University of Essex

Detecting Malaria Parasites in Red Blood Cells using Machine Learning

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Most of all, I would love to thank my close family for their constant support throughout my education. I would not have been able to reach this point without them.

Abstract

Malaria has a major impact on global health, with an estimated 229 million cases and more than 409,000 deaths worldwide in 2019 alone. Most of these cases occur in less economically developed countries where the testing facilities are poor. Typically, the malaria testing procedure requires microscopists to manually count the malaria parasites in red blood cell samples. The calibre of this process depends on the proficiency of the microscopist and facility quality. Therefore, to eliminate human error and increase testing speed, Machine Learning (ML) can be used to automate the testing process.

I specifically utilise a Convolutional Neural Network (CNN) to classify red blood cells as either parasitized or healthy. To iteratively increase my classifiers' accuracy, I use a broad range of ML techniques such as: data augmentation, regularisation, and feature map visualisation. Using these techniques, the model has so far achieved an accuracy of 95.6% on previously unseen test samples.

To accommodate the classifier, I design a convenient application with an intuitive interface. It is vital that the application has wide accessibility, as its main use is in less economically developed countries. Consequently, the application can be used on almost any device.

Contents

Frequently Used Acronyms

ML → Machine Learning

CNN, ConvNet → Convolutional Neural Network

DL → Deep Learning

ReLU → Rectified Linear Unit

RGB → Red, Green, Blue (whilst referring to an image)

UI → User Interface

WHO → World Health Organisation

RDT → Rapid Diagnostic Test

NIH → National Institutes of Health

Main Text

Context & Literature Review

Introduction

Artificial Intelligence (AI) has the potential to revolutionise the healthcare sector, as it has the capability to use and interpret information in a similar manner to human cognitive functions. Additionally, it has the added power of being proficient at handling large quantities of data. One form of AI, Machine Learning (ML), has led to advances in the use of AI in medical diagnosis. Accurate ML algorithms have the capability to increase efficiency where human error is inevitable in medical settings, identify costly medical errors, reduce costs, and ease the workload of overburdened doctors. Within medicine, ML has been identified as having transformational capabilities in less developed countries. These countries are often lacking in medical facilities and specialists. A specific area in which ML could make a real difference is the accurate diagnosis of malaria. Many developing countries face the ongoing challenges of malaria epidemics and could benefit from malaria classification using an accurate ML model.

The Effect of Malaria

Malaria has a major impact on global health. It's a blood disease caused by Plasmodium parasites, which are transmitted through an Anopheles mosquito bite [1]. In 2019, there was an estimated 229 million cases of malaria worldwide [2]. This seems to be very consistent year on year; with 225 million cases in 2009 [3] and 212 million cases in 2015 [4]. The majority of cases occur in less economically developed areas. For instance, 94% of cases occur in the World Health Organisation (WHO) African Region, this can be visualized via figure 1 [2]. According to the WHO [2], only five countries account for more than 51% of all malaria cases. These include Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%), Mozambique (4%), and Niger (3%). Figure 2 displays the global percentage distribution of each country's malaria cases.

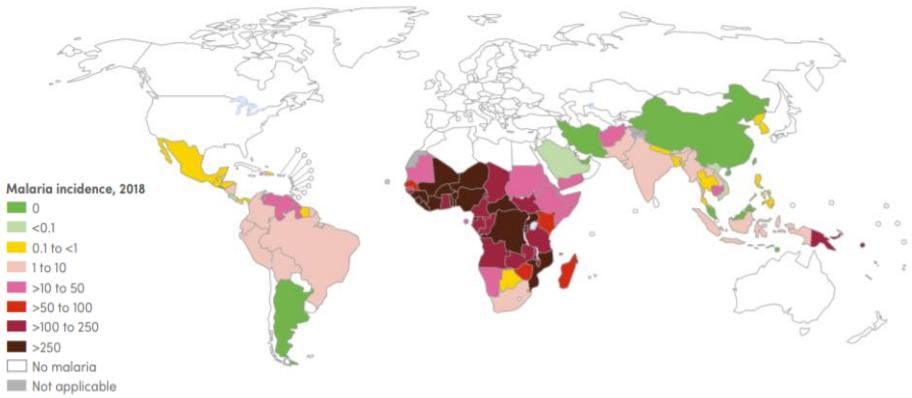

Fig 1. Map of malaria case incidence rate (cases per 1000 population at risk) by country (2018) [5].

