Continuous Medial Representation of Brain Structures Using the Biharmonic PDE

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Abstract

A new approach for constructing deformable continuous medial models for anatomical structures is presented. Medial models describe geometrical objects by first specifying the skeleton of the object and then deriving the boundary surface corresponding to the skeleton. However, an arbitrary specification of a skeleton will not be "valid", unless a certain set of sufficient conditions is satisfied. The most challenging is an equality constraint on the skeleton specification that must hold along certain curves on the skeleton. The main contribution of this paper is the observation that the biharmonic partial differential equation can be used as means to parameterize the space of skeletons that satisfy this equality constraint. Another contribution is the ability to represent skeletons using triangular meshes, which provides added flexibility for modeling. The approach is demonstrated by generating continuous medial models for subcortical structures as well as white matter fasciculi.

Key words: Medial Representation, Skeletons, Deformable Models, Computational Anatomy, Shape Analysis

1 Introduction

Medial representations (m-reps) (Pizer et al., 2003a; Joshi et al., 2002) and the more recent continuous medial representations (cm-reps) are deformable geometric models that describe anatomical structures by explicitly defining the topology and shape of a structure’s skeleton and then deriving the geometry of the structure’s boundary from the skeleton. Models are subsequently
Deformed to fit target data by modifying the parameters defining the skeleton. Deformable medial modeling has been used in a variety of medical imaging analysis applications, including computational neuroanatomy (Yushkevich et al., 2007), cardiac modeling (Sun et al., 2008a), and cancer treatment planning (?). The primary appeal of medial modeling is that it enables shape features derived from skeletons to be used in statistical analysis, e.g., for comparing the shape of anatomical structures between cohorts. Principal among these features is thickness, defined here as the distance between the skeleton and boundary, a feature of great importance in neuromorphometry. Other features, such as the curvature of the skeleton, can also be highly descriptive of the local shape properties of an object (Yushkevich et al., 2001). Another attractive feature of deformable medial modeling is the ability to define a natural shape-based coordinate system over the interiors of structures, which leads to natural applications in structure-specific normalization and statistical mapping (Yushkevich et al., 2007, 2008).

Medial modeling should be distinguished from skeletonization (Kimia et al., 1995; Ogniewicz and Kübler, 1995; Nüf et al., 1996; Golland et al., 1999; Siddiqi et al., 1999b,a; Thompson et al., 2003; Bouix et al., 2005), an approach where the skeleton is derived from the boundary representation deterministically. The difference between skeletonization and medial modeling is summarized in Fig. 1. Skeletonization has limited utility in morphometric analysis studies because the number and configuration of the branches in the skeleton (commonly referred to as branching topology) is highly sensitive to boundary noise. In the case of anatomical structures, branching topology is likely to vary between subjects, requiring the skeleton to be simplified (or pruned) prior to performing shape analysis. By contrast, deformable modeling can assure that the topology of the skeleton representation remains the same for all subjects in the study. The drawback of this approach is that the deformable medial models can only offer an approximate representation of the underlying anatomical structures. However, in practice the representation error is small in comparison to the errors associated with the segmentation of anatomical structures in medical images (Styner et al., 2003a; Yushkevich et al., 2006).

The premise of continuous medial modeling is that the specification of the skeleton must be given as a continuous manifold (or a set of manifolds) — or as a discrete mesh that can be successively refined towards a continuous limit. The boundary derived from the skeleton by inverse skeletonization should also be a continuous surface (or refinable towards a continuous limit). Most importantly, the “actual” skeleton of this boundary surface should be the same as the “synthetic” skeleton specified by the model. This last requirement leads to a set of non-linear equality constraints that the synthetic skeleton must satisfy along curves that bound its component manifolds, as well as a set of inequality constraints that the skeleton must satisfy at every point (Yushkevich et al., 2006). In deformable modeling applications these constraints lead to severely
Fig. 1. Skeletonization vs. medial modeling. Left: A 3D object and the skeleton derived by skeletonization. The color map on the skeleton is the “radius scalar field” $R$ or, equivalently, the distance to the closest boundary point. Right: medial modeling, which is, essentially, the opposite of skeletonization. A deformable parametric medial model is defined as a surface or set of surfaces, and the boundary is derived analytically using “inverse skeletonization,” (see Eqn. 2). The model is then deformed to maximize fit between its boundary and the object of interest. Since the medial model is parametric, it can be flattened, i.e., mapped to a 2D domain; not so for skeletonization. The key difference between skeletonization and medial modeling is that the former computes exact skeletons, but does not guarantee that the branching topology of the skeletons is consistent across individuals; the latter computes approximate skeletons, but guarantees the same topology for all individuals, allowing effective statistical analysis.

over-constrained optimization problems because the number of points where they must be satisfied is infinite (or at least, very large), while the number of coefficients (or control points) defining the skeleton is finite and, preferably, small.

