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Deep Learning-Based Object Detection And Bacteria Morphological Feature Extraction For Antibiotic Mode Of Action Study

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***Abstract*—The increasing prevalence of antimicrobial resistance (AMR), as microorganisms develop resistance to antimicrobial drugs, has emerged as a critical concern in infection treatment, resulting in a rising death toll. Assessing the effect of drugs can provide insights by studying the morphological change of bacteria after drug treatment. However, utilizing conventional techniques such as CellProfiler for long-term and large-scale sample experiments is impractical due to the manual processes involved. To address this challenge, we proposed a deep learning-based object detection model for predicting the type of antibiotic treatment and automatically extracting bacteria morphology. Our model combines YOLOX and two Cascade R-CNNs using weight box fusion to enhance performance. It achieves an mIOU of 0.753 and mAP of 0.699 higher mAP compared to CellProfiler (mAP = 0.218). In addition, we use a computer vision approach to extract bacteria morphological features including cell membrane, DNA, and color intensity to classify the treated antibiotic which achieves comparable performance to CellProfiler (F1-Score = 0.75, 0.79 respectively). We believe our work can be used as an automatic tool to enhance the efficiency of antibiotic prediction and extracting cell profiles for AMR applications. Our code and web application are available at https://github.com/biodatlab/bacteria-detection.**

***Index Terms*—Deep learning, Object detection, Ensemble Method, Weighted-Box Fusion, Antibiotics, Antimicrobial Resistance**

I. Introduction

Antimicrobial resistance (AMR) is a critical issue where bacteria develop resistance to antibiotics, resulting in ineffective treatments. With 1.2 million deaths attributed to AMR in 2019 [1], projections indicate that this number could rise to a staggering 10 million within the next 30 years [2]. Previous AMR studies include the development of new drugs or Macromolecular synthesis (MMS) assays to determine bacterial inhibition pathways [3]. However, such approaches require time and experimentation. Recent research has shown that imaging and using morphological features of bacteria, such as *Escherichia coli* (*E. coli*), can indicate the specific inhibition pathways of antibiotics which can scale the understanding of AMR [4].

One approach to determining the bacteria morphology is utilizing CellProfiler, an open-source software for extracting and clustering cell features. CellProfiler uses machine learning (ML) for quantitative analysis of images by extracting the features of bacteria that can be used to predict potential inhibit pathways or treated antibiotics [5]. Nevertheless, CellProfiler still requires manual work to adjust the original microscopic images. Deep learning (DL) based methods can solve this problem especially when there is a large number of data, for example, Faster R-CNN [6], YOLOv2 [7], and YOLOv3 [8] have been used for automating the detection of cells such as cancer cell counting [9], detection of Campylobacter bacteria and phagocytic activity of leukocytes [10], and blood cell detection [11]. DeepBacs also demonstrated using YOLOv2 with various types of bright-field and fluorescence images to detect growth stages of *E.coli* cells and antibiotics phenotyping [12]. However, YOLOv2 still has limited performance in biomedical images due to its grid-based architecture which performed poorly on densely packed cell colonies [7].

Modern object detection models such as Cascade R-CNN [13], HRNet [14], and YOLOX [15] have shown remarkable performance in various detection tasks. They have been particularly successful in tasks such as white blood cell detection [16], parasitic egg cell detection [17], and cervical cell detec-

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tion [18]. Given their capabilities, it is reasonable to explore the potential of these approaches in detecting bacteria after antibiotic treatment and analyzing their morphology.

In this work, we proposed a deep learning-based object detection and automatic feature extraction from bacterial microscopic images that outperformed the traditional technique, CellProfiler, in both speed and accuracy. We collected 900 images of untreated *E. coli* after being treated with seven well-known antibiotics, including Ampicillin, Ciprofloxacin, Rifampicin, Tetracyclines, Mecillinam, and Kanamycin. We trained the object detection models including Cascade R-CNN and YOLOX and combined the predictions using the ensemble method. Our approach achieves higher mAP than using the CellProfiler. In addition, we used a computer vision approach to extract essential morphological features such as cell membrane characteristics, DNA distribution, and color intensity. The feature extraction achieved comparable performance in downstream antibiotic classification tasks compared to CellProfiler. Our technique could be used for automatically identifying antibiotics and extracting morphological features for further analysis of AMR.

