HIERARCHICAL BRAIN MODEL FOR COREGISTRATION
A Physical Model for Analysis of Brain MRI Data

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Abstract: A ubiquitous problem in coregistration of brain images is that individual sulci and gyri vary considerably between individuals, both with respect to location and shape as well as for simple existence of particular sulci. The underlying assumption of most coregistration processes is that one structure can be smoothly morphed to exactly resemble another structure if enough parameters are used. Although in a strict sense this may be true for intersubject brain registration, due to differing structures the result may not be as meaningful as desired. The proposed approach offers a groundbreaking alternative to the standard approach of continuously deformable coregistration algorithms, introducing instead a hierarchical structure of related nodes (a "nodetree") to model the brain structure using grey-matter and white-matter masks. Additionally, a proposal is made for using the nodetree structure for coregistration, employing a novel locally discontinuous but focused registration to more accurately align and compare corresponding features. This approach can provide a framework for identifying structural differences, with a goal of relating them to functional differences. Although this method uses the brain as an example, it is quite general and not limited to the brain, or even to medical images.

1 INTRODUCTION

Current mainstream coregistration packages for medical images use variations of one of two basic approaches: a) whole-brain voxelwise or volumetric registration which minimizes a cost function summarizing the average difference between two 3D volumes (Woods et al, 1998), or b) registration of discrete points or features, with the transforms for nearby unmarked voxels determined by interpolation (Pelizzari et al., 1989). A feature common to both of these approaches is to treat the structure as a continuous 3-dimensional object, so that although voxels may get stretched or distorted, neighboring voxels remain neighbors. One result of this assumption is that missing or extra structures in either the target or object volume determines the ultimate accuracy of the procedure. To date, increases in accuracy have been achieved by using a larger number of parameters to improve local fits, but the fundamental assumption is that one structure can be smoothly morphed to become identical to another. In brain imaging, frequently there is not a 1-to-1 intersubject correspondence of structures, so

even if an algorithm is able to smoothly morph one object to achieve a good pixel-intensity match with another, the result is not always desirable (Fig. 1).

Current approaches to brain coregistration are limited to a large extent by the underlying similarity of the structures to be registered, in that there is no acknowledgment or allowance for missing or extra structures. For example, a common but difficult problem is to accurately register a brain containing a tumor to a standard brain template. A more subtle but also more ubiquitous problem is the fact that individual gyri and sulci vary considerably between individuals, both with respect to location and shape as well as for simple existence of particular gyri. Current coregistration approaches can reshape a gyrus with some success, but do not address the fact that a gyrus present in one individual may be missing in another. The sensitivity of a multi-subject functional activation study [e.g. functional Magnetic Resonance Imaging (fMRI) or Positron Emission Tomography (PET)] is directly related to the accuracy of combining and examining the same functional signal from a group of subjects, and anatomical variation is emerging as one of the
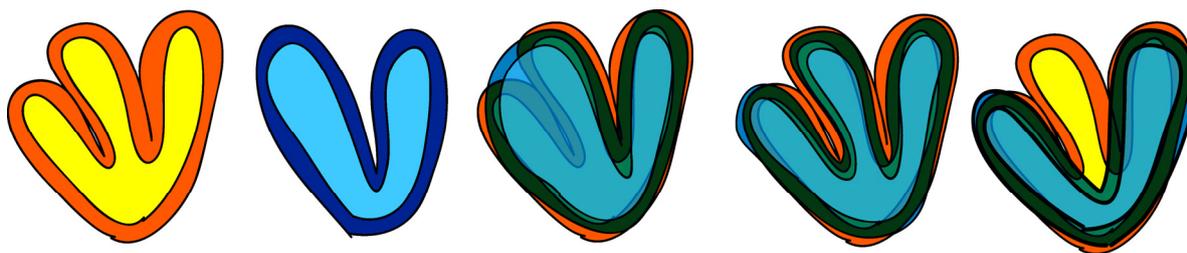
Figure 1: Cartoon showing two different cortical-like structures (1a, 1b) that cannot be meaningfully morphed to achieve a similar shape. Cartoons 1c, 1d demonstrate typical results expected from a continuously deformable coregistration model. 1c: a fit using fewer parameters might result in a single gyrus from the object image (blue) spanning two gyri in the target image (orange). 1d: a fit using a large number of parameters could deform the single gyrus to achieve an accurate pixel intensity match, but there may not be a physiological justification for splitting a single gyrus into two. 1e: an example of a more physiologically plausible scenario, where two gyri should match but there is an "extra" or unassigned gyrus. This result is quite difficult to obtain for current smoothly morphing algorithms.