A number of solutions to addressing this challenge have been proposed. In (Yushkevich et al., 2003), the authors adapted the shape of the domain on which the skeleton is defined so as to force the equality constraints to hold along its boundary. This method is limited to single-manifold skeletons and also presents difficulties for establishing correspondences between models fitted to different instances of a structure. In (Yushkevich et al., 2006), skeletons were defined as solutions of a Poisson partial differential equation (PDE) with a non-linear boundary condition that incorporates the equality constraint. The advantage of the PDE is that it provides a bijective mapping from a subset of a vector space to the space of synthetic skeletons satisfying the equality constraint, allowing linear statistical analysis; but the approach has its limitations: solving the non-linear Poisson equation is computationally expensive.
and the idea does not extend to skeletons with multiple branches. More recently, Terriberry and Gerig (2006) used a specially modified subdivision surface scheme to force local geometry near the edges of skeletal manifolds to satisfy the equality constraint. The technique can handle medial branching. One limitation of this approach is that it requires skeletons to be defined using meshes with quadrilateral elements. The method proposed here, by contrast, is independent of the type of approach used to model skeleton manifolds: it can be implemented using b-splines, Fourier harmonics, radial basis functions or, as we choose to do, using Loop subdivision surfaces which have triangular elements.

The main contribution of this work is to use the biharmonic PDE $\Delta^2 u = f$ to create a high-dimensional mapping from some vector space to the space of synthetic skeletons satisfying the required equality constraints. Unlike the Poisson PDE used for this purpose in (Yushkevich et al., 2006), the higher-order biharmonic equation can incorporate the equality constraints as linear boundary conditions, leading to a simpler, more robust numerical problem. Furthermore, the mapping defined through the biharmonic equation is not limited to single-manifold skeletons.

The paper is organized as follows. The necessary background on medial geometry and inverse skeletonization is given in Sec. ?? . The new approach based on the biharmonic equation is presented in Sec. ?? . Examples that use the new approach to model various brain structures are shown in Sec. ?? . The discussion in Sec. ?? focuses on future applications of the technique and possible improvements.

2 Background

This section summarizes some of the main properties of skeletons. Facts from medial geometry are given without proof, and we refer the reader to Damon’s extensive work for a more mathematical treatment of the subject (Damon, 2003, 2004, 2005).

2.1 Blum Skeleton Definition

In what follows, we use Blum’s definition of the skeleton (Blum, 1967), which was originally given in two dimensions but has a three-dimensional equivalent that has been studied extensively in the recent literature (Nackman, 1982; Vermeer, 1994; Giblin and Kimia, 2003, 2004; Pizer et al., 2003b; Damon, 2003, 2004, 2005).
There are several ways to define the Blum skeleton of an object: as the crest of the distance transform from the boundary; as the shock set of the Eikonal PDE; or, as we do below, as the locus formed by the maximal inscribed balls.

**Definition 1** A closed bounded set \( O \subset \mathbb{R}^3 \) is called a geometric object if it is homeomorphic to a ball in \( \mathbb{R}^3 \) and if its boundary, denoted \( \partial O \), is a smooth generic surface. Following (Giblin and Kimia, 2003), the term generic means devoid of singularities that can be removed by applying a small perturbation to the surface.

**Definition 2** A ball \( B \) is called a maximal inscribed ball (MIB) in a geometric object \( O \) if \( B \subset O \) and there exists no ball \( B' \neq B \) such that \( B \subset B' \subset O \).

**Definition 3** The skeleton of a geometric object \( O \) is the locus of points in \( \mathbb{R}^3 \times \mathbb{R}^+ \) formed by the centers and radii of all MIBs in \( O \).

The locus formed by the centers of the MIBs in \( \mathbb{R}^3 \) is a Whitney stratified set (Damon, 2005), i.e. a set formed by one or more manifolds with boundary connected along their boundaries. We will refer to these manifolds as medial manifolds. We will use the term medial seam to refer to portions of medial manifold boundaries that are shared by multiple medial manifolds, and use the term medial edge to refer to the remaining, non-shared portions of medial manifold boundaries. We will use the term radial scalar field to refer to the field formed by the radii of the MIBs along the medial manifolds. A simple example of a branching skeleton is shown in Fig. ??, with medial edges and seams pointed out.

Giblin and Kimia (2004) prove that points that generically occur on skeletons of geometric objects fall into five distinct classes, which are characterized by the order and multiplicity of contact between the MIB and the object’s boundary: (1) points on the interior of medial manifolds, where the MIB is tangent to the object’s boundary at two points; (2) points on medial edges, where the MIB is tangent to the boundary at one point and has third-order contact with the boundary; (3) points on medial seams, where the MIB is tangent to the boundary at three points; (4) points at seam-edge intersections; and (5) points at seam-seam intersections. Giblin and Kimia (2004) also point out that the geometry of points at edges and seams of medial manifolds is the limit case of the geometry of points on the interior of medial manifolds. For example, one walks along the medial manifold towards a point on the medial edge, the points of tangency between the object’s boundary and the MIB centered at one’s location will get closer and closer to each other, collapsing to a single point once the medial edge is reached.
2.2 Skeleton-Boundary Relationship

An analytic relationship between the skeleton $S$ of an object and its boundary $B$ can be established on the basis of the mapping between the centers of MIBs and the points of tangency between the MIBs and $B$. Every point on $B$ is associated with a single point on $S$, since there can only be one MIB tangent to $B$ at a given point. Conversely, every point on $S$ is associated with one, two or three points on $B$, depending whether it lies on the medial edge, medial interior or medial seam. The bitangency is the generic case, and the other cases are limit cases of the bitangent MIB geometry.

