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Modeling and Simulation of Heat Distribution in Human Skin Caused by Laser Irradiation

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Abstract: Study of light-based skin rejuvenation needs prospective insights of mechanism of laser tissue interaction. A well-built model plays a key role in predicting temperature distribution in human skin exposed to laser irradiation. Therefore, it not only provides guidance for in vitro experiment, but also facilitates parametric studies of clinical treatment.

In this project, three tasks were completed:

Firstly, a new time-dependent mathematical model is built up to study dynamic thermal responses of human skin to laser irradiation. This model is a combination of three parts: MC (Monte Carlo) Simulation, which provides photon distribution; MATLAB data processing, which calculates heat generation rate from MC output; COMSOL modeling, compute real-time temperature change.

Secondly, an experimental setup was built with 976nm laser diode of 1Watt and 4mm beam diameter. Based on the guidance of simulations, the system is designed to be in the best configuration, both for the requirement of experiment and for transportation.

Thirdly, the mathematical model was validated by performing experiments with the experimental setup and ex vivo human skin. Two temperature measurement techniques were applied: thermocouple measurement and thermal camera measurement.

Results derived from both experiment and simulations are compared.
According to analysis, we may draw the conclusion that the model can serve as a reliable tool for predicting temperature distribution of human skin sample under laser irradiation, and it will facilitate parametric study of laser in skin rejuvenation. In addition, the innovative structure of the present model offers great probability to be further improved, by adjusting input parameters, boundary conditions, as well as functionality of the model. We believe that a further revised model, in the future, will be an even more powerful tool for improved treatments of skin rejuvenation.

Conclusions:

In this project, we constructed the model by combining Monte Carlo Simulation with COMSOL model for the first time, and innovatively create a new profile of modeling. This model provides guidance for carrying out ex vivo experiments, and in return, is proved by experiments for its validity and reliability. In the work of this project, result in each experiment is correct and reliable. Therefore, we can draw the conclusion that the present model can serve as a good tool to predict temperature distribution in human skin under laser irradiation, and will facilitate parametric study of laser in skin rejuvenation[]. In addition, the innovative construction of the present model offers great probability to be further improved, by adjusting input parameters, boundary conditions, or functionality of model. We believe that a further revised model, in the future, will be an even more powerful tool for better treatment of skin rejuvenation.
Contents

Acknowledgment ................................................................................................................. 9

Abstract ................................................................................................................................. 10

1. Introduction ......................................................................................................................... 11
   1.1. Preface ............................................................................................................................. 11
   1.2. Skin rejuvenation ............................................................................................................ 11
       1.2.1. Ablative skin resurfacing ......................................................................................... 11
       1.2.2. Non-ablative dermal remodeling .............................................................................. 11
       1.2.3. Fractional Photothermolysis .................................................................................. 12
   1.3. Research Background .................................................................................................... 12
   1.4. Research contents and objectives ................................................................................ 12
   1.5. Thesis Structure ........................................................................................................... 13

2. Skin Optics .......................................................................................................................... 14
   2.1. Overview of skin optics .................................................................................................. 14
       2.1.1. Photon propagation in skin ..................................................................................... 14
       2.1.2. Two tasks in skin optics .......................................................................................... 15
   2.2. Introduction of human skin .......................................................................................... 15
       2.2.1. Structures of skin tissue .......................................................................................... 15
       2.2.2. Skin optical properties ............................................................................................ 16
   2.3. Skin optical parameters ............................................................................................... 17
       2.3.1. Measuring optical parameters ................................................................................ 17
       2.3.2. Theoretical estimation of optical parameters ............................................................ 18
       2.3.3. Optical parameters in our simulation ...................................................................... 20
   2.4. Laser - tissue interaction .............................................................................................. 21
       2.4.1. Light transport of collimated light ......................................................................... 21
       2.4.2. Monte Carlo Simulation ......................................................................................... 22
       2.4.3. Summary .................................................................................................................. 23

3. Thermal Response of skin .................................................................................................. 25
   3.1. Introduction .................................................................................................................... 25
   3.2. Heat balance in skin tissue ........................................................................................... 25
       3.2.1. Tissue heat gain ....................................................................................................... 25
       3.2.2. Tissue heat transfer ................................................................................................. 26
       3.2.3. Thermal energy storage .......................................................................................... 27
       3.2.4. Bioheat transfer equation ....................................................................................... 27
       3.2.5. Tissue thermal properties ....................................................................................... 28
       3.2.6. Summary .................................................................................................................. 28
4. Numerical modeling and Simulation .................................................. 30
   4.1. Introduction ...................................................................................... 30
   4.2. skin model ....................................................................................... 30
   4.3. Model Structure .............................................................................. 30
      4.3.1. Optical parameters ................................................................. 30
      4.3.2. Thermal parameters ............................................................... 31
   4.4. Mathematical Model ....................................................................... 31
      4.4.1. Model construction ................................................................. 31
      4.4.2. Monte Carlo (MC) Simulation ................................................. 32
      4.4.3. MATLAB data processing ..................................................... 33
      4.4.4. COMSOL Modeling ............................................................. 33
   4.5. Research based on the Model ........................................................ 35
      4.5.1. Heating and cooling by water bath ......................................... 35
      4.5.2. Laser irradiation study ............................................................ 38
   4.6. Summary ......................................................................................... 44

5. Temperature measurement and model validation ................................. 45
   5.1. Introduction ...................................................................................... 45
   5.2. Temperature measurement techniques ......................................... 45
      5.2.1. Thermocouples ....................................................................... 45
      5.2.2. Infrared temperature measurement ........................................ 46
   5.3. Materials .......................................................................................... 48
      5.3.1. Skin tissue ................................................................................. 48
      5.3.2. Reagents .................................................................................. 48
      5.3.3. Equipment ............................................................................... 49
      5.3.4. Software ................................................................................ 49
   5.4. Experiment Preparation ................................................................. 49
      5.4.1. Build up Laser system ............................................................. 49
      5.4.2. Modify Laser beam ................................................................. 50
      5.4.3. Power calibration ................................................................... 52
   5.5. Methods .......................................................................................... 53
      5.5.1. Preparation of skin specimen .................................................. 53
      5.5.2. Laser irradiation experiment ................................................... 54
      5.5.3. Perform simulations and analyze the results ......................... 56
   5.6. Results and Analysis ....................................................................... 57
      5.6.1. 4cm×1cm×1mm model ............................................................ 57
      5.6.2. 3cm×2cm×6mm model ........................................................... 63
   5.7. Conclusion ....................................................................................... 67

6. Application ......................................................................................... 69
   6.1. Room condition irradiation ............................................................ 69
   6.2. Choose cooling method to keep temperature .................................. 70
   6.3. Irradiating while applying water bath cooling .................................. 72
6.4. Summary ..................................................................................................................... 74

7. Discussion ....................................................................................................................... 75
    7.1. Choice of sample size in simulation and experiment ............................................. 75
    7.2. Water bath heating and cooling ............................................................................. 75
    7.3. Simulation of larger and small sample ................................................................... 76
    7.4. Model Improvement ............................................................................................... 76
    7.5. Model application .................................................................................................. 76

8. Conclusion and Outlook .................................................................................................. 78

References .......................................................................................................................... 80
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Abstract

Study of light-based skin rejuvenation needs prospective insights of mechanism of laser tissue interaction. A well-built model plays a key role in predicting temperature distribution in human skin exposed to laser irradiation. Therefore, it not only provides guidance for in vitro experiment, but also facilitates parametric studies of clinical treatment. In this project, three tasks were completed:

Firstly, a new time-dependent mathematical model is built up to study dynamic thermal responses of human skin to laser irradiation. This model is a combination of three parts: MC (Monte Carlo) Simulation, which provides photon distribution; MATLAB data processing, which calculates heat generation rate from MC output; COMSOL modeling, compute real-time temperature change.

Secondly, an experimental setup was built with 976nm laser diode of 1Watt and 4mm beam diameter. Based on the guidance of simulations, the system is designed to be in the best configuration, both for the requirement of experiment and for transportation.

Thirdly, the mathematical model was validated by performing experiments with the experimental setup and ex vivo human skin. Two temperature measurement techniques were applied: thermocouple measurement and thermal camera measurement.

Results derived from both experiment and simulations are compared. According to analysis, we may draw the conclusion that the model can serve as a reliable tool for predicting temperature distribution of human skin sample under laser irradiation, and it will facilitate parametric study of laser in skin rejuvenation. In addition, the innovative structure of the present model offers great probability to be further improved, by adjusting input parameters, boundary conditions, as well as functionality of the model. We believe that a further revised model, in the future, will be an even more powerful tool for improved treatments of skin rejuvenation.

Key words: skin rejuvenation, laser irradiation, heat distribution, Monte Carlo Simulation, COMSOL model
1. Introduction

1.1. Preface

The fast development and progress of laser techniques enable its broad applications in modern medicine, in areas of diagnostics, therapy and surgery. Among these, laser-based cosmetic surgery is the most rapidly evolving area. The underlying mechanism is thermal effect of photon skin interaction in response of visible and near-infrared laser light. The extent of thermal destruction of tissue is governed by heat deposition caused by photon absorption in skin tissue, heat transfer and temperature dependent rate reactions. Therefore, a reliable tissue model and simulation method is needed to choose treatment parameters properly and to predict the outcome of the photothermal effect. In this thesis, a time-dependent mathematical model is built up to study dynamic tissue thermal responses to laser irradiation. Moreover, a laser irradiation system was built up and experiments in the lab are carried out to validate the model.

1.2. Skin rejuvenation

The ultimate goal of the thesis is to provide a reliable prediction tool for in vitro experiments to study skin rejuvenation. Therefore, it makes sense to have a brief idea about the perception and classification of skin rejuvenation. The interaction of pulsed and continuous wave lasers with skin in dermatological applications can be categorized into three treatment modalities: ablative skin resurfacing, non-ablative dermal remodeling and fractional photothermolysis [ii].

1.2.1. Ablative skin resurfacing

Ablative laser cosmetic surgery vaporizes the top layer of the skin and the skin upon healing reveals a fresh new surface layer. Since the targeted chromophore is water, CO2 laser or Er:YAG laser are commonly used because of strong water absorption in the far-infrared wavelength range [iii]. The process of recovery is slow because the keratinocytes from healthy skin have to migrate for longer path to append for healing. Besides, side effects of this method include edema, infection, pigmentary changes, and scarring. Ablative skin resurfacing is primarily used to treat chronic photoaging, characterized by rhytides, dyschromias, and lentigines [iv].

1.2.2. Non-ablative dermal remodeling

Differently, the absence of epidermal damage in non-ablative dermal remodeling results in decreased recovery time. This method selectively damages dermal tissue by the process of selective photothermolysis, leaving the skin surface intact [iii]. This is achieved by using appropriate laser irradiation parameters: wavelength, energy density, pulse duration, spot size and spatial profile, as well as cooling the epidermis during irradiation. It is believed that this "upside-down" thermal injury denatures dermal collagen and stimulates collagen growth to promote healing response [iv,v]. The result is skin thickening and tightening. Mid-infrared laser, which are generally weakly absorbed by water, is applied. These type of laser include Q-switched 1064nm Nd:YAG lasers, 585nm pulsed-dye lasers, 976nm diode lasers, 1320nm long-pulsed Nd:YAG lasers, 1540nm Er:Glass lasers and 1440nm diode laser [v,vi].

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1.2.3. Fractional Photothermolysis

Fractional photothermolysis utilizes wavelengths at 1550nm and 2940nm to create micro wound patterns separated by areas of unaffected healthy tissue [ii, iii]. The pattern and depth of thermal impact is controlled by computer programs. The healthy areas surrounding wounds contain viable cells that promote rapid healing. It is a new concept for skin treatment and tends to achieve desired effects without side effects associated with ablative surgery [iii-v].

1.3. Research Background

The aim of this research is to provide a reliable tool to guide in vitro experiments to perform parametric study of laser irradiation on human skin. In other words, it is a prerequisite to study selective photothermal interaction. There are several strengths to use simulation techniques as an important assistant method.

- The process of building the model makes theoretical preparation for in vitro research. It enables in-depth understanding of thermal response of human skin under laser irradiation.
- A well designed model predicts dynamic temperature change of skin tissue precisely, thus provides guidance for designing in actual experiments in advance.
- A validated model can be applied to do further innovative research in this field.
- Generally, a well designed mathematic model is an economical, direct and flexible assistant tool for in vitro research.

1.4. Research contents and objectives

The work flow of the project is presented in Figure1.1. Contents of the research include:

1) To have an in-depth understanding of the application of the research, and to prepare for the project.

   Literature study is the major task for this objective. The study includes the following aspects:
   - To acquire background knowledge about skin resurfacing for understanding the application of the model.
   - To understand conception about skin optics, and to find out skin optical parameters for use in Monte Carlo simulation.
   - To learn theoretical basis of Monte Carlo simulation.
   - To investigate previous people's modeling work in related field.

2) Build up a model based on literature study and available resources.

3) Use the model as guidance for actual experiment. Simulations are performed and results are analyzed.

Two situations are considered: water bath heating and laser irradiation. The desired skin temperature is 45°C and 60°C in both situations. There are three major objects when performing simulation.

- To obtain better time control of the experiments to achieve desired temperature.
- To choose appropriate laser parameters for performing the experiment.
- To compare different cooling methods in simulation either before or after validation of the model.
4) Build up a laser irradiation system for experiments. The system should be designed to be in best configuration, not only to meet experimental requirements, but also be easy to transport.

5) Perform actual experiments to validate the model.
   - Perform irradiation of skin sample with practical size and measure temperature of skin sample based on two techniques: thermocouple measurement and thermal camera measurement.
   - Compare the result with simulation. Adjust input parameters of the model based on experimental conditions.
   - Try to illustrate the validity of the model based on comparison.

6) Further parametric study based on the validated model.

![Figure 1.1 Work flow of the project]

1.5. Thesis Structure

The thesis is composed of the following chapters:
Chapter1 gives a brief introduction of project background, project content and objectives. Chapter2 introduces background knowledge of skin optics, which plays a key role in modeling light distribution in skin. Chapter3 illustrates thermal conduction theory. It serves as basis for thermal analysis of laser-tissue interaction. Chapter4 formulates the numerical model in detail. Simulations based on the model were also explained. This chapter is a meaningful extension and practice of theories presented in Chapter2 and Chapter3. Chapter5 describes temperature measurement techniques and ex vivo experiments for model validation. Chapter6 introduces the applications based on the validated model. Chapter7 discusses some particular questions that should be answered and emphasized in this thesis. Chapter8 gives conclusion and outlook of the thesis project.
2. Skin Optics

2.1. Overview of skin optics

Understanding how light is propagated inside human skin tissue is the first step of modeling light interaction with skin. Then it is essential to find out the rate of heat that is generated in the skin tissue, thus it should be clarified how many photons are absorbed per second by the chromophore inside skin tissue. In this chapter, skin optical properties will be introduced and methods to calculate proper value of optical parameters are presented.

