AUTOMATIC LIVER TUMOR DIAGNOSIS WITH DYNAMIC-CONTRAST ENHANCED MRI

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ABSTRACT

Dynamic-Contrast Enhanced MRI (DCE-MRI) is currently used as a complementary diagnosis tool to assess the malignancy of the liver tumor, called *hepatoma*, *hepatocarcinoma*, *hepatocellular carcinoma* or *adult primary liver cancer*. This paper proposes a set of features and computation methods to extract them in order to design a classifier for automatic diagnosis of the *hepatoma*.

It is shown that the *Maximum*, *WashIn* and *WashOut* rates of the perfusion curves at each voxel obtained from DCE-MRI are adequate discriminative features to automatically classify the tumors with respect to its malignancy.

A dynamic discrete linear pharmacokinetic (PK) model is used to estimate the perfusion curves from the noisy observations, based on the multi-compartment paradigm. The arterial response to the contrast agent bolus injection, called *arterial input function* (AIF), is also estimated since no arteries are available in the neighborhood of the tumor.

The compensation of involuntary movements of the patient, such as the respiratory activity, during the acquisition process is performed using a *Mutual Information* (MI) based registration algorithm with non-rigid transformations. The tumor is isolated in a small region of interest in order to speed up the analysis and the tumor itself is segmented using an active contour algorithm.

The classification of the tumor is based on the mean and variance values of the *Maximum*, *WashIn* and *WashOut* rates of the perfusion curves inside the tumor.

Tests using real data are used to illustrate the ability of using these features to classify the tumor with respect to its malignancy.

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

1. INTRODUCTION

The *primary liver cancer* or *hepatoma* is one of the most lethal forms of cancer and therefore early detection with non-invasive techniques, such as MRI or ultrasound, is desirable and very useful from a clinical point of view.

Dynamic-Contrast Enhanced MRI (DCE-MRI) in clinical practice is used to get information about the malignancy of tumors. In this technique a bolus injection of a contrast agent, usually *gadolinium-DTPA* (Gd), is given to the patient. A set of MRI volumes are acquired, after the injection, and the perfusion of the contrast agent, at each voxel, is followed along the time.

Malignant tumors are known to have an active angiogenesis around them. SFor this reasons they are surrounded by wider, more permeable and higher number of vessels when compared with healthy tissue. Therefore, in cancer tissues a rapid and high amplitude *WashIn* rate followed by relatively rapid *WashOut* is observed. Conversely, in the benign tumor or normal tissues slower *WashIn* and *WashOut* rates are observed. The maximum of the uptake is also higher in malign tumors than in benign ones and normal tissues.

In this paper a physiological based *pharmokinectics* model is used to estimate the perfusion curves from the noisy observations and the *Maximum*, *WashIn* and *WashOut* rates computed [1]. This procedure is time consuming and computational demanding. To speed up the algorithm only small *regions of interest* (ROI) containing the tumor are processed, without decreasing the spatial resolution as shown in Fig. 1. However, the price paid for this reduction on the overall processed volume is an increased difficulty on the registration step because less anatomical details are available to make the alignment.

The registration of the several acquired volumes is needed to allow, as accurately as possible, to follows each intensity voxel along the time without mixing information from different voxels. The main causes of geometric distortions, that leads to this mixture, are the involuntary movements of the patient such as the respiratory activity, during the acquisition process. The registration is performed using the *Mutual Information* (MI) criterion with non-rigid transformations.

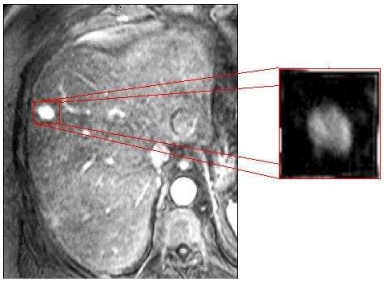

Fig. 1. ROI selection.

