Improving Tuberculosis Diagnostics using Deep Learning and Mobile Health Technologies among Resource-poor and Marginalized Communities

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***Abstract*— Tuberculosis (TB) is a chronic infectious disease worldwide and remains a major cause of death globally. Of the estimated 9 million people who developed TB in 2013, over 80% were in South-East Asia, Western Pacific, and African. The majority of the infected populations was from resource-poor and marginalized communities with weak healthcare infrastructure. Reducing TB diagnosis delay is critical in mitigating disease transmission and minimizing the reproductive rate of the tuberculosis epidemic. The combination of machine learning and mobile computing techniques offers a unique opportunity to accelerate the TB diagnosis among these communities. The ultimate goal of our research is to reduce patient wait times for being diagnosed with this infectious disease by developing new machine learning and mobile health techniques to the TB diagnosis problem. In this paper, we first introduce major technique barriers and proposed system architecture. Then we report two major progresses we recently made. The first activity aims to develop large-scale, real-world and well-annotated X-ray image database dedicated for automated TB screening. The second research activity focus on developing effective and efficient computational models (in particularly, deep convolutional neural networks (CNN)-based models) to classify the image into different category of TB manifestations. Experimental results have demonstrated the effectiveness of our approach. Our future work includes: (1) to further improve the performance of the algorithms; and (2) to deploy our system in the city of Carabayllo in Perú, a densely occupied urban community and high-burden TB.**

Keywords*— tuberculosis; diagnosis; deep learning, deep convolutional neural networks, mHealth; mobile computing; Perú

I. Introduction

Tuberculosis (TB) is a chronic and infectious disease that affects the most disadvantaged populations and involves complex treatment regimes. It remains a major public health problem with more than 9 million estimated new cases and 1.5 million deaths every year, worldwide [1]. Of the estimated 9 million people who developed TB in 2013, over 80% were in South-East Asia, Western Pacific, and African [2]. The majority of the infected populations was from resource-poor and marginalized communities with weak healthcare infrastructure. This is unacceptable considering TB is curable and preventable. Efforts to eliminate the TB epidemic are challenged by the persistent social inequalities in health, the small number of local healthcare professionals, and the weak healthcare infrastructure found in resource-poor settings. The global health community has confronted the situation by focusing on developing and testing effective vaccines, improving the diagnosis process, and promoting patient adherence to the medical treatment.

Reducing the TB diagnosis delay is critical in mitigating disease transmission and minimizing the reproductive rate of the TB epidemic. The ultimate goal of our research is to reduce patient wait times for being diagnosed with this infectious disease by developing a socio-technical system solution to the TB diagnosis problem. Specifically, we aim to design a user-centered, mobile device-based computing system to significantly expedite the TB diagnosis process by developing novel image processing and machine learning techniques to analyze chest X-ray images. Our study will be conducted in the city of Carabayllo, a densely occupied urban community and high-burden TB area in Lima, the capital of Perú.

Mobile computing techniques offer a unique opportunity to accelerate the TB diagnosis among resource-poor, marginalized communities with weak healthcare infrastructure and systems. However, real-world mobile computing tools and applications in TB-related clinical practice with the capacity of accurate TB screening using mobile devices are rare. A wide gap between the technological advancements and the real-world clinical practices is caused by two major barriers: (1) *the first barrier* is the lack of large-scale, real-world, well-annotated, and public available X-ray image database dedicated for automated TB screening. For example, the majority of existing X-ray image databases, such as ImageCLEF [3], JSRT Digital Image Database [4], and ANODE Grand Challenge Database [5], were created mainly for one or two specific TB manifestations (e.g., pulmonary

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nodule). To the best of our knowledge, there is no large-scale, real-world, and public available chest X-ray dedicated for TB diagnosis with high-quality annotation; (2) *the second barrier* is the lack of mobile devices-based computing system that can offer accurate diagnosis by analyzing the chest X-ray images. The use of computer-aided chest radiography for TB screening and diagnosis [6-14] has been limited due to the modest sensitivity and specificity, and high inter- and intra-observer differences in reporting of radiographs [8]. Hence, the automatic screening for TB in chest radiographs is still a challenging task and an open research problem [8]. Furthermore, there is very few reported research on using mobile device to capture and analyze the chest radiograph images for computer-aided TB diagnosis [8].

