Segmentation of Breast Cancer Tissue Microarrays for Computer-Aided Diagnosis in Pathology

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Abstract—Computer-Aided Diagnosis (CAD) systems for pathologists can act as an intelligent digital assistant supporting automated grading and morphometric-based discovery of tissue features that are important in cancer diagnosis and patient prognosis. Automated image segmentation is an essential component of computer-based grading in CAD. We describe a novel tissue segmentation algorithm using local feature-based active contours in a globally convex formulation. Preliminary results using the Stanford Tissue MicroArray database shows promising stromal/epithelial superpixel segmentation.

I. INTRODUCTION

Most carcinomas are graded in clinical practice by pathologist determined visual morphologic parameters of malignant tissues such as tubule/lumen/structure formation, nuclear mitotic activity and nuclear grade or atypia [1]. Automated or assisted grading would be an important component of Computer-Aided Diagnosis (CAD) systems for pathologists. CAD systems can act as a digital assistant to highlight suspicious areas for further scrutiny, offer a second opinion, reduce variability between experts and labs, support larger number of cases, improve the workflow, organize case studies for teaching and learning. A newly emerging role for CAD in pathology is to bootstrap discovery of new morphometric phenomenology. Some of the key components of an overall digital pathology CAD system are shown in Figure 1 and include data acquisition and management that incorporates slide preparation, digital scanning, virtual microscope visualization toolsets for large data handling, image analysis pipelines customized for different cancers or diagnostic tasks, machine learning for CAD expert systems and prognostic evaluation. The image analysis processing pipeline component within pathology CAD systems consist of several modules including: 1) image normalization, 2) tissue segmentation, 3) feature extraction, 4) classification and grading. Accurate tissue segmentation is a critical component of automated grading and survival analysis.

One recent example of CAD supporting automated discovery of new morphometric phenomenology is the recent work of Beck, et. al. [2]. In this study computer-aided analysis of breast cancer tissue microarray specimens using more than 6600 image derived morphometric features, combined with image classification and machine learning resulted in the C-Path software identifying that morphological changes in stromal tissues surrounding the tumor, correlates highly with patient survival, even more so than the morphology of cancerous epithelial regions and other diagnostic factors. This was an unexpected association in breast cancer that is not part of standard clinical practice and was driven by bottom-up automatic image-based segmentation and feature extraction. The importance of stromal morphology offers an interesting hypothesis for further testing and validation. Of course the role of stromal features in breast cancer will need a great deal of additional independent investigation, clinical confirmation across a wider study group and connection to the underlying cancer genomics, biomarker regulation and molecular mechanisms.

In this work we present a novel automatic image segmentation system to distinguish between stromal and epithelial regions in breast cancer tissue based on hematoxylin and eosin (H&E) stained histopathology images collected as tissue microarrays or using whole-slide imaging. This can be used as the first phase towards automated cancer grade labeling and ultimately patient survival prediction studies.

II. TISSUE SEGMENTATION USING LOCAL FEATURE FITTING BASED ACTIVE CONTOURS

The proposed image segmentation approach is an extension of our multichannel Chan and Vese model [3], [4], [5], [6] to segment color images composed of textured regions which was previously used to segment prostate cancer imagery. Utilizing the chromaticity-brightness (CB) model [7] we first decompose the given image and then use two different feature fitting terms to drive the level set based active contour segmentation. Note that the underlying geometric structure of a color image is usually present in the brightness (intensity) channel [8]. We utilize a hybrid feature fitting using the smoothed gradient image computed from the brightness channel, to capture strong intensity variations in the neighborhood of edges, combined with local histogram based weights (see Figure 2). That is, the smoothed gradient image of the brightness channel is weighted by the local histograms computed around each pixel of the intensity channel alone. This provides an adaptive force for the active contour to wrap around strong discontinuities. Following the success of region scalable fitting energy terms [9] in capturing spatially varying regions, we utilize local features in the remaining chromaticity channels to capture smoothly varying color fields. Further, our method is based on the globally convex formulation of Chan et al [10] and is implemented using the efficient dual minimization approach of Chambolle [11].
Let $\Omega$ be an open and bounded set in $\mathbb{R}^2$, and $I : \Omega \to \mathbb{R}^N$ be the input multichannel image. In what follows, we study the traditional color images $N = 3$, $I = (I^1, I^2, I^3)$ where the three spectral channels can be (Red, Green, Blue) bands or other color coordinates such as YUV or HSV and the general multichannel case follows in a straightforward way.