The exact segmentation of the tumor tissue inside the ROI is performed by using the *gradient vector flow* (GVF) active contour algorithm proposed in [2] after performing edge-detection filtering. Only the voxels inside the contour are processed and the respective perfusion curve parameters are estimated. The global parameters used to characterize the tumor are obtained with statistics computed over the data inside the contour. This is the reason why is important to obtain an accurate segmentation of the tumor.

The classification of the tumor is based on the mean and variance values of the *Maximum*, *WashIn* and *WashOut* rates of the estimated perfusion curves inside the tumor.

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2. DATA ACQUISITION AND PROCESSING

The overall characterization of the tumor is performed in five steps

1. Acquisition and ROI selection

   A patient underwent DCE-MRI with paramagnetic contrast agent Gd imaged with a Siemens Sonata scanner using the "Vibe FS tra BH post iPat" protocol, a T_1 weighted imaging sequence. The quantity of contrast media, intravenously automatically injected in the arm, was around 20-25 ml, during 5-30s. The large magnetic moment of the Gd enhances the local fluctuating magnetic field and thus reduces its longitudinal relaxation time constant, which leads to signal enhancement on T_1 weighted images. The contrast agent is injected a few seconds before the the first post-contrast image acquisition and typically six volumes (maximum size 589x413x125) are acquired after the bolus injection at each 30 seconds as shown in Fig. 2. The time delay between the pre-contrast and the first pos-contrast images is around 120 seconds. The voxel size varies from $0.456 \times 0.456 \times 2\ mm^3$ to $0.78 \times 0.78 \times 3\ mm^3$. Breath-hold is needed to minimize organ motion during the acquisition process and therefore the patient is asked to hold its breath between acquisitions. The data used in this paper was provided by the Department of Radiology at the Erasmus MC in Rotterdam.

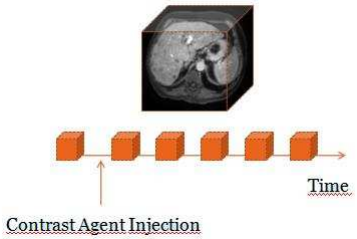


Fig. 2. Acquisition protocol.

   From the complete acquired volume a small cubic ROI containing the tumor to be inspected is manually selected by a specialist. This selected ROI is applied to all volumes of the sequence. Here, the cropped size is about $50 \times 40 \times 10$ for small tumors and $80 \times 90 \times 16$ for larger ones.

2. Registration

   A registration procedure is needed to compensate for organ and tissue displacements and involuntary movements of the patient mainly caused by the respiratory activity. The main goal is to make it possible to extract the time course associated to each voxel without interference of the neighborhood. Here a registration procedure using the MI criterion and a non-rigid transformation are used. The interpolation method is B-splines based [3] and the optimization method is the regular step gradient descent. Here the *Mattes MI* is used and the performance of the alignment algorithm strongly depends on the estimation of the joint intensity density distributions of both volumes to be aligned. In order to speed up this procedure neither all voxels are used nor all intensity gray levels are discriminated. However, a minimum amount of data and number of bins (gray level intervals) is needed to not degrade the performance of the algorithm [4].

   The alignment of all volumes is performed in a pair-wise basis by computing the following non rigid transformation

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

   where $f_p(x) = f(x, t_p)$ and $f_q(x) = f(x, t_q)$ are two volumes from the data sequence and MI is defined as $MI(u, v) = h(u) + h(v) - h(u, v)$ where $h(z) = -E_z(\ln p(z))$ is the entropy of z and $E_z()$ is the expectation operator.

   Several difficulties must be overcome such as the amount of samples and bins and the strategy of alignment. In fact, different results are obtained if each pair of consecutive volumes is aligned, all volumes are aligned with a reference volume or random pairs are selected for alignment. All these problems were addressed by the authors in the scope of this work (details in [5]).

3. Segmentation

   A segmentation step was needed to separate the tumor voxels from the background and collect the voxels from the tumor in order to estimate the perfusion curves. The images were pre-processed with *Canny* edge-detector filter and the snake was manually initialized inside the tumor. The active contour is smoothly attracted to the edges due to the equilibrium between the internal forces (tension and rigidity) and external forces (*gradient vector flow* field). The segmentation was performed on the first post-contrast images from the time series and the result was used on the following registered images.

