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A Framework of Predicting Drug Resistance of Lung Tuberculosis by Utilizing Radiological Images

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***Abstract*—Drug-resistant tuberculosis (TB) has been a persistent death thread of human health for hundreds of years. The increasing emergence of drug resistance and extensively drug-resistant Mycobacterium TB raise researchers attentions. And how to predict drug-resistant lung TB quickly and effectively has become a big challenge. This paper reviews the major prediction methods of drug-resistant lung tuberculosis appeared in recent years. Specifically, we survey the development of prediction methods of lung TB drug resistance, lung region segmentation, and features selection in different radiological images (CT and X-ray images). Furthermore, we summarize a framework which is suitable for the prediction process based on previous literatures. However, this process need human participation and the accuracy rate is not very high. Thus, to address this problem, we introduce deep learning algorithms into this field and present a proved framework to predict automatically, due to the superior performance of deep learning techniques in other medical image analysis fields, and get a high accuracy.**

Keywords—lung tuberculosis classification; drug resistance; transfer learning

I. Introduction

Tuberculosis (TB) has affected human beings for thousands years and has been a persistent thread of public health, after discovery of Mycobacterium tuberculosis (M. tuberculosis) [1]. Nowadays, with the development of medicines, the drug resistance of lung TB has become a serious problem because a patient may be more difficult to cure once his or her organisms become resistant to two or higher levels of standard drugs [2].

Actually, the phenomenon of drug-resistant TB appeared in 1944, when soon after the use of drug for treatment of tuberculosis [3]. Theoretically, drug resistance should not exist when three or more effective drugs are used in combination. However, at the beginning, this phenomenon happens due to human mistakes, including wrong use of single drug, inappropriate doctor prescription and few patient adherence to treatment.Then, the drug-resistant tuberculosis spread and finally represent original virus (see Fig. 1).

In order to better treat TB patients, doctors need to identify whether their lesion is drug resistant and which standard drugs it is resistant to. In 2015, an expending rapid testing and detection of cases has been proposed by WHO to tackle the global crisis of drug-resistant TB [4]. And the introduction

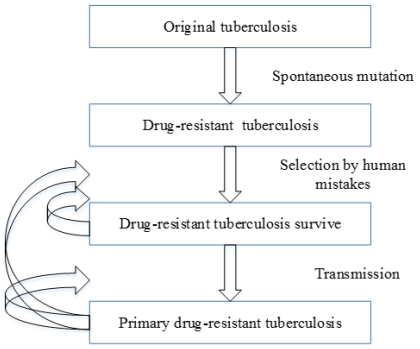

Fig. 1. The development of drug-resistant tuberculosis.

of new treatment methods of drug-resistant TB could make a diagnosis earlier and prevent the spread of drug-resistant M. TB effectively [5]. However, these methods still do not solve many challenges of drug-resistant TB [6]. This process is time-consuming, labor-intensive, and subjective. To solve these problems, image-based computer aided diagnosis has been introduced to this field recently.

In this paper, the contributions are summarized as follows:

- we present a literature review of so far predicting drug-resistant lung TB by utilizing image data (CT and X-ray images) semi-automatically or automatically.
- we propose a framework of these prediction methods.
- we introduce deep learning to predict drug resistance of lung TB and test proposed method on imageCLEF2017 tuberculosis datasets.

II. Overview of Prediction Methods

A. Maintaining the Integrity of the Specifications

Diagnosis of drug-resistant lung TB has received extensive attention of researchers in recent years. The datasets contain 2D and 3D radiological images, including both CT images and X-ray images. And some competitions about prediction drug resistant TB, such as imageCLEF 2017, have also been held this year.

In 2013, researchers examined the feasibility of using radiological images (X-ray and CT images) to predict lung TB drug resistance. They do segmentation firstly. Then, by employing

man-made extracted features and several classifiers, the best accuracy reached 75% [7]. After that, researchers try to find more effective features, which means these features are correlated with drug resistant. And they find that CT images and X-ray images have different correlated features respectively [8]. However, these prediction methods are semi-automatically due to some of features involved are not extracted from images, such as weight, recurring treatment, etc.

To address these drawbacks, V. Kovalev et al. [9] choose to only use features extracted from images to predict drug-resistant lung TB. In other words, the problem of prediction of lung TB drug resistance is treated as a pattern recognition problem, and the best prediction performance presents 75.7%.