A. Globally convex model

The convex formulation of the traditional vector valued Chan and Vese model [3], amounts to solving the minimization problem [10]:

$$
\min_{0 \leq u \leq 1} \left\{ \mu \int_{\Omega} |\nabla u| \, dx + \sum_{i=1}^{3} \int_{\Omega} \lambda_i R^i(x, c^i) \, u \, dx, \right\} \tag{1}
$$

where $u : \Omega \to [0, 1]$ is a function of bounded variation, $u \in BV(\Omega)$ and $R^i(x, c^i) = (I^i - c^i_{\text{in}})^2 - (I^i - c^i_{\text{out}})^2$ which is known as the image fitting term. The vector $c^i = (c^i_{\text{in}}, c^i_{\text{out}})$ represents the averages (mean values) of each channel $I^i$, respectively inside and outside of the segmentation contour. The parameters $\lambda_i$ are positive scalars weighting the fitting terms $R^i(x, c^i)$. The total variation term (first term in Eqn. (1)) keeps the segmentation curve regular. It can be shown that for any $\lambda_i \geq 0$, there exists a minimizer $u$ of (1), which is a global minimum [10]. The energy functional is homogeneous of degree one in $u$ and has a global minimizer by restricting $u$ such that $0 \leq u(x) \leq 1$.

Since the Chan and Vese model relies on mean gray values of the input channel $I^i$ alone (for each channel $i$), it can neither capture the spatially varying intensity regions nor textured regions. In this paper we extend the globally convex Chan-Vese model (1) to support more general fitting terms and to handle textured regions across multiple channels.

B. Decomposition-based fitting terms

First we use the chromaticity-brightness (CB) decomposition which provides the intensity or brightness $B : \Omega \to [0, L]$ computed as $B = |I|$, where $L$ is the maximum intensity value, and the chromaticity channels $C = (C^1, C^2, C^3) : \Omega \to \mathbb{R}^3$ where $\mathbb{R}^3$ is the unit sphere in $\mathbb{R}^3$.

a) Intensity and edge-based feature fitting: Image discontinuities such as edges are of major geometrical structures and are primarily present in the brightness channel alone. We introduce a brightness-based edge feature fitting term using local histograms and the smoothed gradient image to capture objects differentiated by strong discontinuities (see Figure 2). For a given gray-scale image $B : \Omega \to [0, L]$, let $N_{x,r}$ be the local region centered at $x$ with radius $r$. Then the local histogram of a pixel $x \in \Omega$ and its corresponding cumulative distribution function are defined by

$$
P_x(y) = \frac{|\{z \in N_{x,r} \cap \Omega \mid B(z) = y\}|}{N_{x,r} \cap \Omega} \quad F_x(y) = \frac{|\{z \in N_{x,r} \cap \Omega \mid B(z) \leq y\}|}{N_{x,r} \cap \Omega} \tag{2}
$$

for $0 \leq y \leq L$, respectively. Local histograms provide a general local first-order statistical model of the image intensity values around a pixel without making simplifying...
assumptions. We define the following measurable function
\( \omega: \Omega \rightarrow \mathbb{R} \), such that for each \( x \in \Omega \)
\[
\omega(x) = \int_0^L F_x(y) \, dy,
\]
which allows us to get a weight of how much non-homogeneous intensity is present in a local region \( \mathcal{N}_{x,r} \) of a given pixel \( x \in \Omega \). Given an image with texture information, it is possible to extract major regional textures using a weighted and smoothed gradient image, see Figure 2. Then, a new input feature channel is defined by the product
\[
\tilde{B} = \omega \times |\nabla B|_\sigma
\]
where the lower sub-script \( \sigma \) in (4) means a smoothed version of the corresponding indexed function. The smoothing is done by a Gaussian kernel \( G_\sigma(x) = (2\pi\sigma)^{-1}e^{-\frac{|x|^2}{2\sigma^2}} \). The new weighted input channel uses the smoothed gradient to differentiate the object boundaries with the help of local histograms computed within each pixel neighborhood that assists in distinguishing edges between textured foreground and the background. Thus the modified brightness fitting term we use is
\[
F_B(x, c) = (\tilde{B} - c_{in})^2 - (\tilde{B} - c_{out})^2.
\]

b) Chromaticity based localized fitting: As can be seen in Figure 2 the chromaticity channels exhibit inhomogeneities and are spatially varying in nature. Following [9], we utilize a sum of region scalable fitting terms
\[
F_C(x, c) = \sum_{i=1}^3 \left[ |G_\sigma \ast C^i_{in} - c^i_{in}|^2 - |G_\sigma \ast C^i - c^i_{out}|^2 \right]
\]
to capture chromatic regions in the scene efficiently.

