. Consequently, the surface warp $\mathbb{W}_{\mathbb{O}}: v^{\infty}\{f_i(\mathbf{A};\mathbb{O}^*)\} \rightarrow v^{\infty}\{f_i(\mathbf{P};\mathbb{O}^*)\}$ will be given by

$$\mathbb{W}_{\mathbb{O}}:(r,\varphi,\theta) \rightarrow (r^*, \varphi+[\mathbf{D}\varphi(\varphi,\theta)], \theta+[\mathbf{D}\theta(\varphi,\theta)]) \;\forall\; (r,\varphi,\theta) \in v^{\infty}\{f_j(\mathbf{A};\mathbb{O}^*)\}, \qquad (15)$$

where r^* is the point on $v^{\infty}\{f_i(\mathbf{P};\mathbb{O}^*)\}$ at steric angle $(\varphi+[\mathbf{D}\varphi(\varphi,\theta)],\theta+[\mathbf{D}\theta(\varphi,\theta)])$, and where the angular shifts $[\mathbf{D}\varphi, \mathbf{D}\theta](\varphi,\theta)$ are calculated for the deformation of the surface $v^{\infty}\{f_i(\mathbf{A};\mathbb{O}^*)\}$.

VII. Volume Warp Calculation: Extension of 3D Deformation Fields between Surface Systems

For simplicity, let's now denote by $\mathbb{F} = \{S_i\}_{i=1toN}$ the family of N surfaces in the left half-space of the atlas on which surface warps are now defined (N=11, here). In other words, $\mathbb{F} = \{S_i\}_{i=1toN} = \mathbb{O} \cup \{M_i\}_{i=1to6} \cup \mathbb{I}$, where $\mathbb{O} = v^{\infty}\{f_i(\mathbf{A};\mathbb{O}^*)\}$ is the external cortex, $\{M_i\}_{i=1to6}$ are the deep sulcal meshes, and $\mathbb{I} = \{V_i\}_{i=1to4}$ are the meshes representing components of the lateral ventricle, all in the left half-space of the atlas. Now let the region between $\mathbb{I}$ and

$\mathbb{O}$ in the atlas be called $\mathbb{A}$, and the region in the target image lying between $v^{\infty}\{f_j(\mathbf{P};\mathbb{I}^*)\}$ and $v^{\infty}\{f_i(\mathbf{P};\mathbb{O}^*)\}$ be called $\mathbb{P}$. Since the surface warps $\mathbb{W}(S_i)$ are already specified for mapping the ventricular system and cortex from atlas to target scan, we need to interpolate a *volume warp* $\mathbb{W}:\mathbb{A}\rightarrow\mathbb{P}$ which is at least continuous, and agrees with the surface warps $\mathbb{W}(S_i)$ when warping points on the surfaces S_i in the atlas. For each surface, we denote associated displacement maps by:

$$\mathbb{W}_i'(\mathbf{x}) = \mathbb{W}_i(\mathbf{x}) - \mathbf{x}, \forall \mathbf{x}\ \mathbf{e}\ S_i, \forall S_i \in \mathbb{F}. \qquad (16)$$

For convex closed surfaces $S\ \mathbf{e}\ \mathbb{R}^3$, we can show that for each point $\mathbf{p}$ exterior to S, there is a unique *nearest point* $\mathbf{np}_S(\mathbf{p})\ \mathbf{e}\ S$ such that $d(\mathbf{p},\mathbf{np}_S(\mathbf{p})) = inf\{d(\mathbf{p},\mathbf{p}_S)\ |\ \mathbf{p}_S\ \varepsilon\ S\}$, [where $d(\mathbf{p},\mathbf{p}_S)$ is the Euclidean distance between $\mathbf{p}$ and $\mathbf{p}_S$]. Accordingly, let $\delta_S(\mathbf{p})$ be this shortest distance from $\mathbf{p}$ to S. Similarly, for our non-convex surfaces $S_i \in \mathbb{F}$, let $\mathbf{np}_i(\mathbf{x})$, (for an arbitrary point $\mathbf{x}$ in the atlas), denote the nearest point on surface S_i to $\mathbf{x}$, and let $\delta_i(\mathbf{x}) = d(\mathbf{x},\mathbf{np}_i(\mathbf{x}))$ be the 3D distance of $\mathbf{x}$ from this nearest point, with the proviso described in *note 4* for cases where there is no unique near point.[4]

