Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

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Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

submitted by Adam John Guy for the degree of Doctor of Philosophy (PhD) of the University of Bath

December 2004

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Adam Guy
Abstract

An introduction to the use of microwaves for medical applications is given, with a comparison between different modalities for heating tissue, such as radio-frequency and laser based techniques. The background to the design and construction of applicators using finite element packages is also explained and this knowledge is demonstrated in the design, construction and testing of novel systems to treat psoriasis and varicose veins. The psoriasis treatment system is hyperthermia based, whilst the varicose veins treatment employs ablation, thus giving an insight into two different means of inducing a therapeutic effect using heat. Thermal analysis of the heat induced by the applicators is demonstrated by numerical solution of the diffusion equation by finite difference approximations and Green’s function analysis, with the results being validated against bench models. The results of testing of the psoriasis system on three patients are given, including the first quantitative assessment of the relationship between skin temperature and blood perfusion levels for both psoriatic and healthy skin at hyperthermic temperatures. The varicose veins treatment is minimally invasive, and is the first microwave based treatment for varicose veins.
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Chapter 1: Introduction and background

1.1 Introduction

Heating tissue can have a variety of effects depending on the temperature and the length of time for which that temperature is held. It can temporarily stop cell replication (Herman, 1977), coagulate blood vessels (Carbonell, 2003), cause tissue shrinkage (Trembly & Keates, 1991) and, of course, induce cell death (Borelli, 1990). The resulting cell death, and the effects resulting from further heating, such as carbonisation and vaporisation, are commonly referred to as ablation (LeCarpentier, 1993), and are useful for treating a wide variety of complaints. Some of the modalities available to achieve heating in tissue include direct contact heating, (Chung, Xiao & Ryan, 2002), heating induced by laser beams (Navarro, 2001), ultrasound induced heating (Tyreus, Nau & Diederich, 2003), the direct application of radio-frequency (RF) electromagnetic waves (Scott, 2001) and the application of RF energy via an argon plasma (Miyazawa, 2000).

Achieving the desired effect on the tissue relies on producing a particular temperature profile within the tissue for a given length of time. The fact that each modality delivers energy to the tissue through a different method of action means that each modality will lend itself to producing different temperature profiles over different timescales. Different modalities are therefore inherently suited to producing different effects, and hence for the treatment of different conditions. In addition, the use of a particular modality has an impact on the engineering of the device and system used to deliver the heating, which can also be an important consideration in where and how the treatment system can be used. A review of the most commonly used modalities, together with their features and advantages and disadvantages are given in sections 1.2.1 to 1.2.6. A summary is given in table 1.1. The majority of these modalities have been reviewed by Williams and colleagues (2004).
1.2 Thermal medical treatment modalities

1.2.1 Contact heating

Possibly the superficially simplest method of achieving tissue heating is through contacting the tissue to be heated with a hot surface or hot fluid. Thermal conduction is then relied upon to carry the heat into the tissue. This has the advantage of being likely to be relatively easy to implement in terms of system engineering, as the technology required to achieve heating of fluids or surfaces is unlikely to be as complex as that required for other heating modalities. In addition, the maximum temperature rise in the tissue will not exceed the temperature of the fluid or surface used, due to the fact that thermal conduction alone is used to carry heat through the tissue. This means that an accurate upper limit on tissue temperature can be set if the surface temperature is known. This differs from other heating modalities where the heating is induced in the tissue itself, making the maximum tissue temperature more difficult to accurately predict. This effect can be important for treatments that have tight safety limits on temperature, such as treatments that must not produce steam, or must achieve cellular damage without causing cell death.

The fact that contact heating relies on thermal conduction alone also has significant disadvantages. Above all, it cannot produce ablations of significant depth without the use of very high surface temperatures and is slow to create deep ablations compared to other modalities such as microwaves and RF. A major limiting factor in this regard is the level of blood perfusion, which has the effect of cooling the tissue and hence limiting ablation depth even more. In addition, if a surface is used to provide this heating, any small gaps between the surface and the tissue will result in significantly less transfer of heat and so result in a significantly smaller ablation depth than predicted by thermal analysis. This problem can be overcome through the use of a fluid, but this introduces the difficulty of safely delivering the hot fluid to the treatment site without causing collateral damage, containing it once in place and then removing it again. One example of the use of contact heating in medicine is in removing the lining of the uterus, called the endometrium, by inserting a hot saline filled bag into the uterine cavity (Baldwin, 2001). Removal of the endometrium using heat is called endometrial ablation.
1.2.2 Laser
Lasers light with wavelengths of between 1000-3000nm are typically used for heating tissue. Lasers heat the tissue directly, and very superficially, leading to difficulty in assessing and controlling the maximum tissue temperature achieved. However, they offer potentially superficial heating at high temperatures over a small treatment area. The minimum depth of ablation is around 20μm according to LeCarpentier et al. (1993) with maximum ablation diameters of between 1-3cm if heating is maintained (Iizuka, 2000). In addition, no contact with the tissue is required to achieve the heating and the energy can be delivered down very narrow (600μm) optical fibres with minimal losses.

On the other hand, the small size of the heated area of tissue makes ablating large areas slow, as this can only be achieved by passing the heated spot over the surface to be treated. It is therefore not ideal for treating large areas due to the significant time that is required. The fact that the power delivery is from a virtually point source also means that carbonisation of the tissue can result when trying to achieve large ablation volumes (Iizuka, 2000), due to the maintenance of very high temperatures in a small volume of tissue, followed by a reliance on thermal conduction to carry the heating out further. As with direct contact heating, this reliance on thermal conduction limits ablation volumes compared to ultrasound, RF and microwave based modalities and leads to the need for very high superficial temperatures to try and achieve a larger depth of thermal penetration within an appropriate length of time, if required for an application that necessitates large ablation volumes such as tumour ablation. Some examples of lasers being used in medicine are their use in eye surgery due to their very focussed heating, their use to cause veins to occlude by causing localised damage to the vein wall, and in cancer treatment, where they have been used to ablate tumours.

1.2.3 Ultrasound
Ultrasound is very widely used in imaging, but high intensity ultrasound can also be used to produce significant tissue heating. Frequencies of between 1-15 MHz are typically used with heating over depths of up to 5cm (Tyreus, Nau & Diederich,
Higher frequencies are absorbed more readily, so giving smaller depths of penetration, with lower frequencies resulting in deeper penetration. This ability to vary the depth of over which the tissue is heated means that there is significantly more flexibility in determining the required therapeutic temperature profile, as thermal conduction alone is not relied upon to deliver the heat. In particular, heating over a significant depth of tissue means that large ablation volumes are theoretically possible without the need for the development of extremely high temperatures, as thermal conduction is not the only method of delivering heat into the tissue. This means that ultrasound heating is well suited for the ablation of tumours.

Unfortunately, ultrasound applicators have difficulty maintaining efficiency as the probe heats up, even for relatively modest temperature rises. Direct contact with the tissue is also needed to deliver the ultrasonic waves and the use of a coupling medium (such as ultrasound gel) can be required to achieve efficient coupling between the ultrasonic transducer head and the tissue. Both of these effects lead to a significant lack of efficiency and high reflected powers, particularly as the probe temperature rises due to heating of the surrounding tissues. This limits ablation volumes to around 3cm diameter. Also, relatively large applicators of around 2.2 to 4mm diameter are required to create these significant ablation volumes (Tyreus, Nau & Diederich, 2003), which is large in comparison to RF and laser applicators which are generally around 1-2mm in diameter. An additional disadvantage is that ultrasonic absorption is directly related to tissue protein content, which can vary significantly between tissues. It will therefore selectively heat some tissues more than others, such as bone, nerves and scar tissue. This makes ultrasonic ablation impossible in areas close to bone.

1.2.4 Radio-frequency
Radio-frequency based heating is the most widely used method of heating tissue. Alternating currents at frequencies of around 450 - 1000 kHz are used to cause heating due to the passage of the current through the tissue. This means that two electrodes are required to allow currents to run between them. In a bipolar system, the two electrodes are placed near each other on the applicator, so the current is relatively well confined to the region around the applicator. In a monopolar system, currents run
between the applicator and a large pad attached to the patient, often located on their thigh. The current is most intense at the applicator, and becomes increasingly diffuse for tissue closer to the pad. This therefore limits heating to the area around the applicator.

The relatively low frequencies used, when compared to microwave frequencies, means that wires can be used to deliver the energy, and this has significant advantages from an engineering point of view. Applicators can be made very narrow and with minimal energy losses on route to the treatment site. The heating induced by the currents is less superficial than that produced from lasers, but significantly shallower than heating from ultrasound, making it potentially suitable for treating a wide range of conditions.

However, the more limited heated volume of tissue that results when compared to ultrasound induced heating means that ablation volumes are intrinsically smaller than those available from ultrasound induced heating. This is due to the greater reliance on thermal conduction to expand the ablation, and the need to limit power delivery to the applicator to prevent excessive temperatures and charring around the applicator. In addition, tissue desiccation resulting from prolonged heating causes the impedance of the tissue to change in the tissue surrounding the applicator. This has the effect of lowering energy delivery to the tissue, so limiting ablation volume. In an attempt to remedy this and expand the ablation volume, multiple electrodes have been used emerging from a single applicator. This has resulted in unpredictable larger ablation volumes and leads to recurrences when used to treat cancerous tumours as the entire tumour has not been successfully ablated (Scott et al., 2001).

### 1.2.5 Argon plasma coagulation

An extension on the use of radio-frequency heating is the combination of radio-frequency heating with an argon plasma. The plasma allows conduction between the electrode and the tissue without the need for direct contact of the electrode on the tissue. This expands the region of heating whilst still allowing the use of a small probe. This gives very shallow, even burns of around 400μm according to Miyazawa.
(2000) without vaporisation of tissue. Naturally, this also means that it does not lend itself to ablating large volumes, and it is primarily used to stop bleeding from surface blood vessels.

1.2.6 Microwave

Microwaves offer many of the advantages for heating tissue that other modalities offer, due to the fact that it can heat both large and small volumes (Swift, 2003). In this respect it is similar to ultrasound, but does not have some of the major drawbacks associated with the use of ultrasound. Despite this, it has been used surprisingly infrequently. This may be due to the difficulties in producing efficient antenna designs. In fact, microwaves applicators have the potential to offer very efficient designs that can produce uniquely large ablations (Wonnell et al., 1992). As with ultrasound, the depth of tissue heating can be altered through altering the frequency of operation. Frequencies of around 1-10GHz are used with tissue penetration depths between several millimetres and several centimetres. In addition, the absorption of energy by tissue due to microwaves is relatively uniform as it is dominated by the water content of the tissue, which is relatively uniform across tissues. This greatly reduces selective heating effects, allow heating in areas much closer to bone than is possible with ultrasound. Finally, direct contact between the applicator and the tissue is not a necessity to ensure efficient microwave radiation into the tissue.

There are some potential drawbacks however. In particular, large applicators are generally required to achieve efficient designs (2-5mm in diameter). This is considerably larger than many RF and laser applicators. Also, as with radio-frequency ablation, tissue desiccation due to extended treatment times can result in a reduction in energy delivery due to changes in tissue properties. However, careful antenna design can minimise or eliminate this effect and ensure good efficiency throughout a treatment.

Microwaves have the potential to be used to treat many different conditions. Possibilities include tumour ablation, coagulation of blood vessels and endometrial ablation.
<table>
<thead>
<tr>
<th>Method of action</th>
<th>Contact</th>
<th>Laser</th>
<th>Ultrasound</th>
<th>Radio-frequency</th>
<th>Argon plasma</th>
<th>Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thermal conduction</td>
<td>Absorption of photons</td>
<td>Mechanical agitation of tissue caused by ultrasonic waves</td>
<td>Resistive heating induced by the impedance of the tissue</td>
<td>Application of high frequency current via ionised argon gas</td>
<td>Agitation of polar molecules such as water</td>
</tr>
<tr>
<td>Typical frequencies</td>
<td>n/a</td>
<td>1000-3000nm</td>
<td>1 – 15 MHz</td>
<td>450 - 1000 kHz</td>
<td>Radio frequency</td>
<td>1 - 10 GHz</td>
</tr>
<tr>
<td>Advantages</td>
<td>Simpler technology required</td>
<td>Very targeted heating</td>
<td>Large volumes ablation</td>
<td>Small applicators possible</td>
<td>Creates very shallow, even burns - 400µm.</td>
<td>Efficient and quick Large ablation volumes possible</td>
</tr>
<tr>
<td></td>
<td>Maximum tissue temperature known if surface temperature known</td>
<td>Energy deliverable via narrow fibres</td>
<td>Depth of penetration can be controlled by frequency choice</td>
<td>Power deliverable via narrow wires</td>
<td>Coagulated material remains in place</td>
<td>Depth of microwave penetration can be controlled by frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No contact with tissue required</td>
<td>Widedly used and accepted</td>
<td>Direct contact not required</td>
<td>Small probe</td>
<td>Predictable heating patterns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal losses en route to treatment site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Difficult to deliver heat to treatment site</td>
<td>Small ablation volumes</td>
<td>Large applicators required for optimal performance</td>
<td>Unpredictable for larger ablation volumes</td>
<td>Large ablations not possible</td>
<td>Large applicators required compared to RF and laser to deliver significant power levels</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>Virtually point source can lead to carbonisation when trying to achieve larger ablation volumes</td>
<td>Energy absorption related to tissue type leading to selective heating</td>
<td>Becomes inefficient as applicator temperature rises</td>
<td>Cannot cope with high levels of blood loss</td>
<td>Tissue desiccation can result in impedance changes resulting in lower energy delivery</td>
</tr>
<tr>
<td></td>
<td>Only small ablation volumes possible</td>
<td>Small heated spot size makes ablating areas slow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical medical uses</td>
<td>Endometrial ablation</td>
<td>Eye surgery</td>
<td>Tumour ablation</td>
<td>Venous occlusion</td>
<td>Coagulation of surface blood vessels</td>
<td>Tumour ablation</td>
</tr>
<tr>
<td></td>
<td>Venous occlusion</td>
<td>Treatment for thread veins and acne</td>
<td>Blood vessel coagulation</td>
<td>Endometrial ablation</td>
<td>Sterilisation</td>
<td>Endometrial ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood coagulation</td>
</tr>
</tbody>
</table>

1.2.7 Table 1.1: A summary of the major thermal medical treatment modalities
1.3 Introduction to microwaves

Microwaves are electromagnetic waves in the frequency range from around 300 MHz to 300 GHz, with corresponding wavelengths in vacuum of around 1m to 1nm. For medical purposes, frequencies of around 1 to 10 GHz are used with wavelengths in tissue of about 1cm. Much of the electromagnetic spectrum (figure 1.1) is routinely used for medical purposes, and the increasing use of microwave therapy is a natural extension.

![Figure 1.1: The electromagnetic spectrum](www.spacetoday.org/DeepSpace/Telescopes/GreatObservatories/Chandra/ChandraSpectrum.html)

Microwave heating is fundamentally controlled by the degree of attenuation of the waves. Since our bodies are mostly water and there is relatively little variation in water content between different tissue types, microwave heating is predictable (see section 2.2.3). Microwaves can also be used at different frequencies to give different depths of penetration and with different shaped antennas to give different field patterns. The absorption efficiency of the microwaves by water also means that relatively low powers can be used to produce large ablation volumes relative to other techniques for heating tissue.

1.4 The history of electrosurgery

The possibility of heating tissue using high frequency currents was first noted by Thompson (1889), who noticed heat in his wrists when currents from his early high
frequency generator were passed through his hands after they were immersed in saline. Jacques Arsene d'Arsonval (1891 & 1893) applied various high frequency currents to human subjects in 1891, and found that frequencies in excess of 10kHz did not produce neuromuscular stimulation, thus allowing the use of high frequency currents to heat tissue in-vivo. D'Arsonval's equipment was modified by Oudin to create sparks that would cause superficial tissue destruction. Riviere (1900) used this equipment to successfully treat an ulcer in 1900, and Pozzi (1909) reports successful use of the equipment to treat skin cancer, claiming that the modality could selectively destroy tumour cells. Doyen (1909) reports the successful use of a return path electrode that was connected to the patient. This produced a more penetrating and effective current. Clark (1911) achieved the first desiccation of tissue, once again with the Oudin current generator, but with a multiple set of electrodes in order to create a multiple set of sparks, rather than a single electrode. The most major advance undoubtedly came from William Bovie (1928). He successfully worked with Harvey Cushing, a neurosurgeon, to create an electrosurgical device that gained widespread acceptability (Goldwyn, 1979).

The use of both bipolar and monopolar radio-frequency has advanced steadily since then, with many medical devices based on the use of radio frequency currents. The use of even higher frequencies was not possible until the development of the magnetron during World War II. Since then the possibility of heating tissue using microwave ovens has been widely exploited. The use of microwaves for medical treatments is also becoming more widespread. The principles of operation of four commercial systems are given below. These demonstrate four successful ways of applying microwave therapy.

1.5 Current microwave therapies

1.5.1 Microwave endometrial ablation (Microsulis® MEA™ - “MEA”)

This treatment is for a condition called menorrhagia, which is heavy menstrual bleeding experienced by up to 19% of women of reproductive age (Snowden & Christian, 1983). This condition frequently leads to a hysterectomy, which is an operation that carries a high degree of morbidity (7% according to Kelly, 1998) and
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even mortality (Baldwin, 2001). MEA uses high frequency microwaves to ablate the lining of the uterus, called the endometrium. This has been a highly successful treatment and to date has been used in approximately 36,000 operations. Some major aspects of the treatment design are given below.

In figure 1.2 is the applicator. This has an 8.5mm diameter shaft which is designed to be able to be inserted into the uterine cavity through the cervix. It has a metal handle that is held by the surgeon, into which are connected a coaxial cable and a data cable. The coaxial cable delivers microwaves from a microwave generator to the applicator, with the data cable feeding back treatment data from the applicator to the treatment system.

![Figure 1.2: The MEA applicator showing the handle with connections for microwaves and data, the shaft that delivers microwaves from the handle to the tip, and the tip itself.](image)

When the treatment is started microwaves at 9.2 GHz are delivered to the applicator causing microwaves to radiate from the tip. The depth of penetration of the microwaves at this frequency is around 2mm, as shown by the plot of microwave tissue absorption around the tip, shown in figure 1.3. This is chosen specifically in order to target the endometrium, by ensuring that power is deposited over the depth of the endometrium. The depth of heating is therefore tailored to the treatment requirements, and this depth of heating is determined by the choice of microwave frequency. The exact radiation pattern of the microwave tip is determined through
computer modelling of the interaction between the applicator and the surrounding tissue, giving results such as those shown in figure 1.3. The use of computer simulation packages also allows the development of efficient applicator designs.

Figure 1.3: A microwave tissue absorption plot of the MEA applicator tip. The tip diameter is 8.5mm, with significant microwave absorption over the first 2mm of tissue.

Once an efficient applicator has been designed and the radiation pattern assessed by computer simulation, prototype applicators can be built. The actual heating pattern that the applicator produces can then be assessed in tissue phantoms, such as those described in section 2.5.5. The heating pattern over time for a stationary MEA applicator is shown in figure 1.4.

Figures 1.4a-e: The heating pattern of an MEA applicator evolving over time. The applicator is bedded in a clear tissue phantom gel called PAG, with added surfactants that turn the gel opaque at a predetermined temperature.
In order to ablate the whole lining of the endometrium, the applicator needs to be swept around the inside of the cavity. This is controlled by the surgeon attempting to maintain a temperature of between 75°C and 85°C at the tip. This temperature is fed back from the applicator to a system, where the temperature is displayed on an attached screen (Cronin & Sharp, 1995). A typical temperature profile and the concurrent progress of the treatment are shown in figure 1.5.

![Figure 1.5: The MEA treatment procedure including a typical temperature profile as seen by the surgeon, and the treatment progress](image)

In order to minimise patient risk considerable efforts are made to characterise applicator temperature profiles, together with their resulting effects. For the case of MEA this means simulating the temperature profiles that will result from surgeons using the temperature feedback described above. The temperature is measured by a thermocouple located at the tip, as shown in figure 1.6. Safety is ensured by limiting the maximum potential burn depth through setting an upper limit on temperature, and this has been shown to limit the maximum possible burn depth to 8mm. In the event that the temperature exceeds 90°C the system cuts microwave power to the applicator, and before every treatment the wall thickness of the uterus is measured using ultrasound to ensure that it is greater than 8mm.
This treatment has effectiveness ratings comparable with surgical removal of the endometrium (Bain, Cooper and Parkin, 2002), but is faster and has considerably lower complication rates. A typical treatment takes around 3 minutes.

### 1.5.2 Microwave tissue ablation (**Microsulis® MTA™ - “MTA”**)

MTA is currently in use for the treatment of liver cancer, but could potentially be used to treat other cancers. These initial trials are being conducted in liver because liver has the advantage that it can re-grow. A tumour in the liver can therefore be ablated along with a safety margin of surrounding tissue. The entire area will then necrose (Swift, 2001), and be replaced over time. Moving on to treat tumours located in other areas will require more care, as the burn will need to be carefully controlled in order to minimise damage to adjacent healthy tissue.
The applicator consists of a radiating monopole antenna, shown in figures 1.7 and 1.8, that is surgically inserted into the area to be ablated. Power is then applied. The resulting ablation can be monitored in real time through ultrasound, or by temperature measurement at the edge of the volume to be treated. The frequency used is 2.45 GHz, which gives a depth of microwave penetration of around 2 cm. This is in order to give a large possible ablation volume. Ablation volumes can be up to around 7 cm in diameter, with a typical ablation lasting 5 minutes. An ablation in ex-vivo liver is shown in figure 1.9. Three different monopole antenna applicators are shown in figure 1.10, together with a flat-ended applicator that is used to treat tumours that have reached the liver’s surface. The flat end of this applicator can be applied to the tumour on the surface to ensure that no surface tumour cells are spared during a treatment, as may have been the case if the tumour had been treated from the inside using a monopole antenna.

1.5.3 Microwave treatment of thread veins (Veinwave™)
This treatment consists of a fine needle that is inserted into thread veins. These are common swollen superficial veins that can be unsightly, as shown below in figure 1.11. Veinwave is therefore a cosmetic procedure. The needle is pushed vertically through the skin, and through the vein. Once the needle is in position, microwave power at 18 GHz is applied for around 1 second. This causes coagulation of the blood at the part of the vessel where the needle is located and thereby occludes it at that
point. This causes the whole vessel to disappear as blood can no longer be carried through the vein. A small red mark will appear where the needle was inserted, which will disappear over time.

![Thread veins](Figure 1.11)

1.5.4 Microwave treatment for benign prostatic hyperplasia (Prostatron®)

Benign prostatic hyperplasia (BPH) is a chronic enlargement of the prostate. Enlargement of the prostate over a man’s lifetime is very common with 20% of men in the 40-50 age group, rising to 80% of 70-80 year olds showing at least microscopic evidence of BPH. According to Kang (2004), 25-50% of these present clinical symptoms. This generally occurs when the size of the prostate results in occlusion of the urethra. The current gold standard treatment for this is to surgically resect parts of the prostate trans-urethrally, called TURP. This can result in chronic bleeding and therefore carries with it a high level of morbidity including a 6.8-10% incidence of deep venous thrombosis and a 0.2-2.2% reported incidence of pulmonary embolus according to Bell and colleagues (1999). The prostatron aims to reduce the volume of the prostate by ablation. The applicator is inserted into the urethra and guided up to the relevant position. Microwave power is then applied at a frequency of 915 MHz for 28.5mins. In order to ensure sparing of the urethra, the shaft of the applicator is water-cooled. The maximum tissue temperature reached is reported as being around 65°C. Both rectal and urethral temperatures are monitored throughout the treatment to ensure they are spared.
Chapter 2: Microwave and thermal analysis

2.1 Introduction

Chapter 1 described the advantages that microwave heating can offer for heating tissue compared to other methods. Despite this, and perhaps surprisingly, microwave based treatments have been used relatively infrequently. This may be because of the difficulty in designing and building efficient applicators that can reliably and accurately deliver their energy. Overviews of some of the few microwave based treatments currently in clinical use were described in section 1.5.

As mentioned in the review of MEA (in section 1.5.1), considerable efforts need to be made to accurately characterise the temperature profiles resulting from any treatment. This is because of the need to minimise potential risks to patients, as well as to be able to demonstrate to regulatory healthcare authorities how the treatment achieves its effects, and how potential risks have been mitigated. Computer simulations and bench testing provide the major means of achieving this.

The use of computers starts with the use of finite element packages to design the applicator and ensure high efficiency with minimum power reflected. Optimising the efficiency of the applicator is important because it maximises the treatment effects available for a given microwave power and enhances safety by ensuring that applicators will not be able to deliver more power to the tissue than expected. This is because they are already delivering all or very nearly all, the energy supplied to them. An efficient applicator is described as being “well matched”, as the match of the applicator is the degree to which it delivers the energy supplied to it into the tissues.

The use of the finite element package also allows the pattern of microwave absorption in the tissue to be characterised. The thermal profile resulting from this absorption can then be simulated using various methods. Finite difference simulations, Green’s function simulations and the use of finite element packages are described in this work. Finite difference simulations (described in section 2.5.2) offer a quick method of simulating temperature rises, particularly for simple geometries that only require simulation in 1 dimension such as planes, infinitely long cylinders, and spheres. They
are used in chapter 3 to simulate the thermal profile resulting from microwave heating of skin, and in chapter 4 to assess the thermal profile resulting from heating of a vein. Green’s functions (described in section 2.5.3) offer the ability to model more complex microwave absorption patterns, but assume a homogenous, isotropic environment of infinite extent. This is applicable for treatments where temperature rises are sufficiently small that significant changes in tissue properties will not occur as the tissue heats up, and especially where the applicator is removed from the tissue once the heating has occurred. This is because the effect of the applicator itself on the thermal profile will be minimised in this case. A Green’s function is used in chapter 4 to modelling the heating of a microwave applicator inside a vein. Finally, the use of finite element packages (described in sections 2.5.4, 2.5.5, 2.5.6 and 2.5.7) allows a much more comprehensive thermal analysis to be performed, incorporating the effect of the applicator itself and changing tissue properties. The effects of temperature measurement devices themselves can even be incorporated. A finite element thermal model is used in chapter 4 to assess how effectively a temperature measurement probe can measure the temperatures surrounding it. However, such thorough analyses can be complex to set up, computationally expensive and do not generally lend themselves well to moving applicators.

Once the thermal analysis has been performed, the tissue damage that is predicted to result from the simulated temperature profile can be assessed through application of the Arrhenius equation to the predicted temperatures at a given location in the tissue. This is described in section 2.6 and is used in chapter 4 to quantify thermal damage as a result of tissue heating in a vein heated by a microwave applicator.

At all stages the results of the simulations can be validated through bench testing as described in section 2.7. For example, the efficiency of the applicator can be checked using reflected power measurements and calorimetry. Also, after the temperature profile has been simulated, the model can be validated by comparing measured and predicted temperatures at specific points around the applicator. Finally, following the application of the Arrhenius equation to the temperature profile, the predicted degree of tissue damage can be assessed. For temperatures sufficient to cause cell death, the
region of cell death can be validated against liver obtained from a butcher. Cellular
damage can also be evaluated through microscopic examination of cellular structure,
as well as staining to show the presence or absence of enzymes required for cellular
survival. Examination of the cellular structure is known as histology, and the major
relevant aspects are described in section 2.7.9.

All the simulations naturally rely on good material properties data to provide
successful predictions. The relevant microwave and thermal tissue properties used in
this work are given in sections 2.2.3 and 2.4.4 respectively.

Section 2.2 gives an introduction to how electromagnetic radiation can cause heating
in tissue and how the interaction between the electromagnetic radiation and the tissue
is characterised at microwave frequencies.

2.2 Complex permittivity

2.2.1 Introduction
The interaction between microwaves and the media through which they pass is of
crucial importance in hyperthermia. The effect on electromagnetic (EM) waves of
propagating through various media can be described by solution of Maxwell’s
equations for a plane wave. A comprehensive analysis is available from Sadiku

The relevant properties of the medium are specified by the permittivity $\varepsilon$, permeability
$\mu$ and conductivity $\sigma$. It is usual to express permittivities and permeabilities in terms
of relative permittivities $\varepsilon_r$ and permeabilities $\mu_r$. This is the ratio of the permittivity
or permeability of the medium to the permittivity $\varepsilon_0$ or permeability $\mu_0$ of free space.
Since none of the media considered in this work have magnetic properties, the relative
permeability can be left as 1. Relative permittivity is also known as the dielectric
constant. For this analysis a plane wave propagating through free space, as well as in a
lossless dielectric, in a good conductor and in a lossy dielectric, will be considered.
Assuming a linear isotropic homogenous uncharged medium, Maxwell’s equations can be expressed as,

\[
\nabla \cdot \bar{E} = 0 \quad 2.1 \quad \nabla \times \bar{E} = -\mu \frac{\partial \bar{H}}{\partial t} \quad 2.2
\]

\[
\nabla \cdot \bar{H} = 0 \quad 2.3 \quad \nabla \times \bar{H} = \sigma \bar{E} + \varepsilon \frac{\partial \bar{E}}{\partial t} \quad 2.4
\]

Taking the curl of equation 2.2,

\[
\nabla \times (\nabla \times \bar{E}) = -\mu \nabla \times \frac{\partial \bar{H}}{\partial t} = -\mu \frac{\partial (\nabla \times \bar{H})}{\partial t},
\]

and substituting in equation 2.4 and applying the identity

\[
\nabla \times (\nabla \times \bar{A}) = \nabla (\nabla \cdot \bar{A}) - \nabla^2 \bar{A},
\]

gives,

\[
\nabla (\nabla \cdot \bar{E}) - \nabla^2 \bar{E} = -\mu \frac{\partial}{\partial t} (\sigma \bar{E} + \varepsilon \frac{\partial \bar{E}}{\partial t}).
\]

The medium is uncharged, so using equation 2.1 and rearranging gives,

\[
\nabla^2 \bar{E} - \mu \sigma \frac{\partial \bar{E}}{\partial t} - \mu \varepsilon \frac{\partial^2 \bar{E}}{\partial t^2} = 0.
\]

In one dimension this can be expressed as,

\[
\frac{\partial^2 \bar{E}}{\partial z^2} - \mu \sigma \frac{\partial \bar{E}}{\partial t} - \mu \varepsilon \frac{\partial^2 \bar{E}}{\partial t^2} = 0. \quad 2.5
\]

Assuming linearly polarised plane wave solutions of form,

\[
\bar{E} = E_0 e^{(\omega t - k z)} i.
\]

where \( \omega = 2\pi f \) and \( k=2\pi/\lambda \), then,

\[
\frac{\partial \bar{E}}{\partial t} = i\omega \bar{E} \quad \frac{\partial^3 \bar{E}}{\partial t^3} = -\omega^3 \bar{E} \quad \frac{\partial^3 \bar{E}}{\partial z^2} = -k^3 \bar{E}.
\]
Substituting into equation 2.5 gives,

\[-k^2 \vec{E} - i\omega \sigma \mu \vec{E} + \varepsilon \mu \omega^2 \vec{E} = 0\]

\[\therefore k^2 = -i\mu \sigma \omega + \varepsilon \mu \omega^2\] \hspace{1cm} 2.7

This result leads to different outcomes for each case of the four media given above.

