Cancer area characterization by non-parametric clustering

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Abstract

The application of machine learning techniques to open problems in different medical research fields appears to be stimulating and fruitful, especially in the last decade. In this paper, a new method for MRI data segmentation is proposed, which aims at improving the support of medical researchers in the context of cancer therapy. In particular, our effort is focused on the processing of raw output obtained by Dynamic Contrast-Enhanced MRI (DCE-MRI) techniques. Here, morphological and functional parameters are extracted, which seem indicate the local development of cancer. Our contribute consists in organizing automatically these output, separating MRI slice areas with different meaning, in a histological sense. The technique adopted is based on the Mean-Shift paradigm, and it has recently shown to be robust and useful for different and heterogeneous segmentation tasks. Moreover, the technique appears to be predisposed to numerous extensions and medical-driven optimizations.

1 Introduction

Segmentation is a vast and complex domain, both in terms of problem formulation and resolution techniques. It consists in formally translating the delicate visual notions of homogeneity and similarity, and defining criteria which allow their efficient implementation [Petitjean, 2002]. The goal is to partition the source data into meaningful pieces, i.e. those parts corresponding to the different entities, in the physical and semantical sense of the application envisioned. Roughly speaking, the segmentation methods can be categorized into two main classes: *edge-based* and *region-based* [Petitjean, 2002]. In the former, features corresponding to part boundaries are first detected and then regions are built, each one formed by sets of points delimited by the same boundary. In the latter, points sharing the same similarity property are grouped together. In particular, three are the most popular approaches to region-based segmentation: *split-and-merge* methods, identified by a top-down paradigm; *region-growing* methods, that adopt a bottom-up paradigm, and *clustering-based* methods, based on the projection of the points onto a higher dimensional space where the clusters (i.e., segments) are recovered by defining some particular distance functions [Jain *et al.*, 1999a].

In this paper, we apply a recently proposed clustering-based technique for the analysis of data, which considers as leading framework the Mean Shift (MS) clustering paradigm, proposed in [Comaniciu and Meer, 2002]. The main underlying idea of such non parametric approach is that the data space is regarded as an empirical probability density function to estimate. The MS procedure operates by shifting a fixed size estimation window, i.e., *the kernel*, from each data point towards a local mode, denoted, roughly speaking, as a high concentration of points. The points converging to the same mode are considered as belonging to the same region.

Although MS has shown to be a powerful technique for several research fields such as image and video segmentation, tracking, clustering and data mining [Comaniciu and Meer, 2002; Collins, 2003; Georgescu *et al.*, 2003], very few work has been derived from it in the context of medical multidimensional data segmentation.

In this paper, the MS paradigm is applied to perform segmentation of multidimensional data, obtained using Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI). Briefly speaking, DCE-MRI techniques represent non-invasive ways to discover symptoms of local tumor growth, based on a manually-driven feature extraction step that operates on the MRI imagery.

As explained in the following, our method bring two advantages to the current state of the DCE-MRI analysis. First, it permits a more accurate feature extraction step, that here operates in an *automatic* fashion. Second, it permits to fasten the analysis itself, ensuring a higher throughput, that turns out to be useful in the case of massive analysis.

The rest of the paper is organized as follow. In Section 2, an overview of the previous work done in the context

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of medical data segmentation is provided; subsequently, in Section 3, the necessary medical background is provided, considering the classical DCE-MRI experimental methodology, in the contest of the tumor development monitoring. This section will elucidate the nature of the data managed; moreover, here it will be possible to deeply understand the advantages brought by our method. In Section 4, the Mean Shift procedure is explained, connecting it with a classical pattern recognition procedure, i.e. the Parzen Windows estimation method. In Section 5, the technical details of the proposed method are reported. Results are shown in Section 6, also compared with a state of the art method, and, finally, Section 7 concludes the paper.

