Author's response to reviews

Title: Automatic Segmentation of Meningioma from Non-Contrasted Brain MRI Integrating Fuzzy Clustering and Region Growing

Authors:

Thomas M Hsieh (monhsian@ntu.edu.tw)
Yi-Min Liu (min@cycu.org.tw)
Chun-Chih Liao (d95548001@ntu.edu.tw)
Furen Xiao (xfr@xals.net)
I-Jen Chiang (ijchiang@ntu.edu.tw)
Jau-Min Wong (jmwong@ntu.edu.tw)

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Author's response to reviews: see over
Dear Sir:

First of all, we would like to express our gratitude for your initial acceptance of our submitted manuscript on your journal and give us the opportunity to revise our draft. We are also deeply grateful to obtain the highly valuable and instructive comments of the two reviewers. Overall, we have made a major revision on our paper according to the suggestions made by two reviewers as follows. A point-to-point reply to the questions of the first reviewer is as follows:

Reply to reviewer #1

Reviewer #1 stated as follows:

In this study, the authors use an automatic fuzzy c-mean clustering technique for Meningioma segmentation from anatomical MR images and compare the method to manual and semi-automatic readings. In 29 patients, the results show diagnostic accuracy values in the range of 70-90%.

The paper addresses an issue of obvious clinical and methodological interest, i.e. reducing the user-dependence of tumor identification and delineation. However, while the authors should be acknowledged for using elegant tools for assessment of tumor regions, the manuscript in its current form has several methodological shortcomings as well as limitations in terms of structure and language. The main critique is related to reproducibility. As discussed below, based on limited descriptions, it is very hard for readers to reproduce or adapt the proposed technique.

Major Compulsory Revisions:

1. The first paragraph in the Introduction section can be removed. A more to-the-point focus on the current status of MR brain tumor segmentation and available manual and automatic methods may be in order. Is the proposed method a novel approach? Are there other techniques that may provide similar results? Other examples of fuzzy clustering in medical brain tumor imaging?

Reply:

The first paragraph in the Introduction section is rewrite, irrelevant already-known content had been removed. Related works regarding the current status of MR brain
tumor segmentation had been briefly introduced. Also other approach using the FCM clustering algorithm was reviewed. Comparison had been made between these works and our procedure.

2. The manual reference method is not well described. How was the manual tumor reading performed? By whom? Using what criteria?

Reply:
The manual reference method were performed by two board-certificated neurosurgeons, also our co-author (CL and FX), the detailed had been add to the material and method section. A further discussion is also made.

3. The authors state that T1-w post Gd images were used for the reference method, but not for the segmentation method. What was the rationale behind this? For comparison, shouldn’t the same images be used for both techniques? Contrast enhanced Meningiomas typically have a ‘dural tail’ – how was this accounted for in the reference and segmentation methods?

Reply:
The main purpose of our study is to develop an automatic algorithm which could effectively detect the tumor from MR images, and be of clinical use. So we hope our GT could be as resemble to the margin of true tumor as possible. As the contrasted image is more detectable by the human eyes, so we choose T1-w post Gd images as material for the reference method, in order to decrease the man-made error, despite this modality is not used in our automate pathway. Since comparing the efficiency of automatic method with manual method is not our objective, so this measure is adequate. We do see some “dural tail” in the contrast enhanced MR images, but this is no problem to our expert. And since only non-contrast images were used in automatic method, so our system will not encounter this problem.

4. The MR imaging sequence parameters (TR, TE, matrix size, etc), magnetic field strenght, coil system and MR vendor need to be listed.

Reply:
The MR imaging sequence parameters and other necessary spec. had been listed in the first part of the material and method section.

5. If edema is a problem for the segmentation routine, what about including FLAIR images? Or diffusion? Also, because of the extensive contrast uptake usually seen in Meningiomas, will including DSC or DCE imaging help? This needs to be discussed.
Since the purpose of our research is to prove that satisfactory result could be achieved by using only two type non-contrasted MR images. However, to effectively solved the edema problem, more MR sequence like FLAIR images may included as materials, or newer MR imaging technique as DSC and DCE may be incorporated in the future work. This had been discussed in the 2nd section of our discussion.

6. The Materials & Methods section consists of a large theory section on FCM. For better reading, background information that is not specific for this manuscript may be referred to only, or used in an appendix. The literature on FCM clustering (or similar methods) on brain tumors is extensive. The authors should focus on the parts of the proposed segmentation routine that is new compared to previous work.

Reply:
The FCM method had been concise in the Materials & Methods section, the reference had been updated, newer more-related had been added.

7. The pre-processing paragraph is not well described and difficult to reproduce. How was the co-registration procedure performed? Using what algorithm? What about the re-slicing routine? (Interpolation, etc). Were the patient scan orientations geometrically aligned before imaging? What about image intensity normalization?

Reply:
The detailed of the pre-processing paragraph is added into the Material and Method section. Fortunately, none of our image series need to do the re-slicing work in this research. However, if needed, usually we used the Analyze™ (Analyzedirect Inc. Overland Park, KS) in our lab. All patients were examined under well-geometrically aligned orientations. A expert radiologist confirmed there is no intensity in-homogeneity in our images, therefore no need for intensity normalization. This statement had been added to the Data section at the beginning of the Method section.

