Detection of diabetic foot with infrared thermography

Muhammad Adam Abdul Rahim

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NANYANG
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**DETECTION OF DIABETIC FOOT WITH
INFRARED THERMOGRAPHY**

MUHAMMAD ADAM BIN ABDUL RAHIM

SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING

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DETECTION OF DIABETIC FOOT WITH INFRARED THERMOGRAPHY

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

By

MUHAMMAD ADAM BIN ABDUL RAHIM

School of Mechanical and Aerospace Engineering

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Diabetic foot is among the major complications of Diabetes Mellitus (DM) that can results in ulcerations. An early detection and appropriate treatment can prevent traumatic outcomes such as lower extremity amputation. Furthermore, studies have shown that temperature fluctuations on the plantar foot can be related to diabetic foot complications. Since the time of Hippocrates, human body temperature is being associated to health. Thermography is a non-invasive imaging method employed to view the thermal patterns using Infrared (IR) camera. In addition, it allows the qualitative and visual documentation of temperature fluctuation in vascular tissues. Absolutely, IR thermography can play a crucial role in the medical field, especially for detection of diabetic foot disease. Nonetheless, such strategy is yet to be established and many circumstances still unsolved.

The first challenge is analysing the thermal changes because the risks of ulceration are associated to the rise in plantar temperatures. Nevertheless, the attempts to identify the spatial patterns of temperature remains difficult because there are extensive forms of thermal patterns. This complicates the classification process. In addition, the interpretation of thermographic patterns may be difficult due to inadequate details, even in healthy subjects, and classification techniques on the thermographic patterns. Moreover, there is no objective approach in allocating the thermogram to certain classes. Recent studies proposed the temperatures of one foot and contralateral foot to be measured and compared, and the diabetic foot risk regions are detected by the defined threshold. However, this is only applicable in without ulceration or amputation cases and in asymmetric thermal changes.

Therefore, this research developed a novel computer aided detection (CAD) system for diabetic foot using nonlinear features extracted from plantar foot thermograms. A total of 33 healthy volunteers and 33 non-neuropathy diabetic patients are recruited from Ngee Ann Polytechnic (**NPIRB-P0175-2017-ECE-AMA6**) and Singapore General Hospital (SGH), Diabetes & Metabolism Center (DMC) (**CIRB Ref: 2016/3044**) respectively. The thermograms acquired are pre-processed by segmenting the plantar foot regions using polygon and then proceed to warp all the segmented plantar foot regions into uniform size. Afterward, the warped grayscale foot images are decomposed using Discrete Wavelet Transform (DWT) and Higher Order Spectra (HOS) prior to extracting texture and entropy features. The features values from left and right foot are subtracted. Subsequently, student t-test is applied on the resultant features to select and rank the significant features. Lastly, the 27 significantly ranked features (p value < 0.0001) are fed independently into support vector machine (SVM) classifier. The developed methodology achieved maximum classification accuracy of 89.39%, positive predictive value of 96.43%, sensitivity of 81.81% and specificity of 96.97% using only *five* features.

The findings of this research will redound to benefit the diabetic patients considering that IR thermography has the potential to detect diabetic foot early. The rising occurrence and burden of diabetic foot disease prove the need for more efficient and reliable early detection methods. Thus, the developed thermography-based CAD system can be an adjunctive diabetic foot screening tool in clinics to effectively assist podiatrist in decision making and diagnosis processes. This is important as early detection of diabetic foot may prevent future complications. Equally important, this research will help to unveil critical areas in image processing techniques that many

diabetic foot studies have yet to explore. Thus, the development of new and improve methodology on early diabetic foot detection.

The future research intends to acquire and work on more plantar foot thermograms clinical data, which will include diabetic neuropathy patients. This is to extensively study and ascertain the variations in the plantar foot thermal imaging patterns and distributions among the healthy subjects and, diabetic subjects without and with neuropathy. Further, future research plans to develop a novel three classes methodology on diabetic foot detection with the implementation of enhanced image processing and statistical analysis methods that can efficaciously interpret and analyse the huge and diverse plantar foot thermograms data.

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NOMENCLATURES

$A(n)$	Approximation coefficient
$A(f_1, f_2)$	Bispectrum
b	Bias
c	Speed of light in vacuum (m s ⁻¹)
$C(i, j \Delta_x, \Delta_y)$	Co-occurrence matrix
D'	Pixel coordinates of the source image
D	Pixel coordinates of the destination image
$D(n)$	Detailed coefficient
d	Degree of polynomial kernel
E_b	Overall emissivity of black body (W/m ²)
E_λ	Radiation emitted by real object (W/m ²)
$E_{\lambda, b}$	Spectral emissivity power of black body as a diffuser (W/m ²)
$E[]$	Expectation operation
F	Feature space
f	Frequency (Hz)
$f(x, y)$	Image
g	Grey levels
g_c	Grey level intensity values of center pixel
g_p	Grey level intensity values of P points
h	Planck constant (J s)
$H(n)$	High pass filter
H_i	Normalized intensity histogram

I	Spectral intensity ($\text{W cm}^{-2}\mu\text{m}^{-1}$)
I_i	Imaginary part of integrated bispectrum
I_r	Real part of integrated bispectrum
k	Boltzmann constant (J K^{-1})
$K(m)$	Bispectral invariant
$K'_{k_{i+1}} K'_{k_i}$	Pairs of lines represented on source image
$K_{k_i} K_{k_{i+1}}$	Pairs of lines represented on the equivalent destination image
L	Number of gray level in the image
$L(n)$	Low pass filter
$LBP_{P,R}$	Rotation invariant measure
M	Rows of the image
m_{uv}	Two-dimensional moment
m	Gradient
N	An input space
N	Columns of the image
N_i	Intensity values
n	Sampling factor
n_{uv}	Normalized central moment of order $(u + v)$ for $u, v = 0,1,2 \dots$,
P	Points selected on the circumference
$PS(f)$	Power spectrum
$P(i, j)$	Probability for a pixel gray level i to be at distance $(\Delta x, \Delta y)$ from pixel gray level j
P_x, P_y	Partial probability density functions
R	Radius

$S(f)$	Fourier transform of signal $s(nT)$ where integer index is n and sampling interval is T
T	Absolute temperature (K)
$TEM_{(i,j)}$	Texture energy measurements (TEM) filters
U	Uniformity measure
$x(k)$	Original signal input
$x(n)$	A two-dimensional signal
Δx	Distances among the pixels in the directions of x
$\bar{x}$	Image centroid
$\{x_i\}$	A set of points
w	Weight vector
Δy	Distances among the pixels in the directions of y
$\bar{y}$	Image centroid
ε	Emissivity; ratio of radiation emitted by real object E_λ to the radiation emitted by black body $E_{\lambda,b}$ at same temperature (T)
λ	Wavelengths (m)
μ_x	Mean of P_x
μ_y	Mean of P_y
μ_{uv}	Central moment
ρ	Distance of the line from origin
σ	Stefan-Boltzmann constant ($\text{W/m}^2 \text{K}^4$)
σ_x	Standard deviation of P_x
σ_y	Standard deviations of P_y
θ	Angle from horizontal

CHAPTER 1. INTRODUCTION

1.1. BACKGROUND

Diabetes mellitus (DM) is a serious, chronic metabolic disorder due to lack of insulin production by the pancreas, or ineffective use of insulin by the body [1]. Insulin is a hormone secreted by the beta cells of pancreas that regulates blood glucose. Over time, elevated blood glucose levels may result in serious complications to various parts of the body [1]. This includes damaging the kidneys, eyes, heart, nerves and blood vessels. Consequently, these complications affect the quality of life, cause disability and premature death. The typical symptoms of DM include weight loss, blurred vision, dehydration (polydipsia), frequent urination (polyuria), hunger, and tiredness.

The World Health Organization (WHO) reported a total of 3.7 million deaths in 2012 relating to blood glucose levels. Of these, 1.5 million deaths are caused by DM while the remaining 2.2 million deaths are due to high blood glucose which increases the risk of heart and other diseases. Moreover, majority of these deaths (43%) are premature, occurring below the age of 70, and accounts for 1.6 million of the global deaths [2].

Equally important, WHO reported that estimated 422 million of the global adults (age 18 and above) had diabetes in 2014. Almost half of these cases were reported from Pacific and Southeast Asia countries [2]. Furthermore, the number of diabetic patients has risen for the past few decades, from 108 million in 1980 to the present numbers in 2014. In fact, 40% of this rise

in diabetes is approximately because of the growing population and aging, 28% results from the specific-age prevalence, and remaining 32% due to the combination of both [3].

The global diabetes prevalence across all income groups has increased considerably for the past thirty years, reflecting the global rise in the obesity populations. Indeed, the global diabetes prevalence has nearly doubled since 1980, rising from 4.7% to 8.5% in 2014 [3]. In addition, diabetes prevalence in low and middle-income nations is more rapid compared to high income nations for the past decades. In this case, eastern Mediterranean countries experienced the highest increase in diabetes prevalence of about 13.7% [2].

Absolutely, proper control and management of diabetes are important to prevent the development of chronic complications. Diabetic foot as illustrated in **Figure 1.1** is among the serious complications of diabetes characterized as bacterial infection, foot ulceration, and deep tissue destruction due to neuropathy and peripheral arterial disease of the lower limb [4]. Moreover, diabetic foot related complications result in higher hospitalization incidences compared to other chronic complications of diabetes [5]. The inadequacy of diabetic foot to sustain stress exposed the foot to the various complications, which may possibly lead to amputation. An estimated 90000 amputations are performed every year in the United States of America (USA) because of diabetic foot related complications [6].

In any case, diabetic foot ulcers (DFUs) are among the most common foot complication that affect about 15% of the diabetic populations [7]. Diabetic patients are

12% to 25% at risk of developing foot ulcers in their lifetime [8, 9], with nearly 85% of the lower limb amputations are resulted from non-healing foot ulcers [10]. The primary risk factors leading to the development of foot ulcers are neuropathy and peripheral arterial disease of the lower limb [11]. Almost 50% of the diabetic patients with foot ulcers will have neuropathy, nearly 20% of them will have insufficient arterial blood perfusion, and about 80% of them will have both conditions [12, 13]. Nonetheless, other risk factors may also involve, which include abnormal biomechanics of foot and ankle, limited joint movement and low resistance to infection [14].

Many studies have shown that temperature variations on the plantar foot areas can be due to diabetic foot complications [15-21]. The infrared thermometry [15-18], liquid crystal thermography (LCT) [19-22] and infrared thermography [23-27] are among the available methods for measuring temperature. The IR thermometry is a temperature monitoring method that measures the temperature of the various points on the feet [17]. Nevertheless, the IR thermometry method becomes difficult and insufficient when measuring the temperature at many points on the foot. In contrast, the LCT method produces a colour reaction relative to the temperature of the skin surface, which touches the thermochromic liquid crystals [28]. Despite being cheap and providing visualization of plantar thermal distribution, LCT is a contact method that has slow responsivity and thus, may not be useful for certain applications [29].

The infrared thermography is a fast, non-invasive and non-contact method that allows the visualization of plantar temperature distribution. Further, the infrared thermography is passive whereby no harmful radiation passes through the body but instead capturing only body heat radiation [29]. It limits the unnecessary contact and

pressure that may affect the temperature reading and mitigate the spread of infection through the apparatus [26]. Moreover, it permits the measurement of temperature distribution of the whole foot regardless of the shapes or surfaces, particularly the medial arch which is a non-contact surface of the foot. For this purpose, the applications of infrared thermography have significantly increased over the years especially in the study of diabetes foot related complications [30]. The infrared thermography is used to observe morphology of the skin temperature pattern, which is influenced by the blood perfusion. In conditions where blood circulation at the peripheral limbs are reduced, or ischemic, there will be a change in the temperature patterns [30].

Figure 1.1: Illustrations of healthy and diabetic foot. The normal foot having healthy blood vessels with good blood circulation and conversely damage of blood vessels in the diabetic foot can cause tissue damage which could lead to amputation.

1.2. MOTIVATION OF RESEARCH

Without a doubt, diabetic foot plantar analysis using infrared thermography has been successful. The infrared techniques allow rapid capturing of large number of pixels, or picture elements [31]. Individual pixel at the respective point denotes the temperature value. Collectively, these pixels create an image illustrating temperature distribution on the foot plantar. Nevertheless, there are two main challenges that remain unsolved in the progression of diabetic foot detection using infrared thermography.

The first challenge is analysing the thermal changes. The risks of ulceration are particularly linked to the rising plantar temperatures. However, attempts to identify spatial patterns of temperature remains hard because of extensive variations in the thermal pattern and distribution especially among diabetic patients, which complicates the classification process. In addition, the interpretation of plantar foot thermographic patterns may be difficult due to insufficient details and classification techniques on these thermographic patterns. Moreover, there is no objective approach in allocating the thermogram to the specific classes. Despite studies reporting similar temperature distribution in healthy foot, there has been no representative pattern for this group yet. Nagase et al. [26] and Mori [32] investigate the foot plantar thermal patterns of healthy and diabetic subjects and qualitative classified them according to the concept of angiosomes. Both studies reported that high foot plantar temperatures can be an early indication of pre-ulcer inflammation. However, this analysis is performed based on experts' visual perception.

The second challenge is detecting diabetic foot risk regions. Several studies proposed that the temperatures of one foot and contralateral foot are to be measured and compared, and the risk regions are detected based on defined threshold. Nonetheless, the proposed analysis is only applicable for without ulceration or amputation cases and, for asymmetrical thermal changes. There will be no region to compare if patient has total or partial foot amputation and also, the risk regions cannot be detected if the same complications are present on both feet. Peregrina-Barreto et al. [33] proposed a method that approximate regional foot plantar temperatures in diabetic patients and identify the abnormal differences. The approximation is only applicable for asymmetrical changes even though it could identify hotspots. Nonetheless, the study does not provide details with regards to the status of the entire foot. Liu et al. [34] proposed an automated technique that detect diabetic foot problems by comparing same points on both feet to estimate the abnormal differences. Nevertheless, the study encounters several limitations which include difficulty to detect small hotspots at initial stages, insufficient reference when contralateral foot cannot be compared, estimation of abnormalities depends on contralateral comparison among feet and, analyse only certain foot plantar areas instead of whole foot.

Therefore, continuous development of algorithms is needed to better identify and analyse the variation of thermal patterns in diabetic foot. With capable computing machines and improved algorithms, the degree of reliability and detection accuracy could be enhanced. In this research, the above-mentioned challenges are considered and novel methodology is developed to overcome them. Still, there are challenges faced by the current methods. First, the polygon method employed for plantar foot segmentation is not able to enclose the entire foot boundary, in particular the curve areas. For some

thermograms, the temperature of the feet and background is almost similar, which makes manual segmentation process difficult. To overcome these, more polygon points are placed on the foot boundary that improve delineation of curve areas. Also, all the thermograms are adjusted to a standard temperature scale range that provide sufficient thermal contrast between the foot and background for delineation process. The second challenge is to effectively capture relevant information from the foot images despite subtle sudden variations between adjacent pixels. Consequently, advanced image processing methods are implemented that decomposed and extracted features from the foot images. The DWT and HOS decomposition methods are able to capture subtle pattern variations in the pixels and, the non-linear interaction in the phase coupling and frequency components respectively. Thereafter, texture and entropy features extracted the underlying relevant information from DWT and HOS coefficients. The last challenge is the nonlinear boundary encountered by the classification method due to the nonlinear nature of bio image data. Hence, the nonlinear data cannot be simply separated using linear classifier. For this purpose, SVM classifier together with nonlinear kernels such as polynomial and radial basis function (RBF) are used to map the nonlinear data into higher dimension space that reliably discriminate the two classes.

1.3. OBJECTIVES AND SCOPES

The current research aims to develop a novel computer aided detection (CAD) system for diabetic foot using nonlinear features extracted from plantar foot thermograms. A detection system that is capable to reliably detect and analyse the variations in thermal pattern and distribution on the foot plantar of healthy subjects and non-neuropathy diabetic patients. Importantly, quantitative image processing

techniques are implemented to accomplish the abovementioned objective in this study and that the developed system would also consist of classifying the feet thermogram.

This system aims to attain the following scopes:

1. To enable semi-automated segmentation of the feet from the background (region of interest)
2. To standardise the size of feet images prior to subsequent analysis
3. To implement in depth image processing analysis
4. To extract and determine the distinct features for classification process
5. To provide automated classification of the feet thermogram

1.4. ORGANIZATION OF THESIS

The organisation of this thesis is presented as follow. Chapter 2 presents the literature review on the diabetic foot studies using plantar pressure and infrared thermography analysis, the infrared thermography background and its applications in the medical field and lastly the methodology of computer aided diagnosis (CAD) system. For chapter 3, the materials and methodology used to develop the proposed diabetic foot CAD system are described in detail. The results yielded by the proposed CAD system are covered and discussed in chapter 4. Lastly, the conclusion and future work are discussed in chapter 5.

CHAPTER 2. LITERATURE REVIEW

Diabetic foot complications can be prevented by early detection and proper clinical treatment. Based on International Working Group on the Diabetic Foot (IWGDF) risk category [35], diabetic patients need to screen their feet at least once annually to detect foot at risk of ulceration. The feet examination comprises of medical history and foot examination and, neuropathy assessment [35]. Nonetheless, these conventional clinical techniques usually are not able to identify sufficient changes in the skin integrity until ulceration has actually occurred [36]. Therefore, this research discussed the various proposed studies that potentially evaluate and diagnose diabetic foot related complications early using mainly plantar pressure and infrared thermography.