2 Previous Works

In the realm of medical data segmentation, several works have been introduced, especially for MRI clustering and classification [Windishberger *et al.*, 2003; Dimitriadou *et al.*, 2004; Zhang and Chen, 2004; Wismuller *et al.*, 2006; Arulmurgan *et al.*, 2005; Wei and Yang, 2005; Jain *et al.*, 1999b; Scarth *et al.*, 1995; Castellani *et al.*, 2005]. Most proposed methods are based on the *K-Means* algorithm [McQueen, 1967; Han and Kamber, 2000]. In [Windishberger *et al.*, 2003; Zhang and Chen, 2004], a variant of the K-Means has been implemented, called *fuzzy C-Means* (FCM) [Scarth *et al.*, 1995; Jain *et al.*, 1999b; Dimitriadou *et al.*, 2004]. Such variant takes advantages of fuzzy logic algorithms to enhance clustering performance. In particular, the FCM algorithm assigns pixels to fuzzy clusters without labels. Unlike the hard clustering methods which force pixels to belong exclusively to one class, FCM allows pixels to belong to multiple clusters with varying degrees of memberships. In [Windishberger *et al.*, 2003] the clustering of MRI time series have been performed for the identification and separation of artifacts as well as quantification of expected novel information on brain activities. In [Zhang and Chen, 2004] the authors focused on the methodological aspect of the *fuzzy C-Means* by introducing a kernel-induced distance metric and a spatial penalty on the membership functions. The proposed approach has proved to be more robust to noise and other artifacts with respect to standard algorithms. In [Castellani *et al.*, 2005] the authors proposed a DCE-MRI clustering approach, coupled with a Information Visualization module, in which a Bayesian development of the K-Means was applied. Here the add-on is that the number of the clusters is automatically computed; the algorithm is similar in spirit to the X-Means algorithm proposed by [Pelleg and Moore, 2000]. In [Dimitriadou *et al.*, 2004], a quantitative comparison of MRI cluster analysis has been reported.
With respect to the proposed evaluation, the results clearly show that approaches based on k-means algorithm perform significantly better than all the other methods.
More complex techniques have been proposed in [Wismuller *et al.*, 2006; Arulmurgan *et al.*, 2005; Wei and Yang, 2005] which are based on neural networks or genetic algorithms [Jain *et al.*, 1999b; Han and Kamber, 2000], but they are time consuming and therefore are not suitable for interactive applications.

3 The DCE-MRI analysis

The main purpose of DCE-MRI analysis is to accurately monitor the local development of cancer, eventually subject to different treatments.
The traditional criteria to assess the tumor response to treatment is based on the local measurement of tumor size change. This phenomenon is due to the local *angiogenesis*, i.e., the process of growth of new vessels which provide the tumor tissue with nutrients. In consequence, various angiogenesis inhibitors have been developed to target vascular endothelial cells and to block tumor angiogenesis.

Recently, a different and more appealing indicative symptom of the cancer development has been analyzed, i.e. the tissue vascularization [Marzola *et al.*, 2004]. Roughly speaking, vascular effect may precede, by a remarkably long time interval, the effect on tumor growth. For these reasons, the assessment of antiangiogenic compounds requires imaging methods that can detect early vascular alterations.

DCE-MRI techniques play a relevant role in this field [Marzola *et al.*, 2004]. The final aim is to provide quantitative measures that indicate the level of vascularization in the cancer tissue, eventually treated with antiangiogenic compounds, in a *non-invasive* way.
Roughly speaking, the DCE-MRI analysis can be divided in the following steps (see Fig.1)[1]: 1) injecting macromolecular contrast agents in the tissue being analyzed; 2) producing MRI image sets of different slices of the tissue; 3) extracting morphological and functional parameters such as *fractional plasma volume* (fPV) and *transendothelial permeability* (kPS), that model the tissue vascularization; in practice, to each point of the MRI image is associated a pair consisting of fPV and kPS values; 4) manually selecting a Region Of Interest on the MRI slices, in order to isolate the highly vascularized local tumoral area; usually this area is ring-shaped and separates a necrotic area (that lies in the center of the ring) from the external healthy portion of the tissue; 5) averaging the values of fPV and kPS in such ring-shaped area, obtaining for each slice a couple of fPV and kPS mean values, that indicate the overall level of vascularization. This process has been recently tested using a well-known anti-cancer treatment [Marzola *et al.*, 2005], evidencing that the fPV and kPS parameters well describe the effectiveness of the treatment, as checked by additional histological analysis; as we see in the following, we take as experimental data-set the one coming from this research.