C. Combined local feature fitting model and minimization

We combine the different local feature measurements into a single energy functional composed of the weighted luminance edge information with the chromaticity-based region information. Thus, the active contour based scheme we propose can be written as a variational energy minimization problem with a total variation regularization component,
\[
\min_{0 \leq u \leq 1, c} \left\{ \mu \int_\Omega |\nabla u| + \int_\Omega (\lambda_B F_B + \lambda_C F_C) \, u \, dx \right\} \tag{7}
\]
where \( \lambda_B \geq 0 \), \( \lambda_C \geq 0 \) are the tunable parameters for the brightness and total chromaticity feature fitting terms respectively.

A fast numerical scheme based on Chambolle’s dual minimization technique [11] for total variation regularization is implemented for solving the proposed minimization problem in Eqn. (7). We follow the approach of Chan et al [10] by considering the corresponding unconstrained convex minimization functional (with \( \mu = 1 \)) to find the global minimizer of the energy functional using an iterative scheme with fast convergence [12] is described elsewhere.

III. TISSUE MICROARRAY (TMA) SEGMENTATION RESULTS

The digitized breast cancer biopsy cores were obtained from the Stanford TMA database [2], [13] (http://tma.stanford.edu/tma.portal/C-Path). The cores are 0.6mm in diameter (a very small portion of a whole slide image), scanned at 20X using an ArioI scanner with the central 720 \times 1128 region extracted from a larger 1440 \times 2256 image of a TMA core. In all the experiments reported here, the parameters were fixed at \( \delta t = 1/8 \), \( \sigma = 10 \), \( r = 10 \), \( \lambda = 1 \) and \( \theta = 1 \). The tunable brightness and chromaticity parameters were equally weighted as \( \lambda_B = \lambda_C = 0.5 \).

Figure 3 shows five sample tissue segmentation results produced by the proposed local feature active contour method for varying amounts of stroma and epithelium. The TMA breast cancer images are from the NKI training set of type malignant ductal carcinoma [2], shown along with pathologist labeling of stromal and epithelial superpixel regions shown in green and red colors respectively. The feature fitting brightness weighted edges and chromaticity energy terms are shown color-coded followed by the proposed two-class algorithm segmentation result. Qualitatively the automatic segmentation of stromal and epithelial superpixel regions are reasonably consistent with expert labels, for a diverse range of tubule formation vs sheets, and offers a good starting point for classification-based refinement. The last column shows the region contours overlaid on the original TMA image highlighting the region separation prior to classification.

IV. FUTURE WORK & DISCUSSION

In this paper, we present a new texture segmentation scheme driven by local feature energy terms, using the globally convex formulation. Our scheme uses local density functions to model texture information in the luminance channel and combines this with smoothed gradient edge information. By utilizing a localized feature fitting for the chromaticity channels we obtain a combined model which helps in segmenting textured regions effectively. Extensions include edge profile-based active contours [14] for textures.

The proposed local feature-based active contour method works well for identifying stromal and epithelial superpixel regions in our preliminary tests. Quantitative validation using the full Stanford TMA dataset is in progress. Robustness and scalability to a wider range of clinical data also needs to be tested. The tissue regions produced by the proposed segmentation algorithm constitute the support regions for later stages of the CAD system including machine learning and pattern recognition as described in Figure 1.

The overall goal of the system is to develop an automatic grading capability and to determine the patient prognostic value of morphological features within the stroma and epithelia sections of the cancerous tissue. Our image analysis segmentation pipeline within the framework of digital pathology can lead to bottom-up automated discovery of novel morphometric phenomenology with clinical significance. The proposed system will facilitate verification of the role of stromal features in breast cancer along with clinical confirmation
across a wider study group and connection to the underlying cancer genomics and molecular mechanisms.

REFERENCES