

ASSESSING AUTONOMOUS NERVE FUNCTION

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By

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ABSTRACT

This thesis proposes a method of detecting autonomic neuropathy in low-income countries using an infrared camera. Access to healthcare is often limited in low-income countries delaying the detection of neuropathy. If neuropathy can be detected in the earliest stage, often the autonomic state, damage to motor and sensory nerves can be prevented. To develop the method for detecting autonomic neuropathy, first the autonomic system was researched, followed by looking into the effects of neuropathy on the autonomic system to discover what physical properties might be measured with the detection device.

Four affected physical properties were determined through literature research: blood flow, blood pressure, skin resistance, and skin temperature. Of these properties, skin temperature was found to be the most promising based on a literature study, as it seemed to be both easily measurable and relatively independent of other bodily functions. Then the constraints of healthcare in low-income countries were examined and devices that work within these constraints were identified. Of these, the infrared camera showed the most promise, because of its ease of use and cost to accuracy ratio.

A single-subject study was performed to test the restorative capacity of the autonomous system by deliberately changing the temperature of the hand with a heating and cooling agent. Four locations were used on both hands, and both palmar and dorsal side of the hand, using different doses of the agents. The temperature change of the skin was measured using an InfraRed (IR) camera.

A large variation in results was found, but the results did show some evidence for structural differences in the temperature normalization between the affected and unaffected hand. The palmar side shows a stronger reaction than the dorsal side. The cooling agent seems to be more effective, but there are some caveats attached to its use. An interesting observation is that the most noticeable difference between left and right was measured in an area of low circulation. This gives some indication that this area has the most difficulty with returning to the neutral state.

Conclusion: This research shows that skin temperature variation as a result of applying heating or cooling agents to the skin can be measured using an infrared camera, suggesting that minor variations in skin temperature as a result of neuropathy can also be measured, further research with more test subjects should be done.

1 INTRODUCTION

According to the World Health Organization (WHO) more than 200,000 new cases of leprosy, also known as Hansen's disease, are reported each year in over 120 different countries [1]. -Leprosy can be effectively treated when detected using a regiment of antibiotics [2]. This has led to a great reduction in leprosy cases in the world.

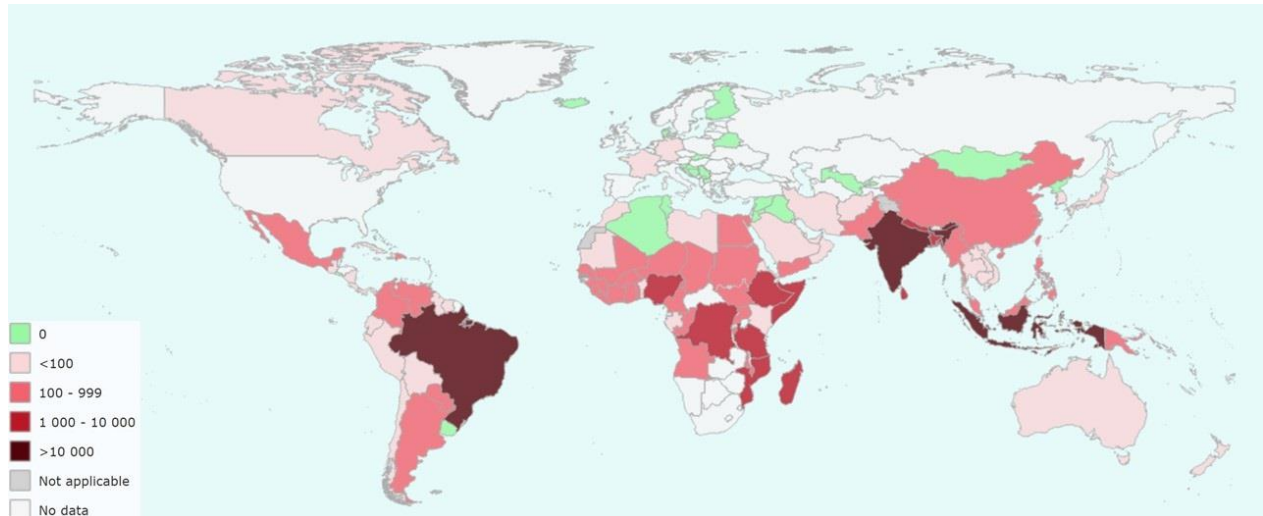


Figure 1: New cases of leprosy in 2021 [3]

As Figure 1 shows, leprosy has been mostly eliminated from the developed countries and the main hotspots are in South America, Asia-Pacific, and Southwest Asia. These countries have in common that access to healthcare is often limited. This means diagnosis is often late and irreversible damage has already been suffered.

Leprosy is a disease that damages nerves. It damages the nerves in an asymmetrical pattern and is generally limited to the extremities[4]. Most often it tends to affect the autonomous nerves before the sensory nerves[5].

To prevent permanent damage, it is important to diagnose leprosy early so that treatment can be administered as quickly as possible[5]. Since leprosy first affects the autonomous system before affecting the sensory system[6], this means that if the damage to the autonomous system can be measured, it can be used to diagnose leprosy before damage to the sensory system can occur.

To assess autonomous function in a low-income setting, different constraints apply compared to assessing autonomous function in a higher-income setting. Autonomous nerves are generally assessed using large expensive devices. Two main methods are used nerve conduction tests (NCS) and Electromyography (EMG)[7] both of these are impractical for low-income settings where the devices used for these methods are not easily accessible.

1.1 RESEARCH QUESTION

The autonomous function is not only damaged by leprosy but also by other types of nerve damage. Therefore, the research question has been made broader by looking at the assessment of autonomous

nerve damage in low-income settings but has been limited to the upper extremities. This has led to the following research question:

“Is it possible to detect asymmetrical neuropathy at an early stage by assessing the autonomic function of the upper extremities using existing (non)medical devices in a low-income country?”

This research question consists of various subparts. Sub-questions have been formulated to answer the various parts of the research question. Each sub-question is followed by a clarification of what the question is trying to answer.

1. What physical properties can be used to assess autonomic function?

Before neuropathy can be detected it is important to look at how autonomic function can be assessed. To do this it is useful to look at what physical properties are controlled by the functions of the autonomous system.

2. What is the relation between autonomic function and (asymmetrical) neuropathy?

The answer to this question will show how neuropathy can disrupt autonomic function. This will help clarify how neuropathy disrupts autonomic function and help with discovering how this disruption might be assessed.

3. How does neuropathy affect the upper extremities?

Here the effects of neuropathy are examined on the upper extremities. The focus will mostly be on the hand region, but the rest of the upper extremities will also be examined.

4. What are the constraints imposed by a low-income country setting?

Here the limitations imposed by a low-income setting are further expanded upon. Not only in terms of costs but also training and practicality. This gives a list of constraints that possible devices need to fit within.

5. Which (non)medical devices are suitable for assessing autonomic function?

With the above questions answered a list of requirements can be created to find suitable devices. The potential devices are gathered and graded with this list of requirements. Then the most suitable device is chosen to be used in testing.

6. Is it possible to detect neuropathy using the found devices?

Here the devices found in the previous sub-question are tested for their potential usefulness. To do this the property they extract is determined and test protocols are made. These tests are then performed in a pilot test that will determine the feasibility of the devices as a means of assessing neuropathy.

1.2 REPORT STRUCTURE

First, the clinical background of leprosy and autonomous nerve damage will be examined. Next a list of suitable devices and the constraints that limit them are discussed. After this, the experimental design will be explained. Then the results will be analyzed and lastly, a discussion of the found results is made.

2 CLINICAL BACKGROUND INFORMATION

To assess autonomous function and possible damage done to it, it is important to know what exactly the autonomous system is and how it may be damaged by neuropathy. The original question that led to this research was to assess autonomous function with existing low-cost devices in patients suffering from leprosy. Therefore, the analysis of the autonomous function is placed into the context of leprosy. To do this, first leprosy is examined and how it affects the body after that autonomous function is assessed and the physical properties that are affected by disruption of autonomous function.

2.1 LEPROSY

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by a bacterium, *Mycobacterium leprae*. It predominantly affects the skin and peripheral nerves and can be effectively treated with multidrug therapy[8].

2.1.1 Transmission

Leprosy is transmitted by droplets from the mouth and nasal passages, and possibly by skin-to-skin contact. Prolonged contact is needed for transmission [9]. The incubation time of leprosy can be very long ranging from 1 to 20 years, averaging around 5 years [10]. An estimated 95% of the world's population is not genetically inclined to the disease, but there is some variation in the degree of immunity to the disease [11].

2.1.2 Symptoms

The main symptoms of leprosy can be divided into symptoms of the skin and symptoms of the nerves [12]. Symptoms of the skin include the onset of redness and swelling, as well as lesions. The symptoms of the nerves may include pain or tenderness, numbness, loss of nerve function, and muscle weakness [13].

2.1.3 Diagnosis

Three cardinal signs are mainly used to diagnose leprosy: anesthetic skin lesions, enlarged peripheral nerves, and acid-fast bacilli [14]. Of these, the nerve thickening is indicative of possible neuropathy. The anesthetic skin lesions can be seen after physical examination, for the other two symptoms multiple tests are available.

To find acid-fast bacilli a smear test may be employed. This is taken from nasal, mucosa, ear lobe, and/or skin lesions [15]. Then a Ziehl-Neelsen stain is used to make the bacilli visible proving infection. Another option is to take a skin biopsy and stain it using the Fite-Faraco technique [16]. To test the nerves a monofilament test may be used. This consists of filaments being run over the suspected affected region with varying thickness testing for sensitivity.

Leprosy may also present in a purely neural way. This complicates diagnosis because there are no lesions to observe [17]. Because only the nerves are affected detection is usually delayed until sensory nerves have been affected. This might lead to permanent disability, as treatment has less effect when this stage of the disease is reached.

2.1.4 Treatment

Originally patients diagnosed with leprosy were required to take antibiotics their entire life until Multi-drug therapy was introduced in 1982 [18]. This proved to be very effective and is only required to be

taken for about a year according to the WHO. After treatment, both physical and social limitations may remain, as damaged nerves may not recover and stigmata of once having suffered leprosy may never go away [19].

2.2 AUTONOMOUS FUNCTION

Autonomous function is controlled by the autonomous nervous system. To increase the understanding of autonomous functions first the entire autonomous nervous system will be examined. After this, the focus will be shifted to the peripheral nervous system and then the physical properties associated with the autonomous nervous system are discussed.

2.2.1 Autonomous nervous system

The autonomous nervous system (ANS) is responsible for all involuntary actions of the body. This includes digestion, heart rate, respiratory rate, pupillary response, urination, and sexual arousal [20]. It is also the primary motivator for the flight-or-flight response.

The ANS consists of three different parts: the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system [21]. The sympathetic nervous system is responsible for the fight-or-flight reactions, the parasympathetic nervous system is responsible for feed-or-breed reactions, and the enteric nervous system is responsible for the gastrointestinal system.

The sympathetic and parasympathetic nervous system work closely together and are integral to keeping the ANS in balance. Initially, it was thought that the sympathetic system was responsible for "excitatory" responses while the parasympathetic is responsible for the "inhibitory" responses, this however has been disproved. The next distinction that is still generally held is that the sympathetic system is responsible for quick responses, such as accelerated heart rate and pupil dilation, and the parasympathetic system is responsible for slower dampening responses, such as decreasing heart rate and respiration. Although this is not entirely true of the sexual arousal aspect of both systems [20].

2.2.2 Autonomous peripheral nervous system

The peripheral nervous system (PNS) is the nervous system that is not part of the brain, brainstem, and spinal cord. Neuropathy usually occurs in the peripheral system and this is why the focus lies on the peripheral system [22]. This focus on the PNS means that of the physical properties controlled by the ANS, only three main functions remain. The main autonomous function of the PNS is the control of the dilation and constriction of veins and arteries, skin wrinkling, and control of the sweat glands of the peripheral system [20].

2.2.3 Physical properties influenced by the autonomous peripheral nervous system

The main autonomous function of the PNS is the control of the dilation and constriction of veins and arteries, skin wrinkling, and control of the sweat glands [23]. The physical properties associated with these functions will be discussed to what extent they influence the autonomous nerve system.

Sweating is a form of thermoregulation for the body as a means of temperature reduction while under heat stress [24]. Sweat glands are, like hair follicles, cutaneous appendages. Sweat is 80% water combined with minerals and salts. Neuropathy disrupts the function of sweat glands and leads to lower sweat production or even the absence of sweat production [25]. This disrupts the function of sweat glands to reduce body temperature which could be measured to assess autonomous function through

electrical resistance of the skin. Sweat is conductive because the presence of NaCl, with conductivity increasing with higher NaCl concentrations [26]. With less sweat, the concentration of NaCl will be lower this decreases conductivity. This conductivity can therefore be linked to neuropathy through skin resistance, as it will be lower as less sweat is produced. It is important to keep in mind that autonomous function is not the only driving force behind sweating stress and anxiety may also trigger a sweat response, especially in the hands and feet. [25].

Skin wrinkling is the appearance of reversible undulations on the surface skin. It is a result of vasoconstriction and is part of the sympathetic nervous system [27]. The wrinkling of the skin creates a topological landscape that may be measured to assess autonomic function.

An important mechanism of the autonomous nervous system is the control over the dilation and constriction of the arteries and veins which is important for body homeostasis [28]. Three main physical properties can be linked to this dilation and constriction of veins and arteries.

Blood pressure, the first of these properties, is controlled by the arterial baroreflex and autonomic nervous system [29]. When the blood pressure is changed by for example movement or a change of elevation, the body will try to maintain blood pressure by constricting and dilating veins and arteries. This can be disrupted by neuropathy leading to measurable differences, as the body will not react as effectively to these changes in blood pressure [30].

Linked to blood pressure is the property of blood flow. Blood flow is the speed at which blood flows through the arteries. Depending on such factors as dilation/constriction and blood pressure the blood flow will be altered. If one or more of these factors are influenced by neuropathy, blood flow will also be changed. When measured this may allow for assessment of autonomous function.

Lastly, an important physical property controlled by dilation and vasoconstriction is temperature. Skin temperature is controlled through sweat, and dilation and constriction of vessels [31]. Vasodilation and sweating are combined to reduce temperature while vasoconstriction allows the body temperature to rise [32]. The body prefers to be in homeostasis which is disrupted by neuropathy. This means that somebody affected by neuropathy will have a more difficult time maintaining and or recovering their body temperature [33]. By assessing the body's ability to maintain or restore skin temperature possible damage to the ANS might be detected.

2.3 NEUROPATHY

To see how the ANS might be influenced by neuropathy it is important to examine neuropathy. First neuropathy as a whole is examined then the different types of neuropathy, the asymmetrical neuropathy, and lastly, the relationship between neuropathy and autonomic function is explored.

2.3.1 Neuropathy

The definition of neuropathy is: "A nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body [22]." Neuropathy is a disease of the nerves found in different parts of the body. Neuropathy is most often found in the peripheral system and the cause of neuropathy is varied, it can be genetic, infection-related, or the result of trauma [34].

2.3.2 Types of Neuropathy

The types of neuropathy can be defined by how and which parts of the body they affect. The common types of neuropathy are symmetric polyneuropathy, single and multiple mononeuropathy, and radiculopathy [35]. Symmetric polyneuropathy is when many or most nerves of the peripheral system are affected symmetrically. This means that all the nerves of the peripheral system are to some degree damaged and that this damage is the same severity on the left and right sides of the body [35]. In the case of mononeuropathy only one (single) or a few (multiple) nerves are affected although this can be symmetrical it is most often asymmetrical [35]. Radiculopathy is more commonly known as a pinched nerve [36]. When for example a nerve gets crushed between the vertebrae of the spinal cord damage can occur leading to neuropathy in the nerves along the spine.

2.3.3 Asymmetrical Neuropathy

In asymmetrical neuropathy, the damage to the nerve is not mirrored in the median plane [14]. This means that when for example a nerve in the left hand is affected, the same nerve is not affected in the right hand. The human body prefers to be in homeostasis this means that generally, the body tries to maintain the same conditions in every part of the body. Because of this, it is possible to use the unaffected body part to diagnose the affected body part. As throughout the body the same reaction to a stimuli of the autonomous nerve system should take place. This makes the diagnosis less reliable on a universal "normal" scale, that might not be true for the current patient in a healthy condition. If, for example, the asymmetrical neuropathy in the left pink is severe, the pink will have little feeling and can be easily identified as a site of possible neuropathy. However, when the neuropathy is not as severe this becomes more difficult; is it neuropathy or simply a person that has lower than usual feeling in their extremities? However, if the sensitivity of the left pink is compared to that of the right pink possible neuropathy can be detected earlier in case of asymmetrical neuropathy.

2.3.4 Neuropathy and Autonomic Function

There are three types of nerves; motor nerves, sensory nerves, and autonomic nerves [23]. Neuropathy affects all three of these nerves. With neuropathy, the usual order in which these are affected are first the autonomic nerves, then the sensory nerves, and last the motor nerves [37]. The autonomous nervous system consists of mostly involuntary, non-conscious, actions and reactions which means that most people don't notice damage to this system until it has reached the sensory nerves. Damage to the sensory function or motor function is noticed more quickly by the person suffering from neuropathy. To increase the chance of discovering neuropathy in an early stage, and thus preventing further damage, the testing of the autonomous nervous system should be introduced and expanded upon. By testing the physical properties found in the previous chapter and comparing them across the median plane the chances of discovering neuropathy in an early stage might be possible.

2.4 EFFECTS OF NEUROPATHY

With the relationship between neuropathy and the autonomic nervous system (ANS) established it is now time to examine how neuropathy affects the ANS. To do this first the general effects of neuropathy are discussed. Then the regions most often affected are discussed focusing on the regions affected by leprosy.

2.4.1 Symptoms of Neuropathy

As mentioned in the previous part there are three types of nerves. The autonomic nerves, the sensory nerves, and the motor nerves. All of these nerves may be affected by neuropathy. The effects of neuropathy depend on which type of nerve is affected. Before describing the symptoms first the function of each nerve type will be examined. The autonomic nerves are responsible for regulating unconscious activities such as digestion, sweating, etc. The sensory nerves are responsible for conducting sense signals. These include such things as pressure, heat, and pain. The motor signals are responsible for conducting the signals for conscious movement.

Depending on which type of nerve is damaged certain symptoms will be present. When the autonomic nerves are damaged the following symptoms can be present [38]:

- Heat intolerance
- Excessive sweating or not being able to sweat
- Bowel, bladder, or digestive problems
- Drops in blood pressure, causing dizziness or lightheadedness

In the sensory nerve the following symptom may be present [39]:

- numbness and tingling in the feet or hands
- burning, stabbing, or shooting pain in affected areas
- loss of balance and coordination

And in the motor nerves [40]:

- muscle weakness, especially in the feet

The symptoms associated with the motor and sensory nerves are generally easier to notice than those associated with the autonomic nerve. Picking up a hot pan and not feeling it is a clearer indication of issues than not sweating as much as you used to.

2.4.2 Affected regions

As mentioned in the previous part the cause of neuropathy is varied. The regions that are affected depend on the cause of the neuropathy and where it is located. In theory, any part of the peripheral system may be affected by neuropathy depending on its cause. The original question this report was made for asked if it was possible to find a low-cost method of assessing autonomic function in leprosy patients. For that reason, it makes sense to take a closer look at the regions often affected by neuropathy as a result of leprosy.

Three cardinal signs are mainly used to diagnose leprosy. These are anesthetic skin lesions, enlarged peripheral nerves, and acid-fast bacilli [14]. Of these, the nerve thickening is indicative of possible neuropathy. The nerves commonly involved with leprosy are the following: the great auricular nerve (which runs from the bottom of the ear to the clavicle), the ulnar nerve (which runs from the shoulder to the hand on the inside of the arm), this nerve thickens usually above the elbow or below the dorsal cutaneous branches at the wrist, median and superficial radial nerves, the lateral popliteal, superficial peroneal, posterior tibial, and sural nerves [41] [42]. This thickening is often visible and/or palpable.

3 SUITABLE DEVICES AND CONSTRAINTS

3.1 CONSTRAINTS

To diagnose neuropathy two methods are generally used in conjunction [7]. The first is a nerve conduction test (NCS). This test uses electrodes to send an electric signal through a nerve and measure the response. The second method is electromyography (EMG). In EMG a small needle is inserted in the muscle to measure response. These tests provide a reliable way of diagnosing neuropathy but require costly machines to perform the tests. There are other methods, but these are often expensive, dependent on very specific conditions, or require highly trained users. This thesis was based on a question from a leprosy physician working in Nepal. He asked if it was possible to find a way of detecting possible neuropathy using cheap readily available devices. As an example, he gave a moisture meter to see if neuropathy, which can influence sweating, would give different results for a healthy versus an unhealthy limb. To broaden the scope of the question it was then rephrased to: are their devices available in a low-income setting to detect possible neuropathy? To be able to answer this it is important to look at what kind of constraints a low-income setting will impose. This chapter will aim to answer that question by first looking at what a low income setting is, next what financial restraints this imposes, then the training restraints, and lastly the practical restraints.