1. Free space
In free space the medium is non-conducting therefore \(\sigma = 0\).

Therefore from equation 2.7,

\[k^2 = \varepsilon \mu \omega^2.\]

Since group velocity is given by \(\omega/k\) and \(\varepsilon = \varepsilon_0\) then,

\[\frac{\omega}{k} = \frac{1}{\sqrt{\varepsilon \mu}} = \frac{1}{\sqrt{\varepsilon_0 \mu_0}}.\]

The speed of the wave is therefore \(\frac{1}{\sqrt{\varepsilon_0 \mu_0}}\), which is the speed of electromagnetic radiation in free space, called \(c\). As there is no imaginary component to \(k\) the wave does not decay, unlike in situations 3 and 4 below. Free space is therefore \textit{lossless}.

2. Lossless dielectrics
A medium where the relative permittivity is real and greater than unity is a lossless dielectric. In this case \(\varepsilon = \varepsilon_0 \varepsilon_r\). As for a wave propagating in free space \(\sigma = 0\), leading as before to,

\[\frac{\omega}{k} = \frac{1}{\sqrt{\varepsilon \mu}}.\]
Since \( \varepsilon = \varepsilon_0 \varepsilon_r \), then

\[
\frac{\omega}{k} = \frac{1}{\sqrt{\varepsilon_r}} \cdot \frac{1}{\sqrt{\varepsilon_0 \mu_0}}.
\]

The speed of the wave is therefore reduced by \( \frac{1}{\sqrt{\varepsilon_r}} \) from \( c \). Since the frequency is constant, the wavelength is also reduced by a factor \( \frac{1}{\sqrt{\varepsilon_r}} \).

3. Good conductors

If the medium is a good conductor then \( \sigma \approx \infty \), therefore \( k \) is now complex and heavily dominated by the \(-i\mu\sigma\omega\) term. Splitting \( k \) into real and imaginary parts,

\[ k = k_R + ik_I \]

and substituting into equation 2.6 gives,

\[
\bar{E} = E_0 e^{i(\sigma t-k_z z-k_x x)} \hat{z}
\]

\[ = E_0 e^{i(\sigma t-k_z z)} e^{-k_x x} \hat{z} \quad 2.8 \]

Therefore, any degree of conductivity in the medium causes the wave to decay exponentially with distance.

4. Lossy dielectric

A lossy dielectric is a medium which may be partially conducting, with \( \sigma \neq 0 \). It may also be an insulator at low frequencies, yet still cause electromagnetic wave attenuation at high frequencies, such as Teflon at optical frequencies. This is because of the loss mechanisms that can occur when an EM wave passes through a lossy dielectric medium that are frequency dependent.
As shown by the case of a good conductor, any medium that allows a net movement of charge will decay a plane EM wave. However, as the frequency increases attenuation is also caused by the excitation of various microscopic modes in the medium. For tissue at microwave frequencies, the overriding effect is that as the field varies, the polar molecules of which water is made up attempt to orientate themselves with the oscillating electric field. The frictional forces that result cause energy to be lost as heat. At higher frequencies still, bound charges are excited by the waves, also causing oscillation and causing energy to be lost as heat. At yet higher frequencies, quantum effects become increasingly important as photon energies become sufficiently high to cause electron promotions. Since all of these losses are over and above any losses directly attributable to movement of free charges, the lossiness of the medium at microwave frequencies is represented by making the relative permittivity complex, so \( \varepsilon_r = \varepsilon' - i\varepsilon'' \). Since \( \varepsilon \) is now complex, \( k \) is also complex, once again leading to equation 2.8, even in the absence of net charge movement. Complex permittivity together with conductivity therefore encapsulates all the losses in the medium.

Conductivity here is low frequency conductivity, interpreted in tissues as that due to ionic conduction through extracellular space (Duck, 1990). Some authors use an alternative description in which the losses due to conductivity are subsumed into the complex permittivity. However, this prevents a distinction being made between ionic conduction, which is important for the heating caused by currents at RF frequencies, and losses due to the mechanisms given above at higher frequencies such as microwave frequencies.

Due to the fact that the various factors that influence EM wave attenuation are frequency dependent, complex permittivity values are not constants and vary with frequency and temperature. Some typical variations for complex permittivity values with frequency are given below in section 2.2.3.
As demonstrated above, there is an exponential decrease in wave amplitude with distance travelled in a lossy medium. Ignoring time dependence and assuming that the frequency is sufficiently high that losses due to ionic conduction in tissue may be ignored gives

\[ E_z = E_0 e^{-\alpha z}, \]

where \( E_0 \) is the magnitude of the electric field at distance 0, \( E_z \) is the magnitude of the electric field at distance \( z \), and \( \alpha \) is a constant given by,

\[
\alpha = \omega \sqrt{\frac{\varepsilon'}{2\varepsilon^2} \left[ 1 + \left( \frac{\varepsilon''}{\varepsilon'} \right)^2 - 1 \right]},
\]

as derived by Sadiku (2001: pp418-419). \( \alpha \) is the attenuation coefficient and the imaginary component of \( k \). \( 1/\alpha \) gives the 1/e amplitude attenuation depth, i.e. the point at which the wave has attenuated to 36.8% of its initial value. Since the power of a wave is given by the amplitude squared,

\[ P_z = P_0 e^{-2\alpha z}. \]

For a plane wave the power penetration depth is therefore half that of the amplitude penetration depth.

Since the distinction between a good conductor and a lossy dielectric is not easy to make, a distinction is made through reference to the solution of the EM wave equation. Equation 2.7 above is

\[ k^2 = -i\mu\sigma + \varepsilon \mu^2. \]
For a good conductor $\sigma \approx \infty$, therefore the $-i\mu\sigma\omega$ term dominates $k^2$ and $\epsilon\omega \ll \sigma$.

Conversely, for a good dielectric $\sigma \ll \epsilon\omega$. Taking the ratio of $\sigma$ and $\epsilon\omega$ defines $\tan \theta$ (Sadiku, 2001: pp421-422), where $\tan \theta$ is known as the loss tangent and is given by

$$\tan \theta = \frac{\sigma}{\omega\epsilon}.$$

A small loss tangent therefore describes a good (low-loss) dielectric, whilst a large loss tangent describes a good conductor or highly lossy dielectric. The loss tangent can also be shown to be equal to the ratio of the imaginary to real parts of the complex permittivity (Sadiku, 2001: p422). So,

$$\tan \theta = \frac{\sigma}{\omega\epsilon} = \frac{\varepsilon''}{\varepsilon'}.$$

### 2.2.2 Measurement of complex permittivity

A variety of techniques have been used to measure complex permittivity at microwave frequencies. Waveguide techniques are popular for the measurement of permittivity generally, but are not necessarily very well suited to the study of tissue since they require the placing of a sample of known thickness within the waveguide, as performed by Hagmann and Gandhi (1982), Dudeck and Buckley (1992), Abdulnour, Akyel and Wu (1995) and Sphicopoulos, Teodoridis and Gardiol (1985). As the sample must make firm contact all around the waveguide and the thickness of the sample must be accurately known, this is not an ideal measurement technique for biological samples, particularly since biological tissues tend to be very lossy, hence requiring thin films. Alternatively, it is possible to contain the samples in a cell (Szwarnowski and Sheppard, 1977), or place the sample at the end of an open ended waveguide as performed by Alekseev and Ziskin (2000), but this is still not ideal.

Another commonly used technique is measurement of the perturbation of the resonance of a cavity, as described by Raveendranath and Mathew (1996). This has the disadvantage that measurements can only be made at a single frequency.
The technique that lends itself best to the measurement of tissue complex permittivity is through characterisation of the reflection from the end of a coaxial line probe in contact with the medium to be analysed. This has been used by Raicu, Kitugawa and Irimajiri (2000) on skin, Hoshi and colleagues (1998) on teeth, Staebb and Misra (1990) on a variety of tissues, and Clegg (2002) on a variety of tissues. This technique is particularly convenient as it requires little or no sample preparation, and can be carried out in-vivo. The probe needs to be calibrated before use (Misra, 1990), and the measurement is dominated by the material in very close proximity to the tip (Tofighi and Daryoush, 2000). This tends to prevent its use on hard surfaces, but it is ideally suited to most biological tissues.

One additional technique that is not widely used is the free space technique. This was used by Ma and Okamura (1999) to measure the complex permittivity of sawdust in a container at 9.4GHz. This requires planar samples of known constant thickness that are large enough to intercept an entire microwave beam.

### 2.2.3 Complex permittivity values

Some complex permittivity measurements of interest made by Clegg (2002) using the flat ended coaxial cable technique are given in figure 2.1. As can be seen in figure 2.1, the real and imaginary parts of the relative complex permittivity for all tissue types and the tissue phantom gel PAG, are relatively similar. This is because they are all primarily composed of water. Fat, on the other hand, has significantly different complex permittivity values. The attenuation depths that these complex permittivity measurements give are shown in figure 2.2 and table 2.1, calculated using equations 2.8 and 2.9. This figure and table show that microwave absorption increases with frequency over the range 1-10GHz, and that the minor differences in tissue complex permittivity values between the non-fat tissue types shown in figure 2.1 has a limited impact on microwave tissue absorption. Fat, on the other hand, does have a significantly different complex permittivity and a much reduced degree of microwave absorption compared to other tissues, with a corresponding increase in attenuation depth between the frequencies of 1-10GHz.
Figure 2.1: Real and imaginary parts of complex relative permittivity for the tissue phantom polyacrylimide gel (PAG) and several tissue samples. The real parts are positive and the imaginary parts are negative. Clegg (2002)

Figure 2.2: 1/e penetration depth for the tissue phantom polyacrylimide gel (PAG) and several tissue samples Clegg (2002)
2.45 GHz 7 GHz 9.2 GHz

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>2.45 GHz</th>
<th>7 GHz</th>
<th>9.2 GHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAG</td>
<td>12.14 mm</td>
<td>2.22 mm</td>
<td>1.48 mm</td>
</tr>
<tr>
<td>Porcine Aorta</td>
<td>9.75 mm</td>
<td>2.69 mm</td>
<td>1.84 mm</td>
</tr>
<tr>
<td>Human Skin</td>
<td>9.07 mm</td>
<td>2.27 mm</td>
<td>1.51 mm</td>
</tr>
<tr>
<td>Porcine Fat</td>
<td>17.33 mm</td>
<td>6.96 mm</td>
<td>5.22 mm</td>
</tr>
<tr>
<td>Porcine Liver</td>
<td>10.04 mm</td>
<td>2.85 mm</td>
<td>1.92 mm</td>
</tr>
</tbody>
</table>

Table 2.1: 1/e penetration depth values for the tissue phantom polyacrylimide gel (PAG) and several tissue samples

Clegg (2002)

2.3 Waveguide modes and coupling

Waveguides channel electromagnetic waves along predetermined paths. The waveguides used in the work described in this thesis are coaxial cable and hollow metal pipe. Coaxial cable consists of a centre conductor surrounded by a dielectric and clad in an outer metal sheath. In a coaxial cable both the electric and magnetic fields are at right angles to the direction of propagation, as shown in figure 2.3. This is called the transverse electromagnetic or TEM mode. Only waveguides with two or more conductors can carry this mode and unlike modes carried by other waveguides, it has the advantage that it has no low frequency cut off. However, in theory although it can carry any frequency, it becomes increasingly lossy as the diameter of the coaxial cable goes down and as the frequency increases.

![Figure 2.3: The electric field (shown in red) and magnetic field (shown in green) of coaxial cable carrying the TEM mode in axial and longitudinal cross section.](image)

The metal pipe is generally either rectangular or circular and can be filled with a dielectric. It can only operate in either transverse electric TE or transverse magnetic TM form. This means that either the magnetic or the electric fields are perpendicular...
to the direction of energy travel, but not both. This is because at the surface of any good conductor the tangential component of the electric field must be zero and the normal component of the magnetic field must be zero. This cannot be true for both the top and side walls as would need to be the case if propagating a wave in TEM mode. Therefore either the electric or magnetic fields can be transverse. Not being able to carry a TEM mode also means that these waveguides have a low frequency cut-off point. Frequencies below this point cannot propagate, and the excitation dies away exponentially with distance down the guide.

For a circular waveguide, the wave equation can be solved in cylindrical polar coordinates to yield a general solution which is in terms of the Bessel equation, and therefore has an infinite number of roots, and is of a particular order \( n \) (see Cronin, 1995). Any particular solution of order \( n \) and root \( l \) is called a mode. In addition to this, Bessel’s equation has two independent solutions, so there are two sets of modes of the same orders and roots. One set describe the TE modes and one the TM modes. These are denoted by \( \text{TE}_{nl} \) or \( \text{TM}_{nl} \). \( n \) equates to the number of full wave patterns around the circumference of the guide, whilst \( l \) refers to the number of half wave patterns across the diameter. As an example, the electric field patterns of the \( \text{TM}_{01} \) mode are shown in figure 2.4.

\[ \]

Figure 2.4: The electric field (shown in red) and magnetic field (shown in green) of circular metal pipe waveguide carrying the \( \text{TM}_{01} \) mode in axial and longitudinal cross section.

One important reason for visualising the fields of waveguide modes is because a waveguide is usually fed or excited by another waveguide such as a coaxial cable. In order to achieve good coupling and minimal reflection when two different waveguides
are connected, E and H fields need to be produced by the driving waveguide in the second waveguide that are similar to the E and H fields of the mode that is intended to be excited in the second waveguide. For example, this means that a coaxial cable will naturally couple effectively into a circular metal pipe waveguide if the centre conductor is positioned such that it will excite the $\text{TM}_{01}$ mode in the metal pipe waveguide. This is because the fields patterns produced by the centre conductor when positioned protruding into the metal pipe as shown in figure 2.5 will naturally tend to excite the $\text{TM}_{01}$ mode.

Figure 2.5: The electric (shown in red) and magnetic fields (shown in green) at the transition between a coaxial cable and a circular metal pipe waveguide. The diagram furthest to the left shows the field pattern of the TEM mode in a cross section of coaxial cable. In the centre is shown the extension of the centre conductor into the circular metal pipe waveguide and the resulting electric fields in longitudinal cross section. On the right are shown the electric and magnetic fields of the $\text{TM}_{01}$ mode in the circular metal pipe waveguide. The similarity of the field patterns and orientation of the centre conductor in the metal pipe allows good coupling to be achieved between the two waveguides.
2.4 Thermal analysis

2.4.1 Thermal models of biological tissue

Thermal conduction is described by the diffusion equation. For the 3 dimensional case where temperature is a function of position and time, \( T(x,y,z,t) \), the diffusion equation is

\[
\nabla^2 T - \frac{\rho C}{k} \frac{\partial T}{\partial t} = -\frac{P}{k}, \tag{2.11}
\]

where \( k \) is the thermal conductivity, \( \rho \) is density, \( c \) is the specific heat capacity and \( P \) is the source term measured in Wm\(^{-3} \). The derivation of this equation for the one-dimensional case is given in appendix 1.

For the thermal analysis of clinical microwave heating, the source term, \( P \), can now be broken into three parts. Firstly there is the deposition of microwave power. This is commonly expressed in W/kg, and is described as a Standard Absorption Rate or SAR. Secondly, there is blood cooling. Finally there is the internal heat generation due to metabolic processes, which gives,

\[
P = \rho_{t}SAR - \rho_{t}\rho_{b}c_{b}m(T - T_{b}) + \rho_{t}Q, \tag{2.12}
\]

where \( \rho_{t} \) is the density of the tissue, \( \rho_{b} \) is the density of blood, \( c_{b} \) is the specific heat capacity of blood, \( m \) is the volumetric flow rate of blood per unit mass of tissue, \( T_{b} \) is the temperature of the perfusing blood and \( Q \) is the metabolic heat generation, measured in W/kg. Multiplication of the metabolic heat generation and SAR by \( \rho_{t} \) converts the power gain per kg of tissue to power gain per cubic metre of tissue. Similarly, \( \rho_{t}\rho_{b}c_{b} \) is required to convert the units of \( m(T-T_{b}) \) into power loss per cubic metre of tissue.
Inserting equation 2.12 into 2.11 and re-arranging gives Pennes’ (1948) bio-heat equation, which for the 3-dimensional case is,

\[
\frac{\rho_c c_i}{k} \frac{\partial T}{\partial t} = \nabla^2 T - \frac{\rho_c c_b m}{k} (T - T_b) + \frac{\rho_s}{k} SAR + \frac{\rho_Q}{k}.
\]

Pennes’ equation was first developed through his study of temperature in the resting forearm of human subjects. Thermocouples were passed through the arms in order to measure temperature as a function of depth within the arm. Anaesthetic was not used in order that it would not affect the results. Pennes showed temperature differences of 3-4 °C between the skin and interior of the arm. His model proposed that metabolic heat generation is homogenous throughout the tissue. Blood perfusion was also taken to be homogenous and the perfusing blood simply heats or cools the tissue through the micro-vasculature in proportion to its temperature difference with the local tissue. There is assumed to be no energy transfer either before or after the blood passes through any point. Chato (1980), Chen and Holmes (1980) and Lemons, Weinbaum and Jiji (1987), have all questioned the validity of Pennes’ model, as he makes the assumption that blood enters the micro-capillary bed at arterial blood temperature, and effectively that no heat exchange occurs in the arteries. Alternative models have been developed by Wulff (1974), Klinger (1974), Chen and Holmes (1980) and Weinbaum, Jiji and Lemons (1984). These all attempt to take into account the vascular architecture. The first three models propose that larger vessels are modelled separately from smaller vessels and tissue alone. Weinbaum, Jiji and Lemons attempt to model the vasculature based on anatomical observation.

Despite the development of other more complex models, Pennes’ original bioheat equation remains very widely used, particularly since it allows analytical solutions to be sought. Wissler (1998) returned to look at Pennes’ original data in order to re-evaluate his work. Although he demonstrated some flaws in Pennes’ work, he demonstrated that with improved computations, Pennes’ model was a very good fit to the experimental results. Arkin, Xu and Holmes (1994) assessed Pennes’ model in different regions of vascular architecture and concluded that it was effective in
regions of numerous small, but thermally significant, vessels. Xu, Chen, Holmes and Arkin (1991) found in a comparison between Pennes' model, the Chen-Holmes and the Weinbaum-Jiji model, that the Chen-Holmes and Pennes results were virtually identical, which leads to the recommendation of the use of Pennes' model due to its greater simplicity. All the other models suffer from additional complexity and the need to evaluate additional parameters. Charney (1992) provides a comparison of all the major bioheat transfer models.

A major simplification is possible if the heated volume is small relative to the body. It can be assumed that the metabolic processes are sufficient to maintain homeostatic equilibrium at body temperature before heat is applied. The temperature of the blood is also assumed to be fixed at this initial temperature. Since the heated volume is small relative to the body as a whole, the metabolic processes can be neglected and all temperature rises are relative to the initial body temperature with blood circulation acting to return the tissue to body temperature. The absolute temperature can therefore be characterised purely in terms of a relative temperature rise.

2.4.2 Temperature dependent properties
All the differences between the various models are related to differences in their handling of blood perfusion. However, there are other temperature related factors that also need to be taken into account. At temperatures above approximately 60°C (Iizuka et al., 2000), coagulation will cause cooling through blood perfusion to be stopped. At higher temperatures, steam generation starts to become important. This has two effects. Firstly, it helps limit the maximum temperature reached in the tissue due to the latent heat of vaporisation of the water. Secondly, it can also actively push hot water and steam out through blood vessels, which may possibly extend the burn relative to model predictions.

The tissue specific heat and thermal conductivity will also change with temperature (Valvano and Chitsabesan, 1987), and is likely to change quite radically as the tissue begins to dessicate at high temperatures. In terms of the heat input to the tissue, the
applied SAR and match of a microwave applicator is also likely to change as the
dielectric constant of the tissue changes as a result of the tissue heating up.

2.4.3 Measurement of thermal properties
Values for the key properties of specific heat capacity and thermal conductivity are
commonly derived through the use of thermal probes such as thermistors that act both
as a heat source and a temperature sensor (Balasubramaniam and Bowman, 1977 and
Valvano, 1984). The thermistor is placed at the tip of a plastic catheter. It is then
inserted into the tissue and heated (Chen, 1981), Holmes and Chen (1983) and
Valvano, 1983). Both the electrical power delivered and the resulting temperature rise
are simultaneously measured. The resulting temperature profile is a function of the
thermal conductivity, specific heat capacity, power delivered and the blood perfusion,
and unfortunately it is not possible to calculate all the required unknowns directly.
Either the perfusion or the specific heat or the thermal conductivity is required in
order to calculate the others (Arkin, 1986). In-vitro experiments are performed to
allow the specific heat and thermal conductivity to be derived, or the blood supply
must be occluded in-vivo. This allows the specific heat capacity and thermal
conductivity to be derived in the absence of blood perfusion. The perfusion can then
be derived.
### 2.4.4 Thermal tissue properties

Some thermal tissue properties are given below in table 2.2.

<table>
<thead>
<tr>
<th>Material</th>
<th>Density (-\rho) (\text{kgm}^{-3})</th>
<th>Specific heat capacity (-c) (\text{J kg}^{-1} \text{K}^{-1})</th>
<th>Thermal conductivity (-k) (\text{Wm}^{-1} \text{K}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>1050 -1070</td>
<td>3600 J kg(^{-1}) K(^{-1})</td>
<td>0.467-0.527 Wm(^{-1})K(^{-1})</td>
</tr>
<tr>
<td>Bovine</td>
<td>3370 J kg(^{-1}) K(^{-1})</td>
<td>Robinson (1972)</td>
<td>Bovine</td>
</tr>
<tr>
<td>Duck (1990)</td>
<td></td>
<td></td>
<td>Poppendiek et al. (1966)</td>
</tr>
<tr>
<td>PAG – polyacrylimide gel</td>
<td>1030 kgm(^{-3})</td>
<td>4187 J kg(^{-1}) K(^{-1})</td>
<td>0.41 Wm(^{-1})K(^{-1})</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>1110-1190</td>
<td>3150,3280 J kg(^{-1}) K(^{-1})</td>
<td>0.293 Wm(^{-1})K(^{-1})</td>
</tr>
<tr>
<td>1116 kgm(^{-3})</td>
<td></td>
<td>3530,3710 J kg(^{-1}) K(^{-1})</td>
<td>0.385-0.393 Wm(^{-1})K(^{-1})</td>
</tr>
<tr>
<td>(dermis) Duck (1990)</td>
<td></td>
<td>(epidermis) Robinson (1972)</td>
<td>Van der Staak et al. (1968)</td>
</tr>
<tr>
<td><strong>Vessels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human Arteries</td>
<td>1050-1075</td>
<td>3528 J kg(^{-1}) K(^{-1})</td>
<td>0.476 Wm(^{-1})K(^{-1})</td>
</tr>
<tr>
<td>Human Veins</td>
<td>1056 kgm(^{-3})</td>
<td>Derived from thermal diffusivity 1.27 x 10(^{-7}) m(^{2}) s(^{-1})</td>
<td>Derived from thermal diffusivity 1.27 x 10(^{-7}) m(^{2}) s(^{-1})</td>
</tr>
<tr>
<td>Duck (1990)</td>
<td></td>
<td></td>
<td>Van Gemert et al. (1986)</td>
</tr>
<tr>
<td><strong>Fat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human Breast</td>
<td>917-939</td>
<td>2250,2400 J kg(^{-1}) K(^{-1})</td>
<td>0.200-0.246 Wm(^{-1})K(^{-1})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2600 J kg(^{-1}) K(^{-1})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lehmann &amp; Johnson (1958)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2680-3920 J kg(^{-1}) K(^{-1})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Robinson (1972)</td>
<td></td>
</tr>
<tr>
<td><strong>Silica</strong></td>
<td>2200 Kg m(^{-3})</td>
<td>740 J kg(^{-1}) K(^{-1})</td>
<td>1.38 Wm(^{-1})K(^{-1})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plastic (polythene)</strong></td>
<td>940 Kg m(^{-3})</td>
<td>1900 J kg(^{-1}) K(^{-1})</td>
<td>0.47 Wm(^{-1})K(^{-1})</td>
</tr>
</tbody>
</table>

Table 2.2: Thermal properties of relevant materials

As can be seen, there are quite significant differences between published results for both specific heat capacity and thermal conductivity even in the same tissue types. This is likely to be due to the difficulties in obtaining accurate measurements for the reasons described in section 2.4.3. However, as with complex permittivity values, thermal property values appear to be fairly similar across tissue types, bearing in mind the uncertainty inherent in the measurements themselves. This is with the exception of fat, which is consistently reported as having lower thermal conductivity, specific heat capacity and density values than other tissue types.
2.5 Simulations

2.5.1 Introduction
Unfortunately, the electromagnetic field pattern is not the heating pattern. Thermal conduction carries heat away from the region being heated and blood cooling will also alter the degree of heating. This transfer of heat is governed by the diffusion equation. This can be solved using a variety of methods including analytical techniques, finite element and finite difference methods. Finite element solutions require specialist computational analysis programs, but a quick and quantitative estimation of temperature in both space and time can be achieved using simple finite difference techniques.

2.5.2 Finite difference simulations
Finite difference methods simply approximate differentials by calculating gradients numerically. The gradient at any point in $x$ can be estimated by evaluating the absolute value of that equation at points on either side of the chosen point at a distance of $+h$ and $-h$. The approximate gradient will, of course, be the difference between the values of the function evaluated at these two points divided by $2h$. This is called a centred approximation. This naturally means that finite difference approximations are based on grids. In this case the grid spacing is $h$. As $h$ gets larger, the approximation becomes less accurate. The error in this approximation will be of the order of $h^2$. This standard approximation is given by Chapra and Canale (1998) and is,

$$
\frac{\partial T_{i,j}}{\partial x} \approx \frac{1}{2h} (T_{i+1,j} - T_{i-1,j})
$$

where,

$$
T_{i,j} = T(x_i, t_j) \quad \text{and} \quad x_{i+1,j} = x_{i,j} + h.
$$

Double differentials can also be approximated numerically using

$$
\frac{\partial^2 T_{i,j}}{\partial x^2} \approx \frac{1}{h^2} (T_{i+1,j} + T_{i-1,j} - 2T_{i,j}).
$$
The centred approximation relies on being able to evaluate the function on either side of $x$. Boundary conditions are therefore required. These specify the value, or the gradient of the function, at the extreme edges of the grid i.e. $x = 0$ and $x = L$ when the grid runs from 0 to $L$. These effectively set the reference frame for the rest of the approximations.

Since this is a system that evolves in time, time is also represented on the grid with a spacing of $n$. The temperature profile at any point $t + n$ is governed by the temperature profile at $t$. However, the temperature profile at $t + 2n$ is as yet unknown when the profile at $t + n$ is approximated. A simpler approximation is therefore used. This simply evaluates the temperature difference between points $t + n$ and $t$ and divides by the step size $n$. This requires an initial temperature profile at $t = 0$ rather than boundary conditions in order to give a temperature profile to start from. Since the gradient is evaluated over fewer points the error increases relative to a centred approach and is of the order of $n$. The approximation is therefore,

$$\frac{\partial T_{i,j}}{\partial t} \approx \frac{1}{n}(T_{i,j+1} - T_{i,j})$$

where,

$$T_{i,j} = T(x_i, t_j) \quad \text{and} \quad t_{i,j+1} = t_{i,j} + n.$$  

This numerical description is called a forward time centred space approach.

Not only does the error increase as $h$ and $n$ increase, but the errors can reach a point where they make the algorithm unstable. This is important since there is a trade-off between accuracy and speed. As $h$ and $n$ increase, the speed of the approximation increases since there are now fewer points in the grid, at the expense of accuracy. Fortunately computers are now sufficiently powerful to run the algorithms used for the temperature calculations in this thesis quickly, even with small grid spacings. The
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stability requirement according to Chapra and Canale (2002) for this simple forward time centred space approach is given by

\[ \frac{1}{2} > \frac{kn}{h^2} \]

where \( k \) is the thermal conductivity. This requirement also ensures convergence.

2.5.3 Green's function simulations

Another common method for the solution of PDEs, such as the diffusion equation, is by the use of Green's functions, as described by Courant and Hilbert (1953).

The SAR applied to the tissue can be visualised as a set of impulse heat sources, or "source points". Each impulse heat source will cause a temperature rise at a point in space that is a function of the tissue properties, time and the distance between the heat source and the point where the temperature is measured. The point at which the temperature rise is required is the "field point". Let \( G(d, t) \) denote the temperature rise of the tissue at any distance \( d \) from the source point at time \( t \), where \( t \) is measured from the impulse. This is the Green's function kernel, which is effectively a solution for the case in which the medium is assumed to be homogenous except at one point.

For the case of a infinite homogenous medium, the Green's function \( G(d, t) \) as described by Yeung (2001), is given by

\[ G(d, t) = \frac{\alpha \rho_c}{k(4\pi \alpha t)^{3/2}} e^{-\frac{d^2}{4\alpha t}} e^{-\alpha t} \]

where \( \alpha \) is given by \( \frac{k}{\rho c} \), and \( \nu \) is a lumped perfusion parameter given by \( \sqrt{\rho_s \rho_c c_b m/k} \). \( m \) is the volumetric flow rate of blood per unit mass of tissue. The factor \( \rho_s \rho_c c_b \) is required to convert \( m \) into units of Wm\(^{-3}\).
Once the Green's function kernel is obtained, linearity is then assumed and this allows superposition of the solutions from single impulses to give solutions for the defined heat source distributions over the required time. The total temperature rise at a point in space caused by a source distribution $SAR$ is therefore given by the volume integral of $G$ over the full range of source points in the region $SAR$, taking into account that the magnitude of the point source heating described by $G$ is a unit magnitude. The $SAR$ therefore needs to be convolved with $G$ in order to give the correct magnitude of heating. This gives the temperature rise from a single impulse of heat with the distribution $SAR$. The entire expression then needs to be integrated over time to give the temperature rise that will be induced by the $SAR$ being applied for a length of time. For the case in which the applied $SAR$ is defined in cylindrical polar coordinates, the temperature rise $\Delta T(r_0, t')$ at a point in space $r_0$ after a length of time $t'$ during which the $SAR$ has been applied, is given by

$$\Delta T(r_0, t') = \int \int \int G(r_0 | r', t) SAR(r, \theta, z) r \, d\theta \, dz \, dr \, dt$$

where $r_0$ is the field point located in space at $(r_0, \theta, z_0)$, $r'$ are the source points located at $(r, \theta, z)$, and $r_0 | r'$ is the distance between the source points and the field point.

