Challenges and Practical Pathways for the Clinical Translation of Deep Learning-Based Nuclei Segmentation in Breast Histopathology

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Abstract: Histopathological diagnosis of the breast highly depends on the characteristics of the cell nuclei. Thus, accurate segmentation of nuclei is regarded as the critical foundation in computational pathology analysis of breast tissue. During the past few years, deep learning techniques have made great breakthroughs in the research of nucleus segmentation in breast histopathology. In particular, they can obviously demonstrate strong advantages for complex feature extraction and high-performance pixel-wise prediction. Moreover, deep learning has been proved to show remarkable potential in quantitative pathology, lesion recognition, and computer-assisted diagnosis. However, previous investigations based on publicly available datasets and controlled experiments encounter numerous limitations during the process of clinical practice. The present review mainly discusses the development of deep learning techniques applied to the segmentation of cell nuclei in breast histopathology. It comprehensively introduces the theoretical background and research mechanism of this field. Besides, it summarizes the current status of the research from the perspective of deep learning models, supervision method, and clinical direction. Based on this, this paper makes an analysis of the main problems associated with nucleus segmentation in breast histopathology. Such problems include data heterogeneity and inadequate standardization, substantial workload of manual annotation and poor consistency of the ground truth, insufficient model interpretability, and lack of workflow integration and external validation. In order to overcome the mentioned problems, this paper outlines a number of possible improvement directions. These directions include multicenter construction of data, stain normalization, weakly and semi-supervised learning, structured interpretation of prediction, external validation, and human-computer collaboration. According to this review, a change of the research focus on nucleus segmentation in breast histopathology could be observed. In addition to the traditional pursuit of improved accuracy, generalizability, interpretability, and clinical practicability will gradually attract attention in this field.

Keywords: Breast Histopathology; Nucleus Segmentation; Deep Learning; Digital Pathology; Clinical Translation

1. Introduction

The breast tumor diagnostic process is strongly dependent on nuclear morphometric parameters including size, shape, atypia, and spatial distribution of cell nuclei. These parameters play an important role in the determination of the breast tumor grade and type. They can be used to conduct quantitative histopathological analysis and computer-aided diagnostics. According to the study conducted by Veta et al., detection and analysis of microscopic features including cell nuclei form the key component of breast cancer histopathology images analysis [1].

Conventional techniques for nucleus segmentation largely rely on thresholding, edge detection, and morphological operations. Such conventional techniques usually exhibit poor stability when applied to breast histopathology images due to variations in staining, overlap between nuclei, and vague boundaries. The advent of deep learning has led to considerable advancements in nucleus segmentation by enabling better feature extraction and per-pixel predictions under challenging conditions. U-Net is one such technique that was developed by Ronneberger et al., which is used extensively

for nucleus segmentation tasks [2].

Despite considerable success demonstrated by deep learning-based nucleus segmentation methods in experimental research, the translation to clinical practice still raises significant concerns. Tizhoosh and Pantanowitz identified limitations in data availability, lack of external validation, and poor clinical workflow integration as critical problems within digital pathology artificial intelligence [3]. Similarly, Bera et al. highlighted that clinical utility in pathology artificial intelligence requires not only adequate model performance but also interpretation, repeatability, and inter-institutional portability [4]. In light of these perspectives, this review examines deep learning-based nucleus segmentation in breast histopathology. The paper provides an overview of technological background and existing achievements. The current limitations and possible improvements will also be discussed.

2. Technical Foundations and Research Mechanisms of Deep Learning-Based Nucleus Segmentation

The purpose of nucleus segmentation is to detect the region of each nucleus in the histopathology image and to distinguish individual nuclei when they are adhering or overlapping. The nuclei in the breast histopathology image generally have characteristics such as small size, indistinct boundaries, high morphological diversity, and dense packing. Other factors such as staining differences and complicated tissue background also influence this process.

The technical background initially starts with pixel-wise dense prediction models. FCNs were introduced by Long et al., where convolutional neural networks are extended to perform semantic segmentation tasks. These models can be trained to predict pixel-wise class mapping [5]. Such an architecture forms the core structure for cell nuclei segmentation. The model is designed to segment the region occupied by cell nuclei based on deep learning-based feature extraction.

According to this approach, the multi-scale fusion of features in medical image segmentation is further emphasized. According to Zhou et al., the semantic disparity between the encoder and decoder has an influence on fine structure reconstruction. The nested skip connections help enhance the fusion of features in UNet++. This helps increase the efficiency of the segmentation process especially when dealing with small objects or boundaries [6]. It is relevant to nuclei segmentation.

