REVIEW ARTICLE

Prior Integrated Segmentation for Brain Structures: A Review

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ABSTRACT

Over the past few years, challenges remain in producing an accurate brain structures segmentation due to the imaging nature of Magnetic Resonance images, that is known to exhibit similar intensity characteristics among subcortical structures such as the hippocampus, amygdala and caudate nucleus. Lack of a distinct image attributes that separate adjacent structures often hinders the accuracy of the segmentation. Therefore, researches have been directed to infer prior knowledge about the possible shape and spatial location to promote accurate segmentation. Realizing the importance of prior information, this focused review aims to introduce brain structures segmentation from the perspective of how the prior information has been utilized in the segmentation methods. A critical analysis on the methodology of the brain segmentation approaches, its' advantages and issues pertaining to these methods has been discussed in detail. This review also provides an insight to the current happenings and future directions in brain structure segmentation.

Keywords: Image segmentation, Brain structures, Magnetic Resonance Imaging

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INTRODUCTION

The advancement in brain imaging modalities, namely brain Magnetic Resonance (MR) imaging has enabled the clinicians to have a closer view at the brain anatomy and its functionality in a non-invasive manner (51). Brain MR imaging potential has promoted early detection of abnormalities and tracking of disease progression. However, with its rapid growth, comes an enormous number of medical datasets that a clinician needs to analyse and delineate manually. This process is known to be intensive, laborious and time consuming, especially for delineating small subcortical brain structures such as the hippocampus, amygdala and caudate nucleus. Besides that, manual delineation is often associated with interrater and intrarater variability, which may lead to the issue of reliability in the delineated structures. Hence, the need for automated segmentation solutions arises as a precondition for accurate analysis of these structures.

Despite considerable breakthroughs thus far, effective segmentation of the brain structures is still known to be very challenging owing to its image characteristics. In brain MR images, most of the small subcortical brain structures are observed to exhibit very weak or unclear boundary definitions at some fragments of the boundary (44, 47). This happens due to almost similar intensity characteristic between adjacent structures. A poorly defined boundary usually leads to the ambiguity of the exact location representing the actual boundary, which is the major deterrent in achieving accurate segmentation.

Observation of conventional clinical practices shows that medical experts are often able to identify and delineate a target structure accurately based on the image information found explicitly from the medical image combined with the prior known information about a structure such as the size, shape and its' spatial location. The prior information usually is of assistance in cases of incomplete image information (34). Similar to manual expert delineation, a key step in developing a robust automated image segmentation is to enrich the segmentation process with prior information, especially the shape and spatial location of the target structure.

Hence, in this review, it is aimed to present the brain structures segmentation approaches that have utilized prior information. The focus of this article is to provide an insight into the nature of prior information been used and the various ways of incorporating the prior information in the segmentation. The remainder of this paper is organized as follows: Section 2 describes

various approaches of brain structures segmentation that employ prior information. Then, Section 3 summarizes these prior integrated segmentation approaches by highlighting their advantages and disadvantages. Finally, this paper provides a conclusion by discussing the challenges and potential directions for future research in brain structures segmentation.

BRAIN STRUCTURES SEGMENTATION

The literature on brain structure segmentation projects five main genres, based on how the prior information has been utilized. This prior information, covering mostly shape and spatial priors have been modelled and inferred in the segmentation. Generally, brain structure segmentation can be classified into manual or semi-automatic, fuzzy spatial relation-based, atlas-based, statistical shape model-based and machine learning-based. Table I summarizes these segmentation approaches, with the target brain structures that have been segmented.

Manual or Semi-automatic

Manual or semi-automatic segmentation approaches proceed from information provided by the user about landmark points of the brain structures. These landmark points can be in the form of mouse clicks either inside, or on the boundary of the target brain structure (24, 31, 45, 38). The landmark points may also be obtained using a set of predefined rules describing the approximate location of the target structure in relation to adjacent structures (39). Generally, these landmark points provide information about the approximate location, which is necessary for initializing a segmentation process.

A majority of the manual or semi-automatic segmentation approaches require users to manually indicate the landmark points within a region of interest. This is to create an initial contour for deformable models, including level set (24, 39, 45) and snake (38). Although, an approximate spatial location has been provided by the user for these deformable models, the contour deformation still might not evolve to the actual