2.1.1. Photon propagation in skin

The characteristics of photon propagation include scattering and absorption events within skin tissue, and reflection and transmission at boundaries. Figure 2.1 indicates probable photon propagation pathways in skin.

![Figure 2.1 Random paths of most photons in tissue](image)

Photons can be absorbed by chromophores (e.g. melanin in epidermis, hemoglobin and water in dermis [vi]) and deposits its energy in skin tissue. Scattering event, which changes the direction of photon propagation, is another important phenomenon, especially at visible and near-IR wavelength range (400nm-1200nm). Besides, photons can be totally internally reflected at the tissue-air interface; or they can be remitted out of the tissue. These events, in corporation, determine photon energy distribution inside skin tissue after laser irradiation at certain wavelength $\lambda$ with constant power $P$ over the laser beam radius $w$. 
2.1.2. Two tasks in skin optics

There are two major problems to solve in skin optics:

1) Estimate the optical properties of tissue. These properties include:
   (i) Absorption coefficient $\mu_a$
   (ii) scattering coefficient $\mu_s$
   (iii) anisotropy coefficient $g$
   (iv) refractive index $n$

   Among these parameters, (i) and (ii) equals the average number of absorption and scattering events per unit path length of photon travel in tissue, (iii) represents the average cosine of the scattering angles, and (iv) defines the velocity change of light traveling from vacuum(air) into the medium[7]. All these coefficients are wavelength and temperature dependent. They can provide calculation basis for the second task.

2) Find out the rate of energy deposition per unit area at some position $r$, which is considered as fluence rate ($\psi(r)$). This task can be solved by Monte Carlo simulation, transport equation and diffusion approximation.

An exact evaluation of light propagation in tissue requires a correct model that characterizes the tissue structure and optical properties. For our case, a model should be built to match the sample characteristics in a realistic way. Therefore, to simplify the case to a certain extent, we consider skin to be a multi-layered structure, with each layer assumed to be isotropic and homogeneous.

2.2. Introduction of human skin

In this part, we will introduce biological characteristic of skin structure and constituents, and how they affect the propagation of light.

2.2.1. Structures of skin tissue

The skin is a complex heterogeneous medium, where the texture, blood and pigmented contents are spatially distributed variably in depth. The skin mainly contains three visible layers: epidermis, dermis and hypodermis. The structure of skin is presented in Figure 2.2.
The epidermis can be subdivided into two sub-layers: non-living, also called stratum corneum, and living epidermis. Stratum corneum (about 0.01-0.02mm thick \([x]\)) consists of only dead squamous cells, which has relatively low water content. Living epidermis (about 0.027-0.15mm thick \([x]\)) contains most of the skin pigmentation, melanin, which is produced in melanocytes. It is composed of four layers: stratum basale, stratum spinosum, stratum granulosum and stratum lucidum \([x, xi]\).

Dermis is a vascularized layer with a thickness of 0.6-4mm. Due to the distribution of blood vessels, skin dermis can be subdivided into four layers \([xii]\): the papillary dermis (150um thick), the upper blood net plexus (100um thick), the reticular dermis (1-4mm thick) and deep blood net plexus (100um thick). The fluence rate of blood decreases as we get deeper into the skin.

The hypodermis is a subcutaneous adipose tissue of up to 3cm thick in the abdomen \([vii, xii]\). It is formed by aggregation of fat cells containing stored lipids in form of a number of small droplets. There are blood capillaries, nerves and reticular fibrils among fat cells and providing metabolic activity to the fat tissue.

### 2.2.2. Skin optical properties

**Absorption**

The epidermis propagates and absorbs light. Due to the low water content of epidermis, the absorption property mostly comes from a natural chromophore, melanin, which is mainly produced in stratum basale. The melanin absorption level depends on the volume fraction of epidermis occupied by melanosomes, which varies from 1.3% (lightly pigmented specimens) to 43% (darker pigmented specimens) \([x]\).

For dermis, in the visible spectral range, main chromophores are the blood hemoglobin \([xiii]\). Absorption of hemoglobin is defined by the hemoglobin oxygen saturation, because both oxy- and de-oxy hemoglobin have slightly different absorption spectra. In the IR spectral range absorption properties of skin dermis are determined by the water absorption.

Absorption of hypodermis is characterized by a negligible absorption of light and most light reaching this layer is reflected back to the upper layer \([xii, xiv]\).

In general, the absorption property of the whole skin is defined by the hemoglobin and water of the skin dermis and melanin of the skin epidermis.
Scattering
The scattering property of human skin is composed of two parts: surface scattering and subsurface scattering [x]. Surface scattering is caused by the folders in the stratum corneum. It follows Fresnel equations. As the result, about 5-7% of the light incident on the stratum corneum is reflected back to surrounding environment [x]. The remaining portion of light is further transmitted to the internal tissue. There are two other types of subsurface scattering occurring within the skin layers: Mie and Rayleigh scattering. Epidermis is characterized as forward scattering media [xii]. Melanin particles, such as melanosomes (>300nm in diameter), is approximately the same size as wavelength of light, so it exhibits mainly forward scattering due to Mie scattering[xiv]. In dermis, the scattering properties of the skin are defined by the scattering properties of the reticular dermis because of the relatively big thickness and comparable scattering coefficients of the reticular dermis [x, xii, xiv]. Collagen fibers (cylindrical with about 2.8um in diameter) lead to Mie scattering, while smaller scale fibrous structures and other micro-structures are responsible for Rayleigh scattering [x]. Light is scattered multiple times inside the dermis before it is either transmitted to another layer or absorbed. This means that the spatial distribution of the backscattered light quickly becomes diffused.

2.3. Skin optical parameters
Finding out skin optical parameters is one of the two major tasks in skin optical research. It is the prerequisite for modeling photon distribution under laser irradiation. There are two methods to determine skin optical parameters: measurement by experiments or theoretical estimation from other people’s experiments.

2.3.1. Measuring optical parameters
The double integrating sphere system is often used to measure the skin optical properties in vitro [xiii]. It measures the diffuse reflectance $R_d$ and the diffuse transmittance $T_d$ simultaneously, and then calculates the absorption and isotropic scattering coefficients using the inverse adding-doubling program. This iterative program estimates the reflectance and transmittance from a set of optical parameters until the calculated reflectance and transmittance match the measured values [x, xiii]. Inputs that should be provided into the program are also values for the anisotropy coefficient $g$ and refractive index $n$ of the sample. Figure2.3 shows the construction of the system.
Figure 2.3 Construction of the double integrating sphere apparatus [xiii]

For measuring the in-vivo optical properties of the skin, a method that used a transient temperature measurement technique was developed [xiv]. Under insignificant heat conduction (exposure time \( t_0 \ll \) characteristic thermal diffusion time \( \tau \)), the slope of peak temperature response to very short pulses versus time gives a measure of the absorption coefficient \( \mu_a \) [xv]:

\[
\Delta T(r, t) = \frac{\Phi(r, z = 0^+, t) \mu_a t}{\rho C}
\]

\( \Delta T(r, t) \) [°C] is the temperature change during the short pulse; \( \Phi(r, z = 0^+, t) \) [W/m²] is the fluence rate below the surface; \( C \) [J/(kg·K)] is heat capacity; \( \rho \) [kg/m³] is skin tissue density; \( t \) [s] is the exposure time. \( \Phi \) is approximately equal to the incidence flux \( (1-r_s)E(r,t) \), where \( r_s \) is the specular reflectance. Because the irradiance used in this measurement was constant during the laser pulse and had a top-hat shape, the irradiance at \( r=0[E(r=0, t)] \) was \( \frac{P}{\pi \omega^2} \) [W/m²], where \( P \) [W] is the input power, and \( \omega \) [m] is the radius of the laser beam. In general, the absorption coefficient can be estimated according to the slope of the peak temperature response curve during the first 100ms of irradiation, for instance.

2.3.2. Theoretical estimation of optical parameters

Empirical equations to calculate optical parameters are summarized theoretically based on skin components and experimental data [x, xiv].

Absorption coefficient of epidermis

The absorption of melaninless epidermis and bloodless dermis is a baseline absorption coefficient \( \mu_{a\text{ base}} \) [cm⁻¹]. It can be expressed as a function of wavelength. This formula is based on measurements of bloodless rat skin using an integrating sphere calibrated with phantom measurements [xiv]. It is considered that rat skin optics is quite similar to that
of neonatal skin.

\[ \mu_{a_{\text{base}}} = 0.244 + 85.3e^{-(\lambda-154)/66.2} \]  \hspace{1cm} (2.2)

Where \( \lambda \) [nm] is laser wavelength. In epidermis, since melanin is the major chromophore, which exhibits stronger absorption at shorter wavelengths, absorption estimation of melanosome should also be considered. The estimation should consider absorption of single melanosome molecule and concentration of melanin in skin. Based on various published studies \([x-xiv]\), a single melanosome has an absorption coefficient \( \mu_{a_{\text{mel}}} \) [cm\(^{-1}\)] stated as:

\[ \mu_{a_{\text{mel}}} = 6.6 \times 10^{11} \lambda^{-3.33} \]  \hspace{1cm} (2.3)

The volume fraction of the epidermis occupied by melanosome, \( f_{\text{mel}} \), is roughly estimated based on measurements:

<table>
<thead>
<tr>
<th>Volume fraction of melanosome in epidermis [xiv]</th>
<th>Light-skinned adults</th>
<th>Moderately pigmented adults</th>
<th>Darkly pigmented adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_{\text{mel}} )</td>
<td>1.3-6.3%</td>
<td>11-16%</td>
<td>18-43%</td>
</tr>
</tbody>
</table>

Therefore, net epidermis absorption coefficient \( \mu_{a_{\text{epi}}} \) [cm\(^{-1}\)] is approximated by combining the baseline absorption and melanin absorption.

\[ \mu_{a_{\text{epi}}} = f_{\text{mel}} \times \mu_{a_{\text{mel}}} + (1-f_{\text{mel}}) \times 11 \times \mu_{a_{\text{base}}} \]  \hspace{1cm} (2.4)

**Absorption coefficient of dermis**

Similar to epidermis, hemoglobin absorption and baseline absorption constitute dermis absorption \([x, xiv]\). Baseline absorption coefficient is given in equation (2.2). Absorption of blood can be obtained from Wray et al. 1998\([xiv]\).

Assume blood to be uniformly distributed in the skin. A typical value assumed as fraction volume of blood \( (f_{\text{blood}}) \) is 0.2% \([xiv]\). Therefore, net absorption of dermis is evaluated as

\[ \mu_{a_{\text{derm}}} = f_{\text{blood}} \times \mu_{a_{\text{blood}}} + (1-f_{\text{blood}}) \times \mu_{a_{\text{base}}} \]  \hspace{1cm} (2.5)

A more delicate approximation should specify a depth profile for blood in dermis.

**Scattering coefficient of skin**

Scattering coefficients of epidermis and dermis is considered to be the same, since epidermis is very thin, and keratin fibers in epidermis possess similar scattering behavior with collagen fibers in dermis \([x, xiv]\).

Scattering coefficient \( \mu_s \) [cm\(^{-1}\)], incorporating anisotropy factor \( g \), gives reduced scattering coefficient:

\[ \mu_s' = \mu_s (1-g) \]  \hspace{1cm} (2.6)
where $g$ is defined as the mean cosine of deflection angle due to a scattering event. Typical values of $g$ are in the range of 0.7-0.95 for skin tissue \([xii, xiv]\), and vary with wavelength. $\mu_s'$ is used to describe the diffusion of photons in a random walk of step size of $1/\mu_s' [\text{cm}]$, where each step involves isotropic scattering. Therefore, for the common case of photon diffusion involving many scattering events, which is typical in visible and near-infrared wavelength range, $\mu_s'$ is quite applicable. Scattering of skin is composed of Mie scattering by large cylindrical dermal collagen fibers and Rayleigh scattering by small-scale structure such as collagen fibers and other cellular structures. In spectral range 600-1500nm, for many tissues, $\mu_s'$ decreases with wavelength according with a power law \([x, xiv]\)

$$\mu_s' = a \lambda^{-w}$$

(2.7)

Where $w$ characterizes the mean size of tissue scatterers and defines the extent of reduced spectral of scattering coefficient. Based on the measured reduced scattering coefficient spectrum, formulas of Mie scattering $\mu_s'_{\text{Mie}} [\text{cm}^{-1}]$ and Rayleigh scattering $\mu_s'_{\text{Rayleigh}} [\text{cm}^{-1}]$ is given respectively as following:

$$\mu_s'_{\text{Mie}} = 73.7 \lambda^{-0.22}$$

(2.8)

$$\mu_s'_{\text{Rayleigh}} = 1.1 \times 10^{12} \lambda^{-4}$$

(2.9)

Therefore, estimation of $\mu_s' [\text{cm}^{-1}]$ of the whole skin is the combination of both factors, which is\([xiv]\)

$$\mu_s' = \mu_s'_{\text{Mie}} + \mu_s'_{\text{Rayleigh}} = 73.7 \lambda^{-0.22} + 1.1 \times 10^{12} \lambda^{-4}$$

(2.10)

### 2.3.3. Optical parameters in our simulation

Absorption and scattering coefficients in our experiment, in the simulation phase, is obtained by firstly calculate by equations (2.2)-(2.10), and then reliability of the data is validated by checking measured data from literatures \([x-xiv]\). The optical data used in our experiments are listed in the following table.

<table>
<thead>
<tr>
<th>$\lambda$ [nm]</th>
<th>$\mu_a$ [cm$^{-1}$]</th>
<th>$\mu_s$ [cm$^{-1}$]</th>
<th>$\mu_s'$ [cm$^{-1}$]</th>
<th>$g$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>532</td>
<td>1.28</td>
<td>322.57</td>
<td>0.9</td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>632</td>
<td>0.6</td>
<td>247.31</td>
<td>0.9</td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>976</td>
<td>0.38</td>
<td>174</td>
<td>0.9</td>
<td>1.38</td>
<td></td>
</tr>
</tbody>
</table>

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2.4. Laser - tissue interaction

After finding out skin optical parameters, light transport in skin can be simulated using several methods. Two methods are introduced here: Transport equation and Monte Carlo Simulation.

2.4.1. Light transport of collimated light

Collimated light normal to the surface has a small portion of the light reflected back, with the remaining light attenuated in the tissue by absorption and scattering. The resulting spatial light distribution assumes to follow Beer’s Law of exponential attenuation [vii]:

\[ I(z) = I_0(1-R)e^{-\mu_t z} \]
\[ \mu_t = \mu_a + \mu_s \]  \hspace{1cm} (2.11)

\( I(z) \) [W/m²] is fluence rate of collimated light at position \( z \) [m] in the tissue. \( I_0 \) [W/m²] is intensity of incident light striking the surface. \( \mu_t \) [cm⁻¹] is attenuation coefficient, which is the summation of absorption coefficient \( \mu_a \) [cm⁻¹] and scattering coefficient \( \mu_s \) [cm⁻¹].

