Analysis of Malignancy Using Enhanced GraphCut-Based Clustering for Diagnosis of Bone Cancer

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Abstract

Osteosarcoma and Ewing's sarcoma are very common bone tumors, and its biopsy is characterized with spatial distributions of osteoblasts, osteocytes, and osteoclasts. Any abnormal growth found in these three cells can be either cancerous or benign. This paper presents enhanced GraphCut-based clustering framework to ascertain malignancy level

in hematoxylin and eosin (H&E)-stained histopathological images. This approach executes iterative GraphCut method to extract foreground objects from biopsy image. Usually, iterative GraphCut needs user interaction to initialize segmentation process. But in enhanced GraphCut method, this initial data is manually generated using standard image processing tools. By doing this, experiment shows that quality of proposed segmentation result is improved. After segmentation of all tissue cells, its categorization is done through color and topological characteristics. Therefore, domain-specific methods such as color-based clustering, mathematical morphology, and active contour are used for feature extraction. This computed features are used to quantify the characteristics of malignancy and classify them as normal, benign, and cancerous using multiclass random forest framework. Proposed method is compared with earlier methods which yields 90% of classification accuracy.

References

1. Who cancer updates, cancer-world health organization (2017a). http://www.who.int/cancer

2. American cancer society cancer facts and figures, American cancer cociety publication (2017b). https://www.cancer.org

3. Heymann, D.: Bone cancer, Primary bone cancers and Bone Metastases. Elsevier Health Sciences (2014)

Google Scholar

4. Ghaznavi, F., Evans, A., Madabhushi, A., Feldman, M.: Digital imaging in pathology: whole-slide imaging and beyond. Ann. Rev. Pathol. Mech. Dis. **8**, 331–359 (2013)

Article Google Scholar

5. Thiran, J.P., Benoit, M.: Morphological feature extraction for the classification of digital images of cancerous tissues. IEEE Trans. Biomed. Eng. **43**(10), 1011–1020 (1996)

Article Google Scholar

6. Weyn, B.: Automated breast tumor diagnosis and grading based on wavelet chromatin texture description. Cytometry **33**(1), 32–40 (1998)

Article Google Scholar

7. Einstein, A.J., Wu, H.S., Sanchez, M., Gil, J.: Fractal characterization of chromatin appearance for diagnosis in breast cytology. J. Pathol **185**(4), 366–381 (1998)

Article Google Scholar

8. Antony, P.J., Vandana, B.S., Alva, S.R.: Visualisation of tissue cells from bone histopathological images for cancer diagnosis: a review on current status in digital histopathology. Int. J. Biomed. Eng. Technol. **24**(2), 133–153 (2017)

Article Google Scholar

9. Veta, M., Pluim, J.P., Van Diest, P.J., Viergever, M.A.: Breast cancer histopathology image analysis: a review. IEEE Trans. Biomed. Eng. **61**(5), 1400–1411 (2014)

Article Google Scholar

10. Cloppet, F., Boucher, v.: Segmentation of overlapping/aggregating nuclei cells in biological images. In : Pattern Recognition, 2008. ICPR 2008. 19th International Conference on, IEEE, pp. 1–4 (2008)

Google Scholar

11. Fatakdawala, H., Xu, J., Basavanhally, A., Bhanot, G., Ganesan, S., Feldman, M., Tomaszewski, J.E., Madabhushi, A.: Expectation-maximization-driven geodesic active contour with overlap resolution (emagacor): application to lymphocyte segmentation on breast cancer histopathology. IEEE Trans. Biomed. Eng. **57**(7), 1676–1689 (2010)

Article Google Scholar

12. Beevi, S., Nair, M.S., Bindu, G.R.: Automatic segmentation of cell nuclei using krill herd optimization based multi-thresholding and localized active contour model. Biocybernetics Biomed. Eng. **36**(4), 584–596 (2016)