2.1. PLANTAR PRESSURE ANALYSIS

The plantar pressure measurement has been widely implemented in many studies and clinical practices. The main purpose is to distinguish the walking patterns of various clinical groups and analyse the impact of foot wears, orthotic supports and surgeries [37]. The plantar foot sole can be divided into 10 areas [38] as illustrated in **Figure 2.1**. Patient is characterized as diabetic neuropathy if no sensation is experienced on at least one of the four areas, namely 1st toe and, 1st, 3rd and 5th metatarsophalangeal joints. Equally important, the mechanical nature of human foot while on dynamic and static loading is better understood using pedobarography. The representative dynamic foot plantar (kPa) images of healthy and diabetic foot with and without neuropathy are shown

in Figure 2.2(a)-(c). The studies on the distributions of plantar foot pressure in diabetes patients are summarized in Table 2.1.

Figure 2.1: Separation of the plantar foot sole into 10 areas which represent the (1) medial heel; (2) lateral heel; (3)(4) midfoot; (5)(6)(7) metatarsophalangeal joints; (8) interphalangeal joint; and (9)(10) lesser toes.

Figure 2.2(a)-(c): The representative dynamic foot plantar images (kPa) of (a) healthy foot, (b) diabetes foot with neuropathy, and (c) diabetes foot without neuropathy.

Table 2.1: Plantar pressure (kPa) analysis.

Author (Year)	Methodology	Findings
Frykberg et al, 1998. [39]	<ul style="list-style-type: none"> • Clinical foot assessments: <ul style="list-style-type: none"> ○ Semmes-Weinstein monofilament ○ Biothesiometer • F-scan mat system • Statistical analysis: <ul style="list-style-type: none"> ○ X^2 test ○ Student t test ○ Wilcoxon's rank sum test ○ Analysis of Variance (ANOVA) ○ Univariate and multivariate logistic regression 	<ul style="list-style-type: none"> • High plantar foot pressure and peripheral neuropathy are the main risk factors for diabetic foot ulceration • Neuropathy having higher impact on foot ulceration
Abouaesha et al, 2001. [40]	<ul style="list-style-type: none"> • Neuropathy assessments • Optical pedobarograph • Planscan: <ul style="list-style-type: none"> ○ Plantar tissue thickness • Statistical analysis: <ul style="list-style-type: none"> ○ Pearson's test ○ Student t test 	<ul style="list-style-type: none"> • The relationship between dynamic foot pressure measurements and plantar tissue thickness are significantly inversed
Prabhu et al, 2001. [41]	<ul style="list-style-type: none"> • Clinical foot assessments: <ul style="list-style-type: none"> ○ Semmes-Weinstein monofilament • Plantar pressure 	<ul style="list-style-type: none"> • Statistical analysis of the parameter mean values from various parts of the plantar feet of diabetes neuropathy patients showed distinct patterns
Caselli et al, 2002. [42]	<ul style="list-style-type: none"> • Neuropathy assessments: <ul style="list-style-type: none"> ○ Sensory test ○ Biothesiometer • Joint mobility evaluation: <ul style="list-style-type: none"> ○ Goniometer • Plantar pressure measurements: <ul style="list-style-type: none"> ○ F-scan mat system • Statistical analysis: <ul style="list-style-type: none"> ○ Analysis of Variance (ANOVA) ○ Fisher's test ○ Kruskal-Wallis test ○ Univariate and multivariate logistic regression 	<ul style="list-style-type: none"> • The fore (F) and rear (R) foot pressures are observed to be elevated in diabetes neuropathy foot • Severe diabetes neuropathy group has high F/R foots pressure ratio <ul style="list-style-type: none"> ○ Indicates unbalanced pressure distribution with increasing severity of neuropathy
Gefen et al, 2003. [43]	<ul style="list-style-type: none"> • MRI • FE analysis software package (ANSYS): 	<ul style="list-style-type: none"> • Diabetes feet injury is most likely to develop in the deeper tissue layers

	<ul style="list-style-type: none"> ○ Construction of planar models of the foot ○ Stress analysis ○ Tension ○ Compression ○ deformations <ul style="list-style-type: none"> • Plantar tissue elasticity measurements 	<ul style="list-style-type: none"> • Tissues around the distal bone prominences of medial metatarsals are highly vulnerable
Abouaesha et al, 2004. [44]	<ul style="list-style-type: none"> • Plantar tissue thickness • Optical pedobarograph: <ul style="list-style-type: none"> ○ Plantar pressure • Receiver operating characteristic (ROC) analysis 	<ul style="list-style-type: none"> • The results showed that tissue thickness values of 11.05, 7.85, 6.65, 6.55 and 5.05 mm in the 1st to 5th metatarsal heads respectively predict plantar pressure with specificity ranging from 52% to 84% and sensitivity ranging from 73% to 97%
Grimm et al, 2004. [45]	<ul style="list-style-type: none"> • Clinical foot assessments • Pedobarograph: <ul style="list-style-type: none"> ○ Plantar pressure 	<ul style="list-style-type: none"> • The study observed an increase in plantar pressure with respect to time and centralized near the sites that commonly vulnerable to ulcerations
Pataky et al, 2005. [46]	<ul style="list-style-type: none"> • Clinical foot assessments • Force sensing resistors sensors: <ul style="list-style-type: none"> ○ Plantar pressure parameters • Statistical analysis: <ul style="list-style-type: none"> ○ Descriptive statistics ○ Paired t test ○ Regression analysis ○ Analysis of Variance (ANOVA) ○ Fisher's test 	<p>Diabetes</p> <ul style="list-style-type: none"> • Big toe and the 5th metatarsal head showing significant increase in plantar pressure and prolonged plantar pressure duration for every step • Plantar pressure is lowest under the heel and contact plantar surface is greatly reduced in the diabetes group • Anterior displacement of weight bearing while walking is observed in the diabetes patients without sign of any problems
Rahman et al, 2006. [47]	<ul style="list-style-type: none"> • Quantification of sensation: <ul style="list-style-type: none"> ○ Semmes-Weinstein monofilaments • Pedobarograph analysis: <ul style="list-style-type: none"> ○ F-scan sensor • Calibration • Static parameters: <ul style="list-style-type: none"> ○ Percentage medial impulse • Fourier domain analysis <ul style="list-style-type: none"> ○ Analysis of Variance (ANOVA) 	<ul style="list-style-type: none"> • Parameters implemented with Analysis of Variance (ANOVA) achieved more than 95% confident interval with excellent P-values for all the categories

Acharya et al, 2008. [48]	<ul style="list-style-type: none"> • Quantification of sensation: <ul style="list-style-type: none"> ◦ Semmes-Weinstein monofilaments • Pedobarograph analysis: <ul style="list-style-type: none"> ◦ F-scan sensor • Calibration • Discrete wavelet transform • Artificial neural network • Gaussian mixture model • Statistical analysis: <ul style="list-style-type: none"> ◦ Analysis of Variance (ANOVA) ◦ Receiver operating characteristic (ROC) 	<ul style="list-style-type: none"> • The study obtained classification results of 100% sensitivity and more than 85% specificity
Bacarin et al, 2009. [49]	<ul style="list-style-type: none"> • Clinical foot assessments: <ul style="list-style-type: none"> ◦ Semmes-Weinstein monofilament • Pedar-X insoles from Novel system: <ul style="list-style-type: none"> ◦ Plantar pressure 	<ul style="list-style-type: none"> • High plantar pressure in both diabetes neuropathy patients with and without history of foot ulcers compared to normal subjects • Diabetes neuropathy with history of foot ulcers do influence the distribution of plantar pressure • Increased load under the rear foot and midfoot, and increased in plantar pressure while barefoot walking
Acharya et al, 2012. [50]	<ul style="list-style-type: none"> • Sensation quantification: <ul style="list-style-type: none"> ◦ Semmes-Weinstein monofilament • Preprocessing • Image analysis: <ul style="list-style-type: none"> ◦ Continuous wavelet transforms (CWT) ◦ Principal Component Analysis (PCA) ◦ Fuzzy Sugeno classifier ◦ Statistical validation 	<ul style="list-style-type: none"> • 93.7% accuracy • 100% sensitivity • 83.3% specificity
Fawzy et al, 2014. [51]	<ul style="list-style-type: none"> • Medical history • Clinical assessment • Foot assessment • Neurological assessment • Plantar pressure measurement • Biochemical studies • SPSS for statistical analysis 	<ul style="list-style-type: none"> • Diabetes neuropathy patients with or without ulcerations have high peak plantar pressure • Risks for ulcerations due to elevation in plantar pressure variables particularly the forefoot peak plantar pressure, forefoot/ rear foot (F/R) ratio and forefoot peak pressure gradients

2.2. INFRARED THERMOGRAPHY

The thermography is a non-invasive imaging technique employed to record the thermal patterns using infrared (IR) camera. It allows qualitative and visual documentation of temperature variations in the vascular tissues. Indeed, the advancement in IR camera technology has revolutionised the field of measuring temperature whereby it is now being widely used for medical purposes [29].

2.2.1. BACKGROUND OF INFRARED THERMOGRAPHY

The human beings are regarded as homeotherms with the capability to sustain inner body temperature regardless of the variations in surrounding temperature by altering heat loss and heat production rates [52-54]. Indeed, this is achieved by the thermoregulatory mechanism of the human body, namely behavioural adjustments to the surrounding temperature and autonomic nervous responses. The autonomic nervous responses include the cutaneous vasomotor and sweating responses for heat loss [52]. Therefore, any unusual changes to the body temperature can be an indication of a disease.

In fact, the first use of thermobiological diagnostic began around 480 BC, discovered in the writings of Hippocrates [55]. Basically, colour changes of the mud placed on the abdomen of a patient is studied during drying. The regions where the mud is observed to have dry first are considered to indicate some underlying body part pathology.

Many physical achievements have elucidated the reasons for these phenomena throughout history. The discovery and acquisition of thermal radiation from the human body by William Herschel in the early 1800s was a huge stepping stone [56]. Based on the physical laws, any object which includes the human body, with a temperature higher than absolute zero (-273 K) emit electromagnetic radiation, called infrared radiation [57]. In addition, the human skin has an emissivity within the wavelength range of 2-20 μm and an average peak of 9-10 μm .

Despite this knowledge, it was in 1934 that Hardy et al. [58] explained the physiological characteristics of infrared emitted from the body surface. He further mentioned that the skin thermal properties and physiological activities are affected by numerous factors. Particularly, this is because the skin helps in regulating the core body temperature. Nonetheless, the presence of disease will cause these factors to change. Thus, infrared measurement can be utilized for diagnostic reasons. With this fundamental knowledge, infrared thermography was introduced to the medical sciences as a potential imaging modality [59]. The infrared thermography was first present to the modern medicine by Lawson in 1956, which later discovered the relationship between breast carcinoma and increasing skin temperature [60]. Afterwards, the potential and feasibility of infrared thermography are explored as an instrument to be utilized for breast lesions study [61]. The infrared thermography measures the temperature, or the temperature distribution using infrared radiation emitted from the body surface, that creates an image known as thermogram. The acquired 2 dimensional (2D) thermogram is a distinct representation of temperature distribution by capturing the reflected infrared radiation from the body in the presence of external infrared energy origins [62]. The infrared thermography is a non-contact, non-invasive and fast approach of measuring

temperature. Further, infrared thermography offers real time visualization of temperature distribution on the body surface without affecting the surface temperature [62].

2.2.2. THE PHYSICS OF INFRARED THERMOGRAPHY

A black body is defined as one that absorbs all the energy reaching it but reflect none back [63]. Based on the Planck's law, the spectral intensity I of thermal radiation at temperature T and at all wavelengths λ from black body in relation to wavelength is defined as:

$$I_{\lambda,b} (\lambda, T) = \frac{2\pi hc^2}{\lambda^5 (e^{\frac{hc}{\lambda kT}} - 1)} \text{ W cm}^{-2} \mu\text{m}^{-1} \quad (1)$$

where h is the Planck constant (6.626×10^{-34} J s), k is the Boltzmann constant (1.381×10^{-23} J K⁻¹), c is the speed of light in vacuum (2.998×10^8 m s⁻¹), λ is the wavelength (m) and T is the absolute temperature (K).

The spectral emissivity power of black body as a diffuse emitter is given by:

$$E_{\lambda,b} (\lambda, T) = I_{\lambda,b} (\lambda, T) = \frac{\frac{A_1}{A_2}}{\lambda^5 (e^{\frac{\lambda T}{1.439}} - 1)} \quad (2)$$

where $A_1 = 2\pi hc^2 = 3.742 \times 10^8$ W $\mu\text{m}^4/\text{m}^2$ and $A_2 = hc/k = 1.439 \times 10^4$ μm K.

The integration of Planck function with respect to all the frequencies results in attaining the Stefan-Boltzmann's law relating to the overall emissivity of black body [64]:

$$E_b = \int_0^{\infty} \frac{A_1}{\lambda^5 (e^{\frac{A_2}{\lambda T}} - 1)} d\lambda = \sigma T^4 \quad (3)$$

where σ is the Stefan-Boltzmann constant ($5.67 \times 10^{-8} \text{ W/m}^2 \text{ K}^4$).

For a black body, the overall energy emitted per unit area is directly proportional to the fourth power of its absolute temperature. The radiation emitted by most real objects are often partial to that emitted by black body of the same wavelength and temperature. The emissivity ε is defined as ratio of radiation emitted by real object E_λ to the radiation emitted by black body $E_{b,\lambda}$ at same temperature (T) [64]:

$$\varepsilon(T) = \frac{E_\lambda(T)}{E_{b,\lambda}(T)} \quad (4)$$

From Eq. (4), the Stefan-Boltzmann's law can be rewritten for real object in relation to emissivity as:

$$E = \varepsilon \sigma T^4 \quad (5)$$

As shown in Eq. (5), the energy radiated by real object is proportional to the surface temperature, which is then captured by the infrared detectors. Nevertheless, the detected energy relies on the surface emissivity coefficient. This coefficient ranges from 0 (non-emitting) to 1 (fully emitting) depending on the material [65]. In this case, the human skin has an emissivity coefficient of about 0.98 ± 0.01 at normal angles [31].

2.2.3. MEDICAL APPLICATIONS

The infrared techniques allow rapid capturing of large number of pixels, or picture elements [31]. The individual pixels at respective point denote the temperature. Collectively, these pixels create an image illustrating the surface temperature distribution. The advancement in infrared camera technology, in terms of resolution and response time has transformed the field of measuring temperature and is now being extensively used for medical purposes [29]. Essentially, temperature changes linked to certain diseases are detected by viewing the temperature distribution of the body using infrared thermography. The infrared thermography has been employed in various medical studies, namely vascular disorders [66-69], rheumatoid arthritis [70], breast cancer [71-75], muscular pain [76, 77] and dry eye [78, 79]. Also, infrared thermography has been widely used for diabetes detection such as to analyse body temperature variations [80] and metabolic parameters [81], estimate blood glucose [82], detect temperature variations in hypoglycaemia [83], and compare infrared thermography with biochemical assay methods [84]. In fact, infrared thermography has been commonly used in the studies of diabetic foot problems detection based on the temperature distribution of plantar foot as shown in Table 2.2-2.5.

2.3. INFRARED THERMOGRAPHY (TEMPERATURE)

ANALYSIS

In this research, the proposed diabetic foot studies using IR thermography are categorized into four types of analysis. They are separate lower limb temperature, asymmetric temperature, temperature distribution and independent thermal and physical stress analysis. The individual analysis is briefly described:

2.3.1. SEPARATE LOWER LIMB TEMPERATURE ANALYSIS

The summary of studies performing temperature analysis on separate lower limb using IR thermography is presented in [Table 2.2](#). Ammer et al. [\[85\]](#) studied the statistical relationship between the hotspots on the plantar and the development of callus, toe nail onychomycosis and foot deformities. However, the method proposed is not useful to detect skin changes normally present in the diabetes feet. Melnizky et al. [\[86\]](#) investigated the development of thermal gradient inversion among the type 2 diabetes patients and the correlation between temperature gradient and, blood glucose level, feet deformation, limited range of motion and nerve conductivity measurements. The study observed that almost half of the diabetes patients have affected temperature gradient on the leg but could not explained the caused. Nishide et al. [\[87\]](#) employed ultrasonography and thermography to determine the latent inflammation around the foot callus and studied the correlation between inflammation observed in callus and, with or without diabetes. The proposed methods may be useful to detect early ulcerations in diabetes patients with calli. Bharara et al. [\[88\]](#) present a quantitative thermography method using thermal index on a single case report of diabetic foot ulcer assessment and

correlate with the standard wound measurement method. Nevertheless, the index analysis requires more patients. Bagavathiappan et al. [23] explored the relationship between type 2 diabetes neuropathy patients and foot temperature using IR thermography. The study revealed that IR thermography may be applicable as an additional screening device to evaluate high risk diabetes feet.

Table 2.2: Separate lower limb temperature analysis.

