Segmentation of dynamic contrast-enhanced MR-images of post chematherapy Ewing's sarcoma with a pharmacokinetic model and a neural network

M. Egmont-Petersen*, R.J. van der Geest *, H.A. Vrooman*, P.C.W. Hogendoorn***, H.J. van der Woude**, J.P. Janssen*, J.L. Bloem**, J.H.C. Reiber*

Leiden University Medical Center
*Division of Image Processing, Dept. of Radiology,
**Department of Radiology
***Department of Pathology
P.O.B. 9600,
2300 RC Leiden, The Netherlands
Email: michael@lkeb.azl.nl

Keywords: Pharmacokinetic analysis, perfusion analysis, nonlinear filtering, neural networks, bone tumors.

1 Introduction

Most patients with Ewing's sarcoma undergo neoadjuvant (preoperative) chemotherapy before surgery is performed. Generally, chemotherapy reduces the size of the tumor which makes the subsequent treatment more successful. MR-imaging aims at monitoring the effect of chemotherapy by identifying areas of vital remnant tumor. An MR-examination includes *static* T1- and T2-weighted MR-images as well as *dynamic*, contrast-enhanced T1-weighted MR-images. Whereas the static MR-images are used to estimate the volume of intra- and extra-osseous bone tumor, the dynamic contrast-enhanced MR-sequence indicates which parts of the tumor are highly perfused by blood. In general, malignant bone tumors are highly perfused. Moreover, these lesions are heterogenuous (sometimes multifocal) containing viable as well as nonviable (necrotic) parts. The only way to reliably distinguish viable from nonviable tumor tissue is by performing a perfusion study by dynamic contrast-enhanced MRI [1].

The temporal images (typically 45-55) per MR-slice obtained from contrast-enhanced MR-imaging using the contrast tracer GdTP need to be analyzed before a distinction is possible between viable and nonviable tumor. Important perfusion characteristics of tissue are *wash-in*, *wash-out* and *maximal enhancement* of blood. Each characteristic is modeled with a separate *pharmacokinetic parameter* for each individual voxel using a two-compartment pharmacokinetic model. This facilitates a classification of tissue into viable and nonviable tumor on a voxel-by-voxel basis.

Our approach reduces the information of the MR-signal to 3 pharmacokinetic characteristics, an operation that might retain information which contributes to the distinction between viable and nonviable tumor. In this paper, we compare the segmentation results obtained using the estimated parmacokinetic parameters with the segmentation result obtained from a feed-forward neural network that is trained to segment areas with viable tumor. The gold standard is obtained from matched histologic studies of the postoperative specimen.

2 Two-compartment pharmacokinetic model

In this section, we derive the two-compartment model that is used to differentiate viable from nonviable tumor. One compartment is the intravascular blood whereas the other is extracellular compartment surrounding the tumor cells.

The presence of MR-tracer causes local magnetic field fluctuations which results in reduced relaxation times, T_1 and T_2, of heavily vascularized tissues, see [2]. The total signal enhancement is linearly related with the tracer concentration in tissue C_e via the bulk longitudinal relaxation time T_e:

$$s_0(x,y) + \boldsymbol{s}(x,y) = \frac{1}{T_e} = \frac{1}{T} + \alpha\, C_e \tag{1}$$

whereby the reduction of T_2 relaxation time is neglected. The parameter T is the relaxation time of the tissue in the absence of tracer and α the tissue- and frequency dependent relaxivity, $s_0(x,y)$ the signal intensity in the absence of tracer. The signal intensity after the tracer has arrived in the tissue (voxel) is proportional to T_e

$$s_0(x,y) + \boldsymbol{s}(x,y) \propto 1 - e^{-\frac{T_r}{T_e}} \tag{2}$$

When the recovery time T_r is small compared to T_e, this exponential function can be approximated with a linear equation $s(x,y,t) \cong \beta T_e$, $t \in \{0, t_{\max}\}$. Assuming that the infusion of contrast tracer is a Dirac pulse and no wash-out takes place, the concentration of tracer follows a step function, which can be approximated by the differential equation

