Cerebral Cortical Thickness Estimation using the TINA Open-Source Image Analysis Environment

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Abstract. This paper gives an overview of the use and development of the TINA open-source medical image analysis environment, with respect to the determination of human cerebral cortical thickness estimation from magnetic resonance images. The ultimate aim of TINA is to provide a validated system where the source code and datasets are freely available in order to allow peer-validation of published results.

1 Introduction

The determination and characterisation of human cerebral cortical thickness has enormous potential use in the assessment of the severity and progression of pathology and of the processes of normal brain ageing. Grey matter (GM) volume loss is seen throughout adulthood to old age [1] and increased cortical thinning relative to control subjects has been implicated in various degenerative diseases, such as Alzheimer's disease [2], and Multiple Sclerosis [3].

Cortical thickness estimation from MR images is a non-trivial process, and various approaches may be adopted (eg, measuring the distance between corresponding points of active shape models fitted to the grey matter boundaries [4], using diffeomorphic field lines [5]). The approach we have taken in the paper presented at MICCAI 2005 [6], outlined in figure 1 and described in detail in [7] was carried out using the TINA open-source medical image analysis environment, which is freely available under the GNU lesser general public licence either as a tarball of the source code (updated daily) from the TINA website (www.tina-vision.net/software.php) or by anonymous access to a CVS repository.

2 Introduction to TINA

TINA provides the algorithms and tool interfaces for a variety of image processing and medical image analysis tasks. It is written in the C language (please see www.tina-vision.net/faq.php for the reasons for this choice) and is primarily intended for use on GNU/Linux, although runs natively on other platforms, for

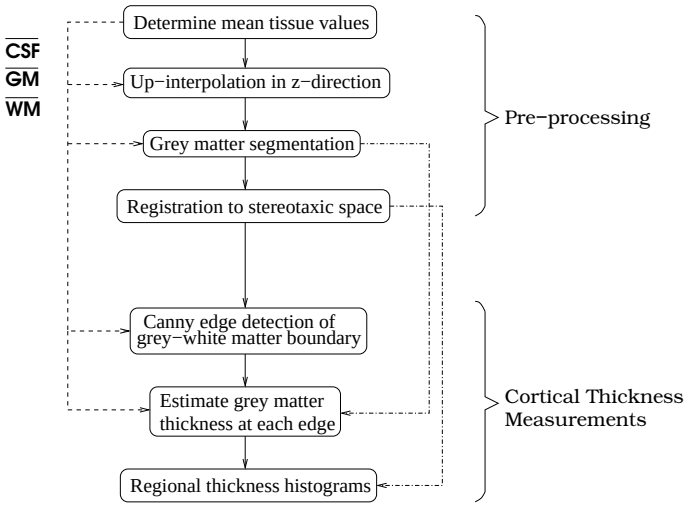

Fig. 1. Flow chart of processes involved in cortical thickness estimation.

example, MacOS and Solaris. It is also possible to run TINA under Microsoft Windows. TINA has functionality for single/multiple image input and output of various "industry standard" formats (such as DICOM), as well as raw data images where the format is unknown. Images may be manipulated using an "image calculator", which provides an interface to commonly used image transformation algorithms, such as image arithmetic, filtering etc. In addition, TINA has toolkits dedicated to medical image analysis, principally rigid co-registration of two datasets, MRI tissue segmentation, and analysis of MR perfusion, permeability, quantitative flow and fMRI. Both user and developer therefore have available an integrated suite of tools which allow a highly modular approach to the development of new algorithms or processing techniques. This re-use of code is preferable to starting from scratch when a new technique is required, and contribution of developer's code back into either the core repository or project directories ensures that the code generated from short-term research is maintained for future use, and is not lost when the project ends. For example, considering the cortical thickness technique shown in figure 1, the pre-processing stages use existing toolsets of TINA, and the actual cortical thickness stage combines new code for the specific task of estimating grey matter thickness with previously existing functionality for edge detection and for histogramming distributions.