Reference (Year)	Methodology	Findings
Ammer et al, 2001. [85]	<ul style="list-style-type: none"> Physical examination of feet Neurological assessment Thermal imaging Single Measure Intraclass Correlation Mann-Whitney U-test 	<ul style="list-style-type: none"> No relationship between skin changes and increased skin temperature
Melnizky et al, 2002. [86]	<ul style="list-style-type: none"> Physical examination of feet Nerve conduction test Thermal imaging SPSS 10.0 for statistical analysis 	<ul style="list-style-type: none"> A pathological temperature gradient was detected on the right limb of 36 diabetes patients (mean pathological gradient: $-0.27 \pm 0.68K$ vs $-1.84 \pm 0.81K$) whereas 39 patients on the left limb ($-0.77 \pm 1.15K$ vs $-1.49 \pm 1.21K$) No correlation between temperature measurements and nerve conduction
Sun et al, 2005. [27]	<ul style="list-style-type: none"> Electromyography for sympathetic skin response (SSR) test Thermal imaging Compute average temperature of six sub regions on each healthy sole Analyze sole temperature normalization relative to forehead temperature of diabetes patients SPSS for statistical analysis 	<ul style="list-style-type: none"> Highest temperature ($29.3 \pm 0.9^{\circ}C$) in the arc areas and lowest for the toes ($26.2 \pm 1.2^{\circ}C$). Diabetes patients without sympathetic skin response (SSR) had higher mean plantar temperature ($27.6 \pm 1.8^{\circ}C$) compared to those with SSR ($26.8 \pm 2.2^{\circ}C$) Equilibrium temperature is achieved at mean

		plantar temperature (27.8±1.0°C) after 15 minutes
Sun et al, 2006. [89]	<ul style="list-style-type: none"> • Seattle Wound Classification system • Thermal imaging • Electromyography for sympathetic skin response (SSR) test • Neurological assessment • SPSS for statistical analysis 	<ul style="list-style-type: none"> • At risk diabetes patients with pre-ulcerative skin and without SSR had highest mean foot temperature (30.2±1.3°C) compared to diabetes patients without SSR (27.9±1.7°C), diabetes patients with SSR (27.1±2.0°C), and normal subjects (26.8±1.8°C)
Sun et al, 2008. [90]	<ul style="list-style-type: none"> • Seattle Wound Classification system • Thermal imaging • Electromyography for sympathetic skin response (SSR) test • Neurological assessment • Nerve conduction test • SPSS for statistical analysis 	<ul style="list-style-type: none"> • At-risk class is 13.4 times more likely to develop plantar ulcerations than the diabetes patients with and without SSR during the 4-year period
Nishide et al, 2009. [87]	<ul style="list-style-type: none"> • Ankle Brachial Index (ABI) • Toe Brachial Index (TBI) • Achilles tendon reflex and vibratory perception • Semmes-Weinstein monofilament test • Thermography • Ultrasonography • Fisher's exact probability test • Mann-Whitney U-test • SPSS for statistical analysis 	<ul style="list-style-type: none"> • Ultrasonography and thermography detect inflammation symptoms in 10% of the calli in diabetes class whereas no inflammation detected in the normal class.
Bharara et al, 2010. [88]	<ul style="list-style-type: none"> • Thermal imaging • Thermal index • Image J Software 	<ul style="list-style-type: none"> • Thermal index/ wound inflammatory index moved from negative to positive (p<0.05) prior to reaching zero
Bagavathiappan et al, 2010. [23]	<ul style="list-style-type: none"> • Anthropometric measurements • Glycated hemoglobin (HbA1c) • Neuropathy assessment • Vascular sufficiency assessment • Thermal imaging • SPSS for statistical analysis 	<ul style="list-style-type: none"> • Diabetes neuropathy patients recorded highest foot temperature (32 – 35°C) than non-neuropathy diabetes patients (27 – 30°C) • Higher mean foot temperature (MFT) for Diabetes neuropathy patients

-
- No relationship between MFT and glycated hemoglobin
-

2.3.2. ASYMMETRIC TEMPERATURE ANALYSIS

The skin temperature distribution of healthy individuals is naturally symmetry whereas an asymmetry skin temperature distribution possibly indicates abnormality [53]. Evidently, Gatt et al. [91] observed that the skin temperature of similar areas in contralateral limbs is symmetrical in terms of pattern and magnitude by using IR thermography.

The studies on asymmetric analysis of diabetic foot thermograms are summarized in Table 2.3. Kaabouch et al in [36, 92-94] proposed an asymmetry analysis based method for detection of inflammation and predicting foot ulcerations risk using IR thermography. All the proposed methods can detect and determine inflammation and ulcers accurately and rapidly. Alternatively, Kaabouch et al. [95] proposed an asymmetry analysis-based scalable scanning technique that provides a valid comparison of both feet, particularly the different sizes and shapes. The implemented scalable scanning method yield fewer false abnormal regions and, the genetic algorithms effectively crop the feet from background and eliminate most noise. A preliminary case study is demonstrated by Liu et al. [96] whereby the effectiveness of proposed dermal thermography is evaluated as a screening instrument for early detection of ulcers. Nevertheless, segmentation of the feet from the background remains challenging because the foot, especially the toes, has a lower temperature compared to other body parts. Peregrina-Barreto et al. [33] presented a technique that provides quantitative

details with regards to the abnormal temperature differences between the symmetrical areas of the feet and inside of the foot. The proposed method able to provide a reliable complimentary information to assists clinicians in early identification of foot ulcers risk. van Netten et al. [97] studied the various cut-off values for skin temperature in identifying diabetes foot problems and to decide the urgency for treatment. The proposed method yields low specificity, which may result in over diagnosis. Nevertheless, the left and right foot mean temperature difference may be sufficient marker to determine urgency for treatment. Liu et al. [34] initiated a technique that involved asymmetric analysis together with colour images segmentation and, non-rigid landmark based registration B-splines among the right and left feet. The method implemented able to significantly detect diabetic foot ulcers with high accuracy, which also includes all the Charcot foots in the database.

Table 2.3: Asymmetric temperature analysis.

Reference (Year)	Methodology	Findings
Harding et al, 1998. [98]	<ul style="list-style-type: none"> • Infrared imaging • Radiography 	<ul style="list-style-type: none"> • Out of the 26 diabetes patients with positive thermograms, 21 of whom are confirmed with osteomyelitis by radiological evidence • Positive thermogram is described as at least 0.5°C rise in temperature of the affected foot skin with respect to the contralateral foot sole
Kaabouch et al, 2009. [92]	<ul style="list-style-type: none"> • Infrared imaging • Segmentation <ul style="list-style-type: none"> ◦ Genetic algorithm • Geometric transformation • Asymmetry analysis 	<ul style="list-style-type: none"> • Able to detect and determine inflammation and ulcers accurately and rapidly
Kaabouch et al, 2009. [93]	<ul style="list-style-type: none"> • Infrared imaging • Automatic thresholding: <ul style="list-style-type: none"> ◦ Histogram ◦ Clustering ◦ Entropy 	<ul style="list-style-type: none"> • Genetic algorithm yields superior thresholding results • Low and high order statistics effectively enhance the

	<ul style="list-style-type: none"> ○ Object attribute ○ Genetic algorithms • Geometric transformation • Asymmetry analysis • Features extraction 	asymmetry analysis in detecting foot abnormalities
Kaabouch et al, 2010. [94]	<ul style="list-style-type: none"> • Infrared imaging • Segmentation: <ul style="list-style-type: none"> ○ Genetic algorithm ○ Moment ○ Entropy ○ Iterative ○ Otsu's method • Geometric transformation • Asymmetry analysis 	<ul style="list-style-type: none"> • Genetic algorithm produces superior thresholding results
Kaabouch et al, 2011. [36]	<ul style="list-style-type: none"> • Infrared imaging • Segmentation: <ul style="list-style-type: none"> ○ Histogram ○ Clustering ○ Entropy ○ Object attribute ○ Genetic algorithms • Geometric transformation • Asymmetry analysis and abnormality identification • Features extraction 	<ul style="list-style-type: none"> • Genetic algorithm produces superior thresholding results • Low and high order statistics effectively enhance the asymmetry analysis in detecting foot abnormalities
Liu et al, 2013. [96]	<ul style="list-style-type: none"> • Infrared imaging • Foot segmentation: <ul style="list-style-type: none"> ○ Active contours without edges • Feet registration • Abnormal detection 	<ul style="list-style-type: none"> • Active contours without edges method acquire reasonable result • Automated detection of pre-symptoms ulceration by computing temperature difference of the feet • 2.2°C as the clinical relevant difference
Peregrina-Barreto et al, 2013. [99]	<ul style="list-style-type: none"> • Infrared imaging • Color characterization • Foot angiosomes and color classification 	<ul style="list-style-type: none"> • The temperature estimate difference between corresponding angiosomes can be used to screen for abnormality
van Netten et al, 2013. [100]	<ul style="list-style-type: none"> • Infrared imaging • Mean temperature of whole foot and regions of interest 	<ul style="list-style-type: none"> • Mean temperature of contralateral and ipsilateral foot is the same in patients with localized problems • Temperature at ROI was more than 2°C compared to the similar area in contralateral foot and to the mean of the entire ipsilateral foot

		<ul style="list-style-type: none"> • Mean temperature differences between the contralateral and ipsilateral foot was more than 3°C in patients with diffuse problems
Peregrina-Barreto et al, 2014. [33]	<ul style="list-style-type: none"> • Infrared imaging • Color characterization • Temperature estimated difference • Hot spots detection 	<ul style="list-style-type: none"> • HSE capable of detecting abnormal small areas in the early phase that were not detected by ETD estimator
van Netten et al, 2014. [97]	<ul style="list-style-type: none"> • Infrared imaging: <ul style="list-style-type: none"> ○ Color image ○ Thermal image • Clinical foot assessments • Kruskal-Wallis test • Receiver operating characteristic (ROC) curve and area using SPSS 	<ul style="list-style-type: none"> • Optimal cut-off value for skin temperature in identifying diabetes foot problems was difference of 2.2°C between contralateral spots, with 76% sensitivity and 40% specificity • Optimal cut-off values for skin temperature to decide the urgency for treatment was difference of 3.5°C between left and right foot mean temperature, with 89% sensitivity and 78% specificity
Vilcahuaman et al, 2014. [101]	<ul style="list-style-type: none"> • Infrared imaging • Image processing: <ul style="list-style-type: none"> ○ Chan and Vese active contour algorithm ○ Iterative closest point (ICP) 	<ul style="list-style-type: none"> • In the clinical study, 10% of the diabetes patients had signs of significant hyperthermia on the foot plantar with temperature difference of more than 2.2°C
Vilcahuaman et al, 2015. [102]	<ul style="list-style-type: none"> • Infrared imaging • Image processing: <ul style="list-style-type: none"> ○ Radon transform ○ Chan and Vese active contour algorithm ○ Compute Mean temperature ○ Iterative closest point (ICP) 	<ul style="list-style-type: none"> • High risk group had significantly higher temperature (32±2°C) than medium risk group (31±2°C) • In the study, 9 out of 82 diabetes patients had significant hyperthermia
Liu et al, 2015. [34]	<ul style="list-style-type: none"> • Infrared imaging • Foot segmentation: <ul style="list-style-type: none"> ○ Machine learning for color image segmentation ○ Segmentation evaluation • Registration optimization • Asymmetric analysis 	<ul style="list-style-type: none"> • The study yielded an accuracy of 95% with 35 out of the 37 diabetic foot ulcers identified • All three Charcot foots are successfully detected.

Kaabouch et al, 2016. [95]	<ul style="list-style-type: none"> • Infrared imaging • Genetic algorithms • Asymmetry analysis-based scalable scanning 	<ul style="list-style-type: none"> • Genetic algorithms effectively crop the feet from background and eliminate most noise • Scalable scanning method yield fewer false abnormal regions
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2.3.3. TEMPERATURE DISTRIBUTION ANALYSIS

Indeed, many studies have observed similar skin temperature distribution on the feet of healthy individuals compared to varying temperature distribution in diabetes patients. In 1991, Chan et al. [20] described the temperature distribution on the feet of healthy individuals as symmetric butterfly pattern in which the highest temperature is at the arc and lowest at the toes.

The summary of studies on temperature distribution analysis is shown in [Table 2.4](#). Nagase et al. [26] and Bharara et al. [103] proposed a characterization method of plantar thermography patterns based on foot planar angiosomes concept. The disadvantages in these studies may be bias of variations in the control group due smaller number of participants. The gender and age are unmatched in the control group, which may lead to confounding factors for data interpretation. Besides, the proposed manual classification method of 20 categories may be complicated for clinical purposes. Oe et al. [104] studied the thermography data of patients with osteomyelitis and diabetes foot. The limitations are that the morphology analysis of thermography patterns may be subjective and possibility affected by the surrounding environment, expertise of the researcher and patients' detail biasness. Furthermore, the diagnosis of osteomyelitis is based on MRI without performing biopsy of the tissues or bone. Thus, the pathophysiology condition that underlie the ankle pattern cannot be fully understand.

Mori et al. [32] proposed a system that characterized plantar thermal patterns with image segmentation technique based on mode seeking technique. The drawbacks are that variations biasness may be present in the control group because of the smaller number of participants. The gender and age are unmatched in the control group, which may lead to difficulties for data interpretation. Moreover, the proposed method only focused on the fore region of the thermographic patterns. Hernandez-Contreras et al. [105] proposed a characterization technique to distinguish the thermal patterns of normal and diabetes patients. The proposed technique analysed the regions of high temperature, the localization and distribution. The analysis using pattern spectrum yields reasonable results. Nonetheless, the technique is unable to offer detail relating to the position of these regions. Again, Hernandez-Contreras et al. [106] proposed a characterization technique to distinguish the thermal patterns of normal and diabetes patients. The technique comprised of plantar area and hotspots segmentations, hotspots characterization and pattern classification, which obtained an average classification rate of 94.33% with the extracted features.

Table 2.4: Temperature distribution analysis.

Reference (Year)	Methodology	Findings
Branemark et al, 1967. [107]	<ul style="list-style-type: none"> • Infrared imaging • Clinical assessment 	<ul style="list-style-type: none"> • Abnormal emission patterns from hand and feet of all diabetes patients • Reduced emission on the metatarsal and toes areas
Nagase et al, 2011. [26]	<ul style="list-style-type: none"> • Infrared imaging • Conceptual classification comprising of 20 categories of plantar thermography patterns 	<p>Normal</p> <ul style="list-style-type: none"> • 48 feet (or 75%) are characterized to the seven categories and the remaining 16 feet characterized as atypical • The Id category (butterfly pattern) is mostly identified with 30 feet (or 46.9%) <p>Diabetes</p>

		<ul style="list-style-type: none"> • 225 (or 87.2%) diabetes feet are characterized to 18 categories and the remaining 33 feet (or 12.8%) as atypical • The IIa category (medial and lateral plantar arteries undamaged) is mostly identified with 101 feet (or 39.1%)
Oe et al, 2013. [104]	<ul style="list-style-type: none"> • MRI scans • Infrared imaging • Ankle-brachial index (ABI) • Toe-brachial index (TBI) • Nerve conduction velocity • SPSS for statistical analysis 	<ul style="list-style-type: none"> • Ankle pattern is mostly common in patients with osteomyelitis • Sensitivity = 60% • Specificity = 100% • PPV = 100% • NPV = 71.4%
Mori et al, 2013. [32]	<ul style="list-style-type: none"> • Ankle-brachial index (ABI) • Toe-brachial index (TBI) • Achilles tendon reflex • Semmes-Weinstein monofilament test • Vibratory sensation test • Infrared imaging • Image partitioning algorithm • T test or chi square test 	<p>Normal</p> <ul style="list-style-type: none"> • 47 feet are characterized to the four categories and the remaining 17 feet characterized as anomalous • The type 1 (butterfly pattern) (44%) is mostly identified <p>Diabetes</p> <ul style="list-style-type: none"> • 198 diabetes feet are characterized to six categories and the remaining 60 feet as atypical • The type 2 (46%) is mostly identified
Bharara et al, 2014. [103]	<ul style="list-style-type: none"> • Clinical assessment • Semmes Weinstein monofilament • Vibratory perception threshold • Infrared imaging 	<p>Normal</p> <ul style="list-style-type: none"> • Subjects are mostly represented by Id category (Butterfly Pattern) during measurements with 47.2% at rest, 13.8% at post stress and 27.8% at recovery <p>Diabetes</p> <ul style="list-style-type: none"> • Subjects are mostly represented by IIa category (medial and lateral plantar arteries undamaged) during measurements with 50% at rest, 50% at post stress and 28.57% at recovery

Hernandez-Contreras et al, 2015. [105]	<ul style="list-style-type: none"> • Infrared imaging • Grayscale characterization • Arch segmentation based on histogram distribution • Mathematical morphology 	<p>Normal</p> <ul style="list-style-type: none"> • Butterfly pattern is presented in the subjects and pattern spectrum is same as oval • Mean percentage of pixels for control group is highest in quadrant 4 with 88.05% <p>Diabetes</p> <ul style="list-style-type: none"> • Pattern spectrum is irregular due to the dissimilar pattern • Mean percentage of pixels is 28.87% for diabetes group in quadrant 3.
Hernandez-Contreras et al, 2015. [106]	<ul style="list-style-type: none"> • Infrared imaging • Grayscale characterization • Foot segmentation • Temperature pattern • Mathematical morphology • Pattern spectrum • Multilayer perceptron • K-fold cross validation 	<ul style="list-style-type: none"> • Proposed technique achieved average classification rate of 94.33%

2.3.4. INDEPENDENT THERMAL AND PHYSICAL STRESS ANALYSIS

The goal of independent stress analysis is to study the reaction of body thermoregulation system under applied thermal and/or physical stress. The stress may include soaking the body part into cold or hot water, or mechanical stress like running or walking.

