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Methodological Review

Symmetry and asymmetry analysis and its implications to computer-aided diagnosis: A review of the literature

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ABSTRACT

Although clinicians have long sought to integrate computer-aided diagnostic (CAD) systems into routine clinical practice, it has proven to be extremely difficult to perform fully automated algorithmic analyses on lesions, based solely on the information contained in images. To increase the utility of computerized tools, it would be intuitive to incorporate anatomical and pathological knowledge and heuristics to help the system draw diagnostic inferences. In neuro-imaging applications, for example, one way to perform this knowledge integration is to uncover symmetry/asymmetry information from the corresponding regions of the head and to explore its implication to positive clinical findings. To correctly quantify asymmetric patterns in brain images, however, the symmetry axis, or the symmetry plane, needs to be appropriately oriented in space; i.e., the symmetry plane needs to be correctly identified either manually or using computerized methods. This review will provide an overview of the current state of knowledge of both symmetry axis/plane detection, and asymmetry quantification in neuro-images.

1. Introduction

The advances in computer technologies, over the last decade or so, are catalyzing the development of modern computerized schemes for lesion detection in radiological images. One major challenge, however, is that computers generally lack sufficient perceptibility and intelligence in terms of discovering pathological patterns, which hinders the decision making process. Since it is known that anatomical knowledge plays an indispensable role in computer vision and artificial intelligence [1–3], integrating anatomical knowledge into the computer system holds great promise for facilitating decision making and improving patient care.

Based on the assumption that the brain exhibits a high level of bi-fold symmetry (Fig. 1) and that this symmetry is violated in the presence of pathological conditions, many researchers have been motivated to construct a symmetry-based paradigm for automatic localization and segmentation of brain lesions. The framework of this methodology is based on the hypothesis that the systematic correlation between asymmetry and pathologies can be a key to the improvement of existing detection algorithms. Integrating symmetry and asymmetry information as the prior knowledge or heuristics into a computer-aided diagnostic (CAD) [4–6] system, ought to enhance the system performance in the analysis of brain pathologies.

To correctly quantify asymmetric patterns in brain images, however, the symmetry axis, or the symmetry plane, needs to be appropriately oriented in space. This enables the system to correct the possible misalignment of radiological scans, and to evaluate hemisphere-wise asymmetry.

Therefore, this review paper has two main focuses. In the first part, the existing state-of-the-art methodologies for identifying the symmetry axis/plane of a given set of brain images will be investigated. In the second part, the discriminating capacity of symmetry/asymmetry in the context of extracting pathological findings in various radiological applications will be explored. In other words, to achieve the goal of using asymmetry as a pathologic index to assist CAD, we need to first solve an image registration problem, followed by a pattern recognition and segmentation problem. With respect to research significance and clinical significance, the ideas discussed in this paper, for a set of particular neuro-applications, might have much more general applicability for CAD in many other highly symmetrical parts of the human body, including the breasts and the limbs; more details can be found in Section 6.

2. Background

2.1. Computer-aided diagnostic system

Subjective, empirical assessment of medical images is generally performed manually by radiologists, which is a time consuming and tedious task. The outcome is usually operator-dependent. In the era of radiologists hanging and reading films on the alternators, the inspection of the scans was prone to errors owing to visual

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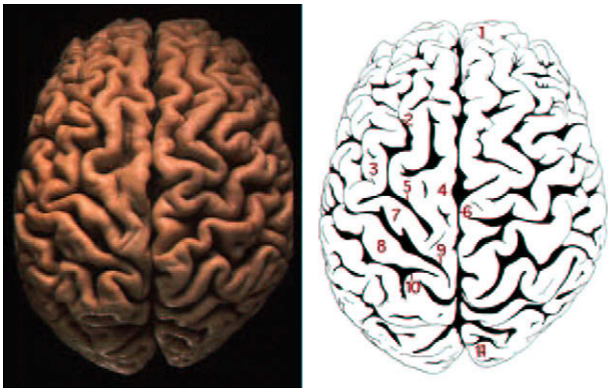

Fig. 1. The brain torque demonstrates that the brain is largely symmetrical, but not perfectly symmetrical: The right frontal lobe (1) is larger than the left one, and the left occipital lobe is larger than the right one (11). This illustration is adapted from [7].

exhaustion after long hours of reading, or to limited experience of the radiologists.

Digital imaging has revolutionized the field of medical imaging and has led to the development of sophisticated computer hardware technologies (e.g., data storage, transmission [8] and display [9]), and specialized software (e.g., registration tools [10] and expert systems [11,12]) that empower physicians to better distinguish abnormalities, characterize findings, supervise interventions, and predict prognosis. The advances in the hardware, in particular, over the last decade or so, are catalyzing the development of modern computerized schemes for lesion detections in radiological images. These techniques and methods, collectively called computer-aided diagnosis (CAD), are bringing about a new era in which computers are assisting a wide spectrum of applications in medical domains. In fact, CAD has become one of the major research subjects in medical imaging and diagnostic radiology [4].

