PARAMETER ESTIMATION FOR A BIOLOGICAL SYSTEM : MODEL AND EXPERIMENTATIONS

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Abstract: Temperature evolution and skin burn process in biological samples exposed to laser radiation are investigated in this communication. A one-dimensional multi-layered model is presented and transient temperature is numerically estimated using a finite difference method. A damage function corresponding to the extent of burn injury and using the Arrhenius assumptions is proposed. Two experimental benches are presented in order to estimate human skin optical and thermal properties.

Keywords: Biomedical systems, Mathematical model, Parameter estimation, Optical properties, Thermal diffusivity, Partial differential equation.

1. INTRODUCTION

During the past decades lasers have found many applications in the civilian or medical community (therapeutic technique, medical diagnostic etc..) as much as in the military community (battlefield). If significant researches efforts have been done on ocular injuries, skin damages have been less investigated. As a consequence, efforts for a better understanding in the areas of laser-skin interactions, skin characteristics and burn injuries are required.

An easy way to determine how light interact with the skin is the numerical simulation. Thus, according to existing models, temperature evolution in skin exposed to laser has been estimated and linked to a predictive numerical model of burn injury. Nevertheless, significant differences on mathematical input parameters values found in previous published studies generate discrepancies in the predictions.

A numerical design of experiment have been performed, so as to determine which factors crucially affect the models. The results have oriented the use and adaptation of two (optical and thermal) benches to our identification needs. The optical one is devoted to diffuse reflection and transmission measurement. For various wavelengths, it allows in vitro samples optical properties measurement and calculations. The thermal one based on a periodic heating method will authorise measurement of diffusivity in vivo.

The aim of this paper is to present a general context where the effect of laser interactions with the skin should be determined. In the following paragraph, a mathematical model of laser-skin interaction for temperature evolution and damage threshold is presented; simulated results are exposed. Then optical bench principle is described. The results on a lipid solution use as skin substitute are presented . In addition, the thermal bench is also introduced.

2. MATHEMATICAL MODEL

Let us assume that the human skin can be considered as a homogeneous three layered structure. The optical, physical and thermal properties are different in each of the three layers (epidermis, dermis, hypodermis). The transient temperature distribution in the tissue (affected by a laser aggression I_0) is described by the Penne's bio-heat equation (Pennes, 1948) where $\theta(x,t)$ the temperature depends on x the space variable and on t the time variable (Ng *et al.*, 2000, 2002) ; (Diaz *et al.*, 2001). In equation (1), optical properties (scattering and absorption) are taken into account:

$$\forall(x,t)\in[0,L]\times[0,t_f]$$

$$\rho_i C_i \frac{\partial\theta(x,t)}{\partial t}-k_i\Delta\theta(x,t)=$$
$$\omega_{bi}\rho_{bi}C_{bi}\left[\theta_a-\theta(x,t)\right]+\beta_i I_0(t)\exp(-\beta_i x) \quad (1)$$

where $(i=e)$ corresponds to the epidermis layer, $(i=d)$ the dermis, $(i=h)$ the hypodermis, and $(i=b)$ the blood.

Table 1. Notation and units

	model parameter	units
L	skin width	$[m]$
t_f	time limit	$[s]$
ρ	volumic density	$[kg.m^{-3}]$
C	specific heat	$[J.kg^{-1}.K^{-1}]$
k	thermal conductivity	$[W.m^{-1}.K^{-1}]$
ω	blood perfusion	$[kg.m^{-3}.s^{-1}]$
θ_a	artery temperature	$[K]$
λ	laser wavelength	$[m]$
$\beta(\lambda)$	extinction coefficient	$[m^{-1}]$
I_0	surfacic flux	$[W.m^{-2}]$
h	convection coefficient	$[W.m^{-2}.K^{-1}]$
T_{ext}	external temperature	$[K]$

Initial condition is :

$$\forall x\in[0,L] \qquad \theta(x,0)=\theta_a \qquad (2)$$

On the skin surface, where the laser radiation occurs, a convective transfer condition is considered :

$$\forall t\in[0,t_f] \qquad \theta(0,t)=h\left(\theta(0,t)-\theta_{ext}\right) \qquad (3)$$

Inside the human body, at the external surface of the hypodermis, temperature is assumed to be constant and equal to the initial temperature.

$$\forall t\in[0,t_f] \qquad \theta(L,t)=\theta_a \qquad (4)$$

Continuity of temperature and temperature gradient is considered at each interface Γ .

