Short Paper

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Abstract

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Introduction

Intracerebral hemorrhage (ICH) is a neurological condition that results from a blood vessel rupturing into the tissue and possibly extending into the ventricles of the brain. The use of X-ray computed tomography (CT) scans allows clinicians and researchers to qualitatively and quantitatively describe the characteristics of a hemorrhage to guide interventions and treatments. CT scanning is widely available and is the most commonly used diagnostic tool in patients with ICH (Sahni and Weinberger 2007). The volume of ICH has been consistently demonstrated to be an important diagnostic predictor of stroke severity, long-term functional outcome, and mortality (Broderick et al. 1993; Hemphill et al. 2001; Tuhrim et al. 1999). ICH volume change is also a common primary outcome (Anderson et al. 2008, 2010; Qureshi et al. 2011; Mayer et al. 2005) and secondary outcome (T. Morgan et al. 2008; Anderson et al. 2008; T Morgan et al. 2008) in clinical trials. Moreover, the location of the ICH has been shown to affect functional outcome in patients with stroke (Rost et al. 2008; Castellanos et al. 2005). Thus, quantitative measures of ICH (e.g.~volume, location, and shape) are increasingly important for treatment and other clinical decision.

ICH volume can be estimated quickly, for example, using the ABC/2 method (Broderick et al. 1993). In this method, a reader chooses the slice with the largest area of hemorrhage. The length of the intersection between this first axis and the hemorrhage is denoted by A. The next step is to draw an orthogonal line at the middle of the segment of length A in the same plane that contains the largest hemorrhage area. The length of the intersection between this second orthogonal axis and the hemorrhage is denoted by B. The reader then counts the number of slices where hemorrhage is present (C). The volume estimate is $\frac{A \times B \times C}{2}$, which is an approximation of the volume under the assumption that the hemorrhage shape is well approximated by an ellipsoid (Kothari et al. 1996). As this method is relatively easy to implement in practice, it can be used to quickly produce rough estimates of hemorrhage volume (Webb et al. 2015).

Although ABC/2 is widely used; Divani et al. (2011) found that the measurement error associated with the ABC/2 method were significantly greater than those using planimetry, which requires slice-by-slice hemorrhage segmentation by trained readers. Planimetry is much more labor intensive and time consuming, but it more

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accurately estimates the true ICH volume compared to the ABC/2 approach, especially for irregularly shaped ICH and for smaller thickness (i.e.~higher resolution) scans.

Another problem that has not been discussed in the literature is that ICH may change over time. The shape of the ICH may initially be well approximated by an ellipsoid but the approximation may become increasingly inaccurate over time as the lesion changes shape, migrates through the surrounding tissues, or breaks down. Surgical interventions that target the removal of ICH may also change the shape of the ICH or cause additional bleeding.

Moreover, the ABC/2 method has been shown to consistently over-estimate infarct volume (Pedraza et al. 2012) and may have significant inter-rater variability [Hussein et al. (2013)}. Therefore, a rapid, automated, and validated method for estimating hemorrhage location and its volume from CT scans is highly relevant in clinical trials and clinical care. Accuracy is accompanied by increase of both diagnostic and prognostic value.

Methods have been proposed for segmentation of ICH using magnetic resonance images (MRI) (Wang et al. 2013; Carhuapoma et al. 2003). However, in most clinical settings CT, not MRI, is the image of choice. Furthermore, MRI sequences and protocols may vary across sites and there is no general, standardized, agreed-upon MRI protocol for ICH standard-of-care. Thus, there is a need for ICH segmentation that relies only on CT scan information, is reliable, reproducible, available, and well validated against planimetry.

We propose an algorithm that can estimate the probability of ICH at the voxel level, produce a binary image of ICH location, and estimate ICH volume. We will compare our predicted ICH maps to the gold standard – manual segmentation. Several methods have been presented for automated methods for estimating ICH from CT scans (Prakash et al. 2012; Loncaric, Cosic, and Dhawan 1996; Loncaric et al. 1999; Pérez et al. 2007; Gillebert, Humphreys, and Mantini 2014). These methods include fuzzy clustering (Prakash et al. 2012; Loncaric, Cosic, and Dhawan 1996), simulated annealing (Loncaric et al. 1999), 3-dimensional (3D) mathematical morphology operations (Pérez et al. 2007), and template-based comparisons (Gillebert, Humphreys, and Mantini 2014). Unfortunately, no software for ICH segmentation is publicly available.

