**Severity of Illness Measures of Rheumatoid Arthritis
Using Thermal Infrared Imaging**

by

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ABSTRACT

This research presents thermal infrared (TIR) imaging systems as a potential effective tool for physicians to diagnose and treat Rheumatoid Arthritis (RA). TIR images were taken of 18 control subjects and 13 patients diagnosed with RA by a rheumatologist. Mathematical measurements were extracted from the joints in the hand, wrist and knee images and analysed with statistical tests to show differences between the control and patient groups. The 2nd metacarpophalangeal, the 3rd metacarpophalangeal and the knee were the joints that showed the greatest statistical difference between control subjects and patients. The best measurements extracted from the TIR images were variance, maximum-minimum temperature difference and mode/maximum temperature ratio. RA patients were classified successfully into three RA severity groups using a ratio measurements calculated from the raw data of the images. Finally, the effect of age on the TIR measurements of the control and the patient groups was found to be weak.

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LIST OF ACRONYMS

ATR	Automated Target Recognition
DIP	Distal InterPhalangeal
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
HDI	Heat Distribution Index
HRUS	High Resolution Ultra Sound
IL-1	InterLeukin-1
IR	InfraRed
MCP	MetaCarpoPhalangeal
MIRG	Medical Information-technologies Research Group
MRI	Magnetic Resonance Imaging
MTP	MetaTarsal Phalangeal
NSAIDs	NonSteroidal Anti-Inflammatory Drugs
OHREB	Ottawa Hospital Research Ethics Board
PIP	Proximal InterPhalangeal
RA	Rheumatoid Arthritis
STD	Standard Deviation
TI	Thermal Index
TIR	Thermal InfraRed
WHO	World Health Organization
X-Ray	Radiography

CHAPTER 1

1 INTRODUCTION

This chapter begins by introducing the motivation of this thesis and the statement of the problem. It continues with a detailed background of rheumatoid arthritis - definition, epidemiology, pathophysiology, symptoms, diagnosis and treatment. Such detail on rheumatoid arthritis disease is necessary to better understand the specific requirements of thermal infrared imaging analysis in future chapters. This chapter ends with the thesis objectives and outline.

1.1 Motivation

In 2000, the World Health Organization reported Rheumatoid Arthritis (RA) as the 31st worst leading cause of “Years Lived with Disability” at a global level (Symmons 2006). RA is a disabling disease, more so than lower limb osteoarthritis. The disability can begin early and rise in a linear fashion (Hochberg 1992, 498-502). Within ten years of onset, 50% of patients in developing countries are unable to hold down full-time jobs (Brooks 1997). RA also reduces life expectancy by 5 to 10 years (Guedes 1999, 492-298). 300 000 Canadians, 2.1 million Americans and approximately 260 000 French citizens are

currently diagnosed with RA. There is therefore a huge need to find a tool that can better assist doctors in diagnosing and treating people inflicted with RA.

The motivation of this research is to use InfraRed (IR) thermal imaging to provide quantitative assessment of joints to assist physicians in diagnosing RA very early on and in monitoring treatment via the deterioration of the joints. This would be a major innovation in Canada and worldwide. IR imaging technologies are safe non-ionizing tools that are inexpensive, non-invasive and capable of examining multiple joints per image in a reasonable scanning time period. Replacing the current RA modalities - Magnetic Resonance Imaging (MRI) and High Resolution Ultra Sound (HRUS) - by IR technology would have a major impact on the Health Care System. For instance, thermal IR tests would release expensive imaging tests, such as MRI, for other medical applications thus reducing the wait times for these procedures.

Furthermore, IR imaging would improve the prognosis of RA patients by detecting the disease early and allowing the doctor to employ an aggressive treatment at an early stage. A better prognosis means an RA patient with controlled pain and a slower progression of the deformation of the joint. Therefore employing IR technologies would greatly improve the quality of life of patients and allow them to remain active for a longer period of time. They could remain employed and be contributing members of society for a longer period of time.

Moreover, IR imaging techniques can help physicians in managing and treating a patient's pain and disease progression by quantifying the inflammation

of each joint during the medicated period. This would diminish the length of the “trial and error period” for finding a first or second line medication match for the RA patient by making the process more efficient by quantifying the trial results for physicians. In addition, IR technologies could identify when a patient is in remission or in a flaring period to help the doctor adjust doses when needed. The goal of the physician is to achieve the lowest possible level of disease activity. IR image measurements could therefore show physicians when the treatments are effective.

Overall, IR thermal imaging is a technology that should be explored as an application to assist physicians in diagnosing and managing RA because of its great potential impact on the Health Care System and on society as a whole.

1.2 Definition of Rheumatoid Arthritis

RA is an autoimmune disease triggered by the exposure of a susceptible host to a microbial antigen. The body’s immune response to this antigen causes a systemic inflammatory response which leads to polyarthritis manifested mainly in the synovial membrane of joints and chronic inflammation of the tissue around the joints. Other organs of the body such as the lungs or eyes may also be affected. This inflammatory reaction releases inflammatory mediators that cause damage to the synovial membrane, the cartilage and the bone. The end result is cartilage loss, joint damage and functional impairment of the joints. Damage to the joints can occur early in the disease and be progressively leading to the deformation of the joint (Lipsky 2008). It will therefore be important that the IR

thermal technology be able to detect not only bone changes, but soft tissue changes as well - especially damage to the synovial membrane. This will allow the thermal infrared camera user to differentiate between degenerative osteoarthritis (bone and cartilage damage) and RA (inflammation of the synovial membrane). The figure below illustrates a normal synovial joint.

Figure 1-1: Normal Synovial Joint

1.3 Epidemiology of Rheumatoid Arthritis

The prevalence of the disease worldwide ranges from 0.3 to 2.1%. It affects women three times more than men and all races are affected equally. The prevalence increases with age while sex differences decrease with age. RA can begin at any age, but 80% of patients develop RA between the ages of 35 and 50. The incidence of RA is more than six times greater for women between 60 to 64 years of age compared to women between 18-29 years of age. Recent studies have shown that the incidence and the severity of RA may be diminishing. This may be a reflection of more aggressive therapeutic interventions. Furthermore, studies have shown a genetic predisposition to RA

since it is common to observe first degree relatives of patients with RA to also be diagnosed with RA (Lipsky 2008). This epidemiologic information helped determine the inclusion and exclusion criteria of our participant database and supported the engineering analysis and discussions of the results. These criteria will be specified in chapter 3 of methodology and the analysis and discussions are presented in chapter 5.

1.4 Pathophysiology of Rheumatoid Arthritis

The exact cause of RA is unknown. However, many studies have explored how the body's immune system functions and interacts to cause autoimmune diseases such as RA. The immune system's role is to seek and destroy antigens that invade the body by producing antibodies that target the invader. People with autoimmune diseases produce antibodies that mistakenly attack specific tissues of their own body.

RA begins with the exposure of an immunocompromised host to an unknown antigen. The antigen is presented to the body via macrophages resulting in the proliferation of T-cells – a type of immune cell lymphocyte. Cytokines are released by the T-cells which activate the proliferation of B-cells – another type of immune cell lymphocyte. The B-cells produce the auto-antibodies that attack the unknown antigen but that also attack the body's synovial membranes. An inflammatory reaction ensues and the cartilages along with the bone are damaged. The resulting joint inflammation causes swelling, stiffness, redness and pain in the joints (El-Gabalawy 2001).

Alongside the production of the auto-antibodies by the B-cells, the macrophages release a chemical mediator - interleukin-1 (IL-1). IL-1 causes the proliferation of synovial cells, the activation of cartilage remodelling cells – chondrocytes – and the proliferation of blood vessels in the synovial membrane. The synovial cell proliferation leads to the disorderly growth of the synovial membrane which results in a pannus that invades the neighbouring cartilage ultimately leading to cartilage and bone destruction. The activated chondrocytes excessively release cartilage digestive enzymes which lead to the degradation of cartilage and eventually of bone. Finally, the proliferation of blood vessels in the synovial membrane increases the vascular permeability of the joint membranes resulting in synovial oedema – the excessive accumulation of synovial fluid in the synovium of the joint. This increased vascularisation also leads to the accumulation of B- and T-cells in the synovium which further contributes to the joint inflammation and damage (Haraoui 2001). The figure below exhibits the joint changes in RA.

Figure 1-2: Pathological Features of Rheumatoid Arthritis

The above figure, illustrates the main pathological feature of RA – synovitis – the inflammation, proliferation and invasion of the synovial membrane. In the normal joint, the synovial lining layer is one to two cells thick with blood vessels found in the deeper layers of the loose connective tissue of the joint. In RA, the lining layer is six to ten cells thick with an increased number of blood vessels. Another pathological observation in the figure above is the cartilage and bone degradation. The erosion is primarily found in the pannus region where the fibrous capsule of the joint that is lined with the synovial membrane meets with the cartilage and bone.

The specific pathophysiology of the disease is important to understand when interpreting the IR thermal images. The next chapter presents passed research that shows that IR thermal images reveal evidence of chemical changes subcutaneously, such as the release of inflammatory chemical mediators in RA (Ring 1970, 337 and Collins 1970, 386). Synovial oedema can also change the intra-articular temperature and would therefore show a change in the skin surface temperature and be evidence of disease activity (Bacon 1976, 51-65). Furthermore, IR imaging modalities can detect cellular proliferation and increase in vascular flow, which are the pathophysiological evidences of an RA pannus (Nielsson 1980, 516-528).

1.5 Symptoms of Rheumatoid Arthritis

The degree of the symptoms of RA depends on the degree of the tissue inflammation. Patients with RA are identified as having “active” disease when

the body tissues are inflamed. “Remission” occurs when the symptoms of the disease are absent and the inflammation subsides. Remission can arise with treatment or without and can last weeks to years. The symptoms of RA can return and inflammation can become active at any time. This is called a period of “flare”. The course of RA can greatly vary from patient to patient with periods of remissions and flares.

When RA is active, the systemic symptoms may include lack of appetite, fatigue, low-grade fever, muscle and joint aches and stiffness. Muscle and joint stiffness appear more commonly in the morning for more than an hour and after periods of inactivity. Joint inflammation is common during flare periods, where joints are warm, red, painful, swollen and tender. It is important to note that the progression of the disease and the degree of damage to the joints does not necessarily correlate with the degree of pain, stiffness or swelling present in the joints.

RA affects multiple joints in a symmetrical bilateral pattern (affecting both sides of the body). The small joints of the hands, the wrists and the feet are usually affected. These joints more specifically include the proximal interphalangeal (PIP) joints, the metacarpophalangeal (MCP) joints, the wrist and the metatarsal phalangeal (MTP) joints. The distal interphalangeal (DIP) joints are not affected by RA. The figures below clearly display the location of these joints.

Figure 1-3: Bones of the Hand

Figure 1-4: Bones of the Foot (A) Anterior View (B) Lateral View

Chronic inflammation can result in damage to the body tissues, cartilage and bone. Consequently, there is a loss of cartilage; erosion and weakness of bones and muscles; and ultimately joint deformity, destruction and loss of function.

RA is systemic and therefore can involve the inflammation of other organs and areas of the body, not only joints. The glands of the eyes and mouth can be inflamed causing dryness to these areas. Inflammation of the pleura of the lung – pleuritis – can cause chest pain and coughing. Rheumatoid nodules (firm lumps of inflammation) can also be found in the lung tissue itself. Asymptomatic

rheumatoid nodules can be present around the elbows and fingers. Inflammation of the heart's pericardium – pericarditis – can cause positional chest pain. An inflamed and enlarged spleen can cause anemia as well as a decrease in white blood cells. Anemia leads to fatigue, dizziness or lightheadedness, palpitations, difficulty breathing (dyspnea), headache and pallor. A decrease in white blood cells makes the patient more susceptible to infections. Blood vessel inflammation – vasculitis – is a rare and serious complication of chronic rheumatoid disease which can lead to tissue death. Tissue death can be identified as tiny visible black areas around the nail beds or as leg ulcers (O'Dell 2008, chapter 15).

Thermal IR images can detect RA symptoms such as swelling, inflammation, heat and redness. It has also been proven that pain can be detected by this non-invasive technology (Herry 2004, 19). This thesis will go on to prove that these symptoms are quantifiable via IR thermography measurements. The systemic RA changes above, such as nodules and vascular changes, may be useful in understanding the temperature distribution spikes and anomalies around the observed joints and limbs.

1.6 Diagnosing Rheumatoid Arthritis

The diagnosis of RA is done by a doctor by initially reviewing the patient's history and performing a physical exam. The doctor carefully takes note of the patient's symptoms and performs the classical examination technique of palpation to examine the joints for inflammation and deformity, the skin for

nodules and other parts of the body for signs of inflammation – redness, enlargement, warmth and tenderness.

The doctor also identifies the distribution and the range of motion of the affected joints. The distribution of the inflamed joints is important in the diagnosis of RA. RA does not have a predilection for weight bearing joints. The small joints of the hands (the proximal interphalangeal (PIP) joints and the metacarpophalangeal (MCP) joints), the wrists, the metatarsal phalangeal (MTP) joints of the feet and the knees are often the target and are inflamed in a symmetrical pattern (meaning both sides of the body are affected). When only one joint unilaterally is inflamed, the diagnosis of RA is more difficult and requires other tests.

Figure 1-5: The Joint Distribution of Rheumatoid Arthritis and Osteoarthritis

The physician may request blood tests to help confirm the diagnosis. These tests can show abnormal serum antibodies, including a serum antibody called the rheumatoid factor which is present in 80% of RA patients. Citrulline antibody and antinuclear antibody are also frequently found in patients with RA. Another blood test called the sedimentation rate is used to observe the speed at which the red blood cells sink to the bottom of a test tube. The sedimentation rate is an indicator of inflammation and increases during flare periods and decreases during remission periods. The C-reactive protein blood test is also used as an indicator of inflammation. Since many inflammatory and autoimmune diseases can produce abnormal rheumatoid factor, citrulline antibody, antinuclear antibody, sedimentation rate and C-reactive protein results, these tests alone cannot be used to diagnose RA.

RA is difficult to diagnose early since patients in the very early stages of the disease may present without apparent joint swelling. The doctor can use imaging techniques such as High Resolution Ultra Sound (HRUS) and Magnetic Resonance Imaging (MRI) to reveal inflammation that is not apparent by the classical examination technique of palpation. Radiography (X-ray) cannot detect soft tissue inflammation, but can provide information with regards to bone destruction and joint deformation at later stages of the RA disease (Bohndorf 1996, 399-407). The radiography image will show an erosive pattern in general. The figure below demonstrates more specifically the radiographic features of an RA joint.

Figure 1-6: Radiographic Features of an RA Joint

In the above figure we can identify the following progressive RA features:

- 1- Diffuse joint space narrowing
- 2- Marginal or central erosions
- 3- Minimal subchondral sclerosis
- 4- Joint effusion (fluid build-up)
- 5- Osteopenia (lower bone density)
- 6- Periarticular soft tissue swelling

The diagnosis of RA is therefore based on the history of the patient's symptoms, the distribution of the inflamed joints, the serum results of the blood tests and the imaging findings. In 1987, the American College of Rheumatology developed revised criteria for the diagnosis of RA. These criteria demonstrate a

sensitivity of 91–94% and a specificity of 89% when used to classify patients with RA compared with control subjects with rheumatic diseases other than RA.

Table 1-1: American College of Rheumatology's Criteria for the Classification of Rheumatoid Arthritis (Arnett 1998, 315-324)

Criterion		Definition
1	Morning Stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2	Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3	Arthritis of hand joints	At least 1 area swollen (as defined above) in wrist, MCP, or PIP joint
4	Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5	Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7	Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

For classification purposes, patient are diagnosed with RA if they satisfy at least 4 of these 7 criteria. Particularly, criteria 1 through 4 must have been present for at least 6 weeks (Arnett 1998, 315-324).

The statement of the problem will compare all the RA diagnosis methods described above to the TIR imaging diagnosis tool for RA. No other tool is at

once safe, non-ionizing, inexpensive, non-invasive and capable of examining multiple joints per image in a reasonable scanning time period.

1.7 Treatment and Therapy of Rheumatoid Arthritis

RA has no known cure. The objective of RA treatment is to diminish joint inflammation, to reduce the pain and the symptoms of the patient, to maximize joint function and to prevent the destruction and deformation of the joint.

There is consensus among doctors that early diagnosis of RA and initiation of aggressive therapy early in the course of the disease can greatly diminish RA progression and in some patients could even lead to drug free remission. It is therefore important to diagnose the disease and to intervene in its very early stages to have a better prognosis (Bykerk 2009).

Optimal treatment of RA involves a combination of patient education, rest, joint-strengthening exercises, joint protection, and medications. Patients are treated according to their disease activity, the type of joints that are inflicted, their age, their overall health and their occupation/lifestyle. When a combination of these approaches and medications are ineffective, some patients with severe joint deformity may require surgery (Bernard 2003).

1.7.1 First line medications

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylate (Aspirin) and ibuprofen (advil, motrin) are used to reduce tissue inflammation, pain and swelling (O'Dell 2008, chapter 16). Patients respond differently to different NSAID medications; therefore, the doctor usually tries several NSAID

drugs before identifying the most effective drug with the least of side effects. These include stomach upset, abdominal pain, ulcers and gastrointestinal bleeding.

During flare periods or when NSAIDs are not effective at treating the disease, corticosteroid medications are given orally or injected directly into the joint (O'Dell 2008, chapter 16). These are more potent in reducing inflammation and maximizing joint function, but can have serious side effects which include weight gain, facial puffiness, thinning of the skin and bone, easy bruising, cataracts, risk of infection, muscle wasting, and destruction of large joints. In addition, discontinuing the treatment of corticosteroids abruptly can lead to flares or other symptoms of withdrawal.

1.7.2 Second line medications

First line medications reduce joint inflammation and pain; however, they do not directly prevent joint destruction or deformity. To prevent progressive damage to cartilage, bone, ligaments and neighboring soft tissues disease-modifying anti-rheumatic drugs (DMARDs) are used (American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines 2002, 328-346). These are slow-acting medications taken over long periods of time at varying doses and may take weeks to months to become effective. The goal of DMARDs is to promote remission and consequently directly impede the progression of joint destruction and deformity. A combination of second line medication can be used, and like the first line medication, the doctor may need to

try different drugs before the treatment is optimal. Some examples of DMARDs are hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine).

Immunosuppressive medications suppress the body's immune system and can be used for treating RA. Immunosuppressive drugs are usually given to patients with aggressive RA or with serious complications of inflammation because of its potentially serious side effects. Methotraxate is a popular immunosuppressive medication used as an initial second line drug. It is important to note that immunosuppressive medications can reduce bone marrow function and cause anemia, low white cell count and low platelet counts. Specifically, methotraxate can sometimes lead to cirrhosis and allergic reactions in the lung. Cyclosporine, another immunosuppressive drug, can cause kidney damage and high blood pressure. These side effects are the reason these drugs are prescribed in low doses and in combination with anti-inflammatory medications (O'Dell 2008, chapter 16).

The efficacy of first and second line treatments can be detected using IR thermography (Ring 1974, 353). This information will be presented in the chapter 2 literature review of this thesis. Furthermore, the awareness of the medication pathways will facilitate the analysis and discussion in chapter 5.

1.8 Statement of the Problem

It is critical to diagnose a patient with RA very early in the course of the disease, first to prevent the non-reversible and permanent damage to the synovial joint, and second to allow the doctor to intervene early with an

aggressive therapy. The prognosis of a diagnosed RA patient is better when discovered and treated early (Bykerk 2009). For that reason, the doctor's goal is to diagnose the disease as early as possible, even before the first clinical signs are apparent – pain and swelling. Imaging techniques can be a solution to this difficulty allowing the physician to visualize the joints in further detail to make an early diagnosis for treatment.

As seen previously, diagnosis is particularly difficult early on in the disease. During this stage, the patient may not present with the apparent RA symptoms - joint swelling, redness, pain, warmth, tenderness. Therefore, it is important to be able to combine the classical examination technique of palpation – which may not detect RA very early on – with imaging techniques that are able to visualize the bone and the soft tissues of the joint; more particularly the synovial membrane. It is also important to clearly identify the distribution of the affected joints to distinguish between RA and other arthritic diseases, such as osteoarthritis. Imaging techniques can help determine the state of the synovial membrane and the distribution of the involved joints. Furthermore, imaging techniques can eliminate diagnostic inter-physician and intra-physician variations. The clinical evaluation – history and physical exam – is subject to observer variations and is limited to the expertise of the individual performing the evaluation. Doctors therefore have an interest in using imaging tools to help facilitate the diagnosis of RA (as verbally stated by the co-investigator of this study – Dr. Jacob Karsh, Rheumatologist at the Ottawa Hospital – Riverside Campus) (Dr. Jacob Karsh, Personal Communication, September 22nd 2009).

The diagnostic serum tests explained above cannot be used alone to identify RA. No single marker has been shown to predict RA outcome well. Therefore imaging procedures still remain the best diagnostic tool used by physicians to identify and assess RA.

Magnetic Resonance Imaging (MRI) and High Resolution Ultrasound (HRUS) are the two imaging tools that are currently used by doctors to diagnose RA. MRI is an imaging technique using radio frequency pulses and a powerful magnetic field to visualize the internal structures of the body – bone, organs, soft tissues, etc. It produces very high quality images with a great contrast between different soft tissues (Sugimoto 2000, 569–575). However, the MRI imaging procedure requires the patient to remain perfectly still while the images are being recorded. MRI exams include multiple sequences that last several minutes each. The entire exam duration is time consuming ranging from 15 minutes up to 45 minutes. Patients with RA, who may be experiencing severe pain or discomfort, may find this procedure very long and difficult. There are also some restraining contraindications to MRI: claustrophobia or anxiety, internal defibrillators or pacemakers and cochlear ear implants. Furthermore, MRI procedures are expensive and the wait times are long. In Ontario, the average patient waits 120 days before having an MRI imaging session (Government of Ontario 2009). High Resolution Ultra Sound (HRUS) is an imaging technique that emits high frequency sound waves into the body and creates an image based on the measurements of the echoes returned from the inner tissues. HRUS can view soft tissue thus is a tool that is able to visualize swelling and inflammation. It is

also less expensive and more available than MRI; however, HRUS produces lower quality images than MRI. According to Dr. Jacob Karsh, there are ongoing investigations examining the diagnostic utility of HRUS since it is limited to a fewer number of joints (Dr. Jacob Karsh, Personal Communication, September 22nd 2009). It is for these reasons that there is a need of an imaging method that is inexpensive, non-invasive, not limited to only imaging a few joints and that is capable of examining multiple joints at a time for the assessment of RA.