limiting factors in functional comparisons (Juch et al., 2005). This paper seeks to establish a framework for applying established skeleton-based, hierarchical registration techniques to anatomical medical images, and subsequently to related functional data.

The nodetree method is based on a variant of the Medial Axis Transform (MAT), which seeks to define a skeleton representative of the major features of an image. The medial axis (MA) (Blum 1967) is described as the locus of the centers of all bi-tangent circles contained within a shape. Here, the term "MA" is used as shorthand for the MAT skeleton. A useful feature of the MA is that the skeletal pixels are connected, so shape features such as length are easily computed. Pixels in a MA skeleton can be ranked post-hoc according to how many branches radiate from them, so that node points can be easily identified. However, one of the lingering problems with the MA and related approaches is a lack of robustness (see e.g. Parker 1997). Small changes in the overall structure can lead to large changes in the final MA structure, which makes it difficult to apply this approach to a variety of situations. A number of variants have been proposed to address this shortcoming, such as a recent method using a Bayesian probabalistic approach to estimate a skeleton shape (Feldman & Singh, 2006), and which seems to be more robust to noise and minor perturbations. However, this and similar approaches have not yet been widely tested on medical images.

A major advance in the MA with respect to medical imaging was a generalization to 3 dimensions (Sherbrooke et al. 1996). Further refinements were added by Amenta and Kolluri (2001) to develop a 3D medial axis from a union of overlapping balls. In this case, the medial axis is not a series of lines, as in the 2D case, but rather a group of vertices that define a closed surface in space. Ranjan and Fournier (1996) proposed using a union of balls to describe a volume, and furthermore they developed a method to coregister two similar structures by finding the closest spatial match between corresponding pairs of balls.

One of the major benefits of a hierarchical skeletal model is that the various branches may be moved independently of one another. This concept underlies much of the computer animation field, where a skeletal model is wrapped with an outer surface so changes in the orientation and shape of the skeleton can be propagated to the surface structures (see e.g. Gagvani et al. 1998). This process has an innate hierarchy, since movements to one element of the skeleton (e.g. the forearm) lead to predictable changes in subservient elements (e.g. the hand).

The nodetree approach combines many of these aspects, including ideas from the MA, the union-of-balls, and the hierarchical skeleton. Unlike a MA, the nodetree does not need to include all pixels connecting the nodes. The goal is to produce a hierarchical skeleton to which volumetric data can be associated in a robust and logical manner. The nodetree is a collection of nodes with essential properties of location, spatial domain, and lineage. All other properties can be derived from these, including internode distance, object distance, and included pixels.