3.1.1 What is a low-income setting

A low-income setting is somewhat hard to quantify. According to the government of the United States of America, a low-income individual is someone whose family's taxable income from the preceding year did not exceed 150% of the poverty level amount [43]. The World Bank's definition of a low-income country is a country in which the gross national income per capita is \$1085 or less [44]. These definitions give an indication of the income of a person in a low-income setting, but that is not the only characteristic defining a low-income setting.

A second important characteristic is access to healthcare. Healthcare access is the ability to obtain healthcare services such as prevention, diagnosis, treatment, and management of diseases, illnesses, disorders, and other health-impacting conditions. The level of access is determined by affordability and convenience. A country that has free healthcare, but builds its hospitals on top of mountains does not have good access to healthcare. Conversely, a country with a hospital on every corner but the simplest healthcare procedure costs more than the average citizen makes in a year and also has low access to healthcare. For the low-income setting discussed here access to healthcare is considered low. In this case, both affordability and convenience will be assumed to be on the low end of the spectrum.

3.1.2 Financial Constraints

The financial aspect of a device can be divided into two components. The first component is the initial cost. The initial cost consists of the cost of purchase, the cost of installing the product, and the cost of training personnel to use it. To make the device financially functional the initial cost should be \$1,000 or less. This number has been established based on the experience of practicing medical personnel in a low-income country.

The second aspect is maintenance costs. These costs include material costs and the cost of a technician to do the maintenance. This cost should be \$500 or less per year.

3.1.3 Training Constraints

Aside from the financial constraints, there are also constraints related to the person using the device. In a low-income setting, there is often a limited pool of specialists and training is more often broad than specialized. It is therefore important to limit the complexity of the device to make it easier to operate and more broadly used. Basic medical training can be assumed for a potential user making this the maximum of how much training is needed for the device. A similar limitation is added to the difficulty of maintenance for the device. The maintenance of the device should be easy enough that it can be kept operational without needing a specialist.

3.1.4 Practical Constraints

Aside from the financial and training constraints, there are also some practical constraints to be mindful of. One of these is the distance from a potential patient to a specialist capable of determining neuropathy. Access to hospitals in a low-income setting is often limited by distance. This means that tests are more often done on location or in out hospitals where resources are limited. This puts a size constraint on any possible devices. The device should be portable and require minimal outside power. Ideally, the device would fit in a portable case and have enough battery life or batteries to last at least a day without charging.

3.2 SUITABLE DEVICES

In the previous chapters, a list of requirements has been created for a device that can be used to assess neuropathy in the autonomic system. Because the search for possible devices is not limited to devices currently used in a medical setting it is important to not only examine devices but also the underlying properties that can be measured. These properties have been examined in a previous chapter. For each property first currently used medical devices are examined and then possible alternatives are looked at. Lastly, the most promising devices are selected and these will be tested for suitability. The devices and the most promising devices were found in the literature study in Appendix A.

3.2.1 Physical properties

In the first chapter, the following physical properties were determined. Temperature, blood flow, blood pressure, skin resistance, and skin topology. The physical properties that are examined are all linked to a lesser and greater degree. This means that some devices described below may measure a different physical property to get the described physical property.

3.2.1.1 *Blood Flow*

The autonomous system controls the restriction of blood veins and arteries as a result of outside influences. These changes to veins and arteries lead to changes in blood flow. Blood flow can be defined as the volume of blood moving through a certain area during a set amount of time. To assess blood flow it is necessary to use a method that measures these three variables. Currently, three methods are commonly used to measure blood flow. The electromagnetic blood flow meter is based on the principle of Faraday's law of electromagnetic induction. This states that a conductor flow will create a magnetic field. Blood, due to its iron content, is a conductor. This means that if a magnet is placed around an area through which blood flows a change in the magnetic field will occur. By measuring this change the flow of the blood can be determined. The ultrasonic blood flow meter uses ultrasound to determine blood flow. It consists of a source, reflector, and receiver. The received signal will be different depending on the flow. This is due to the Doppler effect. The last method is the nuclear magnetic resonance blood flow

meter. It uses a similar principle as the electromagnetic blood flow meter but uses a method similar to an MRI. This method is mostly outdated and is not often used.

The devices used to employ these methods are large expensive devices. This makes them unsuitable for use in a low-income setting. Alternative devices that measure flow are difficult to find. Some devices can measure the flow in tubes and pipes, but these are difficult to adapt to precisely measure the blood flow in different veins and arteries. A possible device to measure blood flow is a pulse-oxy meter. This medical device is used to determine the amount of oxygen in a person's blood. It does this by shining a light through the finger and measuring how much light is absorbed by the oxygen-rich red blood cells. In theory, if the oxygen level of the blood in a non-affected region is known then it should be possible to determine the blood flow. This would require access to the raw data from the device. Again precision is an issue and the device can only be used on digits, making other neuropathy hot spots difficult to assess.

3.2.1.2 Blood Pressure

Dilation and constriction of arteries and veins will influence blood pressure. Measuring blood pressure locally and comparing it on the median plane allows for the detection of neuropathy. Blood pressure is a commonly measured property in a medical setting. Different types of blood pressure monitors are available. Digital blood pressure monitors are often used on the wrist, but they can also be placed on the finger or upper arm and are activated simply by pressing a button. They read the blood pressure automatically based on variations in the volume of blood in the arteries. When taking blood pressure measurements on the wrist, it's important to keep the hand level with the heart. Otherwise, it can affect the readings. Digital meters can sometimes be inaccurate and produce unreliable readings, especially in people with certain heart rhythm problems or arteries that have hardened due to arteriosclerosis. A sphygmomanometer consists of a cuff that is inflated with air, a pressure meter, and a stethoscope.

Because blood pressure tests are well-established in medical science. Looking for a non-medical device does not make a lot of sense. When applying blood pressure tests for diagnosing neuropathy it is important to establish a normal and to change the blood pressure with a test where blood pressure change is expected. A possible test is having the person stand up and measure the blood pressure before and immediately after.

3.2.1.3 Temperature

The temperature in the upper and lower limbs, especially in the hands and feet, is controlled by the autonomous nervous system and more specifically by constriction and dilation. Although body temperature can vary from person to person and in different environments it is symmetrical in the upper and lower limbs [45]. This means that asymmetrical autonomous nerve damage can be discovered by comparing the temperature of left and right upper or lower extremities.

Body temperature is used in diagnostic medicine to check for possible problems in the body. Usually, the temperature of interest is the average or core body temperature. Currently thermography is already used in diagnostics for a variety of issues ranging from breast cancer, to personality testing [46]. Thermography can also be used to assess autonomous function. It has been tested in diabetes [47] and leprosy [48]. The tests are generally between healthy subjects and leprosy patients. However, because leprosy is asymmetrical it can be tested by comparing left to right. Here the precise temperature is less important and the difference in temperature for left and right is the important property because this might indicate damage to the autonomic system. Skin temperature is the physical property that needs

to be measured. Various devices can measure temperature. The most promising devices are an infrared camera and liquid crystal thermometers. The infrared camera is often used in the inspection of buildings and IT infrastructure. The camera has a screen that shows the temperature of whatever it is pointed at showing temperature differences. When used to measure skin temperature it offers a good view of differences between upper and lower limbs making it easier to compare the left and right sides. A liquid crystal thermometer is an interesting option they are most commonly known for their use in mood rings. These rings supposedly change color based on the mood of the wearer. In truth, the rings change depending on temperature. This makes these types of rings perfect for at-home testing where a left-right comparison can be easily done by a person without any medical training. A downside is that commercially available mood rings are easily influenced by outside forces and only show a color. These colors may differ on what type of liquid crystal is used and currently, no exact color-to-temperature chart seems to exist.

3.2.1.4 Skin resistance

Sweating significantly influences skin resistance by adding a saline fluid to the skin surface. Normal skin resistance is determined by several factors. The makeup of the skin itself, the pressure that is applied to it, the wetness of the skin, and the contact area. The wetness of the skin is influenced by sweat and environmental conditions. Again a left-right comparison can be done to diagnose possible neuropathy. The sweat itself could also feasibly be measured, but as noted in the literature study of Appendix A these tests require strict environmental conditions which are difficult to establish in a low-income setting.

To measure skin resistance a possible device is a moisture meter. These devices are cheap, commercially available devices usually used to measure the moisture content of the wood. It uses two prongs that are inserted into the wood to measure the moisture content. This could be used on the skin (without piercing or breaking the skin) to compare the skin resistance left and right.

3.2.1.5 Topology

When the skin wrinkles the topology of the skin changes. Valleys and hills form which can be measured using the right device. The topology of the skin is of interest to dermatology and cosmetic medicine. There are various devices used in the material sciences that can pick up differences in topology using light reflection or sound. To score this topology the picture then will need to be analyzed and quantified. This is most easily done by a computer and would require a lot of man-hours if done by a person. Aside from a picture, an impression could also be made of the skin topology, either in a soft material or with an ink print similar to fingerprints.

Skin wrinkling is an autonomic function but compared to the other physical properties described above it requires quite a long time to initiate. The analysis of the topology also requires a lot of time or expensive equipment. These characteristics make this physical property unsuitable for the intended purpose.

3.2.2 Device Criteria

As mentioned before the previous chapters have established the criteria the device that will be tested needs to conform to. These criteria are as follows. Easy to use; the device should require no special training and should not be more difficult to employ than a standard thermometer. Easy to maintain, no special training is required for maintaining the device. Low initial cost, it should cost no more than \$1,000. Low maintenance cost, should cost less than \$500 per year to maintain. The device should be portable. The device can supply results on-site.

3.2.3 Chosen Devices

Using the above criteria and using the Harris profile from the literature study in Appendix A, see Figure 2 the following devices were selected for testing. The infrared scanner, the mood ring, and the moisture meter. Of these, the focus will be on the infrared scanner as the most promising device.

	Blood Pressure				Skin Wrinkling				Temperature				Sweating				Blood Flow			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Clinical Significance		X						X				X				X		X		
Accuracy of measurement				X		X						X			X					X
Ease of measurement			X					X			X			X						X
Difficulty of implementation				X			X				X				X					X
Time to measure			X		X						X		X							X

Figure 2: Harris profile from Literature study in Appendix A

The infrared scanner was picked as the most promising device because most models are handheld and offer the possibility of testing both sides of the body at once. Furthermore, it investigates the most promising physical property, temperature, and there are models that have the required precision while staying within the determined price range.

The mood ring was picked due to its ease of use and availability. The device measures temperature and it is very cheap. The moisture meter was picked because the initial question asked by the physician was if this might be a useful device. Because this device is also cheap and can be easily integrated into the testing procedure for the infrared scanner and the mood ring.

4 METHODS

To see if the chosen devices might be used to diagnose possible neuropathy it is necessary to test them. First, the conditions in which the experiment is performed will be described. Then the experiment and the used materials themselves will be described for the three chosen devices.

4.1 CONDITIONS

This research is meant to be an exploration of possible applications of the infrared camera, the mood ring and the moisture meter. This means there are certain limitations and conditions surrounding the tests. An important limitation is that the test was not performed in a low-income country on people with diagnosed neuropathy. Instead, this test was designed to see if measurements can be done and show significant results to continue this line of research.

Because the test person doesn't have neuropathy the test needed to be modified. This was done by using a vasodilator and a vasoconstrictor gel to disrupt the autonomic system and measure the return to homeostasis. The tests were performed under no special environmental conditions and the environmental conditions were not monitored or regulated.

4.2 EXPERIMENT

The experiment performed is an investigative experiment meant to offer insight into the use of an infrared camera, mood ring, and moisture meter as a diagnostic tool. The tests were performed on a single subject to narrow down the options for a bigger scale test. To achieve this the restorative power of the autonomous system was tested by deliberately changing the body temperature of the hand with heating and cooling agents. Both sides of the hand were tested, palmar and dorsal, using different amounts of heating and cooling agents.

As the mood rings available did not fit the fingers of the adult test person, this measurement device was excluded from the experiment during the test phase. And therefore not further described in this experiment.

4.2.1 Materials

The materials used in the experiment are as follows:

- Cooling agent: 1% Menthol (Ethos).
- Warming agent: Tiger Balm Red
- IR camera (FLIR E75), this infrared camera is on the higher end of both the price and precision spectrum.
- Precision scale measuring in grams with an accuracy of 0.01 gram up to 200 grams
- Moisture meter (Pattfield)
- Tripod that holds the IR camera.
- ResearchIR software to control the camera and process the pictures.
- Excel, for data processing.
- Laptop, this runs the ResearchIR software that controls the camera and allows pictures to be processed.

- Disposable gloves
- USB to USB-b cable
- Mood ring (koning import)

4.2.2 Setup

The test subject was put in a seated position with hands and forearms resting on the table and given a rest period of 10 minutes before the start of the test. The IR camera was placed on the tripod which was placed on the table with the camera aimed at the hands of the test subject. The IR camera is connected to the laptop via a USB to USB-b cable. The laptop runs the ResearchIR software to control the camera. See Figure 3 and Figure 4.

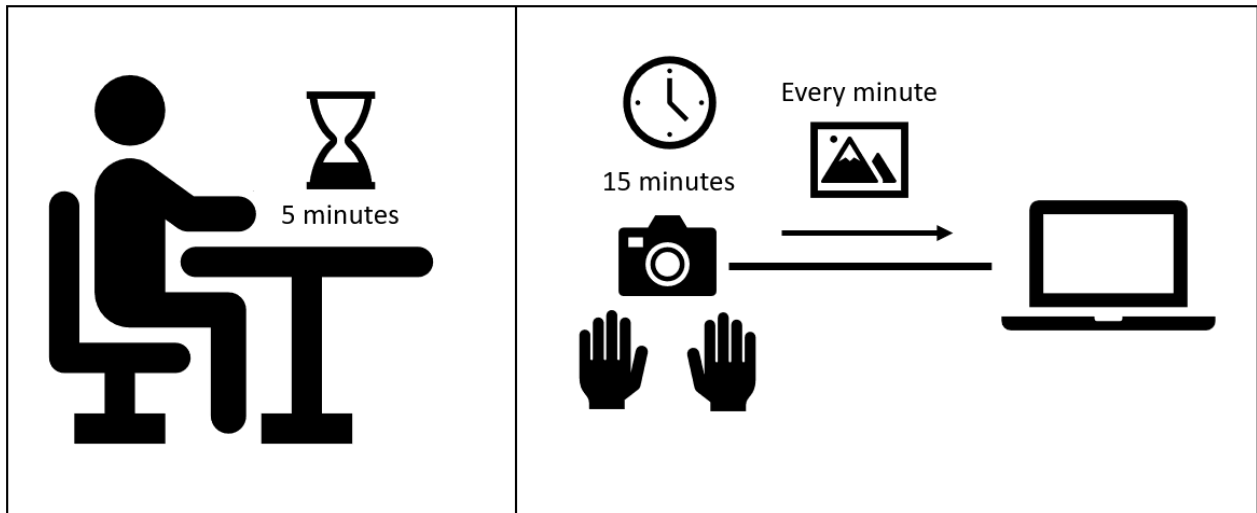


Figure 3: Experimental Setup. The test subject had a an acclimation period of 5 minutes with the arms in the test position. The hands and forearms were resting on the table. The camera was mounted on a tripod and for 15 minutes every minute a picture of the hands was taken. The camera sent the pictures to the laptop running the ResearchIR software.

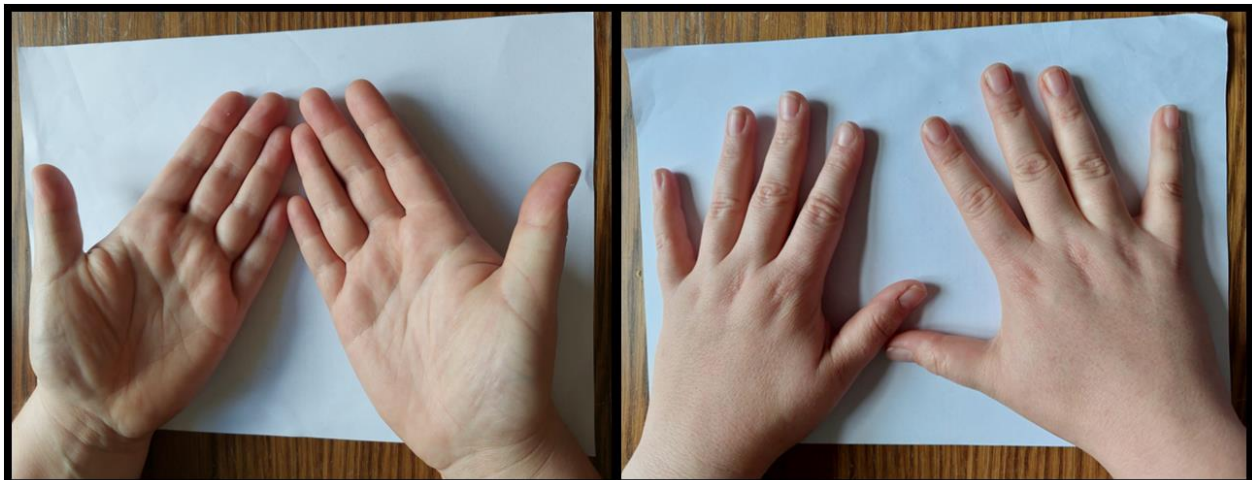


Figure 4: Position of the hands during the experiment. Left the palmar side up, right the dorsal side up.

4.2.3 Exploratory tests

Before the test was performed explorations were made to determine the timing and dosage for the tests. It was found that after five minutes of rest, the temperature of the hands seemed to stabilize. For

the heating and cooling agents, it was found that the cooling agent was less effective than the heating agent so different doses were needed. No conclusive differences concerning the application of the palmar or dorsal side of the hand were found and therefore it was decided to test both sides. During the exploratory test, it became apparent that the mood rings were ill-suited for the designed test. They were sensitive to outside influence and the color ranges are greater for some temperatures than others making precision an issue [49]. This made comparison between the left and right sides very difficult. Because of this no test results were obtained for the mood ring and it was not used in the final experiment. The major effects of the agent are done after 15 minutes and that is the length of the test.

4.2.4 Test parameters

Twelve tests were designed. Six on the palmar side of the hand and six on the dorsal of the hand. Three different quantities of the two agents were applied to each side. The tests were performed in a randomized order and each test was performed with a rest period in between. Table 1 shows the test number, the side of the hand, the type of agent, and the dosage used.

Table 1: Test number, side, agent, and dosage.

Test number	Side of the hand	Agent	Dose (g)
1	Dorsal	Cooling	0.1
2	Dorsal	Cooling	0.2
3	Dorsal	Cooling	0.3
4	Palmar	Cooling	0.1
5	Palmar	Cooling	0.2
6	Palmar	Cooling	0.3
7	Dorsal	Heating	0.03
8	Dorsal	Heating	0.07
9	Dorsal	Heating	0.1
10	Palmar	Heating	0.03
11	Palmar	Heating	0.07
12	Palmar	Heating	0.1

To obtain more information and minimize the influence of the previous test multiple runs were done. All tests were performed three times in a randomized order as shown in Table 2.

Table 2: Test order for the three runs

Run 1	Run 2	Run 3
10	11	11
9	12	1
6	3	4
2	2	8
3	1	2
8	7	12
4	6	6
1	4	7
7	9	9
11	10	3
12	8	5
5	5	10

4.2.5 Steps

The following steps were done for each test:

1. The Test subject spends five minutes stabilizing the skin temperature.
2. A picture was taken at the start as a zero condition. The moisture meter is used to measure skin moistness.
3. Then the agent was applied, and the required weight was measured out on the precision scale and applied while wearing the gloves.
4. For The next 15 minutes every minute a new picture is taken with the IR camera of both the left and right hand. At the same time, the moisture meter is used to measure the moistness of the skin.
5. Then a minimum of 15 minutes of rest time is observed before the next test is done.

These steps were followed every step and between each run, extra time was taken with a minimum of 8 hours of rest in between.

4.2.6 Analysis

To analyze the measurements taken as described above the following steps were taken. Each test was performed three times as shown in Table 1 of Section 4.2.4. The results found were then averaged over the three tests to minimize environmental influences. The resulting average was then normalized to the begin value found at the start of each individual test. This helps visualize the change of temperature with regards to the original temperature of the hand showing if and how much the hand has normalized to its original temperature at the start of the test.

