Quantitative Analysis of Dynamic Contrast-Enhanced and Diffusion-Weighted Magnetic Resonance Imaging for Oncology in R

March 1, 2011

Associate Editor

General Comments

- Generating the pdf document from Sweave includes information on different machines (where the creation has been done). Thus the audit.trail in Fig.10 should be edit slightly in the final version (working directory).

  Thank-you for this comment. We are happy to manually edit the audit trail for final publication.

Specific Comments

- Can the grey scale contrast be enhanced in the images?

  TO DO!

Reviewer #1

We would like to thank the reviewer for all his/her comments and suggestions.

Minor Remarks

1. A colour scale would aid interpretation of the various quantitative figures.

   TO DO!

2. The authors are not entirely consistent about the use (or not) of a subscript in relaxation time variables such as T1; e.g. at the bottom of page 2, "T1" is written both with and without a subscript.

   We have adopted the notation "T1" and "T2" throughout the manuscript.

3. A little more explanation of the final aim of the processing (i.e. maps of estimated kinetic parameters, etc.), and an indication of the reasons that they are important in oncology, would be helpful in the overview at the beginning of §2, to make it clearer to the reader where the manuscript is going. It is also not entirely clear how the steps laid out there link to one another, and it would be useful to make this a bit more explicit.

   TO DO!

4. Some terms seem not be defined before first use. It's not clear to me exactly what m_0 and R_10 each represent on page 3; "transverse relaxation time" is used on page 3 but without explanation of the meaning of "transverse" (likewise "longitudinal"); again on page 3, it is not necessarily obvious which of S(t) and S(0) is pre-contrast, and which post-contrast; B1 is used several times in §2.3 but not defined; in §3, pulse duration and

separation are discussed but without any explanation of what these pulses are. I realise that many/most readers may know about these terms, but defining them, or avoiding their use entirely if they aren't really needed, would make the paper more accessible.

Thank-you for pointing this out. Text has been added, with references, to explain the parameters m_0 and R_{10}. Text has been added/modified to better explain relaxation times/rates. Text has been added/modified to better explain the magnetiziation fields B0 and B1.

5. The URL for ITK is given as ikg.org on page 4. This should be corrected.

   Fixed.

6. After equation (7), the paragraph begins, "A long repetition time (TR <= 5T1) ...". Should this sign not be ">="?

   Fixed.

7. The discussion of anisotropic diffusion in §3 seems odd, since equation (29) includes only a scalar diffusivity term, and therefore can represent only isotropic diffusion. Also in this section, the prescription to ignore measurements with b <= 100 s/mm2 is a bit too general: the suitability of particular data will depend on the application. "The diffusion of water ..." (beginning of the third paragraph) should be "The diffusivity of water ...". Note also that diffusivity is temperature-dependent, so "at room temperature" or similar should be added.

   We have re-worded the first sentence of §3 in order to provide a clear, concise statement about diffusion-weighted imaging. We are confused by the reviewer's comments, since the Stejskal–Tanner formula is well known and provides an estimate of the apparent diffusion coefficient (ADC) via the parameter D. We have taken the recommendation of $b \leq 100$ s/mm^2 from **?**. We acknowledge that not everyone may agree with this viewpoint, but the authors on this publication do represent a very knowledgeable group. We have changed "diffusion" to "diffusivity" and also added the phrase "at room temperature" to the text.

8. In the Bayesian estimation procedure, is there a particular reason for using the median rather than the mean of the posterior distribution as the summary statistic?

   The median is a more robust summary statistic and is frequently used as the point estimator in Bayesian inference. The posterior median is prefered since it is typically closer to the posterior mode (the Bayesian analog to the maximum-likelihood estimator of location) than the posterior mean (**?**).

9. In §4.2, the authors state that "... high ADC values correspond to pure isotrpic diffusion of water molecules in the tissue". This is misleading: isotropy and apparent/mean diffusivity are distinct characteristics.

   The text has been modified to better reflect the physical interpretation of high ADC values.

10. It's not clear to me what the authors mean by "... the indirect nature of MRI data acquisition". Perhaps this could be clarified.

    Text has been added to better explain what we mean by this statement.

Reviewer #2

We would like to thank the reviewer for all his/her comments and suggestions.