The summary of studies based on independent thermal and physical stress analysis prior to thermogram acquisition is presented in **Table 2.5**. Fushimi et al. [108] studied the vasoreactions of peripheral arteries to cold stimuli on the hands of normal and diabetes subjects by recording the temperature changes in the toes using IR

thermography. The pattern for abnormal temperature changes is classified into 3 types, namely increasing, decreasing and flat. The atherosclerosis of peripheral arteries is highly related to the abnormal vasoreaction of toe arteries following the application of cold stimulus on both hands. The advantage of this study is that cold stimulated IR thermography helps to assess the peripheral atherosclerosis condition. Fujiwara et al. [109] evaluated the blood flow in the skin of diabetes patients using IR thermography before and after soaking the lower limb into cold water. The study confirmed that lower skin temperature recovery rate in diabetes patients is because of causal factors such as peripheral arterial sclerosis, abnormal blood coagulation fibrinolysis and sympathetic nerve dysfunction. Hosaki et al. [110] proposed a novel and nonintrusive diagnosis method for peripheral circulation in diabetes patients. The study found that the results for peripheral circulation in diabetes patients obtained using Laser-Doppler blood flowmetry and thermography are correlated. The study showed that these methods can determine diabetes patients with poor peripheral perfusion. Balbinot et al. [111] assessed the specificity and sensibility of plantar thermography in diagnosing diabetes patients with polyneuropathy by utilizing heart rate variability (HRV) as a reference. Evidently, the plantar thermography is applicable in diagnosing diabetes neuropathy early, especially the autonomic and small fibres that are related to sub clinical condition. Nonetheless, this is a cross sectional study that includes sensitive test. Barriga et al. [112] proposed a computer aided detection system for pre-clinical stages of peripheral neuropathy based on thermograms analysis. The study confirmed that cold stimuli and IR thermography can successfully identified patients with microvascular abnormalities. Najafi et al. [113] studied the dynamic fluctuation in plantar temperature with respect to the pre-defined steps taken by the diabetes and peripheral neuropathic patients with and without Charcot neuroarthropathy. There are several disadvantages in this study.

The development stage of Charcot foot is not controlled in this study whereby some patients may be in the coalescence phase. Moreover, the offloading foot wear is not standardized and hence, unable to sufficiently performed stratified analysis by stage and type of offloading foot wear. Lastly, due to the technology drawbacks, a short hold-up is needed to analyse the plantar temperature after each gait. Balbinot et al. [114] compared the plantar temperatures and analysed the plantar re-warming index repeatability after cold stress on two separate days and groups, diabetes and normal. The proposed study observed good repeatability between two days presented by the re-warming index after cold stimuli. However, the drawbacks are the small sample size because this is a pilot study and does not involved neurophysiological study to assess the existence of diabetes peripheral neuropathy. Further, the clinical assessment performed does not identified diabetes patients with neuropathy. Yavuz et al. [115] studied the statistical correlation between the plantar stresses and increases in foot plantar temperature after exercise using IR thermography. The disadvantages are the small number of participants that does not include diabetes patients. Also, there are more female subjects in this study and the size of the customized pressure shear instrument restrict the shear measurements of the whole foot. Agurto et al. [116] proposed a technique for classification of diabetes peripheral neuropathy patients using IR thermography and independent component analysis (ICA). The limitations of this study are that some initial frames are not considered for analysis and some areas, particularly the toes, present artefacts which requires stabilizing the toes to avoid significant movements.

Table 2.5: Independent thermal and physical stress analysis.

Reference (Year)	Methodology	Findings
Fushimi et al, 1996. [108]	<ul style="list-style-type: none"> • ECG • Ankle pressure index • Infrared imaging • Ultrasonic imaging 	<p>Normal</p> <ul style="list-style-type: none"> • All subjects had normal pattern <p>Diabetes</p> <ul style="list-style-type: none"> • 43 had normal, 19 increasing and 26 decreasing and 24 flat patterns
Fujiwara et al, 2000. [109]	<ul style="list-style-type: none"> • Infrared imaging • Ankle-brachial index • Doppler meter • Motor nerve conduction velocity • Sensory nerve conduction velocity • ECG • Schellong's test • Photo-dispersion method • ANOVA with Neuman-Keuls multiple comparison test 	<ul style="list-style-type: none"> • Smaller skin temperature drops in diabetes patients compared to normal subjects after immersing into cold water • Diabetes patients had lower skin temperature recovery rate due to causal factors such as peripheral arterial sclerosis, abnormal blood coagulation fibrinolysis and sympathetic nerve dysfunction
Hosaki et al, 2002. [110]	<ul style="list-style-type: none"> • Infrared imaging • Laser Doppler blood flowmeter • Hot loading at 36 °C • Cold loading at 20 °C • Compute recovery ratio 	<ul style="list-style-type: none"> • Recovery ratios for the 27 diabetes patients were in the range of 0-93.5% and the average was 34% • Blood flow and recovery ratio were correlated ($r = 0.634$, $p < 0.0001$) • Ratio of blood flow after cold loading over the blood flow after hot loading was in the range of 38.1% - 122% and average of 80.6%. • This ratio and recovery ratio is correlated ($r = 0.502$, $p < 0.0001$)
Balbinot et al, 2012. [111]	<ul style="list-style-type: none"> • Clinical assessments: <ul style="list-style-type: none"> ○ Michigan inventory ○ Achilles reflex test • Heart rate variability • Infrared imaging: <ul style="list-style-type: none"> ○ Before and after cold stress test ○ Thermal recovery index 	<p>Diabetes</p> <ul style="list-style-type: none"> • Interdigital anisothermal method performed better than thermal recovery index with 46.2% specificity and 81.3% sensitivity <p>Prediabetes</p>

	<ul style="list-style-type: none"> ○ Interdigital anisothermal • Electromyography • Statistical analysis: <ul style="list-style-type: none"> ○ Receiver operating characteristic (ROC) curve ○ Kappa coefficient ○ Student t test ○ Mann-Whitney U test 	<ul style="list-style-type: none"> • All three tests achieved 25% specificity and 80% sensitivity equally
Barriga et al, 2012. [112]	<ul style="list-style-type: none"> • Infrared imaging • Motion tracking of thermal features • Exponential curve fitting 	<ul style="list-style-type: none"> • Diabetes neuropathy patient recorded recovery rate of 2% at the two toes and approximately 0.4% at the heel • Normal subject recorded high recovery of 4% at the medial arch as compared to less than 1.5% in the diabetes neuropathy patient
Najafi et al, 2012. [113]	<ul style="list-style-type: none"> • Two pre-defined paths of 50 and 150 steps • Infrared imaging • Image processing • Student t test • ANOVA 	<ul style="list-style-type: none"> • In Charcot neuroarthropathy group, the decreased in temperature for non-affected foot is 1.9 folds more than the affected foot • Plantar temperature for both foot in Charcot neuroarthropathy group significantly increased beyond 50 steps and remain higher on the affected foot at 200 steps
Balbinot et al, 2013. [114]	<ul style="list-style-type: none"> • Clinical assessments: <ul style="list-style-type: none"> ○ Michigan neuropathy screening instrument (MNSI) ○ Semmes-Weinstein monofilament ○ 128Hz vibratory sensibility ○ Achilles tendon reflex • Infrared imaging: <ul style="list-style-type: none"> ○ Pre- and post-cold stress test • Data analysis: <ul style="list-style-type: none"> ○ Rewarming index • Statistical analysis: 	<ul style="list-style-type: none"> • Significant difference in the average temperatures of normal subjects between the two days before and after cold stress test compared to no difference in the average temperatures for diabetes patients • Rewarming index of both groups did not differ between the two days

	<ul style="list-style-type: none"> ○ Shapiro-Wilk test ○ T test ○ Bland-Altman limits of agreement plot 	
Yavuz et al, 2014. [115]	<ul style="list-style-type: none"> • Walking on pressure shear plate <ul style="list-style-type: none"> ○ Stress data • Treadmill walking • Infrared imaging: <ul style="list-style-type: none"> ○ Pre- and post-exercise • Peak shear stress and peak resultant stress • Statistical analysis: <ul style="list-style-type: none"> ○ Pearson's r 	<ul style="list-style-type: none"> • Significant correlation between temperature rises and peak shear stress ($r=0.78$) • Increased in plantar temperature can predict the site of peak resultant stress and peak shear stress in 39% and 23% of the subjects
Agurto et al, 2015. [116]	<ul style="list-style-type: none"> • Cold stimulus • Infrared imaging • Independent component analysis (ICA): <ul style="list-style-type: none"> ○ Preprocessing ○ Subsampling ○ Registration ○ Co-registration ○ Time alignment ○ Feature extraction ○ ICA decomposition 	<ul style="list-style-type: none"> • Components 2, 6 and 8 significantly differentiate the normal and diabetes peripheral neuropathy patients • Higher recovery rate in normal subjects for component 6 • Diabetes peripheral neuropathy patients have lower temperature recovery rate in most parts of the foot plantar

2.4. METHODOLOGY OF CAD SYSTEM

Computer aided detection (CAD) plays a crucial role in analysing the IR thermograms. On the contrary, human assessment of IR thermograms are prone to errors due to negligence, tiredness and repeated works. Furthermore, diagnosis accuracy may be affected by the limitations of human visual perception like optical illusions [117]. Besides, some healthcare institutions may not have sufficient clinicians for diagnosis. Therefore, the development of CAD system is necessary to overcome these constraints. Recent breast cancer detection studies have proposed IR thermogram image processing algorithms with enhanced detection accuracy based on the following approaches: segmentation, feature extraction and classification [73, 118-120].

The development of CAD system requires the understanding of system structure and design patterns. The system structure is described by introducing the respective design stages required to develop a general IR thermography-based CAD system. The design stages and the logical association among them are illustrated by the block diagram in Figure 2.3. The block diagram is separated into online and offline systems. In the offline system, the thermograms are first preprocessed and the grayscale features extracted using various methods. Next, the extracted grayscale features are statistically analyzed to determine the significant features and subsequently classified using various classifiers. The significant features and the ground truth of each thermogram class are used to train the classifier. The result is a set of classifier parameters that links the significant features with the ground truth. Similarly, in the online system, thermograms are preprocessed and then the same significant features identify in the offline system are computed for the testing set of images.

Figure 2.3: Block diagram of thermogram-based CAD system that consists of the design stages and the logical association among them. The block diagram is separated into online and offline systems.

2.4.1. PREPROCESSING

Pre-processing handles the non-uniformity of thermograms, for instance the different sizes and forms of region of interest (ROI). Hence, the thermal images may need to be uniformly resized using method such as warping [121]. The thermal image is warped to an image whereby the ROI is transformed into a standard size and form. This allows all the plantar foot temperature data to be analysed on a common basis. There are two image warping techniques, (i) forward and (ii) reverse mappings [121]. The former technique scans the source image pixel by pixel before putting them into suitable locations on the destination image; whereas the latter technique scans the destination image through the individual pixel before sampling the appropriate pixels of the source image [122]. Tan et al. initially selected the ocular region and then reverse mapped all the thermal images into standard form prior to subsequent analysis [123].

2.4.2. FEATURE EXTRACTION

The feature extraction is an important process in capturing significant information from the images. The higher order spectra (HOS), discrete wavelet transform (DWT), textures and entropies techniques can be implemented to extract features [124]. These techniques are concisely described:

2.4.2.1. HIGHER ORDER SPECTRA (HOS)

The HOS is made up of higher order moments with an order of two or more. In addition, HOS include nonlinear combinations of higher order moments, referred as cumulants. The bispectrum and trispectrum are the third and fourth order spectra respectively [[125](#)]. Equally important, features related to third order spectra can be used to extract details for automated diagnosis of disease [[126](#), [127](#)]. In any case, Radon transform must be performed on the thermogram prior to extracting the greyscale features using HOS. This is to convert the 2-dimensional (2D) thermograms into 1-dimensional (1D) signals at different angles [[128](#)].

2.4.2.2. DISCRETE WAVELET TRANSFORM (DWT)

The DWT can be used to capture the location and frequency of features in the thermogram. Essentially, this information assists the CAD system to determine the features of interest. In the thermographic pattern of breast cancer, the features have sharp borders. These sharp borders yield high frequency coefficients with high degree of spatial accuracy whereas smooth edges produce low frequency coefficients with low location accuracy [[129](#)]. The coefficients are acquired by down sampling the signal through a series of high and low pass filters [[130](#), [131](#)]. The output of the high and low pass filters are detail and approximation coefficients respectively. Mookiah et al. combined one texture and two DWT features to compute the nonlinear changes in normal and malignant breast thermograms [[132](#)].

2.4.2.3. TEXTURE

The changes in texture result in an entirely new pattern for feature collection. The textural features compute the coarseness, pixel regularity and smoothness in an image [133]. Hence, textural features are meaningful. The Local Binary Pattern (LBP) [134], Law's Texture Energy (LTE) [135, 136], Gray Level Co-occurrence Matrix [137] and Hu's invariant moment [138], can be implemented to extract useful details for the differential diagnosis of healthy and disease groups.

2.4.2.4. ENTROPY

The entropy computes the irregularities of pixel intensity distribution in the thermogram. Moreover, entropy allows deep understanding on the nature and extent of irregularities and revealed the degree of disordered of the image pixels. The entropy is categorized as non-Shannon and Shannon [139]. The dynamic range of Shannon entropy is relatively lower compared to non-Shannon entropies. Therefore, non-Shannon entropies is significantly effective in approximating the scatter regularity and density. The Kapur, Yager, Renyi, Vajda and Fuzzy entropy are examples of non-Shannon entropies employed to extract features for automated diagnosis of disease [140-142].

2.4.3. STATISTICAL ANALYSIS

The statistical analysis is part of quantitative approach to knowledge. In the development of thermography-based CAD systems, statistical analysis is employed to sum up the data and comprehend the data generating processes. This is normally done by creating a mathematical model that allows the inference of the data generating processes. Moreover, the statistical analysis provides an alternative approach to measure confident in the inferences [[21](#), [26](#), [111](#)].

2.4.3.1. FEATURE SELECTION

The Student's t test can be implemented to identify the significant features by analysing the p value. The p value specifies if the means of the two groups are different statistically [[143](#)]. The feature with lower p value is clinically significance [[144](#)]. Moreover, the feature performance for CAD systems is analysed by ranking the p value in an ascending order and then individually fed the ranked features into the classifier till maximum classification result is obtained.

2.4.4. CLASSIFICATION

The automated classification techniques are important in solving statistics and machine learning difficulties of deciding the class for new finding. Indeed, classifiers have been extensively implemented in many CAD systems [[145](#)]. The supervised algorithms require training data that consist of findings where the ground truth is accessible. In general, the classification techniques extract the distinct information from

training set. This information extraction process is referred to as learning phase. Thereafter, the information extracted is utilized in the classification stage to determine the class for the new finding.

2.4.4.1. SUPPORT VECTOR MACHINE (SVM)

The SVM classifier train and generalize training information for an extensive range of classification complications. The technique determines the hyperplane that acts as a decision surface. The hyperplane divides the data points belonging to the classes with maximum margin. Positively, SVM can yield significant accuracy particularly in difficult conditions. This include high dimensional and nonlinear datasets and, little cases to train the model [[145](#), [146](#)]. For a nonlinear data, the boundary problem is also nonlinear. Thus, to overcome such data, kernels can be used to help map the nonlinear input data to high dimensional space [[147](#)]. The various kernel functions used are linear, second and third order polynomial and Radial Basis Function (RBF).

2.4.4.2. CROSS VALIDATION

In cross validation process, the classifier is assessed with a training dataset [[148](#)]. The dataset is divided randomly into k equal portions. Each portion consists the same number of samples from the two classes [[149](#)]. For the first fold (iteration), $k - 1$ data portions are utilised for training and the remaining for testing the classifier. The iteration is done again $k - 1$ times using a different testing dataset and the remaining folds for training dataset each time. The cross validation procedure is employed to develop classifier for thermography-based CAD system [[71](#)]. In offline system, classification

results are evaluated based on performance measures, namely False Negative (FN), False Positive (FP), True Negative (TN), True Positive, Specificity (Spec), Sensitivity (Sen), Accuracy (Acc). This evaluation assists in choosing the most suitable classification algorithm for online system.

2.5. SUMMARY

This chapter provides an overview on the literatures that are relevant in this research. The [section 2.1](#) summarizes the proposed diabetic foot studies based on plantar foot pressure analysis. The plantar pressure measurement is widely used to distinguish the walking patterns of various clinical groups and to analyze the impact of foot wears, orthotic supports and surgeries. Also, to better understand the mechanical nature of human foot while on dynamic and static loading. Nonetheless, the continuous pressure, shearing and weight bearing during walking may result in rising plantar foot pressures and further include skin breakdown and the formation of callus. This leads to blistering in which the epidermis is dried and hence predisposed to fissure and tear. Besides, the presence of subcutaneous tissues atrophy impaired the capacity of the foot to absorb impact while walking [[150](#)]. Therefore, plantar pressure analysis may not be applicable and comfortable for diabetes patient.

Meanwhile, [section 2.2](#). gives an overview of infrared thermography, namely the background, physics and medical applications. In general, thermography is a non-invasive imaging technique employed to record thermal patterns using infrared (IR) camera. It allows qualitative and visual documentation of temperature variations in the vascular tissues. Indeed, the advancement in IR camera technology has revolutionised

the field of measuring temperature whereby it is now being widely used for medical purposes, which include diabetic foot studies [29].

For this purpose, diabetic foot studies based on infrared thermography analysis are summarized and discussed in [section 2.3](#). In essence, studies have shown that temperature variations on the plantar area can be associated to diabetic foot complications. These studies are further categorised based on the analysis conducted, in this case separate lower limb temperature, asymmetric temperature, temperature distribution and, independent thermal and physical stress analysis. [Section 2.3.1](#). presents a separate lower limb temperature analysis representing range of temperatures for various study groups. This analysis cannot determine the specific risk regions associated to diabetes foot complications. The asymmetric temperature analysis in [section 2.3.2](#). performed plantar temperature comparison between one foot and the contralateral foot. However, this analysis cannot identify risk regions if same complications are present on the same area of both foot. Also, this analysis requires patients to have both foot fully intact (without any past amputation). The temperature distribution analysis in [section 2.3.3](#). does not compare the plantar temperature between feet but instead, studied each foot independently. Despite studies showing same plantar temperature distribution in normal subjects, there has been no representative pattern for this group thus far. In addition, plantar temperature distribution in diabetes patients are irregular and variety in patterns. This complicates the classification process. The independent thermal and physical stress analysis in [section 2.3.4](#). analysed the plantar temperature reaction to the applied external stimulus. The temperature is evaluated by analysing separately before and after the application of external stress. Nevertheless, the external stress applied may result in subjects feeling uncomfortable and inconvenient.