Table I: Brain structures segmentation approaches

Approaches	Authors	Target Structure(s)
Manual/Semi-automatic	Shen et. al. (37)	Hippocampus
	Yushkevich et. al. (45)	Caudate nucleus, lateral ventricle
	Siadat et. al. (38)	Hippocampus
	Xiang and Shuqian (44)	Hippocampus
	Karsch et. al. (24)	Corpus callosum, lateral ventricle, hippocampus
Fuzzy Spatial Relation-based	Barra and Boire (4)	Thalamus, putamen, head of caudate nucleus
	Zhou and Rajapakse (49)	Thalamus, putamen, caudate nuclues, hippocampus, amygdala
	Colliot et. al. (15)	Ventricle, caudate nucleus, thalamus
	Atif et. al. (3)	Caudate nucleus
	Nempont (32)	Caudate nucleus
	Scherrer et. al. (35)	Gray matter, white matter, cerebrospinal fluid, putamen, caudate nucleus, thalamus
Atlas-based	Warfield et. al. (42)	Cortical gray matter, subcortical gray matter, cerebrospinal fluid, myelinated white matter, unmyelinated white matter
	Carmichael et. al. (10)	Hippocampus
	Heckemann et. al. (20)	Amygdala, lateral ventricle, hippocampus, thalamus, palllidum, corpus callosum, gyrus, orbitofrontal cortex
	Van der Lijn et. al. (29)	Hippocampus
	Ciofolo and Barillot (12)	Brain hemispheres, cerebellum, caudate nucleus, putamen, pallidum, thalamus
	Artaechevarria et. al. (2)	18 brain structures, including lateral ventricle, caudate nucleus, putamen, nucleus accumbens, pallidum, thalamus, amygdala, hippocampus
	Aljabar et. al. (1)	Lateral ventricle, caudate nucleus, putamen, nucleus accumbens, pallidum, thalamus, amygdala, hippocampus, brainstem
	Chupin et. al. (11)	Hippocampus, amygdala
	Wolz et. al. (43)	Thalamus, putamen, caudate nucleus, hippocampus, amygdala, nucleus accumbens
	Sabuncu et. al. (34)	White matter, cerebral cortex, lateral ventricle, hippocampus, thalamus, caudate nucleus, putamen, pallidum, amygdala
	Collins and Pruessner (14)	Hippocampus, caudate nucleus
	Coupe et. al. (18)	Lateral ventricle, hippocampus
	Lotjonen et. al. (30)	Hippocampus
	Bishop et. al. (5)	Hippocampus
	Cardoso et. al. (9)	Whole brain structures, including hippocampus, amygdala, caudate nucleus, nucleus accumbens, putamen, thalamus, pallidum
	Gao et. al. (19)	Hippocampus, caudate nucleus
	Kwak et. al. (26)	Hippocampus
	Wang et. al. (41)	Hippocampus
	Zarpalas et. al. (47)	Hippocampus
Statistical Shape Model-based	Tsai et. al. (39)	Ventricle, lenticular nucleus, caudate nucleus
	Tu et. al. (40)	Hippocampus, caudate nucleus, putamen, ventricle
	Patenaude et. al. (33)	Caudate nucleus, nucleus accumbens, pallidum, thalamus, amygdala, hippocampus, brain stem, putamen
	Hufnagel (22)	Putamen
	Gao et. al. (19)	Hippocampus, caudate nucleus
Machine Learning-based	Bao and Chung (53)	Thalamus, putamen, pallidum, hippocampus, amygdala, caudate
	Shakeri et. al. (37)	Thalamus, caudate, putamen, pallidum
	Mehta et. al. (32)	Thalamus, putamen, pallidum, hippocampus, amygdala, caudate, accumbens area
	Kaisar et. al. (50)	Thalamus, putamen, pallidum, hippocampus, amygdala, caudate, accumbens area
	Milletari et. al. (54)	Thalamus, putamen, pallidum, hippocampus, amygdala, caudate, accumbens area, brain stem, midbrain
	Ganaye et. al (55)	Cerebrospinal fluid
	Rajchl et. al. (56)	Cortical, subcortical structures

boundary of the target structure. This is because of the incomplete spatial information, which does not contain information on the expected region of interest that the structure may encompass within an image. A complete spatial information describing the possible range of the region of interest is important to stop the contour evolution at the most probable boundary. Besides that, the landmark points also do not exhibit in detail the respective structure's shape. Hence, with incomplete spatial and shape information, the deformable models often face problems in accurately segmenting the target structures.

It is safe to assume that the human intervention in manual or semi-automatic segmentation approaches is performed by highly skilled experts in human anatomy. This is to ensure precise landmark points initialization so that the expected segmentation results are satisfactory. However, despite this, expert user input may not be fully reliable as interobserver variability may exist where different experts may have different perceptions. This might result in different placements of landmark points even when segmenting the same structure, and this may lead to variation in the segmentation results.