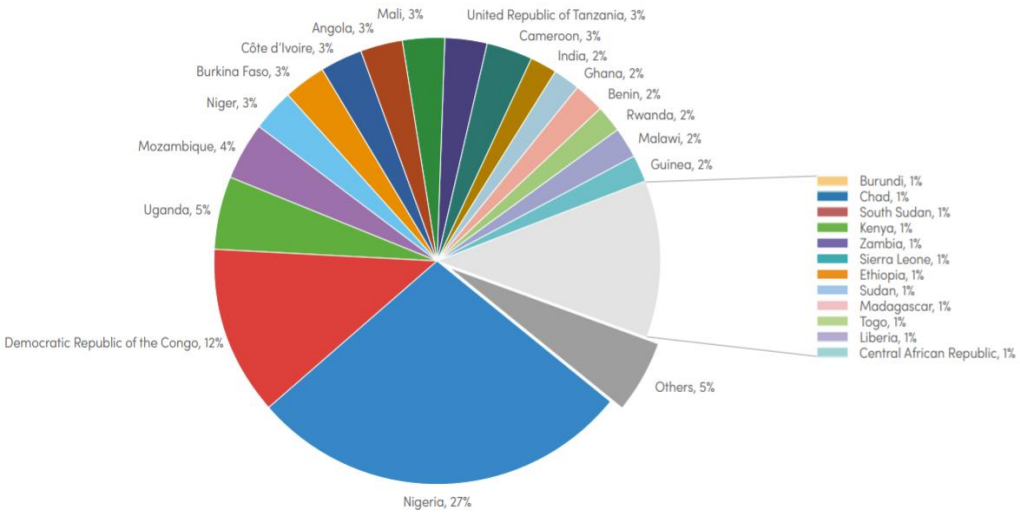

Fig 2. The distribution of malaria cases per country (2019) [2].

This, however, doesn't tell the whole story as yearly there is a considerably high number of malaria deaths. In 2019 there were an estimated 409,000 deaths worldwide, with 384,000 of these deaths (~93%) originating in the WHO African region [2]. Furthermore, the majority of deaths, 84%, were recorded in children under the age of 5 years [2]. Although these figures have significantly reduced from 736,000 deaths worldwide in 2000, automated classification would aid the crucial testing process. Thus, reducing the number of fatalities.

There are 5 different species of Plasmodium (single-celled parasites) that cause malaria in humans. These are: Plasmodium falciparum, malariae, vivax, ovale and knowlesi [1]. It is estimated that in 2018, 99.7% of malaria cases in the WHO African Region were caused by the Plasmodium falciparum parasite. Whereas, Plasmodium vivax is more likely to be found outside of Africa, accounting for 75% of malaria cases in the WHO Region of the Americas [6].

Testing for Malaria

The WHO [7] recognises two main methods of diagnostic testing: Microscopy and Rapid Diagnostic Testing (RDT). Microscopy is the most frequently used form of malaria diagnostics, in most large health clinics & hospitals, which necessitates hundreds of millions of blood films being examined by a trained microscopist every year. This process involves the manual counting of parasites and infected red blood cells. Microscopic diagnostics are not standardized. Consequently, testing relies solely on the experience/skill of the microscopist [8] [9]. In less economically developed countries, the microscopist only has access to a small number of resources and a poor-quality controlled environment. RDT is an alternative form of malaria testing that quickly detects malaria parasites (antigens) in an individual's blood. This method of testing is generally used in more remote areas, where there is limited access to microscopy equipment and expertise [10] - Unfortunately, this testing method has some degree of inaccuracy. Various studies have been carried out to ascertain the

accuracy of RDT's. For example, a study carried out among under 5's in Nigeria in 2015 resulted in an overall diagnostic accuracy of only 79% [11]. As a result, both methods can lead to an incorrect diagnosis, thus leading to one of two outcomes:

- False positives: defined as incorrectly tested as positive, when negative. This leads to undue stress, the unnecessary use of anti-malaria drugs, and the possible suffering from side effects. These can sometimes be extreme and complicated [11].
- False negatives: defined as incorrectly tested as negative, when positive. Subsequently, treatments are not used, which leads to chronic stages of the disease or even death [11].

Why Automate the Testing Process using AI?

