Describing Simulation of Upcoming Wounds for Testing the Bad Mat Device

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Abstract

In 2019, the diabetes mellitus prevalence was estimated to be 1.1 million people in the Netherlands. A common complication of diabetes is the development of Diabetic Foot Ulcers (DFUs). Diabetic Foot Ulcers have a high chance of becoming infected and approximately 20 per cent of the DFU infections will lead to some stage of amputation. For this reason, it is important to detect DFUs in an early stage to prevent infection and further development of these wounds. To detect DFUs in an early stage the feet should be checked daily. However, this is not as simple because patients do not always have the motivation and sometimes even not the possibility to check their feet. Therefore, a device which measures the temperature differences at the feet to track upcoming wounds will be developed. However, this is quite difficult because, for about 40 per cent of the patients, these wounds recur within one year, 60 per cent within three years and 65 per cent within five years. So there is a low chance of recurrence and there is little known about how the development of upcoming wounds works in diabetic patients and little is known about the temperature differences in these wounds.

Risk factors for developing DFUs are neuropathy (damage of the nerves in the feet through nitric oxide blocking and the Maillard reaction), peripheral artery disease (PAD, systemic atherosclerosis in the coronary and cerebral arteries leading to obstruction of the blood vessels which leads to poor circulation resulting from endothelial dysfunction, inflammation, platelet aggregation and vascular smooth muscle cell dysfunction), mechanical stress (development of pressure points which may lead to callus), immunopathy (due to hyperglycaemia and results in infections which leads to poor diabetic control). When a DFU develops, only in the first few days of wound healing an increase in temperature can be observed. A temperature difference of 2.2 °C between both feet indicates an upcoming ulcer. Neuropathy gives larger temperature differences in wound healing, but in general, neuropathy leads to higher mean foot temperatures. It is not clear what the influence of PAD is on temperature measurements of DFUs and on the feet itself. Researchers do not agree on this subject. (Upcoming) DFUs under callus cannot be observed by eye, but can with thermography.

Due to the small chances of measuring upcoming wounds and to better understand the process and variances of upcoming wounds, the DFUs should be simulated. To be able to simulate upcoming wounds, a 3D silicone foot phantom has been developed with heated tubing through the foot. Hereby, a first model with 1 tube has been moulded to prove the working principle of leading tubes with warm water through the foot to simulate the temperature distribution in the foot. Further research needs to be performed to optimize the temperature distribution and to vary the temperature to simulate upcoming diabetic foot ulcers.

Contents

1 Introduction

In 2019, the diabetes mellitus prevalence was estimated to be 1.1 million people in the Netherlands [1]. Worldwide, the prevalence is estimated at 537 million people between 20 and 79 years old in 2021 [2]. Diabetes mellitus results from either hyposecretion or hypoactivity of insulin [3]. Long-term, patients can develop vascular and neural problems which can lead to e.g. strokes, kidney shutdown, blindness, impaired bladder function and peripheral neuropathy [3]. The last, neuropathy, can lead to loss of sensation in for example the feet. In diabetes, one of the most common complication is Diabetic Foot Ulcer (DFU). Usually, it results from underlying neuropathy, peripheral vascular disease, poor glycemic control or poor foot care [4]. This complication has an estimated lifetime incidence of 19 to 34 per cent in diabetic patients. More than 50 per cent of the DFUs become infected and approximately 20 per cent of diabetic foot infections will eventually lead to some stage of amputation. [5]

To detect DFUs in an early stage, daily checks should be carried out. However, patients often have low motivation for these daily checks and sometimes it is even impossible for patients to check the bottom of their feet themselves. Researchers have attempted to diagnose DFUs at a pre-stadium by measuring the temperature of the surface of the plantar side of the foot to identify abnormal temperatures. This can be a sign of an increased risk of DFUs. Currently, the University of Twente and ZiekenhuisGroep Twente (ZGT) are working on a technology to measure temperature differences at the diabetic foot to detect possible DFUs at an early stage. This so-called Bath Mat (Figure 1) measures the temperature distribution of both the foot's dorsal and plantar sides. This is performed by placing the foot on a mat, taking an image from the dorsal side of the foot (direct measurement), subsequently removing the foot from the mat and taking an image from the thermal footprint left on the mat made of memory foam (indirect measurement of the plantar side) [6].

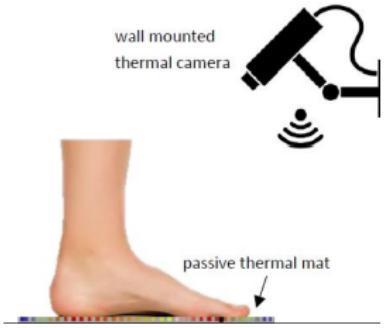


Figure 1: *Set up of Bat Mat with a thermal camera. BRON*

However, it is known that the skin sometimes warms up before a wound develops, but sometimes it does not. Also, due to calluses, it may be difficult to measure temperature differences in these wounds. Moreover, for about 40 per cent of the patients these wounds recur within one year, 60 per cent within three years and 65 per cent within five years [5]. This means for a group of 10 patients, 1 patient may develop a wound after measuring 10 patients each day for half a year (183 days). This makes it difficult to predict the upcoming wounds in a clinical setup. Therefore, it is urgent to simulate the moment the wound develops. To simulate this, it is important to understand the process of how a wound develops, what the principle of cold and warm wounds is and what the influence of calluses is on the temperature change at the surface of the skin. The main question which should be answered during this internship will be:
How do foot ulcers in patients with diabetes mellitus develop especially in the pre-stage? How can the foot ulcer development process be simulated?

Subquestions:

- What are important factors that contribute to the development of a Diabetic Foot Ulcer (DFU)?
- What mechanisms cause the foot to heat or cool down in DFUs?
- What is the influence of calluses on temperature measurements of foot ulcers at the skin surface?
- What temperature difference can be measured during the different stadia in the development of wounds?
- How can the temperature change related to DFU development be simulated? What are the requirements to simulate the foot ulcer development process?

2 Diabetic Foot Ulcers

Diabetic foot ulcers (DFUs) are (open) wounds that do not heal well or keep returning [7]. 19 to 34 per cent of diabetic patients develop a DFU and thereby it is the most common complication of diabetic mellitus patients [5]. DFUs result from underlying neuropathy, peripheral artery disease, poor glycemic control, cellulitis and/or poor foot care. Patients with diabetes and blood circulation issues, heart disease, obesity, a foot condition, kidney disease or certain lifestyle behaviours like using alcohol are at higher risk of developing DFUs. The area of the foot where DFUs usually occur are the places of pressure points and where repetitive trauma occurs. [4, 7]

2.1 Classification

DFUs can be classified based on the severity of the wound. In an early stage, the wound is still closed and the skin looks irritated and red when pressure is applied. This irritation will not go away when the pressure is relieved (Figure 2). In the next stage, the skin is broken for the first time, but still superficial. The wound looks like a blister or shallow crater and it is painful and tender. In stage three, the ulcer penetrates deeper into the tissue. It is possible that the patient will not feel pain due to severe nerve or tissue damage. The last stage is characterized by the observation that the ulcer reaches muscles, bones and tendons. Also in this stage, is it possible that the patient cannot feel pain. Infections or other serious complications may occur such as Staphylococcus. In hospitals, the Texas classification system is helpful to indicate the severity of the ulcer and is helpful to predict amputation. The system is based on the depth of the ulcer and whether the ulcer is infected or whether the patient has an ischemic foot. This divides the patients into four groups (Figure 3). The severity may also be classified in a classification system based on the size (area, depth), sepsis, arteriopathy and denervation of the ulcer. This system is called the S(AD)SAD system and is more used by audits. This classification contains five elements to which a grade between zero (not applicable) to three (worst) is given according to severity, size (area and depth), infection, ischemia and neuropathy as shown in Figure 4. All these five elements together will give an overview of how severe the ulcer is.

