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Developing Computer Controlled Laser Systems for Double Blind Acupuncture Trials

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Certificate of Authorship and Originality

I certify that this thesis has not been previously submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also verify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged.

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Acknowledgement

Writing this thesis has been a long project, longer than I had originally expected, as with life things don't always go as planned. The loss of my greatest mentor, my mother Prof. Carole Rogers occurred during this project. Losing Carole was a severe loss in more ways than one, not just for me but for the University and the Acupuncture profession as a whole. My promise to Carole to see this out became one of my major motivations to keep going, even though without her the task seemed impossible at times. Therefore I dedicate this work to her memory.

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Abstract

Title: Developing Computer Controlled Laser Systems for Double Blind Acupuncture Trials

Background: Double blind clinical testing is considered critical for advancing most areas of medical research. Much of the acupuncture laser and Low Level Laser Therapy (LLLT) research lacks double blinding and suffers from poor trial design. While some research studies have shown a potential increased clinical effect in visible wavelength laser trials visible wavelength lasers are generally overlooked in research, due to the difficulties with double blinding.

Objectives: This study sought to design, construct and test a system that could randomise, control, monitor and record the delivery of visible laser in real-time, and allow for double blinding.

Method: The study utilised a novel approach to incorporate computer controlled lasers within opaque hoods. An optical sensor feedback was incorporated to objectively measure the delivery of laser in a double blinded randomised controlled trial (RCT) situation.

The equipment was designed and tested for future researchers to operate with a minimum of training.

The initial testing was designed around a *proof of concept* study using the equipment to stimulate Pericardium 6 (PC 6) with a visible (635 nm) 10 mW laser while monitoring changes in Heart Rate Variability (HRV). We only sought to trial the equipment under laboratory conditions to see if a double blind condition could be achieved. It was beyond the scope of this study to undertake a RCT of the effects of PC 6 on HRV.

Results: The equipment was successful in maintaining double blind conditions. Laser was delivered and monitored in real-time, the operational parameters were recorded and test participants reported no discomfort associated with the use of the equipment. The

computer successfully controlled the random delivery of laser. The test participants and operators were at no time aware of the state of the laser. The operators reported no difficulties in using the unit.

Conclusion: A laser research tool was successfully created and the study demonstrated the system's unique ability to overcome all the difficulties identified for visible laser wavelength double blind research.

The system is currently designed with two laser hoods to allow for bilateral acupuncture point testing. Future improvements could include additional laser hoods for multiple acupuncture point treatments. Construction of alternate hoods would allow for testing of different wavelengths including infrared and different laser power levels.

The system combines double blind testing with physiological monitoring, which allows researchers to record the physiological effects that accompany laser therapies.

Chapter 1 Introduction

1.1 Background to the Study

Almost since the invention of the first working laser by Theodore Maiman in the 1960s (Bromberg 1988), there have been ever increasing attempts to use it as a therapeutic instrument both for conventional medical use and in acupuncture therapy. Mester et al (1971) demonstrated the physiological and wound healing effects of a ruby laser during the 1960s (1971). Further experiments using 12-25mW Helium Neon (HeNe) type lasers on acupuncture points, were carried out in the Soviet Union between 1970-72 (Plog 1980 in Whittaker 2004).

Since the 1970s, laser acupuncture and Low-Level Laser Therapy (LLLT) have both gradually gained acceptance as legitimate forms of therapy (Whittaker 2004). According to Whittaker (2004) research increased through the 70s and 80s due to the increasing availability of lasers, unfortunately many studies lacked proper randomisation and controls (2004). Despite its widespread acceptance of clinical effectiveness there has been little high quality research to date to determine the true value of these forms of laser therapy. Whittaker (2004, p. 69) stated: "The known ability of laser irradiation to induce cellular effects at sub-thermal thresholds provides impetus for further research". Much of the research conducted so far however, has been poorly designed clinical research trials that lack an objective scientific approach. Hence the need for more rigorously designed research, employing double blinded and randomised controlled trials (RCTs) to evaluate the effectiveness of laser as a therapeutic tool. The use of well-designed RCTs will meet the increased demand for evidence based medicine as the use of these forms of therapy increase.

Examination of the literature suggests that the majority of research claiming an RCT design, employing a double blind method, has been flawed. Many of the common problems include a lack of proper blinding techniques (as shown in table 3 eight papers where studies were not blinded) rendering the conclusions of many studies questionable. Non-reporting of wavelength (as shown in table 1 four papers did not include

wavelength used) make it impossible to accurately reproduce the research or even apply clinically where positive results have been reported.

As shown in Chapter 2 table 2, with 13 positive to 3 null results for visible laser and over 10 papers with positive results to 9 papers with null results for infrared laser, there would appear to be evidence to suggest that visible spectrum lasers may have a greater clinical and biological effect as a therapeutic tool over non-visible infrared lasers. Despite indications that the visible spectrum may have greater benefits, much of the research has employed infrared laser. This is because non-visible spectrums aid in maintaining double blind conditions.

For purposes of acupuncture research, the best type of laser to use in terms of wavelength, power, dosage and time of exposure are all questions that still require definitive answers, and remain an area of continued debate amongst researchers. The overall aim of our research is to provide the necessary equipment and study design to allow researchers to effectively answer some of the questions above, particularly in relation to the challenge of double blind testing of visible spectrum lasers.

1.2 What is Laser?

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation. Another common acronym used interchangeably with laser is LLLT (low-level laser therapy). LLLT is simply a differentiation of the power of the laser unit used in therapy. LLLT units are generally limited to outputs below 500mW.

There are three basic characteristics of laser which differentiate it from normal light.

1) It is *monochromatic*, meaning it has a single wavelength and colour. It is assumed that different cellular structures are stimulated by different wavelengths of light.
2) It is *coherent,* meaning that the radiation is inherently synchronistic. That is, the photons are spatially coherent and unidirectional. It is this characteristic that allows laser to maintain a small spot size over distance. The biological significance of this property is unclear.

3) It is *collimated*. In other words there is a lack of divergence in the beams of light which also contributes to the maintenance of a small spot size over long distances. Since the radiant power of the laser unit is fixed, the intensity of radiation is decreased over distance. Consequently, the distance of the laser from the treatment site will affect the intensity of irradiation.

1.3 LLLT

Laser essentially has three therapeutic factors.

1) *Absorption* is dependent on the wavelength and power of the laser unit. The energy absorbed is proportional to the qualities of the tissues. According to Weber (2007, p. 143): "The diffusion of light particles leads to a kind of photon fog that causes an enlargement of the beam in the tissue, thus limiting the penetration depth". The depth of penetration will also depend on the condition of the skin, its hydration and the blood and fat content in the dermal layer. The depth of penetration and absorption is also affected by the power output or intensity of the laser, the wavelength and time of exposure.

2) *Thermal effects* of laser will also be dependent upon wavelength and power of the unit. In some cases there can be elevation in tissue temperature, dehydration, coagulation of proteins and thermolysis. Although this effect would be at power and dosage levels far in excess of the lasers used for LLLT and therefore not a therapeutic effect employed by LLLT. LLLT (Low-level Laser therapy) uses laser at power levels below 500 mW to treat a range of medical conditions from musculoskeletal pain and soft tissue damage, to skin conditions and wound healing. This is differentiated from higher power lasers used for cutting and ablative techniques e.g. surgical laser for cornea modification or ruby laser for tattoo removal

3) It is the *non-thermal effects* of laser that appear to have the most therapeutic relevance to LLLT. According to a meta-analysis of 31 relevant papers, done by Peplow et al (2010) it is claimed researchers have evidence that laser therapy: provides pain relief through stimulating the release of endorphins and

enkephallins, reduction of inflammation, increase in blood flow to tissues, stimulation of wound healing, stimulation of tissue regeneration, reduced scarring and control of suppurative diseases of skin.

1.4 LLLT and Laser Acupuncture

LLLT is predominantly used as a local therapy for soft tissue injury. It is used outside of any specialised diagnostic framework and this is the difference between LLLT and laser acupuncture, which is applied according to Chinese medicine diagnostic frameworks. Laser acupuncture applies laser technology using Traditional Chinese Medicine (TCM) diagnostic frameworks and its acupuncture points and channel systems. In this context, laser treatment is applied more systemically than the symptomatic approach commonly used by LLLT (non TCM) therapists.

TCM uses systems of diagnosis and treatment developed over thousands of years. It involves the use of meridians to move Qi (Chinese concept of energy) around the body. Treatment is effected through the manipulation of various forms of Qi via the acupuncture points or herbal prescriptions. The selections of acupuncture points or herbs are based on various diagnostic systems, which in turn are based on extensive clinical observation of the patient. These observations include the pulse rate and quality, tongue, strength of voice, manner and mood with questions regarding sleeping patterns, diet, bowel function, urination etc. Identified signs and symptoms are then categorised into diagnostic patterns. These patterns guide the choice of acupuncture or herbal prescriptions.

The essential aim of the acupuncture practitioner is to rebalance the flow of Qi through the meridians. The purpose is to treat the patient rather than the disease. This requires an assessment of the overall factors affecting patient health rather than identifying a disease. For example, to a TCM practitioner an infection might be viewed as a weakness of the Wei Qi, the defence energy (immune response) rather than the specific infection by an opportunistic virus. An acupuncture practitioner may then use laser on

specific acupuncture points as an alternative to using needles to boost the Wei Qi (immune response).

Since laser is painless there is an obvious benefit to patients that are unable to tolerate needles, through phobia, age or illness. There is an added benefit in terms of prevention of blood borne cross infection. It could also be argued that since the aim of the acupuncturist is to adjust the patient's Qi, a form of energy, the use of an energy-based instrument such as laser is a logical extension to acupuncture therapy in place of physical mediums such as needles.

1.5 Laser as a Substitute for Needles

According to a meta-analysis done by Baxter referring the treatment of myofascial pain, postoperative nausea and vomiting and for the relief of chronic tension head-ache; "Laser acupuncture would appear to represent an effective form of acupuncture for the management of the conditions and could be considered as a viable alternative to more traditional forms of acupuncture point stimulation". (Baxter, Bleakley & McDonough 2008, p. 65).

Some researchers argue that laser should not be considered equivalent to acupuncture: Vickland (2006, p. 7) states "So called laser acupuncture, which in a strict traditional sense is not acupuncture at all, should be considered a different technique to manual acupuncture and should be used in acupuncture studies with caution". Proponents of this argument suggest that without needles it cannot be acupuncture, and strictly speaking this is correct. Whether an acupuncture point is stimulated with a beam of light or a stainless steel needle, Qi (the Chinese medical concept of energy upon which acupuncture therapy is based) is still affected.

Regardless, laser has been used by acupuncture practitioners as a therapeutic and research tool since the 1970s. The first use of laser acupuncture is credited to Friedrich Plog in 1973, however there was less well known work done in the now defunct USSR conducted from 1970 (Whittaker 2004). Although laser was not used by ancient

practitioners of acupuncture this may be more due to the lack of the available technology at the time rather than the willingness for experimentation.