For a Gaussian beam, light distribution in the tissue is modified version of equation (2.11) [vii]:

\[ I(r, z) = I_0(1-R)e^{(-r^2/(2\sigma^2(z)))}e^{-(\mu_a+\mu_s)z} \]  \hspace{1cm} (2.12)

The gradient of intensity is described as [xvi]:

\[ Q(r, z) = \frac{\partial I(r, z)}{\partial z} = \mu_a I(r, z) + \mu_s I(r, z) \]  \hspace{1cm} (2.13)

The first term describes heat deposition due to absorption, and the second term describes light variation due to scattering. Therefore, when absorption is assumed to take place only in the direction of the incident beam and the intensity of light decreases exponentially with depth, heat deposition is equal to the absorption coefficient times the light intensity. According to this theory, heat generation of Gaussian beam irradiation is assumed to be [xvi]:

\[ Q(r, z) = \mu_a I_0(1-R)e^{-r^2/(2\sigma^2(z))}e^{-(\mu_a+\mu_s)z} \]  \hspace{1cm} (2.14)

For a non-ideal medium where scattering takes a large part, using Monte Carlo Simulation is more accurate in predicting light propagation [vii].
2.4.2. Monte Carlo Simulation

Monte Carlo Simulation provides a rigorous approach for prediction of photon transport in a non-ideal media, which more closely to skin sample used in ex vivo experiments. It samples photon propagation variable from a well-defined probability distribution. Generally, the simulation process goes as follows [vii, xvii]: A photon is launched and reaches the top of the skin. It propagates a certain step size $s$, with a rotation angle $\psi$ and deflection angle $\theta$, to an interaction site and deposits a portion of its energy to the site. The amount of energy deposited is determined by the optical parameters of skin tissue. The parameter, photon weight $W$, is defined for this purpose, weight changes after an energy deposition happens [vii]:

$$\Delta W = W \frac{\mu_a}{\mu_t}$$

(2.15)

Where $\Delta W$ is the change of photon weight; $W$ is photon weight, $\mu_a$ [cm$^{-1}$] and $\mu_t$ [cm$^{-1}$] are absorption coefficient and attenuation coefficient, respectively, as defined before. When the value is below a predefined threshold, the photon is terminated. Then a new photon is launched and the process is repeated. Figure 2.4 shows the flowchart of implementing Monte Carlo simulation.

![Flowchart of Monte Carlo Simulation](image)

*Figure 2.3 a simplified flow diagram for the Monte Carlo Simulation*
1) Selecting step size \( s \)
For a certain type of tissue with absorption coefficient \( \mu_a \) and scattering coefficient \( \mu_s \), the step size is given as [vii, xvii]

\[
s = \frac{-\ln(\zeta)}{\mu_i}
\]

(2.16)

Where \( \zeta \) is a random number in the interval \((0, 1]\), and \( \mu_i \) is the attenuation coefficient.

2) Selecting deflection angle, \( \theta \)
The probability distribution of \( \cos \theta \), in which \( \theta \) varies in the interval \([0, \pi]\) is described by the galactic scattering function [vii, xvii]:

\[
P(\cos \theta) = \frac{1 - g^2}{2(1 + g^2 - 2g \cos \theta)^{3/2}}
\]

(2.17)

The anisotropy factor \( g \) is the average value of \( \cos \theta \). Therefore, for each random step, the deflection angle is determined using the distribution in equation 2.17[vii]:

\[
\cos \theta = \begin{cases} 
\frac{1}{2g} [1 + g^2 - \frac{(1 - g^2)^2}{1 - g + 2g \zeta}] & \text{if } g > 0 \\
2 \zeta - 1 & \text{if } g < 0
\end{cases}
\]

(2.18)

3) Selecting Anzimusal angle, \( \phi \) [rad]
Anzimusal angle is defined as symmetrical photon deflection from initial axis of propagation. It is uniformly distributed within the interval \([0, 2\pi]\) [xvii].

\[
\phi = 2\pi \zeta
\]

(2.19)

4) Photon propagation
Snell’s law and Fresnel reflectance at the boundary are used to determine if the photon is reflected back or injected into the next layer [xvii]. If a photon is reflected back, the photon would travel in the same layer, the step size will be changed to

\[
s' = s_0 \mu_{i0} / \mu_{i1}
\]

(2.20)

Where \( \mu_{i0} \) [cm\(^{-1}\)] and \( \mu_{i1} \) [cm\(^{-1}\)] are the interaction coefficients for the new layer and the original layer, respectively. After launching all the photons, the Monte Carlo simulation is completed. An absorption power density matrix is generated with each element representing absorbed power density at each location. Therefore, the result of Monte Carlo Simulation can be used as the heat source for the thermal diffusion process.

2.4.3. Summary
In this chapter, skin optics is introduced by solving two tasks: determine skin optical
parameters and calculate energy deposition in each site of the skin tissue. Solving the first problem is the prerequisite for solving the second problem. Theoretical and experimental methods to obtain skin optical parameters were introduced, while light transport equation and Monte Carlo Simulation methods were described for solving energy distribution problem. Study of skin optics lays the foundation for modeling of laser-skin interaction.
3. Thermal Response of skin

3.1. Introduction

Skin optics determines energy deposition in skin tissue during laser irradiation. However, deposited heat at the application site will be transferred to surrounding structures. The rate of heat transfer depends on the physical organization and chemical composition of the skin. Thermodynamic modeling of laser-tissue interaction should take the whole process into account.

Heat transport mechanism in human skin has been developed by previous studies [vii, xv, xvii]. This chapter gives a general introduction of the physical and mathematical basis for biological heat transfer. Heat generation, heat transfer equation will be introduced.

3.2. Heat balance in skin tissue

According to principle of conservation of energy, we know that in a closed system, which, in our case, is a certain tissue volume, the energy balance can be specified in the following equation [vii]:

\[
Q_{\text{gain}} = Q_{\text{storage}} + Q_{\text{loss}} + W
\]  \hspace{1cm} (3.1)

The equation denotes that the rate of heat gained is determined by heat storage in the tissue, heat loss to adjacent tissue by convection and conduction, as well as heat exchange with the surrounding environment by evaporation, radiation, convection and conduction.

3.2.1. Tissue heat gain

Laser irradiation of skin tissue leads to energy deposition inside skin. As illustrated in Chapter 2, when laser beam irradiates a tissue, part of its energy is reflected from the surface. The rest of the energy penetrates into the tissue where it is either absorbed or scattered by the tissue. The absorbed photons contribute to energy deposition, the amount of which depends on laser wavelength and optical properties of the skin tissue. Therefore, heat generation rate per unit volume, when exposed to laser irradiation, is laser energy deposition \( S(r,t) \) [vii, xvii]:

\[
q(r,t) = S(r,t)
\]  \hspace{1cm} (3.2)

where \( q(r,t) \) [W/m\(^3\)] is heat generation rate per unit volume, and \( S(r,t) \) [W/m\(^3\)] is energy deposition per unit volume; \( r \) [m] is the spatial coordinate set. To obtain the rate of heat gain within a volume \( V \), the contribution of all tissue elements should be summed up:

\[
Q_{\text{gain}} = \int_V q(r,t) dV
\]  \hspace{1cm} (3.3)

\( Q_{\text{gain}} \) [W/m\(^3\)] is the total energy gained by laser irradiation within a certain tissue volume. Besides, heat energy can be obtained through heat transferred from adjacent tissue.

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Mechanism of heat transfer will be introduced in the following part.

3.2.2. Tissue heat transfer

Heat transfer occurs whenever there is temperature difference exists [vii, xvi]. The second law of thermodynamics states that the direction of the spontaneous heat flow is from regions of higher temperature to those of lower temperature [xviii]. The speed of heat transfer is determined by the amount of temperature difference between the regions. There are three modes of heat transfer: conduction, convection and radiation. The concepts and fundamental equations of these three modes will be introduced in detail.

Conduction

Direct physical contact is the prerequisite for heat conduction. It may happen in either a solid or fluid medium. In solids, conduction of heat is realized by both lattice vibration and the migration of free electrons. In stationary fluids, random translational and internal vibration of molecules leads to collisions heat conduction [vii]. Mathematically, heat conduction obeys Fourier law of heat conduction[vii, xviii], which states that the amount of thermal energy conducted through a medium, \( Q \) [J], is directly proportional to: \( A \) [m\(^2\)], the cross section area perpendicular to the heat conduction direction; \( (T_2 - T_1) \) [K], the temperature difference across the medium; and \( \Delta t \) [s], the time duration of heat conduction. \( Q \) is inversely proportional to \( \Delta L \) [m], the length across the medium through which heat is conducted. The equation is [vii]

\[
Q = -kA(T_2 - T_1)\Delta t / \Delta L
\]

(3.4)

where \( k \) [W/(m·K)] is thermal conductivity of the medium, expressed in units of energy per unit length, time and temperature difference.

The rate of heat conduction \( Q_c \) [W], through a certain volume with the surface envelope of area \( dA \) [m\(^2\)], should be an integral form of equation (3.4):

\[
Q_c = -\int_k kV T (r, t) \cdot n dA
\]

(3.5)

Where \( n \) is the unit vector normal to \( dA \). In the laser irradiation problem, conduction is the most important mechanism in analyzing transient temperature response to the laser irradiation. It can be easily coupled to the laser heat deposition term in the energy balance equation.

3.2.2.2 Convection

Convection is transfer of thermal energy due to bulk motion of the fluid [xix]. It plays a key role in heat transfer between a solid and a moving fluid. The heat flow \( f \) [W/m\(^2\)], between a solid and fluid is governed by Newton’s law of force [vii]:

\[
f = h(T_2 - T_1),
\]

(3.6)

where \( h \) [W/(m\(^2\)K)] is the convective heat transfer coefficient; \( T_1 \) [K] and \( T_2 \) [K] are the temperatures of the solid surface and bulk fluid, respectively, outside the boundary layer. A model of convection heat transfer in tissue \textit{in vivo} should consider blood perfusion rate. According to Fick’s principle, the amount of substance taken up by an organ per unit time is equal to the arterial level of the substance minus the venous level times
the rate of blood flow. Therefore, the heat transfer rate is formulated as:

\[ q_b = \rho_b c_b w_b (T_{\text{art}} - T_{\text{vein}}), \]  

(3.7)

where \( w_b \) [W/m\(^3\)] is the average volumetric blood perfusion rate, \( T_{\text{art}} \) [K] and \( T_{\text{vein}} \) [K] are the temperature of artery blood and venous blood, \( \rho_b \) [kg/m\(^3\)] and \( c_b \) [J/(kg·K)] are density and heat capacity of blood, respectively. Since we study laser tissue interaction \textit{in vitro}, convection issue is not included in our model.

**Radiation**

Radiation is defined as thermal energy transfer via electromagnetic wave action between non-contacting objects \textsuperscript{[vii]}. No medium is required for energy transport. Thermal emissivity is a function of radiation wavelength, surface temperature, and roughness. A black body is a perfect emitter radiating energy at any wavelength for a given emitter temperature. It is a perfect absorber with no reflection of thermal energy. According to Sten-Boltzmann law, the total emission energy of a blackbody, \( E \) [W/m\(^2\)], is \textsuperscript{[vii, xx]}

\[ E(T) = \sigma T^4 \]  

(3.8)

where \( \sigma = 5.67 \times 10^{-8} \text{[W/(m}^2\cdot\text{K}^4]} \) is the Stefan-Boltzmann constant; \( T \) [K] is the temperature of the blackbody. In circumstances of laser irradiation, this term will not be considered in the heat balance equation because the contribution from intrinsic radiative heat transfer processes is negligible.

**3.2.3. Thermal energy storage**

When heat generation and consumption process is not balanced, heat storage occurs inside tissue, which contributes to temperature rise. The total rate of stored thermal energy is \textsuperscript{[vii]}

\[ Q_{\text{storage}} = \int \rho c \left( \frac{\partial T(r,t)}{\partial t} \right) dV \]  

(3.9)

Where \( \rho \) [kg/m\(^3\)] is density of tissue, \( c \) [J/(kg·K)] is specific heat and \( T(r,t) \) [K] is temperature change at particular location and time. Therefore, temperature change rate is determined by heat storage and the intrinsic heat capacity of tissue.

**3.2.4. Bioheat transfer equation**

From heat balance equation, we deduce the bioheat transfer equation \textsuperscript{[vii, xiii, xv, xx]}

\[ \rho c \frac{\partial T(r,t)}{\partial t} = \nabla [k\nabla T(r,t)] + \rho c w_b [T_{\text{art}}(r,t) - T(r,t)] + S(r,t) \]  

(3.10)

For cylinder summery problems, the heat transfer equation has the form \textsuperscript{xiii, xv, xx]

\[ \rho c \frac{\partial T}{\partial t} = S + \frac{k}{r} \frac{\partial T}{\partial r} + \frac{1}{r} \frac{\partial}{\partial r} \left( k \frac{\partial T}{\partial r} \right) + \frac{\partial}{\partial z} \left( k \frac{\partial T}{\partial z} \right) \]  

(3.11)

Where \( T \) [K] is the temperature at specific heat and time, \( S \) [J] is the laser irradiation...
energy, \( \rho \text{[kg/m}^3\text{]} \) is the density, \( c \text{[J/(kg·K)]} \) is the specific heat, and \( k \text{[W/(m·K)]} \) is the thermal conductivity.

The bio-heat transfer equation should be solved based on boundary conditions. There are initial boundary condition and appropriate boundary condition [vii.]. The former specifies temperature throughout the tissue at the initial time, while the latter mainly contains two forms [vii, xxiv]:

- Prescribed temperature. The surface temperature of a boundary is specified to be constant or a function of coordinate or time. It is an example of Dirichlet boundary condition.
- Prescribed heat exchange. The rate of heat flux across a boundary is specified to be constant or a function of a boundary coordinate or time. It is an example of a Neumann boundary condition.

The solution of the bio-heat equation gives dynamic temperature of the tissue.

### 3.2.5. Tissue thermal properties

Tissue transfer process is decided by the thermal properties of tissue. There are some techniques to measure thermal properties. For example, constant-temperature heating technique firstly measures the baseline tissue temperature, and then a variable voltage is controlled by feedback circuit to maintain the average thermistor temperature at a predefined constant. Then thermal properties were calculated from their relationship with thermistor power.