Due to the complexity of the resulting integrals, a numerical solution method can be required. The commercial program Mathcad® can be used to generate the solution.

### 2.5.4 Finite element (FE) simulations

Correctly matching the applicator to the tissue at the chosen treatment frequency and ensuring the correct field pattern is extremely difficult without the help of a finite element package such as Ansoft HFSS (High Frequency Structure Simulator, 2003) or ANSYS version 8.0 (2003). Theory gives guidelines as to the approximate shape to make the applicator, whilst the fine tuning is conducted by building and testing the applicator in the computer, as, for example, in figure 2.6. The results from a particular simulation allow the design to be altered and improved. This saves making and testing each particular design, and hence saves time. Furthermore, all the dimensions of a design can be parameterised. This allows either automated optimisation of the design
dimensions, or a batch analysis with the dimensions stepping through a range between pre-determined limits.

It is also possible to perform finite element thermal analyses, including mapping of the heating induced by an applicator generated by an electromagnetic solution into a thermal solution, or even coupling of the two solutions in ANSYS. This allows both the microwave properties and the thermal properties to be optimised.

FE analysis involves four underlying steps. Firstly, the region to be solved is divided into a finite number of subdivisions, or elements. The governing equations for the elements are then derived. All the elements are then assembled into a matrix which is finally solved to obtain the required unknowns for each element. The procedure for generating and solving a FE simulation is described below.

2.5.5 Initial decisions
There are three initial decisions to be made:

a) What to model
There is always a trade-off between computation time and model completeness. The more detail that is included the longer the simulation takes, but the greater the chance of obtaining a solution that is an accurate reflection of reality. It is therefore very
important to assess correctly what is required, and what can be approximated or ignored.

b) How to model it

It is often possible to take advantage of symmetry when modelling. In order to take advantage of this, the geometry, loading conditions and material properties need to be symmetric. There are four different types of symmetry that can be applied. Axisymmetric, rotational, reflective and repetitive. Axisymmetric means complete symmetry around a central axis, so that model can become two dimensional. Rotational means that there are repeated segments around a central axis. Reflective means that one half of the model is the mirror image of the other half. Finally, repetitive means that segments are repeated along a straight line.

c) Choice of element type

This is partly governed by the point above. Depending on the different degrees of symmetry in the model, different element types need to be used. A two dimensional axisymmetric model would require two dimensional axisymmetric elements that take this symmetry into account. Naturally, the correct element type for the dimensionality of the problem needs to be chosen, such as whether to use line elements, shell elements, two dimensional or three dimensional elements. The element shape can also be determined. For example, the elements can be brick shaped, tetrahedral, quadrilateral or triangular. In addition, the element type must be suitable for solving the problem, for example, thermal, electromagnetic or structural.

2.5.6 Preprocessing

In general the following five steps are required:

a) Creating the model geometry

This can be approached in two basic ways – bottom-up, and top-down. Bottom-up means defining keypoints in space. These are then joined by lines, which in turn are linked together to form areas and volumes. In the top-down approach, basic volumes called primitives are defined through a minimal set of commands. These are then operated upon using Boolean operations, to create the required geometry. Both approaches can be combined in the course of creating a particular geometry.
b) Defining the materials
This simply means applying the relevant properties to all the volumes in the geometry. These can have temperature dependence in ANSYS. It is important to use the same units as those used in the creation of the model, as definition of the units is not required to obtain a solution.

c) Meshing the model
This is an important step in the creation of the model as the model geometry created earlier plays no part in the actual solution. Only the mesh created within the geometry will be used to generate the solution. The greater the mesh density the more likely it is for the solution to be accurate. However, this has to be set against the additional computation time required when solving larger matrices. In order to assess the areas that need refinement and maximise accuracy, the mesh density can be increased in areas of importance after an initial trial solution has been obtained, as shown in figures 2.7a & b. This can be done manually or automatically. In a thermal solution, areas of high thermal gradient are the areas that may benefit most from mesh refinement. In a HF solution, areas of high field intensity will benefit most from a finer mesh. Automatic mesh generation and refinement saves time in the short term when generating the model, but may well cause refinement in areas that are not required, adding significantly to the computation time.

![Figures 2.7 a & b: Increasing number of elements in the dielectric of a varicose veins applicator modelled in HFSS as the mesh is refined](image-url)
d) Applying loads
These are the model constraints and boundary conditions. For high frequency solutions typical loads are port excitations and radiation boundary conditions. For thermal solutions, heat flux, fixed temperature areas, adiabatic surfaces, radiating surfaces, convecting surfaces and internal heat generation loads are often used.

e) Solving
The solution of an ANSYS model is performed in loadsteps. This is defined as one set of loading conditions for which a solution can be obtained. For a thermal solution a loadstep lasts for a given time. Within each load step the solution is broken down into substeps. So for a thermal solution a new solution would be generated at each substep. Once again there is a trade-off between computation time and solution accuracy. More substeps will give a more accurate result, but result in longer solution times. At the end of each loadstep different loading conditions can be applied. For example, in a thermal solution, the SAR of an applicator can be removed after a given time period in order to allow both heating and cooling to be modelled. The thermal properties of the tissue can also be made temperature dependent.

It is also possible to change the solution type from one loadstep to another. For example, once the SAR and match of an applicator have been derived from an electromagnetic solution, ANSYS allows the SAR to be directly mapped into a thermal model. This transfer of data from one solution to another is applicable when the two interactions are loosely coupled. This means that one of the simulations is considerably less influenced by the changes induced from the results of the other one than vice versa. This situation can be iterated, though, so that the thermal changes can be used to alter the SAR and match, which in turn are fed back into the next thermal analysis. In other words the microwave properties of the tissue have been made temperature dependent.

2.5.7 Post-processing
Once a solution has been generated, the results generated need to be filtered to obtain only the information of interest. This is typically achieved through the use of contour
plots on cross sections, animations and graphs of relevant data at points of interest. Correct interpretation of the results is crucial and it is, of course, always important to relate the model output to reality. It may be necessary to re-examine the implementation of the model.

2.6 Use of the Arrhenius equation to estimate cell damage

2.6.1 Introduction

The degree of damage to the cell is a function of both temperature and the length of time for which the temperature is maintained. A higher temperature for a shorter time is therefore equivalent to a lower temperature for a longer time. The influence of temperature and time on cell damage has been studied by Borelli (1990) in tests on baby hamster kidney (BHK) cells between 43.5°C and 57°C. It was concluded that as a general rule of thumb, a decrease in temperature of 1°C requires a 1.8-fold increase in heating time to achieve the same percentage of cell survival. The absolute level of cellular damage for a particular length of time at constant temperatures of 43.5, 46, 50, 54 and 57°C were also given by Borelli.

In reality, the temperature experienced by tissue at any given point is not constant, but is a function of time $T(t)$. In this case the degree of thermal damage can be quantified by use of the Arrhenius equation, as first performed by Moritz and Henriques (1947) using

$$
\Omega(\tau) = \ln \left( \frac{C(0)}{C(\tau)} \right) = \int_0^\tau A e^{-E/RT(t)} \, dt
$$

where $\Omega(\tau)$ is the degree of tissue damage at time $\tau$, $E$ is an activation energy, $R$ is the universal gas constant (8.314 J/mole/K) and $A$ is a rate parameter. $T(t)$ is in Kelvin and $C(\tau)$ is the proportion of cells surviving at time $\tau$.

This equation is widely used for quantifying the progress of chemical reactions and has been used almost without modification for quantifying hyperthermia induced tissue damage. In chemistry, the activation energy is the minimum energy required by
a molecule to react with another molecule. The $e^{-E/RT(t)}$ term comes from the Maxwell-Boltzman distribution and gives the likelihood that the two molecules will be carrying this minimum energy. As is to be expected, this probability rises with temperature. The rate parameter can be visualised as giving a likelihood that the two molecules will successfully meet to allow a reaction to take place. A comprehensive introduction to the Arrhenius equation and its use in quantifying the progress of chemical reactions is given by Zubay (1993).

An important assumption of the Arrhenius equation is that for a constant temperature the decrease in surviving cells as a function of time will be an exponential decay since

$$C(t) = C(0) e^{-E/RT(t)}.$$

For a fixed temperature, activation energy and rate parameter $A e^{-E/RT(t)}$ will be a constant. In this case letting $R = A e^{-E/RT(t)}$ will give

$$C(t) = C(0)/e^{Rt}.$$

This model therefore assumes that at a fixed temperature cellular survival decays exponentially, and the rate of this decay is a function of the temperature and the chosen activation energy and rate parameter. There are two problems with this approach. Firstly, for quantifying tissue damage the values of $E$ and $A$ have no physical meaning. Secondly, as shown in section 2.6.2, cellular survival has been shown to decrease at a greater than exponential rate at a fixed temperature, bringing into question the validity of this approach to quantifying thermally induced tissue damage. However, the Arrhenius equation is very widely used and there are no commonly accepted alternatives.

$E$ and $A$ are parameters that need to be determined from data such as Borelli's, such that omega is unity at the point of irreversible tissue damage. This is taken to be when cell survival rates are at 37%. Published values include $E = 430,000 (+/-.85,000)$.
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J mole$^{-1}$ and $A = 5.6 \times 10^{63} (\pm 8 \times 10^{12}) s^{-1}$, used by Baldwin (2001). Iizuka (2000) uses values of $E = 506,400$ J mole$^{-1}$ and $A = 2.984 \times 10^{80} s^{-1}$. The wide variation in values means that a very wide range of possible conclusions for burn depth can be drawn. Indeed, even the uncertainties on the values for $A$ and $E$ given by Baldwin (2001) are so large as to render the given values as meaningless.

### 2.6.2 Fitting Arrhenius equation parameters to published data

Since published values for $A$ and $E$ are so highly variable, values of $A$ and $E$ for use in this work were found from looking back at the original data on cell survival over time at fixed temperatures from Borelli. Borelli's results are plotted below in figures 2.8a-e, with the fraction of cells surviving plotted on a log scale on the y axis in blue, against time. The increasing gradient of the line shows that the rate of cell death does in fact increase faster than exponentially over time. As mentioned earlier, this means that the Arrhenius equation cannot therefore be made to fit the entire curve, no matter what values of $A$ and $E$ are chosen. However, since the most important part of the curve is the upper part, which is where the vast majority of the cell death takes place, values for $A$ and $E$ can be chosen to most accurately describe this part of the curve. Using values for $E$ of $5.064 \times 10^5$ and $A$ of $8.5 \times 10^7$ gives the pink lines in figures 2.8a-e. This shows that there will be a slight overestimate in the percentage of cell death up until the point at which cell survival reaches approximately 37%. If heat is applied for longer that this, then cell death rates increase dramatically relative to the Arrhenius predictions. This therefore fits well with 37% cell survival representing tissue death, as any slight degree of heating beyond this point will cause a greater level of tissue death than predicted by the Arrhenius equation using the chosen values for $E$ and $A$. There is a good agreement between the Arrhenius predictions and all the experimental data available, which is over the range of temperatures from 43.5°C to 57°C. This represents agreement over three orders of magnitude in terms of time.
Figure 2.5a: Experimental cell survival data (blue) compared to the fitted Arrhenius equation (pink) at 43.5°C

Figure 2.5b: Experimental cell survival data (blue) compared to the fitted Arrhenius equation (pink) at 46°C

Figure 2.5c: Experimental cell survival data (blue) compared to the fitted Arrhenius equation (pink) at 50°C
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Figure 2.5d: Experimental cell survival data (blue) compared to the fitted Arrhenius equation (pink) at 54°C.

Figure 2.5e: Experimental cell survival data (blue) compared to the fitted Arrhenius equation (pink) at 57°C.
2.7 Bench testing

2.7.1 Introduction

A variety of bench test models are used to characterise applicators, including the tissue phantom polyacrylamide gel (PAG), gelatine based gels, egg white, foam and water loads, ex-vivo animal liver and ex-vivo human samples. Histology can then also be performed on the ex-vivo animal and human samples. All of these have very similar microwave dielectric properties, thus allowing the match to be tested using the network analyser and in all cases except for the foam load, the heating pattern to be visualised. They cannot, of course, take into account the effects of blood cooling, but they are an extremely valuable tool for the development and testing of applicators.

2.7.2 Temperature logging

In conjunction with these models, temperature logging is often required. This is performed in two ways. For temperature measurements outside of the microwave field standard thermocouples, such as those shown in figures 2.6 and 2.8, have been used. These are connected to an analogue to digital converter to allow temperature-logging, as shown in figure 2.7, which interfaces with a computer to log the data. For measurements inside the microwave field, Luxtron® optical fibre temperature measuring probes have been used in conjunction with Luxtron’s 3201 and 720 data collection systems. Once again, these are interfaced with a standard PC in order to log the data.

Fibre optic temperature sensors are not affected by the microwave field as the probes contain no metal parts, but in regions of rapidly changing field intensity, there can be a slight delay in their response, as explained in section 4.8.4.
2.7.3 Calorimetry
A definitive measurement of the output power of a device can be made through calorimetry. The applicator is placed in a known volume of water held in an insulated container and power applied for a known time. The temperature rise is measured. Knowing the specific heat capacity of water together with the volume heated, the length of time that heat is applied for and the temperature rise, allows the power output of the applicator to be calculated. The volume of water surrounding the applicator needs to be sufficient to prevent significant levels of microwave leakage. The penetration depth of the microwaves at the frequency being used therefore needs to be taken into account in the design of the calorimeter. If the power input to the applicator is known, the efficiency of the applicator can also be calculated.

2.7.4 Network analyser measurements
A network analyser compares the microwave signal that leaves the analyser and is incident on a test device with either the signal that is transmitted through the test device, or the signal that is reflected from its input. Of most importance for the work in this thesis is the reflection coefficient, called “S11”. This consists of both a magnitude and phase. For characterisation of applicator efficiency only the magnitude is required and this is commonly referred to as the “match”. For calculation of the complex permittivity of materials, accurate measurement of magnitude and phase is required. The ratio of the magnitude of reflected to incident power is generally displayed in dB. An applicator with an S11 of -10dB therefore reflects 10% of incident power. This is normally the minimum required for an applicator to be described as “well matched”. Such a level is, of course, arbitrary.

2.7.5 Polyacrylamide gel (PAG)
Initial testing of applicators is often performed in PAG. This is a transparent, jelly-like, high water content gel that is clean, easily storable, reusable and has similar dielectric and thermal properties to tissue (Andreuccetti, 1988). It can also have surfactants added to it that become opaque at a predetermined temperature (Yamura, 1982). This enables heating patterns to be visualised, as shown in figures 2.12a and 2.12b. It has a major advantage over other phantom materials in that it can stand the
temperatures that are achieved during microwave ablation without melting. Appendix 2 gives details of the process used to make PAG.

Figures 2.12a & b: Applicator heating patterns being tested in PAG  Clegg (2002)

2.7.6 Egg white
Egg white has been a commonly used microwave tissue phantom material. It has the advantage that it is non-toxic and gives a very visible white heated volume. On the other hand it is difficult to prepare large quantities and is therefore only useful for heating small volumes. Another disadvantage is that convection is possible, which distorts the perceived heating pattern. However, it can be ideal for presentations.

2.7.7 Foam and water loads
These consist of open cell foam that is moistened until wet, but not sodden. This means that the applicator surroundings are wet, but the water cannot convect, so allowing the temperature of the water surrounding the applicator to rise. It is ideal for testing the temperature response of applicators and also allows the match to be assessed.

2.7.8 Ex-vivo animal liver
Liver has the useful property of blanching at a temperature of around 50 °C, as shown in figure 2.13, in addition to possessing the correct dielectric properties and thermal properties. This makes it ideal for evaluating the likely size of the burn in-vivo. The
liver is typically warmed in a water bath to 37°C, after which the experiment is carried out. Pig’s liver is typically used due to its lack of vessels. Unfortunately it consists of relatively thin lobes of around 3cm in thickness. This is insufficient for large burns and experiments conducted at low frequencies. It also makes it difficult to section into thin slices and there is also the possibility that surface cooling will influence the result. Ox liver is available in large pieces, but the vascular architecture is of greater calibre, which often results in less clear-cut results than otherwise would be available.

![Figure 2.13: A well defined burn in liver](image)

### 2.7.9 Ex-vivo human samples and histology

Human tissue that has been removed from consenting patients can also be used to perform tests. These have the advantage that they will replicate in-vivo conditions as closely as possible, with the exception of course, of blood perfusion. Also, if it is still within 10-15 minutes of being removed, the tissue will still be alive. The burn can then be induced, followed by fixation of the sample in liquid nitrogen. The resulting histology that can be performed should give a realistic idea of the likely extent of the burn in-vivo. If the tissue sample is already dead, then a burn can still be done and histology performed, but it is likely to be an underestimate of the likely burn in-vivo, since only the gross destruction of cells will be recorded.

For investigation of gross damage to cells, loss of collagen birefringence is commonly used, as described by Thomsen (1989). Polarised light is shone through a thinly sectioned piece of tissue, and examined under a microscope. Thermally undamaged tissue with high collagen content appears bright, as shown below in figure 2.14, whilst damaged tissue appears dark, as shown in figure 2.15.
Unfortunately, microwaves are a well-known method of fixing tissue (Kok and Boon, 1990 and Yamashiki et al., 2003), and the changes that result in a change in collagen birefringence, also require a threshold level of time and temperature. This means that the changes that may be expected to be observable to demonstrate cell death are only visible after much higher levels of thermal damage than are required to kill the cell. A more subtle, but still common technique checks for the activity of a mitochondrial enzyme called succinic dehydrogenase (SDH) (Swift, 2003 and Yamashiki, 2003). Succinic acid and a stain called nitrotetrazolium blue is added to the tissue, and in areas where the enzyme is still functioning the enzyme catalyses a reaction to convert the stain to an insoluble pigment. The stain is then washed away with water, but remains fixed in the areas of viable tissue. The live areas are therefore left stained blue, as shown below in the uterus in figure 2.16.
Certain cells are low in SDH, such as veins, so an alternative, but similar test is used to check for the viability of another enzyme called NADH. Once again, nitrotetrazolium blue is used to check the outcome of the test. A typical outcome is shown in figure 2.17. The vein on the right was not thermally damaged, whilst the one on the left was.

![Vein Images](image_url)

Figure 2.17: A thermally damaged vein (left), alongside a non thermally damaged one (right) (Metcalfe, 2004)

It is important to recognise that whilst the viability test demonstrates the degree of damage inflicted upon a particular enzyme, this does not prove cell death since it is impossible to be sure that the cell cannot recover.
Chapter 3: Psoriasis

3.1 Introduction

3.1.1 Background

Psoriasis is a chronic skin inflammation caused by abnormally quick skin cell reproduction. Ortonne (1996) has shown that the cell cycle is reduced from 311 hours to 36 and the skin cell transit time, which is the length of time it takes for the skin cells to travel from the base of the epidermis to the surface, is decreased from 28 days to just 4. Psoriasis presents in a variety of forms, but around 80% of sufferers have plaque psoriasis, such as that shown in figure 3.1, which leads to red thickened areas with silvery scales. It also presents differently in different individuals, and ranges from very mild intermittent attacks to the severe and chronic. It can even change from one type to another over a patient’s lifetime. It tends to appear on the elbows, knees, small of the back and other areas that are regularly flexed, such as the hands and feet (Ashcroft, Po & Griffiths, 2000). Fortunately for sufferers, it tends not to appear on the face, except in the most serious cases.

Figure 3.1: Chronic plaque psoriasis

The exact cause is unknown but it appears to be due to a damaged immune system response that manifests itself cutaneously. Psoriasis often appears aggressively at around 20 years of age, but can appear at any time. It can also appear later on in life at around 60, at which point it tends to be less aggressive (Ashcroft, Po & Griffiths, 2000). There is a large genetic component to the disease. Children with no psoriatic parents, but first-degree relatives who do suffer from the disease, have a 4% chance of
inheriting it. According to Swanbeck and colleagues (1997), if one of the parents is a sufferer then the risk rises to 28% and if both parents are sufferers then the risk rises to 65%. The disease is therefore likely to be caused by multi-site genetic defects. There are several proposed genetic linkages with one in particular standing out. The marker Cw6 was present in 85% of individuals with early onset psoriasis in a study by Tilikainen and colleagues (1980). Monozygotic twins, however, only have a 72% chance of sharing the condition (Farber & Nall, 1971), so genetics is certainly not the only culprit. Stress, physical injury, infection and the use of drugs are also known contributory factors (Ashcroft, Po & Griffiths, 2000).

Psoriasis is a surprisingly widespread disease with around 1-2% of the population affected, according to the results of a questionnaire survey in the US by Farber and Nall (1974). This means that there are around 1 million sufferers in the UK and around 4-5 million in the US. It is also an extremely unpleasant affliction. Rapp and colleagues (1999) found in their study that “Patients with psoriasis reported a reduction in physical and mental functioning comparable to that seen in cancer, arthritis, hypertension, heart disease, diabetes and depression.” Despite being so common and unpleasant there is relatively little research interest as it is both non-life threatening and notoriously difficult to treat. There is no cure at present, and treatment therefore focuses on limiting the disease. Current treatments can be divided into three basic categories – topical agents, phototherapy and systemic agents. Topical means that the treatment is restricted to the skin, whilst systemic means that the treatment is applied throughout the body. Creams are therefore topical agents, whilst drugs that are injected or taken orally are systemic.

### 3.1.2 Current psoriasis treatments

First-line treatments are generally topical. The simplest treatment is simply an emollient. This aims to reduce the itchiness and scaliness of the plaque. Steroidal creams, coal tar and anthralin are commonly used for patients with mild to moderate psoriasis. They tend to be messy and ineffective however, with a response rate of around 50%. For more serious cases of psoriasis UV therapy (PUVA) and oral anti-cancer drugs such as Methotrexate are given (Boreham, Gasmann and Mitchel, 1995). However, these more effective treatments also have potentially more serious side
effects. The dangers of UV radiation are well known (Ashcroft, Po & Griffiths, 2000),
and psoriatics can only have a limited number of courses of treatment over their
lifetime. Since psoriasis is a disease involving cellular proliferation, anti-cancer drugs
provide the most effective treatment, but they are also the most harmful, with possible
serious and long-term side effects (Duhra, 1993).

3.1.3 Hyperthermia for the treatment of psoriasis

Hyperthermia means heating tissue to sub-lethal temperatures, and is a promising
candidate for psoriasis treatment. It was extensively tested in the 1970s and 1980s
when attempts were made to heat psoriatic plaques to between 42°C and 45°C with
ultrasound (Orenberg, 1980), infrared radiation (Westerhof, 1987), water (Orenberg,
1986) and exothermic pads (Urabe, 1981). These temperature levels are sufficient to
induce a response, whilst still being below the pain threshold. This is reported as
being 46°C by Cook (1952) who heated subjects using microwaves at 3GHz.
Microwave therapy would provide another treatment option for small, and also
possibly larger, area chronic plaque psoriasis, and remove the need for patients to be
exposed to high doses of potentially carcinogenic UV radiation.

The mechanisms that produce a response to hyperthermia are unknown, but excessive
heat is well known to prevent cell replication by inhibiting DNA, RNA and protein
synthesis (Westerhof, 1987). Heating produces heat shock proteins such as p53
(Conner, 1977) that are known to slow the cell cycle. Another possibility is that
localised heating may have an effect on the immune system, thus directly altering an
underlying cause of the psoriasis. It could be that both effects are important in treating
psoriasis. Cancer is also a hyperproliferative cell disease, like psoriasis, and
hyperthermia has been shown to be a clinically effective cancer treatment in mice by
Herman (1977).

Skin cells are formed at the base of the epidermis, the stratum basale, (indicated in
figure 3.2) and move up from there to form the other layers of the epidermis. Psoriatic
cells do not appear to adequately respond to spatial limitations. They therefore end up
effectively producing what would be a large sheet of cells in the relatively small area
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

of the plaque. This leads to an even more irregular base than in healthy skin. The cross section through a psoriatic plaque shown in figure 3.2 shows just how irregular the epidermis can be. The heating needs to penetrate down to the base of the epidermis in order to be as effective as possible. This undulation makes delivering the heat effectively more difficult, since there is high blood flow in these folds, and the pockets of skin that hang down will be well cooled by the blood flow surrounding them. In fact, cutaneous blood flow in plaques is around ten times higher than in healthy skin according to Kemp and Staberg (1983).

Figure 3.2: A cross section through a psoriatic plaque. The stratum basale is arrowed in the picture and is visible as a thin layer of dark purple cells. The epidermis starts at the stratum basale and includes all the layers from the stratum basale to the surface. (http://www.jichi.ac.jp/usr/path/athos/gifs/i90853.gif)

In order to maximise treatment effectiveness, the superficial 3mm of the skin needs to be heated to a therapeutic temperature according to Orenberg (1986). This is typically between 42 and 45°C. However, if the skin surface is maintained at a therapeutic temperature, hyperthermia induced by simple hot pads, water contact and infra-red heating hyperthermia systems can result in insufficient heat conducting down to ensure a therapeutic effect over the crucial 3mm (Orenberg, 1986).
Ultrasound does induce heating in the tissue and appears to produce an improved therapeutic response compared to exothermic pads. Urabe and colleagues (1981) produced a clinical response in 16-45 days using pads at temperatures of 42-43°C, whilst an ultrasound hyperthermia system produced a response in an average of six treatments given over a two week period at a temperature of 43°C (Orenberg, 1980).

Since microwaves also deliver heat directly into the tissue, they offer the opportunity to replicate, or perhaps even improve upon, the results achieved by ultrasound heating. Microwave hyperthermia was demonstrated by Keddy-Grant (1990), who treated three volunteers with microwaves at 2.45 GHz. One was successfully treated, and remained psoriasis free during the three-month follow-up period. The other two volunteers withdrew from the trial due to uncomfortable deep heating. The promise of microwave therapy therefore appears to have been demonstrated, but only at an inappropriate frequency that will cause significantly deeper heating than is required.

As shown in table 2.1, the 1/e penetration depth of microwaves at 2.45 GHz is 9mm. This is significantly greater than the 3mm of heating that is thought to be optimum. It should therefore be possible to perform a very similar treatment to those of Urabe and Keddy-Grant, but using microwaves at a more appropriate frequency. This should replicate their results with similar efficacy but with less side-effects.

On the other hand, given the apparent success of hyperthermia for treating psoriasis, it is unclear why research appears to have been discontinued. The results of the ultrasound trial by Urabe and colleagues (1981) in particular appear to be very promising. One possibility is that the production of a commercial treatment system is not economic due to the complexity required of such a system. In addition, the fact that only a limited area can be treated by ultrasound therapy would make this treatment modality too time-consuming to be used in the case of most patients. This is because psoriatics are likely to have multiple plaques located all over the body. The same may also be true of microwave based treatments, but additionally, the withdrawal of 2 out of 3 subjects in the only published microwave based trial would almost certainly discourage further research in this direction. It is also possible that all the studies were very careful in their patient selection, and hyperthermia would not prove to be as effective as other interventions in a randomised controlled trial.
3.2 Aims of the research

It should be possible to maintain the advantages of a microwave treatment whilst preventing the problem of deep-heating that occurred for Keddy-Grant, by altering the frequency used in the treatment to a higher value than 2.45GHz and so reducing the penetration. The aim of this work therefore consists of three fundamental parts. Firstly, to assess the most appropriate frequency at which to conduct a treatment using a thermal model. Secondly, to develop a system that will be able to provide a treatment at this frequency. Finally, to test the system in psoriatic volunteers which should allow an assessment of whether the chosen higher frequency can eliminate the problem of painful deep heating, and hence possibly provide an improved treatment for psoriasis.

3.3 Finite difference modelling

3.3.1 Introduction

The amplitude of an electromagnetic wave decays exponentially as it passes through tissue. The rate at which the decay occurs is determined by the chosen frequency and the complex permittivity of the tissue as explained in section 2.2. At 2.45 GHz the field intensity has dropped to around one third of its initial value after 18mm in human skin. It is therefore understandable that any hyperthermia treatment conducted at this frequency could induce painful deep-heating.

3.3.2 Model development

In order to study the influence of microwave frequency on the heating induced in the skin, a thermal analysis of the problem was conducted by numerical solution of the bioheat equation given in section 2.4.1 in one spatial dimension. The equation that was solved was

\[ \frac{\rho_i c_i}{k} \frac{\partial T}{\partial t} = \frac{\partial^2 T}{\partial x^2} + \frac{\rho_i c_i m}{k} (T - T_b) + \frac{\rho_i}{k} \text{SAR}, \]

where \( T \) is the temperature of the tissue in °C, \( \rho_i \) is the density of the tissue, \( \rho_b \) is the density of blood, \( c_b \) is the specific heat capacity of blood, \( m \) is the volumetric flow
rate of blood per unit mass of tissue, $T_b$ is the temperature of the perfusing blood and SAR is the microwave induced heating, measured in W/kg. Values for the various tissue properties involved in the model are therefore required as given in section 3.3.2.1-a, including a value for blood perfusion as given in section 3.3.2.1-c. In addition, values for the microwave power deposition are required as given in section 3.3.2.1-b.

This equation differs from the pure bioheat equation due to the fact that metabolic heat generation has been neglected. This is because the heated volume is sufficiently small that any effects on metabolic heat generation are assumed to be negligible. Furthermore, metabolic processes are assumed to be sufficient to maintain homeostatic equilibrium at body temperature before heat is applied. The initial temperature is therefore assumed to be the subcutaneous tissue temperature.