The novelty of the nodetree is in the integration of the MA and union-of-balls ideas to create a skeleton. The particularly innovative aspect is the subsequent coregistration approach it will enable which is not spatially continuous, but rather which recognizes that different structures (e.g. brains) may have different spatial structures performing the same function. Current alternatives which attempt to
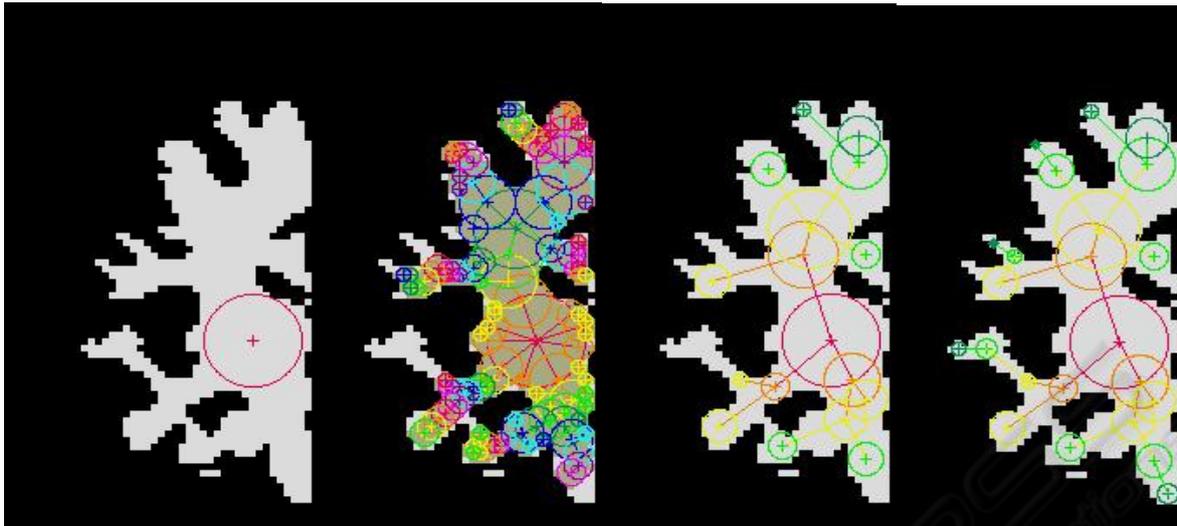
Figure 2: Creation of a nodetree in the left hemisphere of a coronal section. (2a): The initial node is created by filling the region near a seed point with the largest possible circle. (2b): Children nodes are added to each node until the structure is filled. The brown color shows pixels that are included inside a node. The color of each node indicates its rank or generation number, repeating in order over red, orange, yellow, light green, green, light blue, blue, purple, and magenta. (2c): The nodetree is pruned to remove small and/or redundant nodes, leaving behind only nodes needed to define the WM structure. (2d): Six additional nodes (green and dark green) have been added manually using a semiautomated GUI in order to define the structure more accurately.

match such disparate structures using a continuous model reduce the achievable accuracy of coregistrations and also reduce the sensitivity of related functional activation analysis. This paper seeks to develop a framework for addressing and facilitating the comparison of objects with topologies and/or morphologies which are not mutually deformable.

2 METHODS

2.1 Nodetree Properties

Construction of a nodetree for the brain starts with a binary image of the White Matter (WM) tissue, which can be readily obtained using standard neuroimaging software , e.g. BET (Smith 2002). The nodetree attempts to model the WM projections (gyri) to the cortical Gray Matter (GM) surface. To be useful as a medium for identifying specific cortical structures and for intersubject registration, there are several fundamental properties that each nodetree should have:

1) Each gyrus should be principally represented by one major node at the distal end (apex);
2) There should be a node at every gyral opening and branch point;

3) Lines connecting nodes must stay within the tissue type;
4) The size of each node should be relative to the volume of surrounding WM;
5) Node importance is directly related to node size;
6) Each node must have only one parent.

This semantic description will be used as the guiding principal behind the nodetree algorithms. Current standard skeletal approaches were unable to yield the desired characteristics, leading to the development of the current nodetree approach.

2.2 Nodetree Algorithm

A prototype software program has been developed to create and prune a 2D nodetree. Ultimately, a fully 3D implementation is desired, but the software and examples presented in this paper are for the 2D case, in order to simplify initial algorithm development and display of results.

The algorithm starts with a seed-point that all subjects can be expected to have, such as the center of the largest WM region. The largest possible circle is drawn within this region (Fig. 2a) and assigned a rank of 1. This circle defines a "node" whose properties include the location, radius, rank, and a unique identification number. In the second step, the edge pixels of this circle are used as seed-points for

a new set of circles or "child nodes". For each node, the goal is to create a family of children nodes centered on the parent's edge pixels, and to retain only children nodes which are large and do not overlap other sibling nodes. Proceeding from the largest child to the smallest, siblings within each child node are eliminated, leaving a few larger children surrounding the parent. The children nodes are assigned a parent node as an additional innate property, and several convenience properties, such as an "arm length" or distance to the parent node. This process proceeds iteratively until the entire object is filled with nodes (Fig. 2b). The full node-set can be saved for later use.