Figure 1: Photo of moxibustion

As an interesting parallel, moxibustion involves the heating of acupuncture points by burning a herb Artemisia vulgaris, often in the form of a cigar like stick that is held one or two centimetres from the point (non direct) or in the form of small 'cones' that are applied directly to the skin. Chinese moxibustion is widely accepted as a technique that uses the same channel and point systems as acupuncture. There have been studies that attempt to reproduce the heating effect of moxibustion with laser. Their outcomes indicate that radiation from moxibustion has a similar wavelength to that of infrared LLLT.(Shen 2005) There have also been studies done with laser that attempt to reproduce the heating effect of moxibustion, Xueyong used a Carbon Dioxide Laser in the 10.6 um wavelength at 200mW for knee osteoarthritis to reproduce a moxa like effect and reported a positive result (Shen et al. 2009). Similarly, a study done by Zerdo et al (2007, p. 40) that used high intensity laser on kidney 3 on rats concluded that "In this study, heat therapy with laser was as effective as needle therapy in producing anti-nociceptive effects".

Since the first use of laser to stimulate acupuncture points in 1970, there has been an integration of laser as a painless substitute for needles. Chinese medicine has a history development stretching back over 2000 years, and the empirical nature of its evolution and practice makes the integration of laser an almost natural technological step in the continuing development of acupuncture techniques. In the field of LLT, an example would be the recent adoption of the shorter wavelength "violet laser" for therapeutic purposes Litscher et al (2009, 2010; 2010; 2010) and Wang et al (2011). According to Eisenberg (2001) alternative therapies often adopt therapeutic techniques before research is done into their safety of efficacy. Consequently there is a need to understand the effects of laser within the context of "acupuncture" from both modern scientific and TCM perspectives.

1.6 Laser Research Delimiters

In reviewing the literature, it was found that the vast majority of studies failed to provide a clear differentiation of the clinical effectiveness or otherwise of various power levels, treatment times or wavelengths of the lasers employed in their RCTs. Many such reporting issues were noted by Whittaker, who stated:

> *Although the therapeutic use of laser acupuncture is rapidly gaining in popularity, objective evaluation of its efficacy in published studies is difficult because treatment parameters such as wavelength, irradiance, and beam profile are seldom fully described* (2004, p. 69).

By far the largest identified problem in laser RCT studies revolves around the issue of double blinding. Research utilising lasers that function in the visible part of the spectrum for example, consist largely of non-blinded studies. When research participants and the researchers applying the laser intervention were not blinded, the study outcomes reporting clinical effectiveness are open to criticism. As Ian Relf et al (2008, p. 384) stated that "Laser machines delivering visible red light (e.g. using 630 nm laser diodes) are not suitable for double blind trials because both the patient and operator can see when the laser is switched on".

To remove the visible laser spectrum in RCTs would leave the reported therapeutic values of lasers in the visible parts of the spectrum untested, and to potentially deny patients an effective therapy.

1.7 Aims of This Study

This study aims to identify and address the problems with testing laser as a therapeutic tool and placebo for double blind research, in order to address the issues of:

1. Concealment when using visible spectrum laser to enable double blind testing of visible wavelengths.

2. Monitoring of delivery, to address the problems of monitoring and recording of the actual delivery of the intervention even when using non visible laser wavelengths.
3. Consistent dosage of laser through precise timing of laser delivery.
4. Eliminating human error in randomisation while still maintaining the ability to check the randomisation actually used at the end of the study.
5. Provide the ability to record the procedure's success or failure and to allow later independent analysis of these data.
6. Ease of use for the operator to eliminate as much human error as possible within future RCTs and participant comfort with the equipment..

1.8 Objectives of This Study

The study will develop a computer system to meet the aims stated above. This will effectively allow for triple blind testing of LLLT and laser acupuncture therapy. The use of computer controlled and monitored equipment will allow research into visible laser, and by utilising interchangeable laser hoods invisible spectrum laser without limit to specific power, dosage or time factors.

This study will test and evaluation the new system under laboratory/clinical conditions, but will not undertake a full blown RCT.

1.9 Methods

A systematic review of relevant laser research literature was undertaken to establish current practices, equipment used, and effectiveness of laser as a therapy, and the strengths and deficiencies of past research done to date.

A custom computer controlled laser interface coupled with a control programme was designed and created to overcome the problems identified in conducting quality double blind research of laser therapy.

The final design required the incorporation of:

1. two opaque hoods to obscure light output with a laser and optical detection sensor mounted in each hood, allowing masked operation of the laser or concealment of control inactivation of the laser in blind testing.
2. computer controlled random delivery of the laser, thus reducing human error as a factor from the randomisation process.
3. a computer controlled method for recording of the parameters of the procedure in detail and saving results for later confirmation and analysis.

A trial of the system was carried out under mock laboratory conditions and evaluated for effectiveness of the design and its ability to meet the aims and objectives of the study.
A thorough and detailed description of the unit's function can be found in chapter 3.

1.10 Benefits of This Study

This study will contribute to knowledge in the field by:

1. Developing a double blind research methodology that allows for true double blind testing even within the visible laser spectrum.
2. Stimulate research and academic discussion as to the effectiveness or otherwise of laser therapies.
3. Expand the functionality of the UTS-ARL (Acupuncture Research Laboratory)
4. Addressing the need for evidence based medicine.
5. Providing the means to obtain repeatable experimental techniques that can be utilised by future UTS researchers.
6. Adding to the body of professional knowledge in relation to laser and evaluation of acupuncture point function.

Chapter 2 Literature Review

A review of the literature was undertaken using the following databases: PubMed, Cochrane, CamMed, Google Scholar, Academic Search Premier, Alternative Press Index, CINAHL, Computers & Applied Sciences Complete, EBSCOhost, Health Source and the UTS Library. The review was structured in terms of the key factors important to the design of quality clinical trails using laser as an intervention. These include: wavelength, blinding, dosage, time, laser output power, randomisation, laser delivery methods and monitoring and recording systems. The source literature was examined in terms of the quality of reporting and validity of results and the information used to inform the design of this study.

2.1 Wavelength

Figure 2: The visible spectrum

Wavelength determines the colour and visibility of the laser output. Figure 2 shows the visible part of the spectrum as related to the wavelength. The different wavelengths used for laser therapy result in different levels of absorption and reflection in body tissue. Laser therapy has utilised wavelengths from 405nm to 10.6um well beyond the visible spectrum that ends around 700nm..

According to Nussbaum et al (2003, p. 33) “The therapeutic window lies in the wavelength range of approximately 600-950 nm, over which the penetration depth varies by more than a factor of three”. This suggests that the variation in wavelength should have distinctly different physiological effects.

Nussbaum et al (2003, p. 35) further stated that “It is the common view that different mechanisms underlie the effects of red and infrared lasers. Infrared absorption leads to increased vibrational states of molecules”. He goes on to state “ In contrast, visible wavelength irradiation are thought to cause electronic excitation of the photo-acceptor

molecules". This would suggest that there is a direct transfer of energy affecting cellular structures. For example, photoacceptor molecules such as cytochrome c oxidase are thought to be central in this process. According to Karu (2010, p. 607) "cytochrome c oxidase is the terminal enzyme of the respiratory chain in eukaryotic cells, mediating the transfer of electrons from cytochrome c to molecular oxygen". Nussbaum et al (2003) statements also imply that the different wavelengths associated with different types of lasers, will have differing therapeutic effects. Consequently the null effects in some RCTs may be related to the type of laser in use being inappropriately matched with the condition being treated.

The importance of wavelength as a factor in the therapeutic effect can best be demonstrated by comparative studies. Barbosa et al undertook a comparative study of 30 mW lasers using visible 660 nm and infrared 830 nm wavelengths on the healing effects to a crushing lesion of the sciatic nerve in rats. The researchers reported a better result with the use of the visible 660 nm wavelength leading to the conclusion that:

> *One can observe that the use of a GaAlAS laser at 660 nm provided early functional nerve recovery in comparison with that of the other groups, suggesting a beneficial effect of laser on the process of nerve regeneration over the time period evaluated* (2010, p. 428).

Although the study of nerve regeneration in rats cannot be considered direct proof of an equivalent therapeutic effect in humans, it does demonstrate the potential for a difference in effect between infrared and visible wavelengths in terms of possible biological effects.

To determine the appropriate wavelength to use in this study, a review of the wavelengths used and their reported outcomes are noted in the following tables.

Table 1 shows the various wavelengths used in laser acupuncture and LLLT studies. Many studies in the field of LLLT failed to provide the wavelength used in their trials, making the reproduction of their research impossible.

Table 1: Visible wavelengths and unrecorded by number of reviewed papers

Wavelength	Acupuncture Laser	LLLT	Total
None Stated	Three (Quah-Smith, Tang & Russell 2005; Stump & Roberts-Retzlaff 2006; Wozniak et al. 2003)	One (Mulcahy et al. 1995)	Four
Visible Wavelengths			
405 nm	Five (Litscher 2009, 2010; Litscher et al. 2010; Litscher & Lu 2010; Wang et al. 2011)	Nil	Five
632 nm	Four (Aigner et al. 2006; Brockhaus & Elger 1990; Jadwiga & Dominik 2004; King Ce Fau - Clelland et al. 1990)	One (Emshoff et al. 2008)	Five
670 nm	Four (Schlager, Offer & Baldissera 1998; Siedentopf et al. 2002; Siedentopf et al. 2005; Stockert et al. 2007)	Nil	Four
685 nm	Four (Litscher 2004; Litscher et al. 2004; Litscher, Wang & Wiesner-Zechmeister 2000; Valchinov & Pallikarakis 2005)	Nil	Five

Table 1: (cont): Infrared wavelengths by number of reviewed papers

Wavelength	Acupuncture Laser	LLLT	Total
Infrared Wavelengths			
780 nm IR	Two (Hotta et al. 2010; Meireles et al. 2010)	Nil	Two
785 nm	Nil	One (Kazemi-Khoo 2006)	One
810 nm	One (Hausmann 2008)	Nil	One
830 nm	Five (Ebneshahidi et al. 2005; Glazov et al. 2009; Gottschling et al. 2008; Gruber et al. 2002; Trumpler et al. 2003)	Four (Basford et al. 1998; Chow, Heller & Barnsley 2006; Hegedus et al. 2009; Tascioglu et al. 2004)	Nine
904 nm	Three (Haker & Lundeberg 1990; Lavies 1998; Yurtkuran et al. 2007)	Two (Gür et al. 2003; Gür et al. 2002)	Five
980 nm	Nil	One (Kazemi-Khoo 2006)	One
1.06um	Nil	Two (Basford, Sheffield & Cieslak 2000; Basford, Sheffield & Harmsen 1999)	Two
10.6um +650nm	One (Shen et al. 2009)	Nil	One

The variety of wavelengths used for therapy and research demonstrates the need for comprehensive research to determine the appropriate wavelength for laser acupuncture and LLLT. As the different wavelengths result in different physiological effects, there is a wide scope for this type of research.

Table 2 shows whether a positive therapeutic result was reported in the literature. It is interesting to note that studies using visible wavelengths had a higher ratio of positive results over null result, where the outcome was either no change or a continuation of symptoms as before. Where no result was found the dosage levels were all at the extreme low range due to very short treatment times.