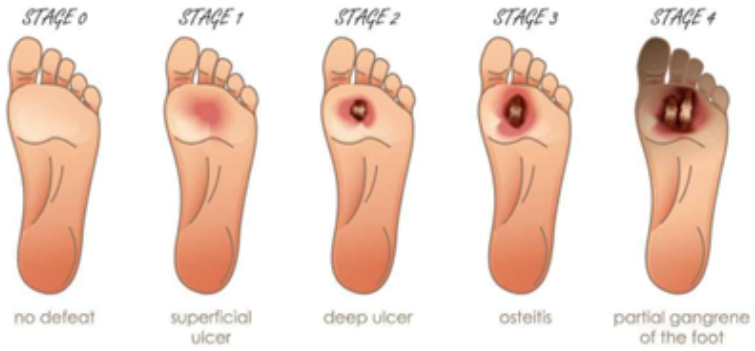


Figure 2: *Different stages of diabetic foot ulcers with stage 0 no ulcer observed up to stage 4 where a severe ulcer can be observed with bone contact. Adapted from [8]*

	Grade 0	Grade 1	Grade 2	Grade 3
	Pre- or post-ulcerative site	Superficial wound not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Ulcer penetrating to bone of joint
Lesions without infection or ischemia				
Infected/non-ischemic lesions				
Ischemic noninfected lesions				
Ischemic infected lesions				

Figure 3: *Texas classification system based on the depth of the ulcer (horizontally) and whether there is an infection and/or ischemia (vertically). Based on [9]*

Grade	Size		Sepsis	Arteriopathy	Denervation
	Area	Depth			
0	Skin intact	Skin intact	None	Pedal pulses present	Pin pricks intact
1	< 1 cm^2	Superficial	Surface	Pedal pulses reduced or one missing	Pin pricks reduced
2	1-3 cm^2	Tendon, periosteum, joint capsule	Cellulitis	Absence of both pedal pulses	Pin pricks absent
3	> 3 cm^2	Bone or joint space	Osteomyelitis	Gangrene	Charcot

Figure 4: *The size (area, depth), sepsis, arteriopathy and denervation system to describe the severity of the diabetic foot ulcers. To each element, a grade can be given from 0 (not applicable) to 3 (very much applicable). Based on [9]*

2.2 Risk factors

Multiple risk factors increase the chance of developing DFUs. These include peripheral neuropathy, peripheral arterial disease, mechanical stress and previous ulcers and/or amputation. In the following paragraphs, these risk factors will be described (except for previous ulcers and/or amputations).

2.2.1 Peripheral neuropathy

60 per cent of the DFUs [10] is caused by neuropathy. Diabetic neuropathy is a condition where the nerves are damaged significantly in the legs and feet. As the sensory nerves are damaged, the body's feeling decreases and patients cannot feel injuries or infections. The most common types are peripheral neuropathy

and autonomic neuropathy. Peripheral neuropathy impaired the feet and legs in the first stadium, and later also the hands and arms. Common symptoms are reduced pain and temperature feeling, muscle weakness and severe foot problems such as ulcers and damage to the bone. Due to muscle weakness, there can be an imbalance between flexion and extension of the feet new pressure points and abnormal bone growth. This can result in a breakdown of the skin which may lead to ulceration. Autonomic neuropathy affects the autonomic nervous system which controls for example sweating, blood pressure and heart rate. This type of neuropathy is recognized by hypoglycemia unawareness, orthostatic hypertension, difficulties swallowing and increased or decreased sweating. Decreased sweating can cause dry skin which contributes to ulceration.

Neuropathy is associated with 2 mechanisms, namely nitric oxide blocking and the Maillard reaction between sugars and amino acids. Hyperglycemia blocks endothelial nitric oxide synthase activation which results in an inhibition of the production of nitric oxide. This leads to an increase in reactive oxygen species, especially superoxide which is converted to hydrogen peroxide. Hydrogen peroxide is then converted to a highly reactive and damaging hydroxyl radical which can bind to nitric oxide. This process affects the vasoconstriction response, platelet aggregation, inflammation and atherothrombosis formation. [10, 11] The Maillard reaction is a complex reaction between reducing sugars and amino groups of biomolecules which leads to the production of advanced glycation end products (AGEs). These AGEs have a role in the pathogenesis of atherosclerosis. The production of some enzymes is increased due to hyperglycemic conditions. These enzymes, aldose reductase and sorbitol dehydrogenase, convert glucose into sorbitol and fructose through the polyol metabolic pathway. In this pathway, nicotinamide adenine dinucleotide phosphate (NADPH) is further reduced, which results in NADPH depletion which affects the normal synthesis of important antioxidants. Both the increase in reactive oxygen species and the NADPH depletion play a crucial role in the pathogenesis and complications of diabetes. Next to that, neuropathy affects the production of nerve growth factors substance P and calcitonin gene-related peptide. These neuropeptides promote cell proliferation, production of growth factors and chemotaxis, thereby important for wound healing and a decrease in neuropeptides may lead to a DFU. [10, 11, 12]

2.2.2 Peripheral artery disease

Peripheral artery disease (PAD) is caused by systemic atherosclerosis in the coronary and cerebral arteries. Atherosclerosis, the narrowing of the blood vessels, can progress to an obstruction of the vessels and thereby cause a reduction of blood flow to and from the organ or limb. This limits the ability to deliver nutrients and remove waste. With a lack of perfusion hypoxia arises which is a lower partial pressure of oxygen in the tissue than normally [13]. Hypoxia together with an infection, pain, or hyperthermia can cause a poor healing outcome for DFUs [13]. Major risk factors of PAD are diabetes mellitus, hypertension, smoking, and hyperlipidaemia. [14]

Mechanisms associated with PAD are endothelial dysfunction, inflammation, platelet aggregation and vascular smooth muscle cell (VSMC) dysfunction. Endothelial dysfunction affects microcirculation, leading to changes in the proliferation of endothelial cells, the thickness of the basement membrane, a decreased synthesis of nitric oxide (NO), increased blood viscosity, alterations in microvascular tone and finally a decreased blood flow. [10] Vascular endothelium is a characteristic of atherosclerosis in diabetic patients which arises from different pathogenetic factors. Firstly, the dormant polyol pathway is activated by chronic hyperglycaemia which causes an increased oxidative stress from reactive oxygen species. This is caused by the consumption of cofactor nicotinamide adenine dinucleotide phosphate and also by reduced glutathione. Chronic hyperglycaemia has also other effects, namely causing the production of advanced glycation end-products, thereby stimulating inflammatory cytokines and growth factors that certainly result in vascular injury. Next to that, chronic hyperglycaemia induces the activation of protein kinase C. This affects the activation of proinflammatory genes such as nuclear factor kB, which causes in the end an induction of the production of NO, which influences vasodilation and protects the blood vessels from the wound. NO reduces

inflammation and plays a role in the inhibition of VSMC migration and platelet activation. All in all, this causes leucocyte chemotaxis, adhesion and migration into the intima and a higher endothelial permeability which results in inflammation. Secondly, when the endothelium is injured, activators of platelet adhesion, activation and aggregation play a role. Together with hyperglycaemia, the glucose uptake by platelets is not checked and there will be abnormalities of coagulation. This includes for example an inhibition of antithrombin and protein C concentration, impaired fibrinolytic function and an excess PAI-1 production. Thirdly, due to the effects hyperglycaemia has on endothelial injury and intima inflammation, hyperglycaemia also plays a role in VSMC dysfunction. VSMC migration and proliferation are initiated by proinflammatory mediators such as vascular endothelial growth factors and cytokines in the inflammatory place of the intima. VSMC together with endothelial foam cells result in fatty streaks which become an atheromatous plaque. This plaque can grow so large that it can obstruct the blood vessel thereby reducing the blood flow. [10, 14]

2.2.3 Mechanical stress

Mechanical stress on the foot can cause a transformation of the anatomical structure, which may lead to deformities such as abnormal bone growth and pressure points. This can lead to a DFU. Also, metatarsal fat pads become stranded. This reduces the cushioning result of the metatarsal heads such that pressure points arise which leads to the formation of callus. Callus can induce skin damage and lead to DFUs. When patients also have neuropathy, the loss of sensation and limited joint mobility in the foot can lead to abnormal biomechanical loading of the foot which produces pressure in some areas and causes the production of callus in those spots. [10]

2.2.4 Immunopathy

Diabetic patients have a weaker immune system compared to healthy people. The previously explained hyperglycaemia plays here a large role in causing an elevation of pro-inflammatory cytokines and impairment of chemotaxis, phagocytosis and intracellular killing. The immune system has lowered leukocyte activity, inappropriate inflammatory response and a disruption of cellular immunity. Some parts of the foot are interconnected and due to the weak response to infections, the infection may spread to other parts of the foot. All of this together causes a longer and weaker response to injury which may also lead to more severe ulcers and complications. Also, the infection adversely affects diabetic control. This results in a repetitive cycle which leads to uncontrolled hyperglycemia that worsens the response to an infection. [10]

3 Temperature in wound development

3.1 Normal wound healing

Wound healing can be described in 3 phases: inflammation, proliferation and remodelling [15, 16]. These phases overlap in time. This requires close cooperation of growth factors, matrix components, different cells, cytokines, proteases and protease inhibitors. The first phase of wound healing is always acute inflammation [17], which includes vascular response (blood coagulation and hemostasis) and cellular events (supplying growth factors and antimicrobial and cytokine release that coordinate the movement of cells and tissue for the repair of the wound). This phase normally takes about 2 days, but can take up to 2 weeks in some cases. and begins when platelets come in contact with exposed collagen, a haemostatic plug will form and neutrophils are entrapped and aggregated whereafter the coagulation cascade starts. Clotting factors are released, which form a matrix at the site of the damage. Around day 3, there is a peak in the level of proteases. These proteases are a vital part of the healing process and are regulated by enzyme inhibitors. [15, 16]
Early in the inflammation phase [16], local vasodilatation, blocking of lymphatic drainage, and blood and fluid in the extravasation into the extravascular space causes redness, swelling and a temperature increase of the skin. The increasing temperature of the skin comes from endogenous pyrogens which act on the central nervous system (anterior hypothalamus) in response to inflammation and/or enzymatic autolysis of tissue [18, 19]. A wound with normal healing has an increased temperature in the first few days and should return to a baseline within a period of two weeks [20].