With respect to software, although clinicians have long sought to integrate CAD systems into routine clinical practice, a readily usable software system that can efficiently characterize lesions is still a rarity even in major research hospitals. It has seemed to be extremely difficult to perform an algorithmic image analysis on lesions, given the limitations of available intelligence systems. To empower the computerized systems, it would seem intuitive to incorporate knowledge and heuristics of disciplines such as anatomy and pathology, to help the system draw diagnostic inferences. One strategy for development of techniques for lesion detection is based on understanding the process of radiologists assessing images—such as how radiologists can discover lesions, why they may miss some abnormalities, and how they can distinguish between benign and malignant lesions [13].

2.2. Brain abnormality detection

Brain images of a variety of modalities can disclose anatomical (MR, CT), functional (PET, SPECT), or physiological (CTP, MRP) information that is crucial to the diagnosis and treatment of patients (Fig. 2). Automated detection and segmentation of brain abnormalities spans several decades of research, and still remains a challenging problem. To facilitate fully automated segmentation, it is known that image information alone is insufficient [14] to successfully differentiate between target organs, abnormal tissue, and the background. For example, statistical classification methods may fail when a brain lesion shows insufficient contrast against its background, or presents highly inhomogeneous patterns.

On the other hand, in medical images of most state-of-the-art modalities, absolute values only provide a reference in terms of

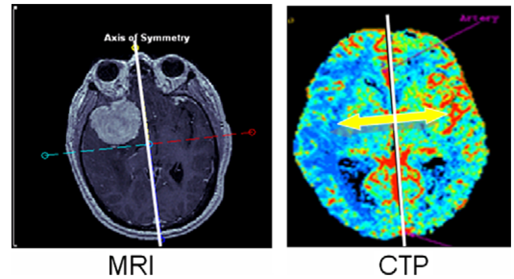

Fig. 2. Asymmetries exhibited in tilted image modalities such as magnetic resonance image (MRI) and CT perfusion images (CTP). When a clinician looks at those images, he or she consciously or subconsciously (1) identifies the symmetry axis/plane (2) compares the abnormality with the healthy side of the brain.

dissecting pathologies. The inter-individual and inter-equipment variations, even under controlled settings, are often so high that it is impossible to directly draw inferences upon the absolute values. Finding statistically significant *relative* values may provide more insights for detecting and quantifying brain abnormalities in computerized analysis.

One way to examine the relative values, particularly in brain images, is to uncover symmetry/asymmetry information from the corresponding regions of the head, and to explore its implications with respect to positive clinical findings (see Fig. 2). The hope is that, with the integration of this information into classification algorithms, a more knowledge-driven and potentially successful diagnostic interpreter can be created.

2.3. Neuro-images: misalignment in clinical settings

A common phenomenon in radiological scanning is that many neuro-imaging devices produce disoriented brain images; the scanned brain images are somewhat tilted and distorted [15]. Tilt and distortion can mislead visual inspection, and often yield false clinical interpretation, since slices of the brain images are no longer representing homologous structures within the same coronal or axial level [7]. The tilt of the head is often observed in the device during the scanning process, however, is not always tractable. Common reasons include, but are not limited to, immobility of patients, inexperience of the technicians, and imprecision of calibration systems [16].

Correcting the tilt of the head is equivalent to realigning the mid-sagittal plane (MSP) with the center of the image lattice. The MSP is defined as the plane that best separates the brain into two halves [7]. It is evident that the re-adjustment of the MSP from the geometrical misrepresentation yields more sensible data assessment either by a human expert or a computer program that is based upon hemisphere-wise cross referencing.

2.4. Symmetry and its clinical implications

Morphologically speaking, a normal human head exhibits a high level of bilateral symmetry, although it is not perfectly symmetrical [17]. Corresponding regions of two hemispheres have approximately identical anatomical properties, and also have comparable, if not identical, physiologic (e.g., blood perfusion) properties. The degree of asymmetry has long been thought to be helpful for suggesting a pathological condition and/or providing a diagnostic cue for clinicians. For example, abnormal asymmetry in the brain indicates a wide range of pathologies, such as stroke, bleeding and tumor. Radiologists routinely use symmetry/asymmetry as one of the most discriminating features, in conjunction with other characters such as location, neighborhood relationship, and shape, to assess abnormalities in brain images.

Functionally speaking, the brain is functionally asymmetrical and each side of the brain assumes distinctive functions. For instance, in most individuals, the left hemisphere is more active in linguistic tasks, while the right hemisphere is specialized for non-verbal tasks such as visual perception [18]. The degree to which anatomical asymmetry correlates with functional asymmetry remains questionable, but it is evident that morphological differences between hemispheres, however slight, occur systematically in normal brains. One example would be that the right frontal lobe is expected to be bigger than its left counterpart [18]. In any case, however, one has to be aware of the existence of normal asymmetry might potentially confound the process of extracting abnormal asymmetry.