Let $b^+$ and $b^-$ denote the points of tangency between $B$ and a bitangent MIB with center $m$ and radius $R$. It can be shown (e.g., (Damon, 2004; Yushkevich et al., 2006)) that $b^\pm$ can be expressed analytically in terms of $m$ and $R$, as follows:

$$b^\pm = m + R\tilde{U}^\pm,$$

where $\tilde{U}^\pm$ are the unit outward normal vectors to $B$ at the points $b^\pm$. These normals are given in turn by

$$\tilde{U}^\pm = -\nabla_m R \pm \sqrt{1 - |\nabla_m R|^2} \tilde{N}_m,$$

where $\tilde{N}_m$ is the unit normal of the medial manifold at $m$ and $\nabla_m R$ is the Riemannian gradient of $R$ on the medial manifold. Recall that the centers of bitangent MIBs lie on the interior of medial manifolds in $S$ (i.e., not on the edges or seams); thus $m$ and $R$ are continuous and differentiable in the neighborhood of a bitangent MIB.

Let us now consider the limit behavior of (2) as we approach the edges and seams of medial manifolds. As noted above, the MIBs centered along medial edges are tangent to $B$ at a single point. For $B$ to be continuous, this requires $b^-$ and $b^+$ to collapse to a single point as the medial edge is approached. That, in turn, requires the coefficient of $\tilde{N}_m$ in (2) to be 0, leading to the following condition:

$$|\nabla_m R| = 1 \text{ along medial edges.} \quad (3)$$

A similar situation occurs at medial seams. The seam is shared by three medial manifolds, so as we approach a point $m$ on a medial seam, we have $m_1 \rightarrow m$, $m_2 \rightarrow m$, and $m_3 \rightarrow m$. For the boundary to be continuous, the six MIB tangency points $b_1^+, b_2^+, b_3^+$ must collapse to three points: $b_1^+ \rightarrow b_2^-, b_2^+ \rightarrow b_3^-$ and $b_3^+ \rightarrow b_1^-$, as illustrated in Fig. ???. This requirement can again be expressed in terms of the gradient of $R$, as follows:

$$\nabla_{m_{i\rightarrow i+1}} R - \nabla_{m_{i\rightarrow i+1}} R = \sqrt{1 - |\nabla_m R|^2} \tilde{N}_m, \quad (4)$$
where \( i = 1, 2, 3 \) and \( \oplus, \ominus \) denote addition and subtraction modulo 3.

In addition to the three cases examined above, there are two special situations at seam-edge and seam-seam intersections that can be treated as limit cases of corresponding conditions.

### 2.3 Inverse Skeletonization

In deformable medial modeling, models for anatomical structures are formed as follows: first, a *synthetic skeleton* is defined as a collection of manifolds with a scalar radius field; second, the boundary of the structure is derived from the synthetic skeleton using relations (1) and (2); lastly, the parameters defining the synthetic skeleton are modified to maximize the match between the model and the structure of interest (as Fig. 1 illustrates). Central to this scheme is the problem of *inverse skeletonization*: under which conditions does a synthetic skeleton \( S_{\text{syn}} \) happen to be the geometrical skeleton of some object \( O \)? It is easy to devise examples where inverse skeletonization fails, i.e., of synthetic skeletons for which (1) and (2) give discontinuous or self-intersecting boundary surfaces (see Fig. 4 in (Yushkevich et al., 2006)).

For single-manifold synthetic skeletons, the sufficient conditions for inverse skeletonization are given in (Yushkevich et al., 2006). These conditions consist of the nonlinear equality relation (3) and several inequality constraints. From the point of view of continuous modeling, the equality constraint presents a much greater challenge than the inequality constraints. If the medial manifold in \( S_{\text{syn}} \) is defined using a finite set of continuous basis functions, there are as many degrees of freedom as there are basis functions, while there are infinitely many points at which the equality constraint (3) must be satisfied. This leads to a severely overdetermined system, which is the main challenge of continuous medial modeling. For skeletons with multiple medial manifolds the situation is similar, with (4) becoming an equality constraint that must be satisfied along medial seams.

### 3 Methods

#### 3.1 Fundamental Problem of Continuous Medial Modeling

Continuous medial modeling relies on our ability to generate valid synthetic skeletons (those satisfying the necessary equality and inequality constraints) and to perform gradient descent optimization in the space of valid synthetic
skeletons. More formally, we pose the fundamental problem of continuous medial modeling in the following form: find a continuous differentiable mapping from a vector space onto the space of all synthetic skeletons satisfying equality constraints (3,4).

