LIVER TUMOR ASSESSMENT WITH DCE-MRI

Liliana Caldeira and João Sanches

Instituto de Sistemas e Robótica / Instituto Superior Técnico
1049-Lisbon, Portugal

ABSTRACT

Dynamic-Contrast Enhanced MRI (DCE-MRI) is used in clinical practice to assess liver tumor malignancy. An algorithm to get information for automatic classification of tumors is presented. The *Maximum* value and *WashIn* and *WashOut* rates, obtained from the perfusion curves measured from the DCE-MRI images, are used in the classification process. The perfusion curves are described by a linear discrete pharmacokinetic (PK) model, based on multi-compartment paradigm where the input is the bolus injection. The *arterial input function* (AIF) that is usually estimated in the closest artery is assumed here to be the response of a second order linear system to the bolus injection. Therefore, the complete chain is modeled as a third order system with a single zero.

The alignment procedure is performed by using the *Mutual Information* (MI) criterion with a non-rigid transformation to compensate the displacements occurred during the acquisition process.

It is shown that the *Maximum* values and the *WashIn* and *WashOut* rates of the perfusion curves in malignant tumors are higher than in healthy tissues. This fact is used to classify them. Furthermore, it is also shown, that inside the tumor, the parameters associated with the perfusion curves for each pixel (time courses) present a higher variance than in the healthy tissues, which may also be used to increase the accuracy of the classifier.

Examples using real data are presented.

Index Terms— DCE-MRI, Pharmacokinetic Model, Perfusion Curve, Registration

1. INTRODUCTION

Dynamic-Contrast Enhanced MRI (DCE-MRI) is used in clinical practice to get information about the malignancy of tumors. Malignant tumors are known to have an active angiogenesis around them. So wider, more permeable and higher number of vessels can be found around malignant tumors when compared with healthy tissue or non malignant ones. In this case an increased contrast agent uptake is observed. Therefore, the revealed contrast kinetics parameters may be used to characterize the tumors as malignant or benign [1]. Malignant tissues generally have an earlier contrast uptake, with rapid and large increasing when compared with benign tissues, which in general show a slower uptake. Cancer demonstrate rapid and high amplitude agent uptake, meaning large *WashIn*, followed by relatively rapid decreasing agent concentration, meaning large *WashOut*, while benign or normal tissue have smaller *WashIn* and *WashOut*. The maximum of the uptake is also higher in malign tumors than in benign. Therefore, the estimation of the perfusion curves may be used to classify the tumors.

Correspondent author: Liliana Caldeira (llcaldeira@gmail.com).This work was supported by Fundaão para a Ciência e a Tecnologia (ISR/IST plurianual funding) through the POS Conhecimento Program which includes FEDER funds.

The traditional procedure to classify liver tumors uses *liver function tests* and liver *biopsy*. This last one is an invasive procedure presenting the risk of spreading the cancer along the biopsy needle pathway.

DCE-MRI is the preferred technique to assess tumor vascular characteristics because it is non invasive. However this is usually computationally intensive due to the huge amount of data generated by the MRI equipment which make them not appropriated in clinical practice.

The processing time may be reduced by decreasing the volume of the ROI containing the tumor in the DCE-MRI data without decreasing the spatial resolution, as shown in Fig. 1). A small ROI with small temporal resolution dataset is used in this work. This reduction speeds up the alignment and analysis algorithms but increases the difficulty in the registration because less detail landmarks are available.

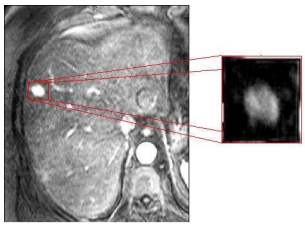

Fig. 1. Selection of a ROI

The signal intensity profile enhancement, after and before the contrast administration, along the time is used to estimate the perfusion curves. There are two ways to quantify perfusion. The first is based on the analysis of signal intensity changes, called *tissue relaxivity* or *semiquantitative*. The second is based on the contrast agent concentration change using pharmacokinetics (PK) models. Semiquantitative are straight forward to calculate but it is not completely supported on physiological reasons. PK models are therefore preferred [2].

However, first, the patient motion occurred during the acquisition due to respiratory and cardiac activity must be compensated [3, 4].