1.9 Thesis Objectives

The main objective of this thesis is to explore IR imaging as a possible inexpensive non-invasive method to diagnose and treat RA. Thermal IR (TIR) systems would make the diagnosis process more efficient since it would reduce the length of the imaging procedure given that some images would be able to examine multiple joints at a time. For example, one single IR image of the hand can at once evaluate 15 joints - the 5 MCPs, 5 PIPs, 5 DIPs joints and the wrist. Thermal IR (TIR) imaging can also quantify the inflammation and severity of the affected joint to assist physicians in treating their RA patients.

The first objective of this thesis is to determine if it is possible to discriminate between the control group and the RA group. The second objective is to identify the joints to examine in a clinical setting that best determine if a participant has or does not have RA. The third objective of this thesis is to identify the best mathematical calculation of the data to assess the presence or absence of RA. The fourth objective is to determine if thermal IR images can be

used to classify the RA patients into three severity groups – high degree of RA, moderate degree of RA and low degree of RA. The final objective of this thesis is to observe the effect of age on the thermal IR measurements.

1.10 Thesis Outline

The introduction has covered the thesis motivation, the statement of the problem, a detailed background on rheumatoid arthritis, and the thesis objectives and outline.

Chapter 2 presents a literature review beginning with thermal infrared imaging. This section covers the electromagnetic spectrum, blackbody radiation and emissivity, Planck's law and Wien's displacement law, and Stefan Boltzmann's law. The chapter goes on to explore the past research in infrared thermography. Afterwards, a section on clinical infrared thermography gives an overview on general medical applications and rheumatoid arthritis applications of thermal infrared technology.

Chapter 3 discusses the methodology used in this research thesis. It covers the extensive ethics review process that was completed to begin this project, followed by the recruitment process of the participants. A description of the infrared system and the setup that was used for the imaging procedure is given. The chapter continues with the collection of data methodology which covers the thermal infrared protocols and recording procedures. It concludes with an explanation of the analysis of data.

Chapter 4 begins by displaying the resulting datasets derived from the raw data measurements extracted from the thermal infrared images. The chapter goes on to apply the Lilliefors Normality Test to observe if the modified raw dataset distributions (called matrices within this thesis) are Gaussian. Then hypothesis tests are done to show the statistical significance of the results to see if each thesis objective can be met.

Chapter 5 states the contributions to knowledge of this thesis work. It will end with some proposed future work.

CHAPTER 2

2 LITTERATURE REVIEW

This chapter presents a literature review beginning with thermal infrared imaging – the electromagnetic spectrum, blackbody radiation and emissivity, Planck's law and Wien's displacement law, and Stefan Boltzmann's law. The chapter goes on to explore the past research in infrared thermography. Afterwards, a section on clinical infrared thermography gives an overview on general medical applications and rheumatoid arthritis applications of thermal infrared technology.

2.1 Thermal Infrared Imaging

2.1.1 Electromagnetic Spectrum

The electromagnetic spectrum is divided into wavelength bands. Thermographic cameras detect radiation in the infrared spectral range. The infrared band is subdivided into four sub-bands: near infrared (0.75 to 3 μm), middle infrared (3 to 6 μm), far infrared (6 to 15 μm) and extreme infrared (15 to 100 μm) (FLIR Systems 2004).

Figure 2-1: Electromagnetic Spectrum (FLIR Systems, 2004)

Military researchers developed this technology for the purpose of using thermal IR cameras for night vision and human detection in war situations. Consequently, most thermal IR cameras function in the far infrared range since the infrared signal at these wavelengths travel best through smoke, smog, dust, humidity and other possible distortion factors in the environment.

2.1.2 Blackbody Radiation and Emissivity

All surfaces heated at a temperature above zero degrees Kelvin (°K) or - 273 degrees Celsius (°C) emit electromagnetic radiation. A blackbody is an object that can perfectly absorb all radiation at any wavelength and that can equally emit all possible wavelengths of energy (Kirchhoff's law). The emissivity of a material is a measure of its ability to absorb and radiate energy. It is the ratio between the power radiated by the material and the power radiated by a blackbody at the same temperature as seen in Equation 2.1.

$$\varepsilon_0(T) = \frac{W_0(\lambda, T)}{W_b(\lambda, T)} \quad (2.1)$$

A blackbody has an emissivity of $\varepsilon = 1$. The emissivity of an object depends on the temperature, wavelength and direction. However, it is possible to consider it a constant within a determined temperature range, bandwidth and cone of direction (Wolfe 1965, Hudson 1969 and Gaussorgues 1994).

Treated surfaces have an emissivity ranging from 0.1 to 0.95. For instance, an oxidized or painted surface has an emissivity of approximately 0.90 whereas a highly polished surface, such as a mirror, has an emissivity below 0.1. Human skin has an emissivity resembling that of a blackbody – estimated between $\varepsilon = 0.97$ and $\varepsilon = 0.98$ – within the 8-14 μm range (the far infrared range). In the 3-5 μm IR region (the middle infrared range), the emissivity of the skin decreases and is more prone to environmental artefacts (Anbar 1994). Therefore, measurements of the skin using thermal IR techniques should be performed in the 8-14 μm range to achieve a higher accuracy of results.

2.1.3 Planck's Law and Wien's Displacement Law

The radiation emitted by a blackbody can be described through Planck's law. The following equation represents the spectral distribution of the radiation from a blackbody (FLIR Systems, 2004):

$$W_{\lambda b} = \frac{2\pi hc^3}{\lambda^5 \left(e^{\frac{hc}{\lambda kT}} - 1 \right)} \times 10^{-6} [\text{Watt} / \text{m}^2 \mu\text{m}] \quad (2.2)$$

where $W_{\lambda b}$ is the blackbody spectral radiant emittance at wavelength λ , c is the velocity of light (3×10^8 m/s), h is the Planck's constant (6.626×10^{-34} Joule sec.), k is the Boltzmann's constant (1.380×10^{-23} Joule/K), T is the absolute

temperature (K) of a blackbody and λ is the wavelength (μm). Planck's radiation law describes how, as the temperature increases, the peaks of the radiated spectrum move towards shorter wavelengths and the radiation power emitted increases. This effect is seen in the figure below, which plots the spectral radiant emittance as a function of wavelength for various temperatures.

Figure 2-2: Emissive Power of a Blackbody at Different Temperatures and Wavelengths According to Planck's Radiation Law (FLIR Systems, 2004)

The location of the peaks can be expressed by differentiating Planck's law with regards to λ and finding the maximum. This is known as Wien's law (FLIR Systems 2004):

$$\lambda_{\max} = \frac{2898}{T} [\mu\text{m}] \quad (2.3)$$

where $\lambda_{\max}$ is the maximum emissive power and T is the temperature (in °K).

Wien's formula describes the common observation that colors vary from red to

orange to yellow as the temperature increases. Consequently, at room temperature (300 °K) the maximum emissive power is attained at a wavelength of 9.7 μm , in the far infrared region of the electromagnetic spectrum. This correlates with what was stated earlier – that the body’s radiated power is significant in the 8-14 μm , the far-infrared spectrum. The figure below shows the Planckian curves from 100K to 1000K. The dotted line represents the maximum radiant emittance at each temperature according to Wien’s displacement law.

Figure 2-3: Planckian Curves Plotted on Semilog Scale (FLIR Systems, 2004)

2.1.4 Stefan Boltzmann’s Law

The Stefan-Boltzmann’s law represents the total emissive power or the total radiant emittance (W_b) of a blackbody. This formula is obtained by integrating Planck’s equation from $\lambda = 0$ to $\lambda = \infty$ and is as follows (FLIR Systems 2004):

$$W_b = \sigma T^4 [Watt / m^2] \quad (2.4)$$

where $\sigma = \frac{2\pi^5 k^4}{15c^2 h^3} \approx 5.670 \times 10^{-8} [Watt / m^2 K^4]$ is the Stefan-Boltzmann's constant.

Graphically, W_b is the area below the Planck curve at a particular temperature. From Equation 2.4, the power emitted by the human body at room temperature (300 °K) with a surface area of approximately $2m^2$ is 1 kW.

The amount of energy that is reflected by an object is determined by the reflectivity coefficient ρ_λ . The reflectivity is calculated as follows:

$$\rho_\lambda = 1 - \varepsilon_\lambda \quad (2.5)$$

A blackbody has a reflectivity of 0, since all the radiation is absorbed and emitted. When a gradient of temperature is applied to a blackbody and if only radiative heat transfer is considered, the Stefan-Boltzmann's law becomes:

$$W_b = \sigma (T_b^4 - T_s^4) [Watt / m^2] \quad (2.6)$$

where T_b is the temperature of the body (in Kelvin) and T_s is the temperature of the surroundings (in Kelvin).

From Planck's law (equation 2.2) and the emissivity equation (equation 2.1) it is possible to directly calculate the temperature of a body knowing the measured emitted power of that body at a specific wavelength. However, when an object has an emissivity less than unity the reflectivity of that body must be taken into account when calculating the temperature of that object from the measured total energy emitted from that body. For this reason, it is desirable to measure objects that have an emissivity as close to unity as possible for a higher

accuracy of temperature measurement (Anbar 1994). Since the skin has an emissivity close to that of a blackbody, the adjustment needed to account for the reflectivity of the skin is negligible, especially when the temperature of the environment is lower than that of the skin and the angle of viewing of the measurement is less than $\pi/4$ (Jones 1998, 1019-1027). It is important to note that in a clinical setting, it is possible to assume that the reflectivity has no effect on the direct link between the measured energy radiated by the object and the temperature of that object since the environment's temperature is controlled to be lower than that of the skin and the viewing angle is ensured to be less than $\pi/4$.

2.2 Past Research in Infrared Thermography

Over the past 50 years, Thermal Infrared (TIR) imaging has been applied to many fields such as military, veterinary and electronic maintenance applications (Ernisse 1997, 2593-2603 and Huang 2005, 3281-3288). From the 1960's to the 1980's, medical thermal imaging applications were investigated. Promising results were found in research such as pain assessment, breast cancer and arthritis (Collins 1974, 113-115; Aubry-Frize 1981 and Gautherie 1983, 74-92). The major limitations found in the early work included physical restrictions of early systems (large size, heavy weight, cooling requirements), subjectivity of the thermographic interpretations, limited power of computers for the imaging analysis, lower sensitivity and high cost of IR systems. These issues prevented the widespread applications of TIR imaging in the medical field until recently. The renewed interest in clinical IR thermography is due to the

advances in IR technology, computers for analysis and standard protocols for examination. New IR systems are physically compact, cost less, have a higher thermal and spatial resolution, and have faster frame and processing rates. Today's computers also have faster processing speeds and high definition monitors for the IR analysis. This combination allows a higher quality of digital IR imaging for medical applications. Furthermore, since the mid 1990's standards for medical IR thermography examinations have been agreed upon (Ring 1995, 1697-1698). On the other hand, the issue of interpreting the higher quality IR images remains. Clinical experts trained in the interpretation of thermograms are the current standard in medical applications. However, the ability of the eye to identify the subtle temperature variations and recognise digital distribution patterns is not very good. It has also been shown that the use of pseudo-colours to improve human interpretation is not a good solution given that humans are subject to psychological effect of hot and cold colours (Anbar 1991, 479–484). Our group has introduced a method to improve IR interpretation by applying recovering processes for the contour of images to reduce noise and improve the low contrast. We also developed a segmentation process to identify abnormal regions on the IR surface of the body (Herry 2007, Herry 2008). Our group intends to incorporate this approach to the clinical application of assessing RA.

2.3 Clinical Infrared Thermography

It is possible to define clinical infrared thermography or thermal infrared imaging as the recording of the temperature distribution of the human body (or

body areas) using infrared radiation emitted by the surface of that body – for example the skin (Jones 1998, 1019-1027). TIR images can provide valuable information on the physiology of the human body, since a major part of the energy radiated by the human body goes through the skin and can be detected by thermographic sensors in the infrared range of the electromagnetic spectrum (Houdas 1982). Some examples of information that can be analysed are neurological activity, vascular flow and distribution, rheumatic activity and abnormal growths in oncology provided that the temperature changes can be seen on the surface of the skin. Thermal IR images can provide a general indication of location and/or sources of pathologies of anatomical nature (Anbar 1991, 479-484). Using thermocouples, Horvath and Hollander have shown that the intra-articular temperature of RA patients can be used as a guide to the severity of inflammation (Horvath 1949, 469-473). Bacon et al. have demonstrated that measurement of mean skin temperature could be used as a measure of disease activity (Bacon 1976, 51-65). Furthermore, Ring et al. and Collins and Cosh have shown that variations in skin temperature over areas of chronic inflammation correctly reflect the chemical and cellular changes in rheumatoid arthritis (Ring 1970, 337 and Collins 1970, 386).

Many studies, such as Goodman et al. and Uematsu et al., have shown that since the skin temperature distribution of a normal healthy individual exhibits a contralateral symmetry, it is possible to identify some abnormalities when the temperature distribution shows asymmetrical patterns (Goodman 1986, 195–202; Uematsu 1985 and Uematsu 1988, 552–555). However, in some pathological

diseases – such as rheumatoid arthritis – this might not always be helpful because the thermal dysfunctions are usually exhibited bilaterally. In cases where the disease is present bilaterally, the expert interpreting the thermographic image must find other signs of abnormalities in the temperature distribution and its patterns (Hooshmand 2001, 53-65). Interpreting the IR image is one of the most difficult processes in IR applications since the expert interpreter needs to understand the complexity of the pathology and the underlying processes that cause the thermal distribution dysfunction. (It is for this reason that Chapter 1 covers detailed information on the pathophysiology of RA.) Thus, the sensitivity and the specificity of the interpretation technique is greatly dependant on the pathological application of the IR technology.¹

2.3.1 General Medical Applications of TIR Technology

The early literature on medical application of TIR technology focused on interpreting thermographic images and identifying abnormal thermal variations on the surface of the skin. This was done via visual evaluation of grey-level and/or pseudocoloured thermal images using isothermal functions, by identifying hot or cold regions within a Region of Interest (ROI) and by asymmetrical analysis (Aubry-Frize 1982, 82-83; Hooshmand 2001, 53-65; Hubbard 1985, 26-35; Poussart 1988; LeRoy 1985 4-13; Kim 1995, 1699-1700; Goldberg 1986; Thomas 1990, 268–273; Ellis 1989). Head and Lipari studied the thermal

¹ The sensitivity is defined as $sens. = \frac{TP}{TP + FN}$ and the specificity as $spec. = \frac{TN}{TN + FP}$ where TP, TN, FP and FN are true positive, true negative, false positive and false negative respectively.

distribution on the surface of breasts for breast cancer risk assessment. They analysed the images by manually selecting a large ROI along the contour of the entire breast using anatomical reference points and splitting each large ROI into four smaller ROIs (Head 1997, 681–684 and Lipari 1997, 673–676). Complex methods of boundary detection have been studied and successfully implemented for breast segmentation to allow automation (Ng 2001, 12-16 and Scales 2004, 1737-1740). Other techniques of ROI automation have been attempted using military Automated Target Recognition (ATR) techniques (Irvine 2002, 31-40). The major obstacle in implementing military ATR to the clinical setting is the nature of the target of study. In a military setting, the shape of the ROI is already known, whereas in the clinical setting, the shape of the region of pain/tumour/joint is not always the same. The shape and size of the diseased region can vary from patient to patient and even within one patient over time.

Once the region of interest is selected, statistical analysis is performed on the selected ROI. This analysis mostly includes thermal detection of maximum and minimum temperature regions and first-order statistics (mean, median, standard deviation). Histograms are also used to graphically represent the temperature distribution in discrete time. Studies were also done to assess the effect of scaling on temperature variations and accuracy by varying the size of the ROI (Goodman 1986, 195-202 and Lipari 1997, 673-676).

Moreover, to ensure the accuracy of medical TIR readings it is important to implement the correct protocols and standards – control of the environment (temperature, reflectivity, humidity, etc.) and control of thermal characteristics of

the skin (no lotions or creams, no extreme exercise, no hot/cold beverages prior to the examination, etc.) (Ring 1995, 1697-1698; Jones 1998, 1019–1027 and Herry 2004). The intensities of IR images depend on the object's temperature and surface properties and on the surface's orientation and wavelength. These properties are not always uniform across one surface where the temperature is uniform. As mentioned previously, environmental factors at the time of imaging greatly influence the IR images that are collected; however, in a clinical setting, these factors can be managed and controlled. Furthermore, controlling the room at ambient temperature (approximately 20 °C) increases the sensitivity of the skin's surface temperature to subcutaneous vascular flow when a cooling period is implemented (Stolwijk 1976, 40-51). Thus, it is recommended that prior to the TIR imaging procedures, the subject remains in the room at ambient temperature for a cooling period in order that the skin's radiating energy best reflects the blood flow and other cellular activity under the skin.

2.3.2 RA Applications of TIR Technology

Collins and Ring used a Thermal Index (TI)² calculation based on the isothermal temperature difference to quantify the measurement of synovitis (Collins 1974, 113 and Ring 1974, 353). The TI they introduced reflects the mean temperature in a determined ROI. Collins and Ring were able to show that

² The Thermographic Index is measured from the expression: $\frac{\sum(\Delta t \times a)}{A}$; where Δt is the difference between the measured isothermal temperature and the lowest common isotherm recorded, a is the area occupied by isotherm (cm²) and A is the total area of the thermogram (cm²).

IR thermograms of the knees, hands and feet can be used to identify patients with RA and as an assessment tool for the disease. They showed that the TI decreased with treatment and that the TI increased during a flare episode of RA. Using a larger sample group and the t-test, Bird, Ring and Bacon's publication confirmed Collins and Ring's findings that thermography can be used to assess inflammation of the synovial membrane and to evaluate the effectiveness of an RA treatment (Bird 1979, 36-39). They studied the effect of intra-articular injection drugs on the state of RA knees and concluded that the TIR images showed improvements in the patients after the treatment was initiated.

In 1983, Salisbury et al. suggested a new method of interpreting the IR information to detect RA abnormalities in the knee, wrist, elbow and ankle joints (Salisbury 1983, Salisbury). He demonstrated that the quantification of synovitis by TIR imaging should be based on dysfunctional thermal patterns rather than by indexes, such as the TI, that are based on absolute skin temperature values. The skin's surface temperature is greatly affected by many factors such as metabolic rate, consumption of very hot/cold beverages, calorie intake, emotional state, circadian variation, physical activity, environment temperature and humidity, etc. (Reinberg 1976, 128-139) Salisbury et al. therefore introduced a Heat Distribution Index (HDI) that would be a representation of pattern and spread of the temperature distribution over the surface of a joint. They went on to prove that the HDI correlated better with joint inflammation and synovitis than Collins and Ring's TI. The TI proved to be less significant in identifying the presence of inflammation and was even less significant in identifying

inflammation in afternoon TIR readings. The TI is more variable and less reproducible than the HDI, since it is greatly affected by the patient's circadian rhythm and the environment in which the images are taken. The HDI was able to identify a normal thermal distribution in the absence of inflammation in the knee, ankle, wrist and elbow joints. Alternatively, inflammation of the synovial membrane was repeatedly detected by the HDI analysis and these results were not affected by the time of day of the TIR readings. Salisbury et al.'s HDI is calculated based on the relative frequency distribution of the thermogram via a 256 grey level TIR image. A ROI of interest is delimited to cover the joint to be analysed. A pixel count is made at each grey level within the ROI and each resulting number is divided by the number of pixels in the ROI. Normal joints present a narrower relative frequency distribution (lower standard deviation) than a diseased joint. Salisbury et al. also added that the distribution of heat over a normal joint results in a positive temperature gradient from the centre to the periphery of the joint. For example, when observing the lateral view of the knee, the temperature increases from the knee's patella (or knee cap) to the back of the knee joint periphery – the patella having the lowest temperature. They also noted that normal joints do not have localised areas of increased temperature – hot spots. An abnormal joint with synovitis can therefore be described as a joint presenting with a negative thermal gradient with localized hot spots within the joint's ROI.

Devereaux et al. supported Salisbury et al.'s work by stating that the HDI significantly correlates with other RA evaluation methods – the Ritchie articular

index (a graded assessment of 26 joint regions to assess tenderness plus a 44 joint count to assess swelling), grip strength, morning stiffness, erythrocyte sedimentation rate and pain score (Devereaux 1985, 434-437). They confirmed, using the product moment coefficient correlation test, that the thermographic HDI is a sensitive, reproducible, quantifiable method of analysis that gives results comparable to the current methods of assessment. In addition to its high correlation, TIR imaging using the HDI technique avoids complications that the current methods do not, such as invasiveness, interobserver variability, high cost, circadian variation, etc. Devereaux et al. also demonstrated that the HDI can be used to confirm if the disease is more severe or better controlled by observing patient's progress over time.

De Silva et al. compared the use of TIR imaging (using the HDI analysis procedure) to the clinical assessment and to the radioisotopic imaging methods of evaluating RA (De Silva 1986, 277-280). Using Spearman correlation coefficients, they found a high correlation between the HDI and the radioisotopic imaging method in rheumatoid arthritic knees. The HDI also significantly correlated with every aspect of the clinical assessment – swelling, tenderness, morning stiffness, joint score – except for pain.

Other research, such as Ilowite et al's, went on to validate the above findings and further confirm that the thermographic HDI is the best method to assess inflammation of the synovial membrane for RA diagnosis (Ilowite 1992, 343-346).

In this thesis we analyse the 2nd and the 3rd MCPs, the 2nd and the 3rd PIPs, the wrists and the knees based on the temperature distribution methodology introduced by Salisbury and supported by many others. The temperature distribution pattern is analysed to see if abnormal localized regions of increased or decreased temperatures can be used to classify participants with RA. Moreover, histogram functions and the relative frequency of hot/cold regions were explored as another method of distinguishing patients from control subjects.

CHAPTER 3

3 METHODOLOGY

Chapter 3 discusses the methodology used in this research thesis. It covers the extensive ethics review process completed prior to beginning this project, followed by the recruitment process of the participants. A description of the infrared system and the setup that was used for the imaging procedure is given. The chapter continues with the collection of data methodology which covers the thermal infrared protocols and recording procedures. It concludes with an explanation of the analysis of data.