Our research team, which includes computer scientists and health scientists from both U.S. and Perú, has proposed to develop a mobile device-based computing solution to overcome the aforementioned barriers. As the first step of developing such a system, we will introduce the two major progresses we recently made. The first aspect is related to the development of large-scale, real-world and well-annotated X-ray image database dedicated for automated TB screening. The second aspect is focusing on developing effective and efficient computational models to classify the image into different categories of TB manifestations.

The rest of the paper is organized as follows. Section 2 introduces the background information and related work. In section 3, we introduce the two progresses we had made in more detail. Section 4 concludes the paper and point out future directions.

II. Backround and Related Work

In this section, we will first introduce the power of mobile computing in healthcare (*sub-section A*). Then we will discuss the related work in developing chest X-ray image database (*sub-section B*), as well as related work in computer-aided system to screen the chest radiography image for TB diagnosis (*sub-section C*).

A. The Power of Mobile Computing in Healthcare (mHealth)

Point of care delivery is critical for the success of any application in the clinical healthcare environment. In Perú, as in many developing countries, a mobile device-based computing solution is very suitable within the context of resource-poor communities in Lima, Perú. The unique characteristics of the mobile devices such as its pervasiveness and low cost provide them the opportunity to support and enable smart care decision making in a connected health scenario for automatic health scenario for automatic tuberculosis screening.

1) mHealth in Perú: In a recent review of the mHealth literature published in Perú, Ruiz et al. [15] showed that mobile health interventions have enormous potential to improve access and the quality of health services in Perú, increasing the effectiveness of public health programs and reducing healthcare costs [15]. Out of 19 papers selected, most of them showed a positive impact, and four were about tuberculosis. It is important to notice that most of them were implemented as pilot projects ([15]). However, the majority of the papers demonstrated that mobile health interventions are well accepted by the population and well-developed projects might contribute to reduce the gap in public health, reducing limitations such as lack of resources (human and logistic) in heath care centers, high dispersion of the population and lack of infrastructure (roads, transportation and Internet connectivity).

2) mHealth for TB Diagnostics: During the last few years, mobile phones have been successfully used for diagnosis of tuberculosis [16]. In Perú, Zimic et al. [17] proposed a relatively minimal investment with mobile phones to facilitate the diagnosis of tuberculosis using a low cost Microscopic Observation Drug Susceptibility (MODS) in remote settings where a lack of trained personnel may otherwise be a limitation [17]. Nowadays, with the advances in mobile processors, images taken by a cell-phone can be immediately processed and analyzed with the help of smart algorithms. Today's global wireless infrastructure also allows transmission of a wide variety of tuberculosis images (such as X-rays) to remote locations for telemedicine diagnosis. Therefore ubiquitous cell-phone based applications can provide unique opportunities to combat tuberculosis, especially in developing countries [18].Recently, Schwartz et al. [19] assessed the diagnostic accuracy of digital photographs of plain film chest X-rays obtained using a mobile phone in Botswana. The authors concluded that digital photographs of chest X-rays obtained via a mobile phone equipped with a digital camera are comparable to plain film chest X-rays [19].

3) The need of a timely tuberculosis diagnosis in Perú

In Perú, tuberculosis remains as a serious public health problem. A successful treatment plan requires a proper diagnosis, in addition to good knowledge about drug susceptibility [20]. Reducing the tuberculosis diagnosis delay is critical in mitigating disease transmission and minimizing the reproductive rate of the tuberculosis epidemic. Different factors impact delays in tuberculosis diagnosis [21], such as: patient health seeking behavior, healthcare centers with poor infrastructure and equipment, inadequate resources and information systems (mostly paper-based), lack of (or inexistent) documented processes, and lack of human resources as part of a multidisciplinary tuberculosis team.

B. Related Work in Developing Chest X-ray Image Database

While there are some evaluation efforts in TB screening tests on developing countries [22, 23], to the best of our knowledge, there is no large-scale, real-world, well-annotated, and public available X-ray image database dedicated for TB screening diagnosis. Most of the existing research [6-14] in the area of computer-aided TB screening employed small data sets for evaluation and validation. Most of the datasets have less than 200 images. There are a few large data sets, such as ImageCLEF [3], JSRT Digital Image Database [4], and ANODE Grand Challenge Database [5], have over tens of thousands images. However, they only include one or two aspects of TB manifestations (e.g., pulmonary nodule). Without a large scale data sets with high qualify annotation, it will be very difficult to determine the efficacy of existing and proposed approach when applied to real-world clinic data. Furthermore, dedicated image annotation software tools and database storage software that can support the manipulations of the X-ray images are needed to facilitate the image annotation and image management.