In clinical practice, the evaluation of tumor is done mostly by human observation specially in the liver where several types of lesions can occur. Highly vascularized tumors, having several arteries around them, are very visible in the arterial phase, during the first 30 seconds after injection [5]. The arterial phase is the most important to assess the malignancy and therefore is the phase that experts observe with more detail. The ultimate goal of this to develop an automatic tool to help the medical doctor in the diagnosis of liver tumors.

In this paper, a PK model is estimated from the observed intensity profiles in a Statistical framework in order to deal with the noise

corrupting the observations. The estimated PK models are used to compute a noiseless perfusion curves whose maximum, washIn and washOut parameters are used in a classifier to classify the tumor malignancy.

The paper is organized as follows. Section 2 describes the acquisition protocol and section 3 the registration procedure. In section 4 the PK model used is described as well the respective parameter estimation algorithm. Section 5 shows the results using real data and section 6 concludes the paper.

2. ACQUISITION

A total of 3 patients underwent DCE-MRI with contrast agent Gadolinium (Gd) imaged with a Siemens Sonata scanner using the "Vibe FS tra BH post iPat" protocol. The quantity of contrast media, automatically injected intravenously in the arm, is around 20-25 ml. Contrast agents such as *Gd* are paramagnetic leading to inhomogeneities in the magnetic field and therefore the signal will be brighter. There are two types of bolus injection: rapid (5-10 sec) and slow (20-30 sec). The contrast agent is injected seconds before the the first pos-contrast image acquisition. Each dataset is composed by a sequence of six volumes (maximum size 589×413). The first is pre-contrast and the rest is pos-contrast with 30 seconds between them. The time delay between pre-contrast and pos-contrast images is around 120 seconds. The voxel size varies from $0.456 \times 0.456 \times 2\ mm^3$ to $0.78 \times 0.78 \times 3\ mm^3$. The data used in this paper, provided in DICOM format, was provided by the Department of Radiology at the Erasmus MC in Rotterdam. A scheme is displayed in Figure 2.

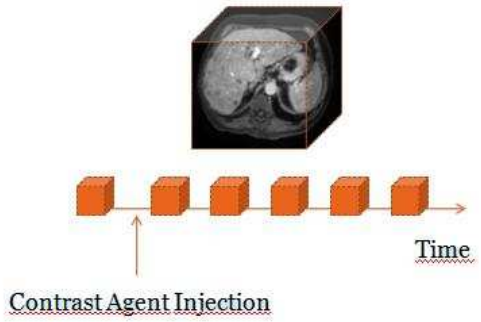

Fig. 2. Acquisition protocol.

The same rectangular ROI, containing the tumor, is used in all sequence images. The cropped size is about $50 \times 40 \times 10$ (Data Set 1 and 2) for small tumors and $80 \times 90 \times 16$ for the larger ones.

To minimize organ motion, breath-hold is asked during acquisitions and patients "catch their breath" between acquisitions.

3. REGISTRATION

The registration procedure performed in the volumes is needed to compensate organ and tissue displacements occurred during acquisition. The motion of the patient due to respiratory and cardiac activity may invalidate the results, because in a pixel by pixel analysis each single time course associated with each pixel along the acquisition time must be completely individualized.

In order to reduce the processing time, a small ROI is selected from the whole volume. The small dimensions of these volumes makes practical the use of non-rigid transformations which are usually more demanding from a computational point of view than the rigid ones, because intensive interpolation operations are involved. The interpolation method is B-splines based [6] and the optimization method is the regular step gradient descent. The alignment procedure is based on the *Mattes MI* criterion and the number of spatial samples used to estimate the marginal and joint histograms, as well the number of its bins, are manually defined. Here, the MI [7] criterion is maximized by geometrically transforming each volume in a pairwise basis

$$\widehat{T}_{p,q} = \arg\max_{T} MI\left[f_p(x), f_q(T(x))\right] \tag{1}$$

where $f_p(x) = f(x, t_p)$ and $f_q(x) = f(x, t_q)$ are two volumes from the data sequence. This process is the main source of the computational burden associated to the whole algorithm. The MI, used as alignment criterion, is defined as follows:

$$MI(u, v) = h(u) + h(v) - h(u, v) \tag{2}$$

where $h(z) = -E_z(\ln p(z))$ is the entropy of z and $E_z()$ is the expectation operator.