In diabetic patients with emerging ulcers, a comparison is often made between both feet to determine whether a temperature difference of more than 2.2°C can be observed [21]. An increased temperature at the place of a DFU may be present up to a week before the DFU develops. With off-loading the development of an ulcer may be prevented [21].

3.2 Chronic wounds

In some wounds [16], the inflammation persists for months to years. They remain 'stuck' in a chronic inflammation state, characterized by neutrophil infiltration and increased protease activity [15]. These wounds are called chronic wounds. Characteristics of these wounds [16] are that a wound can be sealed by death tissue, contains foreign material which cannot be removed or is contaminated with pathogens. Due to the prolonged inflammatory phase, an excess of proteases and inflammatory cytokines are released. It is yet not clear how changes in wound fluid correlate with local factors such as tissue perfusion, heat and pH changes. Risk factors [12] for such wounds are for example, venous insufficiency, infection, oxygenation, stress, venous stasis disease, pressure ulceration, diabetes, vasculitis and ischaemia. Chronic wounds [16] are usually not characterized by redness, swelling or a temperature increase. In research of Kruse [22], even a temperature decrease of about 5 degree Celsius was found in chronic wounds compared to the core temperature due to impaired blood supply and oxygenation. Underlying comorbidities together with local stimuli may prolong the inflammatory phase [15]. Increased pain and wound size are reliable markers of wound infection in chronic wounds. Also, a sudden increase in temperature (1.1°C) can also be a sign of infection [22, 23].

4 Influences on temperature measurements

4.1 Influence of Neuropathy

Patients with severe neuropathy have a significantly larger skin temperature gradient compared to patients with smaller degrees of peripheral neuropathy. However, these patients do not have significantly higher plantar pressures [24]. An elevated mean foot temperature gives an indication of an increased risk for neuropathic foot ulceration. As shown in Figure 5, the temperature difference is quite high in week 1 of the DFU treatment (after patients had received primary care) and the temperature difference decreases over time. A smaller difference in temperature is observed when the surface area of the ulcer decreases [24, 25].

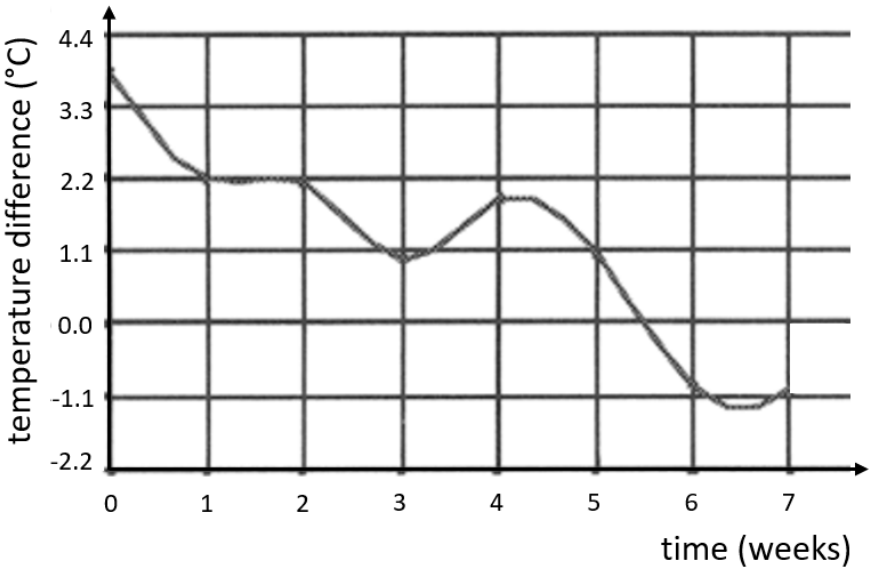


Figure 5: *Mean temperature differences between the ulcerated foot and contralateral extremity over time during treatment (with a cast) of a diabetic, neuropathic foot ulcer. Adapted from [24].*

4.2 Influence of PAD and Ischaemia

A lot of research has been performed on the influence of ischaemia and PAD on wound healing, but researchers do not share the same conclusion. In research of A. Gatt [26, 27, 28] found a higher forefoot temperature (28.3 °C versus 26.2 °C) in diabetes patients with PAD compared with diabetes patients without PAD. M. Carabott [29] also found significantly higher forefoot temperatures in patients with mild and severe PAD. Between mild and severe PAD, no difference was found. In this research, patients with foot ulceration were excluded. So, the research only looked at the influence of PAD on foot temperatures. S. Spiliopoulos [30] looked at patients with and without diabetes and with and without critical limb ischaemia. Thereby was found that there were differences in temperature between measurements of the patients with and without diabetes, but with critical limb ischaemia. However, there was a significant difference in temperature measurements between the control group and patients with neuropathic ulcers. The patients with critical limb ischaemia had a significantly lower temperature (29 °C versus 33 °C). Shuxin Li [23] looked at ischaemic chronic wounds. In these wounds, a lower temperature was found, probably due to the decreased blood flow to the wound. Other researchers [25, 31] also looked at critical limb ischaemia and PAD. These researchers studied mostly literature. In all of these researches, a decrease in temperature was found or assumed due to insufficient blood flow and a slow healing process.

Both A. Gatt and M. Carabott expected a decrease in temperature. In the discussion, M. Carabott [29] gives the following explanation: "An explanation for high heat emissivity could be due to an alteration in normal mechanisms that regulate temperature in the feet. Local ischaemia may lead to disruption of sympathetically mediated noradrenergic vasoconstriction, leading to increased flow to the cutaneous vessels rather than through the deeper arteries, thus leading to this higher heat emissivity." In short, instead of blood running through the deeper arteries which are blocked, the blood would run through the cutaneous vessels which would give higher heat emissivity at the skin. This should be performed with arteriogenesis [32], which describes the enlargement of existing collateral vessels due to increased shear stress due to higher blood flow through those vessels. However, this does not come naturally in PAD patients. It is probably possible to activate arteriogenesis when patients increase their cardiac output by exercising. Next to that, angiogenesis, the formation of new capillary vessels, could be a possibility that the temperature increases in patients with PAD and ischaemia. However, diabetes mellitus causes impaired angiogenesis, so limits the adaptive angiogenesis response and remodelling process [33]. All in all, an increase in temperature does not seem logical.

4.3 Influence of callus

Callus is defined as "localized hyperplasia of the horny layer of the epidermis due to pressure or friction" [34]. Callus is the most important cause of ulceration in the diabetic foot. About 82 per cent of the ulceration was caused by callus formation. However, only 11 per cent of the places with callus formation results in ulceration [35]. In neuropathy, there is also a relatively high chance of ulceration under the callus. In the regions around the callus, temperature changes may be observed when there is inflammation. These are so-called 'hotspots' and can progress to ulceration. In the regions with thick callus, it is difficult to observe inflammation by eye. However, when using non-contact thermography an increase in temperature can be observed when there is (latent) inflammation under the callus. Bilateral comparison is difficult since the callus can be often found at the same place on both feet, but inflammation under the callus on one foot can be visualized with thermography. [34, 35] When there is no inflammation visible, the callus cannot be separated with thermography [36].