Let $\gamma_i(\mathbf{x})\ \varepsilon\ [0,1]$ be defined as the set of weights $\{1/\delta_i(\mathbf{x})\}/\sum_{i=1\ to\ N}\ \{1/[\delta_i(\mathbf{x})]\}$. Here, the numerator controls the weight exerted by the i^{th} surface in the final deformation at point $\mathbf{x}$, and is designed to be smaller when the surface is a larger distance $\delta_i(\mathbf{x})$ from $\mathbf{x}$; the denominator normalizes the resulting set of weights so that they sum to 1 at every $\mathbf{x}$ [31]. A simple 'weighted-average' volume warp is illustrated in Fig. 6 (*left panel*). The appropriate transformation of the atlas is given by the 3D displacement field:

$$\mathbb{W}'(\mathbf{x}) = \sum_{i=1\ to\ N}\ \gamma_i(\mathbf{x}).\mathbb{W}_i'(\mathbf{np}_i(\mathbf{x})),\ \forall \mathbf{x}\ \mathbf{e}\ \mathbb{A}. \qquad (17)$$

[The global warp would then be $\mathbf{x} + \mathbb{W}'(\mathbf{x}) = \mathbb{W}(\mathbf{x})\ \mathbf{e}\ \mathbb{P}$.] This function, however, is not in general continuous. We therefore propose an alternative definition for $\mathbb{W}'(\mathbf{x})$, which is not only continuous, but also allows $\mathbb{W}'(\mathbf{x})$ to be influenced by a range of surface points on each of the surfaces S. As before, let $i = 1$ to N, and let $\delta_i(\mathbf{x}) = d(\mathbf{x},\mathbf{np}_i(\mathbf{x}))$. Let $r_c = min\{R_c, min\{\delta_i(\mathbf{x})\}_{i=1\ to\ N}\}$, where R_c is a constant, and consider the closed sphere $\mathbf{r}\ \mathbf{e}\ \mathbf{B}(\mathbf{x},r_c)$, for each $\mathbf{x}\ \mathbf{e}\ \mathbb{A}$. This is shown in Fig. 6 (*right panel*). Then let

$$\mathbb{W}'(\mathbf{x}) = \sum_{i=1\ to\ N}\ \gamma_i(\mathbf{x}).\mathbf{D}_i'(\mathbf{np}_i(\mathbf{x})),\ \forall \mathbf{x}\ \mathbf{e}\ \mathbb{A}, \qquad (18)$$

where the $\mathbf{D}_i$ are *distortion functions* generated by each surface, given by

$$\mathbf{D}_i(\mathbf{x}) = \frac{\int_{\mathbf{r}\in B(\mathbf{x};Rc)}\ w_i(\mathbf{x},\delta_i(\mathbf{r})).\mathbb{W}_i'(\mathbf{np}_i(\mathbf{r}))\ \ \boldsymbol{dr}}{\int_{\mathbf{r}\in B(\mathbf{x};Rc)}\ w_i(\mathbf{x},\delta_i(\mathbf{r}))\ \ \boldsymbol{dr}}; \qquad (19)$$

the *weight functions* $w_i(\mathbf{x}, \delta_i(\mathbf{r}))$ are defined as

$$w_i(\mathbf{x}, \delta_i(\mathbf{r})) = exp\ (-\{[d(\mathbf{np}_i(\mathbf{r}),\mathbf{x})]/\ \delta_i(\mathbf{x})\}^2). \qquad (20)$$