8. The authors say that the method provide high diagnostic accuracy values as long as the 5 patients in which the method failed are excluded. The rationale behind this exclusion is not well understood, nor the criteria for the exclusion. Any method will obtain high accuracy if the cases that fail are removed. The authors say that the patients that fail usually had ‘significant edema tissue’. What is the limit for significant edema tissue? Was there a test for this? For a reader
trying to adapt this method, it will be very hard to know when the method is expected to fail.

**Reply:**
This description had been rewritten in the “Result” section and also at the first and second section of the discussion. The true meaning we want to express is that, even with 5 failed cases, our automatic method had been proved to have good result compare to the related research. The failure cause were unimunous due to edema tissue, this imply that, if we could exclude the edema case during patient selection, the overall results could be further improved greatly.

9. The authors show values of ‘percent match’ and ‘correspondence ratio’. As long as values of true/false positives/negatives are derived, why not include values of sensitivity and specificity? And maybe more important, assess the reproducibility (test-retest) of the manual and automatic method? In general, in terms of reproducibility (and speed), an automatic method should be superior to a manual method.

**Reply:**
In our research, the result compare the system and result had been calculate true/false positives/negatives are derived. So it is not difficult to calculated the sensitivity and specificity, which are frequently used in medical research. The reason we adopted the PM and CR value rather than the sensitivity / specificity because more frequently used in research the computer science, more robust in presentation, easy to compare with the related literature. The reproducibility of our two observer were calculated and the result were add to the “Result section”. A discussion regarding the reproducibility of automatic pathway and manual method were also been made.

10. A symmetry measure was used to locate the tumor. How is this dependant on tumor size and whether or not the tumor is shifted towards one of the hemispheres? As the authors briefly point out in the Background section, there are issues related to this approach. How many tumors were in the midline?

**Reply:**
There are total 6 cases of midline tumor, and was all successful detected by our system. The detailed of this method had been added in the “Method” section and also been discussed in the “Discussion”.

11. The semi-supervised procedure is not well described. Based on the results, it looks like this was performed late in the automatic tumor segmentation routine. Is
this a critical step for the analysis?

Reply:
Actually, the semi-supervised procedure is not a critical procedure. In the last stage of our knowledge-based procedure, we face the problem of have to select the groups, had notice 5 cases difficult. So, curious how far our algorithm could go, this alternative is added for comparison. Semi-supervised method was introduce to see if the result can be more perfect. It is the automatic pathway our core in the research. This explanation had been added in the Method as well as in the Discussion section.

12. The concept of ‘logistic calculation’ needs to be described.

Reply:
Actually, it should be addressed as “logical” or “”. Correction had been made.

13. Morphological image processing section; erosion and deilation operations were used to clean the binary image. What if the tumor is not homogenous and a ‘solid’ object because of calcifications etc?

Reply:
Since in our research the morphological operation were placed in the final stage, after the FCM clustering, region growing, and KB selection, so all the images will be binary. In this stage, the original in-homogenous tumor will looked like image with some small holes within, these small holes will be filled using dilation operation. Tumor mass with calcification will probably be classified into more than one image groups, and will be merged at the last stage of the KB-selection procedure.

14. Table 3; three patients/values seem to be different between the semi-supervised and the automatic method. What happened here? Who are the 5 patients that did not obtain a satisfactory result?

Reply:
In original table 3 (Now presented in the form of diagram as Figure 9, as suggested by Reviewer #2), slightly different of the PM and CR values between automatic pathway and semi-supervised alternatives were observed in 3 cases. This is due to during the final stage of the KB selection; some of the image group were eliminated manually in the semi-supervise method but preserved in the automatic pathway. This had been discussed in the discussion section. A new table showing the results of our automatic pathway had been added, and the 5 failed cased were listed in this table.
15. The authors state that the semi-supervised method was significantly better than the automatic method. Using what test? P-value?

Reply:
A paired t-test was used to verify the significance of the difference, P-value on PM and CR were all < 0.05. The details had been added into the Method and Results section.

16. The manuscript is sometimes difficult to read and lacks consistency. The Background section has sentences that belong in Materials & Methods (‘In order to effectively eliminate the fragment...’) The Result section has text (statistics) describing how the study was performed which should be in the Materials & Methods section. Also, results are discussed in the Results section instead of in the Discussion section.

Reply:
The draft had been major revised and some paragraph had been re-located in order to demonstrate more reasonable arrangement. Part of the content in introduction was relocated into the method section, and some content in result had move to the discussion section.

17. The Discussion section is short and only a single reference is included related to the choice of cluster number. First, the Discussion section should state the main findings of this study. What makes this method stand out compared to other methods reported in the literature? The results should be compared with previous work, and the accuracy of the method (and the reference method) should be discussed in detail. Also, the clinical usefulness of the proposed method should be discussed.

