Techniques and Applications of Dynamic Contrast Enhanced Magnetic Resonance Imaging in Cancer

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***Abstract*—We first discuss several key technical issues associated with quantitative dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), and then provide examples of DCE-MRI in oncology. In particular, we examine the importance of both active and passive delivery of the contrast agent to the tissue under investigation, and repeatability/reproducibility in DCE-MRI studies. We then discuss examples of how DCE-MRI can assist in assessing and predicting therapeutic response in the neoadjuvant setting.**

I. Introduction

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) involves the serial acquisition of T_1-weighted images before, during, and after the injection of a paramagnetic contrast agent [1]. As the contrast agent arrives at a region of interest it changes the tissue's native T_1 as a function of the concentration and distribution of the contrast agent. Thus, images acquired during this process lead to a signal intensity time course that can then be analyzed with a pharmacokinetic model to return estimates of parameters related to tissue physiology including K^{trans} (the volume transfer constant, related to perfusion/permeability), v_e (the extravascular extracellular volume fraction), v_p (the plasma fraction), and k_{ep} (the efflux constant). These parameters are relevant when studying, for example, tumor induced angiogenesis. In order to perform this modeling three fundamental entities are required: 1) a baseline map of the tissue's native T_1 value(s), 2) the time rate of change of the concentration of contrast agent in both a feeding artery (the so-called arterial or vascular input function) and the tissue of interest, and 3) a pharmacokinetic model to analyze such data. We discuss items 2) and 3) before turning our attention to the repeatability and reproducibility of the methods. Lastly, we examine how DCE-MRI can be used to assess and predict the response of cancers to neoadjuvant therapy.

II. Subtleties of DCE-MRI measurement

A. Characterizing the Arterial Input Function

A particular difficulty associated with quantitative DCE-MRI analysis is the identification of the arterial input function (AIF). The AIF is a measure of the contrast agent concentration in the plasma, and is a necessary component for quantitative modeling as it provides the "input" to the system. The AIF can be measured *via* blood sampling, but this requires frequent, rapid sampling which is often uncomfortable in the clinical setting, and unrealistic in the preclinical setting given the small blood volume of the mice most frequently used in such studies. An alternative to blood sampling is the use of an image-derived AIF, but the difficultly associated with this approach is two-fold. First, a major vessel must be visible in the desired field of view and this is not always feasible given the region of interest. Secondly, the AIF displays rapid uptake and washout of the contrast agent; thus, in order to capture the relevant curve characteristics, the temporal resolution must be sufficiently fast. Unfortunately, this necessarily limits the spatial resolution of the acquisition. A common approach to avoid individual AIF acquisition is to employ a population AIF, whereby a similarly situated population of patients is utilized to generate an average AIF, which can then be applied to future patients [2-7]. This eliminates the need to measure the individual AIF and allows for increased spatial resolution. Loveless *et al*. demonstrated that, in the preclinical setting, use of a population AIF did not significantly alter quantitative results as compared to the patient-specific AIF [4]. Parker *et al.* [7] and Li *et al.* [3] demonstrated similar results in the clinical setting, wherein using a population AIF increased the reproducibility of the quantitative parameters. Another commonly utilized approach which eliminates the need to acquire a patient-specific AIF is the reference region (RR) approach [8-10]. The RR approach utilizes a well-characterized tissue, such as muscle, to provide a second differential equation describing contrast agent concentration compartmentalization over time. This second equation allows for the elimination of the AIF, and results in a solution for the ROI that depends on the characteristics of the reference region.

Each of the above mentioned methods have their own strengths and weaknesses and care must be taken to select a method that is appropriate for the experiment at hand. The choice in input function is frequently determined by 1) the presence of a feeding vessel in the field of view, and 2) the required spatial resolution of the experiment. If high spatial resolution data is needed, this precludes the acquisition of high temporal resolution data so that a population averaged AIF or reference region approach is warranted. This is also the case if a feeding vessel is not available in the field of view. However, if high spatial resolution data is not required

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and a feeding vessel is available in the field of view, then direct measurement of the AIF is possible.