4. Perfusion curves parameters estimation

5. Feature extraction and classification

   These last two steps are addressed in the next section.

3. MODEL ESTIMATION AND FEATURES EXTRACTION

The PK model used for DCE-MRI is compartmental based in the sense that it is derived on assumptions about the dynamics of the contrast agent perfusion process and the water exchange rates between tissue compartments. It is assumed that the tissue comprises two main distinct compartments: the *intra-vascular plasma volume space* and the *extravascular extracelular space* (EES) as displayed in Figure 3.

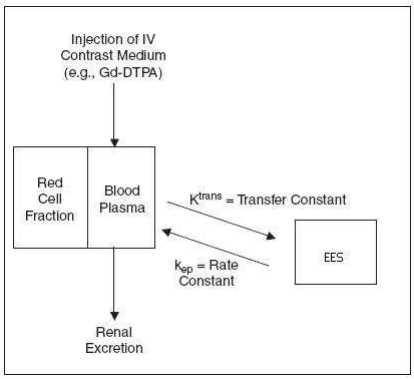


Fig. 3. PK Model

The generalized kinetic model, describing the evolution of contrast agent concentration with time, is defined by the following differential equation [6],

$$dC_t(t)/dt = K_{trans}C_p(t) - K_{ep}C_t(t) \quad (2)$$

where C_t and C_p are the concentrations 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 *WashIn* and *WashOut* rates among others are the preferred parameters in clinical practice for sake of simplicity [7].

The equivalent discrete system is obtained by approximating the derivative by the difference $dC(t)/dt \approx C(n) - C(n-1)$ leading to the following discrete transfer function (see Fig.4)

$$D_2(z) = \frac{C_t(z)}{C_p(z)} = \frac{\beta}{1-\alpha z^{-1}} \quad (3)$$

where $\beta = K_{trans}/(1-K_{ep})$ and $\alpha = 1/(1-K_{ep})$.

The input of the PK model is assumed to be the AIF, an approximation to C_p, and the output is the observed contrast agent concentration, C_t, inside the tumor. The concentration itself is not usually available but it can be estimated from the image intensity. In the case of a low-molecular weight contrast agent such as Gd the relation is simple,

$$z(n) = z(0)(1 + gC(n)) \quad (4)$$

where $z(n)$ is the signal intensity, $C(n)$ is the correspondent concentration value, $z(0)$ is the baseline intensity before the contrast agent injection and g is a parameter depending on the tissue and contrast agent. Since the value of the parameter g is not usually available, the following signal is used $y(n) = gC(n) = z(n)/z(0) - 1$ which linearly depends on the concentration $C(n)$ [8].

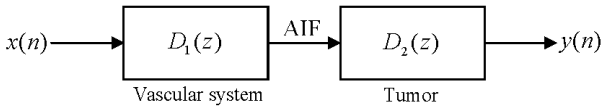


Fig. 4. Overall transfer function

The input of the PK model, the AIF, is usually estimated in a visible artery [8]. This strategy is not accurate when the artery is far way from the tumor region. Furthermore, in this case, no arteries are available because only a small ROI is being processed. Therefore the AIF is also estimated by assuming a transport transfer function from the arm up to the plasma space in the tumor tissue. The early Tofts and Kermode model assumes an bi-exponential AIF that corresponds to a two poles and one zero discrete *linear time invariant* (LTI) system.