This allowed the expected temperature profile at different microwave frequencies to be predicted by using a finite-difference discretisation in time and space, and a forward-time-centred-space approach, as given in section 2.6. The grid spacing was selected to be 0.1mm in space, which imposed a constraint on the spacing in time to be less than 0.044s in order to ensure stability. For simplicity, the spacing in time was chosen as 0.01s. A fixed temperature boundary condition was placed at a depth of 5cm with the temperature set at the subcutaneous temperature. At the surface a symmetry boundary condition was used, with an extra term to account for power loss due to surface cooling through convection. This cooling term also requires characterisation, and this is described in section 3.3.2.1-d. It does, of course, assume that the heated area is an infinite flat plane. This model is given in detail in appendix 3 and all the key tissue properties used in the model are given in table 3.4.
3.3.2.1 Parameter derivation

a) Tissue properties

The tissue properties given in table 3.1 were taken from Duck (1990) for use in the model.

<table>
<thead>
<tr>
<th>Tissue property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>$\rho = 1133 \text{ kg m}^{-3}$</td>
</tr>
<tr>
<td>Specific heat capacity</td>
<td>$C = 3417.5 \text{ J kg}^{-1}\text{K}^{-1}$</td>
</tr>
<tr>
<td>Thermal conductivity</td>
<td>$k = 0.360 \text{ Wm}^{-1}\text{K}^{-1}$</td>
</tr>
</tbody>
</table>

Table 3.1. Tissue properties used for the computer modelling (Duck, 1990)

b) Microwave heating

The microwave heating was described by an exponential decay, the rate of which was determined by the complex permittivity of the tissue, and the frequency, as described by Sadiku (2001). The complex permittivity of skin at different frequencies is given in figure 2.2. The relationship between power absorption and depth is therefore

$$P_x = P_0 e^{-2\alpha x},$$

where $P_0$ is the power absorbed per unit volume at the surface, $P_x$ is the power absorbed per unit volume at depth $x$, and $\alpha$ is the attenuation coefficient defined in section 2.2.1.

The total power input per unit area ($P_t$) is therefore given by

$$P_t = \int_0^\infty P_x \, dx.$$

Plotting $e^{-2\alpha x}$ for human skin at 2.45, 7 and 9.2GHz gives the graph of normalised SAR against depth shown in figure 3.3, which is equivalent to power absorbed per unit volume since the power absorption is normalised and the density is a constant.
c) **Blood cooling**

The blood cooling was simply described by a uniform rate of heat loss that was directly proportional to the temperature difference between the blood temperature and the tissue temperature. Using Klemp and Staberg’s (1983) blood perfusion value for psoriatic skin of \(63.5\text{ml} 100\text{g}^{-1}\text{min}^{-1}\) and Duck’s (1990) value for the density of human skin of \(1133\text{kg m}^{-3}\) gives

\[
\frac{\partial T}{\partial t} = -0.012 \times (T - T_b),
\]

where \(T\) is the temperature of the tissue in °C and \(T_b\) is the constant blood temperature.

d) **Surface cooling**

i) **Introduction**

It would theoretically be possible to calculate the degree of heat loss at the skin’s surface if the surface temperature were known and the perfusion level known. Since, however, in-vivo perfusion levels are uncertain, it is not possible to use temperature measurements of skin to evaluate the degree of heat loss. Therefore a tissue phantom

---

Figure 3.3: Power absorbed as a function of depth in human skin at three frequencies
was used to try and evaluate the rate of heat loss that would occur on the patient’s skin, assuming that the skin was in contact with air at an ambient temperature, as the tissue phantom has zero perfusion. PAG tissue phantom (described in section 2.10.1) was used as its surface is naturally slightly damp, and can be expected to have similar thermal properties to the surface of sweating human skin.

**ii) Method**

A round sheet of PAG tissue phantom of 2cm thickness and 20cm in diameter was immersed in a water bath at 37°C until warmed through. It was then raised to the surface until the surface was just above the water level, and a Luxtron temperature measurement optical fibre was taped to the centre of the surface of the PAG disc. The temperatures were then logged as the surface cooled. This approach was taken as it meant that the situation could be closely modelled using the 1D finite difference thermal model, with the heat loss coefficient (defined in equation 3.1) as the only unknown parameter. The properties of PAG used in the evaluation are listed in table 3.2. The model therefore consisted of a 2cm thick layer of PAG with the lower end having a fixed temperature boundary condition of 37°C. The starting temperature of the entire layer was 37°C. Surface cooling was assumed to follow Newton's Law, which states that the rate of heat loss is assumed to be directly proportional to the temperature difference between the surface and the ambient temperature, and is directly proportional to the surface area. This is valid for both forced and natural convection according to Jones (2000) and can be expressed as

\[ q = hA (T_s - T_{\infty}), \]  

3.1

where \( q \) is the heat lost from the surface, \( A \) is the area, \( T_s \) is the temperature of the surface, \( T_{\infty} \) is the bulk temperature of the fluid and \( h \) is the constant of proportionality called the heat transfer coefficient.

The surface cooling heat transfer coefficient was then adjusted manually to give the best possible fit to the logged temperature cooling data.
Polyacrylamide gel

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (Bini, 1984)</td>
<td>( \rho = 1030 \text{ kg m}^{-3} )</td>
</tr>
<tr>
<td>Specific heat capacity (Bini, 1984)</td>
<td>( C = 4187 \text{ J kg}^{-1} \text{ K}^{-1} )</td>
</tr>
<tr>
<td>Thermal conductivity (Bini, 1984)</td>
<td>( k = 0.41 \text{ W m}^{-1} \text{ K}^{-1} )</td>
</tr>
<tr>
<td>Complex permittivity (7 GHz) (Clegg, 2002)</td>
<td>48.2 - 21.8</td>
</tr>
</tbody>
</table>

Table 3.2. PAG properties used for the computer modelling

An analysis was also made of the effect of forced air cooling on the heat transfer coefficient in exactly the same way as for natural convection alone. As before, a flat sheet of PAG was heated in a water bath, then raised just above the water line and the surface temperature fall measured. However, this time air was blown onto the surface from a small fan as shown in figure 3.4.

Figure 3.4: Experimental set-up for relating heat transfer coefficients to forced air cooling rates
The rated airspeed through the fan was 0.849 ms\(^{-1}\) at a voltage of 12V. The airspeed was assumed to vary in direct proportion to the fan speed cubed, as described by Graebel (2001), the resistance of the fan was assumed to be a constant, and the airspeed was assumed to vary in direct proportion to the power input, as shown in table 3.3. Several different voltages were applied to the fan and once again, the heat loss at the surface was evaluated by best fit to the measured data. The aim was therefore to allow a quantitative relationship between airflow speed and the heat loss through surface cooling to be derived.

<table>
<thead>
<tr>
<th>Voltage applied to fan</th>
<th>Power input (arbitrary units)</th>
<th>Fan speed (arbitrary units)</th>
<th>Air flow speed (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3V</td>
<td>0.0625</td>
<td>0.39685</td>
<td>0.337</td>
</tr>
<tr>
<td>6V</td>
<td>0.25</td>
<td>0.63</td>
<td>0.535</td>
</tr>
<tr>
<td>9V</td>
<td>0.5625</td>
<td>0.825</td>
<td>0.7</td>
</tr>
<tr>
<td>12V</td>
<td>1</td>
<td>1</td>
<td>0.849</td>
</tr>
</tbody>
</table>

Table 3.3: Air flow speed derivation

**iii) Results**

In the absence of forced air cooling, using a value of 224.3 Wm\(^{-2}\)K\(^{-1}\) for the heat transfer coefficient in the model gave the result shown in figure 3.5. This provides a good fit to the experimental data and therefore provides a value for the likely surface heat loss of sweating human skin through convection alone.
As can be seen, the value of $224.3 \text{ Wm}^{-2}\text{K}^{-1}$ gives a good fit over a considerable length of time during a transient response, giving confidence in the value. For the forced air-cooling, the best fits between the model and the experimental results that were obtained are given in figure 3.6.
Once again, a good degree of concurrence was possible between the modelled and measured results. Plotting the air flow speeds against the fitted heat transfer coefficients shown in figure 3.6 gives the graph shown below in figure 3.7.

Figure 3.7: Airflow speed over tissue phantom against surface cooling coefficient. The confidence intervals are based on the maximum and minimum surface cooling coefficients that can reasonably be fitted to the measured data shown in figure 3.6

This allows the airflow speed that would be required to obtain a given heat transfer coefficient to be estimated. This therefore gives meaning to the values for heat transfer coefficient and in particular gives meaning to the results of the thermal modelling given in section 3.3.4 that predict an optimum heat transfer coefficient to try and obtain the most effective thermal profile.
e) Model parameters summary

In summary, the properties given in table 3.4 were used in the modelling.

<table>
<thead>
<tr>
<th>Tissue (Skin)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Density*</td>
<td>( \rho = 1133 \text{ kg m}^{-3} )</td>
</tr>
<tr>
<td>Specific heat capacity*</td>
<td>( C = 3417.5 \text{ J kg}^{-1} \text{K}^{-1} )</td>
</tr>
<tr>
<td>Thermal conductivity*</td>
<td>( k = 0.360 \text{ Wm}^{-1} \text{K}^{-1} )</td>
</tr>
<tr>
<td>Blood perfusion*</td>
<td>( \omega = 63.5 \text{ml100g}^{-1} \text{min}^{-1} )</td>
</tr>
<tr>
<td>Complex permittivity (2.45 GHz)*</td>
<td>56.3 - i16.3</td>
</tr>
<tr>
<td>Complex permittivity (7 GHz)*</td>
<td>49.2 - i21.6</td>
</tr>
<tr>
<td>Subcutaneous temperature</td>
<td>36.5°C</td>
</tr>
<tr>
<td>Surface cooling (convection only)</td>
<td>( h = 224.3 \text{ Wm}^{-2} \text{K}^{-1} )</td>
</tr>
</tbody>
</table>

Table 3.4: Tissue properties used for the finite difference thermal modelling of psoriatic skin (*Duck, 1990, †Clegg, 2000, ‡Klep and Staberg, 1983)

### 3.3.3 Solution optimisation

Initially an optimum solution was sought using a hill-climbing algorithm. (Given in appendix 4). This simple algorithm was tried first due to its simplicity and due to the problem only requiring optimisation of three parameters – the power, frequency and surface cooling coefficient. It compares the solutions that result from using different sets of parameters against a pre-set target solution (Goldberg, 1989). A value is then assigned to each trial solution, which is given by the sum of differences between the pre-set optimum and the target squared, as given by equation 3.2.

The object of the program is to minimise this value. It starts with a trial solution and finds the value associated with that solution. It then varies these starting parameters slightly and finds the value associated with the new solution, whilst also retaining the original parameters. The parameters out of the two possibilities that give the better solution survive to the next generation. These surviving, more appropriate, parameters are also varied slightly, and then their value compared again to their parent
parameters. Once again, the more suitable parameters survive to the next generation, and so on. The value attached to a given trial solution is therefore

\[
Value = \sum_{0}^{n} (T_i^{\text{optimum}} - T_i^{\text{trial}})^2,
\]

3.2

where \( T_i \) is the temperature at each point in the finite difference grid and \( n \) is the number of grid points in the spatial dimension.

In order to speed up program execution, the algorithm starts with a temperature profile that is the target solution. In other words, the initial conditions for the simulation are set as the target. The simulation is then run for one cycle, which is 10 milliseconds of simulation time. If the parameters were perfect, then the temperatures would not deviate from the optimum in any way, since the target is the required solution in the steady state. The greater the change over this one cycle, the less appropriate this set of parameters would be. This method greatly speeds up program execution times. Rather than starting at body temperature with each trial solution and waiting several minutes for the steady state to be reached, the suitability of any solution can be found in one cycle.

For the treatment of psoriasis, the optimum solution would be a step function with a temperature of 43°C over the superficial 3 millimetres and normal body temperature below that, which is impossible to achieve. Setting the target as a step function results in the algorithm either tending towards zero power, or infinite power with a very low frequency. In order to get a useful result from the algorithm the target needs to be at least approximately achievable.
The target was set using a best fit approximation using Microsoft Excel, by picking the surface to be 43°C, the temperature at 1.5 mm to be 44°C and the temperature at 3 mm to be 43°C, with a rapid drop in temperature down to body temperature after that. This gave the equation shown in figure 3.8 for temperature as a function of depth, which is

\[ T = 1.56 \times 10^9 x^5 - 8.08 \times 10^{-7} x^4 + 0.000147 x^3 - 0.0109 x^2 + 0.21x + 42.968, \]

where \( x \) is the depth in mm.

This is clearly unrealistic at depths of below 10 mm, but this is unimportant since the parameters that the algorithm varies will have little to no influence so deep below the surface. The lower boundary condition of 36.5°C also prevents the algorithm from being able to try to approximate the profile below 10 mm in depth. Closer to the surface however, the profile is appropriate, and it is this that the algorithm approximates the trial solutions to.

In order to check that the solution was converging to a consistent set of parameters, the algorithm was run several times starting with various different values.
3.3.4 Results

a) Optimum solution with surface cooling

The optimum parameters were consistently found to be a power input of 3875Wm\(^{-2}\) at a frequency of 5GHz, with a heat transfer coefficient of 330 Wm\(^{-2}\)K\(^{-1}\) with the air at 20°C. The value for surface cooling of 330 Wm\(^{-2}\)K\(^{-1}\) is equivalent to an air speed of only around 0.5ms\(^{-1}\). It is interesting to note, however, that most of the improvement in the error came from the extra air cooling as shown in figure 3.9. Variations in frequency and power had a smaller effect. 3875Wm\(^{-2}\) equates to a power input of 15W for the applicator described in section 3.4.3. The surviving parameters in each generation are shown in figure 3.9 for a typical optimisation run.

![Figure 3.9: Optimisation of frequency, power and surface cooling parameters over 3000 generations](image)

The temperature profile after 5 minutes starting from body temperature using the optimised parameters is shown below in figure 3.10. This is very close to the required profile.
Figure 3.10: Simulated temperature profile using optimised parameters after 5 minutes of heating

b) Optimum solution without surface cooling

Since the degree of air-cooling required to obtain the required profile is minimal, an investigation was then conducted without this parameter. Figure 3.11 shows the predicted profile that would be induced by heating due to simple thermal conduction from surface heating, compared to that induced by heating at both 2.45 GHz and 7 GHz. A frequency of 7 GHz was chosen because it was predicted to give a temperature of 42°C at a depth of 3mm. This should therefore give a therapeutic treatment over the top 3mm of the skin, whilst not being therapeutic at below 3mm, and not requiring any form of extra surface cooling. The likely effectiveness of the treatment compared to simple thermal conduction should be increased because of the higher temperatures reached below the surface. It also should reduce the likelihood of causing unnecessary pain due to heating below the epidermis when compared to a treatment at 2.45GHz, due to the more targeted heated depth.
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

3.4 The treatment system

3.4.1 Introduction

In view of the additional complexity that would be entailed by incorporating a forced air-cooling system, together with the limited effect that it was predicted to have, the decision was made not to incorporate forced air cooling into the treatment system. A system was therefore required to safely heat human skin to a pre-set hyperthermic temperature using the predicted optimum frequency of 7 GHz. The design that was settled on was based on readily available equipment linked together, with a custom made applicator and custom feedback control. The overall system configuration is shown in figure 3.12, with a description of the system components given in section 3.4.2.
The temperature of the skin was measured using the Luxtron fibre optic thermometer, the tip of which was taped onto the skin. The measured temperature was then fed back to the computer where a feedback algorithm would alter the power of the source to maintain the set-point temperature. A travelling wave tube amplifier then amplified this source output, which was connected to the applicator through a standard coaxial cable. The power meter simply provided a check on the output power of the amplifier. The mains supply to all components was delivered through an isolation transformer in order to meet medical electrical equipment safety standard EN60601.

### 3.4.2 System components

The microwave source consisted of an oscillator to generate low power microwaves at the required frequency, as shown below in figure 3.13. The microwaves were then amplified by an amplifier, shown in figure 3.15. The surface temperature was measured using a fibre optic temperature sensor (figure 3.14) taped to the skin. The measured temperature was fed back to a standard PC, which altered the power output from the source using a feedback algorithm. The program also logged the skin temperature and source power output. The feedback and control algorithm was
created in Agilent Vee, which is a commercially available data acquisition and instrument control program.

Figure 3.13: The source Hewlett-Packard HP8350B sweep oscillator combined with a HP83592A RF plug-in

Figure 3.14: The Luxtron fibre optic thermometer – model 3201

Figure 3.15: The amplifier - an ETM SC band travelling wave tube

Since the power output at the applicator was determined by the power input from the source, the power output at the applicator needed to be characterised for the source and amplifier combination over the range of output of the source, and for various appropriate levels of amplifier gain, as shown in figure 3.16.
The power output from the source was logged along with the set-point temperature and the actual skin temperature by the PC. Figure 3.16 therefore allowed the power available to the applicator to be derived from the logged power outputs recorded for the source.
3.4.3 The applicator

Since the computer modelling showed that 7 GHz seemed the optimum frequency to choose, an applicator needed to be designed that would deliver microwave radiation at this frequency. It also needed to fulfil a variety of design criteria. It had to be tolerant to movement relative to the surface and needed to give predictable, preferably even, heating over the aperture, whilst ideally allowing the skin to be in contact with air. This was modelled using the finite element package HFSS (High Frequency Structure Simulator).

The fundamental applicator design chosen was basically an air filled metal pipe waveguide. The edges of the metal cylinder can be placed on the skin to prevent radiation leakage, and since the heated area will only be in contact with the air, potential allergy related problems and perspiration build-up between the applicator and the skin should be minimised. It also allowed the design to retain the possibility of being adapted to incorporate forced air-cooling if later required.

The applicator was designed to use the TM_{01} mode because this mode is easily excited when fed by a coaxial cable, as described in 2.3. This is because of the similarities between the field patterns of the TEM mode of coaxial cable and the TM_{01} of the waveguide. To successfully excite the TM_{01} mode the centre conductor of the coaxial cable needs to be extended into the waveguide in line with the waveguide, and in the centre. This therefore fixes the position of the centre conductor, as shown in the cross section through the design given in figure 3.17. The diameter of the applicator was then chosen according to the requirements of the mode. Using the formula given by Cronin (1995, p85), the TM_{01} mode at 7GHz is cut-off in air at a radius of 1.64 cm. This means that a circular waveguide with less than this radius will not carry the TM_{01} mode. The cut-off radius for the next mode, the TM_{11} mode, is 2.61 cm. The radius of the waveguide was therefore chosen to be mid-way between these two values at 2.2 cm. A Perspex plate was incorporated around half-way down the waveguide as a tuning device. The length of the centre conductor extension into the waveguide and the thickness and position of the Perspex plate were then altered manually within HFSS to minimise the magnitude of the reflection coefficient at 7GHz. In order to
ensure patient safety and conform to the relevant electrical safety standards, the applicator was covered with a machined uPVC jacket, both inside and out. The base of the applicator was covered in moulded silicone rubber. This prevented direct patient contact with any metal parts that were connected to the system.

Figure 3.17: Psoriasis applicator. Dimensions in mm

Some theoretical and experimental test results are shown in figures 3.18-3.20
Figure 3.18 shows the match of the applicator against a range of loss tangents and permittivities. This was carried out to give an indication of the tolerance of the applicator’s match to changes in skin complex permittivity, thus ensuring that the applicator would not be sensitive to small changes in complex permittivity, allowing increased safety and reliability in use and comparability to bench test data from experiments in PAG. Small changes may arise due to measurement errors of the complex permittivity of skin, and also temperature dependence of complex permittivity. As can be seen in figure 3.18 the match is predicted to be better than -10dB for almost all combinations. The limits of the tested combinations are fairly arbitrary, but were chosen such that they comfortably bracket the permittivities and loss tangents of both PAG and skin, which are 49 and 47 respectively, with loss tangents of 0.44 and 0.46. In figure 3.19 the magnetic field vector is shown, demonstrating that the applicator is operating in TM$_{01}$ mode.
Figure 3.20: The applicator heating pattern shown using an LCD sheet overlying a tissue phantom (PAG). Blue is 44°C, green is 43°C, yellow is 42°C and red 41°C. The heated area is 4.4cm in diameter.

Figure 3.20 is a photograph of an LCD sheet, which was placed on the surface of a block of PAG and heated with the applicator in order to give a visual indication of the heating pattern. As is to be expected, the TM_{01} mode results in minimum heating in the centre of the waveguide, with the maximum power input to the tissue being approximately half way between the centre and the circumference of the applicator. In order to ensure that the optical fibre was placed somewhere on this line of maximum heating, paper templates were used to mark the position of the tip of the fibre optic cable using a pen, and hence the required position of the applicator on the skin before treatment.

Figure 3.21: Predicted reflection coefficient (S11) against frequency from HFSS compared to measured S11 against frequency.
The S11 values between 5 and 10GHz are very similar to the predicted values from the HFSS simulations, as can be seen in figure 3.21, but the low S11 at 7GHz was actually found at 6.95GHz. Since conducting all experimentation at 6.95GHz would have a negligible effect on the results, all further experimentation was actually conducted at 6.95GHz. The finished applicator is shown below in figures 3.22a & b. It was then attached to a flexible arm using the machined connection on the side of the applicator, in order that it would be self-supporting when in use.

As mentioned earlier, in order to conform to the relevant electrical safety standards the applicator was covered with a machined uPVC jacket, both inside and out. The base of the applicator was covered in moulded silicone rubber and the connectors were covered in a rubber boot. The entire system was tested at the Leicester Royal Infirmary Medical Physics Department and passed the electrical safety requirements of EN60601.

### 3.4.4 Temperature control
Temperature control in this system is critical. Over 45°C could cause a burn, but the tissue also needs to be at over 42°C to be effective. Furthermore, this temperature needs to be reached within several minutes after the start of treatment, and with no overshoot. The system is also unpredictable since different power levels will produce a different response depending on the amount of energy that has been put in
previously, and on the blood perfusion level. If the tissue is just warm at the surface, then more energy will be required to reach any higher set temperature than if the tissue is thoroughly warmed through already.

A very common form of standard feedback controller is a PID controller, as described by Astrom and Hagglund (1988). It was therefore decided to use this as the basis of the temperature control algorithm. This is made up of proportional, integral and derivative control (hence PID), or any combination of these, except for purely derivative control, as described by

\[
\begin{align*}
U_1(t) &= K_p e(t) \\
U_2(t) &= K_i \int e(t) dt \\
U_3(t) &= K_d \frac{de(t)}{dt} \\
U(t) &= U_1(t) + U_2(t) + U_3(t)
\end{align*}
\]

where \( K_p \), \( K_i \) and \( K_d \) are gain constants, \( e(t) \) is the error and \( U(t) \) is the control variable. \( e(t) \) is given by \( r - y \), where \( r \) is the set point and \( y \) is the measured value.

In the case of purely proportional control, the first term of the algorithm alone is used, so \( U_1(t) = K_p e(t) \). In this case the control variable is simply proportional to the error between the measured and required values. This has a fundamental disadvantage for use in this application, however. This is that as the error goes to zero, the control variable also goes to zero. This means that there always needs to be an error in order to provide a non-zero control signal. In this application, a constant amount of power needs to be applied to maintain the required temperature. It is possible to adapt the proportional control term to include an extra constant, so \( U_1(t) = K_p e(t) + C \). This will therefore mean that the control term will be non-zero even when the error is zero. However, in this application the required value of the constant is unknown and will depend on the steady state power level required for each treatment. The proportional control term was therefore not used in this implementation.
The integral control term gives no set point error (Astrom and Hagglund, 1988) making it ideal for this application. When implemented in a situation in which the measured values are sampled, the integral term can be approximated from the terms shown above according to Astrom and Hagglund (1988) using

\[ U_2(t_n) = U(t_{n-1}) + K_i e(t_n), \]

where \( U_2 \) is the control variable, \( K_i \) is a gain constant and \( t_n \) is the time at discrete time interval \( n \).

Finally, the derivative term can be used to speed up the response of the algorithm (Astrom and Hagglund 1988). The error term given above is made up of the difference between the set point and the measured point

\[ U_3(t) = K_d \frac{de(t)}{dt} = K_d \left[ \frac{dr}{dt} - \frac{dy}{dt} \right]. \]

However, set point \( r \) is normally constant, and thus will not contribute to the derivative term. \( y \) is the measured value. The derivative term can therefore be implemented as

\[ U_3(t) = K_d \frac{dy}{dt}. \]

In the discretised case where the measured values are sampled, this can be approximated by

\[ U_3(t_n) = K_d (y_n - y_{n-1}), \]

where \( U_3 \) is the control variable, \( K_d \) is a gain constant, \( t_n \) is the time at discrete time interval \( n \) and \( y_n \) is the measured value at discrete time interval \( n \).
Both integral and derivative control was implemented in the control algorithm in order to try and obtain fast acting and accurate temperature control.

Setting the gain constants and deciding which terms to include is an empirical procedure. Extensive experimentation is therefore vital. In order to speed up this process the finite difference thermal analysis program described above was used. This meant altering the power input over time by using different combinations of formulae and gain constants. Before starting this manual tuning of the gain constants, an experiment was performed to check that the results would be meaningful. The complete psoriasis treatment system was set-up to warm room temperature PAG using a control algorithm with purely integral control. The gain constant was set using the computer model such that it was predicted to give a very slow response, but with decaying oscillations. The system was then run over the same time period as the computer model to allow a comparison of the predicted and measured results. The actual and predicted surface temperatures are shown below in figure 3.23.

Figure 3.23: Modelled feedback algorithm response (pink) against measured response (blue) in PAG

The degree of overshoot in the simulation is considerably lower than in reality, but the similarity was sufficient, especially considering the very long timescale, to allow use of the model to try different feedback algorithms and adjust the gain constants. Each
computer simulation took only a few seconds, saving an enormous amount of experimental time and effort.

This initial trial had a very long settling time and a high degree of overshoot. The addition of derivative feedback, together with careful tuning of the gain constants, allowed the degree of predicted overshoot to be reduced to acceptable limits, and the set-point temperature to be reached in an acceptable time period. However, all this careful tuning meant that the system was no longer robust. Changing the degree of blood cooling had a dramatic difference on the settling times and overshoot. In figure 3.24 the response was good, but multiplying the perfusion by a factor of 10 meant that the same algorithm was unable to reach 37°C even after 2 minutes.

![Figure 3.24: Modelled temperature response of an integral and derivative (ID) feedback algorithm (blue) using a fixed set temperature of 43°C (pink)](image)

This problem was solved by using a moving set point that ramps up at the required rate to the treatment temperature. The ID (integral and derivative) controller is used to keep the surface temperature as close as possible to this moving set point. It effectively prevents a massive overshoot thus allowing the feedback control to be speeded up. In the computer models this was an extremely effective means of temperature control. The actual temperature was quickly within about 0.1 of a degree of the set point, and was extremely robust to changes in perfusion and temperature, as shown in figure 3.25.
Figure 3.25: The effect of high gain and a moving set point temperature on the surface temperature and power input.

In reality the results were not as good as the simulations, but were a massive improvement on having a fixed set point. As shown in the bench test result in figure 3.26, which was carried out on PAG, a therapeutic temperature can be safely reached in around 3 minutes, or even less. The chosen algorithm was,

\[ P_n = P_{n-1} + ((T_{scr} - T_n) \times P_{n-1} \times K_i) - ((T_n - T_{n-1}) \times P_{n-1} \times K_d), \]

where \( K_i = 0.2 \) and \( K_d = 0.8 \).

Figure 3.26: Bench tested result in PAG using the optimised feedback algorithm.
The final algorithm varies slightly from the textbook versions given above in that each term is multiplied by the power level. This was incorporated so that the feedback response would increase or decrease proportionately to the power level. Low power levels would therefore have proportionally lower changes in power, for the same changes in temperature.

Further investigation showed that the noise in the surface temperature data was influencing the algorithm. The Luxtron data varied by around +/-0.5°C. Adding this random variation into the feedback in the computer model allowed the modelling to be even more representative. This is illustrated in figure 3.27, and allowed further refinement of the gain constants to remove this influence.

Figure 3.27: Comparison between modelled feedback algorithm performance and feedback algorithm performance in use

The modelling showed that the power varied considerably during treatment, although the temperature stayed constant. To damp out this noise a reduction in both gain constants by a factor of 20 was required. However, this also had the unwanted effect of preventing the treatment temperature from being reached quickly without any overshoot. The solution was to start with the previously chosen gain constants, but to reduce them exponentially during the warm-up phase so that the algorithm became
progressively more damped, as shown in equations 3.4 and 3.5. This allowed both a fast warm-up and steady power during treatment.

\[ K_t = 0.19 \times (2^{-t/100}) + 0.01 \]  
\[ K_d = 0.76 \times (2^{-t/100}) + 0.04 \]

where \( t \) is time in seconds.

### 3.5 Bench characterisation in a tissue phantom (PAG)

#### 3.5.1 Introduction

The system was also characterised on PAG without the temperature feedback control. There were three aims to this experiment. Firstly, to find the relationship between the power input used in the model and the power input to the applicator. This was performed because the heating over the heated region of the applicator is not even, meaning that the power input as measured by the power meter cannot be accurately related to a power input per unit area at the point at which the optical fibre tip is placed. Secondly, once this calibration factor is determined, to check that the computer model predictions correlate well over a range of power levels with the measured results, and finally to attempt to estimate the likely degree of error inherent in the system through assessing the degree of error between the model and the system.

#### 3.5.2 Method

The experiment was performed by using a paper template to position both the fibre and applicator such that the tip of the fibre was at the point of maximum heating on the surface of a sheet of room temperature PAG as shown in figures 3.28 and 3.29. A fixed power level in the region that was likely to be approximately appropriate for therapeutic heating was then applied. After 2 minutes power was cut and the block allowed to cool. This was repeated for a range of appropriate powers. The PAG was left to re-equilibrate to room temperature between experiments, and a new position on the sheet used each time, but the average starting temperature of the block did increase gradually over the course of the experiments. Once this data was obtained the finite difference computer model program was run and the power input adjusted such
that a calibration factor was obtained that would allow a reasonable fit of all the predictions to the results.

**3.5.3 Results**

All the experimental results, together with the fit from the model that matched them all best are shown in figure 3.30.

![Figure 3.28: The paper template used to locate the fibre relative to the applicator](image1)

![Figure 3.29: The applicator in position on the PAG](image2)

Figure 3.30: Model predictions fitted to experimentally measured temperatures for a range of power levels.
3.5.4 Analysis

As can be seen there is a good degree of correlation between the model and the measured results for both heating and cooling, over the whole range of appropriate power levels, and a range of starting temperature. This is despite the fact that the model describes the heating and cooling of an infinite plane. The heated area of the applicator therefore appears to be sufficiently large not to be grossly effected by this approximation. The power level on the model was adjusted to best match the experimental results and give a mean error of 0°C. This gives a standard deviation of 0.555°C. A histogram of the temperature differences is shown in figure 3.31. This gives 95% confidence that a modelled temperature will be within +/- 1.1°C of the measured temperature. This degree of confidence was then also applied to the experimental results in-vivo.