B. Incorporating the Effects of Contrast Agent Diffusion

Another point of consideration in quantitative DCE-MRI analysis is that the delivery of contrast agent (CA) to the region under study may not be done so actively; that is, the contrast agent may arrive by passive diffusion. Standard quantitative approaches, such as the Tofts-Key model [1], do not consider the effect of extravascular diffusion of the CA. However, diffusion has the potential to have a significant effect on contrast agent distribution and the observed pharmacokinetics in heterogeneous regions, as is often the case in tumor-bearing tissues that typically possess much variation in vascularity and necrosis. Acknowledgment of this shortcoming has led to the development of approaches to account for inter- and intra-voxel CA diffusion. Pellerin *et al*. developed a finite difference model to analyze the effect of inter-voxel CA diffusion on quantitative DCE analysis [11]. Their model that incorporated inter-voxel diffusion by assigning domain diffusion coefficients, allowed for quantitative analysis of K^{trans} and v_e in the presence of diffusion. When analyzing DCE-MRI data in a xenograft model, the standard Tofts-Key method resulted in unphysiological values of v_e; however, the results showed an improvement in the data when diffusion was considered. Fluckiger *et al*. worked to improve the practicality of this approach, by developing a less computationally intensive algorithm to include the effects of inter-voxel diffusion [12]. Their "diffusion compensated" Tofts-Key model allowed for voxel-specific diffusion coefficients that were not dependent on the surrounding voxels; the model showed improved results over the standard Tofts-Key model. Jia *et al*. utilized a factor termed the contrast agent diffusion coefficient (CDC) to evaluate diffusion in colorectal liver metastases [13]. The approach consisted of evaluating the rate of gradient decrease in the signal intensity of similarly-behaving regions. Their work showed that the CDC was a repeatable value which was able to describe the heterogeneity of the tissue.

There is a growing awareness in the field that passive diffusion of contrast agent in the region under investigation can adversely affect the estimate of pharmacokinetic parameters. As these are the very parameters that have been shown to be of use in clinical studies, maximizing the accuracy with which they can be attained is of great import. Thus, the effects of contrast agent should be accounted for in certain settings. Of course, the precision at which these measurements can be made is also of great relevance.

III. Repeatability and Reproducibility of DCE-MRI

With the increasing use of DCE-MRI to characterize specific aspects of tumor physiology, it is imperative to assess the reproducibility in order to gain an understanding of the expected error within each imaging measurement. An example of DCE-MRI test-retest is shown in Figure 1 in which K^{trans} parametric maps of a central tumor slice are displayed for two separate imaging sessions (within one week) of a patient with breast cancer. K^{trans} was calculated by fitting the dynamic signal intensity for each voxel using the standard Tofts-Key model [1]. The importance of such data is that one wants to be able to establish the range outside of which any observed changes can be safely assumed to be due to changes in biology and not errors in the measurement process. In the figure it is clear that, in this patient, while the trends are quite similar the absolute values of the pixels are different. Repeatability and reproducibility analyses attempt to characterize this issue.

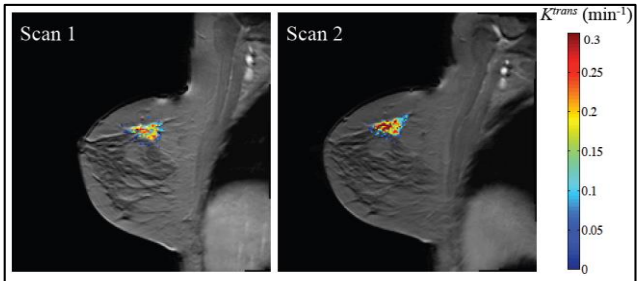

Figure 1 shows K^{trans} maps obtained on the same breast tumor at two imaging sessions within one week. Observe how the general pattern of K^{trans} values matches, but there is variation. This example stresses the importance of establishing the repeatability of DCE-MRI during longitudinal studies.