Fuzzy Spatial Relation-based

Fuzzy spatial relation-based segmentation approaches rely on linguistic information provided by medical experts regarding brain structures relative spatial locations as a source of prior information (36, 33, 3, 15, 49, 4). Fuzzy set theory pioneered by Zadeh (46) has proven to be suitable to formalize linguistic knowledge into fuzzy set representation. Using fuzzy set theory, a set of linguistically defined spatial relations, that includes topological, directional and distance from a given reference structure are modelled as a fuzzy set individually and fused using fusion operators to define a final fuzzy map (7). This fuzzy map is a probabilistic map where each voxel is assigned with a probability value in the range of 0 to 1. Voxels in the fuzzy map with values approaching 1 represent a high degree of satisfaction to a predefined set of spatial relations. Thus, the obtained fuzzy map provides a spatial information indicating that voxels with higher probability as belonging to a target structure.

Barra and Boire (4) was among the earliest to use fuzzy spatial relation-based approach by first segmenting the target brain MR image into gray matter, white matter and cerebrospinal fluid tissues using a possibilistic clustering method. The output of the clustering is a fuzzy map that denotes the membership of a voxel belonging to the respective tissues. Then, a set of spatial relations of a target structure in reference to the ventricular system are modeled as fuzzy maps. All the available fuzzy maps are then fused using logical operators to produce a final fuzzy map. Finally, segmentation of a target structure is performed by thresholding of voxels with membership values greater than 0.8. Several extended works have adapted the resulting fuzzy map to provide initialization for level set (33, 3) and snake (15). Besides that, the fuzzy map also has been incorporated as an external force in these methods to constrain the contour deformation to be within the voxels with high probability values.

However, it should be noted that a spatial relation needs to be defined starting from a reference structure, which in most cases is the ventricular system. Therefore, it is the reference structure that needs to be accurately presegmented beforehand to enable subsequent segmentation of the target structure. Furthermore, segmentation of small brain structures, such as the hippocampus and amygdala usually require an extensive set of spatial relation definitions, which include not only ventricular system as the reference structure, but also other related brain structures. Thus, this may involve multilevel or hierarchical presegmentation of all the related brain structures so that a set of fuzzy maps, when fused together, will contain accurate representation of the target structure's spatial information (36, 33). Generally, it is observed that the obtained fuzzy map using a single spatial relation with the ventricular system as reference is only able to provide a very rough approximate of the spatial information (15). Whereas, the fuzzy map using a set of spatial relations between few reference structures is able to produce a more compact spatial information, and yet lack with accurate shape information (6). Thus, with the presegmentation issue of multiple structures which is often hard to be achieved, the fuzzy spatial relation-based approaches are seen to receive less explorations to segment brain structures.

Atlas-based

As an effort to enrich prior information with more accurate spatial and shape information, a fully automatic segmentation was introduced through atlas-based approaches. These atlas-based approaches exploit expert knowledge encoded in the form of a single or multiple training data as the source to infer prior information. Each training data comprises of a training image, and it's corresponding preannotated labelled binary image, with voxels being labelled as 1 for belonging to target structure and 0 for background. In the literature, the training image and its labelled binary image are also interchangeably referred to as atlas image, and it's labelled atlas image, respectively (8, 23).

For the scope of this review, the term training image and labelled training image will be used to refer to the source of prior information herein. As illustrated in Fig. 1, atlas-based segmentation involves three major stages: (i) Image registration. (ii) Label propagation. (iii) Label fusion.

In the image registration stage, volumetric registration procedure is utilized to maximize the degree of agreement between training images and the target image

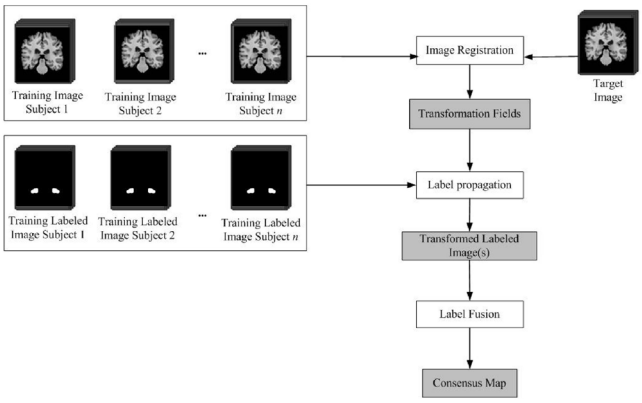

Figure 1: Overview of atlas-based segmentation approach

with an intention to find reliable correspondences between the training and the target images (13). This registration procedure ensures that the training images are translation, rotation and scale invariant with respect to the target image. The resulting correspondences from the registration stage is also known as displacement or transform fields. In the label propagation step, the displacement fields are applied to the respective labelled training images to extrapolate the labelled training images to the coordinate space of the target image. Then, an additional stage of label fusion is carried out if multiple training data are used in the image registration and label propagation steps. The label fusion step assembles the multiple transformed labelled training images into a final consensus map, which can be in the form of a topological or probabilistic map (8). The topological map characterizes voxels of value 1 as belonging to the target structure, whereas probabilistic map defines the probability of a voxel of belonging to the target structure.