These weight functions, which are monotone decreasing with respect to $\delta_i(\mathbf{r})$, control the degree to which $\mathbb{W}'(\mathbf{x})$ is influenced by points on the surrounding surfaces S_i, depending on their distance from **x**. In another approach, Moshfeghi *et al.* [32] compute the distortion at **x** due to surface points **z** by using a weight function $exp\{-(\ \mathbf{x}-\mathbf{z}\ /\beta)]$. They supply the arbitrary constant β manually, and integrate for all **z** on the surface. We prefer to select R_c, as this limits the support of the integrand and therefore permits efficient computation. The resulting algorithm is also *cooperative*, in that many common elements of the arrays $\mathbb{W}_i'(\mathbf{np}_i(\mathbf{r}))$ are used to calculate the distortion functions $\mathbf{D}_i$ for **x**, and for other points close to **x,** avoiding extra evaluation.

As before, we define $\mathbf{x} + \mathbb{W}'(\mathbf{x}) = \mathbb{W}(\mathbf{x})$ **e** $\mathbb{P}$. Separate 3D displacement vectors are calculated for every voxel in the image lattice, resulting in a transformation of extremely high dimension (typically 384x256x384x3 ≈ 0.1 billion degrees of freedom). The warp $\mathbb{W}$ specifies the final warped version of the left side of the atlas. Identical fitting and transformation routines are also applied to the corresponding developmental surfaces in the *right* hemisphere of the atlas, and the union of these two transformations specifies the *final warped version of the atlas*.

VIII. Implementation and Results

A battery of tests was carried out to evaluate the behavior of the algorithm on a wide range of real and simulated data. In the tests that follow, the starting image (previously referred to as the atlas, **A**) will be referred to as the *reference* image, and this will be warped onto a *target* image of the same dimensions.

(a). Simulated Data

Fig. 7(a) shows a single 384x256 pixel 2D slice image containing a hollow gray object, with a black regular grid ruled over it every 16 pixels. This image was copied 256 times, in the direction of viewing, to create a single 384x256x256 3D reference image. A similar copying procedure was applied to the image shown in Fig. 7(b), creating a 3D target image of $384x256^2$ pixel resolution. The target object shown (Fig. 7(b)) has the same external boundary as the reference object, but the left and right hand sides of its internal boundary have been contracted to coincide with a cylinder of radius 80 pixels, whose axis runs perpendicular to, and through the center of, the 2D section shown. Manual outlines of the inner and outer surfaces of the reference and target objects were digitized, converted to parametric mesh form, and used to constrain the deformation of the reference image onto the target. Fig. 7(c) shows the result of this deformation in the form of a 2D axial section through the warped 3D image. Note that the reference object is carried accurately through this relatively large deformation, and is brought into register with the target object. The magnitude of the 3D deformation field was also calculated by the warping algorithm and a 2D slice through this field is shown in the form of a color-coded map (in the coordinate system of the target image) in Fig. 7(d). Note that this smooth warping field is not perfectly symmetrical, because the object boundaries constraining the warp were contoured manually.

(b). Warping of 3D MRI Brain Volumes

Two 3D (384x256x384 resolution) T_1-weighted fast SPGR (spoiled GRASS) MRI volumes were acquired from a patient with clinically determined Alzheimer's disease (Fig. 8(a)), and an age-matched normal subject (Fig. 8(b)). The 3D MRI volumes were acquired on a GE Signa 1.5T clinical scanner with TR/TE 14.3/3.2 msec, flip angle 35°, FOV 25cm and contiguous 1mm thick axial slices covering the entire brain. The two scans were corrected for differences in relative position and size by transformation into standardized Talairach stereotaxic space, using the steps specified in the Talairach atlas [33]. (This transformation is by no means a prerequisite for warping, but it was applied here to test the ability of the algorithm to recover subtle non-linear anatomic differences between scans which cannot be factored out by readily-available *linear* stereotaxic transformations.) Parasagittal slices from both 3D volumes are shown, each taken at a level 7.0 mm left of the midsagittal plane. To aid visual comparison, several structural boundaries, taken from the same sagittal slice of the target scan, are shown superimposed on the reference scan. Note, in particular, the large difference between the two anatomies in the extent of the lateral ventricle at this level, and the differences in the cortical boundaries, especially in frontal areas. Note also the far less convoluted cingulate sulcus, atrophied cerebellum, and more ventral position of the posterior calcarine sulcus in the target scan.

