



## Numerical analysis of heat transfer in biological tissues irradiated by pulsed laser: Treatment of angioma, condyloma and trachea tumors

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### General Note



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## ABSTRACT

This paper deals with thermal impact analysis on biological tissues. Human tissues are illuminated by laser rays. We adopt an exponential-temperature-dependence of the heat conductivity. This action leads to an increase in temperature and finally to the removal of the unwanted tissue. The procedure should avoid causing damage to the neighboring healthy tissues. We have demonstrated that, heat transportation process is defined by a highly nonlinear diffusion equation. In this study we have developed a numerical technique, based on the DOPRI5 fourth-and-fifth-order Runge-Kutta variable step integrator, to elucidate the transfer of thermal energy of laser radiation incident on biological tissue. The temporal profile of the temperature distribution on the biological tissue is investigated. We have demonstrated that, maximum temperatures are reached, immediately, after the triggering of the tissue irradiation. Then, this temperature gradually decreases as the distance increases. We have obtained that the duration of laser application, as well as the intensity of the incident laser, impacted seriously the size of the tissue affected by heating and the maximum temperature attainable during the process.

**Keywords:** Biological tissues; Laser treatment; Nano-heat diffusion; DOPRI5 Runge-Kutta integrator

## 1. INTRODUCTION

During the irradiation of the tissue by pulsed lasers, different types of interaction can be observed, among which thermal effects have larger contribution. So, laser irradiation is followed by the temperature distribution through the tissue. In this paper, we intend to study the process of heat generated by laser light and transferred into biological tissues for a therapeutic purpose. Since the creation of the first working laser (Maiman, 1960; Townes, 2003; Townes, 2007), lasers have been presented as more appropriate light sources in the medical fields, thanks to their directivity, their monochromaticity and their pulsed mode. Very recently, in 2011, another technique of lasers production was proposed by Simo and Caputo (2011). The authors have shown that double-ionization of helium atom by strong fields, leads to high-order harmonic generation (HHG). They used Neodymium-doped yttrium aluminum garnet, Nd:YAG and Titanium-sapphire, Ti:Sapph, as incident lasers. This method allowed them to produce harmonics in the order of 427th and 479th for Nd:YAG and Ti:Sapph, respectively.

Use of lasers in medical area has increased over the years especially in surgery, in the process of cancer diagnosis and treatment, in dermatology, in prostatectomy and in many other medical systems. For instance, lasers have been involved in repairing damaged retinæ, thereby protecting many people from blindness. Neodymium:YAG infrared laser light have been largely used in biological tissue (Auth, 1981; Regan, 1980). Nowadays, carbon dioxide laser and Neodymium:YAG are used in surgery to cut into tissues, to treat certain tumors (Kiefhaber, 1977; Anderson, 1981; Hofstetter, 1980). In the same vein, we can also refer to the publication of the following celebrated papers (Duarte, 2008; Goldman, 1990; Costella, 2008; Thomas, 2008; Batal et al., 2012; Ansari et al., 2013). It should be recalled that tissues, the components of the human organism, are made up largely of water. Thus, the CO<sub>2</sub> laser is well appropriate in human body because water absorbs the frequency of this laser very well. Among the many benefits of using CO<sub>2</sub> we can also mention the shorter surgery time and the less risk of infection. CO<sub>2</sub> laser is requested in several fields of medicine. For instance, it is used for skin resurfacing, a procedure during which the skin is vaporized to promote collagen formation (Barton, 2014). It is also requested for the treatment of certain skin diseases. It is the case of hirsuties papillaris genitalis: Here, the process leads to the deletion of bumps or podules to give homogeneity and clarity to the skin. Nowadays, the CO<sub>2</sub> laser is known to be the more appropriate laser for biological tissue where cutting or hemostasis is achieved photo-thermally (Vogel et al., 2003; Vitruk, 2014; Fisher, 1993; Fantarella et al. 2014).

The determination of the thermal distribution in tissue and precisely on the treatment site is our primary objective. Steps should be taken to avoid contaminating healthy cells around the defective area. So, we should avoid that energy derived from the laser beam flows, by conduction, from the affected target zone to the neighboring healthy cells which are at lower temperatures. Thus, a total control of the heat distribution is required. Our main objective is to confine the generated heat only on the altered portion of the tissue. The chosen focused laser beam should produce precise ablation at the desired location with minimal collateral damage.