In this paper, we strongly improve the process above, providing an automatic method of data segmentation; the proposed technique is applied to this particular kind of analysis, but we suppose it can be also applied in general in the DCE-MRI context. In detail, we focus on steps 3), 4) and 5); our method takes as input the functional parameters fPV and kPS obtained in step 3); in an automatic fashion, it is able to segment areas that experimentally corresponds to the tumoral area extracted by hands in step 4); note that originally this step was driven by histological and physio-

[1] The procedure listed above comes from the investigation detailed in [Marzola *et al.*, 2005], that in turn presents additional similar researches

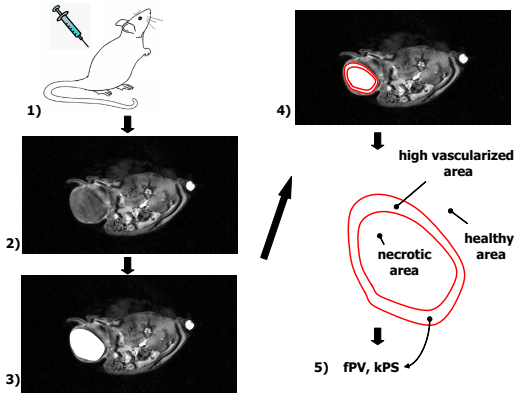


Figure 1: DEC-MRI analysis: example of DEC-MRI analysys procedure; 1) contrast agent injection; 2) MRI image acquisition 3) kPS,fPV extraction; for clarity, here the bright zone highlights the tumor4) ring shape ROI drawing by hand; 5) mean kPS,fPV values computation

logical a-priori considerations, being the ring-shaped zone segmented by hand by an human operator.

The advantage brought by the proposed approach is twofold: firstly and mostly important is that, given a DCE-MRI slice, we provide a region of points composed by an ensemble of fPV and kPS values that individuate separate groups; note that the partition is histologically meaningful, and not relies on a-priori manual settings. Secondly, such a segmentation is produced automatically and quickly (5 seconds, versus the 4-5 minutes needed for an accurate manual setting), thus fasting the analysis process listen above.

4 Mean Shift

The Mean Shift procedure is a dated non-parametric density estimation technique [Fukunaga, 1990; Comaniciu and Meer, 2002]. The main underlying idea is that the data feature space is regarded as an empirical probability density function to estimate: therefore, a big concentration of points that fall near the location $\mathbf{x}$ indicates a big density near $\mathbf{x}$.

The theoretical framework of the mean shift arises from the Parzen Windows [Duda *et al.*, 2001] basic expression, i.e. the kernel density estimator, that is

$$\hat{f}(\mathbf{x}) = \frac{1}{n}\sum_{i=1}^{n} K_{\mathbf{H}}(\mathbf{x}-\mathbf{x}_i) \tag{1}$$

where $\hat{f}(\mathbf{x})$ represents the approximated density calculated in the d-dimensional location $\mathbf{x}$, n is the number of available points and

$$K_{\mathbf{H}}(\mathbf{x}) = |\mathbf{H}|^{-1/2} K(\mathbf{H}^{-1/2}\mathbf{x}). \tag{2}$$

Here above, $K_{\mathbf{H}}$ can be imagined as a weighted window used to estimate the density, dependent on the kernel K and the symmetric positive definite $d \times d$ bandwidth matrix $\mathbf{H}$. The function K is a bounded function with compact support (for full details, see [Comaniciu and Meer, 2002]); the bandwidth matrix codifies the uncertainty associated to the whole feature space.