Besides, with deep learning methods, especially convolutional networks, have been used for analyzing medical images rapidly in recent years [10]. Several researchers also apply deep learning concepts in TB drug resistance prediction field [11].

III. Framework of General Prediction Methods

Based on the description in Section I, we have summarized so far TB drug resistance prediction methods in a framework, which basically completes the forecast process (see Fig. 2).

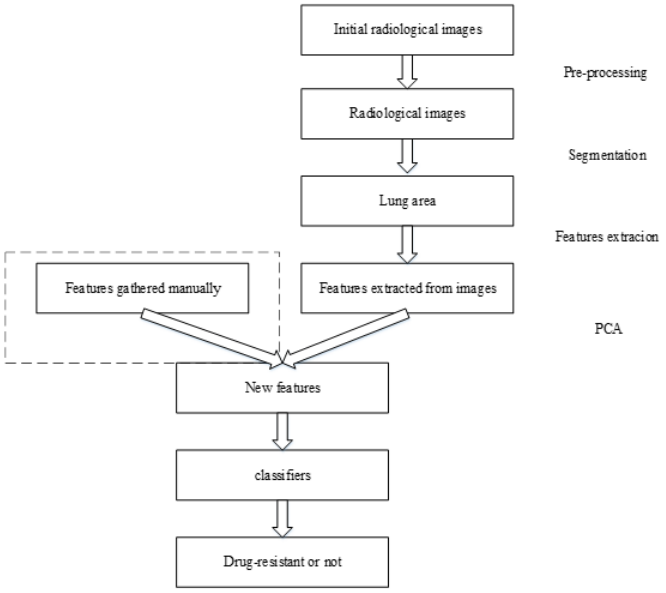

Fig. 2. The framework of basic prediction methods of TB drug resistance.

As we can see in Fig. 2, both semi-automatic (contains part of gridlines) and automatic prediction (without part of gridlines) are shown in the framework. Researchers first do pre-processing, such as resizing images to uniform sizes, contrast enhancement, etc. [12]. Secondly, they segment lung region in order to extract certain features. After extracting features, it is necessary to use the Principal Component Analysis (PCA) to reduce the number of features. Then we get new features, and combine them with other features (gathered manually). Send them to classifiers together to train the classifiers. Then apply these well-trained classifiers to predict target lung images, and finally get the results finally.

Based on the framework, the rest of the paper is organized as follows. Section III-A reviews the methods of lung region segmentation. Section III-B presents features used in radiological images (CT and X-ray images respectively). Section IV shows a new framework of prediction method using deep learning. And Section V tests the proposed methods and analysis the results. Section VI gives the conclusion.

A. Lung Region Segmentation

Image segmentation is known as one of challenge problems in medical image processing and analysis [13]. Specifically, target objects segmentation is the first stage during the whole process, and may affect the following steps severely. In TB drug resistance prediction process, there are two types of images need to segment, CT and Xray images. However the methods of two kinds of images do not have some differences.

Generally speaking, these segmentation methods could be divided into two main categories. One is segmentation using deep learning methods [14], [15] and convolutional neural networks [11]. The other part is methods using morphological characteristics [16], [17] (e.g. border, prior shape, low level features, etc.) and filters [12] (e.g. shadow filter, multilevel thresholding etc.) and this part methods show diversity. Both two main methods present a high accuracy (over 90 percent) in lung region segmentation.

B. Features Extraction

In this section, we will first review common features used after segmentation, and then discuss the significant features of CT and X-ray images respectively.

On the one hand, doctors and researchers usually choose three main standardized data from forms (Excel spreadsheets) [6]: General characteristics of studies (consist of age, country, city, low or high drug-resistant TB rate, year, risk population status, etc.), Principal findings, and Technical details.

On the other hand, researchers also extract features from input radiological images. As we known, a proposed work need extract maximum distinguishable features from lung images [18]. However, digital images are difficult to extracted features due to low contrast, large variation in density, and varying size [19]. For commonly known 2D features, Kovalev V. et al [20] choose features including co-occurrence matrices, Local Binary Patterns (LBP), extended multi-sort, gradient magnitude, and anisotropy image properties. Homma N. et al [21] select image features such as outputs of N-quoit filter, average pixel value, variance pixel value, and entropy pixel value. Nitin S. et al [19] employ low pass filter, high pass filter and point processing techniques. For 3D images, extended multi-sort, multi-dimensional co-occurrence matrix [22] are proved to be powerful and flexible enough [7]. And some researchers use descriptors of four-dimensional matrices [23] and counting frequency of triplets of pixels mutual occurrence [7] to describe X-ray lung images. And for describing CT

lung images, they employ sixdimensional matrices, gradient magnitudes, and mutual angles between gradient vectors [7].

