

Classification for Pathological Images Using Machine Learning

Project Plan

Chi Ian Tang

Supervisor: Dr. S. M. Yiu

27 September 2017

Contents

1	Introduction	3
1.1	Background	3
1.2	Problem Statement	3
1.3	Objectives	3
1.4	Related Works	3
1.5	Outline	4
2	Scope and Deliverables	4
2.1	Project outcomes	4
2.2	Data labelling tool	4
2.3	Automated diagnostic system for bacterial vaginosis	4
2.4	A report on limits and general strategies of applying machine learning techniques in medical context	4
3	Methodology	5
3.1	Prerequisites	5
3.1.1	Hardware	5
3.1.2	Software	5
3.1.3	Data	5
3.2	Image Processing	5
3.3	Classification	6
3.4	Interpretation	6
3.5	Performance Evaluation	7
4	Project Management	7
4.1	Role and Responsibilities	7
4.2	Risks	7
4.2.1	Low Quality Specimen Image	7
4.2.2	Different Staining Techniques	7
4.2.3	Low number of training samples	7
4.3	Project Schedule	7
4.3.1	Preparation Stage	7
4.3.2	Summer Internship	8
4.3.3	Final Year Project	8
5	Conclusion	9
6	References	10

1 Introduction

1.1 Background

Bacterial infection is very common medical condition in human, and several pathogens were found to be responsible for the development of malignant tumors [1]. Bacterial vaginosis (BV), one of the most common bacterial infection in the vagina, was estimated to affect tens of millions of people in the US alone [2]. The prevalence of this infection varies by countries, and can be as high as 50% [1], and studies have shown that this infection increases the risks of being infected with human immunodeficiency virus [1, 3]. The Nugent Score System [4], which involves the investigation of gram-stained vaginal smears from patients, is considered to be the Gold Standard in diagnosing bacterial vaginosis from various sources [1, 5, 6]. In addition, diagnostic microscopy is also the main diagnostic method of parasitic infections, including Malaria, in major hospitals [7, 8] .

1.2 Problem Statement

Diagnostic microscopy, however, requires a considerable amount of training and skills, where the accuracy often depends on how experienced the microscopist is [6, 9]. Furthermore, it could be rather time-consuming since it involves human diagnosis, and hence could be expensive for patients. In the light of the prevalence and consequences of aforementioned infections, an automated process could reduce the dependence on human expertise and provide a more affordable way to perform diagnosis.

1.3 Objectives

This project aims to explore the possibilities in employing machine learning and computer vision techniques in diagnostic microscopy, such that an integrated, automated diagnosis system for bacterial vaginosis will be developed, and the time and cost of bacterial vaginosis diagnosis could be reduced.

In addition, general strategies as well as limitations of applying machine learning and computer vision techniques in medical context will be explored, such that this project could be used as a guideline for future projects using similar techniques.

1.4 Related Works

A number of recent studies made use of a range of computer vision and machine learning techniques on diagnostic microscopy. In particular, Quinn et al. [10] explored the use of convolutional neural networks in detecting several infections including tuberculosis and hookworm. Kraus et al. [11] combined convolutional neural networks and image segmentation with multiple instance learning. These studies showed that deep learning techniques had a range of advantages in diagnostic microscopy and saw significant improvements over traditional techniques.

1.5 Outline

The rest of the project plan starts by showing the scope and the deliverables of this project. Following that is the methodology that we employ in this project, in order to implement the corresponding components of the deliverables. The project management information is provided in the next section, followed by a short conclusion.

2 Scope and Deliverables

2.1 Project outcomes

This project focuses on exploring the strategies in applying machine learning techniques in medical context. In particular, an automated system for diagnostic microscopy of bacterial vaginosis is the main problem that this project focuses on. Related tools including data collection, image processing and model training tools will be developed. The general strategies of applying such techniques will be proposed using the implemented system as a sample.