Semantic segmentation alone is unable to address the issue of nuclear adhesion. Instance segmentation is now the main focus of research. He et al. have introduced Mask R-CNN, which integrates object detection with semantic segmentation of pixels. The model facilitates instance segmentation [7]. In terms of pathologic images, instance segmentation has enabled the process to go beyond nuclear region detection and move towards nucleus instance identification.

Geometric constraints have been utilized to overcome the problem of distinguishing neighboring nuclei. For example, Naylor et al. have suggested distance map regression, which learns structural properties continuously from the nucleus center to the nucleus boundary. As a result, distance map regression facilitates the distinction between overlapping nuclei [8]. Additionally, Graham et al. proved in their study of HoVer-Net that horizontal and vertical offsets of each pixel concerning the nucleus center facilitate instance separation [9]. Therefore, it can be concluded that the current main emphasis of nuclei segmentation is on structural learning.

The presence of orientation and rotation in pathological image morphologies is evident. According to Veeling et al., the typical convolutional neural network cannot capture such characteristics fully [10]. The introduction of rotation-equivariant convolution addresses such an issue. Based on this, it can be concluded that nucleus segmentation should depend on both network architecture and morphological prior encoding.

Conclusively, the research methods for nucleus segmentation using deep learning involve three critical components. Firstly, pixel-wise predictions are made using a fully convolutional network architecture. Secondly, improvements have been made in boundary prediction through the use of multi-scale feature integration. Finally, adjacent nuclei are separated by means of instance segmentation and structural modeling. Nucleus segmentation has progressed from an elementary process of region detection to a holistic task of semantic interpretation, instance prediction, and structural modeling.

3. Current Research Status of Nucleus Segmentation in Breast Histopathology

3.1 Research Progress by Model Type

Based on the structure of the model, nucleus segmentation algorithms may be classified into three major groups: semantic segmentation models, instance segmentation models, and boundary or structure-aware models.

As for semantic segmentation approaches, they concentrate their efforts on pixel-wise classification. Such algorithms conduct the process of image segmentation with the help of predicting probability maps of nuclear regions. DeepLab series was introduced by Chen et al. The algorithm uses dilated convolutions to make the receptive field large enough. This helps to enhance contextual modeling with retaining resolution [11]. Semantic segmentation models demonstrate high recall rate in detecting nuclear regions. However, such methods do not possess instance differentiation capability. As a result, they tend to make adhesion mistakes in cases where the nuclear density is very high. Thus, these models cannot be employed for final segmentation but rather serve as pre-processing tools for coarse segmentation or detection purposes. Instance segmentation models include object-level modeling techniques. They aim to conduct image segmentation at the level of individual nucleus separation. Kirillov et al. designed the Mask R-CNN++ framework based on Mask R-CNN. The authors emphasize the necessity of instance-level segmentation in complex images [12]. With regard to pathology images, these models provide individual nuclear instances. However, the results of such models heavily rely on the quality of detected candidate regions. They demonstrate some cases of missing detection in scenes with densely distributed small targets. Furthermore, the detection paradigm has high costs in terms of computing when applied to ultra-high-resolution pathological images. Boundary/structure awareness models were proposed to overcome these problems. One example is the work conducted by Chen et al., which resulted in DCAN (Deep Contour-Aware Network). DCAN improves the process of separating adjacent nuclei via joint modeling of nuclear regions and boundaries [13]. The core concept of these models is explicit boundary or structural modeling. Thus, the network not only learns to identify whether a certain region belongs to a nucleus or not, but also how nuclei can be differentiated. In comparison with semantic segmentation models, structure-aware algorithms prove more effective in cases with nuclear adhesion. In conclusion, we may say that different model types focus on different aspects of the problem.

3.2 Research Progress by Supervision Strategy

In terms of the supervision strategy, existing studies focus on fully supervised learning, weakly supervised learning, and semi-supervised learning.