As we mentioned above, there may be different suitable descriptors aimed at X-ray and CT images. Besides, some features may not describe the lung images very well and could not perform well. Thus Kovalev V. et al. [8] do the comparison tests, and find five mutually uncorrelated components after the principal component analysis with Kaizers criterion. For CT lung images, component PC3, patients weight, and presence of recurring treatment are correlated with TB drug resistance significantly. While, for X-ray lung images, component PC6 and presence of recurring treatment are correlated with drug-resistant TB tightly. And we can find that there is no factor about patients weight compared with CT images.

IV. Prediction Process with Deep Learning

In recent years, medical imaging has been coming into the Big Data camp [24]. And the medical images analysis has attracted attention of researchers. As we mentioned in Section 4, the gradual method to learn features from data is using handcrafted features. However, the trend is that the whole prediction process is automatic. Thus, deep learning algorithms have rapidly employed in medical images analysis. The most successful model is convolutional neural networks (CNNs) and it has been done since 1980 [10]. And the networks have already applied to medical image analysis in 1995 [25]. And Bengio et al. [26] introduce a kind of CNNs trained end-to-end only. Now they are widely used in medical image analysis field. However, deep learning methods are not introduced to lung TB image analysis.

Specific speaking, with the help of deep neural network, our method extracts the effective features from the CT images, which replaces the manual feature extraction part in the previous algorithm structure. In this paper, we choose VGG16 model as feature extractor. Combining it with the frame graph Fig. 2 in the previous section III, we can get the whole framework of the method using the depth neural network, as shown in Fig. 3).

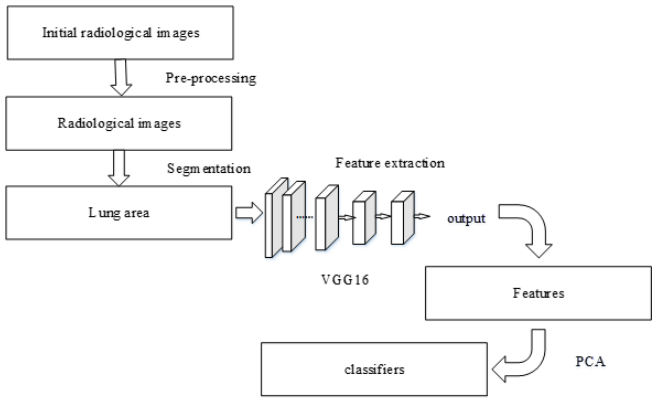

Fig. 3. The framework of basic prediction methods of TB drug resistance using deep learning method (VGG16).

From Fig. 3, we can see that the whole process is divided into three main steps: image preprocessing, feature extraction (VGG16 model) as well as processing (PCA), and classification (SVM).

- Preprocessing of CT Images: In order to deal with the features of 3D image better, it is necessary to convert the 3D image into multi-view and multi-level 2D images. Masks are used to leave the foreground part (lung region), and then images are enhanced to strengthen the texture information.
- Feature Extraction: The processed data is input into the pre trained improved VGG16 model on imageNet.In the next section, we'll give you a detailed explanation of this part.
- Classification: In this process, we choose to use two ways to classify input images: SVM and depth learning neural network (SOFTMAX). This is because in the subsequent comparative experiments, we find that SVM and SOFTMAX have good performance in some specific methods respectively. For SVM classifier, because of dividing feature extraction and classification into two steps, we can add manual features, and combine it with features extracted before. For SOFTMAX classifier, the method using it is more efficiently, because it combines feature extraction and classification together. In the following experiments, we test these two different methods.

A. Feature Extraction with VGG16

In this part, we choose the VGG16 model because the number of patients in this project is not so large, though each patient's CT images size are large. In this case, simple network structure will help avoid overfitting. In the preprocessing stage, each patient will be described by a series of pictures, therefore, after extracting features with VGG16, each patient will have a high-dimension and sparse feature matrix. To address this, we proposed three kinds of methods based on previous framework architecture.

The first one is to use pre-trained VGG16 model to extract features, and make full use of network context feature information. After that, we choose PCA for principal component analysis, and select the most important part of features to represent each patients sample image, see Fig. 4.