2.2 Data labelling tool

A simple auxiliary tool for labelling the microscopic images was developed to facilitate detailed data labelling, which will then be used to train machine learning models. This allows the user to load an image and perform labelling by clicking the interest areas, and export all labels in a single file for further processing.

2.3 Automated diagnostic system for bacterial vaginosis

The first main objective of this project is to develop an automated diagnostic system for bacterial vaginosis with desirable accuracy, similar to that of a human. Most of the components will be written in Python and Lua, and a simple wrapper user interface will be developed. A trained classifier will be the core of this system, with other processing modules supporting the overall flow of the system, including image processing, segmentation, interpretation tools. This system will allow the user to select images and get predictions on degree of infection.

2.4 A report on limits and general strategies of applying machine learning techniques in medical context

After the development of the aforementioned diagnostic tool, limits including number of training samples required, the time required to train the model in the development of such systems will be explored. Furthermore, the recommended architecture of the machine learning module, techniques in image pre-processing will also be discussed in the report if time allows. Finally, the lesson learnt from developing such tool will be included in the report such that this system can act as an example in applying machine learning in medical microscopy.

3 Methodology

In this project, images of stained blood films acquired from microscopes will be processed and used as inputs. Typically, the process involves following stages: image pre-processing, segmentation, and classification [12]. An interpretation of the classified segments of images is then carried out afterwards. This requires both hardware and software support. In addition, for the classification task, images annotated with positions and types of bacteria, as well as the degree of infection (on a scale from 0 to 10, also known as the Nugent Score [4]) by microscopists / experts will be used. The aim is to develop a model with high accuracy in estimating the degree of infection by examining a blood film image through different image processing techniques and machine learning models.

3.1 Prerequisites

3.1.1 Hardware

The access to GPUs (Graphical Processing Units) will be required for training machine learning models.

3.1.2 Software

Machine learning, computer vision and graphics libraries will be required in order to reduce the time spent in developing such tools and to focus on the development of the diagnostic tool. A number of wide-available libraries including Torch, PyTorch, Tensorflow, etc. are identified and the programming languages used will be Python and Lua.

In addition, Java will also be used to develop assistant programs for microscopists in annotating the images.

3.1.3 Data

Images of stained smears of varying degrees of bacterial vaginosis infection will be provided by the medical experts which are collected with the consent from the patients. Also, images of bacterial colonies will also be provided by the medical experts.

3.2 Image Processing

Different image processing techniques will be employed to reduce the variations between training samples and hence to increase the reliability of our machine learning models. This will involve the following stages:

1. **Pre-processing**

At this stage, variations between images due to different background lighting, degree of staining and image acquisitions techniques will be calibrated. Images may vary in illumination level, scale, noisiness, etc. Noises in images can be removed by applying Gaussian filters, or other morphological filtering methods.

Illumination level, on the other hand, can be effectively calibrated by subtracting an empty film (control image) [12], thresholding or analysing the histogram and apply

histogram transformation. Finally, the variations in the scales of images, if not handled properly, could result in meaningless estimations from the model. This can be solved when the magnification of the microscope is known. However, if the information is not available, we can rely on the assumption that healthy human red blood cells and platelets have similar sizes and a more advanced technique called granulometric analysis can be used to estimate the sizes of the cells and scale accordingly [12]. Different combinations of aforementioned techniques will be explored in this project.

2. Segmentation

Segmentation mainly involves dividing the image into areas of interest. This can be done by separating the image into foreground and background, or a hierarchy of separation down to object level [12]. However, these techniques usually cannot achieve perfect separation of cells, especially in a thick blood film image, due to the nature of overlapping cells. An alternative is directly selecting stained pixels and feed the local neighbourhood into the classifier using the Sliding-Window method.