This is a very general statement of the problem. We can make it more specific (and more strict) by requiring that the mapping to be identity for the medial manifolds themselves, and restricting our attention to the radial part of the mapping: given a set of connected medial manifolds \( \mathcal{M} \in \mathbb{R}^3 \) (a Whitney stratified set), find a mapping from some vector space to the set of all radial fields \( R \) defined over \( \mathcal{M} \) that satisfy (3,4). As we show below, this problem has a solution.

3.2 Single-Manifold Case

We begin with the single-manifold case, where \( \mathcal{M} \) contains a single medial manifold \( \mathbf{m} \). Let \( \partial \mathbf{m} \) denote the boundary of \( \mathbf{m} \) and let \( \gamma(s) : [0, L) \to \mathbb{R}^3 \) be its parametric form, parameterized by the arclength \( s \), where \( L \) is the length of \( \partial \mathbf{m} \). Let \( \vec{T}_\gamma(s) \) be the unit tangent vector along \( \gamma \) and let \( \vec{\nu}(s) \) be the outward unit normal vector along \( \gamma(s) \), i.e., \( \vec{\nu} \perp \vec{N}_\mathbf{m} \) and \( \vec{\nu} \perp \vec{T}_\gamma \). Note that

\[
\nabla_{\mathbf{m}} R = R_s \vec{T}_\gamma + R_{\vec{\nu}} \vec{\nu},
\]

where \( R_s \) and \( R_{\vec{\nu}} \) denote the partial derivative of \( R \) with respect to \( s \) and \( \vec{\nu} \), respectively. This expression allows us to rewrite the equality constraint (3) as

\[
R_{\vec{\nu}} = -\sqrt{1 - (R_s)^2},
\]

where the sign is negative because \( R \) increases in the inward direction from the medial edge. The central idea of this paper is the observation that if we were to be given the value of \( R \) along the edge \( \gamma \), i.e.,

\[
R|_\gamma = \tau(s)
\]

then, together, the specification (6) and the constraint (5) have precisely the form of the Dirichlet boundary condition for a fourth-order PDE. This fact allows us to define \( R \) on the interior of the medial manifold \( \mathbf{m} \) as a solution of the fourth-order biharmonic PDE.

It turns out more convenient to define such a PDE not in terms of \( R \) itself, but in terms of \( \phi = R^2 \). Let \( \rho \in L^2(\mathbf{m}) \) be a two-dimensional scalar field on \( \mathbf{m} \) and let \( \tau \in L^2(\partial \mathbf{m}) \) be a one-dimensional scalar field on \( \gamma \), such that \( \tau > 0 \)
and $|d\tau/ds| < 1$ everywhere on $\gamma$. Then let $\phi$ be the solution of

$$
\Delta^2_m \phi = \rho, \\
\phi|_{\gamma} = \tau^2, \\
\phi,\nu|_{\gamma} = -2\tau \sqrt{1 - (d\tau/ds)^2},
$$

where $\Delta_m$ denotes the Laplace-Beltrami operator (LBO) on the manifold $m$. This equation is known as the first biharmonic equation Glowinski and Pironneau (1979).

Provided that the solution $\phi$ is non-negative everywhere on $m$, it is easy to verify that $R = \sqrt{\phi}$ satisfies the equality constraint (3) on $\partial m$. Ensuring that $\phi > 0$ is non-trivial: while the maximum principle for the biharmonic operator can give us a sufficient condition, this condition is too restrictive to use in practice because it excludes a wide range of positive solutions. In practice, however, there is no difficulty staying in the range of positive solutions in the course of deformable modeling.

The PDE (7) is a linear operator

$$
\phi = \Psi(\rho, \tau), \quad \text{where} \quad \Psi : L^2(m) \times L^2(\gamma) \to L^2(m).
$$

The existence, uniqueness and stability of the first biharmonic equation ensure that the mapping $\phi = \Psi(\rho, \tau)$ is defined everywhere on its domain, is one-to-one, and is differentiable. Conveniently, the operator $\Psi$ maps zeros to zero, i.e., if $\rho = 0$ everywhere on $m$ and $\tau(s) = 0$ everywhere on $\gamma$, then $\phi,\nu$ vanishes on $\partial m$ and $\phi = 0$ is the solution of the PDE (7). Interestingly, we define the PDE in terms of $\phi = R$ rather than $\phi = R^2$, we would lose this attractive property. Another attractive reason for choosing $\phi = R^2$ is that for an ellipsoid, the simplest 3D object with a single-manifold medial axis, $\Delta \phi$ is constant on $\Omega$ and $\Delta^2 \phi = 0$. This is not the case for $\phi = R$.

### 3.3 Numerical Solution

Implementing medial modeling based on the biharmonic PDE involves choosing an appropriate representation for the manifolds composing the medial

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1 Indeed, taking the square of the second boundary condition in (7), substituting $\sqrt{\phi}$ for $\tau$ and noting that

$$
|\nabla_m \phi|^2 = (\phi,\nu)^2 + (\phi,s)^2 \quad \text{on} \ \partial m,
$$

we get $|\nabla_m \phi|^2 = 4\phi$ and, by the chain rule, $|\nabla_m R|^2 = 1$. 