We provide a completely automated pipeline of analysis from raw images to binary hemorrhage masks and volume estimates, and provide a public webpage to test the software.

Introduction

Data

Participants and Imaging Data

We used CT images from patients enrolled in the MISTIE II (Minimally Invasive Surgery plus recombinant-tissue plasminogen activator for Intracerebral Hemorrhage Evacuation) stroke trial (T. Morgan et al. 2008). We analyzed 641 scans taken prior to randomization and treatment, corresponding to the first scan acquired post-stroke for 641 unique patients. Inclusion criteria into the study included: 18 to 80 years of age and spontaneous supratentorial intracerebral hemorrhage above 20 milliliters (mL) in size (for full criteria, see Mould et al. (2013)). The population analyzed here had a mean (standard deviation (SD)) age of 59.1123245 (11.3240557) years, was 58% male, and was 59.8, 33.1, 3.7, 2.2, 0.9, 0.2, 0.2. CT data were collected as part of the Johns Hopkins Medicine IRB-approved MISTIE research studies with written consent from participants.

The study protocol was executed with minor, but important, differences across the 1 sites.
In head CT scanning, the gantry may be tilted for multiple purposes, for example, so that sensitive organs, such as the eyes, are not exposed to X-ray radiation. This causes scan slices to be acquired at an oblique angle with respect to the patient. Gantry tilt was observed in 0 scans.

Slice thickness of the image varied within the scan for 0 scans.

For example, a scan may have 10 millimeter (mm) slices at the top and bottom of the brain and 5mm slices in the middle of the brain. Therefore, the original scans analyzed had different voxel (volume element) dimensions. These conditions are characteristic of how scan are presented in many diagnostic cases.

Hemorrhage Segmentation and Location Identification

ICH was manually segmented on CT scans using the OsiriX imaging software by expert readers (OsiriX v. 4.1, Pixmeo; Geneva, Switzerland). After image quality review, continuous, non-overlapping slices of the entire hemorrhage were segmented. Readers employed a semiautomated threshold-based approach using a Hounsfield unit (HU) range of 40 to 80 to select potential regions of hemorrhage (Bergström et al. 1977, smith_imaging_2006); these regions were then further quality controlled and refined by readers using direct inspection of images. Binary hemorrhage masks were created by setting voxel intensity to 1 if the voxel was classified as hemorrhage, regardless of location, and 0 otherwise.

Image Processing: Brain Extraction, Registration

CT images and binary hemorrhage masks were exported from OsiriX to DICOM (Digital Imaging and Communications in Medicine) format. The image processing pipeline can be seen in Figure~**??**. Images with gantry tilt were corrected using a customized MATLAB (The Mathworks, Natick, Massachusetts, USA) user-written script ({http://bit.ly/1ltIM8c}). Images were converted to the Neuroimaging Informatics Technology Initiative (NIfTI) data format using `dcm2nii` (provided with MRIcro (Rorden and Brett 2000)). Images were constrained to values −1024 and 3071 HU to remove potential image rescaling errors and artifacts. No interpolation was done for images with a variable slice thickness. Thickness was determined from the first converted slice and the NIfTI format assumes homogeneous thickness throughout the image. In a future release of `dcm2nii`, called `dcm2niix`, interpolation will be done for scans with variable slice thickness and gantry-tilt correction will be performed automatically.

All image analysis was done in the R statistical software (R Core Team 2015), using the *fslr* (Muschelli, Sweeney, et al. 2015) package to call functions from the FSL (Jenkinson et al. 2012) neuroimaging software (version 5.0.4), and the *ANTsR* package to call functions from the ANTs (Advanced Normalization Tools) neuroimaging software (Avants et al. 2011).

Brains were extracted to remove skull, eyes, facial and nasal features, extracranial skin, and non-human elements of the image captured by the CT scanner, such as the gantry, pillows, or medical devices. Removal of these elements was performed using the brain extraction tool (BET) (Smith 2002), a function of FSL, using a previously published validated CT-specific brain extraction protocol (Muschelli, Ullman, et al. 2015).

Front matter

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