The WHO states [10], *'Early and accurate diagnosis of malaria is essential for both rapid and effective disease management and surveillance. High-quality malaria diagnosis is important in all settings as misdiagnosis can result in significant morbidity and mortality'*. Consequently, automating the testing process using AI has a large role to play in accurately diagnosing malaria, as it has many advantages over its manual counterparts. For example, Dr. Petru Manescu from UCL Computer Science [12] explains that Microscopy, the visual inspection of malaria blood samples, relies heavily on the disposal of skilled technicians and is also time-consuming and open to human error caused by fatigue and workload pressures. AI malaria classification allows more patients to be tested in a shorter amount of time, as the workload will be reduced on the microscopists. This allows the microscopists to work on higher-level consultative tasks. Furthermore, reducing the workload will reduce the costs of testing, thus making it more accessible to remote areas. Additionally, AI diagnostic methods require less specialist laboratory equipment making it less costly and more obtainable in remote locations. With an accurate model, the testing process can be more reliable as human error is eliminated. Testing accessibility (within remote areas) is vital, especially due to concerning figures found in the WHO Malaria Report 2019 [5]:

'Testing was also worryingly low in children who were brought for care, with 30% or less being tested in Cameroon, the Democratic Republic of the Congo and Nigeria.'

It should be noted that Nigeria accounted for ¼ of all malaria cases in the same year (2018) [5].

Machine Learning

Machine Learning (ML) is a subset of Artificial Intelligence based on the idea that systems can identify patterns within data and make decisions with little human interaction [13]. ML systems learn using some form of data, for example, images of cats and dogs could be used to teach a system what both animals look like. Generally, ML algorithms are categorized as either supervised or unsupervised. We may use supervised learning algorithms where pre-specified data labels are used by the ML algorithm when learning to classify data. For instance, an algorithm would be fed

images of cats and dogs with labels (‘cat’ or ‘dog’). It will learn what each species looks like using these labels. On the other hand, unsupervised learning algorithms are used when the provided data is unlabelled [14]. Machine Learning algorithms require minimal human intervention, and thus, can minimise or eliminate the risk of human error. There are many forms of image classification algorithms, however, Convolutional Neural Networks (CNNs) are one of the most prevalent and would be valuable for detecting malaria parasites in red blood cells.

Convolutional Neural Networks

Convolutional Neural Networks are highly popular for image classification problems and incredibly influential in ML. Although neural networks have been around for decades, there was a breakthrough in 2012 with a CNN labelled ‘AlexNet’ [15] [16]. This was a Convolutional Neural Network designed by Alex Krizhevsky (with Ilya Sutskever and Geoffrey Hinton) who substantially improved on previous CNN error rates. They entered a variant of their model into the ILSVRC-2012 competition, achieving a winning top-5 test error rate of 15.3%, compared to 26.2% achieved by the second-placed entry [15]. Due to the vast improvements of CNNs in recent times, I’ll be looking deeper into their mechanisms and applying them to this problem.

A Convolutional Neural Network learns, or ‘trains’, similarly to a child; it is taught a subject using examples and learns from its misclassifications. CNNs attempt to abstract features when propagating towards the deeper layers. For instance, edges may be detected in the first layers, simple shapes in the second layers, and finally higher-level features in the following layers (such as an animal’s face) [17]. CNNs are biologically inspired by Hubel and Wiesel’s 1962 experiment [18]. Hubel and Wiesel found that individual neurons ‘fired’ based on their orientation and that they had a columnlike architecture, which together could produce visual perception. This structure and idea of neuronal cells looking for specific characteristics is the high-level basis of CNNs [19].

CNN Architecture

The following section discusses the main layers used in a Convolutional Neural Network and how they aid the main functionality of a CNN. Understanding how the architecture is formed is crucial to designing an effective CNN. Moreover, it provides a clearer picture of how CNNs classify images, or in this case how it classifies red blood cells as either parasitized or healthy.

Convolutional (Conv): The convolutional layer applies multiple filters (kernels) to an image, which each identify different features. To do this a filter convolves (slides) around an image (see figure 3) and adds together all the products of the corresponding pixels. The output of this creates a feature map (also known as an activation map) that aids learning and in turn decides an image’s class. As you would expect this is the most important layer in the CNN.

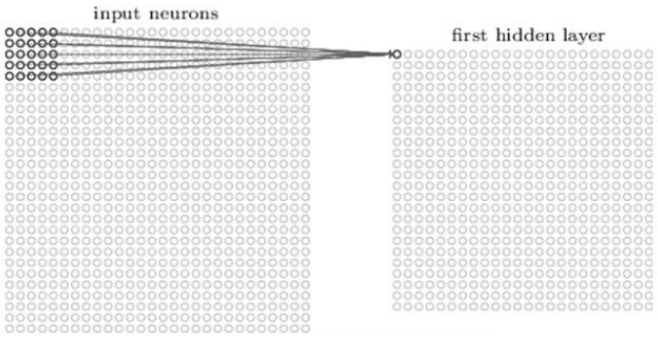

Fig 3. Visualization of a filter convolving around an input volume to produce a feature map [19].