In the case of particular radial symmetric kernels (see [Comaniciu and Meer, 2002]), K can be specified using only a 1-dimensional function, the *profile* $k(\cdot)$, equal for each dimension. Moreover, if we assume independence among the feature dimensions and equal uncertainty over them, the bandwidth matrix can be rewritten as proportional to the identity matrix $\mathbf{H} = h^2\mathbf{I}$. Under such hypotheses, Eq. 2 can be rewritten as:

$$\hat{f}_{h,k}(\mathbf{x}) = \frac{c_{k,d}}{nh^d}\sum_{i=1}^{n} k\left(\left\|\frac{\mathbf{x}-\mathbf{x}_i}{h}\right\|^2\right) \tag{3}$$

where $c_{k,d}$ is a normalizing constant, n is the number of points available, and $k(\cdot)$ is the kernel profile; in Eq.(3) it is easy to note that $k(\cdot)$ models how strongly the points are taken into account for the estimation, in dependence with their distance h to $\mathbf{x}$.

Mean Shift extends this "static" expression, differentiating (3) and obtaining the gradient of the density, i.e.:

$$\hat{\nabla} f_{h,k}(\mathbf{x}) = \frac{2c_{k,d}}{nh^d}\left[\sum_{i=1}^{n} g\left(\left\|\frac{\mathbf{x}_i-\mathbf{x}}{h}\right\|^2\right)\right]\left[\frac{\sum_{i=1}^{n}\mathbf{x}_i g\left(\left\|\frac{\mathbf{x}_i-\mathbf{x}}{h}\right\|^2\right)}{\sum_{i=1}^{n} g\left(\left\|\frac{\mathbf{x}_i-\mathbf{x}}{h}\right\|^2\right)} - \mathbf{x}\right] \tag{4}$$

where $g(x) = k'(x)$. In the above equation, the first term in square brackets is *proportional* to the normalized density gradient, and the second term is the *Mean Shift* vector, that is guaranteed to point towards the direction of maximum increase in the density [Comaniciu and Meer, 2002]. Therefore, starting from a point $\mathbf{x}_i$ in the feature space, the mean shift produces iteratively a trajectory that converges in a stationary point $\mathbf{y}_i$, representing a mode of the whole feature space.

5 The proposed method

Our segmentation method can be thought as a clustering process, derived from the approach proposed in [Comaniciu and Meer, 2002]. Briefly speaking, the first step of such process is made by applying the Mean Shift procedure to all the points $\{\mathbf{x}_i\}$, producing several convergency points $\{\mathbf{y}_i\}$. A consistent number of close convergency locations, $\{\mathbf{y}_i\}_l$, indicates a mode μ_l. The labeling consists in marking the corresponding points $\{\mathbf{x}_i\}_l$ that produces the set $\{\mathbf{y}_i\}_l$ with the label l. This happens for all the convergency location $l = 1, 2, \ldots, L$.

In this paper, we consider each point of the MRI as a d-dimensional entity, living in a *joint domain*. In specific, each $\mathbf{x}_i$ is composed by the pair $\mathbf{x}_s \in \mathcal{R}^2$ of spatial coordinates relative to the x,y image axes (the *forming the spatial sub-domain*) and the pair $\mathbf{x}_c \in \mathcal{R}^2$ of fPV and kPS coefficients (forming the *coefficients sub-domain*). For each sub-domain we assume Euclidian metric.

In order to explore the joint domain, a multivariate kernel is used [Comaniciu and Meer, 2002; Wang *et al.*, 2004], that has the form

$$K_{h_s,h_c}(\mathbf{x_i}) = \frac{C}{h_s^2 h_c^2} k\left(\left\|\frac{\mathbf{x}_{i,s}}{h_s}\right\|^2\right) k\left(\left\|\frac{\mathbf{x}_{i,c}}{h_c}\right\|^2\right) \tag{5}$$