$$x\in\Gamma_{e\leftrightarrow d},\forall t\in[0,t_f]$$
$$\begin{cases} k_e\dfrac{\theta_e(x,t)}{\partial x}=k_d\dfrac{\partial\theta_d(x,t)}{\partial x} \\ \theta_e(x,t)=\theta_d(x,t)\end{cases} \qquad (5)$$

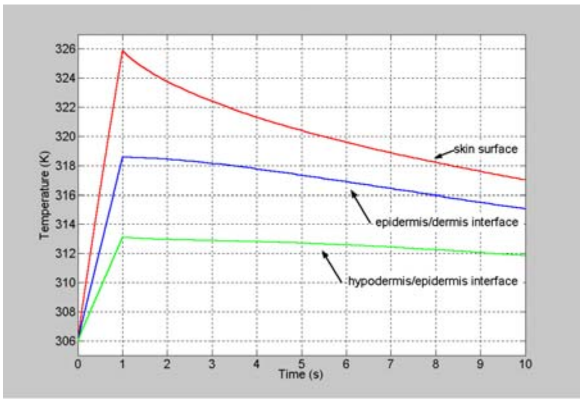

Fig. 1. Temperature evolution.

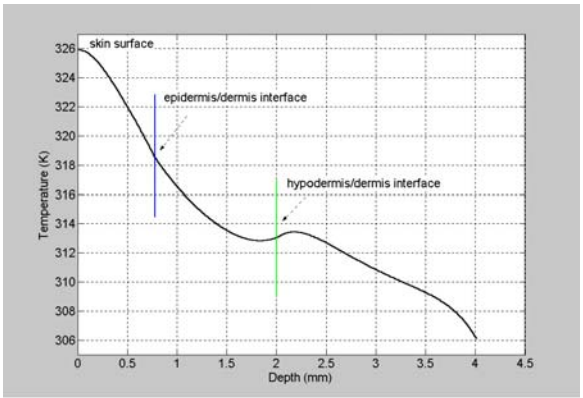

Fig. 2. Temperature spatial distribution at $t=1s$.

$$x\in\Gamma_{d\leftrightarrow h},\forall t\in[0,t_f]$$
$$\begin{cases} k_d\dfrac{\partial\theta_d(x,t)}{\partial x}=k_h\dfrac{\partial\theta_h(x,t)}{\partial x} \\ \theta_d(x,t)=\theta_h(x,t)\end{cases} \qquad (6)$$

Equations (1-6), lead to the formulation of a partial differential equation system solved by a finite difference method. Such a numerical tool is useful for the prediction of temperature increase in the human skin and the evaluation of potential damages. On figure 1, temperature evolution for a laser radiation exposure (duration $1s$; $I_0=130\ kW.m^{-2}$) is shown. On figure 2, temperature distribution is shown at the end of the exposure ($1s$).

3. PREDICTION OF SKIN BURN INJURY

In the standard clinical classification the depth of damaged tissue is considered in order to estimate the injury degree:

- First-degree burns are also known as superficial burns and involve only the epidermis. Basal layer (epidermis-dermis interface) is preserved. An example of a first-degree burn is sunburn.
- Second-degree burns are also known as partial thickness burns and involve both the epidermis and the dermis. Second-degree burns are divided into superficial second-degree burns (superficial partial thickness burns) and deep second-degree

burns (deep partial thickness burn), depending on the depth of tissue injury. In the first case the epidermis and the basal layer are concerned. The second case corresponds to damages observed on superficial dermis (in addition to the basal layer and the epidermis destruction).

– Third-degree burns are also known as full thickness burns since the entire epidermis layer and the entire (or nearly all) dermis layer are destroyed.

Henriques was a pioneer in the area of thermal injury and proposed that the amount of skin damage could be locally predicted on the basis of an Arrhenius-type function:

$$\Omega(x,t) = A\int_0^t \exp\left(\frac{-E}{R\theta(x,t)}\right)d\tau \qquad (7)$$

The value of the damage function Ω is linked to the standard clinical classification of the burn injury severity. Thus, for $\Omega = 0.53$ a first degree burn is obtained; $\Omega = 1$ is a second degree burn, and $\Omega = 10^4$ is a third degree burn. Several formulations have been proposed in order to improve the burn prediction efficiency by empirically adjusting pre-exponential factor (A) and activation energy (E), see (Henriques, 1947) (Fugitt, 1955) (Stoll *et al.*, 1959) (Wu, 1982). Nevertheless, corresponding to the same time-space dependent temperature distribution, distinct injury degrees are predicted by these models. Thus, burn criterion has to be carefully considered for the evaluation of skin behavior during a laser radiation exposure. On figure 3, evolution of predicted damages is shown from a simulated temperature behavior corresponding to laser aggression described in figures 1 and 2. In the laser radiation field, medical researches have been done in order to predict ocular injuries due to laser beam. From this various literature, a great dispersion in model parameters ranges or in burn criterion formulation is encountered. Effect of model parameters inaccuracies has been studied in (Jiang *et al.*, 2002) and (Lormel *et al.*, 2004): on one hand, to estimate the effect of model inaccuracies on temperature prediction, and on the other hand to compare the damage function formulations.

