Unobtrusive Monitoring System for Adherence to Glaucoma Eye-Drop Treatment

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“Coincidence is God’s way of remaining anonymous.”

– Albert Einstein

This thesis is dedicated to my dearest parents, Mr Yadollah Kalhor, Dr Mehri Najafi Sani and my beloved brother, Dr Nima Kalhor for their endless love, support and encouragement throughout my life.

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Abstract

Glaucoma is the second most common cause of blindness and the leading cause of irreversible vision loss worldwide. Glaucoma is an eye condition that mostly occurs due to high intraocular pressure and requires immediate treatment. If not treated, it can lead to blindness. The main method to treat glaucoma involves reducing the pressure inside the eye. The available treatments for treating glaucoma include medications, laser procedures and incisional surgery. Treatment of glaucoma is greatly dependent on the type that a patient is experiencing. Though, eye drops are often the first treatment option when dealing with glaucoma. Should eye drops not work, then alternative surgical treatments can be used. The problem with glaucoma patients is that it's difficult to determine whether treatment is failing because the eye drop is not an effective treatment for them or because they don't adhere to their treatment.

For assisting the clinician, this project will seek to build a possible solution that will address adherence and compliance issues leading the clinician to take more effective decisions for the patient and thus better-quality clinical outcomes. Currently a number of solutions exist to judge and evaluate effective compliance. These range from manual observations to some form of electronic monitoring that seek to establish how well the patient has been keeping track of their medication.

This project and thesis will seek to review glaucoma as a medical disease and its impact upon society as a whole. It will also present a solution that will incorporate a paper-thin electronic wrap that would be situated on the bottle with a view to making this as inexpensive as possible. The electronic device or system will be capable of revealing more details to a clinician such as how often the device is used and when it will be squeezed.

The next step of this thesis is to design a system to identify correct compliance among these patients. Overall, the outcome of this project resulted in the creation of an electronic monitoring device in the form of a flexible PCB which, given its

software, is capable of noting down basic compliance metrics. None of this, however, confirms if the drop actually entered the eye. Advancing on this work, a system was built to accurately determine if a droplet entered the eye utilising vision technologies.

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Chapter 1

Introduction

Glaucoma is a neurodegenerative condition which more often than not, progressively affects the eyesight of patients due to increased intraocular pressure (IOP) [1]. Vision that has been lost to glaucoma cannot be recovered [2]. The related topic of interest in this research is the continuing monitoring of treatment regimes, such that patients can retain a good level of sight for life.
It is predicted that glaucoma could affect over 110 million people globally by 2040. There are studies that state that countries in Asia and Africa may have higher rates of the disease and that, for example, certain ethnicities will have higher rate per head of population [1]. After cataracts, glaucoma is the second most common cause of blindness around the world. Yet, glaucoma is the leading cause of irreversible vision loss globally, which is why it plays an important role in public health [3, 4]. In the UK 1 million patient visits to eye clinics and other ophthalmic facilities every year are reported as being related to glaucoma. It is expected, due to factors such as the aging population and longer life expectancies, that glaucoma will have increased economic impact. Currently, in the UK, 9-12% of people over 65 years old are diagnosed with glaucoma [5].

There are reported debates from the ophthalmic profession, going back as far as far as 50 years, about definitions such as compliance (and hence non-compliance) and adherence (and hence non-adherence). These will be reviewed more completely in Chapter 2. For now, and in simple terms, a given patient will

have been prescribed an on-going regime of eyedrops within their treatment. There are benefits to the ophthalmic professional of monitoring and assessing how closely (or otherwise) the regime is being followed. It is widely accepted amongst the medical community that poor compliance results in worse patient outcomes. In a wider sense, non-compliance is then, of course, a significant drain on the resources of the health system of any country. The range of factors in play are reviewed in Chapter 2. It is reported that problems experienced by both clinicians and patients stem from existing tools being limited in scope. Such tools need to be capable of both managing and monitoring drug compliance. Statements to the effect that new tools and techniques should be developed using new and innovative ideas and technologies are the motivation for this thesis. There have been huge and increasingly rapid developments in many technologies worthy of consideration for this application. Items of direct interest, but not limited to, include the smaller physical size and increased performance specifications of modern single chip microcontrollers/microprocessors, flexible (and wearable) electronics including printed circuit boards and batteries, local communications protocols, memory storage and datalogging devices and a range of microelectromechanical system sensors and vision systems. To conclude this introduction (and using an example from the wider review presented later) there are broad expectations for electronic monitoring systems. They are required to provide information regarding adherence to ocular hypotensive medications among glaucoma patients. As a basic requirement they should provide information such as the time and date for each instance of the medication being applied by the patient, to lead to a better understanding of adherence behaviours. It is argued that the ultimate goal is challenging. For example, a reported study (more details in section 2.2.3) utilised video recording of patients self-administering their eye drops. The results presented stated that 18% of patients missed their eyes when dispensing their eye drops, and only 60% of patients administered the correct number of drops. Around 65% of patients dirtied the bottle by touching it to their eyes. So, sensing of an eyedrop leaving a bottle and correctly entering an eye would be the ultimate system. In this thesis, several technical solutions to these issues are considered.

1.1 Research Aims

There are two main aims of this research. One aim is to develop a small, low-cost almost disposable electronic device that can record when an eye drop bottle is being squeezed and subsequently relay that information to a clinician. For the designed electronic system, requirements are an ultra- low power, embedded microcontroller circuit with suitable control, data storage and communications (for data retrieval) facilities. There was an expectation, given the required power supply and sensing components, that both analogue and digital circuit aspects would need optimisation. This is referred to as System I in subsequent chapters. The second aim is to develop a more advanced image-based system that can confirm the inclusion of an eye drop in the eye by developing a range of LabVIEW vision tools that can suitably detect droplet inclusion. This is referred to as System II in subsequent chapters. Either system must ensure that there is no change in eye drop usage by deterring the patient and allow future clinical trials to further evaluate the technologies and their application.

1.2 Thesis Structure

The structure of the thesis is as follows: -

- The remainder of Chapter 1 provides a summary of the biology of the eye. The nature of the glaucoma disease and its impact along with a review of treatments and medication regimes is also presented.
- Chapter 2 reports on the considerations of approaches in defining terms of drug compliance. A review of reported methods of measuring compliance is included.
- Chapter 3 presents an overview of a small electronic system that can record when the eye drop bottle is squeezed.
- Chapter 4 provides a review of soft flexible battery technology and follows with evaluation and testing of one of these batteries. It also explains the

software required for performing the testing and evaluates results of the battery in different situations and circumstances.

- Chapter 5 assesses suitable sensors that are of an interest to this project. It follows up with testing on different shapes of sensors. Moreover, it goes into detail with regards to calibration of the sensor and covers the results.
- Chapter 6 highlights the electronic design of this project. It evaluates the suitable microcontroller for the purpose of this project. It then expands and describes the programming of said microcontroller and how the setting up of the microcontroller for programming should be. This continues with a description of the programming of an NFC module for data transfer. Then it covers final design stage of the flexible PCB.
- Chapter 7 presents a vision system that identifies a successful eye droplet on the eye. This chapter covers different tasks regarding image processing including histogram, grayscale and vision filters. There is also plenty of programming options to explore and the presentation of successful test data.
- Chapter 8 includes the conclusion of this thesis and further research works.

1.3 Eye Biology

The human eye is an awesome construct and array of multiple sensors that constitute one of the most important sensory systems known to man. The majority of a humans' information about their external environment is collected by the eyes. It is argued that sight, in that respect, is more important than any other senses for humans [6]. The eyeball is made up of three layers/coats, three compartments and contains three fluids. The three layers are the outer fibrous layer, the middle vascular layer and the inner nervous layer. The three compartments are the anterior chamber (the space between the cornea and the iris), the posterior chamber (the space between the iris, the lens and zonule) and the vitreous chamber (the space behind the lens and zonule). The three

intraocular fluids are termed as aqueous humour, vitreous humour and blood. Clinically, the eye is considered as two segments. The anterior segment involves all structures from and including the lens outwards and the posterior segment contains all structures inwards of the lens [7]. The following sections provide further detail for the three layers. The different parts of the eye are highlighted in Figure 1.1.

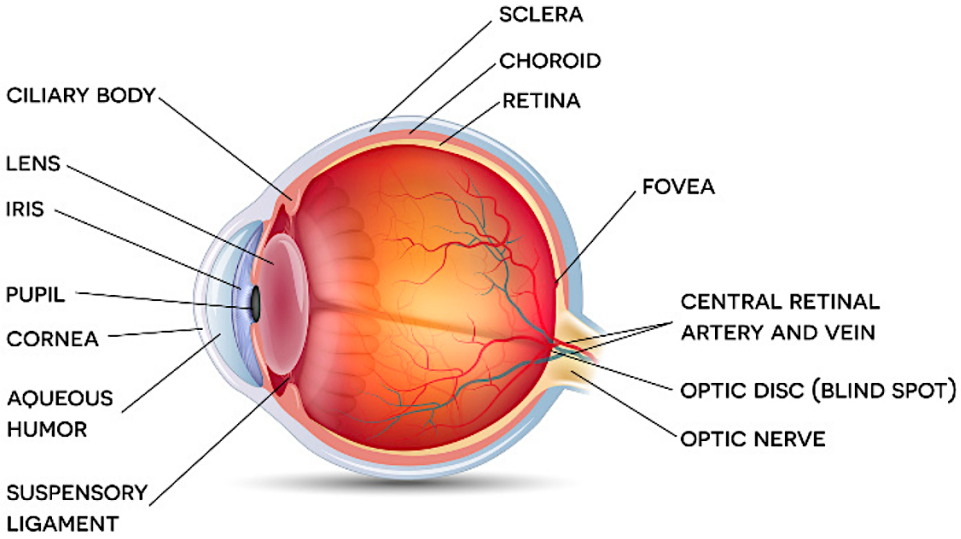


Figure 1.1: Structure of the eye [8].

1.3.1 The Outer Fibrous Layer

The external layer of the eyeball (i.e., the outer fibrous layer) includes the sclera and the cornea which are the toughest parts of the eye and withstand normal internal pressures of 13 to 19 mmHg (the conventional unit used). The shape and maintenance of eye dimensions are achieved by this IOP which leads to a sharp vision [9]. The cornea is the transparent surface which protects the inner parts of eye against any structural damage. The cornea refracts entering light which is then transmitted, through the lens, to the retina [7, 10]. The sclera which surrounds the cornea is dense with a white exterior part that protects the internal structures of the eye [11, 12].

1.3.2 The Middle Vascular Layer

The middle layer (i.e., the vascular layer) which contains the iris, the ciliary body and the choroid is responsible for eye nourishment. The ciliary body controls the thickness of the lens and the iris, which is the coloured part of the eye, controls the amount of light that enters the eye. The aperture at the centre of the iris is the pupil whose size is adjusted by the iris. The size of the pupil decreases when near vision is needed and increases when far vision is required [12]. The choroid within the vascular layer provides oxygen and nourishment for the inner layer of the eye. It also prevents light from reflecting internally [10, 12].

1.3.3 The Inner Nervous Layer

The inner layer (nervous layer) of the eye is the retina, at the back of the eye, and which has a complex structure of neurons. The light that is received by the retina is converted into chemical energy which in turn stimulates the optic nerves. These nerve signals from the eye are sent to the brain for processing via the optic nerve [10, 13].

1.4 How the Eye Works

Prior to a description of glaucoma and its effects, a description of the normal functioning of the eye is presented. Light enters the eye through the cornea, this is then directed through the pupil, behind which the lens is situated. As light is propagated through these structures and through to the lens, it is then focused onto the retina which contains photoreceptor cells [14]. There are two types of cells within the retina: rods and cones. The rods which are very sensitive to light are able to regulate black and white vision. The cones are sensitive to colour and function in bright light. The three types of cones can be named as red, green and blue. A range of visual wavelengths can be detected by each type of cone and not just the specific colours implied by their conventional names. When the eye sees

an object, the light enters a region called the fovea. The fovea is filled with cones which provide sharp vision. The rods which are placed outside the fovea are mostly responsible for peripheral vision. The rods and cones convert the light into a series of complex electrical signals which is then transferred to the brain via the optic nerve, leading an image to form [12, 15]. Figure 1.2 illustrates how the eye works when light enters.

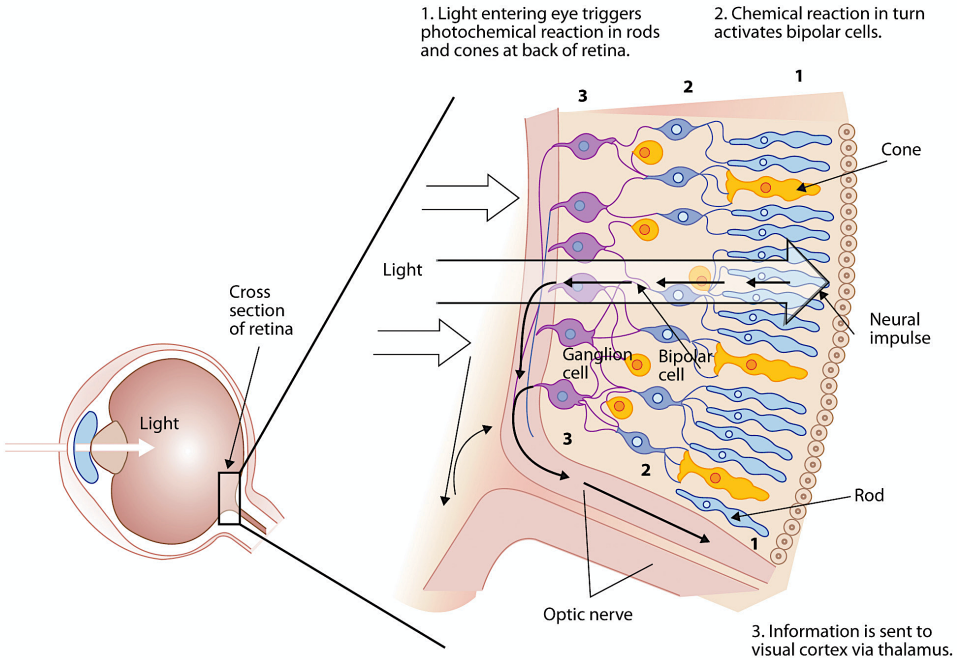


Figure 1.2: Reaction of eye to light [14].

1.4.1 Visual Accommodation

Visual accommodation is the name of the process whereby entering light remains focused on the retina, via the curvature of the lens. Rays from the top of the image hit the bottom of the retina and equally rays from the bottom of the image hit the top. There is also an opposite reaction from left to right of the image. The effect is that the image on the retina becomes flat, backward and upside down. The final observation of the image is 3D in nature, since the brain reinterprets and corrects

the image to become the right way up and deliver special sense awareness. In such a situation, the brain effectively is behaving like a graphics processing unit [14]. Figure 1.3 displays how an image appears on the retina.

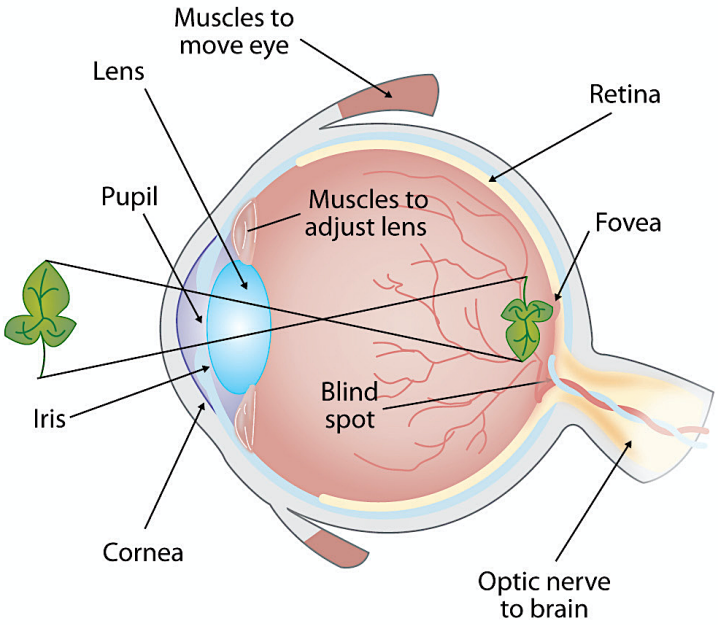


Figure 1.3: Normal Visual accommodation [14].

1.5 What Is Glaucoma?

Glaucoma is an optic neuropathy that can be due to several reasons such as increased IOP which can eventually lead to blindness [16]. Increased IOP is either because of too much fluid build-up in the eye or blocked drainage channels of the eye [17]. Another way to define glaucoma is that it's a condition that causes advanced neuropathy in the optic field which is classified by structural changes to the optic disk leading to functional changes in one's visual field [1]. Glaucoma typically is not identified in the early stages of the disease as no symptoms are initially presented and no complaints are made from the patient until the more

advanced stages of the disease. It's predicted that up to 50% of patient with this disease remain undiagnosed and the number of patients is even higher in developing countries [2]. In addition to IOP, there are other factors that can increase the risk of developing glaucoma. These include, but are not limited to; age, race, family history, diabetes, refractive error (such as myopia), corneal thickness, drug-induced glaucoma (such as steroids), migraine, and obstructive sleep apnoea syndrome [18, 19].

1.6 Types of Glaucoma

Given the anatomical and pathophysiological conditions of the affected eye, glaucoma is mainly categorised as open angle glaucoma (OAG) and angle closure glaucoma (ACG). Other types of glaucoma include, normal tension glaucoma and congenital glaucoma. Glaucoma occurs either in primary or secondary form. The differentiation between primary and secondary glaucoma is that the primary form of glaucoma develops without an identified cause. In contrast, with secondary form of glaucoma there are underlying ophthalmic or medical conditions which causes the development of glaucoma. As such, OAG can be divided into primary open angle glaucoma and secondary open angle glaucoma. Secondary open angle glaucoma includes patients with pigment dispersion syndrome. ACG can be either primary or secondary (such as neovascular). Congenital glaucoma includes both primary and secondary congenital glaucoma which the latter is related to other disorders, for instance aniridia [20-23]. The angle between the cornea and the iris in the anterior chamber when discussing glaucoma topics is referred to as just the angle. The aqueous humour fluid drains out through the trabecular meshwork which is located in the angle between the cornea and the iris. When the aqueous humour is not able to drain away from the eye due to obstruction within the drainage system, the fluid builds up thus the IOP increases. In OAG (as shown in Figure 1.4), the anterior chamber angle is open however, in ACG (as shown in Figure 1.5), the anterior chamber angle is closed [22, 24]. ACG is more serious than OAG as it might develop quickly

alongside with pain as such this type of glaucoma requires immediate medical treatment [25].

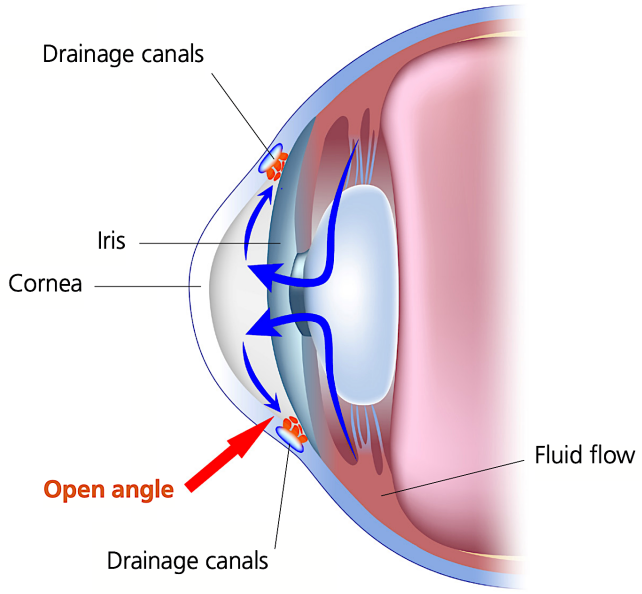


Figure 1.4: Fluid flow in open angle glaucoma [26].

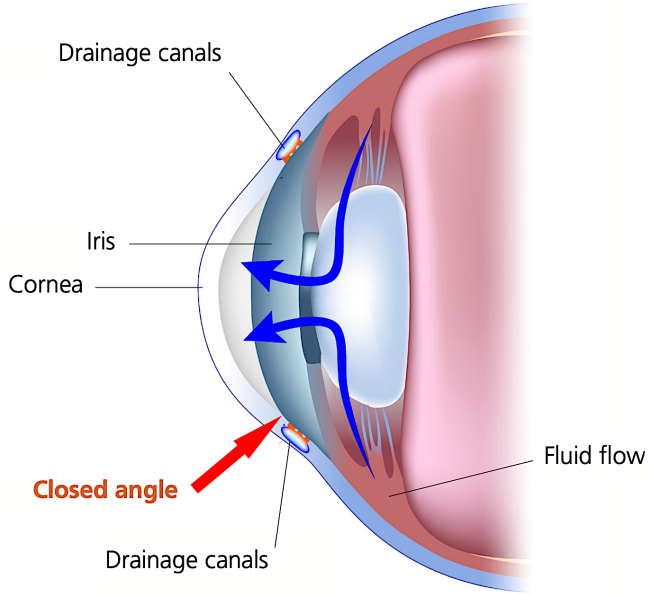


Figure 1.5: Fluid flow in angle closure glaucoma [26].

1.6.1 Primary Open Angle Glaucoma

Primary open angle glaucoma (POAG) is the most common type of glaucoma among all cases of glaucoma. It is suggested that 57.5 million people are estimated to have this type of glaucoma globally [27]. POAG includes both adult-onset disease (above 40 years of age) and juvenile-onset disease (between 3-40 years of age) [23]. There are expected risk factors relating to POAG. The risks increase among those with a family history of the disease, those of black race, patients with diabetes, Hispanic descent and amongst the elderly [16, 28]. Occasionally POAG is referred as silent thief of sight as patients with POAG frequently do not have any symptoms until the optic nerve is damaged. However, if signs of glaucoma are detected on regular eye tests, prevention of the optic nerve damage is probable [29, 30]. POAG is treatable if it is detected at an early stage, however, if visual field damage is sustained, then this is irreversible. Successful intervention is largely dependent on early diagnosis via examination of the optic disc, retinal nerve fibre layer, and visual field [31]. The degree of visual loss damage caused by POAG can be classified in four different ways; mild, moderate, severe and indeterminate [32, 33].

1.6.2 Normal Tension Glaucoma

It is important to note that 25%-50% of POAG cases develop without IOP being above normal range, however, damage to the optic nerve occurs. This type of glaucoma is termed normal tension glaucoma (NTG). As such, NTG is a subdivision of POAG with IOP less than 22mmHg. This type of glaucoma is more common among east Asian ancestries. Abnormal retinal blood flow to the optic nerve plays a significant role in NTG [34-37].

1.6.3 Primary Angle Closure Glaucoma

Primary angle closure glaucoma (PACG) is more visually damaging than POAG. It has been anticipated that 67 million people are diagnosed with primary glaucoma globally and one third of them have PACG [38]. The populations who are at most risk of PACG include the elderly and east Asian ancestries. It is also reported that women are at higher risk for this type of glaucoma [39, 40]. The understanding of PACG has improved significantly in the last two decades, so the danger of the disease is better known globally. In PACG, angle closure is the main problem, and high IOP is subordinate to angle closure. To a degree, PACG can be prevented if the method of angle closure is stopped at the early onset of the disease [41]. Due to confusion in classification of PACG, based on initial discrepancies in terminology and nomenclature, Foster et al developed a standard definition which relies on the progression of disease. PACG can happen in a range of angle closure disorders which includes primary angle closure suspect (PACS), primary angle closure (PAC) and primary angle closure glaucoma (PACG) itself [39, 42]. According to the American Academy of Ophthalmology, all the three categories (PACS, PAC & PACG) have 180 degree or higher iridotrabecular contact (ITC). It has been stated that a person with 180 degree or more of ITC is at risk to develop ACG. Both PAC and PACG suffer from high IOP. However, there is no sign of optic neuropathy in PAC unlike PACG [38, 43].

1.6.4 Congenital Glaucoma

It is very distressing when a child is given a diagnosis of glaucoma, one that is akin to a diagnosis of cancer. The impact upon the patient and their family as can be imagined is severe. The rate of congenital glaucoma is 1 out of 18,500 births in the UK [44]. The symptoms of congenital glaucoma can be viewed when the child is in the early stages of life. The symptoms of this type of glaucoma includes; sensitivity to light, large eyes, red eyes, cloudy eyes and watering eyes [17]. The common form of congenital glaucoma is primary congenital glaucoma (PCG)

which is a rare condition that occurs around 1 in 10,000 babies [45, 46]. PCG is due to abnormal development of the anterior chamber angle when decreasing the aqueous humour outflow resulting in increased IOP. The majority of PCG occurs intermittently, however, it can be inherited. PCG can be divided into three categories based on the age of presentation. These include; new born onset (between birth and age one month), infantile onset (between age one month and 24 months) and late onset (after 24 months) [47].

1.6.5 Secondary Glaucoma

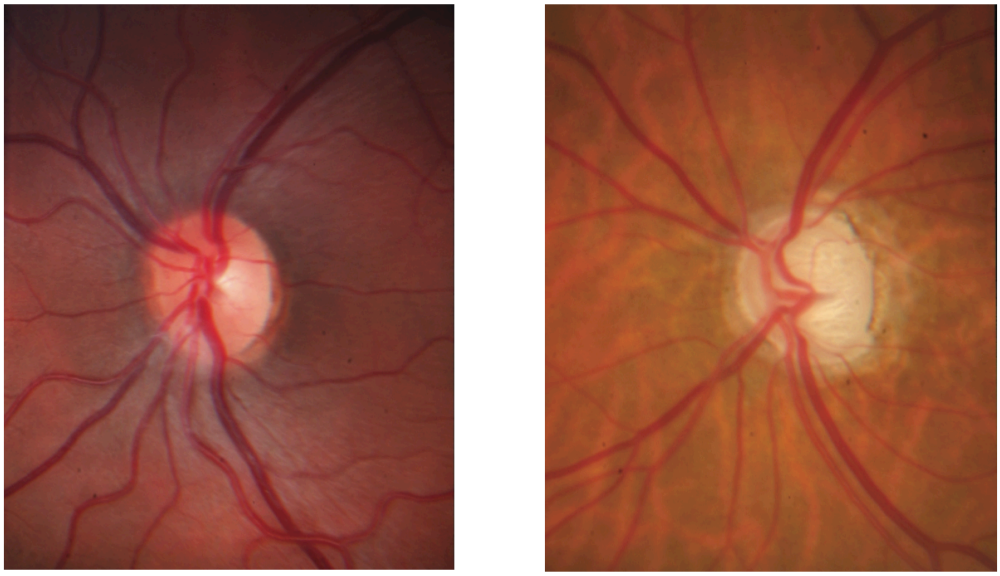
Secondary glaucoma is the result of complications due to; inflammation, neovascularization, trauma, cataract and ophthalmic disorders, so different types of treatments are required to deal with this form of glaucoma [48-50]. Based on the primary pathology, secondary open angle glaucoma includes, but is not limited to, pseudoexfoliative glaucoma and pigmentary glaucoma. Some form of secondary angle closure glaucoma involves neovascular glaucoma and some form of secondary glaucoma can occur either open angle or angle closure such as uveitic glaucoma [51].

1.7 Diagnosis of Glaucoma

Generally, glaucoma happens in both eyes however, the progression of the disease starts in one eye before proceeding to the next. In order for the ophthalmologist to recommend proper treatment, it is essential to determine which type of glaucoma a patient is experiencing. The following tests performs by ophthalmologist in order to diagnose glaucoma accurately during comprehensive glaucoma evaluation [17]:-

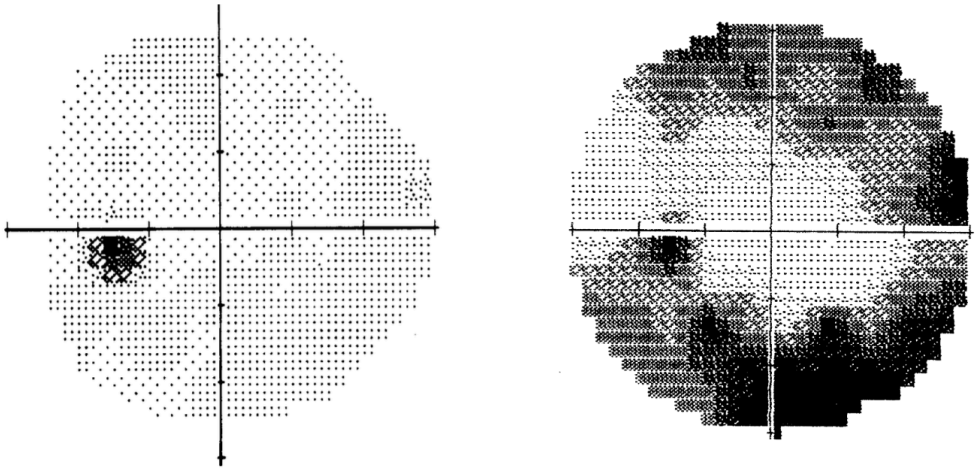
- Tonometry
    - Measuring IOP
- Ophthalmoscopy

    - Examination of the optic nerve (as shown in Figure 1.6)
- Perimetry test
    - Measuring the field of vision (as shown in Figures 1.7 and 1.8)
- Gonioscopy
    - Examine the drainage angle and drainage area of the eye
- Pachymetry
    - Measuring the thickness of the cornea



(a) (b)

Figure 1.6: Ophthalmoscopy examination. Healthy optic nerve (a) and damaged optic nerve within glaucoma (b) can be observed [26].



(a) (b)

Figure 1.7: Perimetry test. A normal visual field (a) and a visual field with vision loss within glaucoma (b) can be observed. Black and darker grey areas illustrate vision loss. As there is no vision in optic disc, thus it displays black in both visual fields which is normal [26].

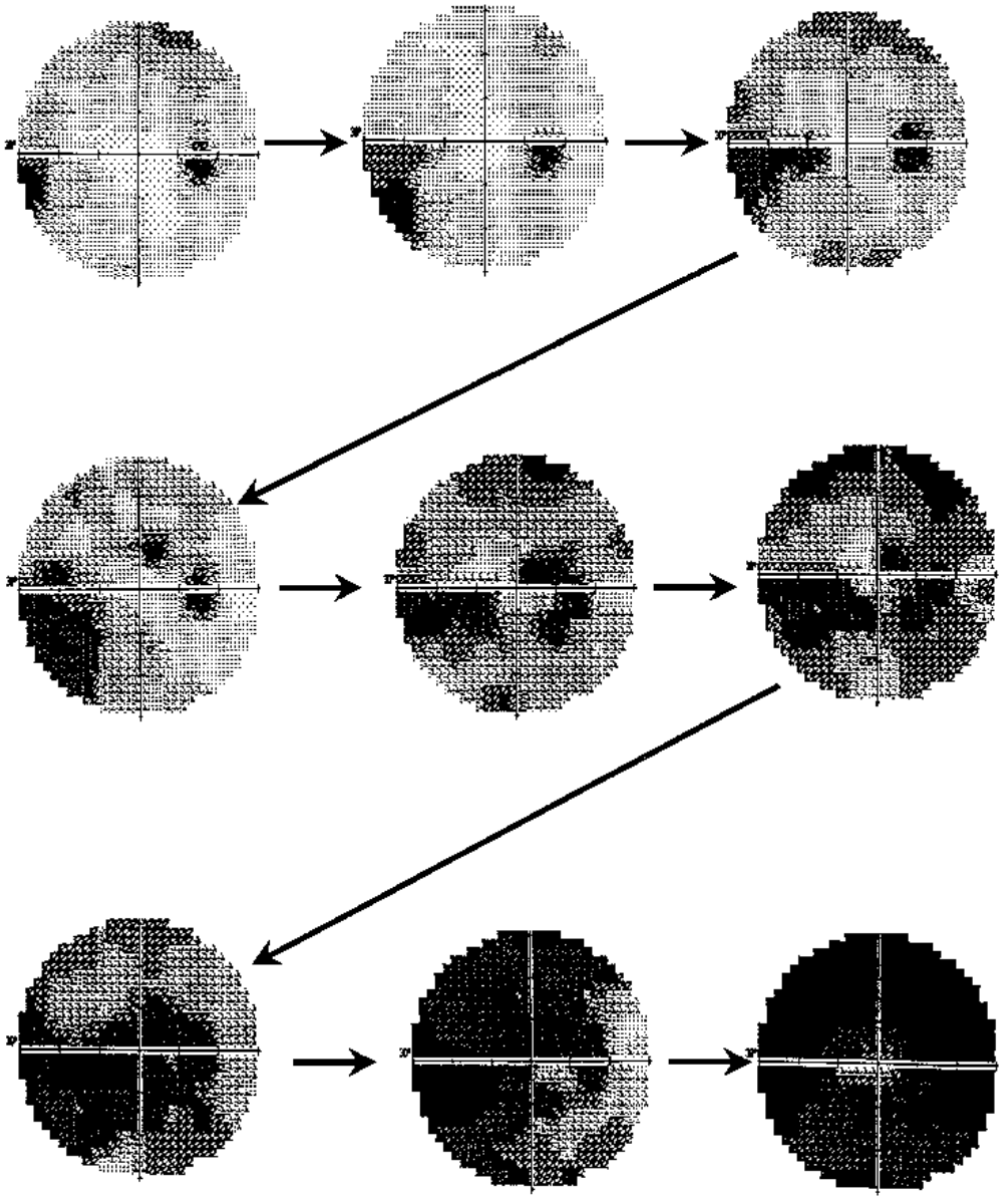


Figure 1.8: Perimetry test. An example of typical glaucoma based visual field progression from early stage to advanced glaucoma visual field loss [52].

1.8 Treatment of Glaucoma

The main aims for treating glaucoma include preventing or slowing-down further visual field loss and safeguarding the quality of life. The death of neuronal cell is irreversible and no cure is available. When this happens it's the main reason for blindness. The reduction of life's quality connected with glaucoma may happen earlier than it's been assumed before, so early diagnosis and treatment of the disease are of great importance. In most patients, early treatment can assist to stop the progression of the disease. Even though with proper treatment, still up to 10% of patients lose their vision. IOP is the major risk factor of retinal ganglion cell (RGC) loss and the level of disease severity as such lowering IOP should be a priority. Reducing of IOP is the only verified method for treating glaucoma. Results from some clinical trials have proven the benefit of decreasing IOP in order to slow down the progression and development of disease [2, 28, 53]. The ultimate goal for glaucoma patients is to maintain their sight and vision. The type of treatment is dependent on several factors including the type of glaucoma, visual prognosis and ocular and/or systemic comorbidities [21]. There are different treatments available for glaucoma patients in order to reduce IOP. The available treatments include medications, laser procedures and incisional surgery. At the beginning of treatment, the majority of patients receive topical ocular hypotensive drops [54]. Treatment plans for OAG relies on controlling IOP; one of the treatment plans is to target and resolve IOP based on patient age, level of IOP and severity of disease. IOP treatment strategy is arbitrary in nature and would need regular assessment and monitoring in order to decide its effectiveness [55]. The treatment of PAC and PACG includes a laser procedure and medications to reduce the pressure inside the eye. Though in case the disease not be controlled by either of these treatments, then surgery (often trabeculectomy) would be recommended [56]. The treatment for children affected by glaucoma is slightly different to that for adults. More frequently used eyedrops can cause serious risks for children. For instance, it's been indicated that brimonidine drops cause central nervous system depression in children [2]. Laser treatment has a limited impact in treating congenital glaucoma. The most

recommended treatment for treating most forms of this type of glaucoma such as PCG is surgical trabeculotomy [57].

1.8.1 Eye Drops

This treatment is the one that is applicable to the author's research. During, and certainly at the beginning of treatment, the majority of patients receive topical ocular hypotensive drops [54]. The use of topical medications is a popular form of treatment that has been around for over a century. In the context of high IOP, it can have significant advantages such as low initial costs and minimal invasiveness [58]. IOP lowering eye drops decreases IOP either by increasing aqueous humour outflow and/or by reducing the amount of aqueous humour fluid produced in the eye. There are five common drug classes available which include; prostaglandin analogues, beta blocker, carbonic anhydrase inhibitors, alpha adrenergic agonists, and cholinergic agents [21, 55, 59, 60].

1.8.2 Surgery

Surgical treatment would be recommended as a treatment when medicines and laser treatment fail to treat glaucoma [62]. Generally, glaucoma surgery is performed under local anaesthetic, however occasionally it can be carried out under general anaesthetic [61]. According to the National Eye Institute (NEI), there are different types of surgery for treating glaucoma patients. These involve trabeculectomy, minimally invasive glaucoma surgery (MIGS), and glaucoma implant surgery [62].

Trabeculectomy

Trabeculectomy is a common surgical procedure for glaucoma patients. The purpose of which is to increase the outflow of fluid from the eye, leading to

reduction of pressure inside the eye [61]. This will be performed by making a tiny opening in the top of the eye under the eyelid. Generally, OAG is treated with this type of surgery [62].

MIGS

MIGS is a new and less invasive type of surgery. Since the procedure is quicker and the recovery time is faster, it is generally becoming a much more accepted form of surgery. Microscopic equipment is applied to create tiny incisions to reduce eye pressure in this type of surgery [61].

Glaucoma Implant Surgery

Glaucoma implant surgery can be applied to treat various kinds of glaucoma, such as congenital, neovascular, and glaucoma caused by an injury. It is carried out by implanting a tiny tube onto the sclera, leading to extra fluid in the eye draining away [62].

1.9 Summary

Glaucoma is the second most prevalent cause of blindness around the world, which is an eye condition that mostly occurs due to high pressure inside the eye, that requires immediate treatment. If it's not treated, patients will get visual field loss that eventually leads to blindness. Glaucoma can be divided into two main types, OAG and ACG. Other types include NTG and congenital glaucoma. The primary method to treat glaucoma involves reducing the pressure inside the eye. The available treatments include medications, laser procedures and incisional surgery. Treatment of glaucoma is very much dependent on the type that a patient is experiencing. However, eye drops are often favoured, particularly at the earlier stages of treatment. A clinician will determine which treatment is

usually the most appropriate. The current research can potentially support and facilitate modern methods of monitoring compliance of applying eye drops. The next chapter provides details of compliance and related topics.

Chapter 2

Compliance

2.1 Introduction

This chapter will seek to go through a number of definitions in relation to compliance including non-compliance, adherence, non-adherence and persistence. Compliance to therapy can be chiefly defined as how well aligned the patients' behaviour is to their prescribed medical advice. Similarly, non-compliance can be defined as the degree to which patient behaviour is poorly aligned with medical advice [63]. Challenges exist in the sense that patients will not comply due to lifestyle factors. These include financial reasons and non-compliance due to a failure on the part of a patient to say no to harmful choices, such as a poor diet for example [64]. The impacts of non-compliance might be serious in elderly patients. Some patients in this range might take more medication than prescribed in misconception that it will increase the rate of their recovery. The use of multiple drugs is really common in elderly patients. It's been estimated that up to 25% of elderly take at least three drugs [65]. There are simple practical issues medical professionals face such as patients that have an inability to read, lack of understanding of what they should do or maybe inappropriate care arrangements. So, it is imperative that the physician takes the time out to speak with their patients understand their individual needs and assess them accordingly [64]. It is commonly accepted amongst the medical

community that poor compliance leads or results in worse patient outcomes. Other effects include, drug resistance and a prolonged use of therapy that will not be as successful should the prescribed regimen be followed. Thus, the patients must take their prescription at the correct time and manner to meet the standards of compliance and they need to keep doing it for the entire duration of the drug treatment plan [63, 66]. It's also worth noting that the non-compliance is a major drain onto the health system of any country. Some might say that it is a waste of valuable resources however the way forward is to argue for a solution and prevention of non-compliance [64].

Drug compliance as a study has been around since drugs themselves have existed and been given to patients. It has been reported that up to 20% of patients do not collect their prescribed medication and fail compliance right from the start of their treatment. There is a chance that even the patients who collect their medication may not take their medication. The data on these patients can be quite sketchy and percentile figures vary from 10 – 90% thus having different rates of compliance. It is stated that these depend on many factors such as keenness of doctor, the disease being cured, and awareness of the patient of the importance of the disease [67]. Overall there are factors that can effect drug compliance for instance, the perceived threat presented to the patient from the disease or the doctors own willingness and resolve to tackle the symptoms in the first place [68]. Patients based on accepting of their diagnosis and starting their treatment can be classified in to four categories. Non-compliers can be defined to patients who don't accept their diagnosis and their needs to treatment. While partially compliant patients are those who accept their diagnosis and treatment, but they don't carry out the recommended treatments satisfactorily in order to improve their health. The third category which is rare is over complier patients who take repeat actions in excess of what is recommended to them. Adequate compilers are defined to those patients who follow health advice sufficiently to control their disease [69]. The families of patients can usually play an important part in enforcing drug compliance. Some patients are unable to administer drugs themselves and this should be accounted for when designing a system in order to take into account for the problems mentioned previously.

Discrepancy or the measure thereof is where two different reporting systems are employed and the disparity between both is reported. Indeed, Friedman et al [70] clearly states that when an electronic system reports back a compliance rate of 76% patients themselves reported a manual reporting of 97%. Techniques, that use a double reporting facility are incredibly useful in judging or assessing the disparity between two results and thus methods that employ this use within one system should be investigated further. The expectation to patient compliance must also be kept realistic as a 100% rate of compliance is very hard to achieve unless experiments are designed in such a way that the patient is kept in strictly controlled conditions. More importantly, it is currently very difficult to verify and establish how compliant patients actually are and statistics are very limited as there isn't one single database or system that can provide supporting statistics. The problem of non-compliance is certainly there, however it's exceptionally difficult to measure, as there are a limited number of tools available. As such useful tools that can and should be developed with new innovative ideas on detection and sensory feel are most welcome to the field. A major problem which is usually experienced by both clinicians and patients is that the current tools, which are capable of both managing and monitoring drug compliance are limited in scope. These do not account for the different methods of dispensing but rather typically look at compliance through ingestion. By looking at drug efficacy, it is possible to determine the rate of compliance. There is a clear link to how the effectiveness of drugs are in comparison to the level of compliance. Should patients have been monitored to have full compliance it is then possible to say that the prescribed drug has failed. Essentially drug efficacy can be shown to be normally distributed [71]. This is relevant as it shows all drugs have an optimal point of efficacy and requires fundamental balance to achieve good clinical outcomes.

2.2 The Concept of Adherence and the Differences to Compliance

The terms of compliance and adherence are preserved as equivalent by nurses. The majority of which use the definition of Haynes and World Health Organisation (WHO) to clarify the terms of patient compliance and patient adherence individually. The effort to define compliance was started by physicians Sackett and Haynes in the late of 1970. They reviewed the published papers regarding compliance however in a conference that took place, disagreements were expressed on how to define it. While Sackett proposed the terms ‘adherence’ and ‘therapeutic alliance’ these terms were not accepted and the members put forward the term compliance which described as; 'the extent to which the patient’s behaviour (in terms of taking medications, following diets, or following other lifestyle changes) coincides with medical advice'. This definition remained for about two decades later. As explained by Sackett : 'the term fits and it amply describes the extent to which the patient yields to health instructions and advice, whether declared by an autocrat, authoritarian clinician or developed as a consensual regimen through negotiation between a health professional and a citizen' [72]. These points of view from Sackett and Haynes are fundamentally important to arrive at the definition of medical drug compliance. It shows a level of thought and fundamental reasoning that was achieved via consensus in the medical community. Whilst consideration was given to adherence and the fundamental differences it wouldn’t be till much later that it was seriously taken on board.

The medical community has been trying to adopt the term of adherence which suggests the patient is willing and amenable to the clinicians’ recommendations instead of compliance which suggests simply following guidelines. Adherence is a complicated problem that can be affected by various number of reasons such as the patient, type of therapy, pre-existing conditions, health system effectiveness and social and economic factors. According to the WHO, adherence is defined as ‘the extent to which a person’s behaviour, corresponds with agreed recommendations from a health care provider’. Additionally, adherence can also

involve a patient's overall healthcare application [73]. One of the patterns that has been identified within this literature review is the inconsistent nature in defining adherence. There are many different descriptions and it's worthwhile that the scientific community can agree and stick to a universal standardised definition. This will help and assist in describing the methods used in adherence and ensure the eminence, legitimacy and dependability of the methods and data analyses used [74]. As a result, the view held within this section is that adherence is an important measure that needs addressing within the realms of drug compliance. The stricter a drug regime is adhered to, the better the patient outcomes will be. Adherence can be measured by a degree which a patient obeys treatment plans as agreed without any break within treatment however, this varies from persistence [75]. Persistence is another term, individual and meaningful in its own right and separate from that of compliance and adherence. It can be referred to as the ability to 'persevere in continuous taking medications such as steadfastly in administering eye drops even though they sting and make the patient's eyes red'. Even though the terms of adherence and persistence are very much alike but still there are some differences among them. For instance, if a patient prescribes to take medication once a day but instead takes it every other day for the rest of prescribed course then the patient would be 50% adherent and 100% persistent [76]. The cost of poor adherence and persistence is expensive. It is suggested that a good scenario of patient medical adherence is estimated to be 75% and of these, 9% of all prescription are such that the script is not filled. Moreover, as the treatment plan is continued, adherence and persistence rates fall further with time. These range from 20% to 64% with reported findings suggesting patients that take a script discontinue treatment within 6 months [75].

2.2.1 Introducing Non-adherence

An important topic within the subject of compliance is adherence. According to the WHO report [77] "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any

improvement in specific medical treatments." This statement is important as a fact as it shows how the medical community takes adherence as a subject very seriously. It can be said that a patient is complying with their medication regime but what is not answered is how well they are adhering to the specific terms that have been set or laid out by the clinician. This gives rise to another component referred to as non-adherence. Non-adherence as a whole has the following consequences: -

- Waste of resources from the medication, both from production capacity and financially.
- Progression of the disease, so the medical situation worsening for the patient.
- Increased use of other medical and/or social resources as a consequence such as more hospital visits or use of nursing homes [78-80].

From another perspective, non-adherence can imply the failure of taking prescribed medication as well as discrepancy, missing doses, and failing to refill the medication [81].

2.2.2 Understanding Different States of Non-adherence

Many types of non-adherence exist; however, the description is without question. It must also be noted that in all types there are many similarities. The first type is primary non-adherence also known as non-fulfilment adherence which written prescription by providers are never filled or started by patient. The second type of non-adherence is called non-persistence which patients decide to stop taking medication after starting it without talking about it with a physician. The non-persistence is not usually deliberate and is as a result of miscommunication regarding treatment plans between the patients and providers. The third type of non-adherence is known as non-conforming which includes a number of behaviours that the prescribed medication isn't appropriately taken by the patient [78, 82]. These involve: -

- Missing doses
- Taking medication at wrong time
- Incorrect doses
- Taking more medication than prescribed

2.2.3 Evaluating Non-adherence

The challenge of non-adherence to therapy or treatment remains as a major concern among universal healthcare. Former US surgeon general C. Everett Koop indicated famously, 'Drugs don't work in patients who don't take them'. It's been anticipated that non-adherence annually cost between 100- 300 billion dollars in the United States and lead to around 125,000 deaths every year. Non-adherence to medication is an issue for many chronic health conditions such as glaucoma due to treatment not being effective. It's being reported that a wide range of 16-67% of glaucoma patients don't adhere to their medications and even less than a third of patients remained on their primary therapy after a year [73]. Around half of the patients who start glaucoma medications stop them within 6 months, even though patients who try to keep to their eye drop medication, research has shown poor performance. In a recent study, 140 glaucoma patients were video recorded during installing their eye drops into their eyes. The result presented that 18% of patients missed their eyes when dispensing their eye drops, and only 60% of patients administered the correct number of drops. Around 65% of patients dirtied the bottle by touching it to their eyes. Another research group of 324 glaucoma patients discovered that 20% of patients indicated that no one had guided them how to use their medications [83].

The impact of non-adherence can be stark. From the cost of the medicines to the long-term impact on the patient. In the most serious of cases there is a real risk of death should patients not adhere to their regimen. It is important to note that skipping vital doses of glaucoma medication will cause damage to the optic nerve and eventually cause vision loss. The same can be said for medications related to

the heart, vascular system and overall infection control. Should appropriate medication not be properly adhered to the consequences can be dire [77]. Generally speaking, patient adherence to glaucoma treatment plans is more often than not, quite poor. Having said that, it is strongly advised that regular attendance to clinical visits to perform monitoring activities such as visual field analysis and to examine medication efficacy takes place. It is already well known and established that using medication and intervening on an early basis to perform surgery greatly improves patient outcomes. Hence a better adherence to such appointments and drug regimens will improve outcomes [84]. A study that was used to establish a measure of adherence within glaucoma medication was conducted by Sleath et al [85]. It set out a method to record adherence and patient eye drop technique via direct observation, using a 6 and 10-point evaluation in relation to the medication and eye drop instilment. It held that patients who were less than 80% adherence measure, had a significantly higher defect within their vision. As such a conclusion is that health care providers should work to improve adherence in order to produce better patient outcomes.

2.3 Solutions to Improve Adherence

In order to improve adherence, there are several methods that can assist glaucoma patients. This can be achieved by improving enthusiasm and knowledge by emphasising the importance of adherence and persistence. Simple and practical steps such as providing a guideline to read at home or writing down the steps of using all drops can be incredibly beneficiary, it may be an idea to use a diagram. Moreover, the following actions can safeguard and ensure a better outcome which include; conducting frequent evaluations of the treatment regimen, providing training and monitoring of the patient eye drop technique, questioning patients regarding adherence and persistence and helping patients to adapt the treatment regime for their lifestyles [86].

Another method to improve adherence is applying medication reminders [87]. An electronic monitoring device that is combined with a reminder mechanism,

perhaps a link with one's phone would allow physicians to indirectly measure adherence and hopefully decrease patient amnesia [88]. It is stated in [87], according to Boland et al, adherence improved 35%, from a base rate of 54% to 73% by using telephone or text reminders. However, it's really important to select a proper type of reminder, as Saeedi et al discovered that email and text reminders are usually appropriate for young patients [89, 90]. Unfortunately, most patients don't realize the impact of non-adherence until the damage has been done. Another method to improve this issue is to provide a reward or an incentive in order to increase adherence. Giuffrida et al even paid cash gifts to their participants of the study to review different treatment plan effectiveness. These references state that 10 out of 11 studies indicated significant improvement in adherence among patients. Still, these studies were not focused on glaucoma patients and fluctuated across studies. More research is needed in order to obtain a new and smart way to cost-effectively improve medication adherence [91, 92].

2.3.1 Measuring Medication Adherence Among Glaucoma Patients

Adherence to glaucoma treatment changes notably with the age of patients. Elderly patients form a large portion of the glaucoma population, and they are particularly vulnerable to non-compliance [93]. However, younger patients appear to comply less because of an active family routine which leads the patients to forget to use their eye drops. Subsequently working behaviours causes the patients to be away from home for a long period of time further adding to adherence issues. Understanding the importance of taking medications can be affected by the patient's lack of education, as younger patients see glaucoma with the view that it is an older person disease. Moreover, limitation of time during working hours may prevent them to request their repeat prescriptions. It seems elderly patients especially those above 90 years age collect more prescriptions than they actually need. This is due to difficulty these patients have in order to instil medications, which cause eye drops to go to waste and eventually the patients run out of medications before the due date to refill, so the number of

collections of repeat prescriptions increase [94]. Topical medications are a good starting therapy in most patients. However, studies have indicated that using many such medications in order to target IOP is essential [95]. It's accepted that the use of eye drops for a lot of patients is quite challenging and there is always an increase in the risk of non-adherence, this eventually leads to the treatment to being less effective [96]. In comparison to oral medication, ophthalmic medication presents a more complicated task. It requires a degree of more skill than just ingesting a pill. Such skills include manual coordination and ability to correctly conclude a successful eye drop. Not all patients have such capabilities when it comes to self-administration and this is further compounded with age. It is clear that when the complexity of the treatment is increased such as adding a second eye drop adherence falls drastically [97]. Patients with two or more glaucoma medications are expected to experience difficulties with: -

- Remember to take their eye drops
- Side effects of their medications
- Suddenly too many eye drops come out
- Abnormal dosing times

In order to overcome these difficulties, providers should reduce the demands required from patients which also leads to better medication adherence [98]. Near one third of patients who are prescribed eye drops for the first time, stop collecting their prescribed eye drops within one year. Yet a noteworthy number of patients who collect their prescriptions, do not adhere well as prescribed. Stated rates change, as studies imply a non-adherence rate around 23 - 90%, however electronic monitoring systems indicate a non-adherence rate of 3- 40% [99]. It is stated in [122], according to Konstas et al, 15% of glaucoma patients were not aware of their non-adherence. The patients were actually taking their prescribed medications however they failed to apply their eye drops appropriately. Another factor that can be named for non-adherence is poor understanding of the disease. Better understanding of glaucoma disease can certainly improve adherence. It was also revealed that only 50% of patients knew the meaning of glaucoma and only 25% of patients understood enough that

blindness is an outcome [100]. A study by Stryker et al suggests four classifications of barriers which can affect negatively on glaucoma treatment adherence. These include provider factors, situational/environmental factors, medication regimen factors, and patient factors. Firstly, in studies of glaucoma, the relationship between the patient and provider is considered as a potential hindrance hence communication and trust issues are certainly important. Secondly, medication regimen factor such as number of medications, number of doses for each medication, and the instruction of taking each medication have shown difficulty in adherence. Additionally, patient factors such as race, gender, age, education, family history and socioeconomic status have a direct effect on glaucoma adherence treatment [84]. Even though some barriers such as medication's cost, poor health conditions might be impossible for providers to manage however, other activities that can be undertaken to improve adherence. These involve patient understanding of the disease, the communication within the doctor-patient relationship and developing systems for keeping adherence in check [101].