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model and then defining a finite differences scheme that allows us to solve the
PDE numerically as a sparse linear system.

3.3.1 Numerical Representation of Medial Models

Our choice of representation for the medial manifolds is Loop subdivision sur-
faces (Loop, 1987). This representation is simple, can be defined on an arbi-
trary domain and, with a small modification, can be used to represent multi-
manifold medial models. In the Loop scheme, a coarse-level triangular mesh is
successively subdivided, converging to a continuous limit surface. Subdivision
involves splitting triangles into four by inserting a new vertex in every edge.
The coordinates of the new vertices, as well as the coordinates of the vertices
retained from the previous level, are computed at each iteration using simple
arithmetic rules (Loop, 1987). Edges in the mesh can be designated as crease
dges, and special rules are used at these edges to generate a crease in the
limit surface (Biermann et al., 2000).

In deformable modeling, the model must be defined by a set of coefficients
which can be modified in order to deform the model (Fig 1). In our Loop-based
scheme, the coefficients are used to specify the coarse-most mesh \((V^0, T^0)\),
where \(V\) denotes the vertices and \(T\) are the triangles. Each vertex \(i\) is a
tuple of coefficients: \(V^0 = (m_i^0, \rho_i^0, \tau_i^0)\), where \(m_i^0 \in \mathbb{R}^3\), and \(\rho_i^0\) and \(\tau_i^0\) are
scalars, corresponding to the boundary conditions of (7). Although we are
only interested in the values of \(\tau\) along \(\gamma(s)\), i.e., at the edges of the medial
manifolds, it is more convenient to define \(\tau_i^0\) at each vertex and to ignore its
values an non-edge vertices.\(^2\)

While the mesh \((V^0, T^0)\) serves as the specification of the deformable model’s
coefficients, the model itself, in theory, is given by the limit surface of Loop
subdivision. In practice, however, we approximate this limit surface by apply-
ing a finite number of subdivisions, i.e., using the mesh \((V^k, T^k)\) as a digital
representation of the skeleton \(m\) and scalar field \(\rho\) and \(\tau\). The level of sub-
division \(k\) is chosen empirically. During model fitting, \(k\) is usually between 1
and 3, depending on the density of \((V^0, T^0)\). Once the model has been fitted
to the target object, \(k\) may be increased to generate a high-quality model.

3.3.2 Spectral Deformation for Medial Manifolds

In practice, when fitting models to anatomical data, we do not always want
to optimize directly over the vertices of the coarse-level mesh \((V^0, T^0)\). In our

\(^2\) In the Loop subdivision scheme, the vertices computed along the edges of a child-
level surface only depend on the edge vertices in the parent-level surface, so having
dummy \(\tau\)-values defined at non-edge vertices has no effect on the PDE solution.
experiments, the control mesh will typically have around 100 vertices, which is too many parameters to optimize in the early stages of model fitting. Instead, we leverage spectral decomposition of the control mesh to allow greater global control, leading to a more efficient coarse-to-fine strategy.

Spectral decomposition involves defining an orthogonal basis on the control mesh \((V^0, T^0)\), so that the mesh can be deformed smoothly by modifying the coefficients of a small number of basis functions rather than the vertices of the control mesh. The natural approach to defining an orthogonal basis on an arbitrary 3D mesh is to use the eigenfunctions of the Laplace operator, which is the generalization of the Fourier basis on the plane (as well as the spherical harmonics basis on the sphere). The Laplace eigenfunction basis has become a popular tool for mesh compression and deformable modeling (Karni and Gotsman, 2000; Rustamov, 2007), and has found applications in computational neuroanatomy (Thompson et al., 2004; Chung et al., 2005; Qiu et al., 2006).

Our implementation of the Laplace eigenfunction basis follows the approach prescribed in (Belkin and Niyogi, 2003), using a variant the authors call “simple-minded”, where the Laplace operator is defined based on mesh topology rather than using mesh coordinates. Specifically, the Laplace operator for a function \(\psi\) on the mesh is estimated at the vertex \(i\) as

\[
\Delta \psi|_i = -\psi_i + \frac{1}{\|N_1(i)\|} \sum_{j \in N(i)} \psi_j ,
\]

where \(N_1(i)\) denotes the one-ring of \(i\), i.e., the set of vertices adjacent to \(i\) by an edge. The alternative is to take the eigenfunctions of the Laplace-Beltrami operator on the mesh, as we do in (10) below for solving the biharmonic PDE. However, the advantage of the “simple-minded” approach is that the basis does not change as the model deforms, making it unnecessary to solve a large sparse eigensystem at every iteration of deformable modeling. In practice we have found the current approach to work well, so we took advantage of it’s relative inexpensiveness.

