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A RECURSIVE AND MODEL-CONSTRAINED REGION SPLITTING ALGORITHM FOR CELL CLUMP DECOMPOSITION

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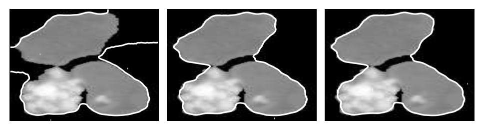
Abstract

Decomposition of cells in clumps is a difficult segmentation task requiring region splitting techniques. Techniques that do not employ prior shape constraints usually fail to achieve accurate segmentation. Those using shape constraints are unable to cope with large clumps and occlusions. In this work, we propose a model-constrained region splitting algorithm for cell clump decomposition. We build the cell model using joint probability distribution of invariant shape features. The shape model, the contour smoothness and the gradient information along the cut are used to optimize the splitting in a recursive manner. The short cut rule is also adopted as a strategy to speed up the process. The algorithm performs well in validation experiments using 60 images with 4516 cells and 520 clumps.

1. Introduction

Peripheral blood examinations using light microscopy are commonly used to diagnose diseases and quantify their severity by detecting infected cells (red blood cells (RBCs) and/or white blood cells), counting them differentially and measuring the relative population of the infected cells. The first step to automate the examinations using image analysis is to segment cells. However, as there are large variations in coloration, illumination and image quality during sample preparation and imaging, cell segmentation robust to these variations is difficult to achieve. An even more difficult task is to separate the cells in the aggregated cell clumps that inevitably appear in these images.

Without prior knowledge, bottom-up segmentation techniques using primitive features often fail to separate cells in the clumps appropriately. For example, when encountering a contour branch, naïve level-set methods [11] do not know whether a split should occur. This limitation is demonstrated in Fig. 1, where surface evolution stabilizes after 1000 iterations and stops at the external contour of the clump of three cells.



(a) 300 (b) 1000 (c) 2000

Figure 1. Segmentation results using a level-set method after different iterations.

In this paper, we build a probabilistic cell shape model and introduce a new cell splitting algorithm based on object function minimization. We consider the model, the gradient information along cuts and the contour smoothness of separated objects in the object function. The short-cut rule is adopted to speed up the searching of splitting candidates. We identify clumps and splitting cuts by checking the model compatibility of decomposed regions. We review related work in Section 2. The new algorithm is described in Section 3. Experiments are presented in Section 4. Lastly, we summarize our work in Section 5.

2. Related work

The decomposition of cell clumps requires tailed region splitting techniques. Existing techniques can be categorized into erosion-based [12, 7], contour concavity analysis [10, 8], watershed-based [2, 13, 3] and model-based [9, 1]. Erosion-based methods erode the boundaries of binary regions so that fused regions can be shrunk and separated from each other. It is also not known beforehand how much erosion is needed to split each local clump. Contour concavity analysis is based on the intuitive assumption that constituent clump parts

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are normally convex, and such a split should occur at the concave parts of the contour. The short-cut rule [15] requires the splitting cut to be the shortest path to pass through for possible cuts. The rule-based methods are usually fast. However using of rules alone may not be able to handle complicated clumps. Watershed transforms are often used to find the watershed of basins based on the Euclidian distance transform of binary images. The classical watershed techniques assume disk-like objects and cannot separate objects when they are fused beyond a certain point. The watershed approaches are based on binary images and often generate fragmented splits.

In general, these techniques that do not use prior knowledge perform worse than those using prior knowledge. Much research has been devoted to model-guided cell segmentation by assuming prior models for cells. A model-based segmentation method is proposed in [4]. Based on local adjacent consistency, it constructs hyper-quadric curves to fit the detected contours. An assignment matrix is used to convert the segmentation problem into a constrained optimization problem. A drawback is that model-based techniques are normally computationally expensive.

Combining rules and models may achieve fast and accurate cell splitting as demonstrated in [9] where the short-cut rule and a statistical shape model are applied to guide the grouping and splitting of regions based on a separate step of over segmentation. In [9], the authors firstly construct a single-object model use a cost function involving the model to identify clump candidates. The then deform the model to fit the clump and decide the splitting plans. However, as they do not model clumps, such a process is problematic in coping with large clumps and occlusions. Cloppet and Boucher [3] discuss the segmentation of overlapping nuclei cells as well by optimizing the right set of markers for watershed-based segmentation using established overlapping templates and aggregating templates. Díaz *et al.* [5] assumed a binary cell template and use template matching to recursively decompose cell clumps.

3. Methodology

We first introduce the objective functions and then describe the algorithm.