Comments

1. P.1 - Why is it called dcemriS4 if it also does diffusion weighted image processing? DTI?

   The **dcemriS4** package originally only contained mathematical models for DCE-MRI, but since DWI has become quite popular in oncology additional functionality has been included to allow ADC estimation.

2. P.2 Many, many "?" question marks throughout the pdf file.. missing references, etc..

   This was a problem with the `Sweave` procedure used by the associate editor. All citations/references have been checked and are valid in the manuscript.

3. P.2 "DWI quantifies the deviation of diffusion from isotropy" This statement is not true.. DWI using equivalent strength gradients in the three orthogonal directions at varying strengths to measure the isotropic free diffusion path length in tissue. While technically the DWIx, DWIy, DWIz components could be examined individually, it is the trace of these that provides an isotropic path length mediated by cellular restrictions to the random Brownian motion. i.e. The apparent diffusion coefficient (ADC) maps generated from a DWI acquisition contains no information about the degree or direction of anisotropy but will provide essential information on regions of infarct as well as boundaries and differentiation of cystic from malignant lesions.

   TO DO!

4. p.2 - "Deviations from isotropy (anisotropic diffusion) in tissue is then used to infer biological information; e.g.,detection, disease progression, treatment response." Should be "are then used to infer"... really only applies to white matter disease, i.e. degeneration or destruction of the fiber tracts..

   Changed.

5. p.2 "Typically, several structural sequences are performed (both T1- and T2-weighted) after the patient has been positioned in the scanner." - Not needed..

   Removed.

6. p.4 "For computational reasons, we follow the method of ?" Which method and why?

   This was a problem with the `Sweave` procedure used by the associate editor. All citations/references have been checked and are valid in the manuscript.

7. Also, will you confirm what relaxation values you will be using for various Gadolinium chelates at differing field strengths.. in blood or plasma?

   This is a good point. We supply a fairly generic value for r_1 by default, but we leave it up to the user to check which value is appropriate for their gadolinium chelate and field strength. I am aware of a document by Dr. Val Runge, presented at the 2009 ISMRM I think, that provides a nice table of gadolinium chelates and their properties. However, I do not know how to reference such a unpublished document.

8. P.5 Should the actual command line R-code actually be included in the text or an appendix?

   We believe strongly that the R code should be interwoven with the text and not placed at the end of the manuscript in an appendix.

9. P.6 "By defining regions of interest (ROIs) in FSLView we may construct a mask that separates voxel belonging to the 10 unique gels." should be "separates voxels"

   Fixed.

10. P.7 Need to reference Weinmanns original paper on AIF's.

    I believe it is cited.

11. P.8 - Figure 3 - Why not just use a linear increase during bolus injection ($t < \tau$) (assuming that a power injector is used at a fixed rate) and then a single/bi-exponential afterwards? This is done routinely in PET. Should also show an actual AIF from a human subject and representative fit..

    We have thought about using a PET-like alternative to the parametric models for the AIF from the DCE-MRI literature. One advantage of our current set of parametric models is that they have analytical solutions, when convolved with the compartmental model, and thus offer computational efficiency. This could be done for the linear-plus-single/double-exponential model, but we have not investigated it.

12. P.11 "To increase computational efficiency draws from the posterior distribution are implemented in C and linked to R." What draws from the posterior distribution??

    As stated in the same paragraph, samples from the posterior PDF are drawn. We replaced the sentence with "To increase computational efficiency sampling from the posterior distribution is implemented in C and linked to R.".

13. P.13 "Contrast is generated when the diffusion of molecules in tissue prefer a specific direction" Please see comment #3 as DWI/ADC maps do not contain directional information. Contrast may be obtained in the core infarct of an ischemic stroke in regions of isotropic diffusion.

    TO DO!

14. P.13 Might also mention higher diffusion b-values (i.e. > 1000 s/mm2) to examine slow/fast components of diffusion related to intra/extracellular diffusion.

    Do you have a reference for this? As it stands we are taking guidance from **?**. We would be happy to add more information regarding b-values with appropriate references.

15. P.13 Was even a paper out a few years back touching on diffusion in DCE analysis. Pellerin M, Yankeelov TE, Lepage M. Incorporating contrast agent diffusion into the analysis of DCE-MRI data. Magn Reson Med. 2007 Dec;58(6):1124-34.