C. Related Work in Computer-aided System to Screen the Chest Radiography Image for TB Diagnosis

The research activities in the area of computer-aided image analysis for tuberculosis (TB) screening from X-ray image can be broadly divided into two categories: (1) the first category is the computer-aided screening and scoring algorithms using chest radiographic features for the TB diagnosis [6-13]. Research activities in this category focus on developing different types of visual features and classification algorithms to score and screen different types of TB manifestations. Most of the papers employ texture features (e.g., Local binary patterns (LBP) [24, 25], Daubechies wavelets [26]) or geometry features (e.g., circularity, Hessian shape features). The classification algorithms employed in these papers range from simple threshold-based approach or k-nearest neighbors (K-NN) algorithm to more complicated methods, such as Decision tree and Support Vector Machine (SVM); (2) the second category of related work is focusing on X-ray image categorization on the organ and pathology level [14]. The main stream methodology in this area is based on local patch representation of the image content (e.g., visual bag of words (Visual BoW) approach). This type of dense sampling of simple features are then feed to non-linear kernel-based classifier, such as SVM classifier. The ultimate goal is to discriminate between healthy and pathological cases. It is also shown that this type of methods can successfully identify specific pathologies in a set of chest radiographs

III. Proposed Approach

The main objective of our research is to design and deploy a reliable, safe and secure, simple to use, and power efficient mobile phone-based cloud computing system to screen the chest radiography image with improved accuracy and reader consistency. As shown in figure 1, our proposed system utilizes traditional client-server (CS) architecture, which includes a client using mobile devices (e.g., smartphone, as shown in the left rectangle in Figure 1), and a remote server (e.g., server at Amazon AWS cloud computing services [27], as shown in the right rectangle in Figure 1). The client and server are communicated via Wi-Fi and/or cellular network with data encrypted using Secure Shell (SSH) to ensure the security and privacy.

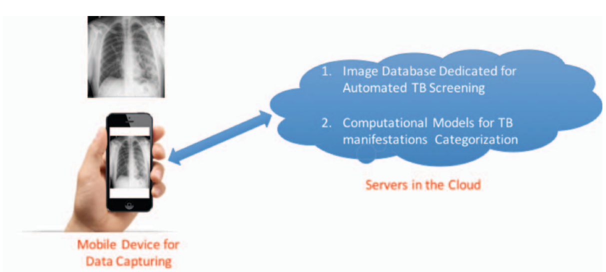


Figure 1. Overview of the proposed mobile phone-based system for improving the TB diagnosis.

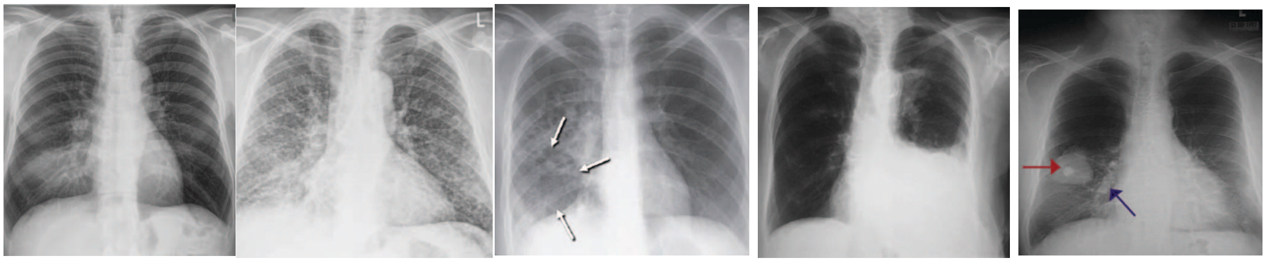
In this paper, we will focus on the introduction of the two major processed we have made recently. As shown in the right side of Figure 1, the first activity is to develop a large-scale, real-world and well-annotated X-ray image database dedicated for automated TB screening. The second research activity focus on developing effective and efficient computational models to classify the image into different categories of TB manifestations. We will introduce this two progresses in the following two sub-sections.

A. To investigate, develop, and evaluate a large-scale, real-world, and well-annotated, chest X-ray image database and related software tools

1) Technique Challenges: The main challenge in this component includes: (1) where and how to gain access to the real-world, large scale TB screening images with detailed diagnostic descriptions; (2) to determine the types of TB manifestations we should target and how we can use these manifestations to annotate each X-ray images; and (3) to develop dedicated annotation software and database management software package for reviewing the chest radiography, locating important contents, annotate them, and extract the annotated contents for research, teaching, and training purposes.

