

Learning Approach to Analyze Tumour Heterogeneity in DCE-MRI Data During Anti-cancer Treatment

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Abstract. The paper proposes a learning approach to support medical researchers in the context of in-vivo cancer imaging, and specifically in the analysis of Dynamic Contrast-Enhanced MRI (DCE-MRI) data. Tumour heterogeneity is characterized by identifying regions with different vascular perfusion. The overall aim is to measure volume differences of such regions for two experimental groups: the treated group, to which an anticancer therapy is administered, and a control group. The proposed approach is based on a three-steps procedure: (i) robust features extraction from raw time-intensity curves, (ii) sample-regions identification manually traced by medical researchers on a small portion of input data, and (iii) overall segmentation by training a Support Vector Machine (SVM) to classify the MRI voxels according to the previously identified cancer areas. In this way a non-invasive method for the analysis of the treatment efficacy is obtained as shown by the promising results reported in our experiments.

1 Introduction

In the context of cancer imaging, machine learning techniques are becoming important to automatically isolate areas of interest characterized by heterogeneous tumoural tissues. In particular, the identification of tumour heterogeneity is crucial for diagnosis and therapy assessment. In this paper, tumour morphology and functional perfusion are obtained by Dynamic Contrast Enhanced MRI (DCE-MRI) techniques. We propose a learning-by-example approach[1] to classify tumoral regions characterized by heterogeneous vascular perfusion. In fact, DCE-MRI techniques represent noninvasive ways to assess tumour vasculature, that are accepted surrogate markers of tumour angiogenesis [2]. Data are analyzed with the aim of investigating the volume changes in the identified regions for both untreated and treated tumours. The proposed analysis is based on three main phases: (i) features extraction from raw time-intensity curves, (ii) representative tumour areas identification, and (iii) overall voxel-by-voxel classification. In the first phase, few robust features that compactly represent the response of

the tissue to the DCE-MRI analysis are computed. The second step provides a manual identification of tumour samples that are representative of the typical tumour aspects. Such samples are carefully and manually chosen by medical researchers on a small portion of input data by observing the different behavior of the time-intensity signals within different kind of tumoural regions (i.e., necrotic or still alive zones). Finally, in the third step, a Support Vector Machine (SVM) is trained to classify voxels according to the regions (i.e., typologies of tumour tissue) defined by the previous phase. In this way, the SVM is able to automatically detect the most discriminative characteristics of the manually identified regions by extending such capability to classify unseen subjects.

Several works are based on the use of machine learning techniques for DCE-MRI tumour analysis [3,4,5,6]. In [3], a visual data-mining approach is proposed to support the medical researchers in tumoral areas characterization by clustering data according to the transendothelial permeability (kPS) and fractional plasma volume (fPV). Although kPS and fPV are accepted estimate of tissue vasculature, their instability under small perturbation of the chosen pharmacokinetics model was proved [4,5]. Therefore, different works are addressed the idea of analyzing directly the raw signals by exploiting possible other compact parameters of the curve shapes. As an example, in [4] the raw signals of the DCE-MRI voxels are analyzed in the context of musculoskeletal tissue classification, where the classification is carried out by introducing a thresholding approach. In [5] the authors propose the use of the Mean Shift algorithm [1] for the clustering of breast DCE-MRI lesions. In particular, voxels are clustered according to the area under the curve feature. Since the results are over-segmented, an iterative procedure is introduced to automatically select the clusters which better represent the tumour. Similarly, in our previous work [6], tumoral regions are characterized by combining Mean Shift clustering[1] with Support Vector Machine (SVM) classification. In the present work we extend the basic framework proposed in [6], to asses the treatment efficacy of anticancer therapies.

2 Materials and Methods

Tumours were induced by subcutaneous injection of human carcinoma cells in nude mice ($n = 11$). Ten days after cells injection animals were randomly assigned to the treated ($n = 6$) and control group ($n = 5$). Animals belonging to the treated and control group received an experimental drug and vehicle, respectively, for a period of 7 days. All animals were observed by MRI before (time T_0) and after the treatment (time T_1). A further group of mice ($n = 5$) bearing the same kind of tumour was used in the training step of the classification procedure. Animals were examined using DCE-MRI as described [2]. To account for tumour heterogeneity, seven classes have been fixed by combining a-priori knowledge of medical experts with the observation of signal shape behaviors (see A-G in Figure 1):

- **Classes A, D**, are characterized by a contrast agent wash-out (i.e., clear defined peak followed by a decrease). These regions correspond to very active

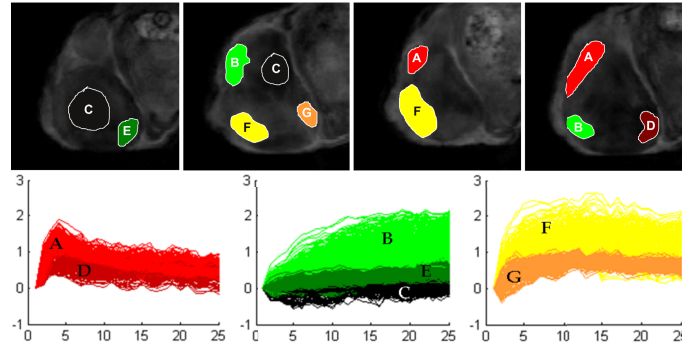


Fig. 1. Sample regions used for SVM training. Seven classes (A-G) were chosen. Source data used to select the sample regions (TOP), and the relative DCE-MRI curves of the whole training set are reported (BOTTOM).

areas where the tumor is still alive. Regions A and D differs by the value of maximum intensity.