It is also believe that thermal properties of skin tissue depend strongly on the amount of water content in the tissue [vii, xv]. It is considered that the specific heat \( c \text{[J/(kg·K)]} \), thermal conductivity \( k \text{[W/(m·K)]} \), and density \( \rho \text{[kg/m}^3\text{]} \) vary linearly with water content according to the following relationships xv:

\[
\rho = (1.3 - 0.3w) \times 10^3 \\
C = (1.55 + 2800 \frac{w}{\rho}) \times 10^3 \\
k = 0.06 + 570 \frac{w}{\rho}
\]

where \( w \) is the water content. Water content of 80% in dermis and 30% in epidermis is assumed. Due to time and experimental limit, we utilize thermal properties based on empirical data as well as formulas presented above. Thermal properties also vary with temperature. Since there is no significant change within 100°C, we consider the coefficients to be constant in our simulation.

### 3.2.6. Summary

In this chapter, thermal transfer theory in skin tissue is illustrated. The heat transfer equation is deduced from laws of thermodynamic and three mechanism of heat transfer: conduction, convection and radiation are introduced. In addition, bio-heat transfer equation is formulated and methods to derive thermal properties of skin tissue are illustrated. After preparation theories of skin optics and thermal response of skin, we will discuss
the numerical modeling of laser-skin interaction in detail.
4. Numerical modeling and Simulation

4.1. Introduction

In study of laser treatment, for the purpose of choosing the treatment parameters properly and correctly predicting the outcome of the photothermal effect, a reliable numerical model is needed. As illustrated in previous chapters, both energy deposition by laser irradiation and heat transfer in skin affect dynamic temperature change. Therefore, both heat generation and heat diffusion process should be taken into consideration in the model. People have tried several methods for constructing a well-designed model [xiii, xv, xvii, xxi]. Gamborg et al used a CCD camera to measure energy storage, and analyzed the following heat transfer using FEMLAB [xxi]. J. J. Crochet et al applied Monte Carlo method to simulate heat generation in skin, while using finite difference method for heat diffusion process [xvii].

A new model combining Monte Carlo simulation with COMSOL modeling is presented here. The principle is the same: to use absorbed energy in tissue as the heat source to fit into heat transfer equation for calculating heat diffusion process. Monte Carlo method can effectively simulate absorption and scattering distribution of photon in skin tissue, thus provide spatial distribution of energy generation. COMSOL software, on the other hand, serves as a fast and accurate tool for finite element analysis.

In this chapter, the construction of the model will be represented in detail, followed by research on three topics through simulations based on the model.

4.2. Skin model

A good skin model, when combined with well designed mathematical model, makes up a reliable numerical model. For reasonable simplification, we consider human skin as a layered structure, with each layer to be homogeneous medium. The structure and property of the model should be defined according to our in vitro experiments.

4.3. Model Structure

The skin sample model is assumed to be 1.2mm in thickness and 2mm in diameter. We consider the skin to be a two-layered structure with epidermis layer and dermis layer. The epidermis layer is considered to be 0.05mm thick while the dermis layer is 1.15mm thick. Figure4.3 shows a 2D axis-symmetric model and a 3D model derived from the 2D model.

4.3.1. Optical parameters

Optical parameters used in the skin model in this project are listed in Table4.1. These data are obtained from literature [vii, xii] and are further validated by calculation as stated in section 2.3.

<table>
<thead>
<tr>
<th>(\lambda) [nm]</th>
<th>(\mu_a) [cm(^{-1})]</th>
<th>(\mu_s) [cm(^{-1})]</th>
<th>g</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>532</td>
<td>1.28</td>
<td>322.57</td>
<td>0.9</td>
<td>1.38</td>
</tr>
</tbody>
</table>
4.3.2. Thermal parameters

Thermal parameters used in the skin model are listed in Table 4.2. Similar to optical parameters, these data are derived from literature [vii, xv, xvii] and are further validated by calculation as stated in section 3.4.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Density [kg/m³]</th>
<th>Thermal conductivity [W/(m*K)]</th>
<th>Specific heat [J/(kg*K)]</th>
<th>Initial temperature [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>epidermis</td>
<td>1200</td>
<td>0.24</td>
<td>3590</td>
<td>37</td>
</tr>
<tr>
<td>dermis</td>
<td>1200</td>
<td>0.45</td>
<td>3300</td>
<td>37</td>
</tr>
</tbody>
</table>

4.4. Mathematical Model

Monte Carlo simulation was used to acquire information of heat generation in tissue, and finite element method was applied for calculating heat diffusion during and after laser irradiation.

4.4.1. Model construction

Figure 4.1 shows architecture of the model. The model is composed of three parts: Monte Carlo Simulation, MATLAB data processing and COMSOL modeling.
Monte Carlo Simulation gives the number of photons absorbed in each location, and the result is exported to MATLAB data processing part, where the heat generation rate is calculated, and serves as the heat source in COMSOL model. The solution of heat transfer function in COMSOL gives the dynamic temperature distribution in skin tissue. In the following, each part of the model will be introduced in detail.

4.4.2. Monte Carlo (MC) Simulation

MC method used here is performed in Linux System. Input is defined in .csv format file and calculation command is sent to the calculation center. The result is imported to MATLAB for further processing.

MC Input

There are two kinds of input for MC simulation. One is optical parameters, including absorption coefficient $\mu_a$, scattering coefficient $\mu_s$, anisotropy coefficient $g$, and refractive index $n$. The parameters we used in the MC simulation are presented in Table 4.1. Another input defines experimental conditions. For example, the sample size, laser parameter, and the number of photon launched. Table 4.3 shows an example of inputs of the second category.
Table 4.3 example of Input of experimental conditions

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>976 nm</td>
<td>2000</td>
<td>2000</td>
<td>1200</td>
<td>Top-hat</td>
<td>2</td>
<td>1</td>
<td>10⁶</td>
</tr>
</tbody>
</table>

MC Output
MC simulation considers the skin tissue to be divided into 51×50×50 voxels (Figure 4.2). The reason to choose 51 as the number of bins on x axis is that the central slice can be easily extracted in the later MATLAB data processing part (section 4.3.3). Accordingly, the output of MC simulation is a 51×50×50 matrix, with each element representing number of photons absorbed inside each voxel.

Figure 4.2 voxels in MC simulation

4.4.3. MATLAB data processing
In MATLAB data processing part, output of MC simulation is transformed into heat generation rate to fit the bio-heat equation in COMSOL modeling.

The following equation is used [xvii]:

\[ q = P_{abs} \times P_{laser} = \frac{N_{local}}{N_{total}} \times P_{laser} \]  

(4.1)

Where \( q \) [W/m³] is a matrix representing heat generation rate in each location; \( P_{abs} \) is photon absorption probability; \( P_{laser} \) [W] is laser power; \( N_{local} \) is the absorbed photon number in each location, obtained by MC simulation; \( N_{total} \) is launched total number of photons, predefined in MC simulation. After \( q \) is obtained, data from a slice in the volume is extracted to fit the 2D geometry in COMSOL (Figure 4.3 (a)).

4.4.4. COMSOL Modeling
In COMSOL Modeling part, a cylinder geometry model should firstly be built up to fit the size of the model in previous two parts. Then physical properties and boundary conditions should be defined, and data from MATLAB data processing part are imported as the heat source item.
Geometry of the model
In COMSOL, a 2D axis-symmetric model (Figure 4.3(a)) is built up for fast calculation speed. Then using extrusion coupling variables and rotation, a 3D model of cylindrical shape is built up (Figure 4.3(b)).

(a) (b)
Figure 4.3 (a) 2D geometry axis-symmetric model (b) 3D model generated by rotating 2D model

Heat Transfer Equation
Heat transfer equation used here in heat conduction calculation in COMSOL is [\text{\ref{eq:heat_equation}}]:

\[ \delta_n \rho C_p \frac{\partial T}{\partial t} - \nabla \cdot (k \nabla T) = Q \]  

(4.2)

Where \( \delta_n \) is time scaling coefficient, \( \rho \) [kg/m\(^3\)] is the density, \( C_p \) [J/(kg\cdot K)] is the specific heat, \( Q \) [W/m\(^3\)] is the heat source, and \( k \) [W/(m\cdot K)] is the thermal conductivity.

COMSOL Input and Output
There are three kinds of input information:
1. Heat generation rate in each voxel as heat source item.
2. Skin thermal properties, as presented before.
3. Boundary conditions, including initial temperature, and boundary temperature conditions, such as constant temperature value or heat flux between boundaries and external environment.

Output of COMSOL modeling is real time temperature of skin tissue. Plots of temperature change with time and temperature distribution can provide information in an intuitive way.
4.5. Research based on the Model

Three topics of study were carried out based on the model constructed:
1. Simulation of heating and cooling by water bath
2. Study of Laser irradiation on skin under room condition
3. Research on laser irradiation with cooling methods applied

In the following we will introduce these three studies in detail.

4.5.1. Heating and cooling by water bath

Simulation carried out in this study is to provide guidance for actual experiments. As required by the experiment, the initial temperature of skin sample is 37°C. It is heated up to a desired temperature by water bath, kept at the temperature for 2-3 seconds, and then cool down to 37°C. The desired temperatures are 45°C and 60°C.

Methods
Simulation method in this study is to firstly build up a model in COMSOL as illustrated previously. For simplicity, boundary condition of skin model is set as constant temperature of 45°C and 60°C.

Target
Since the target of the simulation is to acquire time information of situation heat diffusion process, so that we can have better control of time in actual experiment, there are two classes of information we need:
1) Dynamic temperature change within the skin sample. We obtain the information of how long the sample takes to wholly achieve the desired temperature and fall down to the original temperature.
2) After the center of the tissue arrives at the desired temperature, how long has other part of the sample stayed at the particular temperature. It can be seems as “time districts”, which actually provides very direct viewing of temperature distribution in the sample.

Results
Figure 4.4 shows a central slice in the sample and several important points that were chose to show the results.

Figure 4.4 a central slice in the sample
Temperature change with time
Dynamic temperature changes of 5 points along the center line OB are plotted in Figure 4.5. In addition, Table 4.3 shows how long the sample takes to wholly achieve the desired temperature. Center point O is chosen for judgment since it takes the longest time to reach the final temperature. From the results, we get the following information:

- Temperature rising speed is fast in the beginning, and it gets slower gradually. It makes sense because the larger temperature difference, the faster heat conduction occurs.
- The point more approaches the surface of the sample has faster temperature changing speed.
- To keep the sample at 45°C and 60°C for 2 seconds respectively, we should immerse the sample in 45°C water bath for 8 seconds and 60°C water bath for 9 seconds, respectively.

Figure 4.5 water bath heating and cooling (a) temperature change of 5 points along depth for 45°C (b) temperature change of 5 points long depth for 60°C
### Table 4.3 Time to arrive at desired temperature for water bath heating and cooling

<table>
<thead>
<tr>
<th>Desired Temperature [°C]</th>
<th>Threshold [°C]</th>
<th>Time to final temperature [s]</th>
<th>Time to begin cooling [s]</th>
<th>Time to arrive at 37 °C [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>0.2</td>
<td>6</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>60</td>
<td>0.2</td>
<td>7</td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>

Time districts

Figure 4.6 shows information about time districts in this figure. We can acquire two aspects of information from these figures.

- After the center has stayed at 45°C for 2 seconds, the surface has stayed at 45°C for 8 seconds; while for 60°C, when the center reached 60°C for 2 seconds, the outmost part has kept at 60°C for 9 seconds.

- There are more time districts in 45°C case than in 60°C case, which implies that the heat transfer is faster in latter case. This makes sense because the speed of heat transfer is determined by two factors: temperature difference and thermal property of the material. With the similar material, the larger the initial temperature difference, the faster heat transfer can be achieved.
4.5.2. Laser irradiation study

The main target of this study is to give guidance for the laser irradiation experiment by choosing the best method and parameters. Requirement of the study is the same with water bath heating and cooling: to heat up the skin tissue to 45°C and 60°C, trying to keep the temperature for 2 to 3 seconds. There are three aspects to investigate in this study:

1) Compare different simulation methods
2) Choose suitable laser parameters
3) Find out laser irradiation time to heat up the sample to desired temperature and study suitable cooling method.

Compare simulation models

Two models are used in this study. The first model is the one we introduced in this chapter. It combines Monte Carlo simulation with COMSOL modeling. The second model is to assume weakly scattering in the skin so that scattering can be neglected, and use Beer’s law to describe light propagation.

1) Model 1
Model 1 utilizes Monte Carlo Simulation combined with COMSOL. Firstly to use MC to simulate photon absorption, and then apply MATLAB to calculate heat generation, which serves as heat source in COMSOL, which provides heat diffusion process and gives dynamic temperature of the skin tissue.
2) Model 2

Model 2 is only constructed in COMSOL. As introduced in Chapter 2, photon energy distribution in tissue under collimated laser beam irradiation can be described by Beer’s Law. Heat is converted from local absorption of photon energy. The localized heat source \( S \) \([W/cm^3]\) at position \((r, z)\) and time \(t\) is proportional to absorption coefficient \(\mu_a(z)\) \([1/m]\) and local fluence rate \(\Phi(r, z, t)\) \([W/m^2]\) in tissue [vii,xvii,xv].

\[
S(r, z, t) = \mu_a(1-r_s)v(r, t)\exp(-\mu_a z)
\]

Where \(E(r, t)\) \([W/m^2]\) is irradiance and \(r_s\) is specular reflectance on the skin surface. Top-hat distributed irradiance was used in the model to approximate the laser profile [xxx].

\[
E(r, t) = \frac{P}{\pi\omega^2}
\]

Where \(P\) \([W]\) is the radiant power and \(\omega\) \([m]\) is radius of the laser beam.

3) Model parameters

To compare these two models, the same parameters are used. 976nm, 1W laser with fiber diameter of 2mm are assumed to be laser diameters. The specular reflectance \(r_s\) is considered to be 4.75%, according to measurement of in-vitro mini-pig skin at the air/epidermis interface by a spectrophotometer [xii]. Skin optical parameters and thermal parameters in Table 4.1 and Table 4.2 are used in both models.

4) Results

Figure 4.7 shows the temperature increase of 7 points along line AB (Figure 4.4). We can see that there are two differences between these two models.

- Temperature difference between different points along depth at a certain time in model 1 is much larger than that of model 2.
- Temperature changing is faster in Model 1 than in Model 2.

The result makes sense because Model 2 is an ideal model without considering reflection and scattering of light. Since light distribution in this case is considered to be distributed according to Beer’s law, much of the photon that is actually scattered inside and reflected from the boundaries are considered to be lost. That explains why the heating speed of Model 2 is much slower than model 1. To acquire more realistic results, model 1 should be used in our simulation.
Figure 4.7 compare temperature change of points long central axes with two models (a) temperature of 7 points along depth for model 1 (b) temperature of 7 points along depth for model 2

Table 4.4 Time to achieve desired temperature for Model 1 and Model 2

<table>
<thead>
<tr>
<th>Model</th>
<th>Time to reach 45°C [s]</th>
<th>Time to reach 60°C [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.4</td>
<td>6.2</td>
</tr>
<tr>
<td>2</td>
<td>2.6</td>
<td>7.7</td>
</tr>
</tbody>
</table>
Compare lasers
Based on the model, we should decide which laser should be applied for actual experiment. There are lasers of 4 different wavelengths available in our lab. Other laser parameters are assumed to be the same. Figure 4.8 shows temperature change of different lasers, based on simulations.
There are two criterions for us to judge which laser is our best choice.

