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Robust whole-brain segmentation: Application to traumatic brain injury

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ABSTRACT

We propose a framework for the robust and fully-automatic segmentation of magnetic resonance (MR) brain images called "Multi-Atlas Label Propagation with Expectation–Maximisation based refinement" (MALP-EM). The presented approach is based on a robust registration approach (MAPER), highly performant label fusion (joint label fusion) and intensity-based label refinement using EM. We further adapt this framework to be applicable for the segmentation of brain images with gross changes in anatomy. We propose to account for consistent registration errors by relaxing anatomical priors obtained by multi-atlas propagation and a weighting scheme to locally combine anatomical atlas priors and intensity-refined posterior probabilities. The method is evaluated on a benchmark dataset used in a recent MICCAI segmentation challenge. In this context we show that MALP-EM is competitive for the segmentation of MR brain scans of healthy adults when compared to state-of-the-art automatic labelling techniques. To demonstrate the versatility of the proposed approach, we employed MALP-EM to segment 125 MR brain images into 134 regions from subjects who had sustained traumatic brain injury (TBI). We employ a protocol to assess segmentation quality if no manual reference labels are available. Based on this protocol, three independent, blinded raters confirmed on 13 MR brain scans with pathology that MALP-EM is superior to established label fusion techniques. We visually confirm the robustness of our segmentation approach on the full cohort and investigate the potential of derived symmetry-based imaging biomarkers that correlate with and predict clinically relevant variables in TBI such as the Marshall Classification (MC) or Glasgow Outcome Score (GOS). Specifically, we show that we are able to stratify TBI patients with favourable outcomes from non-favourable outcomes with 64.7% accuracy using acute-phase MR images and 66.8% accuracy using follow-up MR images. Furthermore, we are able to differentiate subjects with the presence of a mass lesion or midline shift from those with diffuse brain injury with 76.0% accuracy. The thalamus, putamen, pallidum and hippocampus are particularly affected. Their involvement predicts TBI disease progression.

1. Introduction

With an estimated annual global incidence of 6.8 million cases, traumatic brain injury (TBI) imposes a significant burden on patients, their families, and health services (Irimia et al., 2012). Usually caused by sudden acceleration/deceleration or focal impacts, the lesions caused can be focal as in the case of contusions or more diffuse (diffuse axonal injury (DAI)) (Meythaler et al., 2001; Warner et al., 2010b). It is common for patients to have a combination of these. After the acute injury secondary processes including complex metabolic cascades, alterations in cerebral blood flow and raised intracranial pressure may occur contributing to the burden of injury. It is well recognised that complex pathophysiological processes including secondary Wallerian-type degeneration continue to occur months to years after the initial insult (Meythaler et al., 2001; Ding et al., 2008; Warner et al., 2010a). In order to improve treatment stratification and patient outcomes, as well as more accurately predict outcome, we need

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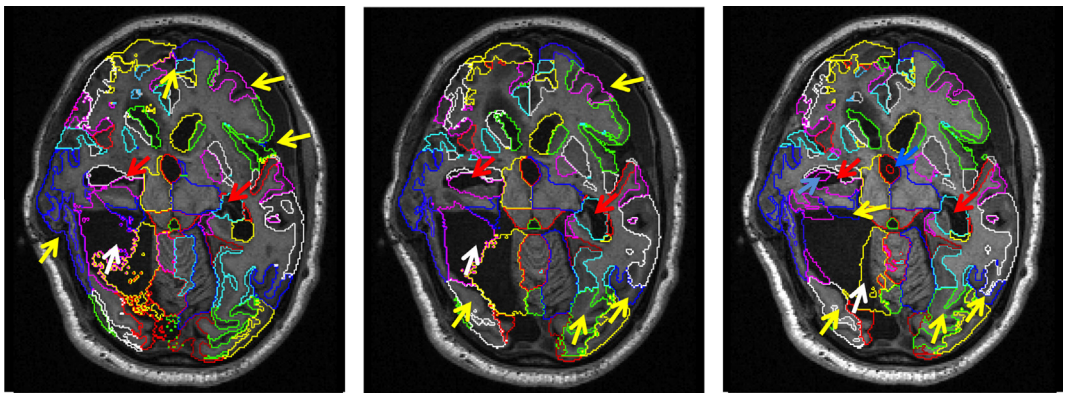

Fig. 1. Example of segmentation results obtained on a subject with highly abnormal brain configuration. Segmentations calculated with MAPER using majority voting (left, Heckemann et al. (2010)) and SyN (Avants et al., 2008) from the ANTs toolkit using either majority voting (middle) or the joint label fusion (right, Wang et al. (2013)). Red arrows: substantial oversegmentation of the hippocampus; yellow arrows: inaccurate cortex segmentation due to gross brain deformation; blue arrows: ventricles incorrectly labelled as background; white arrows: region of missing tissue prohibits reasonable one-to-one mapping of the atlases. Segmentation contours are shown in a colour scheme that provides good colour contrast between neighbouring structures. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to better understand the complexity and heterogeneity of TBI both in the acute and chronic stages.