We shall develop a numerical technique for analyzing the classic problem of thermal diffusion in biological tissues. These investigations shall account for the spatial and temperature-dependence of the heat distribution. The Runge-Kutta 4-5 numerical method is used to simulate the heat manifestation in the biological tissue. We focus our attention on the analysis of the spatial profile of the temperature distribution at successive time periods. These investigations intend to propose protocols for a radiation treatment of three pathologies, namely: angioma, condyloma and the tumor of the trachea altering living tissue.

The paper is organized as follows: We present the model in the next section. Section three stands for the implementation of the DOPRI5 fourth-and-fifth-order Runge-Kutta variable step integrator for the numerical investigations. In this section, computational results are followed by discussions and commentaries. Section four is devoted to the conclusion of the paper.

## 2. THE MODEL

### 2.1 Presentation of the model

This paper deals with the problem of heat transfer in nanostructures such as biological tissues. Here, heat is generated by laser irradiance on biological tissue. We ambition to study the thermal effects and the thermal distribution of laser on faulty tissue. The main characteristics of the laser-tissue interaction that should be taken into account in biomedical domain are thermal changes induce by the tissue-light interaction. Thermal effects of laser rays can lead to the following phenomena, according to the degree and the duration of tissue heating:

- Hyperthermia: Associated to temperatures ranging from 41° to 44°. Changes in enzymatic processes yields cell death for some tens of minutes of irradiation.
- Coagulation: Associated to temperatures ranging from 50° to 100° C°. We can observe desiccation, blanching, and a shrinking of the biological tissues due to the denaturation of protein molecules and collagen. The duration period of laser irradiation being around a second.
- Volatilization: Associated to temperatures above 100° C. The defective substance is completely removed. The various constituents of tissue disappear in smoke during a short time period of about one tenth of a second.

Thermal action on biological tissue is accompanied by the denaturation of protein molecules. Then, follows a significant increase in membrane permeability of mitochondrial. All these manifestations lead to the ultimate stage: the vaporization. The human body can then get rid of the unwanted substance.

We plan to conduct our investigations in view of the treatment of three pathologies that manifest themselves by the multiplication and the presence of undesirable organs. let's list them: the angioma, the condyloma and the tumor of the trachea. Let's make a rough presentation of these diseases.

- A. Angioma is a benign tumor which results mainly from the formation of conglomerates of blood vessels, known as hemangioma or lymph vessels known as lymphangioma. Although considered benign, its presence in certain location of the body can be very bothersome to the patient. In most cases, the removal is the only way to get rid of this pathology. In this contribution, we focus our attention on the protocol of removal by laser treatment. We believe that this technique can limit the risk of alteration of healthy cells.
- B. Condyloma manifests itself by the occurrence of warts, swollen rashes or grayish bumps on the surface of the body. The manifestation of Condyloma in men is characterized by presence of genital bumps dark in color. There are visible in the vicinity of the urethra, scrotum, rectal and penis region. Among women, on the other hand, the event of Condyloma is dictated by the appearance of warts in the area surrounding the vaginal aperture. The principal means of contacting this disease is the Human Papilloma Virus (HPV) Infection. This disease has a direct connection with disorderly sexual relations. People who are at risk from these pathology also include people suffering from too much stress, those who drink alcohol and those who smoke tobacco. The laser irradiation technique removes the unwanted tissue effortlessly. This method is a painless way of Condyloma removal; unlike the direct ablation of the altered area, by a surgical excision, which will require the use of anesthesia to alleviate pain.
- C. Trachea can be subjected to two different forms of tumors, namely:
  - a benign tumor, not cancerous and
  - a malignant tumor in a cancerous form.

Whatever the form of the tumor, this pathology always causes breathing problems to the patient. Respiratory difficulties emerge due to the fact that the manifestation of these unwanted organs can contribute to a significant decrease of airflow into the lungs by narrowing the opening of the trachea. Nowadays, there are various methods of removing the trachea tumor. In this paper, we are interested on the radiation treatment. Laser therapy requires appropriate laser choice. We need a highly focused beam of light to shrink or remove the tumor. In this sense, cancer cells are killed. This process leads to the vaporization of the tumor.

## 2. 2 Derivation of the heat-diffusion equation

The phenomena of heat transport occurring often in daily life, engineering applications and scientific research are governed by the famous Fourier's law of heat conduction (Fourier, 1808).

$$q = -\kappa \nabla T \quad (1)$$

Where  $q$  is the heat flux density,  $\kappa$  the thermal conductivity and  $T$  the temperature.