Fig. 8(c) shows the result of warping the reference anatomy into the shape of the target. (Due to the high degree of cerebellar atrophy, the cerebellar surface was also used to control the deformation field in this case.) 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 of the cerebellum. Both global and local differences in anatomy have been accommodated by the transformation. Note also the smooth continuation of the deformation throughout the rest of the anatomy (*cf*. the effect on the phantom grid in Fig. 7(c)). Next, the two in-slice components of the 3D volumetric warp were applied to a regular grid drawn on the reference image before warping. This grid was then passively carried along in the resultant deformation. The complexity of the recovered deformation field is shown by its effect on this grid in Fig. 8(d). Note especially the large deformation of the transformed grid 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.

The generic surface decomposition of the target anatomy is shown in Fig. 3. To monitor the smooth transition to the surrounding anatomy of the deformation fields initially defined on the surface systems, additional software was developed to represent the magnitude of the warping field on 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 results of this experiment are shown in Fig. 8(e). Note the smooth continuation of the warping field from the complex anatomic surfaces into the surrounding volume architecture of the target brain. As expected, the deformation is particularly pronounced in the frontal, ventricular and cerebellar areas.

(c). Inter-Modality Warping of 3D Cryosectioned Brain Volumes onto 3D MRI Brain Volumes

The capacity of the warping algorithm to warp 3D anatomic imagery acquired in one modality (high-resolution cryosection imaging) onto a target scan from another modality (3D SPGR MRI) was also tested. A normal, *post mortem* human head was cryoprotected and sectioned at 50 μm increments, and the specimen blockface was digitally imaged at 1024^2 pixel resolution [34]. The resulting image sequence was reformatted (after down-sampling) to generate a 384x256x384 24-bit full-color reference volume, which was subsequently transformed into Talairach stereotaxic space. This 3D digital reference volume was warped onto the same 3D target volume as was used in the 3D MRI-to-MRI test (Fig. 8(a)). Fig. 9(a) shows a sagittal slice from the cryosectioned head, taken 7.0 mm left of the midsagittal plane. Outlines of the target MRI volume (shown in Fig. 9(a)) are superimposed on the anatomy to illustrate the anatomic differences before warping. Note especially the smaller cuneus and ventricles in the cryosection image (Fig. 9(a)), as well as a greater degree of arching in the *corpus callosum* and numerous differences in sulcal morphology at this level.

The result of warping the 3D cryosectioned image into the shape of the target MRI anatomy is shown in Fig. 9(b), with the same cortical and ventricular landmarks of the target anatomy superimposed. Note, in particular, the reconfiguration of the sulci (which would only be possible with a high-dimensional warping technique), and note the degree to which the reference *corpus callosum* is deformed into the shape of the target *callosum.* The result of applying the in-plane components of the recovered deformation to a regular grid in the same space as the reference anatomy is shown in Fig. 9(c). Note how different the deformation field is from that observed in the MRI-to-MRI experiment.

(d). Accuracy of the 3D Warp

The ability of the warping algorithm to correctly deform anatomic images into structural correspondence was assessed by manually labeling pairs of well-defined corresponding points in a range of reference and target scans. The distance between these pairs of anatomically homologous points was then compared before and after the warping algorithm was carried out. The results of this test, for landmarks both near to and far from the control surfaces, are presented in Table 1 (N=6, for each of the 8 structures). The algorithm reduced the discrepancy between anatomic landmarks to as little as 0.5-2 mm, even for structures whose initial coordinates were up to 5 mm from their counterparts in the target scan.