Two values of particular interest when assessing reproducibility are the repeatability coefficient (r) and the 95% confidence interval (CI) of the mean; these statistical values are useful in, for example, a treatment response study as they define a level above which a significant change due to therapy can be inferred. The repeatability coefficient r defines the expected limit of variability between two scans on the same subject in 95% of the cases. More specifically, this value defines the difference between scans that can be attributed to measurement error as opposed to physiological changes in an individual. The 95% CI provides a reproducibility measurement of the group mean for any specific parameter. The within-subject coefficient of variation (wCV) has also been used to evaluate reproducibility as it provides a measure of the variability within subjects; however, it is not as useful as r or 95% CI when interpreting treatment response data.

Table 1 (next page) summarizes the reproducibility results from several clinical and preclinical DCE-MRI studies in various types of tumors [14-18]. The reproducibility statistics for K^{trans} seem to vary among the clinical and preclinical studies; for example, r was 0.26 min^{-1} in patients [14], and ranged from 0.005 min^{-1} to 0.22 min^{-1} in rodent models of cancer [16-18]. This large range could be due to several variables, although it is most likely due to differences in data acquisition and analysis protocols. Ferrier *et al*. [17] and Barnes *et al*. [16] used a power injector for contrast agent administration whereas Galbraith *et al*. [14] and Yankeelov *et al*. [18] used manual injections. Galbraith *et al*. hypothesized that using a power injection to administer the contrast agent would significantly improve reproducibility, and the data in Table 1 (next page) support this hypothesis.

The variability associated with v_e appears to be less

TABLE I. Repeatability and reproducibility findings for DCE-MRI

Reference	Tumor type	Parameters	Statistic	Findings
Galbraith [14]	Various (kidney, liver, lymph node, pelvis chest)	K^{trans}	*r*	0.26[a] min^{-1}
				(-45 to +83%)
			95% CI	-14% to + 16%
			wCV	24%
		v_e	*r*	0.08
			95% CI	±6.0%
			wCV	8.5%
Jackson [15]	Glioma	K^{trans}	wCV	7.7%
		v_e		6.2%
Barnes [16]	human breast cancer xenograft	K^{trans}	*r*	0.076 min^{-1}
			95% CI	±16%
			wCV	17%
		v_e	*r*	0.11
			95% CI	±7.3%
			wCV	8.00%
Ferrier [17]	rat brain tumor	K^{trans}	*r*	0.005 min^{-1}
			95% CI	±12%
Yankeelov [18]	murine breast tumor	K^{trans}	*r*	0.22 min^{-1}
			wCV	20%
		v_e	*r*	0.204
			wCV	19%

r, repeatability coefficient, CI, confidence interval; wCV, within-subject coefficient of variation

sensitive to the mechanism of contrast agent injection, as v_e had better reproducibility than K^{trans} in all but one of the studies summarized in Table 1. For example, the 95% CI ranged between ± 6.0% and ± 7.3%, while the wCV ranged between 6.2% and 8.5% [14-16]. Reproducibility in terms of *r* and wCV is similar between K^{trans} and v_e in [18].

In addition to measuring reproducibility at a single institution, it is also imperative to investigate the error associated with DCE-MRI protocols across institutions in order to facilitate multisite trials. There have been only limited efforts at determining multisite reproducibility for quantitative DCE-MRI protocols and this is the subject of several ongoing efforts. Importantly, such investigations are also ongoing in other imaging modalities including FDG-PET. Only when such statistical issues are determined can we truly have confidence that the measurement is ready for, e.g., multi-site clinical trials. As there has been much success at single site trials, this is a problem to address.

IV. Clinical Applications in the Neoadjuvant Setting

In the neoadjuvant setting, cancer patients receive therapy to reduce tumor burden to a size more amenable to surgery. Neoadjuvant therapy also provides an opportunity to observe tumor sensitivity to a particular regimen [19]. However, if it were possible to determine that the primary tumor is unresponsive, the treatment could be changed to another, potentially more effective approach thereby avoiding unnecessary side effects and toxicities. DCE-MRI is one such method that has been proposed to accomplish this task. For example, the I-SPY TRIAL [20] scanned 216 women with breast cancers at four time points: prior to the start of anthracycline-cyclophosphamide (AC) chemotherapy, prior to the second cycle of AC chemotherapy, between AC treatment and taxane therapy, and just prior to surgery. This study showed that the rate of change of the tumor volume and the signal enhancement rate (SER) between therapeutic regimens yielded an area under receiver operating characteristic curve (AUC) of 0.72 and 0.71, respectively.