The strategy used in the alignment procedure is relevant for the final result and depends on the type and dimensions of the volumes. Here the simple strategy of align all volumes with a reference one, e.g., the middle one, is used. More complex strategies were tested with better results, e.g., large number of alignments between random selected pairs of volumes until convergence is achieved. The comparison between several strategies is not presented here by limitations of space and for sake of simplicity.

4. ESTIMATION

PK models make assumptions about the contrast agent perfusion process and the water exchange rates between prescribed tissue compartments. The PK models developed for DCE-MRI are compartmental models, that is, they assume that the tissue comprises several distinct compartments. These models assume that the contrast agent is distributed between two main tissue compartments: the *intravascular plasma volume space* and the *extravascular extracelular space* (EES) as displayed in Figure 3.

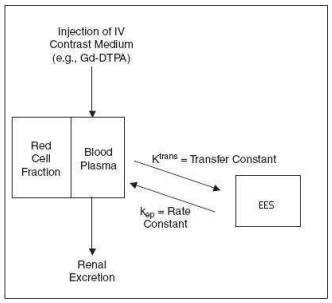

Fig. 3. PK compartmental model

The generalized kinetic model describing the evolution of contrast agent concentration with time by the following differential equation [7]

$$dC_{tumor}/dt = K_{trans}C_p - K_{ep}C_{tumor} \tag{3}$$

where C_{tumor} and C_p are the concentration of the contrast agent in EES and plasma space, respectively. K_{trans} and K_{ep} are constants that may be use to classify tumors. However, usually the *Wash* rates among others are the preferred parameters in clinical practice for sake of simplicity [8].

Several PK models have been proposed for DCE-MRI and the specific model depends on the contrast agent physicochemical and pharmacological properties. Gadolinium based contrast agents (type 2) cannot cross the cell membrane and enter the cells, but pass out the capillaries, because they have a low-molecular weight [7].

The PK model is estimated from the *arterial input function*, AIF ($\hat{C}_{tumor}$), and the observed contrast agent concentration ($\hat{C}_p$). This last one is not usually available. Therefore, a relation between intensity values, which are available, and concentrations is needed. In the case of a low-molecular weight contrast agent this relation is simple, $s(t) = s(0)(1 + gC(t))$ where $s(t)$ is the signal intensity, $C(t)$ is the correspondent concentration value, $s(0)$ is the baseline intensity before the contrast agent injection and g is a parameter depending on the tissue and contrast agent. Since measurements of the g parameter are not available, the following signal is used $y(t) = gC(t) = s(t)/s(0) - 1$ which linearly depends on the concentration $C(t)$ [9].

The way the AIF is determined is different from model to model. The early Tofts and Kermode model assumes an AIF bi-exponential fuction which may be described by a second order *linear time invariant* (LTI) system. The AIF is usually estimated from measures of one of the arteries around the tumor [9], but this can provide wrong information since it can be quite far from the tumor.

The overalll PK model used in this paper [7], relating the agent concentration with the bolus injection, is a third order LTI system with three real poles and a real zero, where the equation (3) and the AIF transfer function displayed in Figure 4 are incorporated.

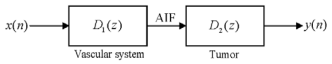

Fig. 4. Overall system.

The transfer function of the discrete time PK model is

$$H(z) = \frac{Y(z)}{X(z)} = \frac{K(1 - dz^{-1})}{(1 - az^{-1})(1 - bz^{-1})(1 - cz^{-1})} \quad (4)$$

The correspondent difference equation is

$$y(n) = Kx(n) - Bx(n-1) - \sum_{k=1}^{3} A_k y(n-k) \quad (5)$$

where $0 \leq n \leq N-1$, $A_1 = 1 - a - b - c$, $A_2 = ab + ac + bc$ and $A_3 = -abc$.

Let $Z = \{z(0), z(1), ..., z(N-1)\}^T$ be the N dimensional vector with the noisy observations of the signal $y(t)$, expanded by a polynomial fitting method, $U = \{u(0), u(1), ..., u(N-1)\}^T$ is the bolus injection signal and $\theta = \{K, B, A_1, A_2, A_3\}^T$ is the vector of parameter to be estimated by minimizing the following energy function $E(Y, U, \theta) = \|Z - Y\|_2^2$ where Y is the response of the system described by the difference equation (5).