(e). Computation Speed

The computation of 3D deformation fields relating two anatomies was greatly accelerated by carrying out the calculations on a multi-scale/multi-resolution 3D octree-spline grid [35]. This hierarchical data structure and multi-resolution strategy permit rapid coarse-to-fine refinement of the deformation field, and the generation of intermediate images using 3D spline interpolation. Within minutes, reasonable estimates of the final deformed images can be generated on demand, for specified slices throughout the warped reference volume. As the resolution of the octree-mesh is increased, the algorithm adjusts finer and finer details as subtler differences between the reference and target anatomy are accommodated. A 1152-parameter 3D spline estimate of the deformation of a single 2D slice is typically obtained within 240 seconds on a standard 200 MHz DEC alpha workstation. 30 minutes of computation time are required to compute a 6912-parameter estimate of the 3D deformation field for warping a full volume (calculations being performed on a regular octree grid of size 16x12x12).

IX. Discussion

We have devised, implemented and tested a fast and spatially accurate technique for calculating the high-dimensional deformation field relating the brain anatomies of an arbitrary pair of subjects. The resulting 3D deformation map can be used to quantify anatomic differences between subjects or within the same subject over time, and to transfer functional information between subjects or integrate that information on a single anatomic template.

In the past, comparing data from different subjects or patient subpopulations has been made difficult because cortical topography and the internal geometry of the brain vary so greatly. 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 [18]. Conversely, the same algorithm can be used to transfer all the information in a 3D digital brain atlas onto the scan of any given patient, while respecting the intricate patterns of structural variation in their anatomy. Such deformable atlases [5,6,7] can be used to carry 3D maps of functional and vascular territories into the coordinate system of different patients, as well as information on tissue types and the boundaries of cytoarchitectonic fields and their neurochemical composition. Thirdly, 3D warping algorithms provide a method for calculating local and global shape changes and give valuable information to scientists studying normal and abnormal growth and development [36].

As in the massively-parallel viscous fluid model [5,17-19], and unlike some other warping approaches, our *surface-based* strategy allows for large deformations while maintaining the continuity and connectivity of the warped image. Chen surface constructs are used to efficiently initialize 3D active surface snakes, which then automatically extract from both scans the developmentally fundamental surfaces of the ventricles and cortex. The analysis of extremely complex cortical topography in 3D image ensembles is made easier by building a generic surface structure to model the internal cortex. Sclaroff and Pentland [37] first proposed a model recovery framework which incorporates wavelet-

based displacement maps to add fine detail to a solid model described by deformable analytic implicit functions. In our formulation, surface-based displacement maps are fundamental to Chen surface construction [26] and to the definition of the 3D warp on connected systems of parametric surfaces. These models permit efficient storage of local shape and deformation details at different scales [37], and subsequently allow a compact representation of anatomic variability [8,9]. The parametric form of the underlying surface models, as well as the positive definite Jacobian property [38] of the derived volumetric warp, enable us to derive statistics on the mapping of surfaces and volumes, using standard 3D statistical machinery [8,9] and the theory of Gaussian random fields [10]. This approach has recently allowed us to develop a surface-based aid for the detection and mapping of subtle abnormalities of shape and volume in the brains of patients with metastatic tumors [10]. Finally, recent developments in our laboratory have enabled pre-mortem anatomical/functional scanning and *post mortem* cryosection imaging of the same individual [39]. 3D warping algorithms, which correct for global and local *post mortem* anatomic change, will, in the very near future, allow direct correlation of 3D neurochemical and cytoarchitectural maps with 3D PET, SPECT and functional MRI data obtained from the same individual *in vivo* [40].