The fully supervised approach requires a huge number of annotated pixels. It remains the mainstream technical path. Caicedo et al. found in their early researches that deep learning models work better in cell segmentation comparing to traditional techniques in a fully supervised setting. The segmentation efficiency of these models depends heavily on the quality and size of annotations [14]. Breast histopathological data require high cost and inconsistency in annotation. The problem limits further development of the fully supervised approach. Weakly supervised segmentation attracts considerable attention due to low costs of annotation. Qu et al. propose to perform point annotation in place of pixel-level annotation. This technique enables learning nuclei distribution of tissues under weak label guidance. Point annotation provides effective segmentation with less effort required for annotation [15]. The main idea behind weakly supervised segmentation consists in conversion of segmentation into dense prediction under label constraints. Segmentation accuracy is significantly lower compared to fully supervised methods. The problem becomes more obvious in the case of complex boundaries. The semi-supervised approach utilizes small amounts of labeled data together with huge quantities of unlabeled ones. The method proposed by Bai et al. involves consistency-based regularization for segmentation in pathological images. The unlabeled data help provide additional constraints for outputs using structural properties. The performance of the algorithm relies on the consistency between the labeled and unlabeled distributions [16]. Generally, there is an evident tendency of changing research approaches in supervision

strategies. Researchers start shifting from improvements in segmentation efficiency to reduction of annotation requirements. There is a trade-off between accuracy and annotation cost.

3.3 Research Trends Toward Clinical Application

As research moves from algorithm-oriented evaluation to application-oriented development, nucleus segmentation has revealed certain trends in its clinical usage.

On one hand, multicentric data analysis and cross-domain generalization have become two directions worthy of study. Stacke et al. noted that domain shift was the main reason for limiting the generalization ability of deep learning methods. The statistical discrepancy caused by different data sources would greatly affect the results of models. In the field of breast histopathology, such discrepancies occur due to the staining process and scanning device used. Weakly supervised learning and low-annotation cost learning have become two directions worthy of exploration. It is obvious that pathological annotation requires considerable experience in experts. A purely data-oriented method depending on pixel-wise annotation cannot satisfy the actual requirements. Thus, reducing the dependence on annotation has been an important premise for clinical applications. Another new trend lies in the improvement of the model explainability. Holzinger et al. held the view that in high-risk situations, medical decision-making based on deep learning algorithms had to present interpretable and traceable characteristics. Otherwise, they would not be trusted [18]. In nucleus segmentation, the explainability manifests itself as the direct connection between the segmented result and pathological structures. The integration of AI system into clinical workflow has become another focus. Topol believed that AI algorithms could deliver clinical values only when incorporated into clinical workflow [19].

3.4 Comparative Analysis of Different Research Directions

Various research paradigms exhibit noticeable disparities in terms of efficiency, costs, and applicability.

With regard to model type, semantic segmentation models exhibit straightforward architectures and efficient computational capability. Nonetheless, such models cannot account for nuclear adhesion. On the other hand, instance segmentation models yield outputs that represent individual nuclei. The computational capacity required by such models is high, but their performances depend on detection precision. Structure-aware models yield favorable results in situations with complicated boundaries. Such models possess intricate architectures. In terms of supervision paradigm, fully supervised models generally yield the most accurate segmentation results. Nonetheless, such models entail the most expensive annotation processes. Weakly supervised models significantly decrease the necessity for annotations. Their performances suffer in relation to the analysis of fine-grained boundaries. Semi-supervised models offer a trade-off between fully supervised and weakly supervised models. Their performances depend on data distributions. With respect to clinical applications, high-performing models do not necessarily correspond to high utility. Generalizability, annotation expenses, interpretability, and compatibility with clinical procedures collectively contribute to the practicality of models. Thus, the prevailing trend in contemporary research endeavors is transitioning from optimizing performance metrics based on a single factor to multiple-factor optimization.

4. Major Challenges in Current Research and Possible Solutions

4.1 Data Heterogeneity and Standardization

The images obtained for breast histopathology present high levels of data heterogeneity. The heterogeneity arises due to variations in the staining protocol, scanner, and preparation techniques used at each center. Cross-center distribution shift has a direct impact on the generalization ability of a model. In their early work, Reinhard et al. highlighted the effect of staining conditions in varying the color space distribution. Variations in the color space distribution have adverse effects on the stability of visual appearance-based techniques [20]. From a deep learning point of view, Macenko et al. demonstrated that variation in staining conditions can create a feature distribution shift, hence limiting model performance in multiple datasets [21]. The approaches applied in addressing this challenge fall under two main

categories; data standardization and domain adaptation. Data standardization such as stain normalization will help to minimize distribution differences in the input data, while domain adaptation will assist in alignment of the feature distributions across multiple datasets. An example of domain adaptation is adversarial domain adaptation method proposed by Kamnitsas et al. This approach minimizes the gap in feature distribution between the source and the target domains [22].