3.1 Object functions with shape modeling

To model geometric shape properties of a region/object, we extract eight standard features, namely, the object area, perimeter, major and minor axis lengths of the ellipse, equivalent diameter, eccentricity of the fitted ellipse, extent (the proportion of the pixels in the bounding box that are also in the region) and solidity (the proportion of the pixels in the convex hull that are also in the region). Among the eight region features r_i, $i = 1, .., 8$, the area r_1 is the most convenient to compute. Hence, for each segmented binary object, we first compute r_1 and its likelihood Ω_{area} belonging to a normal cell class ω_N:

$$\Omega_{area} = \log(P(r_1|\omega_N)). \tag{1}$$

If the area is large enough such that the likelihood Ω_{area} is smaller than a certain threshold $T(\Omega_{area})$, we compute other region features r_i, $i = 2, .., 8$, as well as the shape likelihood function Ω_{region} as follows:

$$\Omega_{region} = \log(\prod_{i=2}^{8} P(r_i|\omega_N)) = \sum_{i=2}^{8} \log P(r_i|\omega_N). \tag{2}$$

Both geometry (area and shape) likelihood functions will be used later to guide the segmentation of cells.

The region model given in Eq. (2) is not sufficient to guide region merging and splitting since it considers only the lengths of the major and minor axes, instead of at least eight length measures used in other models [14, 9]. Hence, we introduce two regularization terms, namely, contour smoothness Ω_{smooth} and the split strength $\Omega_{strength}$ (defined below).

The definition of contour smoothness Ω_{smooth} is based on contour curvature κ. Consider a planar curve/contour $\mathbf{s}$ sampled uniformly at the sampling interval δs along the curve. And following [6], we assume ϑ follows the von Mises distribution, which agrees with human perceptual expectations from a psychovisual perspective [6]. With this assumption, we can define a quantity $\hbar(x, y)$, called *surprisal*, to measure the information gain [6], at any point (x, y) on the contour:

$$\hbar(x, y) = -\log \frac{\exp(a_{von} \cos(\vartheta - \frac{2\pi}{\delta s}))}{2\pi \mathrm{Be}(0, a_{von})}. \tag{3}$$

Here, a_{von} is the spread of the von Mises distribution (assumed to equal 1) and $\mathrm{Be}(0, a_{von})$ is the Bessel function of the first kind given parameters 0 and a_{von}. We can prove that surprisal increases monotonically with $|\kappa|$ [6]. It takes its minimum value at $\vartheta = 0$ for straight segments. We define the smoothness of a contour by the mean value of $\hbar(x, y)$ over all (x, y) on $\mathbf{s}$:

$$\Omega_{smooth} = \frac{\delta s}{|\mathbf{s}|} \sum_{(x,y)\in\mathbf{s}} \hbar(x, y) \tag{4}$$

with $|\mathbf{s}|$ being the length of the curve.

It is clear that, a clump of cells should be partitioned along the natural cell boundaries. Most existing cell splitting methods, however, work on binary images or edge maps and do not refer to the appearance of edges along the cuts if they are not detected during segmentation. The implicit assumption is that these segmentation algorithms are good enough to detect all cell edges and there is no need to consider this factor again in cell splitting. For example, Liu and Sclaroff [9] require an over-segmented image as the input to their algorithm, and assume that the segmentation can detect all object boundaries. Hence, in the splitting/merging steps that follow, they do not refer to the original image. In fact, edge detection approaches and some image segmentation techniques often ignore weak edgels to make a crisp decision for image binarization.

The splitting cut strength $\Omega_{strength}$ is defined based on edge strength. The idea of considering the strength of edges near splitting cuts has been used by Cloppet and Boucher [3] to refine watershed-based segmentation. Here we extend it to model-guided cell splitting in gray-level images. To do so, we compute the gradients around all possible valid cuts. For any color image $I(x, y)$, where $g(x, y)$ is its gray level channel and $\nabla g(x, y)$ the gradient, we define the strength of a cut and hence a contour by the mean gradient magnitudes of all points (x, y) on the contour **s**:

$$\Omega_{strength} = \frac{\delta s}{|\mathbf{s}|} \sum_{(x,y)\in\mathbf{s}} |\nabla g(x, y)|. \tag{5}$$

We adopt the intuitive short-cut rule [15] as our strategy, which chooses the cut with minimum length Ω_{cut} among those cuts sharing a common cut endpoint. Our object function is defined by

$$\begin{aligned}\Omega_{model} \;=\; & \beta_1\Omega_{area} + \beta_2\Omega_{region} + \beta_3\Omega_{smooth} \\ & +\beta_4\Omega_{strength} - \beta_5\Omega_{cut}\end{aligned} \tag{6}$$

where Ω_{region} is defined in Eq. (2), Ω_{cut} is the Euclidian distance of the cut, and β_1 to β_5 are the weighting coefficients that are determined experimentally. We aim to find a splitting such that Ω_{model} is maximized.