Here, we are dealing with the process of ultra short laser heat transfer in biological tissue. Therefore, phenomena developed in this model involves very fast lasers and small structure dimensions. Thus, according to the Fourier equation (1), heat crosses the entire tissue instantaneously. Subsequently, the heat diffusion in the system under consideration gives rise to infinite speeds of heat propagation. Loosely speaking, this event is not physically reasonable. In fact, such behavior is not consistent with the requirements of Einstein's theory of relativity which states that the highest speed known to date is that of electromagnetic waves propagating in vacuum. In this sense, more sophisticated model is needed to explain the heat conduction mechanisms in a physically acceptable way in biological tissue. This paradox can be overcome using Cattaneo and Vernotte models (Cattaneo, 1948; Vernotte, 1958).

In order to overcome the problem of infinite velocity of thermal perturbations, let's consider a time lag in the process. In this respect, heat flux should be relaxed by introducing a relaxation time,  $\tau$ , in the Fourier's law:

$$q(x; t + \tau) = -\kappa \nabla T \quad (2)$$

Equation (2) tells us that the existing temperature is well associated at each time period,  $t$ . On the other hand, it is clear that the heat flux manifests itself only a posterior instant, i.e.  $t + \tau$ . Let's have a look at this modified equation of Fourier (2). The left and right sides of the latter are written for two different time moments, i.e.  $t + \tau$  and  $t$ . In order to overcome this difficulty, we decide to expand the left side of (4) into the Taylor series. After neglecting higher order terms of this series, this equation turns into:

$$q(x, t + \tau) = q(x, t) + \tau \frac{\partial q(x, t)}{\partial t} \quad (3)$$

The conservation energy law for the heat flux is given by the following equation:

$$\rho c_p \frac{\partial T}{\partial t} = -\text{div}(q(x, t)) + q_{gen} \quad (4)$$

In this notation,  $q_{gen}$ , stands for the internal heat source.  $\rho$  is the density,  $c_p$  designates the specific heat. Equation (4) together with equations (3) and (2) leads us to the Cattaneo heat transfer equation (Cattaneo, 1948), within the assumption that the thermal conductivity,  $\kappa$ , is a constant quantity. However, in the ongoing work, we consider rather a temperature-dependent thermal conductivity of the biological tissue. In this context, we arrive at the above equation of heat diffusion after some analytical transformations:

$$\frac{\partial^2 T}{\partial t^2} + \frac{1}{\tau} \frac{\partial T}{\partial t} = \frac{1}{\tau \rho c_p} [\nabla(\kappa \nabla T)] \quad (5)$$

Then, in the remainder of this contribution, it is assumed that the thermal conductivity depends exponentially on temperature as:

$$\kappa = \kappa_0 e^{-\frac{E_0}{K_B T}} \quad (6)$$

Where  $E_0$  stands for the activation energy, i.e. the amount of energy which must be provided to the biological tissue to undergo the heating process and the denaturation process;  $\kappa_0$  is the pre-exponential factor and  $K_B$  is the Boltzmann Constant.

## 3. NUMERICAL COMPUTATIONS OF THE HEAT DIFFUSION EQUATION BY THE METHOD OF RUNGE-KUTTA OF THE FOURTH-AND-FIFTH-ORDERS USING THE DOPRI5 CODE AS THE INTEGRATOR

### 3.1 Technique of computation

The nonlinear equation of diffusion (5) describing the transportation of laser energy through the biological tissue does not have an obvious analytical solution. In this context, we opted for a numerical computation. Computations shall be made, making use of

numerical analysis methods. It is a fact that, physically appropriate solutions can only be obtained through well-conducted stable numerical studies. In these circumstances, a considerable number of numerical errors should be discarded. Therefore, errors generated by round off, for instance, should not be amplified. The approximate solution should also remain bounded.