The ultimate goal of brain mapping is to provide a framework for integrating functional and anatomic data across many subjects and modalities. This task requires algorithms to map functional data from different subjects and between modalities onto a single anatomic template, and to map 3D atlases and digital brain databases onto the scans of new subjects. The surface mapping and volume warping algorithms presented here provide a basis for the generation of anatomical templates and expert diagnostic systems which retain and exploit information on inter-subject variations in brain architecture.

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Appendix: Technical Notes

1. *Superquadrics*. Parameters φ and θ correspond to latitude and longitude angles in an object-centered spherical coordinate system, with θ in the *xy* plane, and φ the angle between the *xy* plane and the vector $S(\varphi,\theta)$; a_x, a_y, a_z define the size of the superquadric along the *x*, *y* and *z* directions, and ε_1 and ε_2 are the squareness parameters along the *z* axis and in the *xy* plane respectively.

2. *Spherical Harmonics*. The spherical harmonics $U_{hm}(\varphi,\theta)$ and $V_{nm}(\varphi,\theta)$ are a doubly infinite set of functions forming a separable, orthogonal basis of continuous single-valued functions, complete on the sphere. The surfaces capturable by spherical harmonics must all be *positive functions on the sphere*, which is another way of saying that they must form a closed surface with the origin in their interior, and consist of points which are in one-to-one correspondence with the points of the sphere. A good way to think of them is as functions of radial *direction* (φ,θ), which take values in the range $[0,\infty)$. Since the function $r_\varepsilon(\varphi,\theta)$ will actually be *negative* where the real surface lies inside the fitted superquadric, an arbitrary base value b_0 is added to all sample points so that the interpolated residual surface is strictly positive. b_0 is set equal to $\{a_x+a_y+a_z\}/3$, where the a_i are the lengths of the fitted superquadric along each of the 3 coordinate axes [26]. This sphere of radius b_0 is then subtracted back out again after the spherical harmonic approximation has been carried out.

3. *Active Surfaces*. The equilibrium surfaces are expressed in a discrete basis of continuous functions, these solutions being found [28] by a variational method with finite elements. This technique uses the Finite Difference Method to discretize the Euler-Lagrange evolution equation *in time*, after using a Finite Element Method to discretize this equation *in space*. Spatial discretization is achieved by representing the solution to the associated variational problem analytically, as a finite linear combination of basis functions for the smooth Sobolev space $C^1 \cap H_0^2([0,1])$.

4. *Surface Near-Points*. For non-convex surfaces, there is not in general a unique nearest point $\mathbf{np}_i(\mathbf{x})$ to an arbitrary $\mathbf{x} \in \mathbb{A}$, so in the algorithm, in cases where (for i = 1 to N) there are $n>1$ points $\{\mathbf{np}_{i,k}(\mathbf{x})\}_{k=1 \text{ to } n}$ on S_i with $d(\mathbf{x}, \mathbf{np}_{i,k}(\mathbf{x})) = inf\{d(\mathbf{x}, \mathbf{x}_S) \mid x_S \in S_i\}$, we stipulate that $\mathbb{W}_i'(\mathbf{np}_i(\mathbf{x}))$ is to be replaced by the arithmetic mean

$$(1/n).\sum_{k=1 \text{ to } n} \mathbb{W}_i'(\mathbf{np}_{i,k}(\mathbf{x})). \quad (21)$$

$\delta(\mathbf{np}_i(\mathbf{x}))$ will then be $\delta(\mathbf{np}_{i,k}(\mathbf{x}))$ for any k. Similarly, for $\mathbf{x},\mathbf{r} \in \mathbb{A}$, if there are $n>1$ points $\{\mathbf{np}_{i,k}(\mathbf{r})\}_{k=1 \text{ to } n}$ on surface S_i with $d(\mathbf{r}, \mathbf{np}_{i,k}(\mathbf{r})) = inf\{d(\mathbf{r}, \mathbf{r}_S) \mid \mathbf{r}_S \in S_i\}$, we replace the term $d(\mathbf{np}_i(\mathbf{r}),\mathbf{x})$ by the mean distance

$$(1/n).\sum_{k=1 \text{ to } n} d(\mathbf{np}_{i,k}(\mathbf{r}),\mathbf{x}). \quad (22)$$

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Figures and Figure Legends for
A Surface-Based Technique for Warping 3-Dimensional Images of the Brain:

Fig. 1.