Article Google Scholar

13. Zucker, S.W.: Region growing: childhood and adolescence. Comput. Graph. Image Process. **5**(3), 382–399 (1976)

Article MathSciNet Google Scholar

14. Rother, C., Kolmogorov, V., Blake, A.: Grabcut: Interactive foreground extraction using iterated graph cuts. In: ACM transactions on graphics (TOG), vol. 23, pp. 309–314. ACM (2004)

Google Scholar

15. Huang, C.H.: Semi-supervised color decomposition for histopathological images using exclusive component analysis. In: Machine Learning for Signal Processing (MLSP), 2015 IEEE 25th International Workshop on, IEEE, pp. 1–6 (2015)

Google Scholar

16. Stierer, M., Rosen, H., Weber, R.: Nuclear pleomorphism, a strong prognostic factor in axillary node-negative small invasive breast cancer. Breast Cancer Res. Treat. **20**(2), 109–116 (1991)

Article Google Scholar

17. Dunne, B., Going, J.J.: Scoring nuclear pleomorphism in breast cancer. Histopathology **39**(3), 259–265 (2001)

Article Google Scholar

18. Fuchs, T.J., Buhmann, J.M.: Computational pathology: challenges and promises for tissue analysis. Comput. Med. Imaging Graph. **35**(7), 515–530 (2011)

Article Google Scholar

19. Wang, M., Zhou, X., Li, F., Huckins, J., King, R.W., Wong, S.T.C.: Novel cell segmentation and online svm for cell cycle phase identification in automated microscopy. Bioinformatics **24**(1), 94–101 (2007)

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Analysis of Malignancy using Enhanced GraphCut Based Clustering for Diagnosis of Bone Cancer

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Abstract. Osteosarcoma and Ewing Sarcoma are very common bone tumor and its biopsy is characterized with spatial distributions of osteoblasts, osteocytes, and osteoclasts. Any abnormal growth found in these three cells can be either cancerous or benign. This paper presents enhanced GraphCut based clustering framework to ascertain malignancy level in Hematoxylin and Eosin (H&E) stained histopathological images. This approach executes iterative GraphCut method to extract foreground objects from biopsy image. Usually iterative GraphCut needs user interaction to initialize segmentation process. But in enhanced graphCut method, this initial data is manually generated with using standard image processing tools. By doing this, experiment shows that quality of proposed segmentation result is improved . After segmentation of all tissue cells, its categorization is done through color and topological characteristics. Therefore, domain specific methods such as color based clustering; mathematical morphology and active contour are used for feature extraction.This computed features are used to quantify the characteristics of malignancy and classify them as normal, benign and cancerous using multi class random forest framework. Proposed method is compared with earlier methods yields 90% of classification accuracy.

Keywords: Histopathology , Bone Biopsy ,Cancer Diagnosis , GraphCut , Malignancy Classification

1 Introduction

Cancer is a major cause of death worldwide accounting for 8.8 million deaths in 2015.Primary bone cancers are infrequent, accounting for less than 0.2 percent of all cancers[1]. As per the American cancer society standardization 3,300 people will be pinpointed with bone cancer. Around 1,490 people are expected to lose their life from bone cancer[2]. It is evident from the statistics that bone cancer is spreading across the globe. Therefore, it is pertinent to focus more seriously on research in health sector. Bone tissue is made up of osteoblasts, osteocytes,