The estimation of the model parameters, K, B and A_k is performed with the *Shanks'* method [10]. These parameters θ are used to compute the agent concentration as response to the bolus injection by using the equation (5).

The bolus injection $u(n)$ is not completely known and therefore must be also estimated. It is assumed that

$$u(n) = \begin{cases} 1, & d_0 \leq n \leq d_1 \\ 0, & otherwise \end{cases} \quad (6)$$

where d_0 and d_1 are unknown to be estimated. There are two restrictions: the bolus injection started before the acquisition of the first pos-contrast image and the duration of the injection has to be reasonable ($\leq 40s$). For each perfusion curve several values of d_0 and d_1 are tested and the solution is the one that lead to the minimum mean square error (MSE),

$$[d_0, d_1] = \arg\min_{d_0, d_1} E(Y, U(d_0, d_1), \hat{\theta}) \quad (7)$$

where it was assumed that $y(n) = 0, 0 \leq n < d_0$. It is also forced that the $y(n)$ will approximate zero around 960 seconds after the beginning of the acquisition when the *Gd* contrast agent is taught to be going out of the body.

5. EXPERIMENTAL RESULTS

The perfusion curves of the three datasets were obtained in 36 voxels around the center of the image/tumor. The results using the data sets 1, 2 and 3 are displayed in Figures 5, 6 and 7 respectively. The medical validation in these very few examples have classify the tumors associated with the data set 1 and 3 as malign and the tumor associated with the data set 2 as benign. In these images are represented the estimated bolus signal(yellow), the expanded observation (green) obtained by interpolation of the real observations (red) and the perfusion curves (blue) for all the 36 pixels processed.

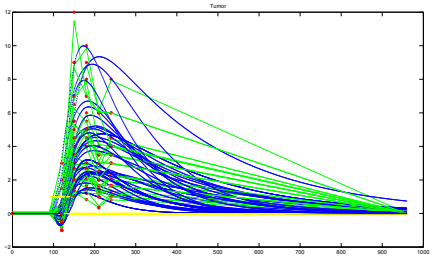

Fig. 5. Perfusion Curves Data Set 1: Observations(red), experimental points (green), bolus injection (yellow) and estimated perfusion curves (blue)

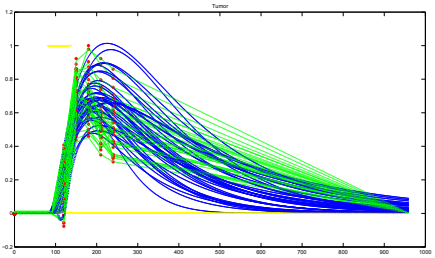

Fig. 6. Perfusion Curves Data Set 2: Observations(red), experimental points (green), bolus injection (yellow) and estimated perfusion curves (blue)

The *Maximum* value and *WashIn* and *WashOut* rates of the perfusion curves for each pixel were computed. It is known that malign tumors are more heterogeneous than benign ones. The computed features can be seen in Figure 8 and different clusters can be seen which can show that these features can be useful in classification.

The mean and variance values of the estimated features for each dataset are also computed and listed in Table 1. These values allow to infer the heterogeneity of the tumor. Dataset 2 presents smaller variances in the three features and the mean values are also smaller.

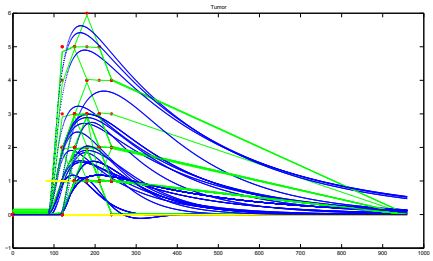

Fig. 7. Perfusion Curves Data Set 3: Observations(red), experimental points (green), bolus injection (yellow) and estimated perfusion curves (blue)

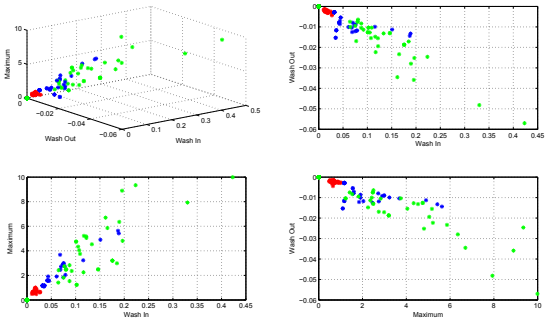

Fig. 8. Features: Data Set 1 (Green), Data Set 2 (Red) and Data Set 3 (Blue)

