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Chromosome Extraction Based on U-Net and YOLOv3

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ABSTRACT Karyotype analysis based on chromosome banding and microscopic imaging is an important means for the diagnosis of genetic symptoms. Chromosome extraction is one of the key steps in karyotype analysis, but it faces some complex situations i.e. chromosome overlaps and adhesions, which are still a challenge for traditional algorithms. Here, we proposed a method for chromosome extraction based on deep learning. In this method, U-Net was used to segment the original micrographs to remove background noise such as nuclei and other interferences. Then YOLOv3 was used to detect and extract each chromosome. Further, U-Net was used again to extract the single chromosomes precisely. The results show that this method can remove effectively the interferences outside the chromosomes, and accurately extract the overlapping and adhesive chromosomes. The accuracy of extracting chromosomes from the raw G-band chromosome images reaches 99.3%. This method is of great significance for the development of automatic karyotype analysis technology.

INDEX TERMS Chromosome extraction, U-Net, YOLOv3.

I. INTRODUCTION

The karyotype analysis method analyzes the microscopic images of chromosomes in the middle division by means of banding technique, and then diagnoses diseases according to the variations in the structure and number of chromosomes. A typical micrograph of chromosomes is shown in Fig.1 (a). Correspondingly, the karyotype map obtained by extraction and classification is shown in Fig.1 (b), which can be used as the basis for disease diagnosis. Obviously, accurately extracting each chromosome from the disordered original micrograph is the prerequisite for successful karyotype analysis. At present, chromosome extraction still mainly depends on trained professionals. However, manual operations are time-consuming and laborious, which are not conducive to the analysis of a large number of samples. Therefore, it is necessary to develop automatic methods. In this regard, several algorithms for chromosome extraction have been proposed in recent years, such as edge detection [1], watershed [2], and geometric methods [3]. Although these algorithms have worked to a certain extent, their processing effects of complex situations, such as chromosome overlaps or adhesions, still need to be further improved. In summary, the development of automatic chromosome extraction based on image processing algorithms faces the following two challenges:

1) Complex background, including nuclei and other interferences, as shown in the blue box in Fig.1 (a).
2) Chromosome overlaps and adhesions, as shown in the red boxes in Fig.1 (a).

In recent years, deep learning [4] has achieved tremendous development and has been applied in various fields including biomedicine. The convolutional neural network (CNN) [5], which is one of the foundations of deep learning algorithms,

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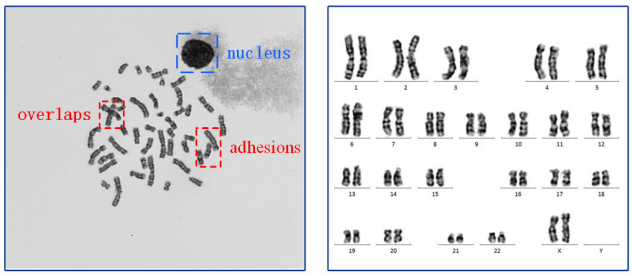

FIGURE 1. Karyotype analysis. (a) Original micrograph; (b) Karyotype map; The blue box shows the nucleus; The red boxes show overlapping and adhesive chromosomes.

possesses a stronger generalization ability than traditional algorithms, because it can learn the key features of the target automatically by training with a large number of samples. Therefore, CNN is potential to provide a more powerful tool to solve the above two problems effectively.

In this article, our main contribution is that we propose an end-to-end method for chromosome extraction based on the optimized combination of YOLOv3 [6] and U-Net [7], which are used for chromosome detection and chromosome segmentation, respectively. This method is able to remove effectively the complex interferences from micrograph background, and to extract accurately the overlapping and adhesive chromosomes, so it is a powerful tool for intelligent extraction of chromosomes.

The rest of this article is organized as follows. The related work is introduced in Section II. Section III presents the overview of chromosome micrograph acquisition and our method for chromosome extraction. The experimental results are described in Section IV and discussed in Section V. Some concluding remarks are placed in Section VI.