2.5. Summary

The research questions posed to this point consist of, for example, can we train the computers toward a new perspective so that they can perceive abnormal structures and equate them as asymmetrical patterns in space? Can we encode the prior knowledge of symmetry into the knowledge base from which we could draw diagnostic inferences and generate faster and more accurate results in identification of pathologic dissimilarities? Can we use asymmetric findings, however evident or subtle, to flag the region of interest, raise the attention from the physicians and thus enhance the practice of radiological scanning?

Based on these research questions, this paper is presented with three main sections: in Section 3, existing methods and techniques in brain pathologies detection and segmentation are explored. In Section 4, I will discuss that in order to uncover asymmetries in head images, methods are needed for the correction of the misalignment commonly present in radiological scans. In Section 5, existing symmetry-based paradigms for automatic localization and segmentation of head lesions will be reviewed.

3. Research in brain pathology detection and segmentation

Medical image segmentation, that is a process of identifying and delineating anatomical structures and other objects in medical images, still largely remains an open problem, in spite of several decades of research from various imaging modalities [19]. There are many brain segmentation approaches which range from low-level image operation such as thresholding, edge detection, mathematical morphology [20], to more sophisticated image processing methods such as statistical classification [21,22], active contours [23], level set [24], fuzzy connectedness [25], and hybrid segmentation methods [26]. A number of review papers [27] can be found in this domain.

However, clinical image analysis indicates that to successfully differentiate between organ and tumor tissue, image information alone is insufficient [14]. For example, if a tumor shows inadequate contrast against the healthy brain tissue, the active contour classification can not be achieved without the manual selection of the seeds to initialize segmentation; hence the method is not fully automated. Other statistical classification methods are also limited due to overlapping intensity distributions of healthy tissue, tumor, and surrounding edema. One taxonomy of medical image segmentation techniques can be presented in Fig. 3. A structure displayed in an image can be segmented and delineated by region-based techniques, boundary-based techniques, or the hybrid of both. Structures that possess discontinuous borders or overlapping internal composition, that are common occurrence in medical images, are likely tocomplicate the segmentation task. Region-based methods further branch into data-driven methods and knowledge-driven methods. Data-driven methods are often supervised and statistical in nature. In data-driven, unsupervised algorithms, techniques such as thresholding and morphology operator, often work as a complementary tool or are intertwined with supervised statistical classifier. Data-driven methods do not explicitly utilize anatomical knowledge in the segmentation tasks.

Knowledge-driven methods, on the other hand, use prior anatomical knowledge about the properties of a structure to guide the segmentation process. These priors are encoded into rules, or transformed into a geographical template (atlas) with tissue labels assigned. For example, in the digital atlas-based segmentation methods [28,29], prior knowledge about normal brain anatomy including the size, shape and location of anatomical structures, is employed. Kaus et al. proposed an adaptive template moderated classification (ATMC) method that combines the statistical classification with anatomical knowledge [14]. The algorithm involves an iterative process of classification of patient's data and nonlinear registration to match the anatomical templates of a digital atlas

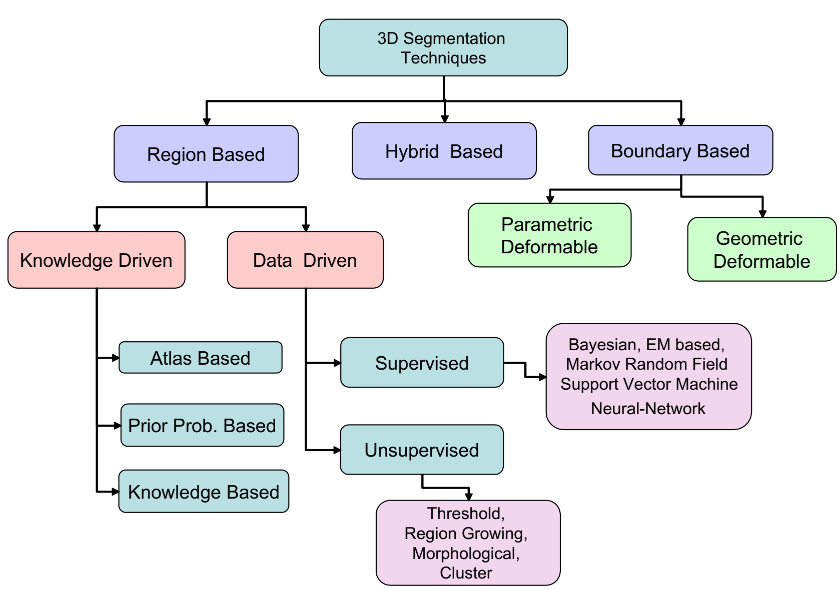

Fig. 3. A taxonomy of existing medical segmentation methods. This model is constructed by the author based on published categorizations on image segmentation techniques.