2) Proposed Approach: To address the first challenge, we established an international research team which include scientists from both U.S. and Peru. One of the core team members is Dr. Jesus Peinado, header of Informatics at Partners In Health at Peru. In the past three years, his team in Peru has collected around 5,000 chest X-ray radiography images captured from real-world TB patients with detailed TB screening descriptions. In addition to that, we also explored the second source of image is the X-ray images from the 2004-2013 ImageCLEF collection, which include over 400,000 medical images, diagnostic annotations, search topics and relevance judgments. The 2004-2007 collection [28-30] contains over 66,000 images from a variety of teaching files annotated in English, French or German. The 2008-2010 collection [31-33] contains over 77,000 images and captions from the medical literature. These images were published in Radiology and Radiographics, two of the journals published by the Radiological Society of North America. The 2011-2013 collection [34-37] includes more than 300,000 image and related text annotation from the biomedical literature (e.g., PubMed).

To address the TB manifestation issue, we worked very closely with our clinical and research collaborators, Dr. Jesus Peinado from Peru and Dr. John Bernardo at Boston Medical Center (BMC) and Boston University School of Medicine (BUSM), to generate a scientific categorization of TB



(a) (b) (c) (d) (e)

Figure 2: (a) Air space consolidation which showing glass opacity with consolidation in the right middle lobe; (b) Miliary pattern with seed-like appearance; (c) Cavity located at the lower lobe (annotated by arrows); (d) Pleural effusion, which is excess fluid that accumulates in the pleural cavity; (e) Calcified granulomata: The red arrow indicates a large 5 cm diameter squamous cell carcinoma of the right lower lobe and there is 1.5 cm bright opacity in the middle of the mass (which is a calcified granuloma). Additional calcified granulomatous areas are medial to the mass, as indicated by blue arrow.

manifestations. As shown in Figure 2, we have identified five TB manifestations. There are some important discoveries (which will serve as important motivations and rational for the proposed approach for image analysis and machine learning techniques) from these images. First, the variety of the TB manifestations is very large. Second, each category of TB manifestation actually indicates the severity of the TB disease. Therefore, algorithms that can recognize and classify the X-ray image into different type of TB manifestation can serve the purpose of screen the X-ray image to understanding the severity of the TB disease.

In addition to developing the real-world database, we also developed annotation software for reviewing the chest radiography, locating important contents, annotate them, and extract the annotated contents for research, teaching, and training purposes. While there are many existing efforts in medical image annotations, [38, 39], there is few open source annotation software dedicated to annotating X-ray image to support automatic screening. Based several existing open source annotation software projects [40], we developed a web-based annotation software. As shown in this figure, this software interface includes three panels. The left most panel contain a list of X-ray images from database. The middle panel is the main annotation panel. The right most panel displays existing annotations of the X-ray image.

B.

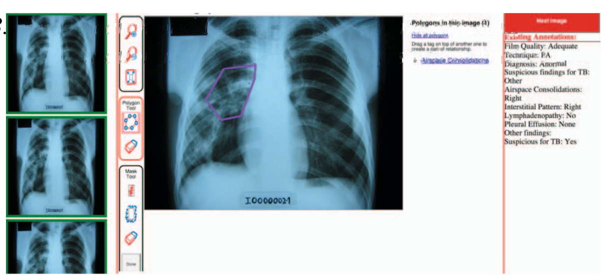


Figure 3: Screenshots of the annotation software

1) Technique Challenges: The The main challenges of automatic TB screening come from the extremely complexity and large variety of the TB manifestations. This is particular true in clinic practice. As we have shown in Figure 2, the variations of TB manifestations can range from subtle military patters to apparent effusions. Via close collaborations and discussions with domain experts, we have discovered that unusual or abnormal TB manifestations affect the texture and geometry of the anatomy. Therefore, most of the existing techniques employ texture and/or geometry features. Usually, different features are useful for different manifestation. For example, texture features, such as Mean, Variance, Entropy, and Third moment, can be employed for detecting infiltration and dense. Local binary patterns (LBP), another type of texture spectrum feature, can be used for cavity detection. Template matching on Fourier domain, a method for geometry feature extraction, maybe useful for detecting the miliary pattern. Hessian shape features, another type of geometry features, could help to detect the nodules. Recently, researchers [6, 9] have shown that combine multiple features can improve the performance of abnormal TB image detection. For example, in paper [9], LBP and histogram of oriented gradients (HOG) are combined for cavity detection. In paper [6], a mixture of Intensity, LBP, and Hessian shape features are employed to measure normal and abnormal patterns in the X-ray image. The literatures have shown that the choice of features play the key role for system performance. Hence, the key issue is how to improve these hand-tuned features. To address these challenges, we plan to explore new solutions based on recent advances in deep learning [41, 42].