3.1 *Ethics Review*

A pilot research proposal was approved by the Ottawa Hospital Research Ethics Board (OHREB) under the title of “Severity of illness measures in rheumatoid arthritis from multi-spectral imaging”. Its principal investigator at the Ottawa Hospital was Dr. Jacob Karsh, a rheumatologist from the Riverside Campus. The co-investigator was Dr. Monique Frize from the Faculty of Engineering and Design at Carleton University. Since the pilot study involved the facilities and the instrumentation at both Carleton University and the University of Ottawa, two more research proposals were submitted and individually approved

by the Carleton University Research Ethics Committee and the University of Ottawa Research Ethics Board. This thesis is part of the first objective outlined in the proposal submitted: “To perform an exploratory pilot test with patients diagnosed with RA to observe the various degrees of inflammation of patient articulations via heat distribution patterns using infrared thermography.” The completion of this study would extend Dr. Frize’s Medical Information-technologies Research Group (MIRG) at Carleton University in infrared thermography.

3.2 Recruitment of Participants

Research participants were patients over the age of 19 years of age of the Ottawa Hospital-Riverside Campus who were diagnosed with RA. They were recruited by their healthcare specialist – Dr. Jacob Karsh – who informed them of the study and asked them if they were interested in participating. Patients of both sexes and of any age were asked to participate in the research study. The exclusion criteria were patients who have joint pain for reasons other than RA; patients who have recently suffered bruising or trauma of the affected joints; and patients with joint sepsis. If patients were interested in the research study, the healthcare specialist provided them with a permission text which they signed to continue with the research process (see Appendix A). This signed permission sheet declared that patients agreed to release their name and contact information to the co-investigators of this study at Carleton University and the

University of Ottawa. The patients were not given any research incentives to participate in the study, and were not coerced into participating in any other way.

Once the permission text was signed, the co-investigator's student, Cynthia Adéa, contacted the patients individually to confirm their interest and to send them "Research Participant Information and Consent Form" documents (see Appendix B). The patients who consented to the study completed the consent form which permitted the usage and storage of the digital IR images of their limbs and joints. No images of participants' faces were taken and no personal information was shared with Carleton University or the University of Ottawa's research teams.

The control participants were subjects over the age of 19 years old recruited at the University Campuses who have not been diagnosed with RA, who were in good general health and who were without pain or symptoms resembling RA. Control subjects were recruited to establish a range of temperature distribution for normal subjects and to provide a baseline for what is identified as normal. The control participants were not given any research incentives to participate in the study, and were not coerced into participating in any other way. They were given the same information package as the RA patients (see Appendix B) and were asked to sign a consent form which permitted the usage and storage of the digital IR images of their limbs and joints. No images of control subjects' faces were taken and no personal information was shared with Carleton University or the University of Ottawa's research teams.

Thirteen patients diagnosed with RA were recruited from the Ottawa Hospital-Riverside Campus and eighteen control subjects were recruited from Carleton University, the University of Ottawa and a few from outside the campuses.

3.3 Collection of Data

3.3.1 Specifications of the Infrared Camera

The ThermoVision A40M Researcher Infrared Camera from FLIR Systems was used to capture the TIR images. This IR camera uses an uncooled microbolometer focal plane array of 320×240 pixels at a refresh rate of 50/60 Hz. It operates in the $7.5\mu\text{m}$ to $13\mu\text{m}$ of the far IR spectral range of the electromagnetic spectrum. The A40M has a 24 mm germanium lens with an anti-reflective coating. The germanium lens renders a field of view that is $24^\circ \times 18^\circ$ with a minimum focus distance of 0.3 m. The camera's spatial resolution is 1.3 mrad, which means that at a distance of 1 m each pixel represents a square of $1.3\text{mm} \times 1.3\text{mm}$. The A40M has a thermal sensitivity of 0.08°C at 30°C and can detect temperature ranges from -40°C to $+120^\circ\text{C}$. The camera was connected to a laptop via a Firewire output connection, thereby capturing sequences of 14 bit digital thermal images at a maximum speed of 60 frames per seconds.

Figure 3-1: A40M Infrared Camera from FLIR Systems (FLIR Systems, 2004)

To see the complete specifications of the A40M IR Camera from FLIR Systems turn to Appendix C.

3.3.2 Infrared Camera and Recording Settings

The software used during the imaging sessions was the ThermaCAM Researcher Pro 2.8 from FLIR Systems. It is via this software that measurement corrections were inputted by the user - the emissivity, the camera distance, the ambient temperature and the relative humidity. The A40M radiometric camera outputs emissivity measurements to the ThermaCAM software which converts the measurements into absolute temperatures while taking into consideration all the input corrections.

The camera settings used for this thesis were as follows. The emissivity was kept constant at 0.98 for the skin. The camera distance ranged from 0.5 m to 1 m and was manually adjusted for every shot via the settings options of the software. The ambient temperature and relative humidity of the environment were measured for each session and were 23 ± 1 °C and 40 ± 2 % respectively for all the sessions. The image intervals for the recording conditions were set at 2, which means 30 images were taken per second during each recording time.

The image presentation box was enabled to allow the user to view the images live and manually adjust the camera for the best shot.

Images were recorded in *.seq format for sequences of images and were subsequently exported into Matlab as *.mat files. The *.mat files contained the temperatures of each pixel of the image and information about the environmental settings.

3.3.3 Medical Thermal Infrared Protocols

Prior to the imaging session, each participant was given these guidelines to follow:

- Do not consume alcoholic beverages twenty-four hours prior to the session.
- Do not consume hot beverages at least one hour prior to the session.
- Do not wear rings, necklaces, anklets and/or bracelets during the session.
- Do not use talcum powder, lotion, drug or deodorant on the skin on the day of the session.
- Avoid prolonged sun exposure at least one week prior to the session.
- Avoid smoking at least two hours prior to the session.
- Avoid any intense physical exercise at least four hours prior to the session.
- Avoid procedures such as electromyography, acupuncture, myelography, transcutaneous electrical stimulation, hot or cold patches, or any other form of physiotherapy at least twenty-four hours prior to the session.

3.3.4 Recording Procedures

The IR thermographic sessions took place in a room without windows to avoid any reflection captured by the camera. There were no shiny or plastic floors and the only lights used were fluorescent lights. The temperature and humidity were measured before and after every session. They were uniform throughout the room and were kept constant throughout the entire session.

The patients and control subjects were asked to apply the medical thermal infrared protocol prior to the session (as described in the previous section). They were also asked to wear a sleeveless shirt and shorts and to remove their socks and shoes to facilitate the imaging of every articulation.

Before the recording session, the participants were placed on a chair with their arms resting to their sides and their bare feet relaxed on a foam carpet for a cooling down period of 15 minutes. During this time, the participants' surface body temperature was cooled sufficiently in a room remaining constant around 23 °C to allow the subcutaneous temperature to be well reflected at the surface of the skin. The participants remained seated without any body parts in contact with one another and without removing their feet from the carpet to ensure that the surface temperature of their skin correctly reflected the internal temperature of the joints and limbs.

The joints of interest were the same for the control subjects and patients with RA - elbows, wrist and hand joints, knees, ankles and feet joints. Each articulation was captured in different anatomical views.

The images of extended elbows were taken in the posterior and anterior view of the frontal anatomical plane. The elbows flexed at 90 degrees were imaged in the frontal plane. The flexed elbows were also imaged in the right and left median plan. See below grey level TIR images that were taken of the elbows.

Table 3-1: Grey Level Thermal Infrared Views of the Elbow

The extended wrists and hand joints were imaged in a single caption in the posterior and anterior view of the frontal anatomical plane. See below grey level TIR images that were taken of the wrist and hand joints.

Table 3-2: Grey Level Thermal Infrared Views of the Wrist and Hand

Images of the extended knees were taken in the posterior and anterior view of the frontal anatomical plane. Captions were taken of both extended

knees at one time and of individual extended knees separately. Images were also captured in the sitting position (knees flexed at 90 degrees) in the anterior frontal view. Captions were taken of both flexed knees at one time and of individual flexed knees separately. The individual flexed knees were also imaged in the right and left median plan. See below grey level TIR images that were taken of the knees.

Table 3-3: Grey Level Thermal Infrared Views of the Knee

Images of the ankles and feet joints were taken in the posterior view of the frontal anatomical plane. Posterior captions were taken of both ankles at one time and of individual ankles separately. Images were also captured in the right and left median plan of the ankles and feet joints. The top and the bottom of the feet were also imaged. The top of the feet were taken at two distances - 0.5 m and 1m respectively. Top views were taken of both feet at one time and of individual feet separately. The bottoms of the feet were taken at the end of the session in two rounds. The first round was captured immediately after the imaging session and the second round was captured after a 5 minute resting and cooling period. During this cooling period, the feet remained propped up and relaxed on a stool to allow the skin surface of the feet to efficiently represent the intra-articular temperature of all the feet joints. See below grey level TIR images that were taken of the ankles and feet joints.

Table 3-4: Gray scale Level Thermal Infrared Views of the Ankle and Foot

3.4 Analysis of Data

To properly analyse the data of the TIR images, it is important to first review the goals of the thesis. The first objective of this thesis is to determine if it is possible to discriminate between the control group and the RA group. The second objective is to identify the best joints to examine in a clinical setting that best determines if a participant has or does not have RA. The third objective of this thesis is to identify the best mathematical calculation of the data to assess the presence or absence of RA. The fourth objective is to determine if thermal IR images can be used to classify the RA patients into three severity groups – high degree of RA, moderate degree of RA and low degree of RA. The final objective of this thesis is to observe the effect of age on the thermal IR measurements.

3.4.1 Converting the Thermal IR Images into Data for analysis

To accomplish the first three goals specifically each *.seq FLIR file is converted into a *.mat MATLAB file using the FLIR software. The image – now a matrix of temperatures in Kelvin – is transformed into a normalized matrix ranging from 0 to 1 using the *mat2gray* function in MATLAB. When the normalized matrix is displayed via MATLAB's *imshow* function, a gray scale image is produced. These images are displayed in gray scale to eliminate any biases that a pseudo-colour image may create when the interpreter is viewing the image. It has been shown that the use of pseudo-colours when interpreting TIR images is not a good practice given that humans are subject to psychological effect of hot and cold colours (Anbar 1991, 479–484).

The Regions of Interests (ROIs) are manually selected from the gray scale image using anatomical reference points and the MATLAB's *roipoly* function. The anatomical reference points are determined by studying the anatomy of each joint to determine the location of the synovial membrane (Moore, 2007). The joints analysed are the 2nd and 3rd MCPs, the 2nd and 3rd PIPs, the wrist and the knee. The main anatomical point that is used to select the region of interest of the knee was the patella. The synovial joint is found underneath the patella. The anatomical points that are used to select the region of interest of the wrist are the pisiform bone – the small pea shaped wrist bone on the inner side (ulnar side) of the forearm – and the base of the thumb – where the trapezium and scaphoid bones are found. Please refer to figure 1.3 for the location of these bones. The anatomical points that are used for the MCP and PIP joints are the

MCP and PIP articulations themselves. The MCP and PIP joints are identified by their ovoid surface. The synovial joint is found directly under the ovoid surface. The images below demonstrate the gray scale matrix of the original TIR image with the manually selected ROIs.

Table 3-5: Regions of Interests Manually Selected for the 2nd and 3rd MCPS, the 2nd and 3rd PIPs, the Wrist and the Knee

Once the joints are identified, MATLAB outputs an array of temperature values which represent the temperature of every pixel within the selected region of interest of the TIR image. The resulting array is a probability distribution of a real-valued random variable.

Measurements are then extracted from these arrays to be analysed: max, min, mean, median, mode, standard deviation, skewness and kurtosis. The max and min measurements refer to the maximum and minimum temperatures within the array of the joint. The mean is the average temperature value of the elements of the array. If there are N elements in the array then the mean value is the sum of all element temperatures divided by N. The median is the

temperature value of the middle element of the joint's array when all the elements of the array are arranged in either ascending or descending order according to their temperature values. If there are N elements in the array, the median is the value of the $(N+1)/2$ element of the ordered values of the array. The mode is the temperature value that occurs most frequently in the array of the joint. The mean, median and mode are measures of central tendency – the location of a distribution. The standard deviation is a measure of dispersion and refers to the variability of the array distribution around the mean value. The skewness and the kurtosis describe the shape of the distribution. The skewness is a measure of the asymmetry of an array's distribution. A symmetric distribution around its mean has zero skewness. In other words, a symmetric array distribution has zero skewness and equal values of mean, median and mode. A distribution is positively skewed if the right tail is longer with $\text{mean} > \text{median} > \text{mode}$. A distribution is negatively skewed if the left tail is longer with $\text{mode} > \text{median} > \text{mean}$. (Salvatore, 2002) The figure below illustrates the different types of skewness.

Figure 3-2: Types of Skewness

The kurtosis is a description of the peak of the array's distribution. A mesokurtic distribution has zero excess kurtosis and has a normal peak around the mean. An example of a mesokurtic distribution is the normal Gaussian distribution. A distribution that is leptokurtic has a positive excess kurtosis and has a more acute peak around the mean with fatter tails. An example of a leptokurtic distribution is the Laplace distribution. A platykurtic distribution has a negative excess kurtosis and has a lower wider peak around the mean with thinner tails. An example of a leptokurtic distribution is the Bernoulli distribution. (Salvatore, 2002) The figure below illustrates the different types of kurtosis.

Figure 3-3: Types of Kurtosis

The literature review has shown that certain measurements (such as max, min, mean, median, mode) extracted from the TIR images are subject to inter-participant variation and many other factors (such as time of day, vascular distribution of the patient, environment, etc.). To eliminate the possibility that a person might simply be naturally warmer or colder than another, these measurements are slightly modified. Inspired by the Heat Distribution Index and Salisbury's research, Ratios, differences and dispersion measurements (variance) are used to compare the control samples and the patient samples. Ratios, differences and dispersion measurements are based on the thermal

distribution of the surface of the skin rather than the exact temperature reading, thus eliminating inter-participant differences. The modified datasets that are used for the analysis were:

Skewness	Max-Min
Kurtosis	$(\text{Mode}-\text{Mean})^2$
Variance	Mode/Min
Mode/Max	Median/Min
Median/Max	Mean/Min
Min/Max	

These modified datasets are referred to as matrices from this point on in the thesis. The matrix is a probability distribution of a real-valued random variable.

Salisbury's HDI is based on the dispersion (the variance) of the distribution of the thermal surface over the joint. In this thesis, many other measures of dispersion are used to characterize different dispersion aspects of the matrix. For instance, the skewness and kurtosis are direct representations of the temperature distribution's shape and thus indirectly represent the dispersion. The variance is the standard deviation (STD) squared and is the typical measurement of dispersion. The $(\text{Mode}-\text{Mean})^2$ is the mode temperature minus the mean temperature squared. It represents the dispersion range between the mode temperature and the mean temperature.

To further explore matrices that eliminate inter-participant variation, ratios are also explored: Mode/Max, Median/Max, Mode/Min, Median/Min and Mean/Min are calculated by dividing the numerator temperature (either mode, median or mean) by the denominator temperature (either max or min). These

ratios normalize the exact temperature value with the participant's own maximum or minimum temperature value. These ratios eliminate the error caused by a naturally colder or warmer participant.

The Max-Min matrix is simply the maximum temperature minus the minimum temperature and represents the temperature range of the joint region. This range is explored to see if the matrix can be used to correctly represent the temperature range of control subjects and RA patients.

The hypothesis is that the dispersion, ratio and difference matrices may be a better representation of the presence or absence of RA in participants.

3.4.2 First Objective – Discriminate Between the Control Group and the Patient Group

To answer the first objective additional data is extracted from the image before the statistical analysis stage. A MATLAB function is used to identify the pixels within the image that ranged from the mode temperature to the maximum temperature. The hypothesis is that the patients have more pixels within this range than the control group since RA patients are warmer at the surface of the affected joint and have abnormal hot spots present. To calculate the amount of pixels from the mode temperature to the maximum temperature, MATLAB's *roicolor* function is used to drive every pixel within that range to 1 and every pixel outside of that range to 0. This produces a binary black and white image that highlights the hot spots and the higher temperature pixels within the TIR image. An example of the binary image is seen below.

Table 3-6: The Binary Image Output of MATLAB's roicolor Function which Highlights the Pixels that are in the Mode to Maximum Temperature Range

In the binary image, the black pixels are cooler than the white pixels. This type of image allows the user to visually see the temperature distribution of the joint and the presence of hot spots. To mathematically quantify the result, the sum of the pixels highlighted are counted and presented as the percentage of the joint that is covered by warmer pixels and/or hot spots.

The hypothesis of the first objective is that the matrices presented above and the percentage of the joint covered by warmer pixels will allow the user to discriminate between the control group and the patient group.

Once the matrices and percentages are extracted and calculated, statistical tests are applied to the results to satisfy the first objective – that the control group is statistically different from the patient group. The first step of the statistical analysis involves testing the distribution of the matrices for normality. If

the matrices are not normally distributed, then the use of tests derived from the normally distribution such as the t-test and ANOVA are invalid (Salvatore, 2002). The current analysis uses the Lilliefors Test of normality (Matlab, 2009). It is applied to the matrix distributions to see if they were Gaussian. The Lilliefors Normality Test is explained in detail in the next chapter. The second step of the statistical analysis applying hypothesis tests to the matrices. If the matrices are normally distributed, parametric hypothesis tests such as the Student t-Test and the Anova Test, would be used to prove the statistical significance of the results. If the matrices are not normally distributed, then non-parametric hypothesis tests, such as the Kruskal-Wallis Test (Salvatore, 2002; Matlab, 2009) and the Ranksum Test (Matlab, 2009), would be used to prove the statistical significance of the results. The hypothesis tests used are explained in detail in the next chapter. To satisfy the first objective, these hypothesis tests should show that the control group matrix distributions are statistically different from the patient group matrix distributions at a significant level of at least 5% ($\alpha = 0.05$) and with a p-value lower than 0.05. The values for α and p are the generally accepted values for statistical significance in hypothesis testing (Salvatore, 2002).

3.4.3 Second Objective – Identify the Joints that Best Determine if a Participant has or does not have RA

To answer the second objective the joints analysed are the 2nd and 3rd MCPs, the 2nd and 3rd PIPs, the wrist and the knee. The hypothesis is that the MCPs and the knees are the best joints in a clinical setting to best determine if a

participant has or does not have RA. Verbal discussions with Dr. Jacob Karsh confirmed that in the majority of RA cases the MCPs are the joints that are most affected early on in the disease - (Dr. Jacob Karsh, Personal Communication, September 22nd 2009). Furthermore, the knees are expected to show good results since past research has shown that the knees are the best joint to observe the presence of RA. The knee is also a larger joint compared to the others resulting in a larger matrix with more elements (since there are more pixels in the TIR image over this joint); therefore the knee matrices should show better statistical results of the thermal distribution.

The MCPs, PIPs and wrists are analysed using the posterior view of the hand in the frontal plane, since the skin surface on the back of the hand is a better representation of the intra-articular temperature. The reason the back of the hand is a better representation is because the skin surface of the palms are subject to more heat transfer when the participant moves around and accidentally touches other body parts or objects. The knees are analysed using the anterior view of the flexed knees in the median plane. The views of the extended and flexed knees in the frontal plane is not expected to be a good representation of the intra-articular temperature since the patella acts as a thick barrier between the joint's temperature and the skin surface temperature. The anatomical views that were used for the hands and knees are shown in the table below.

Table 3-7: Anatomical Views of the Hand and Knee Used for Analysis

The measurements are extracted using the same methods described above and the ratio/difference/dispersion matrices are calculated for statistical analysis. The same statistical tests are applied to the matrices as explained in objective one to prove the statistical significance of the best joint. First, the Lilliefors Normality test is applied to observe if the matrix distributions are Gaussian. Second, the correct hypothesis tests (parametric or non-parametric) are used to prove which joints show the most distribution difference between the control and patient group. To satisfy the second objective, these hypothesis should be tested with a significant level of at least 5% ($\alpha = 0.05$) and with a p-value lower than 0.05. The values for α and p are the generally accepted values for statistical significance in hypothesis testing (Salvatore, 2002).

3.4.4 Third Objective – Identify the Matrix that Best Assesses the Presence or Absence of RA

To answer the third objective it is important to restate the matrices that are used for analysis:

Skewness
Kurtosis
Variance
Mode/Max
Median/Max
Min/Max

Max-Min
(Mode-Mean)²
Mode/Min
Median/Min
Mean/Min

The matrices are expected to show a difference between the control group and the patient group. The hypothesis is that the variance, the max-min, the (mode-mean)² will best represent the thermal distribution dispersion to statistically distinguish between the control and patient group since they are dispersion measurements. The control group is expected to have a larger range of temperatures (a higher variance, a higher max-min and a higher (mode-mean)²) since they are expected to have a distribution that ranges from colder temperatures to the normal temperatures of the joint. The patient group is expected to have a lower variance, a lower max-min and a lower (mode-mean)² since their joints have fewer cold regions and their temperature range will begin at a warmer temperature than the control subjects, thus making the temperature range over the joints smaller than the control subjects.

The values in the matrix go through the same normality and hypothesis testing as explained in objectives one and two. To satisfy the third objective, these hypothesis tests should emphasize the matrices that show the largest statistical difference between the best joints of the control group and the best joints of the patient group at a significant level of at least 5% ($\alpha = 0.05$) and with a p-value lower than 0.05. The values for α and p are the generally accepted values for statistical significance in hypothesis testing (Salvatore, 2002).

3.4.5 Fourth Objective – Classify RA Patients into Three Severity Groups

To study the fourth objective, the best matrices chosen from objective three are extracted from the TIR images of the patient group to represent the thermal distribution of the best joints found in objective two. Dr. Jacob Karsh identified each of the 13 patients as having “high”, “moderate” or “low” degree of RA. The 13 patients are therefore ranked by severity according to Dr. Karsh’s clinical assessment - (Dr. Jacob Karsh, Personal Communication, July 23rd 2009). Then, the elements of the best matrix of the best representing joint are ranked according to their element values. As a result, the patients are ranked by RA severity done by the rheumatologist and ranked by element values within the matrix extracted from the measurements of the TIR image. These two rankings are compared using the Spearman Correlation Coefficient (Salvatore, 2002) to see whether the matrix distribution can correctly rank the patients by severity. The Spearman Correlation Coefficient is explained in detail in the next chapter. To satisfy the fourth objective, the Spearman Correlation Coefficient should show that the matrix ranking of the measurements highly correlates with the severity rankings done by the physician. A high correlation is a Spearman Coefficient greater than 0.5.