Other studies have employed more quantitative DCE-MRI pharmacokinetic models to investigate the ability to predict eventual response in breast cancer. Padhani *et al*. [21] performed DCE-MRI examinations in 25 patients with primary breast cancer before, after the first and after the second cycle of neoadjuvant chemotherapy (NAC) and investigated tumor size, K^{trans}, v_e, and k_{ep}. Both tumor size and change in the range of the K^{trans} histogram after two cycles of treatment were able to predict eventual response with AUCs of 0.93 and 0.94, respectively. Recently Li *et al*. [22] examined 28 patients using DCE-MRI at three time points: pretreatment, post-one cycle of NAC, and just prior to surgery. Semi-quantitative and quantitative physiological parameters were evaluated, including tumor longest dimension, tumor volume, initial area under the curve, SER and SER related parameters, K^{trans}, v_e, k_{ep}, plasma volume fraction (v_p), and the average intracellular water lifetime of a water molecule (τ_i), using three pharmacokinetic models. Among all the parameters, the changes in the SER washout volume and k_{ep} were the best predictors of pathologic complete responders after one cycle of NAC. The SER washout volume yielded an AUC of 0.75, and k_{ep} yielded a maximum estimated AUC of 0.78. Figure 2 shows the k_{ep} maps superimposed on the post-contrast DCE-MRI data at the pre-NAC (1st column), post-1 cycle of NAC (2nd column), and post all cycles of NAC (3rd column) time points for one representative patient achieving pathological complete response (pCR). Note that the mean k_{ep} has decreased from 0.39 min^{-1} at baseline to 0.28 min^{-1} after one cycle of therapy. Li *et al*. also combined the DCE-MRI and diffusion weighted MRI (DW-MRI) data using a simple ratio

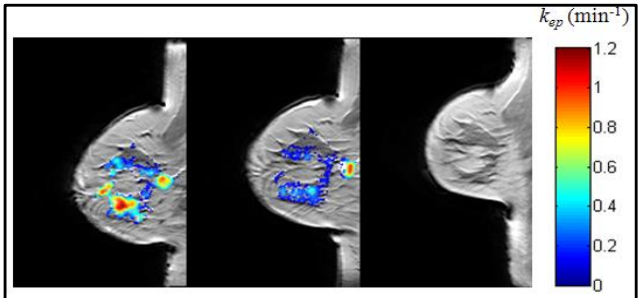

Figure 2 shows the k_{ep} maps superimposed on the post-contrast DCE-MRI data at the pre-NAC (1st column), post-1 cycle of NAC (2nd column), and post all cycles of NAC (3rd column) time points for one representative patient achieving pCR. Observe the significant drop in k_{ep} from the first to second time points.

(k_{ep}/ADC, where ADC is the apparent diffusion coefficient from the DW-MRI data) and showed that the integrated data have a better ability to predict treatment response [23].

There also are studies investigating the predictive ability of the DCE-MRI parameters on other cancers for which neoadjuvant therapy is appropriate. Kim *et al*. [24] performed DCE-MRI on 33 patients with head and neck squamous cell carcinomas before neoadjuvant chemoradiation. K^{trans}, v_e, and τ_i were estimated. It was reported that the average pretreatment K^{trans} was higher in patients achieving a complete response than in those patients who saw a partial response ($p = 0.001$). In the study of Guo *et al*. [25], 69 patients with osteosarcoma were examined using DCE-MRI at week 0, week 9, and week 12. K^{trans}, k_{ep}, v_e, v_p, and the corresponding differences (ΔK^{trans}, Δk_{ep}, Δv_e, and Δv_p) were calculated. It was found that not only K^{trans}, k_{ep}, v_e, v_p significantly decreased from the baseline to week 9 and week 12, but also K^{trans}, v_p, and Δk_{ep} were significantly different between responders and nonresponders.