Like any other chronic diseases, glaucoma has low level of adherence and persistence. White coat adherence which is common among the glaucoma patients refer to those which their adherences increase greatly one week before their appointments with the physician, however, decrease quickly or even stop right after their appointments. White coat adherence cause problems to control IOP over time [102, 103]. It cannot be reasonably expected that someone should follow a patient and observe their administration of eye drops. Pharmacy data is good for a group of people rather than an individual [104].

Differing methods have been used to assess the veracity of adherence to prescribed drugs to glaucoma patients. This includes pharmacy refill records, self-reporting, electronic monitoring and external assisted dosage whereby another health professional such as a doctor or nurse administers and logs the results of drug administration [85]. All of these methods have their positive and negative points. For instance, pharmacy refill records, electronic monitoring and self-reporting do not report back on how successful the actual administering of the eye drop actually was and if the patient actually achieved success with

administering the eye drop. Whereas a qualified health professional would be able to see and verify that the eye drop was successfully administered. In such a case, it's easy to see that when a health professional comes and administers the eye drop in a clinical setting, most likely that of a patient which requires constant care, the logging and verification process can be reliably trusted. The downside to this is that it is a very labour-intensive process. Thus, self-reporting methods tend to show a trend that the patient through no error of their own can possibly erroneously report a false positive. This is evident through the fact these methods tend to have a much higher success rate in comparison to verified methods [105].

2.4 Compliance and Non-compliance

The definition of drug compliance is set out in many different papers. Urquhart states that it is the regime set by a clinician and is a measure for the level of adherence conducted on the part of the patient [106]. Another way of putting it can be set out by Bøgh [107] is the 'degree of correspondence between actual dosing history and the prescribed regimen'. This is dependent on the patients' willingness to conform to the prescribed regime given by the clinician. It is important that patients keep to their prescribed plan as the effectiveness of the medication can be altered by events of non-compliance, thereby hindering the progress of overall treatment. Scientifically, non-compliance is a major problem as it will hinder the progress of treatment. The most imposing question would be how an event of non-compliance can be measured. It is arguable that an event of non-compliance can be defined in degrees of severity. Typically, a clinician will instruct a patient to take their prescription at a certain time within the day. If a patient for example is non-compliant it can be argued that they won't be taking or following this medical advice for a 24-hour period leading to a compliance rate of 0%. This gives rise to the fact that it's also plausible that the patient can be partially compliant, they may not take their medication right there and then but later or earlier than the prescribed time. Others may argue in an absolute fashion either the patient has taken their medication, or they haven't. Either way more

research needs to be conducted into the measure of compliance [106]. Economically, medical non-compliance has imposed a considerable financial burden upon modern health care systems. This burden has been estimated to cost $100 billion each year in the USA [67]. Lack of compliance to medical advice is also a source of ongoing frustration to doctors. Compliance is important as it has been proven that an increased compliance leads to more successful treatment [108]. Methods that help increase compliance involve monitoring. By taking accurate readings of when the treatment was taken and if it was taken to the guidelines proscribed by the clinician it will enable a method whereby feedback can be supplied to the patient and real data can be used to judge how effective the treatment actually is. Sometimes it is difficult to achieve the desired health outcomes even with a high rate of compliance. This is in particular an amplified and aggravating feature when trying to quantify and evaluate the rate of compliance. Studies have shown that when a high level of compliance is achieved, it doesn't always mean a 100% success rate in terms of health outcomes [109].

A result of poor compliance with anti-glaucoma treatment is that a lot of patients still lose their sight. This lack of compliance is often caused by forgetfulness. It is much easier for a patient to say that they're forgetful rather than discuss their actual issues with the medication that they've been directed to take [108, 110]. There are other major reasons too; these include bad application of eye care and poor adherence to medical visits [108]. Side effects of glaucoma medications are another factor that can take precedence on patient's compliance. The side effects can be varied minor localised effects within the eye to more systemic effects that are amplified across the body [111]. With all this information in mind, it is imperative to be able to monitor and look at data for glaucoma patients. Sight when lost is permeant and cannot be simply be re-established after the fact. So subsequent understanding of how good or bad compliance actually is or effectively the quantification of such is critical.

2.5 Methods for Monitoring Adherence and Compliance

Classification used by the WHO for evaluating adherence methods are divided into subjective and objective methods however, many studies have divided them into direct and indirect methods [112, 113]. Direct methods are objective in nature but require a lot of resources both in terms of financial and human. They typically have features such as observing the patient, characterising their method and logging their timing. Moreover, other methods include; the measurements of drug concentration or use of biological markers [114, 115]. Direct methods prove that the drug has actually been taken by the patient. Detection of the drug can take place through biological fluid such as blood or urine. As mentioned before and confirmed by Farmer [116], biomarkers taken with a drug or placebo can be used to ensure that the drug has definitely entered the blood stream. Tests that can confirm this can be done randomly or at defined intervals.

A lot of methods that are used to measure adherence are generally indirect in nature as suggested by Farmer [116], then more so by Bansal and Tsai [114]. Indirect methods can be categorized as: -

- Self-reporting by the patient
- Measurement of the medication
- Electronic monitoring devices
- Prescription record review
- Patient questionnaires
- Clinical Response

Note the differences between a direct and an indirect method of monitoring. A direct method would have a form of verification that would make the result indisputable, typically a form of human verification that takes a significant interest in the patient or one that is able to obtain real-time live data. That's not to say it isn't fool proof or prone to human errors when reporting the results. An indirect method is void of this and usually relies on secondary data after the event of medication has been taken. Even though direct methods are believed to be more verifiable than indirect methods, there are still some practical

considerations regarding direct methods of adherence assessment. For instance, patients might display behaviours of active resistance to taking their medication, or there could be differences in metabolisms that effect on serum levels. Moreover, these direct methods are not suitable for clinical use [71]. One way that monitoring can occur is via pill counting. This is not so much of a hassle to commit to and doesn't cost much either to do. There is however a chance of inaccurate or false measures as the patients may not return the medication left over as told to do so. It is also impossible to verify if the medication is taken as prescribed [115].

Medication Event Monitoring Systems (MEMS) is enthusiastically considered as gold standard for measuring adherence, but they don't actually measure actual medication consumption. Moreover, the system lacks the ability to show the actual time the medication container is opened and closed. Another disadvantage of MEMS is the cost, due to the creation of software and the physical product components. The most common method for measuring adherence is self-reporting by patients. Advantages of such a method are that it's low cost. However, patient's cognitive ability to remember at times can be somewhat impaired and potential inaccuracy in reporting can be named as disadvantage of this method [115]. While adherence to medication remains a common issue in most countries with an advanced medical system, the ways which are being used to observe the behaviour of medication taking, are compared and reassess by a gold standard measure. Self-reported questionnaires (SRQs) and MEMS together can be named as an ideal method to measure medication adherence. The SRQs are simple and yet less expensive compared to electronic monitoring devices (this is reported in more detail in section 2.7) but the accuracy of this method needs to be re-evaluated constantly in order to achieve reliability of SRQ data [117]. Detecting whether an eye drop is successfully administered to the eye is innately challenging. But also determining the level of adherence which is required to lower IOP adequately is still intangible. Earlier studies indicated that levels of adherence when self-reported were considerably higher compared to MEMS [99]. Table 2.1 shows the different testing methods both of direct or indirect and their advantages and disadvantages reproduced from [118].

Table 2.1: Methods of measuring adherence reproduced from [118].

Test	Advantages	Disadvantages
Direct methods Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and 'white-coat adherence', can give a false impression of adherence, expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive, requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient's diaries When the patient is a child, questionnaire for caregiver or teacher	Help to correct for poor recall Simple; objective	Easily altered by the patient Susceptible to distortion

2.6 Compliance Among Glaucoma Patients

Successful compliance among glaucoma patients involves taking the correct amount of medication that has been prescribed by a physician at the appropriate time. The chance of maintaining the remaining eyesight reduces if the patients don't comply as their physicians prescribed. Furthermore, the efficacy of medication can be questioned by the physician which might lead to supplementary medications or avoidable surgery [119]. Non-compliance has an important role in progression of glaucoma and visual field damage. If patients have interruptions during their treatments and restart medications right before their clinic appointments, they might seem to have a decent IOP however they likely have visual field progression due to an interruption in therapy [120, 121]. It's been anticipated that around 10% of visual field defects are the reason of non-adherence [122]. Thus, before changing medications when visual field deterioration is seen, compliance to medications should be proven. So, for the purpose of improving compliance and adherence among glaucoma patients, it's important that physicians identify 'obstacles early on in the treatment plan and plan therapeutic interventions accordingly' [120, 121].

According to Tatham et al [123], there is also the question of correct application. Incorrect technique can lead to a recording of good compliance based on a typical electronic method however this is obviously not the case. It also leaves open the possibility of data fouling. Good compliance and bad application especially in eye drops, it can give the impression of a poor drug response and give the clinician the wrong information. It would also be sensible to further research and suggest an appropriate solution. Patients with glaucoma or retinal disease are most in need of a good compliance regime. Yet as previously discussed the challenge isn't just good compliance but good application alongside it. Identifying both seems to be increasingly crucial [124]. Non-compliance within these patients is pretty common and difficulty in self-administering is high at 50% [125]. For some patients, glaucoma surgery is a solution to prevent compliance problems [126]. Breusegem et al discovered that patients who had trabeculectomy added with

topical ketorolac or fluorometholone had less requirements for postoperative IOP-lowering medication [127].

There are several different aspects that the health care community should understand in order to improve compliance. One of the main factors is that they need to teach patients the steps of how to use their eye drops properly. It's important that assumptions aren't made to this effect. Notwithstanding, patients can be made fully part of their own treatment plans by displaying all options available to them should dosage and side effects be too troublesome. One option is to minimise the dosage rates however, it is important to allow patients to make up their own minds about what's best for them including laser and alternative surgeries. Lastly, it's also really important to arrange an appointment with patients to discuss about dosing techniques, side effects and any other issues. Communications between physicians and patients is an important factor in compliance. Most patients expressed their understandings of the importance of compliance in order to stop progression of glaucoma. Though the risk of going blind is not real to a few patients which shows very poor compliance [119]. The American Glaucoma Society (AGS) has suggested the following for the improvement of compliance [114] : -

- Practical tools and tips such as memory aids, keeping time and tracking tools.
- Modification for bottle design to improve dose application and to keep track of how much product is left in the bottle.
- Better educational materials that will prompt the patient to be more compliant.

However, whilst the AGS has suggested these, better practice can be employed. It must be considered who the main demographic is and the implications of these. Especially in the elderly and those with accessory diseases such as Alzheimer [114].

2.7 Electronic Monitoring

So far it has been established that non-adherence is a major issue in treating disease. It's also safe to say that the debilitating effects have a major impact on patients. It's therefore imperative that a widely accepted solution amongst the scientific community comes to the fore for a method of quantifying compliance/recording compliance outside the clinic. An electronic monitoring system is able to provide information regarding adherence to ocular hypotensive medications among glaucoma patients. Electronic monitoring devices are known as the most accurate methods to determine adherence. An advantage of an electronic monitoring system is it can provide the information regarding time and date, every time the medication has been taken by the patient, so a better understanding of adherence behaviours can be achieved. Whereas, both self-reporting and records kept by the doctor can have different disadvantages such as false records, bad writing and postulations [128]. One of the main issues in being able to design and employ an electronic method of measuring adherence would be the US Food and Drug Administration's (FDA) rules and regulations and the same sorts of things apply for the Medicines and Healthcare products Regulatory Agency (MHRA). These are time consuming and add another dimension to getting approval of a device. It's not only the eye drop medication that must seek FDA approval but the design and special characteristics of the bottle holding the medication. To that end whichever eyedrop bottle that's employed must also be using its certified container. Researchers cannot just use any bottle and due to this fact, a solution must be made that can account for all eye drop bottles. This can be challenging as all eye drop bottles vary in size and shape [104].

Current products on the market include MEMS by Aardex (Figure 2.1) or the Bang & Olufsen helping hand product (Figure 2.2). Each having its unique features with positives and negatives. The helping hand product for instances helps with keeping the drugs in their blister packs so as not to tamper with the drug stability [129].

Figure 2.1: The Medication Electronic Monitoring System (Aardex) [129].

Figure 2.2: The Helping Hand (Bang & Olufsen Medicom) [129].

From research, it has been understood that attempts at different systems have taken place with varying levels of success. One of the major challenges in drug compliance is finding an effective method for monitoring compliance. Systems have been invented in order to deal with monitoring, all of which have their advantages and disadvantages.

It should be noted that similar attempts have been made in the past. For example, a system that was used to monitor eye drop medication by Hermann and Diestelhorst [130] involved the use of a microprocessor and a set of sensors. A tilt sensor would detect the vertical position and a pressure sensor would detect the force applied to the side (as shown in Figure 2.3). The results from the paper are as follows: -

- 15 applications per bottle making 150 total eye drop applications
- 149 correctly identified applications
- Apparatus sensitivity of 99%
- Detection specify of 98%

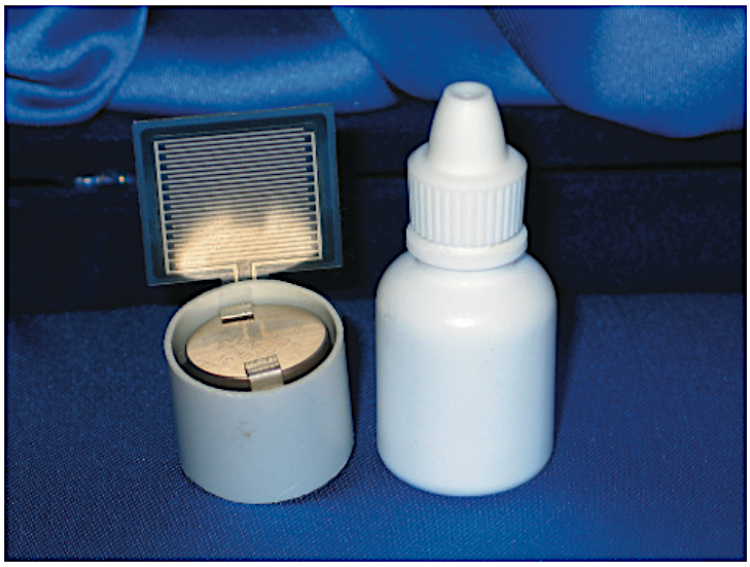


Figure 2.3: System designed by Hermann and Diestelhorst [130].

These results are quite promising however, it cannot be conclusively established that the hardware did produce these results as some manual counting did occur. So therefore, it would only be fair to replicate this in order to verify these results as part of a comprehensive review along with other systems and compare their effectiveness. This will help establish the difference between good systems and bad systems.

Whilst not completely related to eye drop compliance, it's worth looking at different applications. In asthma patients, a key component to their treatment is an inhaler. As such it is now possible to look at the differing details in compliance such as dosage and effectiveness. This is made possible through the use of an electronic spirometer which can analyse the total gaseous intake, given the fact that the medication is taken in a gaseous format. Data is downloaded from the device and the device takes an active role in drug administration. Whilst the device perhaps can give a wealth of insight and accuracy it isn't perfect and is subject to failures [131].

2.8 Training as a Tool to Improve Compliance

The placement of an eyedrop or its administration is commonly referred to as instillation or to instil an eyedrop. A majority of patients are not able to instil their eye drops since eye drop instillation is not taught when they visit a clinic. Within glaucoma patients with visual field impairment, one third of patients who thought that they could instil their eye drops properly, failed to do that when they were monitored and recorded [132]. It would be logical to suggest that one-way compliance and adherence to eye drop instillation in patients can be increased is to evaluate their method of dispensing. Patients that have a successful outcome should be analysed just as much as patients with less than satisfactory outcomes. From these results, it is then possible to determine if training is required and thus if it should be provided. The subsequent results can then be applied to look at the outcome again. One such study did attempt to monitor the effectiveness of patients by using two masked graders and showing that 54.1% of patients had a

poor drop technique. Other observations included that the top of the bottle touched the cornea amongst 15.3% of the group, 27.15% touched the eyelid or lathes with the bottle top out of a group of 85. Moreover, 81.2% could not say if they've actually been shown how to dispense eye drops. These statistics clearly show that training in its own right can be used as a tool to improve compliance [123].

2.9 Electronic Monitoring to Measuring Adherence Within Glaucoma Patients

A study by Boland et al evaluated monitoring for adherence to glaucoma eyedrop [133]. The study involved using a 100ml clear plastic bottle which participants advised to put their eyedrop bottle in it. In case of using more than one eye drop, a second bottle is necessary as no system for monitoring more than one eye drop is available. The MEMS cap (designed by AARDEX Group Ltd) is an electronic bottle cap device which when removed can record the date and time of intended usage providing the eyedrop bottle in stored inside the proceeding container. The participants were guided to keep their eyedrops in the clear bottle and keep the MEMS cap on the bottle unless they need to take their medications once a day. During study visit, by connecting the device to the computer, the event logs could be obtained. Figure 2.4 displays the electronic monitoring system that been used for this study.

The result indicated that 407 out of 491 (82.9%) participants completed 3 months adherence experiment successfully. Around 82.8% of this group took their medication at least 75% of days correctly whom considered adherent. Lack of education, race, having depression and mental problems were the important factors among the non-adherence group. Electronic monitoring for measuring adherence within glaucoma patients reveals that a significant number of patients don't take their prescribed medications which causes higher interocular pressure and eventually leads to a worsening of the disease.

Figure 2.4: Monitoring system for adherence to glaucoma eye drop [133].

Another study by Alan L. Robin et al evaluate adherence among glaucoma patients by using electronic monitoring system [134]. The patients were divided in two groups: those with one drop of prostaglandin analogues usage per day as group one and those with two drops prostaglandin analogues as group two. The experiment took around 60 days. 62 of subjects suffered from OAG or ocular hypertension. Half of the subjects took one medicine and the other half took two medicines each day. An electronic monitoring device to monitor every time the bottle being opened was used (as shown in Figure 2.5). The results indicated dosing errors such as number of under adherence or over adherence events. After the end of 60 days, patients returned the MEMS cap to the clinician, so then the data is transferred to a computer from the cap. The results indicate that in both groups the adherence to one daily eye drop was good with only ≤10% of subjects with more than five dosing errors and mean coverage 97.2% ± 6.1%, however the adherence to the second eyedrop in the second group was poor with 37% of patients with more than five dosing errors and mean coverage of 85.6% ±12.6%. Figure 2.6 presents a map of three hypothetical patients.

Figure 2.5: The picture above displays a standard pharmaceutical prostaglandin bottle with MEMS cap which used to measure adherence of eye drop electronically. The '2' on the cap implies two usages within 24hrs [134].

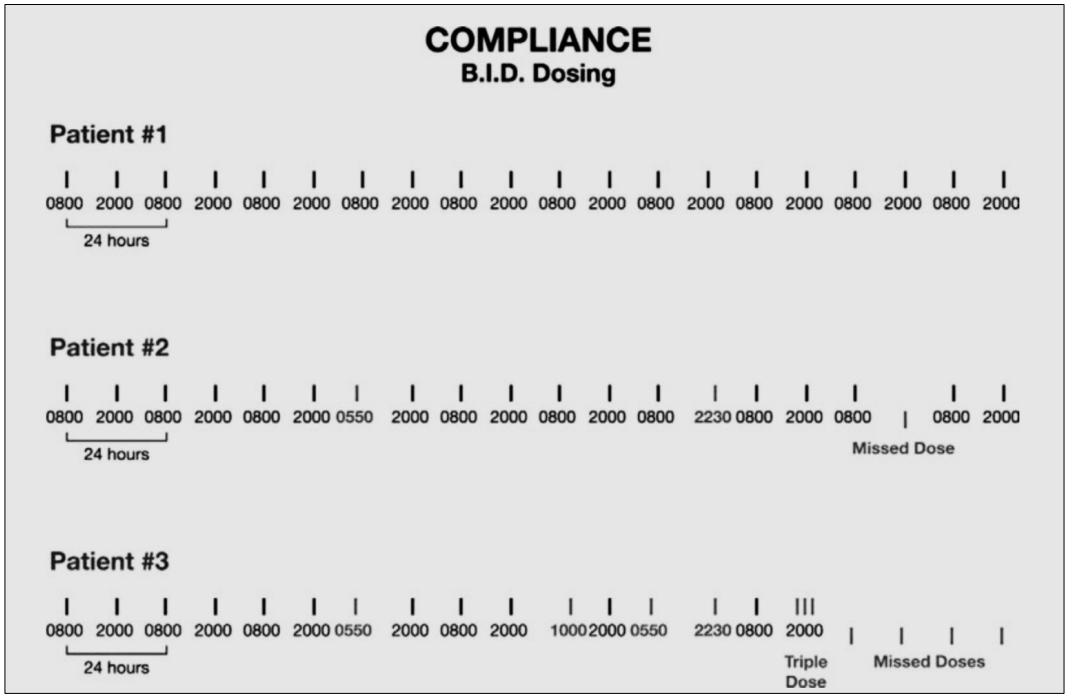


Figure 2.6: Examples of adherence behaviours among the subjects. As it's shown, patient 1 had an excellent adherence. Patient 2 and 3 had early, late and missed doses, however patient 3 had overdosing as well [134].

Unlike the clinical setting, the method of using MEMS cap requires additional stages which include: -

- Open the MEMS cap
- Taking the eye drop bottle out of the container
- Putting back the bottle in the MEMS cap container
- Replacing the MEMS cap

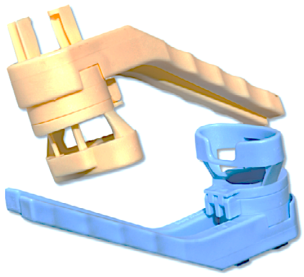
What is really needed is a precise, indirect and non-obstructive method for determining and monitoring adherence [135].

The System I part of this project is similar to the MEMS cap. However, there are some differentiations between the two. First, to use the MEMS cap, patients require training, however an unobtrusive nature of the proposed System I means there is no training needed. Secondly, the MEMS cap can be subjected to record false data. For instance, the patient might open the MEMS cap but then can be distracted to do another task. The System I is not affected by this and records only when eyedrop bottle is squeezed.

2.10 Devices That Facilitate the Administering of Eye Drops

There are a range of different devices that can help with the manual administering of eye drops and thus improving the ability to take adherence and compliance measurements according to the International Glaucoma Association (IGA) and Moorfields Eye Hospital. These are summarised as shown in Table 2.2.

Table 2.2: Selection of devices in the market [136-138].

	
Opticare; a hand-sized dispenser that will aim for the eye in an accurate manner. It is usually good for round eye bottles.	Autodrop; a small device that can be used for a number of eye drop bottles and helps with the aiming of the drop into the eye.
	
Alcon Eyot is designed to fit the shape of bottle and makes it easier to place the bottle over the eye and squeeze it especially for people who have difficulty to squeeze the bottle.	Opticare Arthro; a variation on the device shown and described above but with longer handles for those with hand and arm mobility issues.
	
Dropaid is designed for accurate positioning and easier grip control especially for those with limited thumb movement by using other fingers to hold the levers which squeeze the eye drop out.	Autosqueeze is an addition to the auto drop for those who have issues in squeezing the bottle.

2.11 Other Devices That Facilitate Measuring Compliance

As previously discussed in section 2.2.3 and 2.8, separate reported studies used video recording of patients during self-administered eye drops. It is also explained in detail earlier in section 2.7 and 2.9, that various electronic monitoring devices have been industrialised for measuring adherence and in order to assist patients with their adherence to eye drop treatments. Even thought, these devices are performed to monitor patient's compliance to eye drops, they all fail to express if patient's eye drops actually get into their eyes. Therefore, a main question remains and that is how to be sure that the compliance and adherence to eye drop was successful or more accurately, how can it be certain that the eye drop has been applied correctly and the droplets inserted onto the eye. The answer of these questions can be answered by vision. Nowadays, among all subjects and areas of medical research, the use of imaging, analysis and computer vision are increasingly in demand particularly in the ophthalmology field which are indispensable. A range of diseases and medical conditions can be detected and diagnosed by the use of medical images [139]. A common issue along healthcare staff is to monitor patient's adherence to medications precisely and providing real-time feedback regarding adherence to medications by patients. The majority of available monitoring system on the market concentrate on measuring adherence to pill medications rather than eye drop medications as such it's a major issue for eye drop treatments [140]. It's been suggested that non-adherence among glaucoma patients has a range between 30% to 80%. Along with the development of smart phones, technologies are being utilised to assist with eye drop adherence. Though, the previous electronic monitoring devices had hardware which was clunky, it also had software issues which made them not effective for improving eye drop adherence [141]. Aguilar-Rivera et al develops a "smart drop" bottle alongside wireless technology to deal with the issues occurred in the past. The smart bottle consists of sensing electronic components which detects eye drop administration. Aguilar-Rivera et al 's smart bottle requires no change in the size and shape of eye drop bottle. As shown in Figure 2.7, the way their system works is a thin force sensor that encompasses the bottle leading to the bottom which has the

appropriate electronics. This detects eye drop administration and the data is then transfer wirelessly to a smart phone. The success rate here is claimed to be 100%, this is an interesting possibility [141].

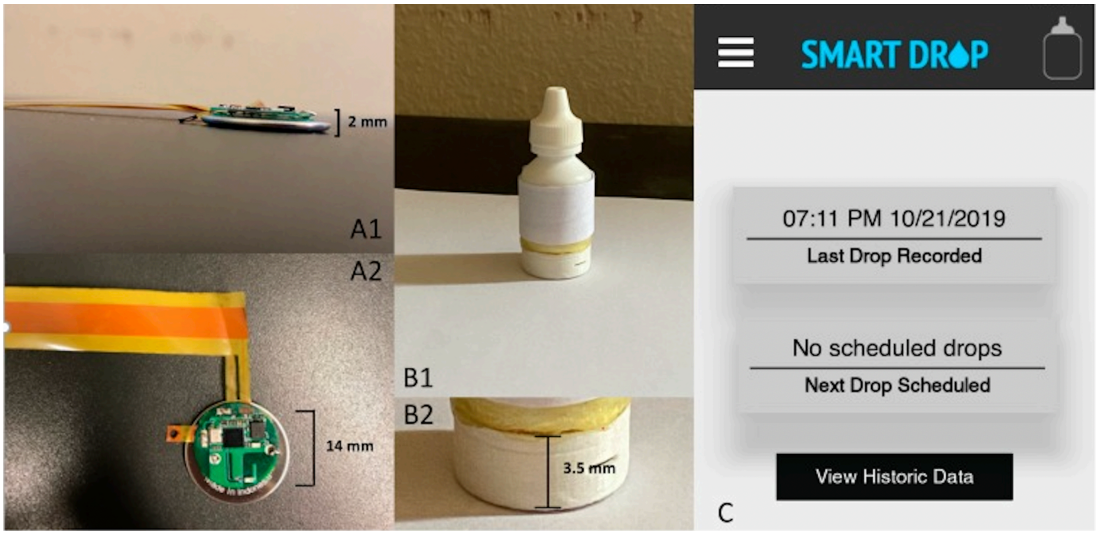


Figure 2.7: A1) Side view of the smart drop system which consists of pressure sensor to detect bottle squeezing and a thin electronic circuit to process the signal and transfer it wirelessly to smart phone application. A2) Top view of the sensor and electronic circuit underneath the bottle. The diameter of the circuit and the battery are around 14 mm in diameter. (B1) Flexible sensor is place underneath of bottle's label and the electronic circuit is placed under the bottle. (B2) Plastic case shelters the circuit and the battery underneath of the bottle. (C) Bluetooth, enables the smart phone app to communicate with the bottle and track eye drop adherence [141].

Aguilar-Rivera et al, the smart drop bottle, is similar to the proposed System I of this research. There are, however, significant differences in the overall design. Both the sensor and electronic circuit of System I wrap around the bottle and are flexible in nature. Also, the smart drop bottle wouldn't tell if the droplet landed the eye unlike System II of this research.

Payne et al, introduces an intelligent bottle sleeve that goes onto an eye drop bottle. What this intelligent sleeve does is to observe the usage of an eye drop by patients and measures fluid level left after applying an eye drop. This information is then transferred to clinicians for review. The sleeve consists of an electronic embedded system which measures the level of fluid in the bottle, the direction of the dropper, the state of the lid (if it's screwed on or off), and difference of angular motion during an application presumably with an accelerometer. The testing of the sleeve took place on ten patients with the age either 65 years old or above and got a rating of 94% success with 0.4 ml resolution. The data of testing transfer to the clinicians via Bluetooth and Wi-Fi in real-time, enabled quick feedback to the patient. These data's enable the clinicians to monitor and log usage of eyedrop by patients in order to make accurate decisions regarding their treatments [140]. Figure 2.8 outlines the overall steps of the system.

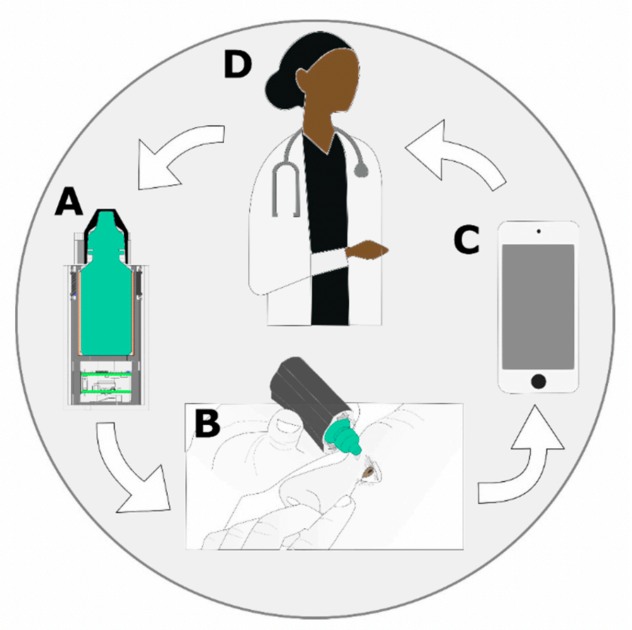


Figure 2.8: (A) The prescribed eyedrop bottle is placed in the intelligent sleeve which is embedded with electronics and sensors. (B) Data from the sensor collects information regarding the usage and the level of fluid in the bottle. (C) Data transfers from the system to a smart phone or any device with Bluetooth connectivity. (D) The clinicians process and analyse the information to be able to make accurate decisions regarding the treatment [140].

Figure 2.9 is the drawing of bottle and sleeve assembly.

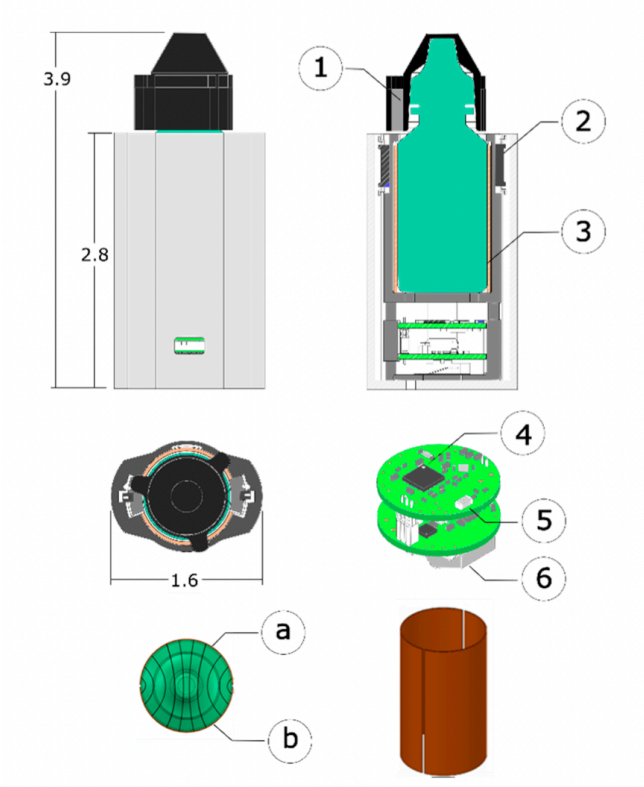


Figure 2.9: (1) Placement of bar magnet in the eyedrop cap. (2) For sensing cap removal, the use of reed switches, are employed. (4) A nRF51422 system on a chip is used with its associated electronics. (5) Bluetooth chip used for data transfer. (6) Coin battery for powering the system. (3) Custom designed capacitive sensor with two rectangular copper sheets surrounding the bottle. Electrical field is measured using this formed sensor highlighted via (a) and (b) [140].

The system described by Payne et al, the intelligent bottle sleeve is like System I and can log usage of an eyedrop application, in terms of placing around the bottle. Use of an accelerometer in their device provides information regarding the orientation of an eyedrop bottle, however it doesn't detect whether the droplet reaches the eyeball.

An experimental study has been conducted by Eaton et al in order to estimate the capability of an innovative, compact, reusable and economical device defined as the Eye Drop Application Monitor (EDAM) which enables the clinicians to make each patient's treatment regime distinct based on their drop performance data. As shown in Figure 2.10, the EDAM device consists of a video monitoring system which records the time and patients' self-administering their own eye drops. As such it is completely independent from any indirect testing methods including, judging the remaining fluid in the bottle via weight and analysing the time an eye drop has been initiated. The clinicians would be able to then notice how much eye drop has been dispensed and how much actually went into the eye. For easy observation, this information then transfers to a computer and database which enables the clinicians to monitor the compliance of patients to eye drop inclusion. The patients also have an advantage to evaluate what they do incorrectly during their eye drop application. The clinicians can then assist the patients to increase the performance of their self-administering or recommend an alternative treatment. EDAM was tested on two different group of patients, the ones who were in clinic and the ones were at home in a period of one week. Self-reporting by patients alongside their prescribed treatment regime has been compared with the results of a video recording via the database which collects significant data including how many drops were distributed and how many were successfully delivered to the eye. The results indicate that the data of both dispensing eye drops and number of drops which ended into the eye were notably different compared to the prescribed treatment regimen [142].

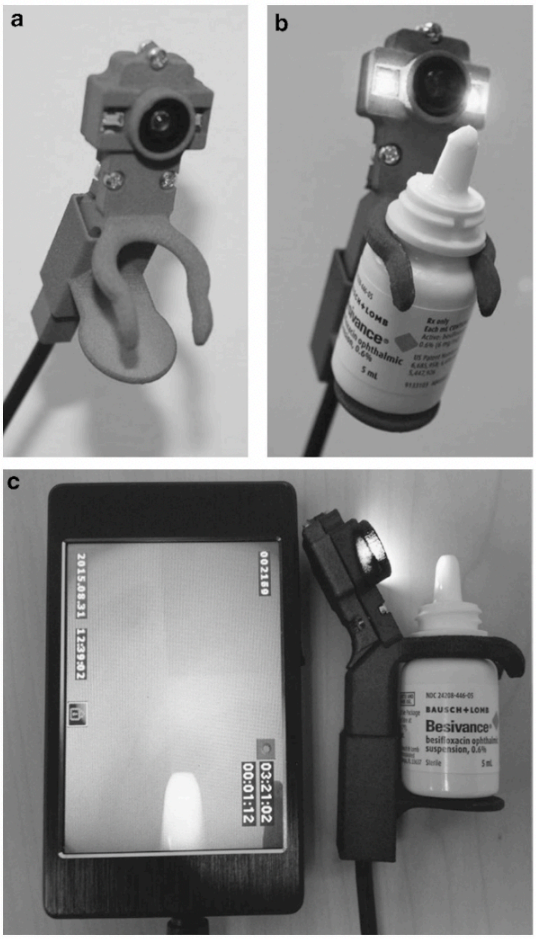


Figure 2.10: The EDAM device. (a) The EDAM with lights off, (b) The EDAM attached to a bottle with lights on and (c) The EDAM with attached bottle connected to the recording device [142].

The EDAM device is similar to System II in that it uses a camera. However, System II stands out since no human interaction is needed in order to check if the droplet successfully reached the eye after an eye drop application. This automatic detection puts the EDAM system as a disadvantage since it requires expensive and time-consuming monitoring by clinicians.

Following the introduction of devices that utilise vision, Nishimura et al created an eye drop bottle sensor system (as shown in Figure 2.11) which takes a motion sensor and smart software to accurately measure compliance of patients with anti-glaucoma ophthalmic solution therapy. The device was tested among 20

patients with OAG which were treated by eye drops in both eyes. The patients were told to dispense eye drops for 3 days and record their drop administration manually. The results of the system including its ability of data collection include the following factors: -

- Data was automatically collated from the eye drop bottle sensors.
- Comparisons were made between the electronic data capture and the self-reported data.
- The data from the electronics indicated 100% eye drop inclusion.

According to Nishimura et al, the data from their device indicates that not only their device can be used by glaucoma patients in order to assist them with their adherence but also it can benefit glaucoma treatment [143].

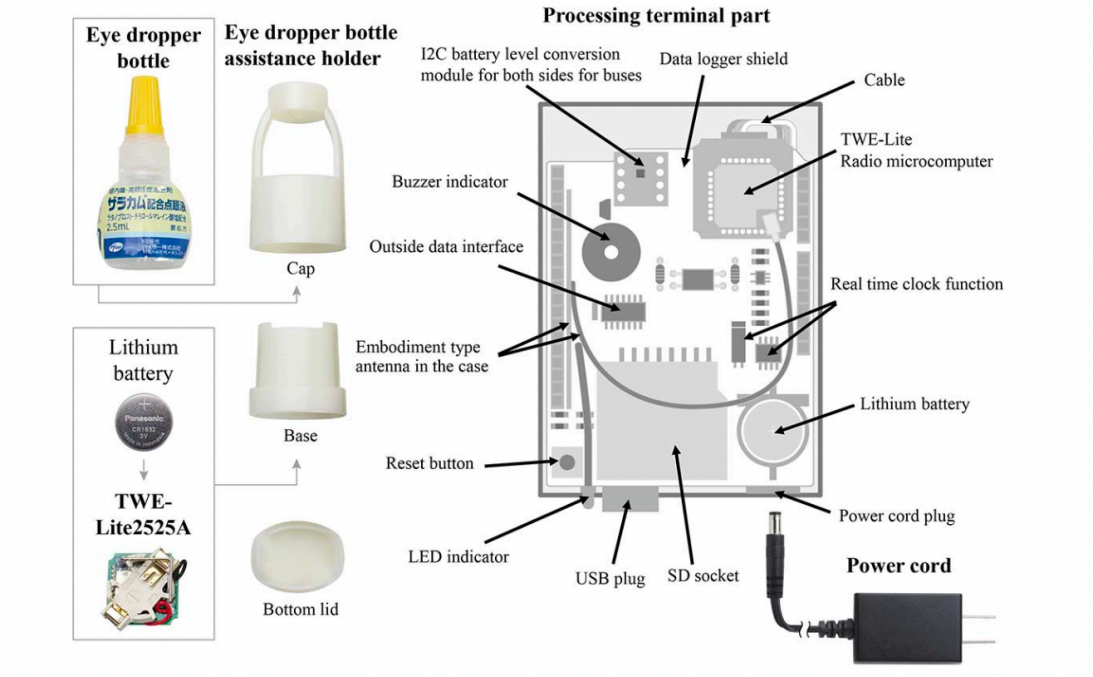


Figure 2.11: Design of the eye dropper bottle sensor [143].

2.12 Summary

The view held within this chapter is that adherence is an important measure that needs addressing within the realms of drug compliance. The stricter a drug regime is adhered to, the better the patient outcomes will be. Adherence measurement can be divided into two categories, with each having its own advantages and disadvantages; direct and indirect methods. The specific interest lies within the electronic monitoring capabilities and how current devices can be improved upon. With further research and development along with combining existing technologies, great advancement can be made in the understanding of the field of compliance. It is apparent however that the scientific community takes the view and believes in solutions such as MEMS and differing electronic monitoring. It is useful and beneficial among patients with serious health conditions which compliance to medications play a major role, including glaucoma patients. There are various methods to improve adherence and compliance to eye drop treatment among glaucoma patients. However, the majority of these methods neither direct or indirect methods fail to confirm if the droplet goes onto the eye after patients have self-administered their eye drops. Vision subjects can assist on this matter and indicate if the droplet is actually reached the eye with no failure scenarios. Few devices introduced in this chapter have not only improved adherence among glaucoma patients but also have assisted monitoring and recording practices of self-administering by patients.

Having reviewed the literature and considered possible options to move forward, it was decided that two extremely different technical solutions be researched. One being a simple, low cost, almost disposable bottle sensor system, the other being a far more advanced vision-based system. The common theme, however, is that they both exploit embedded systems and are not reliant on personal computers. Therefore, they have the potential to be small, compact and be low power.

System I, highlighted in Chapter 3, builds on a small-scale Peripheral Interface Controller (PIC) microcontroller, and advances a proposal from the School of Ophthalmology at Cardiff University. The novelty of this is in the integration of

sensors, microcontroller and near field communication (NFC). This author acknowledges that there are similar systems in use, but the combination of flexible printed circuit boards (PCBs), batteries and NXP based NFC circuits is novel in this context. The closest competitor to System I would be the MEMS cap. However, unlike MEMS, the patients don't need any training regarding the use of the device. Also, MEMS can provide false data regarding taking eyedrop which is not the case in System I.

System II, highlighted in Chapter 7 has a great novelty factor, whilst other studies and papers have looked at similar techniques the application here is fundamentally different. It exploits a more advanced embedded system in the form of the National Instruments (NI) myRIO. It uses a simple webcam and exploits the vision toolkits available in the LabVIEW software suite. A robust detection system for eyedrop delivery is presented in this section and includes a brief summary of an investigation into the use of Artificial Intelligence (AI). The physical delivery platform could be similar to that shown in Figure 2.10 and described in [142]. System II diverges in functionality from that described in [142] such that eye drop inclusion is detected and recorded without the need for subsequent review by a clinician.

Chapter 3

System I- PIC Circuit

3.1 Introduction to Proposed System

From the research that has been conducted, this project will seek to present a possible solution to the problems encountered. The outcome here is to be able to design a system to monitor the compliance of eye drop use in glaucoma patients and help improve patient outcomes. This facet of the work looks at a small, low cost, 'simple', embedded system, sensor and battery configuration that could be mass manufactured and almost disposable. These improved outcomes should come about via better monitoring hence the need for an electronic system that can automatically log data ready for analysis. More data will help enable better clinical decisions to increase drug efficacy.

3.2 Proposed Benefits

As discussed within the literature review in detail the benefits of having a monitoring system would mean that more data can be gleaned and the subsequent efficacy of the drug can be analysed better.

A summary of possible benefits include: -

- Ways to assess the accuracy of results.
- Occurrence of eye drop instillation.
- Analyse the occurrence false positives.
- Learning about the measurand for compliance to treatment.
- Understanding the amount of force required for typical eye drop inclusion.
- No form-factor change from the shape of original bottle (paper-thin).
- The unobtrusive nature of the system which will lead to no training required for the patient to use.
- Looking at circuit power consumption and minimising its usage.

Even more so, further work can occur with regards to the data analysis and definitively prove any unknown measurand quantities. Without more research, these can be difficult to determine.

3.3 Circuit Specification

When designing the circuit, several factors should be considered. These include the type of sensors that is needed to gain the required information and to accommodate the nature of the device itself.

The circuit must be: -

- Compact in nature
- Take force measurements
- Log usage
- Transfer data to a clinician

To do these things, the circuit will require a force sensor. There is also a requirement for a suitable microcontroller and battery management system. Not forgetting a wireless communication method such as an NFC device.

3.4 Measurement Data That Is Being Sought

In order to take the appropriate measurement data, the amount of compliance of the user should be quantified. This is achievable by having sensors that can judge if a successful eyedrop has been affected. The method here would be use of a force sensor with a microcontroller logging the data. This data will be transferred by way of wireless communication such as an NFC chip.

3.5 Force Sensor

Investigations have been carried out on appropriate force sensors for use within this project. Later in this thesis more details will be provided on the selection procedure and evaluation process namely in Chapter 5.

3.6 Microcontroller

When selecting the microcontroller, there is a clear ultra-low power consumption requirement. This severely narrowed down the available microcontrollers available on the market. Moreover, the following essential features were needed: -

- Low power demand
    - Used to conserve battery power
- On board comparator
    - For the sensing side of the circuit
- Sleep mode setting
    - Conserve battery power
- I2C communications
    - To connect to the NFC chip and transfer data
- Small in size
    - Keeping the board and its electronics as small as possible

- Limited in number of pins
    - Keep the sizing requirements

After some research of available products on the market the manufacturer, Microchip Incorporated USA, seemed to have a microcontroller that satisfied the initial requirements. Thus, a sample of Microchip's PIC microcontroller option that seemed to satisfy such a requirement was ordered for evaluation.

For the evaluation of the microcontroller very simple programs in C were created and complied to see the ease of use. This involved use of a development board and simple LEDs that can be manipulated to blink as an example. After these were completed, it was determined that the microcontroller would be suitable to the cause.

3.6.1 Crystal Clock

A crystal clock is needed in order regulate the time on the microcontroller so it can sleep and get awoken periodically. This switching of different modes between sleeping and active mode is also needed to regulate the power. The periodic switching allows for the microcontroller to come to a state that can monitor if the device is being used and is in a state whereby the eye drop is being ejected.

3.7 Battery

A thin and flexible battery is required that can be wrapped around the bottle which can withstand the various pressures and stresses of be being manipulated in various ways. Details of this are presented in Chapter 4.

3.8 Wireless Module

One of the most acceptable ways to pass data from the device to a main computer which is capable of transferring data is to use an NFC module. NFC's have shown prevalence in our current daily lives, one great example is for the use of contactless payments which make life convenient and easy to use. However, in this case it is to be utilised in order to improve the lives of patients.

There are two types of NFC's, one is active the other is passive. Active NFCs are circuitry whereby the data is liable to change and needs active components. Passive circuitry is useful when the data is not liable to change and doesn't need active components to function. In this project the data is constantly liable to change and would therefore require active circuitry. The disadvantage to all active forms of devices is that fact that they require power consumption.

NXP Semiconductor in the Netherlands have made an appropriate module that was tested and used in this project as it met the desired requirements such as data storage and small chip design. It should also be noted that the flexibility of the NFC and the passive power nature of the NFC tags gives rise to its use. In fact, the prime reason for using an NFC tag is due to the need that no local power source would be required. An important requirement is the need for extremely low power consumption, this is additionally why the NFC is the obvious way to go as it does not require power for the transfer of data.

3.9 How the Circuit Works

The theory of operation for the overall circuit is that the data from the sensors is collected by the microcontroller. This is then sent over wirelessly through the NFC module. The microcontroller will be programmed to this effect and the data will contain various pieces of information such as date and time of detected bottle usage. The system consists of microcontroller, sensor, NFC, and battery.

A battery management system shall be in place to ensure that the onboard battery doesn't get used too quickly by the active components in the circuit. A simplified block diagram (as shown in Figure 3.1) is shown below which demonstrates the main components to the circuit.

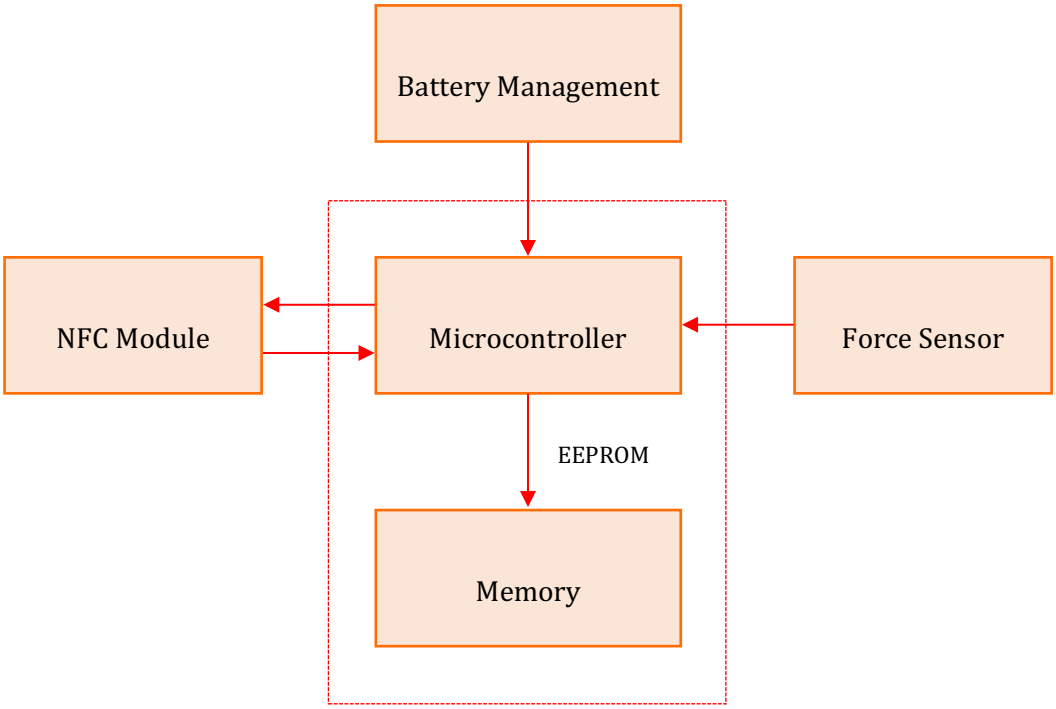


Figure 3.1: Simplified block diagram of overall System I design

3.10 Software Needed

Given the multiple differing systems that were used to form the overall system it is also important to the note the role of software that would be needed to get the system working. Software is needed to be loaded onto the microcontroller which is made in C and all test applications for either evaluating or discovering more information and observing various behaviours for the different parts is made in NI LabVIEW. This is covered in further detail later in this thesis.

3.11 Summary

This chapter provided a brief insight into the components and tools that were available to this project at the time. The focus of research in Chapter 4 focused on the flexible battery which is a relatively new technology at the time of writing. Similarly, Chapter 5 details the various force sensor options that were provided for this work. The choice of PIC and NFC platforms presented in Chapter 6 were largely pre-determined by the originators of this research and as such, there was little scope for reviewing a wide range of alternatives.

Chapter 4

Battery Management

4.1 Introduction to Battery Requirements

The requirements of the battery for the eyedrop bottle application revolve around its thinness, flexibility and charge holding capacity. Ideally the battery should be as thin as possible. More realistically, the flexible circuit board reported in Chapter 6 has a basic (unpopulated) thickness of less than 1 mm. The commercially available battery selected for evaluation (Section 4.3) has a nominal thickness of 0.7 mm. Accordingly, the review provided here considers batteries approaching such thickness values.

In a similar manner the battery should be flexible enough to be wrapped around an eye drop bottle, of 23 mm diameter in this study. There are a number of ways that the implementation of this can be put into effect on a larger scale. The bottle can be supplied to drug manufacturers as an option with this technology or it can be added afterwards during the labelling of the product. Finally, it was deemed that a relatively large charge holding capability is not a critical requirement for the study. The selected battery has a nominal 20 mAh rating and the testing reported in this chapter conformed the sufficiency of this charge rating.

4.1.1 Review of Soft Battery Technologies

It was decided that soft batteries should be considered, reviewed and evaluated, when considering flexible battery technology as no other major commercial alternatives are in place. Further it was deemed important to analyse the behaviour of the battery, for example when subjected to cyclic loading during experiments to simulate eyedrop bottle squeezing.

4.1.2 Fallback Position

A fallback solution was decided in case the soft battery evaluation determined that it's not suitable. The fallback was that a circular standard button ('coin') battery would be used instead. It is, however, reported that for some types of eyedrop bottles, the user should actually apply force to the base of the bottle. Many users may be more familiar with squeezing the sides of their bottles when applying drops. The implication is that the convenient and likely positioning of the button battery would be attached to the bottle base. If this needed to be adopted then it would restrict, for example, any subsequent field studies to only side bottle squeezes.

4.2 Battery Technology

As stated, this research application, for the currently reported research and in the future, will require a thin, flexible and suitably rated battery. Increasingly in the last decade there has been speculation that the flexible electronics market will increasingly manifest new and innovative products. Wendler et al [144] reported on the commercial availability of such devices. They reported on the following companies: -

- Power Paper — At the time of writing, their webpage reported that their core technology had resulted in 90 patents with their battery cells being of the order of 0.5 mm thick with a capacity (per active area) of approximately 5 mAh/cm^2. The continuous current density per active cell area of 0.1 mA/cm^2. The Chinese company, Power Paper is no longer operating.

- KSW- Microtech — At the time of writing, their webpage claimed to set milestones with its smart active label products. They specialised in RFID antenna design and mass production of 13.56 MHz and 868/915 MHz RFID tags. Their Dresden plant was stated to have a production capacity of up to 450 million inlays annually. KSW, is also no longer operating.