Table 2: Comparison of wavelengths used in papers reviewed and response

Wavelength	**Result**	**Null Result**
Infrared 700 nm – 10 um	10 Papers had a result	9 Papers had a null result
Authors IR	(Basford, Sheffield & Harmsen 1999; Butkovic et al. 2005; Chow, Heller & Barnsley 2006; Ebneshahidi et al. 2005; Gottschling et al. 2008; Gür et al. 2003; Gür et al. 2002; Hausmann 2008; Hegedus et al. 2009; Hotta et al. 2010)	(Basford et al. 1998; Basford, Sheffield & Cieslak 2000; Glazov et al. 2009; Gruber et al. 2002; Haker & Lundeberg 1990; Lavies 1998; Meireles et al. 2010; Tascioglu et al. 2004; Trumpler et al. 2003)
Visible 405 nm – 685 nm	13 Papers had a result	3 Papers had a null result
Authors Visible	(Jadwiga & Dominik 2004; Kazemi-Khoo 2006; King Ce Fau - Clelland et al. 1990; Litscher 2004; Litscher 2010; Litscher et al. 2010; Litscher et al. 2004; Litscher, Wang & Wiesner-Zechmeister 2000; Schlager, Offer & Baldissera 1998; Shen et al. 2009; Siedentopf et al. 2002; Siedentopf et al. 2005; Stockert et al. 2007)	(Aigner et al. 2006; Brockhaus & Elger 1990; Emshoff et al. 2008) Note: treatment times were very short on all 3 of these studies with 15seconds per point = 0.075 Joules to 2 minutes per point 1.8 Joules per point

2.1.1 Violet 405 nm

The most recent developments in LLLT have centred on the use of shorter wavelength "violet" lasers around 405 nm. The adoption of the new short wavelength lasers in human trials by researchers such as Litscher could be of concern. At 405 nm these violet lasers are very near the cut off for the Ultra Violet A (UVA) (315 - 400 nm) band. High energy densities are being used, with little regard to possible detrimental effects of wavelengths so close to the UVA band associated with skin cell changes linked to the development of skin cancers. One study by Wang and several by Litscher, use the 405 nm wavelength at 110 mW, without considering the possibility of long term detrimental effects Litscher et al (2009, 2010; 2010; 2010) and Wang et al (2011).

According to Ridley et al (2009, p. 178) "the primary method of damage induction by UVA is thought to occur via an indirect mechanism involving the generation of reactive oxygen species (ROS). These ROS go on to induce DNA damage". Another study by Dr Moon Shong Tang showed that, UVA wavelengths from sunlight will damage the DNA of human melanocyte skin cells leading to a reduced capacity for the cells to repair themselves (2010). Although UVA damage is a continued area of debate amongst researchers and 405 nm is just outside the UVA range, it appears that there have been no long-term animal and or cellular invitro testing before commencing human trials with the 405 nm wavelength.

2.1.2 Visible 405 nm to 685 nm

Historically, the first and most commonly used therapeutic laser in acupuncture laser studies is the Helium Neon (HeNe) which operates in the visible spectrum at 632.8 nm (12-25 mW range). Studies into the effects of HeNe Laser have demonstrated a biochemical influence in mitochondria (the energy producing portion of cells). Greco et al (1989, p. 1428) noted that "HeNe Laser irradiation stimulates the synthesis of all mitochondrial transcription and translation products". Irradiation of cells cultivated in vitro has shown increases in adenosine triphosphate (ATP) of 190% after irradiation with HeNe Laser. (Karu, Pyatibrat & Kalendo 1995). ATP is the source of energy used

in most metabolic processes and hence an increase in ATP could be associated with increases in metabolism and related physiological function.

HeNe Laser has also been reported to effect melanin which is a basic pigment and major epidermal chromophore. In addition to the effects on Melanin the absorptive effect of haemoglobin may have a role in the different physiological effects when exposed to shorter wavelengths of laser due to dominant peaks at 280, 420, 540, and 580 nm with a cut-off wavelength at about 600 nm well below the 700nm where infrared lasers start to operate (Parvin, Eftekharnoori & Dehghanpour 2009)

Based on the information noted in tables 1 and 2 and from scanning the related literature, it is interesting to note that the visible spectrum (405 nm to 685 nm) appears to be the common choice for laser acupuncture therapy. It is also noteworthy that most studies that report a positive clinical result use lasers within this wavelength band.

2.1.3 Non-visible Infrared (IR) 700 nm to 10.6 um

As noted in tables 1 and 2, the distribution of laser acupuncture studies versus LLLT studies using non-visible infrared wavelengths was comparative in number to laser acupuncture versus LLLT studies in the visible 405nm to 685 nm range.

The justification for choosing an Infrared wavelength was not normally reported on the basis of it being an ideal wavelength for treatment. Rather, the non-visible part of the spectrum was often selected in order to maintain a double blind condition for research purposes. This is a common view as noted by Relf et al (2008, p. 383) who states that for research purposes, “laser light is invisible above 770 nm and can be switched off or on without visual recognition by the patient or operator”. This very benefit however comes with an inherent problem. The use of non-visible wavelengths also makes it impossible for the researchers to objectively determine whether the laser dosage was delivered during the intervention. Though desirable for double blind testing, there is effectively no way to measure real time equipment faults.

One possible advantage of IR laser over visible laser is the greater depth of penetration in human tissue. Harrison (1989) investigated the use of laser as a replacement for needles and stated that is had been demonstrated that infrared light at 820 nm has 1.6 times the depth of penetration compared to an equivalent HeNe Laser (1989). This is not direct evidence that increased penetration of infrared would automatically lead to a corresponding increased biological response, thus resulting in a greater therapeutic effect.

2.2 Blinding Analysis

The quality and reporting of attempted double blinding in most of the laser research reviewed suggested that the blinding methods used in many of these studies were questionable at best.

Some examples of poor reporting included:

- Yurkuran et al (2007) where is was not clear if the laser operator was blinded
- Litscher et al (2004) and Schlager et al (1998), were unclear as to why the laser operators or participants would be unaware of the laser
- Brockhaus & Elger (1990) and Stockert et al. (2007), only blinded the data assessors and research participants, but not the laser operators

Table 3 below shows the common blinding strategies employed in a number of laser studies.

Table 3: Blinding strategies as by papers reviewed

Blinding	Laser Acupuncture	Low Level Laser Therapy
Not Blinded	Seven (Hotta et al. 2010; Jadwiga & Dominik 2004; Litscher 2010; Litscher et al. 2010; Litscher, Wang & Wiesner-Zechmeister 2000; Stump & Roberts-Retzlaff 2006; Wozniak et al. 2003)	One (Kazemi-Khoo 2006)
Single Blinded	Nine (Aigner et al. 2006; Butkovic et al. 2005; Ebneshahidi et al. 2005; Hausmann 2008; King Ce Fau - Clelland et al. 1990; Litscher 2004; Shen et al. 2009; Siedentopf et al. 2005)	Two (Gür et al. 2002; Tascioglu et al. 2004)
Double Blinded	Thirteen (Brockhaus & Elger 1990; Emshoff et al. 2008; Glazov et al. 2009; Gottschling et al. 2008; Gruber et al. 2002; Haker & Lundeberg 1990; Lavies 1998; Litscher et al. 2004; Quah-Smith, Tang & Russell 2005; Schlager, Offer & Baldissera 1998; Stockert et al. 2007; Trumpler et al. 2003; Yurtkuran et al. 2007)	Nine (Basford et al. 1998; Basford, Sheffield & Cieslak 2000; Basford, Sheffield & Harmsen 1999; Gür et al. 2003; Hegedus et al. 2009; Hubscher, Lutz & Winfried 2007; Meireles et al. 2010; Mulcahy et al. 1995)

Blind testing controls for bias, and the double-blind trial is the gold standard for clinical research. Double blind studies using acupuncture needles however are impossible to design due to the inability to blind the participant to the needling process. Studies have demonstrated that even pressure on the skin can result in a physiological effect (White, Filshie & Cummings 2001).

To overcome this problem researchers such as Fleckenstein et al (2009) have used sham laser as a control for needles. This too however is problematic because needle-based acupuncture and laser acupuncture use different mechanisms (needle vs. light) which would be obvious to any trial participant and hence introduce some bias. Nonetheless, this study will argue that despite the confounding variables, the use of a laser control has advantages over shallow or sham needling. The challenge posed by blinding visible spectrum lasers, furthermore will be addressed in this study.

One alternative to blinding is the use of an alternative light source such as a red LED light to deceive trial participants and operators as to laser activation. Maloney used red Light Emitting Diodes (LEDs) as a sham control (2010). The difficulty with this method is that a skilled laser operator would recognise the sham nature of the red LED. LEDs emit incoherent light, compared to the coherent light from a laser and the unique speckle pattern induced by laser light looks quite different than light from an incoherent light source. Harris (1995, p. 215),commented that "Even the light from the purest of sources, a single-mode laser, will show wild temporal intensity fluctuations" which results in the uniquely distinct speckle pattern. The speckle pattern is further enhanced by the inherent properties of the skin. Da Silva and Muramatsu (2008) noted that that in a biological tissue such as skin, that a pattern evolves with the phenomenon is called biospeckle. Therfore the use of alternative light sources is problematic for blinding laser operators and research participants.

If the research participants were simply covered with a sufficiently dense material to block the light such that both the participant and laser operator were not able to detect the laser, the problem remains that without visible confirmation or an optical sensor based confirmation as proposed in this study, there is no way to determine if the laser was operational when delivering a therapeutic dose.

2.3 Dosage

Like wavelength, the dosage selected in most research studies often appears to be based on reasons other than proven clinical effectiveness. The range of dosage under review starts at around 0.075 Joules in a study by Aigner et al (2006) using laser acupuncture to treat whiplash injuries. At the high end dosage range, laser is used as an alternative to moxibustion (heating of acupuncture points with burning Artemisia) for arthritis with a dosage of 163.2 Joules (Shen et al. 2009).

According to a meta-analysis done by Baxter (2009) the effectiveness of laser acupuncture depends upon dosage, with mid-range levels of exposure sufficient to produce positive clinical results. Baxter also noted that the negative outcome in regard to change or improvement were clinical studies that tended to use lower dosage ranges of <0.1 Joules. This appears to be confirmed by a general review of the literature as noted in Table 4 below which suggests dosages of around 12 joules would be sufficient to produce a therapeutic effect while maintaining participant safety.

Table 4: Range of dosage delivered by study and the related clinical outcome:

Dosage	Researcher	Therapeutic Result
0.075 J	(Aigner et al. 2006)	Nil
0.2 J	(Glazov et al. 2009)	Nil
0.36 J	(Haker & Lundeberg 1990)	Nil
2.64 J	(Gruber et al. 2002)	Nil
3 J	(Tascioglu et al. 2004)	Nil
6 J	(Hegedus et al. 2009)	Positive
9 J	(Chow, Heller & Barnsley 2006)	Positive
24 J	(Litscher 2004)	Positive
30 J	(Stump & Roberts-Retzlaff 2006)	Positive
163.2 J	(Shen et al. 2009)	Positive

2.4 Time

The common treatment protocol when using acupuncture needles usually involves treatments that last around 20 minutes. The trend with laser clinically is to use a more powerful laser and a shorter treatment time to obtain the same dosage that would have been achieved using a less powerful laser over a greater period of time. This is possible due to the relationships between power, time and dosage as explained below. In order to make comparisons with needle acupuncture that use 20 minute treatment times and keep the total dosage to a safe but effective level it was reasoned a 12 joule per point treatment could be obtained using 10mW lasers, over a period of 20 minutes. Other researchers have also found 20 minutes to be an effective treatment time for laser acupuncture to obtain optimum point stimulation (Weber 2007).