Development of the Human Brain at 2, 3, 5 and 7 Months of Embryonic Age. Due to cellular proliferation during development, the chief structures of the brain are distorted into a characteristic C-shape. The lateral ventricles are continuously transformed (*arrows*) into an arched shape in synchrony with many other structures. These include a major functional unit, located on the floor of the lateral ventricles (*shaded*), consisting of the *caudate* and *putamen*. The *hippocampal formation*, and the *parahippocampal* and *cingulate gyri* of the limbic system are similarly transformed [not shown]. The *hippocampus* arches under the temporal horn of the ventricles (*q.v.*, Fig. 2, *arrow 6*). The two aforementioned gyri are formed on the medial surface of each cerebral hemisphere. (Adapted from [27] and F. Hochsetter, *Beitrage zur Entwicklungsgeschichte des menschlichen Gehirns*, Bd. II, F. Deuticke, Wien und Leipzig, 1929.)

Fig. 2.

The Mature Morphology of the Lateral Ventricles and Cerebral Cortex. (A) represents the human brain as seen from the right hand side, with the right ventricle shaded. When viewed from the front (B), the lateral ventricle 𝕀 (*shaded*) and cerebral cortex 𝕆 (*dashed lines*) in each hemisphere (here, the left one) are seen as nested closed surfaces. The frontal, occipital and temporal extremities (*arrows 1, 2, 3*) and *atrium* (*4*) of the lateral ventricles are shown; the tail of the *caudate* (*5*) and the foot of the *hippocampus* (*6*) project to form the roof and floor of the temporal horn, and the *corpus callosum* roofs over the *atrium* (*7*).

Fig. 3.

Connected Surface Systems used to Control the 3D Warp. The complex internal trajectory of the deep structures controlling the 3D deformation field are illustrated here. Surface models of deep anatomic structures in the right hemisphere of a 3D T_1-weighted SPGR MRI scan of an Alzheimer's patient are shown here, in the context of a

transparent surface-rendered model of the exterior cerebral cortex. Deep sulcal surfaces include: the anterior and posterior rami of the calcarine sulcus (CALCa/p), as well as the cingulate (CING), parieto-occipital (PAOC) supracallosal (CALL) sulci and the Sylvian fissure (SYLV). Also shown are the superior and inferior surface of the frontal horn (VTSs/i) and inferior horn (VTIs/i) of the right lateral ventricle. Color-coded profiles show the magnitude of the 3D deformation maps warping these surface components onto their counterparts in a 3D SPGR MRI scan of a normal, age-matched control subject.

Fig. 4.

Mesh Construction. The outlining process generates a densely-sampled set of points which are known to be located on the internal surface of a sulcus (indicated by *isolated points, above right*). These points, however, are not distributed uniformly on the sulcal surface. Homologous point isolation involves the molding of a lattice-like mesh onto the geometric profile of the surface. The concept is similar to that of a regular net being stretched over an object. The imposition of an identical regular structure on surfaces from different subjects allows surface statistics to be derived. Points on each surface with the same mesh coordinate occupy similar positions in relation to the geometry of the surface they belong to, and are therefore regarded as homologous.

Fig. 5.

3D Displacement Map shown on a 3D Representation of the Right Cingulate Sulcus. Local discrepancies between individual sulci in the atlas and target scans can readily be calculated. Both the magnitude and direction of such surface discrepancies are indicated by arrows that originate at points defined by the mesh in the atlas. Notice that the mesh in this figure contains a reduced number of points for the convenience of illustration. The map shown displaces a representation of the right cingulate sulcus onto the equivalent surface in another 3D brain volume.

Fig. 6.