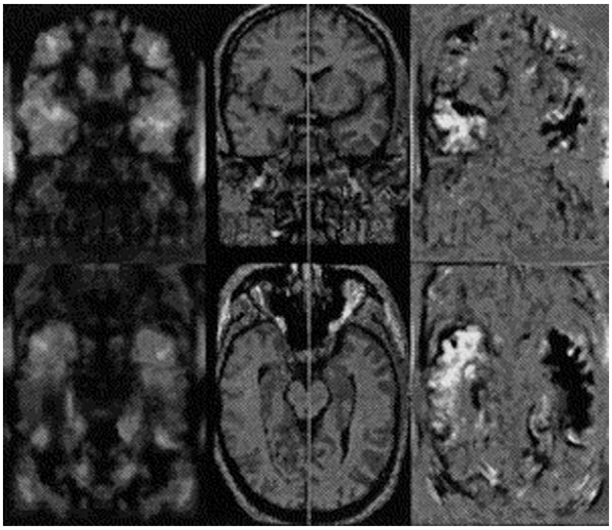

Fig. 4. This figure illustrates the dissymmetry field computation (left, norm of the field) and the application of the $||F||\text{div}(F)$ operator (right) on the realigned image of a real subject (middle). Note that the dissymmetry field is a 3D image. This illustration is adapted from [38].

with the brain anatomy of the patient. Although knowledge-driven methods have shown many advantages over data-driven methods, and the value of symmetry information in interpreting brain pathologies has been fully recognized, most existent knowledge-driven methods to date, surprisingly, rarely use the knowledge about brain symmetry to their advantages. This is because knowledge representation usually requires manual extraction of meaningful information from a population of data and subsequent data encoding of extracted information into a database. This can be a cumbersome process which demands training of a large set of data. In addition, the characteristics of tumors and other brain pathologies are highly variable and heterogeneous, thus representing prior knowledge is not always possible. Encoding symmetry knowledge about the brain can be further complicated by the normal variance of anatomical asymmetries.

4. Research in symmetry axis/plane detection methods

Since symmetry is routinely employed by the neuroradiologists to assist their assessment of brain images, the misalignment of the patient's head in the scanner often leads to false clinical interpretation of the patients' scans. Despite the difficulty in realigning the head at hardware level, a compensational algorithmic (software) plan has fortunately shown promise to make the correction of this disorientation of the head. I will review the existing techniques in this section.

In 2D applications, symmetry axis is defined as the axis best separating a planar brain image into two halves. Various approaches for detecting, analyzing, measuring and applying symmetry in image analysis have been suggested [30–32]. The usual way for determining symmetry axes assumes the object is somewhat elongated so the direction of the axis of least inertia [33] can be used to define the symmetry axes of a 2D planar shape. This is the axis about which the second moment of a thin sheet of material of the same shape is the smallest.

For three dimensional brain images, the symmetry plane is also called mid-sagittal plane (MSP). A vast host of papers investigating ways to resolve the tilt of the head in volumetric brain images can be found in literature where an ideal MSP has been defined as a 3D anatomical structure about which the given volumetric neuro-image presents maximum mirror symmetry [7]. Thus if the MSP is precisely uncovered, the orientation of the head can be resolved and the tilt of the head can be detected and corrected. Based on this rationale, we divide the existing algorithms (to identify MSP) into the following dichotomies: (1) shape-based methods vs. content-based methods, and (2) 2D based methods vs. 3D based methods.

4.1. Shape-based methods vs. content-based methods

Shape-based methods focus on using the geometric landmarks or topological features of the head as a cue to discover the orientation of the symmetry plane, while content-based methods utilize internal signal intensities of brain matters to perform the venue.

One shaped-based example is to use the inter-hemispheric fissure as a simple landmark to extract the mid-sagittal plane. For example, Brummer proposed a method of using the Hough transform to identify cerebral interhemisphereic fissure [34]. Marais extracted the fissure using snakes. Methods using inter-hemispheric fissure enjoy the computational efficiency and robustness against strong internal asymmetries [35]. These methods, however, are sensitive to the presence of a large mass near the fissure, or invisibility of the fissure in some of the image modalities. Liu et al. [16] proposed a method using external surface point cloud as the main features for the hemisphere-wise matching, and the validation of this work is still in the process.

Another branch of shape-based methods is to use inertia matrices to describe the dispersion of a given 3D dataset. This approach, also called the principal component analysis (PCA), deems head as a 3D rigid body with three distinctive principal axes that are orthogonal to each other and about which the moments of inertia are minimized. Those axes are used to characterize rigid bodies by representing the spatial distribution of their mass. Minovic et al. hypothesized that "*Any plane of symmetry in a body is orthogonal to a principal axis*" [36]. Some other authors implemented this idea and presented a method for detecting dominant plane of bilateral symmetry in an image of arbitrary dimension [37]. These algorithms, however, are only tested on the synthesized images or a small number of images of the head. The major obstacle preventing this algorithm from wide adoption in realistic neuro-applications is its deficiencies in handling incomplete dataset. For instance, when the data is truncated or the field of view includes non-head structures (e.g., neck and shoulder), the assumption that the head is ellipsoid-like 3D object is not met and the technique may produce flawed results.