Image Set 1	$50 \times 40 \times 10$ size	12 bins, 1000 samples
	Mean	Var
WashIn	0.1394	0.0054
WashOut	-0.0178	$1.26E-04$
Maximum	4.0655	5.2753
Image Set 2	$40 \times 30 \times 10$ size	12 bins, 1000 samples
	Mean	Var
WashIn	0.0166	$1.57E-05$
WashOut	-0.0024	$3.60E-07$
Maximum	0.7024	0.0161
Image Set 3	$80 \times 90 \times 16$ size	32 bins, 7000 samples
	Mean	Var
WashIn	0.0602	0.0017
WashOut	-0.0083	$1.67E-05$
Maximum	2.0631	1.5174

Table 1. Mean and standard deviation of the estimated features for the three data sets tested. Notice the smaller variance and mean values of data set 2 associated with the benign tumor.

The goal in the future is to extend these tests to a larger number of data sets to design robust classifiers to classify tumors as malign or benign based on this image technique. This goal is extremely important from a clinical point of view.

6. CONCLUSIONS

In this paper, an algorithm to extract features to classify tumors as benign and malign is proposed. The classifier is based on the Maximum and *WashIn* and *WashOut* rates obtained from the perfusion curves estimated from the DCE-MRI images. These three features as well their variances, computed over the pixels inside the tumor, have shown the ability to be used in the classification of the tumors.

A MI based registration algorithm was developed using non-rigid transformations for DCE-MRI datasets. The aligned data is used to estimate the parameters of a PK model from which the perfusion curves are estimated and from which the features used in the classification are computed.

Tests with real data, validated by medical doctors, have been used and shown the ability of the proposed method to classify the liver tumors as being primary malign, called *hepatoma*, or not.

These results are very relevant from a clinical point of view since no automatic established method exist to classify tumors, as already happens for the breast lesions.

In the near future more intensive tests using more data will be used to design a robust classifier.

7. REFERENCES

[1] P.L. Choyke, A.J. Dwyer, and M.V. Knopp, "Functional tumor imaging with dynamic contrast-enhanced magnetic resonance imaging," *Journal of Magnetic Resonance Imaging*, vol. 17, no. 5, pp. 509–520, 2003.

[2] David J Collins and Anwar R Padhani, "Dynamic magnetic resonance imaging of tumor perfusion. Approaches and biomedical challenges," *IEEE Eng Med Biol Mag*, vol. 23, no. 5, pp. 65–83, Sep 2004.

[3] H.J. Leliveld, "Registration of the liver in mr perfusion images using mutual information and automatically generated landmarks," M.S. thesis, Delft University of Technology, January 2006.

[4] KM Langen, DT Jones, et al., "Organ motion and its management," *Int J Radiat Oncol Biol Phys*, vol. 50, no. 1, pp. 265–78, 2001.

[5] J.L. Evelhoch, "Key factors in the acquisition of contrast kinetic data for oncology," *J Magn Reson Imaging*, vol. 10, no. 3, pp. 254–259, Sep 1999.

[6] K. Hameeteman, "An error estimation method for non-rigid, mutual information based liver registration," M.S. thesis, Delft University of Technology, September 2006.

[7] P S et al Tofts, "Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols," *J Magn Reson Imaging*, vol. 10, no. 3, pp. 223–232, Sep 1999.

[8] Yaniv Gal, Andrew Mehnert, Andrew Bradley, Kerry McMahon, and Stuart Crozier, "An evaluation of four parametric models of contrast enhancement for dynamic contrast magnetic resonance imaging of the breast," *Procedings of the 29th Annual International Conference of the IEEE EMBS*, 2007.

[9] M Rijpkema, J H Kaanders, F B Joosten, A J van der Kogel, and A Heerschap, "Method for quantitative mapping of dynamic MRI contrast agent uptake in human tumors," *J Magn Reson Imaging*, vol. 14, no. 4, pp. 457–463, Oct 2001.

[10] John L. Shanks, "Recursion filters for digital processing," *Geophysics*, vol. 32, pp. 33–51, 1967.