3.4.6 Fifth Objective – Observe the Effect of Age on Thermal IR Measurements

To study the fifth objective, the best matrices (from objective three) of the best representative joints (from objective two) are analysed from the control group. The 18 control subjects are ranked by age group: 10-20 years of age, 20-

30 years of age, 30-40 years of age, 40-50 years of age, 50-60 years of age and 60-70 years of age. Then, the elements of the best matrix of the best representing joints are ranked according to their element values. The control subjects are also ranked by age group and ranked by their matrix values. These two rankings are compared using the Spearman Correlation Coefficient to see whether the matrix distribution is highly correlated to the matrix elements. To satisfy the fifth objective, the Spearman Correlation Coefficient should show the extent to which age correlates with the TIR results represented in the matrix distribution. If the Spearman Correlation Coefficient is greater than 0.5, it is possible to state that age is associated strongly to the calculated matrix values derived from the TIR images. If the Spearman Coefficient is lower than 0.5, it is possible to state that age is associated weakly to the calculated matrices.

The following chapter presents the results and analysis of the measurements and matrices extracted from the TIR images.

CHAPTER 4

4 RESULTS AND ANALYSIS

Chapter 4 begins by displaying the resulting matrices derived from the raw data measurements extracted from the thermal infrared images. A discussion of the Lilliefors Normality Test, which determines whether the matrix distributions are Gaussian, follows. In addition, hypothesis tests are done to show the statistical significance of the results to see if each thesis objective can be met.

4.1 Results

All raw data measurements that are extracted from the original Thermal InfraRed (TIR) images can be found in Appendix D. The matrices used for analysis in this chapter are all calculated from the raw measurements.

These raw data measurements were presented at the IEEE International Workshop on Medical Measurements and Applications (MeMeA) in Cetraro, Italy in May 2009. The paper presented entitled "Preliminary Results of Severity of Illness Measures of Rheumatoid Arthritis Using Infrared Imaging" can be found in Appendix F.

The table below shows the average value for each matrix of every joint for the control and patient groups.

Table 4-1: Average Values for Each Matrix of Every Joint for the Control and Patient Group

		Average Value for:				
		Variance	Mode/Max	Median/Max	Min/Max	Max-Min
2nd MCP	Control	0,13997	0,99645	0,99680	0,99430	1,72480
	Patient	0,14211	0,99725	0,99712	0,99378	1,89925
3rd MCP	Control	0,08825	0,99114	0,99738	0,99552	1,35634
	Patient	0,06282	0,99328	0,99781	0,99621	1,15770
2nd PIP	Control	0,07617	0,99771	0,99793	0,99584	1,25547
	Patient	0,07074	0,99776	0,99798	0,99554	1,36027
3rd PIP	Control	0,07945	0,99817	0,99828	0,99562	1,32301
	Patient	0,07504	0,99826	0,99817	0,99517	1,47468
Wrist	Control	0,13762	0,99736	0,99733	0,99406	1,80680
	Patient	0,16193	0,99713	0,99692	0,99337	2,02897
Knee	Control	0,35935	0,98889	0,99579	0,98962	3,15889
	Patient	0,46501	0,98933	0,99644	0,99113	2,69858
		Average Value for:				
		(Mode-Mean) ²	Mode/Min	Median/Min	Mean/Min	
2nd MCP	Control	0,04921	1,00217	1,00252	1,00256	
	Patient	0,04346	1,00350	1,00337	1,00334	
3rd MCP	Control	0,04423	1,00152	1,00186	1,00193	
	Patient	0,02881	1,00155	1,00161	1,00167	
2nd PIP	Control	0,04953	1,00187	1,00209	1,00209	
	Patient	0,15206	1,00223	1,00246	1,00248	
3rd PIP	Control	0,13201	1,00256	1,00267	1,00260	
	Patient	0,02088	1,00312	1,00303	1,00295	
Wrist	Control	0,05378	1,00331	1,00329	1,00319	
	Patient	0,05069	1,00379	1,00358	1,00354	
Knee	Control	0,12981	1,00674	1,00624	1,00602	
	Patient	0,26941	1,00536	1,00538	1,00513	

Please note that the control group's averages are calculated from 36 matrix values (18 control subjects x 2), since each control subject presented two TIR images per joint – the left joint and the right joint. The patient group's averages are calculated from 26 matrix values (13 RA patients x 2). RA is an auto-immune disease affecting the joints bilaterally. As explained in great detail in the introduction chapter, the majority of RA patients show diseased joints on both sides of their body. For instance if the left knee is affected by RA, the patient's

right knee will be equally affected. Therefore, it is justified to include both the left and the right joints of a particular observed region of interest for the matrix distribution. Using both the right and left TIR images increases the sample size of the matrices; thus making the statistical analysis stronger and the matrix distributions more representative of each group.

4.2 *Analysis and Discussion*

Note that all statistical explanations and equations are derived from MathWork's MATLAB Help files and from D. Salvatore and D. Reagle's "Statistics and Econometrics" book from the Schaum's Outline Series of McGraw-Hill Companies (2002).

4.2.1 *First Objective – Discriminate Between the Control Group and the Patient Group*

First, normality is assessed using the Lilliefors Test for all the matrices calculated from the TIR measurements. Lilliefors tests the null hypothesis that the matrix samples come from a normal distribution against the alternative that they do not come from a distribution in the normal family. It is a 2-sided goodness-of-fit test used when the parameters of the distribution are unknown and must be estimated. The Lilliefors test statistic is:

$$KS = \max_x |SCDF(x) - CDF(x)| \quad (4.1)$$

where SCDF is the cumulative distribution function taken from the matrix samples and CDF is the normal cumulative distribution function with the same

mean and standard deviation as the sample matrix (Matlab, 2009). MATLAB's *lillietest* uses a table of critical values computed using Monte Carlo simulation for sample sizes less than 1000 and significance levels between 0.001 and 0.50. The significance level (also known as α or the type-I error) is used to determine the rejection region of the statistical test. Based on α and the degrees of freedom, a critical value is determined and compared to the Lilliefors test statistic stated in the equation above. If Lilliefors test statistic $>$ critical value, then the null hypothesis is rejected. If Lilliefors test statistic $<$ critical value, then the null hypothesis cannot be rejected (Salvatore, 2002). MATLAB outputs four results: *h* value, *p* value, *KS* value and *critical value*. The *h* value is 1 if the null hypothesis is rejected and 0 if it cannot be rejected at the 5% significance level. The significance level is always set to 0.05 in this thesis. The *p* value is the probability of observing an element from the matrix distribution if the null hypothesis is true. The *KS* value is the Lilliefors test statistic retrieved from the equation stated above. The *critical value* is the value that determines the rejection region of the test based on α and the degrees of freedom.

It is important to note that α is a number selected independently of the *p*-value and of the matrix. It is possible to reject the null hypothesis at a statistical significance of α when the *p*-value is smaller than α ; otherwise it is not possible to reject the null hypothesis at level α (Salvatore, 2002).

Random matrices for random joints were selected to see if any of them were normally distributed using MATLAB's *lilliefors* function. The table below shows MATLAB's four outputs obtained by the normality test. A reminder that

the null hypothesis of the test is that the matrix distribution belongs to the normal distribution family; therefore, if h is 1 with a p -value lower than α (where $\alpha = 0.05$), it is possible to conclude that the matrix distribution is not a normal distribution.

Table 4-2: MATLAB Lilliefors Test Results for Randomly Selected Matrices

Participant Type	Joint	Matrix Distribution	MATLAB Outputs			
			h value	p value	KS value	Critical Value
Control Subjects	2nd	Skewness	1	0.0482	0.1503	0.1497
	3rd MCP	Kurtosis	1	0.0020	0.1955	0.1497
	2nd PIP	Variance	1	0.0026	0.1920	0.1497
	3rd PIP	Minimum Temperature	1	0.0040	0.1865	0.1497
Patients	2nd	Kurtosis	1	0.001	0.4422	0.1699
	3rd MCP	Kurtosis	1	0.0346	0.1767	0.1699
	2nd PIP	Maximum Temperature	1	0.0019	0.2226	0.1699
	3rd PIP	Minimum Temperature	1	0.0133	0.1932	0.1699

The results from Lilliefors show that the eight matrices representing the thermal distribution of the joints are not normally distributed (since all the h values are 1) at a 5% significance level ($\alpha = 0.05$). The KS values are all superior to the critical values and the p -values are all lower than α ; therefore it can be confirmed that the matrices are not from the normal Gaussian family.

From the results of the eight randomly selected matrices that were tested for normality, it will be assumed in this thesis that all the matrices are not normality distributed. As a consequence, parametric hypothesis tests cannot be used for the statistical analysis. Instead of the Student t -Test and the Anova Test, the Kruskal-Wallis Test and the Ranksum Test are applied to the matrices.

Second, the Kruskal-Wallis Test and the Ranksum Test are used to show that the control group's matrix distributions are statistically different from the

patient's matrix distributions, showing that TIR images can be used to discriminate between the control and patient groups. The Kruskal-Wallis Test is the non-parametric version of the classical one-way Anova test and is based on the standard Anova table using ranks rather than the numeric values of individual sample points. The test compares the medians of two or more matrices and returns the p-value for the null hypothesis that all samples are drawn from the same distribution (Salvatore, 2002; Matlab, 2009). MATLAB's *ranksum* test, also known as the Mann-Whitney U-test, is similar to the Kruskal-Wallis test. It is a two sided non-parametric test with the null hypothesis that two matrices are independent samples from identical continuous distributions with equal medians, against the alternative that they do not have equal medians. If the null hypothesis of the Kruskal-Wallis and the Ranksum tests are rejected at a significance level of 5% with a p-value lower than 0.05, it is fair to say that the two compared matrices are not from the same distribution and are statistically different (Matlab, 2009).

Every matrix from the control group is compared to every matrix from the patient group for every joint using MATLAB'S ranksum test. The ranksum results are then confirmed via the Kruskal-Wallis test. MATLAB's ranksum test outputs two results: *h* value, *p* value. The *h* value is 1 if the null hypothesis is rejected and 0 if it cannot be rejected at the 5% significance level. The *p* value is the probability of observing an element from the matrix distribution if the null hypothesis is true. If the *h* value is 1, with a p-value lower than 0.05, it is possible to conclude that the matrices of the control group are statistically

different from the matrices of the patient group (Matlab, 2009). The table below demonstrates the two MATLAB outputs from the ranksum test.

Table 4-3: MATLAB's Ranksum Test Results Comparing the Matrix Distributions of the Control and the Patient Group

Joint	Matrix	p-value	h value	Joint	Matrix	p-value	h value
MCP2	STD	0,3828	0	PIP2	STD	0,9346	0
	Skewness	0,0136	1		Skewness	0,1417	0
	Kurtosis	0,9346	0		Kurtosis	0,0962	0
	Mode/Max	0,0105	1		Mode/Max	0,2476	0
	Median/Max	0,0654	0		Median/Max	0,2356	0
	Min/Max	0,7484	0		Min/Max	0,6599	0
	Variance	0,3828	0		Variance	0,9346	0
	Max-Min	0,8171	0		Max-Min	0,5912	0
	(Mode-Mean) ²	0,8521	0		(Mode-Mean) ²	0,2298	0
	Mode/Min	0,0173	1		Mode/Min	0,2021	0
	Median/Min	0,2861	0		Median/Min	0,2356	0
	Mean/Min	0,4603	0		Mean/Min	0,2241	0
MCP3	STD	0,0153	1	PIP3	STD	0,7484	0
	Skewness	0,4786	0		Skewness	0,3360	0
	Kurtosis	0,1969	0		Kurtosis	0,0011	1
	Mode/Max	0,0212	1		Mode/Max	0,3993	0
	Median/Max	0,0361	1		Median/Max	0,3285	0
	Min/Max	0,0047	1		Min/Max	0,4694	0
	Variance	0,0153	1		Variance	0,7484	0
	Max-Min	0,0074	1		Max-Min	0,4162	0
	(Mode-Mean) ²	0,011	1		(Mode-Mean) ²	0,0612	0
	Mode/Min	0,4786	0		Mode/Min	0,4603	0
	Median/Min	0,1055	0		Median/Min	0,7371	0
	Mean/Min	0,0289	1		Mean/Min	0,7371	0
Wrist	STD	0,3747	0	Knee	STD	0,0341	1
	Skewness	0,4248	0		Skewness	0,1585	0
	Kurtosis	0,8404	0		Kurtosis	0,2508	0
	Mode/Max	0,3993	0		Mode/Max	0,2226	0
	Median/Max	0,0796	0		Median/Max	0,0318	0
	Min/Max	0,1226	0		Min/Max	0,0027	1
	Variance	0,3747	0		Variance	0,0341	1
	Max-Min	0,1121	0		Max-Min	0,0026	1
	(Mode-Mean) ²	0,8697	0		(Mode-Mean) ²	0,6635	0
	Mode/Min	0,2129	0		Mode/Min	0,0072	1
	Median/Min	0,4973	0		Median/Min	0,0069	1
	Mean/Min	0,4077	0		Mean/Min	0,0128	1

*MCP2 represents the 2nd MCP, MCP3 represents the 3rd MCP and thusly for the PIP joints.

Note that the Kruskal-Wallis results yield the same results as the ranksum test, thereby verifying the hypothesis test results above.

The table above highlights in gray the matrices where the null hypothesis is rejected at a significance level of 5% with a p-value that was lower than α . These highlighted test results are the ones that were successful in discriminating between the control group and the RA group matrices. Objective one is therefore satisfied since:

- 1- the skewness, mode/max, mode/min matrices of the 2nd MCP are statistically different distributions for the control and patient group;
- 2- The standard deviation (STD), mode/max, median/max, min/max, variance, max-min, (Mode-Mean)², Mean/Min matrices of the 3rd MCP show a statistical difference between the control and patient distributions;
- 3- The control group's kurtosis matrix of the 3rd PIP is statistically different than the patient's kurtosis matrix of the 3rd PIP;
- 4- The standard deviation, min/max, variance, max-min, mode/min, median/min, mean/min matrices of the knee are statistically different distribution for the control and patient group.

To graphically see the difference between the control and patient matrices, histograms are created for a selected matrices mentioned above. These histograms are included in Appendix E, but an example is shown below. The histograms clearly show that the matrix of the patients is shifted differently compared to the matrix of the control subjects. The bin containing the most

elements for the control group is never the same as the bin containing the most elements for the patient group. See example below.

Figure 4-1: Histogram of the Mode/Max Matrix for the 2nd MCP

The histogram shows that the control subjects' 2nd MCP mode/max matrix is shifted to the left whereas the patient's mode/max matrix is more shifted to the right. The bin containing the most elements in the control's matrix is the 0.997 bin whereas the bin containing the most elements in the patient's matrix is 0.999. It is clear that the distributions of the mode/max matrix can distinguish between the control and patient groups.

To further satisfy objective one, the binary images that are produced using MATLAB's *roicolor* function are explored. This function highlights (drives to 1) all the pixels of the TIR image that are within the temperature range from mode to max; and drives to 0 all the pixels outside of that range. The tables below show

the resulting images that are produced by MATLAB'S *roicolor* function for some control subjects and some patients.

Within the control group it is obvious from the binary images below that the knee gradient, as previously discussed in the literature review, are positive from the patella to the inside of the flexed knee. In other words, the patella region has a low thermal temperature and this temperature increases as you get closer to the inside of the flexed knee where the temperature is the warmest. Moreover, there are no evident hot regions within the ROI. It is therefore possible to show via these binary images that control subjects could be identified with a uniform positive temperature gradient and with the absence of evidently abnormal hot regions.

Table 4-4: Grey Images and their Corresponding Binary Images of Control Subjects

From the binary RA patient images below, it is clear that the patient's temperature distribution gradient from the patella to the inside of the flexed knee is not always uniform or positive. In many cases the temperature gradient has spikes and is negative (going from coolest to warmest). Moreover, there are obvious hot spots throughout the joint. It is possible to show via these binary images that RA patients could be identified with a non-uniform temperature gradient and with the presence of abnormal hot regions.

Table 4-5: Grey Images and their Corresponding Binary Images of Patients

The non-uniform and negative thermal gradients seen in the RA patient's images can be explained by the increase in vascularity caused by synovitis and the proliferation of the synovial cells – the pannus. Blood is also shunted from the deep circulation to the subcutaneous circulation also adding to the increase in temperature at the surface of the joint (Nielsson 1980, 516-528). In RA, there are also chemical mediators and an increase in chemical activity within the intra-articular joint due to the inflammation process as explained in chapter 1. All of these pathophysiological aspects can explain the abnormalities seen in the patient TIR images.

Since a visual difference is clear between the control and patient groups, statistical hypothesis tests are applied. The percentage of the pixels highlighted (driven to 1) within the joint surface area was calculated for each patient and control. This percentage represents the area of the joint that contained warmer pixels and/or hot spots. The tables below show the percentages extracted from these binary images for both groups.

Table 4-6: Percentage of Pixels Within the Range Mode to Maximum Temperature Representing the Area of the Joint that is Covered with Warmer Pixels and/or Hot Regions

	Participant #	Number of Pixels within the ROI	Number of Pixels within the Range Mode to Max	%
Control Group	1	8057	2104	26,11
	2	7414	1986	26,79
	3	10972	4737	43,17
	4	12856	4525	35,20
	5	14813	4690	31,66
	6	10753	2774	25,80
	7	9144	5079	55,54
	8	10961	4863	44,37
	9	11531	6587	57,12
	10	16445	9582	58,27
	11	11287	5184	45,93
	12	10706	6459	60,33
	13	9883	2570	26,00
	14	12221	5261	43,05
	15	9046	5688	62,88
	16	10209	2342	22,94
	17	10467	3913	37,38
	18	11969	5976	49,93
	Average % of Control Group			41,80
Patient Group	1	14238	3660	25,71
	2	15852	5743	36,23
	3	14238	10001	70,24
	4	9155	3856	42,12
	5	9673	1664	17,20
	6	14064	2656	18,89
	7	11105	3781	34,05
	8	14081	5422	38,51
	9	11868	7201	60,68
	10	11840	2876	24,29
	11	14216	4818	33,89
	12	7948	2367	29,78
	13	11149	6043	54,20
	Average % of Patient Group			37,37

The control group has more pixels driven to one within the knee region, or a higher percentage covering the knee region, since its mode temperature is generally lower than that of the patient group. Therefore, from the table above, it is possible to state that more pixels fall in the range mode to maximum temperature for the control group than for the patient group.

MATLAB's ranksum test is then applied to the control and to the patient percentage matrix distributions to see if they are statistically different at a significance level of 5%. The ranksum test outputs are h equals 0 and p equals 0.2888. The null hypothesis is not rejected; therefore the percentage of the joint that has warmer pixels and/or hot spots cannot be used to statistically discriminate between the patient and control group. In conclusion, the binary image can only be used as a visual tool to discriminate between control and patient TIR image.

To complete the overall analysis of objective one, a cluster chart is created to identify a potential threshold that could distinguish between the control samples and the patient samples. Since the 2nd MCP's mode/max matrix gave great statistical significant results (using the ranksum test above), its matrix element values were used for the cluster chart. The graph below is the cluster chart of the mode/max matrix of the 2nd MCP joint of the control and patient group.

Figure 4-2: Cluster Chart of Mode/Max Matrix of the 2nd MCP of the Control and the Patient Groups

From this graph, one can see that the highest density of the control group lies around 0,99625 and the highest density of the patient group lies around 0,99825. The averages do not represent the highest density for both groups since many outliers with extreme values do not follow the trend of their respective groups. Explanation for these outliers can be a failure to comply with protocol procedures, the influence of medication or a bad imaging session (imaging technician's error). Therefore, using the high density groupings for the patients and the control subjects, a potential threshold can be seen at around 0.997 to discriminate between the groups.

As this project continues to gather more samples, this threshold will become more and more evident, eliminating the outliers and putting more emphasis on the highest density region of each group. With the small sample set that this thesis is using, an exact value cannot be determined; however, the cluster graph clearly shows that a density trend is forming to see that a threshold will be able to be identified in the future with additional samples.

The results of the matrices extracted from the raw measurements of the TIR image, the visual highlights of the warmer and/or hot spot regions covering the joint of the binary images, and the potential thresholds of the cluster graphs show that it is possible to conclude that the first objective has been satisfied. There are many matrices (listed above) that are able to statistically differentiate at a 5% significance level between the control distribution and the patient distribution. Histograms of these matrices graphically confirm this differentiating capacity. The visual binary images clearly show that a patient could be identified with the presence of hot spots and by a negative temperature gradient from the patella of the knee to the inner flexed knee. The cluster graph demonstrates that a threshold is forming to discriminate between the control samples and the patient samples.

4.2.2 Second Objective – Identify the Best Joints that Best Determines whether a Participant has RA

From the normality Lilliefors tests completed in the first objective, it is assumed that all matrices extracted from the raw measurements are not normally distributed. Therefore, to complete the second goal of the thesis, non-parametric hypothesis tests are used once again. The same ranksum tests are applied to the matrix distributions of the control group and the patient group as explained in the first objective. The results are displayed once again in Table 4.3 from the first objective section.

From the ranksum hypothesis test results displayed in Table 4.3 it is possible to see that the matrices of the 2nd PIP, the 3rd PIP and the wrist cannot differentiate between the control distributions and the patient distributions. Only the kurtosis matrix of the 3rd PIP shows statistically significant results. The joints that best distinguish between the control and patient groups are the 2nd MCP, the 3rd MCP and the knee, since they have many matrices that discriminate between the control and patient distribution at a significance level of 5%.

Refer once again to Appendix E to graphically view the histograms of the matrices of the best representative joints. These histograms show that within the 2nd MCP, 3rd MCP and knee, the matrices of the patients are shifted differently compared to the matrices of the control subjects. The bins containing the most elements for the control group is never the same as the bins containing the most elements for the patient group. One histogram example is shown below.

Figure 4-3: Histogram of the Mode/Max Matrix of the 3rd MCP

Again, this histogram shows that the control subjects' 3rd MCP mode/max matrix is shifted to the left, whereas the patients' mode/max matrix is shifted to the right. The bin containing the most elements in the control's matrix is the 0.9895 bin whereas the bin containing the most elements in the patient's matrix is greater than 0.9975. It is clear from the histogram above that the distributions of the mode/max matrix of the 3rd MCP can distinguish between the control and patient groups.