Atlas-based Segmentation Approaches

Atlas-based segmentation has attracted substantial research interest, with enormous amounts of literature pertaining to brain structures segmentation. Generally, each atlas-based segmentation approaches differ from another either in the type of registration being employed, in the selection of suitable number of training data for label fusion, or in the type of label fusion approach (27).

Type of registration

Normally, the image registration stage involves a single step of rigid or affine registration for finding the correspondences between pairs of training and target images (18, 10). Rigid and affine registration is only able to align the training image to target image with respect to global brain structure characteristics, such as size and coordinate space of target image. Therefore, an additional non-rigid registration is often performed to improve the registration. This twostep registration process is to ensure correspondence at substructures level in the brain (42, 14, 35, 1, 2, 20).

Selection of training data

Early efforts use a single training data that is randomly selected in image registration and label propagation stages (12, 10). The use of a single training data is most likely to face issues of registration errors if there is dissimilarity in inherent intensity and structural variability between the training and target images. Hence, efforts have actively concentrated on using multiple training data in a multi atlas-based segmentation approach. This has been proven to produce better accuracy with reduced error than the single atlas-based segmentation (42, 18, 14, 35, 1). Multi-atlas segmentation uses a set of training data in the registration and label propagation stages and applies a label fusion method to produce the final segmentation. However, not all the training data are highly similar to the target image. Therefore, instead of using all the training data, Coupe at. al. (18) and Collins et. al. (14) adapted global image intensity similarity metrics such as normalized cross correlation and normalized mutual information as a selection criterion to choose only n highly similar training data for the label propagation and label fusion stages. The image intensity similarity metric may be obtained from the image registration stage. If the chosen n is sufficiently large and possibly resembles the target structure, then the final consensus map from the segmentation maybe able to generalize the target structure accurately.

Type of label fusion

Segmentation of a target structure is obtained at the label fusion stage, which is performed by assembling the transformed labelled images using majority voting, weighted fusion or statistical fusion. Majority voting label fusion assumes all or a selected subset of n labelled training images have equal weights. It assigns each voxel a label that most of the labelled training images agree on (14, 20). Instead of using all or a subset of labelled training images in majority voting, another way to improve multi-atlas segmentation accuracy is through the weighted fusion. Weighted fusion may be performed either globally or locally (8). In global fusion, each labelled training image is assigned with a weight that specifies its contribution in the label fusion stage (1). This weight is usually derived from a similarity measurement obtained from the image registration stage. It assumes that globally similar atlas image and target image have high relevance in anatomical similarity. A locally weighted fusion scheme uses voxel wise intensity similarity between training image and target image to determine the weight for every voxel in the labelled training image (42, 18, 35, 2). Locally weighted fusion regards voxels with similar intensity characteristics to also have similar label. The locally weighted fusion has been widely applied in recent years for brain segmentation and has shown to be the best atlas-based segmentation thus far.

Another variation of segmenting a target brain structure

was implemented through statistical fusion, which finds probabilistic estimates of segmentation using statistical models. The STAPLE (for Simultaneous Truth and Performance Level Estimation) algorithm proposed by Warfield et.al. (43) is a type of statistical fusion method for atlas-based brain segmentation. This algorithm simultaneously estimates the segmentation, and the performance level (weight) of each labelled training image contributing to the segmentation using a Bayesian probabilistic framework, optimized with Expectation-Maximization (EM). The EM algorithm iteratively estimates the segmentation (E-step), and the weights defining the contribution of each labelled training images (M-step) until convergence to a local maximum. As an extension to STAPLE, Cardoso et. al. (9) have proposed an integration of local intensity similarity in EM algorithm to segment hippocampus.

Extension to Atlas-based Segmentation Approaches

Instead of solely using atlas-based approaches in computing the final segmentation, it has also been used in combination with supporting methods to obtain the final segmentation. Examples of these supporting methods are level set and classification. This second-level segmentation on top of the atlas-based segmentation mainly focuses on fine-tuning the results from atlas-based segmentation. The second level segmentation methods use image features. Thus, this fine-tuning is necessary to make the segmentation more robust, by making the final segmentation to not only depend upon the training dataset as in atlas-based segmentation, but also the target image characteristics. Usually, the resulting probabilistic map from atlas-based segmentation provides spatial information specifying an approximate spatial location of a target structure. Such spatial information has been used to initialize level set contour evolution (47, 19, 5). Besides initialization, Zarpalas et. al. (47) and Bishop et. al. (5) have included the probabilistic map in the formulation of the level set energy function, in addition to the image-based energies such as edge gradient and intensity. This inclusion of prior information controls the level set evolution from leaking into other irrelevant neighbouring structures. Besides level set, atlas-based segmentation has also been used to provide prior information, which is formulated as an energy function for graph cut (26, 44, 29), Expectation Maximization (30), and Iterated Conditional Modes (11) classification methods to favour voxels having high probability of belonging to the target structure.