3.2 Parsing contours and their convex hulls

The convex hull of a foreground region g_π enclosed by contour c_π in a binary image $g_b(x, y)$ is a convex polygon. The polygonal region enclosed by the convex hull is g_π^c. The complement of the binary region $g_\pi^c - g_\pi$ contains multiple disjoint regions r_π^l, indexed by l. Each r_π^l is characterized by two points on c_π tangent to the convex hull. The two tangent points define s_l^f, which is a segment of c_π. We only consider those regions r_π^l whose s_l^f contains at least one concave point $\breve{u}$ on c_π as we assume region splitting can only occur in such regions. For each $\breve{u}$ on s_l^f of region r_π^l, we choose another point from segment s_j^f of a different region r_π^j, $l \neq j$. The two points form a cut to partition the foreground region g_π. The validity of all possible cuts will be examined subject to the final region splitting to be described next.

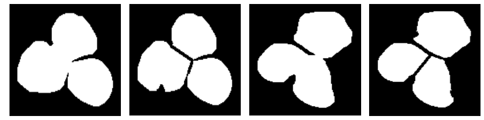
3.3 A recursive and greedy splitting approach

Since we do not know the number of cells in a clump, we have to recursively apply the basic splitting algorithm until there are no more feasible cuts [9]. To do so, we build a binary tree for each shape-invalid clump. For each node, if the object function of any child region is larger than that of its parent node, splitting continues. The best child region is found such that its object function formulated in Eq. (6) is maximized among all possible child regions of the same parent. Two child nodes are then created with the best region as one of them. This procedure is recursively applied.

Note that we have not taken the linear combination of the object functions of all sub-regions as in [9]. We argue that choosing the cut corresponding to the best child region is more appropriate than by finding a cut in the sense of averaging. This is because some constituent cells may have significantly larger deviations from the cell shape model. If a cut is decided based on an averaged value from the deviations of all constituent cells, we could miss the best object-model match and thus not select the best child region.

4. Experiments and results

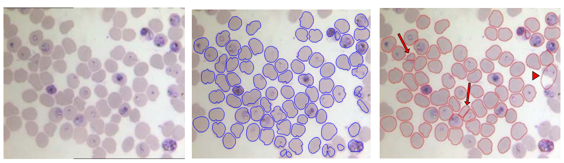
We first build a cell model using 5000 healthy RBCs based on their shape features. The cell shape model is the joint probability density function (PDF) of the eight features. We then use the model to constrain the cell splitting. The parameters used in the object function (Eq. (6)) are determined by using 60 images containing over 4000 RBCs. Their values are $\beta_1 = \beta_2 = 0.2$, $\beta_3 = 0.6$, $\beta_4 = 2.0$ and $\beta_5 = 0.1$. In Fig. 2, two splitting results are shown in Fig. 2(b) and (d) for the clumps shown in Fig. 2(a) and (c) respectively. The clumps are correctly partitioned in both cases.



(a) (b) (c) (d)

Figure 2. Two region splitting examples.

We show the cell segmentation results of two methods in Fig. 3. The objects are first segmented using edge detection followed by edge linking and region filling. Objects are then examined and split if necessary. The original image is shown in Fig. 3(a). The results are given in Fig. 3(b). To have a comparison, we present in Fig. 3(c) another result derived from a rule-based method using ellipse fitting followed by clump splitting using simple rules about cell contours [8]. Two cells (indicated by red arrows) that are over-segmented by the rule-based method are seen in Fig. 3(c). On the right side, there is an improperly segmented object (indicated by the pointing triangle) that includes a substantial amount of background.



(a) (b) (c)

Figure 3. Segmentation results using (a) original image, (b) the proposed method and (c) the rule-based method.

To further demonstrate the robustness of our work, we have tested our method on 60 images containing 4516 RBCs and 520 cell clumps. Some of the clumps are large or contain large occlusions. The measured parameters are average values per image over the 60 images (image size 768×576), with each image containing about 75 RBCs. The average number of over-segmented cells, the average number of under-segmented clumps and the average number of cells in the under-segmented clumps are 1.98 (1.58), 0.88 (1.55) and 2.17 (3.37) for the proposed method (the rule-based method), respectively. Over all, our method performs well. Compared with the rule-based method, it has slightly more over segmentation however much less under segmentation.

5. Conclusion

We have proposed a recursive and model-constrained algorithm for cell clump splitting in this work. We use shape constraints, the smoothness of the object contour and the gradient information along the cut in an optimization framework. To identify possible clumps and splitting cuts, we check model compatibility for each decomposed region. The splitting is recursively performed for the clump. The short cut rule is also adopt as a strategy to speed up the process. The algorithm performs well in validation experiments.

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