Several factors could explain the fact that the PIP joints do not show better statistical results is its small area. The average amount of pixels within the PIP joint is 435 pixels compared to 12 243 pixels in the knee joint. This smaller region makes it more difficult to observe an abnormal thermal distribution and to observe the presence of irregular hot/cold spots. Furthermore, the wrist is taken from the posterior view of the frontal plane. This view might not result in the best

representation of the intra-articular temperature because of barriers that prevent the dissipation of heat to the surface of the skin – for example, hair (especially in men participants) and the pisiform bone. This view is chosen over the anterior view of the frontal plane because in the anterior view the carpal tunnel, containing nerves and ligaments, covers the joint creating more of a barrier for the intra-articular heat to dissipate to the surface of the skin. Other views could be explored to find a better representation of the intra-articular joint of the wrist.

The hypothesis stated in chapter 3 that the MCPs and the knees are the best joints in a clinical setting to best determine if a participant has or does not have RA is therefore accepted. The second objective is therefore satisfied since the matrices of the MCPs and the knees were able to discriminate between the control group and the patient group.

4.2.3 Third Objective – Identify the Matrix that Best Assesses the Presence or Absence of RA

The same ranksum test results are used to satisfy the third objective of this thesis. Referring to the results displayed in Table 4.3, it is possible to identify which matrices extracted from the raw measurements of the TIR images best distinguish between the control and patient groups. Using the best representative joints found in objective two, the mathematical matrices that best rendered statistical differences between both groups are the maximum temperature minus the minimum temperature (max-min), the variance (standard

deviation squared) and the ratio between the mode and maximum temperatures (mode/max). The first and second mathematical matrices – max-min and variance – represent the range and the dispersion of the thermal distribution within the joint. The third mathematical matrix – mode/min – can represent abnormal hot regions that characterize RA disease.

Appendix E graphically displays the histograms of the best representative matrices of the best representative joints (objective two). These histograms show that max-min, mode/max and variance matrices of the 2nd MCP, 3rd MCP and knee can distinguish between the patient and control groups. Their respective histograms are shifted differently and their bins containing the most elements are always different and far apart. One histogram example is shown below.

Figure 4-4: Histogram of the Variance Matrix of the Knee

This histogram shows that the control subject's knee variance matrix is shifted to the right whereas the patient's variance matrix is shifted to the left. The bin containing the most elements in the control's matrix is the 0.385 bin whereas the bin containing the most elements in the patient's matrix is the 0.205 bin. It is clear from the histogram above that the distributions of the variance matrix can distinguish between the control and patient groups.

All the histograms of the best representative matrices found in Appendix E had outlier elements found in the last bin. In all cases but one, the outliers have extremely high values that skew the shape of the histogram. These outliers could be the result of a failure to comply to all the TIR imaging protocols (such as applying lotions to the skin, doing physical activity prior to the session), or a failure to comply to recording protocols (such as body parts touching other body parts causing heat transfers that are reflected at the surface of the skin). Another variable that could have caused outlier elements in the patient group matrices is the influence of first or second line medications taken by the patient. These medications may be in their trial mode, or may be taken because of a flare period. The influence and effect of these first and second line medications are unknown at this stage of the study. In future work on this project, it is expected that these outliers will have less of an impact on the matrix since more participants will be imaged to increase the sample size of the study.

The hypothesis stated in the previous chapter that dispersion matrices will statistically distinguish between the control and patient group can be accepted. In addition to the dispersion matrices – variance and max-min - is the mode/max

matrix that can also statistically differentiate between both group distributions. This can be explained by the fact that abnormal TIR images are not only characterised by their non-uniform thermal distribution, but also by the presence of hot spots. The presence of a hot spot increases the value of the mode temperature, thus making the patients mode/max ratio generally smaller than that of the control group. The third objective is therefore satisfied since the mode/max, the variance and the max-min matrices of the MCPs and the knees were able to discriminate between the control group and the patient group.

The matrix distributions from Table 4-3 that did not reject the hypothesis tests (in others words, they rendered an h value of 0) cannot be used to discriminate between the control and the patient groups. They could not reject the null hypothesis that two matrices are independent samples from identical continuous distributions with equal medians. Therefore the control matrix and the patient matrix have identical distributions with equal medians. Since the matrices are not statistically significant in the context of differentiating between the control subjects and the patients, they cannot be used to answer objectives 4 and 5. Only the matrices that rejected Matlab's ranksum hypothesis test at a significance level of 0.05 can be explored for objectives 4 and 5. Those matrices are the variance, the max-min and the mode/max matrices. Utilising these matrices will statistically validate the results obtained from objectives 4 and 5.

4.2.4 Fourth Objective – Classify RA Patients into Three Severity Groups

First, the patients were classified into three RA severity groups – high, moderate and low. Dr. Jacob Karsh is the specialist who identified each patient within the RA group. His classification is as follows:

Table 4-7: Physician's Assessment of Each Patient and their Corresponding RA Severity Group

Patient #	Sexe	RA Severity	Age
1	M	Low	65
2	F	Low	58
3	M	High	84
4	F	Low	64
5	F	Low	44
6	M	Low	71
7	F	High	79
8	F	Low	40
9	M	Low	68
10	F	Moderate	69
11	F	Moderate	67
12	F	Low	53
13	F	Moderate	64

The patients in the High group are ranked 1 and 2. The patients in the Moderate group were ranked 3, 4 and 5. The rest of the patients in the Low group were ranked from 6 to 13.

Second, the patient's 2nd MCP mode/max matrix is selected for this test since its p-value is very small compared to the variance and max-min matrices. Its p-value is 0.0105 and therefore should strongly represent the degree of severity of the illness of the patients. The table below shows the patient's 2nd MCP mode/max matrix elements ranked from highest to lowest according to their

values. The highest value is given a rank of 1 and the lowest value is given a rank of 13.

Table 4-8: Ranking of the Patient's 2nd MCP Mode/Max Matrix

Patient #	Mode/Max Matrix Elements	Ranking of Mode/Max (from Highest to Lowest)
1	0,99541	12
2	0,997933	4
3	0,998104	2
4	0,997877	5
5	0,998019	3
6	0,990813	13
7	0,997116	8
8	0,997264	7
9	0,99646	10
10	0,996009	11
11	0,996868	9
12	0,997396	6
13	0,998684	1

**This data is taken from the right hand of the patients*

The Spearman Correlation Coefficient is then used to see the extent to which the physician's ranking of severity correlates with the mode/max matrix ranking of the patient (Salvatore, 2002). The Spearman Correlation Coefficient states:

$$SpearmanCoeff = 1 - \frac{6 \sum D^2}{n(n^2 - 1)} \quad (4.2)$$

where D is the difference in rankings and n is the number of samples. The closer the coefficient to 1 the more correlated the rankings. The table below displays the calculations of the Spearman Correlation Coefficient between the physician ranking and the matrix ranking.

Table 4-9: Spearman Correlation Coefficient Calculation Between the Physician Ranking and the Matrix Ranking

Patient #	Mode/Max Matrix Elements	Mode/Max Matrix ranking of Patients	Physician Ranking of Patients by RA Severity	D	D²
1	0,99541	12	12	0	0
2	0,997933	4	7	3	9
3	0,998104	2	1	-1	1
4	0,997877	5	8	3	9
5	0,998019	3	6	3	9
6	0,990813	13	13	0	0
7	0,997116	8	2	-6	36
8	0,997264	7	10	3	9
9	0,99646	10	11	1	1
10	0,996009	11	5	-6	36
11	0,996868	9	4	-5	25
12	0,997396	6	9	3	9
13	0,998684	1	3	2	4

The sum of D^2 is 148 and n 's value is 13, giving a Spearman Correlation Coefficient of 0.593. Since the coefficient is above 0.5, it is possible to state that mode/max matrix elements for the 2nd MCP joint are strongly correlated to the physician's severity classification.

The same analysis is repeated with the patient's 3rd MCP mode/max matrix (p-value of 0.0212), to see if its ranked elements highly correlate with the physician's severity classification. The Spearman Correlation Coefficient calculations resulted in a D^2 of 192 giving a coefficient of 0.473. Since the coefficient is lower than 0.5, it is possible to state that the mode/max matrix elements for the 3rd MCP joint are correlated more weakly to the physician's severity classification.

The same analysis is repeated one more time with the patient's Knee variance matrix (p-value of 0.0341), to observe whether the ranked elements highly correlate with the physician's severity classification. The Spearman Correlation Coefficient calculations resulted in a D^2 of 169 giving a coefficient of 0.536. Since the coefficient is above 0.5, it is possible to state that the knee is also correlated strongly to the physician's severity classification. However, it is important to note, that the knee's correlation coefficient was lower than the 2nd MCP's correlation coefficient. Therefore, the strongest correlation found was the correlation of the patient's 2nd MCP mode/max matrix; which correctly classified the patients within their severity group at a Spearman Correlation Coefficient of 0.593. The graph below graphically demonstrates with increased RA severity there is an increase in the average mode/max value.

Figure 4-5: Average of the Patient's 2nd MCP Mode/Max Matrix Elements by Severity Group

The graph therefore confirms that the patients can be classified into three severity groups using the patient's 2nd MCP mode/max matrix ranking. The fourth objective is therefore satisfied, since the patient's 2nd MCP mode/max matrix ranking highly correlations with the severity rankings of the physician with a Spearman Correlation Coefficient greater than 0.5.

4.2.5 Fifth Objective – Observe the Effect of Age on Thermal IR Matrices

In an attempt to explain the small overlap of elements between the patients and the older control subjects observed in the histograms of Appendix E, the effect of age on the matrices was studied. The Spearman Correlation Coefficient is used to see the extent to which the control subjects' age correlates with the mode/max matrix of the 2nd MCP of the control group. Again, the control's 2nd MCP mode/max matrix was chosen for its low p-value (p equals 0.0105) and its success in distinguishing between the control and patient groups (objectives 1 through 3). The table below shows the control subjects and their corresponding age groups.

Table 4-10: Control Subjects with their Corresponding

Control #	Sexes	Age Group
1	F	20-30
2	F	10-20
3	F	20-30
4	M	20-30
5	M	20-30
6	M	50-60
7	F	50-60
8	M	40-50
9	M	60-70
10	F	60-70
11	M	20-30
12	M	20-30
13	F	20-30
14	M	30-40
15	F	20-30
16	M	20-30
17	F	60-70
18	M	60-70

First, the control subjects are ranked according to their age group. The control subjects in the 60-70 age group are ranked 1, 2, 3 and 4. The control subjects in the 50-60 age group are ranked 5 and 6; and so on.

Second, the control subjects are ranked according to their 2nd MCP mode/max matrix value. The table below shows the control subject's 2nd MCP mode/max matrix elements ranked from highest to lowest according to their values. The highest value is given a rank of 1 and the lowest value is given a rank of 18.

Table 4-11: Ranking of the Control's 2nd MCP Mode/Max Matrix

Control #	Mode/Max Matrix Elements	Ranking of Mode/Max (from Highest to Lowest)
1	0,997819	5
2	0,996318	9
3	0,99797	4
4	0,996923	7
5	0,996463	8
6	0,996196	11
7	0,996057	13
8	0,994762	17
10	0,998375	3
11	0,995535	15
12	0,998791	1
13	0,995277	16
14	0,996206	10
15	0,997702	6
16	0,996122	12
17	0,995632	14
18	0,998566	2

The same equation (4.2) is used to calculate the Spearman Correlation Coefficient between the ranking of the control subjects done by age group and the ranking of the control subjects done by the values of the 2nd MCP's mode/max matrix elements. The table below displays the calculations of the Spearman Correlation Coefficient.

**Table 4-12: Spearman Correlation Coefficient Calculation
Between the Age Ranking and the Matrix Ranking**

Control #	Mode/Max Matrix	Mode/Max Matrix ranking of Control subjects	Ranking of Control subject by Age Group	D	D²
1	0,997819	5	10	5	25
2	0,996318	9	17	8	64
3	0,99797	4	9	5	25
4	0,996923	7	12	5	25
5	0,996463	8	13	5	25
6	0,996196	11	4	-7	49
7	0,996057	13	5	-8	64
8	0,994762	17	6	-11	121
10	0,998375	3	2	-1	1
11	0,995535	15	15	0	0
12	0,998791	1	8	7	49
13	0,995277	16	16	0	0
14	0,996206	10	7	-3	9
15	0,997702	6	11	5	25
16	0,996122	12	14	2	4
17	0,995632	14	3	-11	121
18	0,998566	2	1	-1	1

The sum of D^2 is 608 and n 's value is 18, giving a Spearman Correlation Coefficient of 0.255. Since the coefficient is very low it is possible to state that age is associated weakly with the mode/max matrix of the control group. However, a coefficient of 0.255 is enough to explain the small overlap that is seen between the matrices of the control and the patient group.

The graph below shows that an increased age does not necessarily lead to a higher average mode/max value. The average mode/max value is not highly correlated to age.

Figure 4-6: Average of the Control's 2nd MCP Mode/Max Matrix Elements by Age Group

From the graph above, it is possible to visually see that the correlation is low between the control subject's age and their average mode/max matrix elements. The older age group does not necessarily equate to a higher mode/max reading from the TIR image. However, the 0.255 value can be due to the 60 and over age group, where it is obvious that the average TIR's ratio of mode/max is above the rest of the age groups. Therefore, the over 60 age group may explain the small overlap that is seen between the patient and control samples in the histograms of Appendix E.

An interesting finding is that, the mode/max matrix of the 2nd MCP within the patient group had a Spearman Correlation Coefficient of 0.402 with the age of the patients. This suggests that in the presence of disease, a degenerative factor, the severity RA amplifies the abnormal results of the RA patients.

The pathophysiology of RA can support the statement that with age, a degenerative factor can affect the outcome within the patient group. As previously explained in the first chapter, severe RA causes joint deformity as well as bone destruction. Age and the overuse of the body's joints will make the joint more susceptible to bone destruction and joint deformity. These physiological changes will increase the inflammation of a joint and thus increase the subcutaneous temperature of an affected RA joint.

The fifth objective is met, since the correlation between the ranking of the control subjects by their 2nd MCP mode/max matrix elements and by their age group was studied. It was possible to observe that age does not have much of an effect on the matrices of the control group. However, the Spearman Correlation Coefficient is 0.402 between the ranking of the patients by their 2nd MCP mode/max matrix elements and by their age group. Although the Spearman Coefficient is not greater than 0.5, it is high enough to suggest that there is a weak age-degenerative factor that influences the RA measurements of the patients.

The final chapter of this thesis states the conclusions that can be made from the results and the analysis above, the contributions made to knowledge and suggests future work.

CHAPTER 5

5 CONCLUSION

This chapter states the contributions to knowledge of this thesis work. It will end with some proposed future work.

5.1 Contributions to Knowledge

The first contribution to knowledge was the completion of objective one, that is, the thesis showed that the ratio/difference/dispersion matrices represent correctly the thermal distributions on the surface of the skin. These matrices can distinguish between the temperature distribution of the control group and of the patient group. Moreover, a new method of visually observing the thermal distribution and the presence of hot regions on the knee is presented. Binary images are created using MATLAB's *roicolor* function and they visually illustrate a difference between the control and patient TIR images. The patients' binary images have negative temperature gradients from the patella to the inside of the knee and have abnormal hot regions present. Finally, by representing a highly statistical significant matrix (the 2nd MCP'S mode/max matrix) in a cluster graph this thesis demonstrates a threshold to be determined to clearly discriminate

between the control and patient groups. Distinct highly dense regions were visible in the patient cluster and in the control cluster.

The second contribution to knowledge was the identification of the joints to examine in a clinical setting that best determine if a participant has or does not have RA. The best joints are the 2nd MCP, the 3rd MCP and the knee. These joints statistically showed at a significance level of 5% that they were able to differentiate between the control's matrix measurements and the patient's matrix measurements. This was proven using the non-parametric ranksum and Kruskal-Wallis tests.

The third contribution to knowledge was the identification of the best mathematical calculations of the data to assess the difference between a control and a RA patient. A wide variety of dispersion, ratio and difference matrix distributions were analysed and statistically tested. The best representative matrices of RA are the matrices that characterize the dispersion measurements of the distribution and the matrix ratios that can distinguish between the presence or absence of high temperature regions (via the mode temperature). The best dispersion measurement matrices are the variance and the max-min matrices; and the best matrix representing high temperatures is the mode/max matrix. This was again demonstrated using the non-parametric ranksum and Kruskal-Wallis tests.

The fourth contribution to knowledge was to succeed in classifying the RA patients into three severity groups using the best representative matrix (objective three) of the best representative joint (objective two). The patient's 2nd MCP

mode/max matrix was proven to correlate strongly with the physician's RA severity ranking of the patients; thus proving that the elements within this matrix could be used to classify the RA patients into high, moderate and low severity groups. This was proven using the Spearman Correlation Coefficient.

The final contribution to knowledge was the study of the effect of age on the thermal IR measurements and the resulting calculated matrices. The thesis found that within the control group, age correlates weakly to the 2nd MCP'S mode/max matrix. It is possible to state that age does not greatly affect the extracted measurements of the control's TIR images. Within the patient group, the thesis found that there is a weak but noticeable correlation between the patient's age and their measurements results. Based on this, the thesis found an age-degenerative factor in the patients' RA measurements.

5.2 Future Work

To further the thermal infrared imaging work of the MIRG's research team, it would be necessary to collect data on more patients to increase the sample size of the database. During these imaging sessions, it is recommended to have fixed cameras for imaging to standardize the distance and the zoom of the recorded images. This would allow the amount of pixels within each ROI to be identical in order to more easily compare the analysis results.

Applying image processing techniques to the TIR images would have been useful to eliminate surface effects, such as hair (especially within the ROIs

of male participants' knees and wrists). Filtering and image enhancing techniques could be explored to improve the data extraction for analysis.

Further analysis should be done to refine the assessment of age on the measurements and the calculated matrices. The participants in the control group should also be chosen to represent the RA patient group with respect to age. In this thesis, 70% of the patients imaged were above the age of 60 and only 22% of the control subjects were above that age.

In the future, it would be important that patients be assessed by the physician on the day of the imaging session or soon after/before the imaging session. This would provide necessary medical information with regards to their RA state – “are they in a flare period, are their medications effective in controlling inflammation”, etc. This additional information would serve to further classify patients by severity and would better explain outliers or extreme results. This thesis did not compare IR results with a recent physician's physical examination and therefore did not have all the information to complete an in-depth analysis of the pathophysiology and corresponding RA samples.

Repetitive imaging sessions should also be done to assess the effect of medication on the intra-articular temperature and disease progression. This effect can be assessed by doing repetitive imaging sessions on the same patients during a determined treatment period to quantify via TIR the pain and inflammation of the treated joints. A longitudinal comparison can be made, comparing the thermal IR distribution of the first set of images with the successive ones.

Correlation of IR imaging results should be statistically compared to RA diagnosis gold standards such as MRI and HRUS, which are tools that can correctly classify the normal versus the RA patient. This would further solidify the conclusions stated in this thesis. This comparison would also assess if IR technology can detect inflammation as early on in the disease as MRI and HRUS. As discussed in the introductory chapter, detecting inflammation early would assist in diagnosing RA before the manifestation of clinical symptoms and improve the prognosis of the patient.

As previously stated, this thesis is the first step of a research project that will incorporate multi-spectral imaging to IR imaging as a diagnostic tool for RA disease. This research project will therefore continue with the following objectives. First, incorporating Christophe Herry's work to the IR system would allow the incorporation of automated segmentation and automated extraction of ROI. Future work would also include an automated detection of anomalies within the selected ROI and a classification mechanism between normal and abnormal. The automated system that is envisioned is shown in the figure below.

Figure 5-1: Block Diagram of Christophe Herry's Thesis Research (2008)

Second, to improve the efficiency of the thermal IR diagnostic tool, IR imaging will be combined with multi-spectral imaging to increase its sensitivity and specificity of diagnosis. Multi-spectral imaging would take a sequence of videos with visual cameras to assess the range of motion and level of mobility of the extremities and joints in patients with RA. This would combine two important diagnostic parameters: the distribution and state of the inflamed joints (via IR imaging) and the limitation of motion of the joints (via multi-spectral imaging). This combination of imaging tools would be a highly innovative and promising tool that would be a reliable, quantitative and reproducible means of assessing RA. The ultimate goal is to combine thermal IR technology and multi-spectral imaging and applying it to clinical settings to become a diagnosis-aid that is safe, efficient, inexpensive and easy to operate, and that can be used in health care settings worldwide.

This thesis makes the thermal infrared imaging tool even more a reality as a possible inexpensive, non-invasive and efficient method to diagnose RA. There is more to be explored with thermal infrared technologies; but thus far the results are very promising. One day thermal infrared systems can have a large impact on the quality of life of RA patients, on the Canadian Health Care System and on society as a whole.

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7 APPENDIX A

Permission Text for Potential Participants

Title: Severity of illness measures in rheumatoid arthritis from multi-spectral imaging

I agree that my name and contact information be released to the researchers of the rheumatoid arthritis imaging research project: Dr. Monique Frize, Dr. Pierre Payeur, and their graduate students: Cynthia Lecavalier and Daphne Townsend.

Name (please print): _____

Signature: _____

Contact information:

Address: _____

Email address: _____

Telephone numbers: Home _____
 Office _____
 Fax _____
 Cellular _____

You may contact the student co-investigator Cynthia Lecavalier at (613) 520-2600 ext 5586 or email: clecaval@connect.carleton.ca.

8 APPENDIX B

Research Participant Information and Consent Form

You are being asked to participate in a research study using an infrared (IR) camera (heat images) to determine temperature measurements of limbs. In addition, a series of color pictures using a digital camera will be taken to assess the level of mobility of extremities and joints. The research will be conducted at the University of Ottawa and will be scheduled at a convenient time.

The information collected will not contain pictures of the face and will be kept anonymous.

Purpose and Design

Rheumatoid arthritis affects 300,000 Canadians each year; it involves inflammation and symptoms like redness, swelling, heat, and pain. In this study, we plan to measure the temperature of the joints of patients diagnosed with rheumatoid arthritis and of participants without rheumatoid arthritis using an infrared camera. The assumption is that the infrared pictures of the rheumatoid arthritis patients will show inflammation of tissue or joints. A second test to be

conducted at the same time is the taking of video pictures with digital cameras to assess the extent of movement of extremities and joints of both groups: patients with rheumatoid arthritis and healthy participants. This is a pilot project to assess whether these two types of tests can be helpful as an aid to the early diagnosis of rheumatoid arthritis. These tests may also help to monitor therapy in joint debilitating diseases.

Approximately 15 patients will be involved in this pilot study and 20 to 30 normal subjects.