5 RESULTS

With the two tests performed the results need to be processed. This was done separately for the IR camera and the moisture meter. The moisture meter will be discussed first followed by the results from the IR camera.

5.1 MOISTURE METER

During testing the moisture meter proved uncomfortable and difficult to utilize. The pins the moisture meter uses to measure resistance were experienced as uncomfortable, although no marks or wounds were left by their use. It also proved difficult to consequently measure the resistance at the same spot this was especially difficult on the back of the hand. This meant extra discomfort for the subject during measurement. These factors ultimately lead to the moisture meter being abandoned for measurement and no useful data for analysis was obtained the raw data from the moisture meter can be found in Appendix C: Moisture Meter Raw Data. The moisture meter might still be useful, but this will be further discussed in the discussion.

5.2 INFRARED CAMERA

To analyze the infrared pictures taken with the infrared camera four points were chosen on the dorsal and the palmar side of the hand as shown in Figure 5. The four points were chosen as follows. One point close to the ulnar nerve (1) (a nerve often affected in asymmetrical neuropathy and leprosy in particular), one point that is in an area of high circulation (2), one that is in low circulation (3), and one point just outside the application area to act as a neutral (4). The first picture is taken before application and then one after application and one every minute for 15 minutes showing the progress of disruption and recuperation.

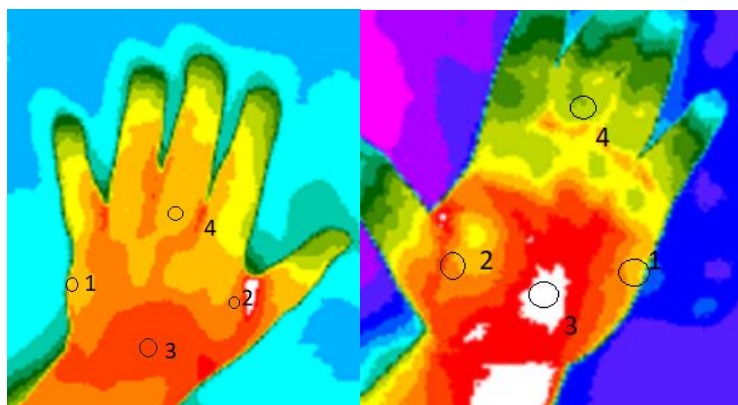


Figure 5: Points of interest on the dorsal and palmar side of the hand

5.2.1 Results

An important note to add to the graphs is that the curve for Test 9 shows some significant abnormal behavior. Part of the data from one of the runs of this test was corrupted and could not be used. This means that for Test 9 only 2 runs were averaged. The test was further troubled by the fact that the 2 runs that were available were done under unusually cold circumstances. Other tests were done under similar circumstances but have averaged out without creating these outliers. To present the data as

complete as possible Test 9 has been included in the results. For the data points used see Appendix B: Temperature data average of three runs. The naming convention for the plotted lines are as follows, TxLyz where x is the number of the test, 1-12, y is the location, 1-4, and z is the side, LS left or RS Right. The horizontal x-axis shows the moments the pictures were taken where 1 is the temperature before application, 2 is the moment just after application and after that a picture for each minute till 15 minutes elapsed. The vertical y-axis shows the temperature difference with the starting value at measurement Point 1. A positive number corresponds with an increase in temperature, a negative number with a decrease in temperature. This leads to the following graphs:

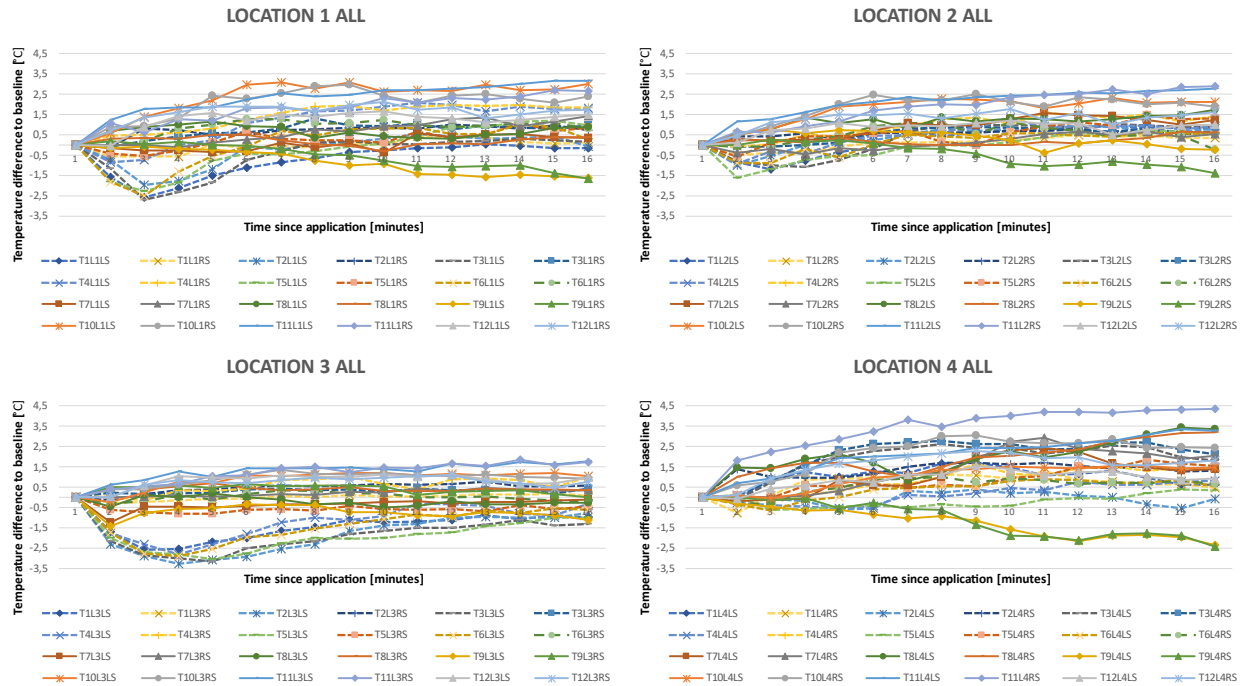


Figure 6: Overview graphs for all locations showing the results from all twelve tests for each specific location. Each line is an averaged test run with the following naming convention: TxLyz where x is the number of the test, 1-12, y is the location, 1-4, and z is the side, LS left or RS Right. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line.

The graphs as shown above show a lot of data and give a first insight. To better understand the data, it will be examined on a more detailed level below. First the left-right results are presented. The left hand was the affected hand, and the right hand was the unaffected control. Then the palmar dorsal results are presented, lastly the heating and cooling results are presented.

5.2.2 Left Right Difference

The first comparison is made between the left and the right hand. The comparisons are made per location starting with location one shown below.



Figure 7: Location 1 Left - Right Difference. Tests 1 to 6 were done with the cooling agent, test 7 to 12 with the heating agent. Each line is an averaged test run with the following naming convention: TxLyLz where x is the number of the test, 1-12, y is the location, 1-4, and z is the side, LS left or RS Right. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.



Figure 8: Location 2 Left - Right Difference. Tests 1 to 6 were done with the cooling agent, test 7 to 12 with the heating agent. Each line is an averaged test run with the following naming convention: TxLyZ where x is the number of the test, 1-12, y is the location, 1-4, and z is the side, LS left or RS Right. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

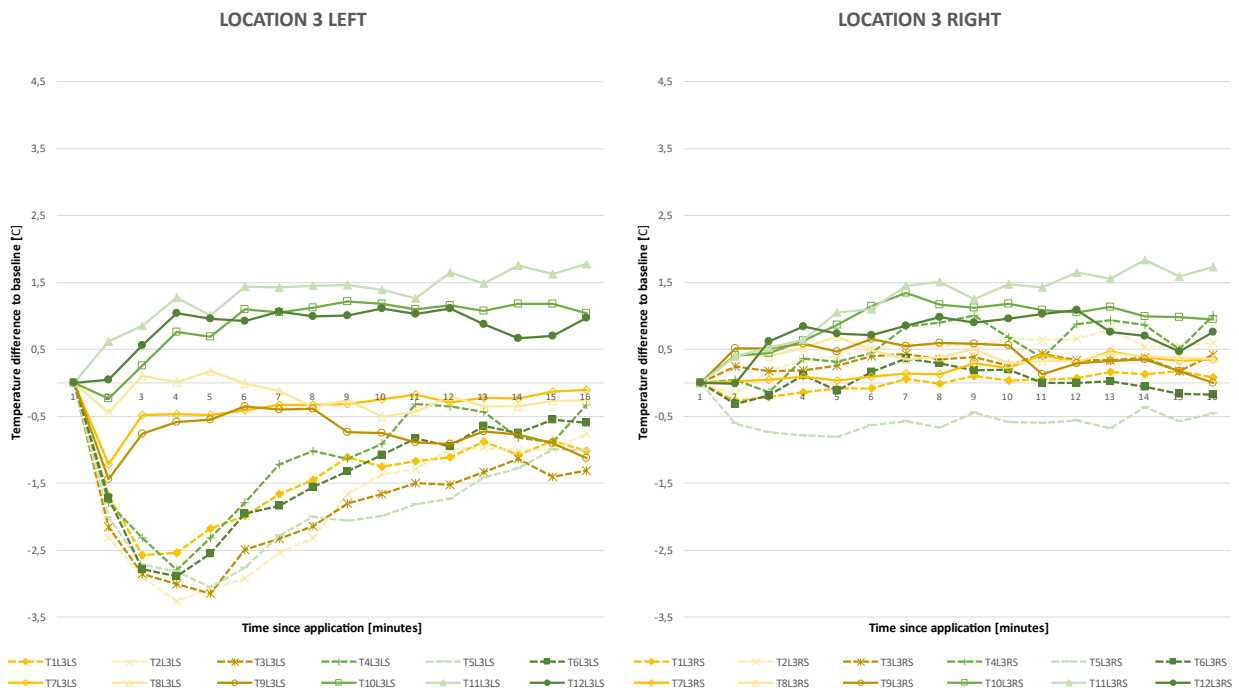


Figure 9: Location 3 Left-Right Difference. Tests 1 to 6 were done with the cooling agent, test 7 to 12 with the heating agent. Each line is an averaged test run with the following naming convention: TxLyZ where x is the number of the test, 1-12, y is the

location, 1-4, and z is the side, LS left or RS Right. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

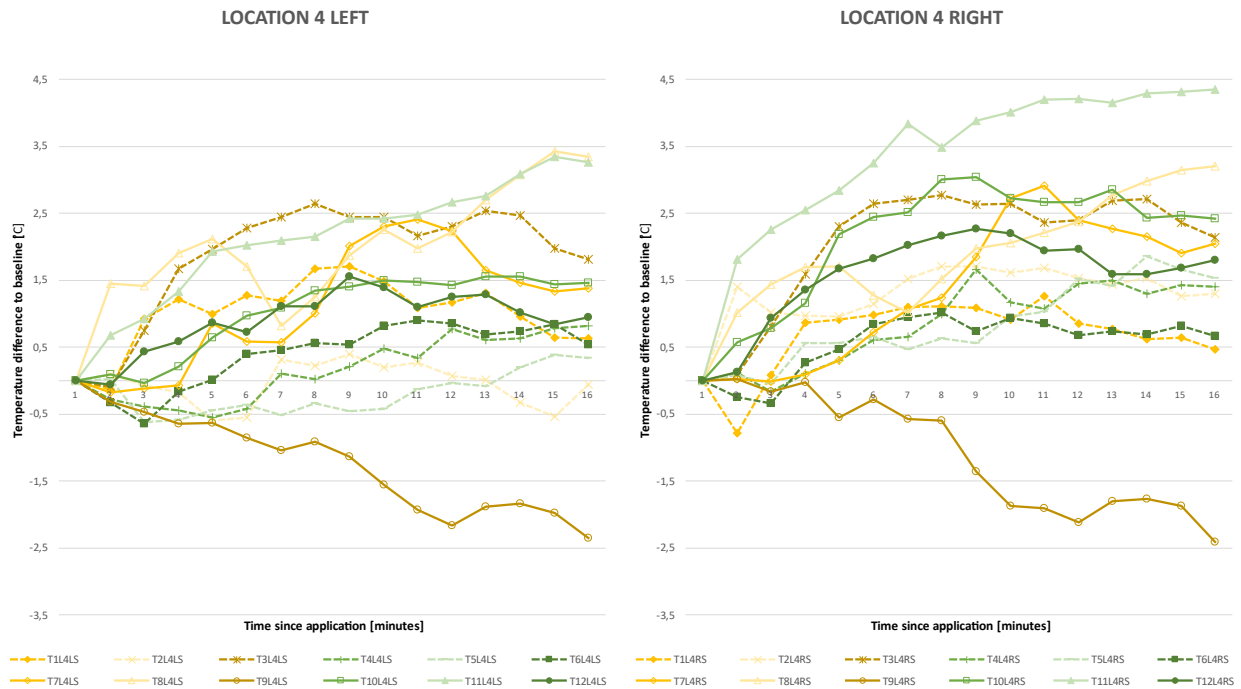


Figure 10: Location 4 Left- Right Difference. Tests 1 to 6 were done with the cooling agent, test 7 to 12 with the heating agent. Each line is an averaged test run with the following naming convention: TxLyz where x is the number of the test, 1-12, y is the location, 1-4, and z is the side, LS left or RS Right. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

5.2.3 Dorsal – Palmar side of hand difference

To examine the difference between the palmar and the dorsal side of the hand, their respective graphs have been placed next to each other. Below the palm and back graphs for the left hand those of the right hand can be found. This allows for both the examination of the difference between the palm and back of the affected hand as well as the unaffected hand.

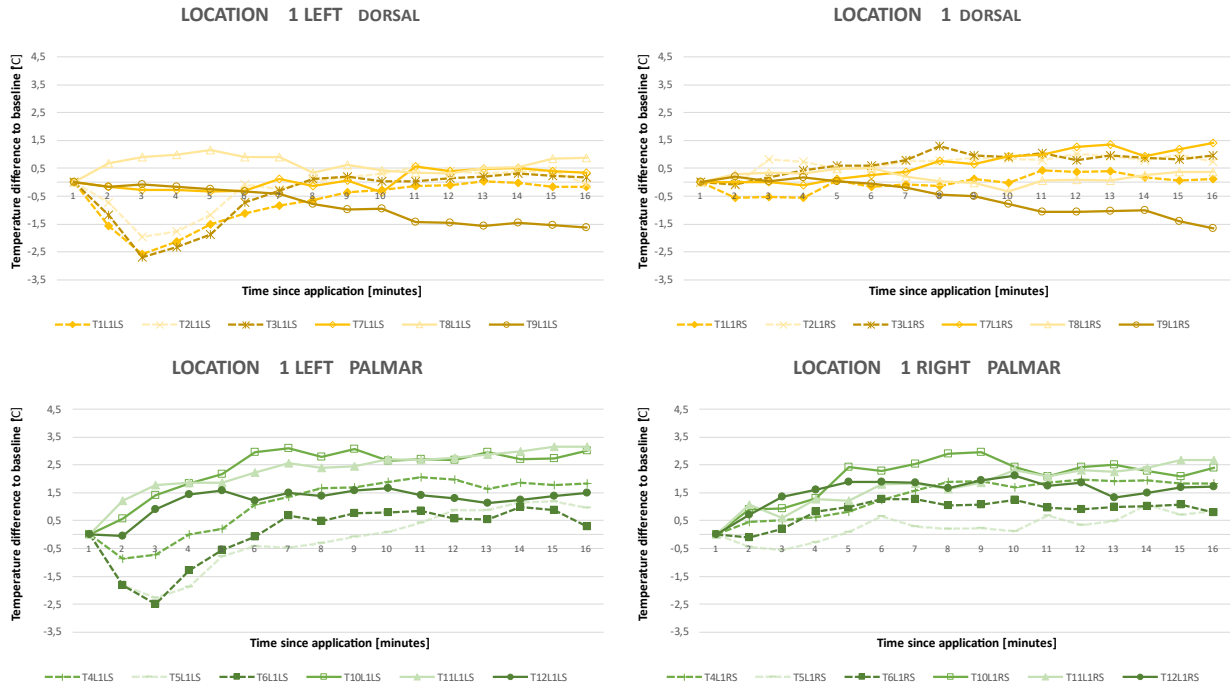


Figure 11: Location 1 Dorsal - Palmar Difference. Tests 1 to 6 were done with the cooling agent, test 7 to 12 with the heating agent. Each line is an averaged test run with the following naming convention: TxLyz where x is the number of the test, 1-12, y is the location, 1-4, and z is the side, LS left or RS Right. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

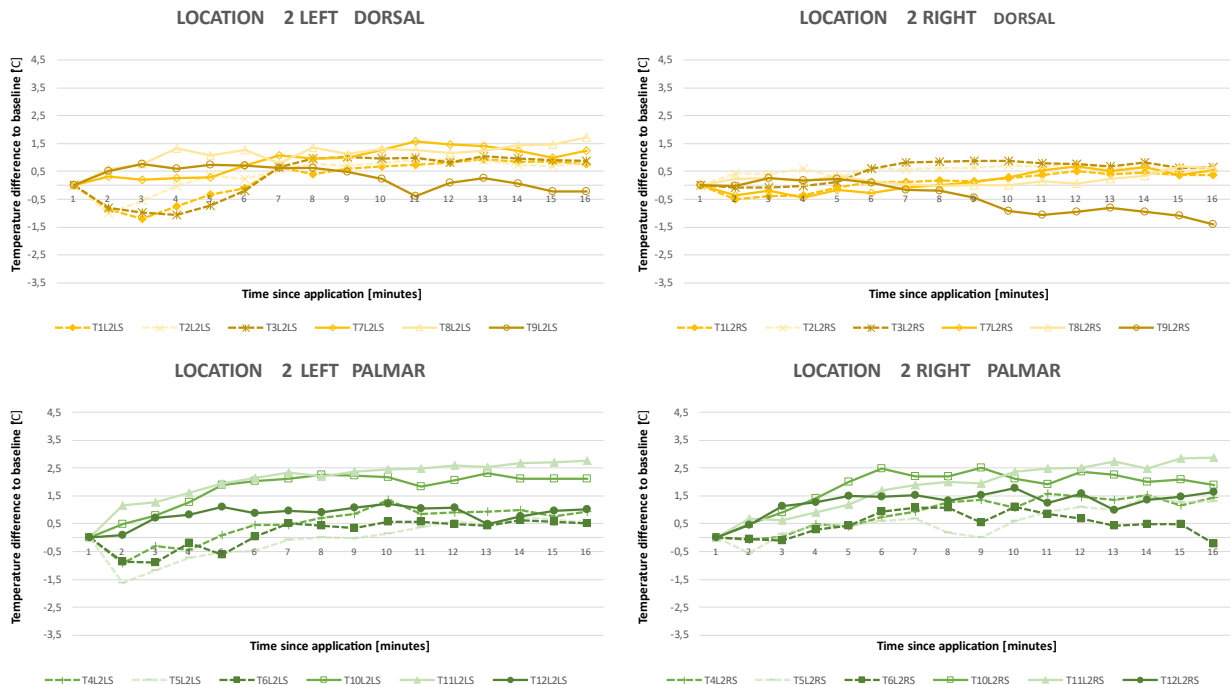


Figure 12: Location 2 Dorsal - Palmar Difference. Tests 1 to 6 were done with the cooling agent, test 7 to 12 with the heating agent. Each line is an averaged test run with the following naming convention: TxLyz where x is the number of the test, 1-12, y is

the location, 1-4, and z is the side, LS left or RS Right. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