4.2 Annotation Burden and Ground Truth Consistency

The accuracy of nucleus segmentation requires fine annotation at the pixel level. Such a process requires a lot of professional pathologists. It is expensive and highly dependent on subjectivity. As Al-Kofahi et al. mentioned, the boundary of nuclei in complex tissue is not always well-defined and objective. There could be significant differences among annotations done by various experts. This question directly impacts the theoretical upper limit of training performance [23]. Scientists have turned their attention toward weak supervision and low-annotation learning to minimize annotation reliance. Rajchl et al. developed a learning framework that employs partial annotations to train segmentation models [24]. In addition, according to Tajbakhsh et al., for medical image processing, in practice, sacrificing some accuracy in annotation while increasing the number of data samples is more beneficial compared to precise but less sample-quantity annotations [25]. Scientists have devised two methods to address the issue of inaccurate ground truth. Firstly, one can design an annotation system based on multiple experts' consensus. Secondly, scientists can incorporate uncertainty modeling into the learning framework. The model could be trained with the distribution of annotations rather than a specific label.

4.3 Interpretability and Clinical Trust

One of the significant problems with using deep learning models clinically is its "black-box" characteristic. As reported by Samek et al., deep models have a good performance in visual tasks. Nevertheless, the decision-making process behind deep models lacks transparency. Consequently, it limits the application of deep learning models in risky situations [26]. If the model is applied in pathological environments, a model without explaining its reasoning for its results will fail to get the trust of the clinical community. Interpretability techniques are thus adopted to solve the problem. Grad-CAM is a technique developed by Selvaraju et al. that uses gradient to create heatmaps related to classes to show the part the model is focusing on [27]. When applying deep learning models for nucleus segmentation task, interpretability techniques can help us examine if the prediction of deep learning models is made from reasonable pathological structure. It was suggested by Caruana et al. that an interpretable model might be more useful than an uninterpretable but high-performing one in clinical applications [28].

4.4 Workflow Integration and Real-World Validation

Most nucleus segmentation methods today are at the level of offline performance assessment. They fail to meet the need for practical integration into clinical workflow. Esteva et al. stressed the importance of validating the artificial intelligence model using practical data, as well as integrating it into clinical workflows to realize clinical value [29]. The model's performance evaluated on publicly available datasets cannot truly reflect its stability during practical use. In addition, there is a need for more demanding criteria for a successful clinical application of a system. Such criteria include high efficiency in computation, traceability of results, and human-computer interaction. According to Price et al., algorithms developed in digital pathology studies should be incorporated into practical pathology information systems to assist clinical decision making [30]. Thus, future research work needs to be devoted to the evaluation of the whole system rather than model performance. Relevant techniques include multicenter external validation, real-world data evaluation, human-machine interaction system design, and integration into digital pathology.

5. Conclusion

There has been significant improvement in deep learning-based nucleus segmentation for breast histopathology. Initially, most studies have concentrated on developing semantic segmentation networks. Recently, more sophisticated models combining instance

analysis and structure modeling have emerged. Previous works have consistently advanced segmentation precision, robustness to challenging conditions, and feature representation capability. This has laid down the technical groundwork for quantitative pathology and computer-aided diagnostics. Nevertheless, the current body of work still mostly operates in experimental conditions and publicly available datasets. There are several factors that prevent the clinical translatability of current works. Heterogeneous data impair the model's generalization capacity. Data annotation costs and variability in ground truth prevent data scalability and quality. Weak interpretability reduces the clinical reliability of the model. Insufficiency in integrating the model with clinical workflow adds to this limitation. This demonstrates that the core issue of nucleus segmentation has transformed from mere performance improvement to systemic challenges in clinical application.

There are some aspects that should be explored by future researchers in order to drive this field forward. First, researchers should focus on developing multicenter and multimodal data sets while integrating standardized techniques and domain adaptation methods to enhance cross-domain performance. Second, researchers should focus on designing weakly supervised and low-annotation training processes in order to decrease reliance on huge amounts of fine-labeled data. Third, researchers should enhance model interpretability and result visualization so that a meaningful correlation could be established between segmentation results and morphological structures of interest. Lastly, there should be more efforts in deep integration of these algorithms into digital pathology pipelines, together with model stability and clinical validation on real data sets. Overall, this algorithmic pipeline for nucleus segmentation based on deep learning is evolving from an algorithm-centered stage towards an application-centered stage where further improvement is not merely associated with model performance but with a balance between data, algorithms, and clinic.

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