Figure 3.31: A histogram of the temperature differences between the modelled and measured bench test results
3.6 In-vivo testing

3.6.1 Aims
The primary aim of the trial was to assess the possibility of using a frequency of 7GHz to treat psoriasis. The set-point temperatures were therefore gradually increased over the 6 treatments in order to assess the likely range of patient acceptability, and in particular, to look for signs of discomfort or deep heating.

3.6.2 Methods

3.6.2.1 Subjects
Subject 1 was a 47 year old woman with chronic plaque psoriasis. Subjects 2 and 3 were 43 and 37 year old men, also with chronic plaque psoriasis. Subject 1 was undergoing tar treatment at the time of the tests, but not in the treated area. Neither of the two other volunteers had undergone treatment in the previous 6 months. Ethical approval for the study was given by the Leicester Hospitals Trust and all subjects gave informed consent to take part.

3.6.2.2 Procedure
Tests were conducted on three volunteers every Tuesday and Thursday for three weeks. This treatment interval was determined by the timings of the dermatology outpatient clinic. Photographs were taken before and after every treatment session. The applicator was placed on the chosen area of skin and the position marked so that the same area of skin could be treated every time. The algorithm was designed to err on the side of caution, which resulted in the mean temperature during a treatment being 0.2°C below the set temperature. The chosen treatment temperature was reached after 3 minutes, and then maintained for 20 minutes. The set temperatures are given below in table 3.5.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
<th>Session 4</th>
<th>Session 5</th>
<th>Session 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td>40°C</td>
<td>42°C</td>
<td>43°C</td>
<td>43°C</td>
<td>43°C</td>
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<td>Subject 2</td>
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<td>42°C</td>
<td>44°C</td>
<td>43°C</td>
<td>43°C</td>
<td>43°C</td>
</tr>
<tr>
<td>Subject 3</td>
<td>41°C</td>
<td>42°C</td>
<td>44°C</td>
<td>43°C</td>
<td>43°C</td>
<td>43°C</td>
</tr>
</tbody>
</table>

Table 3.5: Treatment set temperatures
In the first subject, the applicator was placed on the forearm, in the area indicated in figure 3.32. In the second subject the applicator was placed as shown in figure 3.33. In the third subject, the applicator was placed so as to cover both the plaque and healthy skin, as shown in figure 3.34 with the temperature being monitored on the healthy skin. The treatment set-up is shown in figure 3.35.
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Figure 3.34: The location of the applicator on the third subject. The temperature was measured on the healthy skin

Figure 3.35: The complete system in use
3.6.3 Results

3.6.3.1 Clinical results

All three volunteers completed the trial, and there were no signs of the deep heating that had caused two out of three of the subjects in Keddy-Grant’s (1990) trial at 2.45 GHz to drop out. Despite the limited number of treatments, an improvement was reported by subject 2 after the treatment at 44°C, as shown in figure 3.37. The subject reported a reduction in scaliness and itching, and a noticeable increase in skin softness. There was also a reduction in surface skin temperature from 36.2°C to 33.3°C, indicating a reduction in hyperperfusion. The surface skin temperature over the course of the 6 treatments is shown in figure 3.36. Unfortunately, this improvement was also associated with some blistering within the treated area, as shown to the right of the improved area in figure 3.37. Following this, all treatments were conducted at 43°C.

Figure 3.36: Initial surface skin temperature of subject 2 (psoriatic) over the 6 treatments compared to the surface skin temperature of subject 3 (healthy) over the course of the treatments. The dotted lines are the results of applying linear regression to the data points and are to show the general trend of the data points. A clear downward trend is visible for the psoriatic skin over the course of the treatments, against a slight increase for the healthy skin.
The level of power required to maintain the set temperature was widely different depending on whether the temperature was monitored on healthy or psoriatic skin, as shown in figure 3.38. The difference increased greatly over the temperature range, up to a difference of around 5 times the required power at 43.8°C. Furthermore, on the final treatment the temperature on both the plaque and the healthy skin of the third subject was simultaneously measured during the treatment. This showed that the plaque was between 1.5 and 2°C cooler than the surrounding skin. This meant that it was at between 41.5 to 42°C, which is just under the therapeutic temperature.
3.6.3.2 Blood perfusion analysis

Since both the power input and the surface temperature are known, an assessment can be made of the skin's blood perfusion, and its variation with temperature. The known power input is applied in the finite difference computer simulation and the blood perfusion varied using a feedback algorithm to give the correct surface temperature. Since the surface skin temperature for subject 2 was measured on a plaque, and the skin temperature for subject 3 was measured on healthy skin, the level of blood perfusion for both healthy skin and in a chronic plaque can be assessed.

This analysis predicts a greatly increased level of blood perfusion in psoriatic skin, with the differences increasing with temperature, as shown in figure 3.39. Fitting a linear trend line through the data gives a level of blood perfusion in psoriatic skin as $\omega = 39T - 1510$ whilst the level of blood perfusion in healthy skin is given by $\omega = 2.4T - 90$, where $\omega$ is the blood perfusion in $ml100g^{-1}min^{-1}$ and $T$ is the surface skin temperature. The overall mean error in blood perfusion values at 95% confidence is +/-29%, with a mean error for the blood perfusion in healthy skin at 95% confidence of +/- 32%, and a mean error at 95% confidence in psoriatic skin of +/- 26%.
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Figure 3.39: Predicted blood perfusion level in both healthy (pink) and psoriatic skin (blue). The dotted lines are to show the general trend of the data points and are based on applying linear regression to the data points. The equations of the lines of linear regression are given above in section 3.6.3.2.

This relationship between blood perfusion and surface temperature was then applied to a 2D finite difference model (given in appendix 5) in order to model the case of subject 3, where the healthy and psoriatic skin were equally heated, but the temperature was controlled on the healthy skin. Half the tissue was designated as psoriatic and the perfusion was set according to the equation for perfusion in psoriatic skin, whilst the other half was set as healthy, with the perfusion levels set accordingly. The model was over 10mm along the surface of the skin with the psoriatic to healthy interface at 5mm. At the edges of the plane going down into the tissue, symmetry boundary conditions were imposed, with a fixed temperature boundary condition along the bottom edge of the plane at a depth of 1cm. Power levels were set such that a temperature of 43°C would be achieved at 5mm from the psoriatic to healthy skin interface, on the surface of the healthy skin. The resulting surface temperatures are shown in figure 3.40. The temperatures predicted over the plane are shown in figure 3.41.
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Figure 3.40: Predicted surface temperature levels for the case where psoriatic skin meets healthy skin. The healthy skin was maintained at 43°C.

Figure 3.41: Predicted temperatures for the case where psoriatic skin meets healthy skin. The healthy skin was maintained at 43°C.
The temperature on the surface of the psoriatic skin is predicted to be 41.1°C, which is slightly lower than the temperature measured in reality of between 41.5 and 42°C. This could be because the perfusion levels in subject 3 were lower than those of subject 2, as his psoriasis was not as severe. The predicted perfusion level for subject 3 may therefore be something of an overestimate.

In addition, using the same 2D model, the folds of skin shown in figure 3.2 were modelled to assess whether the greater blood cooling within the folds would be likely to have a significant impact on a microwave therapy. The width of the plaque was guess-estimated to be around 1.5cm. This would give a thickness to the epidermis of 1.7mm with the folds reaching down to around 4.3mm below the surface. The width of each fold was around 1.1mm. These values were put into the model with perfusion values chosen so that the epidermis would have the same perfusion as healthy skin, whilst the dermis would be perfused at the level measured in subject 2. The perfusion levels are shown below in figure 3.42.

![Figure 3.42: The perfusion levels chosen to simulate the folds of psoriatic skin shown in figure 3.2](image-url)
As can be seen in figure 3.43, the effect of the folds is minimal, and so they are predicted to have a minimal impact on any possible therapeutic effect.

3.7 Discussion

Microwave hyperthermia conducted at a frequency of 7 GHz does indeed appear to prevent deep heating when tested in-vivo and therefore represents an improvement over hyperthermia at 2.45 GHz. However, an improvement in patient condition was only reported in the second subject out of the three, and this was associated with blistering of another part of the treated area. This lack of improvement may in part be due to the treatment interval between the Thursday and the following Tuesday being too great. Given that psoriasis can cycle as quickly as every 1.5 days (Coltart & Irvine 1986), the Tuesday treatment may have been largely treating entirely new cells. Overall, the effectiveness of the treatment cannot be accurately assessed due to the limited number of subjects, the limited number of treatments at a therapeutic...
temperature and the long treatment interval between the Thursday and Tuesday treatments.

<table>
<thead>
<tr>
<th></th>
<th>2.45 GHz</th>
<th>7 GHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>One subject had complete clearing of the plaque and had no relapse in the three month follow-up.</td>
<td>Some improvement reported by one subject. Immediate relapse.</td>
</tr>
<tr>
<td>Complications</td>
<td>Deep heating caused two out of three of the subjects to leave the trial.</td>
<td>No deep heating, but blistering in part of the treated area in one subject.</td>
</tr>
</tbody>
</table>

Table 3.6. Comparison between hyperthermia induced by microwaves at two different frequencies.

The direct comparison in table 3.6 between the two frequencies implies that there may be a trade-off between efficacy and patient acceptability. However, given that two out of three of the previous subjects left the trial, any further microwave hyperthermia treatments should clearly be conducted at higher frequencies.

The blistering induced in one of the 7GHz treatments sets an upper limit on treatment time of 20 minutes at a surface temperature of 44°C. However, this complication was also associated with the only reported benefit, indicating how accurately the treatment parameters need to be set. Further refinement of the treatment parameters are necessary, but it appears that a 20 minute treatment at a temperature of between 43°C and 44°C could be effective.

The perfusion results calculated from the tests fit reasonably well with previously published values from Kemp and Staberg (1983). They predicted 6.3ml100g⁻¹min⁻¹ for healthy skin, compared to 63.5ml100g⁻¹min⁻¹ for psoriatic skin. This is well within the 95% confidence limits for the predicted perfusions at the lower end of the temperatures at which the tests were carried out. Both sets of results show an approximate order of magnitude difference between the blood perfusion in plaques and healthy skin. Interestingly, the psoriatic hyperperfusion appears to increase with temperature, up to a maximum of around 15 times the perfusion of healthy skin at around 44°C. This high level of blood perfusion represents a difficulty when using
microwave hyperthermia to treat psoriasis, because of the likely non-uniformity of any treated area. The chosen therapeutic temperature must be the maximum temperature over any treated area. If the treatment area includes any areas of healthy skin, then this will automatically dictate the maximum power output possible. As demonstrated in subject 3, this can lead to the plaque falling just below the temperature needed to induce a therapeutic effect. One possible solution to this is to reduce the blood flow to the treatment area during treatment, either by direct pressure or by applying a tourniquet. Whether such methods would reduce the relative difference in perfusion between areas is uncertain, and complete occlusion of the blood supply would need to be balanced against patient acceptability. Stress is a well-known cause of psoriasis (Ashcroft, Po & Griffiths, 2000), so any treatment that was overly stressful to the patient could well prove to be counter-productive.

3.8 Summary
A thermal analysis was performed to determine the optimum degree of penetration at which to conduct a treatment microwave hyperthermia treatment for psoriasis. This was found to be 7 GHz and a system was designed and built to deliver microwaves at this frequency to the skin. Tests using this system were conducted twice weekly for three weeks on three volunteers. Temperatures of between 40°C and 44°C for 20 minutes were used. All the volunteers tolerated the treatments well, and there were no signs of the painful deep-heating that have been associated with a previous attempt to treat psoriasis by microwave hyperthermia at a lower frequency. There were only limited signs of improvement in one of the subjects however. An assessment was also made of the variation in blood perfusion with temperature in both a plaque and in healthy skin, with the plaque showing significantly higher levels of perfusion. This difference increased with increasing temperature.
3.9 Conclusions

Thermal modelling indicates that microwave hyperthermia treatment conducted at around 7GHz has the potential to offer a more targeted treatment for psoriasis over microwave hyperthermia conducted at lower frequencies. Testing of a system operating at this frequency resulted in a positive response in one patient out of three, but the limited number of treatments and long time interval between treatments means that the effectiveness of the therapy could not be fully assessed. The power levels required to maintain therapeutic temperatures of between 40 and 44°C allowed an assessment to be made of the level of blood perfusion in the tissue of both healthy and psoriatic skin using a finite difference based thermal model. This gave results that fitted well with previously published values and indicates that psoriatic hyperperfusion is approximately ten times greater than the perfusion level in healthy skin and increases with temperature over this range. The level of psoriatic blood perfusion is given by $\omega = 39T - 1510 (+/-26\%)$ whilst the level of blood perfusion in healthy skin is given by $\omega = 2.4T - 90 (+/-32\%)$, where $\omega$ is the blood perfusion in $ml100g^{-1}min^{-1}$ and $T$ is the surface skin temperature. Reducing this difference in perfusion would greatly enhance the efficacy and safety of any microwave based hyperthermia treatment for psoriasis.
Chapter 4: Varicose Veins

4.1 Introduction

4.1.1 Background

Varicose veins are a very common condition. Around 10-15% of adult men and 20-25% of adult women suffer with them according to Adhikari et al. (2000). Leg veins contain one-way valves every few centimetres that help direct blood flow back towards the heart when they are functioning correctly (Goldman and Fronek, 1989). Varicose veins generally occur when these valves fail, either in a superficial vein itself, or in the connecting veins that link the deep to the superficial veins (Labropoulos, 1996 and Evans, 1998). This failure of the valves is known as venous incompetence. The exact process that causes this to result in varicose veins is unclear (Alexander, 1972), but it appears that normal movement in people with failing valves results in chronic increased pressure on the vein walls of the failing vein and those around it, known as venous hypertension (Dodd, 1971). This causes the affected veins to stretch and gives rise to a variety of complications such as pain, skin changes, thread veins, varicose veins and ulcers, as shown in figures 4.1, 4.2 and 4.3. Venous ulceration affects one percent of the western population (Cullum, 2003) and is estimated to cost the NHS £400,000,000 per annum in the UK alone (Ruckley, 1997).
Risk factors for the development of varicose veins are given by Fan (2003), and include age, being of female gender, having a job that involves standing for long periods, having a family history of the disease and previously having suffered a deep vein thrombosis. Obesity is linked to the development of venous incompetence in women, but not men.

Figure 4.2: Skin colouration changes caused by saphenous vein incompetence

Figure 4.3: Ulcer caused by venous incompetence

The greater saphenous vein is particularly prone to failure since it runs all the way from the ankle to the groin and is close to the surface over its entire length. The shorter saphenous vein is also prone to failure due to its superficial location. Both are shown in figure 4.4.
4.1.2 Current techniques for the treatment of venous incompetence

Many sufferers will simply need to elevate their legs regularly to give their veins, and themselves, some temporary relief. Unfortunately however, the progression of the disease cannot be reversed. If the disease becomes serious enough, the only way to obtain relief is by removing or occluding the saphenous vein altogether. This has no negative impact on the patient, as the incompetent vein is failing to perform its function correctly anyway. The deep venous system is also more than capable of making up for any lost capacity. Removal of the vein from the venous system can be performed in a variety of ways. Surgical stripping is the standard technique, but there are several alternatives techniques that aim to be minimally invasive. Two are based on heating the vein from the inside. This is called endovenous ablation or endovenous obliteration, and is performed using a radio-frequency device and with lasers. There is also the injection of a corrosive solution directly into the vein, called sclerotherapy. Introductions to surgical, RF, laser and sclerotherapy based treatments are given in sections 4.1.2.1 to 4.1.2.4.
4.1.2.1 Surgical stripping

Stripping is essentially pulling the vein out. A general anaesthetic is required, making for a more risky and costly operation than anything performed under a local anaesthetic. The traditional treatment and current gold standard for long saphenous vein incompetence is a high tie of the vein at its junction with the deep system in the groin. This is at the point where the saphenous vein meets the femoral vein, called the sapheno-femoral junction. The vein is then stripped using a pin stripper to above or below the knee (Dwerryhouse, 1999). Separate stab incisions are often also used to remove any surface varicosities in a procedure called a phlebectomy (Goren, 1991). The stripping is associated with high rates of both immediate and delayed complications. Blood loss can be high and recovery times are long, around 2 to 4 weeks. This is largely due to post-operative bruising. The rate of recurrence is also high, with 20% of treated patients needing further surgery for recurrence according to MacKenzie and colleagues (2002). This technique therefore leaves considerable room for improvement.

4.1.2.2 VNUS® Closure

The use of radiofrequency based techniques to treat venous incompetence by endovenous saphenous vein obliteration is fairly well established. It involves introducing a catheter, shown in figure 4.5, with sheathable electrodes through an introducer or an open cut-down into the vein. An introducer is a plastic tube that is inserted into the vein in order to aid insertion of the applicator. An open cut-down is where a skin incision is made and the vein pulled up to the surface. An incision is then made in the wall of the vein through which the applicator is fed. Whichever method is used, the applicator is then fed up to the saphenofemoral junction under ultrasound guidance (Rautio et al., 2002). The electrodes are then unsheathed, as shown in figure 4.6, and embed themselves in the vein wall. The applicator is bipolar with the currents running between the collapsible electrodes and the central ball tip. This gives a length of wall heating of between 6 and 8mm when the RF current is applied.
Once the applicator is in position the leg is strongly wrapped in a rubber bandage called an Esmark bandage (shown in figure 4.7), to exsanguinate the leg, as described by Bergan (2002). This is painful, and so a new technique called tumescent anaesthesia has been developed for use under local anaesthetic, which is based on the injection of around 200ml of fluid around the vein (Weiss, 2002). The fluid exerts sufficient pressure to cause the vein to collapse. Power is applied from the RF generator shown in figure 4.8, and the applicator is slowly withdrawn along the length of the vein whilst heating the vein walls to 85°C. A feedback algorithm alters the power to maintain the temperature as close as possible to 85°C. The heating causes the vein to shrink and die. During treatment heparinised saline is fed through a central lumen in the catheter to try and prevent thrombus formation (Weiss, 2002). Heparin is an anti-coagulant drug. Occlusion rates at one year are reported as being 88% by Sybrandy (2002). The advantages of endovenous obliteration are that it requires no general anaesthesia but still gives comparable efficacy to surgical stripping whilst also reducing patient discomfort and undesirable side effects.
Despite the fundamental success of this technique, the pullback rate is very slow, around 2.76 cm/min according to Goldman and Amiry (2002). This is due to the need for thermal conduction to carry heat out through the full thickness of the vein wall, the different layers of which are shown in figure 4.9. Faster drag rates mean that just the inside lining of the vein is seared, without damaging the vein to the maximum possible extent.

One more serious problem with radio-frequency based endovenous saphenous obliteration is the possibility of causing nerve damage. The saphenous nerve runs alongside the vein and is particularly close to it in the lower leg. Paresthesia, defined as numbness or tingling lasting for greater than 6 weeks, followed 15% of treatments on the upper leg and affected 30% of treated lower legs for Chandler et al (2000).
Other papers do not mention paresthesia as a problem, such as those by Weiss (2002), but it is undoubtedly a serious issue. Another problem reported by Merchant (2002) is that of thermal skin injuries. These can be minimised by checking the depth of the vein using ultrasound before treatment, cooling the skin with external cooling pads, and the use of tumescent anaesthesia (Merchant, 2002), as described earlier.

4.1.2.3 Laser
Endovenous laser treatment is also fairly well established and Navarro, Min and Bone (2001) have reported similar success to VNUS. Treatments last around 15 to 20 minutes. The main supplier of such treatments is Diomed with its EVLT procedure. This treatment uses a 0.6mm bare-tipped laser fibre which, like VNUS Closure, is inserted into the greater saphenous vein at either the ankle or the knee through a percutaneous introducer or an open-cut down and fed up to within 1-2cm of the sapheno-femoral junction under ultrasound guidance. At this stage a red light is shone into the fibre to highlight the exact location of the tip. When the fibre is in position, manual compression is applied in order to force the vein against the fibre. 12W is delivered to the vein from a 810nm laser, and the applicator slowly withdrawn with the laser fired at around 3-5mm increments down the length of vein to be treated (Navarro, 2001). This damages the inner lining of the vein wall, called the endothelium (shown in figure 4.9), resulting in clotting and hence causing venous occlusion. The technique can produce extremely high temperatures. Up to 1334°C has been recorded, which in animal models has been shown to cause multiple venous perforations by Weiss (2002). Unlike VNUS Closure it seems to have minimal effect on the tunica externa (see figure 4.9) of the vein (Proebstle, 2002). However, like VNUS Closure, this procedure can be performed under local anaesthetic, especially since Esmark bandages are not used. However, there is the possibility that the more limited damage to the vein wall could lead to higher levels of re-canalisation, which is where the vein re-opens and starts to allow blood flow once more.
4.1.2.4 Sclerotherapy

Sclerotherapy is most commonly used for spider veins, but is also used for varicose ones. It is based on injecting a corrosive solution directly into the vein, that damages the lining of the vessel and hence causes the lining of the vein walls to swell, stick together, and eventually seal shut (Tisi and Beverley, 2003). The vein should then turn into scar tissue. In some cases the vein may need to be retreated. Sclerotherapy does not require anaesthesia. A recurrence rate of 43.8% following treatment with sclerosants is quoted in a 10 year randomised controlled study compared to 0% in the surgery arm of the study (Belcaro, 2000). The potential cost benefits of not requiring surgery when using sclerotherapy are therefore tempered by the need for further treatment. There is also the ever-present danger of the sclerosant escaping systemically.

New developments in the field of sclerotherapy have concentrated on the use of sclerosant foam rather than liquid (Tisi and Beverley, 2003), such as Varisolve®. As with RF and laser treatments, the technique involves canulation of the long saphenous vein and constant ultrasound guidance as the foam is injected. The fundamental aim of the foam is to fill the superficial venous system and so to cause endothelial damage in the same way that traditional sclerosants work, whilst reducing the chances of the sclerosant escaping to the deep venous system.

4.2 Aims of the research

Although both laser and radio-frequency based treatments are available to treat veins endovenously, both techniques have some significant complications and inherent disadvantages that could be overcome with microwave heating, whilst maintaining the efficacy of a thermally based treatment. This is for three main reasons. Firstly, the ability of microwaves to deliver heat into the tissue means that the treatment can be speeded up, whilst still maintaining effectiveness as there is no need to wait for the heat to penetrate. Secondly, microwaves have the advantage that they heat evenly all around the applicator tip, unlike RF based techniques, which should make the technique safer as the maximum depth of thermal penetration can be guaranteed. Finally, the use of dielectrics also allows microwave applicators to be made in
different sizes. Whilst the use of a thick dielectric layer around the tip of a microwave applicator may make the applicator larger and therefore potentially harder to insert, it will also allow more power deposition whilst still giving controlled heating. This is because of the larger circumference of the applicator meaning that the thermal penetration as measured from the surface of the applicator can be the same as for a smaller applicator, but with a greater total power input to the vein. This then offers the chance to maximise efficacy whilst maintaining the same level of thermal penetration and hence safety. Another way of looking at this is that with a larger tip, more of the vein can be in contact with the applicator, therefore meaning that a larger proportion of the vein circumference will be treated. This should therefore maximise treatment efficacy.

The primary aim of this work was to develop a microwave based treatment for varicose veins. This broke down into assessing the likely parameters required for a successful treatment by looking at the most similar successful endovenous product currently available – VNUS Closure. An applicator and system were then developed to deliver a microwave treatment. Characterisation and modelling of this system and applicator were performed both on the bench and in a computer modelling exercise, and finally the system was compared on the bench to VNUS Closure. This demonstrates that the likely effect in-vivo of the treatment will be very similar to VNUS, so giving similar efficacy, whilst still delivering a significantly faster and safer treatment.

4.3 Computer modelling by finite difference approximation

4.3.1 Introduction
As with psoriasis, a simple 1-D finite difference program was written to give an indication of the heating pattern with different powers, applicator lengths, applicator diameters and drag rates (See appendix 6). In particular, the model aims to evaluate the heating pattern successfully used by VNUS, and then tries to replicate approximately the same heating pattern using microwaves, so giving a first indication of the parameters that should be both safe and efficacious.
4.3.2 Method

The heated volume of tissue was assumed to be a cylinder, so the diffusion equation was re-expressed in terms of cylindrical polar coordinates.

The radial part of the diffusion equation in cylindrical polar coordinates is

\[
\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial T}{\partial r} \right) - \rho C \frac{\partial T}{\partial t} = -P(r)
\]

where \( T(r, t) \) is the temperature at distance \( r \) from the \( z \) axis, \( \rho \) is the density, \( C \) is the specific heat capacity, \( k \) is the thermal conductivity and \( P \) is the source term (rate of heat generation or removal).

This equation was solved using finite differences with a grid spacing in time of 0.01 seconds and a grid spacing for radial distance of 0.1mm, using the parameters given below in section 4.3.2.1.

The source term contains only blood cooling and microwave heating terms. The applicator was assumed to be a thermal insulator and so an adiabatic boundary condition was imposed at what would be the tissue applicator interface. An adiabatic boundary condition means that no heat will be lost from the tissue at this boundary.

4.3.2.1 Parameter derivation

a) Tissue properties

The thermal conductivity was available from published data. The density was initially taken as that of water, and the specific heat capacity was taken as being the same as muscle. The properties used are given in table 4.1.

<table>
<thead>
<tr>
<th>( \rho = 1000 \text{ kg m}^{-3} )</th>
<th>Density of water</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C = 3.72 \text{ J kg}^{-1}\text{K}^{-1} )</td>
<td>Human cardiac muscle</td>
</tr>
<tr>
<td>( k = 0.476 \text{ W m}^{-1}\text{K}^{-1} )</td>
<td>Human artery (aorta)</td>
</tr>
</tbody>
</table>

Table 4.1: The tissue properties used for the initial finite difference thermal modelling. The properties of cardiac muscle and aorta were taken from Duck (1990)
b) Microwave heating

As the microwaves are radiating from an infinite cylinder, the energy deposition was taken as being as if from a plane wave, that was reduced in intensity as it spread out from the surface of the applicator by a factor of \( \frac{r}{r+x} \), where \( r \) is the radius of the applicator and \( x \) is the distance from the surface of the applicator.

Based on the above assumption the power at each node in \( \text{Wm}^{-3} \) is given by the formula

\[
P_x = P_r \cdot e^{-2\alpha \frac{r}{r+x}}
\]  \hspace{1cm} 4.1

where \( \alpha \) is the attenuation coefficient given by equation 2.8, \( P_x \) is the power lost to the tissue at any point \( x \) and \( P_r \) is the power delivered to the tissue at the surface of the applicator.

The constant \( P_r \) can be found from the total radiated power \( P_t \) and the heated volume whose length is \( l \) using

\[
P_t = 2\pi r \int_{x=0}^{x=\infty} P_x (r + x) \, dx.
\]  \hspace{1cm} 4.2

Inserting equation 4.1 above gives

\[
P_t = 2\pi r P_r \int_{x=0}^{x=\infty} e^{-2\alpha \frac{r}{r+x}} \, dx.
\]

Evaluating the integral gives

\[
P_t = \frac{\pi r P_r}{\alpha},
\]

and rearranging leads to

\[
P_r = \frac{P_t \alpha}{\pi r l}.
\]  \hspace{1cm} 4.3

Reinserting the constant \( P_r \) from equation 4.3 into equation 4.1 gives the power density in \( \text{Wm}^{-3} \) as a function of distance from the surface of the applicator.
c) Blood cooling

In the absence of specific data on blood cooling, the blood cooling constant was taken as 6.9ml 100g/min. This is the average level of blood perfusion over the entire human body as calculated from the value given by Hoppensteadt & Peskin (1992) for the volume of blood pumped around the body.

4.3.3 Computer program results

Firstly, a VNUS treatment was modelled with the aim of obtaining an appropriate thermal profile to emulate. Chandler and colleagues (2000) give details of the VNUS parameters used to obtain maximal vein contraction whilst minimising nerve damage. The heated region is 6-8mm long, using a power of between 4 and 6 watts and a withdrawal rate of around 3cm/min. The electrodes embed themselves about 1mm into the walls with a vein size of anywhere between 2 and 12 mm in diameter. The temperature is held at 85°C through the feedback mechanism that alters the power input.

The fact that the VNUS applicator uses expanding electrodes makes predicting the thermal penetration of the VNUS applicator using this model likely to be imprecise. This is because the electrodes are unlikely to be evenly positioned around the inside wall of a vein, whilst this model is based on a perfect cylindrical applicator. For the purposes of this simulation, a typical vein under compression was assumed to be around 4 mm in diameter, so the diameter of the applicator was set at 4mm. A frequency of 15 GHz was used to simulate the very superficial heating that is likely to occur from an RF applicator. This equates to a 1/e power penetration depth of around 0.8 mm. Using these two assumptions and a power level of 4.5 watts gave the results shown below in figure 4.10 for temperature in °C against depth over time. The bottom edge of the graph represents the surface of the applicator with radial distance extending out over 5mm. The maximum temperature reached is predicted to be 84°C, which is almost exactly the temperature that is obtained in reality, and this close match between the predicted and actual peak temperatures give credence to the model. The predicted thermal profile for VNUS gives a temperature profile to emulate using
microwave heating, as this thermal profile is known to be both efficacious and have an acceptably low number of side effects.

![Figure 4.10: Simulated RF temperature profile in °C using a frequency of 15GHz, a withdrawal rate of 3cm/min and a power input of 4.5 watts](image)

Since the finite difference model results appear to be reliable, based on their correct prediction of peak temperature, the model was used to provide initial predictions of which parameters would obtain similar temperature profiles, but with faster drag rates, as shown in figures 4.11 and 4.12. Adjusting the drag rate and power input by trial and error yielded the following set of temperature profiles both with a peak temperature of 85°C, and similar temperature profiles to that predicted for VNUS.