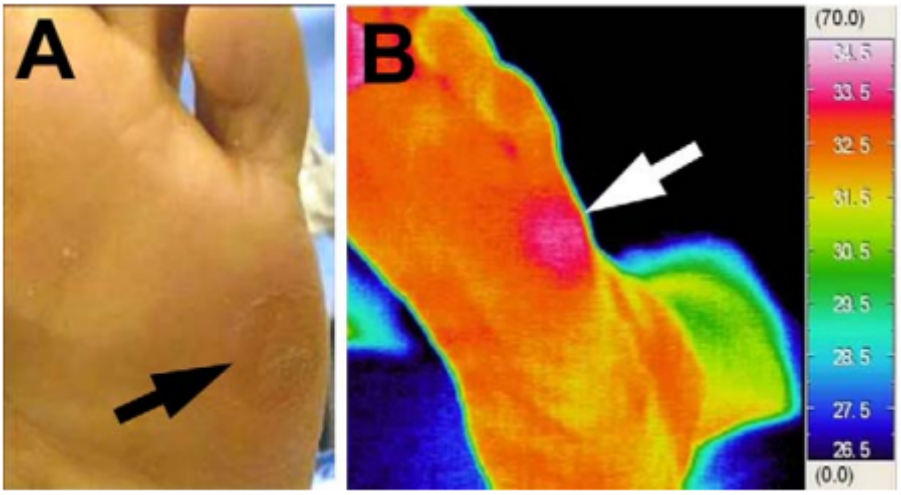
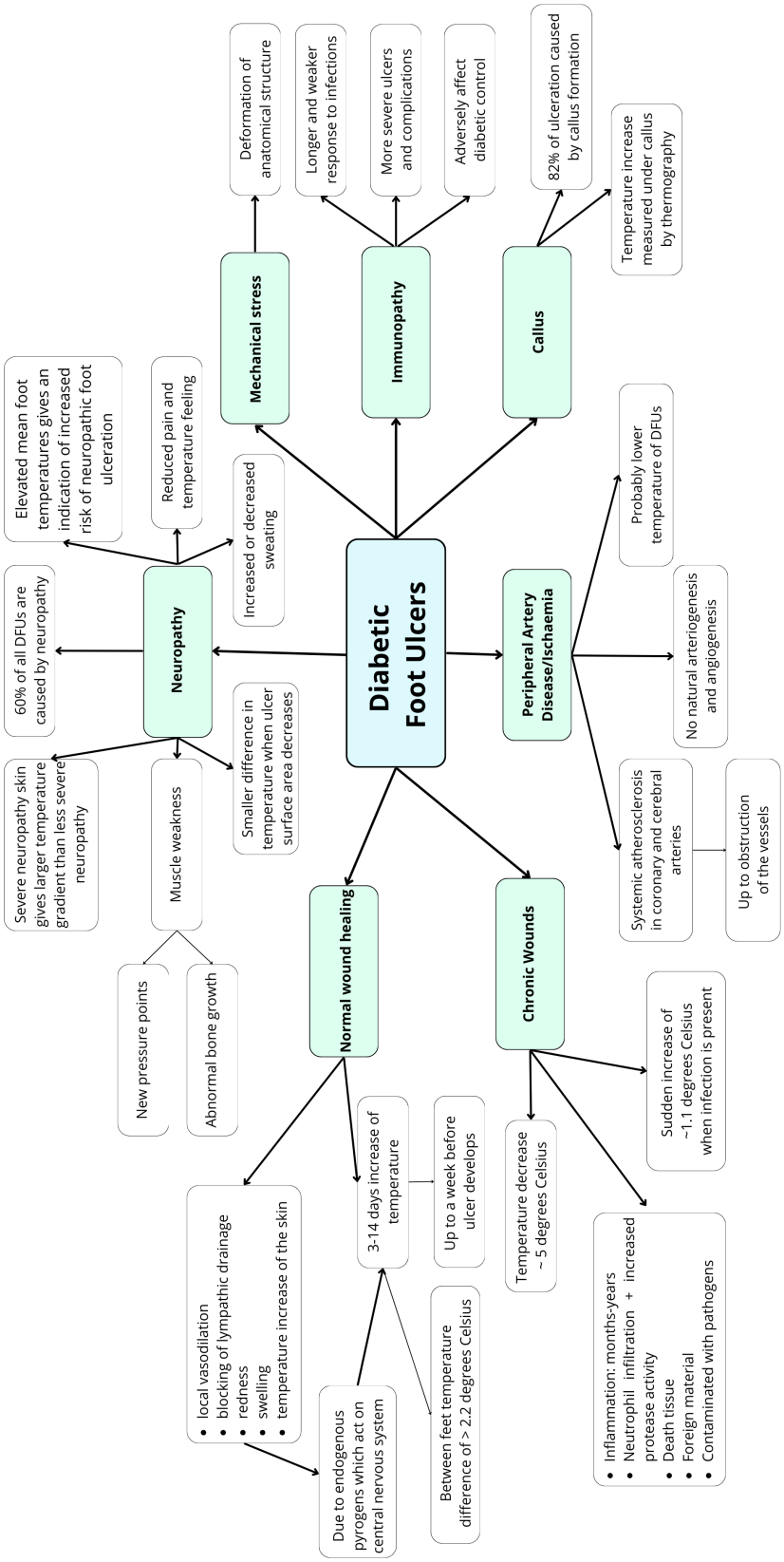


Figure 6: *A) Photograph of a foot with callus (indicated by black arrow). B) Thermal image of a foot with callus (indicated by white arrow). A clear increase in temperature can be observed. [34]*

4.4 Flow cart


Diabetic Foot Ulcers
Neuropathy
Peripheral Artery Disease/Ischaemia
Normal wound healing
Chronic Wounds
Mechanical stress
Immunopathy
Callus
Deformation of anatomical structure
Longer and weaker response to infections
More severe ulcers and complications
Adversely affect diabetic control
82% of ulceration caused by callus formation
Temperature increase measured under callus by thermography
Elevated mean foot temperatures gives an indication of increased risk of neuropathic foot ulceration
Reduced pain and temperature feeling
Increased or decreased sweating
60% of all DFUs are caused by neuropathy
Severe neuropathy skin gives larger temperature gradient than less severe neuropathy
Muscle weakness
Smaller difference in temperature when ulcer surface area decreases
New pressure points
Abnormal bone growth
Probably lower temperature of DFUs
No natural arteriogenesis and angiogenesis
Systemic atherosclerosis in coronary and cerebral arteries
Up to obstruction of the vessels
local vasodilation
blocking of lympathic drainage
redness
swelling
temperature increase of the skin
Due to endogenous pyrogens which act on central nervous system
3-14 days increase of temperature
Up to a week before ulcer develops
Between feet temperature difference of > 2.2 degrees Celsius
Temperature decrease ~ 5 degrees Celsius
Sudden increase of ~1.1 degrees Celsius when infection is present
Inflammation: months-years
Neutrophil infiltration + increased protease activity
Death tissue
Foreign material
Contaminated with pathogens

5 Discussion

Measuring upcoming wounds has multiple difficulties regarding small changes of upcoming wounds and over time no difference in temperature due to going into the stadium of chronic wounds or the fact that the infection may stop. Due to the small chance of an upcoming wound to occur (recurrence of 65 per cent within five years [5]) there is not much known at the first stage of upcoming wounds. It is known that there is an increased temperature due to inflammation up to the first two weeks [20], but there is not yet any information about how much this exactly is. This makes it difficult to observe DFUs in an early stage.
Next to that, there is a great variance in diabetic patients. Some patients have neuropathy, which may cause warmer feet in general. The study of Armstrong [24] shows some information about neuropathy and DFUs, but this is only in the weeks after treatment with a cast and not in an early stage. Studies about patients with PAD or ischaemia and DFUs do not agree on the temperature measurements of the feet of ischemic patients and temperature measurements of DFUs. So, about the DFUs of these patients not much is known, making it difficult to understand the difference in temperature in an early stage.
When a DFU is present under the callus, this cannot be observed by the eye. When measuring with thermography, inflammation under the callus can be observed. For direct measurements (e.g. with a thermometer [37]) on the callus this may be not the case. DFUs under the callus cannot be observed by eye which indicates that the inflammation cannot be measured on the surface, but only under the surface. This explains why research of Aan de Stegge [37] did not find an increase in temperature, but with thermography [34] an increase can be observed.
Due to the difficulties of observing wounds in an early stage, it is difficult to measure patients and create a dataset of different patients with upcoming wounds. Therefore, it is important to create a dataset ourselves with upcoming wounds to let the Batmat recognize whether an upcoming wound occurs or not. This needs to be performed in for example digital simulations or simulations with a prototype/phantom.

6 Conclusion

To conclude, DFUs can be classified into different systems. A lot about Diabetes Mellitus is known just like the development of neuropathy, ischaemia and other causes which influence the formation of DFUs. However, how inflammation and temperature play a role in the development of a DFU is not well known. Neuropathy in general gives higher foot temperatures and higher temperature differences during ulceration. Regarding ischaemia, researchers do not agree on the influence of temperature on the feet and DFUs. Also, not much is known about the early stage of the development of DFUs. Callus can be measured with thermography when inflammation is visible. All in all, foot ulcers develop through different mechanisms and there are multiple risk factors for developing DFUs regarding peripheral neuropathy, peripheral artery disease and ischaemia, mechanical stress and immunopathy. The exact temperature differences could not be found in the literature, so should be further investigated in different situations such as patients with peripheral neuropathy and/or peripheral artery disease or ischaemia.

7 Design

To measure an upcoming diabetic foot ulcer, the feet of 10 patients should be measured each day for half a year and then 1 patient might develop a wound. To have enough measurements of upcoming DFUs, a large group should be measured for a long time to demonstrate that the Bat Mat (section 1) works. This would be very time-consuming. To prevent this, a physical model of the foot can be developed to simulate an upcoming diabetic foot ulcer. In the following paragraphs, requirements for the physical model, sketches and calculations will be drawn and explained.

7.1 Requirements

- The model should be in the shape of the foot.
- The model should have the dimensions of a foot (of a child or adult).
- The temperature should be regulated in different small, local areas.
- The temperature should be distributed as physiology indicates.
- The temperature can be varied over time.
- The model should be able to maintain the same temperature over an hour.
- The model should be able to indicate an ulcer by changing the temperature locally over 2.2 degrees Celsius.
- The model should be made from a strong but flexible material, in such a way that the foot does not plastically deform when an impression is made.
- The model should be able to conduct heat.
- The model should be heated uniformly.
- The model should be able to be heated at both the top and bottom.