3.3 Classification

After the segmentation stage, areas of interests or local frames of the images will be identified. A classifier which distinguishes between target bacteria from the rest, or ideally, into separate categories such as lactobacillus, gardnerella, curved rods, etc. will be developed. In addition, different techniques in determining the number of bacterium in each area of interest will also be explored. Techniques including neural networks, support vector machine and fuzzy logic and others may be employed. Here convolutional neural networks will be used as the main technique:

Convolutional neural network

Since the segmented areas are essentially a part of the image, convolutional neural network is a very good candidate for the classifier. A convolutional neural network starts with an input image and subsequently applies convolutions (filtering) and sub-sampling (max pooling) until the output layer which indicates the likelihood of being in a certain category is reached. During training, the weightings (parameters) in the neurons are adjusted to fit the expected outcome. Using this model, different bacteria can be effectively distinguished and the segmented areas can be categorised into their corresponding classes. A range of hyper-parameters of such model including the number of layers, size of filters, loss function, etc. will also be explored.

3.4 Interpretation

Finally, after identifying the number of different bacteria present in the blood smears, a final data analysis which estimates the degree of infection will be done. The number of bacteria in each category of the Nugent Score System will be identified and an overall interpretation will be made.

3.5 Performance Evaluation

The performance of the models will be evaluated by determining the accuracy of the predictions for images which not used in training the model. A coarse accuracy which is determined by correctly identifying the general degree of infection (Normal, Intermediate and infected), and a fine accuracy which is dependent on the amount of exact matches to the Nugent Score (from 0 to 10) [4] will also be calculated.

4 Project Management

4.1 Role and Responsibilities

This is an individual project where I am the main role in developing the system and responsible for implementing image processing modules, training machine learning models and analysing performance. I will also analyse previous works and integrate into the system, as well as explore new ways to solve the problem and integrate into the system.

4.2 Risks

Although ideally our image processing should be able achieve handle smears collected in various conditions and produce predictions of human-level accuracy, there could be some corner / special cases where our system fails to adapt:

4.2.1 Low Quality Specimen Image

It is possible that the image is under-illuminated or blurred. In such cases, the image processing stage might not be able to calibrate to the standard illumination and fail to identifying areas of interest.

4.2.2 Different Staining Techniques

Separate image processing techniques might need to be employed if different staining chemicals / techniques are used. This requires separate investigation into each technique.

4.2.3 Low number of training samples

The number of labelled smears provided by the medical experts might be low, which might lead to a not-generalised diagnostic tool. This might be mitigated by increasing the size of the training dataset by transformation on the images. However, a clean and sufficient training set is still very crucial to the accuracy of the diagnostic tool.

4.3 Project Schedule

4.3.1 Preparation Stage

Time: February 2017 to June 2017

Acquired background knowledge about diagnostic microscopy, image processing and machine learning during my exchange study at University of Cambridge, including a machine learning project and a course in Artificial Intelligence.

In addition, communicated with Dr. S.M. Yiu on internship arrangements, details of project implementation, etc.

4.3.2 Summer Internship

Time: June 2017 to August 2017

The summer internship started by settling down and finalising the plan for the internship. Learn further knowledge on topics in the first two weeks. The basic frame work of the project is then confirmed, and image processing modules and basic machine learning modules were implemented.

4.3.3 Final Year Project

1. Phase 1

Item	Finished by
Training of first badge of machine learning models and the analysis of their performance	14 September 2017
Meetings with experts from medical background to get feedback for the models	20 September 2017
Development of a simple graphical user interface facilitating data collection suggested by the medical experts	22 September 2017
Submission of detailed project plan and development of project web page	1 October 2017

2. Phase 2

Item	Finish by
Further investigation into image processing modules, especially in terms of segmentation	21 October 2017
Training of second badge of machine learning models based on the new data and new image processing techniques	14 November 2017
Fine-tuning all modules and integration into a working system for bacterial vaginosis diagnosis	31 December 2017
First presentation	8 - 12 January 2018
Submission of interim report	21 January 2018

3. Phase 3

Item	Finish by
Exploration of the limits of machine learning techniques in medical context	14 March 2018
Propose potential improvements and general strategies in applying such techniques	31 March 2018
Final fine-tuning of the integrated diagnosis system	31 March 2018
Submission of final report	15 April 2018
Project exhibition	2 May 2018

5 Conclusion

In this project, we aim to develop an automated diagnostic tool for bacterial vaginosis which makes use of various machine learning and computer vision techniques. This system will then be used as an example to show the general strategies and limitations in the development of diagnostic systems in similar context.