Although patterns of abnormalities have been shown to be predictors of outcome, such use of imaging data is mainly based on expert interpretation of visually inspected X-ray computed tomography (CT) images. Standard models to predict the outcome of TBI patients remain unavailable (Irimia et al., 2012). To assist the understanding of TBI disease progression, accurate quantitative assessment of the structural changes occurring during and after TBI is crucial. Segmentation of structural magnetic resonance (MR) images offers a potential way to gain more insight. For example, in Bendlin et al. (2008) brain volume loss following TBI has been identified using tissue segmentation techniques on structural MR images (MRIs) and diffusion tensor imaging (DTI). In Irimia et al. (2011) an intra-patient time point comparison has been performed on three representative TBI patients using semi-automatic methods for tissue and lesion classification and 3D model generation. Ramlackhansingh et al. (2011) used structural MRI and positron emission tomography (PET) to demonstrate inflammatory processes that remain active for months or years following brain trauma. An overview of existing structural MRI findings in mild TBI is provided in Shenton et al. (2012). Most of the few existing studies (Strangman et al., 2010; Warner et al., 2010a,b) that analyse structural morphometric measures are based on the segmentation techniques available in FreeSurfer (Fischl et al., 2002) and investigate small patient cohorts (Warner et al., 2010a,b). In Warner et al. (2010b) the authors investigate the correlation between structural brain atrophy of 25 patients with DAI and functional outcome. Several brain structures showed significantly increased structural atrophy when compared to a control group 8 months post injury (Warner et al., 2010b). In Strangman et al. (2010), fifty patients that sustained TBI were enrolled in a memory rehabilitation program and their individual progress recorded. The study investigated the predictive value of structural brain volumes with respect to the outcome of the rehabilitation (Strangman et al., 2010). Both studies (Strangman et al., 2010; Warner et al., 2010b) identified several structures, including the thalamus and hippocampus that are particularly affected by TBI and are of significant value when predicting clinical outcome.

The automatic structural segmentation of MR brain scans of TBI patients remains, however, a difficult endeavour as most existing methods lack robustness towards TBI-related changes in anatomy (Irimia et al., 2011, 2012). In the acute phase contusions, the presence of blood, hydrocephalus and/or oedema can greatly affect the ability to accurately segment a brain. In more chronic scans gliosis and atrophy are also often poorly dealt with using currently available segmentation methods. It is this high variability and extent of brain change following a moderate or severe TBI that makes the segmentation task so demanding. An exemplar subject with highly abnormal brain configuration is shown with overlaid automatic segmentations in Fig. 1 to illustrate the difficulty of the segmentation task.

A popular class of automatic segmentation algorithms is multi-atlas label propagation with origins in Rohlfing et al. (2004b) and Heckemann et al. (2006). In multi-atlas label propagation, each of the semi-automatically or completely manually annotated atlases is individually aligned with the unsegmented target image. The propagated segmentations are then merged into a consensus label at each voxel in the target image. Voxelwise label conflicts can be resolved using either simple, unweighted approaches (Rohlfing et al., 2004a; Heckemann et al., 2006; Aljabar et al., 2009) or by weighting individual contributions locally based on the intensity information from the atlas and target images (Artaechevarria et al., 2009; Sabuncu et al., 2010). Alternative fusion strategies based on statistical optimisation have been proposed, with the most popular representative being STAPLE (Warfield et al., 2004) and its modifications (Asman and Landman, 2011, 2013; Landman et al., 2012; Cardoso et al., 2013a). A more detailed overview of atlas-based methods is provided by Cabezas et al. (2011). A particular successful strategy called joint label fusion was recently proposed by Wang et al. (2013). In this state-of-the-art approach, as evaluated in (Landman and Warfield, 2012), segmentation bias is reduced by estimating joint segmentation errors of different atlas pairs (Wang et al., 2013).

Atlas propagation techniques rely on the accurate registration of the atlas and unsegmented MR image to determine the spatial transformation of the atlas labels into the target space. This can be difficult if the target image differs from the available atlases due to the presence of pathology.

Recently, Liu et al. (2014) presented a promising approach based on low-rank matrix decomposition to register multiple images of TBI patients simultaneously to a reference image. In Niethammer et al. (2011), the authors formulated a geometric metamorphosis model to address the challenges arising in the registration of images from TBI, tumour or stroke patients. Other approaches iteratively register and segment the images simultaneously to identify missing correspondences (Periaswamy and Farid, 2006; Chitphakdithai and Duncan, 2010). Based on a seed,