It has been shown that :

– skin thermo physical parameters ($\rho_d C_d$, $\rho_h C_h$, k_e , k_d , k_h) uncertainties do not dramatically affect numerical results. Thus, literature values can be taken into account
– in order to better estimate the temperature evolution in human skin during a laser radiation exposure, it is crucial to carefully estimated $\rho_e C_e$, $\omega_b c_b$, β .

In the following experimental benches for optical and thermal properties estimation are presented.

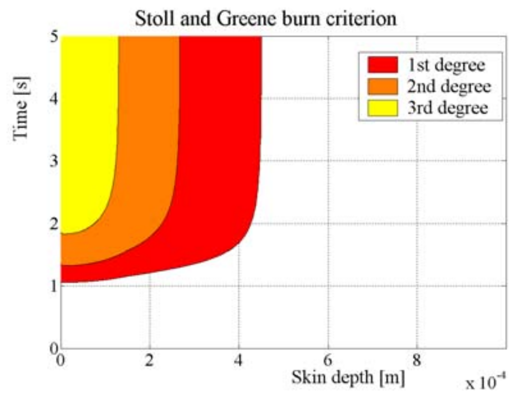

Fig. 3. Damage prediction

4. OPTICAL PROPERTIES DETERMINATION

Determination of extinction coefficient $\beta(\lambda)$ in human skin is quite difficult to perform. An experimental approach based on diffuse reflection and transmission measurements is proposed.

4.1 *Experimental bench*

Measurement of diffuse transmission and reflection is performed using a set up based on a integrating sphere technique (see figure 4). A similar approach is proposed in (Peters *et al.*, 1990) (Du *et al.*, 2001). Two Mercury and Xenon lamps of 150W, two spherical lenses and a monochromator with three gratings rules were used as adjustable light source for wavelengths λ from 300 to 2600nm. The light beam was first collimated and then focused in a slit mounted in front of the monochromator. The monochromator light output was modulated at 1000Hz by a chopper, and collimated. The light scattered by the sample were gathered in an integrating sphere and picked up at the detector port coupled closer to one sphere output. The transmittance coefficient $T(\lambda)$ and the reflectance coefficient $R(\lambda)$ were determined by a comparison method. First, a measure is performed inside the integrating sphere in order to determine the lamp spectrum (considered as input reference : S_1).

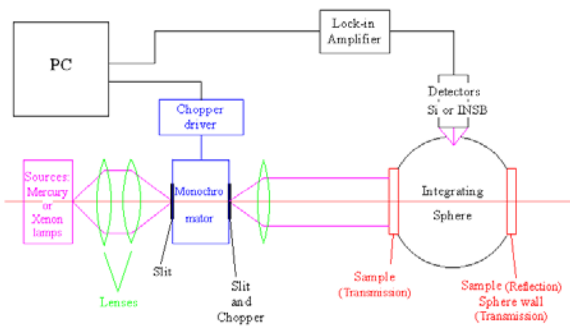

Fig. 4. extinction coefficient measurement set up

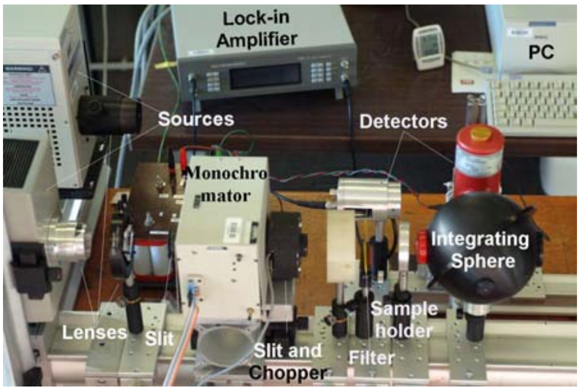

Fig. 5. Optical properties measurement device

Moreover, a calibrated diffuse reflectance sample (S_{ref}) is placed in the outlet port in order to measure the reference reflection coefficient S_2 which depends on the integrating sphere. Then, the studied sample is located in the inlet port in order to measure the diffuse transmission S_T, or in the outlet port for the reflection S_R. Finally, a measurement without any sample in the outlet and inlet ports lead to the determination of S_0, the background signal that depends on the noise in the detection system and on the presence of stay light (Pickering *et al.*, 1993), (Royston *et al.*, 1996). Following equations are considered :

$$T(\lambda)=\frac{S_T(\lambda)-S_0(\lambda)}{S_1(\lambda)-S_0(\lambda)}$$
$$R(\lambda)=S_{ref}(\lambda)\frac{S_R(\lambda)-S_0(\lambda)}{S_2(\lambda)-S_0(\lambda)} \quad (8)$$