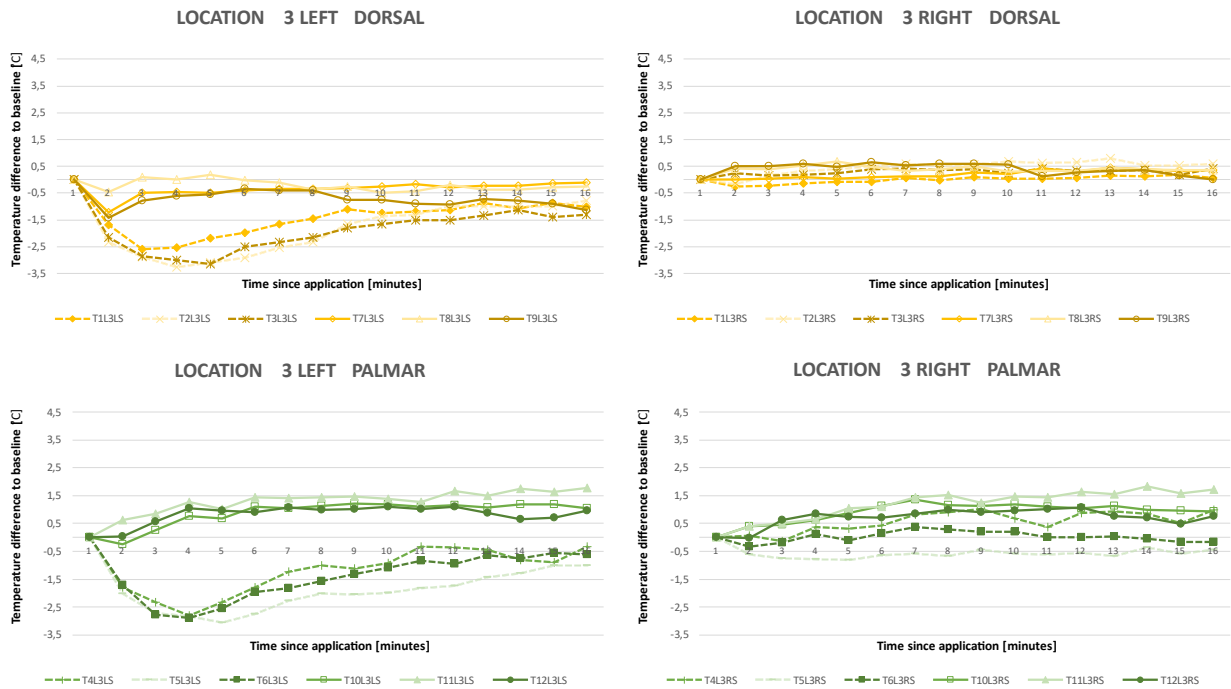


Figure 13: Location 3 Dorsal - Palmar Difference. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the dorsal side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

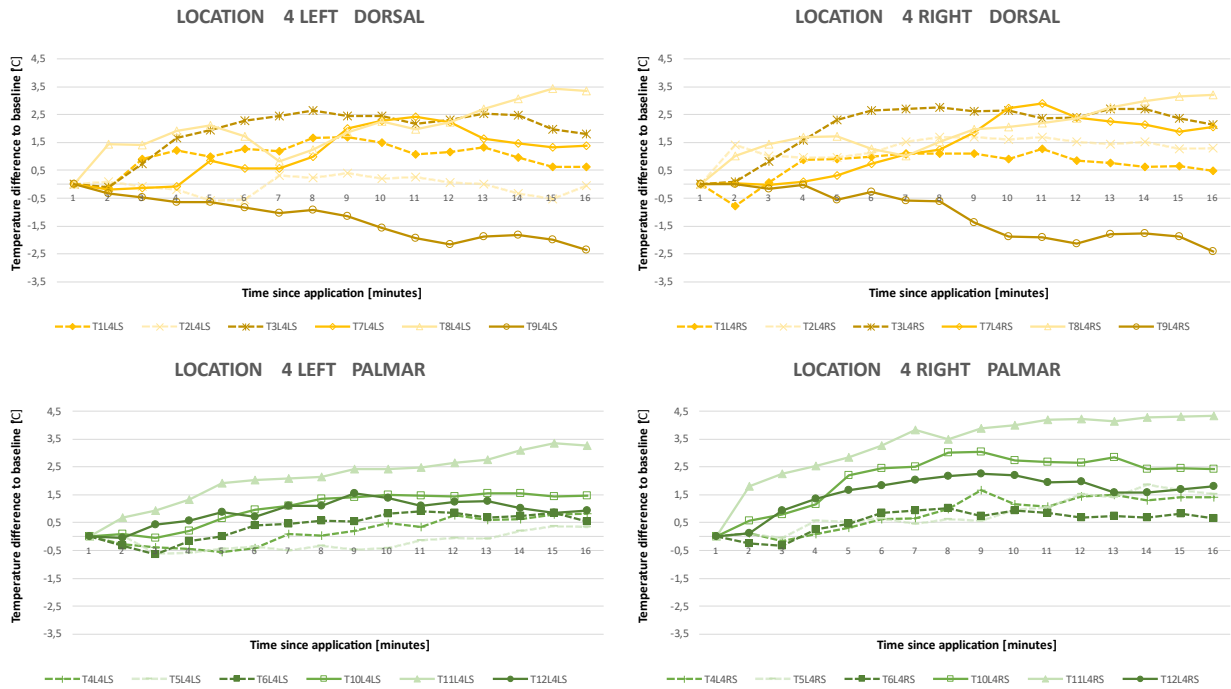


Figure 14: Location 4 Dorsal - Palmar Difference. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the dorsal side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

5.2.4 Cooling Versus Heating

Figures 15 through 18 show the comparison between the cooling and heating. Heating and cooling are compared for both sides at each location. All the graphs show that the cooling agent causes a bigger difference than the heating agent.

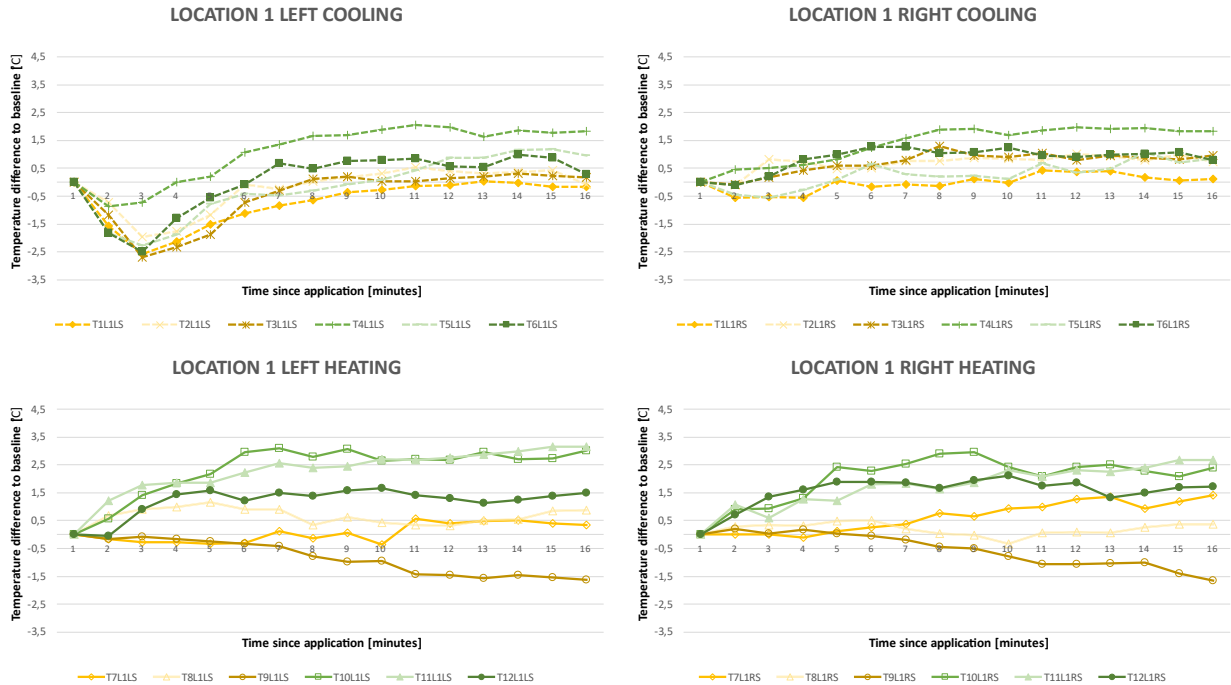


Figure 15: Cooling versus Heating Location 1. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.



Figure 16: Cooling versus Heating Location 2. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the palmar side. The abnormal line T9L2LS belongs to test nine which is unreliable as described earlier.

as described earlier.



Figure 17: Cooling versus Heating Location 3. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the yellow lines the tests where it was applied to the dorsal side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

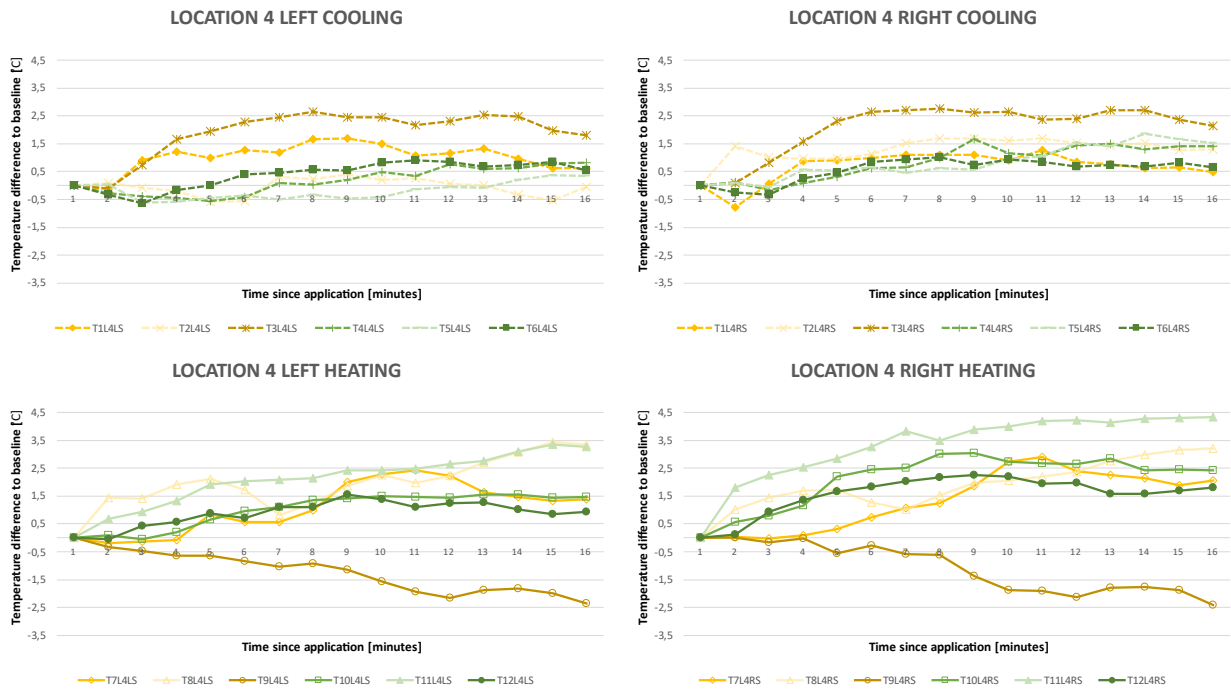


Figure 18: Cooling versus Heating Location 4. The tests with the cooling agent are represented with a dashed line and those for the heating agent with a solid line. The green lines represent tests where the agent was applied to the palmar side and the

yellow lines the tests where it was applied to the palmar side. The abnormal line T9L1LS belongs to test nine which is unreliable as described earlier.

6 DISCUSSION

The previous chapters have shown that it is possible to detect neuropathy while it's affecting the autonomous nervous system. This was shown by first examining the underlying mechanics of the autonomic nervous system and how it is affected by neuropathy. Because the current assessment tools for autonomic damage are expensive and unpractical for use in low-income countries, different options were explored. Ultimately the infrared camera was chosen as the most promising and a single-subject study was performed. In this chapter the results will be compared to those found in the literature, the limitations of the experiment will be discussed, and recommendations for the future will be made.

6.1 RESULTS

6.1.1 Moisture Meter

As discussed in Section 5.1 the moisture meter proved ineffective for the experiment as designed in this thesis. The raw data included in Appendix C contains missing data. At these data points no measurement was possible. This might be caused by the equipment that was used combined with the setup of the test. During the test the applied agents were moisture rich which greatly influences the results from the moisture meter. This does not explain the missing data points.

They can most likely be explained by the used equipment. The moisture meter used was bought at a hardware store and it's intended use was to measure the moisture content of wood. It measures this using 2 spikes that are stabbed into the wood. For practical reasons this was not possible during the tests. This greatly reduces the contact between the points over which the resistance is measured. A possible alternative approach would be to either file down the spikes into a larger surface area or find a different type of moisture or resistance meter to use.

The underlying theory for measuring neuropathy through skin resistance is still sound[50]. For future experiments the setup of the tests will need to be changed to see if a moisture meter can be effectively used in a low income setting.

6.1.2 Infrared Camera

The results from the infrared camera show more promise. Below the results found in the previous chapter will be discussed. This will be done in the same order they were presented in the results chapter.

6.1.2.1 *Left - Right Difference*

A clear difference can be seen between left and right when comparing the first three locations, these are the affected locations with location 4, which was outside of the application area, acting as a control. Of the locations where the agent was applied location 3 showed the most visible reaction, this will be further discussed in 6.1.2.4. The strongest left right difference was visible when the cooling agent was applied.

The left side shows far more reaction than the right side. Especially the cooling agent (Test 1 through 6) show a clear difference with the right side. A second thing to note is that the cooling agent also seems to be normalizing to the starting temperature at the end of the 15 minutes while the heating agent is not yet normalized

Location four shows the most interesting results where right seems to be reacting more than left. However, location four was chosen to be outside of the application area which might go some way to explaining the above data. This will be further discussed in section 6.1.2.4.

6.1.2.2 Dorsal – Palmar side Difference

The results observed above hold for the three locations within the application area, location 3 shows the strongest reaction location 2 the weakest. When comparing the palmar side with the dorsal side a stronger reaction is observed on the palmar side.

Location 4 as seen in the previous results has a wide spread of data. Here it seems that the back of the hand is slightly more impacted, however one must keep in mind that this is the control point so the expected data should be different than those found in the other locations.

6.1.2.3 Cooling – Heating Difference

When comparing the results between the heating and cooling agent it can be observed that the difference between left and right for the cooling agent is more pronounced than that for the heating agent. The heating agent seems to be causing a reaction throughout the body while the effect of the cooling agent seems to be more localized.

A possible explanation for this is that the human body is better at heating up a smaller part of the body than cooling it down. This in general means that a warming effect has a greater influence on the overall body temperature, while the cooling effect can be more easily dealt with locally.

However, two side notes should be made: the first is that the effects of the cooling agent seem to wear out quicker than those of the heating agent and secondly that the dose for the cooling agent is higher than that of the heating agent due to the difference skin absorption. The heating agent saturated the skin more easily than the cooling agent which meant that a lower dosage of the heating agent was used.

6.1.2.4 Location Difference

When looking at the locations it is important to remember why each region was chosen. Figure 5 in the previous chapter shows the location of the 4 points of interest. Location 1 is the point of the nerve that is most often affected by leprosy, Location 2 is a point of high circulation, Location 3 a point of relative low circulation, and Location 4 is chosen just outside the application area. Below a closer look will be taken at the results at each location.

Location 1 shows that the region often affected by leprosy also shows a significant difference between left and right when disrupted. An interesting difference between Location 2 and 3 is that 3 shows the strongest reaction of the 4 locations. Instinctively the greatest reaction would be expected at the point of highest circulation, Location 2, but Location 3 shows the strongest reaction for the cooling agent, and for both the cooling and heating agent it is the most stable location on the right control hand. Location 4 is also interesting and hints at general reaction to the applied agent in the whole body, or at the very least in both hands. The data show chaotic curves at both the left and right side with little to no return to the starting temperature.

In summary, the results from the tests show at least some evidence for there being a measurable difference between the affected, left, and unaffected, right, hand. There is a stronger reaction in the palm of the hand compared to the back of the hand. The cooling agent seems to have a big effect, but there are some caveats attached to its use. An interesting result is that the difference seems to be the

most noticeable in the location with a relatively low circulation. This might indicate that because of the lower density of veins the bodies ability to deal with temperature changes through the autonomic system is worse. This makes sense because with less veins to either supply or disperse heat the time to rectify a thermal imbalance is longer.

The experiment shows that there is a strong suspicion that the cooling cream applied to the palmar allows for measurable differences between the left and right hand. In neuropathy, the skin temperature usually lowers [51]. With more testing it should be possible to reliably measure potential neuropathy using the patient's own skin temperature along the sagittal plane as a reference.

6.2 LIMITATIONS

During this experiment and thesis, several limitations were encountered. The biggest limitation was the lack of access to subjects with known neuropathy. Due to time constraints, it was not possible to go through a medical committee to be able to recruit suitable subjects with known neuropathy instead the choice was made to start a single-subject study. The subject did not have neuropathy so this had to be simulated. The original idea behind the experiment was to simply measure the left right difference in patients suffering from neuropathy. However, the addition of disrupting agents and measuring the recovery of thermal equilibrium makes the experiment more robust even when applied to test subject suffering from neuropathy.

6.3 RECOMMENDATIONS

For future research, the following recommendations are made. These are split into two categories: the first is recommendations for repeating this experiment, and the second is recommendations for future research into detecting possible neuropathy in the autonomous nervous system.

6.3.1 Improving the Experiment

To improve the experiment performed in this thesis the following recommendations are made. During the various runs, the temperature in both hands varied over time. This seems to be an indication that the used waiting time of five minutes for the hands to be at rest might be too short. The recommendation is to increase this time to 10 or 15 minutes to make certain the hands are at rest.

Furthermore, there is a strong suspicion that homeostasis was not yet reached at the end of the 15-minute test period. This might be because the hands were not yet at rest as described above, but to make certain homeostasis is reached it would be beneficial to increase the experiment time by 5 or 10 minutes.

Lastly, the palm-up position, which showed the most promise in the experiment, was experienced as uncomfortable. To improve comfort and prevent interference from involuntary reactions to the feeling of discomfort it would be good to perform the experiment with the hands resting comfortably. Care must be taken however that the armrest does not increase the skin temperature.

With regards to the use of a heating or cooling agent it is prudent to keep in mind the expected reaction in a patient (potentially) suffering from leprosy. Leprosy will interfere with the temperature control done by the peripheral nervous system and will lower the temperature around affected areas. Applying a cooling agent might reduce the area around the affected area to make it seem like the area is not

affected. It might be a good plan to use a heating agent to try and increase the affected area to show the affected areas incapability of increasing in temperature.

6.3.2 Recommendations for future research

For future research, the infrared camera is well suited. To find if the IR camera might be used to detect possible autonomic neuropathy it is important to test on people suffering from neuropathy. A future experiment might be taking pictures of the hands of people with diagnosed neuropathy to compare left and right. If this is combined with a graded severity of their neuropathy, for example by using the nylon monofilament test, a database could be created to detect neuropathy early. This also helps determine the minimum resolution of the infrared camera. An infrared camera with a lower resolution will be less expensive than one with a higher resolution. Which means that if the required resolution is known it will be possible to find the cheapest effective infrared camera.

The next step after this might be to reintroduce the heating and cooling agents to disturb the skin temperature and measure the recuperation ability. The ability to return to homeostasis is an important function of the autonomous nervous system and when one or more limbs show clear deviation from the other limb in the time it takes to return to homeostasis neuropathy might be present.

In future research on diagnosed neuropathy patients, it might be worthwhile to take a second look at the moisture meter as a tool for diagnosing neuropathy. Although the IR camera is the more promising candidate the moisture meter is much cheaper and requires less maintenance. Instead of a moisture meter a different device capable of measuring skin resistance might also be employed. An example of this is the Neurometer which has already been tested on diabetic neuropathy [52].

The mood ring might also be worth a second look. With liquid crystals with a mapped and stable color change it might be possible to create a diagnostic device. If this device can be the size of a mood ring it might be possible to create a self-diagnosis device that does not require a medical professional. This might greatly increase the detection of neuropathy so treatment may start as early as possible.

7 CONCLUSION

The experiment has shown promise for using an infrared camera as a tool to assess possible neuropathy. At the start of the thesis, the following research question was formulated:

“Is it possible to detect asymmetrical neuropathy at an early stage by assessing the autonomic function of the upper extremities using existing (non)medical devices in a low-income country?”

Thermography has been shown to be able to visualize temperature differences between affected and unaffected regions in an experiment where neuropathy was simulated. This shows that an infrared camera might be used in a low income setting to detect neuropathy in an early stage. During the thesis, the various subparts of the main question have been analyzed and answered. It was shown that the main physical properties influenced by the autonomic nervous system are blood pressure, blood flow, skin resistance, and skin temperature. All of these are affected by neuropathy and can be measured in the upper extremities. Currently used devices for the assessment of autonomic neuropathy are generally big and expensive which makes them ill-suited for use in low-income countries. To find a solution to this problem first the constraints of a low-income country were determined followed by an evaluation of possible devices that might function within these constraints.