2.1 User and Developer Support

Development of an algorithm is accompanied by extensive testing and error assessment. This is particularly important when the result of an algorithm is the input to another module, where we may wish to make the assumption that the images have known, homogenous errors [8]. The algorithmic details and results of its

application to data are written up as an internal document and published on the "memos" section of the TINA website (www.tina-vision.net/docs/memos.php). Extracts from these memos often form part of journal and conference publications, so not only are the details of the techniques freely available, but in many cases have also been peer-reviewed. As an aspect of the peer-review process, the TINA website hosts pages detailing current research projects utilising TINA, with the aim that example datasets can be provided to demonstrate the operation of the algorithm. In addition, support is provided through web-based lxr and doxygen code-browsers, Wiki pages and a developer e-mailing list.

The development of TINA as an open-source resource was greatly facilitated by funding from the European Union as part of the IST program under the "Free Software: Towards Critical Mass" call (project number IST-2001-34512).

3 Issues over Validation

There are a multitude of medical image analysis packages available with similar or overlapping functionality, so why should the user choose one over the others? Very often, a requirement for medical image analysis is that the results can be compared to some "gold standard" technique, such as a manual mark-up of an anatomical structure by a trained clinician. However, more often than not, a gold standard does not exist, usually because it is too time consuming or difficult to produce one. An alternative approach is to compare results with those in the medical image analysis literature. In the absence of a gold standard, the user needs to consider whether the assumptions made by the algorithms match the data, whether the processing techniques introduce bias into the results and whether the approach is principled.

3.1 Validation of grey matter thickness estimates

In the case of estimating grey matter thickness, a gold standard of sorts can be obtained by fixing and sectioning an excised brain and manually measuring thickness under a microscope. A comparison with MR can then be performed but there are various methodological complications with this technique which make it less than ideal. Fixation of tissues tends to dehydrate, hence shrink, the tissues; obtaining a 3D thickness from a 2D section requires great care; finally, tissue contrast in MR images of a fixed brain is not the same as in a living brain. As part of the thickness estimation technique, instead of using such a gold standard, we compared the mean results from 13 young (ages 19-53 years) normal subjects in ten regions with results from a semi-automated mark-up method (Kabani et al. 2001 [9]) in 20 subjects(aged 18-40 years), as shown in figure 2. As can be seen, there is good agreement between Kabani's results and ours. The data lie fairly evenly about the line of equality, and there is no significant difference (at $p=0.05$, $df = 31$) between the results from both studies in half of the regions investigated. There would appear to be no systematic bias in either data set to cause the differences seen.

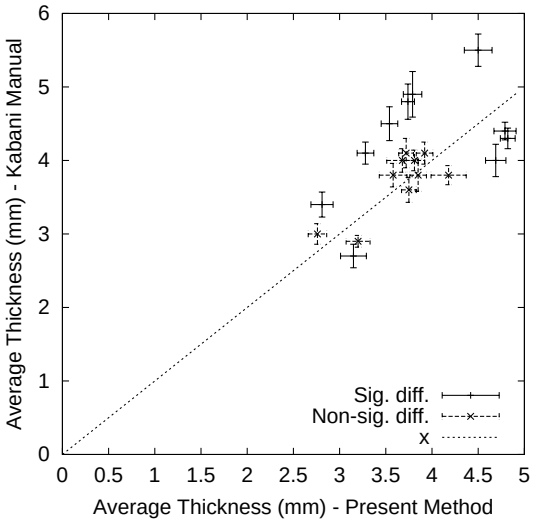

Fig. 2. Scatterplot showing a comparison of results from the present method against a semi-automated manual mark-up. On the x-axis are the average median thicknesses (plus bars illustrating group standard error) from the 13 young normals in this study for the 20 regions; on the y-axis are the mean values from a semi-automated manual mark-up of 20 young normals (Kabani et al. [9]). Crosses with dashed error bars represent those regions where there is no significant difference (using a t-test with significance at p=0.05) between this study and Kabani's, those regions which are significantly different are shown with plusses and solid error bars.