Statistical Shape Model-based

The earlier section presented multiple segmentation approach in which atlas-based segmentation is followed by a second segmentation process as a postprocessing to improve segmentation accuracy. This section introduces another type of segmentation approach that first constructs a prior model from training dataset and then feeds it into a segmentation method. This approach known as Statistical Shape Model (SSM)-based segmentation, is also an automated approach that utilizes training dataset as a source of prior information. However, unlike atlas-based approaches that only produce and use a single by-product in the form of topological or probabilistic map, SSM-based segmentation produces and uses a set of expected anatomical variations that may be present within a given population. Typically, this set of anatomical variations is modelled through Statistical Shape Model. The SSM-based segmentation is a two phases segmentation approach. The overall framework of Statistical Shape Model-based segmentation is illustrated in Fig. 2. It consists of two main phases: (i) SSM construction, and (ii) Segmentation. The discussion on these two phases are detailed in the following sections.

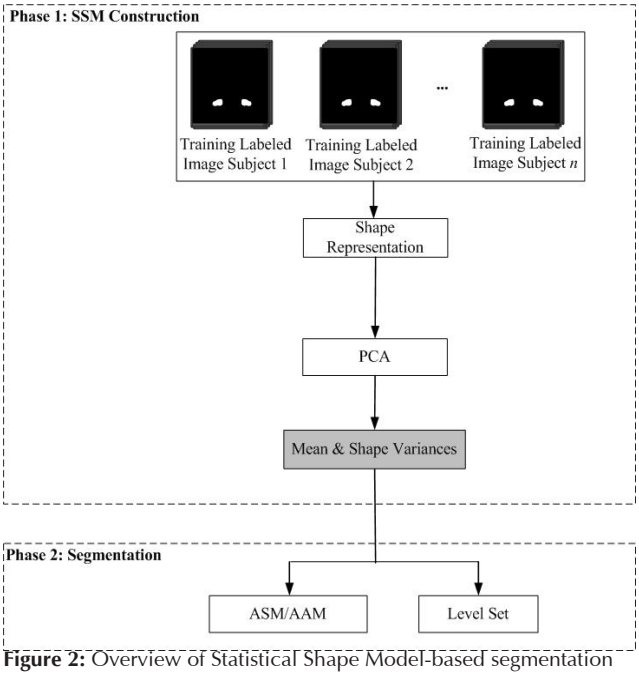

Figure 2: Overview of Statistical Shape Model-based segmentation

Phase 1: SSM Construction

During SSM construction, a preliminary stage of labelled training images parametrization into shape representation, either in the form of points, medial models, spherical harmonics or signed distance maps is involved (21). From these shape representations, a mean/approximate shape and plausible shape variations within the given training dataset are learned using Principal Component Analysis (PCA). In the case of brain structure segmentation, labelled training images have been widely parametrized either as (i) an implicit model of Signed Distance Map (SDM) (28), or (ii) an explicit model of Point Distribution Model (PDM) (17). The following sections discuss these two shape representations, respectively.

Signed distance map

In order to compute the signed distance map shape representation, firstly labelled training images are aligned into a common reference space to remove any variations due to rotations, translations or scaling. This step is

followed by the parametrization of labelled training images into Signed Distance Maps. Then, the mean of SDM is obtained by taking the average of N training SDMs, (S1, S2, …, SN), with mean, $\mu = \frac{1}{N}\sum_{i=1}^{N} S_i$.

This is followed by Principal Component Analysis (PCA) using the mean of SDM to compute modes of shape variations (principal components) within a given training population (28). An estimation of a shape is achieved by taking *k* number of principal components, that describes the most *k* variances of shape in the training population.