Three devices were determined to be suitable, a moisture meter, a mood ring, and an infrared camera. During the preliminary tests, it was determined that the mood ring was not suitable. An experiment was designed for the other two devices. The experiment was a single-subject pilot study into the suitability of the infrared camera and moisture meter. The experiment was done on a healthy subject where homeostasis was disrupted. During the experiment, the moisture meter in its current form proved to be unsuitable for the designed experiment. This left only the infrared camera as a possible device. The results of the experiment showed that there is promise in the infrared camera as an assessment tool, but more testing is required.

Future research should be focused on further expanding on the results found in this thesis. There are two main paths forward for this. The first is expanding the pilot study to more subjects and revisit the mood ring and moisture meter. The second is to use the infrared camera as a diagnostic tool to create a database of possible neuropathy under normal circumstances or use it to measure the return to homeostasis after disruption.

The important thing is that there are devices available that can measure possible autonomic neuropathy in low-income settings. This will help eliminate such diseases as leprosy and make certain that even with limited healthcare options neuropathy can be detected at an early stage.

8 BIBLIOGRAPHY

- [1] "Leprosy (Hansen's disease)." WHO. <https://www.who.int/en/news-room/fact-sheets/detail/leprosy> (accessed 5-MAR-23, 2023).
- [2] H. K. Kar and R. Gupta, "Treatment of leprosy," *Clinics in Dermatology*, vol. 33, no. 1, pp. 55-65, 2015/01/01/ 2015, doi: <https://doi.org/10.1016/j.clindermatol.2014.07.007>.
- [3] "Leprosy World Map." https://apps.who.int/neglected_diseases/ntddata/leprosy/leprosy.html (accessed 05-04-23, 2023).
- [4] W. W. Ooi and J. Srinivasan, "Leprosy and the peripheral nervous system: basic and clinical aspects," (in eng), *Muscle Nerve*, vol. 30, no. 4, pp. 393-409, Oct 2004, doi: 10.1002/mus.20113.
- [5] A. Agrawal, L. Pandit, M. Dalal, and J. P. Shetty, "Neurological manifestations of Hansen's disease and their management," (in eng), *Clin Neurol Neurosurg*, vol. 107, no. 6, pp. 445-54, Oct 2005, doi: 10.1016/j.clineuro.2005.03.007.
- [6] R. T. Vital, X. Illarramendi, O. Nascimento, M. A. Hacker, E. N. Sarno, and M. R. Jardim, "Progression of leprosy neuropathy: a case series study," (in eng), *Brain Behav*, vol. 2, no. 3, pp. 249-55, May 2012, doi: 10.1002/brb3.40.
- [7] E. L. Feldman and M. J. Stevens, "Clinical Testing in Diabetic Peripheral Neuropathy," *Canadian Journal of Neurological Sciences*, vol. 21, no. S4, pp. S3-S7, 1994, doi: 10.1017/S0317167100040671.
- [8] N. Ishii, "Recent advances in the treatment of leprosy," (in eng), *Dermatol Online J*, vol. 9, no. 2, p. 5, Mar 2003.
- [9] S. Araujo, L. O. Freitas, L. R. Goulart, and I. M. Goulart, "Molecular Evidence for the Aerial Route of Infection of Mycobacterium leprae and the Role of Asymptomatic Carriers in the Persistence of Leprosy," (in eng), *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, vol. 63, no. 11, pp. 1412-1420, Dec 1 2016, doi: 10.1093/cid/ciw570.
- [10] L. C. Rodrigues and D. N. J. Lockwood, "Leprosy now: epidemiology, progress, challenges, and research gaps," *The Lancet Infectious Diseases*, vol. 11, no. 6, pp. 464-470, 2011/06/01/ 2011, doi: [https://doi.org/10.1016/S1473-3099\(11\)70006-8](https://doi.org/10.1016/S1473-3099(11)70006-8).
- [11] D. N. Lockwood and P. R. Saunderson, "Nerve damage in leprosy: a continuing challenge to scientists, clinicians and service providers," (in eng), *Int Health*, vol. 4, no. 2, pp. 77-85, Jun 2012, doi: 10.1016/j.inhe.2011.09.006.
- [12] X. Chen, S. Zha, and T.-J. Shui, "Presenting symptoms of leprosy at diagnosis: Clinical evidence from a cross-sectional, population-based study," *PLOS Neglected Tropical Diseases*, vol. 15, no. 11, p. e0009913, 2021, doi: 10.1371/journal.pntd.0009913.
- [13] C. White and C. Franco-Paredes, "Leprosy in the 21st Century," *Clinical Microbiology Reviews*, vol. 28, no. 1, pp. 80-94, 2015/01/01 2015, doi: 10.1128/CMR.00079-13.
- [14] W. W. Ooi, J. J. M. Srinivasan, and nerve, "Leprosy and the peripheral nervous system: basic and clinical aspects," vol. 30, no. 4, pp. 393-409, 2004.
- [15] A. Aggarwal and A. J. I. J. o. M. R. Pandey, "Inverse sampling to study disease burden of leprosy," vol. 132, no. 4, pp. 438-441, 2010.
- [16] K. Eichelmann, S. E. González González, J. C. Salas-Alanis, and J. Ocampo-Candiani, "Leprosy. An Update: Definition, Pathogenesis, Classification, Diagnosis, and Treatment," *Actas Dermo-Sifiliográficas (English Edition)*, vol. 104, no. 7, pp. 554-563, 2013/09/01/ 2013, doi: <https://doi.org/10.1016/j.adengl.2012.03.028>.
- [17] M. R. Jardim *et al.*, "Criteria for diagnosis of pureneural leprosy," *Journal of Neurology*, vol. 250, no. 7, pp. 806-809, 2003/07/01 2003, doi: 10.1007/s00415-003-1081-5.

- [18] R. H. Gelber and J. Grosset, "The chemotherapy of leprosy: an interpretive history," (in eng), *Leprosy review*, vol. 83, no. 3, pp. 221-40, Sep 2012.
- [19] A. Graham, S. Furlong, L. M. Margoles, K. Owusu, and C. Franco-Paredes, "Clinical Management of Leprosy Reactions," *Infectious Diseases in Clinical Practice*, vol. 18, no. 4, 2010. [Online]. Available: https://journals.lww.com/infectedis/Fulltext/2010/07000/Clinical_Management_of_Leprosy_Reactions.4.aspx.
- [20] L. K. J. A. j. o. p. e. McCorry, "Physiology of the autonomic nervous system," vol. 71, no. 4, 2007.
- [21] J. A. Waxenbaum, V. Reddy, and M. Varacallo, "Anatomy, autonomic nervous system," 2019.
- [22] C. Pisciotta and M. E. J. H. o. c. n. Shy, "Neuropathy," vol. 148, pp. 653-665, 2018.
- [23] J. Hubbard, *The peripheral nervous system*. Springer Science & Business Media, 2012.
- [24] K. Wilke, A. Martin, L. Terstegen, and S. S. Biel, "A short history of sweat gland biology," vol. 29, no. 3, pp. 169-179, 2007, doi: <https://doi.org/10.1111/j.1467-2494.2007.00387.x>.
- [25] S. Singaram, K. Ramakrishnan, J. Selvam, M. Senthil, and V. Narayanamurthy, "Sweat gland morphology and physiology in diabetes, neuropathy, and nephropathy: a review," *Archives of Physiology and Biochemistry*, pp. 1-15, 2022, doi: 10.1080/13813455.2022.2114499.
- [26] D.-E. Van Der Merwe, J. B. Ubbink, R. Delport, P. Becker, G. S. Dhatt, and W. H. J. A. o. c. b. Vermaak, "Biological variation in sweat sodium chloride conductivity," vol. 39, no. 1, pp. 39-43, 2002.
- [27] E. P. V. Wilder-Smith, "Water immersion wrinkling," *Clinical Autonomic Research*, vol. 14, no. 2, pp. 125-131, 2004/04/01 2004, doi: 10.1007/s10286-004-0172-4.
- [28] N. Charkoudian, "Skin Blood Flow in Adult Human Thermoregulation: How It Works, When It Does Not, and Why," *Mayo Clinic Proceedings*, vol. 78, no. 5, pp. 603-612, 2003/05/01/ 2003, doi: <https://doi.org/10.4065/78.5.603>.
- [29] E. A. Wehrwein and M. J. Joyner, "Chapter 8 - Regulation of blood pressure by the arterial baroreflex and autonomic nervous system," in *Handbook of Clinical Neurology*, vol. 117, R. M. Buijs and D. F. Swaab Eds.: Elsevier, 2013, pp. 89-102.
- [30] M. J. Joyner, N. Charkoudian, and B. G. Wallin, "A sympathetic view of the sympathetic nervous system and human blood pressure regulation," vol. 93, no. 6, pp. 715-724, 2008, doi: <https://doi.org/10.1113/expphysiol.2007.039545>.
- [31] C. H. J. H. o. c. n. Gibbons, "Basics of autonomic nervous system function," vol. 160, pp. 407-418, 2019.
- [32] J. M. Johnson and D. L. J. F. B. Kellogg Jr, "Thermoregulatory and thermal control in the human cutaneous circulation," vol. 2, no. 3, pp. 825-853, 2010.
- [33] S. Arora *et al.*, "Differences in foot and forearm skin microcirculation in diabetic patients with and without neuropathy," vol. 21, no. 8, pp. 1339-1344, 1998.
- [34] R. Freeman, "Autonomic peripheral neuropathy," *The Lancet*, vol. 365, no. 9466, pp. 1259-1270, 2005/04/02/ 2005, doi: [https://doi.org/10.1016/S0140-6736\(05\)74815-7](https://doi.org/10.1016/S0140-6736(05)74815-7).
- [35] V. Bril, A. Breiner, B. A. Perkins, and D. Zochodne, "Neuropathy," *Canadian Journal of Diabetes*, vol. 42, pp. S217-S221, 2018/04/01/ 2018, doi: <https://doi.org/10.1016/j.cjcd.2017.10.028>.
- [36] E. Casey, "Natural History of Radiculopathy," *Physical Medicine and Rehabilitation Clinics of North America*, vol. 22, no. 1, pp. 1-5, 2011/02/01/ 2011, doi: <https://doi.org/10.1016/j.pmr.2010.10.001>.
- [37] V. P. Shetty, N. H. Antia, and J. M. Jacobs, "The pathology of early leprosy neuropathy," *Journal of the Neurological Sciences*, vol. 88, no. 1, pp. 115-131, 1988/12/01/ 1988, doi: [https://doi.org/10.1016/0022-510X\(88\)90210-9](https://doi.org/10.1016/0022-510X(88)90210-9).
- [38] J. G. McLeod and R. R. Tuck, "Disorders of the autonomic nervous system: Part 1. Pathophysiology and clinical features," *Annals of Neurology*,

- <https://doi.org/10.1002/ana.410210502> vol. 21, no. 5, pp. 419-430, 1987/05/01 1987, doi: <https://doi.org/10.1002/ana.410210502>.
- [39] U. K. Misra, J. Kalita, and P. P. Nair, "Diagnostic approach to peripheral neuropathy," *Annals of Indian Academy of Neurology*, vol. 11, no. 2, 2008. [Online]. Available: https://journals.lww.com/annalsofian/Fulltext/2008/11020/Diagnostic_approach_to_peripheral_neuropathy.4.aspx.
- [40] A. E. Harding and P. K. Thomas, "The clinical features of hereditary motor and sensory neuropathy types I and II," (in eng), *Brain*, vol. 103, no. 2, pp. 259-280, 1980/06// 1980, doi: 10.1093/brain/103.2.259.
- [41] I. N. J. O. IJ and I. ROSY, "Pathology and pathogenesis of leprous neuritis; a preventable and treatable complication," 2001.
- [42] S. V. Khadilkar, R. S. Yadav, and G. J. P. n. Soni, "A practical approach to enlargement of nerves, plexuses and roots," vol. 15, no. 2, pp. 105-115, 2015.
- [43] "Federal TRIO Programs
Current-Year Low-Income Levels."
<https://www2.ed.gov/about/offices/list/ope/trio/incomelevels.html#:~:text=The%20term%20%22low%2Dincome%20individual,of%20the%20poverty%20level%20amount>. (accessed 23-4, 2023).
- [44] "World Bank Country and Lending Groups."
<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups> (accessed).
- [45] R. Vardasca, E. Ring, P. Plassmann, and C. D. J. T. i. Jones, "Thermal symmetry of the upper and lower extremities in healthy subjects," vol. 22, no. 2, pp. 53-60, 2012.
- [46] B. B. Lahiri, S. Bagavathiappan, T. Jayakumar, and J. Philip, "Medical applications of infrared thermography: A review," *Infrared Physics & Technology*, vol. 55, no. 4, pp. 221-235, 2012/07/01/ 2012, doi: <https://doi.org/10.1016/j.infrared.2012.03.007>.
- [47] N. Jasti *et al.*, "Medical Applications of Infrared Thermography: A Narrative Review," *Journal of Stem Cells*, vol. 14, no. 1, 2019.
- [48] A. L. Cavalheiro, D. T. Costa, A. L. Menezes, J. M. Pereira, and E. M. Carvalho, "Thermographic analysis and autonomic response in the hands of patients with leprosy," (in eng), *An Bras Dermatol*, vol. 91, no. 3, pp. 274-83, May-Jun 2016, doi: 10.1590/abd1806-4841.20164612.
- [49] C. Celia, C. Yen, K. Jessica, and L. Jennifer, "Lord of the Mood Rings," 2003.
- [50] A. J. M. Boulton *et al.*, "Dynamic Foot Pressure and Other Studies as Diagnostic and Management Aids in Diabetic Neuropathy," *Diabetes Care*, vol. 6, no. 1, pp. 26-33, 1983, doi: 10.2337/diacare.6.1.26.
- [51] A. L. Cavalheiro, D. T. d. Costa, A. L. F. d. Menezes, J. M. Pereira, and E. M. d. J. A. B. d. D. Carvalho, "Thermographic analysis and autonomic response in the hands of patients with leprosy," vol. 91, pp. 274-283, 2016.
- [52] E. A. Masson, A. Veves, D. Fernando, and A. J. M. Boulton, "Current perception thresholds: a new, quick, and reproducible method for the assessment of peripheral neuropathy in diabetes mellitus," *Diabetologia*, vol. 32, no. 10, pp. 724-728, 1989/10/01 1989, doi: 10.1007/BF00274531.

Leprosy and neuropathy; a literature review

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Abstract—Leprosy can lead to neuropathy. This neuropathy and other neuropathies are a problem across the world and especially in low-income countries. Without regular checkups, it is important to diagnose neuropathy as quickly as possible. Autonomic function assessment can detect possible neuropathy before sensory assessment. To do this a query was used based on a search strategy by the TUDelft library. This literature review first examines leprosy and how it affects the autonomic innervation of the body. Then existing and possibly new ways of assessing autonomous function are discussed and what physical properties might be a good indication of neuropathy. The most useful property is temperature. This can be accurately measured and easily interpreted.

Index Terms—Neuropathy, Leprosy, Autonomic Innervation, Thermal Scanners, Low Income Countries

I. INTRODUCTION

Leprosy is an ancient disease that now is largely considered gone in western countries. However, it is still prevalent in several countries across the globe. The World Health Organization (WHO) reported 202.256 new cases of leprosy last year [1]. Leprosy is most prevalent in Southern America, Africa, and Southeast Asia.

Leprosy is prevalent in lower-income countries where healthcare is less accessible. This complicates the detection, treatment, and eradication of leprosy. To add to this problem a form of leprosy exists that has little to no visible symptoms that affect the nerves and is difficult to detect without expensive, or specialized equipment [2].

In low-income countries, medical resources are not easily accessible. This means that patients with potential neuropathy see medical professionals irregularly. This leads to neuropathies going unnoticed until irreversible damage is done. Therefore, it is important to detect neuropathy as early as possible. A good way to do this is by assessing autonomic function which is damaged before sensory function. This helps prevent permanent disfigurement because of losing sensory function.

Currently, methods used to detect possible neuropathy are impractical for use in low-income countries. It might therefore be useful to explore new ways of assessing autonomic function. This review aims to find a novel way to assess autonomic neuropathy because of leprosy and similar disease. To do this first leprosy is examined, what it is, how it affects the body, and how it is currently diagnosed. After this, a closer look at the autonomous nervous system is taken with a focus on the sympathetic nervous system. Then the currently used

methods of assessing autonomic function are explored and physical properties that might offer novel ways of assessing autonomic function are examined. Then a Harris profile is made to determine which of these properties is most useful to further explore. Lastly, recommendations are made for future research.

II. METHOD

For this literature review, the searching resources guide from the TUDelft library was used [3]. This guide helps build a search query from your main question and subsequently assess the found results. To expand on the found resources snowballing was used to find additional relevant papers and information.

A. Search Query

Two search queries were used. One to explore leprosy and its relation to the assessment of autonomic function, and one to explore the assessment of neuropathies in a more general application. To create the search query first core concepts and their synonyms were gathered these were then combined to form the search query. The first query looked as follows:

TABLE I
CONCEPTS AND SYNONYMS SEARCH QUERY 1

Leprosy	Autonomic Innervation	Measurement
Hansen's Disease	Autonomic Nervous System	Determination
Han* Disease	ANS	Scale
Lepro*	Innervation	Measur* device
		Assessment

TABLE II
SEARCH QUERY 1

Search Query 1.1	"leprosy" OR "Hansen's Disease" OR "Han* Disease" OR "Lepro*"
Search Query 1.2	"autonomic innervation" OR "Autonomic nervous system" OR "innervation" OR "neuropathy"
Search Query 1.3	"measurement" OR "scale" OR "determination" OR "measur* device" OR "assessment" OR "Diagnosis"
Search Query 1.4	[Search query 1.1] AND [Search query 1.2] AND [Search query 1.3]

The core concept and its synonyms were combined into sub-search queries with an OR condition and then combined into the final search query by an AND condition. Table II shows

what the final search query consisted of. This search query was then entered into PubMed giving 311 hits.

For the second search query table III was used to find the concepts and synonyms. For this query, the focus was shifted from leprosy to neuropathy and how they affect the limbs.

TABLE III
CONCEPTS AND SYNONYMS SEARCH QUERY 2

Neuropathy	Autonomic Innervation	Measurement	Limb*
Neuro*	Autonomic Nervous System	Determination	Extremities
Neurological Disorder	ANS	Scale	Hand
	Innervation	Measur* device	Foot
		Assessment	

These concepts and synonyms were then combined into a search query similar to the way it was done for the first search query. This query was entered into PubMed and led to 2250 results.

TABLE IV
SEARCH QUERY 2

Search Query 2.1	"Neuropathy" OR Neuro** OR "neurological disorder"
Search Query 2.2	"autonomic innervation" OR "innervation" OR "Autonomic nervous system"
Search Query 2.3	"measurement" OR "scale" OR "determination" OR "measur* device" OR "assessment"
Search Query 2.4	"limb**" OR "extremities" OR "hand" OR "foot"
Search Query 2.5	[Search query 2.1] AND [Search query 2.2] AND [Search query 2.3] AND [Search query 2.4]

B. Paper selection

In total the search queries have resulted in about 2500 papers. Of course, not all of these will be useful. To find the most relevant papers a selection was made. To do this more easily the papers were uploaded to Rayyan an online platform that allows for easy selection of what to include and what to exclude.

The first selection was done based on title, the papers remaining after this were then further reduced by assessing the abstract of the papers. Papers were selected as appropriate for the first search query if they discussed the assessment of leprosy. Reasons for exclusion were single-patient studies, cohorts, and other studies that did not go into how to assess neuropathy as a result of leprosy.

The second search query had a high amount of results. This search was purposefully vague. The goal of this second search query was to find different assessment methods used with neuropathies that preferably test the autonomic nervous system. These types of assessment methods are rare and by casting a wide net many of these relatively rare methods would be unearthed. The selection process for the papers was the same as for the first search query with a particular focus on finding devices that assess neuropathy.

C. Snowballing

Because no search query is perfect snowballing was used to broaden the scope of papers considered. Snowballing is the process of finding new information from papers mentioned in papers included in the search query. This provides better background on included papers and allows for new avenues of information.

III. LEPROSY

Leprosy has been around for thousands of years. Currently in the western world leprosy is mostly found in idioms and stories however in Africa, South America, and southeast Asia leprosy is still a problem [4]. This chapter will explore the epidemiology of leprosy followed by its pathology, including its classification system. After this, the neuropathy caused by leprosy is examined. Lastly, the cardinal signs of neuropathy and the current assessment of leprosy are discussed.

A. Epidemiology

According to the latest information from the WHO leprosy had 202,256 new cases in 2019 [1]. Leprosy is caused by *M leprae* and has a long incubation period, somewhere between 3 and 10 years [5]. *M leprae* is only found in humans, Nine-Banded armadillo, and three species of primates [6]. The mode of transmission is poorly understood although the suspected mode of transfer is through nasal droplets [7]. There is however also an indication that it might be transferred through environmental means such as soil or food [8].