- Thin Battery Technology — Now known as Blue Spark Technologies. Their webpage [145] summarises their battery range as 1.5V/cell carbon-zinc MnO_2 chemistry, having co-planar architecture and being made from eco-friendly recyclable materials. Specifications include highly flexible, 40 mm bend radius, -30 to +65 deg C operating temperature with energy capacity being dependent on size. Their UT (ultra-thin) range are as thin as 625 microns deliver 5 to 37 mAh of energy (various sizes) at 1.5V. The highest capacity battery has dimensions of 79 x 48 mm (x 625 microns).

- Enfucell — Their webpage [146] reports that the chemistry of SoftBattery® is based on zinc and manganese dioxide, and zinc chloride as an electrolyte.

Enfucell owns the technology for the battery and its manufacturing. The technology enables both various shapes and a wide range of sizes from 1 cm^2 to 100 cm^2. It is stated that SoftBattery® is suitable for low power applications, which require flexible and thin properties. It is noted that their product development services include wireless sensor devices using Bluetooth or NFC transmission technology. Section 4.3 reports this as the selected battery for evaluation.

In addition to the example commercial devices, there are a number of appropriate published research papers suitable for review. Wang et al [147] report on an attempted implement using carbon nanotubes (CNTs). Figure 4.1 shows a fabricated device, alongside a familiar AA battery. The CNT device dimensions and its flexibility can broadly be judged from the experimenter's hand holding the device. Their poster presentation states that typical dimensions are 40 x 30 x 1 mm.

Briefly, they reported that the fabrication included the following stages (reproduced from [147]): -

- Developing formulation comprising of active materials, binder and conductive additives.
- Separator fabrication.
- Formation of homogeneous slurry.
- Electrode formation via coating.
- The battery assembly with separator and current collector.

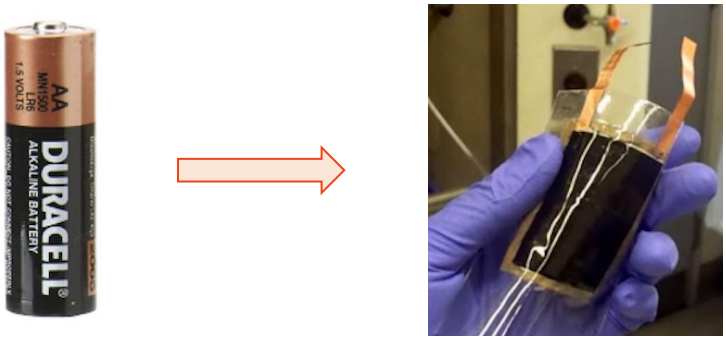
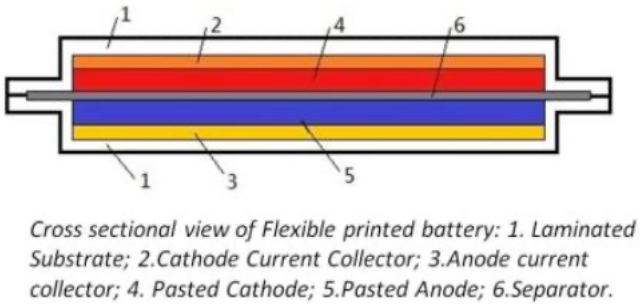


Figure 4.1: Flexible battery (right) with nanostructured electrode as compared to a standard cell (left) [147].

Figure 4.2 shows a cross section and hence the individual components of the battery. For the characterisation of the Zinc-Carbon a nominal voltage of between 1.3 and 1.5V is stated. The battery has 70 mAh capacity and a cut-off voltage of 0.9 V. The authors further claim higher conductivity and battery performance. A longer operating lifetime of 155 h is claimed. However, they note that any defects on the CNT surface caused decreased performance.



Cross sectional view of Flexible printed battery: 1. Laminated Substrate; 2.Cathode Current Collector; 3.Anode current collector; 4. Pasted Cathode; 5.Pasted Anode; 6.Separator.

Figure 4.2: Cross sectional view of flexible printed battery [147].

A common theme in the reported research is that carbon-based materials are key to flexible battery development. This is supported, for example, by Fu et al [148]. The authors also state that another key aspect are structural design mechanisms,

and see intrinsically deformable materials as building blocks for flexible batteries as a way forward. Such building blocks include CNTs, graphene and carbon nanofibers (CNFs). An example of a reviewed and recent development in their paper was for a flexible lithium-ion battery featuring an array of electrode–collector pads electrically connected by serpentine shaped interconnects. In the opinion of the author, it is incredibly important to realise that other materials that can work and are also worthy of further research and investment. Accordingly, this review is intended to summarise the status of the developments of flexible batteries.

In an article [149] the energy density achievable with flexible batteries is discussed. The prime application in mind is the powering of a conventional smart watch. Due to the poor energy density that has been yielded from flexible batteries to date it is argued that a segmented strap approach is a more sensible option. The article quotes Dr Robert Hahn [150] who argues the segmented approach is the way to achieve the migration from a conventional casing mounted battery to a several segment power strap. Thus, certain applications are better served by batteries with much lower flexibility levels.

Another interesting application is wearable medical monitoring devices. Ostfeld et al [151] reported on such a device, where the battery was charged by a solar module and was used to power a pulse oximeter. It is stated that designing a battery that is mechanically flexible and can also provide the required capacity and discharge rate for wearable and wireless electronics is extremely challenging. It is reported that Lithium-ion batteries are often chosen because of their high energy and power density, and stable electrochemical performance. A generic example of their flexible battery design in application is shown in Figure 4.3. The effect of mechanical flexing on the electrochemical performance was reported. The interleaved (with usual discharge cycles) flexing cycles were to bending radii of 3, 2 and 1 inches. The capacity retention for the battery after 20 electrochemical cycles and a total of 600 flexing cycles was reported as 98.8%. Electrochemical impedance spectroscopy (EIS) was used to investigate whether the observed increase in battery impedance was due to the flexing regime.

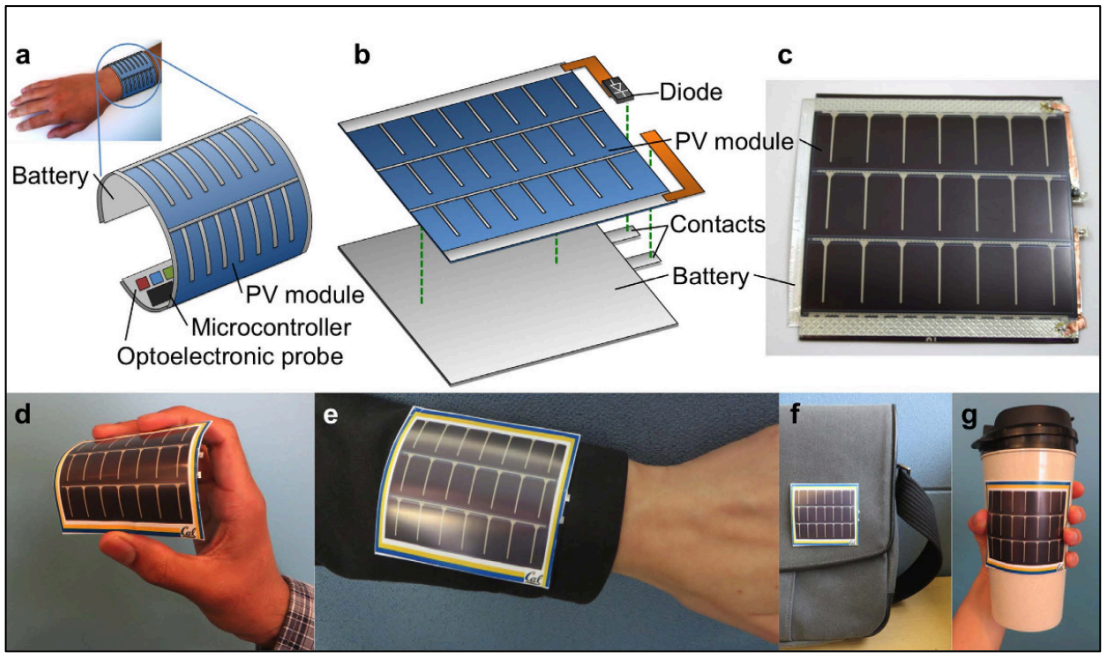


Figure 4.3: The solution and application of the hybrid battery (reproduced from [151]). (a) Activity tracking wristband. (b) System schematic. (c) Physical example of device. (d) Device being flexed and used for testing. (e, f and g) Showcase of different applications on curved areas; sleeve, bag and mug.

One novel idea that has been suggested by Zhou et al [152] is to explore the idea of liquid-based batteries to create the desired flexibility. Although such a design would need a proper way to seal to prevent leakage. It is not hard to imagine how advantageous such a design would be. In fact, in the same paper it is argued that a gel-based anode and cathode could be used.

4.3 Battery Selection

The Enfucell company in Finland manufactures a battery (as shown in Figure 4.4) that was considered and selected for its flexible properties. It must also be noted that this field is quite novel and requires further investigation to advance the limited options. As a result, a set of batteries were ordered for evaluation. Upon evaluation a set of experiments were devised in order to assess the battery

effectiveness. This was done by simulating the conditions, stresses and strains that the battery would be under had it been deployed within the proposed circuit. These stresses and strains include, the curving and wrapping of the battery around the bottle beyond that of what is recommended by the manufacturer. Also pressing and applying force when subjected to the aforementioned condition.

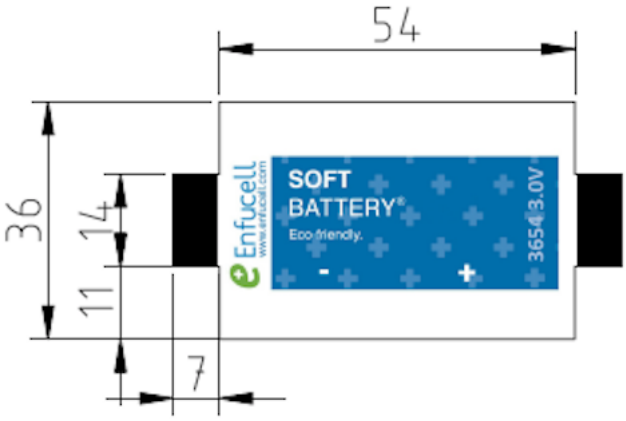


Figure 4.4: Product no. 3654 3.0 V Enfucell battery [146].

4.4 Battery Experiment

Several experiments would be necessary to determine the suitability of the Enfucell battery identified. There were a number of unknown factors with regards to the performance of the battery that needed to be identified and assessed. These can be considered as follows: -

- Can the battery support the loads that are placed upon it?
- What is the reaction of the battery if it is overloaded?
- Does the battery degrade should it experience mechanical stress?
- What are the effects of further mechanical stress than that of which it is already placed?

4.5 Experimental Design

The experiment required the use of a Keysight N6705B DC Power Analyser with a battery source/measure unit (SMU) draining module. This would effectively simulate the changing load that the battery would usually experience in the multiple modes that range from sleep, wake up (WUP) and active modes. It also needed a custom-made program that would control and direct the automatic timings between such modes and if the current drain should simulate an active mode. It is worth noting that an active mode is not always required. The program would also proceed to measure and log both voltage and current with the type of simulated mode. In order to connect to the battery terminals, silver epoxy was used due to the terminals' thin nature and design. This required specialist knowledge and training. Once the batteries were set and hooked to the instrumentation it then became possible to simulate the real-life conditions that it was to be exposed to. This includes the wrapping around a plastic tube that simulates a bottle and the squeezing thereof. The N6705B is able to drain the battery by placing a current load and simultaneously taking a voltage and current reading. The following block diagram (Figure 4.5) shows the layout of the experiment: -

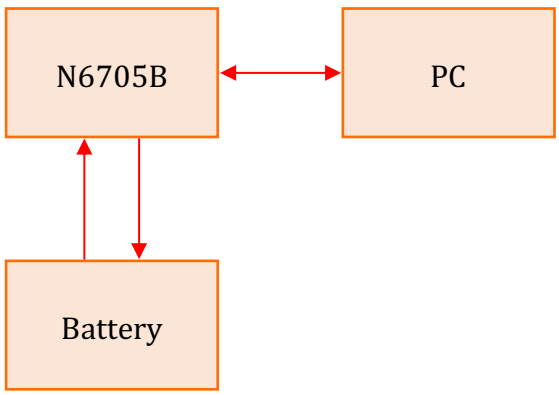


Figure 4.5: Simplified system block diagram of battery test system

4.5.1 Information Regarding N6705B

The N6705B (as shown in Figure 4.6) applies a load onto the battery. As this in turn is active in nature and can be varied to the desired load that is required to maintain a constant current load. This results in the need for a fixed resistance to be obsolete to promote current draw from the battery. It is reasonable to look at the N6705B as a load bearer given that it discharges the battery by attracting electrons to itself. The following behaviours are observed: -

- Discharge of the battery occurs when the electrons from the negative side are attracted to the positive side.
- Convention dictates current flow from positive to negative.
- As time passes the charge that the battery holds decreases, given the formula for charge is Q=It.

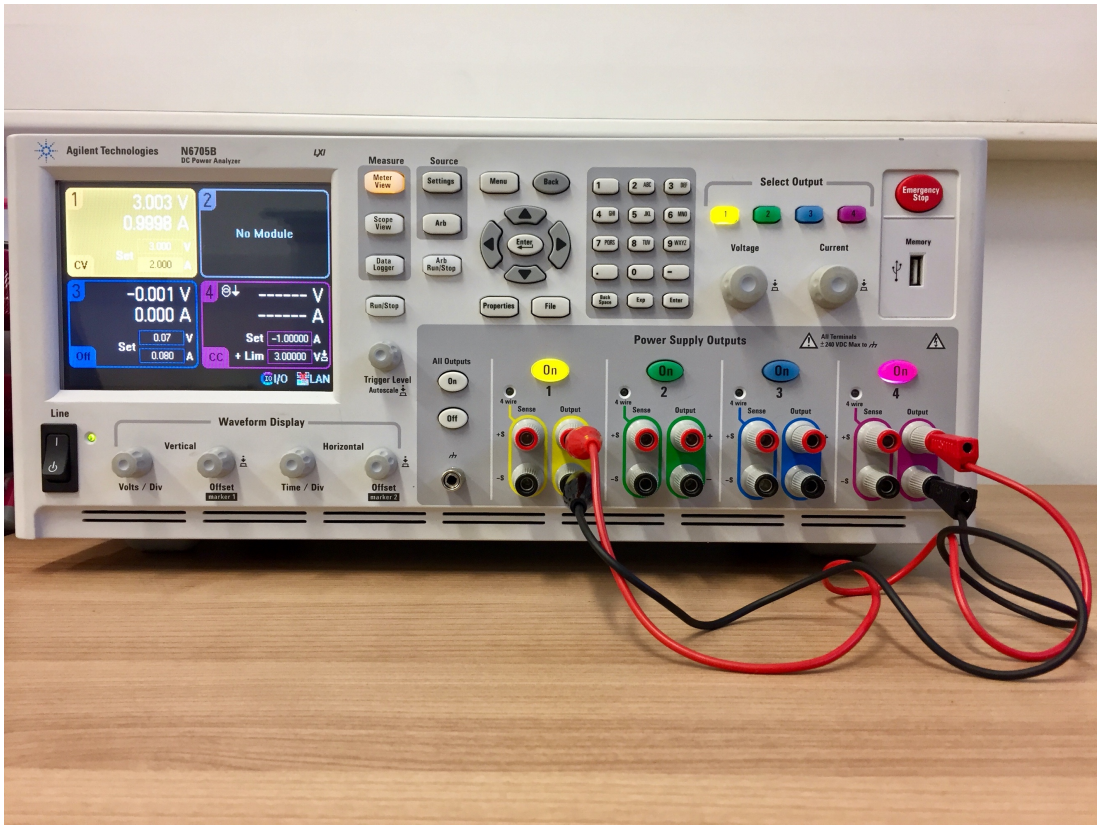


Figure 4.6: The N6705B device

4.6 Experiment Verification

The batteries were assessed in order to observe their reaction when they were to be exposed to these real-life conditions and see if they would hold up to the same standard or similar as advertised when flat, given the requirement of wrapping the battery around the bottle. A number of issues came to light when initially verifying the functionality of the equipment. For instance, training was needed in order to operate the apparatus correctly. The verification in this regard was done via a power supply that simulated the battery.

4.7 Experiment Software Implementation

The software was created in NI LabVIEW. This was a good choice as a family of drivers already existed to interface between LabVIEW and the device. To be clear, the force sensor isn't used in this section of the project nor is the circuit created, only the battery is utilised. One of the major challenges was trying to send the correct commands to the device with the right flexibility. This was resolved with appropriate research into the command structure of the device. A feature of the software given the anticipation to long term testing was to have a strengthened error strategy that will attempt to 'recover' the software automatically should a problem during testing happen. That is to say, if for example the program was suddenly halted due to a power cut, there were redundancies in place to recover on a reboot. Another feature was to try and reconnect to differing I/O devices should there be a connection drop out. The software appropriately makes allowances for long term data logging. The user is able to import the data and make appropriate graphs in Microsoft Excel. The software was created by the author within LabVIEW, a number of steps for software verification were needed. Multiple subVIs were made in a state machine format. When tested with multiple simulations of the different modes or states, some errors were initially picked up upon. These include not taking enough appropriate samples to accurately reflect the signal. Any and all issues resulting from these verifications were fed back and

modifications ensued. The software commits to the following actions in sequential order: -

- Enters sleep mode
    - The software communicates to the instrument and writes an instruction to simulate an electrical load drawing the current demanded for sleep mode from the battery. It takes a measurement from the N6705B and logs it.

- After the set amount of time defined by user in front panel the software goes to WUP mode.
    - The software communicates to the instrument and writes an instruction to simulate an electrical load drawing the current demanded for WUP mode. It takes a measurement from the N6705B, and logs it. The switching between sleep and WUP is done automatically in the defined time on the front panel.

- If the user wants to enter active mode, this is simulated on the front panel.
    - The software communicates to the instrument and writes an instruction to simulate an electrical load drawing the current demanded for active mode. It takes constant measurements until the user exits active mode and logs these too.

The main block diagram (Figure 4.7) is shown in the next page.

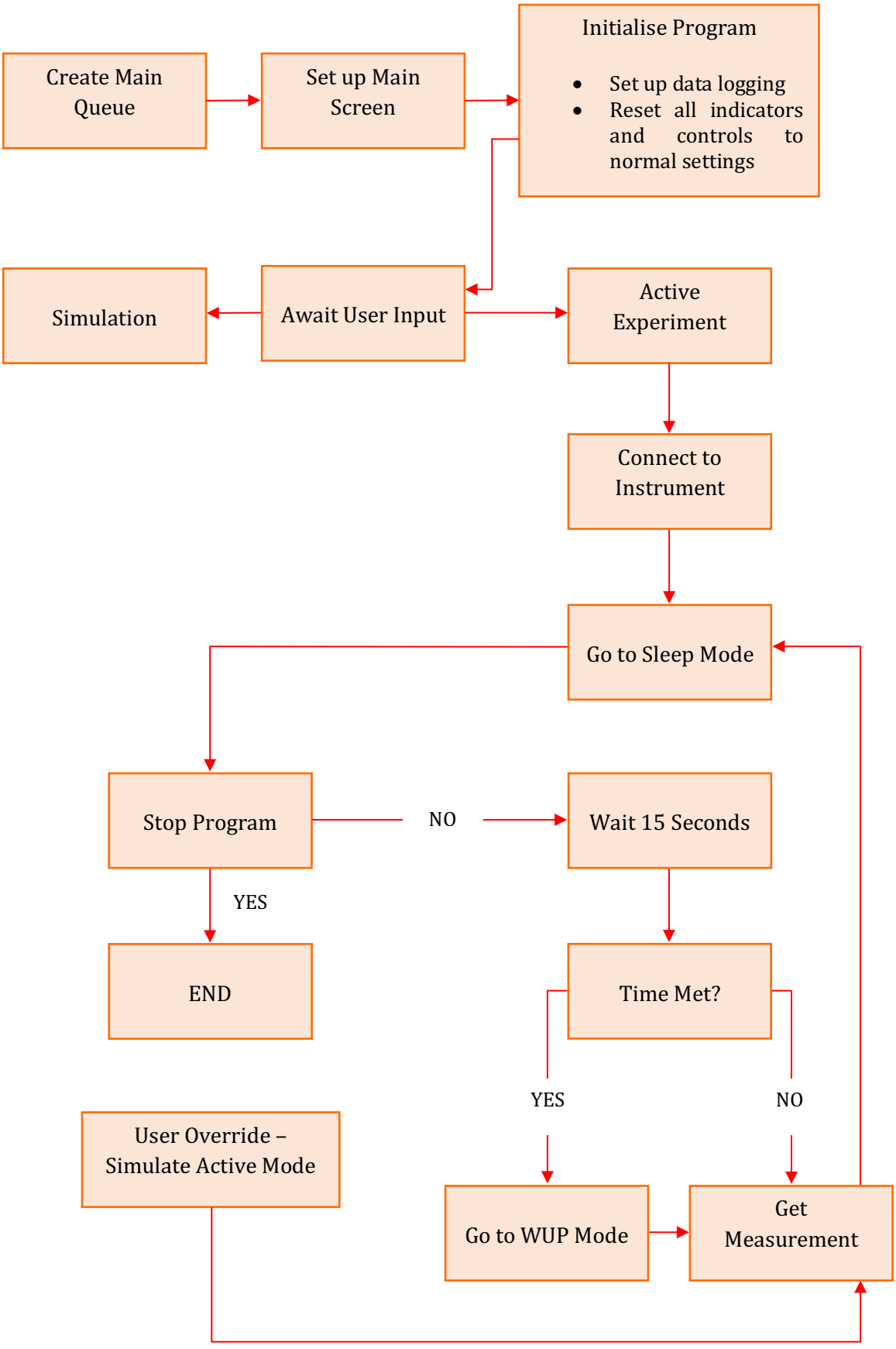


Figure 4.7: Test interface software process diagram. The GUI (front panel) and block diagram are presented in the Appendix A.

4.8 Experimental Results and Data

Initial observations suggest that the battery restricts its voltage output when a higher current demand or load is placed upon it. This might have been the behaviour observed but when placed with simple passive resistors and tested via a multi meter it was shown that the battery displays similar behaviours to being in a short-circuited state. This is true for all batteries, and this was confirmed by using a standard AA battery.

The Enfucell battery had many factors including the stress and strain of curving to consider. The battery also seemed to support very low currents somewhere in the region of no more than 50uA whilst curved, however it's now believed that the maximum output of the battery whilst flat is 1.2mA. This clearly marked difference seems to suggest that permeant damage is caused by excessive bending or shearing of the flexible element as the battery does not recover when released from its curved profile. The manufacturer even states this and says the minimum radius is 25mm otherwise performance is reduced. The expected results that should come from a power source are a maximally flat line at every given power mode for current. So that the current is constant in nature relative to sleep, WUP or active mode. To verify if the software is operating correctly; a check procedure and experiment is implemented. Instead of a battery, a power supply is used in its place that can offer a 3V output with 2A current. The software is set to accept the following settings: -

- 0.5A for sleep
- 1.0A for WUP
- 1.5A for active
- 2 second automatic switching between sleep and WUP.

Normal operation is then allowed to resume and is consistent with what is shown in Figure 4.7 for the sequence of events. The graphs shown in Figures 4.8 and 4.9 confirm that the testing regime is working as expected and the results are consistent with an 'ideal battery'.

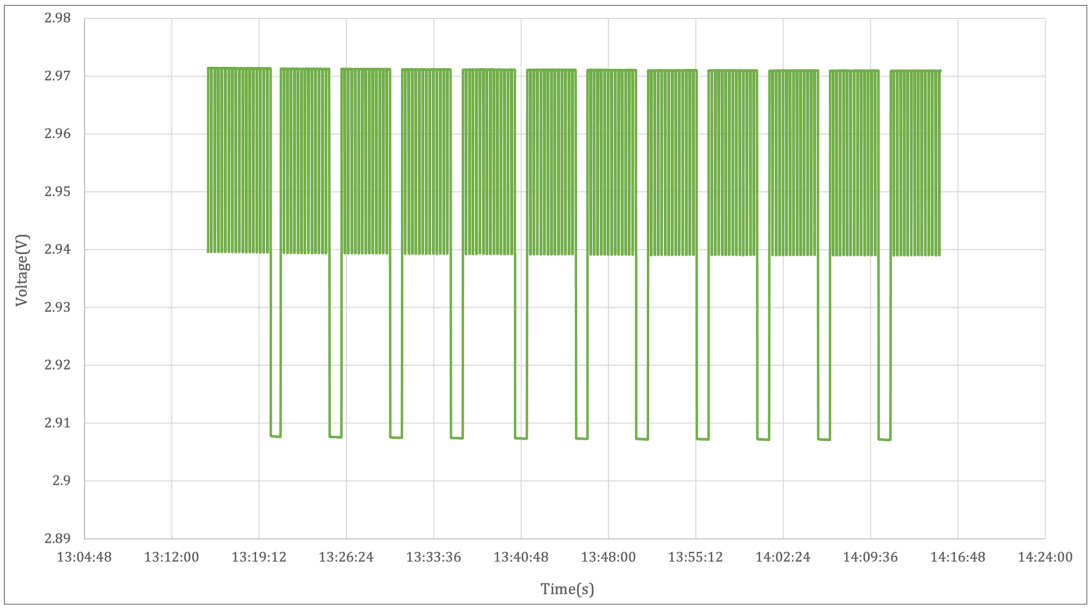


Figure 4.8: Verifying the program with a power supply – Voltage output.

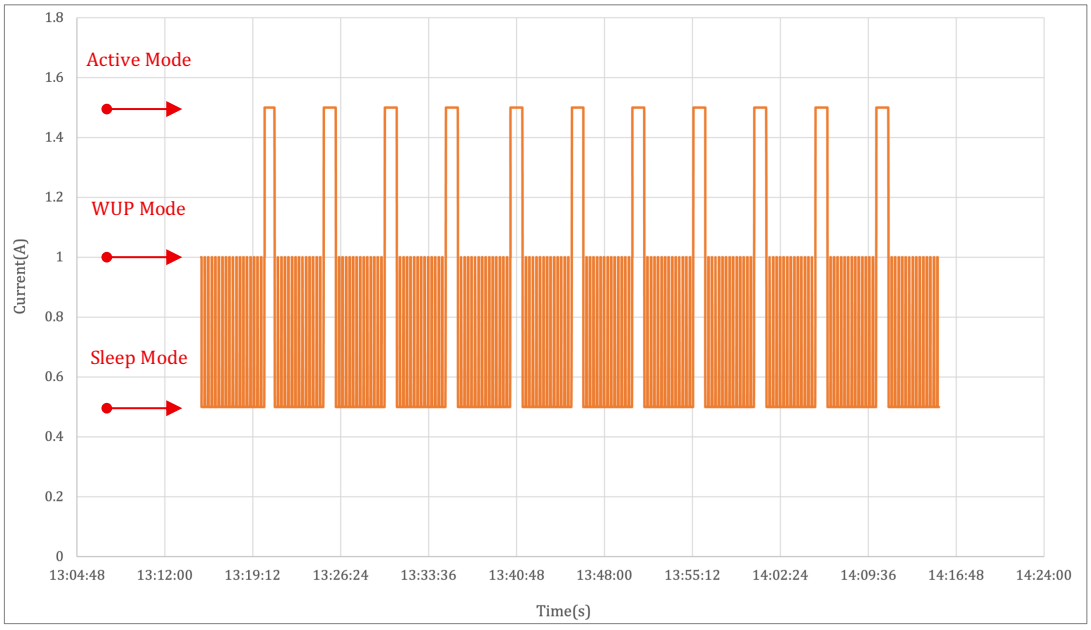


Figure 4.9: Verifying the program with a power supply – Current output.

4.9 Battery Testing

It is now possible to conduct an experiment with the Enfucell battery, having the confidence that the program and instrument work correctly with each other. A series of tests were carried out to assess the voltage and current of the battery as it undergoes discharge. Simply using the system described above, the battery was connected, and a set of figures have been produced that highlight and report the results obtained. Those results are shown in Figures 4.11 through to 4.22 and are self-explanatory. In summary, these figures show the output from the battery using the following parameters: -

- A 15 second cycle time between sleep and WUP mode.
- Set up sleep, WUP and active mode as required.
- Set up; sleep, WUP and active mode as required based on the active components on final circuity as shown in Table 4.1.

Table 4.1: Set up parameters for battery testing

Component	Sleep mode	WUP mode	Active mode
Microcontroller	0.02uA	0.5uA	0.6uA
NFC	155uA	155uA	155uA
Comparator	0.6uA	0.6uA	0.6uA
Voltage regulator	60uA	60uA	60uA
Force sensor	–	–	1mA
Total	0.215 mA	0.216mA	1.216mA

As can be seen from the above table, it is the NFC device that likely draws most of the power based on the datasheet specifications. It is not known if the device does ‘sleep’ as there is no information on this. The active mode currents were quoted for sleep and WUP for worst case scenario. It would be simple to have the microcontroller switch the NFC power line on and off in a further implementation

via a FET transistor. Furthermore, the need for a voltage regulator could be questioned as the components in use are quite robust in terms of their input voltage requirements. A best-case sleep mode current would then be of the order 0.6uA. Finally, the force sensor and comparator resistors could be increased by an order or two in magnitude if the ratio is maintained. A best-case active mode current would then be of the order of around 500uA. These changes could be considered in any follow up research.

4.9.1 Wrapped Battery Testing

A battery was wrapped around a bottle with the same diameter as a normal eye drop bottle. In order to avoid the battery becoming unwrapped, the whole system was attached to the desk with duct tape (as shown in Figure 4.10).

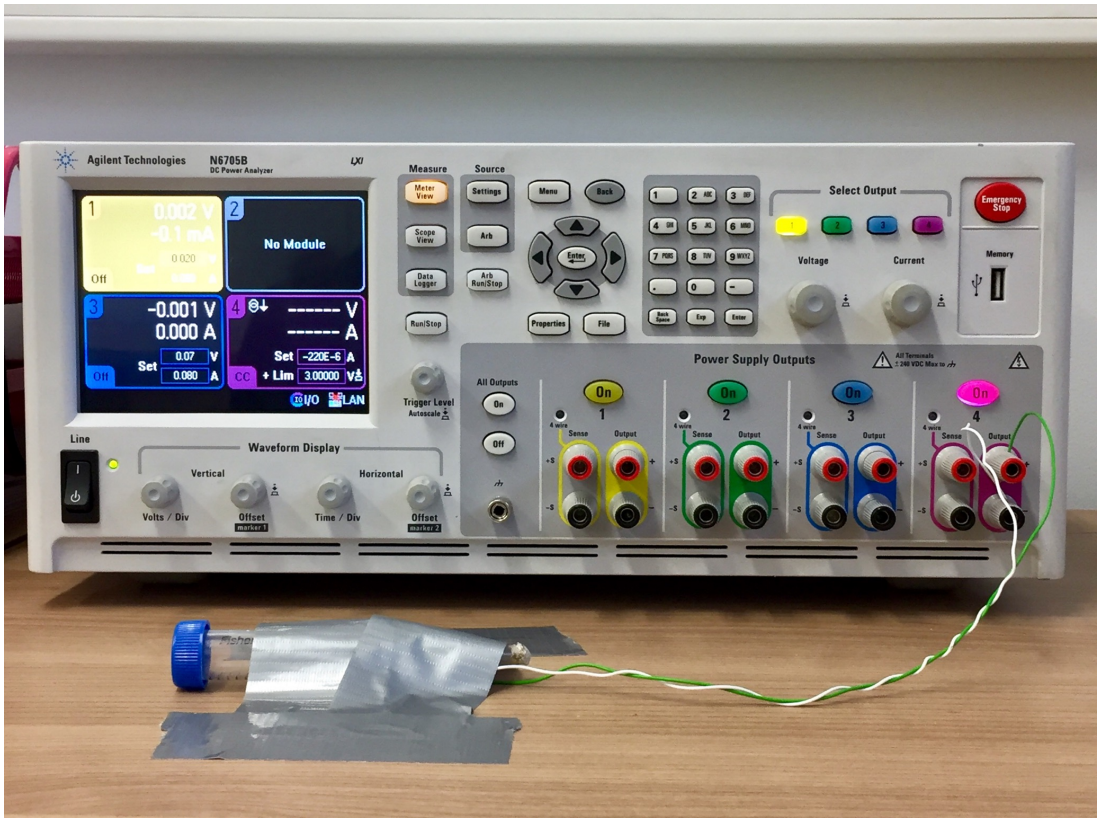


Figure 4.10: Wrapped battery testing

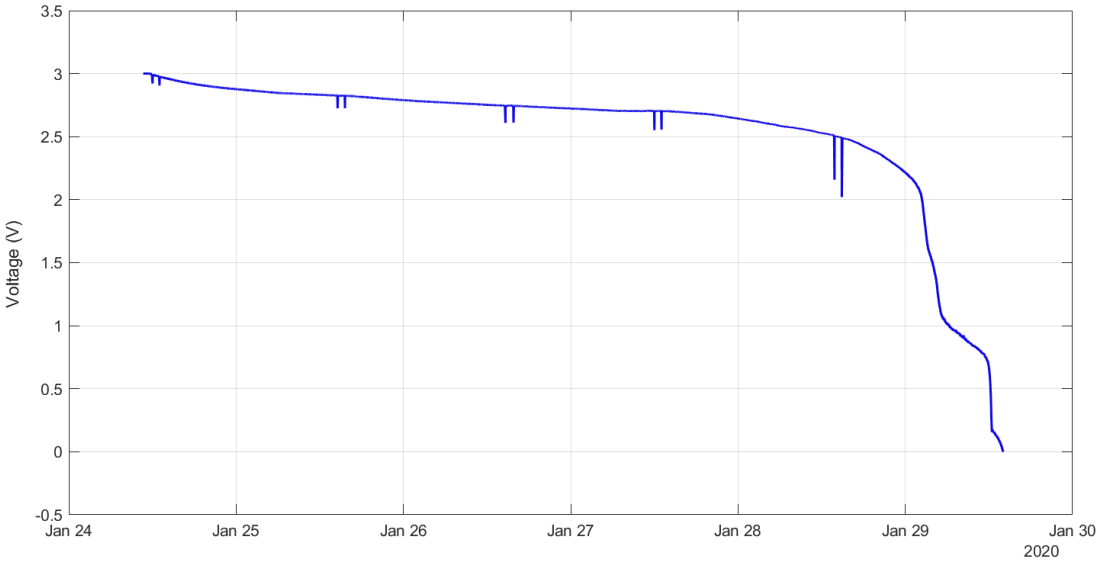


Figure 4.11: Discharging wrapped battery

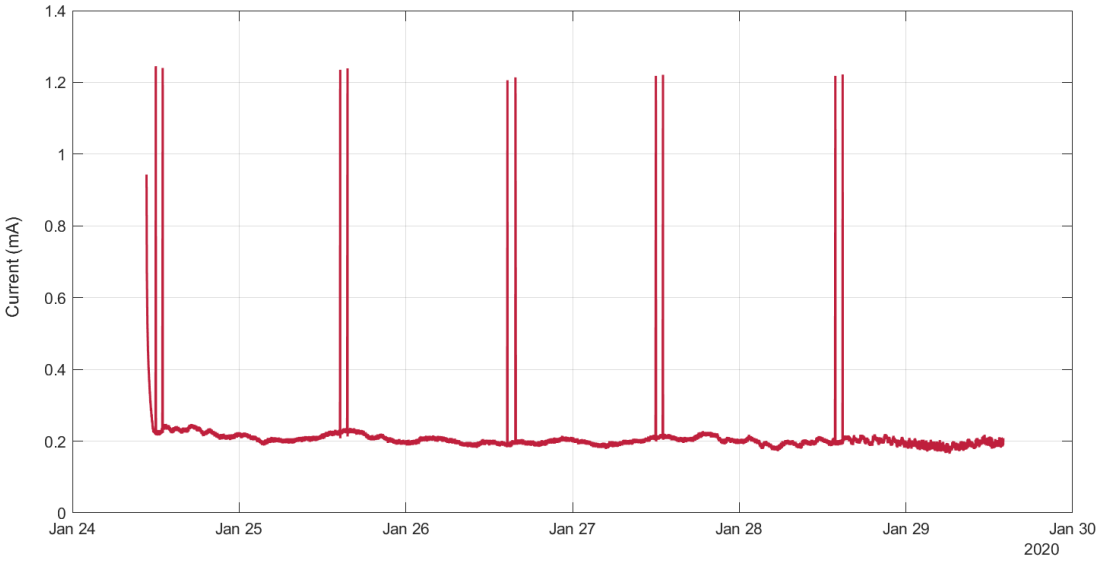


Figure 4.12: Current graph for wrapped battery when changing between different modes. Notice the higher current demand when in active mode and lower demands at WUP and sleep modes.

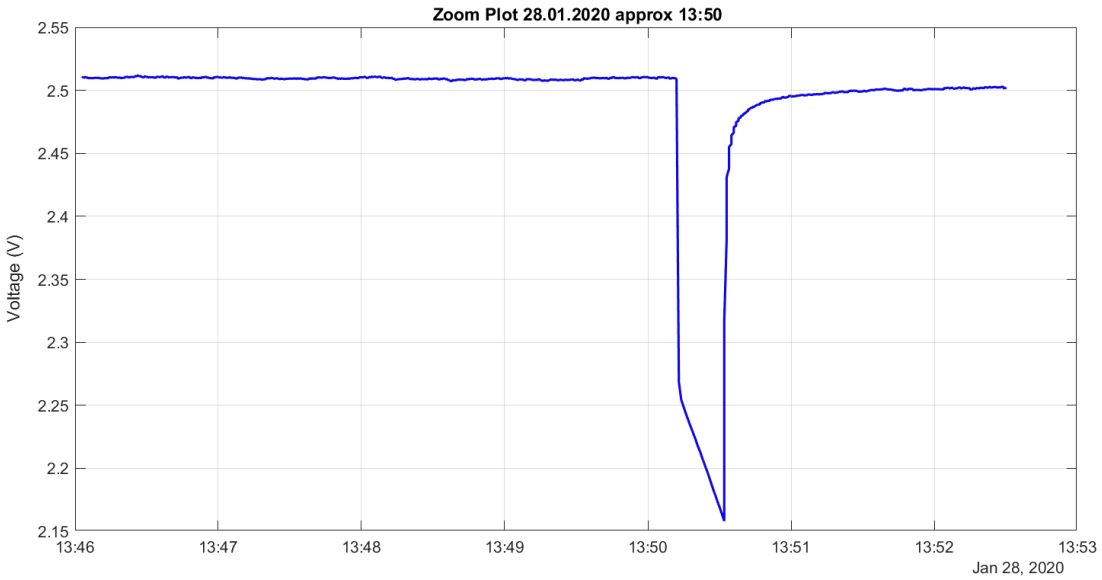


Figure 4.13: Zoom of Figure 4.11 capturing the switching of modes from sleep, WUP to active mode.

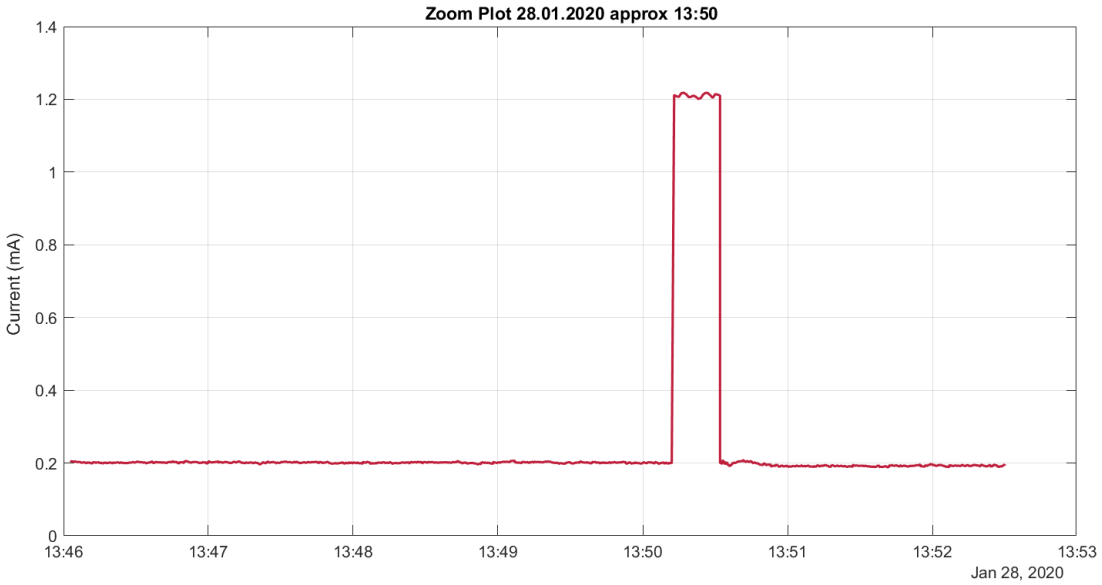


Figure 4.14: Zoom of Figure 4.12 capturing current transitioning from sleep, WUP to active and vice versa.

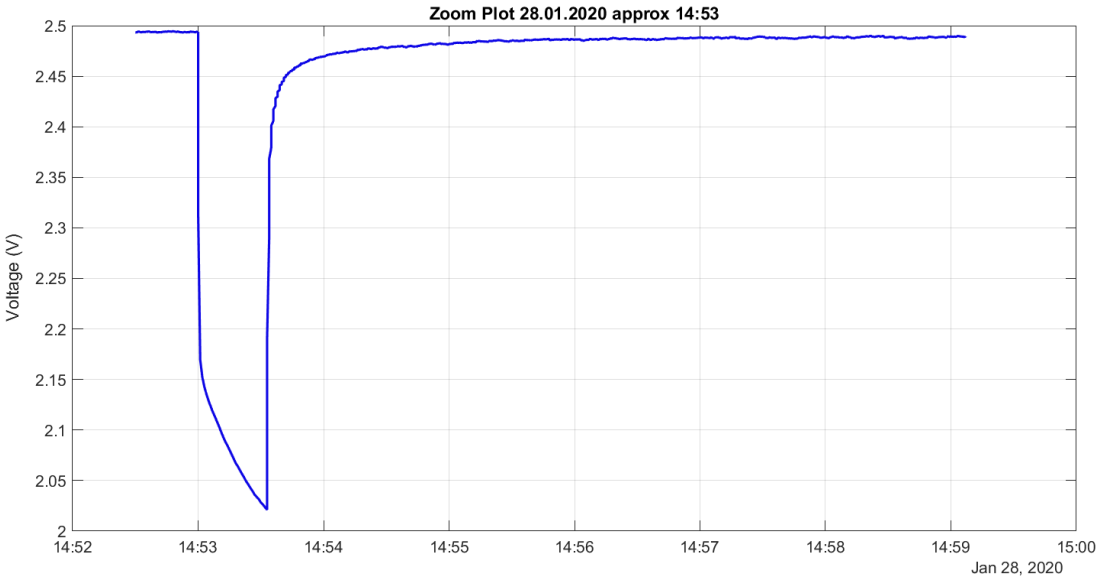


Figure 4.15: Zoom of Figure 4.11, this looks at a different part of the graph but is essentially the same transitioning effect. It shows changes in voltage from sleep to active mode and back again similar to Figure 4.13.

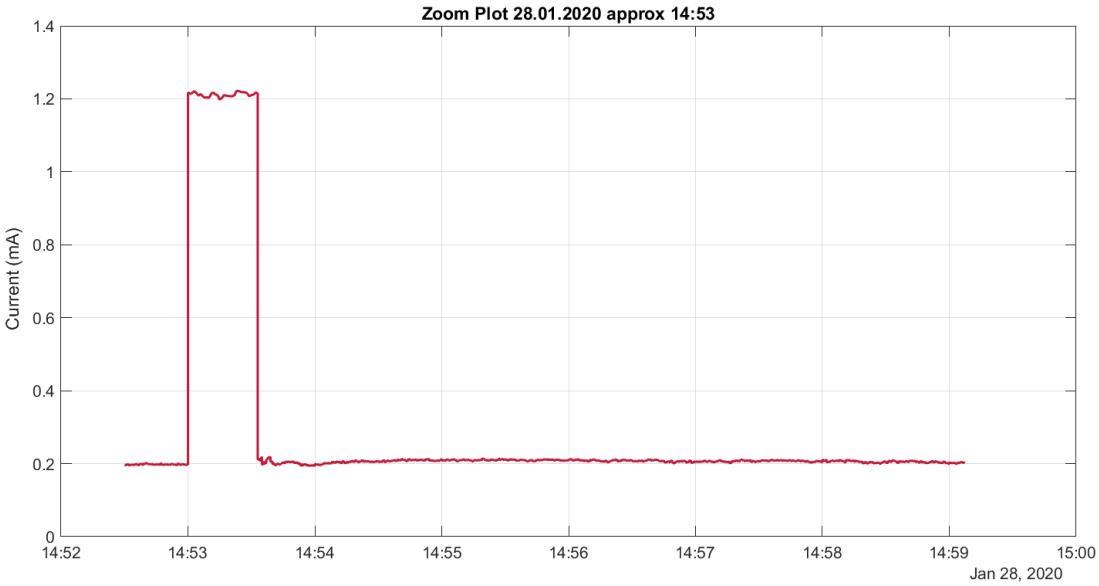


Figure 4.16: Zoom of Figure 4.12 capturing further changes in current between different modes from sleep, WUP to active mode and vice versa.

4.9.2 Flat Battery Testing

In order to see if the performance of the battery was affected by wrapping around the bottle, a testing of a flat battery took place to see the difference between the two batteries. The wrapped battery was bended more than the manufacture specifications allow so it was imperative to see the differences in performance.

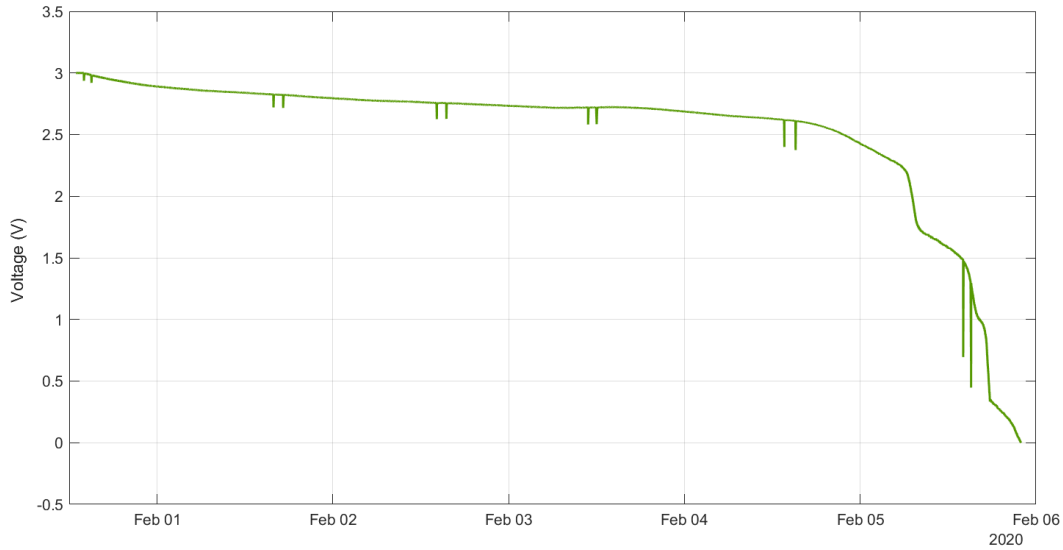


Figure 4.17: Discharging flat battery – The rate of discharge is slower and thus suggests a more effective battery.

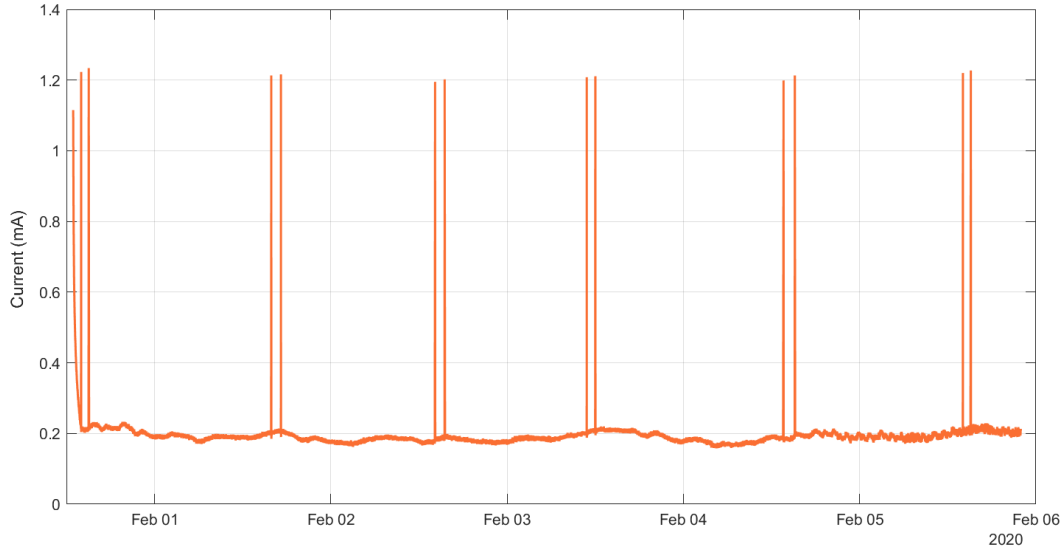


Figure 4.18: Current graph for flat battery, capturing different modes from sleep, WUP to active mode.

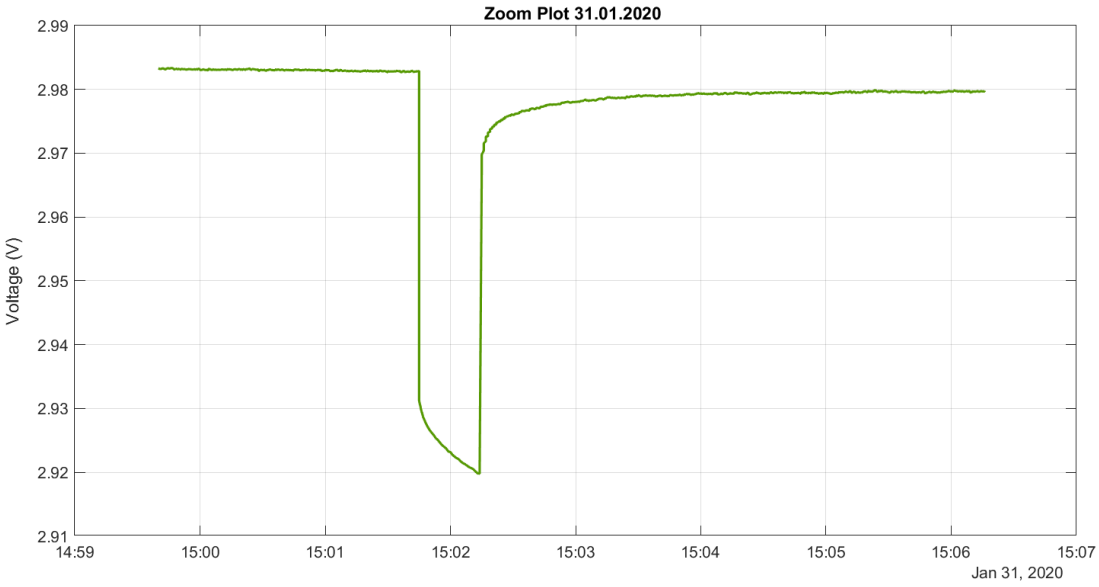


Figure 4.19: Zoom of Figure 4.17 capturing changes in voltage between different modes from sleep to active mode.

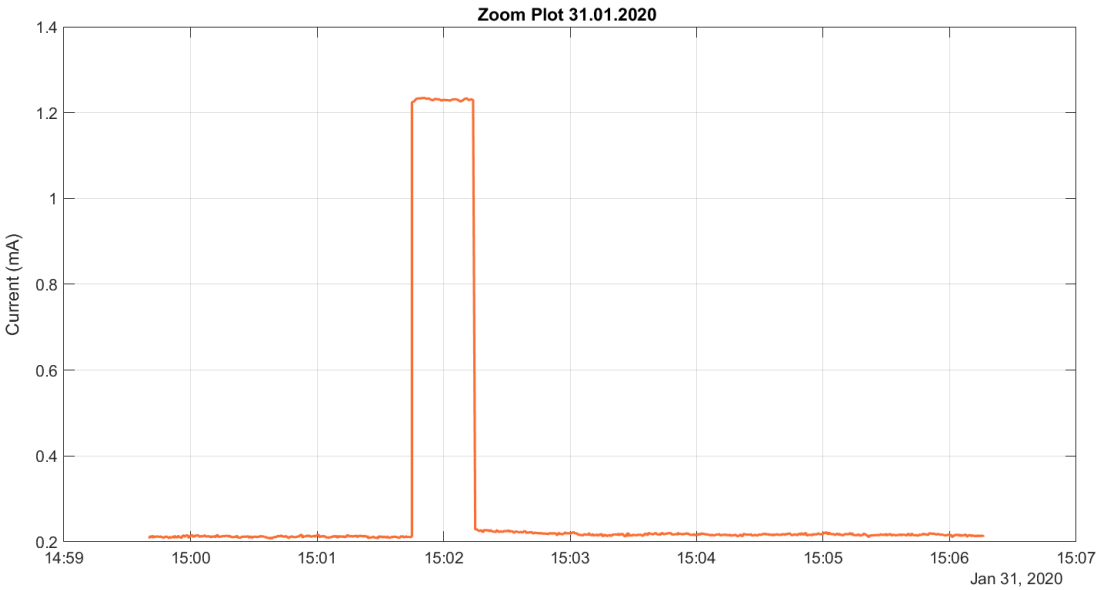


Figure 4.20: Zoom of Figure 4.18 capturing current in different modes from sleep to active mode.