### 3.3.3 Numerical Solution of Biharmonic PDE Using Finite Differences

Glowinski and Pironneau (1979) show that the biharmonic equation on a domain in \(\mathbb{R}^2\) can be reduced to a system of harmonic equations by introducing a new unknown variable \(\omega = \Delta m \phi\) and simultaneously solving for \(\phi\) and \(\omega\). By the same token, the biharmonic equation on the medial manifold (7) can be
written as a system of two harmonic equations:

\[ \Delta_m \phi = \omega, \]
\[ \Delta_m \omega = \rho, \]
\[ \phi |_{\gamma} = \tau^2, \]
\[ \phi, \nu |_{\gamma} = -2\tau \sqrt{1 - \left(\frac{d\tau}{ds}\right)^2}, \]

Using the finite difference method, this equation reduces to a \((2n \times 2n)\) sparse linear system, where \(n\) is the number of vertices in the finite difference mesh. Glowinski and Pironneau (1979) further reduce this system to an \((n \times n)\) sparse linear system and a \((k \times k)\) dense linear system, where \(k < n\) is the number of vertices at the edge of the domain. In our implementation we found that solving the \((2n \times 2n)\) sparse linear system is sufficiently fast not to require further reduction.

The solution of (8) using the finite difference method is complicated by the fact that the Laplace-Beltrami operator (LBO) is defined on a simplicial surface in \(\mathbb{R}^3\) rather than on a planar grid. Many approximations of the LBO have been proposed in the literature. Wardetzky et al. (2007) point out that diversity of proposed operators is due to the fact, which they prove, that no “ideal” digital LBO may be found, i.e., no digital operator may at once satisfy the desirable properties of “symmetry”, “locality”, “linear precision” and “positive weights”. Our solution follows the framework established by Pinkall and Polthier (1993) with robustness modifications by Bobenko and Springborn (2007). This approach satisfies all of the four desired properties except locality (Wardetzky et al., 2007). Since our aim is to get as good an approximation of the solution as possible, we the locality property is the easiest to sacrifice.

In general, the LBO is defined on a mesh as a weighted sum

\[ (\Delta_m \phi)_i = \sum_{j \in N_i(i)} w_{ij} (\phi_j - \phi_i) \]

where \(w_{ij}\) is a weight assigned to each edge in the mesh. Pinkall and Polthier (1993) and later Desbrun et al. (1999) proposed the widely-used cotan formula for \(w_{ij}\):

\[ w_{ij} = \frac{3}{A_i} \frac{\cot \alpha_{ij} + \cot \beta_{ij}}{2}, \]

where \(A_i\) is the sum of the areas of the triangles that share the vertex \(i\), and \(\alpha_{ij}, \beta_{ij}\) are the two angles opposite to the edge \((i, j)\). This expression has been widely used for Laplacian mesh smoothing, minimum surfaces computation and many other applications. However, the weights \(w_{ij}\) can be negative on arbitrary meshes leading to the violation of the maximum principle and other
problems (Wardetzky et al., 2007). Bobenko and Springborn (2007) propose an
elegant solution to this problem by applying intrinsic Delaunay triangulation
to the mesh before computing LBO using the cotan formula. This approach
also ensures that the PDE solution is intrinsic: dependent only on the vertices
of the mesh and not on its triangulation. Intrinsic Delaunay triangulation can
be performed using an efficient intrinsic edge flipping algorithm (Glickenstein,
2005; Fisher et al., 2006), which terminates in finite time and has a unique
solution (Bobenko and Springborn, 2007). Our implementation of the finite
difference method includes the edge flip algorithm.

In addition to the LBO, to solve (8), we require finite difference approximations
of $\phi, \nu$ and $d\tau/ds$ at vertices that lie at the edges of the medial mesh, where
the boundary conditions are defined. We also require an approximation of the
Riemannian gradient $\nabla_m \phi$ for the inverse skeletonization expression (2).

To estimate intrinsic first-derivative quantities of some function $f$ on the mesh
$m$, we start with expressions for tangents to the Loop subdivision surfaces
given by Loop (1987). A pair of tangent vectors $m_1, m_2$ to the limit surface
$m$ at vertex $i$ is given by expressions of the form

$$(m_d)_i = w_{ii,d} m_i + \sum_{j \in N_1(i)} w_{ij,d} m_j, \quad d = 1, 2. \tag{11}$$

The weights $w_{ij,d}$ can be found in the review by Zorin et al. (2000, p.71). Given
these tangent vectors, one can compute at each vertex the covariant metric
tensor $g_{pq} = m_p \cdot m_q$ and the contravariant metric tensor $g^{pq}$, given by the
Einstein notation expression $g^{pq} g_{pq} = \delta_q^p$. The derivatives of $f$ in directions of
$m_1$ and $m_2$ are similarly given by

$$(f_d)_i = w_{ii,d} f_i + \sum_{j \in N_1(i)} w_{ij,d} f_j, \quad d = 1, 2, \tag{12}$$

where the weights $w_{ij,d}$ are the same in both expressions. We can obtain the
Riemannian gradient of $f$ as

$$\nabla_m f = g^{pq} m_p f_{q}. \tag{13}$$

Notice that this expression is non-linear in $f$, so it is unsuitable for finite
difference modeling. However, since the gradient operator does not appear in
the PDE (8) this non-linearity does not pose any problem.