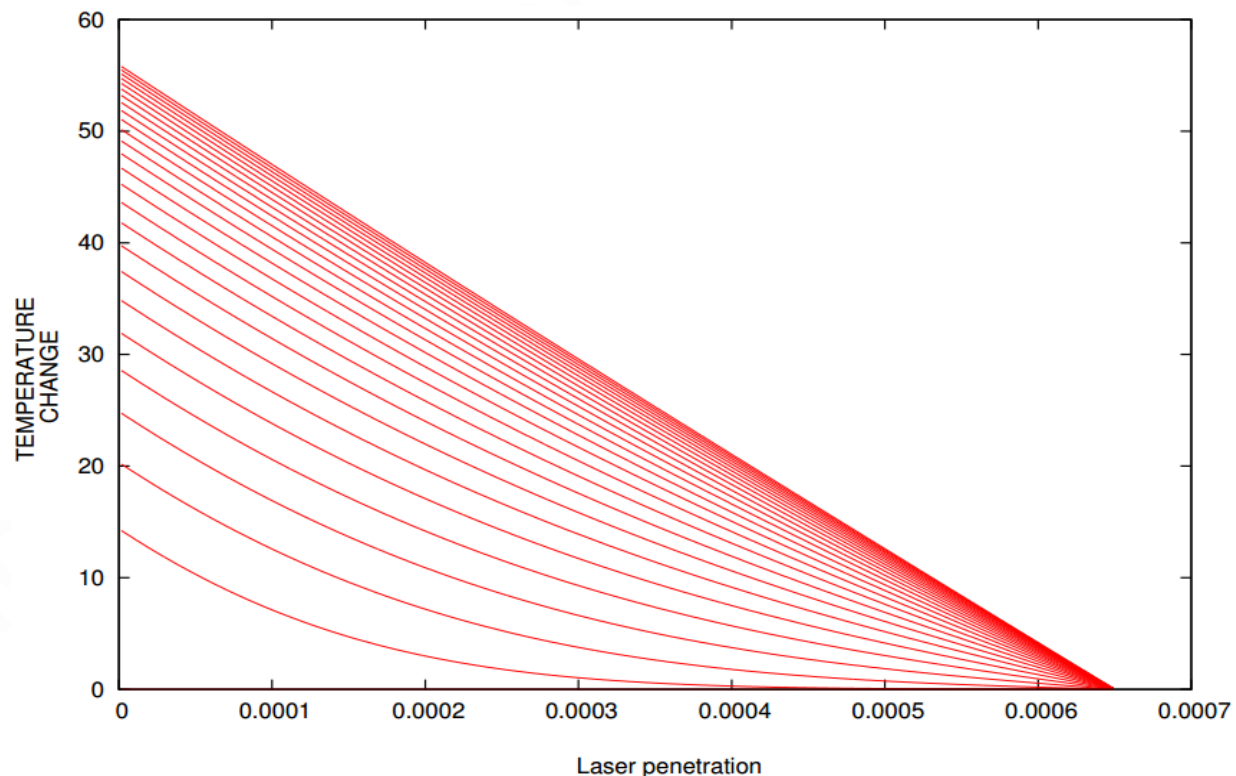
The case of linear problems with constant coefficients can be easily solved by using the well-known mathematical tools of the study of stability (Charner et al 1950, Isaacson et al 1994, Crank et al 1947, Süli et al 2003). Besides, the approach is very complicated for nonlinear problems. Such topics are more difficult to analyze and may require a stronger form of stability. Therefore, it becomes crucial to make use of more appropriate technique for accurately describing the heat distribution in the biological tissue. From our point of view, the Runge Kutta method using DOPRI5 code as the integrator offers excellent accuracy guarantees (Smith 1985, *Journal of Computational* 1986, Hairer et al 1987, Atkinson 1988, Schatzman 2002, Simo et al 2017, Simo et al 2019a, Simo et al 2019b; Simo et al. 2020).

The basis of this method is as follows: the spatial part of the operator is discretized, while the temporal part is keeping as such. Thanks to this solver, one can easily control the local error by varying the time step. This technique allows highlighting a significant increase in the precision of the approximation in time and space independently and easily.