II. MATERIAL AND METHODS

A. Datasets

The dataset was collected using a DeltaVision Ultra fluorescence microscope (100x magnification) at Mahidol University's Institute of Molecular Biosciences. It features *E. coli* bacteria treated with seven common antibiotics and untreated bacteria, totaling 900 images including 100 images per antibiotic class and 200 untreated. Custom modifications were applied using ImageJ to enhance bacterial boundaries. This allowed for easier annotation with Labelme [19], focusing solely on drawing bounding boxes. The labels excluded dead bacteria, usually appearing bright or green. On average, each image contains 61 bacteria, with treated images having around 50 per image and untreated having more than 100. The dataset was split into training (720 images), validation, and testing datasets (90 images each).

B. Model development

We employed various object detection approaches to locate bacteria and predict the corresponding administered antibiotics. The aim was to compare object detection performance with the CellProfiler-based methods.

CellProfiler-based methods: CellProfiler has been widely used as a tool for cell morphology analysis. The general workflow involves modifying raw images into a suitable format using ImageJ. Subsequently, Ilastik, a bioimage analysis software, is used to detect bacteria in the modified images. The extracted features are then processed using CellProfiler. Hierarchical density-based spatial clustering of applications (HDBSCAN) removes outliers and noise from the obtained features. Finally, the cleaned features are used for antibiotic classification using ML approach such as support vector machine (SVM). The cellProfiler-based method is sensitive to low-resolution bacteria images and requires expertise to configure the hyperparameters, making it less suitable to scale the experiments. [20]

Proposed models: We proposed two models to address the limitations of baseline models: Cascade R-CNN [13] with a Res2Net [21] backbone and YOLOX [15]. Cascade R-CNN enhances Faster R-CNN by cascading its detection head and increasing the Intersection over the Union (IoU) threshold, improving detection accuracy. It incorporates the Res2Net backbone for better spatial features and more accurate bounding box predictions compared to ResNet [22], YOLOX enhances YOLOv3 by decoupling the classification and bounding box regression tasks and using an anchor-free algorithm for faster bounding box prediction, resulting in superior object detection performance., both models are enhanced with additional components such as deformable convolutional layers version 2 (DCNv2) [23], Dynamic Head (Dyhead) [24], Path Aggregation Network (PANet) [25], and Side-Aware Boundary Localization [26]. These modifications further improve the models' performance in bacteria morphology classification.

Ensemble Method: The ensemble model combines the results from Cascade R-CNN Res2Net-50, Cascade R-CNN Res2Net-101, and YOLOX. To merge overlapping bounding boxes, we utilized the Weighted Box Fusion (WBF) technique, which employs weighted averaging of bounding boxes. This method provides smoother bounding box predictions compared to traditional non-maximum suppression (NMS). For merging the bounding boxes, we use an IoU threshold of 0.8.

Baseline models: We compared the proposed models with baseline object detection approaches including Faster R-CNN, YOLOv2, and YOLOv3. We chose YOLOv2 [7] and Faster R-CNN [6] since it is frequently used as a baseline in cell object detection tasks and also achieve good performance in detecting bacteria in the fluorescent microscopic image.

Baseline YOLOv2 was developed using the Darknet library [27]. The rest of our models were developed using MMDetection [28]. We applied augmentation including padding, random flipping, shifting brightness-contrast, median blurring, shifting, scaling, and rotating during training. Cascade R-CNN and Faster R-CNN models are training for 200 epochs and YOLOX and YOLOv3 are training for 800 epochs. We selected the model with the best validation score for ensemble prediction. All experiments used GPU NVIDIA 3060Ti.