osteoclasts . A destructive growth in these three primitive biological cells of mesenchymal can reveal cell differentiation and malignant outgrowth[3].
Cancer diagnosis process has several stages such as clinical examination, radiological examination and biopsy for histopathology. Research work in radiology reached its zenith but there is no significant achievement in automation of histopathology. Therefore, the proposed research work emphasizes development of automation tool in histopathology field .There are unique challenges due to the variation in complex tissue structure .By increased bone cancer and advancement in technology data sets are readily available for study[4]. This study is indebted to bone cancer with the data sets of Ewing sarcoma and Osteosarcoma.
Computer-Aided Diagnosis (CAD) systems in Histopathology field benefits the pathologist to mitigate the workload and for accurate diagnosis. Moreover, lack of dataset and technical expertise in this field remained unattended [5, 6, 7].
Increased workload pressure on pathologists and demand for early diagnosis is need of the hour and it is inevitable.This research exploration in pathology paved the way for collection of literature and dataset to carry out automation work and it is acknowledged in the review of literature done in my previous work[8].
Research findings witness the development of several algorithms and novel techniques in exploration for segmentation of cell nuclei. These Segmentation techniques such as mathematical morphology [9], watershed segmentation[10], probability based expectation maximization[11], active contour[12]and region growing methods[13] works on pixel, color and topological feature with its own discrepancies . It is imperative to conclude from the above noted research work that accuracy in segmentation of tissue cell is remarkable.
Grab Cut is considered as one of the image partitioning method; since it requires user interaction by specifying window box around the object of interest. The algorithm calculates the color distribution of the target object and the background with using model based clustering method. The max-flow min-cut method is used to separate foreground and background. Misclassified areas are distinguished and adjusted by rerunning the algorithm. Iterative version of this algorithm has been used for foreground segmentation[14].
Features of segmented images are the component to extract information regarding the state of disease. Pleomorphism, mitotic activity, cell counts determines the diagnosis of cancer[15, 16, 17]. Measurement of nuclei count is required for diagnosis but manual counting of nuclei is too hectic leads to variation in result and it is evident from the research work done by Fuchs stated 42% variation in classification of nuclei by Pathologists[18]. This uncertainty created the necessity for developing automation framework counting tool. Cell identification and classification of digital slide is difficult because of its complicated morphology. Hence, selection of a classifier is important to deal with large dataset[19].Health sector needs higher end technology for easy diagnosis.

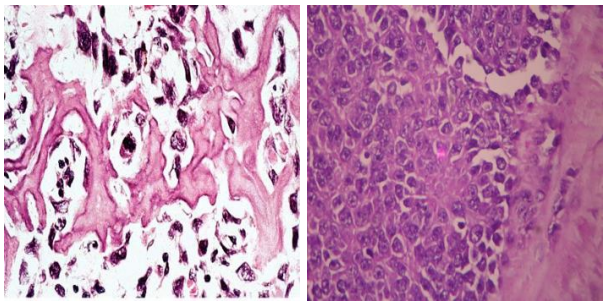
Organization

Next part of this paper is organized as follows. Section 2 describes methods to separate malignant structure regions based on Enhanced GraphCut method.

Feature extraction and classification approach is defined in the same sub section. Accordingly, experimental result discussion narrated in section 3.Finally, summary is outlined and future research perspective is highlighted in section 4.

2 Materials and Methods

H&E stained digital slide of bone biopsy plays pivotal role in this research work. This stained biopsy slide is scanned through a microscope at magnification factor around 40 converts it into digital form approximately giga byte size as illustrated in figure 1(a) and 1(b). Pathologist derives diagnosis observations from the biopsy slide. These findings cater the need of a Pathologist through simplifying diagnosis process with accurate declaration of disease. Data sets are collected from KVG Medical College & Hospital, Sullia, Kasturba Medical College & Hospital, Mangalore and Kidwai Institute of Oncology, Bangalore.



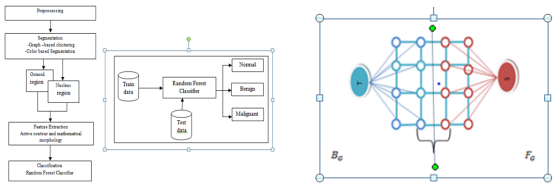
(a) (b)

Fig. 1: Shows H&E stained bone slide (a) Osteosarcoma osteoid with malignant cells(b) Small cell Ewingsarcoma shows large pleomorphic cells

It is essential to study the histology of bone, bone forming cells, ostoid production, mitotic activity, and the common disorder to characterize normal and cancerous image. In Osteosarcoma cell manifold features need to be segmented through automation require the research endeavor. If this research tool succeeds in bone cancer can be applicable for all common types of cancer.
Figure 2a shows diagram of automated system which classifies their malignancy state as normal, benign and cancerous. In this study, we use 140 images of bone biopsy samples and abnormalities are diagnosed through enhanced graphCut based clustering frame work.