![Figure 4.11: Simulated temperature profile in °C for a microwave applicator with a withdrawal rate of 7cm/min at 9.2GHz with a power input of 8 watts](image)
4.3.4 Conclusions

In order to increase the drag rate compared to VNUS, the frequency of operation needs to be lowered whilst simultaneously increasing the power. This is not unexpected as an increase in power will naturally be required as withdrawal rate increases to give the same energy dose per unit length. However, this will result in high peak temperatures close to the applicator surface if the power is not deposited over more tissue. The frequency therefore needs to be lowered as the power and withdrawal speed are increased, in order to prevent excessive temperatures and steam formation. Another way of looking at this is that lowering the frequency of operation reduces the need to rely on thermal conduction to give the required thermal penetration. Similar results to those achieved using RF techniques should therefore be possible when using microwaves, but with much quicker treatment times. Given the encouraging possibilities shown by the initial thermal modelling, an investigation into various possible applicator designs and treatment control methods was conducted.
4.4 Applicator design

4.4.1 Introduction and design requirements
The applicator had to fulfill a variety of design criteria. It had to be sufficiently flexible to allow safe introduction into the vein, whilst not being so flexible as to prevent a small amount of force being applied to the cable during insertion. It had to be easy to insert, and yet ideally it would also fill the vein, thus allowing power to be applied to the entire circumference of the vein wall to improve the likely efficacy of the treatment. It also needed to be robust with no possibility of failure in use or the chance of parts becoming detached in the body. All the exterior faces needed to be medically approved and bio-compatible, with the interior components also being non-toxic. The tip needed to be rounded to prevent snagging or possible perforation of the vein wall during insertion. The exterior also had to be non-stick to prevent clot formation on the surface.

4.4.2 Applicator design iterations
The initial computer modelling exercise had indicated that a treatment could be performed at a frequency of 9.2 GHz with a similar thermal profile to VNUS Closure, but with greater treatment speed. A source was also available at this frequency, so prototype applicators were therefore designed using HFSS to operate at 9.2GHz.

Three basic applicator designs were developed for further testing. Stripped coaxial cable, a dielectric sheathed monopole radiator with a metal tip, and a dielectric sheathed monopole radiator without the metal tip.

4.4.2.1 Stripped coaxial cable
The initial design was simply a stripped piece of coax, cut to the right length to ensure an acceptably low degree of reflection when in tissue and coated in a layer of heat shrink. This gave a reflection coefficient (S11) of around -17dB at 9.2GHz and had the advantage of being extremely simple, inexpensive and robust.
4.4.2.2 Dielectric sheathed radiator with a metal tip

This more complex applicator was designed with the aim of continuing to heat the vein even as it contracted as the applicator was withdrawn. This was achieved by putting a tapering dielectric around the centre conductor together with attaching a metal tip at the end of the centre conductor. This provided a rounded profile to reduce the chances of snagging on valves, but also produced a reasonable amount of heating at the tip. The final closure of the vein would be ensured by this metal tip that was connected to the centre conductor. This performed a dual function as it kept the applicator together and also caused intense fields at the very tip of the applicator. The entire applicator was sheathed in a non-stick medical grade heat shrink called FEP which provided the non-stick, medically approved robust coating. A variety of designs were tried and the two with the most appropriate field patterns at diameters of 3.4mm (shown in figures 4.14 and 4.15) and 4.8mm (shown in figures 4.16 and 4.17) were optimised to give a reflection coefficient (S11) of less than -10dB. The predicted and actual S11 for the 3.4mm applicator between 5 and 10 GHz is shown in figure 4.13. The variations in reflection coefficient for the actual applicator are due to the three metres of coaxial cable between the network analyser and the applicator tip. This is because there is a slight reflection from the tip as well as slight reflection at the connection between the network analyser and the applicator coaxial cable. The two reflections will therefore destructively interfere at certain frequencies and constructively interfere at others. This effect becomes very apparent with long waveguide lengths because the large distance between the tip and the connection to the network analyser means that only a relatively small change in frequency is needed to add an extra half wavelength and so change constructive to destructive interference, and vice versa. The general shapes of the predicted and actual reflection coefficients are similar however with a consistent reflection of less than -10dB between 7.6GHz and at least 10GHz.
Figure 4.13: S11 reflection coefficient (labelled match) in dB against frequency for the 3.4mm applicator from the HFSS model (blue) compared to measured values (red)

The time-average magnitude of the electric field patterns for the two applicators are shown below in figures 4.14 and 4.16. They both have the most intense fields close to the tip, whilst still showing heating further back. The result of this tip heating is shown in surfactant loaded PAG tissue phantom in figure 4.19.

Figure 4.14: The magnitude of the time-averaged electric field of a 3.4 mm diameter applicator with a metal washer tip operating at 9.2 GHz
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

Figure 4.15: Cross section of a 3.4 mm diameter applicator with a metal washer tip operating at 9.2 GHz

Figure 4.16: The magnitude of the time-averaged electric field of a 4.8mm diameter applicator with a metal washer tip operating at 9.2 GHz

Figure 4.17: Cross section of a 4.8mm diameter applicator with a metal washer tip operating at 9.2 GHz
In order to provide feedback on withdrawal, temperature was initially used as a control parameter in the same way as it is used by VNUS. A thermocouple was placed on the ferrule just behind the ferrule/dielectric interface, in the location shown in figure 4.18. A small piece of electrical tape was placed underneath it to help prevent it being heat sunk onto the ferrule, as shown in figure 4.24.

**Figure 4.18:** An exploded diagram of the 4.8mm applicator including the coaxial cable, thermocouple, ferrule, plastic dielectric, washer and FEP jacket

**Figure 4.19:** The heating pattern of the 4.8mm applicator with metal tip in surfactant loaded PAG

### 4.4.2.3 Dielectric sheathed radiator without metal tip

The third type of applicator design to be built had the centre conductor entirely sheathed in dielectric, so removing the heating at the tip. The dielectric was simply held in place by the FEP sheath. These second generation prototypes showed good
microwave performance and were simpler to build than the applicators with a metal tip. A variety of diameters were optimised on HFSS with the aim of providing applicators that would be capable of treating veins of different sizes. Applicators of 3.4mm, 4.0mm, 4.8mm and 6.0mm in diameter were designed and built, as shown in figure 4.24. The interior dimensions of the 3.4mm applicator are shown in figure 4.20, together with the predicted field pattern in tissue in figure 4.21. The 4.8mm applicator is shown in figure 4.22, together with an exploded diagram showing the components of the design in figure 4.23. The 4.0 and 6.0mm diameter designs are similar to the 3.4 and 4.8mm designs.

Figure 4.20: Cross section of the 3.4mm diameter applicator without the metal washer tip designed to operate at 9.2 GHz

Figure 4.21: Time averaged magnitude of the electric field for the 3.4mm diameter applicator without the metal washer tip designed for operation at 9.2 GHz modelled in HFSS. This shows significantly less field intensity at the applicator tip than the dielectric sheathed applicators with a metal tip.
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Figure 4.22: Cross section of the 4.8mm diameter applicator without the metal washer tip designed to operate at 9.2 GHz

Figure 4.23: Exploded diagram of the second generation 4.8mm applicator including coaxial cable, thermocouple, ferrule, \( \varepsilon = 25 \) dielectric and FEP jacket

Figure 4.24: Applicators of 3.4, 4.0, 4.8 and 6mm diameter
Once the range of applicators was completed, clinical opinion was sought as to the ability of the applicators to be introduced into the greater saphenous vein. It was felt that the option should be available to allow insertion through a percutaneous introducer, as well as an open cut-down. The largest commercially available introducer that would be useable with the greater saphenous vein had a internal diameter of 4.67mm. The tip of the 4.8mm diameter applicator was therefore reduced in diameter slightly to 4.5mm in order to allow use with this introducer. The other designs were not taken forward beyond initial bench testing as it was found that the 4.5mm design gave complete heating of the vein wall of veins up to at least 1.2cm in diameter. The design of the 4.5mm applicator is shown in figure 4.25, together with its SAR pattern in figure 4.26 and predicted and actual match over the range 7-10 GHz in figure 4.27.

Figure 4.25: Cross section of the 4.5mm diameter applicator designed to operate at 9.2 GHz

Figure 4.26: SAR of the 4.5mm applicator as modelled in HFSS
The variations in reflection coefficient for the actual applicator are due to the three metre length of cable between the network analyser and the applicator tip, as explained above in section 4.4.2.2. The general shapes of the predicted and actual reflection coefficients are roughly similar however with a consistent reflection of less than -10dB between 8GHz and 9.3GHz. The S11 for this applicator is therefore acceptable at 9.2GHz, as at least 90% of the input power will be deposited into the tissue.

The 3m flexible coaxial cable that the applicator tip was built onto is shown in figure 4.28. The first metre was sheathed in FEP for patient contact. The final 2 metres were sheathed in polyolefin heatshrink to act as an extension and give sufficient reach from the microwave source and system to the operating table when in use.
The tolerances required on the components of the applicator tip to ensure a high yield in production were assessed using HFSS. The results are given in appendix 8.

4.5 Applicator testing

4.5.1 Heat shrink bedded in PAG

4.5.1.1 Aims

A simple and quick way of testing applicator designs was required initially that could determine how effectively a design could induce shrinkage, and allow the testing of a temperature feedback control method.

4.5.1.2 Method

Low temperature heat shrink was set in PAG to simulate the vein in tissue. This shrinks down to half its initial diameter when heated to above 85 °C. The heat shrink tube was filled with ultrasound gel to simulate the blood that would be present in the vein and to allow an acceptably low level of reflected power. All experiments were conducted at room temperature. Both the stripped coaxial cable and the applicators with the metal tip were tested in the heat shrink. The power outputs were chosen according to the parameters predicted by the finite difference computer model.
4.5.1.3 Results

When using the stripped coaxial cable, the tube had a tendency to shrink down onto the applicator and then become jammed there. As the applicator was withdrawn the tube would stay at the same diameter as the applicator. It also had difficulty heating heat shrink of around 4.8mm in diameter due to the small diameter of the applicator.

With the applicators with the metal tip a very high degree of shrinkage could be achieved, as was hoped for. However, this required a very slow withdrawal rate of around 3cm/min to cause maximum shrinkage of the heat shrink. A faster withdrawal rate would result in minimal, if any, degree of shrinkage. There was a distinct cut-off above around 3cm/min where the degree of shrinkage became minimal. This result was disappointing as it implied that a high degree of shrinkage was not possible without the continued application of heat and meant that some of the conclusions from the finite difference modelling exercise given in section 4.3.3 might not be valid. In particular, the ability to obtain the same degree of tissue shrinkage at a faster withdrawal rate by increasing power and reducing frequency might not be possible.

4.5.2 Excised vein bedded in PAG

4.5.2.1 Aims

In order to assess whether the results from shrinking heat shrink in set PAG would be replicated in tissue, the method was extended by the use of stripped human saphenous vein in place of the heat shrink.

4.5.2.2 Method

As with the heat shrink, the vein was suspended in position with a rod holding it in place in the centre of a small waterproof box. The PAG was then poured in and left to set around the vein. The setting of the PAG is an exothermic reaction which raises the temperature to around 50°C. It was then left to cool to 37°C, at which point the experiment was performed. The vein was once again filled with ultrasound gel to simulate blood.
4.5.2.3 Results

The results are shown in figures 4.29 – 4.31.

Figure 4.29: A freshly stripped varicose vein bedded in PAG

Figure 4.30: The same vein after heating

Figure 4.31: The cross-sectioned saphenous vein before and after the treatment

The vein shown in figure 4.29 has shrunk so much that it has actually shrunk away from the supporting gel, as shown in figure 4.30. Note also that one of the perforator veins that joins the greater saphenous has been occluded at the junction. It is not known how effectively other modalities occlude junctions. Sealing these junctions as well as the vein itself may be a key factor in preventing recurrence.

There were however, some negative aspects to this result. Firstly, if the pullback rate was too quick then the heat delivery at the tip was no longer able to apply heat directly to the vein wall, exactly as found with the heat shrink. This lead to a vicious circle. As the vein was not contracting down to the minimum size at the tip any more, it wasn’t heated as strongly, which meant that it didn’t shrink, so that once again heat from the tip was not applied. The critical speed to achieve the maximum level of
shrinkage was similar to RF at around 3cm/min and was slower than the predicted rate at 9.2GHz of 7cm/min. The speed of withdrawal to achieve maximum shrinkage therefore appeared to be dictated by the shrinkage rate of the vein, irrespective of how the heat was applied. This important result therefore appeared to limit the speed of treatment to the same as VNUS’ RF based treatment. However, although immediate venous occlusion would be likely to be preferable from an efficacy point of view, the results of laser treatment show that instant occlusion is not required to achieve lasting results and high efficacy rates. Unlike RF based treatments, microwave heating can still cause irreversible tissue damage even at high withdrawal rates over the full thickness of the vein wall. This is because there is no need to wait for thermal conduction to carry heat through the tissue alone, as the microwaves will heat the tissue directly. This can still be concluded from the initial finite difference modelling exercise described in section 4.3, even if this heating is too rapid to result in significant immediate venous shrinkage.

This led to the further testing of applicators without metal tips. The applicators described in section 4.4.2.2 were not used in further testing, as applicator designs that induced significant heating at the tip to achieve maximum venous shrinkage would not be effective at high withdrawal rates. In addition, the effects of the heating were now focussed on tissue damage levels and burn characterisation, with no further regard for tissue shrinkage. This shift in emphasis from trying to achieve both a significant degree of shrinkage and a controlled burn, to just achieving a controlled burn, allowed more flexibility in applicator withdrawal rate. In particular, considerably higher withdrawal speeds than 3cm/min could now be assessed.

4.5.3 Excised vein in bovine liver

4.5.3.1 Aims
The use of PAG as a model had several disadvantages. Firstly, it caused a temperature rise that would result in vein death as it set, meaning that the effect of a treatment could not fully be assessed. It also set solid and would not shrink with the vein, if required, as heat was applied. Finally it did not show the depth of thermal penetration beyond the vein wall effectively.
The aim of the new model of vein in liver was to build on the results of the veins set in PAG, and focus on burn characterisation alone, rather than both shrinkage and burn characterisation. In addition, it would address the disadvantages of the PAG and vein model and provide a bench model that would be significantly more realistic.

4.5.3.2 Method
An excised long saphenous vein was laid in a sandwich of ox liver and secured at both ends of the vein using sutures. The assembly was wrapped in cling film to simulate the fascia of the leg. This block was then placed in a sealed plastic bag and placed in the water bath and held at 37°C for several hours. The block was removed from the water bath and the plastic bag. The cling film was opened at one end to allow the applicator to be inserted into the vein, or gap between the slices of liver. Immediately before the applicator was inserted a further temperature was taken from inside the block of liver to check that 37°C had been reached. The applicator was inserted into the treatment block until the starting point was reached and a compression weight applied to the experiment block. This consisted of a flat metal plate approximately 1cm deep by 15cm by 30cm. After the treatment was finished the block was left for around 6 minutes prior to opening to ensure that the maximum thermal penetration had occurred.

A range of veins from 1.2cm in diameter down to 3mm in diameter were used in the tests. Only the 4.5mm diameter applicator was tested using this model.

4.5.3.3 Results
The model showed that the 4.5mm applicator was easy to insert in the full range of vein sizes tested, whilst also showing a consistent burn over the full thickness of the vein wall even in the 1.2cm diameter veins. This may be due to the compression pushing the vein onto the head of the applicator. This model was also used to provide validation of the thermal analysis as described in section 4.9.2.1, as well as a comparative test between the 4.5mm applicator and VNUS, as described in section 4.10.
4.6 Treatment control
Irrespective of the applicator, it was vital to provide a method by which the energy
delivered to the vein could be closely controlled. Several ideas were examined.

4.6.1 Temperature feedback
Initially, the use of temperature as a feedback parameter was investigated, with a
thermocouple located on the ferrule of the applicator as shown in figure 4.32, to try
and minimise direct heating.

![Figure 4.32: The location of the thermocouple on the 4.8mm dielectric sheathed applicator](image)

Unfortunately, obtaining accurate temperature feedback was found to be directly
related to the contraction problem found in both the heat shrink and the veins in PAG.
The thermocouple would provide feedback until contact was lost with the vein wall. It
would then cease to read the temperature of the wall and so fail to provide any sort of
useful feedback. In fact, it would typically start to read higher when it was no longer
in contact with the vein wall, causing a quicker withdrawal of the applicator. This
quicker withdrawal would automatically result in less heating and less contraction of
the vein. The only way to break this cycle was to ignore the temperature for a short
while and stop withdrawal, allowing the applicator to regain contact with the vein
wall, before recommencing withdrawal. This was totally unsatisfactory as a treatment
control procedure.
4.6.2 Audible control

In order to remove the temperature feedback problem, a new withdrawal method was devised. Coloured bands were marked on the applicator cable at 1cm intervals. The basis of this was that the surgeon would need to aim to withdraw the applicator so that the bands became visible in time to audible tones from the system. A banded applicator is shown below in figure 4.33. This proved to be a very effective way of controlling burn depth and allowed initial characterisation of the burns and temperatures produced by various withdrawal speeds and power levels. However, since one of the aims of the device was to achieve quicker withdrawal rates, the power level had to be increased relative to VNUS' RF treatment. This would give a potentially excessive burn to the tissue in the event of failure to withdraw the applicator sufficiently. The coloured bands did not therefore offer any means of protecting the patient. Some initial investigations were conducted into using the thermocouple located on the ferrule to provide a temperature trip, similar to that used for MEA (as explained in section 1.3.1). However, an alternative method of control based on direct measurement of the applicator withdrawal was developed using an optical motion sensor.

![Figure 4.33: Coloured bands marked on an applicator cable to allow accurate applicator withdrawal](image)

4.6.3 Optical motion sensor

Due to the inaccuracies of performing accurate temperature measurements of the vein wall using a thermocouple or optical fibre, a new method was designed based on
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direct measurement of applicator withdrawal. This was achieved through the use of optical mouse sensor technology.

4.6.3.1 Optical mouse position sensing

An optical mouse contains a sensor that identifies its position by image recognition. The sensor consists of a light sensitive array, a lens to focus light reflected from the surface under the sensor onto the array, an LED to provide illumination of the surface and a chip to perform the image processing as shown in figure 4.34.

![Figure 4.34: A schematic diagram of the primary components of an optical mouse, including their link to the computer](image)

The chip identifies features visible to the array. It then assesses the position of the same features a fraction of a second later to see if the features have moved. If so, it updates its position internally, and searches for new features. It therefore relies on surface features that can stimulate the light sensitive array sufficiently to be detected by the processing chip. When polled, the chip gives its position in a counts value of units in the x and y plane. The exact units are determined by the distance between the lens and the surface, the speed of movement of the mouse, and the surface which the mouse is placed on. In general, it is to be expected that increasing the distance from the surface to the array will result in a drop in the number of counts per distance moved.

4.6.3.2 The optical motion sensor

Rather than measuring the location of a mouse relative to a surface, the same electronics were used to measure the movement of the applicator cable as it passed through a small housing. This housing was designed to guide the cable through a channel past the optical mouse lens. The sensor is based on a commercially available
optical mouse chip, LED and lens (Agilent ADNK-2620) mounted on custom made circuit board. The circuit board shown in figure 4.35, together with the chip, lens and LED is mounted above the cable in a plastic sensor unit housing as shown in the exploded diagram of figure 4.39. This sensor monitors the location of the cable and relays this information to the system when it is polled. The circuit board was designed and built by Marchwood Technologies Ltd (2004).

For use in this application, the x value that the sensor provides when polled can be disregarded as this relates solely to the rotation of the cable. The update time of the unit is around 2200 times per second meaning that a withdrawal of around $18\text{ms}^{-1}$ will be required before the sensor fails to recognise any features from the previous scan. Since the number of counts is in arbitrary units, it then needs to be related back to real distance through multiplication within the system by a conversion factor. This is more fully explained in section 4.7.3 below. Since the location of the cable is determined by image recognition, the sensor needs the cable to have surface features that it can read. In this case the applicator cable coating is clear, allowing the outer braid of the coaxial cable to be read by the sensor. The use of an optical sensor has the major advantage that neither debris on the cable, nor cable damage, will prevent the chip from calculating position. It is therefore intrinsically reliable.

A variety of design criteria needed to be fulfilled for the housing of the optical mouse chip. The first treatment step would be that the percutaneous introducer would be fed into the vein. Then the applicator would be fed through the introducer and up the vein into position. The housing could then be slid up the cable until it mated with the percutaneous introducer. At this stage the housing could be held in position with surgical tape. This would help to prevent the introducer being forced further into the
vein, and also prevent the sensor from withdrawing along with the cable. The surgeon would then hold the sensor housing in one hand, whilst withdrawing the cable through the housing with the other as the treatment was performed. In the event of a treatment being performed without the percutaneous introducer, the sensor would simply be placed in an appropriate position near the entrance to the vein.

The housing therefore needed to be as small as possible, whilst still large enough to be comfortably held in one hand. It also needed to be slightly rounded for patient comfort and general aesthetics. The same sensor and applicator combination would be used to treat both legs of a single patient, so the housing also needed to be transferable from one leg to another. In addition, both the sensor and housing needed to be disposable.

The housing design was created and prototyped by Kinnier Dufort Ltd (2004), working from the treatment description and design criteria given above. To ensure a match with the introducer, a short recess of the same diameter as the end of the introducer was created on the introducer side of the housing. The final overall housing dimensions were approximately 7cm x 4cm, making it small yet easy to hold. In order to allow the housing to be taped in position, a clip with tape fed through it was designed to be attached to underside of the housing. This meant that the edges of the tape were positioned low on the body of the housing where they met the housing, so helping to give good adhesion. It also meant that a transfer from one leg to another could be carried out if a spare clip and length of tape were provided. After the treatment on the first leg, the clip could be detached, so removing the tape at the same time and allowing the replacement tape to be clipped on for the second treatment.

The cable was guided through the housing on a series of plastic ridges that held the cable up against the base plate and sensor and minimised lateral cable movements. The completed housing design is shown, together with the percutaneous introducer, in figures 4.36, 4.37 and 4.38.
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Figure 4.36: Underside view of the optical motion sensor

Figure 4.37: Top view of the optical motion sensor

Figure 4.38: The optical motion sensor showing the mating joint with the percutaneous introducer
The exploded diagram in figure 4.39 shows all of the major components of the optical motion sensor, and how they fit together. The simplicity of the design and the stacking assembly is designed to aid in manufacturing by simplifying the assembly process as much as possible.
4.7 The system

4.7.1 Overview

The system, which is an adaptation of the commercially available MEA system from Microsulis Medical, is shown in figure 4.40 and consists of a control unit and 9.2 GHz magnetron with a maximum power output of around 50 watts. The pneumatic footswitch is used by the surgeon to turn the microwave power on and off. The optical motion sensor is plugged into the system on the front panel, and the applicator is attached via an N-type connector to the magnetron. The whole system, including the applicator, is called the Microwave Venous Occlusion (MVO) system.

The control unit is based on a standard PC with a touch screen user interface and custom designed software. The software was created by the software company IPL Ltd (2004) working from the specifications described in this section of the thesis together with sections 4.7.2 and 4.7.3.
The applicator is designed to be introduced into the patient with the sensor unit being firmly taped or strapped down in an appropriate position near the site of the applicator introduction. When treatment starts, the applicator is withdrawn and this movement is detected by the sensor. The rate of withdrawal is measured by the sensor and fed back to the surgeon via the system to ensure that the required treatment depth is achieved. The data from the sensor is time-averaged to make the withdrawal rate data usable by the surgeon. In the event that the surgeon moves too slowly, the system cuts power to the applicator.

In order to warn the surgeon that the applicator is approaching the skin and the treatment coming to an end, coloured warning bands were placed on the cable. Firstly a 4cm warning band appears on the cable, followed by 4cm a black stop band. At a withdrawal rate of 17.5cm/min this gives the surgeon and theatre staff 14 seconds to see the warning band and a further 14 seconds to see the stop band. There are two sets of warning and stop bands, as shown in figure 4.41. The yellow and black one is for use with a percutaneous introducer whilst the blue and black one provides a warning when using the system with an open cut-down.

4.7.2 The treatment screen

The treatment screen, shown in figure 4.42, indicates the speed of withdrawal on a speedometer. The background is divided into 4 areas with three different coloured zones, to indicate the optimal, sub-optimal and unacceptable rates of withdrawal. The rates that correspond to each band were determined through the computer modelling detailed in sections 4.7 and 4.8 of this chapter. In the event of the averaged
withdrawal rate dropping into the unacceptable region of below 10cm/min, power is cut to the applicator and the treatment screen replaced with a screen asking the surgeon to withdraw the applicator 8mm. This withdrawal is monitored by the software and the number of remaining millimetres required to complete the 8mm appears on the screen. Once the 8mm has been covered the treatment screen re-appears and treatment can re-commence. This should have no clinical implications as the length of untreated vein will be very short relative to the overall treated length.

Figure 4.42: The user interface screen during a treatment

**4.7.3 Speed averaging**

During use the sensor returns a position value when polled in counts, relative to where it was last re-set. Before the start of every treatment the sensor is reset and then polled every 0.1 seconds once the footswitch is depressed and power is applied. The difference in the counts value between each poll is then multiplied by a conversion factor to give the rate of motion in cm per minute.

The polling interval is important in determining accuracy and is related to the speed of motion of the cable. If the polling interval is so short that very few counts have been accumulated between polls, then discretisation errors will occur as the measured rate will appear to be one of several discrete values. The polling interval was chosen through trial and error to make such errors unrecognisable.
In order to make the feedback useful to the surgeon, the response of the speedometer had to be made sufficiently damped to make the speed that appears on the system screen move smoothly and not cause unnecessary trips. At the same time the response must not be so slow that the system does not trip within an acceptable time period and the speed presented to the surgeon is too slow, so delayed that the feedback is not usable. In order to fulfill these criteria a rolling average calculation was used which presents the mean value of the preceding 26 polling intervals. In other words, the mean value from the previous 2.6 seconds of speed measurement. This gives a smooth response to changes in speed, whilst also giving an effectively instantaneous response to any change in speed. The maximum length of time which the applicator can remain stationary for is therefore the length of the averaging time, i.e. 2.6 seconds. A typical treatment is shown in figure 4.43. The mean averaged withdrawal speed in this treatment is 17.5 cm/min with a standard deviation of 2.2 cm/min. The minimum averaged withdrawal rate is 10.92 whilst the maximum is 23.6 cm/min.

A potential user problem was coping with the response of the speedometer at the start of the treatment. Starting from the minimum value of 7.5 cm/min would entail
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removing the 10cm/min trip level and only imposing it again after a certain length of time. Instead, the treatment screen starts with the needle at the optimum treatment rate of 17.5cm/min with the algorithm assuming that a perfect withdrawal had been maintained even before the start of treatment. The surgeon has to withdraw the applicator before the needle reaches the trip level. This system is quite intuitive and easy to use and ensures that the same safety conditions are imposed throughout the treatment. In the event of no withdrawal at all from a standing start the trip time is 
\[ \left( \frac{17.5-10}{17.5} \right) \times 2.6 = 1.1 \text{ seconds}. \]

4.7.4 System testing

4.7.4.1 The lead screw based withdrawal device

In order to allow accurate withdrawal of the applicator for characterisation of the sensor and system a withdrawal device based on a lead screw was built. The lead screw is driven by a computer controlled stepper motor which rotates accurately at a chosen number of rotations per second. The drive nut runs along the screw and is fitted with a clamp into which the cable can be fitted, as shown in figure 4.44. The sensor is clamped near the end of the lead screw and the cable fitted into the clamp on the drive nut. The cable can then be withdrawn at a constant pre-determined speed when the stepper motor is driven.

Figure 4.44: The mechanics of the lead screw device
4.7.4.2 Motion sensor characterisation

The speed value shown is dictated by the accuracy of the sensor and the calibration factor. This in turn determines the burn induced in the patient. The accuracy of the sensor is therefore crucial.

Initially a single sensor was randomly chosen and withdrawals at various speeds using the lead screw were carried out over a fixed length of 20.9cm. This allowed an assessment of the effect of different withdrawal speeds on distance measurement. The results are shown in figure 4.45.

Figure 4.45: Percentage measurement error in distance over 20.9cm against withdrawal speed for one randomly chosen sensor. The error bars are 95% confidence intervals.

The number of counts measured per unit distance will therefore decrease by approximately 0.5% from the value measured at 10cm/min with increasing withdrawal speed in the likely range of interest of up to 27.5cm/min.

The conversion factor was then assessed through testing ten completed sensors. Each one had an applicator pulled through it at 27.5cm/min and 10cm/min. The mean number of counts from these 20 values was then chosen to calculate the conversion.
factor. The results are shown in scatter diagram in figure 4.46 as an error in distance measurement relative to the mean. The standard deviation is 1.2% and the 95% confidence interval for the mean is +/-0.5%

![Figure 4.46: Percentage error in distance measurement for 20 values from 10 sensors](image)

4.8 Thermal analysis by Green’s function integration

4.8.1 Introduction

The finite difference model described in section 4.3 gave an initial treatment characterisation for VNUS and allowed a first assessment of the likely parameters that would potentially give an effective treatment using microwaves. However, as explained in section 2.1, the fact that this is a medical treatment means that accurate characterisation of potential tissue damage is required, both to minimise risks to patients by allowing accurate setting of treatment parameters, and also to fully explain how the tissue will be affected by the treatment. A more accurate thermal analysis was therefore required, upon which analysis of tissue damage could be built. A Green’s function model was used as this approach lends itself well to modelling this treatment. Firstly, finite difference and finite element based approaches do not lend themselves as well to modelling moving sources. Furthermore, the tissue temperatures reached by this treatment will not be sufficient to cause steam generation, and heating is applied for a relatively short time. The chances of significant changes in tissue properties occurring are therefore minimised. In addition, the applicator is removed from the tissue as soon as heating has occurred, minimising the effect of the applicator itself on the thermal profile. The heated volume is also very small relative to the body. All of these factors support the assumptions required for a Green’s function model to be appropriate, which are that the medium is homogenous, isotropic and infinite.
4.8.2 SAR fitting

An analysis was conducted with the aim of characterising the treatment and placing limits on the withdrawal speed of the applicator. The first step was to transfer the SAR predicted by HFSS to the Green’s function model. The SAR was therefore recorded along various lines parallel to, and radiating outward from, the applicator surface as shown in figure 4.47.

\[
SAR(r, z) = e^{-1000(r-2.25\times10^{-3})} \times SAR_{\text{peak}} \times e^{-10^5z^2},
\]

where \(SAR_{\text{peak}}\) is the maximum value of SAR at the surface of the applicator.
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The expression for SAR was convolved with the Green’s function kernel as described in section 2.3.3 over space and time to give the temperature against time for any chosen depth. The Mathcad worksheet used is given in appendix 7.