C. Model evaluation

The object detection models were evaluated using two main metrics: mean intersection over union (mIoU) and mean average precision (mAP). mIoU can be calculated by the mean of the area of overlap over the area of union for each class (c) as

$$mIoU = \frac{1}{n} \sum_{c} IoU_c \tag{1}$$

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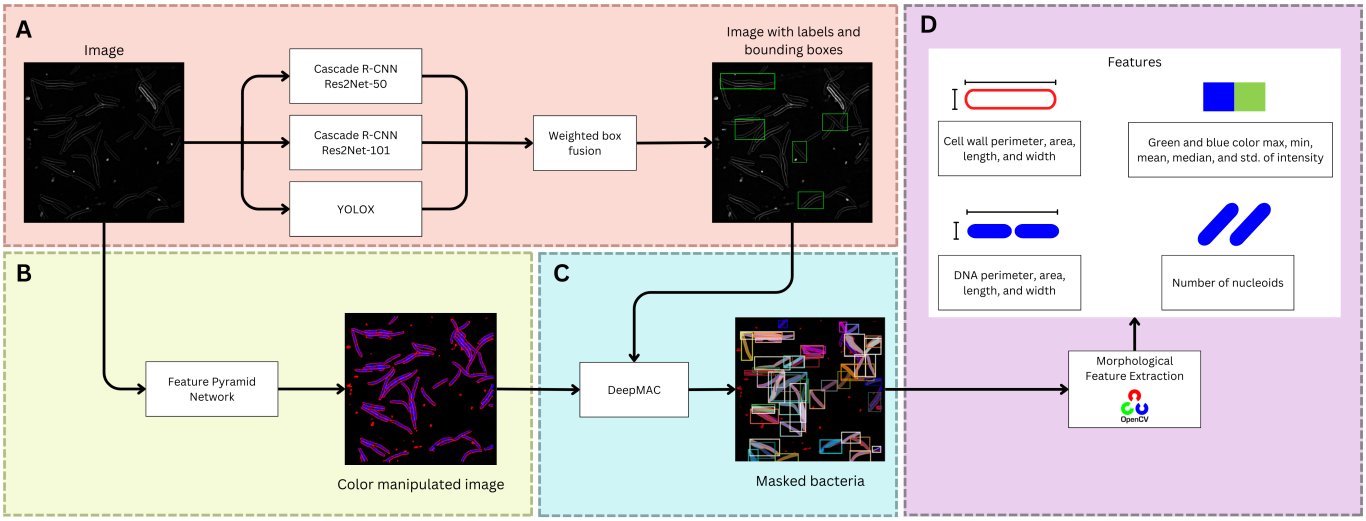

Fig. 1. A schematic of the bacterial cell detection and morphological feature extraction. A. The object detection models detect bacteria and classify the treated antibiotics. The bounding boxes are fused together using weight box fusion. B. Image color is enhanced using Feature Pyramid Network (FPN) [29]. C. DeepMAC utilizes bounding boxes to generate masks. D. Finally, the computer vision approach is used to extract bacteria morphological features such as cell membrane perimeter, cell membrane area, DNA perimeter, DNA area, and color statistics.

where IoU per class can be calculated as

$$IoU_c = \frac{\text{Intersection Area}_c}{\text{Union area}_c} \tag{2}$$

In addition, we used mean average precision (mAP) which is the mean of all average precision (AP) for all predicted classes (c). We used mAP as our main metric since we wanted the model to identify bacteria and their treated antibiotics correctly.

D. Bacteria Feature Extraction

In addition to predicting treated antibiotics, it is crucial to consider the morphological features of bacteria caused by antibiotics. These features play a vital role in predicting how new antibiotics will target bacterial pathways. The feature extraction model extracts specific features from predicted bounding boxes, including the perimeter, area, length, and width of the bacteria's cell membrane, DNA, and color intensity (minimum, maximum, mean, median, and standard deviation of the green and blue color channels) [30]. These features can be used to predict the pathways they target, facilitating the development of new antibiotics.

We employed a three-step process for bacteria feature extraction. First, we used an image from the Feature Pyramid Network (FPN) to manipulate pixel color for the cell membrane and DNA [29] (Figure 1B). Next, we performed instance segmentation from a given bounding box to get a cell mask using DeepMAC [31]. Finally, we extracted 19 morphological features from these masks using OpenCV [32] to obtain cell parameters such as area, perimeter, and dimensions of the segmented regions (Figure 1C).