Activation Function (Nonlinearity): Activation functions are applied to a convolutional layer's output and do not form a new layer alone. It computes a "weighted sum" of its input, adds a bias, and then decides if the neuron should be "fired" [20]. The most prominent activation function is the Rectified Linear Unit, which is referred to as 'ReLU'. In basic terms, ReLU returns 0 if a value is negative, but *X* if a value is positive. A visual representation is found in figure 4 below.

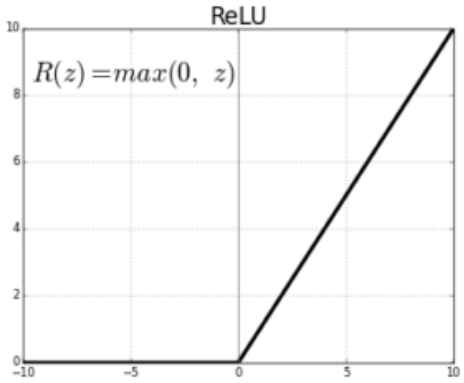

Fig 4. The ReLU Activation Function [21].

Pooling: Pooling layers are used to reduce the spatial size of the representation, thus, also reducing the required computation the network must perform. The best example is max pooling, where the largest number is returned from each *N x N* stride. A visual representation is shown in figure 5.

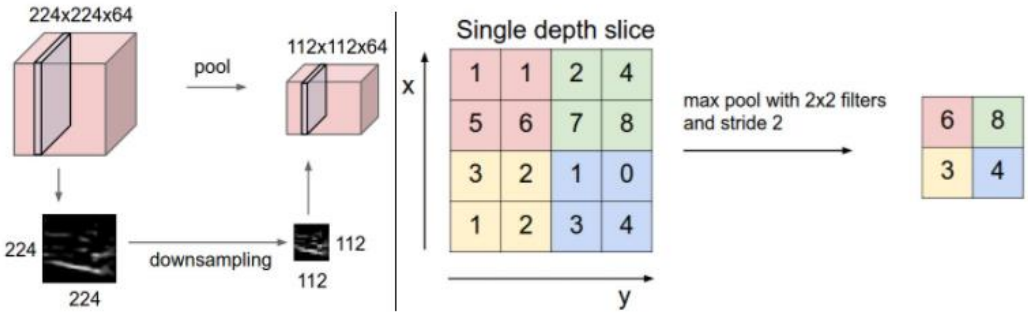

Fig 5. How max pooling works at a high level [22].

Fully Connected: This is the final layer in the network and produces the classification output. This layer takes input from the previous layer and outputs an *N*-dimensional probability vector, where *N* is the number of possible outcomes [19]. In the case of my research, malaria classification only has 2 outcomes, parasitized and uninfected. A fully connected layer works by looking at the previous layer's output and determining which features best correlate to a particular class [19]. These correlations will not be an exact answer; instead, the algorithm will output a weighting of probability. The classification is then made from the maximum of these outputs.

Architecture: An example of how the layers above could be connected is shown using Yann Lecun et al. famous LeNet-5 (1998) [23] (see figure 6). LeNet-5 was specifically designed to classify handwritten digits. Where subsampling occurs in figure 6, pooling would usually take place instead.

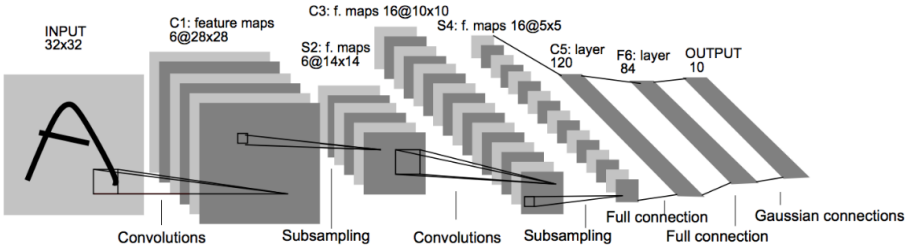

Fig 6. Yann Lecun et al. LeNet-5 (1998) architecture [23].