Content-based methods, treating the head as two halves of gray-level volumes that the intensities of one half can be matched to those of the other half through registration. By geometrically aligning one hemisphere to its reflection the symmetry plane is derived. Typically, an optimization scheme is proposed to seek the maximum value of the similarity measure between hemispheres. Methods vary in this regards; the searching process can, either be global [15] or local [38–40]; the chosen features can be the intensities of the voxels [38], edge images [15], or characteristics of the sampled distributions [41,42].

4.2. 2D based methods vs. 3D based methods

2D based methods extract 2D lines first from each individual slice and then compute the 3D plane from those lines by using standard interpolation technique. For example, some used Hough transformation to compute the longitudinal fissure at each coronal slice [34]; Liu et al. estimated the 2D mid-sagittal axis for each coronal or axial slice, and then computed a 3D plane from set of these lines [15]; Junck et al. used a cross correlation analysis for the detection of the line of symmetry in a transverse positron emission tomography (PET) or SPECT slice [43].

Because these methods process head volume slice-by-slice, the global symmetry of the whole brain is not captured. In case when the head is strongly tilted, the structures displayed in the same axial slice do not reside in the same axial level. The midlines computed independently from each axial slice, are likely to be a misrepresentation of the real symmetry axes, therefore the 3D interpolation of those lines leads to meaningless results.

3D based approaches consider the head volume as a whole mass, hence the plane that maximizes the bilateral symmetry is captured. Minoshima extended Junck's method to 3D, and improved its tolerance to pathological asymmetries by applying the stochastic sign change (SSC) criterion as an index of image alignment [44]. But the results only demonstrated its success in PET image and the performance on MRI and other image modalities remains unknown.

Ardekani conducted iterative search on the unit sphere, in order to find the plane with respect to which the image exhibits maximum cross correlation [39]. In general, the algorithms that are based on local search, enjoy the computational advantage, but are likely to fail in pathological brain images where gross asymmetries happen.

Thirion et al. used the "Demons" algorithm to find the anatomical counterpart via a non-rigid registration method [38]. However, non-rigid registration will provide aberrant matching when a lesion is present only on one hemisphere. The meaningless correspondences can degrade the LS criterion and its minimization. Prima et al. modified this method and computed local similarity measures between two sides of the brain, using block matching procedure [7]. This method generated a robust estimation of MSP other than plain registration based methods.

Contrary to the 2D based methods, when the whole 3D volume is taken into account, the overall gross anatomy of the volumetric brain is used. 3D based methods are less sensitive to the initial condition of the head's orientation and variability of the inter-hemispheric fissure. For most existing 3D methods, however, one common drawback is the computational cost due to the optimization scheme when searching over the 3D space for the maximum matching hemispheres.

The existing work on the MSP detection is summarized as in Table 1. In terms of computational efficiency, one should be aware of if the algorithm is realistic to be implemented in the clinical settings. Generally speaking, content-based algorithms are more time consuming than shape-based methods. Said that, most algorithms do not seem pose a significant threat to be implemented in realistic settings. In addition, a number of techniques can be used to facilitate the computation, for instance, down-sample the volumetric data or employ the multi-scale scheme.

5. Research in brain symmetry and asymmetry analysis

Human head presents a high level of symmetry; however, it is not perfectly symmetrical. Morphological and functional difference between the hemispheres makes the brain slightly asymmetrical. Different aspects of anatomical asymmetry of human brain have been studied. For example, it is recognized that the right frontal lobe is larger than the left frontal lobe, while the right occipital lobe is smaller than its left counterpart [18] (see Fig. 1).

The gross volumetric asymmetries in hemispheres in total, brain compartments, and different intracranial structures were reported in a number of works. For example, 200 normal brains MRI had been studied to contribute to a normative volumetric database and their relations with age and gender were examined [45]. It was found that an asymmetry in the depth of central sulcus has its relationship with handedness and gender [46]. Steinmetz reported a strong correlation between left hemisphere dominance for right-handedness and a large left *planum temporal* [47]. Those studies suggested morphological asymmetries is associated with functional variations in human brain populations. On the other hand, some pathology is strongly linked with abnormalities of brain asymmetry. For example, bilateral reduction of metabolic activity in parietal, temporal, and prefrontal regions is known to be an important feature for diagnosing the Alzheimer's disease [48]. A method of analysis and visualization of cerebral brain asymmetry was reported in [49].

Some research group also tried to quantitatively estimate brain asymmetries. In 2004, Lee et al. investigated hemispheric asymmetry and calculated the fractal dimension (FD) of the 3D skeletonized volume, which represented the cortical folding pattern [50]. They also measured volumes of gray matter and white matter and obtained the hemispheric asymmetries of each measurement. They used MRI dataset from 62 normal adults' brain. This study discovered among normal brains, although hemisphere-wise cortical folding pattern (obtained from FD) presented significant asymmetry, the volumes of WM and GM showed no significant asymmetric changes.

In another paper [51], Kovalev et al. investigated structural brain asymmetry in normal volunteers and in patients with pathological findings using 3D volumetric texture analysis. The algorithm is based on multi-sort co-occurrence matrices that employ intensity, gradient and anisotropy image features. By calculating

Table 1
Existing methods for detecting symmetry planes of brain images.