2.5 Laser Output Power

The output power of a laser is analogous to the brightness of a light globe, the higher the wattage the brighter the output. Utilising a higher wattage will increase the dosage for any given period of time.

Any laser operating at less than 500 mW is considered therapeutically to be a low level laser. Lasers with outputs greater than 500 mW will produce thermal outputs and are commonly used for surgical cauterisation.

Like wavelength, the researchers rationales for choosing a particular power level were unclear in most studies. Some researchers did state that higher power levels were chosen to speed the treatment process as higher power levels will deliver similar dosages in shorter times.

Using the formula Joules / Watts = Seconds we can see 12 J / 0.01W = 1200 seconds or 20 minutes. For example to deliver 10 joules a:

- 10 mW Laser will take 1200 seconds
- 40 mW Laser will take 300 seconds
- 100 mW Laser will take 120 seconds

Table 5 below shows the power ranges of laser units commonly used for clinical research in the literature reviewed. It is important to note that positive therapeutic results are essentially obtained at 10mW or higher.

Table 5: Power ranges utilised in the studies under review

Power	Researcher	Therapeutic Result
4 mW	(Yurtkuran et al. 2007)	Nil
5 mW	(Aigner et al. 2006)	Nil
10 mW	(Schlager, Offer & Baldissera 1998)	Positive
10 mW	(Stockert et al. 2007)	Positive
10 mW	(Siedentopf et al. 2002)	Positive
10 mW	(Siedentopf et al. 2005)	Positive
10 mW	(Gür et al. 2003)	Positive
11.2 mW	(Gür et al. 2002)	Positive
20 mW	(Butkovic et al. 2005)	Positive
24 mW	(Wozniak et al. 2003)	Positive
30 mW	(Gottschling et al. 2008)	Positive
36 mW	(Shen et al. 2009)	Positive
50 mW	(Hegedus et al. 2009)	Positive
50 mW	(Hausmann 2008)	Positive
70 mW	(Meireles et al. 2010)	Positive
100 mW	(Quah-Smith, Tang & Russell 2005)	Positive
100 mW	(Litscher 2010; Litscher et al. 2010)	Positive
100 mW	(Jadwiga & Dominik 2004)	Positive
300 mW	(Chow, Heller & Barnsley 2006)	Positive
500 mW	(Stump & Roberts-Retzlaff 2006)	Positive

When higher power levels are used, the treatment time is reduced to limit the intervention dosage to a safe level. Due to the interrelationships between time, dosage, wavelength and power, the choice of a suitably powered laser for achieving a therapeutic effect needs further investigation. This is confirmed by Whittaker who states that:

> *Many studies have used lasers with insufficient power to reach the targeted acupuncture points. Such major deficiencies indicate that it is possible to make a good argument for the statement that laser acupuncture has yet to be adequately evaluated* (2004, p. 77).

2.6 Randomisation

Randomisation in clinical trials is very important as it reduces bias and false causality. The possibility of introducing human error into the randomisation process is an inherent risk. Current technologies however allow for the minimisation of this risk and these technologies will be utilised in this study's design.

Table 6 notes 41 laser acupuncture and LLLT studies and the method of randomisation employed.

Table 6: Methods of randomisation in the papers reviewed

9 Used no randomisations	(Gruber et al. 2002; Jadwiga & Dominik 2004; Kazemi-Khoo 2006; Litscher 2010; Litscher et al. 2010; Litscher et al. 2004; Litscher, Wang & Wiesner-Zechmeister 2000; Shen et al. 2009; Siedentopf et al. 2005; Stockert et al. 2007)
19 Randomisations were unclear	(Aigner et al. 2006; Brockhaus & Elger 1990; Butkovic et al. 2005; Ebneshahidi et al. 2005; Emshoff et al. 2008; Haker & Lundeberg 1990; Hausmann 2008; Hotta et al. 2010; Hubscher, Lutz & Winfried 2007; King Ce Fau - Clelland et al. 1990; Lavies 1998; Litscher 2004; Mulcahy et al. 1995; Schlager, Offer & Baldissera 1998; Siedentopf et al. 2002; Stump & Roberts-Retzlaff 2006; Wozniak et al. 2003; Yurtkuran et al. 2007)
9 Envelope based randomisations	(Chow, Heller & Barnsley 2006; Gottschling et al. 2008; Gür et al. 2003; Gür et al. 2002; Hegedus et al. 2009; Meireles et al. 2010; Shen et al. 2009; Tascioglu et al. 2004; Trumpler et al. 2003)
1 Flip of a coin based randomisation	(Quah-Smith, Tang & Russell 2005)
2 Computer based randomisations	(Basford, Sheffield & Cieslak 2000; Basford, Sheffield & Harmsen 1999)
1 Device based randomisation	(Glazov et al. 2009)

In Table 6, only one study used a technology based approach to controlling randomisation. Glazov et al (2009) used a method of hardware based randomisation that employed one hundred consecutive settings on a dial that was programmed into the circuitry of the laser device in a random pattern at the time of manufacture. Only 50 of

these settings would result in production of a laser beam when the machine was operated. A shortfall of the design was that the device had no facility to automatically record the particular intervention used (dialled). Hence human error could still be introduced as a mistake in entering the proper code and could possibly corrupt the results. Current advances in computer technologies allow this shortcoming to be easily remedied.

2.7 Delivery System

A number of factors relating to the mechanics of delivering laser can affect the outcome of a study.

Many studies to date use optic fibre to deliver laser resulting in losses of energy. For example, the four studies by Litscher (2004; 2010; 2010; 2004) used a 110 mW laser but the output measured 100 mW, a fibre loss of approximately 10%. Many studies fail to report this and consequently it is impossible to determine the actual output of their devices. Given the noted relationships between power, wavelength, time and dosage, it is not always clear if the reported dosages are accurate and whether reports of therapeutic actions are reliable or reproducible.

HeNe Lasers, commonly used for laser delivery in the 632.8 nm wavelength, use fibre optic cable as the conduit for delivering laser to the acupuncture point. In these units however, it is not just the optic fibre that presents a problem. There is an issue with the High Voltage Power Supply Unit (HV PSU) used to excite the Helium Neon gas medium that generates the laser output. The HV PSU produces an audible high pitched noise which would adversely affect any attempt to use these lasers in double blind studies as the operator could easily determine if a unit was disabled. Technological advances now allow for delivery of wavelengths in the HeNe laser range using silent diode lasers.

2.8 Monitoring and Recording of Intervention

None of the papers in the literature review that claimed to be double blinded used any monitoring or recording of the laser output at time of delivery. Some studies tested laser output periodically throughout the study, while others did not account for possible equipment failure in any way. Only one paper Hubscher et al (2007) controlled the laser with a computer to keep the operator blinded. Most relied on independently disabled equipment to provide the placebo laser.

2.9 Summary

A review of the relevant literature revealed a number of issues and shortcomings in existing studies that will be used to inform the design of the laser system in this study.

The better quality studies attempted to use blinding but then failed to document the equipment used, power outputs, wavelengths, time of treatment, and total dosage. The vast majority failed to measure that the procedure or laser output was actually delivered as intended. There were technical issues noted with the use of optical fibre systems or high voltage power supplies that can adversely affect dosage and other aspects in a trial situation, particularly blinding. Many of these flaws made the research results difficult or impossible to reproduce. At least one study attempted to reduce human error by incorporating a system of randomisation into the laser device. The review also revealed that most of the positive clinical outcomes were related to studies that used visible light lasers (405 nm to 670nm) with mid-range dosages of around 12 joules.

Chapter 3 Design

The following chapter will outline the design process and then present the system designed as part of this study. Schematics and other systems information can be found in the appendices.

3.1 Developing a Computer Controlled Laser System for Double Blind Studies

The aim of this project is to design and test a computer controlled visible laser system for double blind studies. To plan the design, existing laser units were examined for their strengths and weaknesses. A literature review was undertaken to define each of the key parameters to allow for the development of properly randomised and double blinded studies. The objective was to develop a system that is capable of overcoming all the issues identified in the literature review. This has resulted in a novel approach to the defined problems, particularly in using visible light lasers. This chapter outlines the design problems and solutions adopted by this study.

3.2 Design Parameters

3.2.1 Wavelength

Identification of the appropriate wavelength is an important factor in laser therapy as different wavelengths have different physiological effects. The literature revealed that the visible light wavelengths tend to have a greater therapeutic effect, particularly in relation to laser acupuncture. Infrared (IR) or invisible wavelength lasers provide some advantages in terms of blinding, but their therapeutic value is questionable.

Solution

This study will use visible light diode lasers with a wavelength of 635 nm. The 635 nm wavelength was chosen as it was the closest to the common HeNe 632.8 nm range that has proven safety over 40 years of research and clinical use. Shorter wavelengths such as 405 nm have yet to be proven safe. Longer infrared wavelengths have often failed to get results such as those published using the visible spectrum. The unit developed for this study was designed to allow for interchangeable laser heads to test any available wavelengths.

3.2.2 Blinding

Most of the effective blinding methods to date use non-visible laser in the IR range. Blinding is often achieved through disabling of equipment. This however does not overcome issues of operator error such as potential confusion with the use of multiple probes. The issue of effectively double blinding visible spectrum lasers has not effectively been addressed by researchers to date.

Solution

This study has designed a system using opaque hoods (see Figure 3) to shield any visible light. It has the ability to plug in different laser hoods with different types of wavelength and wattage laser diodes and the operation of the laser is controlled by a computer. Each hood contains an optical sensor to determine if the laser was activated. Only the computer knows with certainty, if the laser was active or inactive during the intervention.

The customised software program is capable of indicating to the operator both during and after the procedure that the system was armed and operational (i.e. in a working state). The system however will not indicate whether the laser was active or not (i.e. the working state laser actually delivered the dosage). This aspect of the procedure is automatically recorded for later analysis allowing for up to triple blind testing (blind operator, blind participant and blind data analyst).

3.2.3 Dosage

The literature indicated that mid-range dosages of around 12 joules are the most therapeutically effective. Dosage however is dependent upon other parameters including wavelength, time and power of the laser unit.

Solution

This study uses two 10 mW aluminium-gallium-indium-phosphide (AlGalnP) Laser diodes with the following output specifications:

Wavelength of 635 nm

Collimated beam of 0.355 cm at 0.01 Watts

Beam area of 0.09898 cm^2

Power density of 0.10103 W/cm^2

Using the formula Seconds x Watts = Joules we can calculate the total dosage to be 0.01W x 1200 seconds = 12 Joules

As the laser is delivered by a diode directly mounted into the hood, there is virtually no loss of integrity as would be experienced if the laser was delivered via an optical fibre. Computer control of the total dosage time ensures accurate delivery of laser energy. Use of a hood design also means that the laser diode is held at a fixed distance away from the skin to allow for consistent reproduction of experimental conditions.