1. Since we require homogeneous heating, the temperature difference over depth should be as less as possible.

2. The laser we choose should have appropriate heating efficiency to arrive at our required temperature. On one hand, the heating time should be long enough for us to control; on the other hand, the time should not be too long so that certain efficiency can be achieved.

Due to these two criterions, we can see that both (a) and (c) do not meet the first criteria; (b) and (d) shows homogeneous heating with appropriate heating time, but (b) is more efficient than (d). Therefore, after careful comparison, 976nm laser is the final choice.
**Choose laser parameters**

After choosing the laser wavelength, laser parameters, such as beam diameter and power, are left to determine. Figure 4.9 shows 976nm laser with different beam diameters and powers.

**Figure 4.9** 976nm laser with different laser diameters and powers: (a) 4mm, 1W; (b)
4mm, 2W; (c) 2mm, 1W

Concerning the two criterions listed in section 4.4.2, we can tell that (b) and (c) does not meet criteria1. It is reasonable because both (b) and (c) provide higher fluence rate \( \Phi \) [W/m\(^2\)] at skin surface so that more photon is absorbed at each depth in tissue, leading to higher temperature difference. It is obvious that (a) is the best choice.

4.6. Summary

In this chapter, a numerical model combining Monte Carlo Simulation and finite element analysis in COMSOL is introduced. Based on the model, series of simulations were performed around two topics, study of heating and cooling by water bath, and prepare for further in vitro experiments, by comparing model and choose laser parameters. All these studies provide information from two aspects: 1) predicting temperature change of skin sample in real time, so that enable us to have better time control of actual experiments; 2) prepares for necessary conditions for achieving desired results in actual experiments. The model provides an innovative structure and should be further improved during actual experiment, which will be illustrated in the next chapter.
5. Temperature measurement and model validation

5.1. Introduction

The essential step after modeling and simulation is to perform temperature measurement of skin under laser irradiation to validate the model. Firstly, a set up was built up for laser irradiation and temperature measurement. Secondly, experiments are performed, providing dynamic temperature of skin tissue under laser irradiation. Two temperature measurement techniques are used: thermometer and infrared imaging. In this chapter, temperature measurement techniques will be introduced and structure of the whole set up for experiments will be introduced in detail. In the end, the result of experiments will be analyzed and compared with simulated results.

5.2. Temperature measurement techniques

Temperature is measured by two methods in our experiment by using both thermocouple and infrared camera. The physical principle of these two techniques will be introduced in the following.

5.2.1. Thermocouples

A Thermocouple is made by spot welding two different metal wires together. Probe can be constructed in varies shapes, including round tips, conical needles, and hypodermic needles. The principle of thermocouple is based on Seebeck effect.

**Thermocouple physics**

Seebeck effect occurs when thermal-to-electrical energy conversion happens. On one hand, if the wires form a loop, and the junctions are at different temperatures, a current will flow in the loop. On the other hand, if a loop is broken and the junctions are at different temperatures, then a voltage will develop between the junctions. The current $I$ in the first case and voltage $V$ in the second case are linearly proportional to the temperature difference, if the temperature difference is small.

![Thermocouple structure](Figure 5.1)

Figure 5.1 shows the inner construction of thermocouple. We suppose $N$ is the digital sample derived from the A/D convertor for the unknown tissue temperature, $T$. Extremes of the temperature range ($T_{\text{min}}$ and $T_{\text{max}}$) are used as the reference temperature. $N_{\text{min}}$ and $N_{\text{max}}$ are digital samples at $T_{\text{min}}$ and $T_{\text{max}}$, respectively. Then the following equation calculates the unknown tissue temperature:
temperature from measured digital sample:

\[ T = T_{\min} + (N - N_{\min}) \frac{T_{\max} - T_{\min}}{N_{\max} - N_{\min}} \]  

(5.1)

This equation is based on assumption of linear response. Therefore, it is only suitable for temperature range less than 25°C. For larger temperature range, a quadratic equation should be used:

\[ T = H_0 + H_1N + H_2N^2 \]  

(5.2)

where \( H_0, H_1 \) and \( H_2 \) are determined by calibration of the instrument over the range of interest.

**Thermocouple characteristics and error analysis**

Thermocouples are characterized by: 1) low impedance 2) low temperature sensitivity 3) low power dissipation 4) fast response 5) high stability 6) Interchangeability.

There are mainly several factors which may lead to measurement errors based on thermocouple:

1. **Electrical leakage to the tissue**
   Bare sensors show significant electrode-electrolyte chemical interactions when placed in wet tissue. In addition, it picks up electro-physiologic artifact and 60Hz noise from the tissue. Therefore, coating is critical to ensure a high electrical resistivity and a high thermal conductivity. Selecting a thermocouple with good coating material is fairly important.

2. **Time response**
   In our experiment, transducer maybe either placed in a perfect heat sink (e.g. the probe is directly heated by laser), or be inserted in tissue. In the former case, time response is only determined by the size and thermal properties of the transducer probe, while for the latter, time response is also affected by the thermal properties of the tissue. It is demonstrated that [vii] for a conduction-dominated situation, which is the latter case, the time constant is mostly dependent on probe size, slightly dependent on tissue thermal properties, and nearly independent of the thermal properties of the probe. In this sense, the smaller probe radius, the faster time response we obtain.

3. **Spatial tissue temperature gradient**
   Laser heating in our experiments creates large tissue temperature gradients. The presence of probe with the stainless steel shafts affects the tissue temperature field greatly, due to the mismatch between probe/tissue thermal conductivity. To minimize the error, a shaft with thermal properties similar to tissue should be applied.

4. **Surface measurement errors**
   Laser energy may directly heat thermocouples if it is put under the laser irradiation. Figure plots the temperature measured by a thermocouple under directly laser irradiation. Due to large size of the probe in our case, there are great effects of temperature increase by energy absorption of probe. Therefore, in our experiment, direct shining of laser light on the probe should be avoided.

Based on the analysis above, when the size of thermocouple probe is small compared with sample size, and when it is used correctly, thermocouple has fast response, high repeatability and high accuracy.

**5.2.2. Infrared temperature measurement**

Compared with measuring temperature by thermocouple, thermographic imaging offers a non-
contact method of estimating surface temperature with high spatial resolution. Thermal cameras measures irradiated surface energy in infrared band, which is then used to estimate surface temperature.

**Physical principle**
Thermal infrared emission is caused by the acceleration of charge. The measured signal in thermal imaging comes from photons emitted by the object due to the relaxation of thermally excited atoms and molecules. The two most common imaging bands for measuring emitted infrared energy are 3-5μm and 8-12μm.

![Figure 5.2 Band-limited emissive power for the two common imaging bands in W/m².](image)

Figure 5.2 shows blackbody power distribution between two bands as a function of temperature. The function relationship can be expressed as fifth-order polynomial fits the two curves in the figure:
For 3-5μm band:

\[ E_3 = 1.987 \times 10^{-2} T + 1.1817 \times 10^{-3} T^2 + 9.232 \times 10^{-6} T^3 + 1.3709 \times 10^{-7} T^4 + 1.071 \times 10^{-10} T^5 \]
For 8-12μm band:

\[
E_b = 74.296 + 1.4603T + 8.933 \times 10^{-3}T^2 + 1.4858 \times 10^{-5}T^3 - 7.0592 \times 10^{-8}T^4 + 9.286 \times 10^{-11}T^5
\]

(5.4)

We can see that 8 to 12μm band generally has more signal over 3-5μm band, while noise figure is higher as well, thus the signal to noise ratio over these two bands are about the same.

The surface temperature field, \(T(x,y)\) [K], is subsequently inferred from measurements of surface radiosity, \(J(x,y)[W/m^2]\), which consists of reflected, emitted, and perhaps transmitted flux. According to Kirchhoff’s radiation law, for an incident flux, the sum of the absorbed, reflected and transmitted fractions must be 1:

\[
\alpha + \rho + \tau = 1
\]

(5.5)

Where \(\alpha\) is absorptivity, \(\beta\) is reflectivity and \(\tau\) is transmissivity. It is proved that emissivity \(\varepsilon\) is equal to \(\alpha\) [vii].

The reflected and transmitted portion should be removed during the calibration step. For an opaque surface, \(E_b\), the emitted flux \(f\) [W/m²] or an equivalent blackbody, can be estimated from \(J_m\) by

\[
E_b(T) = \frac{J_m(T, T_w, \varepsilon) - (1 - \varepsilon)E_b(T_w)}{\varepsilon}
\]

(5.6)

Where \(J_m\) is measured radiosity (thermal camera result).

**Errors in thermal imaging method**

For the usual laser irradiation situations, where the enclosure is cooler than tissue temperatures, all the errors in thermal imaging contribute to and under-estimation of the true surface emitted flux component, thus lead to an under-estimation of surface temperature. The possible factors that cause errors are: 1) optical pathway attenuation caused by lens and mirrors; 2) thermal gradients along the optical axis; 3) limited temperature resolution of the image. Compared with thermocouple measurement presented before, non-contact thermal imaging offers better spatial sampling of surface temperature distributions, which can be used to directly verify models of laser tissue interactions.

### 5.3. Materials

#### 5.3.1. Skin tissue

1. 4 cm×1cm×1mm skin sample
2. 3cm×2 cm×1mm skin sample
3. 2mm diameter and 1mm thickness skin sample

#### 5.3.2. Reagents

2. DMEM (Dulbecco’s Modified Eagle Medium)
5.3.3. Equipment

(1) Laser×1: SP-976 laser diode (SHEAU MANN, USA)
(2) Laser driver×1: VUE-MV (VUE METRIX)
(3) Laser cooler×1: Laser 2000 (BENELUX CV)
(4) Detector card ×1 (THORLABS)
(5) Microscope objective×1: OFR, LMH-20X-YAG
(6) Laser holder×1
(7) Teflon plate×1
(8) Translational stage×2
(9) Power meter×1: broadband power/energy meter (Melles Griot)
(10) Thermometer×1: K202 Data logger (VOLT CRAFT)
(11) PC×1 (LG)
(12) Culture dish×4
(13) RVS×1
(14) Infrared Camera×1
(15) Heating instrument×1 (IKAMAG REC-G)

5.3.4. Software

(1) Laser driver software (WinVUE-MV)
(2) thermometer software
(3) ThermaCAM Researcher 2000

5.4. Experiment Preparation

Before performing ex vivo experiment, preparations should be made. Laser irradiation system should be built up and adjusted to meet experiment conditions. Adjustment of the system includes modify laser beam size, measure beam profile, and calibrate laser power.

5.4.1. Build up Laser system

Building up a laser irradiation system is the first step of performing the ex vivo experiments. Figure 5.2 shows the construction of the system. The laser is connected to PC through a laser driver, and the software installed on PC provides powerful controlling functions. Moreover, the laser is attached on the cooling system with a thermal insulation layer in between. Power meter is used to calibrate the power on the surface of skin sample before experiments. Laser light shines on the skin sample, and dynamic temperature is measured by using thermocouple or infrared camera. Software of the thermometer is installed on PC to analyze the result.
5.4.2. Modify Laser beam

According to simulations performed prior to *ex vivo* experiments, laser parameters are predetermined as listed in Table 5.1. Therefore, an optical system should be designed to modify laser beam profile as required.

**Theoretical calculation**

The multimode laser fiber used in this experiment has numerical aperture \( \theta = 0.22 \) and diameter of 105µm. After the beam is expanded by a microscope objective with focal length \( f = 10 \text{mm} \), a laser spot of \( \Theta = 4.4 \text{mm} \) with top-hat intensity distribution will be generated. The sketch shown on Figure 5.3 presents the light path in the optical system. Table 1 compares different parameters of laser fiber and collimated laser beam.

![Figure 5.3 A simplified sketch of the optical system](image)

L = Collimating Lens \( \theta = \) Divergence Angle of LED
LD = Laser Diode \( \Theta = \) Diameter of Collimated Beam

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber Diameter</td>
<td>105µm</td>
</tr>
<tr>
<td>Fiber NA</td>
<td>0.22</td>
</tr>
<tr>
<td>Laser Spot Size</td>
<td>4.4mm</td>
</tr>
<tr>
<td>Beam Expander Focal Length</td>
<td>10mm</td>
</tr>
</tbody>
</table>

---

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The calculation is performed as in the following:

\[ y = \theta \cdot f = 0.22 \times 10 = 2.2(\text{mm}) \]

\[ \varnothing = 2y = 4.4(\text{mm}) \]

### Table 5.1 Laser parameter comparison between original and collimated laser beam

<table>
<thead>
<tr>
<th>Parameter laser</th>
<th>Laser wavelength [nm]</th>
<th>Source profile</th>
<th>Beam radius [mm]</th>
<th>Numerical aperture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser before modification</td>
<td>976</td>
<td>Top-hat</td>
<td>0.105</td>
<td>0.22</td>
</tr>
<tr>
<td>Laser after modification</td>
<td>976</td>
<td>Top-hat</td>
<td>2.2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Beam profile measurement**

The intensity distribution of laser beam is measured by traversing the spot with translational stage over a fixed power meter. The sensor of the power meter is covered by a 200μm pinhole. Measurement is performed every 0.5mm over two dimensions. Figure 5.4 and Table 5.2 shows a uniform spot intensity.
**Figure 5.4** Power distribution over two dimensions (a) the measured power distribution over x-dimension; (b) the measured power distribution over y-dimension.

<table>
<thead>
<tr>
<th>Position1 [mm]</th>
<th>0</th>
<th>0.4</th>
<th>0.8</th>
<th>1.2</th>
<th>1.6</th>
<th>2.0</th>
<th>2.4</th>
<th>2.8</th>
<th>3.2</th>
<th>3.6</th>
<th>4</th>
<th>4.4</th>
<th>4.8</th>
<th>5.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power [mW]</td>
<td>0.1</td>
<td>0.6</td>
<td>3.6</td>
<td>4.5</td>
<td>4.7</td>
<td>4.4</td>
<td>4.6</td>
<td>4.8</td>
<td>4.3</td>
<td>4.5</td>
<td>4.2</td>
<td>3.3</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Position2 [mm]</td>
<td>0</td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
<td>1.6</td>
<td>2.0</td>
<td>2.4</td>
<td>2.8</td>
<td>3.2</td>
<td>3.6</td>
<td>4</td>
<td>4.4</td>
<td>4.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Power [mW]</td>
<td>0.1</td>
<td>0.7</td>
<td>2.2</td>
<td>5.1</td>
<td>4.5</td>
<td>4.8</td>
<td>5.2</td>
<td>4.4</td>
<td>5.3</td>
<td>4.6</td>
<td>4.8</td>
<td>2.8</td>
<td>0.6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

### 5.4.3. Power calibration

To better control the laser power irradiated on skin sample by adjusting laser current, calibration of laser should be carried out to find out functional relationship between the current applied on laser and emitted power. Power meter is used in calibration. From Figure 5.5 we can see that power varies almost linearly with changing current. To obtain irradiated power of 1W on skin surface, as designed in simulation, we need to use electrical current of 1.82A.
5.5. Methods

Based on the well-designed laser system, series of experiments was conducted ex vivo to validate the model. Each experiment follows a similar procedure. In the following, the procedure will be described in detail.