CNN architecture which was previously designed for malaria detection can be found via S. Rajaraman et al. custom CNN model [24] (see figure 7). Similarly, the architecture is based on LeCun & Bengio's (1995) CNN [25], which they advocated for image classification. When designing an initial CNN model, I will take into account my research, in relation to how these architectures have been built.

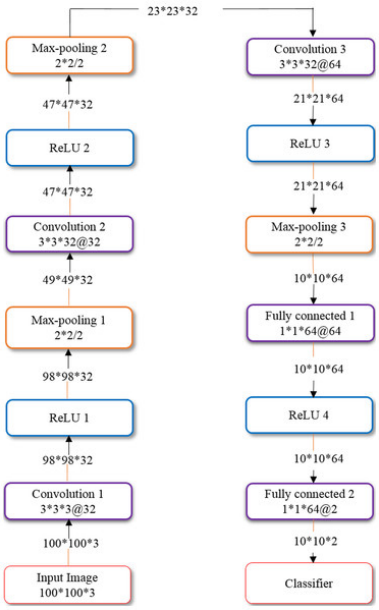

Fig 7. S. Rajaraman et al. custom CNN architecture [24].

Summarised Aims & Objectives

My main project aim is to design and implement a classification tool that identifies malaria parasites in pre-segmented red blood cells. The tool will reduce the workload on microscopists and decrease the need for specialist consultants and equipment. It will reduce testing costs and speed up the process compared to microscopy. In addition, the automated testing process will eliminate human error. These factors will allow less developed countries, where malaria is epidemic, to identify parasitized cases early, leading to less morbidity and mortality.

To achieve these aims, I have outlined the following objectives:

- Design a Convolutional Neural Network using reputable Python ML libraries.
- Through iterative testing, improve CNN model performance (accuracy) using ML techniques.
- When testing the application on unseen samples, the model should achieve a higher test accuracy than the RDT's diagnostic accuracy of 79% (among under 5's in Nigeria, 2015 [11]).
- Create a classification tool that is accessible via almost any device, enabling its use in less developed counties.
- The application should be simplistic to allow easy use for individuals with limited medical knowledge.

Evaluation

The dataset I have selected can be located via the NIH website, please see [26]. The dataset contains 27,558 pre-segmented red blood cells, both from healthy patients and patients infected with the P. falciparum malaria parasite. There is an equal split of infected and parasitized images to reduce bias. All images have been manually annotated by an expert slide reader at the Mahidol-Oxford Tropical Medicine Research Unit in Bangkok, Thailand. When training a CNN model, it is vital to segment the dataset as testing must be done with unseen examples (not used for training the model). Although the segmentation split can depend on the size of the dataset, a good rule-of-thumb, is 80/10/10 [27]. This represents 80% of the dataset for training and 10% for each of validation and testing. Please find a visual example in figure 8.

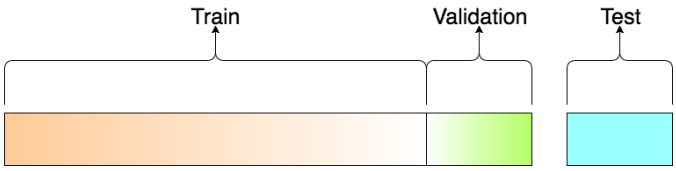

Fig 8. Typical dataset split [27].

To evaluate the performance of the CNN, I use various accuracy metrics, which are calculated as seen in figure 9. To improve upon the CNN model's performance, I utilise the validation partition, to calculate validation accuracy. This metric is used over test accuracy when training to ensure the model can generalise successfully and doesn't just fit to a specific case. However, to evaluate the final model's performance I use the

testing partition to calculate the model's test accuracy. This partition contains unseen samples, which produce an accuracy score for a more real-world scenario.

$$Accuracy = \frac{TrueNegatives + TruePositive}{TruePositive + FalsePositive + TrueNegative + FalseNegative}$$

Fig 9. Accuracy equation [28].

Methodologies

Machine Learning Libraries: TensorFlow (TF) and Keras are two of the most popular and effective Python deep learning libraries. These libraries include all the vital elements for designing and implementing Convolutional Neural Networks. TensorFlow & Keras' modular routines allow for robust ML production whilst still being user-friendly. There are many other Python libraries that are advantageous to the implementation of my CNN. For instance, OpenCV and Numpy are useful for manipulating large datasets and performing intricate mathematical functions with the utmost efficiency. These libraries and more are utilised to implement the classification tool.