where $\mathbf{x}_{i,s}$ indicates the spatial coordinates of the $i-$th point and so on for $\mathbf{x}_{i,c}$; C is a normalization constant, and h_s,h_c are the kernel bandwidths for each sub-domain. These values give to each feature domain the intuitive concept of "importance": strictly speaking, the bigger the related kernel bandwidth, the less important that feature. In other words, a big amplitude of the kernel tends to agglomerate points in few convergence locations, while a small kernel highlights better local modes, encouraging cluster separations.
In this paper, we use the Epanechnikov kernel [Comaniciu and Meer, 2002], that can be described by the profile

$$k(x) = \begin{cases} 1 - x & \text{if } 0 \leq x \leq 1 \\ 0 & \text{otherwise} \end{cases} \quad (6)$$

that differentiated leads to the uniform kernel, i.e. a d-dimensional unit sphere.

6 Experiments

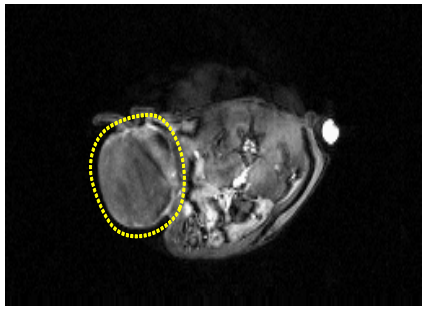
The experiments performed in this paper are related to a series of investigations on the effects of a particular tumor treatment, using DCE-MRI techniques. Here, human mammary carcinoma fragments (13762 MAT B III) were subcutaneously injected in the right flank of 42 female rats at the level of the median-lateral. The details about the experiment outstand the scope of the paper (see [Marzola *et al.*, 2005] for details); anyway, the interesting aspects are the following: 1) after the injection of a contrast compound in the animals, MRI images were acquired for tumor localization and good visualization of extratumoral tissues. The dynamic evolution of the Signal Intensity in MR images is analyzed using a two compartments tissue model in which the contrast agent can freely diffuse between plasma and interstitial space. The kPS and fPV values are obtained pixel by pixel by fitting the theoretical expression to experimental data. After that, data were transferred on a PC for analysis. Images were analyzed on a ring-like region-of interest (ROI) basis to obtain the average value of kPS and fPV within it: in each animal, the central 5 slices of the 3D data set were analyzed.

In our case, we select a reasonable section of the MRI slice, (Fig.2 (a); in principle, the analysis can be applied to the entire slice); in this area, we calculate the related kPS and fPV coefficients (Fig.2 (b) and (c)) and we perform MS segmentation using a uniform kernel for each subdomain.

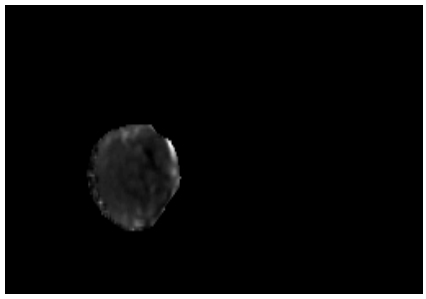
After the normalization of the data, that brought all the values between 0 and 1, the kernel bandwidth widths have been easily chosen. In particular, after some (less than 10) trials the bandwidth values have been set to $[0.3, 0.3, 0.03, 0.06]$ for the spatial (first pair of values), and the coefficient sub-domain (second pair of values), respectively.

The current implementation of the proposed method is working under the Matlab 7 environment. The segmentation process takes ~ 5 sec. each for each MRI slice.

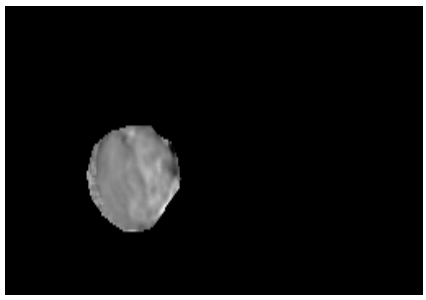
A result obtained for the slice shown in Fig.2 is shown in Fig.3 (b).
As comparative test, we perform the same analysis using the approach based on the Bayesian development of the K-Means, presented in [Castellani *et al.*, 2005]; the result is



(a)



(b)