5.5.1. Preparation of skin specimen

According to the error analysis of thermocouple given in section 5.2, skin sample with diameter of 2mm and thickness of 1.2mm is not suitable for validating the model, due to the comparatively large size of thermocouple probe. To ensure the accuracy of measurement, we choose 4cm×1cm×1mm skin sample and 3cm×2cm×6mm skin sample in experiments. Samples are kept in culture medium and are frozen in -80°C fridge. They are picked out and thaw in room temperature water bath 1 hour before experiment.

Table 5.3 Data corresponding to Figure5.5

<table>
<thead>
<tr>
<th>Current [A]</th>
<th>0</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power [W]</td>
<td>0</td>
<td>0.05</td>
<td>0.12</td>
<td>0.18</td>
<td>0.25</td>
<td>0.32</td>
<td>0.39</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Current [A]</td>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.82</td>
</tr>
<tr>
<td>Power [W]</td>
<td>0.52</td>
<td>0.58</td>
<td>0.65</td>
<td>0.71</td>
<td>0.78</td>
<td>0.84</td>
<td>0.92</td>
<td>0.99</td>
<td>1</td>
</tr>
</tbody>
</table>
### 5.5.2. Laser irradiation experiment

1) Lay the skin sample on top of a Teflon plate, trying to keep the sample as neat as possible.
2) Set a small value of current, e.g. 0.5A, on the laser control software shown in Figure 5.6. Shine the laser from 10cm above the sample. Using the special material card, adjust the laser spot to be located approximate in the center of the sample. Turn off the laser.
3) In thermometer measurement, fix the thermometer probe at a particular site on the sample. The location of the probe is pre-designed before the experiment. In infrared camera measurement, the camera should be adjusted to the same height with the sample to get a side view. At the same time, the laser spot should also be adjusted to shine at the edge of the sample. Focus the sample image in the infrared camera.
4) In thermometer measurement, turn on the thermocouple software (Figure 5.8), and start to record the real time temperature.
5) Adjust the laser current to be 1.82A, ensuring that the power at the surface of skin is 1W.
6) In thermocouple measurement, detect real-time temperature change, and turn off the laser after a certain period of time. In infrared camera measurement, start automatic photographing. It takes 1 photo per 5 seconds.
7) Acquire the data from the thermometer software or images from the infrared camera for further analysis. Freeze the sample in the fridge and clear the table.

**Figure 5.6 Laser control software**

Annotations:
- P=V×I is the power applied on laser;
- Power calibration is to ensure that power shining on the sample is 1W.
Figure 5.7 Thermocouple software

Figure 5.8 Thermal camera software
5.5.3. **Perform simulations and analyze the results**

According to the sample size in experiments, build up 4cm×1cm×1mm and 3cm×2cm×6mm 3D models (Figure 5.9). Input parameters in the models are listed in Table 5.4-Table 5.6.

![Figure 5.9 Model of (a) 4cm×1cm×1mm skin sample and (b) 3cm×2cm×6mm skin sample](image)

**Table 5.4** Skin optical properties used in Monte Carlo simulation [xii]

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>layers</th>
<th>Absorption coefficient $\mu_a$ [1/cm]</th>
<th>Scattering coefficient $\mu_s$ [1/cm]</th>
<th>Refractive index $n$</th>
<th>Anisotropy $g$</th>
</tr>
</thead>
<tbody>
<tr>
<td>976nm</td>
<td>dermis</td>
<td>0.38</td>
<td>174</td>
<td>0.9</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>sub-dermis</td>
<td>1.05</td>
<td>97</td>
<td>0.9</td>
<td>1.38</td>
</tr>
</tbody>
</table>

**Table 5.5** Laser beam parameters used in MC simulation and MATLAB

<table>
<thead>
<tr>
<th>Laser wavelength [nm]</th>
<th>Power reach the surface [W]</th>
<th>Source type</th>
<th>Beam radius [mm]</th>
<th>Number of photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>976</td>
<td>1</td>
<td>Top-hat</td>
<td>2</td>
<td>106</td>
</tr>
</tbody>
</table>
Table 5.6 Skin thermal properties and boundary settings in COMSOL [xv]

<table>
<thead>
<tr>
<th>Model</th>
<th>epidermis</th>
<th>dermis</th>
</tr>
</thead>
<tbody>
<tr>
<td>4cm×1cm×1mm model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermal conductivity</td>
<td>0.24</td>
<td>0.45</td>
</tr>
<tr>
<td>[W/(m²*K)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Density</td>
<td>1200</td>
<td>1200</td>
</tr>
<tr>
<td>[kg/(m³)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat capacity</td>
<td>3590</td>
<td>3300</td>
</tr>
<tr>
<td>[J/(kg*K)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness</td>
<td>0.05</td>
<td>0.95</td>
</tr>
<tr>
<td>[mm]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>dermis</th>
<th>sub-dermis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3cm×2cm×6mm model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermal conductivity</td>
<td>0.45</td>
<td>0.15</td>
</tr>
<tr>
<td>[W/(m²*K)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Density</td>
<td>1200</td>
<td>1000</td>
</tr>
<tr>
<td>[kg/(m³)]</td>
<td></td>
<td></td>
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<tr>
<td>Heat capacity</td>
<td>3300</td>
<td>2675</td>
</tr>
<tr>
<td>[J/(kg*K)]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>Bottom surface</th>
<th>Other surfaces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boundary setting for both models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>heat transfer coefficient</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>[W/(m²*K)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>External Temperature(C)</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Data analysis is mainly carried out by using software. Results in COMSOL can be easily handled to make different plots; Data from thermal imaging can be read and extracted by ThermaCAM Researcher; Temperature data measured by thermocouple is also stored in corresponding software. Generally, data derived from all the three methods can be imported into MATLAB and be compared.

5.6. Results and Analysis

5.6.1. 4cm×1cm×1mm model

Temperature profile at the center of bottom

Firstly, simulation is performed to find out how long the center of the bottom takes to reach our desired temperature 45°C and 60°C (Figure 5.10). Laser is shut off after the sample reaches 60°C. Basic simulation conditions are listed in the Table 5.7. The dynamic temperature data derived from both methods are plotted and compared in Figure 5.11 and Table 5.8, and difference between the two data sets is calculated using the following formula:

\[
d = \frac{1}{N} \sum_{n=1}^{N} \left| \frac{a_n - b_n}{a_n} \right|
\]  

(5.7)
Figure 5.10 Dynamic temperature of the center on the bottom of 4cm×1cm×1mm model

Table 5.7 Important time information in this simulation

<table>
<thead>
<tr>
<th>Model</th>
<th>Initial temperature (°C)</th>
<th>Time to shut off laser (s)</th>
<th>Time to finish data recording (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4cm×1cm×1mm</td>
<td>22</td>
<td>36</td>
<td>200</td>
</tr>
</tbody>
</table>

Figure 5.11 Compare data from simulation and experiments
From this experiment we obtain information from several aspects.

(1) From simulation, we know that with an initial temperature of 22°C, it takes 8.2 seconds and 23.4 seconds to heat the bottom center of a small sample with diameter of 2mm and thickness of 1mm to 45°C and 60°C, respectively, while the 4cm×1cm×1mm sample takes even shorter time. It makes sense because for small sample (sample diameter is 2mm), only a part of the laser energy (beam diameter is 4mm) shines on the sample, and for a thin sample, heat spread quickly along the depth.

(2) Measured temperature increase at the center of the bottom is much faster than data derived from simulation, at the beginning stage. The deviation between the two data sets during the temperature rising phase is 12.7%. It may be due to the reason that the thickness of the skin sample is only 1mm, thus photons transmitting the sample can reach the thermocouple probe. The absorbed energy causes greater temperature increase of thermocouple probe, thus leads to over-estimation of sample temperature.

(3) Temperature increasing speed gets slower after a certain period of time, so that both methods indicate nearly the same time to reach 60°C. This phenomenon may be due to that heat flux at skin surface is much larger than what we assumed in simulation. For example, water evaporation from the skin surfaces has not been taken into consideration in the model.

(4) After shutting off the laser, temperature decrease is much faster in measurement than simulation. On one hand, it may be caused by the fast cooling of probe, and on the other hand, it may be due to large heat flux on air/skin interface.

(5) Based on analysis above, measurement by thermocouple at the center of the top and bottom surfaces could not provide reliable results for validation.

**Two probes measurement**

To verify the deduction above, an experiment using two sensors were performed. A probe is fixed at the bottom of the surface center from the beginning. After reaching 60°C, shut off the laser, and immediately put another probe on top of the skin surface. The experiment is an attempt to see the effects of energy absorption by thermocouple probe.

<table>
<thead>
<tr>
<th>Model</th>
<th>Time to turn on laser[s]</th>
<th>Time to shut off laser and apply another probe[s]</th>
<th>time when the probe has response [s]</th>
<th>time for response [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4cm×1cm×1mm</td>
<td>22</td>
<td>41</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>134</td>
<td>149</td>
<td>150</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>256</td>
<td>268</td>
<td>269</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>378</td>
<td>390</td>
<td>392</td>
<td>2</td>
</tr>
</tbody>
</table>

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From this experiment, we obtain information in the following.

1. Since the attachment between the thermometer probe and skin tissue, heat conduction takes place during laser irradiation. Therefore, the probe and skin possess the same temperature. When the laser is turned off, and, at the same time, the other probe is put onto the same point, theoretically, it should measure the whole temperature decreasing process, overlapping with the data measured by the first probe.

2. From the result we may observe the phenomenon that the highest temperature which is detected by the second probe is much lower than that was measured by the first probe. The difference indicates a lagging period of 1-2 seconds.

3. This experiment did not provide the information to verify the effect of photon absorption by the probe, as expected. However, it offers valuable information about time response of the thermocouple.

6mm from the center of the top surface

To overcome the difficulty of getting reliable data in the first experiment stated above, we have two alternative methods: to avoid direct shining of laser light on the sample and to use a thick sample so that photon cannot penetrate the tissue.

The method we apply in this experiment is to measure the temperature 6mm away from the center of the surface, and the result is compared with simulated result in Figure5.13.
The information we obtained from the experiment is concluded here:

(1) We can see from the figure that the measured data and the simulated data correspond well with each other at the first 70 seconds. The temperature increase in experiment became slower afterwards, while the temperature increase predicted by the model shows almost linear increase. This is reasonable because the probe attaching the surface of skin may not fully contact the sample, and it is also influenced by air flux around, so surface temperature measured by thermocouple tends to be lower than actual value.

(2) According to simulation in 5.6.1.1, achieving 60°C of the center of the bottom requires only 35 seconds, which means that the result of the first 35 seconds of irradiation is meaningful to us. As shown in Figure5.12, two curves derived from experiment and simulation departs from each other after 71 seconds. Reasonably, we may consider simulation results after 71 seconds to be irrelevant in our experiment.

(3) The deviation between the measured data and the simulated data is 1.56% during the first 71 seconds, which shows a good correspondence and correct model.
1cm from the center of the top surface

Another experiment similar to 5.6.1.2 was performed. This time the experimental data and simulated data of the point 1cm away from the center is compared. Initial temperature is 24°C by using heating instrument. Results are shown below.

![Figure 5.14](image)

**Figure 5.14** measured and simulated data of 1cm from the center of the bottom

**Table 5.8** Experiment result

<table>
<thead>
<tr>
<th></th>
<th>Time to reach 25°C[s]</th>
<th>Time to reach 32°C[s]</th>
<th>Difference [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation</td>
<td>104</td>
<td>434</td>
<td></td>
</tr>
<tr>
<td>Experiment</td>
<td>166</td>
<td>436</td>
<td>2.36</td>
</tr>
</tbody>
</table>

The information we obtained from the experiment is presented here.

1. In the temperature rising period, the temperature profile of both cases shows a slight decrease before continuous increase. The reason is that heat has not diffused to the particular site while the air surrounding, which is room temperature (about 20°C), cools the skin. The temperature decreasing at the beginning is larger in experiment than in simulation. This gives us hints that in actual environment, heat flux is larger at air/skin interface than our expectation.

2. After turning off the laser, we can see that during the cooling period, temperature drops more quickly in experiment. This further verifies our opinion of higher heat flux during measurement.

3. The deviation between the two cases during temperature increasing stage is 2.36%, which proves to be reasonable value.
5.6.2. 3cm×2cm×6mm model

Thermocouple measurement

A 3cm×2cm×6mm model was built up and simulations are performed. Figure 5.14 shows the geometry of the model and Figure 5.15 presents temperature prediction of series of points along the central axes based on simulation.

Figure 5.14 model of laser illumination of skin sample with size of 3cm×2cm×6mm

Figure 5.15 Temperature profile of 3cm×2cm×6mm model predicted by simulation
Figure 5.16 Temperature profile of 3cm×2cm×6mm model by thermocouple measurement

To avoid absorption of photon by the probe, we have validated the model by putting the probe a certain distance away from the center of the top surface, the other measurement is to use the thick sample and perform measurement from the center of the bottom. We can obtain the following information from the results:

(1) Temperature measured by thermocouple is similar as that is predicted by simulation. However, measurement value is smaller than predicted value, maybe due to larger heat flux than expected.

(2) Temperature measured by plug the probe into the sample indicates faster temperature increasing speed compared with measured at the bottom of the sample. It makes sense because the former gives the temperature from inside of the sample.
Validation of the model by infrared imaging

Figure 5.17 Temperature profile of 3cm×2cm×6mm model by measurement using infrared camera

Table 5.9 Comparison of temperature data on the surface of skin

<table>
<thead>
<tr>
<th></th>
<th>Time to reach 45°C [s]</th>
<th>Time to reach 60°C [s]</th>
<th>Difference [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation result</td>
<td>29</td>
<td>80</td>
<td>4.1</td>
</tr>
<tr>
<td>Experiment results</td>
<td>22</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

The results are analyzed and summarized in the following.

(1) Data measured by infrared camera, from the surface of the sample, both top and bottom, match well with the simulation result. However, temperature inside the sample shows larger deviation from the measured data. This gives us hint that the optical parameters or thermal parameters in this simulation do not match those of the skin sample in our simulation very well.

(2) Compared with thermocouple, infrared camera provides higher spatial resolution and faster time response, thus can provide a more powerful tool for validating our model.