Therefore, the overall transfer function used in this paper, relating the bolus signal injection in the arm with the contrast agent in the tumor tissue [6] is a three poles and one zero LTI system,

$$H(z) = \frac{K(1-dz^{-1})}{(1-az^{-1})(1-bz^{-1})(1-cz^{-1})} \quad (5)$$

The observation model is the following

$$\begin{aligned} y(n) &= Kx(n) - Dx(n-1) \\ &- Ay(n-1) - By(n-2) - Cy(n-3) \\ &+ \eta(n) \end{aligned} \quad (6)$$

where $\eta(n) \rightarrow N(0,\sigma^2)$ is *additive white Gaussian noise* (AWGN), $A = 1-a-b-c$, $B = ab+ac+bc$ and $C = -abc$ are the parameters of the system to be estimated. The small number of samples of each time course, $L = 6$, is augmented by interpolation in order to generate a large vector of observations $\mathbf{y} = \{y(0), y(1), ..., y(N-1)\}^T$ where $N >> L$. The bolus injection signal, $\mathbf{x} = \{x(0), x(1), ..., x(N-1)\}^T$, is not completely known and is also jointly estimated with the set of parameters $\theta = \{K, A, B, C\}^T$ by minimizing an energy function $E(\mathbf{y}, \mathbf{x}, \theta)$.

The estimation of the parameters, $\theta = \{K, A, B, C\}^T$ is performed with the *Shanks'* method [9,10]. The estimation of these parameters is performed several times for different bolus injection signals

$$x(n) = \begin{cases} 1, & d_0 \leq n \leq d_1 \\ 0, & otherwise \end{cases} \quad (7)$$

where d_0 and d_1 changes each time the vector θ is estimated. The estimated vector $[\hat{d_0}, \hat{d_1}]$ is obtained by

$$[\hat{d_0}, \hat{d_1}] = \arg \min_{[d0,d1]} \|\mathbf{y} - \mathbf{h}(d_0, d_1) * \mathbf{x}(d_0, d1)\|_2^2 \quad (8)$$

where $\mathbf{h}(d_0, d_1) = \{h(0), h(1), ..., h(N-1)\}^T$ is the impulse response of the estimated transfer function $H(z)$ when the input is the signal $\mathbf{x}(d_0, d_1)$.

Three restrictions are imposed for $[d_0, d_1]$: i) the bolus injection starts before the acquisition of the first post-contrast image, ii) $d_0, d_1 > 0$ and iii) the bolus injection duration $d_1 - d_0 \leq 40s$. It is also forced that the $y(n)$ will approximate zero for $t = 960$ seconds after the beginning of the acquisition when the Gd is taught to be going out of the body.

4. EXPERIMENTAL RESULTS

In this section two data sets from a benign and a malign tumors were used to illustrate the application of the algorithm. The data sets were aligned and the tumors segmented with active contours in a single cross-section. The *Maximum*, *WashIn* and *WashOut* rates values were computed from the estimated perfusion curves obtained from the time courses associated with each voxel inside the tumor.

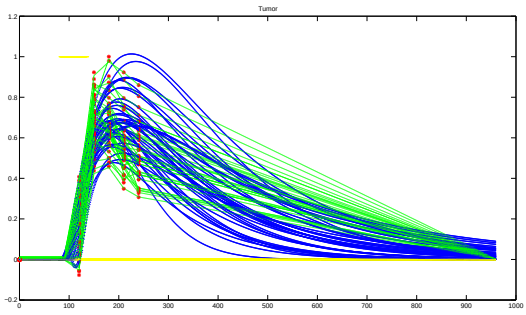
Fig.5 displays the estimated perfusion curves for a benign and a malign tumor. Fig.6 displays the *WashIn* rates for both tumors where it is clear that the malign tumor is more heterogeneous than the benign one.

The three parameters *WashIn*, *WashOut* and *Maximum* of the perfusion curves are displayed in Fig. 7 and their mean and variance are presented in Table 1.

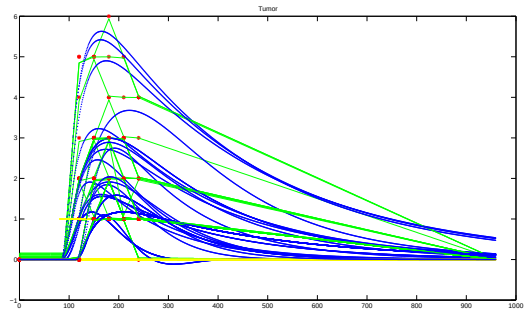
This table shows clearly higher values for the mean and variance values in the case of the malign tumor. In Fig.6 it can be seen that, in terms of *WashIn*, there is higher heterogeneity for the malign tumor. The same effect can be observed in the other parameters.