II. RELATED WORKS

Chromosome extraction is still one of the most challenging problems in karyotype analysis, especially the overlaps and adhesions of chromosomes make the extraction more complicated. Various attempts have been made to develop automatic chromosome extraction methods. For example, Ji [8], [9] proposed a rule-based chromosome extraction method, which automatically found the segmentation paths based on the geometric features and the pixel density analysis. Agam and Dinstein *et al.* [10] regarded chromosome extraction as a low-level identification problem. This method extracts the chromosomes by analyzing the contour of the chromosomes and looking for the points of interest. Yuan *et al.* [3] proposed a method for segmenting adhesive and overlapping chromosomes using shape bump information, pale path and topological analysis. Grisan *et al.* [11], [12] proposed two greedy approaches based on geometric evidence and image information. Saiyod and Wayalun [13] used a hybrid method to find four cut points for separating overlapping chromosomes. Sugapriyaa *et al.* [14] extracted the chromosomes in the form of monomers and clusters using edge detection and the local threshold method. Shen *et al.* [15] first used the K-Means algorithm to extract the separated single chromosomes or chromosome clusters, and then used the watershed algorithm to separate the adhesive chromosome clusters. Minaee *et al.* [16] also divided the segmentation task into two stages. First, the chromosome clusters were found using the surrounding ellipse method, convex hull method, skeleton and end points. Second, the chromosome clusters were further divided into single chromosomes according to the crossing points of the overlapping chromosomes. Recently, Altinsoy *et al.* [17] proposed a fully-automatic raw G-band chromosome image segmentation algorithm, including cleaning background noise by histogram analysis, removing irrelevant objects based on their morphological features, separating touching chromosomes using geodesic grey-scale distance transform, and finding the accurate cutting points for separation of overlapping chromosomes, etc.

To sum up, most of the above methods are based on chromosome contour features and artificially formulated rules for chromosome extraction. Although they can extract chromosomes effectively in most cases, they are still difficult to separate accurately overlapping or adhesive chromosomes, because artificial rules are not always able to work in the complex and diverse chromosome distribution.

In this regard, deep learning may be a promising choice because it can extract chromosomes based on its autonomously learned features rather than artificially formulated rules. In fact, deep convolutional neural networks have been used for chromosome segmentation. For example, Saleh *et al.* [18] improved U-Net by adding a suitable number of layers and implementing TTA to perform the overlapping chromosome segmentation, with an accuracy (IOU) of 99.68%. Altinsoy *et al.* [19] used a U-Net based convolutional neural network to remove the background noise and irrelevant objects in the raw G-band chromosome images, and achieved more accurate result than the local adaptive thresholding method. These encouraging findings showed a tremendous application potential of deep learning algorithms in automatic chromosome segmentation.

In this article, we propose a different strategy from existing methods. Here, we simplify the end-to-end chromosome extraction process into three steps: denoising, preliminary chromosome extraction and precise chromosome segmentation. All these three steps are performed using deep convolutional neural networks. Considering that YOLOv3 is suitable for quickly and accurately identifying small targets [6], and U-Net has a prominent advantage in dealing with a small number of samples [7], we optimize the combination of YOLOv3 and U-Net to segment overlapping or adhesive chromosomes.

III. METHODS

A. ACQUISITION OF CHROMOSOME MICROGRAPHS

The chromosomes were derived from short-term cultured bone marrow cells, which were treated with colchicine. After hypotonicity and fixation, the cells were prepared

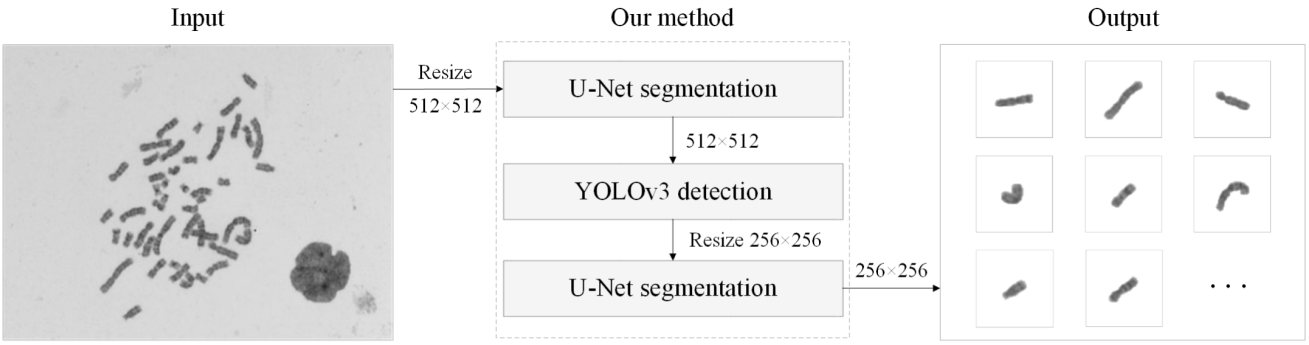

FIGURE 2. Schematic diagram of the method for chromosome extraction.