Because the skin surface temperature variations are extremely subtle and sensitive to environmental changes:

- Do not use talcum powder, lotion, drug or deodorant on the skin on the day of the session.
- Do not consume alcoholic beverages 12 hours prior to the session.
- Do not consume hot beverages at least 1 hour prior to the session.
- Do not use procedures such as acupuncture, transcutaneous electrical stimulation (TENS machine), hot or cold patches, or any other form of physiotherapy at least 24h prior to the session. You should not do any intense physical exercises at least 4 hours prior to the session
- Avoid prolonged sun exposure for at least one week prior to the session.
- Do not smoke at least 2 hours prior to the session.
- Do not wear any rings, necklaces, and bracelets during the session.

The session will take place in a room with the following characteristics:

- Without windows or with covered windows to avoid any reflection.
- Constant uniform temperature between 20 and 25.
- Constant humidity.
- Fluorescent lights.

You will be asked to come to the biomedical laboratory of Dr. Monique Frize at the University of Ottawa (Colonel By Building, Room C507) at a mutually convenient time. Both types of cameras will be available at that location. You need to wear shorts and short sleeve shirt (or change into these in a nearby bathroom).

The skin has to cool at room temperature for 10-15 minutes; then pictures are taken of the joints, hands, feet. For each body region, you will be asked to assume a position facilitating the imaging. For instance, for images of the hands (palm and back), you will be seated on a chair and will be asked to place your hand over a table. For the under-feet view, you will be seated on a chair and raise your leg, with the ankle resting on a stool. For other views, you will be standing.

You will also be asked to move your hands, elbows, knees and feet from time to time. Sequences of images will be taken with an infrared camera and several regular intra-optical video cameras. Both types of cameras will record the sequences simultaneously.

The imaging session is expected to last approximately 30 minutes.

You may be asked to participate for a maximum of three sessions in order to study the stability of the temperature distribution over time. But this is not mandatory to participate in the study. It is totally voluntary.

Are there any risks?

There are no foreseen risks to participants.

If you are a patient diagnosed with rheumatoid arthritis, the research team will capture images of your body parts affected by rheumatoid arthritis. If you are a healthy volunteer, the research team will capture images of several healthy joints and limbs.

There is no direct contact or risk associated with gathering these images.

Are there any benefits to me if I choose to participate? While there are no immediate benefits for you, this study is expected to provide a useful tool for early diagnosis of rheumatoid arthritis.

How will my confidentiality be protected?

Your name will not be used in any publications that may arise from this study. Only group information will be published. No images of the participant's faces will be taken. The consent forms and images will be stored at Carleton and Ottawa Universities research laboratories of Dr Frize and Dr Payeur containing only numbers as reference. The images will be stored in a protected file with user id and password protection. The data will be destroyed five years after the tests are completed.

Withdrawal from the Study

If you are a patient with rheumatoid arthritis, you may withdraw from the study at any time without any impact to the care you are receiving. You can also choose to have your images withdrawn from the study completely.

If you are a healthy participant, you may withdraw from the study at any time. You can also choose to have your images withdrawn from the study completely.

Study Expenses

If you are a patient, you will be reimbursed for parking or bus expenses to attend the session at the University of Ottawa. If you are a student, no compensation will be needed, as you will be on either campus and there is a free bus service between the two universities.

Questions about the Study

You may ask any questions about the research at any time. If you have questions about the research after you leave today you should contact the student co-investigator Cynthia Lecavalier at (613) 520-2600 ext 5586 or email: clecaval@connect.carleton.ca.

If you have any questions about your rights as a research subject, you may contact the Chairperson of the Ottawa Hospital Research Ethics Board at (613) 798-5555, extension 14902 or the University of Ottawa's Research Ethics Board through the Research Grants and Ethics Services at (613) 562-5841, e-mail ethics@uOttawa.ca.

Consent

I have read this Research Participant Information and Consent Form and have had an opportunity to ask my study doctor and the researchers any questions I had about the study.

My questions and/or concerns have been answered to my satisfaction and I agree to participate in this study. If I decide at a later stage in the study that I would like to withdraw my consent, I may do so at any time.

A copy of the Research Participant Information and Consent Form will be provided to me.

Signatures

Name of Participant (please print):

Signature

Date

Student co-investigator: Cynthia Lecavalier

Signature

Date

9 APPENDIX C

ThermoVision A40M Researcher

IMAGING PERFORMANCE

Field of view/min focus distance 24° x 18° / 0.3 m

Spatial resolution (IFOV) 1.3 mrad

Thermal sensitivity @ 50/60Hz 0.08°C at 30 °C

Focusing Built-in focus motor

Detector type Focal Plane Array (FPA), uncooled microbolometer

Spectral range 7.5 to 13 µm

IMAGE PRESENTATION

FireWire output IEEE-1394 8/16-bit monochrome and 8-bit color

Video output RS170 EIA/NTSC or CCIR/PAL composite video

MEASUREMENT

Temperature ranges

Range 1: -40°C to +120°C (-40 to +248°F)

Range 2: 0°C to +500°C (+32 to +932°F)

Optional: Up to +1500°C (+2732°F)

Optional: Up to +2000°C (+3632°F)

Accuracy (% of reading) ± 2°C or ± 2%

Measurement modes Spot, Area, Isotherm, Difference

Automatic emissivity correction
Variable from 0.1 to 1.0

Individual emissivity settings Individually settable

Measurement corrections Reflected ambient, distance, relative humidity, external optics. Automatic, based on user input

POWER SOURCE

AC operation AC adapter 110/220 VAC, 50/60Hz (included)

DC operation 8-30V nominal, <6W

PHYSICAL CHARACTERISTICS

Weight 1.4 kg (3.0 lbs)

Size 207mm x 92mm x 109mm (8.1" x 3.6" x 4.3")

Tripod mounting 1/4"– 20

ENVIRONMENTAL

Operating temperature range -15°C to +50°C (5°F to 122°F)

Storage temperature range -40°C to +70°C (-40°F to 158°F)

Humidity Operating and storage 10% to 95%, non-condensing

Encapsulation IP 40
(Determined by connector type)

Shock Operational: 25G, IEC 68-2-29

Vibration Operational: 2G, IEC 68-2-6

10 APPENDIX D

10.1 2nd MCP Raw Data Measurements

Table 10-1: Raw Data Measurements Extracted from the Control Group's 2nd MCP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	26,1105	24,6853	25,4597	25,5042	25,4580	0,3534	-0,2794	1,9844
	2	28,3482	25,7030	27,1593	27,1930	27,2386	0,6124	-0,1033	2,1580
	3	27,8476	26,9645	27,3119	27,3050	27,2370	0,1473	0,1713	2,7103
	4	30,0950	28,8796	29,2699	29,1995	29,1624	0,2359	1,1101	3,6497
	5	31,9448	30,4923	31,0995	31,0931	30,8663	0,3064	0,1588	2,2105
	6	34,4558	33,0637	33,6921	33,6296	33,2861	0,3598	0,2760	1,9135
	7	31,9741	30,4487	30,9595	30,8778	30,7716	0,3280	0,5527	2,2921
	8	32,8184	30,8655	31,4970	31,4279	31,2164	0,3612	0,6998	2,8610
	9	x	x	x	x	x	x	x	x
	10	32,9767	31,8570	32,3339	32,3496	32,4796	0,2265	0,0531	2,6858
	11	27,5611	25,9822	26,4582	26,3486	26,2190	0,2976	0,9900	3,1782
	12	27,3503	25,4305	26,5945	26,6153	26,9872	0,4126	-0,3342	2,5027
	13	24,4499	22,1455	23,2691	23,2255	23,0450	0,4804	0,2267	2,3356
	14	26,7441	24,3879	25,5904	25,6069	25,6069	0,4945	-0,0251	2,4962
	15	33,3864	32,3649	32,8731	32,8552	32,6824	0,2387	0,0836	1,9904
	16	29,2447	27,5989	28,1753	28,1477	28,0727	0,3244	0,4250	2,5414
	17	32,5950	30,6676	31,3209	31,2675	31,2602	0,3478	0,7991	3,6520
	18	33,0994	32,1115	32,6186	32,6317	32,6606	0,2271	-0,0597	2,0101
LEFT HAND	1	26,2329	24,2346	25,1966	25,1496	24,9796	0,3884	0,3312	2,7780
	2	27,7155	25,5182	26,6314	26,6605	26,6605	0,5214	-0,0739	2,1749
	3	26,6837	24,7830	25,6857	25,6685	25,4382	0,3921	0,2635	2,5750
	4	29,2590	27,3793	28,2671	28,2519	27,9894	0,3828	0,1800	2,1998
	5	32,2273	30,9688	31,6088	31,6689	31,7851	0,2859	-0,4344	2,1899
	6	34,8808	33,1283	33,9226	33,9366	33,2933	0,4055	0,0045	2,0417
	7	32,8696	31,5455	31,8960	31,8363	31,7854	0,2206	1,3763	5,4255
	8	32,9048	30,4474	31,2677	31,2748	31,1215	0,4350	0,7281	4,1835
	9	x	x	x	x	x	x	x	x
	10	33,5432	31,7408	32,2995	32,2556	32,1687	0,2675	1,2854	5,7058
	11	26,7669	24,6901	25,6044	25,5494	25,5993	0,4262	0,4738	2,7667
	12	26,7445	25,0764	25,8706	25,8524	25,8524	0,3327	0,2228	2,4346
	13	24,2248	21,6849	22,9110	22,8877	22,7302	0,5093	0,0442	2,6394
	14	26,5998	23,6092	25,1774	25,2419	24,7829	0,6574	-0,1606	2,0324
	15	33,5796	32,3577	32,8979	32,9056	32,8696	0,2155	0,3059	3,2486
	16	29,2818	27,7119	28,3897	28,3575	28,2377	0,3109	0,2165	2,4786
	17	31,5299	29,9982	30,7524	30,7996	30,4327	0,3546	-0,1281	2,0290
	18	32,9413	31,8214	32,4148	32,4477	32,4586	0,2620	-0,2772	2,1671
Average		29,9702	28,2454	29,0140	29,0007	28,8952	0,3565	0,2677	2,7130

Table 10-2: Raw Data Measurements Extracted from the Patient Group's 2nd MCP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	34,1853	32,5157	32,9144	32,8760	32,7752	0,2123	1,8015	8,9345
	2	34,3468	32,9070	33,5189	33,5539	33,7114	0,2631	-0,0834	2,7726
	3	33,6470	31,7626	32,7416	32,8710	33,0655	0,4647	-0,2646	1,6601
	4	30,0216	28,3053	29,0348	29,0589	29,3783	0,3849	-0,0057	1,8287
	5	29,8801	28,3182	29,2812	29,3025	29,2802	0,3420	-0,4080	2,4527
	6	31,6099	27,4611	29,1036	28,9679	28,8114	0,9284	0,4308	2,3475
	7	34,1497	32,4363	33,2885	33,2890	33,2639	0,2014	-0,0640	3,8788
	8	32,9120	31,7341	32,2329	32,1835	32,0749	0,2439	0,4930	2,4673
	9	31,2683	29,5413	30,2286	30,2426	30,1911	0,2889	0,0198	2,8278
	10	33,9721	31,4287	32,4823	32,4658	32,7470	0,5197	0,2233	2,3592
	11	33,7791	31,7989	32,5586	32,5878	32,8184	0,3941	-0,0181	1,9991
	12	32,6211	31,3234	31,8121	31,8036	31,8254	0,2546	0,3638	2,7489
	13	28,5139	27,5378	28,0228	28,0569	28,1170	0,1676	-0,5022	2,8177
LEFT HAND	1	33,3571	32,3134	32,7815	32,7824	32,7176	0,1961	-0,0138	2,5599
	2	33,7114	31,8063	33,2150	33,2453	33,5610	0,2907	-0,9527	4,4021
	3	34,1972	27,4902	33,4464	33,4965	33,6399	0,4492	-5,7915	57,5579
	4	30,1469	28,3801	29,5020	29,5117	29,5117	0,2609	-0,3176	3,5379
	5	29,3841	27,5893	28,5867	28,5875	28,4455	0,3419	-0,0962	2,3800
	6	28,5128	26,3002	27,2766	27,2760	26,9391	0,4515	0,1988	2,4525
	7	33,6004	32,1542	33,0773	33,1060	33,0126	0,2997	-0,7272	3,1715
	8	33,0844	31,5378	32,3608	32,4148	32,5808	0,3553	-0,1136	1,9768
	9	31,7268	30,2058	30,9235	30,9103	31,3266	0,3486	-0,0327	1,9586
	10	33,8295	31,6325	32,6355	32,6101	32,4658	0,5274	0,1053	2,0062
	11	33,5289	32,1325	32,9158	32,9982	33,0342	0,3331	-0,4642	2,2452
	12	32,4913	31,4327	31,9641	31,9813	32,0502	0,2404	-0,0672	2,1993
	13	29,1401	28,1920	28,6156	28,5737	28,4391	0,1941	0,3605	2,3810
Average		32,2161	30,3168	31,3277	31,3367	31,3763	0,3444	-0,2279	4,9201

10.2 3rd MCP Raw Data Measurements

Table 10-3: Raw Data Measurements Extracted from the Control Group's 3rd MCP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	25,9880	24,4990	25,2549	25,2653	24,9099	0,3747	0,0264	2,0235
	2	28,8054	27,2082	28,1365	28,1678	28,4833	0,3883	-0,2086	1,9324
	3	28,1704	27,0402	27,6344	27,6595	27,7423	0,2372	-0,2217	2,2984
	4	30,3895	29,2887	29,7749	29,7406	29,6297	0,2470	0,3682	2,2880
	5	31,6907	30,3086	30,8597	30,8224	30,6758	0,3011	0,4344	2,3225
	6	34,3919	32,4155	33,1733	33,0996	33,0206	0,4710	0,5141	2,5070
	7	32,3649	30,7349	31,1827	31,1300	30,9985	0,2778	1,0317	4,2677
	8	31,9513	30,6896	31,1362	31,1361	30,8435	0,2498	0,4963	2,7302
	9	x	x	x	x	x	x	x	x
	10	32,5734	31,5226	31,9505	31,9441	32,0746	0,2118	0,2967	2,5494
	11	27,5762	26,8807	27,1890	27,1761	27,0172	0,1694	0,1757	2,0087
	12	27,8551	26,3108	27,1695	27,1765	27,1538	0,2794	-0,3697	3,2960
	13	24,4112	22,8169	23,6351	23,6326	23,4762	0,3256	-0,0919	2,3508
	14	27,3121	25,8369	26,6115	26,6378	26,7897	0,3297	-0,3488	2,3923
	15	32,9127	32,2348	32,4359	32,4372	32,4516	0,1082	0,5938	3,7834
	16	28,9249	27,2517	27,8189	27,7495	27,6140	0,3378	0,6234	2,6660
	17	32,1180	30,5869	31,0833	31,0338	30,8875	0,2834	0,6766	2,9600
	18	33,1855	32,1260	32,5662	32,5380	32,3719	0,2448	0,3700	2,2187
LEFT HAND	1	27,9548	26,5154	27,2260	27,1995	27,0858	0,3569	0,1274	2,0021
	2	28,8129	27,3523	28,1262	28,1226	27,9042	0,3491	-0,0138	2,1087
	3	27,5616	26,1888	26,8446	26,8432	26,6077	0,2789	0,0939	2,4005
	4	29,6000	28,5288	29,1702	29,1772	29,1327	0,2202	-0,3065	2,3702
	5	32,1622	30,6685	31,1935	31,1442	30,7931	0,3027	0,5650	2,6446
	6	34,4487	32,5815	33,3944	33,4007	33,6511	0,4172	0,0447	1,9892
	7	32,5310	31,3926	31,8374	31,7600	31,5965	0,2727	0,7486	2,4340
	8	31,6390	30,2856	30,7270	30,6750	30,5062	0,2576	0,8266	3,2548
	9	x	x	x	x	x	x	x	x
	10	32,7896	31,5517	32,0198	31,9803	31,8062	0,2510	0,4639	2,5095
	11	27,4707	26,2342	26,8916	26,9186	27,0474	0,2874	-0,2636	2,1485
	12	28,0504	26,6077	27,0681	27,0213	26,9417	0,2551	0,8292	3,6955
	13	24,6359	23,2334	23,9262	23,9291	23,7341	0,3178	0,0527	2,1870
	14	27,2970	25,9669	26,6052	26,5960	26,3715	0,3121	0,1191	2,0681
	15	33,0924	32,3649	32,6331	32,6175	32,5021	0,1386	0,3769	2,5512
	16	29,6376	27,8022	28,5544	28,5221	28,2227	0,3862	0,4670	2,6062
	17	31,5445	30,1088	30,5492	30,4988	30,3739	0,2751	0,9564	3,6453
	18	33,1066	31,7052	32,1949	32,1658	31,9955	0,2696	0,5151	2,7192
Average		30,0869	28,7306	29,3110	29,2917	29,1886	0,2878	0,2932	2,5862

Table 10-4: Raw Data Measurements Extracted from the Patient Group's 3rd MCP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	33,7148	32,7104	33,0718	33,0629	32,9479	0,1634	0,6039	3,7875
	2	34,2114	33,1590	33,6750	33,6971	33,9117	0,2670	-0,0658	1,7664
	3	33,4965	32,6184	33,1865	33,1878	33,1662	0,1218	-0,5207	4,0262
	4	30,0953	28,8356	29,2370	29,1853	29,1036	0,2460	1,5795	5,5391
	5	29,9465	29,0944	29,5748	29,6065	29,6953	0,1492	-0,4995	2,6517
	6	30,5062	29,5176	29,8991	29,9022	29,9392	0,2060	0,4202	2,8930
	7	33,7362	32,7968	33,3208	33,3427	33,5504	0,2495	-0,2523	1,7555
	8	32,7681	31,7849	32,2695	32,2558	32,1835	0,1719	0,0768	2,7501
	9	30,8371	29,6671	30,0733	30,0216	29,9257	0,2342	0,7954	3,1084
	10	33,4865	31,8650	32,2666	32,1839	32,1332	0,2519	1,7503	6,5791
	11	33,3069	31,8498	32,4927	32,4796	32,2917	0,3363	0,2096	2,1556
	12	32,6643	31,6147	32,0417	32,0502	32,1298	0,2147	0,1873	2,3189
	13	28,5438	27,9368	28,2591	28,2519	28,1320	0,1193	0,2457	2,4683
LEFT HAND	1	33,3284	32,5229	32,9428	32,9407	32,9695	0,1485	-0,0659	2,8655
	2	33,3387	32,5822	33,0151	33,0223	32,9863	0,1379	-0,6092	3,3563
	3	34,0902	32,8566	33,6180	33,6542	33,7043	0,2345	-0,8674	3,7121
	4	30,7639	29,3486	29,7821	29,6967	29,6079	0,3071	0,9006	3,0437
	5	29,3915	28,6921	29,0793	29,0833	29,0721	0,1437	-0,2263	2,5309
	6	29,2876	27,8077	28,4814	28,4155	28,1533	0,3390	0,4014	2,1294
	7	33,6648	32,5373	33,1810	33,2208	33,5074	0,2846	-0,4192	2,1694
	8	33,0054	31,5159	32,2548	32,2342	31,8647	0,3351	0,2685	2,1979
	9	31,7994	29,4376	30,1800	30,1137	30,1174	0,4380	0,8169	3,5398
	10	33,4435	32,0100	32,5267	32,4658	32,4514	0,3063	0,6538	2,7593
	11	33,4430	32,1325	32,7466	32,6960	32,9335	0,3346	0,2709	1,9305
	12	32,7076	31,4691	31,9673	31,9560	31,9125	0,2450	0,2584	2,4530
	13	29,4667	28,5811	28,9966	28,9690	28,8349	0,1869	0,3749	2,3855
Average		32,1171	30,9594	31,4669	31,4498	31,4317	0,2374	0,2418	2,9567

10.3 2nd PIP Raw Data Measurements

Table 10-5: Raw Data Measurements Extracted from the Control Group's 2nd PIP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	24,1645	22,9971	23,6758	23,7037	23,8445	0,2556	-0,3692	2,2885
	2	25,0006	23,1654	24,1359	24,1845	24,2547	0,4384	-0,2647	2,0702
	3	26,7065	26,0666	26,4829	26,5088	26,5164	0,1115	-1,0337	4,0433
	4	30,0065	28,8796	29,3577	29,3184	29,1327	0,2651	0,4385	2,2370
	5	32,1622	30,8297	31,6574	31,6398	31,5379	0,2405	-0,1575	2,8235
	6	34,5834	33,4723	34,1562	34,1929	34,2924	0,2280	-0,6434	3,1801
	7	31,9886	30,7496	31,2844	31,2322	30,5379	0,3231	0,2941	1,9904
	8	32,8688	31,7626	32,2721	32,2339	31,9948	0,2631	0,2795	2,0386
	9	x	x	x	x	x	x	x	x
	10	33,1850	32,2049	32,6823	32,6527	32,5734	0,1700	0,2976	2,8805
	11	27,2819	25,7909	26,5397	26,5237	26,4629	0,3256	0,1131	2,3854
	12	25,3306	24,1783	24,6459	24,6205	24,4733	0,2401	0,4108	2,3964
	13	20,7094	20,0162	20,3398	20,3473	20,3876	0,1384	0,1624	2,3345
	14	23,9914	22,4619	23,1525	23,1784	23,2334	0,3645	-0,0143	2,0142
	15	33,9864	32,5310	33,4785	33,5582	33,7368	0,3245	-0,8970	2,9950
	16	29,9628	28,6192	29,2112	29,2521	28,6938	0,3328	0,1190	1,9648
	17	33,1132	31,9078	32,5747	32,5734	32,7968	0,2797	-0,1401	2,1567
	18	32,8550	31,6325	32,1400	32,1187	31,9520	0,2531	0,5517	2,9350
LEFT HAND	1	24,5611	23,3588	24,2386	24,2813	24,2968	0,1766	-1,3103	5,3514
	2	25,1709	22,9999	24,0704	24,0596	23,9346	0,5772	0,0452	1,7740
	3	25,0456	24,4268	24,6976	24,6825	24,5973	0,1102	0,2399	2,7099
	4	28,0119	26,2863	26,9189	26,8721	26,7279	0,3410	0,7798	3,2300
	5	32,4441	31,2902	31,8711	31,8577	31,6252	0,2771	0,0158	1,9755
	6	34,8454	33,8724	34,3417	34,3635	34,4487	0,2062	-0,0742	2,4332
	7	32,3216	30,6763	31,6273	31,6328	31,6328	0,1667	-0,3021	8,1294
	8	32,4074	30,8875	31,6825	31,6754	31,4061	0,3058	0,0217	2,2089
	9	x	x	x	x	x	x	x	x
	10	33,1850	31,8860	32,6281	32,6023	32,6023	0,1756	0,4422	4,8155
	11	25,9287	24,5662	25,0524	25,0377	25,2842	0,2772	0,4919	2,6216
	12	26,3032	25,0147	25,5711	25,5765	25,2613	0,3050	0,2818	2,1821
	13	21,2862	20,4198	20,8147	20,7977	20,7736	0,1853	0,1875	2,1033
	14	24,0771	22,7696	23,2827	23,2647	23,1784	0,2372	0,4446	2,8447
	15	33,4795	32,3143	33,2097	33,2359	33,2144	0,1746	-2,0751	9,1976
	16	29,5043	28,1927	28,5862	28,5295	28,4099	0,2556	1,0043	4,0426
	17	32,0746	30,8948	31,4185	31,4206	31,5372	0,2580	0,1484	2,3501
	18	33,0060	31,7415	32,4962	32,5524	32,6461	0,2759	-0,6364	2,7538
Average		29,1632	27,9077	28,5381	28,5377	28,4705	0,2606	-0,0338	3,0429