7.2 Steps to take

In the process of designing a phantom foot model, different steps need to be taken. In this report, the first 2 steps will be elaborated and for the third step, different designs will be explained in the next section.

- **Phantom without tubes**
  Goal: To check if the moulding mechanism can be used for the foot model.
- **Calculations of temperature distribution for one tube**
  Goal: To calculate how the temperature would be distributed over space, the temperature of the water inside the tube and what the setup time is.
- **Phantom with one tube through the foot**
  Goal: To check if the moulding mechanism can also be used for a phantom with tubes and to see the temperature distribution over the foot with one tube and check whether the calculations were right.
- **Sketches for phantom with tubes through the foot**
  Goal: To make sketches to indicate how the tubes should be aligned in a model with multiple tubes.

- **Calculations of temperature distribution for multiple tubes**
  Goal: To calculate how the temperature would be distributed over space, the temperature of the water inside the tubes and what the setup time is for a model with multiple tubes.

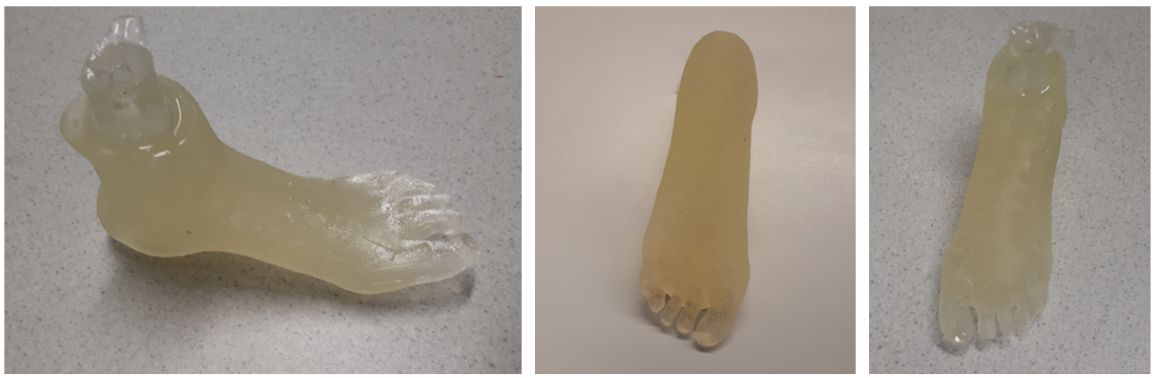
- **Phantom with tubes through the foot**
  Goal: To make a realistic phantom with a good temperature distribution of a healthy subject.

- **Phantom with rotary knobs to regulate the temperature**
  Goal: To make a realistic phantom in which the temperature can be regulated to simulate different cases.

- **Simulate diabetic foot ulcers**
  Goal: To simulate DFUs with a thermal camera and to make a realistic dataset of direct plantar feet images and indirect feet images using the Batmat.

7.2.1 Phantom without tubes

A 3D foot model mould has been 3D printed and filled with silicone. The procedure of moulding and passing tubes through the foot can be found in Appendix A Protocols. First, a model was moulded out of silicone without any tubes through the foot to make a stable model and to get familiar with moulding out of silicone. This model (Figure 7) was the first experiment. The model is about 10 cm in length and 4 cm wide. Remarkable is that there were a lot of air bubbles inside the phantom. This turned out that there were some deformities in for example the hallux (dig I) and at the medial side of the foot. Also, the air bubbles create a decreased uniformity.



A B C

Figure 7: *3D foot phantom moulded out of silicone. A) Medial view of the foot B) Plantar view of the foot. C) Dorsal view of the foot. At the large toe, an air bubble is visible.*

7.2.2 Calculations

To understand the heat transfer through the different materials and setting up the initial temperature, calculations should be performed. The heat of the foot should be isothermally divided. An assumption is made that there is a 1D steady heat conduction through the wall [38].
Through the foot, different tubes are placed. These are placed 1 cm from the bottom of the foot and at a 2 cm distance from each other. In such a way, the heat conductivity through the material can be calculated and an isothermal profile can be created. To analyze the heat transfer, an overview of the situation is displayed (Figure 8). In the middle water is running through a PE tube. The tube is surrounded with silicone and is placed in air at 20 degrees Celsius.

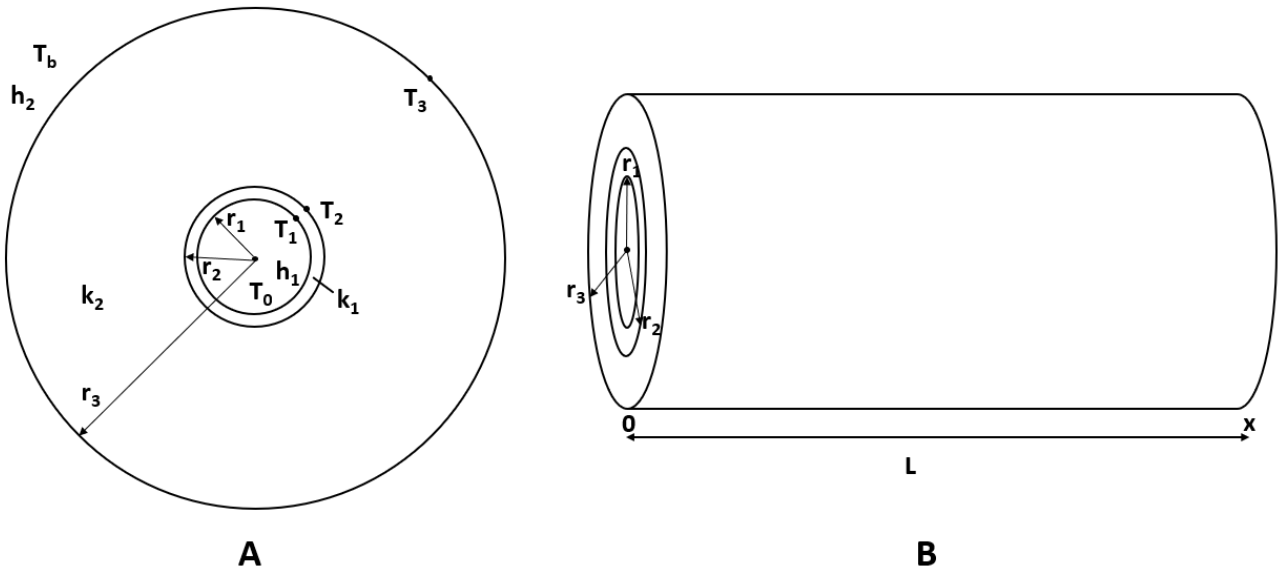


Figure 8: *Overview of the situation A) Intersection of a round phantom where the distance from the tube to air at each point equal is, with r1: the inside radius of the tube, r2: the distance up to the outside of the tube, r3: the distance up to the outside of the phantom model. B) Side view of a round phantom with length L.*

First, the resistance R [m °C W^{-1}] in the different layers of Figure 8 can be formulated as follows:

$$R_{tot} = R_{conv_1} + R_{cycl_1} + R_{cycl_2} + R_{conv_2} \tag{1}$$

with

$$R_{conv1} = \frac{1}{h_1 A_1} \tag{2a}$$

$$h_1 = \frac{k_2 Nu_1}{2r_1} \tag{2b}$$

$$R_{cycl1} = \frac{\ln(r_2/r_1)}{2\pi k_1} \tag{2c}$$

$$R_{cycl2} = \frac{\ln(r_3/r_2)}{2\pi k_2} \tag{2d}$$

$$R_{conv2} = \frac{1}{h_2 A_2} \tag{2e}$$

$$h_2 = \frac{k_2 Nu_2}{2r_3} \tag{2f}$$

with h: heat transfer coefficient [W m^{-2} °C^{-1}], A: Area per length unit [m], k: thermal conductivity [W m^{-1} °C^{-1}], Nu: Nusselt number [-] and r: radius [m]. with Nusselt number defined as follows:

$$Nu = \{0.6 + \frac{0.387 Ra_D^{1/6}}{[1 + (0.559/Pr)^{9/16}]^{8/27}}\}^2 \tag{3}$$

with Rayleigh number (Ra) as follows:

$$Ra_L = Gr_L Pr \tag{4a}$$

$$Gr_L = \frac{g\beta(T_3 - T_b)L_c^3}{v_{kin}^2} \tag{4b}$$

with g: gravitational acceleration [m/s^2], β: coefficient of volume expansion [1/K], L_c: characteristic length (diameter in this case) [m], v: kinematic viscosity of the fluid [m^2/s].