2.1 Preprocessing

Color is one of the predominant factors for malignant analysis. Therefore, preprocessing working in RGB color space. Stain artifacts cleared with using the technique of Gaussian filters method to maintain sharp intensity for separating tissue cells. Image normalization can be done through histogram modification technique. These preprocessing methods provide high quality images.



(a) (b)

Fig. 2: (a)Frame work for bone cancer detection (b) Enhanced GraphCut

2.2 Image Segmentation

The proposed approach introduces enhanced GraphCut algorithm for the segmentation of different tissue cells in digital bone biopsy. This approach has two phases.

1.GraphCut method to extract foreground objects:

Iterative GraphCut algorithm is used to extract foreground objects in biopsy image. First, user should specify the background pixels by selecting desired foreground object in an image. Algorithm does an initial labeling where all unknown pixels are identified as foreground class F_G and all known pixels are set to background class B_G . Now a Gaussian Mixture Model (GMM) is defined which learns and create new pixel distribution. A graph G is made from this pixel clusters in which vertices in the graphs are pixels. Two vertices are selected as seed nodes namely S and T. Every foreground pixel is connected to S and every background pixel is connected to T. The edges are weighted based on pixel similarity. The edges are assigned with minimum cost if there is variance in pixel color .Then a graphCut algorithm is used to segment the graph based on minimum cost function. Once minimum weight edges are removed, the pixels which are connected to S belong toF_G and those connected to T become B_G. The process is continued until it converges. The process of portioning the region as foreground and background is illustrated in figure 2b .

The steps of graphCut process are given in algorithm 1.

2. Color based segmentation method:

To learn the malignancy factors of the different types of bone tissue we run color based segmentation method which quantizes the pixels of foreground component into two clusters. These clusters correspond to pink and blue regions. Pink color represents osteoid deposition and cytoplasm. Starting with user-specified colors of the objects to be segmented, the algorithm estimates the color distribution of the target objects using a nearest neighbor rule. Each resultant cluster corresponds to blue nuclei and pink osteoid deposition. This result is used in the next level to determine the abnormality in the images.

2.3 Active contour and mathematical morphology based Feature Extraction

The proposed approach transforms a segmented tissue component to object domain and pixel domain respectively. The method use edge based active contour method and mathematical morphology to extract lace-like pattern from image

Algorithm 1: Enhanced GraphCut Method

Input : H&E Image,F_G,and B_G where F_G is the foreground which is defined as unknown part of the image and B_G known background region. Foreground selection done manually, so that it covers all types of tissue structures.

Output: Segmentation of foreground I_{out} from image.

1 Initially label foreground F_G and background B_G pixels depends on the input provided.
2 Train Gaussian Mixture Mode (GMM) based on initial labeling, which is used to model foreground and background pixels as two clusters c_1 and c_2.
3 Select node S and T from c_1 and c_2 respectively.
4 Construct a graph wherec_1 pixels are connected to S and c_2 pixels are connected to T through edges.
5 Assign weight to edge depends on pixel similarity. Low weight is assigned if there is variance in pixel color.
6 Use Min-cut algorithm to remove low cost edges.
7 Refine operation until Min- cut algorithm converges.