Methods	Content based vs. shaped based	Extracting feature	2D vs. 3D	Local search vs. global search	Modalities
Brummer (1991)	Shape based	Inter-hemisphereic fissure (IF)	2D	Global: seek longitudinal fissure	MR
Hu and Nowinnski (2003)	Shape based	Inter-hemisphereic fissure (IF)	2D	Local: in the vicinity of IF	MR, CT
Minovic (1993)	Shape based	Principle axes	3D	Global: search the inertia matrix of 3D rigid body	Simulated data and MR
Liu (2006)	Shape based	External surface point cloud	3D	Global	Simulated data and MR
Liu (2001)	Content based	Edge map cross correlation	2D	Global: edge cross correlation	MR, CT
Smith and Jenkinson (1999)	Content based	The ratio of intensity profile	3D	Global: measure the symmetry of the lines orthogonal to the candidate symmetry plane	CT, MR, PET, SPECT
Junck (1990)	Content based	Content cross correlation	2D	Global	PET, SPECT
Ardekani (1997)	Content based	Content cross correlation	3D	Local: on a unit sphere	MR, PET
Prima (2002)	Content based	Content cross correlation	3D	Local: block matching	CT, MR, PET, SPECDT
Volkau (2006)	Content based	Intensity distribution: Kullback–Leibler' measure	3D	Global	MR, MRA, CT

L1 (normalized sum of absolute element-by-element differences) distance, matrices computed for the left and right hemispheres are treated as two feature vectors. It was found that pathological brains are significantly more asymmetric and the variation of asymmetry degree is much wider. It also reported significant gender-related asymmetry difference.

Maes et al., measured the hemispheric asymmetry in cerebral grey and white matter volumes from MR images [17]. The grey and white matter segmentation was conducted through non-rigid registration with the labeled template image. Their findings indicated a slight difference between grey matter volumes left and right, both in normal and schizophrenics. Their study only intended to compare the volume difference of grey and white matters between left and right, hemispheres, it is not applicable to neuro-images where a large lesion is present.

Volkau et al. evaluated asymmetry as a scalar value, using the Jeffery divergence measure [42]. A threshold is set to $T = 0.007$ to achieve minimum number of false positives and false negatives. This study demonstrated the significant statistic dissymmetry in normal brains compared to tumor brains; it however may only provide a gross estimation of asymmetries for it only employed one scalar value to represent dissymmetry. The algorithm does not have the capability for localizing pathologies.

Thirion et al. stated that "the quantification of abnormal dissimilarity can be a powerful tool to detect abnormalities" [38]. They computed a dense 3D dissymmetry fields and compared the relative dissymmetry measure of a patient to a population (see Fig. 4). Thus a 3D significance map was acquired. It aimed to answer the question if a brain tumor is significantly more dissymmetrical than the same region in a normal population. This has been the most systematic discussion to date to compare volumetric dissymmetry between abnormal and normal population. It is worthwhile to notice that acquire large sample of normal brains as control for inter-patient fusion may not be straightforward to implement in a clinical setting [22].

Liu et al. proposed a statistical method for detection and segmentation of acute/subacute ischemic stroke. This technique has been demonstrated and validated on MR images to detect rodent cerebral ischemic stroke, and the results have been compared with post-mortem histological sections (see Fig. 5). They make use of statistical analysis (non-parametric statistical test) on paired windows across hemispheres to identify statistically significant differences between hemispheres [52].

It should be noted that, for any of these algorithms, the tolerance to normal asymmetries is critical to the success of abnormal asymmetry detection. Normal anatomical asymmetries between hemispheres can be statistically significant. Slight geographical misalignment between left and right hemispheres and patient-specific asymmetric patterns in regions of the head can complicate the procedure in differentiating pathological asymmetries from anatomical asymmetries. If there appears a non-trivial normal variation between two hemispheres, it is highly likely that the method will detect unwanted artifacts together with pathological asymmetries.

In another word, asymmetry analysis as a tool for pathology detection cannot be achieved without differentiating normal asymmetries from abnormal asymmetries. In the rodent ischemia model [52], authors pointed out four major types of asymmetries imbedded in brain radiological images should be taken into considerations: (1) normal asymmetry in the image signal intensity, (2) abnormal asymmetry in the image signal intensity, e.g., the presence of tumor; (3) noise due to geometrical misalignment; (4) noise due to in-homogeneity of the signals, e.g., bias fields.

In order to eliminate type (1) and type (3) artifacts, a non-rigid registration process between hemispheres is recommended as a preprocessing step [53]. By doing so, points formerly misaligned will be mapped to their counterparts by a set of geometric affine transformations. Plus, standard noise deduction algorithm may have the promise to remove errors introduced by type (4) noises. Despite the promising results in the preliminary studies, these techniques are still in its infancy: more solid evaluation is required in order to verify the robustness and efficacy of these algorithms.