Multiplying the expression for SAR in equation 4.4 by the density, gives an expression for power deposition in W/m³. Integrating this over the volume of which significant heating occurs gives the total power deposition into the tissue. The value

Figure 4.48: The SAR calculated from HFSS (blue) compared to the approximation used in the Green’s function analysis (red) along a line running parallel to the applicator surface at a distance of 1.75mm

Figure 4.49: The SAR calculated from HFSS (blue) compared to the approximation used in the Green’s function analysis (red) along a line running radially outward from the applicator surface
SAR\textsubscript{peak} can then be adjusted to give the required power output \( P \), which sets the value for SAR\textsubscript{peak} using

\[
P = \int_{-8\times10^{-3}}^{8\times10^{-3}} \int_{-10.25\times10^{-3}}^{10.25\times10^{-3}} (e^{-1000(r-2.25\times10^{-3})}) \times SAR_{\text{peak}} \times e^{-10^{5}r^{2}} \times p_{t} \times 2\pi r dr dz,
\]

where \( p_{t} \) is the density of the tissue.

The temperature rise \( T(r_{0}, t) \) at time \( t \) and at a point in space \( r_{0}(r_{0}, \theta, z_{0}) \), due to an impulse applied to the applicator at \( t = 0 \), is given by the convolution of the Green’s function with the applicator SAR, integrated over the volume over which the SAR applies. The source points are defined by the \( SAR(r, \theta, z) \). For the case in which the applied SAR is an impulse heat source, applied at \( t = 0 \), defined in cylindrical polar coordinates, \( T(r_{0}, t) \) is given by,

\[
T(r_{0}, t) = \iiint_{V} G(r_{0} | r, t) SAR(r, \theta, z) r d\theta dz dr
\]

where \( r_{0} \) is the field point, \( r_{0} | r \) is the distance between the source point and the field point and \( V \) is the volume over which the SAR applies.

The distance between the source and field points for the case where the system is described in cylindrical polar coordinates is given by trigonometry, as shown in figure 4.50 and is given by

\[
r_{0} | r = \sqrt{(r \sin \theta)^{2} + (r_{0} - r \cos \theta)^{2} + (z - z_{0})^{2}},
\]

where the source points SAR are given in cylindrical polar coordinates and the field point \( r_{0} \) is located at \( (r_{0}, \theta, z_{0}) \).
Figure 4.50: The relationship between the source and field points and the distance between them calculated using cylindrical polar coordinates.

For a case of a stationary SAR which is applied for a certain time then the temperature rise $T(r_0, t')$ after time $t'$ is given by the integral over time of equation 4.5

$$T(r_0, t') = \int_0^t \int_0^r \int_0^{2\pi} G(r_0 | r', t) SAR(r, \theta, z) r d\theta dz dr dt.$$ 

However, in order to evaluate the temperature rise after power stops being applied, the integral must evaluate the contribution from the Green's function that would come from the first instance at which power was applied, as well as all the other contributions that come after power was first applied until it was turned off. If power was applied for $x$ seconds, and the temperature rise at $t'$ is required, then the integral will have to evaluate contributions from $t' - x$ until $t'$

$$T(r_0, t') = \int_{t' - x}^t \int_0^r \int_0^{2\pi} G(r_0 | r', t) SAR(r, \theta, z) r d\theta dz dr dt.$$ 

where $x$ is the length of time power is applied for.
To model a moving source, the integral must account for the changing distance between the field point and the source points, as well as the integrating over the correct time. If the source is moving at a constant rate $u$ along the $z$ axis, then the distance will be a function of time, and the time can be specified in terms of distance moved along the $z$ axis from $z_{\text{start}}$ to the final location at time $t$, $z_0(t)$. The integral can then be performed over distance, with the time specified in terms of the distance

$$T(r_0, t) = \frac{1}{u} \int_{z_{\text{start}}}^{z_0(t)} \int \int \int G(r_0, r', t(z_0)) SAR(r, \theta, z) r dr \theta dz dz_0 .$$

As shown in figure 4.51, let $i$ be the length of time since the start of the simulation, at which point the temperature rise is required. If the simulation starts with the source points at some position $z_{\text{start}}$ when $i = 0$, the distance moved after $i$ will therefore be,

$$Z(i) = ui + z_{\text{start}} .$$

Setting the time so that when $Z(0) = 0$ gives a new variable,

$$T(i) = i + \frac{z_{\text{start}}}{u} .$$

Figure 4.51: The relationship between the source and field points over time $T(i)$ and $i$ relative to distance $z_0$. 

Source points adjacent to field point at $z = 0$ and $i = \frac{z_{\text{start}}}{u}$

$T(0) = 0$
Each integral is evaluated with \( i \) fixed, so for every calculation \( i \) is effectively a constant. The integral needs to evaluate the contribution of the source points to the field point going back over time from time \( T(i) \) and position \( Z(i) \). This means that the contribution of the source points to the temperature rise at any fixed point in time \( i \) will be given by the contribution from the Green’s function at position \( Z(i) \) with time within the function set to 0, added to the contributions from the locations of the previous positions of the source points, with the times at which each of these contributions increasing to take into account that these contributions were progressively further and further back in the past.

The distance moved at time \( T(i) \) will be \( Z(i) \), and the time used within the Green’s function must be 0 at time \( T(i) \) with time increasing as the integral is evaluated over positions going back in time. This gives an expression for the time used within the Green’s function to relate position to the length of time in the past that the applicator was at that position

\[
t = T(i) - \frac{z_0}{u}.
\]

The final integral, with limits based on the results shown in figure 4.48 and 4.49 is,

\[
T(r_0,i) = \frac{1}{u} \int_{z_{start}}^{z_{stop}} \int_{2.25 \times 10^{-3}}^{8 \times 10^{-3}} \int_{-\pi}^{\pi} G(r_0,r',T(i) - \frac{z_0}{u}) SAR(r,z) rd\theta dz dr dz_0.
\]

In order to speed up the calculation, after the SAR is far enough away that any further contribution from the SAR is negligible, it is possible to evaluate the integral up until a stop point \( z_{stop} \)

\[
T(r_0,i) = \frac{1}{u} \int_{z_{start}}^{z_{stop}} \int_{2.25 \times 10^{-3}}^{8 \times 10^{-3}} \int_{-\pi}^{\pi} G(r_0,r',z_0) SAR(r,\theta,z) rd\theta dz dr dz_0.
\]
4.8.3 Model validation in PAG

4.8.3.1 Aims
The aim is to validate the temperatures predicted by the model by comparing the predicted temperatures that would be created in PAG with temperatures measured in PAG over a range of relevant withdrawal speeds. This will demonstrate that the model is an appropriate one to use for characterising the treatment.

4.8.3.2 Method
The temperatures predicted by the model were validated against the tissue phantom PAG. A PAG block was created with a 4mm diameter channel running down the centre of it. Optical fibre temperature measurement probes were buried at depths of approximately 1mm, 2mm, 3mm and 4mm from the channel. The exact distance of the centre of each fibre from the edge of the channel was then measured using a travelling microscope. This was focused on the centre of the tip of the fibre, and the position recorded. The microscope assembly was then moved sideways along a track until the centre of the image was on the edge of the channel and the new position recorded. This allowed a more accurate measurement of the position of the fibre relative to the channel to the made. The fibres were measured as being at distances of 0.75mm, 1.5mm, 3.35mm and 4.25mm. The applicator was inserted into the channel and power applied as the applicator was withdrawn past the fibre at a constant speed using the lead screw based withdrawal device. The temperature profiles were recorded for speeds of 10cm/min, 12.5cm/min, 17.5cm/min and 22.5cm/min, so a total of 16 temperature profiles were recorded. The experimental set-up is shown in figures 4.52 to 4.55.
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

Figure 4.52: The PAG temperature validation experimental set-up showing the lead screw withdrawal device together with its computer control, the PAG block and fibre, the magnetron power source, the luxtron optical fibre temperature measurement device and the data logging computer.

Figure 4.53: The PAG block with an optical fibre running into it.

Figure 4.54: A close-up of the applicator tip and optical fibre within the PAG block.
4.8.3.3 Initial results

A small modification was made to the integral that was used to evaluate the temperatures. Rather than integrating around the entire circumference of the applicator from $-\pi$ to $\pi$, the integral was only evaluated from $-\pi/2$ to $\pi/2$. This therefore meant that only heat sources on the side of the channel nearest to the point at which the temperatures were being predicted were taken into account. This was to allow for the fact that heat sources from the other side of the channel would not be able to reach the fibre due to the air gap caused by the channel. The properties of PAG given in table 2.2 were used in the modelling. The initial results for a withdrawal speed of 22.5cm/min at 0.75 and 1.5mm are shown in figures 4.56 and 4.57.

![Traveling microscope](image.png)

**Figure 4.55:** The travelling microscope used to measure the depth of the fibre in the PAG relative to the channel.

![Temperature graph](image.png)

**Figure 4.56:** Comparison between measured (blue) and modelled (pink) values for temperature at a depth of 0.75mm in PAG at a withdrawal rate of 22.5cm/min when first measured.
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

Figure 4.57: Comparison between measured (blue) and modelled (pink) values for temperature at a depth of 1.5mm in PAG at a withdrawal rate of 22.5cm/min when first measured

The model is clearly a good fit the experimental results. However there is a discrepancy between the modelled and measured results for the peak temperatures close in to the applicator. Unfortunately, this discrepancy is important because these high temperatures are largely responsible for creating the burn. It was therefore important to understand from where this difference arose. A static finite element analysis in ANSYS was conducted to investigate the source of this discrepancy.

4.8.4 ANSYS analysis

4.8.4.1 Aims

In ANSYS both the PAG and the fibre were modelled in order to obtain the best possible understanding of the source of the difference. The optical fibre temperature probe used to take the measurements was a Luxtron STB. A close-up of the tip is shown in figure 4.58. Figure 4.59 shows the internal structure of the fibre, as given by the manufacturers.
Although optical fibre measurement probes have the advantage that microwave fields do not directly affect them, their temperature response can potentially lag slightly in regions of high thermal gradient. This is because the fibre itself is microwave transparent, and therefore does not heat up with the surroundings. Instead it relies on thermal conduction to heat the fluorescent dye. However, the dye is located within a plastic jacket, which naturally acts as insulation. Furthermore, the dye is directly in contact with the relatively high thermal conductivity silica core of the optical fibre and therefore has a natural tendency to lag behind temperature changes. This lag is not normally significant, but it was investigated as a possible explanation of the discrepancy between the predicted and recorded temperatures as the MVO applicator passes the fibre.

### 4.8.4.2 Method

A hollow cylinder of 30mm in diameter and 20mm deep was created in ANSYS to represent the PAG used in the validation experiments. The central lumen had a diameter of 4.5mm. Within this cylinder two further cylinders of the same dimensions as those given by Luxtron were embedded to represent the core and cladding of the optical fibre. The material properties given below in table 4.2 were then applied.
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

Table 4.2. The thermal properties applied to the three components of the ANSYS simulations

<table>
<thead>
<tr>
<th>Component</th>
<th>Density</th>
<th>Specific heat capacity</th>
<th>Thermal conductivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyacrylamide gel</td>
<td>1030 kg/m³</td>
<td>4187 J/kg°C</td>
<td>0.41 W/m°C</td>
</tr>
<tr>
<td>Plastic</td>
<td>940 kg/m³</td>
<td>1900 J/kg°C</td>
<td>0.47 W/m°C</td>
</tr>
<tr>
<td>Silica</td>
<td>2200 kg/m³</td>
<td>740 J/kg°C</td>
<td>1.38 W/m°C</td>
</tr>
</tbody>
</table>

In the simulation the fibre was placed at 0.75mm. This was because a noticeable temperature lag between the measured and modelled temperatures was only visible when the fibre was close to the channel. The set-up is shown in figures 4.60a and 4.60b.

Adiabatic boundary conditions were applied to the symmetry plane of the model (the XY plane) and the internal lumen of the cylinder. The outer surfaces were all given fixed temperature boundary conditions of 20°C. The initial starting temperature was also chosen as 20°C. This is effectively an arbitrary starting temperature, as it is the temperature rise (ΔT) that is important.
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

The field generated by the MVO applicator was applied to the PAG for two seconds, and the resulting temperatures at the point within the tip of the fibre where the fluorescent dye is located were determined over 200 seconds. Then the material properties of the fibre were changed to those of tissue, and the SAR was applied both to the PAG and to the fibre for two seconds. Once again the temperature at the same point at the tip of the fibre was determined over 200 seconds. The same mesh was used for both simulations and the node at which the temperature was recorded is shown in figure 4.61.

Figure 4.61. A close-up of the meshed model with the fibre at 0.75mm. The node at which the temperature was recorded is circled.

Two seconds was chosen as the period of time for which the SAR from the stationary applicator was applied, since this is approximately equivalent to the SAR likely to be experienced by the fibre from an applicator moving at the optimal rate of 17.5cm/min.
4.8.4.3 Results

The initial results showed only a very small difference between the temperature at the point of the fluorescent dye, and the temperature in the PAG without the fibre, as shown in figure 4.62.

![Graph of temperatures recorded over 200secs at a depth of 0.75mm by a temperature measurement fibre in perfect thermal contact with its surroundings (red) and in PAG alone without a fibre (blue).](image)

Figure 4.62. Graph of temperatures recorded over 200secs at a depth of 0.75mm by a temperature measurement fibre in perfect thermal contact with its surroundings (red) and in PAG alone without a fibre (blue).

However, this difference was not sufficient to explain the difference seen between the model and the measured results. A second set of simulations was then carried out. An adiabatic boundary condition was applied to the walls of the fibres, leaving only the tip in contact with the PAG. The adiabatic boundary condition prevented energy flow between the fibre and the PAG anywhere except on the flat of the tip. This was to simulate the effect of an insulating air gap around the fibre. This did produce a significant discrepancy between the temperature of the dye and the temperature of the PAG alone, as shown in figure 4.63, which matched very well with the experimental data.
Figure 4.63 Graph of temperatures recorded over 200 secs at a depth of 0.75mm by a insulated fibre and in PAG without a fibre.

This effect can be seen below in figures 4.64 and 4.65, both recorded at 8secs after heat was first applied. Figure 4.64 shows a cross section of the fibre and PAG with all the correct properties, whilst figure 4.65 shows a cross section of the PAG alone.

The fibre can be seen to be cooler than the surrounding PAG in figure 4.62, whilst in figure 4.65, the thermal contours are passing through the former location of the fibre.
4.8.4.4 ANSYS model validity

This model was intended to qualitatively demonstrate that when the fibre is used to measure temperatures in regions of high thermal gradient, such as those experienced at a depth of 0.75mm from the applicator, the intimate contact of the fibre surface with the material in question becomes very important. Validity can be given to the model by comparing the predicted temperatures that would be measured by the fibre when only in contact at the tip, with the actual temperatures measured as part of the Green's function model validation. This comparison is valid because of the relatively fast movement of the applicator past the fibre, and the proximity of the fibre to the applicator. As shown in figure 4.66, the measured temperature profile is very similar to that predicted for the stationary case. Since the temperature predictions are so similar to the measured values, credence can be given to the model that incorporates insulation of the fibre shaft.

Figure 4.66. Predicted temperatures experienced by the fibre at 0.75mm from a stationary applicator compared to the recorded temperatures from a moving applicator for the case where the fibre shaft is insulated from the tissue

4.8.4.5 Conclusions

An ANSYS model has been produced of a stationary MVO applicator heating PAG for 2 seconds with and without a temperature measurement fibre located at 0.75mm.
The simulations were carried out with and without adiabatic boundary conditions applied to the fibre-PAG interface along the length of the fibre shaft. This model indicates that the discrepancy in peak temperature measurements between the measured results and the Green's function model predictions in regions of high thermal gradient is due to the intrinsic nature of the fibre, and additionally, insufficient contact between the fibre and the PAG. It explains why there is a difference between the Green's function temperature predictions and the measured results, particularly for the short period when the fibre is within a high thermal gradient.

4.8.5 Final temperature validation results in PAG
Despite the similarity of the ANSYS analysis results to the measured results at 17.5cm/min, the thermal analysis was still conducted using Green's functions. This is because the ANSYS results do not incorporate movement, so slower withdrawal rates are likely to have an increasing discrepancy between the predicted and measured values. There is also likely to be a growing discrepancy between the predicted and measured values as the fibre moves away from the applicator channel.

However, based on the results of the ANSYS analysis, the temperature measurements were re-done with ultrasound gel injected around the tip of the fibre to try and maximise contact with the PAG. This gave improved results compared to the Green's function analysis predictions, as shown in figures 4.67-4.70 for the results measured using a withdrawal rate of 22.5cm/min.
Figure 4.67: Comparison between measured (blue) and Green's function analysis (pink) values for temperature at a depth of 0.75mm in PAG at a withdrawal rate of 22.5cm/min

Figure 4.68: Comparison between measured (blue) and Green's function analysis (pink) values for temperature at a depth of 1.5mm in PAG at a withdrawal rate of 22.5cm/min
Figure 4.69: Comparison between measured (blue) and Green’s function analysis (pink) values for temperature at a depth of 3.35mm in PAG at a withdrawal rate of 22.5cm/min

Figure 4.70: Comparison between measured (blue) and Green’s function analysis (pink) values for temperature at a depth of 4.25mm in PAG at a withdrawal rate of 22.5cm/min
4.9 Burn depth analysis by use of the Arrhenius equation

4.9.1 Aims
Once confidence had been established in the temperatures predicted by the model, the Arrhenius equation was applied to the temperature results given by the model in order to assess the degree of cellular damage that would result, and in particular, the depth of cell death. The Arrhenius equation and the parameters used are given in section 2.6.

4.9.2 Method
This gives the resulting level of tissue damage at the depth at which the temperature profile was calculated over time as an omega value. Ω = 1 is the value at which permanent tissue damage is taken to have occurred, as explained in section 2.6.2. The maximum values that omega reaches are then recorded at intervals of 0.1mm as shown in figure 4.71 for a withdrawal rate of 22.5cm/min. The exact point at which Ω = 1 can then be interpolated. The maximum value of omega was taken as the final value after 360 seconds for withdrawals of 5 and 7.5cm/min, and 240 seconds for all other results. The growth of omega over time is shown in figure 4.72 for the 5cm/min results and the 10cm/min results. These represent the results that are most likely not to have reached their final values by the end of the simulated time period. As can be seen, the final omega value is clearly close to the omega value that would be recorded at infinity.
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Figure 4.71: Omega values plotted against depth for a withdrawal rate of 22.5 cm/min, allowing the point at which $\Omega = 1$ to be interpolated. The dotted lines show a linear interpolation between the two data points straddling $\Omega = 1$.

Figure 4.72: Omega value growth against time for the two results that are most likely not to have reached their maximum value by the end of the simulation.
4.9.3 Burn validation in liver

4.9.3.1 Aims

In order to validate the model predications for tissue damage, a validation was carried out in bovine liver.

4.9.3.2 Method

An applicator was sandwiched between two pieces of liver that had been heated in a water bath to 37°C, as described in section 4.5.3.2. Power was applied and the applicator was then withdrawn using the lead screw based withdrawal device at 10cm/min, 12.5cm/min, 17.5cm/min and 22.5cm/min. The liver was then left for six minutes to allow the burn to reach the maximum possible extent. The heated track in the liver was cross-sectioned and close-up photographs taken against a scale. The depth of visible thermal damage was then measured at 0.5cm intervals along the heated length and the mean level of visible tissue damage calculated. A typical burn is shown in figure 4.73.

![Figure 4.73: The burn in liver resulting from a withdrawal rate of 22.5cm/min](image)

The model was then run using the properties listed in table 4.3.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho$</td>
<td>1060 kg m$^{-3}$</td>
<td>Mean density of human liver</td>
</tr>
<tr>
<td>$C$</td>
<td>3.370 J kg$^{-1}$K$^{-1}$</td>
<td>Specific heat capacity of bovine liver</td>
</tr>
<tr>
<td>$k$</td>
<td>0.488 W m$^{-1}$K$^{-1}$</td>
<td>Thermal conductivity of bovine liver</td>
</tr>
</tbody>
</table>

Table 4.3: The tissue properties used for the validation of the results from the burn analysis. These were all taken from Duck (1990)
4.9.3.3 Results

The modelled and measured results are compared in figure 4.74.

![Figure 4.74: Modelled burn depths (pink) compared to measured mean burn depths (blue) in ex-vivo bovine liver with 95% confidence intervals for the means](image)

The gradients of the predicted and measured burn depths are very similar, and the predicted and measured burn depths are similar. The predicted burn depths are all slightly greater than those measured, though. However, this is not unexpected as only the level of gross tissue damage is visible and it is probable that the likely depth of tissue necrosis will extend slightly further than that visible in the liver.

4.9.4 Predicted results in-vivo and system parameter choice

Following on from the results of the burn validation, the Green’s function model was re-run using the parameters for the human vein given in table 4.4, for withdrawal speeds of 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25 and 27.5 cm/min, at the ideal, maximum and minimum power levels possible from the applicator. The Arrhenius equation was then applied using the values for E and A given in section 2.4 and validated in the liver, in order to calculate the maximum and minimum depths of cell death in a human vein.
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

<table>
<thead>
<tr>
<th>$\rho = 1056 \text{ kg m}^{-3}$</th>
<th>Density of human veins</th>
<th>Duck, 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C = 3.528 \text{ J kg}^{-1} \text{K}^{-1}$</td>
<td>Specific heat capacity of human aorta</td>
<td>Valvano &amp; Chitsabesan, 1987</td>
</tr>
<tr>
<td>$k = 0.46 \text{ W m}^{-1} \text{K}^{-1}$</td>
<td>Mean of two values for human aorta</td>
<td>Valvano &amp; Chitsabesan, 1987</td>
</tr>
</tbody>
</table>

Table 4.4: The tissue properties used for the thermal analysis in human veins. These were all taken from Duck (1990)

The maximum power level is given by the maximum uncertainty on the magnetron power output, which is $+7.15\%$ and assumes a perfectly matched applicator. This gives an output of 16.9 watts at the tip. The minimum power output is given by the minimum uncertainty on the magnetron power output, which is $-7.15\%$, together with the worst-case match into tissue. The minimum acceptable applicator match measured at the end of the cable is $-16.6\, \text{dB}$, which taking into account the loss in the cable gives a minimum power output of 11.5 watts into the tissue.

Figure 4.75: Predicted burn depth against withdrawal rate for the MVO applicator and system in a vein

These results shown in figure 4.75 were used to assess the safe and recommended limits for applicator withdrawal rate, which are given on the treatment screen as described in section 4.7.2. The model shows that the burn grows greatly for
withdrawal rates under 10cm/min. This was therefore chosen as the safety limit, with the recommended withdrawal rate being between 12.5 and 22.5cm/min. This is equivalent to a burn of between 1.1 and 2.6mm at the target power output of 15 watts. The optical sensor characterisation given in 4.7.4.2 gives a standard deviation of 1.2%. Taking three standard deviations as the maximum degree of error gives an error of +/-3.6%. Based on this error and the maximum and minimum power output levels, the worst case burn with a constant withdrawal is predicted to be 3.0mm depth. At a nominal withdrawal of 22.5cm/min, the minimum burn is predicted to be 0.6mm in depth. If the surgeon stays within the recommended treatment band the burn should be well within 0.6 to 3.0mm as a constant steady withdrawal at 10cm/min is impossible to perform manually. These burn depths are within the levels previously published as being typical of a VNUS Closure treatment, but greater than the thickness of a vein wall, which is around 0.5mm. This should therefore give a safe and effective treatment.

4.10 Comparative bench testing with VNUS

4.10.1 Aims

In order to evaluate the MVO treatment as effectively as possible before a clinical study, a bench model was created to directly compare the established treatment VNUS Closure with MVO.

4.10.2 Method

A stripped human greater saphenous vein was sandwiched between two layers of ox liver. The liver represented the fascia and muscle that surround the vein in-vivo and allowed the extent of the thermal penetration through the vein to be assessed. The vein was sutured to the liver at both ends and the entire sandwich was wrapped in cling film and heated in a water bath to body temperature. The sandwich was then removed and a pressure of 200mmHg applied to represent bandaging and exsanguination of the leg with an Esmark bandage. Treatments were carried out on this model using both VNUS and MVO according to their normal protocols.
4.10.3 Results

4.10.3.1 Macroscopic

A typical comparative result is shown below in figures 4.76. As can be seen, the appearance of the burns is similar. Similar levels of efficacy can therefore be expected to VNUS, but much more quickly.

Figure 4.76: The burn on the right results from MVO, whilst the burn on the left results from VNUS

Figure 4.77: Cross section of the liver from the bench test of the VNUS treatment

Figure 4.78: Cross section of the liver from the bench test of the MVO treatment

The depth of visible thermal penetration through the vein wall into the surrounding liver is minimal for both VNUS and MVO as shown in figures 4.77 and 4.78.
4.10.3.2 Histological

Initial histological analysis of the VNUS burn has also been conducted. An experiment was designed and carried out by Metcalfe (2004) to allow an assessment of the burn resulting from VNUS. Rather than surrounding the vein with liver, a stripped varicose vein was cut into sections and the sections placed one inside the other. The vein was treated within 20 minutes of being removed from the patient in order to make the results as realistic as possible. This allowed heating to be carried out on still live tissue and an assessment of the degree of cell damage through birefringence to be made, as explained in section 2.5.9. This was not carried out with MVO, as microwaves fix tissue, making histological analysis of relatively subtle burns such as these difficult.

Figure 4.79: A cross-section of three lengths of vein placed one inside the other followed by treatment with VNUS closure and histological analysis (Metcalf, 2004)
Interestingly, this shows an asymmetric burn with dark areas at the top and bottom of figure 4.79. The lighter areas show viable tissue. This asymmetry is probably due to the compression applied to the vein causing the electrodes to be crushed together. They therefore no longer fill the vein and do not apply heat evenly to the inside wall. The vein in figure 4.79 was therefore probably crushed from either side, so the actual orientation of the vein in the experiment was probably at 90° to its current orientation on the page. The maximum depth of the burn is uncertain, but it certainly appears to be greater than 1.5mm, as it has penetrated through 3 veins, each of which is around 0.5mm thick.

This result implies that the complete circumference of the vein wall does need to be necrosed in order to cause occlusion. This is important because this situation is similar to the results that can be expected from a smaller, round applicator, such as the MVO applicator, which may also only apply maximum heat to the areas where the vein is directly in contact with the applicator. With very large veins, there may be areas around the applicator that do not get heated, as the applicator does not fill the vein. The VNUS result implies that this may have no impact on treatment efficacy.

4.11 Discussion

Ideally VNUS would have been modelled more extensively in order to evaluate its thermal profile more realistically than with a simple finite difference model. In particular, an investigation of the interesting histological results shown in Metcalfe’s (2004) bench test on VNUS Closure may have justified the use of smaller diameter MVO applicators. However, the histological results do not fit well with the macroscopic burns visible in both the veins and surrounding liver treated by VNUS and this result may well be due to the birefringence analysis not being sufficiently subtle to detect the changes that would result in cell death. In addition, the use of a smaller MVO applicator would mean that the maximum power input would need to be reduced in order to keep the thermal penetration from the surface of the applicator constant. This would probably result in reduced efficacy, but further work would be required to assess this. Linked to this is the question of the range of vein sizes that can be treated by the 4.5mm diameter microwave applicator. All the bench testing has
shown a burn to the complete wall of veins up to 1.2cm in diameter, but there is likely to be an upper limit on treatment size. There is also likely to be a lower limit on treatable vein diameter, but the 4.5mm applicator has been shown to be capable of insertion into veins of only 3mm in diameter. A smaller applicator may gain very little in terms of ease of insertion, but may well be less effective at treating large veins.

Another uncertainty is in the predicted maximum and minimum depths of thermal penetration. The modelling exercise conducted was effectively a worst-case analysis, as no perfusion, or fluid effects were considered. In-vivo there may well be fluids present, both in and around the vein. These fluids, such as blood, could remove heat, and so reduce the thermal penetration. This problem should not occur when the vessel and surrounding tissues are completely ex-sanguinated through compression, but this may well not be completely possible in-vivo. The level of residual blood will be a function of the ability of the clinician to ex-sanguinate the tissues, and can therefore only be assessed through clinical testing.

The manual pullback and feedback control mechanism also means that there will be some variation in pullback rate during the treatment. However, so long as the clinician stays within the recommended treatment band, the range of burn depths should be smaller than that predicted in the modelling. This is because the mean pullback rate will influence the temperature of the applicator, so tending to rob heat from the tissue when moving too slowly and add heat when moving too fast, relative to a steady pullback rate.

Although ultimately the efficacy and safety of the treatment can only be definitively answered through clinical testing, the bench test comparisons with VNUS do provide a very strong degree of confidence in the system.

4.12 Summary
An applicator for the treatment of varicose veins through the occlusion of the greater saphenous vein above the knee has been developed through an iterative development process. A finite-difference model of endovenous heating has been constructed to
show that a microwave applicator could increase the withdrawal rate of an endovenous thermally based treatment from the current 3cm/min using an RF technique, to around 20cm/min whilst still maintaining a similar temperature profile. Due to the ready availability of a source at 9.2 GHz, the possibility of designing an applicator to operate at this frequency was investigated. The resulting applicator has a design frequency of 9.2GHz and is intended for introduction either directly into the vein or through a percutaneous introducer. The burn is controlled by the withdrawal speed of the applicator. This applicator has been integrated into a system which uses an optical motion sensor to measure the withdrawal rate of the applicator by the surgeon. Characterisation of the temperatures induced in the tissue by the applicator, and the resulting burn, has been carried out for a range of speeds. A validated model based on the use of Green's functions to assess the temperatures induced in the surrounding tissue, and the Arrhenius equation to assess the resulting level of tissue damage, was used. This information has been used to determine the most effective and safe range of withdrawal speeds. Comparative bench tests on human veins have been carried out with an established and successful RF based treatment system to confirm that the burns resulting from the use of the applicator and system are likely to be both safe and effective. The first microwave treatment for varicose veins has therefore been developed.