component. The specification for active contour method is input image and a mask. For quick and accurate segmentation result, an initial contour nearest to the object shape is specified. All the identified shapes are then labeled. Morphology opening function is performed to estimate the region between defined lower bound (LB) and upper bound (UB). Finding abnormality in osteoid production alone not defines the state of lesion. Main idea of separating dark blue component is to find out hyperchromatic nuclei. The proposed algorithm is based on finding almost circular object in blue component. The algorithm starts by converting blue components into binary image (B). Finding all connected object in an image and marking each of them with a separate label is called connected region labeling. For analysis of the detected regions it is required to measure the features like area and perimeter. Using these two measures, the object roundness is calculated as given in equation 1.

$$Roundness = \frac{(perimeter)^2}{4\pi area} \tag{1}$$

Geometry, morphology and texture are the low level features are used define abstract concepts such as abnormal mitotic and osteoid production, irregularity of nucleus shape and size. So the relevant features are extracted from segmented image components to build classifier model.

2.4 Random Forest for malignancy level classification

Random Forest is the most popular supervised classification method which works in machine learning for the classification. This serve by building aggregation of decision trees at training time and output the class by taking the majority votes of trees. Training set with tissue component labels is used: osteoid deposit, hyper chromatic nuclei and malignant. Each of this tissue labeled describes specific feature of malignancy. Row in the training set can be a set of attributes to be

used as pattern for matching. This study needs three classes, normal, benign, and cancerous, so it requires multiclass . This frame work assigns test data as three distinct values (namely 1, 2, and 3). An image classified under class 1 is identified as normal, class 2 as benign and 3 as cancerous.

3 Result interpretation

The iterative GraphCut method was tested using a dataset of different bone biopsy images, as shown in Figure 3. The result completely depends on GraphCut initialization, which makes the segmentation results sensitive. To address this issue initial selection of object of are manually built. By performing this efficiency of the graphCut method will be improved by not considering unnecessary image elements. For defining the tissue objects we run the color based segmentation method on extracted foreground component. The foreground component contains two prominent colored areas such as pink and blue. The result analysis can be seen in figure 4 (a) and 4(b).

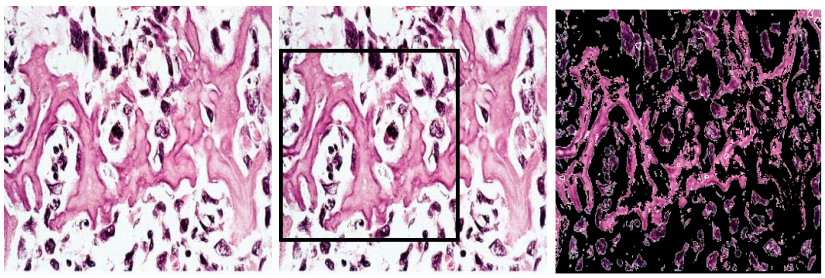
3.1 Classification Accuracy

A total of 140 Hematoxylin and Eosin (H&E) stained histopathological images comprising of osteosarcoma, Ewing Sarcoma and normal bone (includes benign). Total 80 images are used for training purpose remaining images as test set. Training set with tissue component labels is used: osteoid deposit, hyperchromatic nuclei, malignant (pleomorphic and abnormal mitotic) .The corresponding classification accuracy obtained is listed in table 1.These features are trained through multi-class Random Forest give better performance with 90% accuracy. But earlier studies only stressed upon limited features which led to poor performance.

Manual Diagnosis of Test Data (Analysis from Experts)

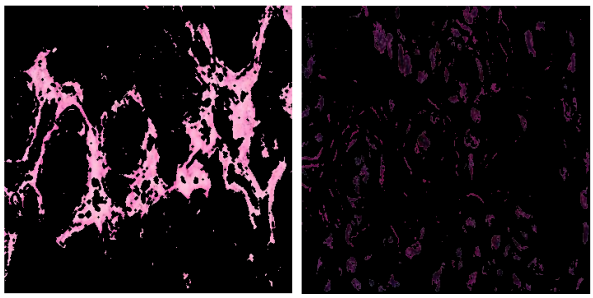
1. Cancerous Bone Image: There are 40 images selected for the study, out of which 20 images are actually having malignant osteoid features and 20 images shows hyperchromatic nuclei pattern. All these images show abnormal mitotic activity also.
2. Normal and Benign Image: Total 20 images selected for the study, out of which 8 images shows normal tissue pattern and 12 images having slightly abnormal tissue pattern stated as benign.