$$\begin{aligned} \lim_{g\to\infty} \quad & \frac{dC_b}{dt} = -g\; C_b(1 - C_b) \\ \lim_{g\to\infty} \quad & C_b = \frac{1}{1 + e^{-g(t-t_0)}} \end{aligned} \tag{3}$$

with t the time and t_0 the moment of local contrast arrival. The wash-out of tracer from the blood compartment is given by the differential equation

$$\frac{dC_b}{dt} = -k_1\; C_b\;, \quad C_b = e^{-k_1\,(t-t_0)}\;, \quad t \ge t_0 \tag{4}$$

with k_1 the transfer rate from the blood to the extracellular space, the second compartment in our pharmacokinetic model. Combining Eq. (3) with Eq. (4) yields the following pharmacokinetic model for the blood compartment

$$C_b = \frac{1}{1+e^{-g\,(t-t_0)}} e^{-k_1\,(t-t_0)} \tag{5}$$

For the extracellular compartment, the concentration of tracer after the bolus has been injected is specified by [2]

$$\frac{dC_e}{dt} = (k_1\; C_b - k_2\; C_e) \tag{6}$$

Combining Eq. (3) with Eq. (6) yields

$$C_e = \frac{1}{1+e^{-g\,(t-t_0)}} \left(e^{k_1\,(t-t_0)} + e^{-k_2\,(t-t_0)}\right) \tag{7}$$

which encompasses Eq. (5) as a special case. This pharmacokinetic model is extended with an amplitude factor a and the MR-signal $s_0(x,y)$ before the tracer has arrived

$$C_e = s_0(x,y) + \frac{a}{1+e^{-g\,(t-t_0)}} \left(e^{k_1\,(t-t_0)} + e^{-k_2\,(t-t_0)}\right) + \varepsilon \tag{8}$$

This function is differentiable and can be estimated for each individual voxel by least square minimization of the residual error ε using the Levenberg Marquart algorithm. The free parameters are the wash-in rate k_1, wash-out rate k_2, maximal enhancement a, local arrival time of tracer t_0 and the initial signal intensity before tracer has arrived in voxel (x,y), $s_0(x,y)$. The constant g is set to 10.

3 Segmentation of MR-images

The best indicator for the effect of chemotherapy that can be obtained from MR-examination is the (decrease in the) volume of viable tumor, an assessment that entails a segmentation of the diagnostic and preoperative *dynamic* MR-images into viable and nonviable tumor. Viable tumor is characterized by both a high amount of vessels and a high perfusion. The many blood vessels supply the dividing cancer cells with enough blood to ensure a high metabolism. The high perfusion of viable tumor is a pharmacokinetic characteristic that is captured well by our two-compartment model (Eq. (8)). The pharmacokinetic parameters contain functional information which is visualized by so-called *parametric images*. By thresholding the wash-in (k_1) image, which indicates the relative wash-in rate per voxel, we can identify the (viable) parts of the tumor where the wash-in rate of tracer is high. This segmentation is compared with a postoperative histologic macro slice – our gold standard – obtained a few days after the preoperative MR-scan. In this histologic slice, which is oriented and positioned as to obtain the best match with the MR-slice, areas containing viable tumor are clearly indicated. The histologic slice is digitized on a color scanner and annotations are made by an experienced pathologist.

We compare the segmentation results obtained from wash-in parametric images with the results obtained from a feed-forward neural network. In general, a feed-forward neural network with one hidden layer is capable of approximating every continuous function to an arbitrary precision when the number of hidden nodes is large enough [3]. Neural networks are trained to classify each individual voxel into viable and nonviable tumor based on the dynamic MR-signal. The networks are trained using a mask based on the annotations from the histologic macroslice. Each neural network obtains as input the intensities of voxel (x,y) corresponding to all time steps, $\boldsymbol{s}(x,y)$. The network output contains the two (complementary) posterior probabilities that the voxel belongs to an area with viable tumor or not, $P(\omega_{\text{viable}} \mid \boldsymbol{s}(x,y))=1-P(\omega_{\text{nonviable}} \mid \boldsymbol{s}(x,y))$.