Point distribution model

In contrast to signed distance map, which is a volumetric-based parametrization approach, point distribution model shape representation only uses a set of representative points, distributed on the surface of the structure. In this firstly, parametrization of labelled training image into point distribution model is performed using triangulation or surface meshing techniques. A set of these points for a training image, which is referred to as training point set, describes the shape of a structure. Each point in the point set is defined by point coordinates in vector form. Then, in an alignment stage, the N training point sets are aligned to a common reference space to eliminate pose variations between shapes. Then, the aligned training point sets are utilized to compute the SSM (17). In order to construct the SSM, importance must be given beforehand to find the exact correspondence between training point sets. An initiation towards SSM construction was carried out by manually comparing one-to-one correspondences between point sets (17). In this approach, coordinates of corresponding points are manually identified by the user and sorted such that the i-th coordinate in the training point set T_N corresponds to i-th coordinate in the training point set T_N. Then, the mean shape is computed by taking the average of the coordinates of N sorted training point sets given by

$$\bar{x} = \frac{1}{N}\sum_{i=1}^{N} T_i, \quad (1)$$

where $\bar{x}$ being the mean shape vector. Then, similar to signed distance map shape representation, PCA is used to calculate the shape variances.

There is one fundamental issue with manual one-to-one correspondence, in which two corresponding landmarks must be precise and refer to identical anatomical locations. Although, finding this correspondence in 2D images manually is achievable, in 3D images, it is very impractical, time consuming and operator subjective procedure, specifically for small brain structures such as the hippocampus and amygdala (21). Therefore, instead of manually assigning a one-to-one correspondence between points on labelled training images, Patenaude et. al. (34) proposed an automatic method of finding the correspondence points. In their work, a population of labelled training images are parametrized as surface meshes by fitting an initial 3D mesh towards the labelled training images. The fitting of an initial 3D mesh, which is chosen to be the most common shape in the labelled training images is performed using a deformation process as in the snake method (25), and closely monitored to make the deformation to lay on the surface of the labelled training images. One main issue here is that the deformation of the initial 3D mesh to labelled training images must maintain consistency between corresponding points across all the labelled training images, so that structured corresponding points are produced. As a solution to this issue, user intervention is still needed to select the common initial 3D mesh and making sure the corresponding points are structured similarly on all the labelled training images.

Foreseeing that automatic one-to-one correspondence between points still requires user intervention, a fully automatic correspondence assignment between points was then proposed using point set registration method. Point set registration method is a local registration process that utilizes only representative points on the surface of a structure and does not require exact one-to-one correspondence assignment beforehand. Originating from the problem of aligning a reference point set to another point set using either rigid, affine or non-rigid transformation, this point set registration is adapted simultaneously to align multiple point sets and construct SSM within an optimization framework. Hufnagel (22) initiated the utilization of point set registration to compute SSM for segmentation. The construction of SSM is preceded by parametrization of labelled training images to training point sets. The parametrization process includes all the voxels on the object surface as the points. Then, a chosen point set from a set of training point sets is assigned as a reference point set. This is followed by pairwise Expectation-Maximization-Iterative Closest Point (EM-ICP) registration between the reference point set and every other training point set. From the EM-ICP registration, the transformation fields from a reference point set to every training point set is computed. In addition, the EM-ICP also calculates correspondence probability between two points from the reference and training point sets. Finally, the correspondence probability is used to compute the mean shape within an optimization framework. Finally, the shape variations are built by performing PCA on the transformations from reference point set to every other training point set and obtaining the eigen-decomposition of the transformation. These eigen-decompositions are then used to compute the shape variations.

Phase 2: Segmentation

The SSM constructed in the first phase is used to guide the segmentation process. Segmentation phase generally involves Active Shape Model and level set methods. Mainly, SSM is formulated as shape prior into these segmentation methods to constrain the segmented results to be within the range of shape variances, defined by the SSM. The following sections describes these label

segmentation methods.

Active shape model

The Active Shape Model (ASM) pioneered by Cootes et. al. (16), is a parametric segmentation method that extends the snake method. ASM incorporates SSM in the form of a point distribution model. SSM is used as a shape prior term in ASM. In addition to the shape information, incorporation of intensity variations in ASM has been introduced through Active Appearance Model (AAM) (16). Similar to shape variations modelling using PCA, AAM also uses PCA to model the mean intensity and intensity variations from a set of training data. Sampling of intensity values from the training dataset is performed at pixel locations along the outer and inner normal direction of each point in the point set. Then, the sample intensity values are used by PCA to model the intensity variations. An application of AAM in brain structure segmentation was proposed by Patenaude et. al. (34), where AAM is formulated in a Bayesian framework. This segmentation approach, termed as Bayesian Appearance Model performs segmentation by maximizing the probability of a shape, given the learned image intensities variations through the conjugate gradient descent scheme. However, one important point to note from all the ASM and AAM is that, the shape representation in PDM does not allow topological changes during segmentation. Hence, the initialization of these models is required to be similar in shape as the target structure and as close as possible to the target structure. This has been one of the major bottlenecks in parametric segmentation methods.