(3) Due to the good temperature resolution of infrared camera, we can analyze the heat diffusion speed along depth. Assume that heat spreads in a semicircular way in depth. Thus we can compare the diffusion area by setting a value, 25°C, as the front of temperature field. For analyzing the thermal camera result, a semicircular area within a certain temperature range can be selected, and the area can be estimated by length of radius (Figure 5.18).

For analyzing the simulation result, data is imported into MATLAB and scatter plotted. The front edge of the temperature field can be drawn to clearly indicate temperature penetration depth (Figure 5.19). Then the heat diffusion speed can be evaluated by calculating the area within a certain temperature range in both cases. Results are listed in Table 5.10.
Figure 5.18 Estimation of the area within a certain temperature range

Figure 5.19 Simulation result plot in Matlab and front edge of temperature field (a) scatter plot of heat distribution in MATLAB (b) front edge of temperature field, the depth of the lowest point gives the radius value
From analysis based on figure 5.19 and data information listed in Table 5.10, we can draw the conclusion for several aspects:

1) Heat diffusion area for both simulation and experiment can be considered to approach each other throughout the time of detection.

2) Heat diffusion speed in simulation is faster than experiment from the beginning, but getting slower and slower throughout the time. It makes sense because the model is assumed to be homogeneous in simulation, so that temperature diffusion area should become smaller and smaller with time, however, in actual experiment, it is not ideal, thus lead to difference.

Table 5.11 shows temperature distribution within 1 mm depth. After 21 seconds, average temperature within the small sample volume increases to 43°C, while after 26 seconds, average temperature increases to 46.5°C. Similarly, to reach around 60°C, about 48 seconds is needed. This can match the result with simulation of 4 cm × 1 cm × 1 mm sample, which indicates that it requires 16.9 seconds and 37 seconds to reach 45°C and 60°C, respectively. The time lagging in thermal camera result is reasonable due to shining of the laser from the edge and optical pathway attenuation, as introduced before.

5.7. Conclusion

In this chapter, model validation process is presented in detail. Two temperature measurement techniques, including thermocouple and thermal camera measurement, are introduced at first, from perspective of physical structure, principle and causes of error. Then experiments based on two practical sample sizes are presented: 4 cm × 1 cm × 1 mm model and 3 cm × 2 cm × 6 mm model. To avoid error caused by absorption of photon energy by thermocouple probe when it is put
underneath a thin sample within the irradiation of laser beam, temperature is measured in two alternative ways: from a certain distance away from the laser spot and underneath a thick sample. In 3cm×2cm×6mm model validation, infrared camera measurement is added, and heat spreading speed are introduced to compare the model. Curves and data derived from simulation and experiments were compared and analyzed. Comparison shows repetitiveness and allowable difference between simulation and measurement. Therefore, we may draw the conclusion that the model is stable and reliable; it has good performance in predicting temperature field in human skin under laser irradiation. However, further improvement of the model is quite feasible and necessary. This aspect will be introduced in the following chapter.
6. Application

In this chapter, applications of the validated numerical model are carried out on study of laser irradiation of small skin samples, with diameter of 2mm and thickness of 1.2mm. The objective of laser irradiation experiments is the same as in water bath heating and cooling: the skin was originally kept in 37°C, it is firstly heated to 45°C and 60°C, kept at the desired temperature for 2-3 seconds, and cooled down to original temperature. This study, again, can be divided into 3 topics:

1. Laser irradiation in room temperature condition
2. Choose cooling methods to keep skin tissue at desired temperatures
3. Laser irradiation with water bath cooling applied

6.1. Room condition irradiation

Figure 6.1 temperature change with time for points along z axis in room condition

Table 6.1 Time to reach desired temperature

<table>
<thead>
<tr>
<th>Time to reach 45°C[s]</th>
<th>Time to reach 60 °C[s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Using the selected laser with the determined laser parameters, which is 976nm laser diode with 4mm laser diameter and 1W power, laser irradiation in room condition was simulated. Initial temperature is 37°C. The boundary condition is set to be T=25°C as external temperature and heat flux coefficient is set to be h=5[W/m²·K], which is considered to be normal room condition. Figure6.1 and Table6.1 show that it takes 8.2 seconds and 23.6seconds, to heat the sample to 45°C and 60°C, respectively.
Figure 6.2 shows temperature distribution along depth (line AB) and horizontal axis (line OC) within 25 seconds. Time interval is 1 second. The temperature at the center of top surface is about 2°C higher than the center of bottom, and the difference between horizontal axes is about 1°C. From these two figures, we can consider the skin sample to be nearly homogeneously heated.

**6.2. Choose cooling method to keep temperature**

A major task of this study is to find out how we keep the skin sample at desired temperature for a short period of time. The idea is to firstly heat the skin sample for 8 seconds, until the temperature of the sample arrives at 45 °C, then irradiating the skin while cooling by water bath for a certain period of time, and turn off the laser for cooling with only water bath. Figure 6.3 shows temperature change of different cooling methods. The left figure represents cooling by immersing the whole sample in water, and the right figures shows heating profile by immersing three sides of skin in water, while leaving the surface of the skin in room condition. We can see that the right figure shows better temperature keeping effect than left figure. However, as presented in Figure 6.4, using the second cooling method, temperature difference can be up to 5 centigrade, thus it does not meet our requirement for homogeneous heating.
The third method for keeping the skin at desired temperature is to apply irradiation until the skin heated to a certain temperature, then turn off the laser and keep the sample in room condition for 2 seconds, and put the sample into water bath of 37°C for cooling. Figure 6.5 shows temperature change with time for 45°C and 60°C, and temperature distribution along z axis within 10 seconds and 25 seconds, respectively. Table 6.2 shows data.

We can find out that temperature drops within 2 seconds after irradiation are 0.5°C and 0.2°C respectively for 45°C and 60°C case, which can be considered to be no change in temperature. Therefore, this method meets our requirement for keeping temperature.
Figure 6.5 Compare cooling in room condition. (a) temperature change with time of heating to 45°C, (b) temperature distribution along z axis of heating to 45°C (c) temperature change of heating to 60°C (d) temperature distribution along z axis of heating to 60°C

Table 6.2 Time results in cooling in room condition

<table>
<thead>
<tr>
<th>Desired temperature [°C]</th>
<th>Irradiation Time [s]</th>
<th>Time to start Water cooling [s]</th>
<th>Temp. drop in 2 seconds [°C]</th>
<th>Time to arrive at 37 °C [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>8.2</td>
<td>10.2</td>
<td>0.5</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>23.6</td>
<td>25.6</td>
<td>0.2</td>
<td>36</td>
</tr>
</tbody>
</table>

6.3. Irradiating while applying water bath cooling

Figure 6.6 shows temperature change of using water bath cooling during laser irradiation. The method is to immerse the skin sample in 37°C water while performing irradiation at the same time. We can see from Figure 6.6 that after a certain period of time, temperature gradient forms in
tissue sample, with different parts of the sample staying at different temperatures. Only the tissue at certain location at skin tissue arrives at the desired temperature.

Table 6.3 shows data information. We can see that around 0.44mm range in depth and 0.3mm range in horizontal axis achieves 45°C; while about 0.35mm range in depth and 0.2mm range in horizontal axis arrives at 60°C. Based on the information we obtained in this study, we may draw the conclusion that laser irradiation while water bath cooling cannot realize homogeneous heating but selective heating instead.
Figure 6.6 Laser irradiation during water bath cooling applied. (a) Temperature change with time of heating to 45°C; (b) temperature change with time of heating to 60°C (c) temperature distribution along z axis for 45°C (d) temperature distribution along z axis for 60°C (e) temperature distribution along horizontal axis for 45°C (f) temperature distribution along horizontal axis for 60°C.

Table 6.3 Data information of laser irradiation during water bath applied

<table>
<thead>
<tr>
<th>Desired temp. [°C]</th>
<th>Laser power [W]</th>
<th>Time to form gradient [s]</th>
<th>Target location on Line AB [mm]</th>
<th>Target location on Line OC [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>2.3</td>
<td>7</td>
<td>0.52-0.96</td>
<td>0-0.3</td>
</tr>
<tr>
<td>60</td>
<td>7</td>
<td>8</td>
<td>0.57-0.92</td>
<td>0-0.2</td>
</tr>
</tbody>
</table>

6.4. Summary

In this chapter, the application of the validated model is carried out on three topics, including finding time information of laser irradiation on room condition and exploring the best cooling method. The study focuses on sample of small size, which is more stable and shows linear result. The model proves its power in efficiency and flexibility. It provides us with reliable predictions of temperature change in skin tissue under laser irradiation.
7. Discussion

In this chapter, some specific issues in the project will be raised and discussed in detail.

7.1. Choice of sample size in simulation and experiment

The sample size we chose at the simulation phase is very tiny sample with diameter of 2mm and thickness of 1.2mm. This preference is due to the accuracy of temperature prediction for small sample. The larger the sample, the more external influence factors exist, thus more non-linear result will be obtained. However, for small sample, linear result will be get, thus easier prediction can be achieved.

However, measuring temperature of sample with tiny size is more difficult than that of larger sample, due to the relatively large size of thermocouple probe, and limited temperature resolution of thermal image. Therefore, larger samples of 4cm×1cm×1mm and 3cm×2cm×6mm are used for validation of the model. The model was validated by comparing the simulation result and experimental result, in each case, and mutually.

7.2. Water bath heating and cooling

Before, ideal boundary condition was used in water bath heating and cooling simulation (see section 4.4.1). The boundaries are directly set at 45°C or 60°C. Due to large heat transfer coefficient of water, the simulation makes sense, but not precise. A non-ideal model is raised up here. Boundary condition is set with heat flux to mimic the actual situation. The external temperature is the desired temperature and heat transfer coefficient $h=500 \ (W \cdot m^{-2} \cdot K^{-1})$.

Figure 7.1 and Table 7.1 gives results. Compared with the ideal boundary case, temperature changing is slower than that of ideal case, which makes sense, because in actual situation, there are heat exchange between the sample boundary and water, and it takes time to heat up the surface of the sample.

![Temperature change with time for non-ideal case](image_url)
Table 7.1 Time to arrive at desired temperature for water bath heating and cooling in non-ideal case

<table>
<thead>
<tr>
<th>Desired Temperature (°C)</th>
<th>Threshold (°C)</th>
<th>Time to final temperature (s)</th>
<th>Time to begin cooling (s)</th>
<th>Time to arrive at 37°C (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>0.2</td>
<td>8</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>60</td>
<td>0.2</td>
<td>9</td>
<td>11</td>
<td>20</td>
</tr>
</tbody>
</table>

7.3. Simulation of larger and small sample

Table 4.6 shows that with an initial temperature of 37°C, it takes 8.2 seconds and 23.6 seconds, respectively, to heat the tiny skin sample, which has diameter of 2 mm and thickness of 1.2 mm, up to 45°C and 60°C. While simulation shows that it takes 4.7 seconds and 13.2 seconds to heat up 4 cm × 1 cm × 1 mm sample to 45°C and 60°C, respectively. Faster temperature increasing speed in the latter case, as we consider, is due to the size of beam diameter shining on the sample. For the tiny sample, 4 mm laser diameter shines only approximately half the power on the sample, while the whole laser power is irradiated on the 4 cm × 1 cm × 1 mm sample. That explains why the larger sample takes only half the time to heat up to the same temperature as the small sample size. To test the assumption, the power in the second case is decreased to be 0.5 W, which is half of the power used in the former case. If the time to achieve desired temperature is nearly the same for both, we may draw the conclusion that the time to heat up the small size is the same as using the larger sample.

7.4. Model Improvement

To compare the result with actual experiment, the model should be modified according to experimental conditions, for example, the sample size. In addition, parameters of the model should be adjusted to improve the coherence of the results. The parameters include:

1. Skin optical parameters and thermal parameters
   Different skin sample has its specific parameters. In chapter 2 and chapter 3, we have introduced methods to measure skin optical parameters. Due to limit of experiment conditions, in this project, sample parameters cannot be measured specifically, but to acquire from literatures. Therefore, both parameters should be adjusted to match the result of simulation.

2. Boundary conditions
   Room conditions in experiment, including heat flux and external temperature, which should be set in the simulation as boundary conditions, cannot be precisely measured. Therefore, they should be adjusted until the result from simulation and experiment matches each other.

7.5. Model application

After a validated model is built up, it can be used for further laser parameter study, for example, beam diameter, power density on the skin surface and pulse duration. In addition, the structure of the model provides a good method for constructing models of laser irradiation on other tissue. For example, laser irradiation study on cells.
8. Conclusion and Outlook

In this project, a mathematic model was built up for predicting temperature field in human skin sample under laser irradiation. This model is made up of three parts:

(1) MC simulation considers the skin tissue to be divided into $51 \times 50 \times 50$ voxels, and output a matrix of the same size, with each element representing number of photons absorbed inside each voxel.
(2) MATLAB data processing. This part transfer the output of MC simulation into heat generation rate to fit the bio-heat equation in COMSOL modeling
(3) COMSOL model. A model with the desired geometry is built up with defined thermal parameters. By setting the boundary conditions and import the heat source function, which is also the result derived from the second part, real time temperature in skin can be calculated.

Based on the model, three topics of research were carried out prior to actual experiment:

(1) Simulation of heating and cooling by water bath. On one hand, to give guidance of time control of the model. On the other hand, to obtain a direct view of temperature distribution in skin.
(2) Study of Laser irradiation of skin in room condition. This study includes compare different models, choosing appropriate laser and laser parameters
(3) Study cooling effects during laser irradiation and choose suitable cooling method.

These studies provide guidance for further actual experiments, which aims to validate the model. A laser irradiation system was built up and laser light was collimated and adjusted as designed. 4cm×1cm×1mm and 3cm×2cm×6mm skin samples are used in the experiment and two temperature measurement techniques are applied: thermocouple and infrared camera measurement. Results derived from both experiment and simulation is compared and small difference is obtained. According to analysis, we may draw the conclusion that the model can serve as a reliable tool for predicting temperature distribution of human skin sample under laser irradiation. The model itself also provides a great variability for modification. It can be improved from the following aspects:

- Better input data. Skin optical parameters and thermal parameters should be more accurate for the model.
  - The parameters are not only wavelength dependent, but also temperature dependent. Optical parameters of skin change a lot with temperature change of skin samples under laser irradiation.
  - These coefficients are also sample-specific. Under allowed experimental conditions, the parameters can be measured for each sample before experiment.

If the changing and the sample-specific coefficient can be incorporated into the model, the accuracy of the model will be largely increased.