Application (User Interface): The user interface is highly accessible and simple to use. It's vital that the classification tool requires the smallest number of resources possible, so that it may be used in less economically developed areas. Taking this into account I create a web application, rather than a mobile application, which is accessible via any device. Consequently, the tools' only access requirement is a device with internet access. To ensure that the user has the best experience when using the tool, I utilise Bootstrap. Bootstrap is a powerful HTML, CSS & JS framework for developing responsive and mobile-first web applications. This framework is very beneficial to ensuring the application works to its full potential on all devices. Furthermore, I utilise the Python Flask library to allow the classification algorithm to interact with the web application.

Legal & Ethical Issues

The growth in the use of AI in healthcare has led to both ethical and legal challenges. In the article, 'Ethical and legal challenges of artificial intelligence-driven healthcare', Gerke et al. identify four ethical and five political challenges of AI [29]. The main ethical issue recognised, the 'informed consent to use', refers to ensuring a patient is aware that AI is being used in the diagnostic process. Therefore, if a microscopist utilises an AI classification application to diagnose a patient, the patient should understand the risks. For instance, the model's performance (accuracy).

The primary legal issue covered, which relates to this project, is 'data protection and privacy' [29]. Therefore, if any patient data is stored it must comply with acts such as the Data Protection Act 2018, which is the UK's version of the General Data Protection Regulation (GDPR). In addition, the dataset used for training the CNN models is publicly available via the NIH website [26]. Thus, I did not need to request its use.

Technical Documentation

The technical documentation contains the main contents of this report. The sections that are covered in the technical documentation are shown in figure 10. Please locate the technical documentation via the 'README.md' file in GitLab:

GitLab: **cseegit.essex.ac.uk/ce301_2020/ce301_harding_kiernan_j_w**

If the link above does not work, please visit the University of Essex's internal GitLab and locate the project using the following information:

Project Name: ***ce301_harding_kiernan_j_w***

Project ID: ***3147***

As a last resort please feel free to contact me via email: ***kjwharding@gmail.com***

Fig 10. The technical documentation contents.

1. **Understanding CNNs in Code**
    - Setting up the Environment
    - Implementing a CNN
2. **Designing Custom CNN Models**
    - Initial Greyscale Model
    - Initial Colour Model
    - Improving the Model
        - Data Visualisation
        - Data Augmentation
        - Regularisation
        - Optimizer Adjustment
        - Feature Map Visualisation
    - Evaluation & Results
    - Discussion
3. **Application Design**
    - Implementation
    - Styling
    - Examples
4. **Installation & Usage**
    - Training Custom Models
    - Application

Project Planning & Management

To manage my project, I employed various tools, such as Jira, Git, and personal timetables/lists. I decided to use a range of management techniques, as some were more suited for the situation or application. When using Jira, I typically used tasks and sub-tasks, which allowed me to produce high-level aims and then provide more specificity with sub-tasks. I appropriately set the issue priority level, story points, due date and commented on any developments or bugs. A good example of how I laid out issues is shown in figure 11. My main project risk was falling behind on the main tasks. Therefore, I always allowed appropriate slack time for each task of approximately 20%, allowing me to easily adapt to any significant project changes. For instance, I came across an issue with installing/running TensorFlow, which took longer than expected to fix. However, due to the added slack time, I did not fall behind. Figure 12 provides a good visualisation of how issues were managed over time. Although Jira was beneficial, I found it to be less valuable when working on a personal project compared to a team project.