3.2.4 Time

Time in terms of duration of exposure to laser will affect dosage. The duration of exposure is determined by the power output of the laser unit. The literature showed that different physiological effects are produced by exposure to different wavelength of laser and that in some cases, physiological effects may be time dependant.

Solution

To allow for appropriate photo-biological processes to occur, this study has determined that a 10 mW laser of 635 nm will deliver 12 joules over a 20 minute period.

Using the formula Joules / Watts = Seconds we can see 12 J / 0.01W = 1200 seconds or 20 minutes.

Under these circumstances, a 20 minute delivery of laser for a human operator to apply using a hand held unit without resting the probe on the patient's skin or moving it away from the point would be extremely difficult. The use of the hood design again counters these problems.

Furthermore this time period reflects the commonly held practice of retaining acupuncture needles for 20 minutes. There is no published research that indicates a 20 minute retention time for needles is any more effective than shorter or longer times. The mere act of lying still for a 20 minute period while undertaking treatment may have physiological effects regardless of the intervention (acupuncture or laser). Consequently a clinical trial design that mimics the standard acupuncture treatment convention of 20 minutes is more useful for making direct comparisons of effect.

3.2.5 Power

Power of the laser unit is an important parameter that affects dosage and time. The literature indicated that more powerful laser units were frequently chosen for the convenience of shorter treatment times, but without consideration of the possible time dependant photo-biological processes.

Solution

The system uses 10 mW diode lasers because they allow for the delivery of a mid-range dosage of 12 joules over a 20 minutes period. At this power level, there will be no local thermal effects that would interfere with blinding of participants. Diode lasers where purposely chosen to overcome issues of power loss through optical cable delivery system as noted in the literature.

3.2.6 Randomisation

Randomisation is an important design element for any clinical trial. Manual systems for randomisation carry an inherent risk of human error.

Solution
The system developed for this study uses a combination of randomisation protocols. In the first instance for a single intervention group, participants would be manually randomised into groups A or B using any suitable method such as permuted blocks. A further level of randomisation is then introduced by the computer which may select either group A or group B to receive the laser, unbeknown to the operator.

If a cross over study was used with two interventions, the computer would record which participants were is group A and which in group B. It would further record which of these groups received the active laser in the first round and then reverse the delivery of the intervention in the second round. Only the computer would be aware which group is being actually treated at any point in time and will record the intervention for later analysis.

3.2.7 Delivery System

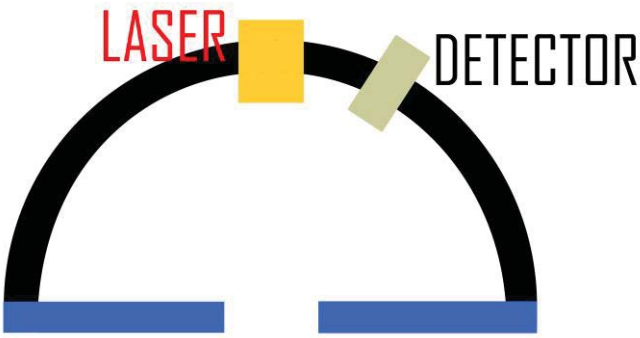
The literature review identified a number of areas for improvement including suitable designs for blinding and improved mechanisms for the delivery of laser.

Solution
The hood design incorporated as part of this study is illustrated in Figure 3. The use of an opaque hood ensures that both the operator and participant are effectively blinded. The distance of the laser from the skin is standardised due to the hood mounting.

The area over the point over test has zero pressure directly applied to it to avoid the effects of manual stimulation. The boot has a soft wide area at the base (shown in blue), to disperse the force across a wide area and to reduce the pressure in any one spot for comfort and to assist in the provision of an absolute light seal.

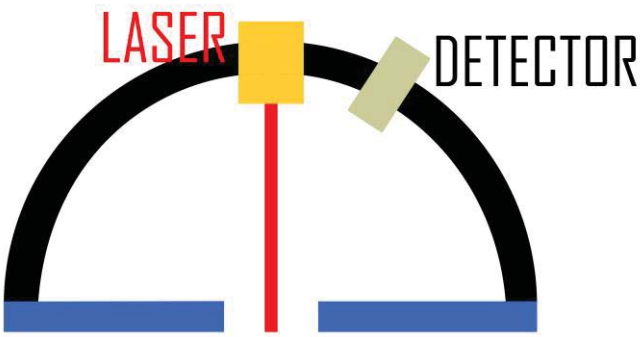
Figure 3: Drawing of the fundamental system design

Hood; laser diode; and optical sensor.



The use of a collimated laser diode means there is insignificant loss of power output compared to laser delivered via a fibre optic cable. It also means that there is a generally deeper penetration of the light as there is less beam divergence. The use of a diode laser circumvents noise issues and related blinding difficulties associated with high voltage power supplies common to HeNe Lasers. An optical sensor detects the successful delivery of the laser.

Figure 4: Drawing of the collimated laser output



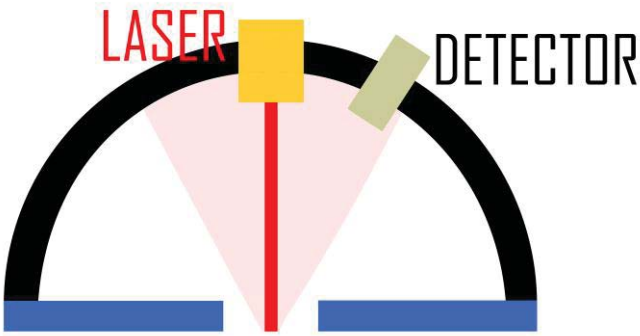
3.2.8 Monitoring and Recording

The literature review showed that no studies engage in any equipment monitoring during the intervention. A few studies tested equipment between interventions. In studies that use disabled equipment, there exists the potential for invalid results due to a mix up in the use of the laser probes.

Solution

The system developed in this study is novel and unique in that it monitors the activity of the laser unit during delivery of the intervention.

Figure 5: Drawing of the detection of the laser activation



Using a computer to oversee the delivery of the laser allows the system to determine with 100% confidence whether the laser was active or not without the operator knowing it at the time of the intervention. The computer monitors the activation of the laser through an optical sensor. The feedback of information from the hood allows the computer to monitor and record whether the laser is active or inactive.

If the laser failed to activate when the computer instructed it to do so or there was a connection error or power failure during the application of the intervention then the computer will inform the operator of that fact. It will tell the operator that the laser has a critical failure. The failure warning will also occur if light enters the hood during the procedure which might happen if a hood was fitted incorrectly.

A warning will not occur if the computer has instructed the laser not to activate when it is delivering a placebo intervention.

In informing the operator the computer won't give away the double blind conditions of the test. The computer will save a successful cycle or unsuccessful cycle to a file with other relevant data. The file is saved automatically named by group and session. If the data file already exists it will not be overwritten. An incremented number is applied to the file so no data can be "accidentally" lost.

3.3 The System and Computer Interface

Figure 6 shows the laser unit with a hood detached and one connected. Safety was a priority in its design. So there is a safety arming key. The power light comes on when there is power to the unit but there are no lights activated when the laser is operating to maintain double blind conditions. The unit operation is completely silent. The laser hoods are 100% opaque with a soft rubber ring to disperse pressure on the skin for comfort and to aid in trapping 100% of the light within the unit during operation.

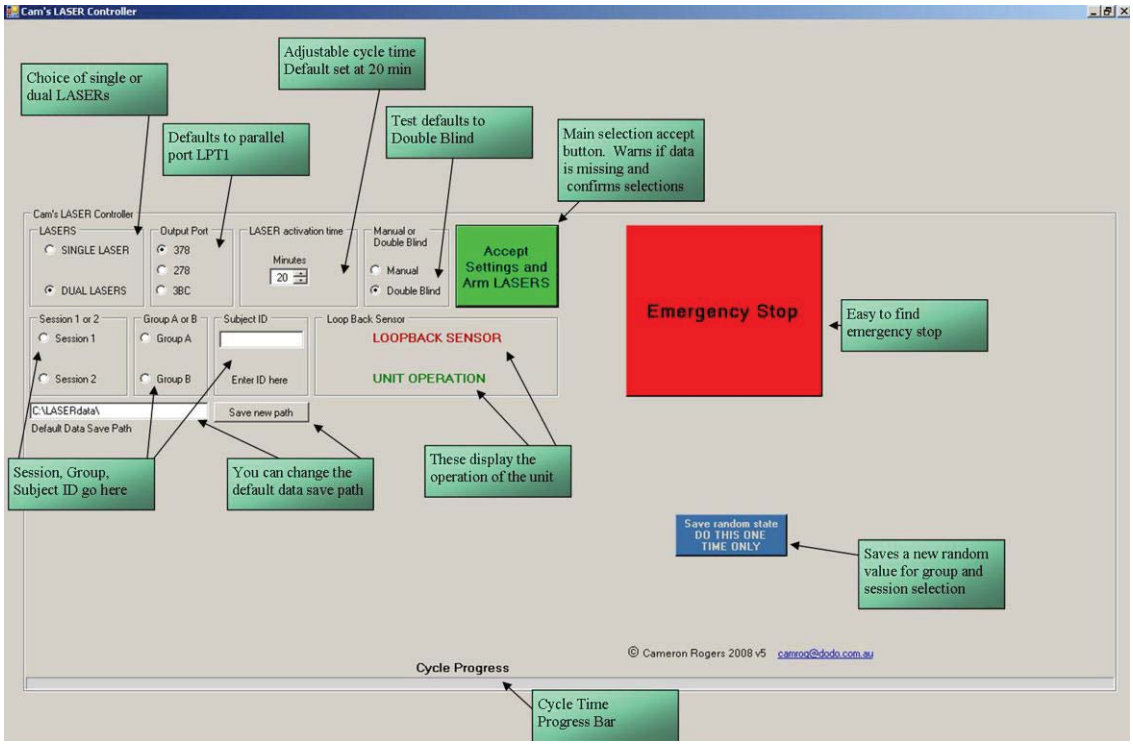
Figure 6: Photo of the prototype laser unit

The specifications for the units are:

Laser Diodes: 635nm / 10mW, <10mW, adjustable focus.
Max Output Power: 10mW
Wavelength @ Peak Emission (min/max): 630-640nm
Operating Current (max): 55mA
Operating Voltage (max): 3V

The computer interface is shown below as a screen shot. Instructions for operating the unit and software can be found in the Appendix A-1.

Figure 7: Screenshot of computer interface



The programme allows the operator to choose single or dual laser activation. The output port that the laser is plugged into can be selected to correspond with the available parallel port. Time/duration of laser activation is selectable. This is an important feature if the laser diodes are to be changed as lasers with different wavelength and power outputs will require adjustment of the time factor to deliver a calculated dosage. Manual operation is possible for testing purposes. Session, group and subject ID fields are used for the recording of blind testing results. The loop-back sensor field displays real-time operation of the Unit but doesn't tell the operator the actual state of the lasers unless in manual mode. The blue button is used once only at the beginning of the study to reset the random state. The programme was designed to be as self-explanatory and simple as possible, with features such as warnings if necessary fields are left blank and automatic incremental renaming of files when saving, in order to prevent accidental data loss from identical file names.