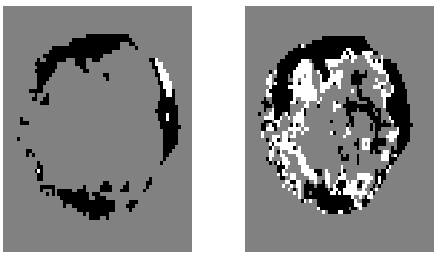


(c)

Figure 2: DEC-MRI: (a) example of MRI slice, where a contrast agent has been introduced into the tissue before the image acquisition; a rough section of the tissue was selected in order to apply our algorithm, highlighted by the dotted circle; (b) intensity image representing the fPV values; (c) intensity image representing the kPS values; in b) and c), the higher the values of the parameters, the brighter the color of the correspondent pixels.

shown in Fig.3 (a). As one can see, our approach identify two clusters: both of them have a different histological meaning; the darker cluster, roughly forming a ring, indicates effectively the zone of the tumor more affected by vascularization. This zone corresponds to the one segmented by hand at steps 4) and 5) of the DCE-MRI analysis discussed in Sect.3. The second cluster, that spreads over the center, indicates another different zone, affected by high permeability with respect to the contrast agent. The result obtained using the X-Means based approach shows slightly only the circular high vascularized ring.

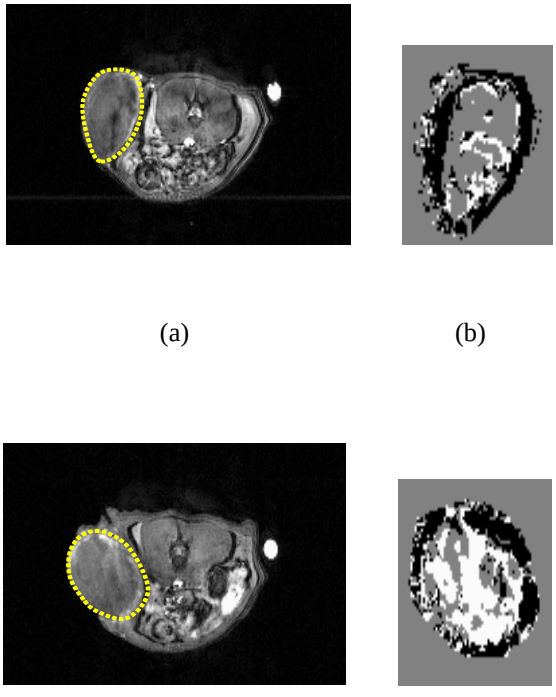
With the same experimental setup, we perform another two tests on the same DCE-MRI data set. As shown in Fig.4 (b) and (d), in both the cases the resulting segmentations show 2 clusters, i.e., an external high vascularized



(a) (b)

Figure 3: Comparative results: (a) the segmentation obtained using the X-means method; (b) our approach

ring and a central necrotic spread zone, with precise histological meanings, as written above.



(a) (b)

(c) (d)

Figure 4: DCE-MRI results: on the left, the MRI images related to two different experiments, with the tumoral zone highlighted. On the right, the resulting segmentations

7 Conclusions

In this paper, we introduce a multidimensional segmentation technique derived by the Mean Shift (MS) procedure, aimed at improving the analysis and the characterization of tumor tissues. Briefly speaking, the multidimensional output obtained by a recent and non invasive tissue analysis, namely, the Dynamic Contrast-Enhanced MRI (DCE-MRI) technique is considered; the output of this technique, composed by spatial, morphological and functional tumor parameters is projected in a joint space, where an *automatic* clustering-based segmentation is performed; this process results in a histologically meaningful partition, that individuates tissue zones differently involved with the development of the tumor. The goals of the proposed method are two: 1) we permit an analysis of the tissue more precise and 2) fast than the manual analysis currently performed; these two results assess that the non-parametric paradigm derived from the MS strategy well behaves with medical segmentation issues, related to the DCE-MRI context. Further research is currently under study, specially devoted to make automatic the phase of kernel selection.

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