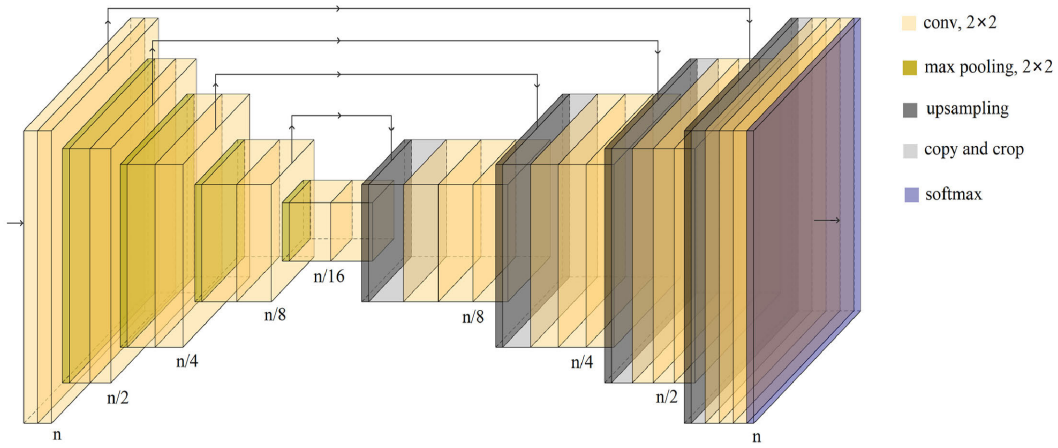

FIGURE 3. Network structure diagram of U-Net.

by the flame drop method and then stained using Giemsa dye (G-banding technology). Finally, the chromosomes were scanned and photographed using a Metafer automatic chromosome scanning workstation (MetaSystems, Germany).

B. THE METHOD FOR CHROMOSOME EXTRACTION

Our method for chromosome extraction based on U-Net and YOLOv3 is shown in Fig.2. Its key steps are as follows: (1) In order to ensure the accuracy of extraction, U-Net is used to remove the nuclei and other interferences in the background of the micrograph before extraction of chromosomes. (2) YOLOv3 is used to detect chromosomes and draw prediction boxes for each chromosome separately. (3) U-Net is used again to extract the chromosome in each prediction box accurately, especially to remove the overlapping or adhesive parts from other chromosomes. Moreover, in order to enhance the generalization ability of this method, we expanded the data before training, including rotation, flip and translation [20].

In our method, U-Net is used to remove the background of chromosome micrographs and the precise extraction of chromosomes. As shown in Fig.3, the U-Net consists of a contraction path (left) and an expansion path (right). The contraction path follows a typical convolutional network structure, which is composed of the 3×3 convolution kernels, the ReLU activation function and the max-pooling layers. In each downsampling step, the number of channels in the feature map is doubled. In the expansion path, each step includes upsampling the feature map, reducing the number of channels of the feature map by half, and concatenating the symmetric feature map in the contraction path. In the last layer, a 1×1 convolution kernel is used for the convolution operation, and each 64-dimensional feature vector is mapped to the output layer of the network.

YOLOv3 is used to detect chromosomes in the micrograph after denoising. As shown in Fig.4, the YOLOv3 consists of three parts: (1) The network for feature extraction; (2) Multi-scale feature fusion; (3) Predictions. First, the network for feature extraction is darknet-53, which is mainly composed of convolution modules and residual blocks. Each convolution module contains a batch normalization layer [21] and a LeakyReLU layer [6], and each residual block contains three convolution layers, a ReLU layer and concatenation operation. In the downsampling of darknet-53, the size transformation of feature maps is achieved by changing the