The programme has been compiled and tested and it can be installed on available versions of the Windows operating systems, i.e. XP, Vista and Windows 7.

3.4 Testing

Ethics approval was obtained to test the equipment on participants in a clinical trial situation (UTS HREC 2008-372).

TGA approval of the device was obtained (GN#127/2009).

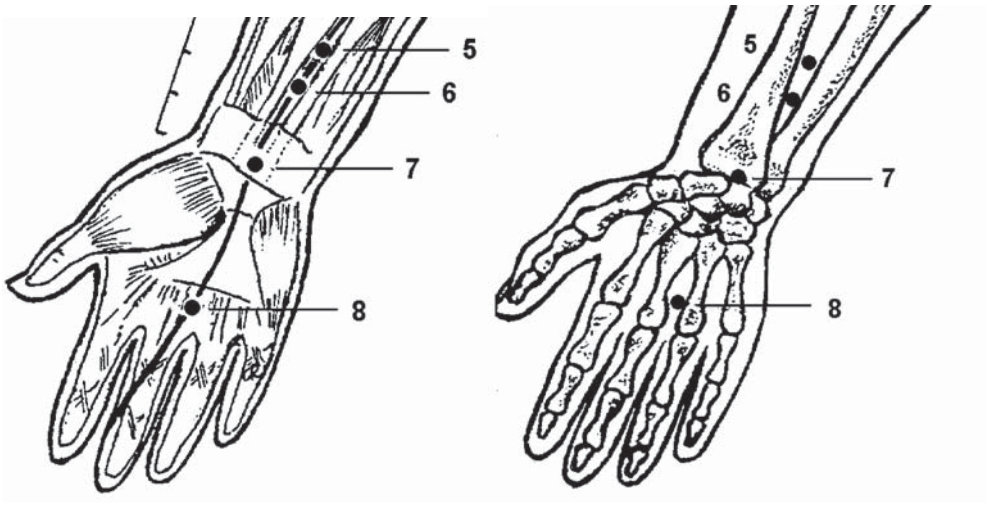
The purpose of testing the equipment under clinical trial conditions was to determine if:

- the system was functional;
- the system was easy to operate;
- that blinding of the operator and participant could be achieved; and
- the hoods/lasers were easy to attach and comfortable for participants to wear.

To achieve this purpose a series of bench tests and mock trial of six healthy participants was designed to test the system on the point pericardium 6 (PC 6).

PC 6 – Neiguan (Inner Gate)
Location 1 cun below PC 5 and 2 cun above the wrist flexure between the tendons (Rogers & Rogers 2009 rev., p. 127)

Figure 8: Point location of Pericardium 6



3.5 Procedure

To mimic trial conditions, the testing was undertaken at the UTS Acupuncture Research Laboratory. As well as the laser, participants were connected to a heart rate variability monitor. Other physiological parameters normally measured would include respiration, electrooculography (EOG), Electroencephalography and electrodermal activity (EDA). These additional measures were not taken as they were unnecessary for the testing stage of this proof of concept design. Furthermore, a full blown RCT using the system was outside of the scope of this Masters project. Participants and operators were asked to complete a simple questionnaire in relation to the ease of use; blinding and comfort (refer to appendix B-2).

3.6 Summary of Design

The aim of this study was to design a system that would allow for the effective double blind measurement of visible laser acupuncture interventions. Through a process of reviewing exiting equipment and literature, the key parameters were identified and design solutions generated. This resulted in a system with the following characteristics:

- A hooded design to allow for double blinding of visible light lasers and standardised positioning of the laser probe from the skin surface;
- An optical feedback system to monitor laser delivery and system faults;
- The use of a 635nm, 10 mW laser diode delivering 12 joules in 20 minutes to:
    - overcome issues associated with thermal detection;
    - loss of photo biological activity due to high power/short dosage periods;
    - noise and loss of power due to optical fibre delivery systems; and
    - reflect clinical conditions and practices
- Computer controlled randomisation of laser delivery; and
- An easy to use hardware and software interface to ensure standardised delivery of laser intervention.

The next stage of the process involved bench testing and mock trails on participants to verify the proof of concept.

Chapter 4 Results

Ethics approval (UTS HREC REF NO. 2008-327A) was gained to test the equipment on participants under clinical trial conditions. As part of the ethics approval registration for the new device was obtained with the Therapeutic Goods Administration (GN#127/2009).

Two naive operators were given a brief, single run through the use of the system and then asked to operate the equipment on three test participants each. They were instructed to run a 10, 15 and 20 minute session. They were then asked to complete a simple survey (see appendix). Test participants were also asked to complete a short survey (see appendices) to determine the success of the blinding and determine the comfort of the hoods.

Although the scope of this study did not include a RCT, ,the test was undertaken in the Acupuncture Research Laboratory under mock trail conditions and participants were connected to heart rate variability (HRV) monitor to provide a sense of a genuine research trial. No data relating to HRV will be presented as part of the study results.

4.1 Outputs From the Laser System

Repeated bench testing of the lasers showed the system to be operational in all design parameters, including detection of failed cycles. Examples of a successful and failed cycle output in the manual mode (used during bench testing) can be seen below. During manual operation the lasers will be active during the test, this is so that equipment testing can be done at anytime without revealing the control of laser inactivation of the blind testing, therefore the group or session will have no effect on the operation of the laser in manual mode and therefore the laser will be activated during the session. Manual mode is purely for equipment and connection testing with a greater detail of feedback to the operator. In double blind mode the system will only report a problem without detail as to the nature of the problem. In manual mode the system gives specific details as to the nature of the failure.

subject ID :
This file saved : 18/11/2011 10:55:41 AM
Number of lasers : Dual LASERS
Cycle success : Cycle Successful
Cycle start : 18/11/2011 10:54:33 AM
Cycle finish : 18/11/2011 10:55:33 AM
Cycle time minutes : 1
Manual or Double Blind : Manual
session : 1
Group : Group A
random value : 1
Programmed by Cameron Rogers 2008 camrog@dodo.com.au ©Cameron Rogers 2008

subject ID :
This file saved : 16/02/2012 11:01:55 AM
Number of lasers : Dual LASERS
Cycle success : Cycle Failure
Cycle start : 16/02/2012 10:55:46 AM
Cycle finish : 16/02/2012 11:00:46 AM
Cycle time minutes : 5
Manual or Double Blind : Manual
session : 1
Group : Group A
random value : 1
Programmed by Cameron Rogers 2008 camrog@dodo.com.au ©Cameron Rogers 2008

In the instance above, a cycle failure was induced by lifting the hood and preventing the detection of the laser's reflection to the feedback sensor, meaning the position of the hood was therefore incorrect.

All laser cycles in the mock trials were successfully completed. Example output files are shown below. One file shows dual lasers were fired, the other a cycle where the lasers were disabled.

subject ID : lab test 1
This file saved : 4/03/2011 12:13:03 PM
Number of lasers : Dual LASERS
Cycle success : Cycle Successful
Cycle start : 4/03/2011 12:01:52 PM
Cycle finish : 4/03/2011 12:11:52 PM
Cycle time minutes : 10
Manual or Double Blind : Double Blind
session : 1
Group : Group A
random value : 0
Programmed by Cameron Rogers 2008 camrog@dodo.com.au ©Cameron Rogers 2008

subject ID : lab test 2
This file saved : 21/03/2012 2:32:47 PM
Number of lasers : LASERS Disabled
Cycle success : Cycle Successful
Cycle start : 21/03/2012 2:12:43 PM
Cycle finish : 21/03/2012 2:32:43 PM
Cycle time minutes : 20
Manual or Double Blind : Double Blind
session : 1
Group : Group A
random value : 1
Programmed by Cameron Rogers 2008 camrog@dodo.com.au ©Cameron Rogers 2008

Based on the outcomes from bench testing and the mock trial, the system is deemed to be technically operational.

4.2 Questionnaire Results

Two simple questionaries were designed. One to determine ease of use for the operator, another to determine the level of comfort for the participant. Both questionnaires also tested for blindness of the experiment. The results are noted in the table below.

Table 7: Operator rating of the system

Operators	Score on a scale of 1(easy) to 10 (very difficult)	
	Operator 1	Operator 2
How easy were the hoods to position?	2	2
How easy were the hoods to attach/fix in place?	1	1
How easy was the computer interface to use/control?	1	1
Were you able to determine if the lasers had fired?	No	No

Both operators found the system easy to use. One operator commented that centering the hoods exactly over the point required some finesse, but that this would likely be overcome with practice. Neither operator was able to determine if the lasers had fired.

Table 8: Participant ratings of the system

Score on a scale of 1 (very comfortable) to 10 (very uncomfortable)	Participants					
	1	2	3	4	5	6
How would you rate the comfort of the hoods when positioned?	1	1	2	1	2	1
How uncomfortable or distracting were the laser hoods over the entire length of the intervention?	1	1	1	2	1	2
Were you able to determine if the lasers had fired?	No	No	No	No	Yes	No

All participants reported minimal discomfort of the hoods both on placement and during the intervention. The minimum time hoods were in place was 20 minutes, the maximum time 40 minutes. Participant 5 claimed to know that the laser had fired on the basis of "a sensation of spreading warmth from the point to the hand". Upon cross referencing with the data files at the end of the trial, it was noted that in that particular instance, the lasers did not fire, suggesting that the sensation was likely a placebo.

On the basis of the bench testing and mock trial, it was concluded that system was operating within designed parameters and that participants and operators were successfully blinded to the visible light lasers.

4.3 Summary

Bench testing and mock trials were completed and proved the system to be successful in relation to operational parameters, ease of operator use, participant comfort, and blinding.

The system is now ready for deployment in clinical trials.

Chapter 5 Conclusion

5.1 Conclusions Drawn from Literature Review

Since the 1960s, physiological effects of various types of laser have been tested and proven, and Low-Level Laser Therapy and Laser acupuncture has gradually gained acceptance as a legitimate form of therapy. The earliest and most promising laser treatments appear to be linked with visible light lasers in the 406nm to 685 nm band. There are however considerable methodological problems in RCT design when using visible light lasers. The purpose of this study was to design a system that overcame these problems.

A review of the literature indicated that the most clinically effective parameters would involve the use of a 635nm, 10 mW laser diode delivering 12 joules in 20 minutes. This ensured that issues of thermal detection would be avoided, that laser was delivered for a sufficient time to allow to photo-biological activation and that the delivery method would reflect common acupuncture needle retention times.

The literature also revealed considerable issues with RCT design including problems with randomisation, blinding, monitoring and recording laser delivery and the reporting of study results.

5.2 The Design Process

This study undertook a systematic process to identify issues with existing laser acupuncture and LLLT RCTs and address each one in the design of a computer controlled system to deliver visible laser under controlled, double blind clinical research trial conditions. In doing so, all parameters that influence the therapeutic effects of laser including power, wavelength, time and dosage were controlled.

The design solutions that are unique to this system include:

- a specially designed hood that ensures blinding of the participant and operator;
- the inclusion of optical sensors into the hood design to detect laser delivery or failure;
- an additional layer of randomisation by the computer controlled system which is blinded to the operator and participant; and
- a computer controlled interface with built-in loop back systems to alert researchers to system failures, while ensuring data integrity through systematic data files saves.