V. Conclusion

DCE-MRI has already made important contributions to clinical science, but there are several technical areas that need to be addressed to enhance the utility of the method.

References

[1] T. E. Yankeelov and J. C. Gore, "Dynamic Contrast Enhanced Magnetic Resonance Imaging in Oncology: Theory, Data Acquisition, Analysis, and Examples," *Curr Med Imaging Rev,* vol. 3, pp. 91-107, May 1 2009.

[2] S. M. Kim, M. A. Haider, M. Milosevic, and I. W. Yeung, "A comparison of dynamic contrast-enhanced CT and MR imaging-derived measurements in patients with cervical cancer," *Clin Physiol Funct Imaging,* vol. 33, pp. 150-61, Mar 2013.

[3] X. Li, E. B. Welch, L. R. Arlinghaus, A. B. Chakravarthy, L. Xu, J. Farley*, et al.*, "A novel AIF tracking method and comparison of DCE-MRI parameters using individual and population-based AIFs in human breast cancer," *Phys Med Biol,* vol. 56, pp. 5753-69, Sep 7 2011.

[4] M. E. Loveless, J. Halliday, C. Liess, L. Xu, R. D. Dortch, J. Whisenant*, et al.*, "A quantitative comparison of the influence of individual versus population-derived vascular input functions on dynamic contrast enhanced-MRI in small animals," *Magn Reson Med,* vol. 67, pp. 226-36, Jan 2012.

[5] D. M. McGrath, D. P. Bradley, J. L. Tessier, T. Lacey, C. J. Taylor, and G. J. Parker, "Comparison of model-based arterial input functions for dynamic contrast-enhanced MRI in tumor bearing rats," *Magn Reson Med,* vol. 61, pp. 1173-84, May 2009.

[6] R. Meng, S. D. Chang, E. C. Jones, S. L. Goldenberg, and P. Kozlowski, "Comparison between population average and experimentally measured arterial input function in predicting biopsy results in prostate cancer," *Acad Radiol,* vol. 17, pp. 520-5, Apr 2010.

[7] G. J. Parker, C. Roberts, A. Macdonald, G. A. Buonaccorsi, S. Cheung, D. L. Buckley*, et al.*, "Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI," *Magn Reson Med,* vol. 56, pp. 993-1000, Nov 2006.

[8] D. A. Kovar, M. Lewis, and G. S. Karczmar, "A new method for imaging perfusion and contrast extraction fraction: input functions derived from reference tissues," *J Magn Reson Imaging,* vol. 8, pp. 1126-34, Sep-Oct 1998.

[9] C. Yang, G. S. Karczmar, M. Medved, and W. M. Stadler, "Estimating the arterial input function using two reference tissues in dynamic contrast-enhanced MRI studies: fundamental concepts and simulations," *Magn Reson Med,* vol. 52, pp. 1110-7, Nov 2004.

[10] T. E. Yankeelov, J. J. Luci, M. Lepage, R. Li, L. Debusk, P. C. Lin*, et al.*, "Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model," *Magn Reson Imaging,* vol. 23, pp. 519-29, May 2005.

[11] M. Pellerin, T. E. Yankeelov, and M. Lepage, "Incorporating contrast agent diffusion into the analysis of DCE-MRI data," *Magn Reson Med,* vol. 58, pp. 1124-34, Dec 2007.

[12] J. U. Fluckiger, M. E. Loveless, S. L. Barnes, M. Lepage, and T. E. Yankeelov, "A diffusion-compensated model for the analysis of DCE-MRI data: theory, simulations and experimental results," *Phys Med Biol,* vol. 58, pp. 1983-98, Mar 21 2013.

[13] G. Jia, C. O'Dell, J. T. Heverhagen, X. Yang, J. Liang, R. V. Jacko*, et al.*, "Colorectal liver metastases: contrast agent diffusion coefficient for quantification of contrast enhancement heterogeneity at MR imaging," *Radiology,* vol. 248, pp. 901-9, Sep 2008.