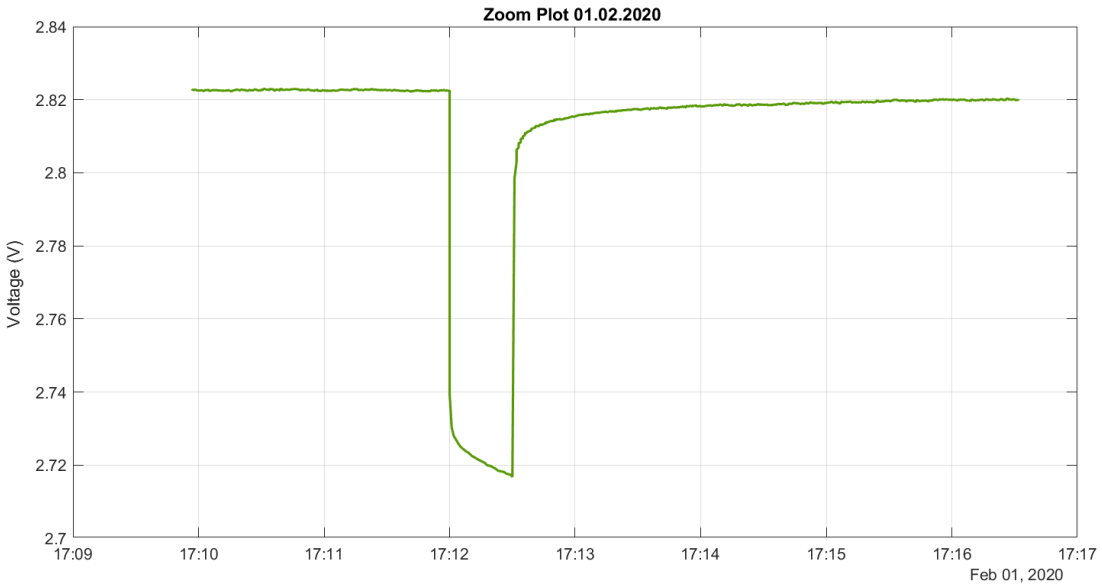


Figure 4.21: Zoom of Figure 4.17 capturing further changes in voltage between different modes from sleep to active mode.

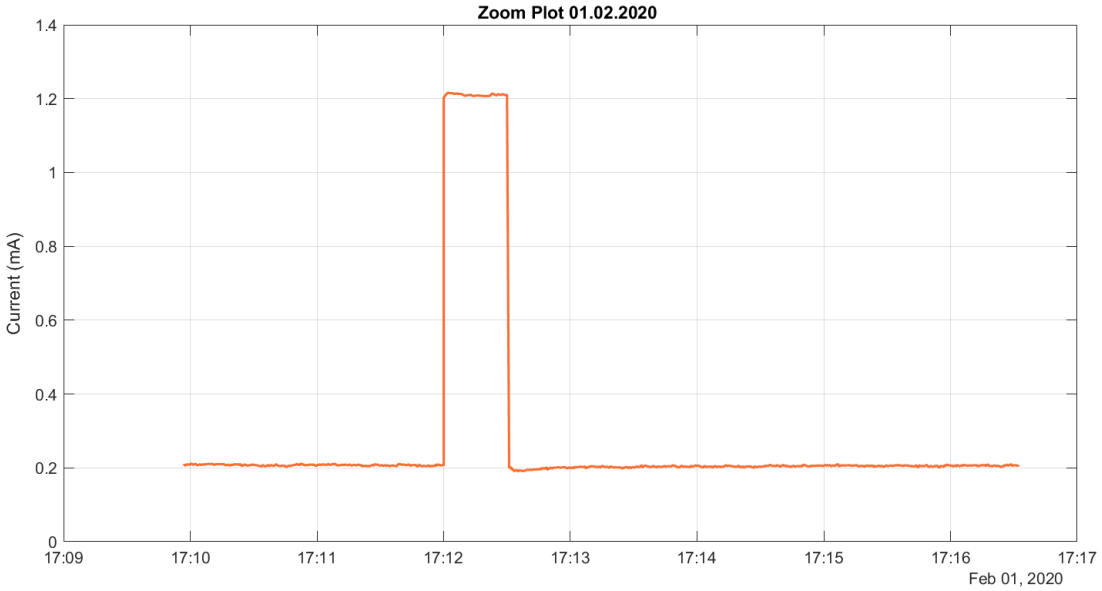


Figure 4.22: Zoom of Figure 4.18 capturing further changes in current between different modes.

4.10 Discussion

It was decided that the time at which the battery voltage first dropped below 2.5 volts would be used as a comparison for the two battery states (flat and curved). It was found that the flat battery crossed this threshold after 104 hours and 37 minutes. The curved battery did so after 99 hours and 32 minutes. In either case, the capacity of this battery all in all is not sufficient for the purpose of this project. At least, a battery with 6 times more capacity is needed to last for a whole month for it to be suitable for this project.

It should be noted that there is an initial spike at the beginning of current graphs. This could possibly be due to the capacitance within the N6705B device needing to charge up or discharge for that matter at the start of a cycle. It isn't believed that this is a response from the battery but more a settling time. However, this hasn't been verified via experimentation.

4.11 Conclusion - Evaluation

The results that were obtained here implied that the current Enfucell device would not be suitable for this application moving forward. Also, it is beyond the scope of this research to design a new commercial battery in the university environment. Future research, possibly with Enfucell could, in principle, realise a suitable battery with sufficient capacity and physical volume.

In terms of establishing power requirements and needs by using the current drainage unit the following parameters apply: -

- For verifying the software, 3V has been used from a separate power supply source.
- The voltage rating has no impediment or effect on the overall experiment as the primary interest is the behavior of current.

One thing that the battery performance testing has made clear is that the battery will seek to compensate when a certain demand outside its usual parameters is placed upon it. For instance, if a higher than usual current demand is placed upon the battery, the voltage will drop to compensate as a result. Whilst the battery will move to satisfy this demand, it cannot be the case to get something for nothing. This makes sense as the battery and all batteries given their nature as a limited energy source will have a maximum power output.

The company tested their products under one current however for this project the behaviour of battery has had to be investigated under different current values, switching at variable rates [146]. The rate of switching could possibly be a point of experimentation to help analyse battery performance.

There are other flexible batteries available in market however with lack of time, budget and availability of equipment, it was not possible to test them all [153]. Note to mention there is a lack of small, flexible batteries with great capacity in the market compared to big, flexible ones, so further research is needed on this category.

Finally, more research and development are needed to get a suitable low charge and flexible battery. However, the button battery will be considered if the flexible batteries in the market don't meet the expectation of the project.

4.11.1 Button Batteries

As a result of the experimentation, given the limited capacity of the flexible batteries, it is necessary to revert to more common battery technology and use a button battery. There are multiple factors to this however the main basis is when consulting with the manufacturer armed with the results generated a number of relevant and interesting points came from the discussion. Given the current demanded by the proposed system, a battery would be needed that offers 6 times more capacity than is currently available. Also, this would occupy a space 6 times

larger. Clearly this isn't a suitable option for the eye drop bottles being considered in this study.

Whilst the current demands are within the manufacturer tolerance it would appear the duration or power capacity is the issue here. This is due to the characteristic 'S' shape curve towards the end of the battery life not being able to supply enough voltage and thus power. When challenged about increasing the energy density within the battery, the manufacturer pointed towards the electrochemical properties and the manufacturer processes that have the limitations which include: -

- Battery density – the material used is manganese oxide this material has a certain amount of energy per weight unit.
- The maximum practical thickness of a soft battery is 0.7mm.
- It is possible to stack batteries however this will impact on how flexible it can be.

The argument here is that with the current chemical composition it's not viable to use a flexible battery. This is fine as a failsafe; an alternative design can be considered and it's that flexibility to think differently which gives the ability to progress with the concept of monitoring for eye drop dispensing and enhancing that aspect. For simple 'concept' testing, use of the button battery does not impact on the evaluation of the overall circuit and also is very cheap and easily replaceable.

Chapter 5

Sensor Evaluation

5.1 Flexible Force Sensors

As covered in Chapter 3, the force sensor is an integral part of this project and in this chapter the processes and procedures for selection, evaluation and calibration will be reported in more detail.

There are a large number of force and pressure-based sensors that are capable of detecting the human touch. This is increasingly true given the major development in sensor technologies driven very much by smart phones and as a result there are a larger selection of sensors that are on offer. Arguably it would have been somewhat unthinkable 20 years ago that a flexible based sensor is a reality today.

A key requirement of the force sensor is that it will need have the ability to be wrapped around the eye drop bottle. This flexibility is obviously not present in a lot of sensors and as such they will be eliminated from evaluation. It is more likely that sensor arrays or grids with IC based sensors are more likely to detect the amount of force in this application. There are some economic considerations of such an advance sensor choice in that it would be more costly and therefore unviable for mass market eyedrop bottle force sensing.

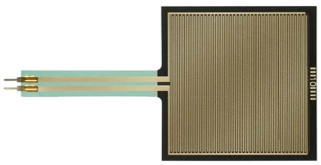
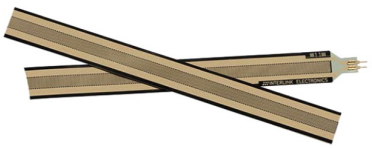
In principle, the force sensor can be capacitive or resistive in nature. Capacitive based sensors are highly accurate and desired for touch-based applications and detection of interaction. However, accuracy is not a pre-requisite here and often, capacitive sensors operate in a resonant circuit which would require additional componentry. It is reasoned that a resistive based force sensor would be a better option for several reasons. Firstly, the cost of these is usually a lot more economical than capacitive options. Secondly, from a power perspective, a small resistive network can be reasoned to have negligible power consumption if high value resistances are used.

A number of manufacturers were considered with the main stumbling block being the flexible nature. Interlink Electronics Inc in the USA. had a line of sensors that had all the desired requirements and as such they supplied a set of samples that formed the first part of experimentation.

5.2 Choice of Force Sensor

These Interlink Electronics sensors were used for the project application. The operation of all sensors in the family with the main variation being the size and shape. Table 5.1 documents the different models within the range of sensors. As will be reported several of the range were evaluated and model 406 was selected. The selection was on the basis of given most complete surface area coverage for the eyedrop bottle. Due to its dimensions the sensor would wrap around the whole bottle and patients pressing all areas of the bottle would still be detected by that sensor.

Table 5.1: Different types of force sensing resistors (FSRs) reproduced from the data sheet and used in testing within the project [154].

Part Type	Description	Part image
Model 400	FSR, 0.2" [5.08mm] Circle	
Model 400 Short tail	FSR, 0.2" [5.08mm] Circle	
Model 402	FSR, 0.5" [12.7mm] Circle	
Model 402 Short tail	FSR, 0.5" [12.7mm] Circle	
Model 406	FSR,1.5" [38.1mm] Square	
Model 408	FSR, 24" [609.6mm] Strip	

5.3 Instrumentation

The initial instrumentation that was used in order assess the FSR sensors comprised of a TL084CN operational amplifier (op-amp) powered by a NI-VirtualBench (VB-8012) power supply on a ±15V configuration. A resistive bridge was also used with the force sensor and a fixed resistor. The output of the sensor circuit was applied to the input of the op-amp and the output of the op-amp was observed on an oscilloscope. The result was immediate, and it was possible to see a change in output on the oscilloscope when a force is applied to the sensor with the same true from the family of sensors. Figure 5.1 and 5.2 shows the test set up and appropriate circuity used to ascertain suitability of the sensors.

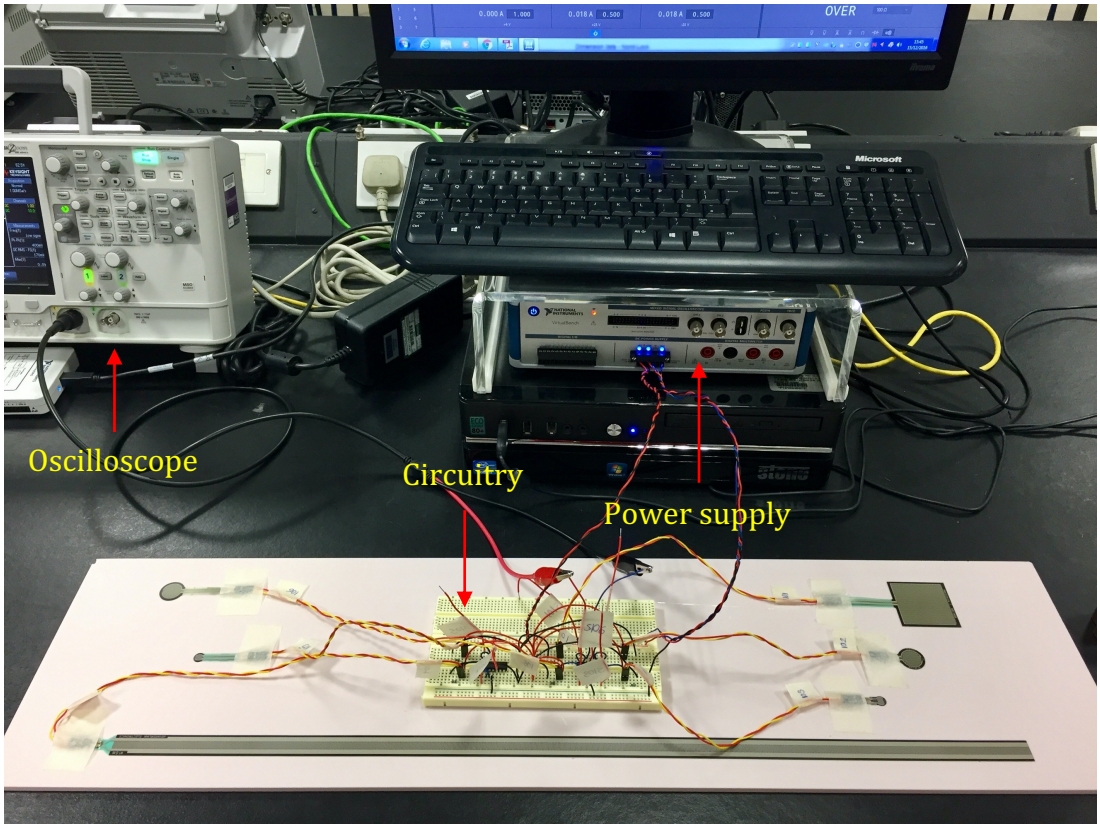


Figure 5.1: A constructed circuit made on a breadboard with a suitable power supply. The output from the deployed sensors of different shapes and sizes are then observed on the oscilloscope.

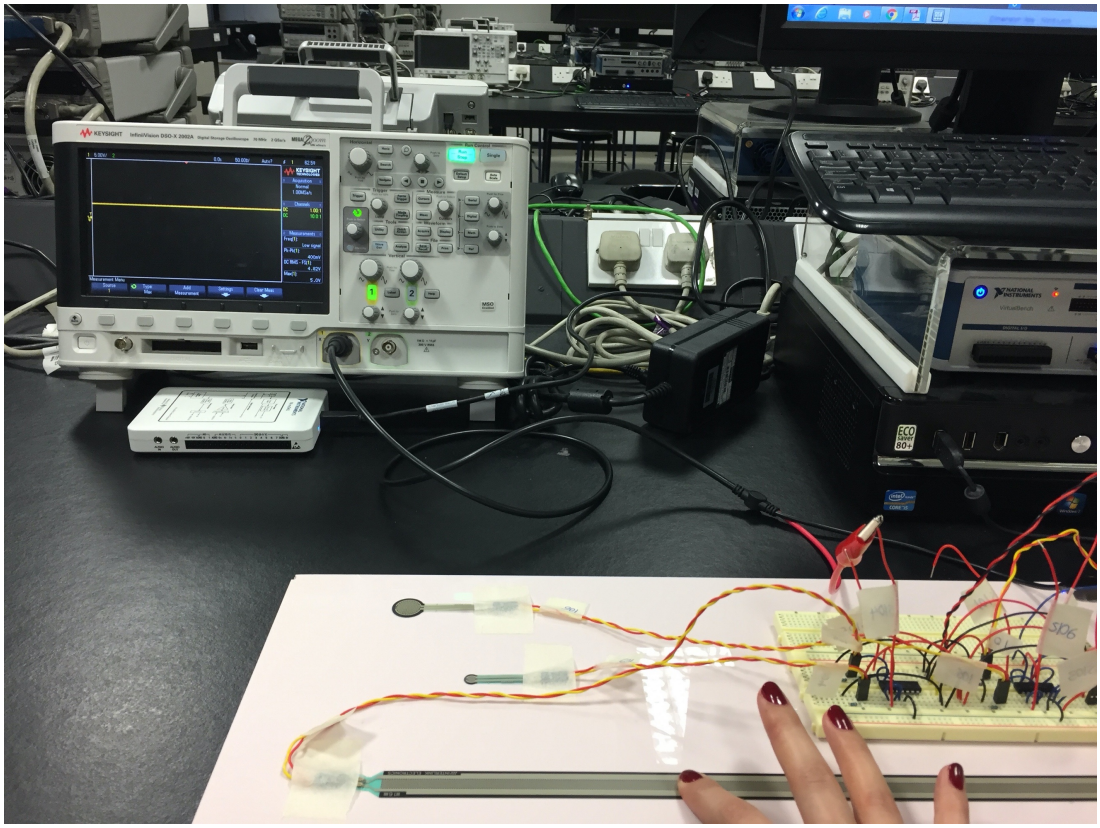


Figure 5.2: Simple check on operation that shows output level high on oscilloscope by exerting force via touch.

Section 5.4 presents the calibration results in more detail and reports on the effect of variable fixed forced application points. Furthermore, once the level of force exerted was established the TL084CN op-amp was replaced with a comparator. This is so a digital signal is effectively supplied to the microcontroller. The comparative line was set to the level of force needed to eject an eye drop from the bottle.

5.4 Results

The circuit shown in Figure 5.3 was replicated 6 times for 6 different sensors and different fixed weights were applied for each sensor. The following section details the results for the sensors.

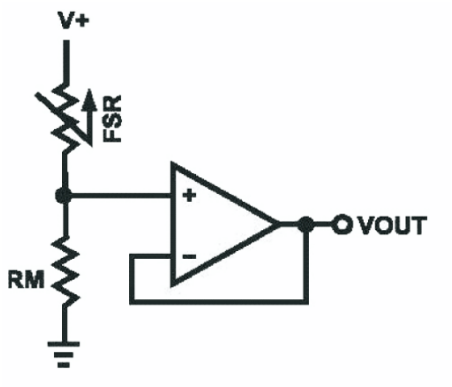


Figure 5.3: Amplifier circuit reproduced from [154].

5.4.1 Model 406 Square FSR

The weights used were of a smaller diameter than the overall sensor dimensions. Hence tests were carried out at placing 5 distinct positions on the sensor, these include top right, top left, bottom right, bottom left and center. For the results shown in Figure 5.4 the results for 3 of the application positions were identical. The results for the other 2 positions can be seen more distinctly in the figure. The figure positions are noted in the figure legend and appropriate curve fits have been applied to the data sets.

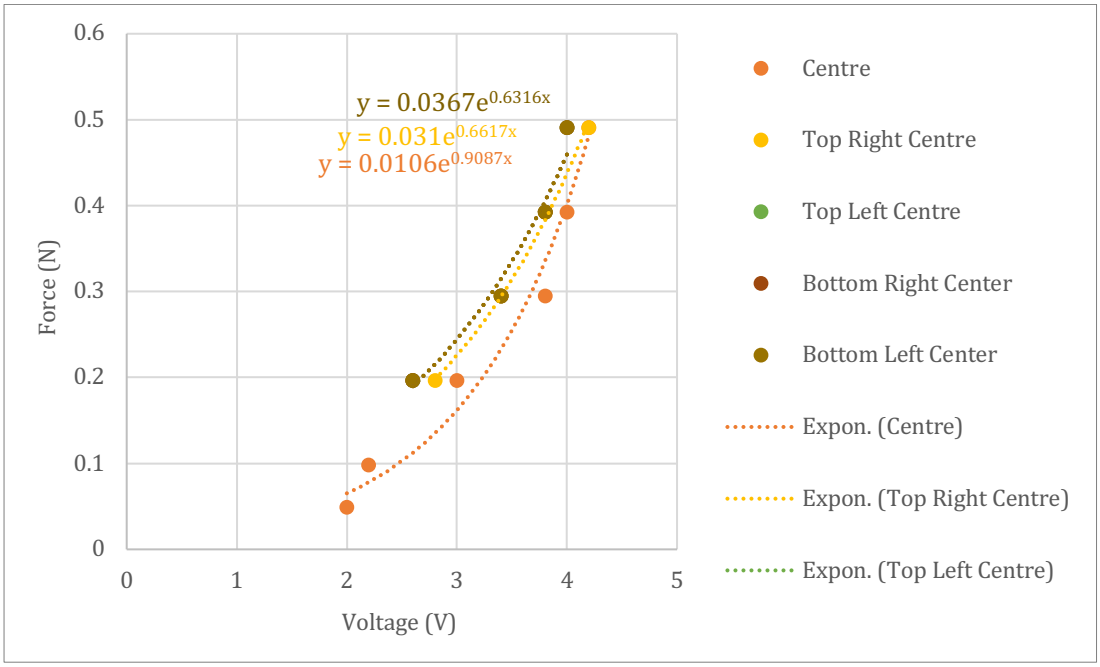


Figure 5.4: Calibration results for Model 406 FSR sensor.

5.4.2 Model 402 Short Tail Round FSR

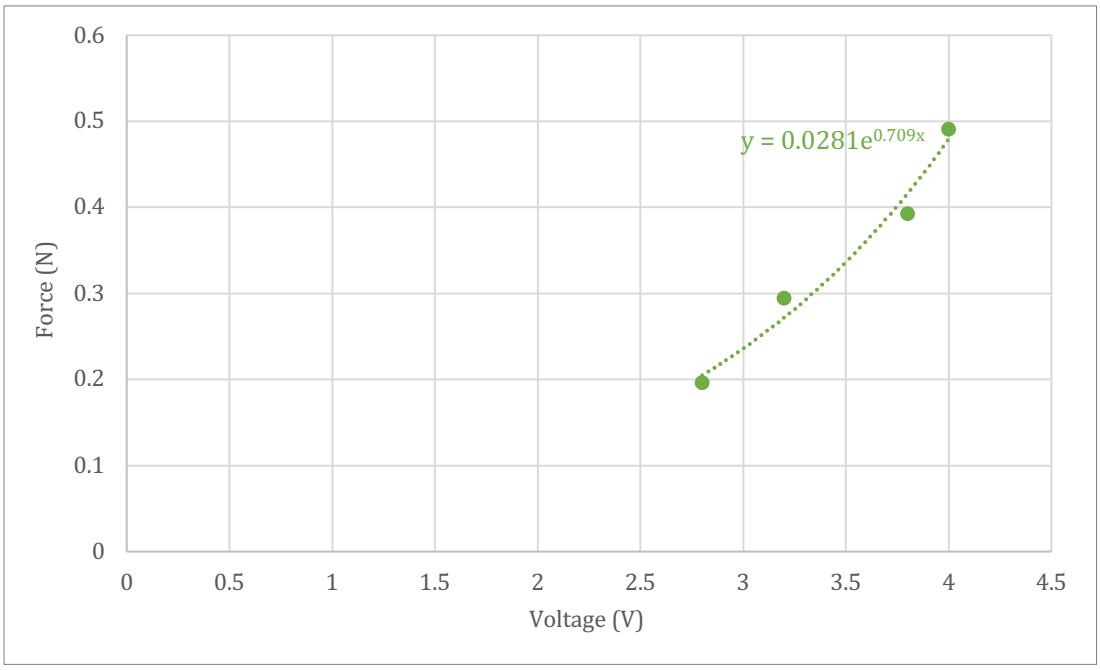


Figure 5.5: Calibration results for Model 402 FSR sensor.

5.4.3 Model 400 Short Tail Round FSR

The results obtained for this model had different characteristics in that there was no visible output for masses below 50gram mass which is 0.4905N of weight. This model, due to its lack of sensitivity, wasn't evaluated any further. Table 5.2 shows the result of the experimentation.

Table 5.2: Result for model 400 short tail round FSR sensor

Weight(g)	V_{OUT} (V)
5	–
10	–
20	–
30	–
40	–
50	3.2

5.4.4 Model 408 Strip FSR

Model 408 as denoted is a strip type FSR and the calibration results this time for three different weight positions are shown in Figure 5.6 and exponential calibration curve fits are detailed in the figure.

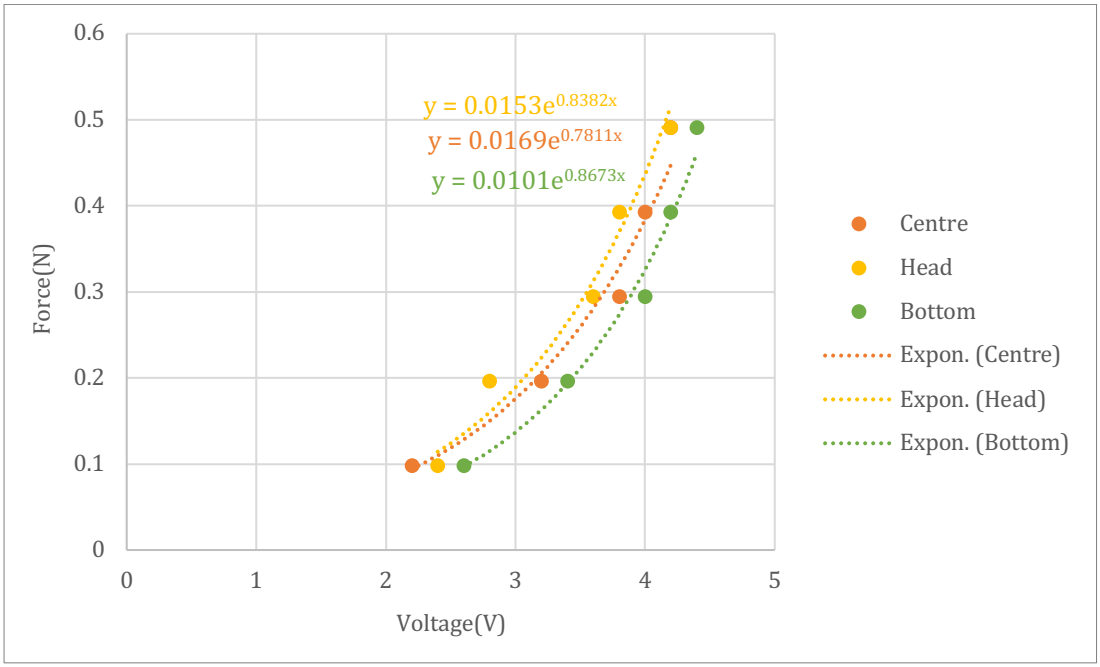


Figure 5.6: Calibration results for Model 408 FSR sensor.

5.4.5 Model 400 Round FSR

Model 400 the round FSR didn't give a discernible output for masses below 50 grams. For completeness Table 5.3 documents the result for this experiment.

Table 5.3: Result for model 400 round FSR sensor

Weight(g)	V_{OUT} (V)
5	–
10	–
20	–
30	–
40	–
50	3.00

5.4.6 Model 402 Round FSR

Model 402 results are shown in Figure 5.7. Due to the physical dimensions of this model, there was only a single positional placement of the masses.

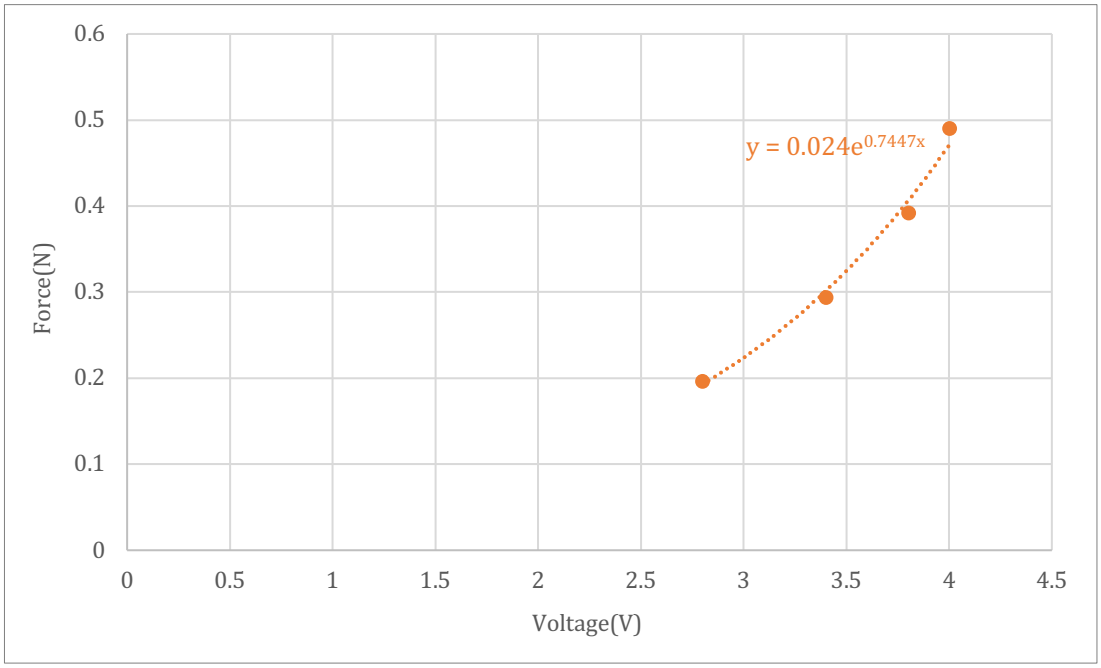


Figure 5.7: Calibration results for Model 402 FSR sensor.

5.5 Evaluation

Upon obtaining technical support from the manufacturer of the FSR sensors that are being evaluated, it was suggested that a force concentrator should be used. This could be something simple in nature such as a circular washer that would fundamentally focus the effect of the mass on the sensitive area and minimise the force on surrounding (non-sensitive) areas. The details of the washer utilised are summarised in Table 5.4. Essentially the calibration weights needed to be balanced on top of the washer which was placed on the surface of the FSR sensor that was being evaluated.

Table 5.4: Washer measurement

Weight	0.0927g
Inner diameter	3mm
Outside diameter	5.8mm
Thickness	1.4mm

It was accepted that the self-weight of the washer would modify the previously obtained calibrations, and in some cases, it was difficult to balance the weights on top of the washer. Figure 5.8 gives a visual indication of the dimensions of the weights used to compare 4 of the 6 force sensors. The other two was impractical to test on given their size and scope.

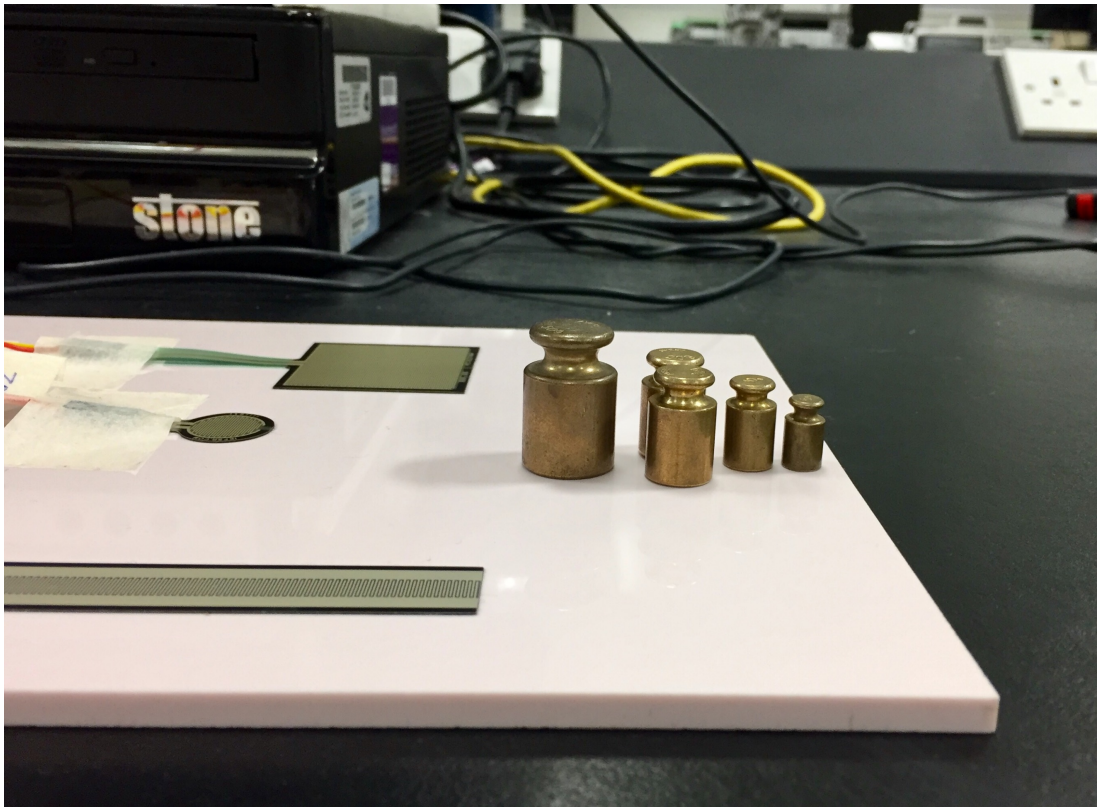


Figure 5.8: Set of fixed weights

5.6 Calibration

Subsequent to the initial evaluation and calibration in the previous section, a more detailed calibration was achieved. Using a Zwick Z050 (50KN) test machine, this enabled a fixed-point force to be applied to the sensors. Again, the voltage output from the sensors was observed and the results reported are initially for tests carried out with the sensors on a flat surface. The circuitry that was used was from the manufacturer's datasheet. The purpose of this experimentation is to establish a calibrated curve profile this is done by using calibrated equipment which in turn establishes the character of the sensor.

It is important to note that the final calibration of the device can only take place when the full circuitry is assembled and applied to the eyedrop bottle. The procedure for this is to exert a fixed level of force in stages onto the device and compare the output with the calibrated experimentation that has been completed from this section. Should the profile be within the same or similar output range it is sufficient to use the profile curve as an adequate reference.

The method that is used is to take the Zwick Z050 (50KN) test machine and add a 2KN load cell which would apply a fixed level force and the subsequent output is then measured via a multimeter. The results were subsequently logged which gave the desired characterisation of the sensor.

The Figures from 5.9 to 5.12 show the result of this calibration experimentation. It also should be mentioned that the result from the manufacturer has been added to the result of experimentation in all figures within the mention range except from 5.9. It was decided that the sensor be tested way beyond the recommended maximum to see if a point of failure could be identified.

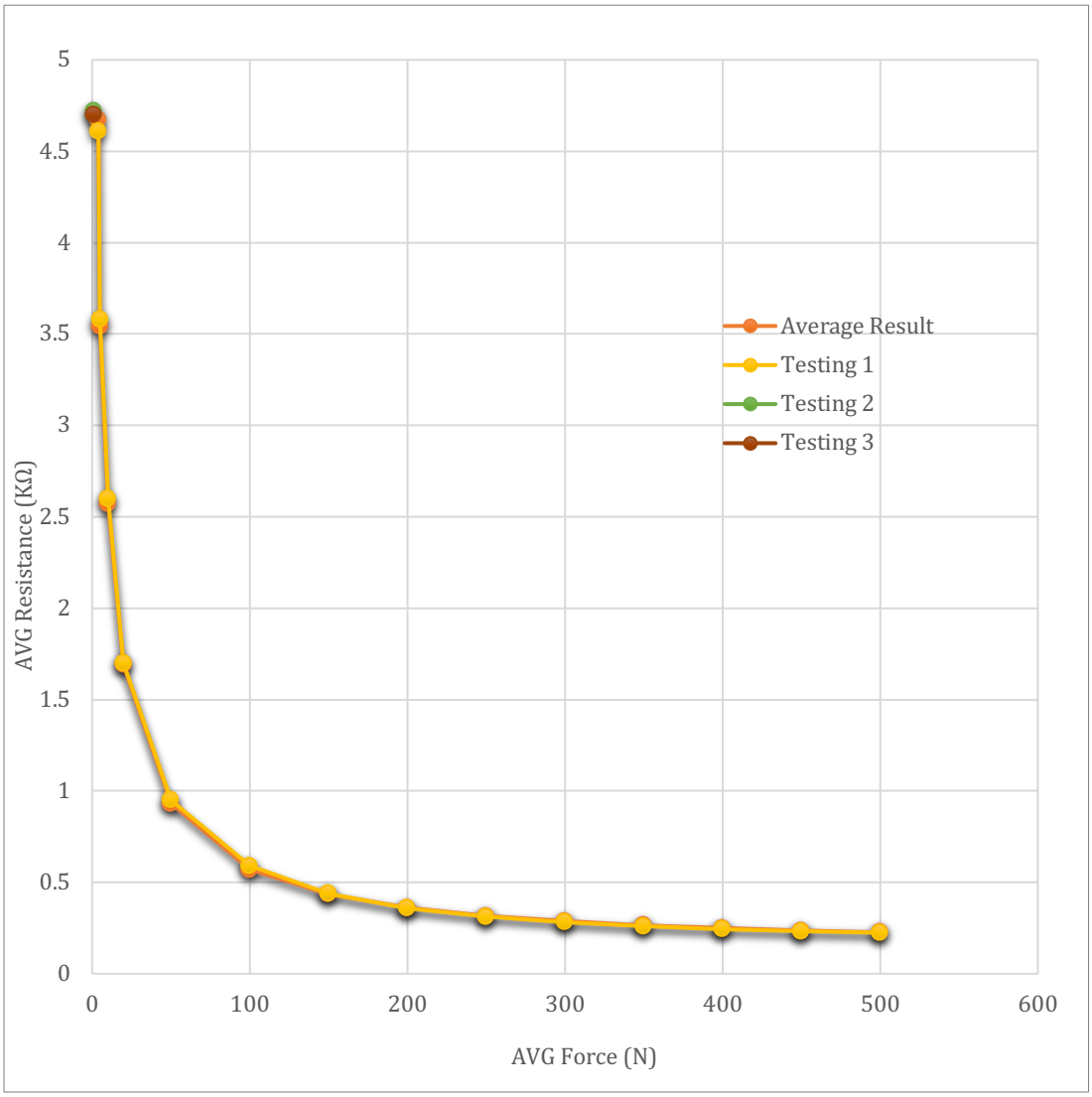


Figure 5.9: Calibration curve obtained from experimentation using a Zwick Z050 (50KN) test machine. This experiment was replicated 3 times to generate an average result and labeled so in the graph. The experimental data is labeled as testing 1,2 and 3.

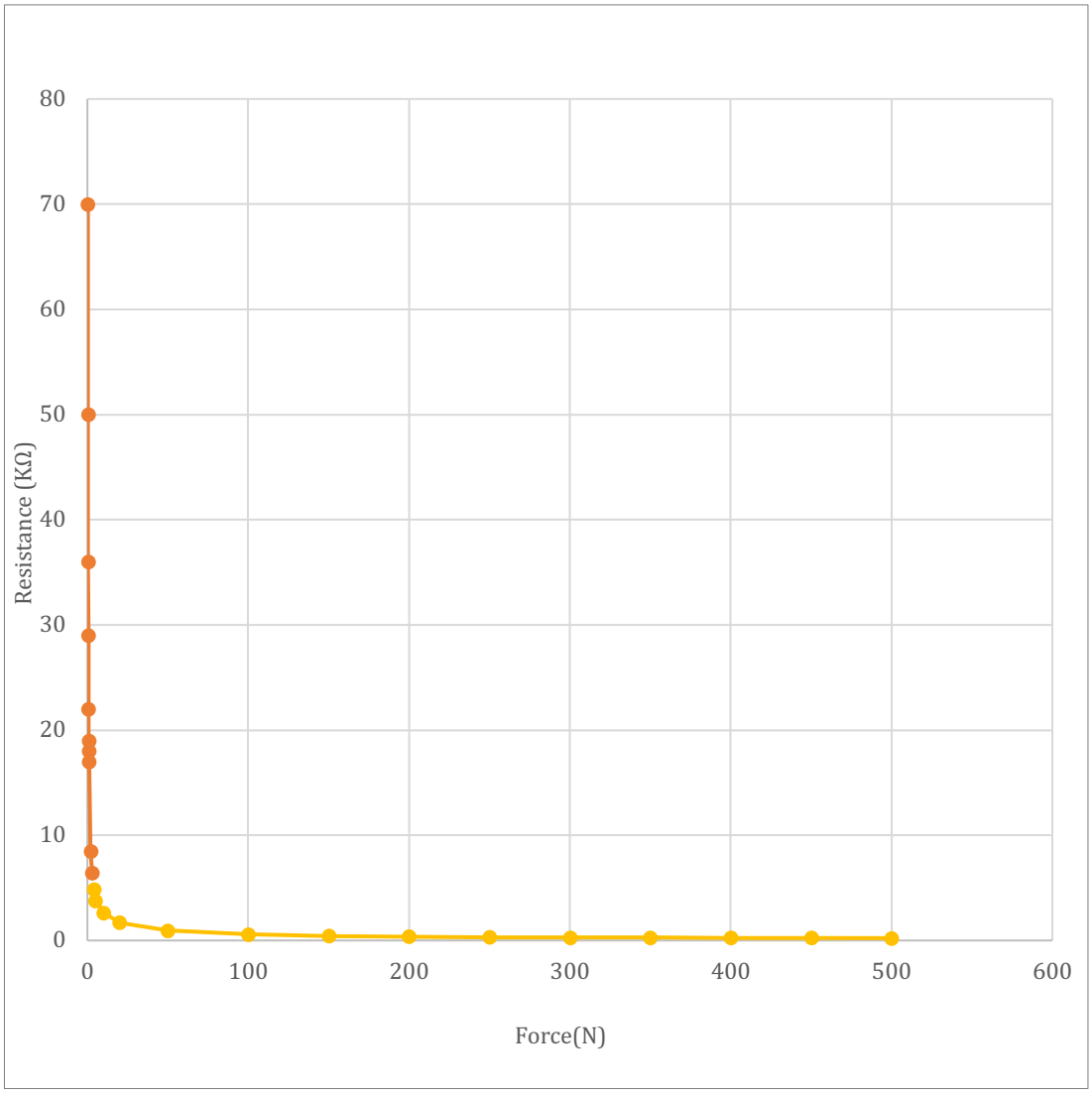


Figure 5.10: The experiment sought to extend the available manufacturer data. The orange line represents the data from the data sheet whilst the gold line represents the experimental data. It can be seen clearly that there is a level of correlation.

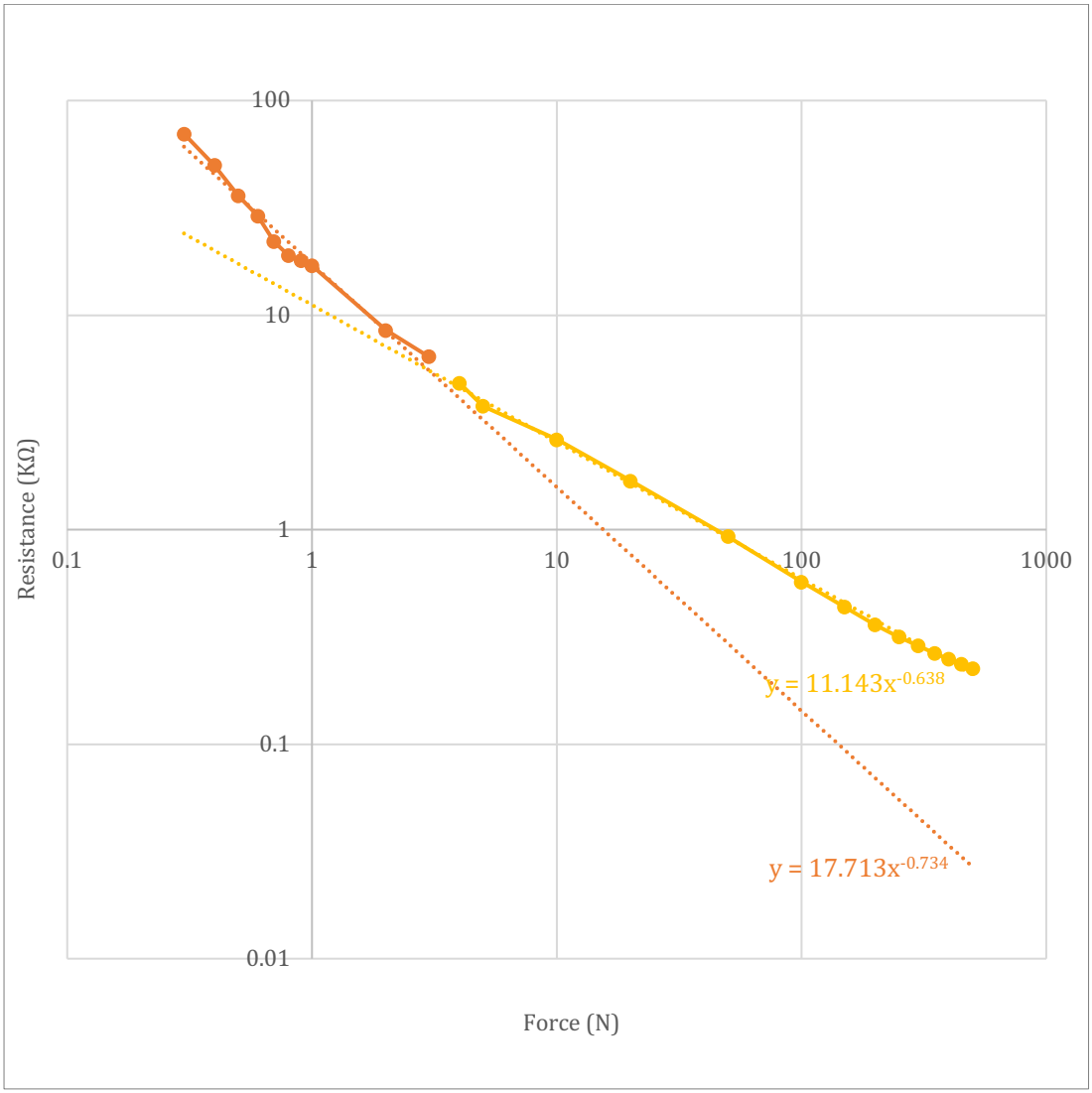


Figure 5.11: Calibration information in a logarithmic scale due to the presentation of data from the manufacturer in the same format.

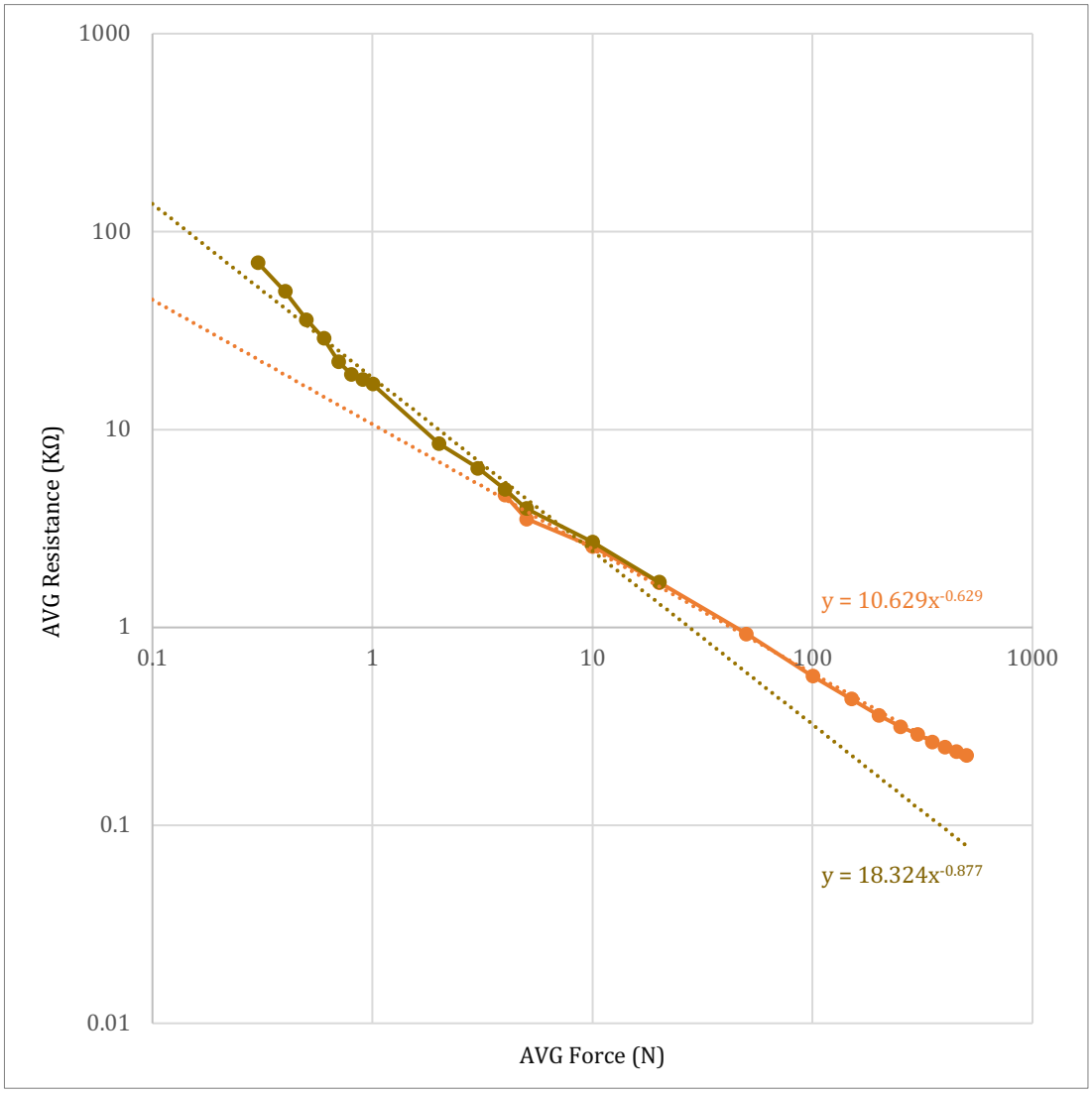


Figure 5.12: A logarithmic scale of manufacturer (brown) and the experimental results (orange). The manufacturer data includes results up to 20N and the experiment for this project was conducted from 4N up to 500N. The conformity of the results indicates a pattern that is consistent and enduring in nature. Also, no sensor failure was observed.

5.7 Determining the Comparator Threshold Voltage

Since the proposed circuit relies on a comparator to detect the squeezing of the bottle, an experiment was devised that would determine the minimum sensor resistance (from squeezing) that would eject a droplet. By using a slot sensor, appropriate amplification and a force sensor (as shown in Figure 5.13) it was possible to determine the minimum voltage generated by the circuit (and hence the resistance) that would cause an eye drop to eject. The slot sensor is a simple LED/photo transistor pair frequently used as limit sensors in mechanical applications [155]. It was used here to detect the presence of a droplet passing between the LED and photo transistor. The experiment took place with different volumetric levels of fluid. It also had different modes of bottle squeezing, i.e., once with the thumb and once with a finger.