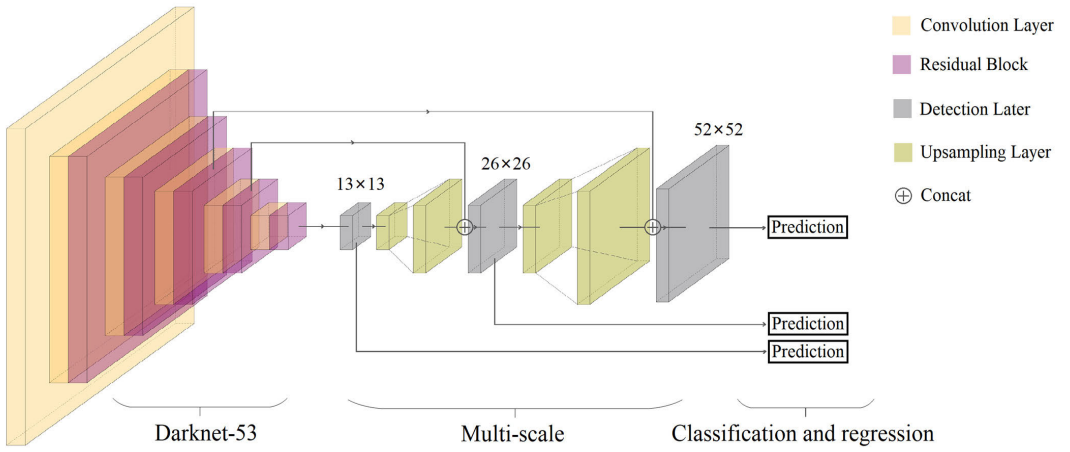

FIGURE 4. Network structure diagram of YOLOv3.

stride of the filters, rather than using the traditional pooling layers. Second, the multi-scale feature fusion draws on the idea of the feature pyramid network [22], that is, deep feature maps and shallow feature maps are superimposed by upsampling to avoid the disappearance of some small-size target features as the network deepens. The size of these feature maps is divided into three levels, namely 13×13, 26×26 and 52×52. Smaller feature maps are used to detect larger targets and vice versa. Finally, in the prediction part, YOLOv3 outputs the prediction results by calculating the classification confidence and coordinates of the targets.

IV. RESULTS

A. DENOISING OF CHROMOSOME MICROGRAPHS

U-Net was used for denoising of chromosome micrographs. The image samples came from 130 measured chromosome micrographs. By rotation, translation and flipping of the original micrographs, the number of the image samples was expanded to 1300, of which 600 samples were used as the training set, 400 samples were used as the validation set, and the rest were used as the test set. Before training, the input micrographs were resized to 512×512 to reduce the amount of calculation. Then the training was carried out on the platform of Nvidia Quadro P600. In the training process, the initial learning rate was set to 0.001, and the Adam algorithm [23] was used for gradient descent.

The results of denoising are shown in Fig.5. It can be seen that both complete and incomplete nuclei (shown in the dotted boxes) can be removed effectively. In addition, some interferences (shown in the solid boxes), whose gray values are very similar to chromosomes, can also be identified and removed accurately. More importantly, the chromosomes maintain their original shapes very well, and no erroneous removal of chromosomes is found during the denoising process. These results demonstrate the excellent performance of U-Net in the denoising of chromosome micrographs.

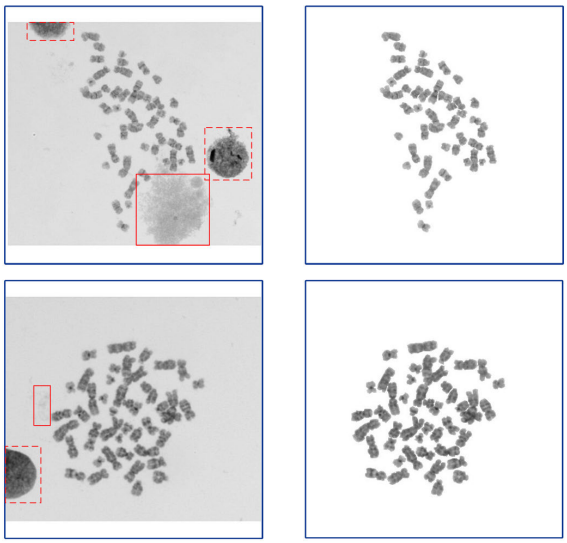

FIGURE 5. Denoising of chromosome micrographs. (a) Original micrographs; (b) Micrographs after denoising.

B. CHROMOSOME IDENTIFICATION AND LOCATION

After denoising, we began to extract chromosomes. In this regard, the key step was to identify and locate chromosomes accurately. Here, YOLOv3 was used to tackle this task.