Reply:
A lot more issues had been added into Discussion section, including the main findings of our study, in depth analysis of the results regarding the accuracy of our system and the reference method. The unique characteristic of our study compared to other related works. The clinical usefulness of our research is also discussed.

18. There are language issues throughout the text. A colleague with English as their native language should read the manuscript to ensure that the words used both accurately and clearly convey the intended meaning.

Reply:
Our revised draft had been sent for professional English edit before this time
Minor Essential Revisions:

1. Histologically, there are many Meningioma sub-types. Did any patients undergo surgery prior to MR imaging? If so, what were the results and why were they included?

   **Reply:**
   In our study, all patients were fresh and didn’t undergo operation for brain tumor.

2. Information on patient age and gender should be included.

   **Reply:**
   Since Information on patient age and gender should be included. For privacy consideration, usually anonymous image data were provided by our medical image department as research used.

3. Did the authors perform any skull-stripping prior to tumor segmentation? If not, could this aid the routine?

   **Reply:**
   In our study, we didn’t perform any skull-stripping prior to tumor segmentation, the effect is not very significant.

4. The computational language used and the time to perform the end-to-end analysis should be clearly stated in the beginning or end of the M&M section.

   **Reply:**
   The computational language and the timing for usage in this research had been added into the M&M section.

5. Symmetrical histogram analysis section: removing pixel grayscale values below 50% seems a bit arbitrary. What about Otsu’s method or similar?

   **Reply:**
   Actually, it is grayscale values below “50”, not 50%, it is our mistake, and had been corrected. This criterion is commonly used in the study of digital image processing, as grayscale below 50 usually had no meaningful data. The Otsu’s method works great in histogram thresholding, and may be used in more complicated situation. But in our relative simple situation, our criterion is enough to generate satisfactory results.
6. Statistics; were the TN, TP, FP and FN values based on pixel-by-pixel analysis?

**Reply:**
The TN, TP, FP and FN values were based on pixel-by-pixel analysis; this notification had been added into the Method section.

7. References; some of the reference titles are not in bold.

**Reply:**
The reference had been renewed, and all mistake had been corrected.

8. The word ‘Hitogram’ in Figure 6 is misspelled

**Reply:**
The misspelled ‘Hitogram’ in Figure 6 had been corrected.

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**Reply to the Reviewer #2**

Reviewer #2 stated as follows.

_In this work, FCM classifier and native region growing are combined to locate tumor regions in non-contrasted T1 and T2 -weighted MR images. The crucial issue is that the paper does not well substantiate the novelty of the proposed approach._

**Reply:**
The draft had been major revised A lot more issues had been added into Discussion section, including in depth analysis of the results, the unique characteristic of our study compared to other related works. The clinical usefulness of our research is also discussed.

_Besides, a lot of the paper is dedicated to present textbook theory (e.g. FCM, evaluation criteria, ....) and giving a reference is much sufficient._ –

**Reply:**
The Background section had been re-written, contents with already-known textbook-like knowledge is deleted, or just mentioned in reference.
Explanations also suffer from language problems - it takes considerable effort to understand such simple things (e.g. “The unsupervised FCM does not require training data, had been frequent used in the segmentation of MR images”, ” At the same time, the contrast-enhanced T1-weighted images (CET1) were use for manual tumor segmentation, the resulting “Ground truth (GT)” will be used for validating the results for brain tumor image extraction later.”, ....)

Reply:
Our revised draft had been sent for professional English edit before this time submission.

- Resolution of equations is extremely distorted.
Reply:
The equation portion had been concise and re-edited. Resolution of equations is improved.

- Definition of Solidity is unclear.
Reply:
Definition of Solidity and the method had been described in more detail, also a figure is given on this issue for better understanding.

- I think that 36 references for such work is so much, especially that authors missed a comparative study with similar works.
Reply:
More irrelevant reference, or reference regarding the basic already-known knowledge were deleted. However, more updated and related works were also added, this make only 4 reference less than old drafts. These newer reference, including the valuable work of our reviewers, were missed or haven’t been published at the time when this research was designed. During our revision, we benefit very much from these newly discoveries.

- What is the used stop criterion for the region growing algorithm?
Reply:
When neighbor pixel is beyond the 2SD, this had been described more detailed in the Method section.

- What is the interest of Table 1?
Reply:
The table 1 had been deleted as it is well-known knowledge and seems redundant.

- Table 3 can be efficiently replaced by curves.

Reply:
- Many parameters are used (for FCM as well for RG). Influence of these parameters on final results should be discussed.

Reply:
These parameters are discussed. The influence of these parameters on final results has been added into the discussion section.

In order to make appropriate revision according to the critical points raised by the reviewers, some of the data had been re-analyzed and new results had been added. The spelling and some grammar errors have been carefully corrected. Furthermore, the final draft is sent for professional English editing.

During our revision, more updated and related works, including the valuable work of our reviewers, had been reviewed. What make us feel encouraging is that, these works all dedicated to solve the challenges we faced in our study, but with different ways of approach. This makes us believe that our study had its unique characteristic, and has the value for been accepted and published in your journal.

Sincerely Yours truly,

Thomas Mon-Hsian Hsieh