Thermogram-based CAD system is eminently essential to interpret the plantar thermograms because the link between diabetic foot and thermal pattern is subtle and, in most cases, nonlinear [151]. Absolutely, knowledge discovery and data mining algorithms can help to improve the thermogram-based diagnosis. Section 2.4. describes the algorithms employed in this research to develop the thermography-based CAD system. These algorithms are from the domains of pre-processing, feature extraction, statistical feature analysis, classification, and result assessment.

CHAPTER 3. MATERIALS & METHODOLOGY

3.1. STUDY POPULATION

This research was conducted on healthy and diabetes without neuropathy groups. 33 healthy subjects and 33 diabetic patients without neuropathy were voluntarily recruited from Ngee Ann Polytechnic, Biomedical Centre, and Singapore General Hospital (SGH), Diabetes & Metabolism Centre (DMC), respectively under similar conditions. The SingHealth Centralised Institutional Review Board (CIRB) has approved for the diabetic foot data collection to be conducted in SGH (CIRB Ref: 2016/3044). Meanwhile, Ngee Ann Polytechnic-Institutional Review Board (NP-IRB) has approved the data collection of healthy foot (NPIRB-P0175-2017-ECE-AMA6). The demographic information obtained from diabetes and healthy groups is presented in **Table 3.1**. For both groups, the participants were informed about this research and informed consent were obtained. In addition, participants with previous amputation, peripheral vascular disease, ischemic heart disease and neurological disorder were excluded.

Table 3.1: Demographic information of healthy and diabetes groups (Mean $\pm$ Standard Deviation).

	Healthy group	Diabetes group
Subjects	33	33
Female	15	15
Male	18	18
Average Age (years)	51.94 $\pm$ 11.25	56.18 $\pm$ 14.71
Average Body Mass Index (BMI) (kg/m²)	23.50 $\pm$ 3.61	25.08 $\pm$ 5.31

3.2. THERMOGRAM ACQUISITION PROTOCOL

The study was conducted in a control room temperature of 20 $\pm$ 1°C and humidity of 55 $\pm$ 5%. The subjects were required to remove their foot wear, socks, and their feet cleaned. Thereafter, the subjects remained seated on the treatment bench in supine position for at least 15 minutes. The purpose is to achieve thermal equilibrium on the feet prior to capturing the passive thermograms. The segmented feet thermograms of healthy and diabetic seen in Figure 3.1(a)-(b) were captured using Thermographic System VarioCAM© hr head 680/30 mm as shown in Figure 3.2. The infrared camera was placed at focus distance of about 1 *meter* away from the feet. The specifications of infrared thermography camera used in this research are presented in Table 3.2. The thermal image of the foot plantar was presented in RGB (Red, Green, Blue) colour space and temperature scale ranging from 20 to 32°C. The infrared camera automatically calibrates the temperature scale based on the coldest and hottest points in the scene. The

thermograms are kept in *.irbis* format after acquisition and then exported to *.bmp* format for subsequent image analysis.

Figure 3.1(a)-(b): The segmented feet thermograms (C°) of (a) healthy and (b) diabetes without neuropathy captured using Thermographic System VarioCAM© hr head 680/30 mm.

Figure 3.2: Infrared thermography camera (Thermographic System VarioCAM© hr head 680/30 mm) to capture the feet of healthy and diabetic subjects.

Table 3.2: Infrared thermography camera specifications.

Detector type	Micro bolometer FPA detector (uncooled)
Detector format	640 x 480 infrared-pixel
Spectral range	(7.5 ... 14) μm
Infrared image rate	50/60 Hz
Temperature measurement range	(-40 ... 1200) $^{\circ}\text{C}$, optionally > 2000 $^{\circ}\text{C}$
Thermal resolution @ 30$^{\circ}\text{C}$	Better than 0.03 K
Measurement accuracy	± 1.5 K, ± 2 %
Standard lens, FOV, aperture angle, minimum focus range, geometrical resolution	30 mm, (53 x 40) cm, (30 x 23) $^{\circ}$, 0.3 m, 0.8 mrad

3.3. METHODOLOGY

In this research, the segmented grayscale foot thermogram is warped into an image whereby the region of interest is transformed into a common size and shape [123]. This process allows the approximation of plantar foot region and the comparison of plantar foot surface data of different sizes to a standard size. The temperature data within the region of interest (ROI) is decomposed using discrete wavelet transform (DWT) and higher order spectra (HOS) techniques that can capture the minute variation between adjacent pixels and, the non-linear interaction in the phase coupling and frequency components [152]. Thereafter, feature values (texture and entropy based) extracted from both decomposed foot images are subtracted and then statistically analysed to determine the significant features for classification. The block diagram of the proposed methodology for diabetic foot detection is presented in Figure 3.3.

Figure 3.3: The block diagram of the proposed methodology using thermal images for diabetic foot detection.

3.3.1. PLANTAR FOOT SEGMENTATION

The plantar foot regions of healthy and diabetic groups are initially segmented from the thermograms. The plantar foot region is manually delineated using polygon with 16 points selected on the foot boundary. These points are connected by straight lines that enclosed the whole plantar foot and represented by returning the information relating to the coordinates. The segmented left foot is then flipped in the same orientation as the right foot for equal comparison prior to subtraction. The delineation and masking of the ROI are shown in [Figure 3.4\(a\)-\(b\)](#) respectively.

(a)

(b)

Figure 3.4 (a)-(b): The plantar foot segmentation process consists of (a) delineation of plantar foot region using 16 polygon points and (b) masking of plantar foot region prior to subsequent analysis.

3.3.2. IMAGE WARPING

In general, image warping transformed the thermal data at the plantar foot surface into standard form. There are two available image warping techniques, (i) forward and (ii) reverse mappings [121]. For forward mapping technique, the source image is being scanned pixel by pixel before putting them into suitable locations on the destination image. In reverse mapping technique, the destination image is being scanned through the individual pixel before sampling the appropriate pixels of the source image [122]. In this work, the image warping technique employed is reverse mapping as to avoid from missing out sampling the relevant pixels.

The warping technique begins with several pairs of lines represented on source image $(K'_{k_{i+1}} K'_{k_i})$ and the equivalent destination image $(K_{k_i} K_{k_{i+1}})$. For every line $K_{k_i} K_{k_{i+1}}$,

$$S = \frac{(D-K_{k_i}) \cdot (K_{k_{i+1}} - K_{k_i})}{\|K_{k_{i+1}} - K_{k_i}\|^2} \quad (6)$$

$$t = \frac{(D-K_{k_i}) \cdot \text{perpendicular}(K_{k_{i+1}} - K_{k_i})}{\|K_{k_{i+1}} - K_{k_i}\|} \quad (7)$$

$$D' = K'_{k_i} + s \cdot (K'_{k_{i+1}} - K'_{k_i}) + \frac{t \cdot \text{perpendicular}(K'_{k_{i+1}} - K'_{k_i})}{\|K'_{k_{i+1}} - K'_{k_i}\|} \quad (8)$$

where D' and D are pixel coordinates of the source and destination images respectively as illustrated in [Figure 3.5](#). The vector equal to and perpendicular to the input vector are given by *perpendicular* ().

In the case of multi-line, the computational method is as following:

For the individual pixel D in destination image,

$$DSUM = 0$$

$$weightsum = 0$$

For the individual line $K_{k_i}K_{k_{i+1}}$,

Get s, t determined from $K_{k_i}K_{k_{i+1}}$

Get D'_{k_i}

Calculate $DS_{k_i} = D'_{k_i} - D_{k_i}$

$Dist$ = nearest distance between D to $K_{k_i}K_{k_{i+1}}$

$$weight = \left(\frac{\|K_{k_i}K_{k_{i+1}}\|^{c_1}}{c_2 + Dist} \right) c_3$$

$$DSUM+ = DS_{k_i} \cdot weight$$

$$weightsum+ = weight$$

$$D'_{k_i} = D_{k_i} + DSUM/weightsum$$

$$destinationImage(D_{k_i}) = sourceImage(D'_{k_i})$$

The nearest distance between D and $K_{k_i}K_{k_{i+1}}$ is $abs(t)$ if $0 < s < 1$. The value equivalent to straight line distance between D and K_{k_i} if $s \leq 0$. It is equivalent to the straight line between D and $K_{k_{i+1}}$ if $s \geq 1$. All these are illustrated in Figure 3.6. In this research, the warped image of each foot has a size of 123 x 278 pixels. The outcome of warped grayscale feet image (246 x 278 pixels) is presented in Figure 3.7.

Figure 3.5: Illustration of a single line pair between source and destination images.

Figure 3.6: An example of three cases on the nearest distance between D and

$$K_{k_i}K_{k_{i+1}}.$$

Figure 3.7: The outcome of warped grayscale feet image (246 x 278 pixels).

3.3.3. HIGHER ORDER SPECTRA (HOS)

The warped grayscale images need to first undergo Radon transform to change the images into one dimensional (1D) data. Radon transform is implemented to detect the features among the two-dimensional (2D) image [153, 154]. The Radon transform converts the lines through an image to points in the Radon backprojection. The individual point in the Radon backprojection is converted from a straight line in the image. For a given function $Z(x, y)$, Radon transform is represented as:

$$RT(\rho, \theta) = \int_{-\infty}^{\infty} Z(\rho \cos \theta - l \sin \theta, \rho \sin \theta + l \cos \theta) dl$$

(9)

The Eq. (9) explains the integral along line l through the image. The distance of the line from origin is ρ and the angle from horizontal is θ . Thus, the two-dimensional signal is converted to one dimensional parallel beam that allow projections at different angles θ . This work used an angle of $\theta = 5^\circ$ to better captures the minute variation between adjacent pixels [152]. The schematic diagram of Radon Transform is illustrated in Figure 3.8.

Figure 3.8: The illustration of Radon Transform. (a) Image and (b) Radon domains.

The higher order spectra (HOS) comprise of third and higher order cumulants and moments spectra that can be represented for random processes and deterministic signals [126]. Equally important, HOS technique is effective in analyzing the nonlinear characteristics of images [126, 154]. In this work, features are extracted from third order statistics which is the bispectrum. The Fourier transform of third order correlation gives the bispectrum and is defined as:

$$A(f_1, f_2) = E[S(f_1)S(f_2)S^*(f_1 + f_2)]$$

(10)

where Fourier transform of signal $s(nT)$ is $S(f)$, expectation operation is $E[\cdot]$, frequencies $(f_1 + f_2)$ conjugates is $S^*(f_1 + f_2)$, integer index is n and sampling interval is T . The expectation operation is practically substituted with an estimate, which is an average of the entire realization of a signal. The relationship remains without expectation operation for deterministic signal as the third order correlation is a time average. In the case of deterministic sampled signal, $S(f)$, which is discrete time Fourier transform, is calculated as discrete Fourier transform (DFT) at frequency samples by fast Fourier transform (FFT) technique. In addition, Nyquist frequency may be used to normalize the frequency f (Hz) within 0 to 1.

The bispectrum can be normalized using power spectra at component frequencies that gives a value within 0 to 1 and also, denotes the level of phase coupling among the frequency components [126]. The normalized bispectrum is defined as follow:

$$A_{norm}(f_1, f_2) = \frac{E(S(f_1)S(f_2)S^*(f_1+f_2))}{\sqrt{PS(f_1)PS(f_2)PS(f_1+f_2)}} \quad (11)$$

where $PS(f)$ is power spectrum. The features in this work is according to the phases of integrated bispectrum [155], which yield HOS coefficients, and is briefly explained below.

Based on the assumption that there is no bispectral aliasing, the bispectrum of real signal is represented as triangle with $0 \leq f_2 \leq f_1 \leq f_2 + f_1 \leq 1$. The integration along straight lines that pass through the origin in bifrequency space results in parameters acquisition. The computational area and integration line are illustrated in **Figure 3.9**.

The phase of the integrated bispectrum on the radial line with gradient equivalent to m is the bispectral invariant, $K(m)$, defined as:

$$K(m) = \arctan \left(\frac{I_i(m)}{I_r(m)} \right) \quad (12)$$

where

$$I(m) = I_r(m) + jI_i(m) = \int_{f_1=0^+}^{\frac{1}{1+m}} A(f_1, mf_1) df_1 \quad (13)$$

for $0 < m \leq 1$, and $j = \sqrt{-1}$. The variables I_i and I_r indicate the imaginary and real part of integrated bispectrum respectively.

The bispectral invariants consist of details relating to the waveform shape within window and are not affected by shifting and amplification and, the robustness against time scale variations. For this research, bispectral invariant features are being used for every 5° . The examples of the resulting bispectrum and bispectrum contour plots of diabetic and healthy left and right foot are shown in [Figure 3.10\(a\)-\(d\)](#) and [3.11\(a\)-\(d\)](#) respectively. The diabetic foot has lower bispectrum amplitude (z-axis) compared to healthy foot and thus lower feature values.

Figure 3.9: Non-redundant area of calculation of bispectrum for real signals.

(a)

(b)

(c)

(d)

Figure 3.10(a)-(d): The examples of the resulting bispectrum and bispectrum contour plots of diabetic foot. Left foot: (a) bispectrum, (b) bispectrum contour. Right foot: (c) bispectrum, (d) bispectrum contour.

(a)

(b)

(c)

(d)

Figure 3.11(a)-(d): The examples of the resulting bispectrum and bispectrum contour plots of healthy foot. Left foot: (a) bispectrum, (b) bispectrum contour. Right foot: (c) bispectrum, (d) bispectrum contour.

3.3.4. DISCRETE WAVELET TRANSFORM (DWT)

The discrete wavelet transform (DWT) transforms a two-dimensional signal $x(n)$ by undergoing through a series of down sampling of low and high pass filters [156]. The low pass and high pass filters are represented by transfer function of $L(n)$ and $H(n)$ respectively as defined in Eq. (14) and Eq. (15). The Daubechies (Db) wavelets are orthogonal wavelets with vanishing moments, which was developed by Ingrid Daubechies [130]. For the Db(n) family, n has to be a positive even number and is also the resulting size of the filters. The Db(n) wavelet has $\frac{1}{2}n$ vanishing moments. For example, the coefficients of 4 tap Daubechies 4 (Db4) are:

$$a = \frac{1 + \sqrt{3}}{4\sqrt{2}}, \quad b = \frac{3 + \sqrt{3}}{4\sqrt{2}}, \quad c = \frac{3 - \sqrt{3}}{4\sqrt{2}}, \quad d = \frac{-1 + \sqrt{3}}{4\sqrt{2}}$$

The octave band pass filter is defined by the low pass $L(n)$ and high pass $H(n)$ filters:

$$L(n) = (a, b, c, d) \tag{14}$$

$$H(n) = (-1)^n L(3 - n) = (d, -c, b, -a) \tag{15}$$

Moreover, the output of high pass filter is known as detailed coefficients while the output of low pass filter is referred to as approximation coefficients. The process of acquiring the detailed $D(n)$ and approximation $A(n)$ coefficients are described with mathematical formulation in Eq. (16) and Eq. (17) respectively.

$$D(n) = \sum_{k=-\infty}^{\infty} x(k)H(2n - k) \quad (16)$$

$$A(n) = \sum_{k=-\infty}^{\infty} x(k)L(2n - k) \quad (17)$$

where $x(k)$ is the original signal input, k is the integer, H is the high pass filter, L is the low pass filter and n indicates the sampling factor.

The frequency resolution can be enhanced by cascading at least two basic filter operations. The cascading is performed by putting the output of first level low pass filter through a similar low and high pass filters combination. The detailed coefficients of the lower level make up the higher-level coefficients. For every level, the frequency resolution is doubled, and the number of samples is halved. The coefficients of last level will comprise of both the approximation and detailed coefficients. The Figure 3.12 illustrates an example of two-dimensional (2D) DWT of two level.

Figure 3.12: An illustration of two-dimensional (2D) DWT decomposition of two level.

For this work, healthy and diabetic foot images undergo two level of DWT decomposition using Daubechies 8 (db8) mother wavelet [157]. The rows are first put through the high and low pass filters to acquire the high and low frequency components. Next, the images are down sampled along the columns by high and low pass filters to acquire the approximation (LL), horizontal (HL), diagonal (HH) and vertical (LH) coefficients of first level. The approximation (LL) is further decomposed until second level in similar procedure. The results of two level DWT decomposition of healthy and diabetic foot thermal images are shown in Figure 3.13(a)-(b). It can be seen that there are not much sudden changes in the second level horizontal coefficient for diabetes as compared to normal. Hence, the feature values are relatively low for diabetes compared to normal foot.

(a)

(b)

Figure 3.13(a)-(b): The results of two level DWT decomposition of two level of (a) diabetic and (b) healthy foot thermograms.

3.3.5. FEATURE EXTRACTION

In this work, texture and entropy based features are extracted from the decomposed DWT and HOS images to identify the differentiation between healthy and diabetic foot cases. The features are Gray Level Co-occurrence Matrix (GLCM) [137], Hu's invariant moment [138], local binary pattern (LBP) [134], Laws texture energy (LTE) [158] and entropies [142, 159-164].