Level set

Compared to ASM and AAM, level set method as a non-parametric method based on implicit representation has shown superiority by allowing topological changes during deformation. A group of researchers (19, 41, 40) demonstrated the use of SSM in the form of signed distance map into the level set method. The SSM utilized as the shape prior, is formulated as an internal energy that controls the deformation of evolving level set contour to be within the range of shape variances defined by SSM. It is often mentioned that shape representation in signed distance map does not form a linear space (22). Hence, the averaging operation of finding the mean shape may not maintain signed distance map characteristics and thus may also lead to inaccurate shape variations. Besides that, the use of signed distance map may not generalize accurately a target structure that differs in shape and size from a set of training structures. In cases of varying local shapes such as brain subcortical structures which are subjected to local anatomical variability across population, the simple averaging operation may only able to provide approximate shape information, and not the actual shape information corresponding to the target structure (19, 41).

As an alternative to using signed distance map in level set, Hufnagel (22) formulated shape prior in the form of point distribution model as shape energy into the level set. Initialization of the level set contour is performed using the mean shape in the form of point distribution model and fitting it to a target data. Fitting the mean shape is carried out using an evolutionary algorithm that finds the best fit mean shape on the target data. This is done by iteratively selecting the best shape from a population of shapes, with the highest fitness of belonging to a target structure boundary defined by edge gradients. Using the best fit mean shape as initialization, level set evolution progresses to find the target structure by maximizing the separation of a structure from the background using regional statistics, while conforming to the shape prior defined by the best fit mean shape. During every contour evolution, the current mean shape is updated by using pairwise EM-ICP registration between the previously obtained mean shape and zero level set of current moving contour. This contour evolution process continues until a convergence criterion (i.e. number of iterations) is met.

Machine Learning-based

Recently, exploration of machine learning-based methods for brain structures segmentation have been actively explored (32, 37, 48, 50, 52). Reported successes of these machine learning-based approaches, especially with the emerging deep learning methods have opened a new horizon for brain structures segmentation (52). The deep learning methods is at advantages compared to the conventional machine learning methods in term of the feature learning process. In conventional machine learning methods, feature learning is supervised in which features are carefully defined and selected by the experts. Whereas, deep learning methods uses unsupervised self-taught learning approach.

Deep learning method is a large artificial neural network, which are inspired by the neuronal structure and functionality of the brain. A deep learning method known as Convolutional Neural Network (CNN) has been actively experimented with brain images. Fig. 3 illustrates the schematic diagram of the CNN architecture for MR brain segmentation. CNN consists of multiple processing layers includes Convolutional layers, Subsampling layers and Fully-Connected layers. The choice of input in the architecture includes 2D patches or 3D volumes extracted from MR images as the input for CNN and the model is trained on these extracted patches and given class labels to correctly classify into its regions such as segmentation of anatomical brain structures (52, 53, 54, 55, 56).

Convolutional layer is used to detect local features at different positions in an input test image by creating convolutional kernels which convolved with the input image with a square filter to produce a feature map.

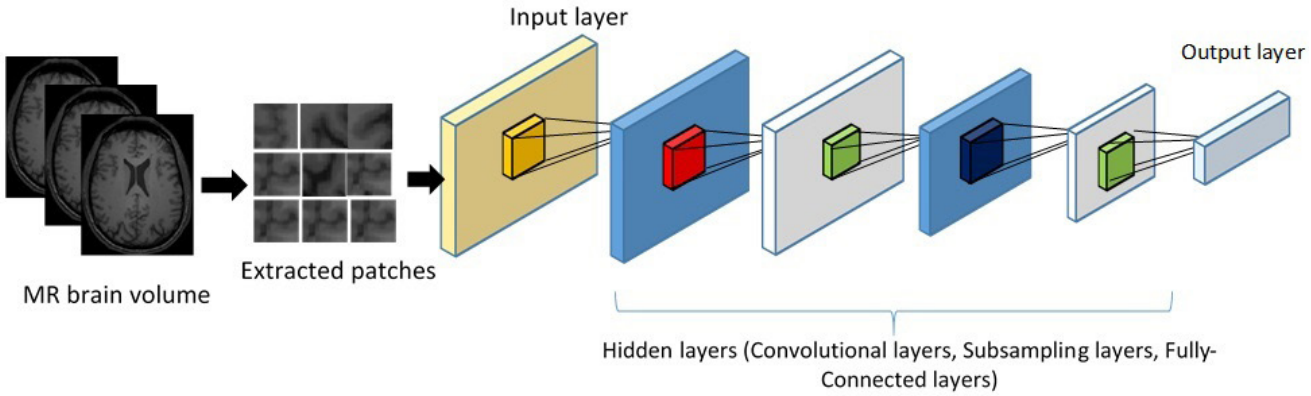

Figure 3: Schematic diagram of the CNN architecture for MR brain segmentation. Image source from https://brain-development.org/ixi-dataset/

Convolutional layer acts as a feature extractor to extract features from the input images. Each of the convolutional layer is followed by a leaky Rectified Nonlinearity Unit (ReLU) as the activation function where the computed weights sum is passed through this non-linearity function.