To evaluate the feature extraction model, we used features from the test images extracted from the proposed model and CellProfiler. Subsequently, we divided each cell's features into train and test datasets with an 80:20 ratio and used SVM for antibiotic classification. Finally precision, recall, and F1-score as the evaluation metrics for comparing the quality of the features from both procedures. This approach aids in assessing the feature quality, which is vital for studying the bacteria morphology.

III. RESULTS

A. Compare the detection performance between models and CellProfiler

The baseline model such as YOLOv2 and Faster R-CNN gives a mIoU of 0.14 and 0.325 and mAP of 0.053 and 0.041 respectively. The baseline model can localize the bacteria but cannot classify them correctly thus getting a low mAP score. The best three-performing models include Cascade R-CNN Res2Net-101, Cascade R-CNN Res2Net-50, and YOLOX. For the single detection model, Cascade R-CNN Res2Net-50 achieves the highest mAP and mIOU of 0.680 and 0.802 respectively (Table I). The ensemble method, which is the means to combine predictions from many different models, was introduced to improve the model performance. The ensemble model was achieved from the combination of the models, which are Cascade R-CNN with Res2Net-101, YOLOX_m, and Cascade R-CNN with Res2Net-50. It results in mAP and mIoU at 0.699 and 0.753 respectively which is higher than CellProfiler with mAP and mIoU at 0.218. The ensemble model can significantly detect more bacteria compared to CellProfiler.

B. Downstream antibiotic classification using bacteria morphological features

We compared automatic feature extraction using the best object detection model to CellProfiler for classifying antibiotic treatments based on cell morphology (Table II). Our model

TABLE I
RESULTS OF EACH MODEL'S PERFORMANCE

Model	mAP	AP_{50}	AP_{75}	AP_M	AP_L	mIoU
CellProfiler*	0.218	0.367	0.225	0.211	0.298	0.218
YOLOv2*	0.053	0.192	0.015	0.048	0.102	0.140
Faster R-CNN*	0.041	0.097	0.031	0.005	0.045	0.325
Cascade R-CNN Res2Net-101	0.652	0.808	0.762	0.677	0.692	0.800
Cascade R-CNN Res2Net-50	0.680	0.82	0.779	0.704	0.628	**0.802**
YOLOX_m	0.621	0.902	0.835	0.711	0.796	0.755
Weighted box fusion	**0.699**	**0.836**	**0.796**	**0.717**	**0.675**	0.753

*Baseline Note — mAP = means average precision; AP_{50}, AP_{75} = average precision at certain IoU value; AP_M, AP_L = average precision across the size of the object; mIOU = means Intersection over Union. Both metrics are used to measure the localization and classification performance of the model.

achieved a similar performance to CellProfiler, with F1-scores of 0.76 and 0.79, respectively. While CellProfiler excelled in precision for certain classes like Ciprofloxacin and Colistin, its recall was lower compared to our model. This suggests CellProfiler's strength lies in feature extraction, but it detects fewer bacteria initially than our model. In summary, our automated model is effective for morphological feature extraction in this context.

TABLE II
PRECISION, RECALL, AND F1-SCORE OF THE DOWNSTREAM ANTIBIOTIC CLASSIFICATION USING CELL FEATURES FROM CELLPROFILER AND PROPOSED MODEL

	CellProfiler			Proposed		
Class	***Precis.***	***Recall***	***F1-score***	***Precis.***	***Recall***	***F1-score***
Amp	0.68	0.83	0.75	0.82	0.75	0.79
Cip	1.00	0.39	0.56	0.82	0.66	0.73
Col	0.80	0.49	0.61	0.83	0.66	0.78
Kan	0.86	0.89	0.87	0.78	0.80	0.79
Mec	0.87	0.87	0.87	0.81	0.45	0.58
Rif	0.97	0.90	0.93	0.86	0.84	0.85
Tet	0.85	0.85	0.85	0.76	0.84	0.80
Unt	0.86	0.96	0.91	0.74	0.82	0.78
Avg	0.86	0.77	0.79	0.80	0.73	0.76

Abbreviations: Precis, Precision; Amp, Ampicillin; Cip, Ciprofloxacin; Col, Colistin; Kan, Kanamycin; Mec, Mecillinam; Rif, Rifampicin; Tet, Tetracycline; Unt, Untreated.