5.3 Results

The results of testing indicated that the system was operational. Operators indicated that the control system was easy to use and the hardware easy to apply in a clinical trial situation. Participants indicated that the hoods were comfortable and not distracting. Double blinding was successful. The researchers found the unit to be especially safe to operate for participants and operators, the opaque hoods stopped any chance of accidental exposure to the laser, coupled with the key interlock and the programme's preoperational checks. Data from the trial was successfully saved and recorded. Randomisation of the groups was successful. The participants were unable to detect the active and control phases of the testing.

5.3.1 Limitations of the Study

While the system met all intended design specifications, a number of possible improvements have been identified.

The provision of more than two simultaneous laser heads would add the ability to test bilateral point combinations. At the moment the system is limited to a single point bilaterally or two points ipsilaterally or contralaterally.

The hood design has some limitations for particular acupuncture points where a full seal around the point may not be possible, e.g. Lung 7, due to the diameter of the current hoods. Additional hoods with differing shapes to counter this can be designed.

There are also current limitations to the programming as the laser hoods are not independently set to deliver or not deliver a laser intervention. Consequently, both laser diodes will either activate or not activate. A simple programming change could be instigated to allow the lasers to randomly activate independently. Such a programming change would allow the comparison of acupuncture point function using a model such as:

- ST36 and ST 30 active vs ST36 and ST 30 non active;
- ST 36 active vs ST 30 non active; or
- ST36 non active vs ST 30 active.

This alternate control program was deemed outside of the scope of this study, but would be a simple matter to instigate. Furthermore, with the addition of physiological testing and the additional hood modules, the system could be applied to the therapeutic testing of a variety of point combinations. Similarly, it would be possible to compare visible lasers with infrared lasers or lasers of different power and wavelength outputs.

Additionally the use of a pulsed laser system could allow for greater depth of point penetration while keeping the total dosage delivered to an acceptable level. The current laser unit is only designed to deliver a continuous beam.

5.3.2 Strengths of the Study

The strength of this study lies in the development and testing of a computer-controlled LLLT system with unique design elements. The system allows for double blind trails of visible light lasers, which has not been effectively achieved in previous studies.

The system design and control interface is flexible and allows for the change in laser dosage through control of the delivery time. The system will allow researchers to incorporate lasers with other wavelengths without compromising the integrity of the

randomisation or blinding. It allows for the development and use of other laser hoods that may be applied to a variety of acupuncture point locations.

Its monitoring and loop back system identifies system failures during the laser delivery. This will allow for the confirmation of the delivery of the intervention and alert the researcher to laser faults.

5.3.3 Summary

The purpose to this study was to develop a system for the double blind delivery of visible laser in a clinical trial situation. Bench testing and a mock clinical trial were devised as a proof of concept. The system was tested to deliver 12 joules over 20 minutes using a 635 nm, 10 mW diode laser to mimic other acupuncture interventions. The equipment has been proven as fit for purpose and can now move to full scale RCT deployment.

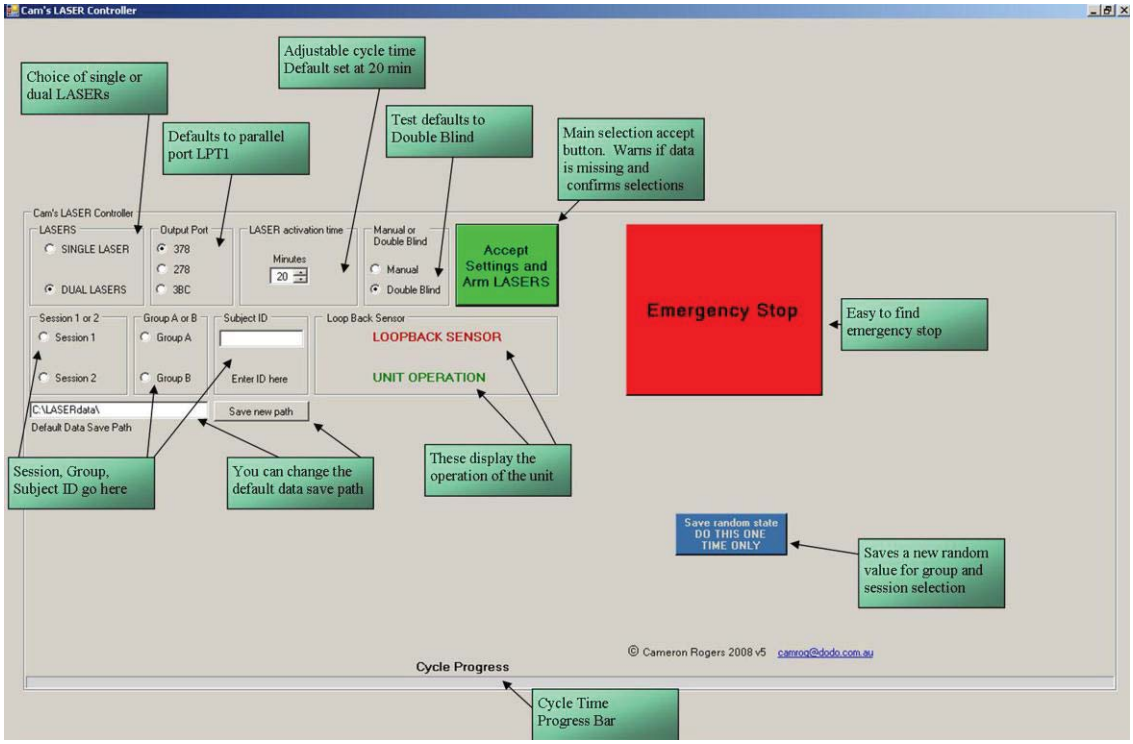
Instructions for the use of the system can be found in appendix A-1

Appendices

Appendix A-1

Laser Controller Operating Procedure Instructions

Figure 9: Illustrated screen dump of laser programme



Any questions regarding operation should be emailed to camrog@dodo.com.au **BEFORE** using this programme or controller unit. This programme is designed to operate **ONLY** the laser control unit that it comes with! **It is not designed for use with any other control unit**. During operation all standard laser safety procedures need to be applied, safety glasses for any person in the operating area etc.

The Controller unit **MUST NOT BE SWITCHED ON** until the controller programme is running. **This step must not be omitted** as there is a slight risk of premature laser activation depending on the computer used. The unit should not be armed until both laser hoods are secured properly and all connections to the computer and laser hoods have been checked and all other safety requirements such as protective goggles are in place.

Appendix A-2

Programme Operation Instructions

The operation of the unit is controlled by eight fields and three buttons with feedback provided by two fields and an output text file that is saved to the default location C:\LASERdata.

Control fields

1. LASERs

   Allows the activation of one or two laser hoods, the default is for two hoods to be activated

2. Output Port

   This value is set at the default 378, corresponding to LPT1 and there should usually be no need to change it, however if you wish to use an alternative parallel port then you can set a different port here.

3. Laser activation time

   Set at a default of 20 minutes. You can alter the activation time of the laser operation here. This represents the total dose time that the laser will be switched on. Therefore using the default time, after 20 minutes the laser will switch off automatically unless stopped by the use of the emergency stop button.

4. Manual or Double Blind

   In manual mode the programme shows much more information, this is for testing and non research use. In Manual mode the laser will always be activated when system is activated. By not deactivating the laser in the test mode the state of the Double Blind will not be revealed and therefore testing of the unit can be carried out at anytime during a study.

   Double Blind operation requires the setting of the following fields such as subject ID and the unit gives only terse feedback during its operation. In Double Blind mode the unit will signal a system problem if the unit is not operating as expected but not the exact nature of the problem where as in manual mode you will see messages on connection failures, laser failures etc.

5. Session

   The session field is for within study crossovers. Session 1 and session 2 reverse the treatment vs. control group selection. So if 10 treatments were required with laser followed by a crossover with 10 treatments without laser for one group and the opposite for another control group, then the first 10 treatments would be conducted under session 1 and the next 10 under session 2. The group that had laser in the first 10 treatments wouldn't then get it in the second and the opposite would be true for the second group.

   If no crossover is require but instead a treatment group and a control placebo group scenario was desired then all interventions would be done as **SESSION 1 ONLY**, thus not resulting in a crossover.

6. Group A or B

   Participants for double blind research should have been allocated into two random groups by any preferred method. The suggested method would be random envelops with a unique participant ID that would put them into group A or B without them needing to know which of the two groups they were actually allocated to.

7. Subject ID

   This area is required for the recording of information to the laser data text file. Example file name; here PART1234 was used as the subject ID so the file was saved as "PART1234 Group A session1 FN0.txt"

8. Default Data Save Path

   This is already set by default at C:\LASERdata\ and there should be little reason to change it. If it is desirable to set a different location to save the data text file then you should use the format for example to a flash drive at F: you would put F:\LASERdata\ then hit the save button. That will mean that the default path will now point to your flash drive on F: and save the data into a directory called LASERdata. You may name the directory anything you desire as long as you don't use the standard illegal characters for directory naming.

Feedback Fields

1. Loop Back Sensors

   This field provides real-time information as to the operation of the unit. Any faults will be reported here. While in double blind mode the feedback is severely limited so as to maintain double blind conditions. In manual mode there is verbose feedback that will report if the lasers are active, if one fails the particular laser that is off, if there is a communication error to the computer etc.
2. Cycle Progress

   The cycle progress bar shows a graphical representation of time elapsed and time to end of intervention in real time. When it reaches the end a message will appear in the Loop Back Sensor field with "cycle success" or "cycle failure" messages if the desired outcome of the intervention failed to happen correctly as determined by the computer.

The Three Buttons

1. Green Button, Accept Settings and Arm Lasers.

   The green button is the main activation button, when you hit this you will be asked if you are sure about your settings and if in double blind mode if any fields have been left blank you will be told to fill them in.

2. Red Button, Emergency Stop

   Clicking on the red emergency stop button immediately shuts off all the lasers and halts the programme.

3. Blue Button, Save Random State

   As it says on the blue button, you should only do this **ONCE!** At the start of the study the blue button resets the random state of the A and B groups. After you hit this button there is no way to tell which of the two groups is now going to get the laser and which is in the control group. This is for double blind testing so the operator is unaware of the intervention.

Appendix A-3

Circuit Function Description

The power supply board provides a stable 5 volt supply to power the switching board and the logic gates within the unit. The second stage of the power supply board provides the stable 3 volts for the laser diodes.

The switching board controls the actual laser activation that is controlled by the logic board.