An important property of nodetree growth is that at each iteration, growth only occurs for nodes created in the previous iteration, and this growth is limited to previously unclaimed regions. We hypothesize that this will produce a natural growth pattern that is reproducible across similar branching structures. This property also helps to ensure that the initial full nodetree has a closed surface.

2.3 Nodetree Pruning

To emphasize its basic shape, the nodetree must be pruned so that only the important nodes remain. In principle, it is desirable for the nodetree algorithm to yield a description of the object which needs little post-processing; however in practice, some level of post-processing (pruning) is required to better emphasize the overall WM structure. Pruning is not a single step, but rather is a series of algorithms which can be varied *ad infinitum* to emphasize various characteristics of the underlying structure.

In the current MRI example, the goal is to represent the overall shape of the WM structures with the fewest number of nodes. It is not necessary (and unlikely) that all WM pixels be contained within a node after this step. An "important" node meets one of the following criteria: it is a) large and in the center of a WM space; b) at the end of a WM gyri; c) at a fulcrum (bend) in a gyral projection or d) at the mouth (opening) of the gyrus into a larger WM region. Specific parameters for each of these criteria can be varied for different effects; for instance, decreasing the minimal acceptable size for a terminal node [criteria b) above] can more accurately model the full extent of a WM gyrus, but perhaps at the expense of indicating the importance of the node terminus based on its size.

A series of automated pruning algorithms were developed to remove small nodes, similar neighboring nodes, and redundant nodes along a straight path (Fig. 2c). Some pruning steps may result in a node changing position and/or radius. Although the goal is for full automation, the nodetree can be adjusted manually to make sure that all arms are filled in and that the nodes are located properly (Fig. 2d). Either manual or automated adjustment of individual nodes is simple, due to the hierarchical compostion of the nodetree. After pruning, the arm-lengths are recalculated and ranks are re-assigned to minimize the number of ranks. A variety of algorithms were developed for the pruning stages, including functions such as: remove dead-end nodes; remove nodes below a specified size; consolidate long runs of nodes by removing nodes that have only a single child; consolidate ranks to remove gaps; remove nodes that are too close to their parents.

3 RESULTS

A nodetree was created for each of 7 normal subjects using a coronal slice of the left hemisphere from the same location after the image data were coregistered to the MNI T1 template (Evans et al., 1993) using registration software from SPM2 (http://www.fil.ion.ucl.ac.uk/spm/) and skull-stripped with BET (Smith 2002). Tissue segment maps were produced using FAST (Zhang et al., 2001). An 8th nodetree was created using the sum-image of the segment maps. Similarity of the nodetrees in Fig. 3 indicates the robustness of this technique across individuals. The differences help to highlight the variation in anatomic structure between individuals.

While there is clearly room for improvement, all of the nodetrees show similarities, and all are able to define the overall shape of the WM, including most of the larger arms.

The nodetree represents a significant data reduction technique. Figure 2a shows a typical 2D image of WM with 1018 WM pixels. The full nodetree (Fig. 2b) contains ~92% of the WM pixels yet is represented by only 126 nodes. The final pruned nodetree (Fig. 2d) contains only 21 nodes, but still captures the shape of the WM structure. This savings is expected to be proportionally even greater for 3D data using a nodetree comprised of spheres. Furthermore, since the pruned structure is represented by so few points, it is very efficient to manipulate the structure.
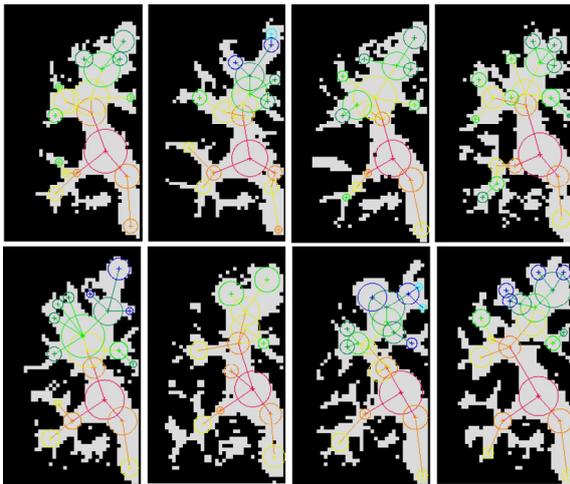
Figure 3: Comparison of nodetrees from 7 different subjects. The nodetree at the upper left was derived from the thresholded WM segment from a sum-image of the individual segment maps, and can be considered as a basis for comparison.