#### 4. RESULTS AND DISCUSSION

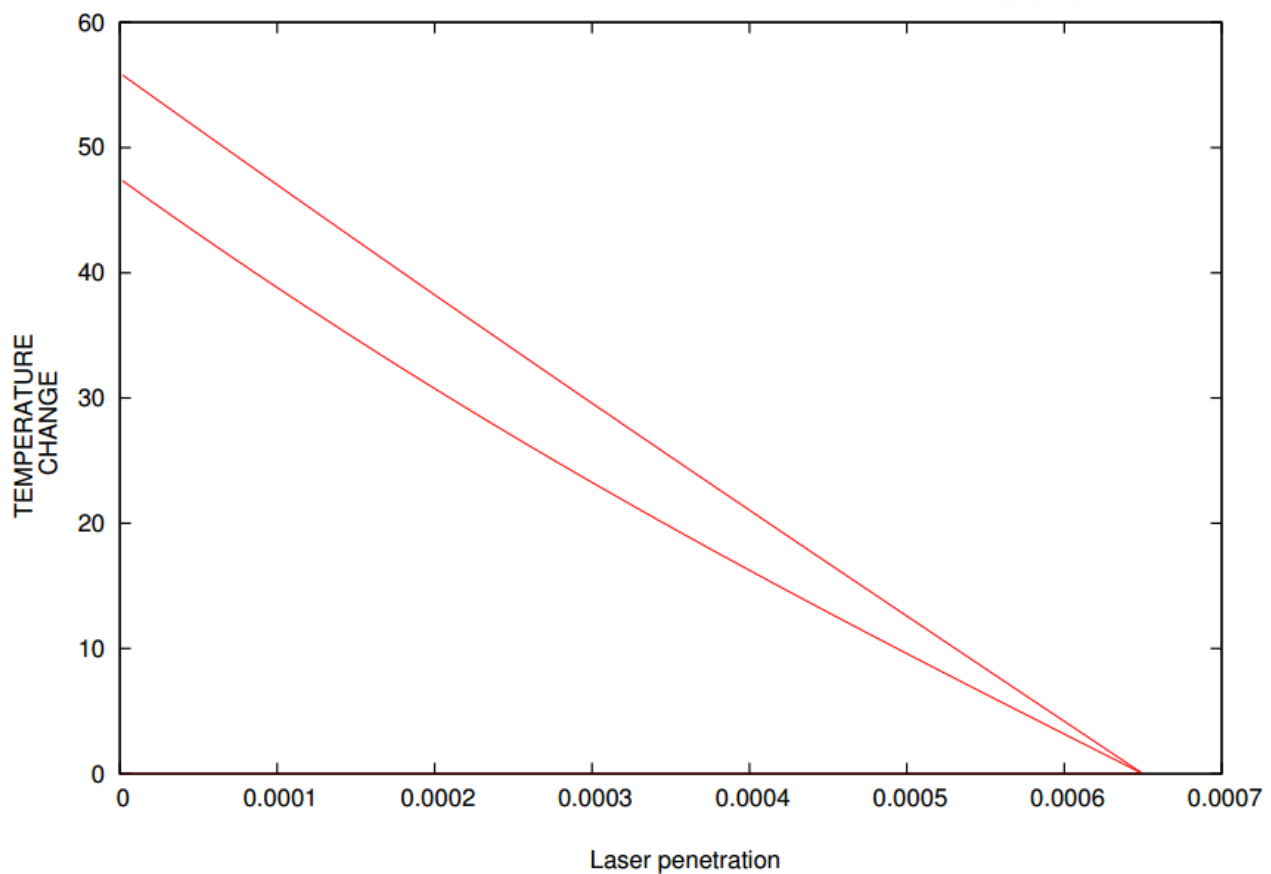
In the framework of the ongoing theoretical treatment, we present in this section some of the results that have been obtained by solving the master equation of diffusion numerically. To achieve this aim, two types of laser are involved in the computational process, namely: Neodymium-doped yttrium aluminum garnet, Nd:YAG and Titanium-sapphire, Ti:Sapph. For a given laser, we have the possibility to follow the progression of the thermal energy along the tissue. It is worthwhile to recognize that human beings are homeothermal organisms. In this sense, their central temperature remains constant regardless of the various forms of fluctuations that could be recorded outside environment. Indeed, human beings organism functions normally and properly at temperature values ranging from 36°C to 37.5°C.

Correspond to optimal conditions for the proper functioning of the organism. The metabolic process that takes place in our organism is achieved preferably around 37°C. Thus, the initial temperature involved in numerical computation is  $T_0 = 37^\circ\text{C}$ . The human body functions normally and optimally under these conditions.



**Figure 1:** Temperature response to the laser treatment of flat angiomas: Pattern of heating of the biological tissue using the Neodymium-Doped Yttrium Garnet laser radiation (Nd: YAG) at a wavelength 1060 nm (0,585 eV) and a the time period  $t_0 = 5,0 \cdot 10^{-12}s$