6 References

- [1] C. Kenyon, R. Colebunders and T. Crucitti, “The global epidemiology of bacterial vaginosis: a systematic review”, *American Journal of Obstetrics and Gynecology*, vol. 209, no. 6, pp. 505-523, 2013.
- [2] E. Koumans, M. Sternberg, C. Bruce, G. McQuillan, J. Kendrick, M. Sutton and L. Markowitz, “The Prevalence of Bacterial Vaginosis in the United States, 2001-2004; Associations With Symptoms, Sexual Behaviors, and Reproductive Health”, *Sexually Transmitted Diseases*, vol. 34, no. 11, pp. 864-869, 2007.
- [3] J. Atashili, C. Poole, P. Ndumbe, A. Adimora and J. Smith, “Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies”, *AIDS*, vol. 22, no. 12, pp. 1493-1501, 2008.
- [4] R. P. Nugent, M. A. Krohn, and S. L. Hillier, “Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation”, *Journal of clinical microbiology*, vol. 29, no. 2, pp. 297-301, 1991.
- [5] B. Sha, H. Chen, Q. Wang, M. Zariffard, M. Cohen and G. Spear, “Utility of Amsel Criteria, Nugent Score, and Quantitative PCR for *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Lactobacillus* spp. for Diagnosis of Bacterial Vaginosis in Human Immunodeficiency Virus-Infected Women”, *Journal of Clinical Microbiology*, vol. 43, no. 9, pp. 4607-4612, 2005.
- [6] [6]R. Chawla, P. Bhalla, S. Chadha, S. Grover and S. Garg, “Comparison of Hay’s Criteria with Nugent’s Scoring System for Diagnosis of Bacterial Vaginosis”, *BioMed Research International*, vol. 2013, pp. 1-5, 2013.
- [7] World Health Organization. (2017, March 14). *Microscopy* [Online]. Available: <http://www.who.int/malaria/areas/diagnosis/microscopy/en/>. [Accessed 2017, September 27]
- [8] K. C. Hazen. (2016, October). *Microscopy* [Online]. Available: <http://www.merckmanuals.com/professional/infectious-diseases/laboratory-diagnosis-of-infectious-disease/microscopy> [Accessed 2017, February 13]
- [9] K. Petersen, “Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, 7th Edition Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, 7th Edition Edited by Gerald L. Mandell , John E. Bennett , and Raphael Dolin Philadelphia, PA: Churchill Livingstone Elsevier, 2009. 4320 pp, illustrated.”, *Clinical Infectious Diseases*, vol. 51, no. 5, pp. 636-637, 2010.
- [10] J. A. Quinn, R. Nakasi, P. KB Mugagga, P. Byanyima, W. Lubega, and A. Andama. “Deep convolutional neural networks for microscopy-based point of care diagnostics.” In Machine Learning for Healthcare Conference, pp. 271-281. 2016.

-
- [11] O. Kraus, J. Ba and B. Frey, “Classifying and segmenting microscopy images with deep multiple instance learning”, *Bioinformatics*, vol. 32, no. 12, pp. i52-i59, 2016.
- [12] F Boray Tek, Andrew G Dempster and Izzet Kale. 13 July 2009. *Computer vision for microscopy diagnosis of malaria*. Malaria Journal 2009 8:153. Accessed from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719653/pdf/1475-2875-8-153.pdf>