. The result of classification model is demonstrated in figure 5(a),5(b) and 5(c). Significance of this study is whatever image used here will be categorized as per the features. Depending upon the output of these the classifier proposed system defines malignancy level as normal, benign and malignant. Precision calculates the result relevancy, while recall determines how many truly relevant results are returned. Fscore is the union metric of precision and recall which measures the reconstruction of degree between precision and recall criteria. For normal images both precision as well as recall has high scores that shows the classifier is returning accurate results. For cancerous images (Class 3) shows high recall relates to a low false negative rate. But slight variation is detected in benign



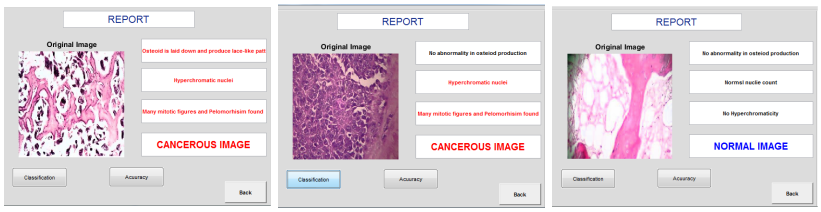
(a) (b) (c)

Fig. 3: Figure shows a) Input Image b) Selection of initial Data c) Foreground Extraction



(a) (b)

Fig. 4: (a) Separation of pink component shows osteoid deposition (b)Separation of dark blue shows hyperchromatic nuclei



(a) (b) (c)

Fig. 5: Automated frame work result for (a) Osteosarcoma (b) Ewingsarcoma (c) Normal image

Table 1: Classification accuracy in the test data set

	Accuracy Measures (%)			
	Recall	specificity	Precision	Fscore
Normal(8)	87	100	100	93.048
Benign(12)	75	93.7	75	75
Cancerous(40)	95	84.2	92	93.47

Table 2: : Evaluation of classification result

Diagnosis Process	**Accuracy**
Earlier work depends on nuclei count	76%
Proposed work	90%

images (Class 2) . The reason is some benign images shows abnormal pattern of tissue cells due to some infections. Hence, classifier assigns this type of images as class 3 instead of 2.

To investigate the effectiveness of proposed method, we compare with earlier method where malignancy state defined by considering only nuclei count. The experiment shows that our method improves the accuracy by 14% as shown in table 2.

4 Conclusion and future work

Clinical approach and manual diagnosis is insufficient to declare disease like cancer. Diversified complex features having different sub-types in bone tissue cells made diagnosis as most challenging one. Hence, automation framework is essential for early and quick accurate diagnosis. Many scholars were tried to explore automation in digital histopathology with limited individual features. This minimal characteristics not enough for defining the state of disease because of complex tissue cells in bone images. To overcome these obstacles proposed research work combined three categories of feature set in bone cancer for classification of malignancy. Therefore, proposed automated tool framework is commendable and accuracy of the work is appreciated by Pathologists.
Any research work is incomplete without complete data set and more focused research group. Adequate data sources with dedicated scholars can contribute their best in this field. Future work is particularly intended to increase the strength of data sources and involvement of good number of domain experts to robust techniques.

References

[1] Who cancer updates, cancer-world health organization, 2017. URL http://www.who.int/cancer.

[2] American cancer society cancer facts and figures,american cancer cociety publication, 2017. URL https://www.cancer.org.

[3] Dominique. Heymann. *bone cancer,Primary bone cancers and Bone Metastases.* Elsevier Health Sciences, 2014.