Deep learning [41, 42] aims to learn multiple levels of representation and abstraction that help infer knowledge from data such as images, videos, audio, and text, is making astonishing gains in computer vision, speech recognition, multimedia analysis, and drug designing. The impact of deep learning is far reaching on applications in medical, social and commercial domains [43-45]. Briefly speaking, there are two main classes of deep learning techniques: purely supervised learning algorithms (e.g., Deep Convolutional Network [46, 47]), unsupervised and semi-supervised learning algorithms (e.g., Denoising Autoencoders [48, 49], Restricted Boltzmann Machines[50, 51], Deep Boltzmann Machines [52]). Our proposed approach is rooted from Deep Convolutional Neural Network (CNN) [53] and Region-based CNN [54].

2) Proposed Approach: Our main objective is to analyze the X-ray images and to screen the chest radiography image with improved accuracy and reader consistency. We convert the screening problem into a classification problem. More specifically, we will investigate effective and efficient computational models to segment the image into smaller region and classify the image region into different category of TB manifestations (e.g., Air space consolidation, Miliary pattern, Cavity, Bronchiectasis, Opaque, and etc). As shown in Figure 4, our proposed approach include the follwing three steps.

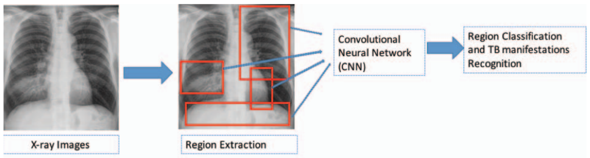


Figure 4: Proposed approach for X-ray image analytics

a) Step 1: Extraction of region proposals: In this step, we will extract regions from the image using different methods like selective search [55].

b) Step 2: Initial Image feature extraction: In this step, we will extract both global and local features from the X-ray images captured by the mobile device. While there exists a large number of global features ranging from color, texture, to edge features, we mainly choose texture and shape features because the cutting edge research in computer-aided TB screening using X-ray imaging have shown that texture and shape features are most effective [6, 9, 14, 24-26, 56-60]. Specifically, we will extract the following global features:

- Gabor features: We will use 48 dimension log Gabor coefficients as features. 24 filters with 6 orientations and 4 scales are used to compute the response, and for each filter response, the first and second moment are extracted
- Local Binary Patterns (LBP) features: We plan to use local binary pattern with uniform patterns extension, which results in a 59-dimension histogram.

For local features, we plan to extract two types of local features.

- The first type of local feature is SIFT features [61] with dense sampling, using 20×20 patches and overlapping windows shifted by 10 pixels. We plan to use the VLfeat library for Dense SIFT extraction.
- The second category of local features is PHOG [62]. We plan to use 3400 dimensional pyramid histogram of oriented gradient with 4 bin histogram and 3 level pyramid (K = 4, L = 3). In addition to feature extraction algorithms, we also have well designed plan for implementation to ensure the software is reliable, simple to use, and power efficient.

c) Step 3: Deep Convolutional Neural Network (CNN)-based X-ray Image Analysis:. Recall in our first step, we have extracted some features from the original image. Hence, we do not need to transmit the entire image. Instead, we resize the image at mobile phone and only transmit the image with much smaller size. In our preliminary test, we reduce the size by half and the results are still acceptable. By doing so, our system will consume substantially less power, compared with transmitting the original image. Another contribution in this component is that we plan to employ the deep convolutional neural networks (CNN) [54, 63] for region classification. Our proposed techniques are rooted from recent advances on deep learning, such as region deep convolutional neural networks [54], which take full use of region features. As shown in Figure 4, there are several steps in this approach:

Extraction of region proposals: In this step, we will extract regions from the image using different methods like selective search [55]. For each region, train a CNN model to calculate the new features for further classification. Please note, before we perform the feature extraction process, the region should be scaled to a fixed size 227x227 (in order to the same vector dimension in our further handling). After the above handling, we should generate a 4096-dimensional feature vector. The features from CNN will be combined with features originally transmitted from mobile phone. We will apply the linear classifier like Support Vector Machine (SVM) [64], the combined features for final region classification and TB manifestations recognition. For the implementation purpose, we use the open source Caffe [65] for training. The training of the proposed CNN approach could include two steps: (a) supervised training on a large dataset using CNN; (b) fine-tuning the CNN feature for detection using a smaller dataset. Our preliminary study has shown the feasibility of the proposed approach for a small group of images. In this study, we plan to extend and refine our preliminary results to large scale, real-word X-ray image datasets.