- **Classes B, E,** reveal a contrast agent accumulation (i.e., increasing trend). Typically, the activity in such areas are very few by evidencing the transition of the tumor toward a necrotic state.
- **Class C,** contains voxels with negligible enhancement, presumably due to necrotic tissue.
- **F and G,** have been introduced to account for intermediate patterns (i.e., initial increasing trend followed by a plateau phase). These regions are likely to correspond to tumor transitions from high active to low active state.

By following the proposed pipeline, few and stable signal features are identified to model the different DCE-MRI curve class. In particular, the following curve characteristics are chosen: time-to-peak (TTP), peak value (PEAK), area under curve (AUC), initial area under curve (AUCTTP), and washout rate (WR).

Therefore, in order to apply a learning-by-example approach, several samples of each identified class need to be fed to the classifier. As mentioned above, such phase is carried out manually by medical experts. Figure 1(TOP) shows some representative regions which are used to build the training set. In Figure 1(BOTTOM) the signals curve of the whole selected samples are reported. Signals are colored according to their respective class by evidencing the expected curve shape. A binary Support Vector Machine (SVM) classifier[1] is used to distinguish among the several tumoral tissue classes. In particular, the SVM is able to automatically detect the most discriminative characteristics of the manually identified regions therefore allowing also the classification of new subjects. Finally, in each tumour, the percentage volumes covered by each of the seven classes have been then calculated to evaluate the time-dependent changes in control and treated tumours. The values obtained have been averaged over the experimental groups and statistically compared by paired t-test.

3 Results

The rate of tumour growth is strongly affected by the treatment; in fact average tumour volume, as determined by MR images, increased from $575 \pm 104 \text{ mm}^3$ to $1821 \pm 191 \text{ mm}^3$ in the control group and from $553 \pm 187 \text{ mm}^3$ to $788 \pm 227 \text{ mm}^3$ in the treated group. Figure 2 shows percentage volumes of the different classes, averaged over the whole experimental group. In the control group there is a significant ($p < 0.05$) increase of the percentage volume covered by the classes C and E (i.e., the less enhancing portions of the tumours). Concomitantly, a significant ($p < 0.01$) decrease of the class F is observed. An increase in the

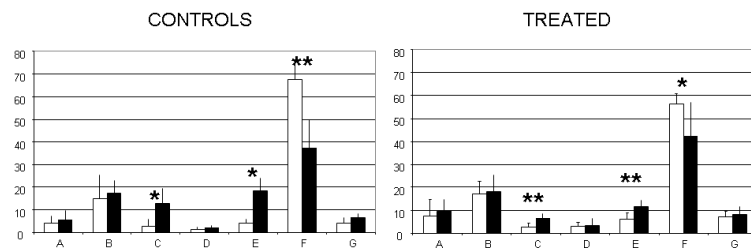


Fig. 2. Percentage volume attributed to each of the seven classes A-G averaged over the different experimental groups (control and treated). White and black bars represent values at time T_0 and T_1 respectively. Asterisks indicate t-test significance at a 0.05 (*) and 0.01 (**).

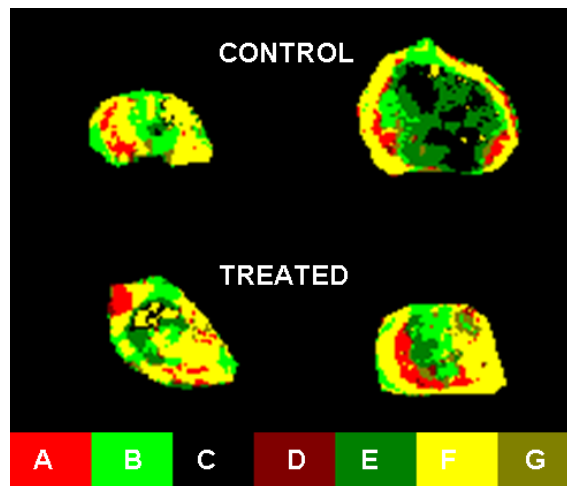


Fig. 3. Segmentation of tumour images in representative control and treated tumours at time T_0 (left) and at time T_1 (right). The colorbar shows the colors used to identify the segmented classes.

scarcely enhanced tissue (necrotic tissue) is typically observed during fast tumour growth. The increase of this tissue is less pronounced in treated tumours as expected from their reduced rate of growth. The percentage volume attributed to A and D classes (wash-out regions that correspond to well vascularized tissue) is not significantly affected by treatment (or normal tumour growth) in agreement with the fact that the biological target of the herein investigated therapeutic treatment is represented by tumour cells and not by vasculature.

Figure 3 shows segmentation of tumour images obtained with SVM in two representative animals (vehicle and drug treated) before and after the treatment. The substantial increase in the necrotic portion of the control tumour, typical of fast growing tumours, can be visually appreciated.

4 Conclusions

In this paper we emphasize the use of machine learning techniques as a mean to produce automatic and meaningful segmentation results in the quantitative evaluation of DCE-MRI data. The proposed approach permits the computation of percentage tumour volumes of above defined regions and to follow their modifications during the treatment with an experimental drug. Our results suggest that this approach can be useful in the analysis of heterogeneous tumour tissues and of their response to therapies.

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