At the vertices along the boundaries and creases of the Loop subdivision sur-
face, $m_1$ is parallel to $\gamma$, the curve that forms the boundary of the subdivision
surface and, thus, perpendicular to the outward normal, $\nu$. Therefore, $f,s$,
where $s$ is the uniform arc length parameterization of $\gamma$, is given by

$$f,s = f,1/\sqrt{g_{11}}, \tag{14}$$
and the normal derivative is given by

\[ f_{\nu} = \frac{g_{11} f_2 - g_{12} f_1}{g_{11} \sqrt{g_{22}}} \].

Plugging in (12) for \( f_1 \) and \( f_2 \) in the above two expressions, we get finite difference expressions for \( f_s \) and \( f_{\nu} \). Finally, substituting \( \tau \) and \( \phi \) for \( f \), we obtain the finite difference expressions for all of the terms appearing in the PDE (8).

With the help of finite difference expressions for \( \Delta_m \phi \), \( \Delta_m \omega \), \( \phi_{\nu} \) and \( \tau_s \), the PDE (8) reduces to the linear system

\[ A \begin{bmatrix} \phi \\ \omega \end{bmatrix} = b, \tag{13} \]

where \( A \) is a sparse matrix. However, the matrix \( A \) may not be of full rank. The reason this happens is that \( \phi \) is fixed at the boundary nodes by the Dirichlet boundary conditions, so the boundary condition involving \( \phi_{\nu} \) imposes constraints on the values of \( \phi \) “just inside” of the boundary. If there are fewer values to satisfy these constraints than there are constraints, the problem will not have a solution. To avoid this problem, we ensure that the meshes used to represent medial manifolds have more vertices just inside of the boundary than there are boundary vertices. To solve the sparse linear system, we use the direct solver PARDISO (Schenk and Gärtner, 2004).

### 3.4 Multi-Manifold Case

### 3.5 Deformable Modeling

The problem of fitting cm-rep models to anatomical structures is described in earlier work (Yushkevich et al., 2006). There are essentially no differences in terms of the objective function between the biharmonic cm-rep model and the earlier Poisson-based model. In most applications, we deform cm-rep models to maximize fit with a binary segmentation of a given target structure. Although there has been plenty of work on using medial representations to directly segment anatomical structures in medical images (Pizer et al., 2003a; ?), segmentation is not the focus of this work. Other applications of continuous medial models include shape-based normalization (Yushkevich et al., 2007), shape analysis (Sun et al., 2008b) and data dimensionality reduction (Yushkevich et al., 2008). For these applications, we typically start with a given segmentation of the structure of interest and require to fit a medial model to it.
We briefly summarize the fitting approach described in (Yushkevich et al., 2006). Model fitting involves numerical optimization, where the objective function consists of an image match term and a set of regularization priors and penalties used to ensure model’s validity. The image match term estimates the Dice overlap between the model and the target structure (this is not easily possible for some other types of deformable models, such as boundary models; however, since medial models allow the entire interior of the model to be parameterized, computing overlap is fast and simple). Soft penalty terms ensure that the model does not self-intersect (a simple penalty on the Jacobian of the $\vec{U}$ vector field in (2) is sufficient in most applications), and that the minimum angle of triangles in the mesh does not get too small. In addition, regularization priors are used to maintain geometrical correspondence when models are fitted to multiple instances of an anatomical structure. A simple regularization prior is penalizes the gradient magnitude of the determinant of the metric tensor the mapping between the deforming model and a target model.

4 Experiments and Results

The aims of this experimental section are (1) to illustrate the ability of cm-rep models to accurately represent natural variability in the shape of anatomical structures; (2) to demonstrate the capacity to perform linear statistical analysis in the space of cm-rep models.

The motivation for the first aim is that cm-rep models are, by construction, a lossy representation for anatomical structures. The branching topology of the skeleton of a cm-rep model is maintained during deformable modeling. Since real-world variability in the topology of the skeletons of anatomical structures is vast, cm-reps can only fit target anatomy approximately. However, it has been found, both in the case of discrete (Styner et al., 2003a) and continuous medial models (Yushkevich et al., 2006, 2008; Sun et al., 2008a), that for some structures, such as the hippocampus, the approximation error is quite small, especially when compared with errors associated with manually or automatically segmenting these structures from anatomical images. In this paper, we again carry out fitting accuracy analysis to ensure that cm-rep models based on the biharmonic PDE perform as well or better than earlier approaches.

The second experimental aim shows off the particular advantages of PDE-based medial modeling. It takes advantage of the fact that the PDE creates a diffeomorphic mapping from a parameter space that is a codimension-0 subset of $\mathbb{R}^N$ to the space of “valid” cm-rep models. This mapping allows us to apply linear operations, such as principal component analysis (PCA), linear discrimination, or shape interpolation to cm-rep parameters and to gener-
ate new “valid” cm-rep instances. Without the PDE, linear combination of cm-rep models would lead to “invalid” instances, because nonlinear equality constraints (3) and (4) would be violated.