Table 10-6: Raw Data Measurements Extracted from the Patient Group's 2nd PIP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	33,2926	32,2483	32,9118	32,9623	33,1060	0,2411	-0,5396	2,3129
	2	34,1900	32,9791	33,7927	33,8259	33,9546	0,2213	-0,9457	3,8211
	3	34,1330	31,9444	32,7004	32,5895	32,3724	0,3737	0,9882	3,5413
	4	29,5561	28,5147	28,9690	28,9548	28,9473	0,2140	0,3809	2,5600
	5	27,8153	26,7037	27,3067	27,3327	27,5667	0,2574	-0,1519	1,9688
	6	28,1608	26,5592	27,1407	27,0831	27,1663	0,3201	0,6853	2,9175
	7	32,6311	30,9753	31,9235	31,9368	31,9803	0,3266	-0,5247	2,8909
	8	33,1992	31,8647	32,6568	32,7105	32,8257	0,3049	-0,8074	3,1125
	9	31,5378	30,0364	30,9003	30,8811	30,6760	0,3150	-0,0482	2,4945
	10	33,3934	31,8722	32,8480	32,9054	31,0276	0,2808	-0,5848	2,8017
	11	33,1563	32,1470	32,6834	32,6599	32,5806	0,2311	-0,0676	2,2293
	12	32,4913	30,2024	32,0495	32,0429	32,0647	0,2236	-2,6959	20,6997
	13	28,0269	26,7279	27,3980	27,3717	27,2962	0,2490	0,0520	2,4629
LEFT HAND	1	34,2493	31,9731	32,7117	32,6095	32,5301	0,4387	1,1993	4,4869
	2	33,3746	31,6606	32,6203	32,5533	32,5172	0,2811	0,1714	2,5976
	3	33,7401	31,7480	32,9545	32,9503	32,9575	0,2852	-0,4021	4,6211
	4	29,4524	28,9548	29,2161	29,2150	29,2150	0,0827	0,2008	3,2241
	5	26,9921	26,0176	26,5885	26,5973	26,4983	0,2146	-0,2251	2,3509
	6	25,9258	24,9185	25,3012	25,2655	25,1962	0,2177	0,5451	2,6524
	7	31,6099	30,6163	31,2975	31,3332	31,3405	0,1795	-1,2540	5,0888
	8	33,2637	31,9953	32,7796	32,7897	32,8185	0,1860	-0,0597	2,9159
	9	31,8430	30,2647	31,2508	31,2391	31,1734	0,2582	-0,4214	3,9464
	10	33,9721	32,3719	33,4775	33,5294	33,8010	0,3385	-0,9874	3,7468
	11	33,3642	32,5012	32,9675	32,9731	33,1563	0,1944	-0,2671	2,2227
	12	33,0959	32,0140	32,5272	32,4480	32,2384	0,2856	0,1967	1,5220
	13	28,6708	27,9593	28,3752	28,3942	28,3942	0,1193	-0,7521	3,4630
Average		31,5822	30,2219	30,9749	30,9675	30,9000	0,2554	-0,2429	3,7174

10.4 3rd PIP Raw Data Measurements

Table 10-7: Raw Data Measurements Extracted from the Control Group's 3rd PIP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	23,9560	22,8315	23,4545	23,4883	23,5784	0,2724	-0,2561	2,0285
	2	25,6722	23,4722	24,6071	24,7215	23,0000	0,5827	-0,2542	1,9003
	3	26,4327	25,7758	26,1384	26,1735	26,7914	0,1542	-0,4916	2,2960
	4	29,8958	29,1847	29,5182	29,4889	29,4074	0,1609	0,3444	2,0702
	5	31,9230	31,0712	31,5652	31,5452	31,3412	0,1746	-0,0039	2,3087
	6	34,6756	33,5295	34,3252	34,3706	34,4629	0,2055	-0,8125	3,2208
	7	31,8943	30,6543	31,4381	31,5019	31,3781	0,2934	-0,7832	2,8567
	8	32,7824	31,2894	32,1107	32,1615	32,4074	0,3824	-0,3170	1,9451
	9	x	x	x	x	x	x	x	x
	10	32,9264	31,9948	32,6008	32,5842	32,5446	0,1580	-0,2833	3,4714
	11	27,4329	26,1121	26,6480	26,6150	26,3257	0,2813	0,5239	2,5163
	12	26,7825	24,8989	25,6722	25,5841	25,4152	0,4094	0,8409	3,0632
	13	20,8057	19,9920	20,3610	20,3392	20,5808	0,2136	0,2387	1,8638
	14	25,0377	22,5075	24,4511	24,4955	24,6901	0,3179	-0,5689	2,6252
	15	33,5939	32,6392	33,2103	33,2574	33,3148	0,2038	-0,4816	2,4218
	16	29,8668	29,2224	29,5288	29,5266	29,4376	0,1231	0,0798	2,2274
	17	32,2917	30,8289	31,7511	31,7590	31,5153	0,2921	-0,3078	2,4830
	18	33,0563	32,5820	32,4068	32,4152	32,5380	0,3051	0,0117	2,0030
LEFT HAND	1	25,0723	24,1567	24,7379	24,7783	24,7860	0,1483	-1,2740	4,8236
	2	25,7799	23,7154	24,8530	24,8526	24,0830	0,0890	0,0883	1,9048
	3	25,1381	24,4423	24,8512	24,8526	24,8526	0,0928	-0,5075	4,8054
	4	27,9743	26,8418	27,3029	27,2659	27,2130	0,1943	1,1226	4,5468
	5	33,0563	31,8432	32,6148	32,6317	32,8190	0,2018	-0,5266	3,1801
	6	34,7534	32,3938	34,2317	34,3777	34,5267	0,4509	-2,0826	7,2341
	7	32,2131	31,1665	31,8101	31,8145	31,7709	0,2198	-0,3384	2,3954
	8	32,5518	31,3988	32,0127	32,0311	32,1035	0,2789	-0,2012	2,1068
	9	x	x	x	x	x	x	x	x
	10	33,0916	32,4579	32,7568	32,7680	32,7608	0,1255	-0,1983	2,4668
	11	27,0020	26,0052	26,5575	26,5542	26,5846	0,1520	-0,0588	3,8001
	12	27,5088	25,5534	26,5039	26,5241	26,7445	0,4317	0,1170	2,1884
	13	21,1503	20,4278	20,7717	20,7656	20,6731	0,1521	0,1211	2,1674
	14	24,6669	23,0842	24,1386	24,2248	24,2870	0,3350	-0,5925	2,5137
	15	33,1929	31,9596	32,8297	32,8408	32,9900	0,2003	-0,6432	3,5083
	16	30,6763	27,9901	30,0173	30,0439	30,0734	0,3815	-1,1189	8,8599
	17	32,2194	30,6750	31,5092	31,5736	31,6099	0,3830	-0,2397	2,1127
	18	32,4586	29,8515	31,9046	31,9883	32,1260	0,3742	-1,6559	6,5996
Average		29,3392	28,0162	28,7997	28,8210	28,7863	0,2571	-0,3091	3,1328

Table 10-8: Raw Data Measurements Extracted from the Patient Group's 3rd PIP Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	33,5289	32,8184	33,0773	33,0773	33,0342	0,1357	0,6941	3,4272
	2	34,2328	33,4104	33,7615	33,7615	33,6685	0,1808	0,3197	2,4467
	3	33,4104	32,0824	32,5392	32,5027	32,4304	0,2007	0,9315	4,0332
	4	30,0953	29,5561	29,5667	29,5635	29,5561	0,1535	0,1560	3,3237
	5	28,2658	26,7645	27,6347	27,6534	27,7023	0,3175	-0,2577	2,6487
	6	28,5202	27,5365	27,8068	27,7475	27,7174	0,1799	1,1686	4,1105
	7	32,6960	30,3792	31,6920	31,7335	32,1470	0,4482	-0,6188	3,2032
	8	33,3712	32,0894	32,8327	32,9551	33,0557	0,3367	-0,5929	1,9303
	9	32,0605	30,9615	31,6659	31,7123	31,7922	0,2169	-0,6887	2,8885
	10	33,3791	31,7924	32,8316	32,8838	32,9054	0,3019	-0,9411	3,6980
	11	33,1921	31,9803	32,8174	32,8328	33,0342	0,2254	-0,5874	2,8505
	12	32,4263	32,5993	31,9120	31,9415	31,9850	0,2403	-0,7377	5,1512
	13	28,3343	27,0086	27,9117	28,0194	28,1245	0,2729	-1,3696	4,1838
LEFT HAND	1	33,3141	32,2339	32,6633	32,6383	32,6599	0,1754	0,7078	3,7320
	2	33,7258	32,1405	33,0166	33,0295	33,0655	0,2652	-0,0546	3,7256
	3	33,1446	27,3540	32,3982	32,4882	32,5389	0,5399	-3,5814	24,3273
	4	30,0585	28,6566	29,7749	29,8076	29,8224	0,1941	-3,2520	16,9999
	5	27,7701	26,5364	27,3070	27,3176	27,1739	0,2133	-0,5223	3,4431
	6	26,6505	24,9803	25,6087	25,5770	25,4886	0,3359	0,4455	2,6146
	7	31,6318	30,4547	31,0550	31,0850	31,1872	0,2206	-0,2871	2,8017
	8	33,1275	31,9300	32,7294	32,7897	32,7969	0,2414	-1,4349	4,6900
	9	32,4293	30,9908	31,6931	31,7195	31,7413	0,2545	-0,3136	2,9421
	10	34,2071	32,0028	33,7279	33,7795	33,8723	0,3043	-1,2187	6,0979
	11	33,5861	31,7190	33,0883	33,0916	32,9623	0,2846	-1,4494	7,2922
	12	33,1892	30,7606	32,3940	32,3541	32,3035	0,3465	0,0880	4,4325
	13	28,8498	28,1170	28,5922	28,6110	28,6708	0,1167	-1,5937	6,6777
Average		31,7384	30,2637	31,1576	31,1797	31,2091	0,2578	-0,5766	5,1412

10.5 Wrist Raw Data Measurements

Table 10-9: Raw Data Measurements Extracted from the Control Group's Wrist Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	30,2050	27,7589	28,9412	28,9812	29,1451	0,4239	0,0795	3,1567
	2	30,6159	29,5064	30,2165	30,2694	30,4170	0,2143	-0,6369	2,5121
	3	30,0806	28,8356	29,5489	29,5709	29,5857	0,2497	-0,2504	2,4466
	4	31,2099	29,5630	30,4687	30,5511	30,6905	0,3239	-0,6040	2,7330
	5	32,5668	30,9322	31,7652	31,7851	31,8505	0,2472	-0,3625	4,4286
	6	34,2000	32,5671	33,5556	33,5653	33,4365	0,2638	-0,4692	3,4082
	7	32,0828	30,3458	31,4071	31,4946	31,5237	0,3505	-1,0118	3,5709
	8	31,8425	30,1236	31,1865	31,2164	31,2967	0,3055	0,3055	3,1960
	9	x	x	x	x	x	x	x	x
	10	32,2845	31,0046	31,6791	31,6972	31,9658	0,2580	-0,2979	2,2263
	11	29,5999	27,2970	28,5659	28,5740	27,9674	0,5275	-0,0042	1,7807
	12	30,2205	27,4635	28,9351	29,0887	29,3486	0,5902	-0,2877	1,9391
	13	27,7945	26,2342	27,1734	27,2593	27,2366	0,3430	-0,5907	2,2589
	14	29,2812	27,3197	28,6492	28,7531	29,0361	0,3945	-1,0059	3,3200
	15	33,2933	31,3489	32,4388	32,4588	32,2637	0,4179	-0,2118	2,2084
	16	29,6524	27,6592	28,8663	28,8951	28,8355	0,3558	-0,9410	4,2062
	17	32,1687	30,2561	31,4165	31,4206	31,3769	0,3449	-0,6344	3,7072
	18	33,0635	31,3777	32,0878	32,0137	31,7343	0,3965	0,3513	1,9741
LEFT HAND	1	30,2935	28,7572	29,1285	29,1004	29,1153	0,1931	2,9045	15,2369
	2	31,1520	29,3650	30,2741	30,2768	30,2916	0,4312	0,0313	1,9514
	3	29,2670	28,3577	28,7009	28,7014	28,7089	0,1144	0,2780	4,0285
	4	30,5511	29,3184	29,9968	30,0655	30,3233	0,2947	-0,3467	1,7962
	5	32,8622	30,7418	32,1231	32,2273	32,4586	0,4351	-1,0711	3,4849
	6	34,6401	32,6319	33,6439	33,6332	33,4580	0,3945	-0,0707	2,3315
	7	32,9990	30,9473	32,1186	32,2565	32,3432	0,4612	-0,5305	2,4064
	8	32,6095	29,7544	30,4107	30,3739	30,4621	0,4568	1,5358	6,3220
	9	x	x	x	x	x	x	x	x
	10	32,6744	30,7336	31,7385	31,7481	31,7626	0,4049	-0,0603	2,2975
	11	29,2293	26,9565	28,1030	28,0875	27,7042	0,4584	0,1314	1,9942
	12	29,9110	27,9303	28,8386	28,6939	28,5894	0,4914	0,2377	1,7607
	13	27,7795	26,3791	27,1845	27,2593	27,2819	0,2472	-0,8275	3,2881
	14	29,4296	27,3499	28,6857	28,8500	29,0807	0,4406	-0,7102	2,3449
	15	33,4437	31,3781	32,5612	32,6103	32,5815	0,4291	-0,4379	2,4750
	16	29,7781	27,9225	29,1167	29,1110	29,0292	0,3353	-0,9689	4,4678
	17	32,2121	30,8948	31,4655	31,3842	31,3186	0,2606	0,7813	2,8732
	18	33,3648	31,9158	32,7281	32,7686	32,7686	0,2658	-0,4532	2,6065
Average		31,2459	29,4391	30,4035	30,4336	30,4408	0,3565	-0,1809	3,2570

Table 10-10: Raw Data Measurements Extracted from the Patient Group's Wrist Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	34,2066	32,1977	33,1474	33,1634	33,2137	0,3134	0,0215	2,7879
	2	34,2684	32,3145	33,5902	33,6757	33,7472	0,3773	-0,7149	2,7312
	3	33,2884	31,1056	32,3249	32,3797	32,4665	0,4096	-0,4979	2,7675
	4	29,9847	28,7685	29,3541	29,3338	29,3189	0,2148	0,3113	3,1018
	5	31,7263	30,1088	31,1276	31,2383	31,2967	0,3623	-0,6427	2,2889
	6	33,9503	32,1398	33,1905	33,1921	33,1706	0,3524	-0,1293	2,5688
	7	34,7956	32,1615	33,6762	33,7576	33,8647	0,4042	-0,5392	3,2532
	8	32,6456	30,8152	31,4377	31,4067	31,5014	0,3320	0,5215	2,7766
	9	31,2318	29,0143	29,9105	29,7854	29,5117	0,4732	0,8039	2,7549
	10	33,8366	32,1549	33,0564	33,0635	32,9413	0,3304	-0,2092	2,4490
	11	33,1347	31,4425	32,3925	32,2990	32,1904	0,3104	0,2612	2,2979
	12	32,5562	30,7533	31,8807	31,9125	31,9632	0,3151	-0,6963	3,3497
	13	32,7470	29,4074	30,8240	30,6978	30,5951	0,6755	0,5330	2,9259
LEFT HAND	1	33,7648	31,9296	32,9132	32,9479	33,2424	0,4176	-0,1749	1,9664
	2	33,3746	31,8063	32,6345	32,6617	32,7267	0,2394	-0,3333	3,3226
	3	33,9831	31,4054	33,2195	33,3530	33,3961	0,4666	-1,5500	4,7620
	4	29,9995	28,3801	29,0712	29,0441	28,9027	0,2831	0,2483	2,8239
	5	30,6310	29,2728	30,0485	30,0720	30,1088	0,1830	-0,3235	3,3593
	6	31,0484	28,6697	29,6175	29,5546	29,4879	0,3722	0,5551	3,0703
	7	34,5901	32,7464	33,6430	33,6219	33,7005	0,4419	0,0778	2,0832
	8	30,3382	28,2529	29,3050	29,3115	29,3115	0,4425	0,0030	2,3523
	9	31,2391	28,8580	30,1481	30,1764	30,5219	0,5025	-0,3939	2,5175
	10	34,2711	32,1042	33,1426	33,1066	33,7153	0,5357	0,0518	1,7211
	11	33,7434	31,9948	33,0708	33,1060	33,1634	0,2512	-0,5258	3,4519
	12	33,5473	30,4451	32,2599	32,3541	32,6643	0,5759	-0,8582	3,6166
	13	32,3936	30,2938	31,4909	31,5670	31,7851	0,4633	-0,4238	2,2843
Average		32,7422	30,7132	31,7876	31,7993	31,8657	0,3864	-0,1779	2,8225

10.6 Knee Raw Data Measurements

Table 10-11: Raw Data Measurements Extracted from the Control Group's Knee Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	30,2493	27,0934	28,7182	28,8543	29,0781	0,5696	-0,3387	2,7822
	2	29,8330	27,8514	29,1100	29,1639	29,3204	0,3243	-1,0887	4,4812
	3	30,3823	27,6369	29,6064	29,6745	29,7189	0,4351	-1,5978	6,4680
	4	33,0060	28,4765	31,0202	31,1515	31,4141	0,8399	-0,4804	2,9319
	5	31,3194	28,8498	30,3849	30,4923	30,6025	0,4187	-0,9371	3,9023
	6	31,9233	28,7535	30,9183	31,0716	31,3124	0,5506	-1,0887	3,7233
	7	31,1884	28,4174	29,9771	29,9628	29,9037	0,5265	-0,3303	2,8037
	8	32,3423	30,2193	31,3156	31,3332	31,3769	0,3390	-0,2411	2,8205
	9	33,0342	30,2267	31,8757	31,8715	31,7771	0,4745	-0,1384	2,7094
	10	30,9168	28,7518	29,5376	29,4879	29,4435	0,2537	1,1037	5,7005
	11	30,6826	26,7517	29,4577	29,6591	29,7035	0,7381	-1,1407	3,7774
	12	30,9250	26,6305	29,0497	29,1184	28,7909	0,9487	-0,2888	2,1461
	13	28,7083	25,6913	27,7761	27,9298	28,2299	0,6067	-1,0905	3,6389
	14	30,6606	26,1121	29,2306	29,3109	29,4147	0,5991	-0,7396	3,6096
	15	29,6450	28,4024	29,1597	29,1556	29,1110	0,1573	-0,2628	3,6784
	16	32,1769	28,3350	30,6243	30,7056	31,4509	0,9255	-0,3442	2,1790
	17	30,9753	28,2957	29,7534	29,8431	30,0277	0,5805	-0,2536	2,1453
	18	31,7626	28,6323	29,9560	30,0130	30,0425	0,5676	-0,0333	2,5365
LEFT HAND	1	31,9546	28,1278	30,1671	30,0943	29,8948	0,5649	0,252	2,9179
	2	31,2692	28,4383	29,6503	29,6549	29,6921	0,3858	-0,0075	3,5097
	3	30,5880	27,3428	29,5864	29,6375	29,6523	0,435	-1,4072	6,3791
	4	32,6894	29,0360	31,0510	31,2172	31,5961	0,7624	-0,4195	2,4765
	5	31,2099	27,9969	29,7904	29,8810	30,3086	0,6447	-0,3787	2,5655
	6	32,3288	29,2670	31,0810	31,1884	31,3562	0,5707	-0,5929	2,7631
	7	31,9523	28,4248	30,0810	30,0955	30,6396	0,6653	-0,031	2,3417
	8	32,5085	29,9613	31,1837	31,2383	31,3186	0,4801	-0,1617	2,4846
	9	32,7608	29,8136	31,6116	31,6390	31,6536	0,4803	-0,6058	3,5678
	10	30,5429	28,5427	29,4554	29,3693	29,3619	0,3285	0,8274	3,2571
	11	30,1904	26,1274	28,6153	28,8127	29,4147	0,8386	-0,7738	2,8185
	12	31,3339	25,9748	28,9712	29,0738	29,8297	1,0518	-0,3539	2,2779
	13	29,8069	26,0968	28,4322	28,5889	28,8574	0,6943	-0,8351	3,2502
	14	30,6679	26,5846	29,1372	29,2738	29,5185	0,7781	-0,6062	2,7147
	15	31,3489	27,9526	29,0225	28,9696	28,8430	0,3935	0,7195	4,7714
	16	31,7637	28,8057	30,5102	30,5222	30,3752	0,6596	-0,2578	2,26
	17	31,4511	29,1911	30,4602	30,4841	30,7556	0,4091	-0,3273	2,7163
	18	32,5668	30,1332	31,8815	31,9448	32,1332	0,307	-0,5449	2,6813
Average		31,2963	28,1374	29,9489	30,0135	30,1644	0,5640	-0,4110	3,2719