    Thank-you for this reference. We were not aware of this paper. It would be difficult to include it at this point in time, since the manuscript is limited to covering the current capabilities of the **dcemriS4** package. This diffusion-perfusion model would be an interesting addition to its functionality.

16. P.13 "Observing an increase in diffusivity.." Need to be cautious here as tumors may show increased ADC due to initial edemic response to therapy followed by decreased ADC as tumors begin to become necrotic or apototic. Additionally, tumor regression would be indicated by a reduction in ADC.. Lastly, ADC values in different tumor types do not all respond the same as well as variation in Tx (XRT, Chemo, etc.).

    TO DO!

17. P.14 "we utilize a binary mask" How was this mask created and what threshold was decided upon to create the mask??

    The binary mask was created using FSLView, the popular viewing software packaged with FSL. A non-expert (BW) placed a square of fixed dimension over several slices that appeared to contain a tumor. No threshold was used to create the binary mask.

18. P.14 "from an appropriate voxel or collection of voxel" should be "voxels".

    Changed.

19. P.14 Although selecting a literature based AIF may be appropriate for some neurological lesions, a population average closer to the feeding vessel of the tumor may be better served for other tumor types outside the brain.

    We agree completely. The literature-based AIF is used for illustrative purposes only. We do not advocate using such an AIF in practice.

20. P.15 a reference to "fritz.hansen" is made in the code.. does this refer to a subject/colleague name?

    The name of this option refers to **?**, who proposed values for the bio-exponential AIF. This work has been cited in the AIF section.

21. P.15 "ve is high at the tumor rim" - Is the maximum value of this parameter constrained? i.e. can there be $> 100\%$ for the extravascular extracellular space?

    The volume of EES is not constrained during estimation. We have discussed this with reviewers when submitting similar analyses to journals in the past. Our position is that the mathematical models used in describing the contrast agent concentration over time are overly simplistic and imposing such a rigid constraint does not benefit the user since it is difficult to believe that the model captures the true biological state of perfusion in tissue.

22. P.15 Likewise is.. ve + vp <1 used as a constraint?

    No, a hard constraint on either of the volume parameters is not implemented during estimation. For more information, please see our answer to the previous item.

23. P.15 "The SSE over the given ROI covers a variety of tissue types" Has this program been tested or applied to non-cerebellar tumor types (i.e, breast, colorectal, prostate.)

    Yes, we have applied these algorithms to breast, head-and-neck and prostate tumors.

24. P.21 "The methodology behind DWI and DTI are virtually identical.. so we will ignore the extra information provide" should be "provided". I understand the statement, but a few sentences about defining the maximum eigenvector of the diffusion ellipsoid with

an figure might be informative for the reader.. although possibly beyond the scope of this article. It might show the orthogonal diameters on the ellipsoid used to calculated the DWI. (Might also mention that all major vendors compute the fractional anisotropy (FA) maps online.)

Fixed. We appreciate the comments from the reviewer, but we do not think that a discussion of diffusion tensor imaging (DTI) is appropriate in this manuscript. We only mention DTI since the RIDER NEURO MRI acquisition contains such a sequence, and we happen to use it for illustrative purposes in DWI.

25. Also, in my experience, the ADC map created from the DTI data set may differ slightly from that acquired with a 3-Trace DWI sequence.

    Thank-you, we have added a sentence that states this fact.

26. P.22 "range of physical units for the ADC values is [0.0005, 0.003]" Interestingly, I have also seen values greater than this due to CSF flow phenomenon.

    Thank-you for your comment.

27. P.22 "isotrpic diffusion" should be "isotropic"

    Changed.

28. In this reviewers opinion, the diffusion component of this package might not be included.. Calculation of apparent diffusion coefficient maps are now created online at the time of acquisition on most major MRI vendors. In addition, the creation of the maps is the result of a straight linear regression which is must less involved than the DCE-MRI analysis presented in this work.

    TO DO!

29. P.26 Are there capabilities available for incorporation of a user-defined AIF taken from the DCE-MRI data set??

    Yes, it is possible to supply a user-defined AIF. We have added a few sentences in the RIDER Neuro MRI example that highlights this feature.