4.1 Hippocampus

4.1.1 Subjects, Imaging and Data Processing

The dataset used in this experiment was graciously provided to us by Prof. Guido Gerig (Department of Computer Science, University of Utah) and Prof. Sarang Joshi (Departments of Biomedical Engineering, University of Utah). The data includes 1.5 Tesla T1-weighted SPGR MRI scans (0.9375 × 0.9375 × 1.5mm³ voxel size) for 87 subjects from a previously published schizophrenia study (Chakos et al., 2005); the subjects included patients with early illness and chronic disease, as well as controls matched by age and gender. The dataset also included left and right hippocampus segmentations, obtained automatically using the Joshi et al. (1997) large deformation diffeomorphic registration method that incorporates expert-placed anatomic landmarks. This segmentation approach is used extensively in brain morphometry (Csernansky et al., 1998) and was shown to have greater interrater reliability than manual segmentation (Haller et al., 1997). This data has been analyzed previously using statistical features derived from boundary and discrete medial representations, and differences in the shape and size of the hippocampus between schizophrenia patients and controls were detected (Styner et al., 2003b; Gerig et al., 2002, 2003).

Hippocampus segmentations were provided in the form of high-resolution boundary surface meshes. We scan-converted and flood-filled these meshes to generate binary masks with the voxel size 0.33 mm³. An initial medial model was constructed using a skeletonization and flattening based procedure described in an earlier paper (Yushkevich et al., 2008, Sec. 3.4.1). The model has 1584 triangles and 853 vertices. Model fitting followed a multi-resolution schedule, with up to 800 iterations with the Laplace eigenfunction basis of size 10 (see Sec. 3.3.2), followed by up to 200 iterations with basis of size 40, up to 200 iterations with basis of size 120 and, finally, up to 200 iterations with direct optimization over each vertex in the model. Fitting time was about 1 hour per model per 2.4GHz CPU.

4.1.2 CM-Rep Fitting Accuracy

Fitting accuracy was evaluated in terms of Dice overlap and mean squared distance between the model’s boundary and target structure’s boundary. The results are listed in Table ??, with earlier results on the same dataset from
Table 1
Accuracy of fitting hippocampus segmentations of deformable cm-rep models. The accuracy obtained using cm-rep models based on the biharmonic equation (BH) is compared to previously published results in (Yushkevich et al., 2006) that used a non-linear Poisson equation (NLP). Each value in the table represents one of five accuracy measures averaged over 89 subjects. The measures include Dice overlap (Dice, 1945) between the interior of the cm-rep model and the segmented hippocampus volume; mean Euclidean distance from the boundary of the cm-rep model to the boundary of the hippocampus; mean distance from the hippocampus to the model; maximum distance (within subject) from the model to the hippocampus; and maximum distance from the hippocampus to the model. The results show a consistent improvement in fitting accuracy with the biharmonic equation approach.

<table>
<thead>
<tr>
<th></th>
<th>Left Hippocampus</th>
<th>Right Hippocampus</th>
<th>Both Hippocampi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BH</td>
<td>NLP</td>
<td>BH</td>
</tr>
<tr>
<td>Dice Overlap</td>
<td>0.977</td>
<td>0.953</td>
<td>0.966</td>
</tr>
<tr>
<td>Avg. Dist. Model to Target (mm)</td>
<td>0.104</td>
<td>0.164</td>
<td>0.111</td>
</tr>
<tr>
<td>Avg. Dist. Target to Model (mm)</td>
<td>0.121</td>
<td>0.187</td>
<td>0.133</td>
</tr>
<tr>
<td>Max. Dist. Model to Target (mm)</td>
<td>1.020</td>
<td>1.214</td>
<td>0.990</td>
</tr>
<tr>
<td>Max. Dist. Target to Model (mm)</td>
<td>1.097</td>
<td>1.381</td>
<td>1.183</td>
</tr>
</tbody>
</table>

Overlap between a fitted cm-rep model and the target hippocampus mask was measured using Dice similarity coefficient Dice (1945), a symmetric overlap measure frequently used to compare agreement between segmentations (e.g., Zou et al. (2004)). Boundary-based criteria describe the average (as well as maximal) distance from the fitted cm-rep models to the corresponding hippocampus meshes and, vice versa, from the hippocampus meshes to the fitted cm-rep models (average and maximal mesh-to-mesh distance is asymmetrical). The means of these maximal and average distances over all subjects are reported in Table ??.
4.1.3 Vector Space Statistical Analysis

4.2 Caudate Nucleus

4.2.1 Subjects and Imaging

4.2.2 CM-Rep Fitting Accuracy

4.2.3 Shape Interpolation

4.2.4 White Matter Structures

4.2.5 Subjects and Imaging

4.2.6 CM-Rep Fitting Accuracy

5 Discussion and Conclusions

References


Damon, J. On the smoothness and geometry of boundaries associated to


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