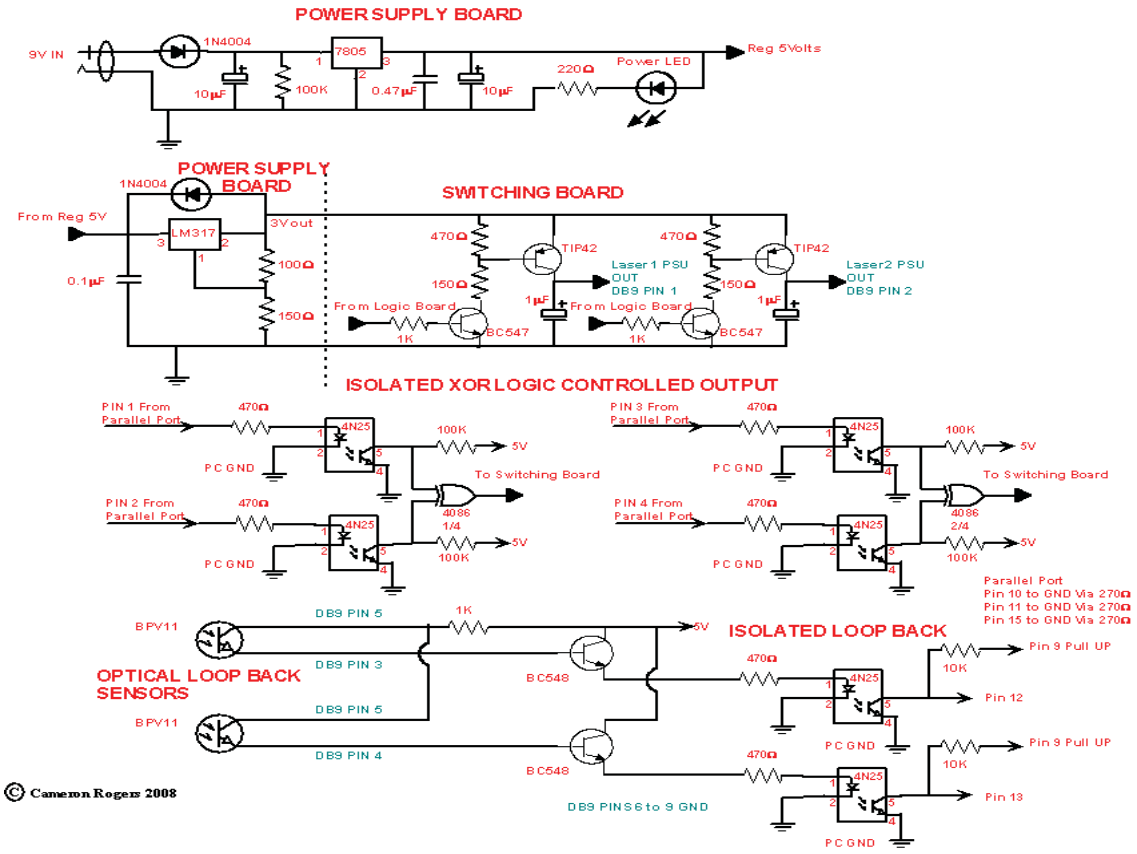
The isolated XOR (4086 exclusive or gate) controlled output board signals the switching board to turn on the lasers when the computer provides the correct signal to do so. The XOR will only turn on the laser if it receives a 1 and 0 at the input gate. It will not switch on if both inputs are high or low to the XOR gate; this is to prevent accidental triggering of the laser output. The 4n25 opto-isolators separate the unit from a direct electrical connection from the controlling computer.

The isolated Loop Back uses BPV11 optical transistors to “see” the activation of the laser and in turn activate the 4n25 opto-isolators via a drive from 2 BC548 transistors. Again this part of the circuit isolates the unit electrically from the computer, instead feeding the information via an optical signal within the 4n25 opto-isolator.

Appendix A-4

Circuit Diagram of Laser Unit

Figure 10: Circuit diagram of the laser computer interface



Appendix B-1

Glossary

A

Absorb To transform radiant energy into a medium with a resultant rise in temperature.

Amplitude The maximum value of the electromagnetic wave the height of the wave.

B

Beam Rays of light travelling together.

Brightness The intensity of a laser beam analogous to the brightness of a light bulb.

C

CO_2 Laser Laser in which the primary lasing medium is carbon dioxide gas. The output wavelength is 10.6 micrometers the output is in the IR band.

Coherence Where light waves are in phase in both time and space.
Monochromaticity and low divergence are two properties of coherent light.

Collimated Light Light rays that are parallel.

Continuous Wave (CW) Constant, steady-state wave with no interruption of the beam.

D

Divergence The increase in the diameter of the laser beam with distance from the source.

E

Electromagnetic Radiation The propagation of electric and magnetic fields through space.

Emission Act of giving off radiant energy after an electron returns to a lower orbit.

Energy The product of power (watts) and duration (seconds). One watt second = one Joule.

F

Failsafe Interlock An interlock a key operated safety mechanism.

Frequency The number of light wave peaks passing a fixed point in a given unit of time.

G

Gas Laser A type of laser in which the laser action takes place in a gas medium eg helium neon lasers.

H

Helium-Neon Laser (HeNe) A laser in which the active medium is a mixture of helium and neon. Its wavelength is usually around 632.8nm.

Hertz (Hz) Unit of frequency in the International System of Units (SI), abbreviated Hz.

I

Infrared Radiation (IR) Invisible to the human eye, electromagnetic radiation with wavelengths which lie within the range of 0.70 to 1000 micrometers.

J

Joule (J) A unit of energy (1 watt-second) used to describe the rate of energy delivery. It is equal to 1 watt-second or 0.239 calorie.

Joule/cm^2 A unit of radiant exposure used in measuring the amount of energy incident upon a unit area.

K

L

Laser An acronym for light amplification by stimulated emission of radiation. A laser is a device which produces an intense beam of light with the unique properties of coherence, collimation and monochromaticity. The device consists of a cavity with mirrors at the ends, and filled with material such as crystal, glass, liquid, gas or dye. .

M

Micron A micro metre which is the unit of length equal to 1 millionth of a metre.

Monochromatic Light Light consisting of a single wavelength.

N

Nanometer (nm) A unit of length in the International System of Units (SI) equal to one billionth of a meter. One nm equals 10^{-9} meter, and is the usual measure of light wavelengths. Visible light ranges from about 400 nm in the purple to about 760 nm in the deep red.

O

Optical Fibre A filament of quartz or other optical material capable of transmitting light along its length by multiple internal reflection and emitting it at the end.

P

Phase When the troughs and peaks of waves coincide and are "locked" together. The result is a reinforced wave in increased amplitude (brightness).

Photon In quantum theory, the elemental unit of light, having both wave and particle behaviour. It has motion, but no mass or charge.

Power The rate of energy delivery expressed in watts (joules per second). Thus: 1 Watt = 1 Joule/1 Sec.

Pulsed Laser Laser which delivers energy in the form of a single or train of pulses.

Q

R

Radiation The process of releasing electromagnetic energy.

Reflection The return of radiant energy (incident light) by a surface, with no change in wavelength.

Resonator The mirrors (or reflectors) making up the laser cavity including the laser rod or tube. The mirrors reflect light back and forth to build up amplification as in a helium neon laser.

S

Semiconductor Laser A type of laser which produces its output from semiconductor materials.

Spontaneous Emission Decay of an excited atom to a ground or resting state by the random emission of one photon.

Spot Size The mathematical measurement of the radius of the laser beam.

Stimulated Emission When an atom, ion, or molecule capable of lasing is excited to a higher energy level by an electric charge or other means, it will spontaneously emit a photon as it decays to the normal ground state. If that photon passes near another atom of the same energy, the second atom will be stimulated to emit a photon.

T

Traditional Chinese Medicine (TCM) Traditional Chinese methods of medical practice, including acupuncture and herbal medicine.

U

Ultraviolet Radiation (UV) Electromagnetic radiation with wavelengths of UV-A (315-400 nm), UV-B (280-315 nm), and UV-C (100-280 nm).

V

Visible Radiation (light) Electromagnetic radiation which can be seen by the human eye. It is commonly used to describe wavelengths which lie in the range between 400 nm and 700-780 nm.

W

Watt A unit of power (equivalent to one Joule per second).

Watt/cm^2 A unit of irradiance used in measuring the amount of power per area of absorbing surface.

Wavelength The length of the light wave, usually measured from peak to peak, measured in unit of the micrometre um (micron) or the nanometre nm.

Appendix B-2

Example Survey Forms

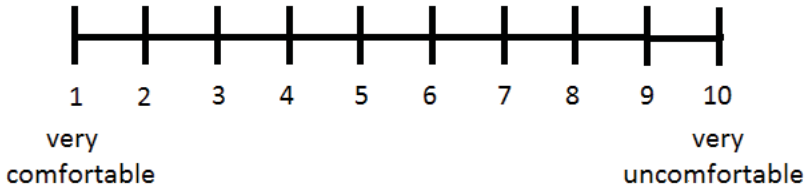
Example Participant Survey Form:

Developing Computer Controlled Laser Systems for Double Blind Acupuncture Trials

Participant Survey

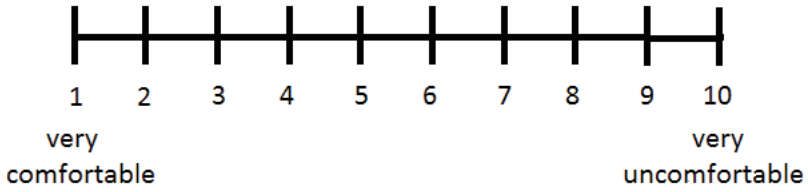
Participant ID:_____

On the scales below, rate the following items:
How would you rate the comfort of the hoods when positioned?



Comments:

How uncomfortable or distracting were the laser hoods over the entire length of the intervention?



Comments:

Were you able to determine if the lasers had fired?

Circle: YES NO

If yes, what led you to believe the lasers had fired?

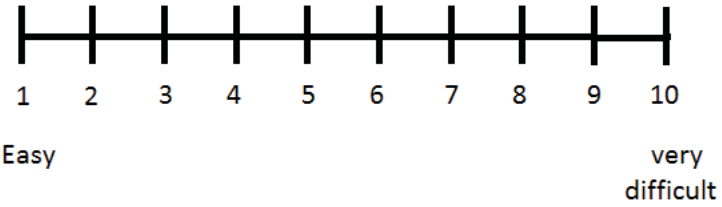
Example Practitioner Survey Form:

Developing Computer Controlled Laser Systems for Double Blind Acupuncture Trials

Practitioner Survey

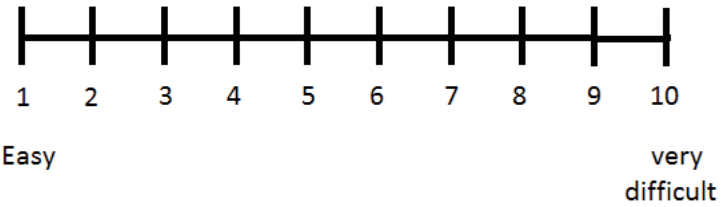
Practitioner ID:_____

On the scales below, rate the following items:
How easy were the hoods to position?



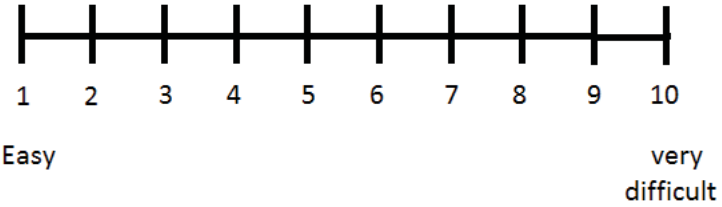
Comments:

How easy were the hoods to attach/fix in place?



Comments:

How easy was the computer interface to use/control?



Comments:

Were you able to determine if the lasers had fired?

Circle: YES NO

If yes, what led you to believe the lasers had fired?

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