6. Discussion

The readily usable software for abnormality analysis of images has hindered the integration of computer-aided diagnosis (CAD) tools in the clinical information system. It is believed that a fast and accurate CAD tool would provide physician with a mechanism

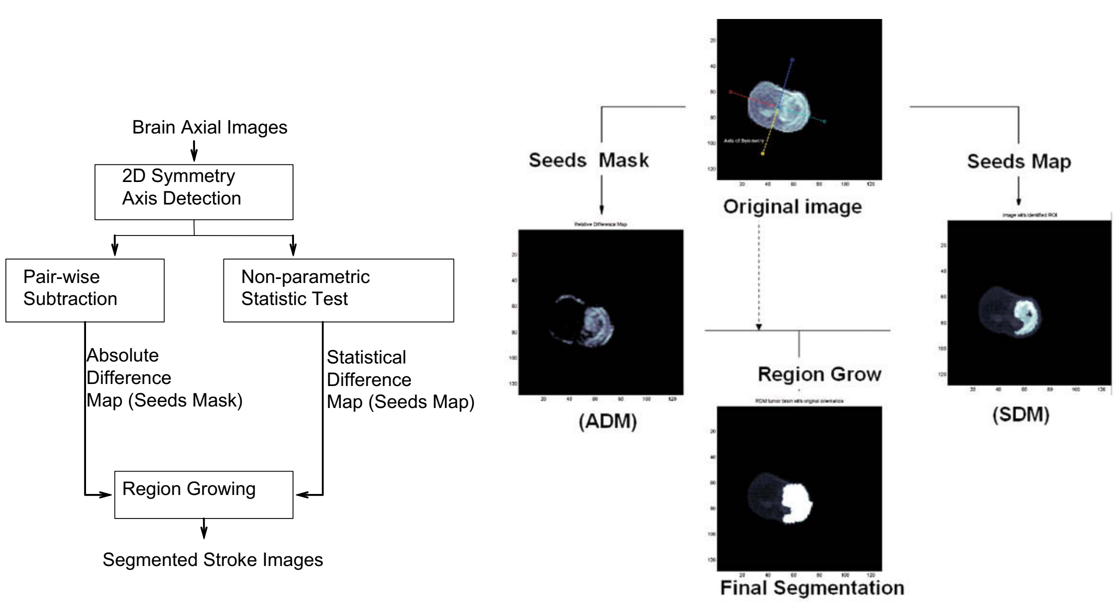

Fig. 5. The proposed segmentation framework illustrated (a) in flowchart (b) in segmenting stroke from rat ischemia stroke models in MRI. The illustration is adapted from [52].

for early detection of important findings that could result in earlier delivery of effective therapy [54]. With isolated image signals yet-to-be linked with the underlining anatomical landscape, each radiological image is treated as a spatial data sheet of pixel values rather than knowledge entries. While we acknowledge the importance of employing knowledge in computer-aided diagnosis, we must also realize, particularly in brain imaging, the systematic correlation between asymmetry and pathologycan potentially improve existing detection algorithms.

In this review, the use of symmetry and asymmetry information in neuro-imaging applications has been explored. The impact of developing a fully automated method for complex characterization and quantification of asymmetry could be far-reaching. To make this process fully automated, future work will need to have the faculty to detect symmetry plane (or axis) and quantify asymmetries sequentially using the computational framework suggested in Fig. 6.

However, with the recognition that sometimes normal hemispherical asymmetries can be as significant as asymmetries caused by abnormal pathologies, we must admit that using asymmetry analysis alone is not always sufficient as a classifier to completely discriminate brain pathologies.

In these cases a hybrid approach is recommended, where symmetry can be used as a spatial prior to facilitate subsequent either region-based or boundary-based segmentation operations. In addition, when the normal asymmetric artifacts are adjacent to the boundary of the lesions, or a brain lesion are cross the midline, or a pair of brain lesions are largely bilaterally symmetrical, additional errors might occur. One solution could be the fusion of images from multiple modalities, each of which provides complementary information concerning the region of interest. The merging of these data channels can yield a cross-referenced mask to filter out connected artifacts (that exhibit similar signal intensities as that of a lesion) and asymmetrical artifacts (that are adjacent to asymmetrical pathologies).

The concepts described in this paper could be potentially generalized from neuro-domain to other regions of the body, as mirror symmetry is a common occurrence in many human structures such as face, breast and limbs. For instance, interpretation of asymmetries in mammograms between the left and right breasts can be used to indicate potential tumor masses. Alterson and Plews proposed a way to perform symmetry analysis on a population of 51 randomly selected patients and demonstrated that automated symmetry detection of symmetry is both feasible and accurate [55]. Because the human body is essentially a symmetrical object, the study of symmetry and asymmetry can significantly deepen our understanding about human anatomy, physiology and pathology; and assist computerized tools to serve better roles in decision making and improving patient care.