The training platform was the same as above, and the numbers of the chromosome samples in the training set, validation set and test set are 13800, 9200 and 4600 respectively. Before training, we pre-trained the YOLOv3 on VOC2007 and obtained a pre-trained model, which can enhance the speed and accuracy of the training. In the training process, the initial learning rate was set to 0.001, and the Adam algorithm was used for gradient descent.

The results of chromosome identification and location are shown in Fig.6. It is obvious that YOLOv3 can detect each chromosome accurately in the micrograph

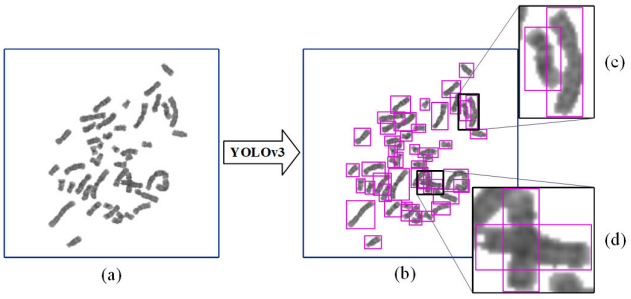

FIGURE 6. Chromosome identification and location. (a) Micrograph after denoising; (b) Chromosome detection; (c) Detection of adhesive chromosomes; (d) Detection of overlapping chromosomes.

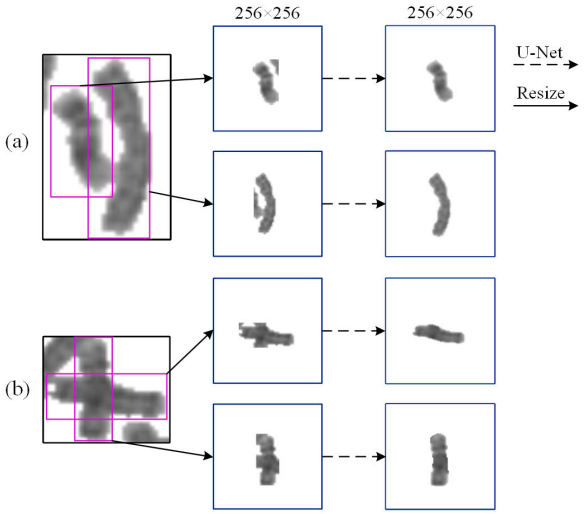

FIGURE 7. Precise extraction of adhesive (a) and overlapping (b) chromosomes. Dotted arrows indicate U-Net; Solid arrows indicate resize operations.

(shown in Fig.6 (b)). In particular, YOLOv3 shows a strong ability to accurately identify and locate adhesive and overlapping chromosomes (shown in Fig.6 (c) and Fig.6 (d), respectively).

C. PRECISE EXTRACTION OF CHROMOSOMES

Although YOLOv3 can identify and locate chromosomes accurately, and then output images of single chromosomes, these images often contain interferences from other chromosomes. Especially for overlapping and adhesive chromosomes, the interferences from other chromosomes are difficult to remove accurately, as shown in Fig.7. Here, U-Net was used again to extract single chromosomes precisely based on the YOLOv3 output images with the size of 256 × 256. In the training process, the initial learning rate was set to 0.001, and the Adam algorithm was used for gradient descent.

The results of precise extraction of chromosomes are shown in Fig.7. It can be seen that in both cases of adhesion (shown in Fig.6 (a)) and overlap (shown in Fig.6 (b)), the interferences from other chromosomes can be identified and removed accurately, and thus the precise extraction of single chromosomes under complex conditions is completed.

D. QUALITATIVE EVALUATION

The accuracy of the chromosome extraction method is quantitatively evaluated by judging whether the single, overlapping and adhesive chromosomes can be correctly extracted. As shown in (1). The accuracy is defined as the ratio of the number of chromosomes extracted correctly ($N_{extraction}$) to the total number of the chromosomes ($N_{overall}$) [17].

$$Accuracy = \frac{N_{extraction}}{N_{overall}} \times 100\% \tag{1}$$

To evaluate the accuracy of our method quantitatively, we randomly selected 50 original micrographs, including 1662 single chromosomes and 638 overlapping and adhesive chromosomes. These samples were well representative and can be used to assess the accuracy of the method. As a result, 2283 chromosomes were correctly extracted, and the accuracy rate reached 99.3%. This result is better than those by other methods, as shown in Table 1.