Table 10-12: Raw Data Measurements Extracted from the Patient Group's Knee Joint

		Max (°C)	Min (°C)	Mean (°C)	Median (°C)	Mode (°C)	STD	Skewness	Kurtosis
RIGHT HAND	1	31,8352	28,9828	30,6760	30,7776	31,0996	0,5633	-0,6414	2,8053
	2	31,6898	29,8763	30,7146	30,7316	30,8564	0,3305	-0,1307	2,4253
	3	31,8352	28,9828	30,6760	30,7776	31,0996	0,5633	-0,6414	2,8053
	4	29,0738	25,9060	28,0741	28,1629	28,2454	0,5395	-1,1527	4,6386
	5	30,7923	28,6024	30,0984	30,2120	30,5576	0,4687	-0,7398	2,6766
	6	31,2748	28,6398	30,1301	30,1751	30,5796	0,4721	-0,4066	2,3680
	7	32,0746	30,6530	31,3990	31,4206	31,5081	0,2433	-0,1090	2,6753
	8	29,8076	27,6595	28,7702	28,7760	28,8878	0,3868	0,1107	2,5216
	9	29,0441	26,7597	27,9101	27,8551	27,7574	0,4155	0,4489	2,7057
	10	31,9810	29,9032	31,1506	31,1880	31,4214	0,3226	-0,5389	3,0899
	11	30,4033	28,9828	29,9602	30,0130	30,0720	0,2136	-1,2839	4,6348
	12	31,2724	28,9586	30,2112	30,2908	30,4745	0,3652	-0,2989	2,3884
	13	30,5438	28,1095	29,3482	29,3480	29,3184	0,3617	-0,1871	3,5468
LEFT HAND	1	32,1325	29,2579	31,0218	31,1872	31,3988	0,6037	-0,7395	2,71
	2	31,4200	29,5205	30,5332	30,5110	30,4669	0,3355	-0,0295	2,64
	3	31,8645	29,4685	30,5154	30,4742	29,8097	0,5694	0,2446	1,9134
	4	28,1704	25,5611	27,3531	27,4409	27,6821	0,4235	-1,1194	4,3429
	5	31,0850	28,7592	29,8999	29,9170	29,8801	0,4175	-0,1652	2,5133
	6	31,0484	28,4754	30,0377	30,1751	30,3297	0,5569	-0,5574	2,4235
	7	31,1434	29,3693	30,4272	30,4474	30,4400	0,2915	-0,5222	3,2053
	8	31,6323	27,1840	29,2335	29,1704	27,1840	0,9486	0,073	2,0262
	9	28,8878	26,9493	28,0124	28,0279	27,9979	0,3666	-0,2073	2,7337
	10	31,7561	22,8927	29,5297	30,5878	30,4703	2,5207	-1,5207	4,4411
	11	31,5372	29,4583	30,2717	30,2414	30,1457	0,3803	0,3999	2,7651
	12	32,7652	29,1966	30,9183	30,9437	31,0972	0,7165	-0,0808	2,4402
	13	31,3485	28,1470	29,4361	29,4000	29,3555	0,4705	0,8634	4,9584
Average		31,0161	28,3175	29,8580	29,9328	29,9283	0,5326	-0,3435	3,0152

11 APPENDIX E

11.1 Histogram of 2nd MCP's Most Statistically Significant Matrices

Figure 11-1: Histogram of the Mode/Max Matrix for the 2nd MCP

Figure 11-2: Histogram of the Mode/Min Matrix for the 2nd MCP

Figure 11-3: Histogram of the Skewness Matrix for the 2nd MCP

11.2 Histogram of 3rd MCP's Most Statistically Significant Matrices

Figure 11-4: Histogram of the Variance Matrix for the 3rd MCP

Figure 11-5: Histogram of the Mode/Max Matrix for the 3rd MCP

Figure 11-6: Histogram of the Max-Min Matrix for the 3rd MCP

11.3 Histogram of the Knee's Most Statistically Significant Datasets

Figure 11-7: Histogram of the Variance Matrix of the Knee

Figure 11-8: Histogram of the Mode/Min Matrix of the Knee

Figure 11-9: Histogram of the Max-Min Matrix of the Knee

12 APPENDIX F

Preliminary Results of Severity of Illness Measures of Rheumatoid Arthritis Using Infrared Imaging

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Abstract—In the first phase of a large project we used an infrared thermographic camera to obtain accurate measurements of body temperature in joints of twelve human normal subjects (control group) and for thirteen patients diagnosed with rheumatoid arthritis (RA) by a rheumatologist. The ultimate goal is to create a low cost effective method to diagnose early synovitis. Temperature measurements of hands were analyzed with first order statistics. Results show significant temperature differences between control subjects and patients for every joint and hand portion measured. Future work will complete the analysis of knees, elbows, ankles, combine infrared imaging (IR) and intra-optical imaging (IO), and incorporate feature extraction and classification approaches to stratify patients into severity of illness prior to, and after receiving treatment.

Keywords- *infrared imaging; thermography; measuring temperatures rheumatoid arthritis patients; comparing with normal subjects.*

I. INTRODUCTION

Over 300,000 Canadians, 2.1 million Americans, and around 260,000 French are currently diagnosed with rheumatoid arthritis (RA), involving inflammation and symptoms like redness, swelling, heat, and pain. Within 10 years of diagnosis, 50% of patients have severe disability and life expectancy reduction from 3 to 18 years. With the aging of the population, the prevalence of chronic

diseases and conditions is expected to increase even more over the next decades. Early diagnosis and treatment of RA could help postpone or prevent serious disability. Currently, diagnosis relies mainly on qualitative evaluation, medical history, examination, and laboratory tests. MRI (Magnetic Resonance Imaging) and HRUS (High-Resolution Ultra-Sound) have been used with some patients to detect early synovitis. However these tests are not readily available to everyone and waiting lists in many countries are very long. Less expensive technologies providing quantitative assessment to diagnose and monitor therapy in joint debilitating diseases would be a major innovation in Canada and in the world. This explains the motivation to develop more accessible approaches for active prevention.

Visual marker-based monitoring systems still remain expensive and complex to operate. As a result, they are found mainly in particular cases in rehabilitation and for research. More tractable non-invasive approaches that simultaneously combine infrared imaging with movement extension measurement should be made available in large clinics and all hospitals to provide access to a major part of the population. Replacing expensive MRI or HRUS by the proposed technology would also have a major impact on the Health Care System; the current tests (MRI and HRUS)

required for early diagnosis of RA could be replaced by the new imaging technique, thus releasing the expensive tests for other applications, likely leading to a reduction of waiting times for these tests. It is anticipated that the system will aid physicians in making earlier diagnoses and delay progression of the disease to advanced stages of deformity or disability, keeping Canadian and French citizens more active, at work and in their personal lives.

Inflammation and limitation of motion are two important parameters to monitor RA, along with pain assessment. The integration of heat distribution on the skin surface along with movement capabilities to be found in one diagnostic tool is innovative and seen as a reliable, quantitative and reproducible means of assessment of RA. This aspect is innovative and promising given that injury to bones, joints and muscles are known to recover slowly. Calibration of the automated measurement with disease level estimated by medical experts will also be possible providing that the correlation is sufficiently high with other clinical assessment tools. The resulting technology will support the translation of knowledge to physicians and other health personnel to help to improve or restore musculoskeletal health with quantitative measurements that can be classified, clustered and analyzed in order to observe tendencies and general trends to be compared with real clinical investigations. The ultimate goal is the integration of the multi-spectral approach into clinical application to become a diagnosis-aid that is affordable, efficient and easy to operate, and that can be widely used over existing health services networks.

From a clinical point of view, the technique of infrared photography may provide utility in several areas of care of patients with RA. a) Early diagnosis; currently, the diagnosis of RA is based on the clinical evaluation, specifically the demonstration of joint swelling by palpation. This method is at best crude and noted for substantial inter-observer and intra-observer variation. Refinement is provided by MRI and power Doppler. However, both of these methods are labor intensive, time consuming, expensive and also subject to the expertise of the individual performing the evaluation. Infrared photography may provide an alternate approach that could detect active inflammation at a time when the joints may

simply be stiff and/or tender but not detectably swollen.

b) Prognosis; currently, the identification of biomarkers of disease severity and predictors of outcome is an area of active research. No single marker has been found to predict outcome well, perhaps with the exception of the persistent elevation of CRP despite therapy. The intensity of the infrared signal may be useful as measure of inflammatory load and a predictor of outcome.

c) Achievement of remission; the ability to suppress the intensity of the infrared signal may speak to adequacy of treatment. Currently, the goal of RA therapy is to induce the lowest possible level of disease activity. Measurements of disease activity rely on clinical parameters; however future goals are not simply to attain clinical remission, but radiographic remission defined as no progression of joint damage. Methods to demonstrate radiographic remission will rely on MRI, which noted above is an expensive approach. Infrared photography may provide an alternative to MRI in defining radiographic remission

Therefore, developing a less costly, non-invasive technology to provide a quantitative assessment of RA and to monitor therapy effectiveness in joint debilitating diseases has been the main motivation behind this work.

II. LITERATURE REVIEW

Over the past 50 years, infrared imaging has been applied to many fields. The major limitations encountered in early work were the lower resolution, large size of sensors, and the limited power of computers for the image analysis [1]. A few clinical studies demonstrate that heat distribution provides a quantitative measure of disease activity and especially of inflammation in knee joints of patients [2], [3], [4]. Correlation has been observed between heat distribution measurement and physicians' assessment based on degree of swelling, warmth, limitation of motion, grip strength, morning stiffness and pain score. Early studies mainly focused on knees and ankles to assess the effect of various treatments on RA patients. In this study, we analysed the temperatures of various joints in the hands, wrist, back of the hand, palm, thumb shaft, for both controls and patients. Our intent was to identify how clearly we could separate patients from controls and to examine which joints are the most indicative of an RA condition in patients.

Anomaly detection in infrared images is a challenging task. Often the key element of an automated anomaly detection system is the segmentation of relevant information from noise and background. Numerous algorithms are available in the literature for the segmentation of visible images, but these differ significantly from infrared images. The intensities of the latter depend on object temperature, object surface properties, surface orientation, wavelength, and are not necessarily uniform across an object, even if the temperature of that object is uniform. The environmental conditions at the time of imaging also influence the resulting images. Moreover, the range of intensities of infrared images is typically much less than for visible images, leading to low contrast, poor resolution, and less texture information. Key features that are successfully used in the processing of visible images cannot be used reliably when dealing with infrared images, thus the segmentation of the latter presents unique challenges and depends greatly on the application considered. Methods developed for automated tracking of military targets [5] or for predictive maintenance [6] do not perform well when translated to applications in medicine. Our group introduced a method based on morphological processing of edge maps using both strong and weak edges to recover the contour of faint parts of the object in low contrast and high noise situations [7, 8, 9]. Promising results were obtained for synthetic images of hands on three types of real backgrounds. The segmentation approach is part of a larger framework for automated identification of abnormal regions in infrared images of the human body and will be integrated into this project at a later stage. To date, our framework was applied to the assessment of pain [10], of musculoskeletal disorders in the arms and hands of computer users, and to capture the evolution of the temperature distribution on pianists' hands and arms during practice. We intend to incorporate this approach to the measurement of joints for diagnosing RA, once the first phase of the study described here is completed.

A second long-term goal is to develop a multi-spectral quantitative sensing approach to assess the severity of RA, combining infrared imaging (IR) and intra-optical imaging (IO). Building on previous work of our team to reconstruct the 3D position of human limbs from a segmented set of synchronized video captures without markers [11], precise gesture estimation can be achieved to

evaluate the range of motion of a subject. It also provides a recording mechanism for temporal comparisons of the subject's capability of movement and dexterity. Our hypothesis is that this combination of infrared and passive intra-optical imaging will help in the early diagnosis of (RA) and to measure the effectiveness of therapy for patients treated for RA. The current paper addresses the first part of the work: measuring and analysing the temperature distribution in various joints of the hands and of other parts such as wrist, palm, and back of the hand. In subsequent work, the analysis will be completed on the other views taken of patients and normal subjects such as elbows, knees, ankles, and feet. Following this step, the superposition of the two imaging techniques will be developed.

III. METHODOLOGY

A. Data collection

Thirteen patients (nine females and four males) diagnosed with rheumatoid arthritis and eighteen control subjects were recruited after receiving the ethical clearance certificate from the hospital and the Universities. Six control subjects were eliminated from the total of eighteen volunteers for this preliminary analysis to maintain a database of subjects who were 50 years old or less; the six were between 60 and 70 years old. In the future, an in-depth analysis will be done with respect to the effect of age on mean temperatures of joints, but a quick observation was that persons over 50 had higher temperatures than younger subjects. All subjects (five females and seven males) and patients followed the protocol: not to use talcum powder, lotion, drug or deodorant on the skin on the day of the session; not to consume alcoholic beverages 12 hours prior to the session; not to consume hot beverages at least 1 hour prior to the session; not to use procedures such as acupuncture, transcutaneous electrical nerve stimulation (TENS), hot or cold patches, or any other form of physiotherapy at least 24 hours prior to the session. They were asked not to do intense physical exercises at least 4 hours prior to the tests, avoid prolonged sun exposure for at least one week, not smoke for at least 2 hours prior to the testing, and not wear any rings, necklaces, and bracelets during the session.

The room had a controlled temperature of around 20 degrees C, with no windows. All test

subjects wore light clothing (short-sleeved T-shirt and shorts); they removed their shoes and socks and were seated in the room without any of their limbs touching the other for a fifteen minute period before images were taken. This is to cool the parts of the body that were covered by clothing and have everyone in the same condition prior to the imaging session. The IR camera uses a solid state uncooled microbolometer focal plane array of 320×420 pixels, operating in the window 7.5µm–13µm of the far IR range of the electromagnetic spectrum. It has a 24mm germanium lens with an anti-reflective coating. This gives a 24°×18° field of view with a minimum focus distance of 30 cm. Its spatial resolution is 1.3mrad. The thermal resolution is 0.05°C at 30°C. The camera was connected to a laptop via a Firewire interface, thereby capturing sequences of 14bit digital thermal images at a set speed of 30 frames per seconds. Images were taken of the hands (dorsal and palm), arms, knees, feet (top and palm).

The preliminary analysis consisted of three steps:

(i) Calculating the mean temperature, the median, and the standard deviation for the twelve control subjects and thirteen patients for the following: Metacarpal Phalangeal (MCP) joints (all of the four joints together enclosed in a quadrilateral); Metacarpal Phalangeal joint of the third finger (MCP3); the third proximal interphalangeal joint (PIP3); the third distal interphalangeal joint (DIP3); the Mid Phalange (MP), the wrist, the back of the hand, and the palm; for the palms, the standard diameter was 120 pixels, which corresponded to approximately 4 cm in diameter. See Figure 1 for a drawing of the hand with the name of each joint. The mean temperatures for each view are presented in Table I with the first column reporting the results for the control group, the second column presenting the results for the patients, and the third column reporting the difference between the former two columns.

(ii) For the patient group, the joint temperatures are reported, as well as the mean temperature of all patients for each of the joints and parts of the hand. This is intended to see if a patient's joint temperatures are higher than, lower than, or equal to the mean temperature for each joint or part of all patients; it is our belief that patients whose joints

are at higher temperatures than the mean temperature for all patients would have more serious inflammation and vice versa for those under the mean temperature. These results are presented in Table II. Of course, in the long run, it is the comparison of a patient's own temperature measures which will be important to determine if the disease is progressing or regressing at each visit.

(iii) The difference of the mean temperature between patients and participants for the right hand and the left hand were calculated for: MCP, MCP3, the wrist, and the back of the hand. The results are presented in Table III.

Since there are between fifty and seventy-five images for each view, for each patient or subject, it was decided that for this preliminary analysis, the twentieth image for each view would be analyzed. The region of interest is identified in the same way for each test and the mean and median is calculated for each. In the future, when the automation of the analysis has been completed, then it will be possible to average the data from all the images taken of each particular view.

Figure 1: Joints of the left hand

During these imaging sessions, measurements were also taken of the following: Inside and outside of the left and right arms in a straight position, then inside and outside the right and left elbows in a bent position; the back as well as a front view of the bent right and left elbows. Similarly, the knee was imaged with the following positions: Back view of left knee and of the right knee, then a front view of these two joints; then inside and outside views of each knee. Finally, each foot was imaged with top view followed by a

view of the sole. However the focus of this paper is mainly the hands; the analysis of all the other measurements will be part of future paper.

(iv) Three patients were retested in April 2009, nearly one year after the first imaging session done between April and June of 2008. Table IV shows the mean temperatures for MCP3, PIP3, and DIP3 taken at two different points in time (spring 2008 and spring 2009) for patient no. 1, 4, and 13.

IV. RESULTS AND DISCUSSION

The results clearly show that the mean temperatures measured with infrared techniques were greater for all patients and all joints and hand parts than for the control subjects; see Table I. Greater temperatures were even seen at the DIPs, joints that are not often involved clinically in RA. On the day of the infrared testing, we did not examine each joint for clinical signs and symptoms of RA such as swelling or tenderness and are therefore unable to provide a correlation between clinical assessment and infrared signal. All infrared imaging tests were done at the University and in order to respect the requirements of the Ethics Review Board, these were to be separate at this time from the clinical evaluation. However, in the future, the new ethics proposal will suggest testing at the hospital facility and all patients will be assessed by a physician, by the imaging, and results compared to MRI tests (as ground truth). For this study, all patients had well established long-term RA and were being treated with disease modifying drugs. The physician's global assessment of disease activity at the time of the patient's visit was that the disease appeared to be less active in some patients (e.g. patients 1 and 2) and very active in another (e.g. patient 7). However, by the time these patients participated in the imaging sessions, their RA status could have changed as indicated by the temperature measurements reported here. The preliminary analysis of the temperature measurements did not discriminate yet among patients with different degrees of clinical activity. Nevertheless, it is also known that clinical evaluation is often inadequate to evaluate joint inflammation except with approaches such as MRI testing. Other analysis approaches including classification techniques will be applied to this data in the near future to assess whether some discrimination of level of disease is possible.

FIGURE 2: MCP LABELS ON A PARTICIPANT'S HAND

FIGURE 3: EXAMPLE OF A PATIENT'S HAND

TABLE I. MEAN TEMPERATURE FOR CONTROL SUBJECTS AND PATIENTS IN VARIOUS JOINTS IN LEFT HAND (DEG. CELSIUS)

Part imaged	Control subjects	Patients	Difference
MCP	28.2	31.5	3.3
MCP3	28.1	31.4	3.3
Wrist	29.7	31.9	2.2
Back hand	29.5	31.6	2.1
PIP	27.2	30.9	3.7
PIP3	27.5	31.0	3.5
DIP	27.0	30.5	3.5
DIP3	27.3	30.6	3.3
MP	27.3	31.0	3.7
Thumb	27.7	31.7	4.0
Palm	30.5	32.5	2.0

TABLE II TEMP. PATIENTS LEFT HAND (DEG. CELSIUS)

Patient	Test date	MCP	MCP 3	PIP3	DIP3	Wrist	Back	MP	Palm
1	Apr. 29	32.9	32.8	32.6	32.8	32.8	33.2	33.6	33.3
2	Apr. 25	32.9	32.9	32.9	32.7	32.5	32.8	33.4	34.3
3	May 8	33.3	33.5	32.3	32.1	33.1	33.4	33.1	33.7
4	Jun. 12	29.8	29.7	29.7	29.2	29.0	30.0	30.0	30.6
5	Jun. 12	28.8	29.0	27.2	25.8	29.9	29.8	28.0	30.0
6	Jun. 13	28.0	28.4	25.5	24.8	29.5	29.4	27.8	29.9
7	Jun. 13	33.1	33.1	31.0	30.2	33.5	33.5	32.2	32.8
8	Jun. 16	32.1	32.2	32.6	32.1	29.2	31.1	32.6	31.8
9	Jun. 17	30.7	30.1	31.6	31.9	30.0	30.8	32.3	31.9
10	Jun. 17	33.1	32.4	33.6	33.3	33.0	33.3	33.7	33.5
11	Jun. 19	32.9	32.6	33.0	32.8	33.0	33.3	33.4	33.4
12	Jun. 21	32.1	31.9	32.3	32.2	32.2	32.5	32.8	32.9
13	Jun. 24	28.9	28.9	28.5	27.8	31.4	30.2	29.1	31.3
Mean		31.4	31.3	30.9	30.5	31.4	31.7	31.6	32.2
SD		1.93	1.83	2.51	2.84	1.70	1.59	2.17	1.46

TABLE III DIFFERENCE OF THE MEAN TEMPERATURE OF TWO HANDS FOR CONTROL SUBJECTS AND PATIENTS (DEGREES CELSIUS)

Part imaged	Control Left	Control Right	Patient Left	Patient Right	Diff. Control	Diff. Patients
MCP	28.2	28.2	31.5	31.6	0.0	0.1
MCP3	28.3	28.1	31.4	31.5	0.2	0.1
Wrist	29.6	29.7	31.6	32.0	0.1	0.6
Back hand	29.4	29.5	31.9	32.0	0.1	0.1

TABLE IV. MEAN TEMPERATURE OF LEFT HAND OF THREE PATIENTS IMAGED AT TWO DIFFERENT TIMES (PATIENTS 1, 4, AND 13): SPRING 2008 (A) and SPRING 2009 (B)

Part imaged	A patient 1	B patient 1	A patient 4	B patient 4	A patient 13	B patient 13
MCP3	32.8	33.3	29.7	27.5	28.9	32.4
PIP3	32.6	33.1	29.7	25.9	28.5	33.4
DIP3	32.8	33.5	29.2	26.8	27.8	33.3

Again, although the physician could not be present at these second tests for patients 1, 4 and 13, it is evident from the tests results that patient 1 suffers from slightly more inflammation from the hand joint temperatures reported in Table IV. Patient 4 seems to be better and patient 13 seems worse.

V. CONCLUSION AND FUTURE WORK

The first phase of this research project enabled us to conclude that there are measurable differences in temperatures of hands in patients versus control subjects, establishing a proof of concept and leading to future work. Moreover it is

interesting to note that subjects do not show much temperature difference between the right and the left hand joints or other hand parts (palm and back of hand), which is expected since they are not suspected of having any abnormality in either hand. For the next phase of the project, physician assessment, infrared imaging, visual imaging, and MRI studies will be collected and compared. Also, building upon C. Herry's work [7], future developments will include feature extraction processed through a pattern recognition system to optimize the classification of outcomes in terms of severity of RA and degree of changes at each visit. An index will be established, independent from the acquisition setup, to classify thermographic measurements into categories of RA diseases that correspond to currently used RA levels, as diagnosed by medical experts. A database will be created over this phase of research on patients already diagnosed with RA.

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