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

March 1, 2011

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.

   TO DO!

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.

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.

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.

TO DO!

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?

TO DO!

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.

TO DO!

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

TO DO!

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?

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

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.

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..

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..

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

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

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

10. P.7 Need to reference Weinmanns original paper on AIFs.

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..

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??

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.

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.

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.

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.).

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

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

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.

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

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?

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

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.)

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.)

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.

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.

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

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.

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