V. DISCUSSION

Chromosome extraction is a prerequisite for automatic karyotype analysis. Due to the complexity and diversity of chromosome distribution, chromosome extraction is still a challenge for many traditional image-processing algorithms based on artificial rules. In contrast, deep learning can analyze images based on learned target features rather than artificial rules, and thus has the potential to provide new powerful tools for solving this problem. At present, image-processing algorithms based on deep learning mainly include image segmentation algorithms and target detection algorithms. The former can segment all targets from the background, but can not distinguish similar targets in the image. On the contrary, the latter can detect each target, but can not extract the target accurately along the contour, making it difficult to extract overlapping and adhesive chromosomes. Therefore, image segmentation algorithms or target detection algorithms alone can not solve the problem of chromosome extraction, and the combination of the two algorithms is required. Mask R-CNN [25]–[27] is a well-known method that combines a target detection algorithm (Faster R-CNN [28]) and an image segmentation algorithm (Fully Convolutional Networks, FCN [29]), and generally requires a huge number of samples for training. In our study, we tried to use Mask R-CNN for chromosome extraction, but the result was not satisfactory (data not shown), which may be related to the relatively small number of chromosome micrographs. Taking this factor into account, we combined U-Net and YOLOv3 for chromosome extraction.

U-Net is an image segmentation algorithm, which can use the underlying features (concatenation of the same resolution) to solve the problem of insufficient upsampling information, and thus has an outstanding advantage in processing medical images with a small number of samples. This is confirmed by our results. As shown in Fig.5 and Fig.7, although the number of samples is relatively small, U-Net has excellent performances in both image denoising

TABLE 1. Comparison of our result with those in the literature.

THE METHODS	SEPARATION OF ADHESIVE CHROMOSOMES	SEPARATION OF OVERLAPPING CHROMOSOMES	NUMBER OF CHROMOSOMES	ACCURACY
Ji (1994) [9] set 1	Yes	No	11279	95.2%
Ji (1994) [9] set 2	Yes	Yes	19719	91.3%
Agam *et al.* (1997) [10]	Yes	Yes	1150	94%
Grisan *et al.* (2007) [11]	Yes	Yes	1380	96%
Grisan *et al.* (2009) [12]	Yes	Yes	6683	94%
Yilmaz *et al.* (2018) [24]	Yes	No	6678	97.8%
Emrecan *et al.* (2020) [17]	Yes	Yes	23374	98.94%
Proposed method	Yes	Yes	2300	99.3%

and precise chromosome extraction. YOLOv3 is a One-Stage target detection algorithm, which regards the target detection as a regression problem, and does not require a complicated process of generating the candidate boxes. Therefore, its detection speed is faster than those of Two-Stage algorithms such as Faster R-CNN [27] and Fast R-CNN [30]. More importantly, YOLOv3 has a multi-scale network that can detect targets of various sizes, so it can avoid missed detections effectively. This is very helpful for detecting targets with large size differences. These advantages make YOLOv3 a powerful tool for chromosome detection. As shown in Fig.6, although the chromosomes have a dense distribution and large individual differences in size, YOLOv3 can still identify and locate each chromosome accurately.

In addition, the quantitative evaluation results further confirm the effectiveness of our method. The results show that the proposed method can extract effectively both adhesive and overlapping chromosomes. The accuracy of the chromosome extraction reaches 99.3%, which is better than the results of other methods in Table 1, indicating that our deep learning-based method has a stronger generalization ability and a wider applicability than the artificial rules-based methods.

VI. CONCLUSION

In this study, we proposed an automatic chromosome extraction method based on the optimized combination of U-Net and YOLOv3. This method includes three steps: First, U-Net is used to remove interferences in the chromosome micrographs. Second, YOLOv3 is used to identify and extract each chromosome. Finally, U-Net is used again to extract the chromosomes precisely. The results show that our method can extract accurately the single, overlapping and adhesive chromosomes from the raw G-band chromosome images, with an accuracy of 99.3%. This method is of great significance for automatic karyotype analysis.

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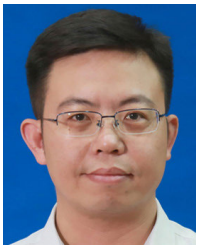

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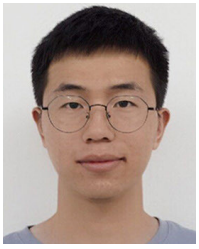

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