5. CONCLUSIONS

In this work, a MI based registration algorithm was developed using non-rigid transformations for DCE-MRI datasets. In this paper, it was presented an algorithm to extract automatically features to build a classifier of the tumor benignancy/malignancy based on the *Maximum* (Max), *WashIn*(WI) and *WashOut*(WO) rates obtained from the perfusion curves measured from the MRI images. It was concluded that the following features $[\mu_{WI}, \sigma_{WI}, \mu_{WO}, \sigma_{WO}, \mu_{Max}, \sigma_{Max}]$



(a) Benign



(b) Malign

Fig. 5. Time Courses inside the tumor. Observations (red), expanded vector (green), estimated bolus injection (yellow) and estimated perfusion curves (blue)

	Mean	Variance
Malign	$40 \times 30 \times 10$ size	12 bins, 1000 samples
WashIn	0.0650	$2.7e-3$
WashOut	0.0067	$1.6e-5$
Maximum	2.1729	1.9
$\|f\|_2/\|f_w\|_2$	2.1739/0.0653	1.9/0.0027
Benign	$80 \times 90 \times 16$ size	32 bins, 7000 samples
WashIn	0.0419	$2.2e-4$
WashOut	0.0037	$1.3e-6$
Maximum	1.3735	$1.5e-1$
$\|f\|_2/\|f_w\|_2$	1.3741/0.0421	0.1546/0.0002

Table 1. Features. $f = [WashIn, WashOut, Maximum]$ and $f_w = [WashIn, WashOut]$

has enough discriminative properties to use in an automatic classifying process. Other parameters can also be extracted from images in order to get more relevant information about the tumors such as shape irregularity and texture analysis in the parameters space. In the future, more data and realistic perfusion models should be used in order to design robust classifiers.

6. REFERENCES

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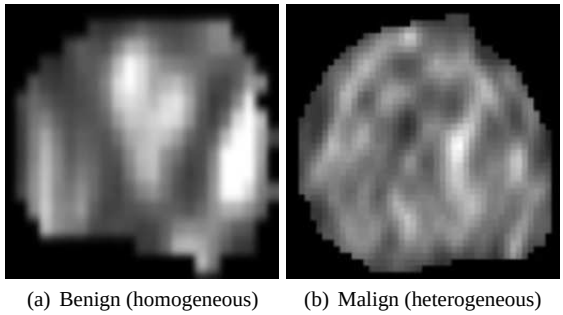

(a) Benign (homogeneous) (b) Malign (heterogeneous)

Fig. 6. Washin map ($WashIn \in [0, 0.1]$).

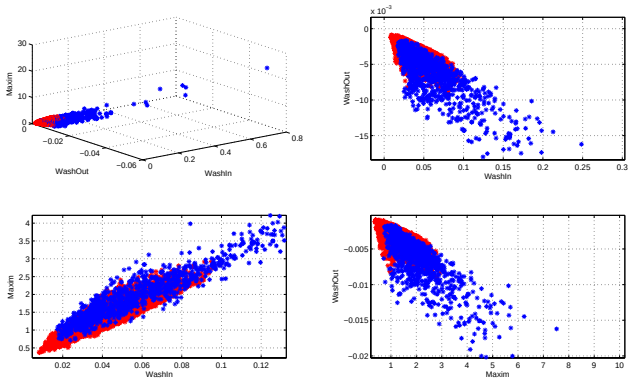

Fig. 7. Feature Representation: Malign (Blue) and Benign (Red). Top Left: (*WashIn*,*WashOut*,*Maximum*), Top Right:(*WashIn*,*WashOut*), Bottom left:(*WashIn*,*Maxim*) and Bottom right:(*Maximum*,*WashOut*)