The heat difference over the length of the tube is calculated in order to understand the heat loss over the length of the tube.

$$\dot{Q} = \rho \dot{V} C_p \Delta T \tag{5}$$

with $\dot{Q}$: heat transfer [W], ρ: density [kg/m^3], $\dot{V}$: flow rate [m^3/s], C_p: heat capacity [J/kgK] and ΔT: temperature difference [K] Next, the energy balance ($E_{in} = E_{out}$) can be formulated:

$$\rho \dot{V} C_p \Delta T = \frac{T_a - T_b}{R_{tot}} \tag{6}$$

and the derivative can be taken:

$$\dot{q} = \rho \dot{V} C_p \frac{dT}{dx} \tag{7a}$$

$$\dot{q} = \frac{-T(x) - T_b}{R_{tot}} \tag{7b}$$

with $\dot{q}$: heat loss over length x [W/m], R_{tot}: resistance [W^{-1} m^{-1} °C^{-1}]; defined in equation 1, $T(x)$: the temperature at a certain point x [°C], T_b: the outside temperature [°C] (see Figure 8). Which gives:

$$\frac{1}{T(x) - T_b} \frac{d(T(x) - T_b)}{dx} = \frac{1}{\rho \dot{V} C_p R_{tot}} \tag{8}$$

$$T(x) = T_b + C_2 e^{-\xi x} \tag{9}$$

with $\xi = \frac{1}{\rho \dot{V} C_p R_{tot}}$
at $x = 0$: T(x=0) $= T_0$, $C_2 = T_0 - T_b$, which gives:

$$\frac{T(x) - T_b}{T_0 - T_b} = e^{-\xi x} = e^{-\frac{x}{\rho \dot{V} C_p R_{tot}}} \tag{10}$$

which can be rewritten to:

$$\dot{q} = \frac{T_0 - T_b}{R_{tot}} e^{-\frac{x}{\rho \dot{V} C_p R_{tot}}} \tag{11}$$

Equation 11 represents the heat loss over the length of the tube at position x. In order to understand how the heat loss is in each layer, the temperature [°C] in each layer at each position x can be calculated.

$$T_{in} = T_b + (T_0 - T_b) e^{-\frac{x}{\rho \dot{V} C_p R_{tot}}} \tag{12a}$$

$$T_1 = T_{in} - \dot{q} R_{conv1} \tag{12b}$$

$$T_2 = T_1 - \dot{q} R_{cycl1} \tag{12c}$$

$$T_3 = T_2 - \dot{q} R_{cycl2} \tag{12d}$$

$$T_{out} = T_3 - \dot{q} R_{conv2} \tag{12e}$$

These last calculations can be plotted with temperature against length x (Figure 9). According to the calculations, the water temperature should be set at 41 °C to achieve a temperature of 30 °C at the outside of the silicone layer. The calculations also show that the water will cool down about 1 degree over a tube of 16 cm.

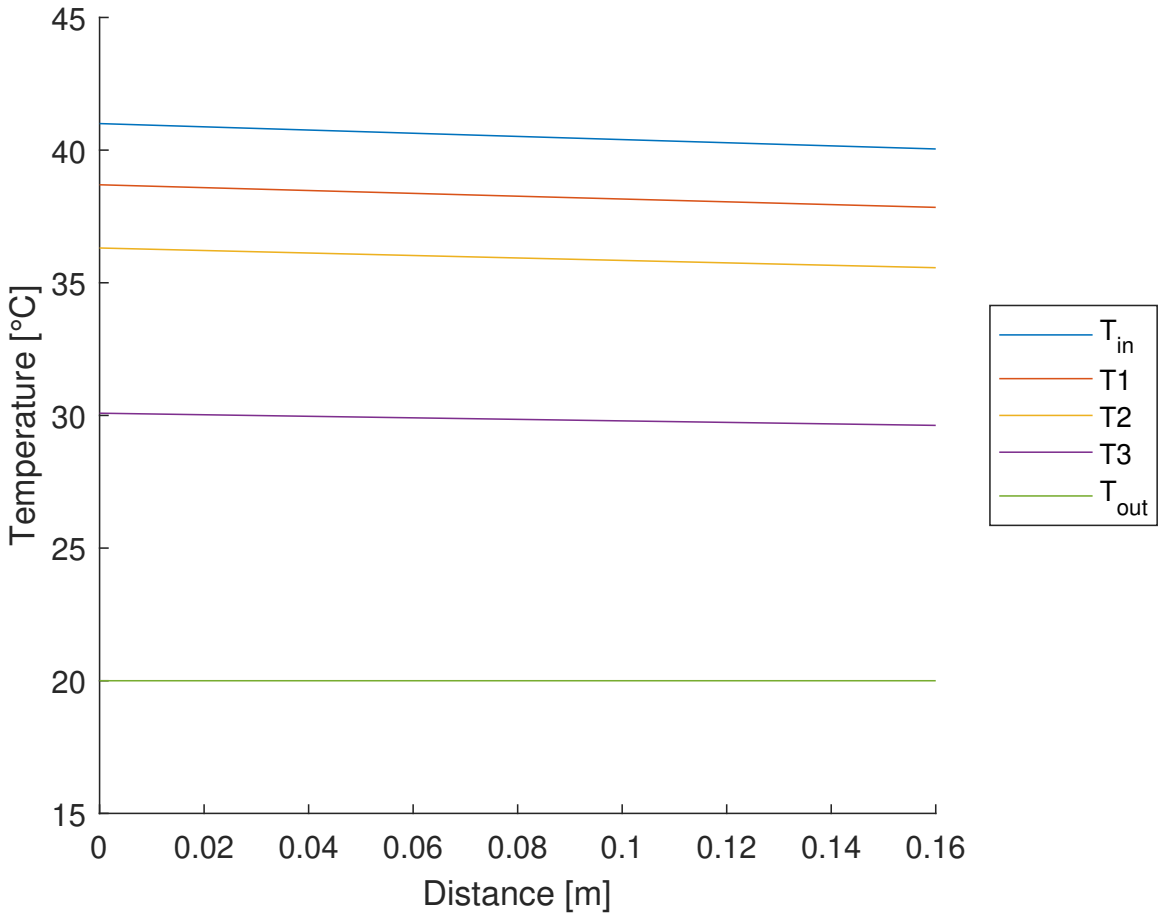


Figure 9: *Temperature distribution over space in different layers along one tube.*

The time it takes to warm up the whole foot up to a stable level should also be calculated. Therefore the total heat difference [J] that needs to be generated should be divided by the heat difference over space. This gives the longest/worst time before a stable situation occurs. This is because of some assumptions, for example, the whole volume needs to be warmed up to a certain mean temperature, the silicone has poor conduction and a cylindrical model is used, while this is not completely true. So, in practice, the time would probably be a bit shorter.

$$\dot{Q}_{tot} = \rho V_{foot} \Delta T C_p \tag{13a}$$

$$\Delta T = (T_2 + T_3)/2 - T_{out} \tag{13b}$$

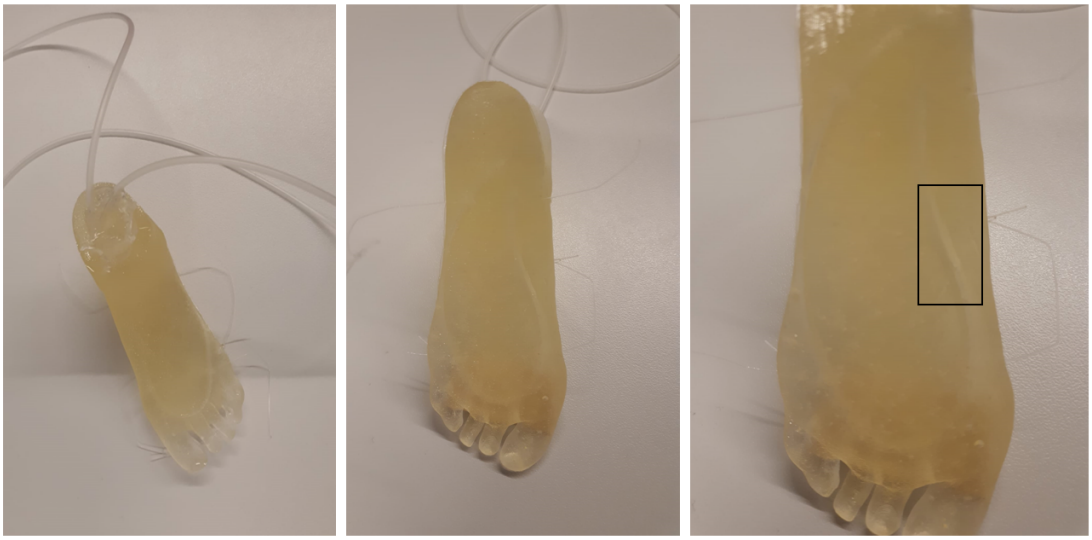
with V_{foot} as the volume of the foot [m^3] and ΔT as the mean temperature difference [K].

$$\begin{aligned} t_{set} &= \frac{\dot{Q}_{tot}}{\dot{Q}} \\ t_{set} &= \frac{3.47 \times 10^3}{1.13} = 3071 \end{aligned} \tag{14}$$

So, the time it takes is about 3071 seconds, which corresponds to 52 minutes.