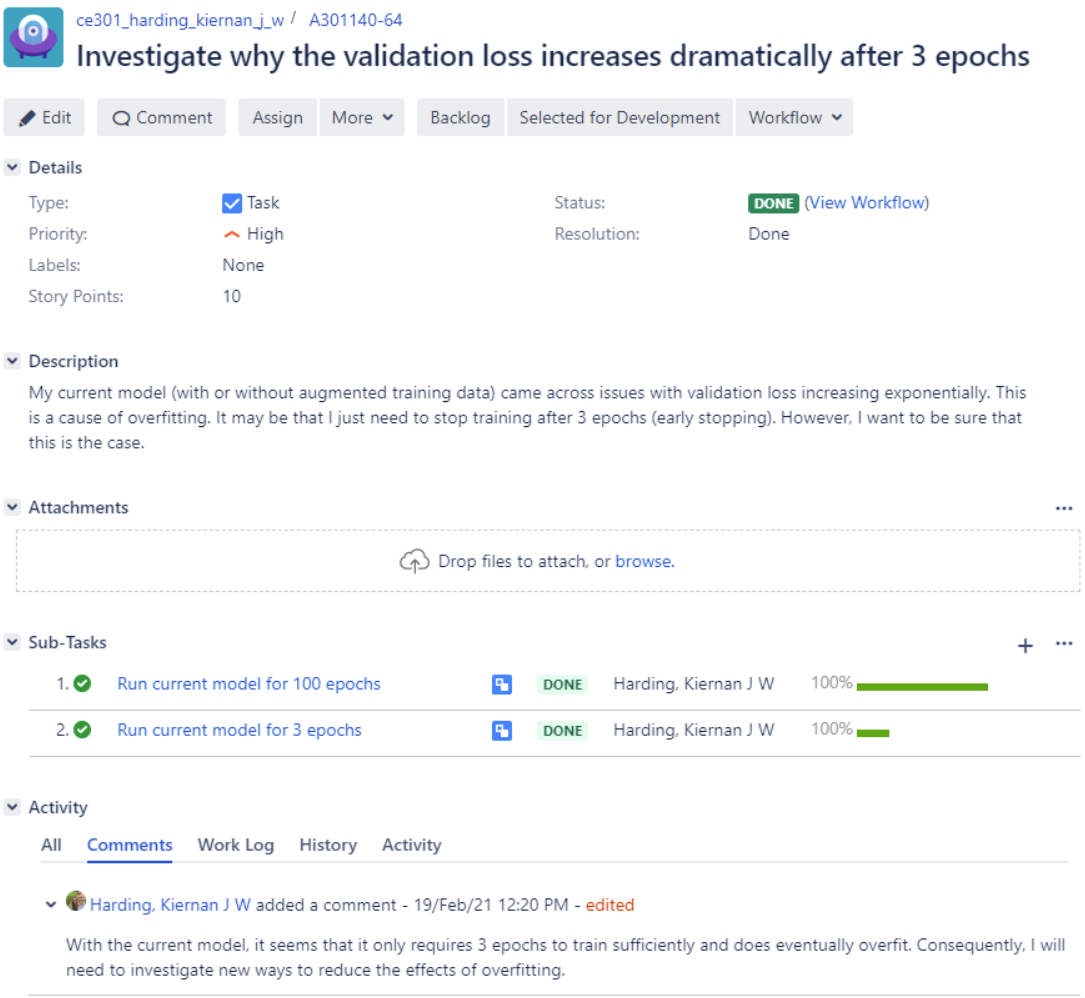

Fig 11. An example Jira issue.

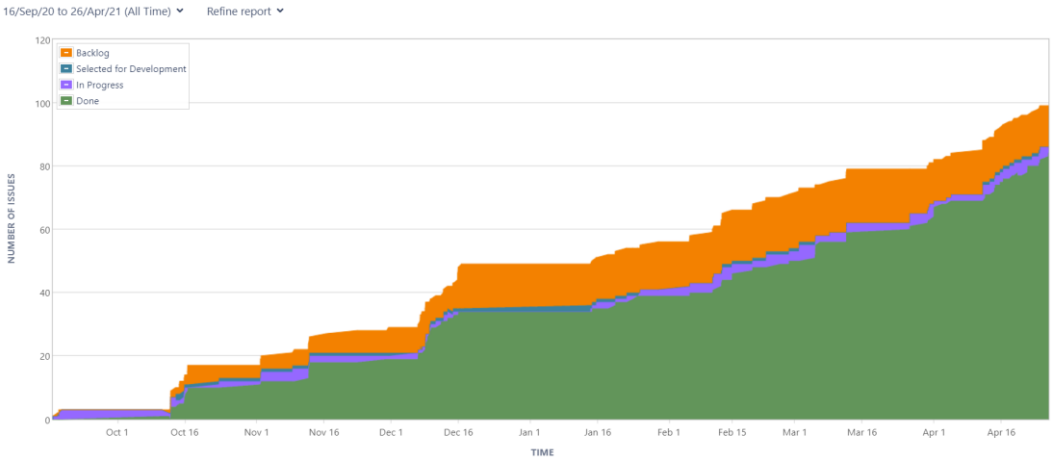

Fig 12. A cumulative flow diagram of issues from Jira (25/4/2021).

I frequently committed to my Git repository for 2 main reasons. To document and keep track of all the major project developments, and to guarantee my work was also saved to an external system. I found Git advantageous when trying to locate older versions of work that had been overridden with an updated copy. Keeping your files organised is essential; I always kept my Git repository well-structured and organised so another individual or I could navigate my project with ease (see figure 13). Moreover, when committing to Git I added meaningful but concise commit messages, which allowed me to locate a specific commit (or version) at a later date.