The extinction coefficient $\beta(\lambda)$ was calculated from the Kubelka and Munk theory ; see (Kubleka, 1948, 1954). Both scattering $S_{KM}(\lambda)$ and absorption $A_{KM}(\lambda)$ coefficients are obtained from the measured diffuse reflectance and transmittance :

$$S_{KM}(\lambda)=\frac{1}{y(\lambda)D}\ln\left[\frac{1-\left(x(\lambda)-y(\lambda)\right)R(\lambda)}{T(\lambda)}\right] \quad (9)$$
$$A_{KM}(\lambda)=\left(x(\lambda)-1\right)S_{KM}(\lambda)$$

where D is the sample thickness and :

$$x(\lambda)=\frac{1+R^2(\lambda)-T^2(\lambda)}{2R(\lambda)} \quad ; \quad y(\lambda)=\sqrt{x^2(\lambda)-1}$$

The extinction coefficient $\beta(\lambda)$ is calculated from previous values according to equation 10 which is considered for thick samples (Van Gemert *et al.*, 1995) :

$$\beta(\lambda)=\sqrt{A_{KM}(\lambda)\left[A_{KM}(\lambda)+2S_{KM}(\lambda)\right]} \quad (10)$$

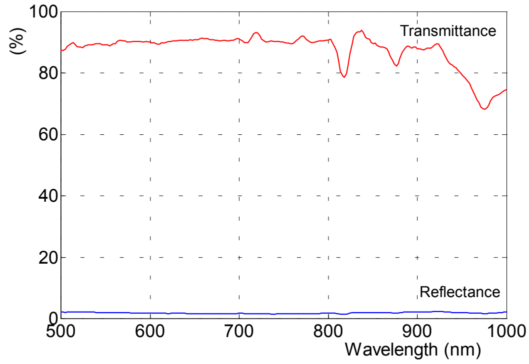

Fig. 6. Measured transmittance and reflectance.

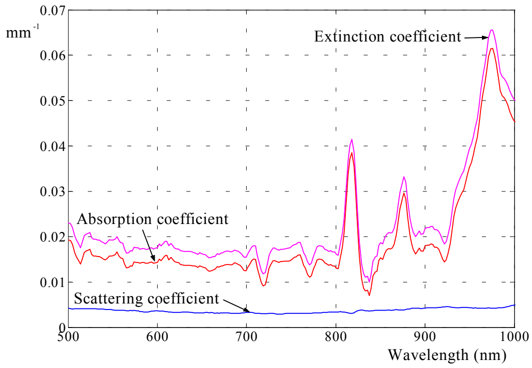

Fig. 7. Absorption, scattering, extinction coefficient.

A high difficulty is encountered since optical properties of the biological sample are not easily separated from sample holder properties. It is important to minimize the effect of the sample holder on the determination of transmittance $T(\lambda)$. In such a way, a minimum absorption coefficient is required for the sample holder.

4.2 Results

The optical properties measurements device has been developed and validated and experiments have been investigated on lipidic skin substitutes. Results are shown on figure 6 and 7.

For biological samples of human skin substitute, this measurement device leads to the determination of extinction coefficient which depends on the laser wavelength. In the following paragraph, thermal properties of human skin is investigated for in-vivo measurements.

5. THERMAL PROPERTIES IDENTIFICATION

In this chapter a technique for the measurement of skin thermal properties is presented. Using a periodic heating method, this technique is devoted to identification of material thermal diffusivity $a=\dfrac{k}{\rho C}$

in $\left[m^2.s^{-1}\right]$, see (Gervaise *et al.*, 1997) for millimetric scale and (Dilhaire *et al.*, 2004) for micrometric applications.

5.1 Experimental bench

The experimental bench is based on a photothermal method whose periodic excitation is localised on a millimeter-scale spot. The distance on which the heat has propagated during a period is called thermal diffusion length $\delta = \sqrt{\dfrac{a}{\pi f}}$ where f is the modulation frequency.