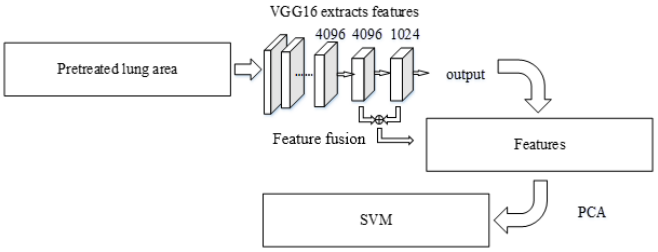

Fig. 4. The framework of a prediction method of TB drug resistance using fixed/fine-tuned VGG16 and SVM.

The seconde one is divided into two different ways. One is to use fine-tuned VGG16 model (denoted by fine-tuned1)

and network context feature information to extract features, and then send them into PCA and SVM classifier to predict drug-resistant TB, see Fig. 4. The other one is to use the same fine-tuned VGG16 model to extract features, and directly put them into SOFTMAX to do classification, see Fig. 5.

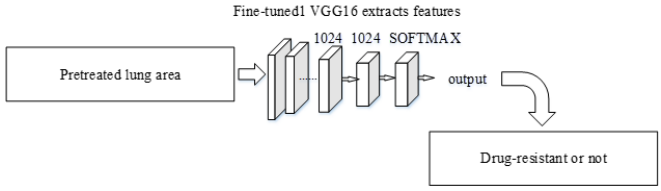

Fig. 5. The framework of a prediction method of TB drug resistance using fine-tuned VGG16 and SOFTMAX.

The last one is to use another fined-tuned VGG16 model (denoted by fine-tuned2), based on the second kind of method, to extract features and do the classification with SOFTMAX, see Fig. 6.

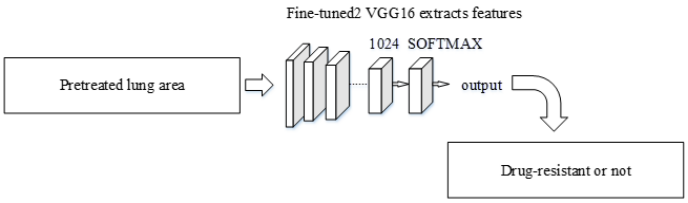

Fig. 6. The framework of a prediction method of TB drug resistance using another kind of fine-tuned VGG16 and SOFTMAX.

V. Experiments and Analysis

In this paper, we chose to perform experiments on the latest competition ImageCLEF dataset, which contains only HIV negative patients without relapse, and these patients belong to tuberculosis drug sensitivity (DS) or multidrug resistance (MDR). The total number of samples are 230, including 134 samples of tuberculosis drug sensitivity (DS), and 96 samples belonging to multi drug resistance (MDR).

We compare our test results with some of the best methods presented in the competition. The results of other algorithm are available in http://www.imageclef.org/2017/tuberculosis. These works trained in 230 samples and tested in 210 samples, while the proposed algorithm is trained in 180 samples and tested in 50 samples, since the test data are only available for groups which participated this challenge. The evaluation standard is the average precision (RCC), which refers to the definition of the average accuracy of the whole dataset, as in 1:

$$RCC = \frac{1}{n} * \sum_{i=1}^{n} RCC_i. \quad (1)$$

where n is the repeated number of experiments.

And the final contrast results are shown as table I, where we can see, the latter two methods we put forward are better than other methods in accuracy.

TABLE I. Contract Results

Methods	RCC(%)
MedGIFTcompetition	51.6
HHU DBScompetition	56.8
FC1024+FC4096+PCA+SVM	55.7
fine-tuned1+PCA+SVM	54.7
fine-tuned1+SOFTMAX	**60.8**
fine-tuned2+SOFTMAX	**64.0**

VI. Conclusion

In this paper, we proposed a general framework to do the classification of lung drug-resistant TB semi-automatically and automatically. To solve the small sample classification problem, with convolutional neural networks, we introduce VGG16 as the basic model. Motivated by deep learning algorithm in other medical field applications, we introduce CNNs in lung drug-resistant TB prediction and give a new framework which could predict TB drug resistance automatically. And we test the proposed methods on ImageCLEF2017 tuberculosis dataset, and get the highest accuracy (64.0%) compared with other methods in competition. In the future, we will test the proposed framework in more test data and tasks.

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