IV. Experimental Results

In this section, we present our experimental results, which includes the data set used in our experiments and the reported accuracy.

The dataset we used is provided by Dr. Peinado (one of the core team members from Perú). This dataset includes 4701 images. There are 453 normal images (from patients without TB) and 4248 abnormal images (from patients with different types of TB manifestations).

The first experiment we conducted is the binary categorization. This means our goal is to classify any X-ray TB image into two categories: normal and abnormal. We adapt the GoogleNet model [53] from Caffe [65] as the pre-training model, which was generated by a supervised training procedure from a very large dataset (ImageNet [66]). Then we use the 4701 images from our Perú collaborators for finetuning. We used 4/5 of the TB images for training and 1/5 of the images for testing, which is corresponding to 3760 images for training and 941 images for testing, respectively. The results (average precisions after certain number of iterations) are listed in Table 1 below. From this table, we can tell that we can achieve 89.6% of accuracy for binary classification (normal/abnormal). Please note, we achieve this performance without using any pre-processing techniques. The input to the system is the raw image pixels. Therefore, this number (89.6%) is very impressive considering the fact that we only using raw pixels.

# of Iterations	10,000	30,000	50,000	80,000	100,000
Average Precisions	*82.8%*	*88.6%*	*89.0%*	*89.5%*	*89.6%*

Table 1: Average precisions for binary classification

The second type of experiments we conduct is multiclass categorization. We use the same GoogleNet model as the previous experiment, and also 4/5 of images for training and 1/5 of images for testing. But in this experiment we add more categories named specific TB manifestation. In these experiments, our goal is to classify the TB X-ray images into multiple categories. Each category is corresponding to one of the TB manifestations. Table 2 below illustrates the characteristics of the data

Category (Name of TB Manifestations)	Total Image #	Image # Used for Training	Image # Used for Testing
Cavitation	1182	946	246
Lymphadenopathy	202	162	40
Infiltration	2252	1802	450
Pleural Effusion	560	448	112

Table 2: Characteristics of the Data Distribution in the Second Experiments

Table 3 shows the results of the multi-class categorizations. From this table, we can tell that we can achieve 62.07% of accuracy for multi-class classification. We believe there are several reasons contributing the low accuracy: (1) The input to the system is the raw image pixels and we did not use any pre-processing techniques; (2) We are performing multiclass categorizations. The intra-class differences are large while the inter-class differences are small. Due to the space limit, we did not draw the table showing the confusion matrix.

# of Iterations	10,000	30,000	50,000	80,000	100,000
Average Precisions	*43.48%*	*61.68%*	*61.92%*	*62.05%*	*62.07%*

Table 3: Average precisions for multi-class classification

V. Conclusions and Future Directions

According to the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), Tuberculosis (TB) is one of the world's deadliest diseases. One third of the world's population is infected with TB. In 2014, 9.6 million people around the world became sick with TB disease. The majority of the infected populations was from resource-poor communities with weak healthcare infrastructure. Mobile technologies have the potential to reduce the burden of TB by providing mobile computing and communication techniques and devices for better diagnosis, treatment and prevention in these marginalized communities. The ultimate goal of our research is to reduce patient wait times to be diagnosed with TB by implementing a socio-technical solution to optimize the diagnosis process. As the first step of this research project, in this paper, we introduce the two major progresses we have made. The first progress is to build a large-scale, real-world, and well-annotated chest X-ray image database dedicated for TB screening. The second progress is to develop effective and efficient computational model for TB manifestation categorization. Preliminary results have demonstrated the feasibility of the proposed approach.

Based on the proposed framework and the preliminary work reported in this paper, our final goal is to produce a scalable solution to improve healthcare system in Perú, and globally, with mobile technologies. We will continue to develop the large scale, real-world X-ray TB database, as well as continuing to improve the performance of the computing algorithms. We will also implement a scalable solution by making the mobile device-based computer-aided system available as an open source software platform. We will conduct field-testing in tuberculosis clinics in the city of Carabayllo (Lima, Perú).

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