A full exploitation of symmetry information of the human body requires knowledge infusion from multiple disciplines (see Fig. 7). We use the term "computational asymmetry analysis" to the subset of all these methods that utilize the computer and information science to uncover the symmetry information quantitatively inside the human body. Computational asymmetry analysis requires multi-disciplinary fertilization that makes this brain pathology assessment meaningful and effective. For instance, the deployment of prior information about brain symmetry can potentially bridge the cognitive association between human experts and computer systems (can the human way of dissecting visual asymmetries be of inspiration to the computer vision algorithm?). It conveys core ideas of an increasingly growing discipline—*cognitive science*. This research also falls into the discipline of modern *artificial intelligence* and *computer vision*, because it engages a machine to "think" like a human and in this "thinking" course, knowledge and heuristics are known to shorten the searching time and reduce the searching space. In addition, this research directly deals with geometric objects such as symmetry axis and symmetry plane therefore it concerns about basic theorems and applied methods in *computational geometry*. Furthermore, *knowledge engineering* is a discipline that involves integrating knowledge into computer systems in order to solve complex problems. Because prior knowledge about symmetry is another form of high level human expertise, we can utilize the advances in this discipline to further aid the understanding

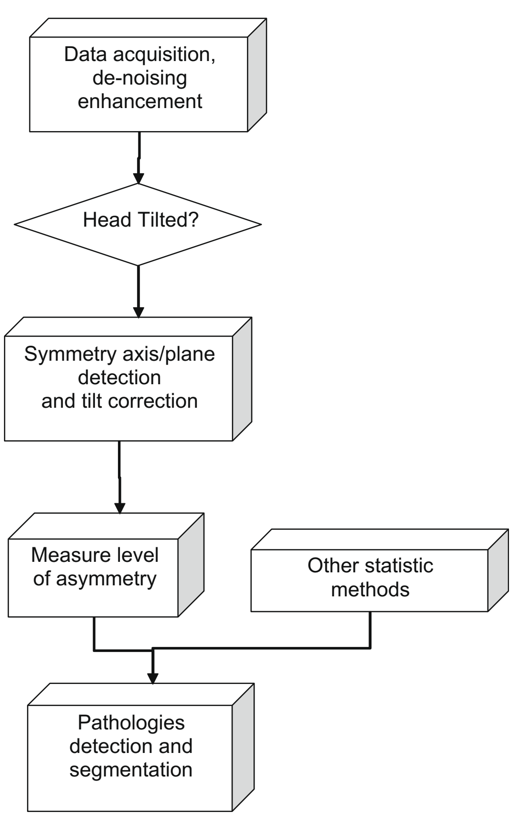

Fig. 6. The generic workflow of the symmetry-based brain lesion detection system. It consists of two main topics: symmetry detection and asymmetry analysis.

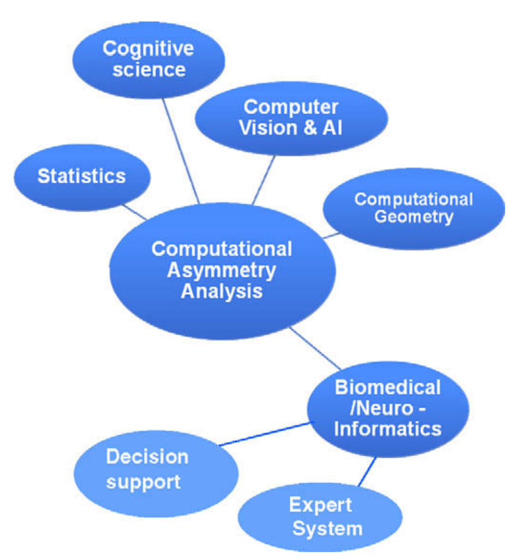

Fig. 7. Computational asymmetry analysis can be deemed as a highly interdisciplinary research, and it can only be enriched via the cross-fertilization with insights from different disciplines.

about human asymmetry. *Neuroinformatics* is a research field that employs development of neuroscience data (structure, function, and physiology), knowledge and application of computational models and analytical tools for the integration and analysis of experimental data and for improving existing theories about the nervous system and brain [56]—the scope of this research also fits with this definition. The analytical tool employed here is imaging algorithms and the mission is to discover brain structural and physiological changes in a pathological condition. Likewise, this research can easily find its course in the disciplinary track of *imaging informatics* and *biomedical informatics*. Other disciplines, such as *anatomy*, *physiology*, and *radiology* can also in one way or the other impart insights into the sphere of symmetry/asymmetry analysis.

7. Conclusion

Based on the hypothesis that the systematic correlation between asymmetry and pathology can be a key to the improvement of existing lesion detection algorithms, this paper explores the state-of-the-art technologies for analyzing brain symmetry and asymmetry. This review has attempted to demonstrate that integrating symmetry/asymmetry information into computer-aided diagnostic (CAD) scheme promises to enhance the system performance in the evaluation of brain pathologies. The hope is that this work will raise greater interest in studying symmetry and asymmetry of human body, leading toward a systematic development of hybrid methodologies, necessarily integrating multidisciplinary knowledge ranging from human anatomy, physiology, pathology to applied engineering sciences such as imaging informatics and biomedical engineering.

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