7.2.3 Phantom with one tube through the foot

After the phantom without tubes, the next step would be to simulate the temperature in the foot by including 1 tube in the foot phantom and leading warm water through the foot. This is performed to show whether the principle of leading warm water through a tube in the foot may work to simulate the normal temperature distribution of a healthy person throughout the whole foot. The tube was placed inside the 3D foot model mould and secured using fishing lines. The procedure can be found in Appendix A Protocols. The final result is shown in Figure 10. During the moulding, the tube was displaced at the top of the mould (anatomical cranial of the calcaneus) which resulted in the tubes coming out of the silicone. This also happened at the bottom of the foot (Figure 10C). The tube was not evenly distributed from the plantar side of the foot. Some parts of the tube were lying closer to the plantar side of the foot than other parts.



A B C

Figure 10: *3D foot phantom moulded out of silicone with 1 tube inside. A) Dorsal view of the foot. B) Plantar view of the foot where the tube is visible. C) Zoomed plantar view of the foot. In the black box is shown that the tube is coming out of the silicone.*

Water was heated up to 42 °C in an isolated beaker and led through the tube inside the foot. The exact protocol can be found in Appendix A. As shown in Figure 11B the foot indeed heats up, especially at the places where the tubes are running through. Comparing Figure 11B and 11C it is shown that the foot model heats up more than the actual foot (28 vs 26 °C). However, despite that the foot is warmer, the toes and calcaneus of the foot are in both figures colder than the rest of the foot. So, this is comparable. In the middle of the foot model, there is one large plane which is heated up whereas in the foot of a patient, only a small part of the middle of the foot is warmer than the rest of the foot.

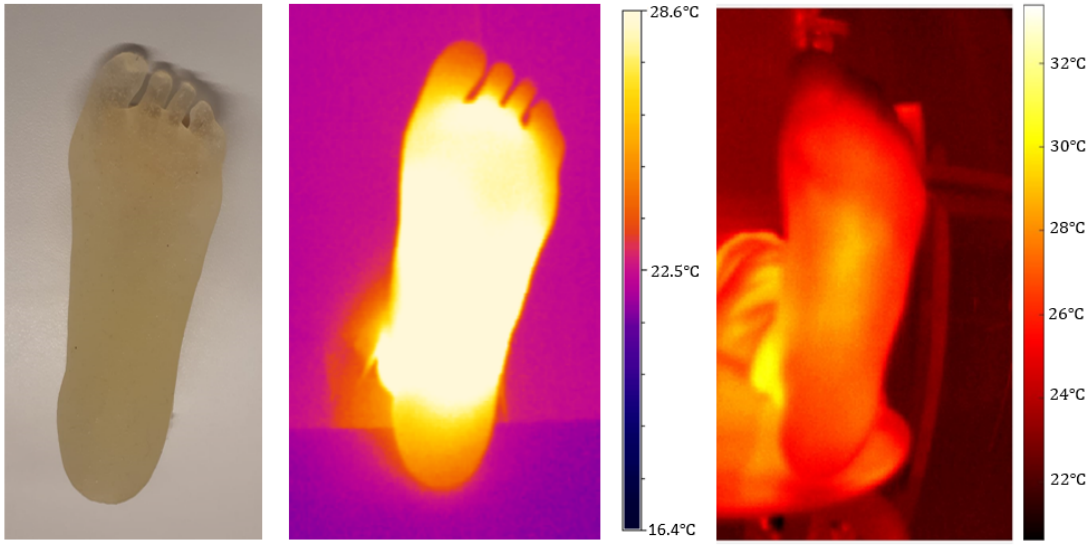


Figure 11: *A) Plantar view of the 3D foot model B) Thermal image of the plantar view of the 3D foot model C) Thermal image of the plantar view of the foot of a healthy person.*

7.3 Sketches for phantom with tubes through the foot

The distribution of heat in the foot can be simulated by inserting different tubes inside a phantom and subsequently passing warm water through the tubes. The insertion of the different tubes can be performed in different ways (Figure 12). Important is that the distribution through the foot is uniform and that the temperature can be regulated. From one large tube, the water should be regulated into different smaller tubes.

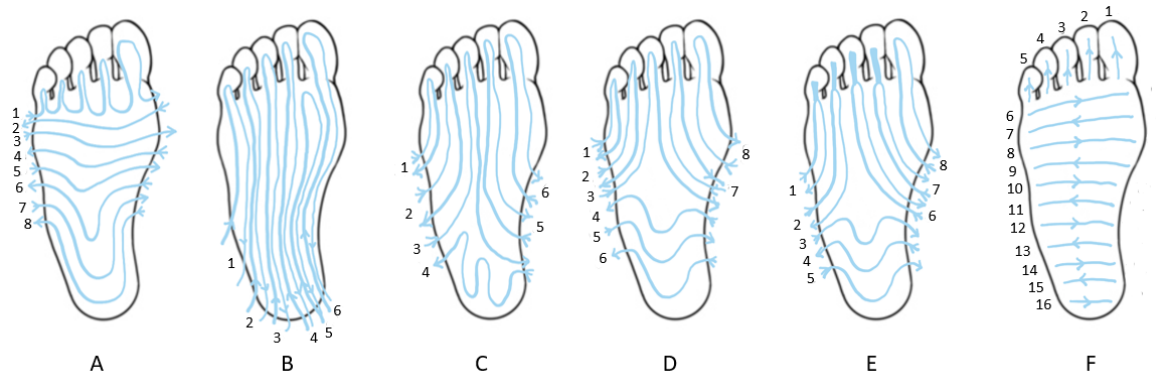


Figure 12: *Different sketches (A-F) of a tube system through the foot to distribute heat through the skin. Arrows indicate the direction of the flow through the specific tube.*

In Figure 12A the temperature would be distributed well through the foot, but a disadvantage is that there is one tube through all of the toes which may be a problem because in toe I and V the temperature is larger than in the other toes. Figure 12B has a tube through every separate toe. However, the temperature in the middle of the foot is also larger than in the toes causing a problem for the distribution of heat through the foot phantom. Next to that, the tubes are quite long which may give the problem that the water will cool down over space. In Figure 12C the tubes are shorter and there are more tubes. This is even more the case in Figure 12D. In sketches A-D, there are tubes through all of the toes. Through the small toes,

it will be difficult to lead the tubes. In Figure 12E, there are small sheets placed against the tubes which conduct the heat from the tubes. However, there are still large tubes through the foot. This gives the final sketch (Figure 12F) where there are smaller tubes through the foot (16 in total). The tubes are led from and towards the top of the foot.
The regulation from one large tube into smaller tubes can be ideally performed by splitting the larger tube into 2 tubes, 2 into 4 tubes, 4 into 8 tubes and eventually 8 into 16 tubes. To get 6 tubes the large tube can be split into 2 tubes and each tube into 3 tubes giving 6 tubes in total. So, this would advocate for sketches C-F. To conduct the heat well and stimulate an uniform flow, bends should not be larger than 180 degrees.

7.4 Discussion

During the moulding process of both phantoms, a lot of air bubbles were observed in the beaker before and in the phantom after moulding. This can be probably caused by stirring with the spoon during the heating process. Different techniques were performed to remove the air bubbles. First, less stirring during the heating process was tried. This resulted in a large clump of silicone in the middle of the beaker. Next, using a vacuum oven was used after the heating process. In the first place, the temperature of the vacuum oven was not turned on. This resulted in a significant temperature decrease during vacuuming which caused the silicone to irreversibly become hard/flexible. When the temperature of the vacuum oven was turned on, the silicone was kept at the same viscosity. However, in the vacuum oven, no removal of bubbles could be observed both when the temperature was turned off and on. This can explained by that the silicone was too viscous to remove the air bubbles. In fish bait making [39] also a vacuum oven is used to remove air bubbles out of silicone. During this process, the removal of air bubbles can be observed by the air bubbles splashing. Another explanation for the fact that the air bubbles did not splash may be that the silicone was only placed for a short amount of time in the vacuum oven and only once or twice vacuuming was applied. The next time, this can be maybe performed longer and more often. It was also tried to knock on the sides of the mould to remove the bubbles. However, unfortunately did not make any difference.
Another problem that occurred during the moulding process was the heating process. It was difficult to measure the temperature during the process. An external thermometer was placed in the silicone. At different places in the silicone, a different temperature could be measured even when stirring was applied. The temperature drops made it difficult to observe when the right temperature was achieved. When the temperature was too low, the silicone was too viscous which made it impossible to mold. The temperature drops may be caused due to the heating from below. The silicone at the bottom becomes warmer sooner than the top layer. Due to the viscosity, it was difficult to stir the silicone from the bottom to the top. This can be tried better in further experiments. Another important point is to mould the silicone at one time into the foot mould. Otherwise, the foot will break when cooled down.
The size of the foot and the flexibility of the tubes made it difficult to align the tubes in the right place. This was currently performed with two fishing lines. This was not enough since some part of the tube was lying at the bottom of the foot and pointing out of the foot. Also, at the top of the mould the tubes could move 'freely' during the moulding process which resulted in the tubes were not aligned evenly and movement of the tubes in the heel. Next time another method for fastening the tubes should be invented or to include more fishing lines.
The distribution of heat was 2 °C too high. This can be solved by decreasing the temperature in the beaker, but furthermore, the temperature distribution was reasonably good in comparison to the patient's foot. To compare this with the calculations it was expected that the temperature should be even higher (28 vs 30 °C). So, the model should be adapted to getting a temperature of about 26 °C on the outside of the foot. Also, the values of for example the tubing are estimated because it was not known which exact material was used. Next to that, different assumptions are made, which made it easier to calculate, but further away from reality. This model should be improved for further research.
Looking at the requirements, a lot of requirements have been fulfilled. The dimensions are still smaller