3.3.5.1. GRAY LEVEL CO-OCCURRENCE MATRIX (GLCM)

For Gray Level Co-occurrence Matrix (GLCM) [137], the image $f(x,y)$ is defined as $M \times N$ grayscale matrix. Every element of the matrix denotes individual pixel intensity of the image. The co-occurrence matrix $C(i,j|\Delta_x,\Delta_y)$ is a probability function estimation of second order. The matrix indicates the frequency of occurrence for a pixel pair with i and j gray levels. The distances among the pixels are Δ_x and Δ_y in the directions of x and y respectively. The co-occurrence matrix is defined as:

$$C(i,j|\Delta_x,\Delta_y) = |\{(r,s), (r+\Delta_x, s+\Delta_y): I(r,s) = i, I(r+\Delta_x, s+\Delta_y) = j\}| \quad (18)$$

where $(r,s), (r+\Delta_x, s+\Delta_y) \in M \times N, d = (\Delta_x, \Delta_y)$ and, $|\odot|$ indicate the number of elements in a set. The probability for a pixel gray level i to be at distance (Δ_x, Δ_y) from pixel gray level j is calculated as:

$$P(i, j) = \frac{c(i, j)}{\sum c(i, j)} \quad (19)$$

In this work, contrast, homogeneity, energy and correlation of GLCM based textural features are computed. The image is defined as $f(x, y)$ and have significant gray level intensities. Then, the GLCM of $N \times N$ is computed where N is the number of gray levels. The GLCM matrix element (i, j, d, θ) is referred as joint probability of i and j gray level which is separated by direction θ and distance d . The features extracted are described as follow:

Contrast:

$$f_{contrast} = \sum_{n=0}^{N-1} n^2 \{ \sum_{i=0}^N \sum_{j=0}^N P(i, j) \} \quad (20)$$

Homogeneity:

$$f_{homogeneity} = \sum_{i=0}^{N-1} \sum_{j=0}^{N-1} \frac{1}{1+(i-j)^2} P(i, j) \quad (21)$$

Energy:

$$f_{energy} = \sum_{i=0}^{N-1} \sum_{j=0}^{N-1} P(i, j)^2 \quad (22)$$

Correlation:

$$f_{correlation} = \frac{\sum_{i=0}^{N-1} \sum_{j=0}^{N-1} (i,j)P(i,j) - \mu_x \mu_y}{\sigma_x \sigma_y} \quad (23)$$

where $\mu_x, \mu_y, \sigma_x, \sigma_y$ are the means and standard deviations of P_x, P_y and P_x, P_y are the partial probability density functions.

3.3.5.2. HU'S INVARIANT MOMENT

The moments and relevant invariants are analyzed to classify the image patterns for many applications. For an image $f(x, y)$, the two-dimensional moment is represented as:

$$m_{uv} = \sum_x \sum_y x^u y^v f(x, y) \quad (24)$$

For $u, v = 0, 1, 2 \dots$, the central moment is represented as:

$$\mu_{uv} = \sum_x \sum_y (x - \bar{x})^u (y - \bar{y})^v f(x, y) \quad (25)$$

where $\bar{x} = \frac{m_{10}}{m_{00}}$ and $\bar{y} = \frac{m_{01}}{m_{00}}$ are the image centroid.

In this work, binary image is considered where m_{00} is the image area. The normalized central moment of order $(u + v)$ is represented as:

$$n_{uv} = \frac{\mu_{uv}}{\mu_{00}^\gamma} \quad (26)$$

For $u, v = 0, 1, 2 \dots$, and where $\gamma = \frac{u+v}{2} + 1$.

Based on the normalized central moment, seven moment values from order three that are invariant to object orientation, scale and position are defined by Hu [138]. The seven moments are described as follow:

$$M_1 = n + n_{02} \quad (27)$$

$$M_2 = (n_{20} - n_{02})^2 + 4n_{11}^2 \quad (28)$$

$$M_3 = (n_{30} - 3n_{12})^2 + (3n_{21} - n_{03})^2 \quad (29)$$

$$M_4 = (n_{30} + n_{12})^2 + (n_{21} + n_{03})^2 \quad (30)$$

$$M_5 = (n_{30} - 3n_{12})(n_{30} + n_{12})[(n_{30} + n_{12})^2 - 3(n_{21} - n_{03})^2] + (3n_{21} - n_{03})(n_{21} + n_{03})[3(n_{30} + n_{12})^2 - (n_{21} + n_{03})^2]$$

(31)

$$M_6 = (n_{20} - n_{02})[(n_{30} + n_{12})^2 - (n_{21} + n_{03})^2] + 4n_{11}(n_{30} + n_{12})(n_{21} + n_{03})$$

(32)

$$M_7 = (3n_{21} - n_{03})(n_{30} + n_{12})[(n_{30} + n_{12})^2 - 3(n_{21} + n_{03})^2] + (3n_{21} - n_{03})(n_{21} + n_{03})[3(n_{30} + n_{12})^2 - (n_{21} + n_{03})^2]$$

(33)

3.3.5.3. LOCAL BINARY PATTERN (LBP)

For local binary pattern (LBP), the feature vector is computed by [134]: A circle neighborhood surrounding a pixel is considered with P points selected on the circumference and radius R . The g_c and g_p are the grey level intensity values of the center pixel and P points respectively, where $p = 0, \dots, P - 1$. Figure 3.14 shows the circular neighbor sets of various P and R values.

Figure 3.14: The circular neighbour sets surrounding a pixel with different points P and radius R values.

The P points are changed as bit stream of 1 and 0 depending on the pixel intensity, greater or less than the center pixel intensity. The computation for LBP code value of center pixel (x_c, y_c) that has intensity g_c is as follow:

$$\text{LBP}_{P,R}^{\text{Original}} = \sum_{p=0}^{P-1} h(g_p - g_c) \quad (34)$$

where

$$h(x) = \begin{cases} 1, & x \geq 0 \\ 0, & x < 0 \end{cases}$$

The LBP is considered uniform if binary pattern has not more than two bitwise changes from 1 to 0 or vice versa with the bit pattern traversing circularly. The examples of uniform patterns are: 011100 (2 changes), 001100 (2 changes) and 111111(0 changes). Therefore, rotation invariant measure, known as $\text{LBP}_{P,R}$, is computed according to the number of changes in the pattern using uniformity measure $U \leq 2$.

$$LBP_{P,R}(x) = \begin{cases} \sum_{p=0}^{P-1} h(g_p - g_c) & \text{if } U(x) \leq 2 \\ P + 1 & \text{otherwise} \end{cases} \quad (35)$$

where

$$h(x) = \begin{cases} 1, & x \geq 0 \\ 0, & x < 0 \end{cases}$$

In LBP, multiscale study on the image is performed through selecting circles of different radius and subsequently, constructing LBP image for the individual scale. For this work, entropy and energy of LBP image are used as features. The LBP image is constructed at various scales ($P = 8, 16$ and 24 with $R = 1, 2$ and 3 respectively).

3.3.5.4. LAWS TEXTURE ENERGY (LTE)

This method uses masks of suitable sizes to differentiate various texture types [158]. The masks are applied onto the image and then approximate the energy within the pass filters area are estimated [158]. The texture energy measures are acquired through *three* one dimensional vectors, namely $L3$, $E3$ and $S3$ which elucidate these following features: level, edge and spot respectively. $L3 = [1, 2, 1]$, $E3 = [-1, 0, 1]$ and $S3 = [-1, 2, -1]$. The convolution between any vertical one-dimensional vector with horizontal one will generate nine two dimensional masks of 3 by 3 size, which are $L3E3$, $L3L3$, $L3S3$, $E3S3$, $E3E3$, $E3L3$, $S3E3$, $S3S3$ and $S3L3$. For instance,

$$L3 \begin{pmatrix} 1 \\ 2 \\ 1 \end{pmatrix} \times E3 \begin{pmatrix} -1 & 0 & 1 \end{pmatrix} = L3E3 \begin{pmatrix} -1 & 0 & 1 \\ -2 & 0 & 2 \\ -1 & 0 & 1 \end{pmatrix} \quad (36)$$

Except $L3L3$, all the masks have zero mean and thus, eight masks zero sum numbered from 1 to 8 are used. Initially, the image is convolved with the individual two-dimensional mask to derive the texture information. For instance, if $E3S3$ is used to filter the image $f(x, y)$, this yields a result of texture image TI_{E3S3} .

$$TI_{E3S3} = f(x, y) \times E3S3 \quad (37)$$

The texture image TI_{L3L3} is used to normalize the other images contrast as shown in Eq. (38). This is to ensure that the resultant images are contrast independent.

$$Normalise(TI_{mask}) = \frac{TI_{(x,y)mask}}{TI_{(x,y)L3L3}} \quad (38)$$

Thereafter, the normalized TIs are passed through the texture energy measurements (TEM) filters. The TEM filters comprised of moving non-linear window average of absolute values as shown below:

$$TEM_{(x,y)} = \sum_{u=-3}^3 \sum_{v=-3}^3 |TI_{(x+u,y+v)}|$$

(39)

In this thesis, the image is filtered with the eight masks and then the energies calculated are used as features. Thus, eight features are derived from the individual eight masks.

3.3.5.5. ENTROPIES

Entropy is implemented to compute the uncertainty in image pixels [142, 159]. In this work, entropy measures [142, 159-164] such as Renyi, Yager, Kapur, Fuzzy, Shannon and Vадja are implemented to measure randomness in the pixel intensity distribution of healthy and diabetic foot images. The image is considered to be $f(x, y)$ that have N_i intensity values, where $i = 0, 1, 2, 3, \dots, L - 1$.

For a given image $f(x, y)$ of size $M \times N$, the normalized intensity histogram (H_i) is calculated as follow [142, 159]:

$$H_i = \frac{N_i}{M \times N} \quad (40)$$

where N and M are columns and rows of the image respectively.

Shannon entropy measures the average information in the image and is calculated as [142, 159]:

$$\text{Shannon entropy} = - \sum_{i=0}^{L-1} H_i \log_2(H_i) \quad (41)$$

where L is the number of gray level in the image.

Renyi entropy is a generalized entropy that has high dynamic range and represented as [160, 161]:

$$\text{Renyi entropy} = \frac{1}{1-\alpha} \log \sum_{i=0}^{L-1} H_i^\alpha, \text{ for } \alpha \neq 1, \alpha > 0 \quad (42)$$

where L is the number of gray level in the image.

Kapur entropy is an enhanced generalization of Renyi entropy represented as [160, 161]:

$$Kapur\ entropy = K_{(\alpha,\beta)} = \frac{1}{1-\alpha} \ln \frac{\sum_{i=0}^{L-1} H_i^\alpha}{\sum_{i=0}^{L-1} H_i^\beta}, \text{ for } \alpha \neq 1, \beta > 0, \alpha + \beta - 1 > 0 \quad (43)$$

where $\alpha = 0.5$ and $\beta = 0.7$ are diversity indices; L is the number of gray level in the image.

Yager entropy is employed to approximate the scatter regularity and density, and is expressed as [162]:

$$Yager\ entropy = 1 - \frac{\sum_{i=0}^{L-1} |2H_i - 1|}{|M \times N|} \quad (44)$$

where N and M are columns and rows of the image respectively; L is the number of gray level in the image.

Fuzzy entropy is calculated in fuzzy set and has different degree of membership in the form as [163]:

$$Fuzzy\ entropy = \frac{1}{|M \times N|} \sum_{j=0}^{g-1} E(h_j) \quad (45)$$

where N and M are columns and rows of the image respectively; g is the grey levels.

Vajda entropy is a unique case of Kapur entropy and is defined as [164]:

$$Vadja\ entropy = v_{\alpha,\beta} = \frac{1}{1-\alpha} \log_2 \frac{\sum_{j=0}^{g-1} h_j^\alpha}{\sum_{j=0}^{g-1} h_j} \quad (46)$$

where $\alpha \neq \beta$, $\alpha > 0$ and $\beta = 1$; $h_j = \{(x_j, \mu_{h_j}(x_j), v_{h_j}(x_j)) | x_j \in X_j\}$ is the fuzzy set in $X_j = \{x_j\}, j = 1, 2, \dots, g-1$; $v_{h_j}(x_j)$ and $\mu_{h_j}(x_j)$ are the degree of non-membership and membership of x to h_j respectively; g is the grey levels.

3.3.6. STATISTICAL ANALYSIS

The statistical analysis is a component of quantitative technique that is employed to develop the proposed system. Also, to sum up the data and comprehend the generating processes. This is normally done by creating a mathematical model that allows the inference of the data generating processes. Moreover, the statistical analysis provides an alternative approach to measure the clinically significant data [21, 26, 111].

3.3.6.1. STUDENT'S *T*-TEST

Student's *t*-test is implemented to determine whether the features extracted are clinically significant by analyzing the *p* value. The *p* value also determines the discrimination between the two groups, in this case healthy and diabetes [143]. A low *p* value provides the confidence that the respective groups is possible to be discriminated by the classifier [144]. In this work, the performance of the feature is evaluated by ranking the features according to the *p* and *t* values. Subsequently, ranked features are input independently into the classifier until maximum accuracy is obtained.

3.3.7. CLASSIFICATION

The automated classification technique is important to solve statistics and machine learning difficulties of deciding the class of new data. Indeed, classifiers have been extensively implemented in many systems [145]. The supervised algorithms require training data that consist of findings where the ground truth is accessible. In general, the classification techniques extract the distinct information from training set. This

information extraction process is referred to as learning phase. Thereafter, information derived is utilized in the classification stage to determine the class for the new finding.

3.3.7.1. SUPPORT VECTOR MACHINE (SVM)

Support vector machine (SVM) as illustrated in [Figure 3.15](#) is a two-class classifier that uses support vectors to solve various classification problems by considering individual classes as a separate problem [[165](#), [166](#)]. For better generalization, the margin width separating the classes are maximized. For a set of points $\{x_i\}$ in n dimensional space, which correspond to class of $\{y_i: y_i \in \{-1, 1\}\}$, the training algorithm will try to place the hyperplane in between the points where $y_i = 1$ and $y_i = -1$. The classification of new pattern x is done by assessing which sides of the hyperplane the points locate.

Figure 3.15: Illustration of support vector machine (SVM). A two-class classifier that uses support vectors to solve various classification problems by considering individual classes as a separate problem.

For this work, SVM classifier with nonlinear kernel function of polynomial and radial basis function (RBF) are chosen. The polynomial and RBF kernels are sufficiently flexible in discriminating the two classes especially when there is a non-linear relationship present among the features. The set of points are mapped into a higher dimension space that allows the separation of the points with a linear hyperplane as shown in [Figure 3.16](#) [165].

Figure 3.16: Mapping the set of points into a higher dimension space that allows the points to be separated using linear hyperplane.

In nonlinear classifier, the function ϕ map the data from an input space N to the feature space F and hence, the discriminant function in the feature space F is described by:

$$f(x) = w^T \phi(x) + b$$

(47)

where $w = \text{weight vector}$ and $b = \text{bias}$.

Assume that the weight vector is illustrated as the linear combination of the training examples, for instance, $w = \sum_{i=1}^n \alpha_i x_i$. Thus,

$$f(x) = \sum_{i=1}^n \alpha_i x_i^T x + b \quad (48)$$

In the feature space, F, it is given as:

$$f(x) = \sum_{i=1}^n \alpha_i \phi(x_i)^T \phi(x) + b \quad (49)$$

where α_i is the dual representation of decision boundary.

For efficient computation in the high dimension feature space F, the kernel function is represented as follow:

$$k(x, x') = \phi(x)^T \phi(x') \quad (50)$$

Based on the kernel function, the discriminant function is given as:

$$f(x) = \sum_{i=1}^n k(x, x_i) + b \quad (51)$$

The *degree d* polynomial kernel is represented by:

$$k(x, x') = (x^T x' + 1)^d \quad (52)$$

For polynomial kernel, the feature space comprises of all monomial with degree less or similar as d . In linear kernel, where $d = 1$, the additive constant is excluded in Eq. (52). Nevertheless, the classifier is more flexible as the degree of polynomial increases.

Equally important, Gaussian Radial Basis Function (RBF) is represented as:

$$k(x, x') = \exp(-\gamma \|x - x'\|^2) \quad (53)$$

The gammas γ , which is $\gamma > 0$, controls the width of RBF and the flexibility of the classifier. The $\|x\|$ is the norm of x given as $\sqrt{x^T x}$.

3.3.8. TEN-FOLD CROSS VALIDATION

Cross-validation technique used a training data set to analyze a classifier [148]. In this research, ten-fold cross-validation as illustrated in Figure 3.17 is implemented to test the classifier. The dataset is separated randomly into ten similar parts whereby each part comprises of the same number of samples from the two groups [149]. The first nine data parts are used for classifier training while the other one part is for testing. The fold is repeated nine times with each time using dissimilar test dataset and the rest as training datasets. The process has been used to design classifiers for thermography based systems [71].

Figure 3.17: Illustration of ten-fold(iteration) cross validation employed to analyse the classifier. The dataset is separated randomly into ten equal parts whereby each part contains the same number of samples.

CHAPTER 4. RESULTS AND DISCUSSION

In this research, various texture and entropy based methods are used to extract features from the HOS and DWT decomposed thermal images to identify the differentiation between healthy and diabetic foot cases. The research findings are discussed in the following sections.