[4] Farzad Ghaznavi, Andrew Evans, Anant Madabhushi, and Michael Feldman. Digital imaging in pathology: whole-slide imaging and beyond. *Annual Review of Pathology: Mechanisms of Disease*, 8:331–359, 2013.

[5] J. P Thiran and Benoit Macq. Morphological feature extraction for the classification of digital images of cancerous tissues. *IEEE Transactions on biomedical engineering*, 43(10):1011–1020, 1996.

[6] Barbara Weyn. Automated breast tumor diagnosis and grading based on wavelet chromatin texture description. *Cytometry*, 33(1):32–40, 1998.

[7] Andrew. J Einstein, Hai-Shan Wu, Miguel Sanchez, and Joan Gil. Fractal characterization of chromatin appearance for diagnosis in breast cytology. *The Journal of pathology*, 185(4):366–381, 1998.

[8] P. J Antony, B. S Vandana, and SathyavathiR. Alva. Visualisation of tissue cells from bone histopathological images for cancer diagnosis: a review on current status in digital histopathology. *International Journal of Biomedical Engineering and Technology*, 24(2):133–153, 2017.

[9] Mitko Veta, Josien PW Pluim, Paul J Van Diest, and Max A Viergever. Breast cancer histopathology image analysis: A review. *IEEE Transactions on Biomedical Engineering*, 61(5):1400–1411, 2014.

[10] Florence Cloppet and Arnaud Boucher. Segmentation of overlapping/aggregating nuclei cells in biological images. In *Pattern Recognition, 2008. ICPR 2008. 19th International Conference on*, pages 1–4. IEEE, 2008.

[11] Hussain Fatakdawala, Jun Xu, Ajay Basavanhally, Gyan Bhanot, Shridar Ganesan, Michael Feldman, John E Tomaszewski, and Anant Madabhushi. Expectation–maximization-driven geodesic active contour with overlap resolution (emagacor): Application to lymphocyte segmentation on breast cancer histopathology. *IEEE Transactions on Biomedical Engineering*, 57(7): 1676–1689, 2010.

[12] Sabeena Beevi, Madhu S Nair, and GR Bindu. Automatic segmentation of cell nuclei using krill herd optimization based multi-thresholding and localized active contour model. *Biocybernetics and Biomedical Engineering*, 36(4):584–596, 2016.

[13] Steven W Zucker. Region growing: Childhood and adolescence. *Computer graphics and image processing*, 5(3):382–399, 1976.

[14] Carsten Rother, Vladimir Kolmogorov, and Andrew Blake. Grabcut: Interactive foreground extraction using iterated graph cuts. In *ACM transactions on graphics (TOG)*, volume 23, pages 309–314. ACM, 2004.

[15] Chao-Hui Huang. Semi-supervised color decomposition for histopathological images using exclusive component analysis. In *Machine Learning for Signal Processing (MLSP), 2015 IEEE 25th International Workshop on*, pages 1–6. IEEE, 2015.

[16] Michael Stierer, Harald Rosen, and Renate Weber. Nuclear pleomorphism, a strong prognostic factor in axillary node-negative small invasive breast cancer. *Breast cancer research and treatment*, 20(2):109–116, 1991.

[17] B Dunne and JJ Going. Scoring nuclear pleomorphism in breast cancer. *Histopathology*, 39(3):259–265, 2001.

[18] Thomas J Fuchs and Joachim M Buhmann. Computational pathology: Challenges and promises for tissue analysis. *Computerized Medical Imaging and Graphics*, 35(7):515–530, 2011.

[19] Meng Wang, Xiaobo Zhou, Fuhai Li, Jeremy Huckins, Randall W King, and Stephen TC Wong. Novel cell segmentation and online svm for cell cycle phase identification in automated microscopy. *Bioinformatics*, 24(1): 94–101, 2007.