B. Pathology

Leprosy is primarily seen as a dermatological condition [9]. It starts cutaneous and prefers the colder regions of the body limiting itself mostly to the extremities [10].

Two classifications systems exist, one scientific and one practical. The Ridley-Jopling classification is the classical more scientific classification that provides insight into the pathology and disease severity [11]. The second classification is that of the WHO. This is a more practical classification that is used in the field to determine the appropriate treatment according to the WHO [12].

1) *Clinical classification:* Ridley and Jopling created a thorough classification that considers the cell-mediated immunity (CMI) of the patient [13]. There are 5 types of leprosy according to this classification:

- 1) Tuberculoid (TT)
- 2) Borderline Tuberculoid (BT)
- 3) Mid Borderline (BB)
- 4) Borderline Lepromatous (BL)
- 5) Lepromatous (LL)

BB is unstable and therefore very rare. Clinical, histopathological, and immunological criteria determine the type of leprosy the patient has. On the tuberculoid side of the classification, patients have a strong antibody production against leprosy. On the lepromatous side, patients are anergic to *M leprae* and antibody production is low [14]. This classification

system is useful for determining which type of leprosy a patient may develop. Which in turn will determine the possibility of nerve function impairment.

2) *WHO classification*: Its main use is determining what type of treatment the patient requires. The classification knows two types: Paucibacillary Leprosy (PB) and Multibacillary leprosy (MB). The classification is based on the number of lesions and the number of nerves that are affected. A patient has PB when he suffers from 1 to 5 lesions and only 1 nerve is involved. A patient has MB if more than 5 symmetrical lesions and 2 or more nerves are involved [15].

There is also a form of leprosy that doesn't fit into the above classification systems. This is pure neuritic leprosy (PNL) which only affects nerves and has no skin lesions [2].

C. Cardinal signs of leprosy

Three cardinal signs are mainly used to diagnose leprosy. These are anesthetic skin lesions, enlarged peripheral nerves, and acid-fast bacilli [10].

Of these, the nerve thickening is indicative of possible neuropathy. The nerves commonly involved with leprosy are the following: the great auricular nerve (which runs from the bottom of the ear to the clavicle), the ulnar nerve (which runs from the shoulder to the hand on the inside of the arm), this nerve thickens usually above the elbow or below the dorsal cutaneous branches at the wrist, median and superficial radial nerves, the lateral popliteal, superficial peroneal, posterior tibial, and sural nerves [16] [17]. This thickening is often visible and/or palpable.

D. Current Assessment

Leprosy is currently assessed by checking the cardinal signs described above. If one or more of the cardinal signs is present leprosy might be present [18]. For each cardinal sign, tests exist to assess these.

For anesthetic skin lesions, the monofilament test is generally used. In this test filaments of various thicknesses are touched to the patient's skin and the patient is asked to pinpoint the location [18]. If the patient cannot pinpoint the location anesthetic skin lesions might be present. Another assessment method tests the temperature sense of the patient. Although this test is still being developed initial tests are hopeful [19].

To assess enlarged peripheral nerves a few tests are possible. The easiest is a visual and/or sensory test. Some enlarged nerves can be easily seen or felt. The nerves may also be tested with nerve conduction studies that show possible neuropathy [20]. Ultrasound imaging is also used to find enlarged nerves. Magnetic resonant imaging is, when available, a good option to image inflamed nerves [21].

To find acid-fast bacilli a Fite-Faraco staining in skin smears or skin biopsies should be done [10]. These should be done on the most active lesions or the lesions that have been there the longest. Another option would be a PCR test to find *M leprae* bacilli.

Of the test described above the monofilament test and skin smears are currently the main tools of assessment in countries in which leprosy is endemic [4].

IV. AUTONOMOUS NERVOUS SYSTEM

The autonomous nervous system (ANS) is responsible for involuntary functions of the body. The autonomous nervous system consists of the sympathetic, parasympathetic, and enteric nervous system. For the assessment of possible neuropathy, the sympathetic nervous system (SNS) is the most relevant to examine.

The SNS is responsible for the body's "flight or fight" response and is also activated by exercise [22]. The SNS affects the vasoconstriction and temperature regulation of the body [23]. Because leprosy mainly affects the extremities only the SNS of the extremities will be examined. The two main parts of SNS, vasoconstriction and temperature regulation, will be further examined below.

A. Vasoconstriction

The SNS controls vasoconstriction to maintain blood pressure under various circumstances. This process mainly involves the skeletal muscles [24]. Little research has been done regarding blood pressure in leprosy patients. A study from 1978 found some correlation between cardiovascular problems and leprosy [25]. However, the size of the study fails to provide definitive proof for causation. The problem might lie in the fact that leprosy affects too small a region around the affected nerve leading to difficulty to detect changes in blood pressure. It might still be possible to assess the constriction of the blood vessels which seems to be true for patients suffering nerve damage in their fingers [26]. A different result of vasoconstriction is skin wrinkling. Skin wrinkling occurs between 5-30 minutes of immersion in water or application of vasoconstrictor cream such as EMLA to the hand palm or foot sole [27]. Here vasoconstriction causes the digital pulp to lose pulp volume leading to wrinkling of the skin [28].

B. Temperature regulation

The body temperature is preferably constant within a small margin [29]. The SNS helps the body to maintain this preferred temperature. It does this through a combination of vasodilation, vasoconstriction, and sweating. Vasodilation and sweating are combined to reduce temperature while vasoconstriction allows the body temperature to rise [30]. Neuropathy can inhibit the mechanisms of the SNS making it more difficult to maintain and restore body temperature [31].

V. ASSESSMENT

Most tools that assess autonomic function are impractical in a low-income country setting. However, by examining the existing tools important physical properties associated with autonomic function can be found. In the second part of this section, these physical properties and their relation to autonomic function will be further examined.

A. Existing diagnostic tools

Currently, the following methods are used in assessing nerve damage. These methods test the autonomic function or at least partially the autonomic function.

1) *Electrographic*: The most commonly used electrographic test used for neuropathies is the sympathetic skin response (SSR) test [32]. These tests work by sending a stimulating current through a peripheral nerve and then measuring the response from the corresponding polysynaptic reflex arch. The amount of stimulation copied is an indication of how well the autonomic function works. This technique only requires a simple electrode to trigger and measure the response. The SSR test however does require a stable room temperature, usually about 26°, where the subject must be 15-20 minutes before the test [32].

Another method is sympathetic microneurography. In this method, a tungsten microelectrode is inserted percutaneously into a peripheral nerve to directly measure the current passing through it [33]. However, this method is time-consuming and difficult making its diagnostic application unpractical [34].

2) *Temperature*: To assess the thermoregulation of someone suspected of neuropathy a thermoregulatory sweat test (TST) may be performed [35]. This test is performed under controlled circumstances in a sauna-like room with a specific temperature and humidity [36]. A special powder is applied to the part of the body being tested that reacts to sweating [37]. A lack of color indicates an inability to sweat and possible neuropathy.

3) *Skin wrinkling*: Another test used to test the SNS is the skin wrinkling test [38] [39]. The test can be performed on the hand palm or the foot sole. The hand palm is the preferred site of the test because it makes for easier grading. First, the hand is either soaked for 5-30 minutes in water, or a vasoconstrictor cream is applied. After this, the wrinkling is graded from 1 to 4 depending on how much wrinkling has occurred [28]. Before testing a reference photo is often made of the hand palm to assist in the grading. A downside to this test is that the grading is subjective making difficult to monitor small changes.

B. Physical properties

To find novel diagnostic tools it is useful to look at the measurable qualities influenced by neuropathy. If the expected physical reaction can be measured, deviation and possible neuropathy can be quantified. Possible ways of measuring these properties are suggested.

Blood Pressure: Although the kidneys are the main determinant of blood pressure, the SNS still contributes and is largely responsible for short-term blood pressure control [40]. A change in vasoconstriction will change blood pressure. Certain movements and exercises have an expected change in blood pressure. This can be measured to assess possible neuropathy. It is important to note that blood pressure should be measured as close as possible to the suspected site of neuropathy.

Skin Wrinkling: As discussed earlier skin wrinkling is controlled by the SNS [28]. It might be possible to redesign the skin wrinkling test to be less subjective. A possible solution would be to compare initial surface area to wrinkled surface area and express this as a percentage. To do this either AI can be employed to compare before and after pictures or it might be possible to use fingerprinting techniques to create before

and after prints. If these prints are made on grid paper it should be possible to determine the wrinkling as a percentage giving a more objective result.

Temperature: Neuropathy can disturb temperature regulation. This means that the temperature of the area around possible neuropathy is divergent from its normal temperature. This exhibits itself in two ways, the temperature is lower than it should be, and two the area is slow to regain its former equilibrium if that equilibrium is disturbed [41].

These two effects can be measured using something like a thermal scanner. A full body map could be made to monitor the patient and detect abnormal temperatures. A more focused thermal scanner, such as those used during the Covid pandemic to monitor for fever, could be used to analyze the area of suspected neuropathy after that area is cooled or warmed to determine how quickly equilibrium can be restored.

Sweating: Sweating is part of the temperature regulation process. Sweat glands are inhibited by neuropathy. The currently used thermoregulatory sweat test requires the patient to be exposed to a specific temperature and humidity for a set amount of time [36]. The test is also an all-or-nothing test. The powder will still color the skin even with relatively little sweat. A test on a scale would allow for monitoring of the patient's sweat response over longer periods. This might help monitor possible neuropathy.

A possible way to measure sweating on a scale is by measuring skin conductance. More sweat equals less electrical resistance and more conductance. A moisture meter might offer a low-cost way of measuring this resistance. A moisture meter is normally used to measure the electrical resistance in wood to determine how dry it is. It uses two prongs and measures the resistance between these two prongs. Likely, this would also work to measure skin resistance and thus conductance. However, skin conductance is difficult to quantify [42] and this new test would need extensive use to build up a database of expected and divergent conductance.

Blood flow: Aside from blood pressure vasoconstriction will also change the flow at which blood moves through veins and arteries. Blood in a dilated vein or artery will travel at a slower pace, conversely, blood will travel faster in a constricted vein. This characteristic is closely related to blood pressure but is distinct enough to warrant a different type of assessment.

A widely used way of measuring blood flow is photoplethysmogram. This method is used in pulse oximetry to measure oxygen saturation of the red blood cells using a light-emitting diode and photoreceptor. Although it measures oxygen it also indirectly measures blood flow [43]. By plotting the oxygen in the blood over time the relative speed of the blood flow can be determined. This can then be used to explore possible neuropathy by performing a motion or sympathetic stimulation where a change in blood flow is expected, but not found.

VI. DISCUSSION

Currently, leprosy, and other neuropathies, are mainly tested using the patient's sensory functions. These sensory functions are not the first functions to be affected by neuropathy. The

autonomic functions of the body parts affected by neuropathy are generally impaired before the sensory functions [9]. Thus it might be wise to shift the diagnosis from sensory to autonomic function. However, as mentioned in the previous section most currently existing diagnostic tools are impractical or unsuitable for use in low-income countries. To remedy this below five physical properties are compared in a Harris profile to find the most suitable for autonomous function diagnosis in low-income countries.

A. Physical Properties

In the previous part, five physical properties were identified as potential means of discovering neuropathy. In this part, these five properties will be compared to determine which one has the most potential to be adapted into a new way of detecting possible neuropathy. To do this a Harris profile is created.

A Harris profile gives a quick visual impression of which concept has the most initial merit. To create a Harris profile first the requirements are identified and ranked by importance. The most important one will be at the top and the least important one at the bottom. Each device is then scored with a 1, 2, 3, or 4 indicating how well they fulfill each requirement. Comparing the center of gravity of the 'tower' creates the concepts can be compared. The higher and more to the right the center of gravity the more suitable the concept is. This allows a simple visual way to compare different ideas at the initial stage.

1) *Requirements:* Before a Harris profile can be made the requirements desired from the physical properties must first be determined. To determine these requirements it is useful to remember the goal of this paper. To find a novel way to assess autonomic function in low-income countries. All the described properties are autonomic functions so the important requirements are how well they can be assessed and if they can be assessed in low-income countries.

Keeping in mind the former the following requirements have been determined. Ease of measurement means how easily can the physical property be measured. If the desired property can only be measured using expensive and/or large equipment or requires difficult to create circumstances its suitability for low-income countries is diminished. Time to measure describes how quickly the desired property can be extracted and examined. A quick test requires less time for a patient this means the incentive to get tested is increased. This will widen the investigation into possible neuropathy increasing the chance of detecting it early. Clinical significance describes what the measured property says about possible neuropathy. If a property can be accurately measured but leaves too much possibility for a diagnosis different than neuropathy it is a less useful property. Although all properties are part of the autonomous function they might not be exclusively linked to the autonomous function. Difficulty of implementation describes how difficult it is to use the property to create a test for possible neuropathy. To maximize the utility of the potential test it should require little to no training before being

used. This includes both measuring the property as well as assessing the obtained results. Accuracy of the measurement, how small of a difference can be detected. If small changes can be monitored accurately possible neuropathy can be diagnosed quicker when periodically tested.

For the order of importance of the requirements the assessment should be prioritized over the application in low-income countries. Although the use in low-income countries is part of the goal, detection of possible neuropathy should be the priority. This means that accuracy and clinical significance are the two top requirements. Of these two clinical significance is the more important one. As mentioned before if no significant possibility of neuropathy can be determined by testing the property it is not a useful property to test. For the requirements related to use in low-income countries ease of measurement should be valued higher closely followed by the difficulty of implementation. The goal of the assessment is to find possible neuropathy as soon as possible. To do this the test should be as widely used as possible. To ensure this the test or device should be easy to add to tools already used in care facilities in low-income countries. This leaves the time to measure as the least important requirement. Reduced time to measure would increase the usability of the test

2) *Harris Profile:* To create the Harris profile the different physical properties should be graded on the requirements described above. It is important to note that this is not an exact grading but rather an indication of suitability. For grading the physical properties some assumptions were made regarding the difficulty of implementation and time to measure requirements. For these requirements, the use of existing devices was assumed and a possible user has some medical training.

Blood: When measured locally abnormal blood pressure may indicate neuropathy. However local blood pressure irregularity might also be the result of general hyper- or hypotension. This limits the clinical significance of abnormal blood pressure. This means that for clinical significance blood pressure scores a 2. Blood pressure can be reliably measured with accuracy allowing small changes to be noticed. For accuracy blood pressure scores a 4. Blood pressure can be fairly easily measured. However, depending on where exactly blood pressure should be measured local topography might impede easy measurement. Therefore it scores a 3 in this requirement. Blood pressure measurements are an established practice that all health care workers should be able to perform therefore it scores a 4. Blood pressure can not be measured instantaneously, but it is quick and therefore scores a 3.

Skin Wrinkling: Skin wrinkling is a prime example of an autonomous Skin Wrinkling: Skin wrinkling is a prime example of an autonomous function it, therefore, scores a 4 on significance. For accuracy skin wrinkling scores a 2. It has degrees of skin wrinkling, but this is very subjective and difficult to objectively quantify. Measuring skin wrinkling is easy no special devices are required and therefore it scores a 4. Skin wrinkling is easy to implement as a test because

TABLE V
HARRIS PROFILE; BLOOD FLOW AND TEMPERATURE BOTH SCORE A TOTAL OF 17 POINTS. TEMPERATURE, HOWEVER, HAS A HIGHER CENTER OF GRAVITY AND IS THEREFORE THE BETTER PROPERTY TO MEASURE.

	Blood Pressure				Skin Wrinkling				Temperature				Sweating				Blood Flow			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Clinical Significance		X						X				X				X		X		
Accuracy of measurement				X		X						X			X					X
Ease of measurement			X					X			X			X					X	
Difficulty of implementation				X			X				X				X					X
Time to measure			X		X						X		X							X

it requires little training to perform. However, judging the amount of wrinkling objectively is difficult and might require more experience. That's why it scores a 3. Skin wrinkling is not a quick test. It may take up to 30 minutes soaking in water to activate the wrinkling reflex and even the vasoconstrictor creams don't significantly reduce this time. Therefore it scores a 1.

Temperature: Temperature is a good indication of autonomous function. Both for abnormalities in skin temperature and abnormalities in returning to a previous temperature. This means it scores a 4. Very accurate thermal scanners that offer a heat map of a larger area already exist allowing small temperature changes to be measured. Here it also scores a 4. Thermal scanners and similar equipment are handheld and readily available making measurements of temperature easy therefore it scores a 3. Measuring the temperature requires no special training, however interpreting the data might require some expertise to assess if measurements are abnormal or not. Because of this slightly more difficult interpretation, it scores a +. If just the skin temperature is measured it can be done almost instantaneously however if the ability to restore temperature is measured it might take significantly more time. Because this falls outside of the scope of this review to determine which method gives the best diagnosis the times are taken on average scoring temperature a 3.

Sweating: Like skin, wrinkling sweating is a good indication of autonomous function. Giving it a clinical significance of 4. The accuracy of measuring the sweating is questionable. No sweat is a good indication of neuropathy, but a little or a lot of sweating does not give useful information. Therefore it scores a 3. Measuring the sweat is not necessarily difficult, but activating the sweat glands has an optimum temperature and humidity. Realizing these might not always be possible and this might complicate the measurement. Taking this into account a - was given. No special training is required to implement the measurement although the same with it being a binary result, sweat or no sweat, makes implementation more difficult. This means it scores a 3. Like skin wrinkling, it takes time to activate the sweat response increasing the time required for this measurement. This is reflected in its score of 1.

Blood flow: Like blood pressure blood flow is not a strictly autonomous function. This makes it less suitable giving it a score of 2. With the photoplethysmogram method described before it should be possible to get an accurate measurement of the blood flow. This leads to a score of 4. Similar to temper-

ature the measurement of blood flow requires no big machines, but the machine is somewhat complicated. It, therefore, scores a 3, just like temperature. The measurement will most likely not be difficult to implement. The measuring device will most likely require little training and the result should be easy to interpret. Leading to a score of 4. This will also be the fastest property to measure. The flow can be quickly read and therefore it scores a 4.

Table V shows the Harris profile for the physical properties. Looking at the Harris profile Temperature is the most suitable of the five properties. It has the same score as blood flow, but has a higher center of gravity. However, it would be unwise to disregard the other properties completely. The Harris profile looks at each property individually and combining them might lead to a better assessment. It might therefore be useful to investigate combinations of the properties. For example, a logical combination would be temperature and sweating. Triggering sweating requires an increase in body temperature, combine this with a test to see how long it takes to return the skin to its original temperature and data can be gathered. Other combinations might also work, but this would be part of future research and falls outside of the scope of this review.

VII. CONCLUSION

The goal of this paper was to find if assessing neurological damage to the autonomous functions as a result of leprosy or other neuropathies is possible. Most neuropathy is assessed using the sensory function of the patient, not the autonomic function. Generally, this is easier, the tests are cheaper, and when done regularly allow for proper monitoring. However, in countries where access to regular medical care is sparse and irregular, it is important to detect neuropathy as quickly as possible to prevent permanent injury or disfigurement. Because autonomic functions are often affected before sensory functions it is useful to assess these functions.

This review has identified five physical properties that may be used to test autonomic function to detect possible neuropathy. Of these properties, the temperature has the most potential for developing a novel way to diagnose neuropathy. This will be further explored in the following project. It is important to note that currently, the properties have only been compared to diagnose possible neuropathy on their own. It is might well be more useful, and practical, to combine different properties to create a new way to diagnose possible

neuropathy. However, this falls outside of the scope of this review and will be done in a follow-up project.