4.13 Conclusions
A finite difference model has been able to show the potential of a microwave based endovenous technique for the treatment of varicose veins. The use of the HFSS finite element package, together with bench testing has allowed the development of a microwave applicator operating at 9.2GHz. Thermal modelling by Green’s function analysis, together with the application of the Arrhenius equation has then allowed the depth of thermal penetration of the applicator to be assessed to within the range 1.1 to 2.6mm. This modelling, together with the use of an optical motion sensor to measure applicator withdrawal rate has the potential to allow both a fast treatment and tight limits on the thermal penetration of the system. The resulting burns appear similar to those from an established but much slower RF treatment. The use of all three computer models, together with validation testing, has allowed the development of a system that should give similar levels of efficacy to the RF treatment, but with
increased safety and speed. This is the first microwave treatment for varicose veins and one of very few minimally invasive treatments, and it has the potential to offer greater speed, efficacy and safety than any other treatment for venous incompetence.
Chapter 5: Conclusions and future work

5.1 Summary

5.1.1 Introduction
This thesis provides a general overview of the major thermal medical treatment modalities, including microwave therapy. A survey of four successful microwave based therapies was given as an introduction to how microwaves can be successfully used to treat medical conditions. The analysis techniques required to develop treatments were also covered, such as an introduction to tissue complex permittivity and microwave absorption, the practical use of finite element packages, thermal analysis by finite difference approximation, Green's functions, the ANSYS finite element package, the Arrhenius equation, bench testing and the use of tissue substitutes.

The analysis techniques given in the introduction were applied in the development and testing of two novel microwave based treatments that are designed to treat two very different conditions: psoriasis and varicose veins.

5.1.2 Psoriasis
A review of the history of the use of hyperthermia in the treatment of psoriasis was conducted. This identified the possibility of improving on the result of one previous microwave trial involving three patients at 2.45GHz by Keddy-Grant (1990) that successfully treated one patient, but caused painful deep heating in the other two. The aim of this work was to build on Keddy-Grant's promising result and optimise the treatment of psoriasis by microwave therapy. The system would be designed to retain the therapeutic effect shown by the use of microwaves at 2.45GHz, whilst removing the deep heating.

A one dimensional finite difference thermal model was developed for a theoretical investigation into the likely performance required by a microwave applicator to be used for treating psoriasis. Data on blood perfusion from Klemp and Staberg (1983), and the thermal properties of skin from Duck (1990) were used in the model. The surface cooling parameter was assessed experimentally through the use of a tissue phantom on the bench, and the microwave properties of skin were taken from Clegg.
According to Orenberg (1986) the most efficacious treatment would be given by a therapeutic temperature of between 42 and 44°C over the superficial 3mm of the skin. The finite difference model developed indicated that to give a temperature of 43°C at a depth of 3mm required a frequency of 5GHz and forced air surface cooling at an ambient air flow rate of around 0.5m/s. In order to err on the side of caution, the parameters required to obtain a temperature of 42°C at 3mm were also assessed. 42°C at 3mm was found to be achievable using a frequency of 7GHz, and with no surface cooling required.

Based on these results an applicator operating at 7GHz, and without surface cooling, was designed using the finite element package HFSS and built. Its microwave performance was characterised using a network analyser, and it was integrated into a system. The heating produced by the applicator was characterised on the bench using a tissue phantom and compared to the model results in order to obtain a level of confidence in the model. This system was then applied to three patients for two treatments per week over three weeks.

In terms of efficacy, the clinical results were disappointing, with a mild improvement visible in only one of the patients. This improvement was also associated with a complication, which was blistering of the skin in part of the treated area. The resulting surface temperature data and power input data, together with the computer model, allowed an assessment to be made of the perfusion levels in healthy and psoriatic skin, and their relationship to skin temperature. This gave novel results on the variation of skin perfusion with temperature at hyperthermic temperatures. A best fit to the results gave the level of psoriatic blood perfusion as \( \omega = 39T - 1510 \), whilst the level of blood perfusion in healthy skin was found to be \( \omega = 2.4T - 90 \), where \( \omega \) is the blood perfusion in \( ml100g^{-1}min^{-1} \) and \( T \) is the surface skin temperature. These results are valid for temperatures of between 40 and 44°C, with a mean error in predicted blood perfusion of +/-29%.

5.1.3 Varicose Veins

As with psoriasis, a review of current treatments was conducted, and the possible means of treating varicose veins using microwaves was assessed. A minimally
invasive, radio-frequency based treatment called VNUS Closure demonstrated that a
minimally invasive endovenous treatment based on heating could provide an effective
treatment. A one dimensional finite difference model was developed to allow an
analysis of VNUS’ thermal effects in tissue. Based on this modelling exercise a
microwave applicator was constructed and bench tested. The design went through a
number of iterations until a design was settled on. This was characterised using a
thermal analysis model based on the use of Green’s functions, and validated against a
tissue phantom on the bench. A discrepancy between the results was explained
through the use of static finite element analysis using the package ANSYS. The
Green’s function analysis was then expanded to include an analysis of the burn likely
to result from the heating by applying the Arrhenius equation to the temperatures
predicted by the Green’s function model. As before, the model results were validated
against a bench model. This model gave a characterisation of the burn resulting from
different applicator withdrawal speeds, showing that with a power output of 15 watts
and a frequency of 9.2GHz, a burn of between 2.6 and 1.1mm would result if the
withdrawal speed was kept between 10 and 22.5cm/min. These limits on withdrawal
speed were incorporated into a system that monitors the withdrawal speed through the
use of an optical motion sensor, and presents this as feedback to the surgeon in order
to achieve a safe and effective treatment. This novel optical motion sensor uses
standard optical mouse components to measure relative position of the applicator
cable as it passes through a custom designed housing, so allowing the speed of
withdrawal to be calculated. The complete applicator and treatment system were
compared against VNUS using stripped human saphenous vein on the bench to
demonstrate the similarity between the effects of the two systems, and hence the
likely efficacy and safety of the microwave based system in-vivo.

5.2 Discussion

5.2.1 Thermal models
The characterisation and modelling of both applicators by computer has proved to be
effective and successful. The finite difference model was simple and quick to run. It
also had the advantage that it was flexible as it was written from the ground up. On
the negative side, it could not easily be made to describe complex or curved
geometries and could become unwieldy as it was made more complex. The Green’s
function model was ideal for modelling moving sources but had the disadvantage that homogeneity of the modelled volume needed to be assumed. Finite element packages have the potential to offer extremely accurate results, as demonstrated by HFSS. The consistent accuracy of the results from HFSS meant that any discrepancy between the simulation and the measured values was likely to be due to incorrect translation of the model into reality. When conducting thermal analysis using ANSYS the effect of the temperature measurement probe itself could even be included, as explained in section 4.8.3. However, modelling of moving sources can become complex and computationally expensive.

5.2.3 Psoriasis
The clinical results were disappointing with only a minor improvement seen in one patient. There are a variety of possible reasons for this. Firstly, the thermal modelling may have been inaccurate. Secondly, the twice-weekly treatment scheduling may have left too great a gap between treatments, allowing complete cell replication to take place during the interval and resulting in each treatment being effectively the same as the first. However, the most likely problem was due to the extreme variation in blood perfusion found between healthy and psoriatic skin. This meant that if healthy skin reached a therapeutic temperature, then the psoriatic skin would not reach it, whilst if the psoriatic skin reached a therapeutic temperature, then a burn would result in any healthy skin within the treatment area. This meant that only the patient with large area plaque psoriasis was effectively treated, and this was the same patient that did show some benefit. However, the safety implications of using a microwave treatment without some means of controlling blood flow are clear.

It therefore appears that whilst the possible efficacy of microwave therapy at 7GHz remains unresolved, the difficulty of controlling dosage using microwave therapy at any frequency without control of blood flow has been shown.

5.2.4 Varicose veins
The modelling exercises described in chapter 4 provide a convincing characterisation of the treatment due to the validation of both the thermal and burn depth analysis on the bench. The probable efficacy of the treatment as a whole is also strongly
supported by the bench comparison of the MVO treatment against an existing treatment with known efficacy and safety in-vivo.

5.3 Suggestions for further research

5.3.1 Fundamental research
There is considerable scope for improving our knowledge of both the microwave and thermal tissue properties, and their relationship with temperature. A comprehensive set of results for complex permittivity and its relationship to temperature in a range of tissue types would also ideally be derived, extending the work of Clegg (2002). Another key parameter is knowledge of blood perfusion levels in different tissues. One possible way of achieving this would be through the use of a probe that was fundamentally similar to that used for the psoriasis experiments. A smaller waveguide could be constructed and a known level of microwave heating applied to the tissue, whilst the surface temperature was measured. The entire device could be modelled in ANSYS and if the thermal and microwave properties of the tissue were accurately known, the perfusion level could be accurately calculated.

5.3.2 Thermal analysis
Improved knowledge of both microwave and thermal tissue properties could be applied to computer modelling in ANSYS to start to utilise its full capabilities. In the first instance, a loosely coupled microwave and thermal solutions could be performed on static models. This effectively means iterating the electromagnetic and thermal solutions over time within ANSYS. This would allow a quantitative analysis of the cooling effect of the tip as well as heating from the applicator shaft. If required, expansion of the various components of the applicator could also be undertaken. If the changes in material properties with temperature were known, this could be incorporated at this stage. The changing SAR pattern and power input during a treatment as the burn evolved could therefore also be predicted. Ideally, this solution would be closely coupled, meaning that the electromagnetic and thermal solutions are generated simultaneously, rather than through an iterative process. Another particularly interesting step would be to quantitatively describe heat transfer as a result of fluid movement. Finally, a moving source could be modelled with all the relevant changes in tissue properties taken into account.
5.3.3 Psoriasis

For psoriasis, there are several possible approaches for continuing the research. One would be to continue with surface microwave irradiation and to examine the possibility of temporarily reducing or removing the blood supply to the area to be treated, as mentioned before in section 3.10. It may be possible to achieve this through direct compression or the use of a tourniquet, or even through the application of drugs. The aim of this would be to remove the temperature differences over the treated area caused by the widely varying levels of blood perfusion in conjunction with the uniform deposition of energy over the skin. However, this may be difficult to achieve without inducing counter-productive levels of patient stress.

Another possible avenue to explore for treating psoriasis with microwaves would be through the application of heat using a Veinwave™ style device, as described in section 1.5.3. This would be inserted into the plaque and heat applied with the aim of occluding the blood supply within the plaque. This may provide relief through two methods of action. One would be to simply reduce the redness of the plaque by reducing the blood supply to the plaque. It may also provide longer term relief by reducing the supply of nutrients delivered by the blood to the cells, and so directly hinder their replication.

5.3.4 Varicose Veins

For veins, the first step would be to examine the results of the treatment as it stands in-vivo in a clinical trial. Follow-up of the patients would allow the effectiveness of the treatment to be quantified, but ideally histological analysis of in-vivo treated vessels would also be conducted. This would allow a direct comparison to the results of the bench tests, Green’s function and the Arrhenius analysis.

The treatment could also be expanded to treat other vessels, such as the lesser saphenous vein and small perforator veins. These would require a considerably smaller applicator. The lesser saphenous vein would also require an even more targeted treatment, due to the close proximity of the saphenous nerve to the vein in the lower leg.
An altogether different treatment technique could also be investigated. Rather than a continuous pull-back down the length of the vessel, the applicator could be kept static and a pulse of heat applied. The applicator could then be withdrawn without any power, and left static in a new position adjacent to the previous one. Another burn could then be put in at this point. As with the current method, the withdrawal could be monitored by the optical sensor. This technique would be a cross between the laser endovenous technique and MVO, and may be ideal for short veins such as perforators.

5.4 Conclusions

The use of the finite element computer modelling package HFSS together with accurate data on microwave properties has allowed the construction, testing and refinement of two very different microwave applicators, with the aim of treating two very common, difficult to treat, and chronic diseases: psoriasis and varicose veins.

The first conclusion is that treatment of psoriasis using microwave hyperthermia is possible, but is limited by large variations in blood perfusion between different regions of the skin. The variations in blood perfusion between healthy and psoriatic skin has been shown to be particularly large, with levels of blood perfusion in psoriatic skin of $\omega = 39T - 1510$ (+/-26%), compared to levels of blood perfusion in healthy skin of $\omega = 2.4T - 90$ (+/-32%), where $\omega$ is the blood perfusion in $ml100g^{-1}min^{-1}$ and $T$ is the surface skin temperature. These results are valid for temperatures of between 40 and 44°C, and fit well with previously published values for blood perfusion in healthy and psoriatic skin derived by a different method. They are also the first results for the temperature dependence of skin perfusion at hyperthermic temperatures.

Secondly, varicose veins can be treated using microwaves with a device and system of the type described. The resulting treatment effect appears to be very similar to an established and effective venous occlusion device, but with a significantly faster treatment time. This is the first microwave based treatment for varicose veins, and one of only a handful of minimally invasive varicose veins treatments.
Finally, modelling can play an important and successful role in the design and characterisation of medical microwave treatments. Thermal analysis of the treatments has been conducted by three different methods, with accuracy sufficient to allow significant characterisation and refinement of the applicators and their use.
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Appendix 1: Derivation of Pennes' Bio-Heat Equation

Heat flux is inversely proportional to temperature gradient so
\[ F(x) = -\alpha \frac{\partial T}{\partial x}, \]
where \( \alpha \) is a constant and \( F \) is the thermal flux.

Also, the energy retained over distance \( \delta x \) in the body is directly proportional to the temperature at \( x \). The rate of change of temperature with respect to time is determined by the rate of energy change at \( x \) giving
\[ \frac{\partial T}{\partial t} = \beta \frac{\partial E}{\partial t}, \]
where \( \beta \) is a constant and \( E \) is energy.

This rate of energy change can be broken down again into two parts. Firstly there is a source term, \( P(x, t) \), that represents power input (or removal) due to internal heat generation (or heat removal). This is directly proportional to temperature. Secondly, there is also energy change due to the rate of change of heat flux with respect to distance. This is inversely proportional to temperature giving
\[ \frac{\partial E}{\partial t} = P - \frac{\partial F}{\partial x}. \]

Inserting 3 into 2 gives,
\[ \frac{\partial T}{\partial t} = \beta \times (P - \frac{\partial F}{\partial x}) \]
and inserting 1 into 4 gives,
Substituting \( k \) for \( a \) and \( 1/\rho C \) for \( \beta \), where \( k \) is the thermal conductivity, \( \rho \) is density and \( C \) is the specific heat capacity gives,

\[
\frac{\partial T}{\partial t} = \frac{k}{\rho C} \frac{\partial^2 T}{\partial x^2} + \frac{P}{\rho C} \cdot
\]

Rearranging, this gives,

\[
\frac{\partial^2 T}{\partial x^2} - \frac{\rho C}{k} \frac{\partial T}{\partial t} = \frac{P}{k} \cdot
\]

For microwave medical thermal analysis purposes the source term, \( P \), can now be broken into three parts. Firstly there is the deposition microwave energy. This is commonly expressed as a standard absorption rate (SAR \((x, t)\)) in watts/kg. Secondly, there is blood cooling. Finally there is the internal heat generation due to metabolic processes.

Therefore,

\[
P = \rho_iSAR - \rho_i\rho_b c_b m(T - T_b) + \rho_iQ, \quad 6
\]

where \( \rho_i \) is the density of the tissue, \( \rho_b \) is the density of blood, \( c_b \) is the heat capacity of blood, \( m \) is the volumetric flow rate of blood per unit mass of tissue, \( T_b \) is the temperature of the perfusing blood and \( Q \) is the metabolic heat generation.

Inserting equation 6 into 5 and re-arranging gives Pennes' (1948) bio-heat equation, which in 3 dimensions is

\[
\frac{\rho_i C_i}{k} \frac{\partial T}{\partial t} = \nabla^2 T - \frac{\rho_i \rho_b C_b m}{k} (T - T_b) + \frac{\rho_i}{k} SAR + \frac{\rho_i Q}{k}. 
\]
Appendix 2: PAG formulation

For a total volume of 500ml mix the two parts and leave to set

**Part 1**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylamide</td>
<td>75g</td>
</tr>
<tr>
<td>MBA (Methylenebisacrylamide)</td>
<td>0.5g</td>
</tr>
<tr>
<td>TMEDA (Tetramethylethelenediamine)</td>
<td>1.92g</td>
</tr>
<tr>
<td>Surfactant (optional)</td>
<td>5g</td>
</tr>
</tbody>
</table>

Add de-ionised water to 450ml

**Part 2**

| AP (Ammonium persulfate)      | 0.65g   |

Add de-ionised water to 50ml
Appendix 3: 1 D finite difference thermal model of skin for assessment of blood perfusion levels (BASIC)

20 PRINT "Enter no of seconds"
30 INPUT S
60 PRINT "Enter watts on power meter"
70 INPUT W
80 PRINT "Enter starting temp"
90 INPUT STEMP
92 INPUT SETTEMP
95 BP = .000001
97 W = W * 100000
100 S = S * 100
110 L = 500
115 TLAST = 36.5
120 DIM T(L, 2)
130 OPEN "C:RESULTS.TXT" FOR OUTPUT AS #1
140 FOR N = 1 TO L
150 T(N, 1) = STEMP
160 FOR N1 = 2 TO (L - 1)
170 P = W * (2.71828 ^ (-442.5 * N1 / 10000))
180 T(N1, 2) = ((T((N1 + 1), 1) - (2 * T(N1, 1)) + T((N1 - 1), 1)) * .0931) + T(N1, 1) + (P / 387202750) + ((STEMP - T(N1, 1)) * BP)
190 NEXT N1
200 T(L, 2) = STEMP
205 T(L, 2) = (.0052 * (20 - T(L, 2))) + T(L, 2)
210 FOR N1 = 1 TO L
220 T(N1, 1) = T(N1, 2)
230 BP = ((T(L, 1) - SETTEMP) * BP * .001) - ((T(L, 1) - TLAST) * BP * .002) + BP
240 TLAST = T(L, 1)
250 IF BP < .000001 THEN BP = .000001
255 IF N / 100 = INT(N / 100) THEN GOTO 275 ELSE GOTO 300
260 REM FOR N1 = 1 TO 50
261 REM PRINT #1, CSNG(T(1, 1)); CHR$(9);
270 REM NEXT N1
275 PRINT T(1, 1);
280 PRINT TP(1, 1);
285 PRINT TP(1, 1);
290 PRINT BP
300 NEXT N
350 END
Appendix 4: 1 D finite difference thermal model of skin with hill-climbing algorithm for treatment optimisation (BASIC)

100 DIM VAR(3, 2)
170 PRINT "Enter starting power"
180 INPUT VAR(1, 1)
190 PRINT "Enter starting frequency in GHz"
200 INPUT VAR(2, 1)
210 PRINT "Enter starting surface cooling constant"
220 INPUT VAR(3, 1)
260 L = 200
263 OPEN "C:RESULTS.TXT" FOR OUTPUT AS #1
265 DIM T(L, 2)
270 VAR(1, 2) = VAR(1, 1)
280 VAR(2, 2) = VAR(2, 1)
290 VAR(3, 2) = VAR(3, 1)
300 PRINT "Enter no of generations"
310 INPUT Y
320 Q = 1
330 GOSUB 470
340 Q = 2
350 GOSUB 470
360 REM ***** START OF MAIN LOOP *****
370 FOR X = 1 TO Y
380 GOSUB 410
390 NEXT X
400 GOTO 900
410 IF DIF(1) >= DIF(2) THEN Q = 1 ELSE Q = 2
420 IF DIF(1) >= DIF(2) THEN R = 2 ELSE R = 1
430 DIF(Q) = 0
440 VAR(1, Q) = VAR(1, R) * ((RND / 10 - .05) + 1)
450 VAR(2, Q) = VAR(2, R) * ((RND / 10 - .05) + 1)
460 VAR(3, Q) = VAR(3, R) * ((RND / 10 - .05) + 1)
470 G = VAR(2, Q) * 10 ^ 9
480 EO = 8.854187 * 10 ^ -12
490 U = 1.256637 * 10 ^ -6
500 ER = 50
510 OM = 2 * 3.14159 * G
520 SIG = 27 * OM * EO
530 Z = (((SIG / (OM * EO * ER)) ^ 2) + 1)^.5 - 1
540 G = 1 / (((Z * U * EO * ER) / 2) ^ .5) * OM)
550 W = VAR(1, Q) * 100000
555 G = G / 2
570 IF X = 0 THEN PRINT "Skin depth is"; G * 1000; "mm"
590 FOR N = 1 TO L
600 T(N, 1) = (((1.572875 * 10 ^ -9) * (N ^ 5)) - (8.081823 * (10 ^ -7) * (N ^ 4)) + (.0001468 * (N ^ 3)) - (.010876 * (N ^ 2)) + (.2101256 * N) + 42.96808)
610 NEXT N
620 T(L, 2) = 35
640 FOR N1 = 2 TO (L - 1)
650 P = W * (2.71828 * (-1 / G) * N1 / 10000)
660 T(N1, 2) = (TT((N1 + 1, 1) - (2 * T(N1, 1))) + T((N1 - 1, 1)) * .09507) + T(N1, 1) + (P / 431261000) + (((35 - T(N1, 1)) * .00012))
670 NEXT N
680 T(1, 2) = T(2, 2)
690 T(1, 2) = (VAR(3, Q) * (20 - T(1, 2))) + T(1, 2)
700 FOR N1 = 1 TO L
710 T(N1, 1) = T(N1, 2)
720 NEXT N1
740 FOR N = 1 TO L
750 DIF(Q) = ((T(N, 2) - (((1.572875 * 10^-9) * (N^5)) - (8.081823 * (10^-7) * (N^4)) +
(.0001468 * (N^3)) - (.010876 * (N^2)) + (.2101256 * N) + 42.96808))^2) + DIF(Q)
760 NEXT N
770 PRINT DIF(R); VAR(1, R); VAR(2, R); VAR(3, R)
775 PRINT #1, CSNG(DIF(R)); CHR$(9); CSNG(VAR(1, R)); CHR$(9); CSNG(VAR(2, R));
CHR$(9); CSNG(VAR(3, R));
776 PRINT #1, CHR$(13);
780 IF X = Y THEN GOTO 790 ELSE GOTO 890
790 PRINT "Continue training?"
800 INPUT E$
810 IF E$ = "N" GOTO 820 ELSE GOTO 300
820 PRINT VAR(1, R); "W"
870 PRINT VAR(2, R); "GHz"
880 PRINT VAR(3, R); "Cooling"
890 RETURN
900 END
Appendix 5: 2 D finite difference thermal model of skin (BASIC)

20 PRINT "Enter no of seconds"
30 INPUT S
100 S = S * 100
118 DIM T1(100, 95)
119 DIM T2(100, 95)
120 DIM BP(100, 95)
121 OPEN "C:RESULTS.TXT" FOR OUTPUT AS #1
123 FOR N = 1 TO 100
124 FOR N1 = 1 TO 95
125 T1(N, N1) = 37
126 T2(N, N1) = 37
127 BP(N, N1) = 1
128 NEXT N1
129 NEXT N
130 FOR N = 50 TO 100
131 FOR N1 = 1 TO 20
132 BP(N, N1) = 0
133 NEXT N1
134 NEXT N
150 W = 5000000
160 OPW = 100
170 FOR N = 1 TO 99
180 FOR N1 = 2 TO 99
185 FOR N2 = 2 TO 94
190 P = W * (2.71828 ^ (-542 * N2 / 10000))
195 IF BP(N1, N2) = 0 THEN GOTO 196 ELSE GOTO 198
196 BPR = ((4.475 * (10 ^ -6)) * T1(N1, 1)) -.0001699
197 GOTO 210
198 BPR = ((7.87714 * (10 ^ -5)) * T1(N1, 1)) -.0030586
210 T2(N1, N2) = ((T1((N1 + 1), N2) - (4 * T1(N1, N2)) + T1((N1 - 1), N2) + T1(N1, (N2 + 1)) + T1(N1, (N2 - 1))) * .093104) + T1(N1, N2) + (P / 387202750) + ((36.5 - T1(N1, N2)) * BPR)
220 NEXT N2
225 NEXT N1
226 FOR N1 = 1 TO 100
229 T2(N1, 1) = T2(N1, 2)
230 T2(N1, 1) = (.0052 * (20 - T2(N1, 1))) + T2(N1, 1)
231 NEXT N1
232 FOR N2 = 1 TO 95
233 T2(1, N2) = T2(2, N2)
234 T2(100, N2) = T2(99, N2)
235 NEXT N2
240 FOR N1 = 1 TO 100
245 FOR N2 = 1 TO 95
250 T1(N1, N2) = T2(N1, N2)
260 NEXT N2
261 NEXT N1
280 IF N / 80 = INT(N / 80) THEN GOTO 285 ELSE GOTO 300
285 T3 = 43
291 OPT = T2(100, 1)
292 OPW = OPW + ((T3 - OPT) * OPW * (.19 * (2 ^ -(N / 80) / 100))) - ((OPT - TLAST) * OPW * (.76 * (2 ^ -(N / 80) / 100)) + .04))
293 IF OPW < .3 THEN OPW = .3
294 IF OPW > 100 THEN OPW = 100
295 TLAST = OPT
296 W = OPW * 4000000
Two Applications of Microwave Therapy: Psoriasis and Varicose Veins

300 PRINT N; CHR$(9); W; CSNG(T2(100, 1)); CHR$(13);
310 NEXT N
320 FOR N2 = 1 TO 95
330 FOR N1 = 1 TO 100
340 PRINT #1, CSNG(T2(N1, N2)); CHR$(9);
350 NEXT N1
360 PRINT #1, CHR$(13);
370 NEXT N2
380 END
20 PRINT "Enter drag rate in cm/min"
30 INPUT DR
40 DR = DR / 6000
50 PRINT "Enter radius of applicator in mm"
60 INPUT R
65 R = R / 1000
70 PRINT "Enter length of applicator in mm"
80 INPUT LENGTH
85 LENGTH = LENGTH / 1000
100 HEAT = LENGTH / DR
130 S = 6000
140 L = 100
150 DIM T(L, 2)
160 PRINT "Enter total number of Watts going into tissue"
170 INPUT W
180 PRINT "Enter frequency in GHz"
190 INPUT G
195 REM ***** Calculate Skin Depth *****
200 G = G * 10 ^ 9
210 EO = 8.854187 * 10 ^ -12
220 U = 1.256637 * 10 ^ -6
230 ER = 50
240 SIG = 27 * OM * EO
250 OM = 2 * 3.14159 * G
260 Z = (((SIG / (OM * EO * ER)) ^ 2) + 1) ^ .5 - 1
270 G = 1 / (((Z * U * EO * ER) / 2) ^ .5) * OM
280 PRINT "Uncorrected skin depth is"; G * 1000; "mm"
290 REM ***** Evaluate power input constant *****
300 G = 2 / G
310 K = (W * G) / (R * 2 * 3.14159 * LENGTH)
320 OPEN "C:RESULTS.TXT" FOR OUTPUT AS #1
330 REM ***** Set Boundary Conditions *****
340 FOR N = 1 TO L
350 T(N, 1) = 37
360 NEXT N
370 T(L, 2) = 37
380 REM ***** Main loop *****
390 FOR N1 = 1 TO (L - 1)
400 P = K * (2.71828 ^ (-G * (N1 / 10000))) * ((R + (N1 / 10000)) ^ -1) * R
410 IF N > HEAT THEN P = 0
420 T(N1, 2) = (T((N1 + 1), 1) - (2 * T(N1, 1)) + T((N1 - 1), 1)) / 7.4 + (T(N1 + 1, 1) - T(N1 - 1, 1)) / (148000 * (N1 + (R * 10)) * .0001) + T(N1, 1) + (P / 370000000) + ((37 - T(N1, 1)) * .000013)
430 NEXT N1
440 T(1, 2) = T(2, 2)
450 FOR N1 = 1 TO L
460 T(N1, 1) = T(N1, 2)
470 NEXT N1
480 FOR N = 1 TO S
490 FOR N1 = 2 TO (L - 1)
500 P = K * (2.71828 ^ (-G * (N1 / 10000))) * ((R + (N1 / 10000)) ^ -1) * R
510 IF N > HEAT THEN P = 0
520 T(N1, 2) = (T((N1 + 1), 1) - (2 * T(N1, 1)) + T((N1 - 1), 1)) / 7.4 + (T(N1 + 1, 1) - T(N1 - 1, 1)) / (148000 * (N1 + (R * 10)) * .0001) + T(N1, 1) + (P / 370000000) + ((37 - T(N1, 1)) * .000013)
530 NEXT N1
540 T(1, 2) = T(2, 2)
550 FOR N1 = 1 TO L
560 T(N1, 1) = T(N1, 2)
570 NEXT N1
580 IF N / 50 = INT(N / 50) THEN GOTO 590 ELSE GOTO 630
590 FOR N1 = 1 TO 50
600 PRINT #1, CINT(T(N1, 1)); CHR$(9); 
610 NEXT N1
620 PRINT #1, CHR$(13)
630 NEXT N
650 END
Appendix 7: Green’s function thermal analysis program for the MVO applicator (Mathcad)

\[ \text{Conversion of dimensions} \]
\[ a = \frac{k}{\rho c_p} \]
\[ \text{Thermal diffusivity} \]
\[ n = 1.235 \times 10^{-7} \]
\[ \text{SAR} = 106(8.23 - 15)^9 \text{ (peak)} \]
\[ \text{Power} = \frac{8.10^{-12}}{1.235 \times 10^{-16}} \]
\[ \text{Power} = 15 \]
\[ \text{Source-field distance squared} \]
\[ f = \text{period} = 240 \]
\[ u = 1.667 \times 10^3 \]
\[ \text{Speed in mm} \]
\[ d = 2.2510^3 \]
\[ \text{Factor} = \frac{1}{4.67} \]
\[ \text{First part of Green's function} \]
\[ \frac{\partial R \text{factor}}{\partial z} = \text{factor} \]
\[ \text{Second part of Green's function} \]
\[ f = \text{period} = 240 \]
\[ u = 1.667 \times 10^3 \]
\[ \text{Depth} = 2.2510^3 \]
\[ f = \text{factor} \]
\[ \text{Output} = \text{green}(u,i) \]
\[ f = \text{power} \]
\[ p = 0.240 \]
\[ \text{Output} = 8.510^7 \sum_{i=0}^{d} \left( \frac{1}{3} \right) \text{ (peak)} \]

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Appendix 8: MVO applicator engineering tolerance analysis

In order to define the acceptable tolerances on the components of the applicator, tolerances of +/- 0.05mm were placed on the diameter and length of the dielectric, the hole for the centre conductor in the dielectric, and the centre conductor length. All combinations of the tolerance extremes were simulated on HFSS. None of the simulations gave a result under -10dB, and the predicted match for 80% of them was under -15 dB, as shown below.

Match results for all the extreme combinations of tip dimensions with a tolerance of +/-0.05mm