4.1. FEATURES SELECTED

The Student's t -test is used to verify the distinct features for accurate discrimination between the healthy and diabetes groups. Table 4.1 shows the statistical analysis result of various features extracted from HOS and DWT decomposed thermal images. From the total 4810 features extracted, only 27 features are significant with p value < 0.0001 and then ranked based on lowest p and highest t values. All the 27 significant ranked features registered higher *mean* value for normal group as compared to diabetes group (Table 4.1). This clearly indicates a discrimination between the *two* (healthy and diabetes) groups. The cH2_LME22 and 2_HOS36 features have the lowest (0.00002) and highest (0.00014) p values respectively. The cH2_LME22 feature is acquired from the 22nd coefficient of law mask energy extracted from the second level horizontal coefficient of DWT. In contrast, the 2_HOS36 feature is obtained from the 36th coefficient of HOS at 5° (2nd angle). Majority of these significant features (25 out of 27 features) are extracted from HOS decomposed images. The HOS is a nonlinear technique that is able to capture the non-linear interaction in the phase coupling and frequency components [167]. The bar plot of 27 significant features ($p < 0.0001$)

extracted from HOS and DWT decomposed thermal images of healthy and diabetes groups are shown in [Figure 4.1\(a\)-\(b\)](#). It is evident that the features extracted exhibit a clear discrimination between the *two* (healthy and diabetes) groups. The healthy foot, with normal blood perfusion, will exhibit more pixel variations on the thermogram and thus, resulting in high feature values. On the other hand, diabetic foot with insufficient arterial blood perfusion will exhibit less or almost uniform pixel variations and hence, the low feature values [\[30\]](#).

4.2. CLASSIFICATION

The 27 ranked significant features are fed individually into the support vector machine (SVM) classifier. [Table 4.2](#) show the classification results using the features extracted from HOS and DWT decomposed thermal images. As shown in [Table 4.2](#), the first column denotes the number of features fed into the classifier. The subsequent four columns indicate the number of True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN). The classification accuracy, positive predictive value, sensitivity and specificity are shown in columns 6,7,8, and 9 respectively. Overall, the SVM RBF classifier obtained maximum classification accuracy of 89.39%, positive predictive value of 96.43%, sensitivity of 81.81% and specificity of 96.97% using only *five* features. As the features become less significance down the ranked, the classification performance also drops as seen in [Table 4.2](#) and [Figure 4.2](#). The plot of accuracy (%) against the number of features using SVM classifier is presented in [Figure 4.2](#). In addition, the evaluate classification performance across the ten folds is shown in [Table 4.3](#) and [Figure 4.3](#).

Table 4.1: The 27 significant ranked features ($p < 0.0001$) extracted from HOS and DWT decomposed thermal images of healthy and diabetes groups.

Feature	Healthy		Diabetes		<i>p</i> Value	<i>t</i> Value
	Mean	Standard Deviation	Mean	Standard Deviation		
cH2_LME22	0.4000	0.2785	0.1611	0.1094	0.00002	4.58514
34_HOS119	0.4314	0.2028	0.2186	0.1819	0.00003	4.48613
3_HOS107	0.4034	0.3023	0.1557	0.1274	0.00005	4.33783
19_HOS56	0.2428	0.2234	0.0665	0.0718	0.00006	4.31662
2_HOS94	0.3166	0.2674	0.1096	0.0813	0.00007	4.25480
36_HOS44	0.4069	0.3055	0.1584	0.1413	0.00007	4.24126
36_HOS52	0.4116	0.3068	0.1624	0.1425	0.00008	4.23241
19_HOS67	0.2219	0.2101	0.0619	0.0603	0.00008	4.20638
36_HOS61	0.4013	0.3015	0.1581	0.1404	0.00008	4.20073
2_HOS93	0.3094	0.2634	0.1075	0.0851	0.00009	4.18867
2_HOS44	0.2966	0.2620	0.0998	0.0709	0.00010	4.16468
cH2_LME21	0.3342	0.2692	0.1250	0.1044	0.00010	4.16127
2d_HOS52	0.2984	0.2642	0.1007	0.0718	0.00010	4.14665
20_HOS4	0.3181	0.2869	0.0916	0.1275	0.00010	4.14497
2_HOS81	0.2947	0.2612	0.0979	0.0821	0.00011	4.12981
36_HOS71	0.3816	0.2891	0.1530	0.1344	0.00011	4.11815
2_HOS61	0.3037	0.2693	0.1045	0.0737	0.00012	4.09874
2_HOS70	0.2878	0.2592	0.0943	0.0807	0.00012	4.09491
36_HOS82	0.3546	0.2697	0.1427	0.1266	0.00012	4.08612
19_HOS37	0.2055	0.1946	0.0611	0.0582	0.00013	4.08317
2_HOS71	0.3134	0.2788	0.1082	0.0775	0.00013	4.07384
2_HOS60	0.2845	0.2576	0.0932	0.0799	0.00013	4.07276
19_HOS46	0.2033	0.2029	0.0549	0.0525	0.00013	4.07032
2_HOS51	0.2825	0.2567	0.0926	0.0794	0.00014	4.05895
2_HOS43	0.2814	0.2562	0.0923	0.0792	0.00014	4.05136
2_HOS82	0.3363	0.3000	0.1163	0.0857	0.00014	4.05105
2_HOS36	0.2811	0.2560	0.0922	0.0791	0.00014	4.04893

(a)

(b)

Figure 4.1(a)-(b): The bar plots of 27 significant ranked features ($p < 0.0001$) extracted from HOS and DWT decomposed thermal images of healthy and diabetes groups.

Table 4.2: The classification results of support vector machine (SVM) classifier using the 27 significant ranked features extracted from HOS and DWT decomposed thermal images.

Number of Features	TP	TN	FP	FN	Accuracy (%)	PPV (%)	Sensitivity (%)	Specificity (%)
2	29	27	6	4	84.85	82.86	87.88	81.82
3	29	27	6	4	84.85	82.86	87.88	81.82
4	25	33	0	8	87.88	100.00	75.76	100.00
5	27	32	1	6	89.39	96.43	81.82	96.97
6	26	33	0	7	89.39	100.00	78.79	100.00
7	24	33	0	9	86.36	100.00	72.73	100.00
8	25	33	0	8	87.88	100.00	75.76	100.00
9	24	33	0	9	86.36	100.00	72.73	100.00
10	26	31	2	7	86.36	92.86	78.79	93.94
11	25	31	2	8	84.85	92.59	75.76	93.94
12	26	32	1	7	87.88	96.30	78.79	96.97
13	26	32	1	7	87.88	96.30	78.79	96.97
14	25	32	1	8	86.36	96.15	75.76	96.97
15	25	31	2	8	84.85	92.59	75.76	93.94
16	24	32	1	9	84.85	96.00	72.73	96.97
17	25	31	2	8	84.85	92.59	75.76	93.94
18	26	30	3	7	84.85	89.66	78.79	90.91
19	23	32	1	10	83.33	95.83	69.70	96.97
20	24	32	1	9	84.85	96.00	72.73	96.97

TP=True Positive; TN=True Negative, FP=False Positive; FN=False Negative;

PPV=Positive Predictive Value.

Figure 4.2: Plot of accuracies (%) against the number of features. This research obtained maximum accuracy of 89.39% using five features.

Table 4.3: Ten-fold cross validation of SVM classifier.

Fold Number	Accuracy (%)	PPV (%)	Sensitivity (%)	Specificity (%)
1	83.33	75.00	100.00	66.67
2	85.71	100.00	66.67	100.00
3	85.71	100.00	66.67	100.00
4	100.00	100.00	100.00	100.00
5	100.00	100.00	100.00	100.00
6	57.14	100.00	25.00	100.00
7	100.00	100.00	100.00	100.00
8	100.00	100.00	100.00	100.00
9	83.33	100.00	66.67	100.00
10	100.00	100.00	100.00	100.00
Average	89.52	97.50	82.50	96.67

PPV=Positive Predictive Value.

Figure 4.3: Plot of fold classification performance (%) against fold number.

4.3. DISCUSSION

Infrared thermography has been effective in detecting diabetic foot related complications based on feet temperature distribution [168]. The various methods used for thermogram analysis are summarised in Tables 2.2 - 2.5. For separate lower limb temperature analysis (Table 2.2), Bharara et al. [88] presented a quantitative thermography method through thermal index for diabetic foot ulcer assessment using a single case and correlated it with the standard wound measurement method. The thermal index/wound inflammatory index moved from negative to positive ($p < 0.05$) before reaching zero. Nevertheless, the index analysis requires more patients. In asymmetric temperature analysis (Table 2.3), Liu et al. [34] proposed a technique involving asymmetric analysis together with colour images segmentation and, non-rigid landmark based registration B-splines of both feet. Their technique can determine diabetic foot ulcers with 95% accuracy (35 out 37), which included all the Charcot foots. Meanwhile for temperature distribution analysis (Table 2.4), Hernandez-Contreras et al. [106] proposed characterization technique to distinguish the thermal patterns of normal and diabetic patients. Their technique obtained an average classification rate of 94.33% using the extracted features. Lastly in independent thermal and physical stress analysis (Table 2.5), Balbinot et al. [114] compared the plantar temperatures and analysed the plantar rewarming index repeatability after cold stress on two separate days for diabetic and normal groups. The rewarming index presented good repeatability after cold stress between two days a week apart in both groups. However, the sample size was small, and the study did not identify diabetic patients with neuropathy.

The majority of these studies presented in [Tables 2.2 - 2.5](#) are based on qualitative analysis and did not implement feature extraction and classification techniques. Indeed, it may not be simple to detect the minute abnormal temperature changes by just visually examining the feet thermogram [\[151\]](#). Therefore, this research develops a novel computer aided diagnosis (CAD) system for diabetic foot (without neuropathy) based on quantitative analysis of plantar foot infrared images. The 27 significantly ranked features ([Table 4.1](#)) extracted from the HOS and DWT decomposed thermal images are input independently into the SVM classifier. Positively, the developed system yielded maximum classification performance of 89.39% accuracy, 96.43% positive predictive value, 81.81% sensitivity and 96.97% specificity using only *five* features.

A total of 4810 (texture and entropy) features are extracted from the HOS and DWT decomposed thermal images. However, only 27 features are significant (p value < 0.0001) and ranked in descending order based on lowest p and highest t values as shown in [Table 4.1](#). A lower p value indicates that the feature is clinically significance [\[144\]](#). Also, p value signifies if or not the means of the two groups are statistically distinct [\[143\]](#). Evidently, the 27 significantly ranked features registered higher *mean* value for normal group compared to diabetes group ([Table 4.1](#) and [Figure 4.1\(a\)-\(b\)](#)). This clearly indicates a discrimination between the *two* (healthy and diabetes) groups and therefore the high classification accuracy yielded by SVM classifier using only *five* significant features.

As can be seen in [Table 4.1](#), most of the significant features extracted (25 out of 27 features) are from HOS coefficients using entropy methods. Indeed, HOS method is able to better captures information relating to the nonlinearity and phase present in the

diabetic foot images [133]. These features are thus highly distinctive and discriminative as compared to DWT. Furthermore, they are significantly robust in noisy environment and hence, effective in capturing the non-linear interaction of the pixels in the phase coupling and frequency domain [152]. Also, it is able to capture the sudden changes in the image efficiently [169]. Equally important, entropy methods are able to quantify the randomness and uncertainty of pixels within the HOS decomposed image [141]. Pixels intensity values that are uniformly distributed will yield less information and thus the entropy is lesser [170]. In fact, the features values are lower for diabetes group compared to normal group as seen in Table 4.1. This indicates that changes in the pixel values of diabetic foot thermograms are subtle and contain less high frequency components. In the diabetes group, the decrease in blood circulation to the foot may be due to developing peripheral arterial disease which result in cold plantar foot thermogram [171]. This is represented with less intensity and subtle variability in the pixels of entire diabetic foot thermogram.

Nonetheless, there are two significant texture features extracted from DWT coefficient, namely cH2_LME22 and cH2_LME21 features. These texture features computed from DWT coefficients in the second level horizontal (cH2) direction (Figure 3.12) have provided highest discrimination. In fact, the computed cH2_LME22 feature is ranked first in Table 4.1. The cH2_LME22 is a texture feature (22nd coefficient of law mask energy) extracted from DWT coefficients in the second level horizontal (cH2) direction. In essence, DWT captures sudden variations in the pixels [152] and the texture methods measure the coarseness, pixel regularity and smoothness in the image [133]. Absolutely, the DWT decomposed thermal images of healthy and diabetic foot will have textural differences which can be measured with texture methods. The higher the

roughness of a surface or texture, the higher the texture feature value will be [133]. In this research, texture features values are registered lower in the diabetes group than normal group (Table 4.1). This may be due to the developing peripheral arterial disease which result in cold plantar foot thermogram that appears less intense and subtle variations in the pixels [171].

The association between diabetic foot and heat pattern on the plantar foot is subtle and often nonlinear [151]. Therefore, the development of computer aided system (CAD) is essential in helping to interpret the plantar thermograms. The knowledge discovery and data mining algorithms may provide improvement to the thermogram based CAD system in various main areas. First, screening clinicians may experience possible visual overloading. With thermogram based CAD system, diagnosis workload can be reduced, and more attention can be given on complicated cases. Thus, enhancing the medical care. Secondly is the inter observer variability. Thermogram diagnosis based on human can be subjective and the qualities may vary extensively. Thus, objective technique based on mathematics and computer science can help in objectifying the diagnosis and decrease the inter-observer variability. Finally, the quality of diagnosis. To a large extent, the progress of thermogram diagnosis based on human depends on training level and experience of the screening clinicians. Meanwhile, the progress of CAD system is based on the software and hardware in which computing machinery is increasingly becoming more potent. Moreover, the software domain progresses by integrating and from developing better image processing algorithms. Hence, CAD system may be able to outperform the clinicians based on cost, accuracy and speed.

The advantages of the proposed methodology are as followed:

1. The proposed methodology does not require extensive computational machinery, which would be considerably easy and simple to operate.
2. The proposed methodology achieved maximum accuracy of 89.39% with minimum 5 features in classifying the two groups. Thus, it is fast and efficient.
3. The SVM classifier is highly robust due to the implementation of 10-fold cross validation technique.
4. The proposed methodology is reliable as the research has taken comparatively the same number of subjects with matching age groups and gender.
5. The proposed methodology does not require any expert training as the results yielded are significantly objective.

The disadvantages of the proposed methodology include:

1. Used only 66 subjects (33 normal and 33 diabetes).
2. Semi-automated system.
3. Infrared thermography is expensive.

CHAPTER 5. CONCLUSION & FUTURE WORK

5.1. CONCLUSION

Diabetes mellitus is a long term metabolic disorder causing problems to the various parts of human body. Indeed, diabetic foot is among the expensive complication causing disability and impairing the quality of life. Furthermore, abnormal superficial temperature changes on the diabetic foot can be observed using IR thermography. Importantly, the applications of IR thermography as a temperature measurement method and hence diagnosing the diseases is growing significantly in the medical field. Majority of the diabetic studies are based on qualitative analysis which involved visual examination and manually interpretation of the thermograms and its features. Without a doubt, this is labour intensive, time consuming and vulnerable to inter-observer variability. Hence, computer aided system may assist in accurate early detection of diabetic foot.

In this research, a novel two-class diabetic foot CAD system is developed using nonlinear features extracted from plantar foot thermograms. The developed system is based on quantitative image processing and statistical analysis techniques. Positively, the developed system achieved a maximum classification performance results of 89.39% accuracy, 96.43% positive predictive value, 81.81% sensitivity and 96.97% specificity using only *five* features. The developed system can be introduced in polyclinics as an adjunct instrument to help the podiatrists to screen and detect potential diabetic foot patients. This will expeditiously provide early treatment and hence

improve the quality of life. Nevertheless, there is still a need to develop better algorithms to reliably detect diabetic foot and its various stages (with and without neuropathy).

5.2. FUTURE WORK

In future, the work can be extended to foot plantar thermograms of diabetes patient with neuropathy. This is because the progression of peripheral neuropathy can increase the risk of diabetic foot ulcerations. Extremely, foot ulcerations are the major cause of lower limb amputation in diabetes patients. Moreover, the risk of mortality for diabetes patients is reported to be higher when the foot ulcerations are developed [172]. Thus, it is crucial to monitor the foot condition of diabetes patients with neuropathy so that preventive actions can be taken.

The IR thermography images of healthy and diabetes subjects, without and with neuropathy can be analysed and classified. Other nonlinear feature extraction and classification methods can be explored for dataset. The receiver operation characteristic (ROC) technique can be used to assess the test's ability to differentiate the diseases cases. The ROC is effective in measuring the diagnosis accuracy (area under the curve) in sufficiently meaningful manner. In general, the implementation of ROC analysis is to choose optimum cut off points to dichotomize a continuous scale. The right selection of cut off points may lower the total false negative and false positive errors. Alternatively, deep learning algorithm [173, 174] may be used instead of the conventional technique of image processing, feature extraction, feature ranking and classification when the database involved is huge.

In this study, knowledge acquired can provide the basis in using thermography-based computer aided detection (CAD) system to effectively diagnose diabetic foot disease as shown in **Figure 7.1**. The developed CAD system can be introduced in

polyclinics and hospitals to provide real time medical support in diagnosing the magnitude of diabetic foot complications using infrared images of the foot. Further, such methods can be extended to other diseases like cancers, wound healing, eye diseases, and bone fractures etc.

Figure 5.1: Stages involve in the development of an alternative CAD system based on plantar foot thermogram to effectively diagnose diabetic foot disease.

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APPENDIX A

Tel: (65) 6225 0488
Fax: (65) 6557 2138
Singapore Health Services Pte Ltd
31 Third Hospital Avenue
#03-03 Bowyer Block C
Singapore 168753
www.singhealth.com.sg
UEN No. 200002698Z

CIRB Ref: 2016/3044

20 December 2016

Dr Tong Weng Kong Jasper
Division of Allied Health Specialties
KK Women's and Children's Hospital

Dear Dr Tong

SINGHEALTH CENTRALISED INSTITUTIONAL REVIEW BOARD (CIRB) APPROVAL

Protocol Title: PLANTAR FOOT THERMOGRAPHY PATTERNS AMONG HEALTHY PERSONS, PERSONS WITH AND WITHOUT DIABETIC NEUROPATHY

We are pleased to inform you that the SingHealth CIRB F has approved the above research project to be conducted in KK Women's and Children's Hospital and Singapore General Hospital.