IV. ERROR ANALYSIS

We observed the false positive predictions in some areas where cells overlap or sit closely in a colony. When the colony is densely packed, the prediction generated by the models may fail to cover all individual bacteria or include an excessively incorrect prediction overall (Figures 2A and 2B). The model also predicted wrongly in the cell-division area where it is hard to distinguish between a single cell or a dividing cell (Figure 2C). The models also overpredicted when the cell membranes of the bacteria were thin and not connected smoothly. (Figure 2D)

V. DISCUSSION

Our work introduces an automated deep learning-based object detection model for studying antimicrobial resistance

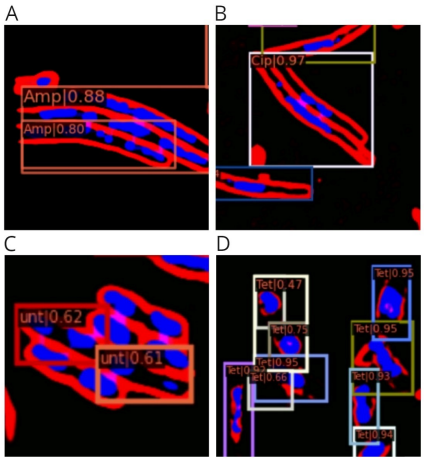

Fig. 2. An example of the model's prediction from different classes that contain errors. A, B. Bacteria treated with Ampicillin and Ciprofloxacin had a dense group of colonies and the model failed to detect some of the bacteria. C. Untreated bacteria had an exceeding number of bounding boxes due to the incomplete cell division D. Bacteria treated by Tetracycline tended to have unclear cell membranes making it hard for the model to detect.

(AMR) in *E. Coli* post-drug treatment. The top-performing model combines YOLOX and two Cascade R-CNNs using a weight box fusion ensemble method, outperforming CellProfiler in terms of mAP and mIoU. These features are then utilized for antibiotic classification, achieving performance comparable to CellProfiler. Additionally, we developed a web application for our model.

Both baseline models exhibit lower mAP in the object detection task due to their simplistic architecture, which hampers the extraction of high-quality spatial features. The low-resolution features hinder the accurate identification of bacteria. Additionally, the models struggle with misclassifying the detected bacteria and have difficulties in precisely localizing the bounding boxes around bacteria colony [33]. Moreover, distinguishing bacteria with a small size poses a challenge for the models that fail to extract the feature at the difference scale such as YOLOv2, leading to inaccurate classification [8].

The single model, Cascade R-CNN based, still lacks the ability to differentiate a colony of densely packed bacteria resulting in false detections. YOLOX tends to overpredict bounding boxes. Another observation is that the ensemble model has a lower overall mIoU score but a higher mAP. This is because the ensemble method fuses the overlapped area from all of the models, resulting in higher AP but the combined boxes get lower mIoU. We can improve the individual model and ensemble parameters to improve the final predictions.

As this model was trained based on E.coli which has its unique morphology, Model training should be required for a different type of bacteria.

Finally, CellProfiler and our proposed object detection-based model were compared. While CellProfiler is good at detecting certain cell characteristics, its detection rate is only 20-30%. In contrast, our approach focuses on detected cells for feature comparison and achieves competitive results. We

encountered occasional inaccuracies in automatic feature extraction using OpenCV based on DeepMac masks, but overall, DeepMac masks performed well, especially in sparse cell areas. However, in densely packed bacteria areas, the mask quality was lower. Future work can improve robustness in such scenarios. Training an instance segmentation model to predict both bounding boxes and masks shows promise for enhancing object detection and mask segmentation [34]. These findings open doors for advanced biomedical image analysis with broad potential applications.

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