4 Experiments

We analyzed the dynamic (preoperative) MR-images from two patients with Ewing's sarcoma. Both patients underwent neoadjuvant chemotherapy followed by limb salvage surgery as specified by the standard protocols used in our hospital. The wash-in parametric image was computed and postprocessed with a 3×3 median filter. A threshold was chosen such that the number of incorrectly classified voxels was minimal. The resulting binary image was compared with the mask image derived from the histologic macro slice.

Neural networks with one hidden layer were trained with back-propagation to classify individual voxels as viable or nonviable tumor. Note that the average intensity $\mu(x,y)$ is subtracted from each signal $\boldsymbol{s}(x,y)$ before being processed by the network. Neural networks with 1, 2, 4 and 6 hidden nodes were trained 3.000 cycles with back-propagation, learning rate=0,0001, momentum=0,5, offline learning.

Table 1. Overall and class-conditional correctness measures [4] for the 2 patients with Ewing's sarcoma computed from the segmentation obtained with the wash-in image and the neural network (test set).

Patient	Segmentation method	Correctness	Cl. cond. correctness (Nonviable)	Cl. cond. correctness (Viable)
EW-1	Wash-in parameter	0,9990	0,9983	0,4133
	Neural network (4 hid.)	0,9992	0,9998	0,5067
EW-2	Wash-in parameter	0,9966	0,9982	0,6633
	Neural network (4 hid.)	0,9984	0,9996	0,7450

The (best) results obtained with the two segmentation techniques are shown in table 1. For both patients, the neural network gives a better segmentation than the wash-in parametric image when computed on voxels that were not included in the training set. The class-conditional correctness [4] of 'viable tumor' is rather low, 0,40–0,66. This is mainly caused by the fact that only the centers of the areas with viable tumor are highly perfused. The border areas containing also viable tumor cells have a lower wash-in rate for both tumors. Fig. 1 shows a dynamic MR-image before the arrival of contrast tracer, 200 sec. after arrival of the tracer, the amplitude and wash-in images.

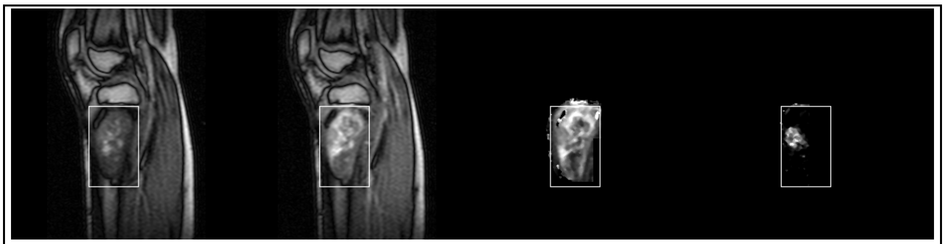

Figure 1. Shows a dynamic MR-image before the arrival of tracer (a), 200 sec. after arrival of the tracer (b), the amplitude parametric image (c) and the wash-in parametric image (d).

5 Discussion

The experiments indicate that the neural network gives a slightly better segmentation result than pharmacokinetic analysis. The neural network obtains all information present in the MR-signal whereas segmentation based on the *wash-in* parametric image captures solely one single feature of the MR-signal. Surprisingly, an acceptable distinction can be made between viable and nonviable tumor from the wash-in parameter alone.

6 Conclusion

In this paper, we investigated two techniques for detecting areas with viable and nonviable tumor based on dynamic contrast-enhanced MR-imaging. We compared the performance obtained from a two-compartment pharmacokinetic model with that obtained from a neural network. Our results indicate that the neural network results in a slightly better segmentation than the wash-in parametric image.

7 References

1. Woude van der HJ, et al.: Musculoskeletal tumors: does fast dynamic contrast-enhanced subtraction MR imaging contribute to the characterization? Radiology, 208(3):821-828, 1998.
2. Hoffmann U, Brix G, Knopp MV, Heß T, Lorenz WJ: Pharmacokinetic mapping of the breast: A new method for dynamic MR mammography. Magnetic Resonance in Medicine, 33(4):506-514, 1995.
3. Funahashi KI: On the approximate realization of continuous mappings by neural networks. Neural Networks, 2:183-192, 1989.
4. Egmont-Petersen M, Talmon JL, Brender J, McNair P: On the quality of neural net classifiers. Artificial Intelligence in Medicine, 6(5):359-381, 1994.