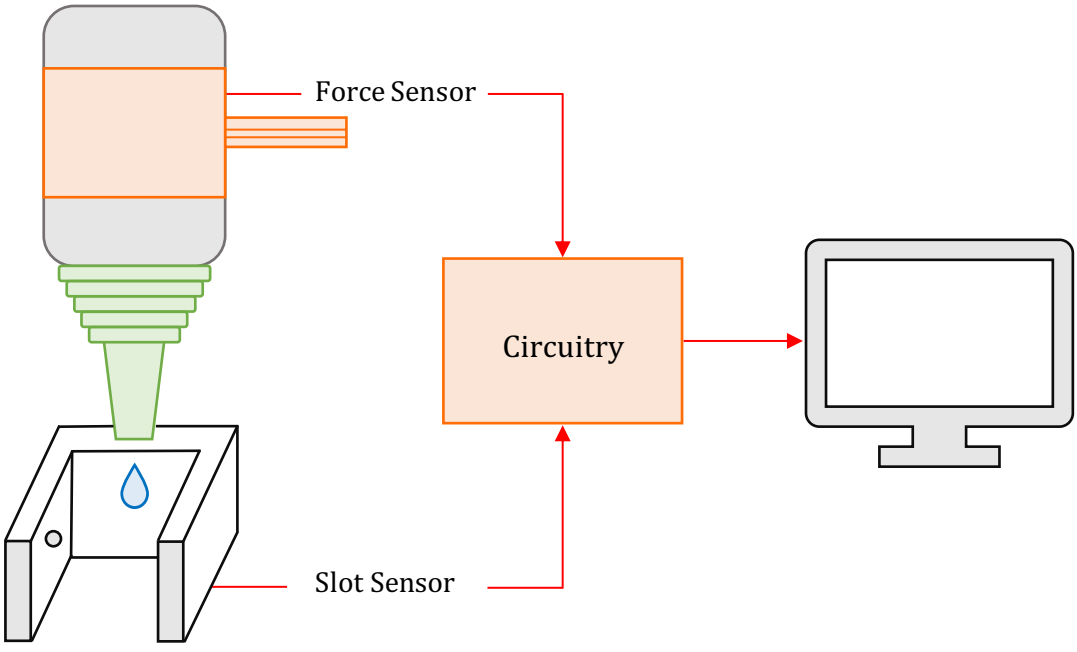


Figure 5.13: The force sensor was wrapped around the bottle, when the bottle is squeezed, the drop from the bottle is detected by the slot sensor. The NI myDAQ and LabVIEW program gets the data from the experiment.

Figure 5.14 through to 5.23 displays the results obtained from a series of experiments where the bottle was squeezed and the voltage output from the force sensor and slot sensor output were recorded and output as a CSV file, displayed in Excel. Different squeezing locations and fluid levels were tested, and the figure captions below summarise these different conditions. Figure 5.24 gathers the results for all experiments for comparison.

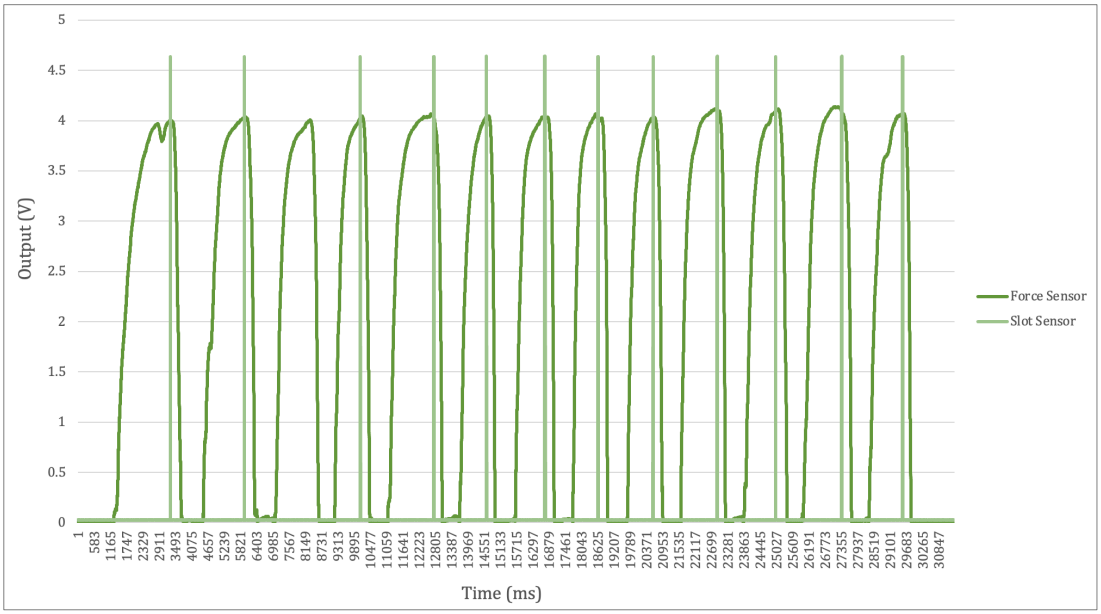


Figure 5.14: Measured output voltage with thumb press when the bottle is full of fluid.

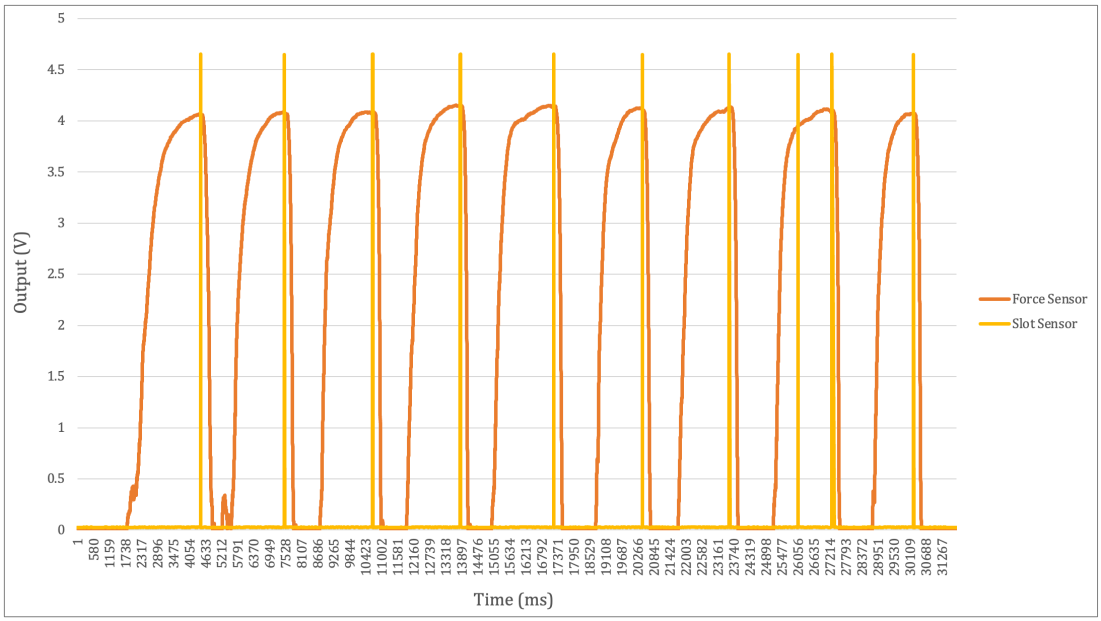


Figure 5.15: Output voltage with thumb when the level of fluid in the bottle is 2cm.

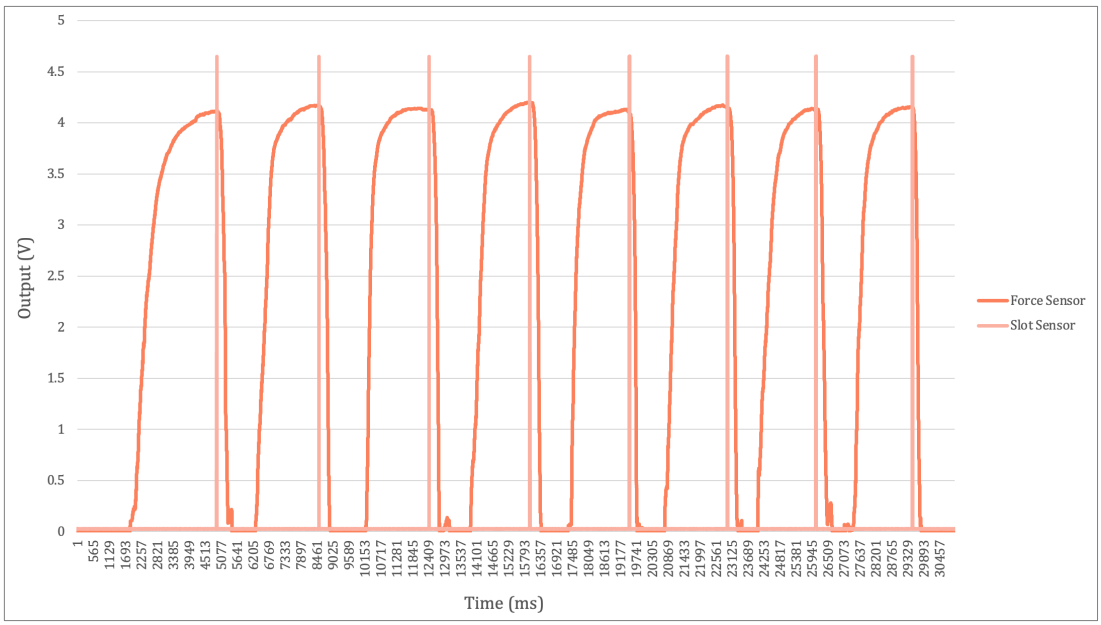


Figure 5.16: Output voltage with thumb when the level of fluid in the bottle is 1.5cm.

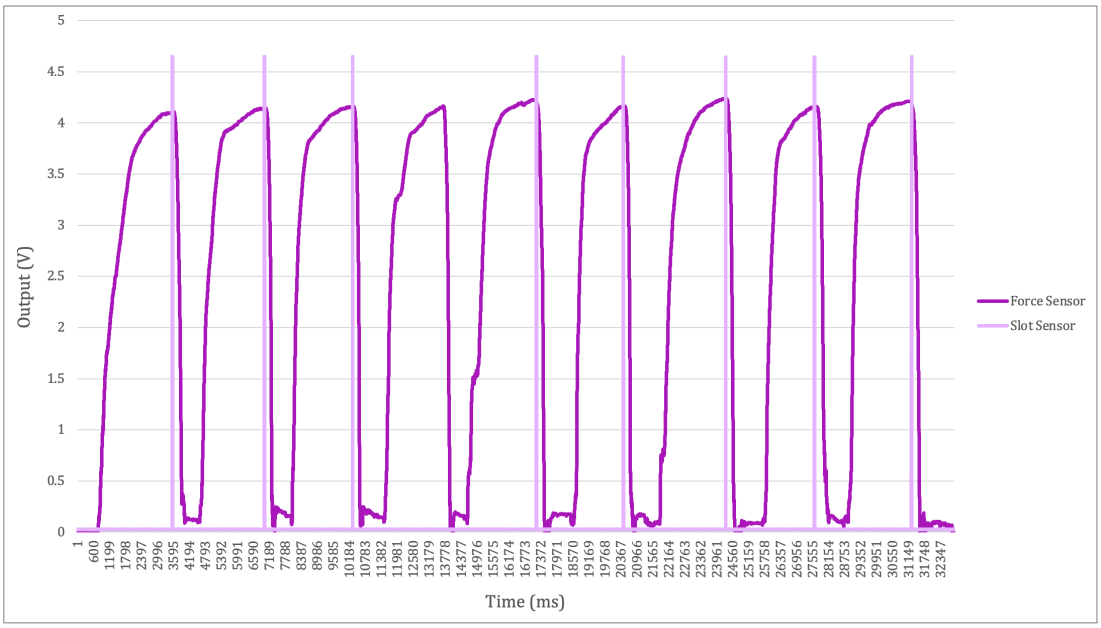


Figure 5.17: Output voltage with thumb when the level of fluid in the bottle is 1cm.

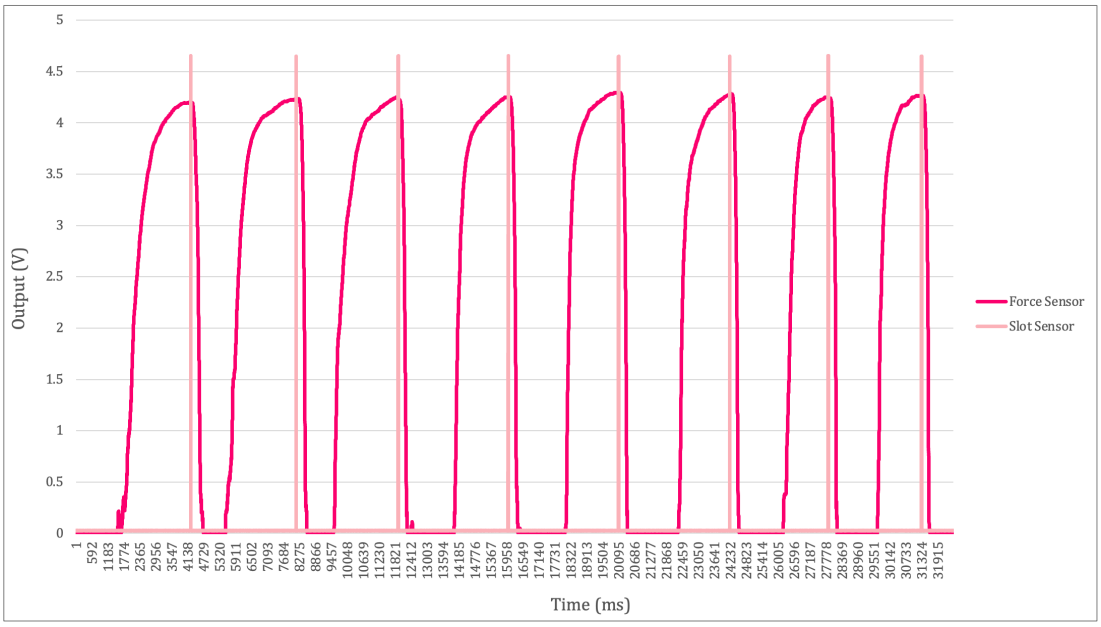


Figure 5.18: Output voltage with thumb when the level of fluid in the bottle is 0.5cm.

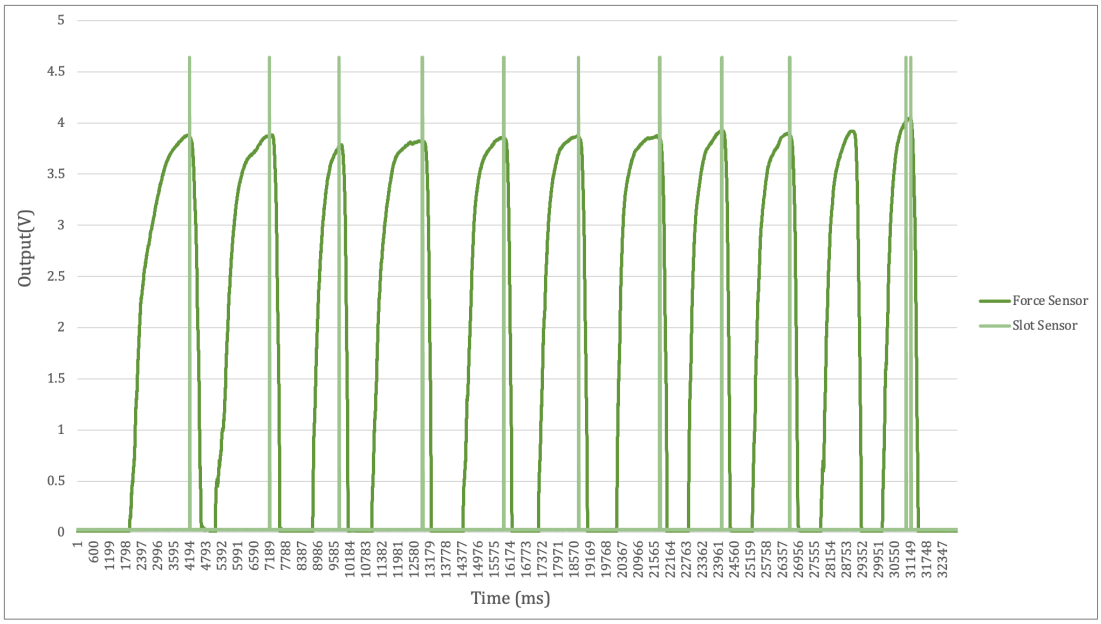


Figure 5.19: Measured output voltage with finger press when the bottle is full of fluid.

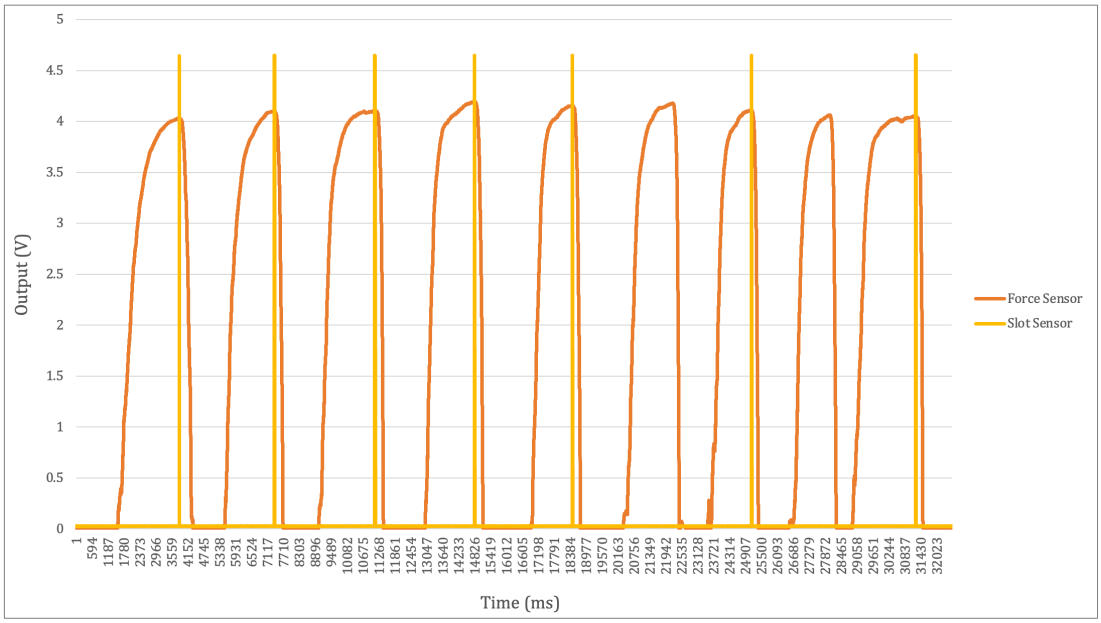


Figure 5.20: Output voltage with finger when the level of fluid in the bottle is 2cm.

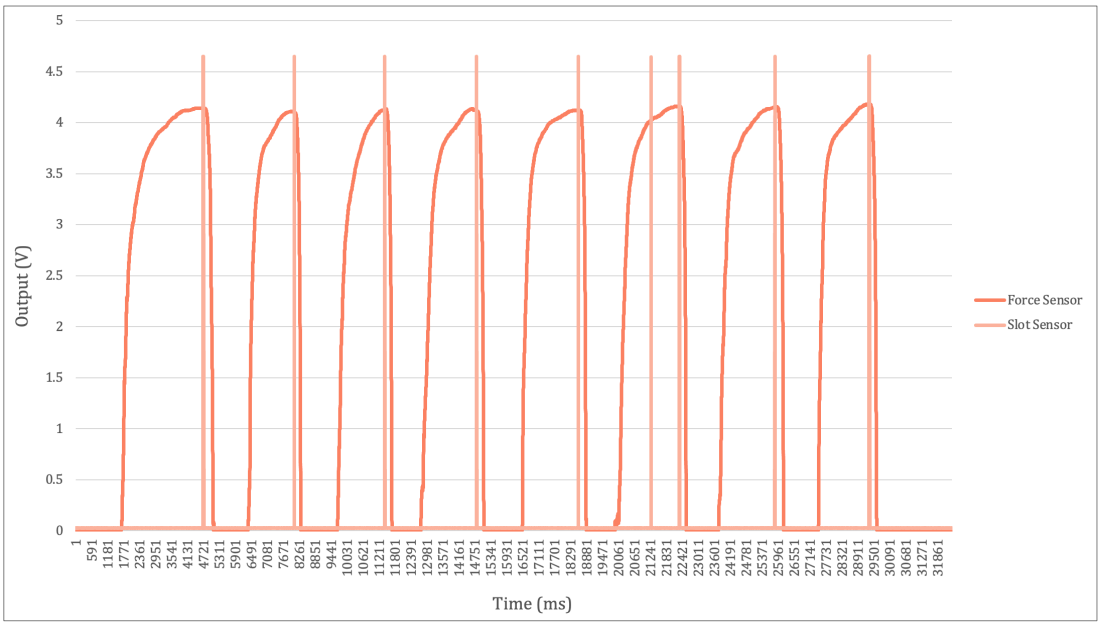


Figure 5.21: Output voltage with finger when the level of fluid in the bottle is 1.5cm.

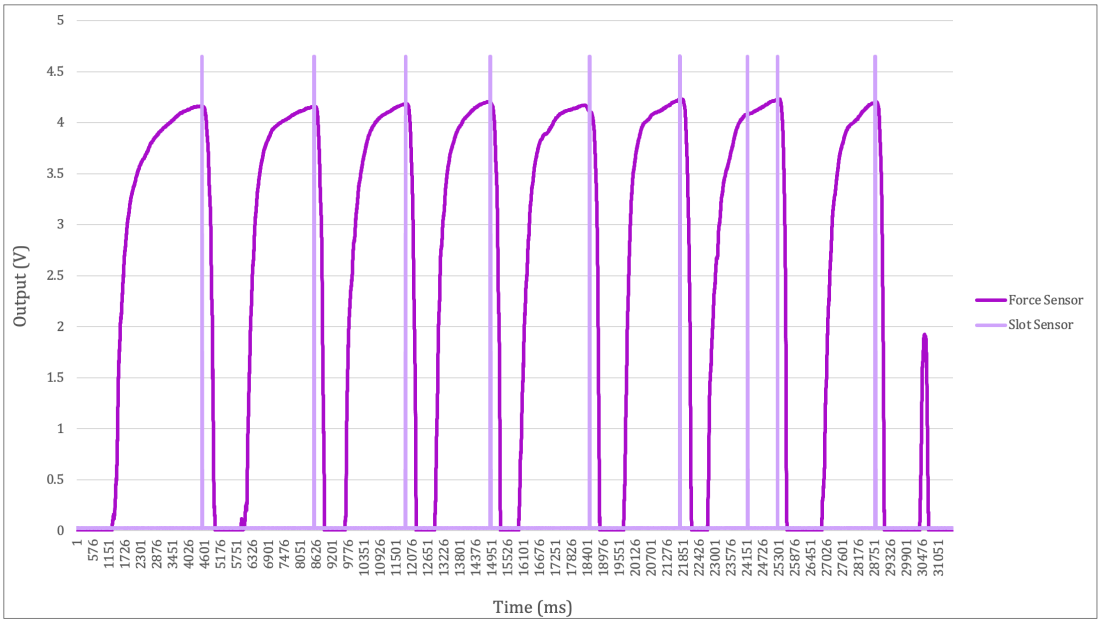


Figure 5.22: Output voltage with finger when the level of fluid in the bottle is 1cm.

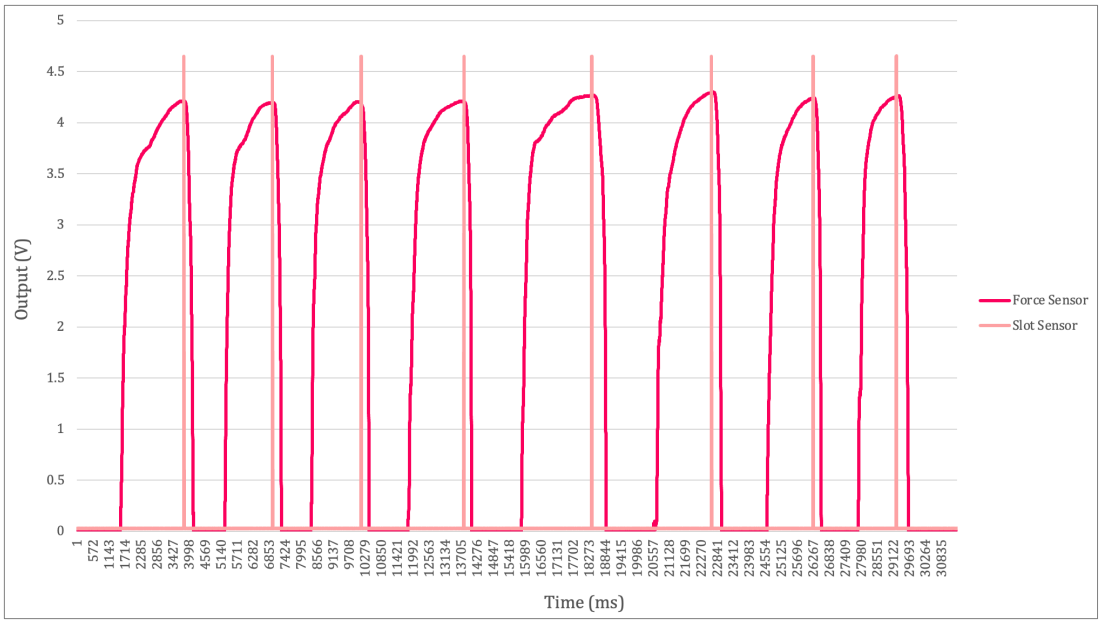


Figure 5.23: Output voltage with finger when the level of fluid in the bottle is 0.5cm.

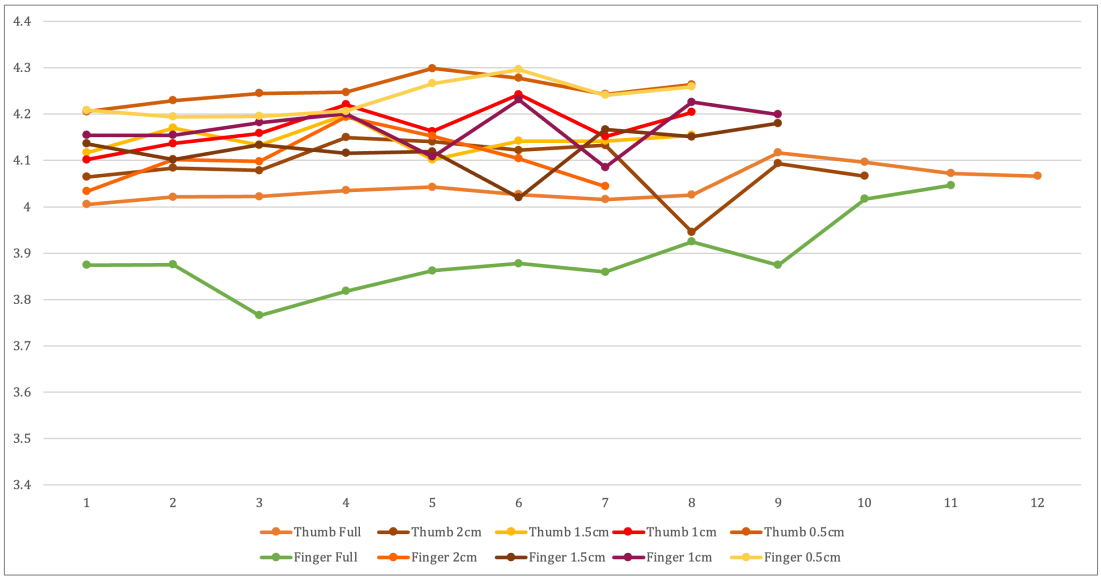


Figure 5.24: Voltage at the point of eye drop ejection, for different fluid levels. Finger and thumb press data also included as highlighted in the figure caption.

Based on the graph above, 3.5 Volts was determined to be output from the amplification circuit, this figure in turn can be applied to the formula to determine the resistance that is generated by the force sensor.

By applying the values now for R_M, V_+ and V_{OUT} the values for resistance expressed by the force sensor can be derived.

$$V_{OUT} = (R_M V_+) / (R_M + R_{FSR}) \quad (5.1)$$

V_{OUT} = 3.5V (Op-amp output voltage)
R_M = 3KΩ (Op-amp feedback resistor)
V_+ = 4.74V (Op-amp supply voltage)

R_{FSR} = 1.05KΩ (Force sensor resistance)

This data is then applied to the force sensor experimentation and the subsequent graph (Figure 5.11), which gives a value of 46.96N. This is the approximate minimum force required to eject an eye drop and the value can be used within the coding section of the microcontroller if needed. This corresponds to a mid-range value of squeeze forces measured for a range of people (17.8N to 160N) as highlighted in [156].

5.8 Further Work and Research

The scope of this project omits some questions that can arise. For example, one question that comes out is how the system would know or sense if the eye drop bottle is in a ready position to perform an eye drop dispense. A simple answer would be to have an accelerometer, this was looked at within the project of an MEng at Cardiff University. The students' project was generated from the work that was completed alongside this project detailed in this thesis and thus assisted in determining the viability of other sensor technologies.

Louis Sherratt [157] shows how the ADXL337 accelerometer chip can be used to determine if the system is in an upside-down state so that it is ready to dispense an eyedrop. The purpose here is not to ascertain if an eyedrop is dispensed but merely to establish its position. Figure 5.25 (reproduced from [157]), shows the dynamic 3 axis output from the accelerometer and the measurable dip from the x axis that determines the system is in a ready state.

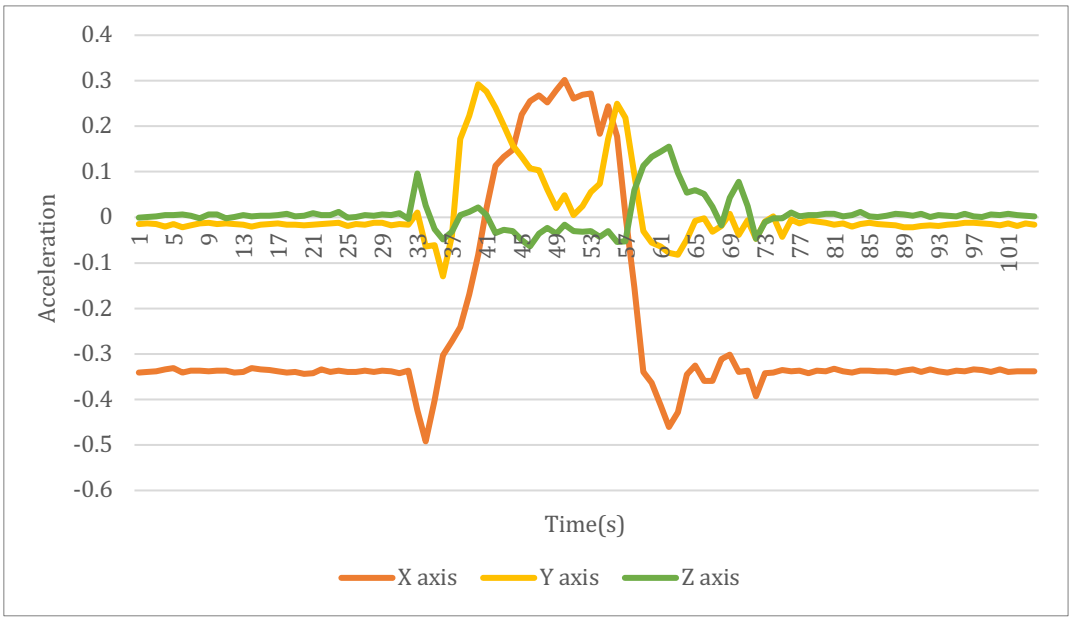


Figure 5.25: ADXL337 accelerometer being inverted with the x axis starting normal to ground.

Rather than considering the full range of analogue outputs from the accelerometer, one improvement would be to have an analogue to digital conversion of the signal connected to a comparator for a simple Boolean (bottle up or down) output. This has the benefit of converting the signal programmatically so that the system will know that the eye drop has been inverted with less power draw.

Additionally, the type of force sensor is also an important point. Within the MEng project effectively a resistive sensor is used however other types of force sensors haven't been considered such as capacitive or piezoelectric types. Sherratt [157] reports that the piezoelectric types will have to have an additional requirement of having active signal amplification and thus had settled on a capacitive type. A further point of investigation is to see the effectiveness of more types of sensors particularly to commit to a cost and benefit analysis of each one that is proposed.

Fundamentally, Sherratt [157] argues for a system with multiple sensing points, which on balance of completing this project is something that is highly recommended as it will improve the accuracy and precision of the device. There is a trade-off here too, more sensors and sensing capability will generate a greater power requirement something that has been a struggle in this project already given the flexible battery requirements. It is also worth considering that a simpler system is lower in cost especially if the intention is that the device is meant for one bottle only.

Moreover, an important point to note in sensing capability to which Sherratt [157] concludes is that there is no definitive way, and it is accepted that it is not possible to know for sure if the eye drop inclusion was or is successful. Such a conclusion would have to be taken via a vision-based processing system which has been successfully put together in the framework of this project (explained in Chapter 7). There is obviously a lot of room and scope for further work that would require more funding. This can entail a process to miniaturise the system, combine both systems together and explore a product or actual dispenser.

5.9 Summary

From the experimentation that has been completed, a profile of the sensor that will be used has been established. This will further aid the effort in constructing the final circuit. It has been established that the calibration profile can be applied to the final circuit which in turn will give rise to the level of force that is required for an eye drop ejection pattern. This force will be different for different bottle types. Parameters such as level of fluid, bottle design and shape will impact on this figure, however ejection was usually achieved around 47N. This is an approximate minimum estimate. This particular sensor is a simple passive component, and its power consumption is largely minimal and constant in nature. Its mailability in terms of its flexible nature gives good grounding to prolong the life of the device too. The squeezing force of around 47N should exclude the possibility of a false report being generated from dropping the bottle for example. The transient nature of such an event would likely be missed by the microcontroller in any case. If this concept were to become a commercial product, the manufacturer would be able to customise a sensor for the purpose of the project which can be utilised in the future work that is outside the remit of this project.

Chapter 6

Electronic Design

6.1 Introduction

The electronic design of this project is very multi-faceted in nature and naturally forms and represents different parts of the overall system with multiple sub systems at play. In order to determine the correct electronic design, it is necessary to restate the requirements of the system and thus deduce what is needed to achieve that. The system should fulfil the following requirements: -

- Sense if the eye drop bottle has been squeezed.
- Must be flexible in nature.
- Be able to last for the life of the eyedrop bottle.
- Log the events of eye drop inclusion.
- Saving the data onto the device ready for transfer.
- Transfer the data gathered to a computer.
- Low in cost for production purposes.

With these points in mind the following essential items are needed in order to satisfy the criteria of the system: -

- Microcontroller
    - A logical brain would be required to direct and dictate the terms of the program.
    - Enough space to store the compiled program and log events that have actively taken place.
    - One that consumes a low amount of power.
    - Be capable of going into a deep sleep mode so to conserve energy for long sustained periods of time.
- NFC
    - An NFC chip is good platform to transfer data.
    - The chip must be low powered in nature and activated when presented to its reader.
- Flexible battery
    - This has been discussed at length in Chapter 4 however it forms an essential part of the circuitry and consideration must be given to the battery capabilities with respect to the final circuitry. If implemented as a commercial product, a suitable battery could in principle be designed, manufactured, and supplied for this application.
- Sensor
    - A sensor platform is needed to detect the event of eyedrop squeezing. This has been discussed before and ultimately some level of customisation would be required. For the purposes of this project the resistance-based force sensors will be used.

6.2 Microcontroller

Within this section a discussion will take place with regards to the microcontroller selection and theory of operation.

6.2.1 Choice of Microcontroller

The features that the microcontroller should have been mentioned in section 3.6. The PIC16LF1828 was selected given its small size and ultra-low power features, which would enable cycling between different power modes. From an early stage it was determined that three power modes will be an appropriate level of power cycling. These are sleep, WUP and finally active mode. A sleep mode would consume the minimal amount of power, whilst a WUP mode would be slightly higher but enough for the microcontroller to determine if WUP should be advanced to active or for it to return back to sleep. As the name suggests, active mode entails the use of all devices for full regular operation. These actions are all taken to save and conserve as much energy as possible.

6.2.2 Microcontroller Evaluation and Circuit Prototyping

The microcontroller would need a phase of development and testing to later on verify and validate the expected functionality that is required from the overall device. The essence or behavior of a microcontroller is that it is programmable to replicate the expected behaviors. The prototyping stage consists of the C programming design and development and the overall microcontroller electronic circuitry. In order to assist with this process for the PIC, a development board called a curiosity board was employed which has the basic features needed to test and carry out development on the microcontroller.

6.2.3 Curiosity Development Board

The curiosity development board is a low-cost evaluation board that enables the design and development of a PIC microcontroller and its associated program. It has onboard devices and ports that allow for physical interaction before deployment. Figure 6.1 displays a curiosity development board with the name of each part.

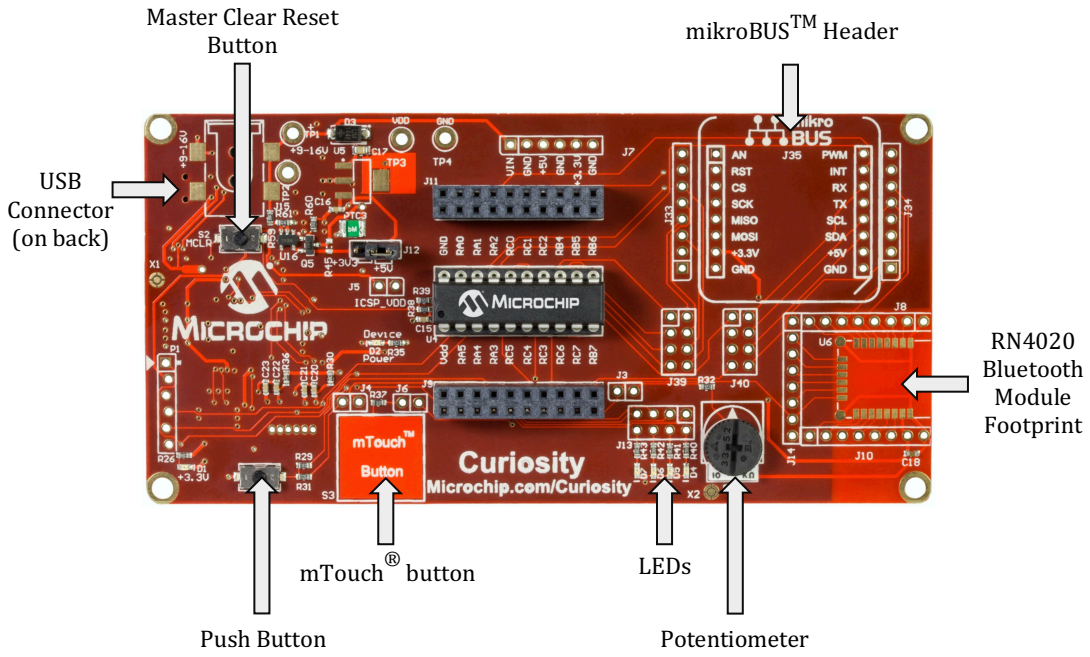


Figure 6.1: Curiosity development board (reproduced from [158]).

6.2.4 C Programming

The C programming of this project was a challenging and essential part especially because of the type of microcontroller that has been used for this project. Each section of C programming had to be tested individually and finally all parts of the program, being tested together. Other microcontrollers such as the Atmel Arduino for example have extensive libraries and open-source examples that make it much easier to develop. Before starting the C programming, it's really important to identify what code is needed to be written and how the program will work. A breakdown of the required major sections are as follows: -

- Reading sensor data
- Data logging
- Time tracking
- Drivers for the NFC chip
- Management of the different power modes

- Awareness of the fact that most the time the device is in sleep mode.
- Wake only to note the passing of time, and if the bottle is squeezed.

The program for microcontroller is written in the MPLABX IDE Integrated Design Environment which is the native environment for Microchip PIC's. The final C program takes 79.36 out of the maximum 256 bytes of available memory and can be referred to in the appendix of this thesis. Virtual code schematics are shown in the following section. The coding includes set up of the PIC and then goes to sleep. The main program of the PIC involves the use of different interrupts, timer interrupt, force sensor interrupt and NFC. The interrupt feature suspends the running code or wakes the system when an interrupt occurs so that a certain task can be executed immediately.

6.2.5 Timer Interrupt

The timer module in PIC microcontroller is basically a counter which counts 'ticks' of the oscillator clock. The frequency of the clock is defined by the external clock circuit. This was necessary to be able to log the time the patient used the eye drop applicator during the day. In the final application, one-hour windows throughout the day would be defined and if the system was used it would be logged as occurring within that one-hour window. Knowledge of the exact time the eye drop was administered was not necessary. During the development and testing phase, 15 second windows were used instead of the full hour. Thereby, a full day of testing could be done within an hour or so.

The PIC microcontroller has different timers however timer 1 is selected due to the presence of the external crystal clock [159]. The timer 1 module is a 16-bit timer/counter. The timer interrupt indicates when 15 seconds has elapsed and eventually when one day has passed. The description here is that half day contains 12 hours which is 43200 seconds. Dividing 43200 seconds by 15

seconds, gives 2880 which is the number of 15 seconds in half day. If the number is below 2880, this represents the morning period and if the number is equal or above 2880, it must therefore mean an afternoon/evening time. The microcontroller wakes up every 15 seconds and goes to sleep within 2ms to save power. The passing of 15 seconds could be verified by setting one of the output pins on the PIC to high briefly. This could be observed with an oscilloscope or via an LED indication if using the development board. The routine for initialising the timer interrupt is listed below: -

- Activate timer1 with internal oscillator.
- Switch to using the external crystal clock.
- Implement a periodic check every 15 seconds.
- Check the interrupts are working for the timer.
- Introduce sleep mode and check again that the interrupts are still working.

The testing protocol for the timer interrupts would be to use a simple incrementor and view the result over an extended period of time to see if the program is keeping track. This was done over an accelerated time stamp to prove the theory of operation as it would have been impractical to wait for the correct time frames that has been designed for the system.

6.2.6 Force Sensor Interrupt

By pressing the force sensor that wrapped around the bottle in the final design the eye drop ejects. The belief is that a patient will squeeze the eye drop twice a day for a month. The information of patients' behaviour will be written to the NFC. The NFC behaves as if it has an external memory. By putting a break point and debugging the code, testing the force sensor interrupt can be achieved. The force sensor connects to PIC via the comparator to the INT pin.

The testing protocol of interrupt lines can take place by simulating the force sensor, this is done using a switch that is wired from a high-power line relative to the microcontroller. An actual test can take place by completing the circuitry and pressing the force sensor on the table. Both methods would confirm interrupt code functionality.

6.2.7 Force Sensor Interrupt Experiment

Another experiment took place regarding how the interrupt of force sensor behaves. There were two types of sensors used, a force sensor and a slot sensor. The force sensor acts when the actual sensor is pressed, and the slot sensor detects when the eye drop ejects from the bottle. By attaching the curiosity board to the comparator circuitry, the experiment is performed to see the interrupt of the force sensor (as shown in Figure 6.2).

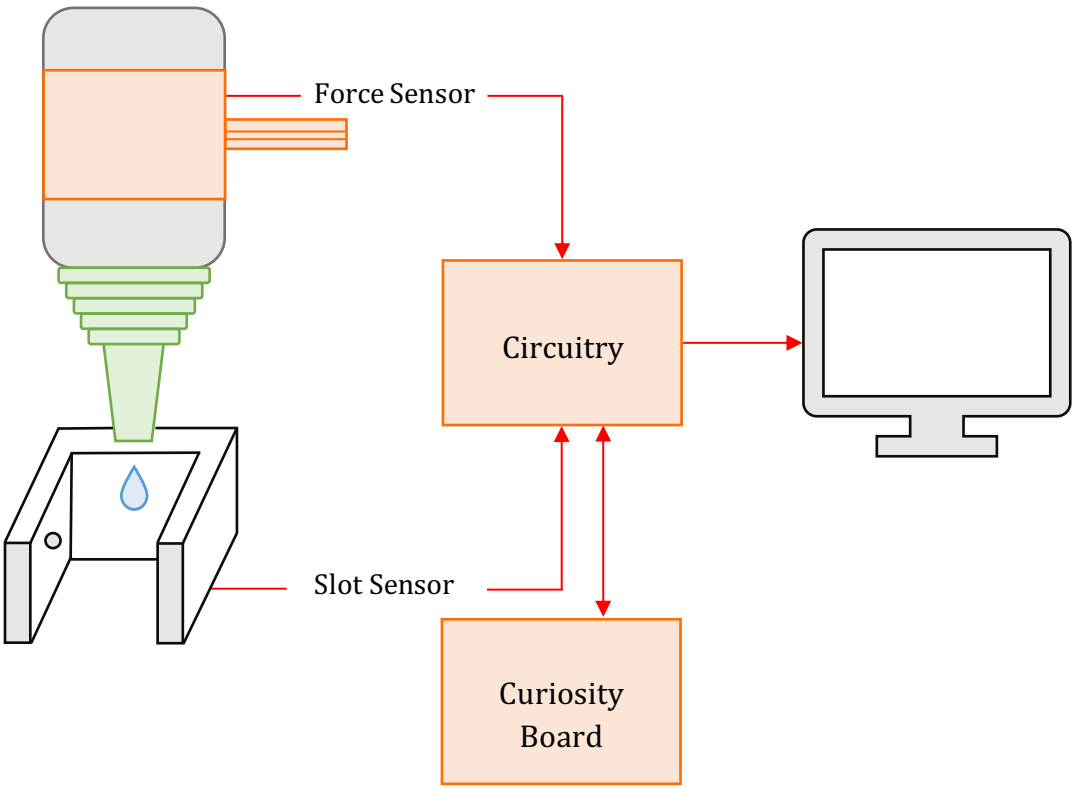


Figure 6.2: Force sensor interrupt testing

To test this setup, two comparator circuits were prepared. One each for the force sensor and slot sensor. The output from the force sensor comparator was connected to the INT pin of the PIC to trigger the interrupt. The analogue output from the force sensor and the two comparator outputs were connected to a NI myDAQ for recording purposes and the output traces are given in the Figures 6.3 and 6.4. Multiple squeezing events can be seen in these figures with the analogue output from the force sensor changing as the squeeze carried out. Also, the corresponding comparator output as the threshold for squeeze is reached. Finally, the ejection of a droplet is captured by the slot sensor and correlates well with the squeeze reaching its maximum.

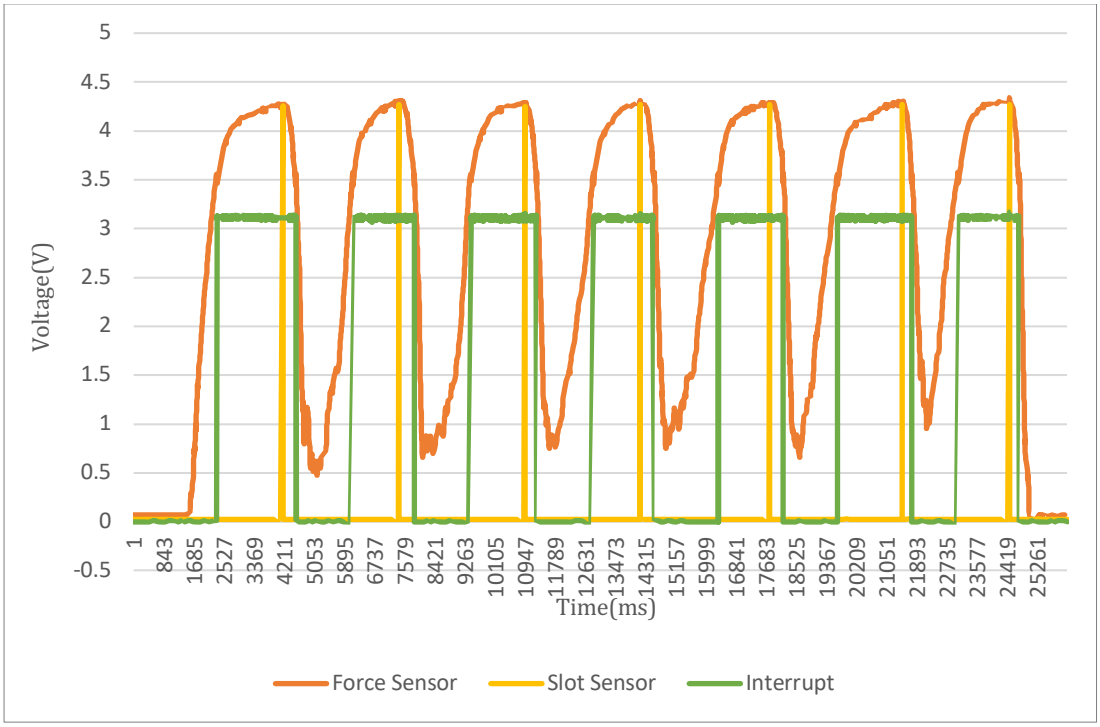


Figure 6.3: Graph showing the interrupt of the force sensor when an eye drop ejected from a bottle. The idea of this experiment is to observe that the interrupt of the force sensor is excited.

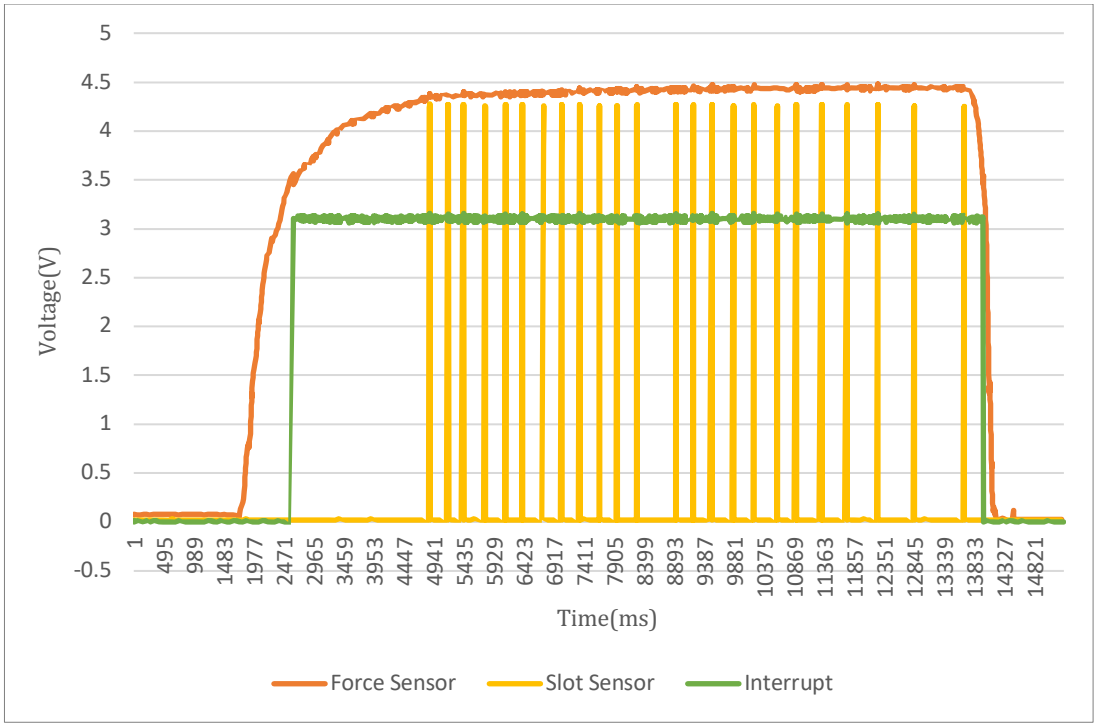


Figure 6.4: Graph showing the interrupt when the force sensor pressed continuously. Multiple droplets can be seen to be ejected.

6.2.8 NFC Interrupt

Before adding NFC chip to the circuit, a switch has been used which simulates the NFC interrupt line. For the need of expediency, the code was accelerated into thinking that one day is the equivalent of 2 mins just to speed up testing. Every minute, the sensor is going to be pressed (compliance), digit 1 will be shown. By not pressing the force sensor (non-compliance) digit 0 will show. The data is going to be written in the electrically erasable programmable read-only memory (EEPROM) of the microcontroller. After debugging and doing the testing for the equivalent of 30 days, the program pauses, and the switch is removed. By looking at the Watch Window of the programming environment, the data that has been written in the EEPROM and READ_data_back can be seen. If for instance someone uses the eyedrop bottle more than 60 times, once they have used it in a half day period, the relevant data bit on the register is changed to 1 and cannot be

reversed. If an interrupt does not happen in a half day period, it stays at 0. Figure 6.5 shows the circuit with switch. Note, the slot sensor is not used from now on.

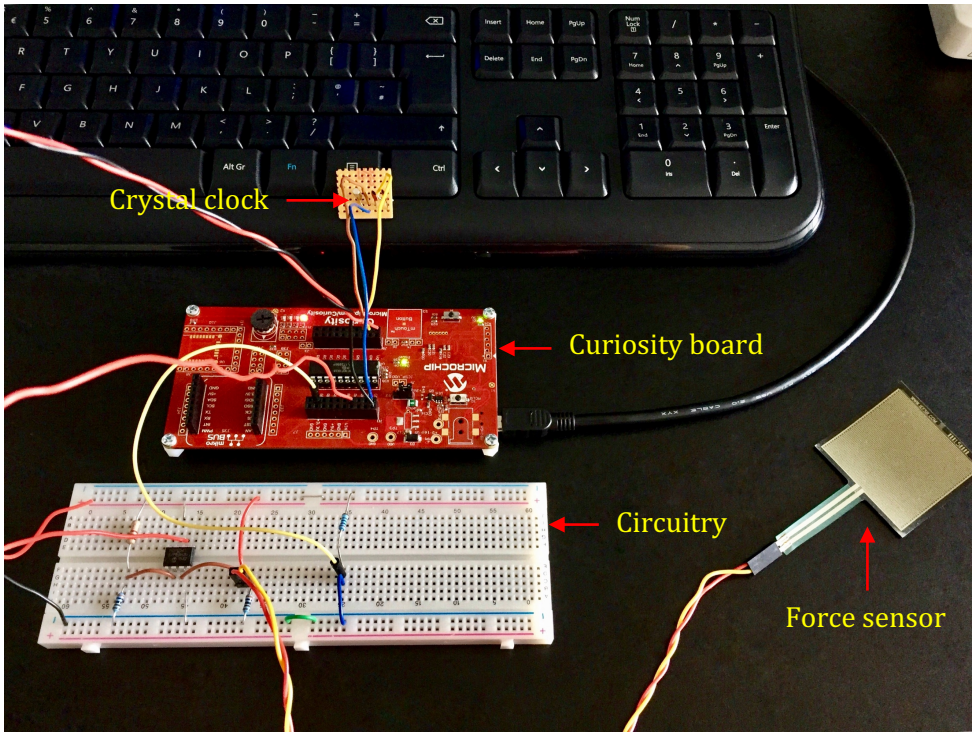


Figure 6.5: Circuit with switch for testing write and read in the EEPROM.