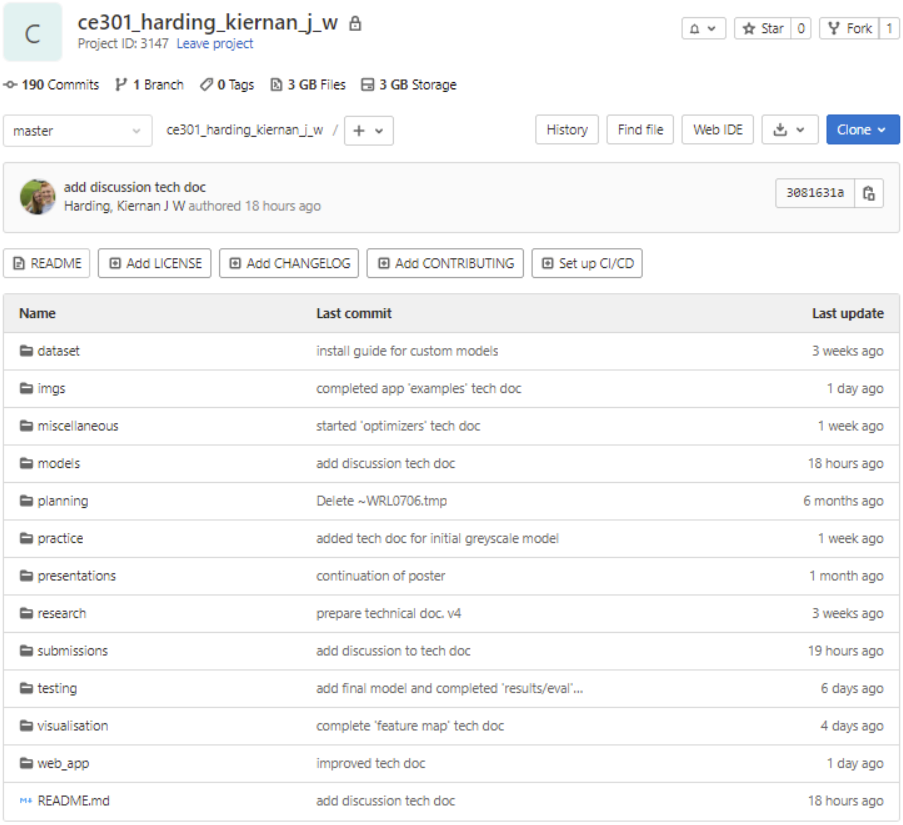

Fig 13. A snapshot of my Git repository (25/4/2021).

Additionally, I used various markdown files to keep track of summarised weekly developments and the results of each CNN model. I believe that all these management methods/tools have been very advantageous to the completion and development of my project. Nevertheless, if I started this project over again and had more time, I would add stretch goals to my project plan. This would allow me to better the project with additional features if I did not require the allocated slack time.

Conclusion

Machine Learning, specifically Convolutional Neural Networks (CNN) have been very effective at detecting malaria parasites in red blood cells. Successfully, I classified pre-segmented red blood cells as either parasitized or healthy, using popular Machine Learning libraries in Python. From achieving an original accuracy of 71.4%, I have vastly improved upon my CNN model, reaching an accuracy of 95.6% on unseen test samples. This accuracy score surpassed my aim of improving upon the RDT's accuracy of 79% [11]. To fit the CNN model with high accuracy, I employed various techniques such as: data augmentation, regularisation, and feature map visualisation. These techniques aided the reduction of overfitting within the classification model, thus, increasing accuracy. I found that these techniques were very successful at improving the model's performance.

To assist the trained model, I designed a highly accessible application that can be hosted locally or on a web server using Flask. I designed the application with simplicity in mind to allow effortless use and navigation. Moreover, the user interface is graphically pleasing, with a serene effect relating to health. The application (including the CNN model) eliminates human error from the classification part of the diagnostic process.

This project was a major success as I had little AI knowledge, and no CNN knowledge prior to its start. My technical knowledge has vastly improved through research and application. To extend this project, I would research further ML techniques to improve the model's accuracy. For instance, this may include a research-based exploration of tweaking specific parameters related to the loss function. Additionally, I would investigate segmenting red blood cells from thin blood smears, allowing the whole classification process to be automated. Currently, malaria can be detected in pre-segmented red blood cells, but ideally, malaria would be detected in a thin blood smear.

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