3.2 Considering assumptions about the data and algorithms

The production of accurate estimates of cortical volume in localised, small structures (for example, the hippocampus) requires that non-rigid registration should accurately co-register the image volume to the target atlas volume. Conventional approaches confound anatomical variation with true volume changes [10], the result of which is that the boundaries of a given structure may be inaccurately placed, giving a large potential error on the volume of the structure. However, the cortical thickness is relatively insensitive to the anatomical regions measured. By sampling the thickness of a given structure many times and taking the median of the thicknesses [6], any inaccuracy in the structural boundary placement will result in a minimal change in the median regional thickness. In the absence of MR image evidence as to the beginning and end of specific structures (in reality, only a continuous ribbon can be seen), it is unneccesary and unreliable (see above) to apply a non-rigid registration for obtaining thickness estimates, instead it is sufficient to use an affine transformation and to use the median thickness as a robust estimate of the average thickness in a structure.

As can be seen, accuracy in thickness estimation is at the expense of not being able to quantify the tissue volumetric data. This issue has been partly addressed in a previous study [11] using techniques based upon monitoring the

relative increases of cerebrospinal fluid (CSF) in coarse regions of the brain. In some respects this thickness technique and the volumetric CSF one are intended to be complementary.

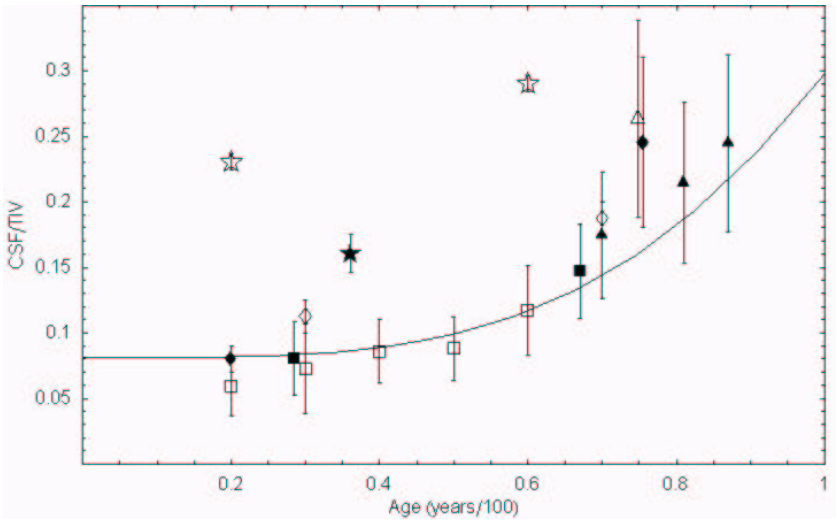

Fig. 3. A plot of CSF volume normalised to total intracranial volume against age. Data are from the following studies: ■ Gur et al. [12], □ Blatter et al. [13], ▲ Mueller et al. [14], △ Coffey et al. [15], ♦ Courchesne et al. [16], ◊ Whitwell et al. [17], ★ Chard et al. [18], unfilled star; Good et al. [19].The solid line shows the expected dependency of CSF volume against age, assuming a Weibull distribution for the rate of increase of CSF.

In terms of validating the CSF data, we derived a biologically valid dependency of the increase of CSF with age using 70 normal subjects aged 19 to 85 [20]. We then compared this curve and our results with results from 8 studies (all using different analysis software and techniques), comprising 1400 normal volunteers in total. The majority of the data from these studies agrees with the fit to our data despite significant differences between studies in the definitions of the measured anatomical volume, the MR acquisition types and the measurement techniques. Note that the studies by Good et al [19] and Chard et al. [18] both show a significant overestimation of CSF volume, by up to 200%, and these are the only two to use Statistical Parametric Mapping (SPM) [21]. As the other studies provide an upper bound on the variation in CSF volume seen due to differences in analysis and scan type, it is unlikely that the results in the SPM papers are due to such variations; instead there must be a more fundamental algorithmic reason for the large overestimation in volume. One speculation as to the cause of this overestimation is the fact that SPM does not model partial volume processes.

4 Conclusions

The major advantages of using the TINA open-source software are that it provides a mechanism for maintaining a record of the work carried out by its users, it accelerates the process of algorithmic design, making the success of short-term projects more feasible, and extensive validation of the algorithms has been performed, so that the user can be confident in the accuracy and reliability of the techniques. The ultimate aim of making TINA open-source is to make the source code, example datasets and algorithmic details all freely available, so that peer review, replication of the techniques and validation of the results reported in our publications can take place.

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