REFERENCES

- [1] "Leprosy (hansen's disease)." [Online]. Available: <https://www.who.int/news-room/fact-sheets/detail/leprosy>
- [2] W. Brandsma, E. Post, I. Wagenaar, K. Alam, V. Shetty, S. Husain, C. R. S. Prakoeswa, M. Shah, K. B. Tamang, J. M. Elling *et al.*, "Pure neural leprosy—mind the diagnosis," *Lepr Rev*, vol. 92, pp. 38–46, 2021.
- [3] 2021. [Online]. Available: <https://tulib.tudelft.nl/searching-resources/making-a-search-plan/>
- [4] C. White and C. Franco-Paredes, "Leprosy in the 21st century," *Clinical microbiology reviews*, vol. 28, no. 1, pp. 80–94, 2015.
- [5] S. K. Noordeen, "Epidemiology of leprosy," in *Mycobacteria*. Springer, 1998, pp. 379–397.
- [6] O. Rojas-Espinosa and M. Løvik, "Mycobacterium leprae and mycobacterium leprae infections in domestic and wild animals," *Revue scientifique et technique (International Office of Epizootics)*, vol. 20, no. 1, pp. 219–251, 2001.
- [7] M. Hatta, S. M. van Beers, B. Madjid, A. Djumadi, M. Y. de Wit, and P. R. Klatsar, "Distribution and persistence of mycobacterium leprae nasal carriage among a population in which leprosy is endemic in indonesia," *Transactions of The Royal Society of Tropical Medicine and Hygiene*, vol. 89, no. 4, pp. 381–385, 1995. [Online]. Available: [https://doi.org/10.1016/0035-9203\(95\)90018-7](https://doi.org/10.1016/0035-9203(95)90018-7)
- [8] L. A. Blake, B. C. West, C. H. Lary, and J. R. Todd IV, "Environmental nonhuman sources of leprosy," *Reviews of infectious diseases*, vol. 9, no. 3, pp. 562–577, 1987.
- [9] S. Khadilkar, S. Patil, and V. Shetty, "Neuropathies of leprosy," *Journal of the neurological sciences*, vol. 420, p. 117288, 2021. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/33360424/>
- [10] W. Ooi and J. Srinivasan, "Leprosy and the peripheral nervous system: basic and clinical aspects," *Muscle nerve*, vol. 30, no. 4, pp. 393–409, 2004. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/15372437/>
- [11] K. Lau, "Neurological complications of leprosy," *Seminars in neurology*, vol. 39, no. 4, pp. 462–471, 2019. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/31533187/>
- [12] W. H. Organization *et al.*, *WHO Expert Committee on Leprosy: fifth report [of a meeting held in Geneva from 19 to 25 October 1976]*. World Health Organization, 1977.
- [13] D. Ridley and W. Jopling, "Classification of leprosy according to immunity," *Int j lepr other mycobact dis*, vol. 34, pp. 255–273, 1966.
- [14] M. de Freitas and G. Said, "Leprous neuropathy," *Handbook of clinical neurology*, vol. 115, pp. 499–514, 2013. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/23931798/>
- [15] F. E. F. Pardo, T. T. Fajardo, R. M. Abalos, D. Scollard, and R. H. Gelber, "Methods for the classification of leprosy for treatment purposes," *Clinical Infectious Diseases*, vol. 44, no. 8, pp. 1096–1099, 2007.
- [16] I. N. J. O. IJ and I. ROSY, "Pathology and pathogenesis of leprosy neuritis; a preventable and treatable complication," 2001.
- [17] S. V. Khadilkar, R. S. Yadav, and G. Soni, "A practical approach to enlargement of nerves, plexuses and roots," *Practical neurology*, vol. 15, no. 2, pp. 105–115, 2015.
- [18] V. Panikar, "Enhanced global strategy for further reducing the disease burden due to leprosy: 2011–2015," *Leprosy review*, vol. 80, no. 4, pp. 353–354, 2009.
- [19] I. Wagenaar, E. Post, W. Brandsma, D. Ziegler, M. Rahman, K. Alam, and J. Richardus, *Early detection of neuropathy in leprosy: a comparison of five tests for field settings*, 2017, vol. 6. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/28859682/>
- [20] J. Garbino, C. Heise, and J. M. W., "Assessing nerves in leprosy," *Clinics in dermatology*, vol. 34, no. 1, pp. 51–8, 2016. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/26773623/>
- [21] P. Pottecher, B. Flageul, E. Sibilleau, J. Laredo, and V. Bousson, "Peripheral hypertrophic neuropathy due to leprosy: ultrasound and mr imaging findings," *Diagnostic and interventional imaging*, vol. 97, no. 4, pp. 471–473, 2016.
- [22] L. K. McCorry, "Physiology of the autonomic nervous system," *American journal of pharmaceutical education*, vol. 71, no. 4, 2007.
- [23] C. H. Gibbons, "Basics of autonomic nervous system function," *Handbook of clinical neurology*, vol. 160, pp. 407–418, 2019.
- [24] G. Grassi, "Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives," *Hypertension*, vol. 54, no. 4, pp. 690–697, 2009.
- [25] H. Khattri, K. Radhakrishnan, S. Kaur, B. Kumar, and P. Wahi, "Cardiac dysautonomia in leprosy," *Int J Lepr Other Mycobact Dis*, vol. 46, no. 2, pp. 172–174, 1978.
- [26] N. Abbot, J. Beck, P. Samson, C. Butlin, P. Bennett, and J. Grange, "Cold fingers in leprosy," *International journal of leprosy and other mycobacterial diseases : official organ of the International Leprosy Association*, vol. 60, no. 4, pp. 580–6, 1992. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/1299714/>
- [27] E. P. Wilder-Smith, "Water immersion wrinkling," *Clinical Autonomic Research*, vol. 14, no. 2, pp. 125–131, 2004.
- [28] —, "Stimulated skin wrinkling as an indicator of limb sympathetic function," *Clinical Neurophysiology*, vol. 126, no. 1, pp. 10–16, 2015.
- [29] H. M. Chinyanga, "Temperature regulation and anesthesia," *Pharmacology & therapeutics*, vol. 26, no. 2, pp. 147–161, 1984.
- [30] J. M. Johnson and D. L. Kellogg Jr, "Thermoregulatory and thermal control in the human cutaneous circulation," *Front Biosci (Schol Ed)*, vol. 2, pp. 825–853, 2010.
- [31] S. Arora, P. Smakowski, R. G. Frykberg, L. R. Simeone, R. Freeman, F. W. LoGerfo, and A. Veves, "Differences in foot and forearm skin microcirculation in diabetic patients with and without neuropathy," *Diabetes care*, vol. 21, no. 8, pp. 1339–1344, 1998.
- [32] P. Kucera, Z. Goldenberg, and E. Kurca, "Sympathetic skin response: review of the method and its clinical use," *BRATISLAVSKE LEKARSKE LISTY*, vol. 105, no. 3, pp. 108–116, 2004.
- [33] J. L. Greaney and W. L. Kenney, "Measuring and quantifying skin sympathetic nervous system activity in humans," *Journal of neurophysiology*, vol. 118, no. 4, pp. 2181–2193, 2017.
- [34] V. G. Macefield, "Sympathetic microneurography," *Handbook of clinical neurology*, vol. 117, pp. 353–364, 2013.
- [35] L. Guttmann, "The management of the quinizarin sweat test," *Postgraduate Medical Journal*, vol. 23, no. 262, p. 353, 1947.
- [36] R. D. Fealey, "Thermoregulatory sweat test," *Clinical Neurophysiology*, 3rd edn. Oxford University Press, New York, pp. 645–660, 2009.
- [37] R. Fealey, "Autonomic dysfunction in spinal cord disease," in *Spinal Cord Disease*. Springer, 1997, pp. 219–227.
- [38] J. Sheskin, S. Sabatto, Z. Yosipovitz, and A. Ilukevich, "Lack of wrinkle formation in the fingertips of patients with hansen's disease. confirmation of previous observations," *Hansenologia Internationalis: hansenase e outras doenças infecciosas*, vol. 8, no. 1, pp. 54–60, 1983.
- [39] C. V. Clark, B. Pentland, D. J. Ewing, and B. F. Clarke, "Decreased skin wrinkling in diabetes mellitus," *Diabetes Care*, vol. 7, no. 3, pp. 224–227, 1984.
- [40] M. J. Joyner, N. Charkoudian, and B. G. Wallin, "Sympathetic nervous system and blood pressure in humans: individualized patterns of regulation and their implications," *Hypertension*, vol. 56, no. 1, pp. 10–16, 2010.
- [41] N. Charkoudian, "Skin blood flow in adult human thermoregulation: how it works, when it does not, and why," in *Mayo clinic proceedings*, vol. 78, no. 5. Elsevier, 2003, pp. 603–612.
- [42] D. T. Lykken and P. H. Venables, "Direct measurement of skin conductance: A proposal for standardization," *Psychophysiology*, vol. 8, no. 5, pp. 656–672, 1971.
- [43] A. Reisner, P. A. Shaltis, D. McCombie, H. H. Asada, D. S. Warner, and M. A. Warner, "Utility of the photoplethysmogram in circulatory monitoring," *The Journal of the American Society of Anesthesiologists*, vol. 108, no. 5, pp. 950–958, 2008.

APPENDIX B: TEMPERATURE DATA AVERAGE OF THREE RUNS

Below the average test results can be found for the 12 tests. The results are the averaged temperature measured over the three different runs for each test. The tables also show the root mean square (RMS) and standard deviation (St. Dev.)

Test 1: Back, Cooling, 0,1g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	30,56	31,60	31,94	31,10
2	28,99	30,74	30,25	30,97
3	27,99	30,39	29,36	32,02
4	28,42	30,84	29,40	32,32
5	29,05	31,27	29,76	32,09
6	29,43	31,49	29,95	32,38
7	29,72	32,26	30,27	32,28
8	29,92	32,01	30,49	32,77
9	30,21	32,21	30,82	32,80
10	30,30	32,29	30,69	32,58
11	30,42	32,33	30,76	32,18
12	30,45	32,43	30,82	32,27
13	30,60	32,55	31,06	32,41
14	30,54	32,44	30,85	32,05
15	30,40	32,45	31,07	31,73
16	30,41	32,36	30,92	31,73
RMS	29,85	31,86	30,53	32,11
St. Dev.	0,83	0,70	0,67	0,52

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	30,58	31,29	32,18	30,74
2	30,02	30,80	31,91	29,95
3	30,05	30,90	31,97	30,81
4	30,02	30,93	32,03	31,61
5	30,63	31,22	32,10	31,65
6	30,41	31,41	32,10	31,72
7	30,50	31,42	32,24	31,84
8	30,44	31,47	32,17	31,85
9	30,70	31,44	32,29	31,83
10	30,57	31,54	32,21	31,65
11	31,00	31,66	32,22	32,00
12	30,95	31,80	32,25	31,59
13	30,97	31,70	32,34	31,52
14	30,74	31,75	32,30	31,36
15	30,65	31,66	32,36	31,38
16	30,71	31,66	32,26	31,21
RMS	30,56	31,42	32,18	31,42
St. Dev.	0,32	0,31	0,13	0,53

Test 2: Back, Cooling, 0,2g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	30,48	31,89	32,49	32,28
2	29,75	30,89	30,17	32,37
3	28,51	31,35	29,59	32,21
4	28,71	31,88	29,22	32,10
5	29,29	32,24	29,41	31,68
6	30,39	32,13	29,56	31,73
7	30,23	32,45	29,95	32,59
8	30,50	32,66	30,17	32,50
9	30,64	32,60	30,83	32,67
10	30,79	32,67	31,12	32,48
11	31,02	32,84	31,20	32,55
12	30,89	32,81	31,49	32,35
13	30,80	32,79	31,51	32,30
14	30,84	32,64	31,47	31,95
15	30,92	32,56	31,49	31,74
16	30,41	32,70	31,72	32,22
RMS	30,27	32,32	30,73	32,23
St. Dev.	0,79	0,56	0,99	0,31

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	30,04	31,25	32,19	30,25
2	29,94	31,68	32,02	31,66
3	30,86	31,66	32,37	31,27
4	30,77	31,85	32,53	31,22
5	30,53	31,54	32,59	31,21
6	30,54	31,88	32,69	31,40
7	30,79	31,82	32,78	31,78
8	30,81	31,88	32,75	31,96
9	30,90	31,87	32,76	31,96
10	30,89	31,95	32,86	31,86
11	30,84	31,94	32,83	31,94
12	31,04	32,01	32,85	31,79
13	30,98	31,85	32,98	31,70
14	30,83	31,90	32,73	31,78
15	31,02	31,77	32,74	31,52
16	30,79	31,84	32,79	31,55
RMS	30,73	31,79	32,66	31,56
St. Dev.	0,32	0,19	0,26	0,43

Test 3: Back, Cooling, 0,3g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	30,33	32,08	32,66	30,38
2	29,16	31,29	30,50	30,29
3	27,63	31,10	29,80	31,13
4	28,01	31,02	29,65	32,05
5	28,46	31,36	29,51	32,34
6	29,60	31,88	30,16	32,66
7	30,03	32,74	30,33	32,82
8	30,45	33,06	30,51	33,03
9	30,52	33,09	30,85	32,83
10	30,37	33,05	31,00	32,82
11	30,36	33,06	31,16	32,54
12	30,48	32,91	31,14	32,68
13	30,54	33,12	31,32	32,92
14	30,64	33,04	31,52	32,85
15	30,55	32,98	31,26	32,35
16	30,50	32,97	31,35	32,19
RMS	29,87	32,43	30,80	32,25
St. Dev.	0,99	0,82	0,81	0,88

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	30,20	31,41	32,34	29,65
2	30,11	31,34	32,58	29,73
3	30,38	31,33	32,51	30,45
4	30,63	31,40	32,53	31,24
5	30,79	31,54	32,59	31,94
6	30,80	32,01	32,73	32,29
7	30,99	32,24	32,77	32,34
8	31,51	32,25	32,69	32,42
9	31,16	32,29	32,72	32,28
10	31,11	32,28	32,59	32,28
11	31,26	32,21	32,76	32,01
12	30,99	32,17	32,68	32,04
13	31,17	32,09	32,67	32,34
14	31,06	32,23	32,71	32,36
15	31,02	32,03	32,52	32,01
16	31,18	32,06	32,76	31,78
RMS	30,90	31,93	32,63	31,71
St. Dev.	0,39	0,38	0,12	0,93

Test 4: Palm, Cooling, 0,1g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	32,03	33,61	34,73	31,25
2	31,18	32,69	32,94	30,97
3	31,31	33,30	32,41	30,87
4	32,03	33,18	31,93	30,80
5	32,25	33,71	32,41	30,70
6	33,12	34,07	32,94	30,83
7	33,40	34,06	33,51	31,35
8	33,71	34,32	33,71	31,28
9	33,73	34,46	33,60	31,45
10	33,91	34,98	33,82	31,73
11	34,10	34,45	34,41	31,59
12	34,00	34,52	34,38	32,02
13	33,68	34,55	34,30	31,86
14	33,91	34,59	33,91	31,88
15	33,81	34,37	33,84	32,03
16	33,86	34,56	34,41	32,06
RMS	33,14	34,10	33,59	31,42
St. Dev.	1,01	0,63	0,83	0,48

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	31,47	32,64	33,11	30,78
2	31,93	32,58	33,16	30,89
3	31,97	32,67	32,97	30,61
4	32,10	33,14	33,48	30,88
5	32,29	33,05	33,42	31,08
6	32,72	33,38	33,55	31,39
7	33,05	33,59	33,95	31,42
8	33,35	33,92	34,01	31,77
9	33,38	34,01	34,12	32,43
10	33,15	33,70	33,79	31,94
11	33,34	34,23	33,48	31,85
12	33,43	34,11	33,98	32,22
13	33,40	34,01	34,05	32,27
14	33,42	34,17	33,97	32,08
15	33,30	33,79	33,61	32,20
16	33,31	34,08	34,11	32,18
RMS	32,86	33,57	33,68	31,63
St. Dev.	0,67	0,58	0,38	0,62

Test 5: Palm, Cooling, 0,2g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	34,37	35,47	35,25	33,55
2	32,56	33,85	33,24	33,58
3	32,11	34,29	32,54	32,93
4	32,51	34,74	32,43	32,96
5	33,60	34,95	32,20	33,10
6	33,95	34,99	32,49	33,19
7	33,91	35,38	32,97	33,04
8	34,08	35,47	33,25	33,21
9	34,29	35,44	33,20	33,09
10	34,45	35,63	33,26	33,13
11	34,81	35,84	33,44	33,42
12	35,26	36,08	33,52	33,51
13	35,25	35,93	33,84	33,47
14	35,54	36,22	33,97	33,75
15	35,56	36,12	34,25	33,94
16	35,35	36,02	34,25	33,89
RMS	34,24	35,41	33,39	33,36
St. Dev.	1,10	0,68	0,80	0,32

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	34,12	34,27	34,62	33,18
2	33,68	33,71	34,01	33,26
3	33,57	34,38	33,88	33,13
4	33,84	34,71	33,83	33,74
5	34,22	34,70	33,82	33,73
6	34,77	34,86	33,99	33,83
7	34,42	34,95	34,04	33,65
8	34,33	34,43	33,96	33,80
9	34,36	34,29	34,18	33,74
10	34,25	34,87	34,03	34,14
11	34,79	35,19	34,02	34,21
12	34,46	35,38	34,06	34,70
13	34,61	35,25	33,95	34,59
14	35,19	35,75	34,25	35,04
15	34,83	35,55	34,05	34,84
16	34,97	35,57	34,16	34,71
RMS	34,40	34,87	34,05	34,02
St. Dev.	0,46	0,56	0,19	0,61

Test 6: Palm, Cooling, 0,3g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	35,30	36,32	35,59	34,50
2	33,48	35,44	33,88	34,17
3	32,80	35,41	32,81	33,85
4	34,00	36,14	32,70	34,33
5	34,74	35,71	33,04	34,51
6	35,21	36,34	33,63	34,89
7	35,98	36,82	33,76	34,95
8	35,78	36,75	34,03	35,06
9	36,07	36,66	34,27	35,04
10	36,10	36,89	34,51	35,32
11	36,14	36,90	34,76	35,40
12	35,85	36,79	34,65	35,36
13	35,83	36,73	34,95	35,18
14	36,29	36,95	34,84	35,23
15	36,18	36,89	35,04	35,34
16	35,58	36,83	34,99	35,04
RMS	35,35	36,48	34,22	34,89
St. Dev.	1,05	0,53	0,86	0,47

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	34,94	35,58	35,43	34,89
2	34,85	35,52	35,11	34,65
3	35,14	35,49	35,24	34,55
4	35,77	35,87	35,55	35,17
5	35,94	36,02	35,31	35,36
6	36,22	36,52	35,58	35,74
7	36,23	36,66	35,79	35,84
8	36,00	36,65	35,72	35,91
9	36,02	36,14	35,62	35,63
10	36,18	36,70	35,62	35,83
11	35,91	36,42	35,42	35,74
12	35,85	36,27	35,42	35,57
13	35,92	36,01	35,45	35,63
14	35,97	36,07	35,37	35,58
15	36,01	36,06	35,26	35,72
16	35,74	35,35	35,25	35,55
RMS	35,80	36,09	35,45	35,46
St. Dev.	0,43	0,44	0,19	0,42

Test 7: Back, Heating, 0,03g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	31,66	33,06	33,22	32,68
2	31,50	33,38	32,01	32,50
3	31,38	33,26	32,75	32,56
4	31,37	33,33	32,75	32,60
5	31,32	33,34	32,74	33,53
6	31,35	33,78	32,81	33,26
7	31,79	34,14	32,89	33,24
8	31,53	34,01	32,89	33,68
9	31,73	34,04	32,90	34,69
10	31,29	34,33	32,98	34,97
11	32,23	34,66	33,05	35,09
12	32,06	34,52	32,93	34,91
13	32,14	34,49	33,00	34,33
14	32,18	34,31	32,99	34,14
15	32,05	34,06	33,09	34,00
16	32,00	34,30	33,12	34,06
RMS	31,72	33,94	32,88	33,77
St. Dev.	0,34	0,51	0,27	0,90

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	30,84	32,52	32,70	31,90
2	30,84	32,15	32,72	31,92
3	30,85	32,33	32,75	31,88
4	30,73	32,08	32,79	31,99
5	30,96	32,36	32,74	32,20
6	31,10	32,24	32,79	32,62
7	31,22	32,43	32,84	32,96
8	31,62	32,52	32,83	33,13
9	31,48	32,63	32,99	33,75
10	31,76	32,81	32,92	34,62
11	31,82	33,05	33,12	34,81
12	32,10	33,19	33,00	34,29
13	32,19	33,02	33,16	34,17
14	31,77	33,18	33,09	34,04
15	32,01	32,90	33,03	33,80
16	32,26	33,06	33,05	33,94
RMS	31,48	32,65	32,91	33,27
St. Dev.	0,54	0,38	0,16	1,05

Test 8: Back, Heating, 0,07g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	30,50	32,29	32,63	30,83
2	31,19	32,87	32,19	32,28
3	31,39	33,07	32,74	32,24
4	31,49	33,62	32,65	32,73
5	31,67	33,36	32,81	32,94
6	31,42	33,56	32,63	32,54
7	31,40	33,08	32,52	31,65
8	30,85	33,65	32,27	32,08
9	31,13	33,43	32,38	32,70
10	30,93	33,59	32,14	33,09
11	30,83	33,56	32,20	32,80
12	30,80	33,46	32,43	33,05
13	31,01	33,55	32,28	33,53
14	31,03	33,73	32,28	33,90
15	31,34	33,75	32,37	34,26
16	31,37	34,02	32,38	34,17
RMS	31,15	33,41	32,43	32,81
St. Dev.	0,31	0,41	0,21	0,91