because it was still a trial and we did not want to spill that much material. The temperature can still not be regulated in different small areas, and it is not yet distributed as physiology indicates. But we can vary the temperature over time, and the temperature can also be stable. Using silicone as a material helps to make the foot flexible but also strong. In such a way the material will not plastically deform when an impression is made. The model can conduct heat, however, the model does not yet conduct the heat uniformly. It was observed that the model was heated both at the top and bottom. Because the tubing was lying more towards the bottom of the foot than the top, the heat was more conducted towards the bottom than the top. In order to improve this even further, the next steps to take should be implemented.

8 Conclusion

A small 3D foot phantom model has been developed, firstly without tubing and then with in order to simulate the heat distribution over a foot and to simulate upcoming diabetic foot ulcers. This is because of the small changes that temperature changes in upcoming wounds can be measured. The working principle of the conductance of heat through warm tubing has been proven. The heat distribution is however still not realistic and should be improved in further research. All in all, the foot ulcer development can probably be simulated through a silicone foot model with warm tubes where the flow rate and temperature towards different places of the foot can be altered. However, only the working principle was proven during this study.

9 Outlook

Literature part
There are still some gaps in research towards temperature differences regarding upcoming wounds, ischaemia and neuropathy. Also, the influence on temperature differences of callus at the surface of the foot is not well known. Next to that, more research should be performed on diabetic wound healing and what the temperature differences are in this process. Moreover, in the literature, not much can be found about how large the differences in temperature are during wound development and healing.

Design part
There are different points which need to be improved to get a realistic model to simulate upcoming wounds. Firstly, during the heating process of the silicone, the temperature should be measured better in such a way that the silicone can be moulded at the right temperature. Next, the removal of bubbles should be investigated to get a uniform silicone model. This can either be performed by further investigating the use of a vacuum oven or by searching for another way. When these problems are solved the next steps in the section 'Steps to take' can be executed. This includes calculations and developing a model with multiple tubes, adjusting the model by implementing a way to simulate foot ulcers, for example by introducing rotary knobs. When the model is further developed a dataset can be created by measuring different upcoming wounds. After that, the simulations can be compared to the wounds of patients. If this is comparable the phantom simulations can be used to develop a self-learning algorithm to detect upcoming wounds.

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Appendices

A Protocols

A.1 Casting foot phantom without tubes

1. Build up the set-up like in Figure A.1. The thermometer of the oil bath should be plugged in in the dashboard of the oil bath and hanged in the oil bath.
2. Turn on the oil bath and set the temperature on 175 °C and the stirrer on 400 rpm.
3. Measure 150 mL of silicone into a beaker.
4. Prepare the mold by taping the edge and tying an elastic around it.
5. When the oil bath of heated, hang the beaker into the oil and clamp the beaker into clamps.
6. Attach a thermometer to the clamps and hang the thermometer in the silicone.
7. Start stirring with a spoon to uniformly heat the silicone.
8. When the silicone is transparent and liquid enough to pour (and before it becomes yellow), the liquid can be molded into the mold. This will be around 160 °C. The molding should be performed with heat gloves. The molding should be performed fast and in one try.
9. After a day the mold can be opened and the silicone foot model can be removed and used for further research.

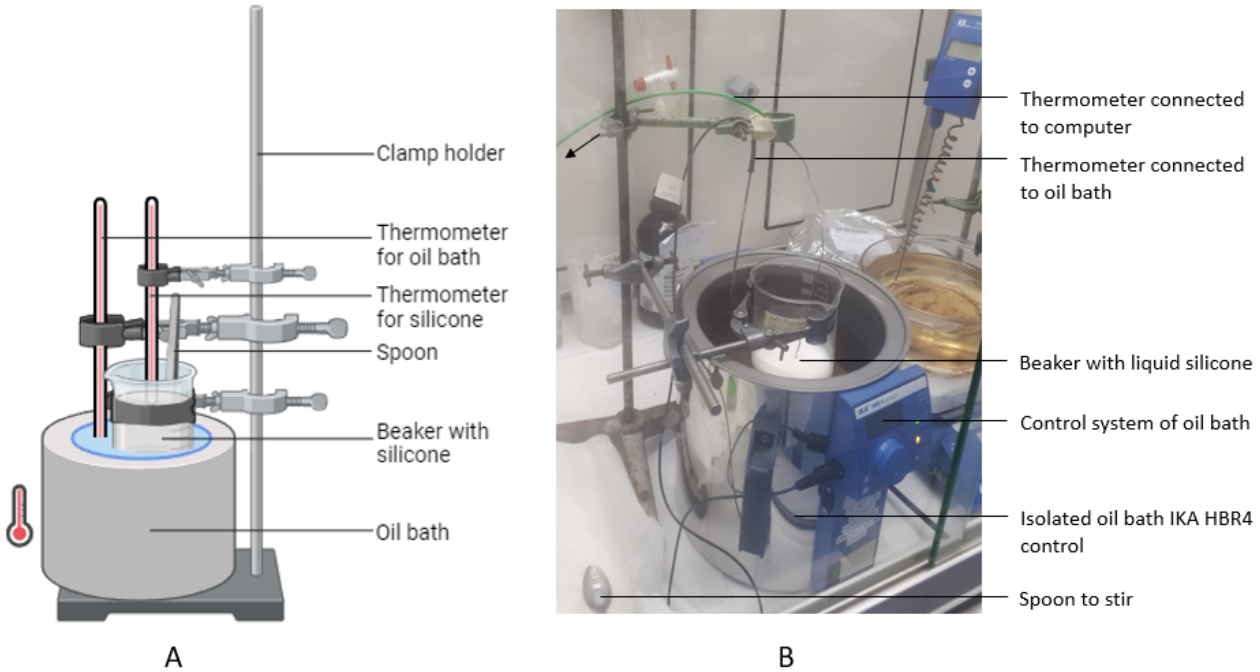

Figure A.1: *Setup for heating silicone in an oil bath A) Schematic overview, B) Overview from lab cabinet.*

A.2 Casting foot phantom with 1 tube

1. Step 1-3 of protocol A.1 should be carried out.
2. Two small fishing lines should be attached around the bottom of the mold whereafter the tube should be attached with small pieces of fishing lines.
3. The mold should be prepared by taping the edge, over the fishing lines, and by tying an elastic around it.
4. Step 6-9 of protocol A.2 should be carried out.

A.3 Measuring the foot with thermal camera

1. Heat up the beaker to 41 °C and turn on the stirrer to 200 rpm.
2. Place the pump above the stirrer in the beaker as in Figure XX.
3. Turn on the pump and let the water pump through the foot until a stable temperature is reached. The beaker and tubing should be isolated with for example radiator foil.
4. Place the isolating boards around the foot and tape the foot in such a way that the plantar side of the foot can be measured.
5. Turn on the thermal camera and take pictures.

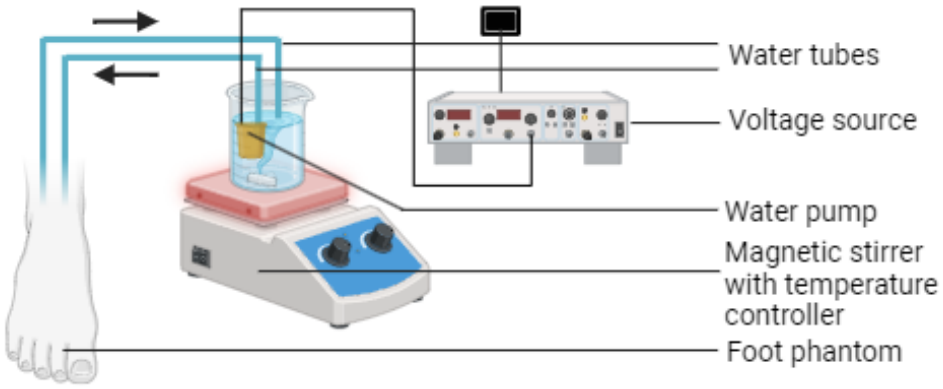

Figure A.2: *Setup for heating of the foot with water and making thermal images.*