In subsampling layer, the use of maximum, minimum or average pooling operation were used aiming to reduce the size of the feature maps by selecting the most responsive neuron from the pooling window. In fully-connected layers, also known as Dense layers is used to combine the outputs of the into a 1D feature vector for final classification.

SUMMARY OF BRAIN STRUCTURES SEGMENTATION

All the brain structures segmentation approaches are compared in detail based on their advantages and disadvantages and have been summarized in Table II. From the material presented in this article, it maybe concluded that manual or semi-automatic segmentation approaches are only able to provide spatial information, which approximates the expected location of a target structure. Likewise, fuzzy spatial relation-based segmentation is also able to provide spatial information. But, the fuzzy spatial relation-based segmentation has a better prior model that also exhibits approximate shape information. However, due to high user intervention in the process of constructing the prior information, these two segmentation approaches have not gained much interest over past few years.

Atlas-based segmentation has successfully dominated most of the medical image segmentation for several years. However, their success in segmenting structures with relatively clear boundaries such as abdominal structures and major brain structures: gray matter and white matter may not be fully extended to small

Table II: Key advantages and disadvantages of various type of brain structures segmentation approaches

Approaches	Advantages	Disadvantages
Manual/Semi-automatic	Simplest and fastest form of integrating prior information.	Accuracy of segmentation subjected to inter-observer variability. Extensive user intervention Lack of shape information.
Fuzzy Spatial Relation-based	Able to model experts' linguistic knowledge into fuzzy models.	Extensive set of spatial relations rules for segmenting a target structure. Requires multi-level or hierarchical segmentation of many reference structures beforehand for accurate prior information definition. Incomplete shape information, without preserving local shape details.
Atlas-based	An automatic segmentation approach, without any user intervention. Provides accurate prior information.	Computationally intensive due to volumetric-based segmentation.
SSM-based using Signed Distance Map	Contains spatial information.	May not be able to generalize accurately a target structure that differs in shape and size from the training population.
SSM-based using Point Distribution Model	Exhibits detail shape information.	Does not inherit spatial information. Computationally known to be less intensive. Representation of shape in PDM does not allow topological changes in ASM and AAM methods.
Convolutional Neural Network	High capacity in dealing with the large dataset. Automatic self-taught segmentation approach. Provide accurate prior information.	High computational complexity due to intensive training phase. Exhibits class imbalance if training dataset is not representative enough.

subcortical structures in the brain. Subcortical structures for example hippocampus with challenging boundary definition often face the issues of oversegmented and undersegmented voxels due to use of general label fusion approaches namely, majority voting and globally weighted fusion (2). A more thorough fusion for producing accurate segmentation is performed by examining voxelwise similarity functions using locally weighted fusion. However, this volumetric label fusion approach only adds to the computational burden.

Statistical shape model-based segmentation using PDM representation has produced some success in segmentation, with less computational burden due to the use of only a set of representative boundary points. However, these methods are still computationally complex because of the use of optimization framework to construct of SSM. Another issue is, the prior model represented through SSM mostly contains shape information and does not inherit the spatial information. This is because the construction of SSM in PDM representation is often performed in a chosen training data coordinate space, and not on the real target data coordinate space. As a solution, an approach of approximating the spatial location of the target structure using the mean shape has been performed using evolutionary algorithm (22) as a postprocessing method.

Convolutional Neural Networks has been proven successful in various medical image segmentation in very recent years with its high capacity in dealing with the large dataset and ability to automatically learn with self-extracted features (53, 54, 56). However, CNN involved high computational complexity due to the intensive training phase. Besides that, a large representative dataset for all type of anatomical structures is required to prevent class imbalance issue.

CONCLUSION

In this paper, a range of segmentation approaches integrating prior information for assisting brain structures segmentation have been presented. The preceding sections have detailed the trends in capturing the prior information and ways of integrating it into respective segmentation approaches. From the review, it may seen that it is very important to integrate prior information into segmentation to achieve accurate brain structures segmentation (27, 23, 53, 54).

However, review on most of the prior integrated segmentation approaches shows that the source of prior information comes from description based on healthy normal subjects. Not much assumptions about abnormal brain structures have been taken into considerations when applying the prior information to patient subjects. Hence, detailed attentions must be given when using prior information in subjects with brain abnormalities. Population specific prior information is another aspect for consideration in the segmentation process.

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