Volume Warp Calculation. Two methods are shown. The simple *weighted-average* method (*left*) can be improved (*right*) by expressing $\mathbb{W}'(\mathbf{x})$ as a weighted linear combination of distortion functions associated with each surface. Within a surface S_i, the relative contribution of each surface point in the projected patch $\{\mathbf{np}_i(B(\mathbf{x};r_c))\}$ 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 $\mathbf{D}_i(\mathbf{x}) = \{\int_B w_i \mathbb{W}_i' \, \boldsymbol{dr}\}/\{\int_B w_i \, \boldsymbol{dr}\}$. The volume warp $\mathbb{W}'(\mathbf{x})$ will be a weighted average of the $\mathbf{D}_i$, depending on the relative distance $\gamma(\mathbf{x})$ of $\mathbf{x}$ from its near-points on each surface.

Fig. 7.

Axial slice images are shown, from 384^2x256 image volumes of (a) a geometric test object, containing nested surfaces, whose dimensions are described in the main text; (b) a target object with the same 3D topology; and (c) the result of warping the test object onto the target. (d) shows the magnitude of the required deformation field (in the coordinate system of the target image) indicating that the test object is carried accurately through this relatively large deformation, and is brought into register with the target object.

Fig. 8.

MRI-to-MRI Experiment. T_1-weighted MR sagittal brain slice images from (a). the target scan and (b). the reference anatomy; (c). result of warping the reference anatomy into structural correspondence with the target; (d). transformation applied to a regular grid in the reference coordinate system. Note that the continuous 1-to-1 mapping property of the warping transformation kept all of the structures connected and prevented them from being broken apart. This accounts for the slight striations seen above the cerebellum in the warped image, since its juxtaposition with the lingual cortex is maintained under the transformation. The deformed grid also shows that structures were not broken apart, because the grid lines are continuous and connected. (e) represents the magnitude of the 3D deformation field on the surface anatomy of the target brain, as well as on an orthogonal plane slicing through many of these surfaces, 7mm into the right hemisphere. Note the smooth continuation of the warping field from the complex anatomic surfaces into the surrounding brain architecture, and the highlighting of the severe deformations in the pre-marginal cortex, ventricular and cerebellar areas.

Fig. 9.

Inter-modality Warping: 3D Digital Cryosection Volumes mapped onto 3D MRI volumes. Sagittal brain slice images from (a) a digitally-imaged, cryosectioned whole human head; (b) the result of warping the cryosectioned head image into structural correspondence with the 3D MRI dataset shown in Fig. 8(a); and (c) transformation applied to a regular grid in the reference coordinate system. Note the reconfiguration of the major sulci, and the degree to which the reference *corpus callosum* is transformed into the shape of the target *callosum*. Note how different the deformation field is from that obtained in the MRI-to-MRI experiment [Fig 8(d),(e)].

Table 1

3D Distance (in mm) between Corresponding Points in Reference and Target Scans.

Structure (*N*=6, for each structure)	Before Transformation	After Transformation
I. *On family of control surfaces*:		

1. Frontal horn, lateral ventricle (anterior tip)	2.27 ± 0.76	0.54 ± 0.38
2. Cuneal point, occipital lobe‡	4.10 ± 1.00	1.26 ± 0.27
3. Marginal branch, cingulate sulcus (superior limit)‡	4.74 ± 0.78	1.29 ± 0.69
II. *Off family of control surfaces*:		
4. Hippocampus (rostral tip)	3.90 ± 1.91	1.32 ± 1.04
5. Superior temporal sulcus (lateral limit)	3.26 ± 0.60	1.88 ± 1.67
6. Insula (posterior limit)	4.25 ± 1.73	2.65 ± 1.35
7. Superior rostral sulcus (frontal limit)‡	3.10 ± 2.38	2.32 ± 1.18
8. Interthalamic adhesion	1.26 ± 0.60	0.85 ± 0.54

‡ *measured at medial wall of hemisphere*

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