Once the simulation testing of the system had been completed, the NFC simulation switch was replaced with an actual NFC chip. The read and write for NFC is being replaced by the read and write of EEPROM. The testing for the whole program is explained as before. The Figure 6.6 shows the final circuitry with the NFC chip.

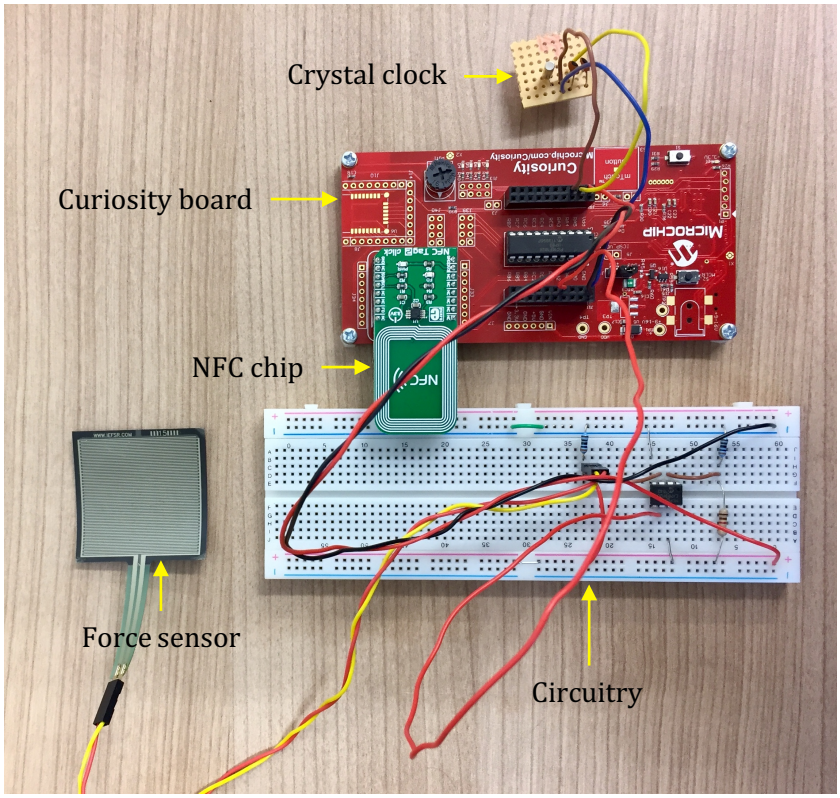


Figure 6.6: Final circuit with NFC chip

In order to test the program, a table is drawn to assist the testing. The table contains morning and afternoon of each day for a period of 30 days. The time period which compliance happens or not is chosen randomly. For instance, if compliance happens in the morning of day one and not occurs in the afternoon the number would be 01. For day two, the compliance happens, the opposite of action of day one would occur that is to say that the number for day two would be 10. So, for day one and two, the final number that expected to observe would be 1001. The integer data type in coding “int” takes 2 bytes/ 16 bits. So, the expectation would be to see binary numbers of 16 bits in length which would correspond to 8 days (morning & afternoon). Day 9-16, 17-24 and 25-32 occur in the next lines. After completing the table, the expectation would be to observe these numbers in a watch window after the testing was completed.

The Table 6.1 illustrates the way the program is tested. The ✓ symbol means the sensor has been pressed and the × mark indicates when the pressing is being

missed. So, the expectation would be to eventually have the results as shown in this table where a clinician can evaluate the patient's adherence. The results start from right to left, for instance morning of day one and then the afternoon of the day one and keeps incrementing accordingly. The Figure 6.7 displays the same results on the watch window of the programming environment.

Table 6.1: Testing the final Program with NFC

Day	AM	PM	Logged_data	Read_data_back (NFC)
1	✓	✓	11011111	10111111
2	✓	✓		
3	✓	✓		
4	×	✓		
5	✓	✓		
6	✓	✓		
7	✓	×		
8	✓	✓		
9	×	✓	11101111	01111110
10	✓	✓		
11	✓	✓		
12	✓	×		
13	✓	✓		
14	✓	✓		
15	×	✓		
16	✓	✓		
17	✓	✓	11101111	01110111
18	✓	×		
19	✓	✓		
20	✓	×		
21	✓	✓		
22	✓	✓		
23	×	✓		
24	✓	✓		
25	✓	×	00001111	10111101
26	✓	✓		
27	✓	✓		
28	×	✓		
29	✓	✓		
30	✓	✓		

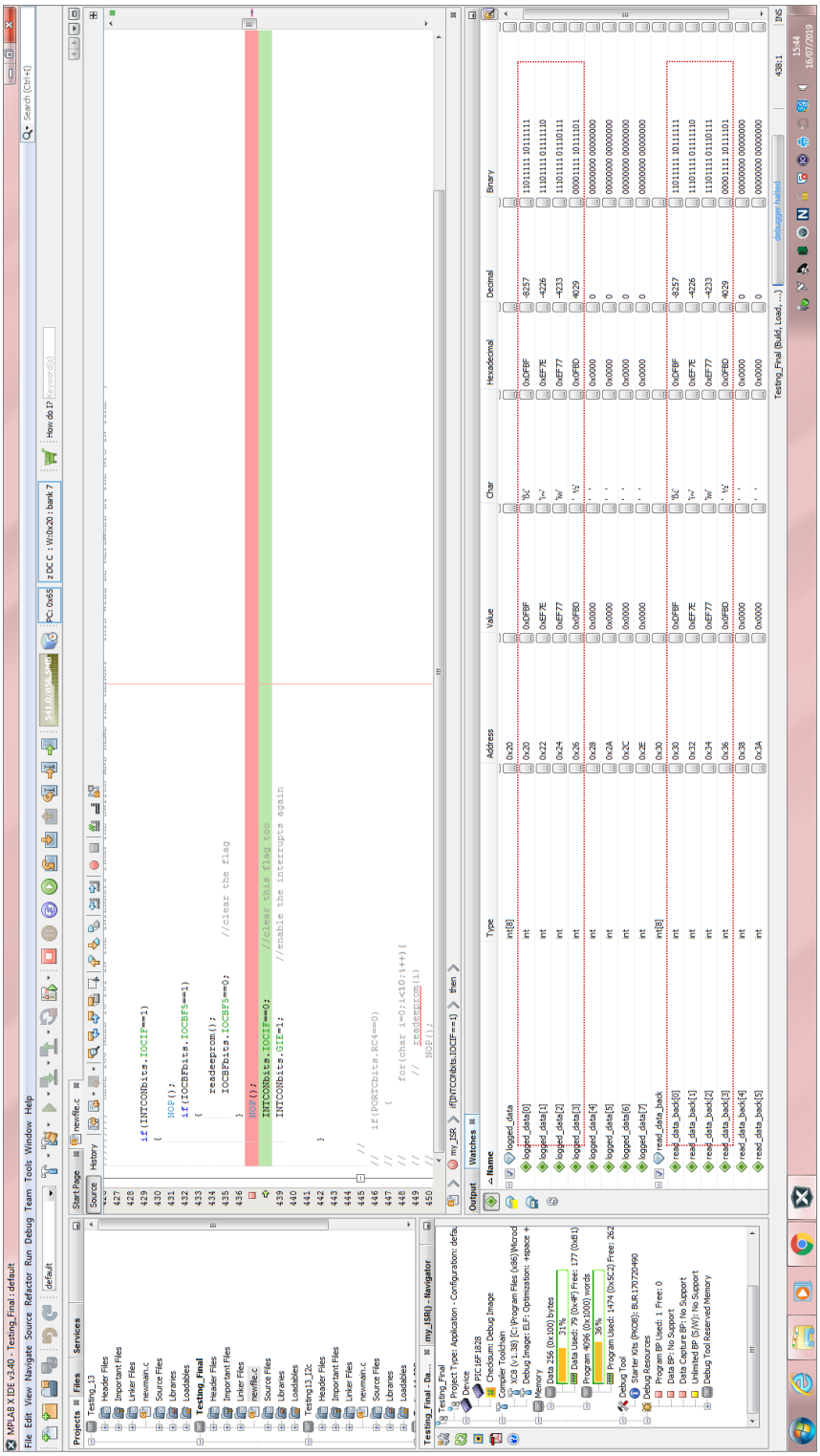


Figure 6.7: The results of the testing on the watch window

6.3 NFC Design and Development

Before engaging in integrating the NFC chip from NXP Semiconductors is it necessary to engage in a stage of design and development to establish the theory of operation of the chip when trying to transfer the data from the chip to a PC. This is done by using the supplied manufacturer demo kit which has a reader and is covered in this section. The intent of this section is to describe the creation of a basic program and prove that a clinician will be able to set up the system, then view the data stored on the system from the last 30 days.

6.3.1 Demo Kit Reader

The theory of operation of the demo kit reader device is noted here. The first step is downloading the NTAGI2C Demo software from the NXP website. Once this is completed and installed and the reader is connected to the PC, the software should be opened and the demo tab should be selected as shown in Figure 6.8.

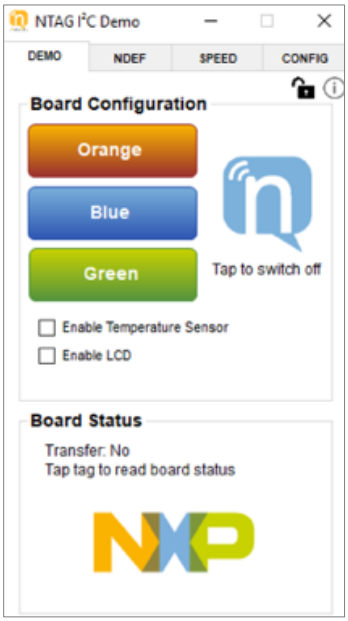


Figure 6.8: The GUI of the NTAGI2C Demo software

Basic diagnostics can be completed to ensure communication to the device, for example turning on or off the LED. Once this has been established it is possible to move on to writing and reading. The NDEF section needs to be selected which in turn enables the read and write sections. Information can be put simply as a text and then can be written to the chip (as shown in Figure 6.9).

Figure 6.9: Writing on NXP

This data that has been written will be acknowledged by the NXP chip when it placed on top of the reader (Figure 6.10).

Figure 6.10: NXP on top of the reader

Then by clicking on Read NDEF, the text that has been written can now be read back (as shown in Figure 6.11).

Figure 6.11: Reading NXP

6.4 Reading and Writing Data to the NFC Chip

An investigation was necessary in order to establish the correct parameters for an external read or write. That said whilst the demo program was able to establish comms, read and write, it didn't provide the method to do it. This was established by looking at the read parameters and the different manuals from NXP. Thus, the programming function operates on the basis of writing to the chip in a structured fashion. From the data sheet and depending on what chip is being used; it is possible to formulate a hexadecimal number from string-based inputs that will then situate on the chip's memory space. The chip would then reply with hexadecimal 90 when a successful operation has taken place.

In order to write data, the data must be converted from a string ACSI based format to hexadecimal based numbers. The data must also be reorganised into 4-byte blocks and an instruction given to which line the data will go to. It is also

good practice to have appropriate termination. Robin Alexander Nissen from CCM-EE company has made some example code in NI LabVIEW which has been repurposed and edited by this author to make it suitable for the needs of this project with the theory of operation that has been established in mind.

A write to the device is achieved by creating a hexadecimal array in LabVIEW with the following at the start: -

FF D6 00 06 04 xx xx xx xx

What is happening here is that the initial write instruction is made using FF D6, with the indication that the write should occur on line 6 with a maximum capacity of 4 blocks. Hence 06 and 04 at the end of the instruction. What would follow, is the hexadecimal data that has been converted from string up to a maximum of 4 blocks of data which is represented above as xx. A successful operation of any kind gives a reply of 00 90 from the device.

With all this information in mind a program is created in LabVIEW that will automatically: -

- Interpret the data that has been applied and convert it from string to hexadecimal.
- Limit the size of a data package that can be written to prevent false or overwriting.
- Increment the position of the data blocks and overwrite the data that currently exists.
- Limit every line of data write to 4 blocks.
- Should an odd last data write occur, this will be padded at the end with 00 till it reaches the 4^{th} block, this can happen when the message that's passed through the algorithm does not reach the last 4 full blocks.

What this would enable is a unique identifier for the patient to be written to the device by a medical professional. After which it will allow the medical

professional to track the data and give appropriate feedback. The software map (as shown in Figure 6.12) gives an easy guide as to what is going on and how it behaves.

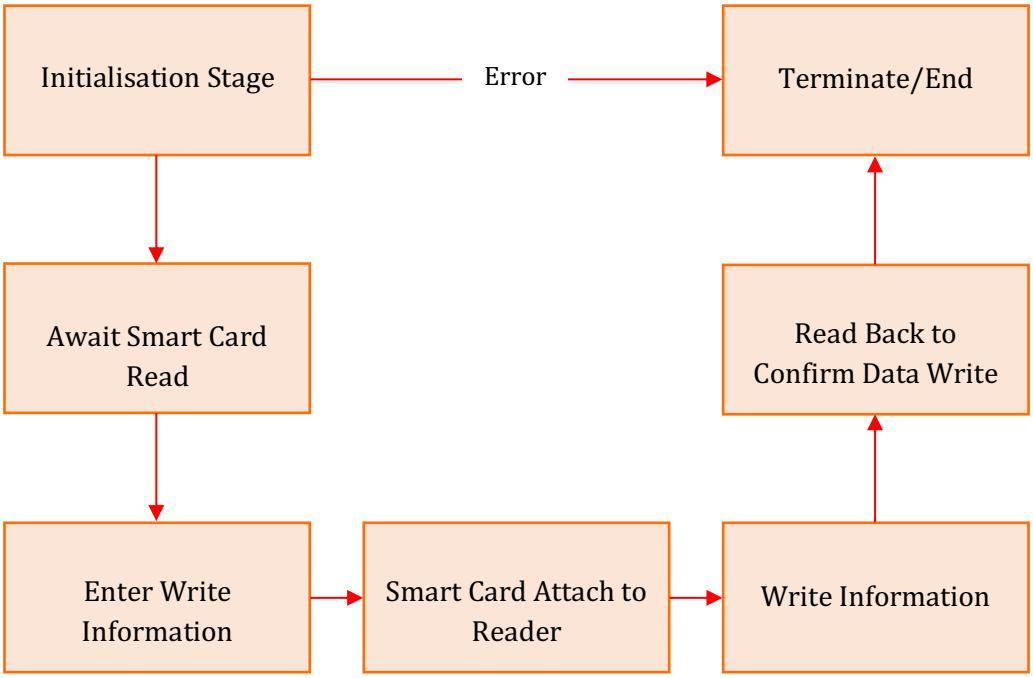


Figure 6.12: Simplified software block diagram

In order to check the program and make sure it's able to transmit from the NFC to the computer, a fall-back option was employed by using the debugging tools and introducing simulated squeezes. It was then observed in the prototype LabVIEW program designed to read the NFC chip the correct memory space and its data in hexadecimal format.

6.5 Final Label and PCB Design

The final label and PCB design was achieved by taking all the knowledge acquired on the component side and combining them. Initially a full schematic of the circuit was created using Altium's circuit maker software. The benefit of this method is that there is a database with common components that can be automatically translated from a schematic to a PCB. Once the circuit was constructed in a schematic format which is shown in Appendix C, this is then ported to a PCB design. The design was altered to suit the specific needs of the project in Altium. Some of the design strategies that have been employed here include the use of a double layer design and flexible fabrication considerations. Consideration had to be given to the constraints within this section of the project. Such as the size of a typical eye drop bottle and the need for it to be wrapped around. It's at this stage implementation can proceed. As can be seen in Figure 6.13, a standard eye dropped bottle with the usable area that the system will be placed.

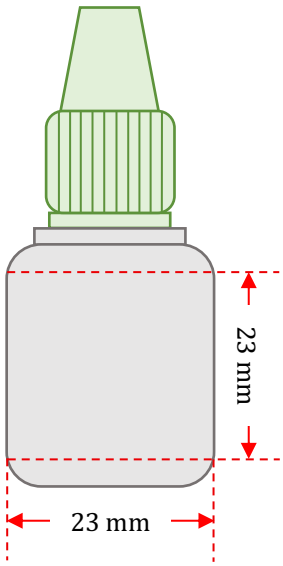


Figure 6.13: Standard size of glaucoma eye drop dispenser bottle with the sketch of used area for the final system. Measurements obtained here can be used to calculate curvature.

As such it is easy to work out the label size as a whole given the constraints by use of πd to figure out the length and the height as a measured quantity to 23mm where ‘d’ would be 23mm. Figure 6.14 shows the final flexible label of the product in block diagram format with all components that will be employed.

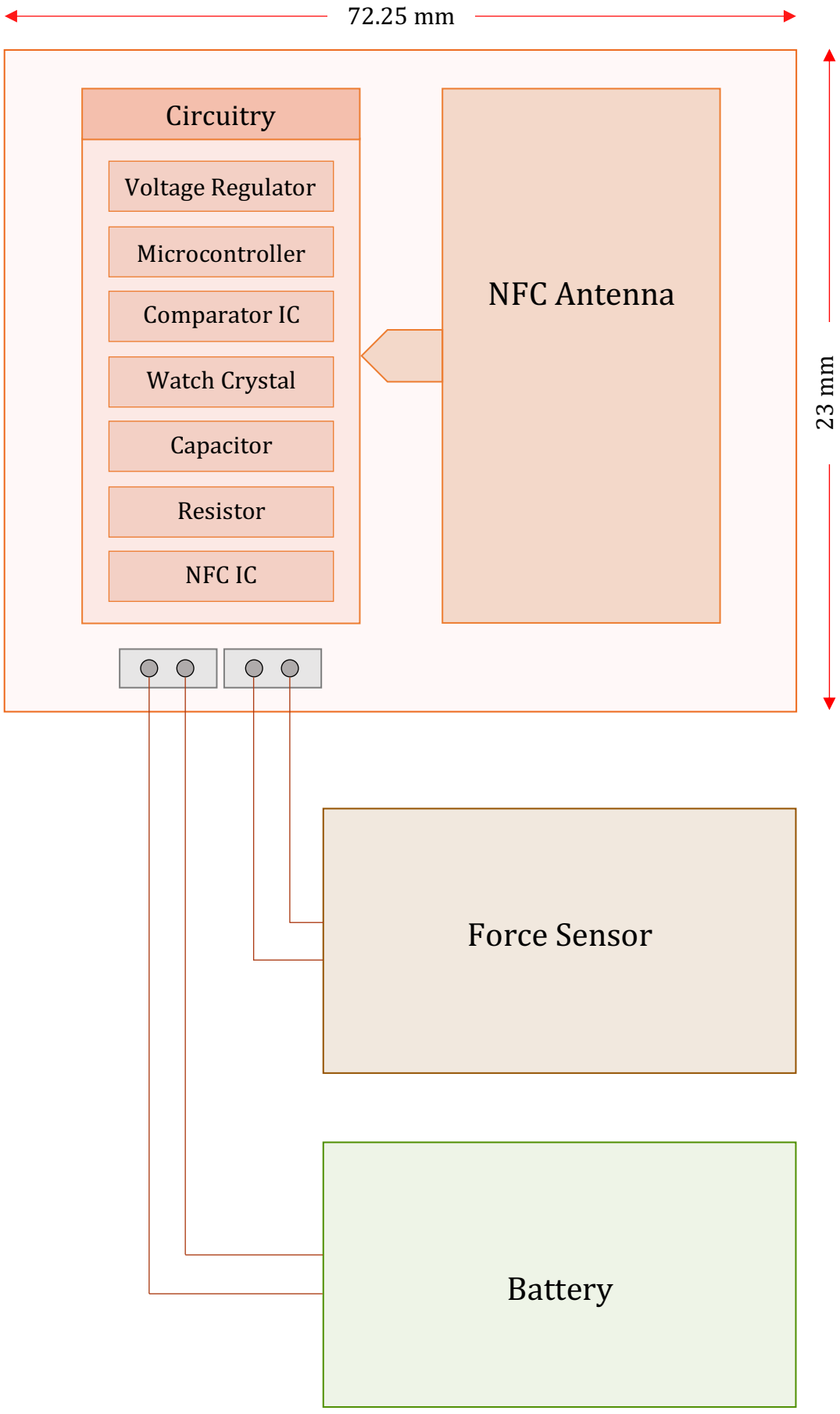


Figure 6.14: Final flexible label

Figure 6.15 shows the final PCB design. After a design iteration review, the antenna and a slight reorganisation of the circuit was implemented. Figures 6.16 and 6.17 show the final manufactured product with different states of evolution. Another idea is for a further iteration of the PCB concentrating on a size reduction. It is possible with refinement that the size of the current PCB can be reduced and thus the programming connectors are done away with, in a mass production environment the microcontrollers will usually be batch programmed then soldered on or a set of contacts would be made on the PCB rather than a full interconnect. In a production run rather than a prototype PCB, programming connectors can be made with flat surface connections for example. This will allow for a better coverage of sensors on the bottle. In short efficiencies can be made but for which are outside the scope of this project.

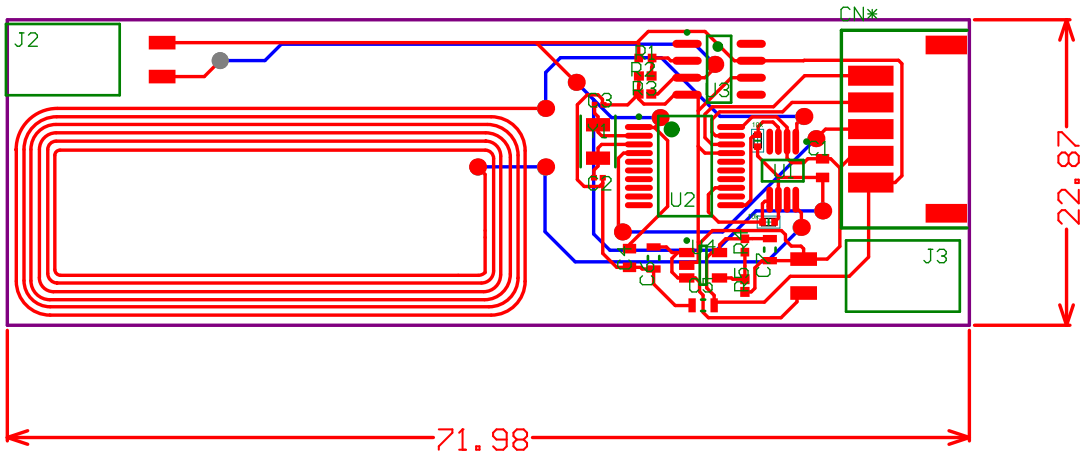


Figure 6.15: PCB design

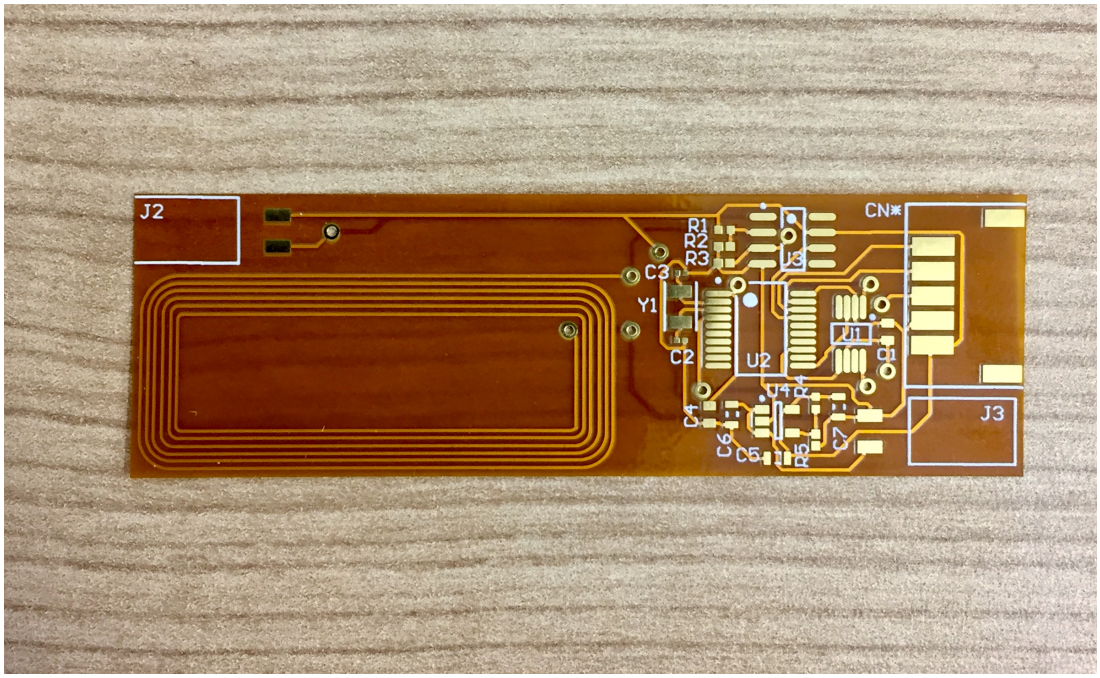


Figure 6.16: PCB from manufacturer

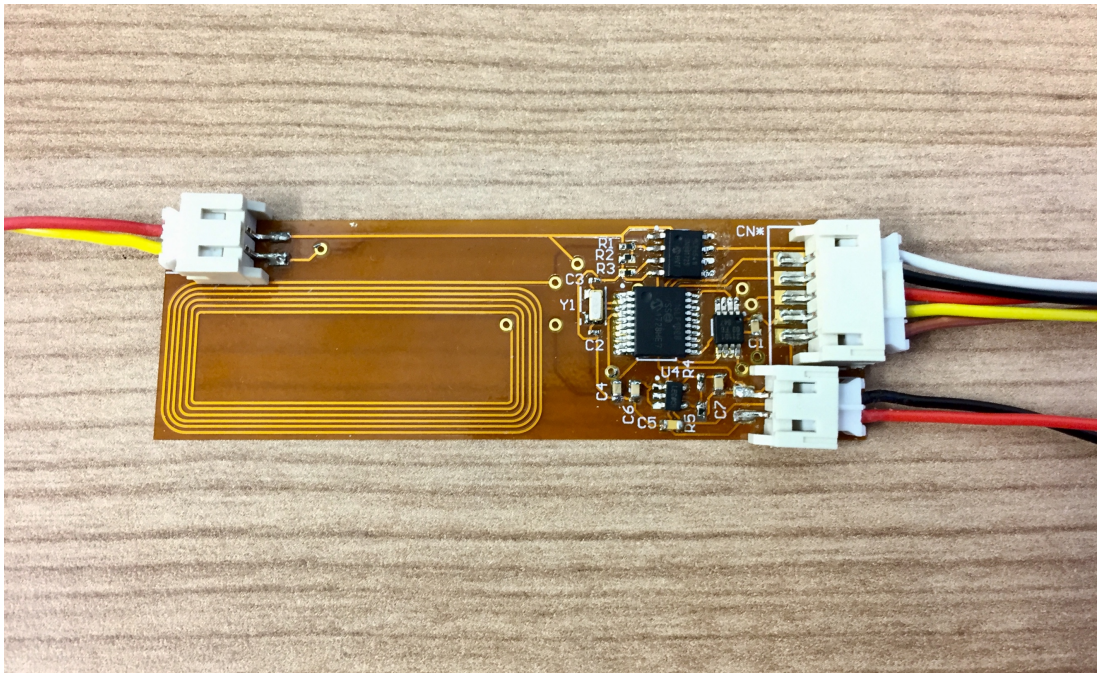


Figure 6.17: PCB with parts soldered

6.6 Testing of PCB

The testing of the PCB commenced once everything was connected correctly. An attempt was made to program the microcontroller. The compiler and the program complained of having low voltage on the device. This in turn triggered the need for further investigation on the final soldered board. It was ascertained that the voltage on the microcontroller was 1.5V against a battery that was outputting 3V through a voltage regulator. This was surprising as the circuit was designed for a voltage regulation of around 2.5V. It was also noted that the battery was degrading much faster than expected and dropping to around 2.5V. After carefully reviewing the design, it was then determined that there was no immediate design fault and through a process of elimination the problem was sourced to the output on the voltage regulator. The design decision towards having the voltage regulator is still valid as the battery through the course of its life will tend to experience a reduction in voltage output which is not reliable when powering a device such as a microcontroller. One would be forgiven for thinking there was an IC issue at this point however, the next course of action was to ensure that the voltage regulator circuit was correctly assembled. This was done by powering down the circuit and checking the resistors forming the voltage divider portion. Upon investigation with a multi-meter, it was proven that the intended resistors were soldered in their opposing places. That is to say, R4 was in the place of R5 and R5 was in the place of R4. An attempt was made to rework this circuit, the resistors were de-soldered and switched around. Unfortunately, and as somewhat expected when this rework was completed, the output from the voltage regulator was wrong. Upon inspection and observation, it was concluded that the resistors were most likely damaged from heat exposure due to rework. This would effectively mean the circuit now on this board is unviable and there is no guarantee that the rest of the components didn't suffer from some form of excess heat exposure. To further complicate matters, a cold solder joint was discovered when investigating the resistors of R1, R2 and R3 which resulted in resistor R1 to fall off. The only logical solution with this number of problems is to have a brand-new soldered board put together. A fall back or back up board that was put together by the university manufacturing team, was

then examined and used. This time with the foresight to conduct checks on the resistors. Ironically it was proven than the resistors on R4 and R5 were wrong from the design these were again reworked and checked. However, when it came to programming the circuit, it did not produce the desired 2.5V to the microcontroller, it was producing 1.8V which was sufficient to conduct programming. Further investigation and checking later on with the new PCB revealed that the wrong formula was used to determine the voltage output. With the current documented resistors, an actual voltage output of 0.8V is expected however by chance the manufacturing team ended up making another mistake but one that worked to the project's favour. This mistake enabled an output of 1.8V. Whilst on the power side of the microcontroller sufficient voltage would be present, there was an issue on the sensor side which when the resistors were probed it was observed that resistors R1, 2 and 3 were identical. This effectively made the sensing component of the circuit useless.

6.6.1 Finding Feedback and Resolving Issues

At this point it was accepted that a complete brand-new PCB was needed to address all these issues. Before this was instigated, a thorough review on the other parts of the circuit had to take place and the following issues were identified on top of what has already been mentioned: -

- The output of the voltage regulator
    - Investigation showed that the output was much lower than expected. This was addressed by revising the resistors used with new understanding from the data sheet. The value of R5 was changed from 5KΩ to 30KΩ. After this, the voltage regulator provided 2.5V.
- Non readability of the data from the NFC
    - Initially the data was not forthcoming. Investigation showed a design flaw that the NFC chip didn't have the appropriate pull up

resistors to it. Once this was addressed, the data then came as expected.

After resolution of all these issues the PCB worked as designed. Some tests were carried out to affirm the correct communication via the NFC and the PC. Each of these tests confirmed the correct operation of the circuit as a whole and could now be mass manufactured for use in potential clinical trials. With some extensive fault finding and re-design, a viable concept was delivered addressing all of the requirements of the proposed system.

6.7 Component Pricing

It has been since the start of this project a desire to have the total cost of the item to be relatively cheap in nature. However, an overriding question is to see whether or not the system is actually possible. To that end it has been proven that the system minimally viable in nature as shown in the bill of materials which leads us to the return of the pricing question. Table 6.2 lists the bill of materials and their respective price for each component. This would be the price for a single item enough to prototype with rather than bulk or quantity purchase. It should also be noted however that should a production run with sufficient quantities take place, then this will lead to significant cost reductions. It must also be stated that in some cases it would be practical to make a custom or specific part which can be requested from the manufacturer. Table 6.3 gives an idea for the sorts of cost savings that can be made given a higher production run.

Table 6.2: The list of individual prices for all materials

Qty	Item description	Unit price (inc. VAT)	Total
1	PCB	£51.74	£51.74
1	Force sensor	£2.85	£2.85
1	Crystal, 32.768KHz	£0.5772	£0.5772
1	Analogue Comparator	£0.432	£0.432
1	LDO Voltage Regulator	£1.2	£1.2
1	RFID IC, NTAG, 13.56 MHz	£1.1304	£1.1304
1	Microchip PIC16LF1828- I/SS	£0.41	£0.41
2	Wurth Elektronik WR-WTB, 2 Way, 1 row, straight PCB header*	£0.989	£0.989
1	Wurth Elektronik WR-WTB, 5 Way, 1 row, straight PCB header	£1.318	£1.318
1	CR2032 Button Battery, 3V	£1.027	£1.027
1	TE Connectivity Female 2 Way Battery Holder	£1.92	£1.92
2	Wurth Elektronik WR-WTB Female Connector Housing, 2mm Pitch, 2 Way, 1 Row*	£0.122	£0.122
1	Wurth Elektronik WR-WTB Female Connector Housing, 2mm Pitch, 5 Way, 1 Row	£0.163	£0.163
9	Wurth Elektronik WR-WTB Female Crimp Terminal Contact 22AWG	£0.154	£1.386
2	SMD Multilayer Ceramic Capacitor, 15 pF*	£0.1075	£0.1075
3	0603(1608M) 100nF Capacitor*	£0.102	£0.102
2	Tantalum Capacitor 10µF*	£1.567	£1.567
1	20kΩ 0402 (1005M) Thin Film SMD Resistor	£0.401	£0.401
1	30kΩ 0402 (1005M) Thick Film SMD Resistor	£0.04	£0.04
1	1.1kΩ 0805 (2012M) Thick Film SMD Resistor	£0.017	£0.017
2	SMD Chip Resistor, 3kΩ*	£0.3624	£0.3624
1	SMD Chip Resistor, 5kΩ*	£3.612	£3.612
2	10kΩ, 0402 (1005M) Thin Film SMD Resistor*	£2.58	£2.58
Grand Total			£74.05

* Minimum order applies.

Table 6.3: The list of quantity prices for 1000 units

Qty	Item description	Unit price (inc. VAT)	Total
1	PCB*	£20.00	£20.000
1	Force sensor	£2.49	£2490.00
1	Crystal, 32.768KHz	£0.3084	£308.4
1	Analogue Comparator	£0.3264	£326.4
1	LDO Voltage Regulator	£0.4584	£458.4
1	RFID IC, NTAG, 13.56 MHz	£0.4236	£423.6
1	Microchip PIC16LF1828- I/SS	£0.326	£326.00
2	Wurth Elektronik WR-WTB, 2 Way, 1 row, straight PCB header	£0.5808	£1128.00
1	Wurth Elektronik WR-WTB, 5 Way, 1 row, straight PCB header	£0.7877	£787.2
1	CR2032 Button Battery, 3V	£0.9216	£921.6
1	TE Connectivity Female 2 Way Battery Holder	£1.068	£1068
2	Wurth Elektronik WR-WTB Female Connector Housing, 2mm Pitch, 2 Way, 1 Row	£0.072	£144.00
1	Wurth Elektronik WR-WTB Female Connector Housing, 2mm Pitch, 5 Way, 1 Row	£0.096	£96.00
9	Wurth Elektronik WR-WTB Female Crimp Terminal Contact 22AWG	£0.1056	£950.4
2	SMD Multilayer Ceramic Capacitor, 15 pF	£0.02	£41.76
3	0603(1608M) 100nF Capacitor	£0.0516	£154.8
2	Tantalum Capacitor 10µF	£0.74	£1488.00
1	20kΩ 0402 (1005M) Thin Film SMD Resistor	£0.06	£60.00
1	30kΩ 0402 (1005M) Thick Film SMD Resistor	£0.0144	£14.4
1	1.1kΩ 0805 (2012M) Thick Film SMD Resistor	£0.0072	£7.2
2	SMD Chip Resistor, 3kΩ	£0.05592	£111.84
1	SMD Chip Resistor, 5kΩ	£0.0834	£83.4
2	10kΩ, 0402 (1005M) Thin Film SMD Resistor	£0.095	£228.00
Grand Total			£31.617

* The PCB company is not able to quote for high quantities unless there is a serious discussion that displays a firm commitment to create an order otherwise, they kindly quoted for 50 units. The price for 50 units will be £1000 or £20 each. This assumption that the price will stay the same probably doesn't hold true however it's the only price on offer.

6.8 Summary

This chapter provided information regarding the electronic design of the final circuitry. The microcontroller programming had been tested and the results showed the program works perfectly. With regards to the reading and writing on the NFC chip, a program had been written in LabVIEW. The testing of program proved the program is able to read what had been written to it. Extensive testing has been conducted and simulated on the breadboard and the curiosity board in terms of proving the theory of operation which till now has produced very good results. The software and hardware have both worked in these environments. The PCB which has been designed and developed is exactly the same in nature as the one created on the breadboard. After few attempts and fixing the issues which were due to the IC chip, the PCB worked. In hindsight, based on the experience that has been gathered after testing, it would be better to test the PCB on a non-flexible board as the flexible one makes the initial testing more difficult when there is an issue or problem present. It must be noted that fixing a mistake on flexible PCB is difficult and liable to cause damage. Furthermore, consideration to solder this PCB by a manufacture with capability for a pick and place machine would avoid soldering errors and on top of that save the time.

Chapter 7

System II- Vision

7.1 Introduction

As previously discussed on Chapter 2, the main challenge regarding glaucoma patients is to know whether or not they adhere to their eyedrop treatment regimen. Prior chapters show a system that can assist the patients on this matter. Notwithstanding another issue that comes to light is how the clinician can determine whether or not the droplet has entered the eye or if the patients are complying successfully.

One possible way to address this issue is to look at another system that can ascertain if the eye drop has been successfully accepted by the eye. It is worth investigating a system that is made from real-time vision technologies.

It is possible to use NI's machine vision technology and apply the well establish vision filters that exist in the market. From the hardware to the software NI offers a range of vision products that are for use in industrial applications. Moreover, by looking at the filters that are known to work for this application, such as Canny filter (described in section 7.7) and comparing them in NI's product offering it's possible to transfer this knowledge and see if it can work in a real-time system.

7.2 Hypothesis

It is imperative to formulate a hypothesis which will give this section of the project the scope and space of development. Given that the eye is more wet after applying eye drop compared to dry eye it is possible to attain some research. From which it's understood the impact of shining differing-coloured lights onto wet and dry surfaces. The reflected image and the wavelengths used represent an opportunity for image processing to occur. Thus, an investigation can take place which will explore the following research opportunities: -

- Design and development of a hardware system capable of image capture.
- Development of an algorithm capable of differentiating between a wet and dry eye.
- Investigation into which colour of light would yield the best result.

7.3 Work Packages

This section of the thesis will describe a system concept that can: -

- To correctly detect application of an eyedrop via a suitable algorithm.
- Evaluate and assess the best vision system most suitable.
- Investigate the different filters that would ideally assist in eye drop detection.

7.4 System Design

The core system consists of a camera to capture the event of applying an eyedrop and then real-time processing is done on the myRIO FPGA device or on a PC using LabVIEW. Much of the development was accomplished on the PC with the LabVIEW software whilst being mindful of the fact that this could be deployed onto a myRIO for potential field trials in future.

A number of pre-defined LabVIEW image processing tools were evaluated in order to assess whether they may be useful in facilitating droplet detection. Research into the use of these tools is summarised in [160] and is used primarily for iris recognition using MATLAB. This process flow was converted into LabVIEW as a means of gaining an insight into how images can be acquired and modified. The MATLAB algorithms described in [160] were implemented in LabVIEW code by this author. A brief summary of these image processing steps follows in the next section.

7.5 Grayscale

Grayscale images are ones that are represented by various shades of grey. An easy way to understand grayscale images is to look at how they're represented. Each pixel is assigned a number from 0 – 255 as an 8-bit binary number. Zero corresponds to black while 255 would mean white and numbers in between are varying shades of grey. If the value is closer to 255 then this is lighter while if its closer to 0 then the pixel would be darker [161]. The code consists of 3 parts: -

1- Read colour image file Apply and change to a pixel map suitable for use in LabVIEW.
2- Apply grayscale settings.
3- Redraw and display in LabVIEW.

The output from the grayscale VI is shown in Figure 7.1.

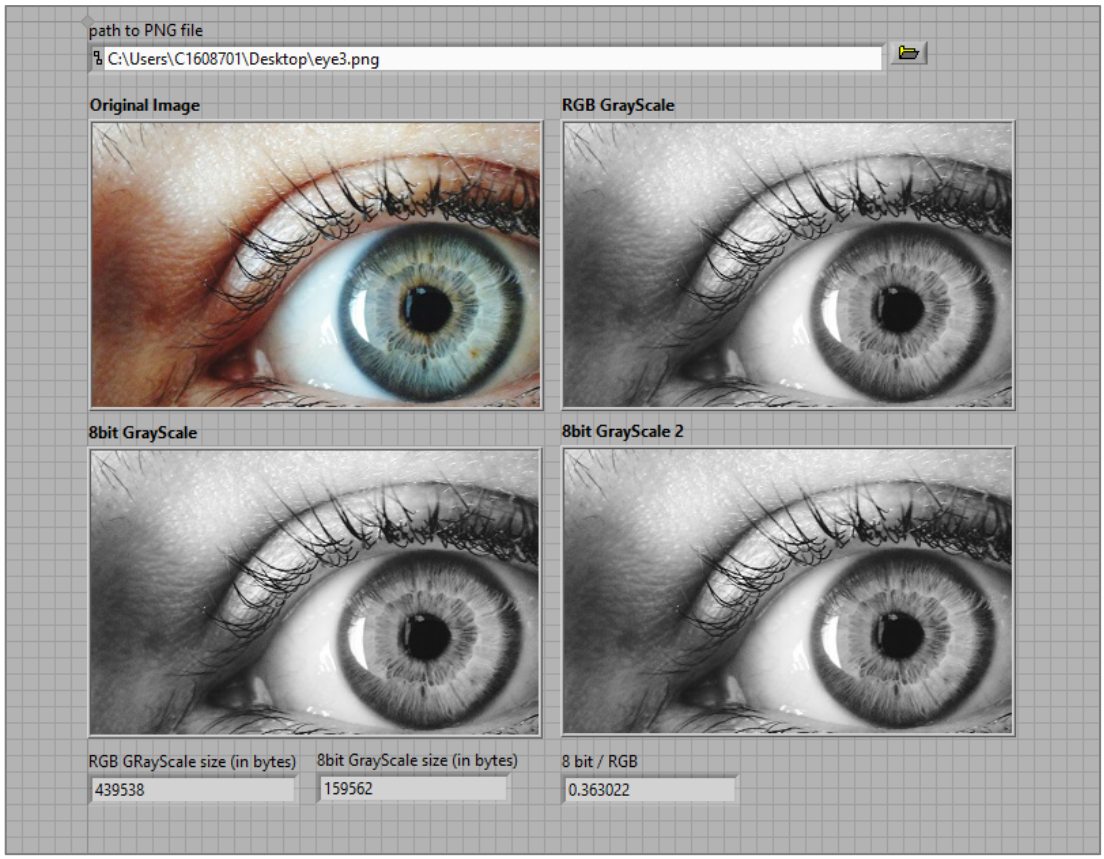


Figure 7.1: Output; the original image taken from [162].

7.6 Histogram

The histogram analysis in image processing represents the distribution of pixels from a dark to light setting. If most pixels were to be within the left side of the diagram, it can be said that the image has more darker pixels. Conversely if the pixels in the image are lighter, then the expectation on the histogram would be to see them on the right. The code includes 3 parts: -

1- This portion of the code imports the image of the eye. It then maps it onto the IMAQ structure ready for processing.
2- In the while loop the last image event is analysed and should there be a change, the histogram is updated. If the user changes the targeting on the front panel the histogram will update accordingly along with the mean and standard deviation.

3- When the analysis is complete then the stop button is pressed and all images are deleted from memory.

The output from the histogram VI is shown in Figure 7.2.

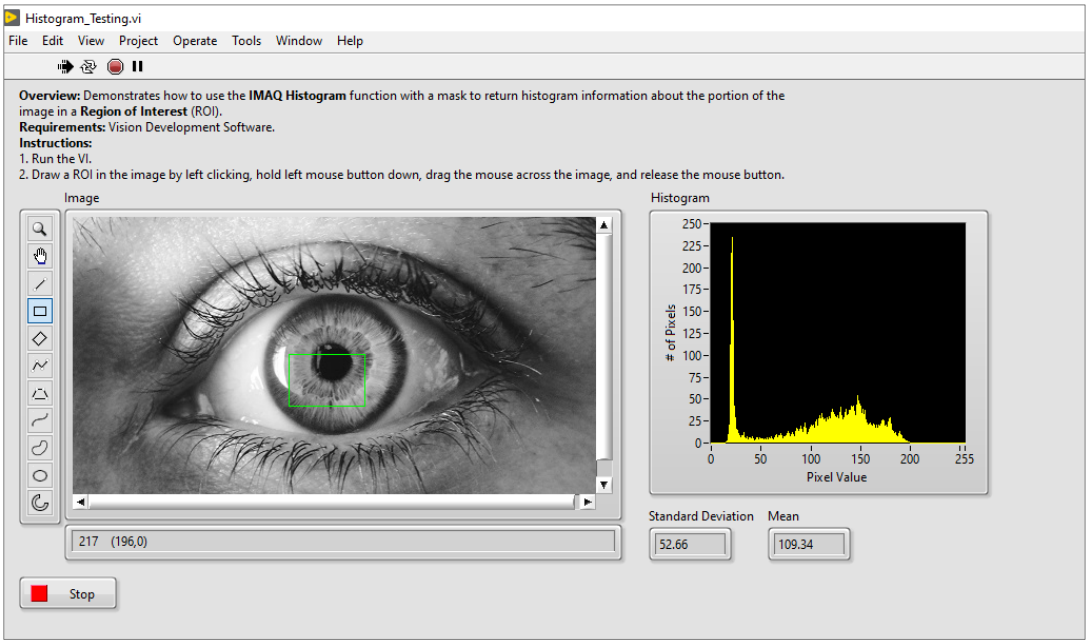


Figure 7.2: Front panel for histogram generation. By selecting the different regions of the eye, it's possible to see the changes in the histogram.

7.7 Canny Filter

A Canny filter is a filter used for edge detection and usually has several steps. These are expertly described by Sekehravani et al [163] and are briefly summarised here. The Steps are image smoothing (noise reduction), gradient calculation, non-maximum suppression, double threshold and edge tracking by hysteresis. Gradient calculation via differentiation is important for picking up the outlines in the image. Non maximum suppression involves taking the pixels individually and looking at their intensity. Double thresholding means to take weaker pixels and strengthen or increase their intensity and then edge tracking

completes the process. It should be noted that image smoothing is the process of suppressing noise within the image. The original image and the output from the Canny filter VI are shown in Figures 7.3 and 7.4.

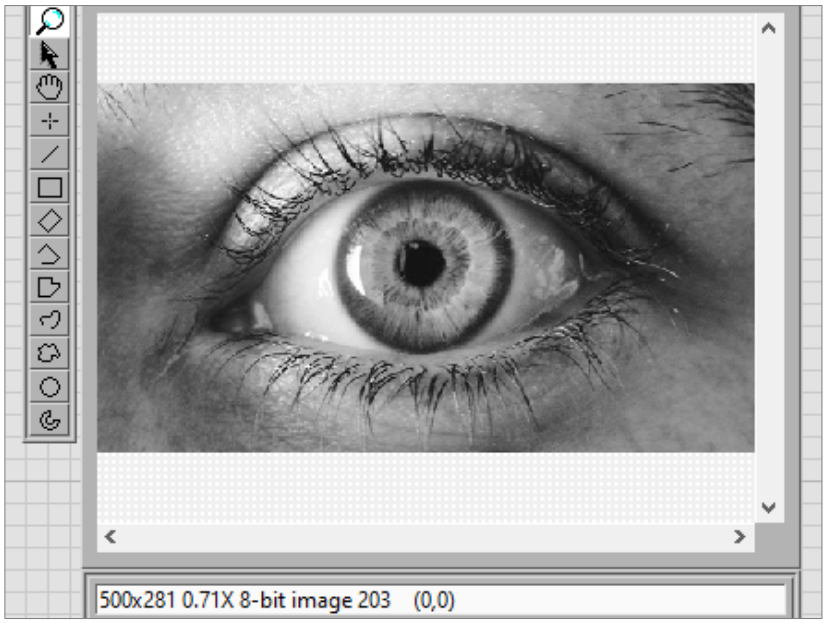


Figure 7.3: Original image

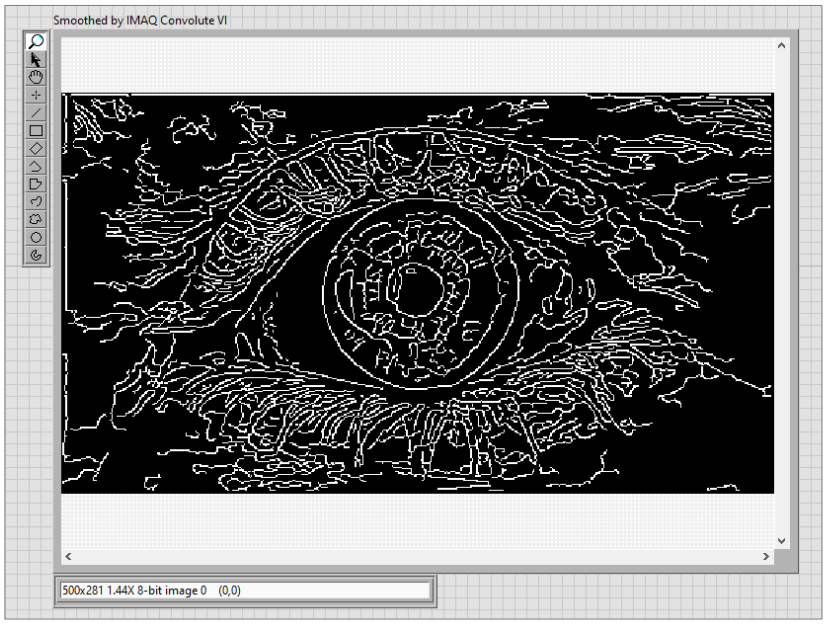


Figure 7.4: Edge detection using Canny filter.

7.8 Processing of Images of Both Wet and Dry Eyes

Having established a basic VI for processing images, images were obtained of an eye using the webcam that was connected to the PC running LabVIEW. The images of a wet and dry eye could then be compared to ascertain any differences. A wet eye was obtained by dropping saline solution into the eye. The output from the Canny filter was then compared. Briefly, the RGB colour image was converted to grayscale before being applied to the Canny filter. A video of the eye dropping process was recorded first and then frames from before and after were chosen as source images for the filter. Figure 7.5 shows the RGB and grayscale image of the dry eye. Following that, Figure 7.6 shows similar for the wet eye.

(a)

(b)

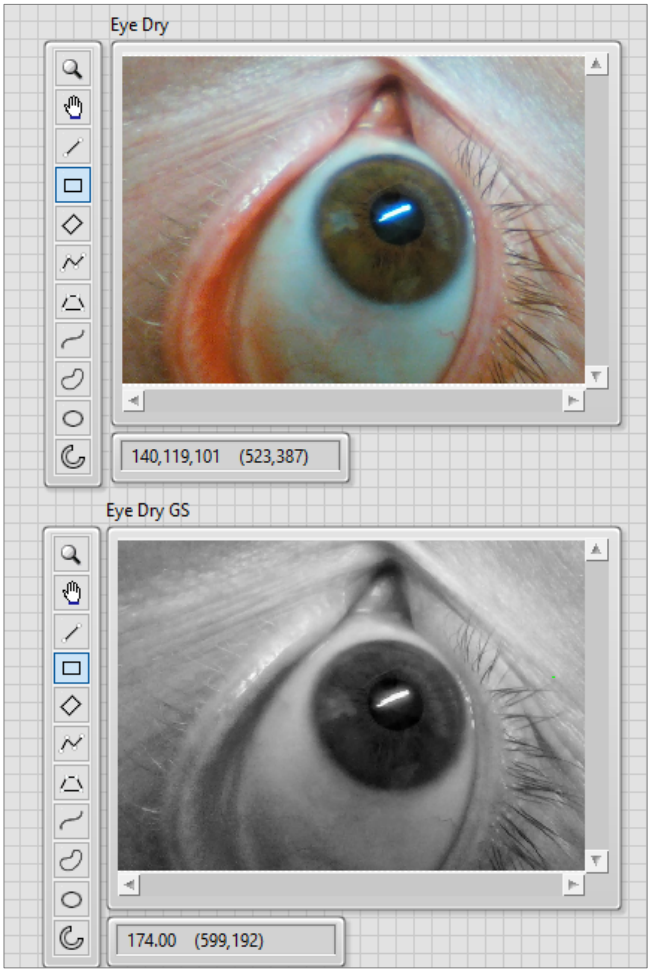


Figure 7.5: Image (a) shows the dry eye without any processing. Image (b) is the grayscale.