The documents reviewed are:

- a) CIRB Application Form dated 15 Dec 2016
- b) Study Protocol dated 1 Aug 2016
- c) Participant Information Sheet and Consent Form: Version 4 dated Dec 2016
- d) Inclusion Exclusion Screening Form
- e) Recruitment Poster: Version 2 dated 2 Dec 2016

The SingHealth CIRB operates in accordance with the ICH/ Singapore Guideline for Good Clinical Practices, and with the applicable regulatory requirement(s).

The approval period is from **20 December 2016 to 28 November 2017**. The reference number for this study is CIRB Ref: 2016/3044. Please use this reference number for all future correspondence.

The following are to be observed upon SingHealth CIRB Approval:

1. No subject should be admitted to the trial before the Health Sciences Authority issues the Clinical Trial Certificate. (only applicable for drug-related studies).
2. The Principal Investigator should ensure that this study is conducted in compliance with the Singapore Guideline for Good Clinical Practice, the ethical guidelines of which are applicable to all studies to be carried out, and to ensure that the study is carried out in accordance to the guidelines and the submitted protocol. The Principal Investigator should meet with his collaborator(s) regularly to assess the progress of the study, and be familiar and comply with all applicable research policies in the Institution.

PATIENTS. AT THE HEART OF ALL WE DO.®

SingHealth Academic Healthcare Cluster
Singapore General Hospital • KK Women's and Children's Hospital
National Cancer Centre Singapore • National Dental Centre Singapore • National Heart Centre Singapore • National Neuroscience Institute
Singapore National Eye Centre • SingHealth Polyclinics • Bright Vision Hospital • Sengkang Health

APPENDIX B

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

You are being invited to participate in a research study.

Before you take part in this research study, the study must be explained to you and you must be given the chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the informed consent form. You will be given a copy of this document to take home with you.

STUDY INFORMATION

Protocol Title:

Plantar foot thermography patterns among healthy persons, persons with and without diabetic neuropathy

Principal Investigator(s):

Heng Li-Wen Marabelle, Senior Podiatrist
Podiatry Department, Singapore General Hospital

PURPOSE OF THE RESEARCH STUDY

You are being invited to participate in a research study on the potential of use of thermograph scan as a tool in assessing neuropathy (nerve damage)

We hope to learn whether thermograph scans is able to give us information on the patient's foot health in terms of circulation and sensation.

You were selected as a possible subject in this study because you have diabetes (with or without sensory loss).

This study will recruit subjects from Singapore General Hospital over a period of 11 months. 66 subjects will be involved in this study.

There will be no samples of tissues, blood and/or body fluids obtained during the course of this study.

When your participation in the study ends, you will no longer have access to the thermography device unless special additional arrangements are made by the Principal Investigator.

STUDY PROCEDURES AND VISIT SCHEDULE

If you agree to take part in this study, you will be asked to fill out a survey form and be tested for neuropathy (sensory loss). Your participation in the study will last 60 minutes. No follow up visits will be required unless specified by the Principal Investigator.

Schedule of visits and procedures:

One 60 minute visit

The screening procedures include checking for sensory loss and autonomic neuropathy affecting your blood pressures.

The study procedures involve taking a thermoscan of your bare feet.

YOUR RESPONSIBILITIES IN THIS STUDY

If you agree to participate in this study, you should:

- Ensure that subjective questions are answered to the best of your knowledge
- Be in good general condition on day of assessment as this may affect neuropathy assessment
- Report any discomfort during assessment
- Follow all test safety instructions given by the assessor during measurement procedure
- Inform the Principal Investigator as soon as possible about any side effects that you may have encountered.

WITHDRAWAL FROM STUDY

You are free to withdraw your consent and discontinue your participation at any time without prejudice to you or effect on your medical care. If you decide to stop taking part in this study, you should tell the Principal Investigator immediately.

If you withdraw from the study for any reason,

- The Principal Investigator will not follow-up to collect any further data from you.

However, the data that have been collected until the time of your withdrawal will be kept and analysed. The reason is to enable a complete and comprehensive evaluation of the study.

Your doctor, the Principal Investigator and/or the Sponsor of this study may stop your participation in the study at any time for one or more of the following reasons:

- Failure to follow the instructions of the Principal Investigator and/or study staff.
- The Principal Investigator decides that continuing your participation could be harmful.

WHAT IS NOT STANDARD CARE OR EXPERIMENTAL IN THIS STUDY

The study is being conducted because it is unclear whether thermoscans would be useful in detecting neuropathy. We hope that your participation will help us to determine whether neuropathy can be assessed in this manner.

POSSIBLE RISKS, DISCOMFORTS AND INCONVENIENCES

- There is a very low risk of skin contamination and/or infection. To minimize this risk, the equipment to measure mobility will be wiped down before and after use on each subject.

POTENTIAL BENEFITS

You will

Be assessed for neuropathy and results explained to you

- Be given a copy of the thermoscan of your feet
- Have the opportunity to discuss your test results with the research team.

ALTERNATIVES

- The current method to assess loss of sensation in the feet is by using the monofilament and neurothesiometer.
- Autonomic neuropathy is assessed by taking the blood pressure at the standing and lying down positions.

PARTICIPANT'S RIGHTS

Your participation in this study is entirely voluntary. Your questions will be answered clearly and to your satisfaction.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you or your legal representative will be informed in a timely manner by the Principal Investigator or his/her representative.

By signing and allowing yourself to participate in the study, you do not waive any of your legal rights to revoke your consent and withdraw yourself from the study at any time.

CONFIDENTIALITY OF STUDY AND MEDICAL RECORDS

Information collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available. Only your Investigator(s) will have access to the confidential information being collected.

However, Regulatory Agencies, Institutional Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public.

By signing the Consent Form, you consent to (i) the collection, access to, use and storage of your Personal Data by Singapore General Hospital, and (ii) the disclosure of such Personal Data to our authorised service providers and relevant third parties for the purpose of future research studies ("Future Studies").

Where required, such Future Studies will be submitted for review and necessary approval by the relevant institutional review board.

“Personal Data” means data about you which makes you identifiable (i) from such data or (ii) from that data and other information which an organisation has or likely to have access. Examples of personal data include medical conditions, medications, investigations and treatment history.

By signing the Consent Form, you also confirm that you have read, understood and consented to the SingHealth Data Protection Policy, the full version of which is available at www.singhealth.com.sg/pdpa.

Data collected and entered into the Screening and Data Collection Forms are the property of Singapore General Hospital. In the event of any publication regarding this study, your identity will remain confidential.

COSTS OF PARTICIPATION

If you take part in this study, the following will be performed at no charge to you:

1. Test for neuropathy – tactile sensitivity (10g nylon monofilament)
2. Test for neuropathy – vibration sensitivity
3. Test for autonomic neuropathy – standing and sitting blood pressures
4. Thermoscan of your feet

You will have to pay for any medical or therapy services not relating to the potential risks, discomforts and inconveniences described above.

RESEARCH RELATED INJURY AND COMPENSATION

The Hospital does not make any provisions to compensate study subjects for research related injury. However, compensation may be considered on a case-by-case basis for unexpected injuries due to non-negligent causes.

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

WHO TO CONTACT IF YOU HAVE QUESTIONS REGARDING THE STUDY

If you have questions about this research study and your rights or in the case of any injuries during the course of this study, you may contact the Site Principal Investigator, Ms Marabelle Heng at 9622 9223.

WHO HAS REVIEWED THE STUDY

This study has been reviewed by the SingHealth Centralised Institutional Review Board for ethics approval.

If you have questions about your rights as a participant, you can call the SingHealth Centralised Institutional Review Board at 6323 7515 during office hours (8:30 am to 5:30pm).

If you have any complaints about this research study, you may contact the Principal Investigator or the SingHealth Centralised Institutional Review Board.

CONSENT FORM	
Details of Research Study	
Protocol Title: Plantar foot thermography patterns among healthy persons, persons with and without diabetic neuropathy	
Principal Investigator(s): Marabelle Heng, Senior Podiatrist Podiatry Department Singapore General Hospital 17 Third Hospital Avenue, Outram Road Singapore 168752 Mobile: 96229223	
Participant's Particulars	
Name:	NRIC No.:
Address:	
Sex: Female/Male	Date of birth _____ dd/mm/yyyy
Race: Chinese/ Malay/ Indian /Others (please specify) _____	

I agree to participate in the research study as described and on the terms set out in the Participant Information Sheet.

I have fully discussed and understood the purpose and procedures of this study. I have been given the Participant Information Sheet and the opportunity to ask questions about this study and have received satisfactory answers and information.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons and without my medical care being affected.

By participating in this research study, I confirm that I have read, understood and consent to the SingHealth Data Protection Policy. I also consent to the use of my Personal Data for Future Research.

_____	_____	_____
Name of participant	Signature/Thumbprint (Right / Left)	Date of signing

To be filled by parent / legal guardian / legal representative, where applicable

I hereby give consent for the above participant to participate in the proposed research study. The nature, risks and benefits of the study have been explained clearly to me and I fully understand them.

I confirm that I have read, understood and consent to the SingHealth Data Protection Policy. I also consent to the use of the participant's Personal Data for Future Research.

Name of participant's
parent /legal guardian

Signature

Date of signing

To be filled by translator, if required

The study has been explained to the participant/ legal representative in

_____ by _____.
Language Name of translator

To be filled witness, where applicable

An impartial witness should be present during the entire informed consent discussion if a participant or the participant's legal representative is unable to read. After the written consent form and any written information to be provided to participant, is read and explained to the participant or the participant's legal representative, and after the participant or the participant's legal representative has orally consented to the participant's participation in the study and, if capable of doing so, has signed and personally dated the consent form, the witness should sign and personally date the consent form.

Witnessed by: _____
Name of witness Designation of witness

Signature of witness

Date of signing

Investigator's Statement

I, the undersigned, certify to the best of my knowledge that the participant/participant's legal representative signing this consent form had the study fully explained and clearly understands the nature, risks and benefits of his/ her/ his ward's/ her ward's participation in the study.

Name of Investigator

Signature

Date

APPENDIX C

Inclusion Exclusion Screening Form (Diabetes Group)

Subject Number	
----------------	--

Demographics

Age	
Sex	
Height	
Weight	
Ethnicity	

Exclusion

Previous amputation	Yes / No
Peripheral Vascular Disease	Yes / No
Ischemic Heart Disease	Yes / No
Neurological Disorder	Yes / No

Eligible for study?	Yes / No
Group allocation	Control
	nDN
	DN

Healthy individuals
Diabetes patients
without neuropathy
Diabetes patients
with neuropathy

APPENDIX D

NGEE ANN POLYTECHNIC PARTICIPANT INFORMATION SHEET & CONSENT FORM

1. INTRODUCTION

You are invited to be a participant in this research study on the potential use of infrared thermography as a tool in assessing the **plantar foot thermography patterns among the healthy persons**. Before you take part in this research study, the study must be explained to you and you must be given the chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the informed consent form. You will be given a copy of this document to take home with you.

2. PURPOSE OF PROJECT

- (a) The purpose of this project is to learn whether thermograph scans is able to give us the information on the patient's foot health in terms of circulation and sensation.
- (b) Participants must fulfill the following criteria:
- The participants have to be healthy.
- (c) Participants will be excluded if:
- The participants have medical history of diabetes.
 - Foot fractures and infection.
 - Ulceration.
 - Amputation.
 - Ischemic heart disease.
 - Peripheral vascular disease.
 - Charcot arthropathy.
- (d) The total number of expected participants is :
- 33 healthy subjects.

3. DESCRIPTION OF PROCEDURES IN THIS PROJECT

- (a) If you agree to participate in this project, you can expect to :
- You will be asked to fill out the inform consent and inclusion/exclusion forms.

<ul style="list-style-type: none"> • Your participant in this study will last about 30 minutes. • No follow up visits will be required unless specified by the Principal Investigator. • The study procedures involve taking a thermoscan of your bare feet. <p>(b) This project is expected to commence on _____ and conclude on _____.</p>
<p>4. RISKS RELATED TO THIS PROJECT</p>
<p>(a) The project has the following risks:</p> <ul style="list-style-type: none"> • As far to our best knowledge, the infrared thermography (IRT) tool is safe, noncontact and noninvasive for clinical applications. Thus, posed no potential risk in this study. • There is a very low risk of skin contamination and/or infection. To minimize this risk, the equipment will be wiped down before and after use on each participant. <p>(b) If you experience discomfort as a direct result of your participation in this project, you will receive care from:</p> <ul style="list-style-type: none"> • The Institution (Ngee Ann Polytechnic) does not make any provisions to compensate study participants for research related injury. However, compensation may be considered on a case-by-case basis for unexpected injuries due to non-negligent causes. • By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.
<p>5. BENEFITS OF BEING IN THIS PROJECT (if any)</p>
<p>Benefits for being in this project are:</p> <ul style="list-style-type: none"> • The participant's foot health will be assessed in terms of circulation and sensation. • Be given a copy of the thermoscan of your feet. • Opportunities to discuss the thermoscan results with the research team.
<p>6. PAYMENT (if any)</p>
<p><u>Note to PI</u></p> <p><i>The NP-IRB recommends each participant to be paid at the end of <u>each</u> visit.</i></p> <p>(a) Amount payable to each participant for their time and transport (where applicable):</p> <ul style="list-style-type: none"> • NA <p>(b) When and how payment will be made:</p> <ul style="list-style-type: none"> • NA
<p>7. CONFIDENTIALITY AND PRIVACY OF DATA</p>

Information collected for this project will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made available to the public.

However, members of the project team, NP-IRB and regulatory authorities will be granted direct access to your original records and data to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you are authorizing such access to your records.

Data collected and entered into the data collection forms are the property of Ngee Ann Polytechnic. In the event of any publication regarding this project, your identity will remain confidential.

8. VOLUNTARY PARTICIPATION/WITHDRAWAL

- (a) **Your participation is voluntary.** If you choose not to participate, it will not affect your current or future relations with the Polytechnic.
- (b) You are free to withdraw from this project at any time.

9. CONTACTS AND QUESTIONS

- (a) The project has been reviewed by the NP-IRB for ethics approval.
 - (b) The Principal Investigator for this project is **Muhammad Adam Bin Abdul Rahim**. For questions or more information concerning this project you may contact him at **90170752** (telephone).
 - (c) If you believe you may have suffered a project related injury, contact **Dr. Tan Jen Hong** at **93598537** (telephone) who will give you further instructions.
 - (d) If you have any complaints about this project, you may contact the Principal Investigator at **90170752** or the NP IRB Secretariat at 6460-6812 or np-irb@np.edu.sg
- You will be given a copy of this consent form and one will be kept in the PI's records file for future reference.**

CONSENT FORM

Project Title (*as in the NP-IRB application form*) :

Plantar foot thermography patterns among healthy persons, persons with and without diabetic neuropathy.

Principal Investigator - Contact Details:

Name: Muhammad Adam Bin Abdul Rahim	Telephone: 90170752
School/Div.: School of Engineering / Electronic & Computer Engineering Division.	E-mail: ama6@np.edu.sg

State any existing medical condition: _____
(*e.g. allergy or sensitivity to any food ingredients, medication or products*)

Note to PI

Please delete or amend any of the following statements, where applicable. Any participant below 21yrs old will require parental/legal guardian consent.

I hereby acknowledge that:

1. I agree to take part in the above stated project.
2. I have received a copy of this participant information sheet that explains the use of my [blood/tissue/data] in this project. I understand its contents and agree to donate my [blood/tissue/data] for the use of this project.
3. I can withdraw from the project at any point of time by informing the Principal Investigator and all my [blood/tissue/data] will be discarded.
4. My only remuneration, if any, is as stated in Section 6 of this Participant Information Sheet and Consent Form.
5. I allow/ will not allow my data to be used for activities other than this project.
6. I allow my child (under the age of 21 years old) _____
(Child's name) to participate in this project.

* This project has been explained to me in _____ (state language), which I understand, by _____ (name of translator) on _____ (date).

Name and Signature (Participant)

Date

Name and Signature (Parent/Legal Guardian)

Date

Name and Signature (Consent Taker)

Date

Name and Signature (Translator)*

Date

**(Please include this section if the project participant is unable to understand English.)*

APPENDIX E

Inclusion Exclusion Screening Form (Control Group)

Subject Number	
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Demographics

Age	
Sex	
Height	
Weight	
Ethnicity	

Exclusion

Diabetes	
Previous amputation	Yes / No
Peripheral Vascular Disease	Yes / No
Ischemic Heart Disease	Yes / No
Neurological Disorder	Yes / No

Eligible for study?	Yes / No
Group allocation	Control
	nDN
	DN

Healthy individuals
~~Diabetes patients~~
~~without neuropathy~~
~~Diabetes patients~~
~~with neuropathy~~

APPENDIX F

JOURNAL PUBLICATIONS

1. **Adam M**, Ng EYK, Tan JH, Heng ML, Tong JWK, Acharya UR. Computer aided diagnosis of diabetic foot using infrared thermography: A review. (2017). *Computers in biology and medicine*, 91, 326-336.
2. **Muhammad Adam**, Tan Jen Hong, Eddie Y K Ng, “The Effect of Diabetes on Cardiovascular System”, *Journal of Mechanics in Medicine and Biology*, Vol. 17, No. 7, World Scientific, (2017), Pp. 1740008 [29 pages]. <http://dx.doi.org/10.1142/S0219519417400085>
3. **Adam M**, Ng EYK, Oh SL, Heng ML, Hagiwara Y, Tan JH, Tong JW, Acharya UR. Automated characterization of diabetic foot using nonlinear features extracted from thermograms. *Infrared Physics & Technology*. 2018 Mar 31;89:325-37.