Although a nodetree can model a fairly complete representation of an object, it should be emphasized that the nodetree is not required to exist in isolation. For detailed analysis of a shape, the original object and its underlying data values may be interrogated as long as nodetree-related spatial transforms are recorded.

Figs. 2b-d illustrate a potential problem for the nodetree: one of the terminal gyri remains unfilled Fig. 2b-c) and has been manually filled in (Fig. 2d). This is a result of the minimal acceptable node size, which in this example is a 5-pixel cross-shape. Using a smaller node (single pixel) or permitting the search to proceed via diagonal pixels (i.e. pixels touching at only a corner) solves this problem, but must be balanced against the increased complexity of the nodetree shape. The non-minimal node size is used in Fig. 2 to highlight this tradeoff, in which a more complex initial nodetree would require additional pruning. In the current implementation, the pruning is insufficiently developed to yield robust results for a very complex nodetree.

Initial attempts to characterize the robustness of the nodetree indicate that it can be quite sensitive to noise in the binary WM representation. For example, a single non-WM pixel in the center of a large WM space will yield a number of small nodes surrounding the non-WM island, rather than the expected single large node. This is really more of a problem related to creation of the initial binary image, and isolated non-WM pixels can easily be removed by standard filtering techniques.

An additional observation is that, while the nodetree is not overly sensitive to minor changes in the edge of a structure, the position of nodes at the end of a gyrus can be sensitive to the width of the gyrus in relation to the minimal acceptable node size. Currently, a dedicated pruning step is needed to minimize this, but further investigation of the growth pattern with respect to this bias is needed.

In order to be useful for anatomical coregistration, a systematic identification of important nodes is required. For example, a template based on a large number of individuals could label those nodes which occur most frequently. Once a WM nodetree has been created, the gray matter cortex could be modeled as an additional layer, as represented in Fig.4.
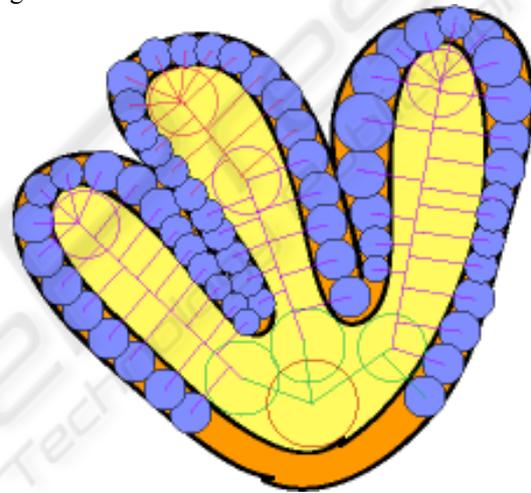

Figure 4: Cartoon showing a 2D scheme for arranging Gray Matter (GM) nodes within cortical GM and for associating them to the White Matter (WM) nodetree. The color of the line connecting each GM node indicates the line segment of the WM it belongs to. The GM nodes have a radius designed to span the cortex at each node's location. Although the GM nodes are depicted as disks in this cartoon, they could be irregularly shaped in order to cover all of the GM yet prevent overlap of node interiors.

4 CONCLUSION

The nodetree algorithm can yield a reasonably similar model of the brain white matter structure across individuals. Further advances, particularly with respect to pruning, are expected to yield improved similarity. The hierarchical structure is well suited as a framework for investigating non-continuous spatial registration approaches.

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