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	31,27	32,18	32,72	30,71
2	31,56	32,40	33,14	31,73
3	31,60	32,43	33,12	32,15
4	31,59	32,31	33,25	32,41
5	31,76	32,51	33,41	32,42
6	31,77	32,32	33,21	31,99
7	31,48	32,21	33,07	31,73
8	31,30	32,16	33,11	32,23
9	31,24	32,18	33,23	32,69
10	30,95	32,18	33,02	32,77
11	31,32	32,33	33,05	32,92
12	31,36	32,25	33,05	33,08
13	31,33	32,40	33,16	33,48
14	31,54	32,51	33,12	33,69
15	31,65	32,85	33,10	33,86
16	31,65	32,81	33,09	33,92
RMS	31,46	32,38	33,11	32,62
St. Dev.	0,22	0,21	0,14	0,88

Test 9: Back, Heating, 0,1g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	29,75	30,10	31,64	29,12
2	29,59	30,62	30,20	28,81
3	29,67	30,87	30,88	28,65
4	29,58	30,69	31,05	28,48
5	29,52	30,82	31,08	28,49
6	29,42	30,80	31,29	28,27
7	29,33	30,71	31,24	28,08
8	28,97	30,72	31,26	28,21
9	28,77	30,58	30,90	27,98
10	28,82	30,34	30,89	27,56
11	28,33	29,70	30,75	27,19
12	28,31	30,18	30,72	26,95
13	28,18	30,35	30,91	27,23
14	28,31	30,15	30,86	27,29
15	28,22	29,89	30,74	27,15
16	28,13	29,88	30,52	26,77
RMS	28,94	30,40	30,94	27,90
St. Dev.	0,62	0,38	0,34	0,73

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	30,42	30,92	31,96	30,11
2	30,62	30,90	32,47	30,13
3	30,46	31,17	32,47	29,95
4	30,60	31,09	32,54	30,09
5	30,44	31,14	32,43	29,56
6	30,38	31,01	32,61	29,84
7	30,22	30,75	32,50	29,54
8	29,97	30,74	32,56	29,51
9	29,92	30,48	32,54	28,75
10	29,64	29,99	32,51	28,24
11	29,37	29,86	32,08	28,20
12	29,35	29,96	32,24	28,00
13	29,38	30,10	32,28	28,31
14	29,41	29,97	32,31	28,34
15	29,02	29,83	32,13	28,24
16	28,77	29,52	31,95	27,70
RMS	29,88	30,47	32,35	29,04
St. Dev.	0,60	0,56	0,22	0,88

Test 10: Palm, Heating, 0,03g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	33,48	34,66	34,69	33,09
2	34,05	35,15	34,46	33,17
3	34,88	35,47	34,95	33,05
4	35,30	35,92	35,45	33,29
5	35,66	36,55	35,38	33,73
6	36,45	36,68	35,79	34,06
7	36,58	36,79	35,75	34,18
8	36,27	36,93	35,81	34,43
9	36,56	36,88	35,91	34,49
10	36,12	36,83	35,88	34,58
11	36,18	36,49	35,79	34,56
12	36,16	36,71	35,85	34,51
13	36,44	36,96	35,77	34,64
14	36,19	36,76	35,87	34,64
15	36,22	36,79	35,88	34,52
16	36,49	36,78	35,73	34,55
RMS	35,83	36,40	35,56	34,10
St. Dev.	0,93	0,71	0,46	0,61

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	33,05	33,62	33,52	32,40
2	33,96	34,10	33,93	32,97
3	33,98	34,53	33,97	33,19
4	34,36	35,03	34,15	33,56
5	35,48	35,62	34,39	34,59
6	35,33	36,09	34,66	34,85
7	35,58	35,82	34,87	34,91
8	35,95	35,82	34,69	35,40
9	36,01	36,13	34,65	35,44
10	35,47	35,75	34,71	35,12
11	35,14	35,53	34,61	35,07
12	35,47	35,97	34,57	35,06
13	35,57	35,87	34,66	35,26
14	35,33	35,62	34,52	34,83
15	35,14	35,72	34,50	34,87
16	35,46	35,50	34,46	34,82
RMS	35,09	35,43	34,43	34,53
St. Dev.	0,81	0,73	0,36	0,94

Test 11: Palm, Heating, 0,07g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	33,89	34,39	34,10	31,64
2	35,11	35,56	34,72	32,32
3	35,66	35,67	34,95	32,56
4	35,76	36,01	35,37	32,96
5	35,76	36,35	35,11	33,57
6	36,12	36,53	35,54	33,66
7	36,44	36,73	35,52	33,73
8	36,28	36,58	35,54	33,79
9	36,35	36,76	35,56	34,06
10	36,60	36,84	35,49	34,06
11	36,57	36,88	35,36	34,12
12	36,66	36,98	35,75	34,30
13	36,75	36,94	35,59	34,40
14	36,89	37,06	35,85	34,73
15	37,05	37,09	35,72	34,98
16	37,05	37,16	35,87	34,90
RMS	36,19	36,48	35,38	33,75
St. Dev.	0,82	0,74	0,46	0,95

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	33,79	33,75	33,24	31,36
2	34,87	34,43	33,64	33,17
3	34,39	34,39	33,76	33,62
4	35,05	34,66	33,88	33,91
5	34,99	34,93	34,29	34,20
6	35,59	35,46	34,33	34,62
7	35,62	35,64	34,68	35,20
8	35,44	35,76	34,75	34,85
9	35,65	35,70	34,48	35,24
10	36,09	36,12	34,71	35,37
11	35,88	36,24	34,67	35,56
12	36,11	36,28	34,88	35,58
13	36,03	36,48	34,79	35,51
14	36,19	36,25	35,08	35,65
15	36,47	36,59	34,83	35,68
16	36,46	36,63	34,96	35,71
RMS	35,55	35,59	34,44	34,72
St. Dev.	0,75	0,89	0,54	1,20

Test 12: Palm, Heating, 0,1g

Left

Minute	Location 1	Location 2	Location 3	Location 4
1	35,45	36,33	35,30	34,04
2	35,40	36,43	35,34	33,98
3	36,34	37,05	35,87	34,47
4	36,89	37,14	36,34	34,62
5	37,03	37,42	36,26	34,90
6	36,66	37,21	36,22	34,76
7	36,95	37,29	36,37	35,15
8	36,82	37,24	36,29	35,15
9	37,02	37,39	36,31	35,59
10	37,11	37,54	36,41	35,43
11	36,85	37,37	36,33	35,14
12	36,74	37,40	36,41	35,29
13	36,57	36,83	36,18	35,32
14	36,69	37,08	35,97	35,05
15	36,84	37,30	36,01	34,88
16	36,94	37,34	36,27	34,98
RMS	36,65	37,15	36,12	34,92
St. Dev.	0,51	0,35	0,35	0,46

Right

Minute	Location 1	Location 2	Location 3	Location 4
1	34,71	35,25	34,67	33,97
2	35,42	35,71	34,65	34,09
3	36,06	36,37	35,29	34,90
4	36,32	36,53	35,51	35,32
5	36,60	36,74	35,40	35,64
6	36,60	36,73	35,38	35,80
7	36,59	36,78	35,52	35,99
8	36,38	36,57	35,65	36,13
9	36,67	36,78	35,56	36,24
10	36,84	37,03	35,62	36,17
11	36,47	36,49	35,69	35,91
12	36,57	36,84	35,75	35,93
13	36,03	36,24	35,42	35,55
14	36,20	36,60	35,37	35,55
15	36,42	36,71	35,14	35,65
16	36,44	36,88	35,43	35,77
RMS	36,27	36,52	35,38	35,54
St. Dev.	0,53	0,46	0,32	0,68

APPENDIX C: MOISTURE METER RAW DATA

Test 1

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	18,5	18,5	1	-	18,8	1	18,4	18,3
2	20,4	18,4	2	20,4	18,6	2	21	18,6
3	19,9	-	3	19,7	18,4	3	19,4	18,4
4	19	18,5	4	18,7	18,4	4	18,9	18,2
5	16	18,5	5	18,8	-	5	18,4	18,5
6	16,9	18,4	6	19	18,8	6	18,3	18,4
7	16,7	18,2	7	18,8	-	7	14,3	-
8	18,8	-	8	18,5	18,8	8	17	18,7
9	18,8	18,6	9	16,5	18,7	9	18,6	18,9
10	18,8	-	10	18,4	17	10	18,8	-
11	18,7	16,6	11	18,5	18,8	11	18,2	18,8
12	18,9	18,5	12	17,7	18,6	12	18,2	18,2
13	19,4	18,6	13	18,2	18,7	13	16,5	19
14	18,8	-	14	18,8	18,9	14	19,4	-
15	18,5	18,5	15	18,3	-	15	18,3	-

Test 2

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	19,9	16,6	1	18,6	18,9	1	18,5	18,6
2	19,7	18,7	2	20,9	15,1	2	20,6	-
3	20,2	19,1	3	20,6	18,2	3	19,4	18,8
4	20,6	15,4	4	20,4	16,2	4	19	18,4
5	20,5	18,9	5	19,3	18,2	5	18,4	18,4
6	20,2	18,7	6	19	18,2	6	18,9	-
7	19,6	18,9	7	18,8	18,4	7	18,1	18,5
8	20	17	8	19,1	14,5	8	18,9	18,6
9	19	18,4	9	19	18,4	9	19,1	18,5
10	19,4	13,2	10	19,6	-	10	19	18,2
11	19,3	18,6	11	19,4	18,7	11	18,8	18,2
12	17,7	18,8	12	18,8	18,4	12	18,7	-
13	19	18,5	13	18,5	18,8	13	19,2	18,7
14	19,3	18,3	14	19,4	18,2	14	18,8	19
15	19	17,4	15	19	-	15	18,8	-

Test 3

Run 1				Run 2				Run 3			
Minute	Left	Right		Minute	Left	Right		Minute	Left	Right	
1	18,3	19		1	18,5	18,7		1	18,2	15,8	
2	19,7	16		2	20,9	18,4		2	22,5	18,6	
3	20,6	17,4		3	20,1	18,9		3	21,2	18,8	
4	19,9	16,6		4	19	18,8		4	20,5	-	
5	19,1	18,3		5	18,6	17,2		5	20,5	-	
6	20	18,3		6	19,3	18,6		6	19	18,8	
7	19,2	18,7		7	18,4	18,5		7	19,6	18,8	
8	19,1	18,7		8	18,3	18,7		8	19	18,4	
9	18,6	18,4		9	18,8	18,8		9	19,1	18,6	
10	18,4	18,6		10	18,2	18,7		10	19	18,7	
11	18,2	-		11	18,7	18,6		11	18,8	18,3	
12	19	18,3		12	18,3	18,7		12	18,8	18,3	
13	18,6	18,4		13	18,5	18,8		13	18,2	18,4	
14	18,2	18,2		14	14,8	18,7		14	19	18,6	
15	19,1	-		15	16	18,8		15	18,9	19	

Test 4

Run 1				Run 2				Run 3			
Minute	Left	Right		Minute	Left	Right		Minute	Left	Right	
1	18,9	18,9		1	18,7	18,3		1	18,8	18,8	
2	20,4	18,6		2	19,4	18,7		2	19	19	
3	19,4	18,8		3	19	18,3		3	19	18,8	
4	19,1	18,5		4	18,8	18,5		4	18,8	19	
5	19,2	18,7		5	18,8	18,8		5	18,8	19,2	
6	19,3	18,6		6	19,1	19		6	19,6	18,8	
7	19	18,4		7	18,6	18,3		7	18,7	18,5	
8	18,8	18,7		8	18,7	18,4		8	19,2	18,6	
9	18,8	18,7		9	19	18,3		9	19,1	18,7	
10	19,7	18,8		10	18,6	18,6		10	18,9	18,4	
11	19,2	18,6		11	18,9	18,8		11	18,7	18,2	
12	18,8	18,7		12	18,5	18,7		12	18,6	18,3	
13	19,1	19,3		13	18,6	18,7		13	18,7	-	
14	18,9	18,8		14	18,6	18,4		14	18,8	18,8	
15	18,7	18,8		15	18,3	19,1		15	18,4	18,8	

Test 5

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	18,7	18,1	1	18,6	18,5	1	19,4	19,2
2	20,4	18,4	2	18,7	18,7	2	20,9	18,7
3	20,4	19,8	3	20,6	18,6	3	19,6	18,7
4	19,4	18,7	4	20,1	18,6	4	18,6	18,7
5	19	18,2	5	19,2	18,4	5	19,7	18,8
6	19,1	17,8	6	19,3	18,6	6	19,4	18,5
7	18,8	18,8	7	18,8	18,4	7	18,8	18,9
8	19	18,4	8	18,8	17,4	8	19,4	18,7
9	19,4	18,6	9	18,8	18,4	9	19,5	19
10	18,8	18,9	10	18,7	18,8	10	18,5	18,4
11	18,8	18,5	11	18,8	18,8	11	18,8	18,6
12	18,6	18,4	12	18,8	18,2	12	19	18,6
13	18,6	17	13	18,9	18,4	13	19	18,8
14	19,1	18,7	14	18,9	18,8	14	19	19
15	18,8	18,2	15	19	18,4	15	19	19

Test 6

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	-	-	1	19	18,4	1	18,5	18,3
2	-	-	2	20,8	18,8	2	23,3	18,6
3	-	-	3	21	18,8	3	20,9	18,9
4	-	-	4	21	19,7	4	22,2	18,7
5	-	-	5	20,9	19,1	5	20,9	18,9
6	-	-	6	20,3	18,8	6	19,9	18,7
7	-	-	7	19,4	18,7	7	18,8	19,2
8	-	-	8	19	18,7	8	19,4	18,9
9	-	-	9	18,8	17,2	9	20,2	18,4
10	-	-	10	19	18,4	10	19,6	18,6
11	-	-	11	19,9	17,4	11	20,1	18,8
12	-	-	12	19,3	18,8	12	18,8	19
13	-	-	13	19,3	18,8	13	19,4	18,9
14	-	-	14	19,3	19,4	14	19,3	18,8
15	-	-	15	18,8	19	15	20,4	18,6

Test 7

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	18,7	-	1	18,7	18,7	1	18,6	-
2	19,2	18,4	2	18,9	18,5	2	18,8	18,7
3	18,3	18,8	3	18,4	-	3	19	18,2
4	18,8	18,7	4	18,6	18,3	4	18,8	18,5
5	18,9	18,6	5	18,8	18,5	5	18,8	18,7
6	18,8	18,2	6	18,7	18,3	6	18,8	18,7
7	19	18,4	7	18,9	18,4	7	19	18,9
8	19	18,6	8	18,3	18,6	8	19,9	-
9	18,6	-	9	18,8	18,7	9	18,8	18,8
10	18,8	18,5	10	18,9	18,7	10	18,8	18,7
11	18,6	18,7	11	18,8	18,4	11	19,3	-
12	18,7	18,3	12	18,5	18,7	12	18,9	18,8
13	18,5	18,7	13	18,7	18,7	13	18,9	18,4
14	18,7	19	14	18,7	18,4	14	18,8	18,9
15	18,6	-	15	18,6	-	15	19,2	-

Test 8

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	18,2	14,6	1	18,3	18,6	1	18,6	18,8
2	18,2	18,5	2	18,7	18,7	2	19,3	18,7
3	18,7	18,5	3	18,4	18,8	3	18,7	-
4	18,7	-	4	18,8	18,6	4	18,7	18,7
5	18,2	18,8	5	18,6	18,6	5	18,8	18,6
6	19,1	18,7	6	18,6	18,6	6	18,6	18,5
7	18,6	18,8	7	18,7	18,5	7	18,7	18,6
8	18,2	18,6	8	18,4	-	8	18,7	18,5
9	18,7	-	9	18,4	18,7	9	18,3	18,7
10	18,5	18,7	10	18,7	18,7	10	18,7	18,8
11	18,5	18,6	11	18,6	18,4	11	18,6	-
12	18,8	18,6	12	18,6	18,8	12	18,8	18,4
13	18,2	18,6	13	18,7	18,5	13	19	18,6
14	19,1	18,2	14	18,4	18,6	14	18,6	-
15	18,3	16,1	15	18,7	19	15	18,8	18,7

Test 9

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	18,4	18,5	1	18,5	18,2	1	18,3	18,7
2	18,8	18,4	2	18,3	18,5	2	19	18,7
3	18,5	18,8	3	18,5	18,8	3	19	18,8
4	18,8	18,6	4	18,5	18,6	4	18,4 -	
5	19	18,4	5	18,8	18,2	5	18,8	18,7
6	18,7	18,5	6	18,8	18,2	6	18,8	18,7
7	18,4	18,6	7	18,6	18,3	7	18,8 -	
8	18,8	18,4	8	18,6	18,8	8	18,7	18,3
9	18,6	18,5	9	18,5	18,7	9	18,8 -	
10	18,3	18,8	10	18,3	18,9	10	18,8	18,7
11	18,9	18,8	11	18,4	18,4	11	18,9	19
12	18,6	18,8	12	18,5	18,4	12	18,9	18,4
13	18,3	18,4	13	18,5 -		13	18,8 -	
14	18,8	18,2	14	18,4 -		14	19,4	18,4
15	18,5	18,7	15	18,3	18,3	15	19,4 -	

Test 10

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	18	19	1	18,6	18,5	1	18,7	18,8
2	19	17	2	18,8	18,6	2	19,2	18,5
3	18,5	17	3	18,3	18,5	3	20,1	18,7
4	18	18,2	4	18,6	18,5	4	19,1	18,4
5	19,4	18,5	5	18,6	18,2	5	19,3	18,8
6	19,1	18,8	6	18,5	18,8	6	18,3	18,1
7	19	18,3	7	18,7	18,7	7	19,1	18,4
8	19	18,8	8	18,8	18,6	8	19,4	18,6
9	19,3	18,5	9	19,1	18,4	9	19,4	18,6
10	19	18,8	10	18,9	18,3	10	19,4	18,7
11	18,8	18,6	11	18,7	18,3	11	19	18,5
12	19	18,8	12	19,1	18,6	12	20,2	18,3
13	18,7	18,8	13	19	18,6	13	19,7	18,6
14	19	18,4	14	19	18,8	14	19,4	18,8
15	19,2	18,5	15	19	18,4	15	19,9	18,8

Test 11

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	19	18,9	1	18,6	18,5	1	18,8	18,1
2	18,9	18,9	2	18,6	18,3	2	18,8	18,8
3	18,9	18,3	3	19,3	18,9	3	18,6	18,7
4	18,9	18,8	4	18,8	18,4	4	18,6	18,4
5	19	18,6	5	18,3	18,8	5	18,8	18,4
6	19	18,5	6	19	18,8	6	18,9	18,4
7	19,3	18,7	7	19,4	18,5	7	18,9	18,5
8	20,4	18,7	8	19,1	18,2	8	18,8	17,8
9	20	18,7	9	19,3	18,7	9	18,5	18,4
10	19,4	18,8	10	19,4	18,8	10	18,4	18,6
11	19,2	18,6	11	19,3	18,8	11	18,6	18,4
12	19,4	18,8	12	19	18,6	12	18,4	18,4
13	18,9	18,7	13	18,9	18,3	13	18,7	18,8
14	19,4	18,8	14	18,8	18,9	14	18,7	18,6
15	19,4	18,4	15	19,4	18,9	15	18,9	18,4

Test 12

Run 1			Run 2			Run 3		
Minute	Left	Right	Minute	Left	Right	Minute	Left	Right
1	19	18,9	1	19,3	18,3	1	18,7	18,4
2	19	19,2	2	18,5	18,8	2	18,8	18,7
3	18,8	18,6	3	20	19,3	3	18,9	18,7
4	18,7	18,7	4	19	18,6	4	18,8	18,7
5	18,7	19	5	18,9	18,3	5	19	18,4
6	18,9	18,5	6	18,8	19	6	18,8	18,3
7	19,1	18,7	7	18,8	18,5	7	18,9	18,8
8	19,4	18,6	8	19,3	19	8	18,8	19
9	18,8	17,9	9	18,8	18,7	9	19,1	18,7
10	20,1	19,1	10	19	18,9	10	18,9	18,3
11	19	18,8	11	19	18,9	11	19,2	18,7
12	19,4	18,8	12	19	18,4	12	19	18,6
13	19,1	18,8	13	19,2	18,3	13	19,3	18,8
14	19,1	18,5	14	19,4	18,4	14	19,7	18,2
15	19,4	18,5	15	18,9	17,8	15	19,7	18,8