[14] S. M. Galbraith, M. A. Lodge, N. J. Taylor, G. J. Rustin, S. Bentzen, J. J. Stirling*, et al.*, "Reproducibility of dynamic contrast-enhanced MRI in human muscle and tumours: comparison of quantitative and semi-quantitative analysis," *NMR Biomed,* vol. 15, pp. 132-42, Apr 2002.

[15] A. Jackson, G. C. Jayson, K. L. Li, X. P. Zhu, D. R. Checkley, J. J. Tessier*, et al.*, "Reproducibility of quantitative dynamic contrast-enhanced MRI in newly presenting glioma," *Br J Radiol,* vol. 76, pp. 153-62, Mar 2003.

[16] S. L. Barnes, J. G. Whisenant, M. E. Loveless, G. D. Ayers, and T. E. Yankeelov, "Assessing the reproducibility of dynamic contrast enhanced magnetic resonance imaging in a murine model of breast cancer," *Magn Reson Med,* vol. 69, pp. 1721-34, Jun 2013.

[17] M. C. Ferrier, H. Sarin, S. H. Fung, B. Schatlo, R. M. Pluta, S. N. Gupta*, et al.*, "Validation of dynamic contrast-enhanced magnetic resonance imaging-derived vascular permeability measurements using quantitative autoradiography in the RG2 rat brain tumor model," *Neoplasia,* vol. 9, pp. 546-55, Jul 2007.

[18] T. E. Yankeelov, L. M. DeBusk, D. D. Billheimer, J. J. Luci, P. C. Lin, R. R. Price*, et al.*, "Repeatability of a reference region model for analysis of murine DCE-MRI data at 7T," *J Magn Reson Imaging,* vol. 24, pp. 1140-7, Nov 2006.

[19] S. F. Sener, "Neoadjuvant therapy for locally advanced cancer," *J Surg Oncol,* vol. 101, p. 282, Mar 15 2010.

[20] N. M. Hylton, J. D. Blume, W. K. Bernreuter, E. D. Pisano, M. A. Rosen, E. A. Morris*, et al.*, "Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy--results from ACRIN 6657/I-SPY TRIAL," *Radiology,* vol. 263, pp. 663-72, Jun 2012.

[21] A. R. Padhani, C. Hayes, L. Assersohn, T. Powles, A. Makris, J. Suckling*, et al.*, "Prediction of clinicopathologic response of breast cancer to primary chemotherapy at contrast-enhanced MR imaging: initial clinical results," *Radiology,* vol. 239, pp. 361-74, May 2006.

[22] X. Li, L. R. Arlinghaus, G. D. Ayers, A. B. Chakravarthy, R. G. Abramson, V. G. Abramson*, et al.*, "DCE-MRI analysis methods for predicting the response of breast cancer to neoadjuvant chemotherapy: Pilot study findings," *Magn Reson Med,* vol. 71, pp. 1592-602, Apr 2014.

[23] A. L. Li X, Chakravarthy AB, Abramson RG, Abramson VG, Farley J, Ayers GD, Mayer IA, Kelley MC, Meszoely IM, Means-Powell J, Grau AM, Sanders M, Bhave SR, Yankeelov TE, "Quantitative DCE- and DW-MRI to Predict the Response of Primary Breast Cancer to Neoadjuvant Therapy," *Proc. Intl. Soc. Mag. Reson. Med. (ISMRM)* p. 3384, 2013.

[24] S. Kim, L. A. Loevner, H. Quon, A. Kilger, E. Sherman, G. Weinstein*, et al.*, "Prediction of response to chemoradiation therapy in squamous cell carcinomas of the head and neck using dynamic contrast-enhanced MR imaging," *AJNR Am J Neuroradiol,* vol. 31, pp. 262-8, Feb 2010.

[25] J. Guo, W. E. Reddick, J. O. Glass, Q. Ji, C. A. Billups, J. Wu*, et al.*, "Dynamic contrast-enhanced magnetic resonance imaging as a prognostic factor in predicting event-free and overall survival in pediatric patients with osteosarcoma," *Cancer,* vol. 118, pp. 3776-85, Aug 1 2012.