- Better boundary conditions. The boundary conditions of the room were not accurately evaluated. They should be adjusted through various tests and based on accurate input parameters.
- More powerful to study laser parameters. Laser parameters that can be studied in this model are beam diameter and laser power. However, laser pulse duration is also a very important parameter. Further improvement should also take this factor into consideration.
- More powerful to study in vivo experiment. In vivo study is quite necessary to study skin rejuvenation. To approach in vivo situation, the model should be modified with improved algorithm. This should be realized by adjusting heat transfer equation.
In this project, we constructed the model by combining Monte Carlo Simulation with COMSOL model for the first time, and innovatively create a new profile of modeling. This model provides guidance for carrying out ex vivo experiments, and in return, is proved by experiments for its validity and reliability. In the work of this project, result in each experiment is correct and reliable. Therefore, we can draw the conclusion that the present model can serve as a good tool to predict temperature distribution in human skin under laser irradiation, and will facilitate parametric study of laser in skin rejuvenation[xxx]. In addition, the innovative construction of the present model offers great probability to be further improved, by adjusting input parameters, boundary conditions, or functionality of model. We believe that a further revised model, in the future, will be an even more powerful tool for better treatment of skin rejuvenation.
References

1. It is recommended to use a tool to manage your references, such as EndNote.
2. This database can be loaded as an add-in for Word.

[ix] http://www.absoluteastronomy.com/topics/Skin
[xv] B. Chen, S.L.Thomsen, Modeling thermal damage in skin from 2000nm laser irradiation, Kournal of Biomedical Optics, 064028
A Appendices

A.1 Inserting equations

Equations appear in many Technical Notes and Reports. This template contains a macro, called InsertEquation, that creates a table in which an equation can be entered via the equation editor and which places the equation number flush right. See the example below. The macro can be called via the shortkey Ctrl-F1 or via the Infoscreen toolbar button.
1. Appendix
   - MATLAB data processing part in the model

(1) 3D model of large sample 4cm×1cm×1mm

%Function main calculate heat generation rate, output a matrix of 50×50×50, with each element representing heat generation rate in each voxel.

```matlab
function DataExport=main
laserPower=1; %laser power
photonNo=1000000; %photon number
X=ReadAbsorbanceYing();
Qrate=HeatCalculate(X,photonNo,laserPower); %calculate heat generation rate
DataExport=[];
format long;
z=linspace(0.001,0,50); %number of data points along z axis
y=linspace(0,0.01,50); %number of data points along y axis
x=linspace(0,0.04,50); %number of data points along x axis
for i=1:50 %list data in 4 columns, %with the first three
column as %the coordinate, %and the last column be the %value of heat generation rate
    for j=1:50
        for k=1:50
            DataExport=[DataExport;x(k) y(j) z(i) Qrate(k,j,i)];
        end
    end
end
return %Function ReadAbsorbanceYing read data file from MC simulation, and reform it into a 50×50×50 matrix.
function [X]=ReadAbsorbanceYing();
%ReadAbsorbanceYing reads a 3D array of double (absorbance layer) from a binary file
```
%Input n: resolution of MC calculation in x,y,z
%       slice : depth below surface
%Output X : absorption array
[simname, pathname] = uigetfile('C:\SkinTest\*.abs', 'Pick an absorption file');
%number of bins as given in the input file
% slice_x = 10;%desired number of slice to be visualized
% slice_y = 10;
% slice_z = 10;
if isequal(simname,0) | isequal(pathname,0)
else
    fid = fopen(strcat(pathname,simname), 'r');
    A = [];
    [A, COUNT] = fread(fid, 50*50*50, 'float');
    ABS = [];
    ABS = reshape(A, [50 50 50]);
    X = ABS;
end

%Function HeatCalculate calculates heat generation rate in each bin, after an event of photon absorption
function Qrate=HeatCalculate(Qskin, photonNo, laserPower)
    skinSize1=0.04; %the size sample [m]
skinSize2=0.01;
    thickness=0.001; %sample thickness [m]
    [length,width,height]=size(Qskin);
    binVolume=(skinSize1*skinSize2*thickness)/(length*width*height); %m3
    Q=Qskin/photonNo; %photon absorption probability
    Qrate=Q*laserPower/binVolume; %heat generation rate (W/m^3)
    return

(2) 2D model of small sample Ø2mm, thickness 1.2mm

%Function main calculate heat generation rate, output a matrix of 51x50x50, with each element representing heat generation rate in each voxel.
function DataExport=main
    laserPower=1;
    photonNo=10^6;
    X=ReadAbsorbanceYing();
    [m,n,k]=size(X);
    Qskin(1:n/2,1:k)=X(26,26:50,:); %extract a piece from the center of the sample
    Qrate=HeatCalculate(Qskin, photonNo, laserPower); %calculate heat generation rate
    DataExport=[];
    DataEpi=[];

    format long
    z=linspace(0.001,0,50);
y = linspace(0, 0.001, 25);

for i = 1:50
    for j = 1:2
        DataExport = [DataExport; y(j) z(i) Qrate(j, i)]; % 3 columns, with
        % first 2 columns
        % coordinates
    end
end
return

function [X] = ReadAbsorbanceYing();

%Function ReadAbsorbanceYing read data file from MC simulation, and
% reform it into a 51×50×50 matrix.
[simname, pathname] = uigetfile('C:\SkinTest\*.abs', 'Pick an absorb-
ance file');

if isequal(simname, 0) | isequal(pathname, 0)
    else
        fid = fopen(strcat(pathname, simname), 'r');
        A = [];
        [A, COUNT] = fread(fid, 51*50*50, 'float');

        ABS = [];
        ABS = reshape(A, [51 50 50]);
        X = ABS;
    end

return

%Function HeatCalculate calculates heat generation rate in each bin,
% after an event of photon absorption
function Qrate = HeatCalculate(Qskin, photonNo, laserPower)
    skinSize = 2; % the size sample [mm]
    thickness = 1; % sample thickness [mm]
    binVolume = (skinSize^2 * thickness * 10^(-9)) / (51*50*50); % m^3
    % photonEnergy = plank * c / (lambda * 10^(-9)); % single photon energy
    Q = Qskin / photonNo; % photon absorption probability
    Qrate = Q * laserPower / binVolume; % heat generation rate (W/m^3)
return

● “Time Zone” plots file

(1) 45°C time zone

load 45_8s
skindata = x45_8s;
final_temp = 45;
[same_dura,num_dura,act_dura]=Process_data2D45(final_temp,skindata);
same_dura=same_dura(2:end,:); %remove the first row, which is time used
figure;
for i=1:length(act_dura)
    hold on;
    scatter(same_dura(:,2*i-1),same_dura(:,2*i),act_dura(i));
end
xlabel('radius');
ylabel('height');
axis([-0.0011 0.0011 -0.0001 0.0013]);
set(gca,'XTick',(-0.0011:0.0001:0.0011));
set(gca,'YTick',(-0.0001:0.0001:0.0013));
legend('2s','3s','4s','5s','6s','7s','8s');
title(['2D plot of time distribution at ' num2str(final_temp) ' Centi-
grade with 8s heating time']);

function process_data2D45 classify zones according to how long it has
stayed at the final temperature
function [same_dura,num_dura,act_dura]=Process_data2D45(final_temp,skindata)
    skindata=skindata(:,2:12);
    [height,width]=size(skindata); %read the size of data
    width=width-3; %only regard the temperature data
    time=zeros(1,height); %initialize a vector to store the
time for each point to stay at the final temperature
    time_step=1; %recorded time step
    for i=1:height
        A=find((final_temp-skindata(i,4:end))<0.6); %find when the point
        %arrive at the final
        %temperature, define a
        %small
t=(width-A(1))*time_step; %calculate the time
        time(i)=t; %store it in vector
    end
    data2=[skindata(:,1:3) %skin-
        time'];
    duration=0:1:10; %all possible time
    intervals
    act_dura=[]; %a vector to store all time inter-
    vals
    num_dura=[]; %that has been actually spent
    for k=1:length(duration)
        if length(find(time==duration(k)))~=0;
            act_dura=[act_dura duration(k)];
            num_dura=[num_dura length(find(time==duration(k)))];
        end
    end
    same_dura=zeros(max(num_dura)+1,2*length(act_dura)); %define a matrix
to points time of est number for m=1:length(act_dura) columns number

same_dura(2:num_dura(m)+1,(2*m-1):2*m)=skindata(find(time==act_dura(m)),2:3);
same_dura(1,2*m)=act_dura(m);

end

return

2. Appendix

- MATLAB data processing part in the model

(3) 3D model of large sample 4cm×1cm×1mm

%Function main calculate heat generation rate, output a matrix of 50×50×50, with each element representing heat generation rate in each voxel.
function DataExport=main
laserPower=1; %laser power
photonNo=1000000; %photon number
X=ReadAbsorbanceYing();

Qrate=HeatCalculate(X,photonNo,laserPower); %calculate heat generation rate
DataExport=[];

format long;
z=linspace(0.001,0.5,50); %number of data points along z axis
y=linspace(0,0.01,50); %number of data points
along y axis
x=linspace(0,0.04,50); %number of data points
along x axis

for i=1:50 %list data in 4 columns,
    for j=1:50 %with the first three
column as
        for k=1:50 %the coordinate,
            %and the last column be
            the %value of heat generation
            rate
                DataExport=[DataExport;x(k) y(j) z(i) Qrate(k,j,i)];
            end
        end
    end
end
return

%Function ReadAbsorbanceYing read data file from MC simulation, and
%reform it into a 50×50×50 matrix.
function [X]=ReadAbsorbanceYing();

%ReadAbsorbanceYing reads a 3D array of double (absorbance layer) from a
%binary file
%Input n: resolution of MC calculation in x,y,z
%      slice : depth below surface
%Output X : absorption array
   [simname, pathname] = uigetfile('C:\SkinTest\*.abs', 'Pick an absorb-
%ance file');
%number of bins as given in the input file
% slice_x = 10;%desired number of slice to be visualized
% slice_y = 10;
% slice_z = 10;

    if isequal(simname,0) | isequal(pathname,0)
    else
        fid = fopen(strcat(pathname,simname), 'r');
        A = [];
        [A, COUNT] = fread(fid,50*50*50,'float');
        ABS = [];
        ABS = reshape(A,[50 50 50]);
        X = ABS;
    end

%Function HeatCalculate calculates heat generation rate in each bin,
%after an event of photon absorption
function Qrate=HeatCalculate(Qskin,photonNo,laserPower)
skinSize1=0.04; %the size sample [m]
skinSize2=0.01;
thickness=0.001; %sample thickness [m]
[length,width,height]=size(Qskin);
binVolume=(skinSize1*skinSize2*thickness)/(length*width*height); %m3
Q=Qskin/photonNo; %photon absorption probabil-
Qrate = Q * laserPower / binVolume; % heat generation rate (W/m^3)
return

(4) 2D model of small sample Ø2mm, thickness 1.2mm

% Function main calculate heat generation rate, output a matrix of 51*50*50, with each element representing heat generation rate in each voxel.
function DataExport = main
laserPower = 1;
photonNo = 1e6;
X = ReadAbsorbanceYing();
[m, n, k] = size(X);
Qskin(1:n/2, 1:k) = X(26, 26:50,:); % extract a piece from the center of the sample
Qrate = HeatCalculate(Qskin, photonNo, laserPower); % calculate heat generation rate
DataExport = [];
DataEpi = [];

format long
z = linspace(0.001, 0, 50);
y = linspace(0, 0.001, 25);

for i = 1:50
    for j = 1:25
        DataExport = [DataExport; y(j) z(i) Qrate(j, i)]; % 3 columns, with the first 2 columns as coordinates
    end
end
return

function [X] = ReadAbsorbanceYing();

% Function ReadAbsorbanceYing read data file from MC simulation, and reform it into a 51*50*50 matrix.
[simname, pathname] = uigetfile('C:\SkinTest\*.abs', 'Pick an absorbance file');

if isequal(simname, 0) | isequal(pathname, 0)
else
    fid = fopen(strcat(pathname, simname), 'r');
    A = [];
    [A, COUNT] = fread(fid, 51*50*50, 'float');
    ABS = [];
    ABS = reshape(A, [51 50 50]);
end
\[
X = \text{ABS};
\]
end

return

% Function **HeatCalculate** calculates heat generation rate in each bin, after an event of photon absorption

```matlab
function Qrate=HeatCalculate(Qskin,photonNo,laserPower)
skinSize=2; % the size sample [mm]
thickness=1; % sample thickness [mm]
binVolume=(skinSize^2*thickness*10^(-9))/(51*50*50); % m3
% photonEnergy=plank*c/(lambda*10^(-9)); % single photon energy
Q=Qskin/photonNo; % photon absorption probability
Qrate=Q*laserPower/binVolume; % heat generation rate (W/m^3)
Return
```

- “Time Zone” plots file

(2) 45°C time zone

load 45_8s
skindata=x45_8s;
final_temp=45;
[same_dura,num_dura,act_dura]=Process_data2D45(final_temp,skindata);
same_dura=same_dura(2:end,:); % remove the first row, which is time used
figure;
for i=1:length(act_dura)
    hold on;
    scatter(same_dura(:,2*i-1),same_dura(:,2*i),act_dura(i));
end
xlabel('radius');
ylabel('height');
axis([-0.0011 0.0011 -0.0001 0.0013]);
set(gca,'XTick',(-0.0011:0.0001:0.0011));
set(gca,'YTick',(-0.0001:0.0001:0.0013));
legend('2s','3s','4s','5s','6s','7s','8s');
title(['2D plot of time distribution at ' num2str(final_temp) ' Centigrade with 8s heating time']);

% function **Process_data2D45** classify zones according to how long it has stayed at the final temperature

```matlab
function [same_dura,num_dura,act_dura]=Process_data2D45(final_temp,skindata)
% skindata=skindata(:,2:12);
[height,width]=size(skindata); % read the size of data
width=width-3; % only regard the temperature data
time=zeros(1,height); % initialize a vector to store the time for each point to stay at the final temperature
time_step=1; % recorded time step
for i=1:height
    A=find((final_temp-skindata(i,4:end))<0.6); % find when the point
    % arrive at the final
end
```
%temperature, define a small difference

\[ t = (\text{width} - A(1)) \times \text{time\_step}; \]

%calculate the time interval
\[ \text{time}(i) = t; \]

%store it in vector
end

%skin-
data2 = [skindata(:,1:3) %time'];
duration = 0:1:10; %all possible time intervals
act_dura = []; %a vector to store all time intervals that has been actually spent
num_dura = []; %a vector to store how many points for each time interval
for \( k = 1: \text{length}(\text{duration}) \)
    if length(find(time == duration(k))) \( \neq 0; \)
        act_dura = [act_dura duration(k)];
        num_dura = [num_dura length(find(time == duration(k)))];
    end
end

same_dura = zeros(max(num_dura) + 1, 2*length(act_dura)); %define a matrix to store classified points with different time of largest value of point number
for \( m = 1: \text{length}(\text{act\_dura}) \)
    %and number of columns
    number
    same_dura(2: num_dura(m) + 1, (2*m-1):2*m) = skindata(find(time == act_dura(m)), 2:3);
    same_dura(1, 2*m) = act_dura(m); %
%the first row is values
end
return