Table 2. Diffusion length estimation

frequency $[Hz]$	diffusivity $\left[m^2.s^{-1}\right]$	diffusion length $[mm]$
$f=1$	$a=4\,10^{-8}$	$\delta \approx 0.1$
$f=0.01$	$a=10^{-7}$	$\delta \approx 1.8$

In the studied configuration, the thermally excited volume does not exceed some mm^3. A biological sample is exposed to a periodic heating. The periodic temperature observed on the surface depends on the distance to the exciting source. Modulus and phase lag of the measured signal are characteristic of the material thermal properties. Analysis of phase lag leads to thermal diffusivity identification. This thermal property is identified by minimising the measurement-calculation difference (Beck *et al.*, 1977), (Walter *et al.*, 2001). Mathematical model is developed in order to simulate the propagation of thermal waves inside the studied biological sample (Gurevich *et al.*, 2003), (Muscio *et al.*, 2004).

The experimental arrangement is shown at figure 8. The heating source originates from a fiber-coupled diode laser system emitting at 1940 nm so as to be absorbed in the superficial layer of the skin. Lens L1 allows adjustment of the gaussian-shaped heating spot size that is about 10-mm in diameter.

The modulation frequency and the power are controlled by a computer. A part of the heating beam is picked up with a beamsplitter and sent to a photodiode the signal of which being used as a phase reference. The sample front face temperature is monitored by an InSb infrared sensor. The sighted zone size is adjusted by lenses L2 and L3; a water-cooled diaphragm placed between them intercepts disturbing hot sources radiation.

A lock-in amplifier measures the phase lag between the temperature sensor and the reference photodiode outputs. For a given set of frequencies, the computer controls the modulation frequency to the laser, waits for the steady-state be attained and read the lock-in amplifier phase output.

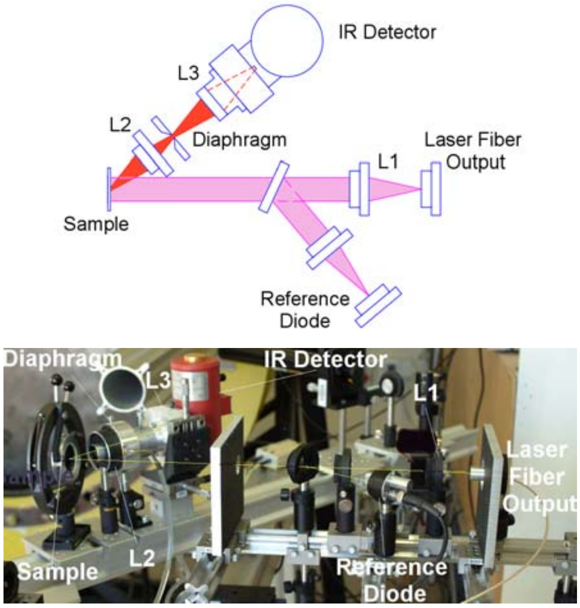

Fig. 8. Thermal properties measurement device

Since time dependent solutions are numerically difficult to estimate, complex temperature is considered and leads to the determination of both phase and modulus in stationary state ; see (Autrique *et al., 2003)*.

The development of the measurement device is actually investigated according to the following step :

- Sensitivity analysis in order to adapt the bench to in vivo measurements. It is crucial to determine laser strength, wavelength and heating frequency for human epidermis and dermis thickness. Damage threshold has to be avoided and temperature increase must be less than 10 degrees.
- Validation on human skin substitute. The measurement device has to be validated and collagen samples are considered (Heitland *et al.*, 2004) ; (Si-Nae *et al.*, 2004).

6. CONCLUDING REMARKS AND PERSPECTIVES

In this communication, the field of laser aggression effect on human skin is investigated. Firstly a mathematical model has been considered and simulation results are presented. From previous studies, it has been shown that in order to validate this predictive tool, it is crucial to carefully estimated several model parameters : an optical property (extinction coefficient in human skin) and thermal properties of several skin layers (epidermis and dermis). An experimental device for optical properties estimation is presented and measurements are carried out for skin substitute. For thermal properties, determination is based on periodic methods. Sensitivity analysis has to be performed in order to determine optimal configurations. An important constraint is to avoid damages on human skin during measurements. Observations on phase lag between heating laser (at a given wavelength) and oscillating temperature lead to the determination of thermal diffusivity. According to the excitation frequency, various skin depth are affected. Thus, superficial property (epidermis) and subcutaneous property (dermis) can be identified with non-intrusive observations.

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