(a)

(b)

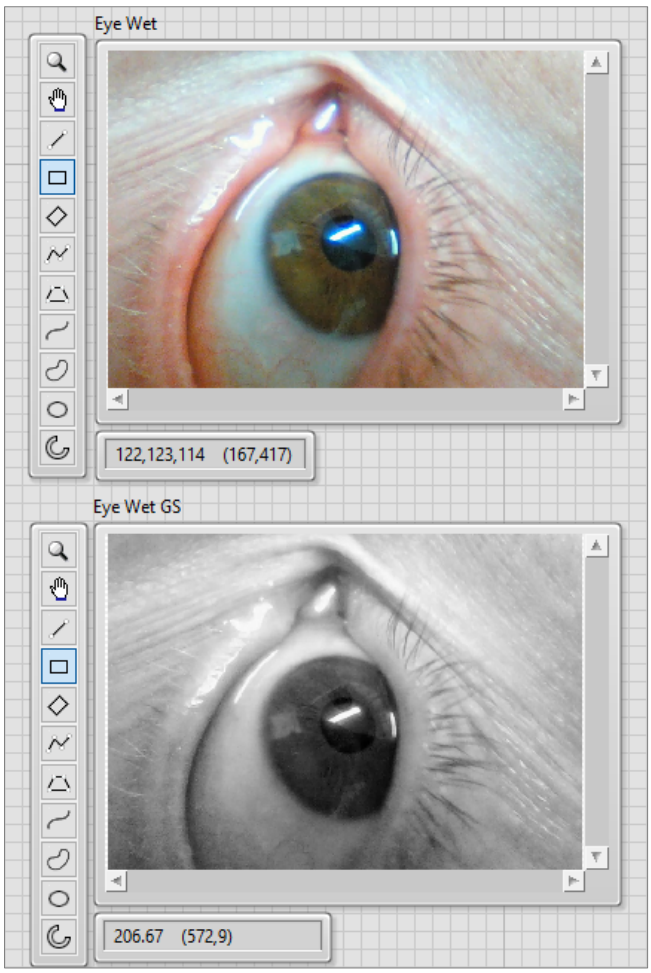


Figure 7.6: Image (a) shows the eye after an application of an eye drop causing it to now become 'wet'. Image (b) is a conversion to grayscale.

The Canny filter output is highlighted in Figure 7.7 for the dry eye and 7.8 for the wet eye. On comparing these two images, an additional feature can be clearly seen in the wet eye image near the upper eyelid. This is an additional surface reflection of the room light from the meniscus that has formed by the droplet that has entered the eye. On closer inspection, another two features may be seen near the tear duct and the lower eyelid where again, a reflection from liquid is present. This was a novel discovery in this research and the possibility of using these reflecting features presented an opportunity to differentiate between wet and dry eyes. These features have been highlighted in the original grayscale image, indicated by the red circles. Figure 7.9 shows these features.

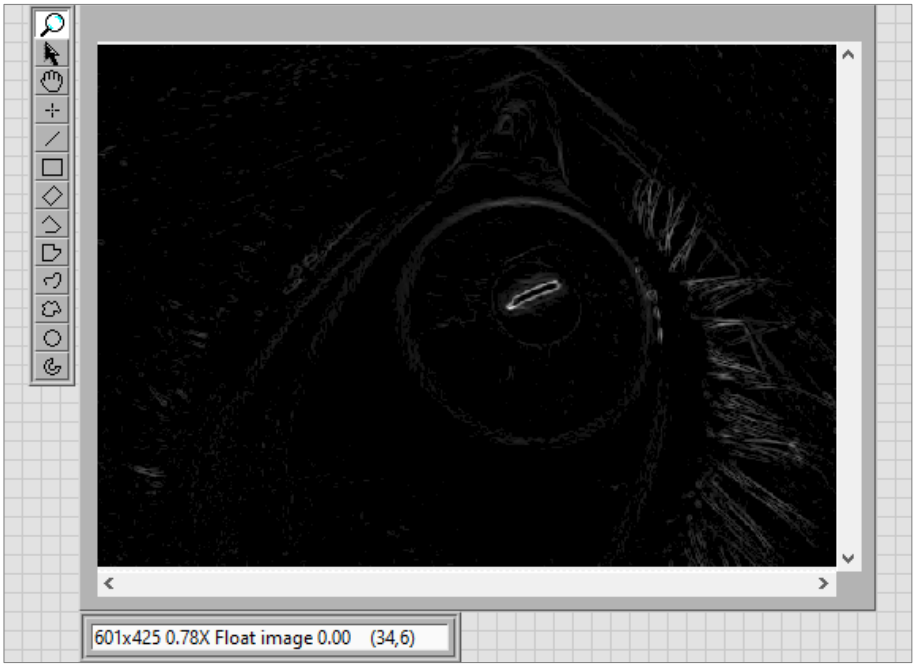


Figure 7.7: Dry eye with Canny filter

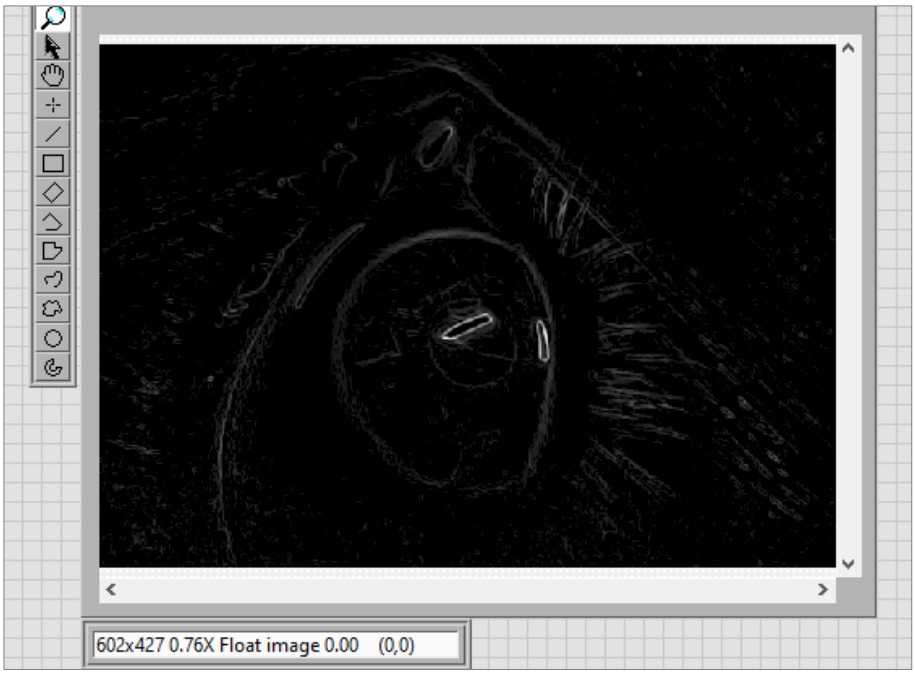


Figure 7.8: Wet eye with Canny filter. Observe the bounded regions around the reflection of the fluorescent light.

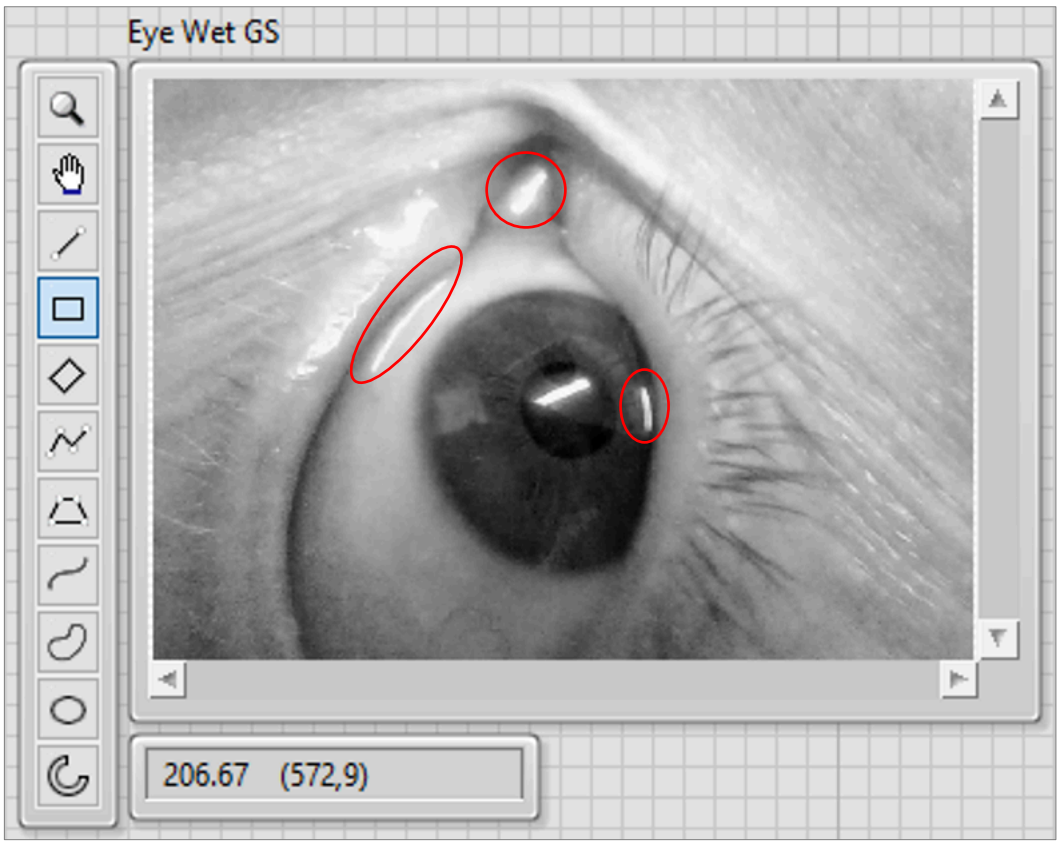


Figure 7.9: Wet eye with highlighted reflections

If one considers the original RGB or grayscale images alone, it may be possible to implement an image comparison algorithm to detect these additional features. In practice, however, as these are 'live' images of a moving and likely blinking eye, a more sophisticated AI tool may be required to detect these features. This possibility remains for future work and a simpler logic-based approach was decided on moving forward. One simple approach that could be implemented in LabVIEW would be to take the Canny filtered images of 7.7 (dry) and 7.8 (wet) and use a simple 'vectorisation' tool. An online version of this [164] was used to convert the images into vector graphics files (Figure 7.10). For the dry eye, a single feature appears in the vectorised image, for the wet eye, two features are visible. The number of features can easily be detected in LabVIEW using the particle detection tool in the image processing toolbox.

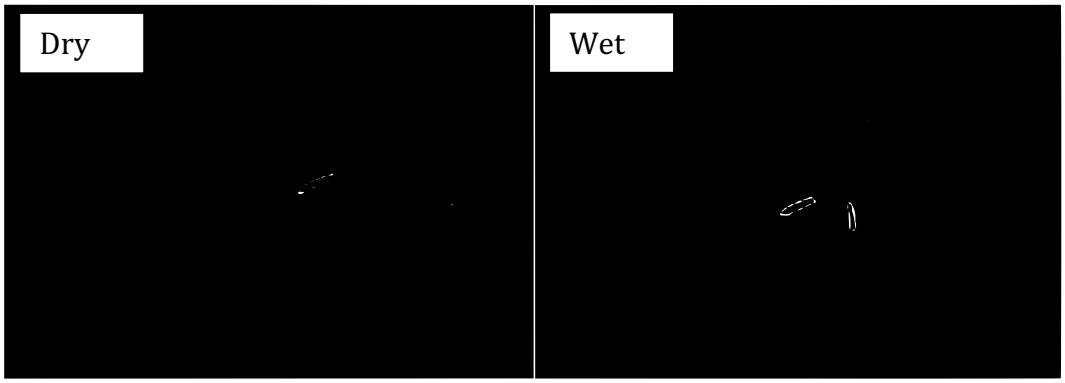


Figure 7.10: Comparison of Canny filtered wet and dry eye images following vectorisation. White areas shown are the highlighted reflections.

With the final application in mind and given the range of sophisticated tools deployable on the myRIO, it should be obvious that some simple image comparison algorithms could be developed to utilise the Canny filter's edge detection capability to develop a robust method of compliance detection.

7.9 Visual Edge Detector for NI myRIO

In order to confirm the viability of the myRIO, a version of the Canny filter VI described above was deployed on a myRIO. The code for visual edge detection already exists and has been made from NI. By attaching a web camera to the NI myRIO the system can generate live edge detection images in real-time. When the image is taken its then processed on board the myRIO looking for edge detection. This information, along with the raw image data is then sent to a network streamed queue. Once in this queue the top-level PC program will display it for the user to see. A separate third part of the program awaits to hear instructions from the host PC program looking for instructions such as terminate the program operation. The snippets of the VI have been shown from Figure 7.11 through to Figure 7.13. Inclusion of these code snippets is intended to highlight to the reader the relative ease in which such a process can be implemented where LabVIEW vision tools are available.

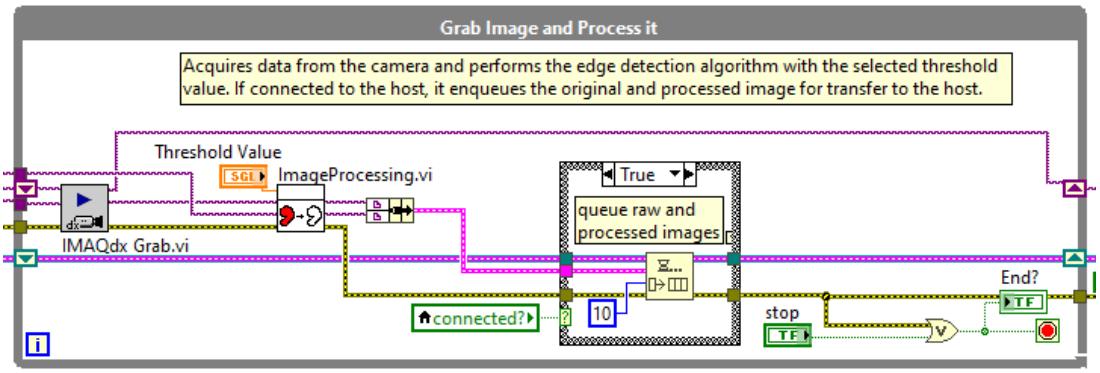


Figure 7.11: Capturing an image from the camera and processing the image.

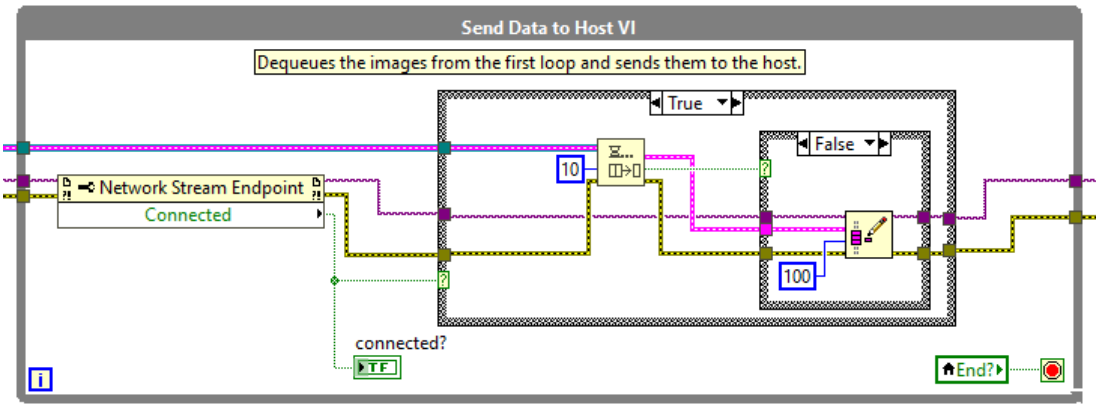


Figure 7.12: Sending the data to host PC

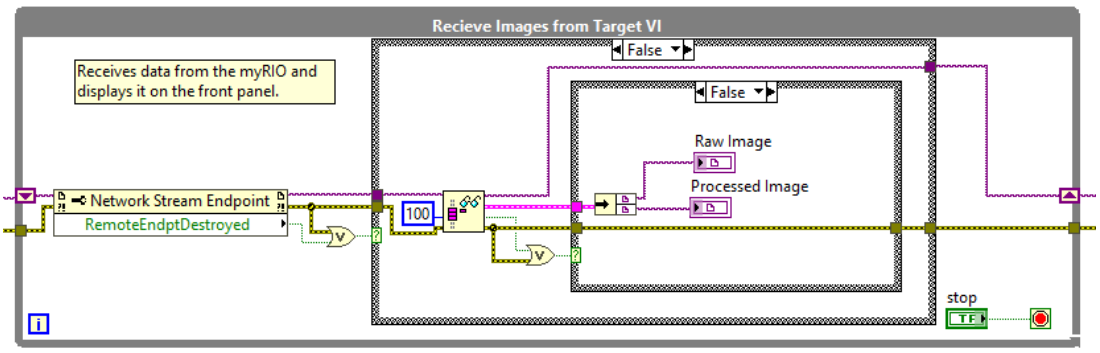


Figure 7.13: Receiving the image from NI myRIO

7.10 Exploiting Light Reflection From the Eye

Following the discovery described at the end of section 7.8 that reflected light sources from the eye might provide a mechanism for differentiating between wet and dry eyes, a simple colour detection algorithm was developed to extract specific colours from the image. The basic idea here is that, given the liquid meniscus around the eye reflects light very well, if a specific colour light is used, then that region can be extracted from the rest of the image. LEDs are perfect light sources for this idea since they are bright and are of 'pure' colour (little spread in emitted wavelengths). Initially a green LED cluster was made of 5x5 individual LEDs soldered onto a PCB. In order to speed up the development process, these images are captured via PC as opposed to myRIO to give maximum flexibility in testing out the theory. Once refined on the PC, it is relatively trivial to deploy the code onto the myRIO as highlighted in section 7.9.

Initially, the histogram of the grayscale images of the wet and dry eye were compared under illumination via the green LED cluster. The flow sequence is highlighted below: -

1. The IMAQ image is created in LabVIEW.
2. This is then converted into a grayscale image.
3. The grayscale image is then run into a histogram.
4. The IMAQ edge detection algorithm is applied.
5. A histogram is then taken from the output of the edge detection algorithm.

The output from this algorithm is shown in Figures 7.14 and 7.15.

(a)

(b)

(c)

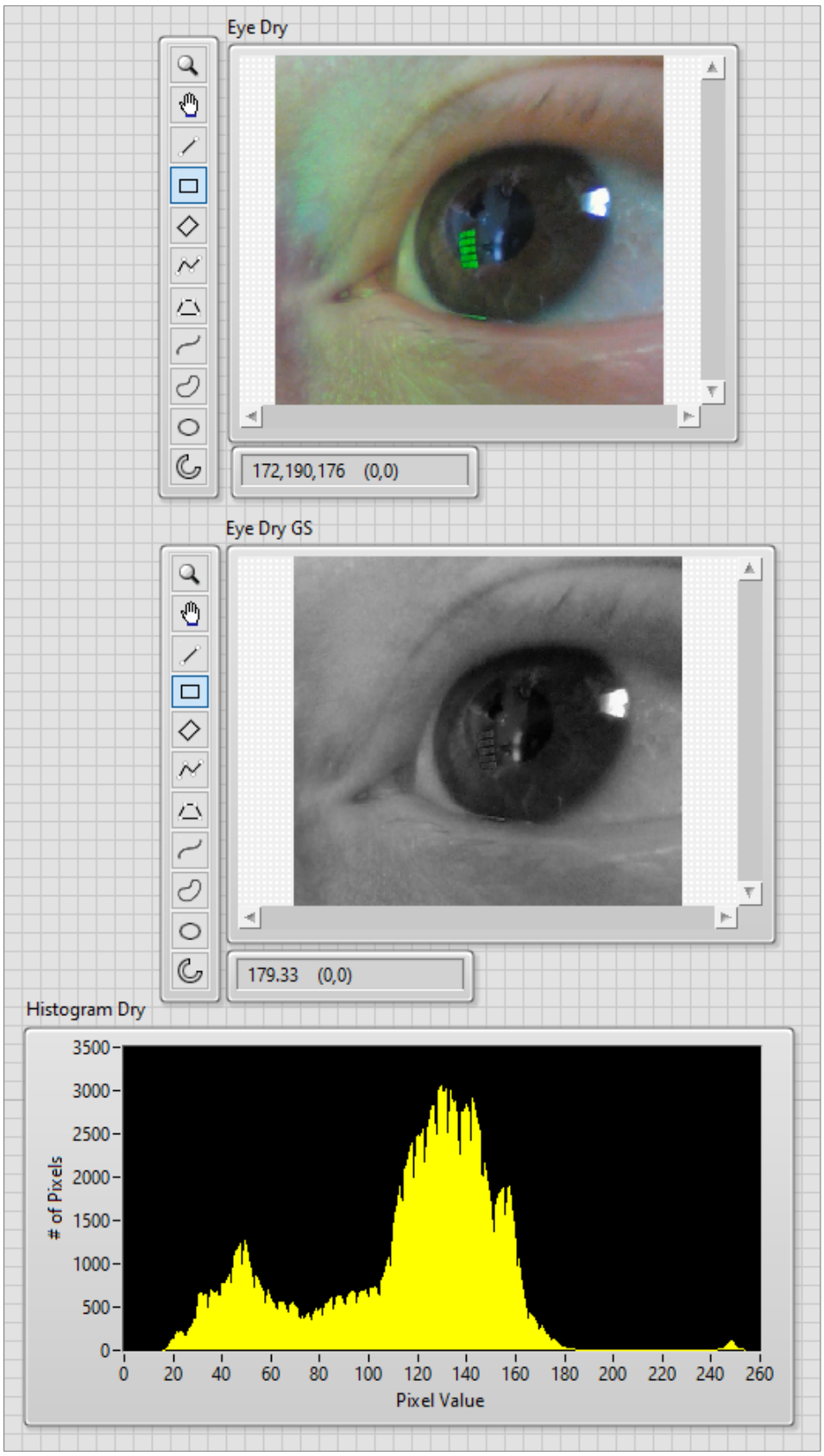


Figure 7.14: Image (a) shows a dry eye as green light is shined onto it. Image (b) is conversion to grayscale and image (c) represents the histogram result.

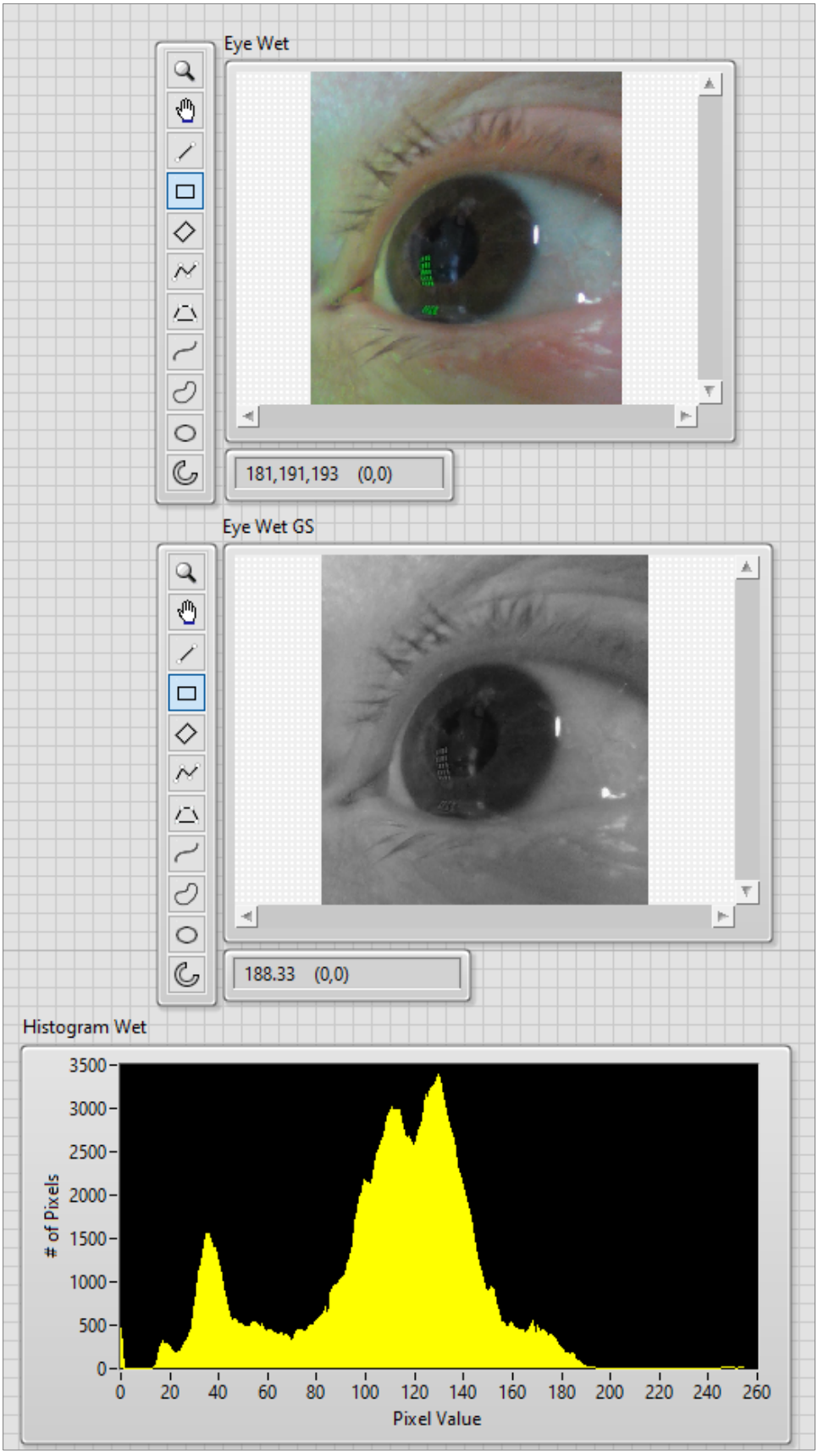


Figure 7.15: Image (a) shows a wet eye as green light is shined onto it. Image (b) is conversion to grayscale and image (c) represents the histogram result.

By looking at the result, there was slight difference between dry and wet eye. However, by concentrating on histogram graphs of two images, there is a limited difference between the two. It isn't distinguishable which eye would represent wet or dry for that matter given what is known about histogram results. Also, there was a lot of variation in room illumination which could account for significant differences in the histogram. What is of significance is the reflection of the green LED cluster from the lower wet eyelid in Figure 7.15 above. Instead of looking at the gray-scaled images and the corresponding histogram, the colour images likely hold more information that can be analysed.

7.11 Colour Filtering

An attempt was made to extract only the green portions of the image with the idea being that in the dry eye, there should only be one region. In the wet eye, there should be more than one region. Surprisingly, there is a lot of green light in the reflection of white light from the sclera. This made the process of isolating only the direct LED reflections difficult. Also, given that the LED source was a cluster and not a single source of illumination, it made the separation of the green only light quite difficult. Future implementations that exploit more sophistication, could ideally search for the LED cluster of 5x5 light sources, however, a more straight-forward approach was taken here. Simply to use a single LED.

A high brightness green LED was embedded into the case of the webcam that was being used to capture the images (as shown in Figure 7.16). Later a blue LED replaced the green one. A 1cm x 1cm hole was made in the body and white tissue paper was used to diffuse the light. The blue LED proved to be extremely robust and generated reliable images.

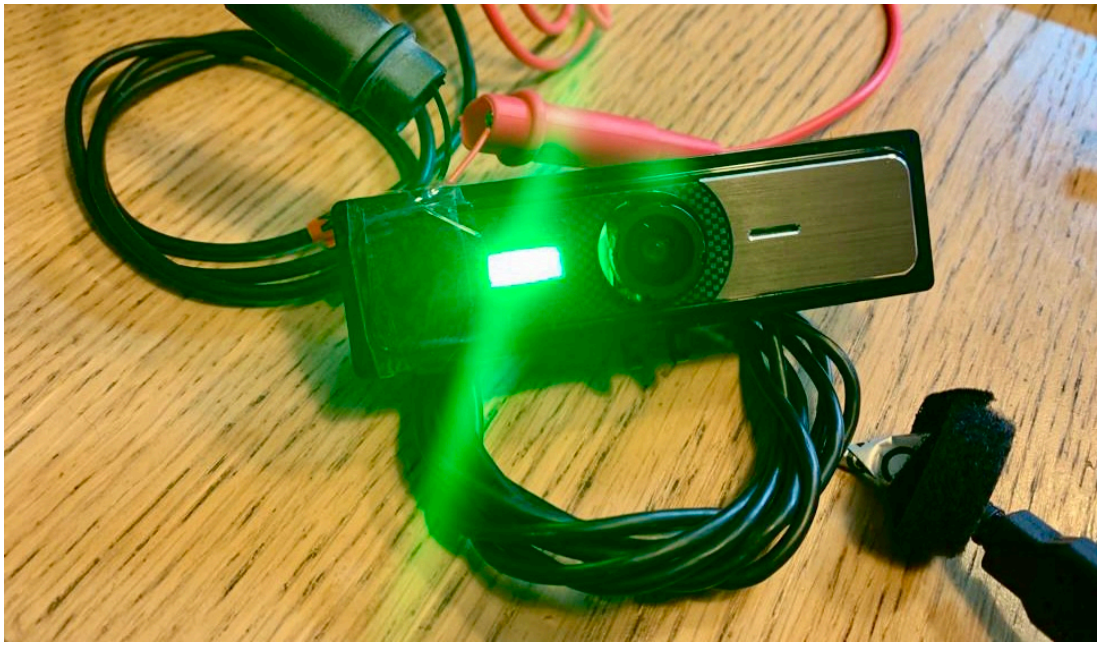


Figure 7.16: LED incorporated into the webcam.

Moving forward, it was decided that a 'real-time' LabVIEW application should be developed that would take a live video feed from the webcam or a pre-recorded video and perform frame by frame image processing. The algorithm developed by this author captured frames from the camera or video and applied a colour filter. This enabled the selection of only the bright blue reflections from the eye from the LED. The criteria for colour selection are as follows: -

Pixels with colours in the range RED [0-15], GREEN [50-255] and BLUE [0-255] are separated from the rest of the image. These regions are filled if necessary and detected by the particle detection tool. The particle(s) is(are) bounded by the red box in the images below. The single particle is from the dry eye in the left-hand image and the two particles are from the wet eye (right-hand image).

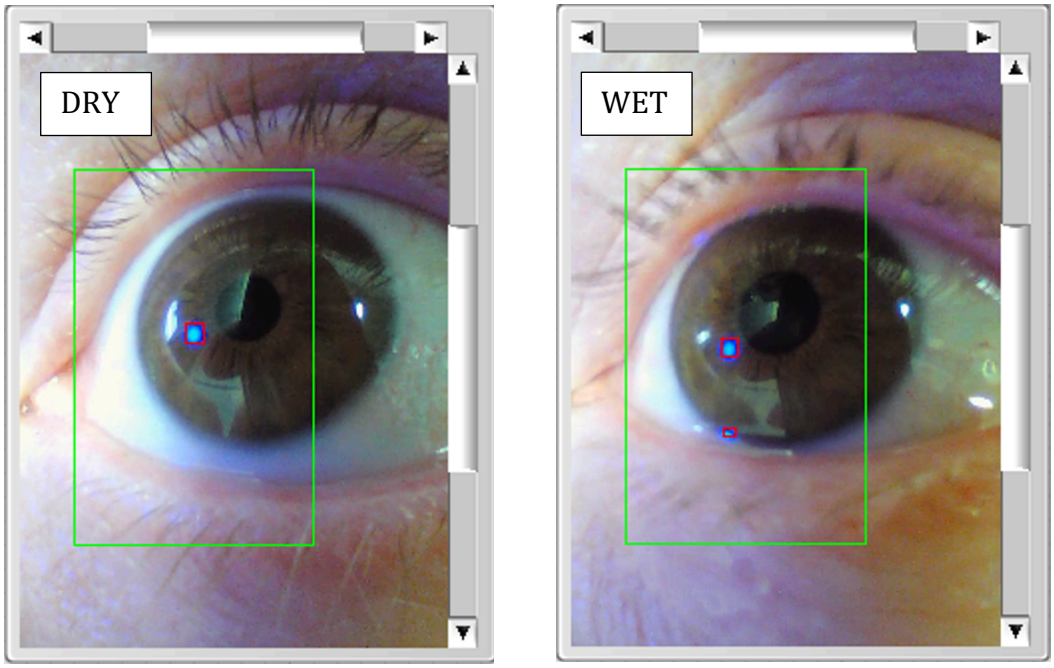


Figure 7.17: Comparison of particle detection generated by the colour filter tool for both wet and dry eye.

The results obtained from this experiment highlight several points. Firstly, the dry eye shows a single reflection of the LED. The region where this reflection occurs is detected by the VI and identified as a single particle. It is assumed that the vast majority of normal eyes would produce this surface reflection. It is possible that some individuals would naturally have a wet eye if the eye is producing tears frequently. However, in the majority of cases, the eye is not going to have the volume of liquid present that is associated with the presence of a droplet. When this additional volume of liquid is added to the eye, surface tension is likely to create a meniscus where additional surfaces are present for reflection. It is clearly shown in Figure 7.17 that the second 'particle' is because of the reflection from the liquid meniscus near the lower eyelid. It is important to note at this point that only one volunteer was used in this study. This being the PhD supervisor, Dr R. Perks. Utilising many individuals as volunteers would have required approval and this would have not been possible given the limitations of this research. Many images of wet and dry eye were obtained and evaluated (over

80 frames of video). A definitive test of these ideas presented here would require the use of many volunteers and many hours of video.

Moving forward with this concept, a simple logic test can be embedded into LabVIEW based on the assumption that a single particle represents a dry eye, and more than one particle represents a wet eye. Furthermore, the absence of a particle represents a closed eye. A summary of the process follows with some detail of the LabVIEW script. Step by step of colour extraction: -

- The colour threshold is first applied. From this it is possible to filter off different colours and vary the threshold of red, green, or blue.
- For investigative purposes, an image array is generated, and the processed image has any 'holes' filled. The centre of the image is obtained too.
- A global report to the image is also taken for analysis purposes.
- Erosions are also looked at to see if a stronger signal processed image can be obtained. This cleans up any 'single pixel' particles in the background.

7.12 Final Implementation of the Colour Extraction and Particle Detection VI

A summary of the colour extraction and particle detection VI comprises of 5 major sections. The first section (as shown in Figure 7.18) reads the video AVI file and bringing that data into LabVIEW. Essential information from the video file is also taken such as the number of frames per second for example.

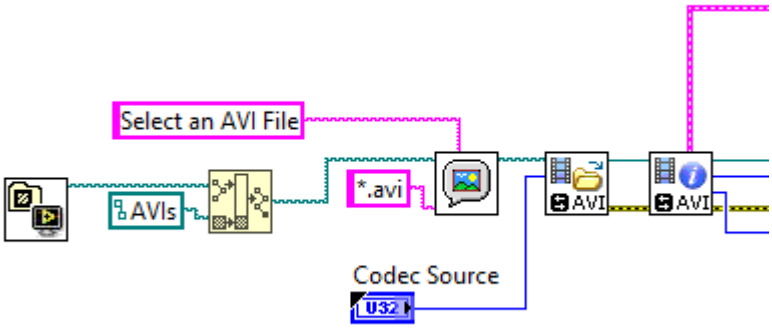


Figure 7.18: Reading video AVI file

The second section involves converting the AVI file into an IMAQ compatible format. Two copies are made, one which is the original source and another whereby intention is that the colour threshold is rendered in grayscale (the picture map for the detected pixels is binary, i.e., true (red) or false (black). Figure 7.19 displays this section of the code.

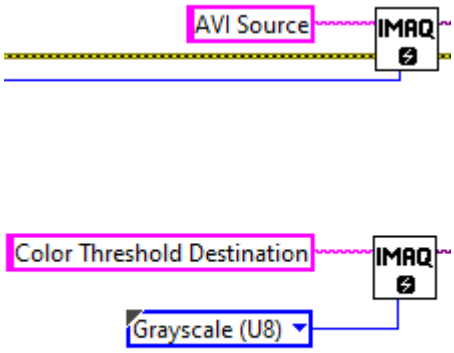


Figure 7.19: Converting the AVI file into an IMAQ

As shown in Figure 7.20, the third section is the retrieval and playing of the image in the loop. This information is in turn passed for the resolution to be ascertained. This is needed as later on; the counting of objects relies on this information.

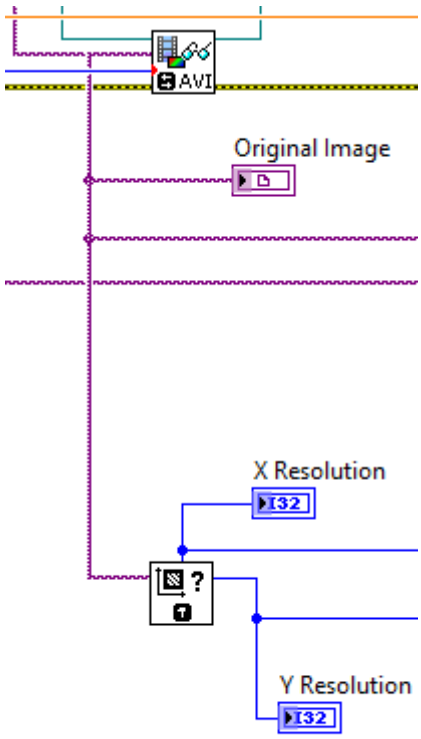


Figure 7.20: Retrieval and playing of the image

The fourth section involves manipulation of the colours in the image. Specifically, the VI isolates pixels that represent the LED reflections. A colour threshold filter is applied which is controlled by the RGB pallet. Figure 7.21 represents this part of the VI.

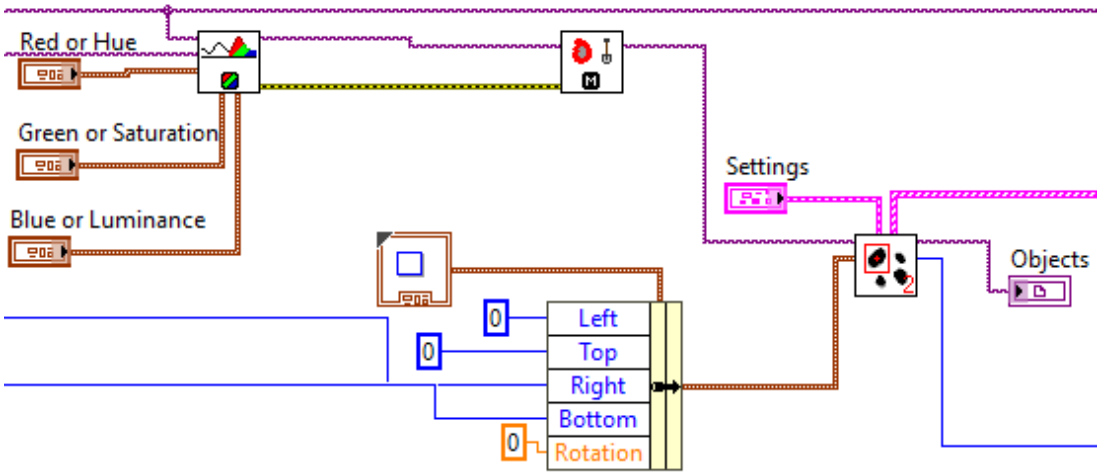


Figure 7.21: Manipulation of the colours in the image

The fifth section as shown in Figure 7.22, is the display or presentation of the algorithm. Both the technical aspect whilst it is at work and the original image at play are shown to the user. It is worth noting that blinking is also detected. This could be a useful indicator of a successful inclusion of an eye drop, especially in patients who blink a lot after applying eyedrops which can cause some of the drops to flow out.

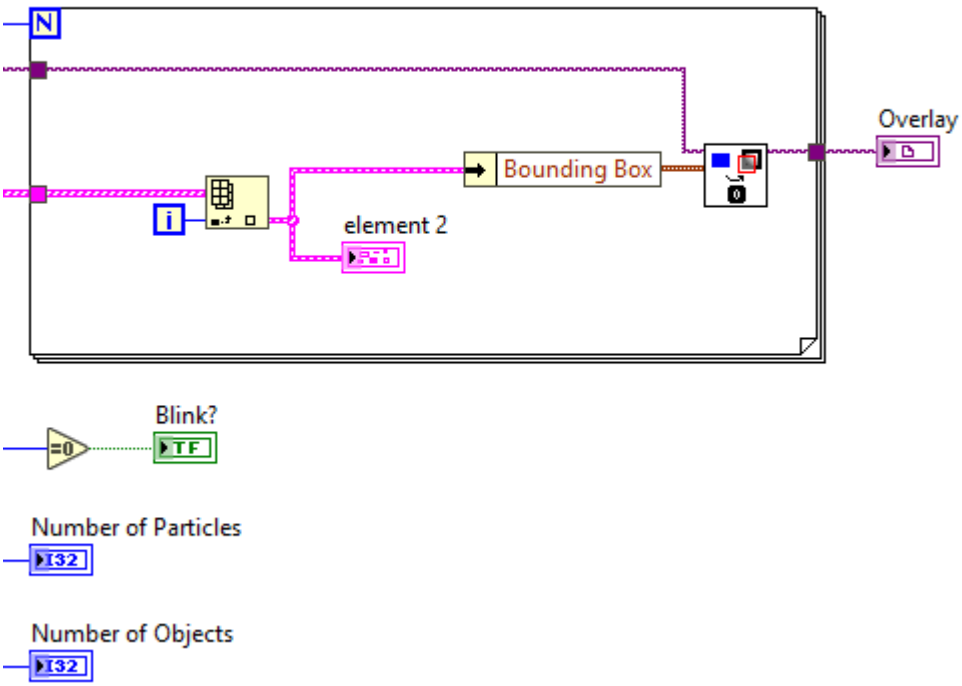


Figure 7.22: Display the algorithm and blink indication

The outcomes are shown from Figure 7.23 through 7.25. These are simply screenshots of the GUI at different stages of the sample video of an eyedrop being administered. In the final implementation of this concept, a signal from the bottle sensor could be used to highlight when the transition from dry to wet eye will occur.

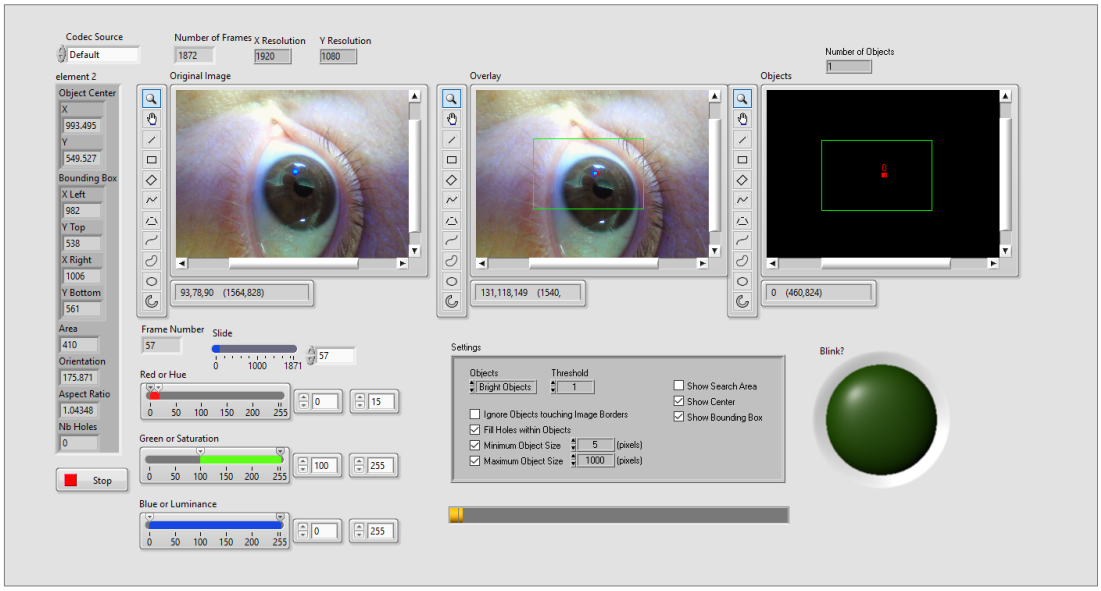


Figure 7.23: Dry eye, note one object or particle detected.

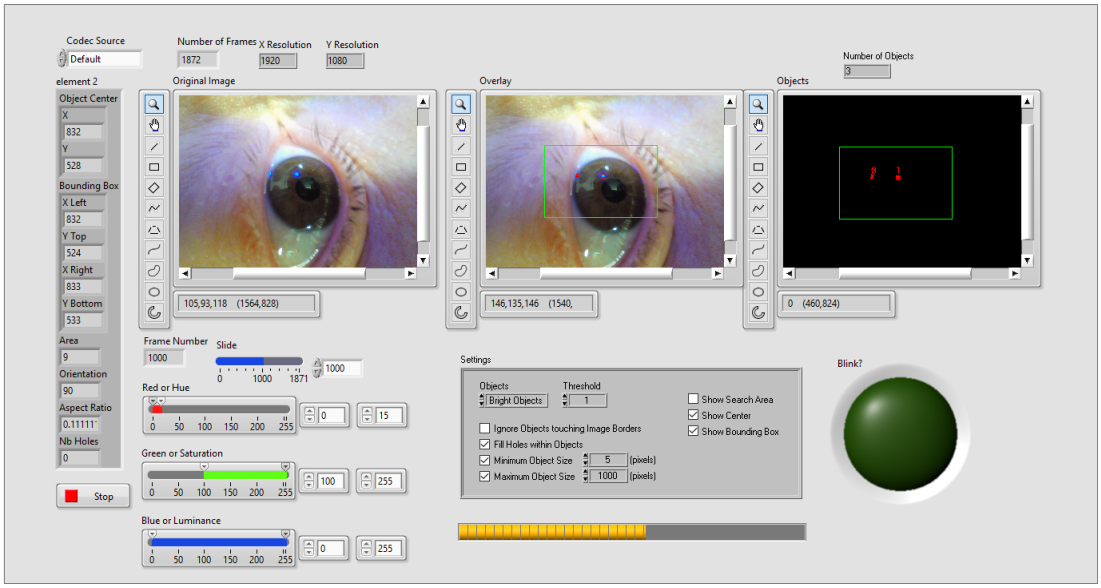


Figure 7.24: Wet eye, note three objects or particles detected.

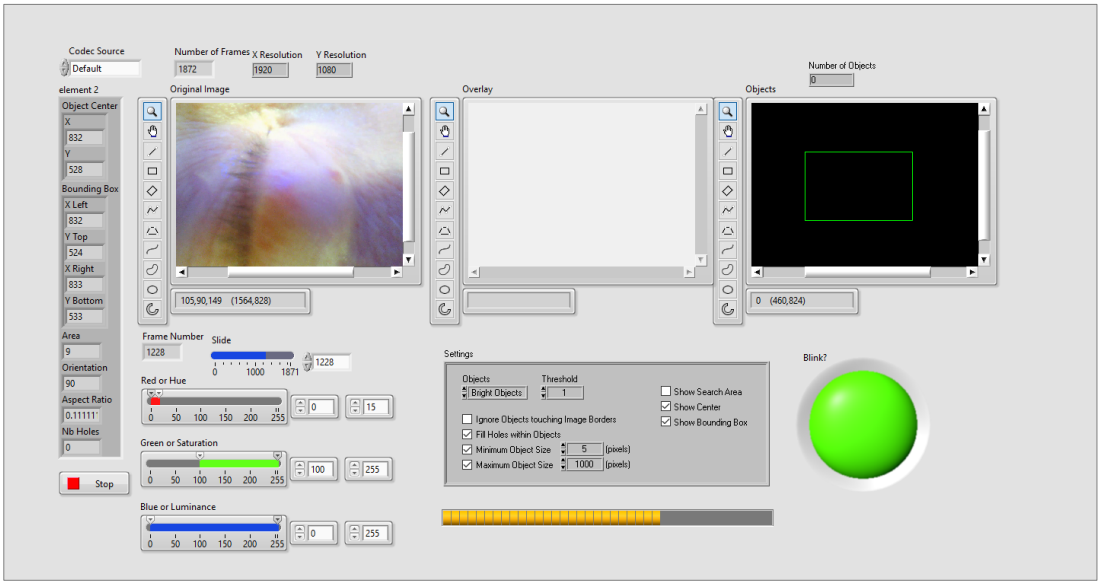


Figure 7.25: Blink capture, the green Boolean indicator highlighting a blink event.

The GUI shown in the images above shows all the controls and outputs from the LabVIEW code. Overall, the system described functions as intended and generates results that are consistent with the idea that specific reflections form the eye and meniscus can be used to detect eye drop inclusion. Even with a handheld camera and fluctuating natural light, the detection of eyedrops in the eye was accurate and reproduceable. Unfortunately, it was not possible to provide proper statistical data on the accuracy of the system as that would require a clinical trial of some form. However, initial testing with this concept looks promising as a concept to develop further.

7.13 AI

In the previous section, the system described used simple logic. This author fully acknowledges that AI tools would likely deliver a much more robust system of droplet detection. This next section summarises a brief work package conducted in collaboration with this author, her supervisor and two visiting undergraduate students from ENSEIRB-MATMECA Bordeaux. Much of the work was carried out

by Anne-Sophie Layoller and Kevin Ronaldo from ENSEIRB-MATMECA, under the direction of this author and her supervisor.

7.13.1 Further Work Package

Written in MATLAB, the project exploited 'transfer learning' [165], using the Alexnet pretrained deep neural network [166]. Initially a data set of 87,000 eye pictures from 37 people and were classified as open eye or closed eye. The figure below highlights the concept. An eye tracking algorithm was used to assist with the classification of the images. Of the 87,000 images, around 20% were used for training. A final data set of 11,943 closed eye images and 10,193 open eye images were used to train the network, taking around 8 hours to complete. The final accuracy of the network with this training data set was 0.9998.

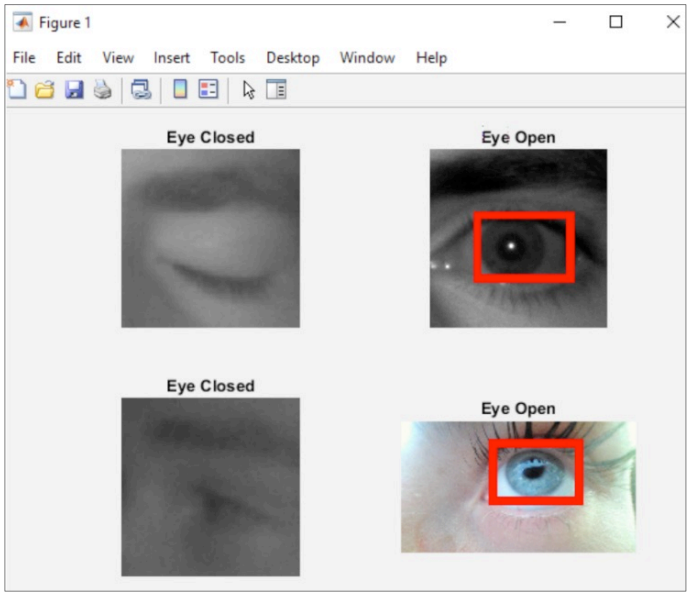


Figure 7.26: Example of a correct classification of eye images

Once this was complete, images of researcher's eyes were correctly classified as opened or closed by the network. These images were obtained from video

footage of the eye opening and closing. This typically consisted of many hundreds of images. This established a platform for developing a method to differentiate between wet and dry eyes. A new class in the dataset was defined containing images of wet eyes following the administration of saline droplets. Video recordings were made, and the frames associated with 'wet' and 'dry' scenarios were separated. This generated 10,887 images of wet eyes for the next training phase. The training process for this took 11 hours. The system was then tested with new images of wet and dry eyes. The accuracy of this was in excess of 0.8, however, eyes can be naturally wet and so a much more extensive training data set would be needed. Overall, this small insight into AI techniques proved extremely useful and can easily be exported onto an embedded system such as a myRIO. Used in conjunction with the non-intelligent implementation described in the previous section, this could deliver an excellent training platform for the Alexnet network.

7.14 Summary

Prior chapters explained in detail, a system designed to assist adherence to eye drop treatment among glaucoma patients. However, a serious question would remain and that is how to be certain the patient complies successfully. For this matter, another system with image processing is required to identify a droplet onto the eye. This chapter involves different tasks in image processing that are required to lead to the final program. The software can be created in NI LabVIEW. LabVIEW offers great modules and packages associated with vision which can help design the whole system and offer solutions. The summarised procedure to achieve this is as follows: -

- Take a grayscale and histogram of an eye image.
- Apply two vision filters, smoothing and Canny to the image.
- Detect the image of an eye before and after applying eye drop using vision filters.

- Investigate and apply LED lighting on the eye for better detection of reflections.
- Use of further filters to extract specific colours.

Chapter 8

Conclusion and Future Work

8.1 Conclusion

This project has covered many different aspects including: -

- A review of glaucoma as a disease.
- The challenges that are faced in treatment and care of patients.
- Possible solutions and the examination of better effectiveness in drug compliance.
- Design and development of a system that can be used to expand and enhance glaucoma drug compliance.
- Design and development of a system that will ascertain for certain eye drop inclusion.
- The evaluation and effectiveness of such a system and the possibilities of further work which will be covered in this chapter.

To summarise and formulate an appropriate conclusion for this thesis, it's worth briefly recapping the key points and takeaways. These include to remember that the failure for eye drop treatment within glaucoma patients is either due to treatments that aren't suitable or because the patients don't adhere to their eye drop treatments. Therefore, a system which monitors drug compliance would be very effective for clinicians.

Glaucoma is considered as the second leading cause of blindness globally. With early detection and monitoring, glaucoma patients can keep their sight, however vision loss due to glaucoma can't be recovered. As an eye condition, glaucoma is generally caused by too much pressure inside the eye, which eventually damages the optic nerve. There are two main types of glaucoma, OAG and ACG. Other types include NTG and congenital glaucoma.

Protecting patient's sight is the most important goal in diagnosing glaucoma therefore some factors need to be tested before diagnosing glaucoma perfectly. These include: -

- Tonometry
- Ophthalmoscopy
- Perimetry test
- Gonioscopy
- Pachymetry

After diagnosing glaucoma, a proper treatment can be suggested by clinicians. Treatment of glaucoma is really dependent on the type of glaucoma. The available treatments include medications, laser procedures and incisional surgery.

Thus, drawing on this review, it is possible to see that the main section of this project has really been the design and development of two prototype systems, one which is capable of being wrapped around a bottle and is thin and flexible in nature. The other system is for monitoring a successful inclusion. This is due to the fact that medication or eye drops would be the initial and most common form of treatment. As has been proven in the course of this project, the prototype has been built and achieved from conception, design, development and final testing. Each stage has had its points of success, but it is necessary to evaluate these.

The conception stage has been fairly simple to envisage and put into action. Early experimentation has proven the possibility of having flexible sensors and prove their limitations. It was also important to research the capabilities of a flexible circuit. In conclusion on this section and in hindsight, one may argue that more

sensors would give a greater sensing capability but the downside to this is the extra power requirements that are needed. These were deliberately minimised including the use of further sensors to judge or ascertain the position of the eye drop bottle. Overall, it can be said this section passed with success and can be subject to further work if need be.

Within the design and development stage, the one omission has been the use of a flexible battery and the power constraints that are in place as a result from the original conception. This has been discussed already earlier in this thesis and unless a specific project is raised to investigate the use and possibility of increasing the power capacity of such a battery, it is not really possible or practical to implement with current technology as it stands.

Otherwise, all other aspects in the design and development stage can be considered a technical success. This is drawn from the fact that there is a working viable program for the PIC microcontroller that is capable of interacting and interfacing with its peripheral devices. There is a clear proven schematic which has been prototyped on a breadboard and also a final flexible PCB design which has been made. This section can be altered or reused depending on the requirements of any further work, however the principles remain solid.

Initial testing and validation proved challenging. After many attempts and refinements with multiple learning events a successful PCB was produced that delivered the intended functionality. If used in a clinical trial in the future, this system has the potential to assist with determining patient compliance. Knowing when the droplet has actually ended up onto the eye, can provide even more compliance information. This is especially provident before replacing the current treatment with a new alternative one, they can be fully aware the current treatment is not appropriate, or the patient didn't comply successfully. In such a case, a vision system is required to be able to indicate that the droplet has been successfully delivered onto the eye. As proven in Chapter 7 this is possible using NI's vision system tools.

One of the things that can be drawn from this project is the suitability and practicality of the suggested wrap around design. It has been noted early on in the project that the more practical way forward would be to have the circuitry and button battery on the underside. This suggestion and approach weren't favoured as it wouldn't explore the possibility of a thin and flexible design. It was also suggested that some bottles have their ejection mechanism on the rear. However other teams in the world have explored this option quoted in the paper titled 'Smart Electronic Eyedrop Bottle for Unobtrusive Monitoring of Glaucoma Medication Adherence' [141] has taken this approach. Their device has a sensing component on the side with the associated circuitry and power on the rear. This in turn will communicate via Bluetooth to a custom app. The approach outlined in this thesis is similar in nature and has the same overall intentions, which is to improve drug compliance among glaucoma patients.

Indeed, there are many different ideas and implementations which are in progress and have been tried. These include the MEMS cap as discussed previously and to outline again, it's an electronic bottle cap device which when removed can record the date and time of intended usage providing the eyedrop bottle is stored inside the proceeding container. The major disadvantage of this system in comparison to an integrated system such as one produced from this project is that it would require a form of training and memory to place the bottle back in the glass container. Whilst its intentions are good it's execution it can be argued is perhaps flawed or creates an additional layer that is subject to error.

Ultimately it can be concluded that this project provides a blueprint for the possibilities in solving and standardising the approach to improving eye drop compliance. It is by no means a final approach and as sensing technology improves in the course of time so will the means to tackle this issue. It is the formulated opinion that in order to come up with a final solution for this problem, an investment would definitely have to be made. This is particularly true should the solution that is being sought is to be generated in an appropriate time frame to fend off competition from other sources.

There have also been a number of key skills have either been gained or enhanced from this project including general engineering skills and a more practical understanding given the level of investiture in the project. These skills include programming on C for a PIC microcontroller, PCB flexible board design, LabVIEW programming, hardware sourcing and selection. Not forgetting the vision programming skills that have been picked up along the way.

8.2 Recommendations for Future Work

As Previously discussed, there are quite a few areas that can be incorporated into future work and future projects as a result of this research. Firstly, the design and development of an integrated eyedrop bottle should be looked at. This is where the circuitry is embalmed into the bottle rather than being an attachment. How this will be achieved is a question that can be addressed in terms of manufacturing and design. It is suspected new manufacturing processes will need to be established that can make this view a possibility. The benefit here would be a generic bottle can be applied across the board instead of just for glaucoma and a licence agreement can be reached on each unit from a business perspective. Secondly, more exploration and credence to the use of more sensors can be incorporated into a new project. This will allow for the evaluation on the effectiveness of a more intelligent system. Such an edit to this program to handle extra sensors wouldn't be too taxing either. Thirdly, a project can be generated that can explore not just drug compliance or eye drop bottles but to all internet of things (IoT) technology. In fact, major advancements can be made in the use of a flexible battery and flexible battery technology. It should be understood that humanity is operating at the peak of its knowledge in this field and it is poorly researched to say the least. The advent of electrification in cars and the use of more flexible and wearable consumables warrant this arena an exciting area to advance and research further. A lot of knowledge and information has been gained from such batteries in this project along with their capability of which the manufacturer was keen to know how far we could push their batteries. Certainly, it would be great to investigate different polymer batteries with a higher degree

of capacity that are flexible than the ones currently on offer in the market. While not totally in the remit of this project it is still an interesting area of the engineering to uncover and discover. Fourthly, a much more integrated system whereby the vision side can communicate with the logging side is of great benefit. It will clearly enhance the system capability. It is also worth expanding the systems overall capability or effectively miniaturising it to do away with the PC for the vision processing side. Finally, it must be made clear that should this blueprint of this project reach a conclusion in the form of production manufacture and marketing, more investment is required and a review of the project will be needed in accordance to FDA and MHRA rules not forgetting that CE marking would be a separate goal. These are quality assurance engineering tasks that need time and investment in order to gain regulatory approval.

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Abbreviations & Acronyms

ACG	Angle closure glaucoma
AGS	American Glaucoma Society
AI	Artificial Intelligence
CE	Conformité Européene
CNF	Carbon nanofiber
CNT	Carbon nanotube
EDAM	Eye Drop Application Monitor
EEPROM	Electrically erasable programmable read-only memory
EIS	Electrochemical impedance spectroscopy
FDA	Food and Drug Administration
FSR	Force sensing resistor
IGA	International Glaucoma Association
IOP	Intraocular pressure
IoT	Internet of things
ITC	Iridotrabecular contact
MEMS	Medication Event Monitoring Systems
MHRA	Medicines and Healthcare products Regulatory Agency
MIGS	Minimally invasive glaucoma surgery

NEI	National Eye Institute
NFC	Near field communication
NI	National Instruments
NTG	Normal tension glaucoma
OAG	Open angle glaucoma
Op-amp	Operational amplifier
PAC	Primary angle closure
PACG	Primary angle closure glaucoma
PACS	Primary angle closure suspect
PC	Personal computer
PCB	Printed circuit board
PCG	Primary congenital glaucoma
PIC	Peripheral Interface Controller
POAG	Primary open angle glaucoma
RGC	Retinal ganglion cell
SMU	Source/measure unit
SRQs	Self- reported questionnaires
UT	Ultra-thin
WHO	World Health Organization
WUP	Wake up

Appendix A

Battery Discharge Test Software

As previously discussed in Chapter 4, the battery discharge software was created in NI LabVIEW. Figure A.1 and A.2 represent the front panel and block diagram.

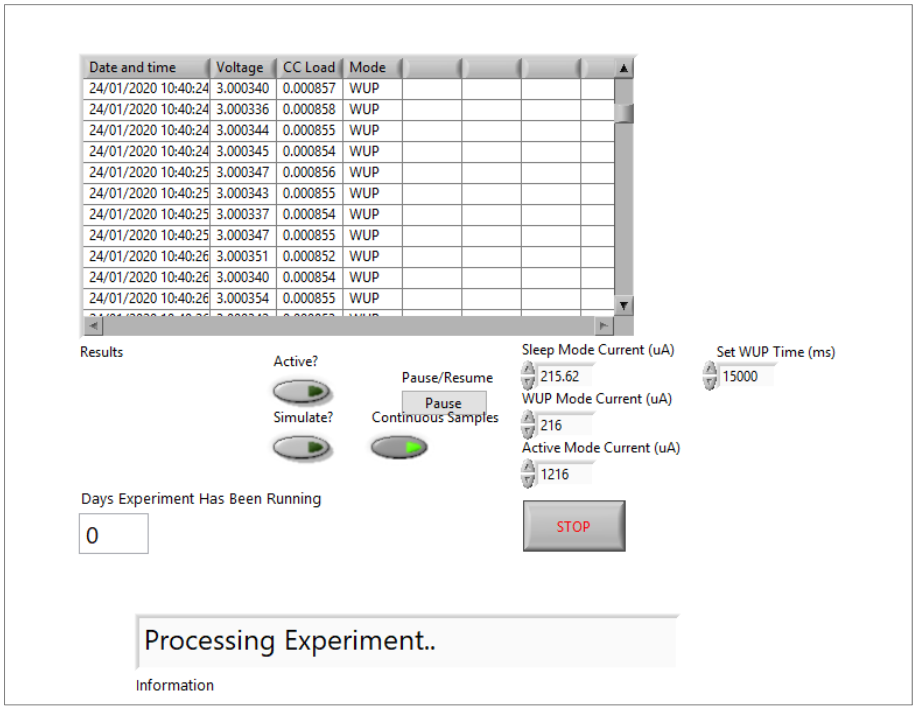

Figure A.1: LabVIEW GUI front panel during testing

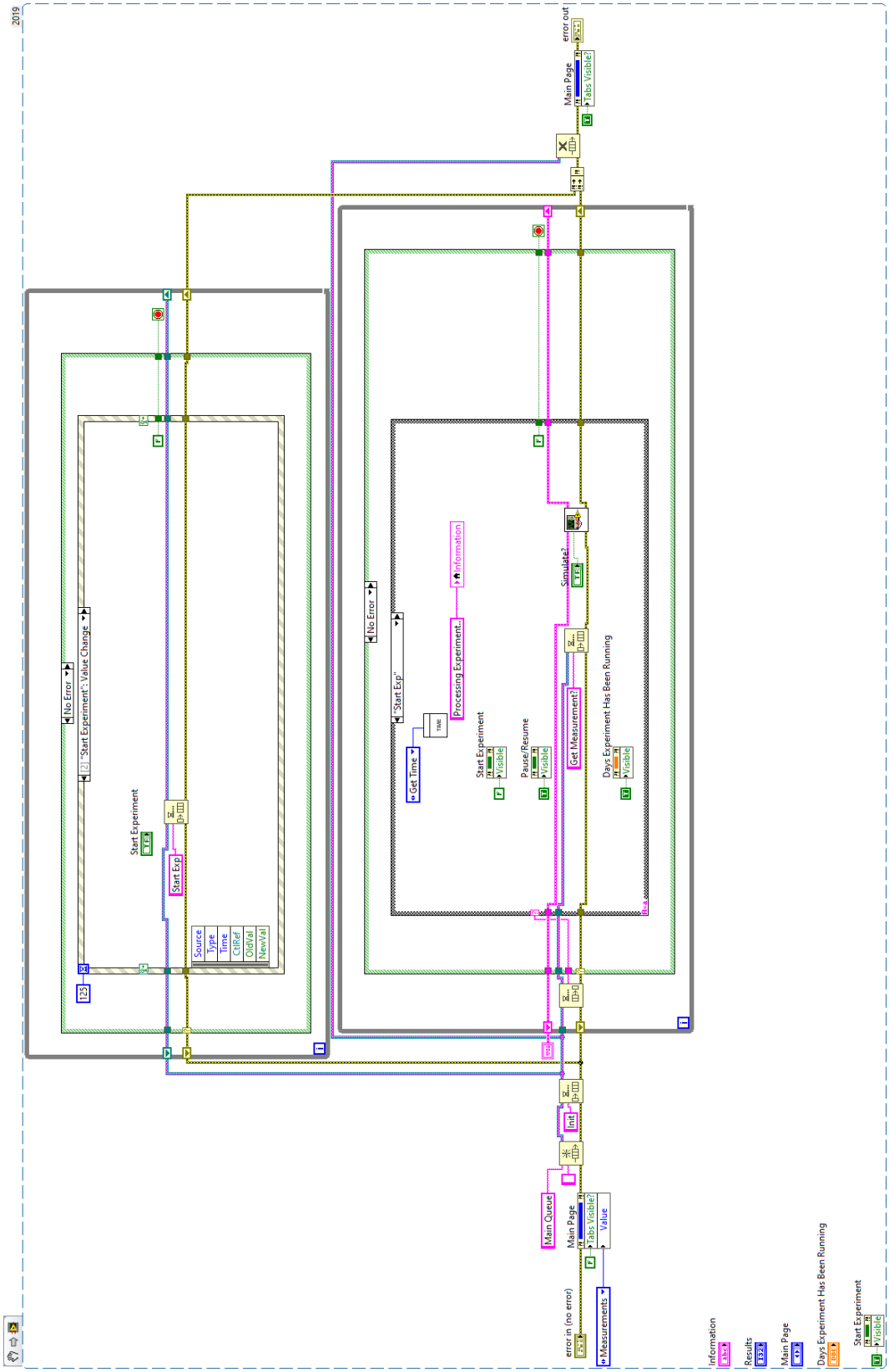

Figure A.2: LabVIEW block diagram

Appendix B

Wrapped Battery Testing With 2 Second Cycle Time Between Sleep and WUP Mode

This experiment took place with exact numbers for setting up different modes like other experiments except with different cycle time between sleep and WUP mode. The tape around the bottle detached during the experiment which after wrapping, the voltage increased however it dropped after a period of time. This incident happened on the 14th of Jan after the first active mode which can be noticed with highlighted circle. It must be noted that should the experiment have been rerun without the mistake, the results wouldn't have significantly changed, and no benefit would have been gained from rerunning the experiment as the curve is characteristic in line with other experimentation.

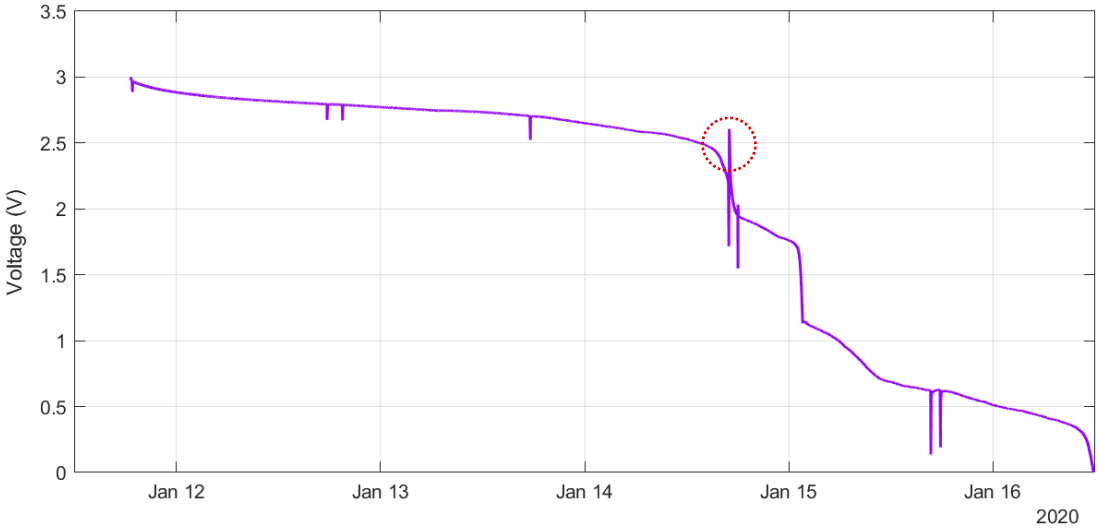

Figure B.1: Discharging wrapped battery

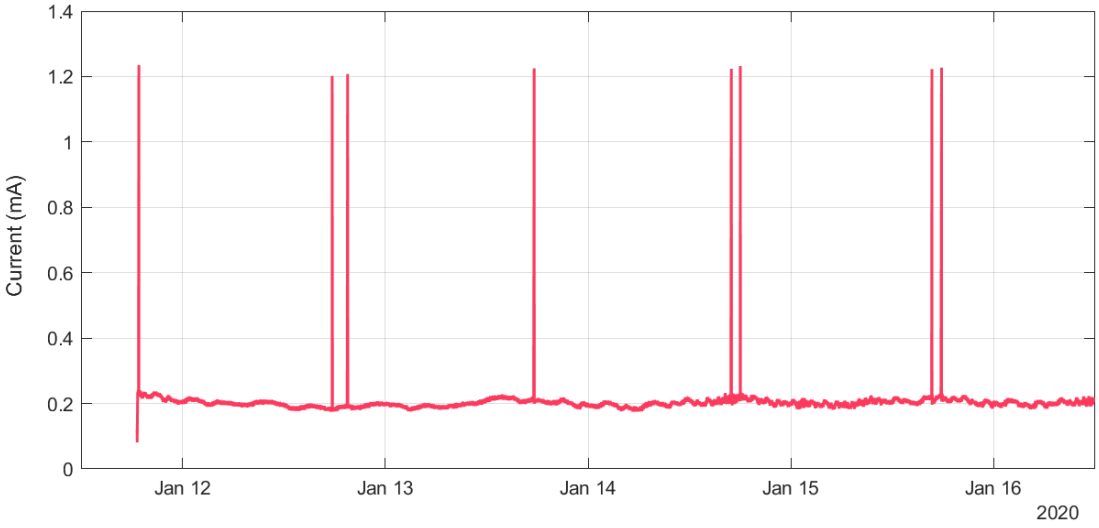

Figure B.2: Current graph for wrapped battery

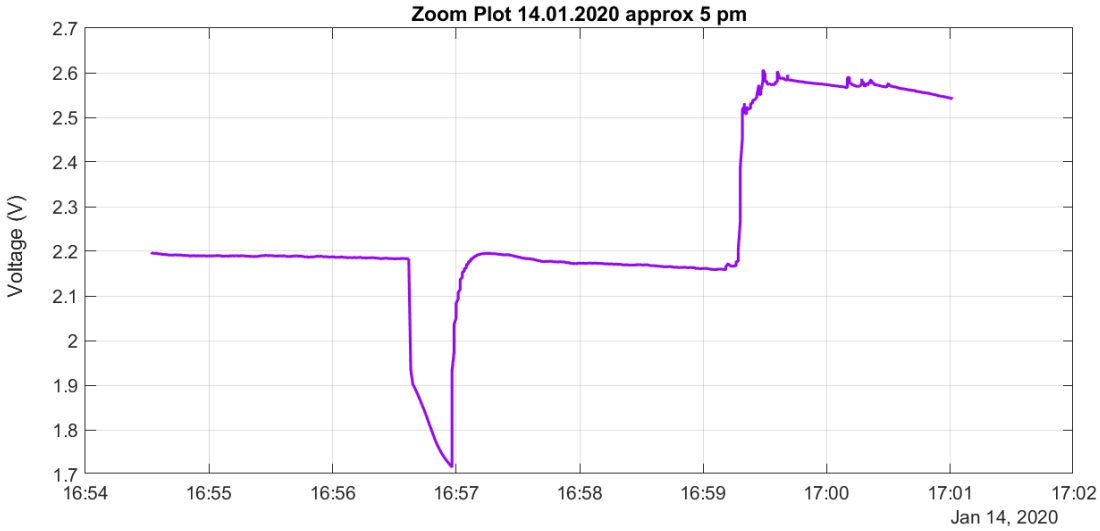

Figure B.3: Zoom of Figure B.1 capturing changes in voltage between different modes.

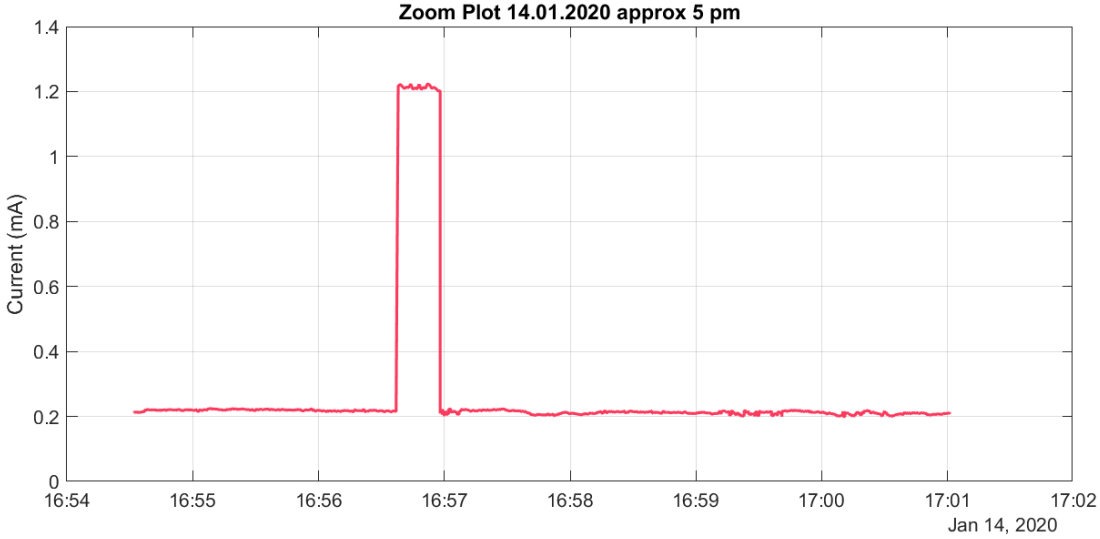

Figure B.4: Zoom of Figure B.2 capturing current in different modes.

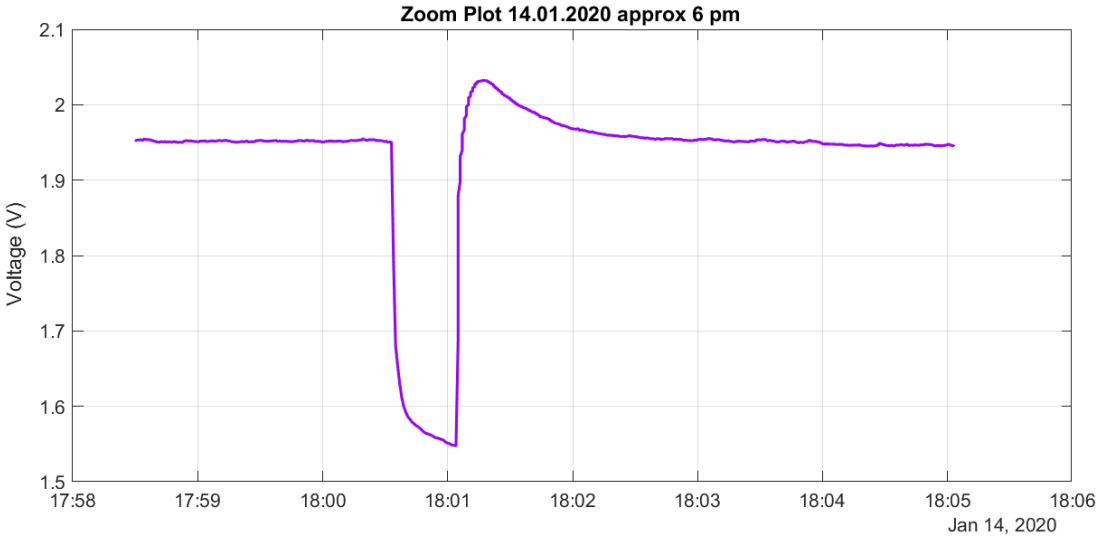

Figure B.5: Zoom of Figure B.1 capturing further changes in voltage between different modes.

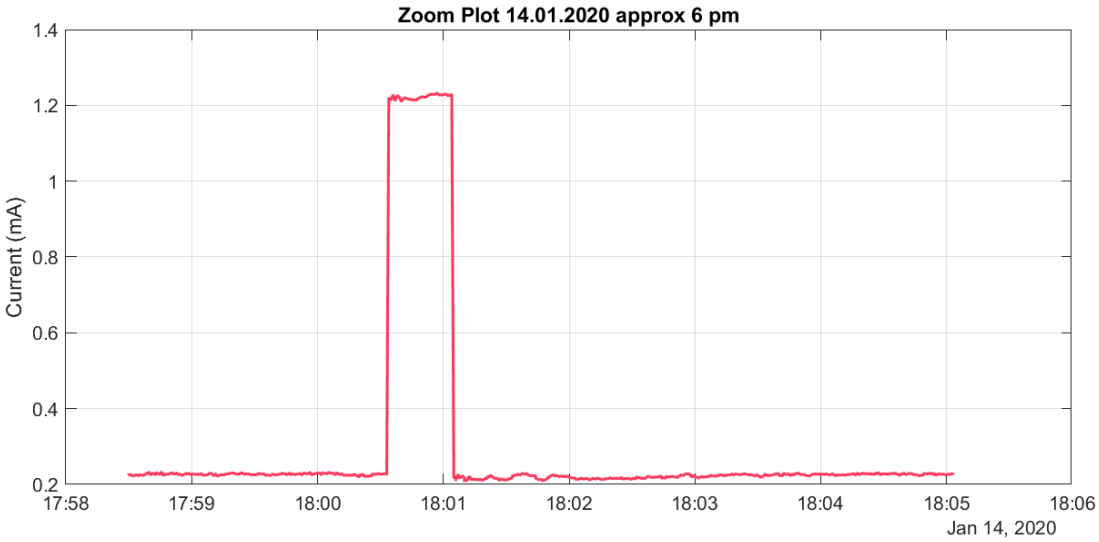

Figure B.6: Zoom of Figure B.2 capturing further changes in current between different modes.

Appendix C

Block Diagram

As previously discussed in Chapter 6, the final block diagram of circuit was designed within the circuit maker. Figure C.1 shows the final block diagram of the system with all components which are involved within the final product.

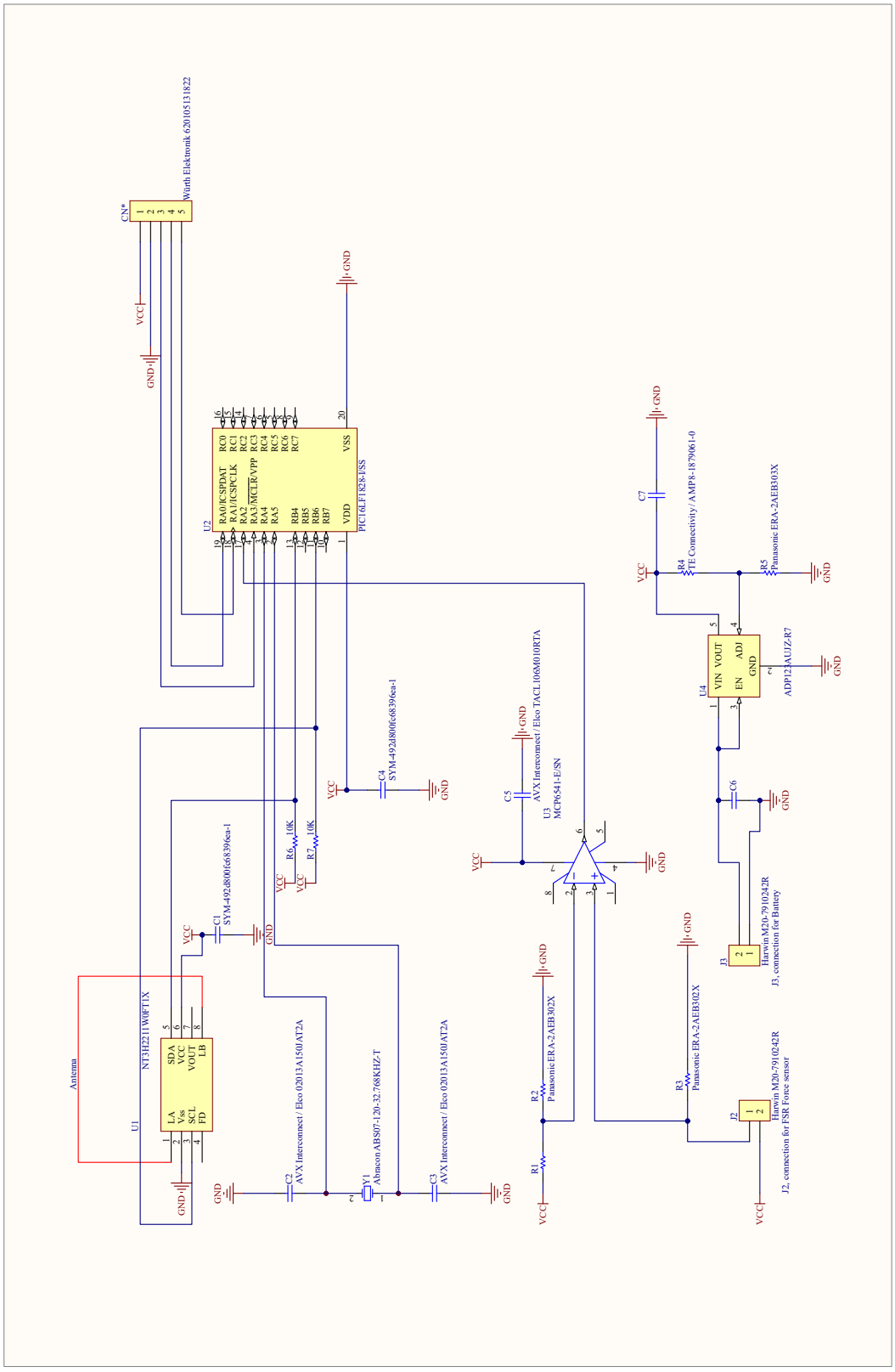

Figure C.1: Final block diagram

Appendix D

C Programming

This section provides the C programming which had been written for the purpose of this project. As mentioned on Chapter 6, before adding the NFC chip to the circuit, a switch had been used which simulates the NFC interrupt line. The data of force sensor either pressed or not pressed, being written and read from the EEPROM of the microcontroller.

This part of program was then excluded from the final program after the switch proceeded to be replaced by the NFC chip. The parts that were included for this simulation purpose have not been removed entirely from the program but merely commented out.

```
#include <xc.h>

#include <pic16lf1828.h>

#define _XTAL_FREQ 4000000

// PIC16lF1828 Configuration Bit Settings



// 'C' source line config statements



// CONFIG1

//#pragma config FOSC = EXTRC      // Oscillator Selection (EXTRC oscillator: External RC circuit connected to CLKIN pin)

#pragma config FOSC = INTOSC    // Oscillator Selection (INTOSC oscillator: I/O function on CLKIN pin)

#pragma config WDTE = OFF       // Watchdog Timer Enable (WDT disabled)

#pragma config PWRTE = OFF      // Power-up Timer Enable (PWRT disabled)

#pragma config MCLRE = ON       // MCLR Pin Function Select (MCLR/VPP pin function is MCLR)

#pragma config CP = OFF         // Flash Program Memory Code Protection (Program memory code protection is disabled)

#pragma config CPD = OFF        // Data Memory Code Protection (Data memory code protection is disabled)

#pragma config BOREN = ON       // Brown-out Reset Enable (Brown-out Reset enabled)
```

#pragma config CLKOUTEN = OFF // Clock Out Enable (CLKOUT function is disabled. I/O or oscillator function on the CLKOUT pin)

#pragma config IESO = ON // Internal/External Switchover (Internal/External Switchover mode is enabled)

#pragma config FCMEN = ON // Fail-Safe Clock Monitor Enable (Fail-Safe Clock Monitor is enabled)

// CONFIG2

#pragma config WRT = OFF // Flash Memory Self-Write Protection (Write protection off)

#pragma config PLLEN = ON // PLL Enable (4x PLL enabled)

#pragma config STVREN = ON // Stack Overflow/Underflow Reset Enable (Stack Overflow or Underflow will cause a Reset)

#pragma config BORV = LO // Brown-out Reset Voltage Selection (Brown-out Reset Voltage (Vbor), low trip point selected.)

#pragma config LVP = ON // Low-Voltage Programming Enable (Low-voltage programming enabled)

void write_eeprom(void); // function declaration void write_eeprom(char myaddress, int mydata)

void LogDayNight(void);

void readeeprom(void);

```
void i2C_wait(void);

void i2c_initialise(void);




// *.*.* GLOBAL VARIABLES *.*.*




//int j=0;

int fifteen_secs_counter=0;

int another_counter=0;

int num_days=0;


int events = 0;

int thishappen = 0;

int anotherevent =0;

int yetanotherevent=0;

//int is 16 bits, we can fit 8 days in each

int dayonetoeight=0;

int daynineto sixteen=0;

int  dayseventeentotwentyfour=0;
```

```
int daytwentyfivetothirtytwo=0;

char myaddress;

// instead of the above, using

int logged_data[8] = {0,0,0,0,0,0,0,0};

int read_data_back[8] = {0,0,0,0,0,0,0,0};




int eepromreadvalue=0;



// *.*.* MY MAIN FUNCTION *.*.*



void main(void) {



   ANSELA=0b00000000;  //all pins we are concerned with digital

   TRISA=0b00101100;   //all pins we are concerned with output



//    OSCCON=0b00000010;  //31kHz int oscilator SYSTEM CLOCK
```

OSCCON=0b00000001; //31kHz ext oscilator USE TIMER INPUT FOR SYSTEM CLOCK

INTCONbits.GIE=0; // ensure no interrupts

PORTCbits.RC0=0; //value is 0

ANSELAbits.ANSA4=0; // sets it to digital

TRISCbits.TRISC5=0;

LATCbits.LATC5=0;

T1CONbits.T1CKPS=3; // 3 is "11" binary - which is what needs to be set to choose prescaler of 1:8

T1CONbits.TMR1CS=2; //YES (01 is internal) external oscillator this is "10" in binary - which is what needs to be set to choose asynchronous counter mode using the external oscillator crystal

T1CONbits.nT1SYNC=1; // asynchronous mode

T1CONbits.T1OSCEN=1; // enables the oscillator, then need to wait a delay before enabling the TIMER1 overall

```
// add a delay here
   for(int i=0;i<1000;i++)
   {
      //do nothing
   }

   ANSELCbits.ANSC0=0;
   TRISCbits.TRISC0=0;

   TRISAbits.TRISA4=1;
   TRISAbits.TRISA5=1;

   T1GCONbits.TMR1GE=0; // it counts regardless of gates function, this might need changing

// setting up the interrupts for the timer
   PIE1bits.TMR1IE=1;
   PIR1bits.TMR1IF=0; // just ensures no flag is set, in case of using interrupts
```

INTCONbits.PEIE=1; // I think I need this in order for the peripheral timer to wake system if timer rollover (executes next instructions, not an interrupt as such)

INTCONbits.GIE=1;

TMR1=4096;

PIR1bits.TMR1IF=0;

T1CONbits.TMR1ON=1;

//setting up the interrupts on the "interrupt on change" inputs (this is the pushbutton switch to be replaced by the NFC)

INTCONbits.IOCIE=1;

ANSELBbits.ANSB5=0;

TRISBbits.TRISB5=1;

INTCONbits.IOCIE=1;

IOCBPbits.IOCBP5=1;

//enabling the interrupt on the INT pin (RA2)

INTCONbits.INTE=1;

OPTION_REGbits.INTEDG=1;

//enabling all the interrupts

INTCONbits.PEIE=1; // I think I need this in order for the peripheral timer to wake system if timer rollover (executes next instructions, not an interrupt as such)

```
  INTCONbits.GIE=1; // MAKE SURE THERE WILL BE INTERRUPTS


//i2c initialisation stuff
  ANSELBbits.ANSB4=0;
  TRISBbits.TRISB6=1;     // input (datasheet pg 274 says define both as inputs)
  TRISBbits.TRISB4=1;     // input

  SSP1CON1bits.SSPEN=1;   //  enables serial port for SPI

  //i2c initialise
  INTCONbits.PEIE=1; // to enable peripherals in general
  PIE1bits.SSP1IE=0; // not going to use interrupts, not now at least
  PIR1bits.SSP1IF=0; // clear the flag anyway
  SSP1CON1bits.SSPM=0b1000; // I2C master clock = Fosc/(4*(SSP1ADD+1))
  SSP1STATbits.SMP=1; //slew rate control disabled
  SSP1STATbits.CKE=0;//##1; //
  SSP1ADD=9;//##3; // should set clock to be Fosc/16

  SSP1CON2bits.RCEN=0;
```

```
 myaddress=0x04;  // this is the address of the block of 16 bytes I want to write
to

 // (Block 0 is unaccessible, and I'm reserving blocks 1-3 for name and date to
be written by the PC nfc interface at initial clinic)

//i2c initialisation stuff




                write_eeprom();



    NOP();


//TRISAbits.TRISA1=0;

   NOP();

    NOP();



 while(1)

 {


    SLEEP();
```

```
      NOP();


   }


}




void interrupt my_ISR(void)

{

   INTCONbits.GIE=0;          //disable all interrupts




/* THIS IS THE 15 SECONDS WAKE UP FROM SLEEP */

   if(PIR1bits.TMR1IF==1)

   { // if timer flag is set

      LATCbits.LATC0=!LATCbits.LATC0;

      T1CONbits.TMR1ON=0;

      PIR1bits.TMR1IF=0;

      TMR1=4096;

      T1CONbits.TMR1ON=1;
```

```
  //  LATCbits.LATC5=!LATCbits.LATC5;


      fifteen_secs_counter++;

      another_counter++;

      NOP();



    if(fifteen_secs_counter>=2*2880)

    {

      // every 15 seconds it will come to this function

      num_days++; //this is incremented 2x per day

      NOP();

      fifteen_secs_counter=0;

      write_eeprom();

    }



}
```

```
if(INTCONbits.INTF)
{ // if positive edge detected on the interrupt pin (FORCE SENSOR)
   INTCONbits.GIE=0; // disable all interrupts
   LogDayNight();
      if(fifteen_secs_counter>2880){
         yetanotherevent++;
      }
   NOP();
   NOP();
   //LATCbits.LATC5 = !(PORTCbits.RC5); //toggle LED

   //LATAbits.LATA5 = !(PORTAbits.RA5); //toggle LED

   INTCONbits.INTF=0;   // clear the flag
   INTCONbits.GIE=1;    // enable interrupts

}
```

```
  if(INTCONbits.IOCIF==1)
  {
    NOP();
    if(IOCBFbits.IOCBF5==1)
    {
      readeeprom();
      IOCBFbits.IOCBF5==0;     //clear the flag
    }
    NOP();
    INTCONbits.IOCIF==0;       //clear this flag too
    INTCONbits.GIE=1;          //enable the interrupts again



  }



  INTCONbits.GIE=1;
}

void LogDayNight(void){
```

```
if((num_days<=32)&& (fifteen_secs_counter<2880) ){

// log it as morning , this will be from 00:00 to 12:00, (first twelve hours of the day)


if(num_days==0){ // first day is day 0

logged_data[0]=logged_data[0]|0b0000000000000001;

}


else if(num_days==1){

logged_data[0]=logged_data[0]|0b0000000000000100;

}


else if(num_days==2){

logged_data[0]=logged_data[0]|0b0000000000010000;

}


else if(num_days==3){

logged_data[0]=logged_data[0]|0b0000000001000000;
```

```
}

else if(num_days==4){
   logged_data[0]=logged_data[0]|0b0000000100000000;
}

else if(num_days==5){
   logged_data[0]=logged_data[0]|0b0000010000000000;
}

else if(num_days==6){
   logged_data[0]=logged_data[0]|0b0001000000000000;
}

else if(num_days==7){
   logged_data[0]=logged_data[0]|0b0100000000000000;
}

else if(num_days==8){
   logged_data[1]=logged_data[1]|0b0000000000000001;
```

```
}

else if(num_days==9){
   logged_data[1]=logged_data[1]|0b0000000000000100;
}

else if(num_days==10){
   logged_data[1]=logged_data[1]|0b0000000000010000;
}

else if(num_days==11){
   logged_data[1]=logged_data[1]|0b0000000001000000;
}

else if(num_days==12){
   logged_data[1]=logged_data[1]|0b0000000100000000;
}

else if(num_days==13){
   logged_data[1]=logged_data[1]|0b0000010000000000;
```

```
}

else if(num_days==14){
   logged_data[1]=logged_data[1]|0b0001000000000000;
}

else if(num_days==15){
   logged_data[1]=logged_data[1]|0b0100000000000000;
}

else if(num_days==16){
   logged_data[2]=logged_data[2]|0b0000000000000001;
}

else if(num_days==17){
   logged_data[2]=logged_data[2]|0b0000000000000100;
}

else if(num_days==18){
   logged_data[2]=logged_data[2]|0b0000000000010000;
```

```
}

else if(num_days==19){
   logged_data[2]=logged_data[2]|0b0000000001000000;
}

else if(num_days==20){
   logged_data[2]=logged_data[2]|0b0000000100000000;
}

else if(num_days==21){
   logged_data[2]=logged_data[2]|0b0000010000000000;
}

else if(num_days==22){
   logged_data[2]=logged_data[2]|0b0001000000000000;
}

else if(num_days==23){
   logged_data[2]=logged_data[2]|0b0100000000000000;
```

```
}

else if(num_days==24){
   logged_data[3]=logged_data[3]|0b0000000000000001;
}

else if(num_days==25){
   logged_data[3]=logged_data[3]|0b0000000000000100;
}

else if(num_days==26){
   logged_data[3]=logged_data[3]|0b0000000000010000;
}

else if(num_days==27){
   logged_data[3]=logged_data[3]|0b0000000001000000;
}

else if(num_days==28){
   logged_data[3]=logged_data[3]|0b0000000100000000;
```

```
        }


        else if(num_days==29){
           logged_data[3]=logged_data[3]|0b0000010000000000;
        }


        else if(num_days==30){
           logged_data[3]=logged_data[3]|0b0001000000000000;
        }


        else if(num_days==31){
           logged_data[3]=logged_data[3]|0b0100000000000000;
        }


      }
     else if((num_days<=32)&& (fifteen_secs_counter >= 2880)){
        // log it as aftenoon , this will be from 12 to 24:00, (second twelve hours
of the day)
        LATCbits.LATC5=!LATCbits.LATC5;
        events++;
```

```
if(num_days==0){
      thishappen++;
   logged_data[0]=logged_data[0]|0b0000000000000010;
}

else if(num_days==1){
   thishappen++;
   logged_data[0]=logged_data[0]|0b0000000000001000;
}

else if(num_days==2){
   thishappen++;
   logged_data[0]=logged_data[0]|0b0000000000100000;
}

else if(num_days==3){
   thishappen++;
   logged_data[0]=logged_data[0]|0b0000000010000000;
```

```
}

else if(num_days==4){
   logged_data[0]=logged_data[0]|0b0000001000000000;
}

else if(num_days==5){
   logged_data[0]=logged_data[0]|0b0000100000000000;
}

else if(num_days==6){
   logged_data[0]=logged_data[0]|0b0010000000000000;
}

else if(num_days==7){
   logged_data[0]=logged_data[0]|0b1000000000000000;
}

else if(num_days==8){
   logged_data[1]=logged_data[1]|0b0000000000000010;
```

```
}

else if(num_days==9){
   logged_data[1]=logged_data[1]|0b0000000000001000;
}

else if(num_days==10){
   logged_data[1]=logged_data[1]|0b0000000000100000;
}

else if(num_days==11){
   logged_data[1]=logged_data[1]|0b0000000010000000;
}

else if(num_days==12){
   logged_data[1]=logged_data[1]|0b0000001000000000;
}

else if(num_days==13){
   logged_data[1]=logged_data[1]|0b0000100000000000;
```

```
}

else if(num_days==14){
   logged_data[1]=logged_data[1]|0b0010000000000000;
}

else if(num_days==15){
   logged_data[1]=logged_data[1]|0b1000000000000000;
}

else if(num_days==16){
   logged_data[2]=logged_data[2]|0b0000000000000010;
}

else if(num_days==17){
   logged_data[2]=logged_data[2]|0b0000000000001000;
}

else if(num_days==18){
   logged_data[2]=logged_data[2]|0b0000000000100000;
```

```
}

else if(num_days==19){
   logged_data[2]=logged_data[2]|0b0000000010000000;
}

else if(num_days==20){
   logged_data[2]=logged_data[2]|0b0000001000000000;
}

else if(num_days==21){
   logged_data[2]=logged_data[2]|0b0000100000000000;
}

else if(num_days==22){
   logged_data[2]=logged_data[2]|0b0010000000000000;
}

else if(num_days==23){
   logged_data[2]=logged_data[2]|0b1000000000000000;
```

```
}

else if(num_days==24){
   logged_data[3]=logged_data[3]|0b0000000000000010;
}

else if(num_days==25){
   logged_data[3]=logged_data[3]|0b0000000000001000;
}

else if(num_days==26){
   logged_data[3]=logged_data[3]|0b0000000000100000;
}

else if(num_days==27){
   logged_data[3]=logged_data[3]|0b0000000010000000;
}

else if(num_days==28){
   logged_data[3]=logged_data[3]|0b0000001000000000;
```

```
    }

    else if(num_days==29){
      logged_data[3]=logged_data[3]|0b0000100000000000;
    }

    else if(num_days==30){
      logged_data[3]=logged_data[3]|0b0010000000000000;
    }

    else if(num_days==31){
      logged_data[3]=logged_data[3]|0b1000000000000000;
    }
    else
    {
      anotherevent++;
    }
  }
  else{
```

```
    }
  }



void write_eeprom()
{
  int i, mydata, j;
  myaddress=0x04;
  NOP();



// Write Data


  SSP1CON2bits.SEN=1; // start condition
  i2C_wait();
  SSP1BUF=0b10101010; //control code 1010101, write 0   (DEVICE ADDRESS)
  i2C_wait();
  while(SSP1CON2bits.ACKSTAT){/*wait*/};
  SSP1BUF=myaddress;
  i2C_wait();
```

```
  while(SSP1CON2bits.ACKSTAT){/*wait*/};
  for(j=0;j<8;j++)
  {
    SSP1BUF=logged_data[j] & 0b0000000011111111;
    i2C_wait();
    while(SSP1CON2bits.ACKSTAT){/*wait*/};
    SSP1BUF=logged_data[j]  >>8;
    i2C_wait();
    while(SSP1CON2bits.ACKSTAT){/*wait*/};
  }
  SSP1CON2bits.PEN=1; //stop condition
    i2C_wait(); //wait for it still (and, ultimately clear the flag)



//          EEADRL=2*myaddress;   // address we want to write to
//          EEDATL=mydata & 0b0000000011111111; // random data to write
//          EECON1bits.CFGS=0; // datasheet
//          EECON1bits.EEPGD=0; //datasheet
//          EECON1bits.WREN=1; // must be set to enable writes
//
```

```
//            INTCONbits.GIE=0; //disabling interrupts

//            // certain sequence needed to for writing to  eeprom

//            EECON2=0x55;

//            EECON2=0xAA;

//            // interrupts must be disabled for this bit of code

//            EECON1bits.WR=1;

//

//             while(PIR2bits.EEIF==0);  //once the write completes it should pass
this line

//            PIR2bits.EEIF=0; // clear the flag

//            EECON1bits.WREN=0; // must be kept clear after finished writing

//

//            EEADRL=(2*myaddress)+1;   // address we want to write to

//            EEDATL=mydata >>8; // random data to write

//

//            EECON1bits.WREN=1; // must be set to enable writes

//            INTCONbits.GIE=0; //disabling interrupts

//            // certain sequence needed to for writing to  eeprom

//            EECON2=0x55;

//            EECON2=0xAA;
```

```
//            // interrupts must be disabled for this bit of code

//            EECON1bits.WR=1;

//

//             while(PIR2bits.EEIF==0);  //once the write completes it should pass this line

//            PIR2bits.EEIF=0; // clear the flag

//            EECON1bits.WREN=0; // must be kept clear after finished writing




        INTCONbits.GIE=1; // enable interrupts

        return;



}



//void readeeprom(char address){

//                        eepromreadvalue=0; // the data we read goes to this variable

//          EEADRL=2*address;  // We want to read address 0 of data memory

//          // according to read instruction of EEPROM

//

//          EECON1bits.CFGS=0;
```

```
//        EECON1bits.EEPGD=0;
//        EECON1bits.RD=1;
//       // data will be available in the next cycle
//        int i=0;
//        while(i<14){
//          i++;
//        }
//        NOP();
//        eepromreadvalue=EEDATL;   // reading data
//        read_data_back[address]=eepromreadvalue;
//
//                        eepromreadvalue=0; // the data we read goes to this
variable
//
//        EEADRL=(2*address)+1;   // address we want to read from
//
//        // according to read instruction of EEPROM
//
//        EECON1bits.CFGS=0;
//        EECON1bits.EEPGD=0;
```

```
//          EECON1bits.RD=1;
//         // data will be available in the next cycle
//          int i=0;
//          while(i<14){
//             i++;
//          }
//          NOP();
//          eepromreadvalue=EEDATL;    // reading data
//                                    read_data_back[address]=read_data_back[address]    |
(eepromreadvalue<<8);
//}



void i2C_wait(void){
   while(!PIR1bits.SSP1IF){/*wait*/}
   PIR1bits.SSP1IF=0; // wait til flag set then clear
}



// Read Data
```

```
void readeeprom(void){

   int i, j;
   myaddress=0x04;



SSP1CON2bits.SEN=1; // start condition
   i2C_wait();
   SSP1BUF=0b10101010; //control code 1010101, write 0
   i2C_wait();
   while(SSP1CON2bits.ACKSTAT){/*wait*/};
   SSP1BUF=myaddress;
   i2C_wait();
   while(SSP1CON2bits.ACKSTAT){/*wait*/};


//SSP1CON2bits.RSEN=1;
  SSP1CON2bits.PEN=1; //stop condition
      i2C_wait(); //wait for it still (and, ultimately clear the flag)
   for(i=0;i<1000;i++){ // a delay
```

```
}
SSP1CON2bits.SEN=1; //start condition



i2C_wait();
SSP1BUF= 0b10101011; //control code 1010101, read 1
i2C_wait();
while(SSP1CON2bits.ACKSTAT){/*wait*/};


 for(j=0;j<8;j++)
{
   SSP1CON2bits.RCEN=1;  // tell the PIC to listen - cleared automatically at the reception of a byte so needs to be IN the loop
   i2C_wait();
   read_data_back[j]=SSP1BUF;   // get data
   SSP1CON2bits.ACKDT=0; // ACK (NACK is 1) ### needs to be 0
   SSP1CON2bits.ACKEN=1; // to send NACK
   i2C_wait(); //## added by me - do I need to wait for the acknowledge flag
   SSP1CON2bits.RCEN=1;  // tell the PIC to listen - cleared automatically at the reception of a byte so needs to be IN the loop
   i2C_wait();
```

```
      read_data_back[j]=read_data_back[j] |  (SSP1BUF<<8);     // get data
      SSP1CON2bits.ACKDT=0; // ACK (NACK is 1) ### needs to be 0
      SSP1CON2bits.ACKEN=1; // to send NACK
      i2C_wait(); //## added by me - do I need to wait for the acknowledge flag
   }
   SSP1CON2bits.PEN=1;   // stop condition
   i2C_wait();

   SSP1CON2bits.RCEN=0;  // stop listening

   return;

}
```