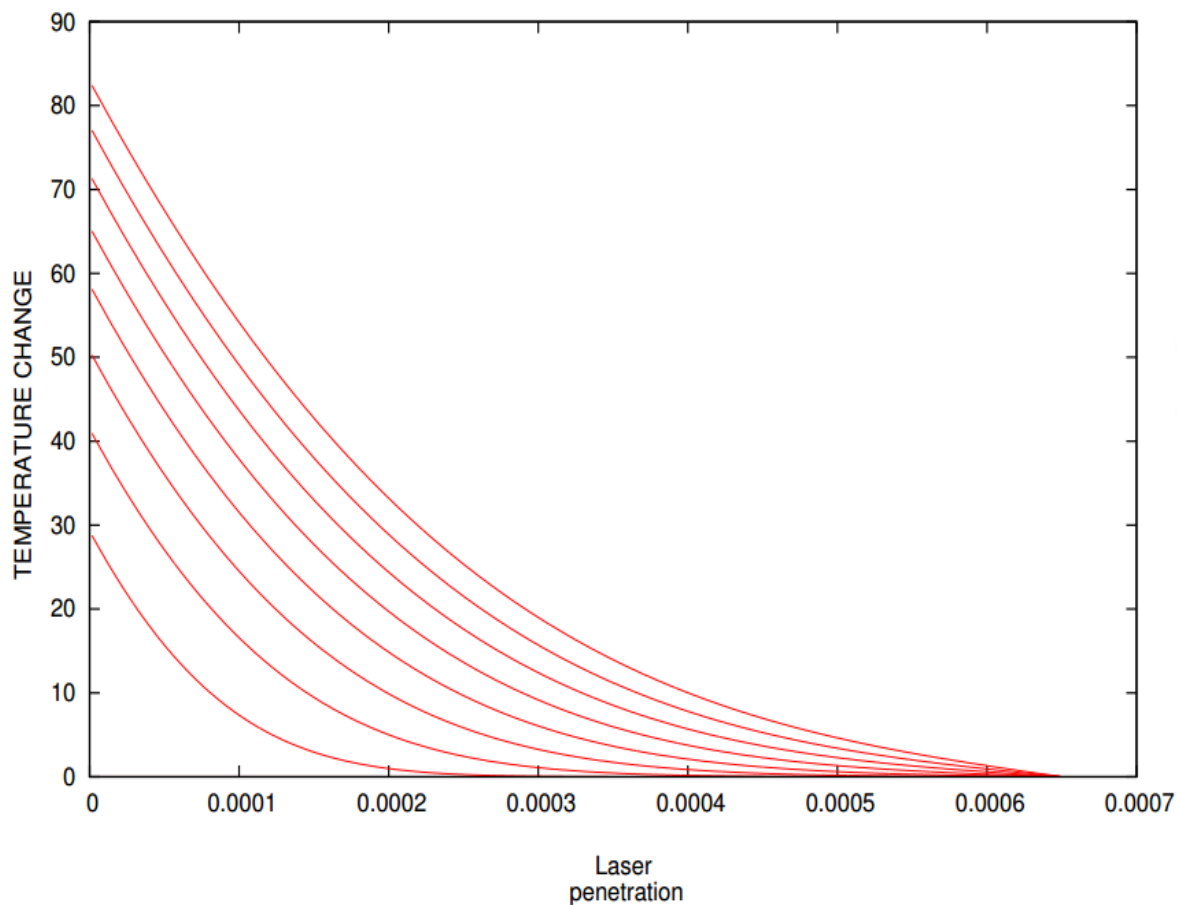
Figure (1) shows the temperature response to the laser treatment of angioma. The implementation of this model is based specifically on the cherry angioma; considered as a benign, dome-shaped cherry-red papule on the trunk (Campbell de Morgan, 2009). This defect consists of a compressible mass of blood vessels. Pattern of heating of the biological tissue using the Neodymium-Doped Yttrium Garnet laser radiation (Nd:YAG) at a wavelength 1060 nm (0,585 eV). This laser is used at a power setting at 80 W and pulse durations sufficient to bring the temperature in the range interval 50 - 100 °C, representing tissue coagulation. Only a small area of the tissue reaches high temperatures (the altered zone). This figure shows the temperature distributions for the biological tissue under consideration along the Ox axis. The above figure tells us that, temperature increases to the maximum, instantly, after process is triggered. Tung (2008) and his colleagues obtained a similar profile when they studied the temperature distributions for the cornea along the radial axis for different time periods. In this circumstance, they make use of radio-frequency currents. So, at the beginning of the heating, the temperature reaches its maximum instantly. When they were investigating on the thermal therapy modeling in biological tissue, Molina and his colleagues (2008) obtained the same conclusion. The plot of the temperature progress over time indicates clearly that maximum temperatures are reached immediately at the beginning of the process. Then, we observed a decrease in thermal energy with the increasing penetration depth of laser.



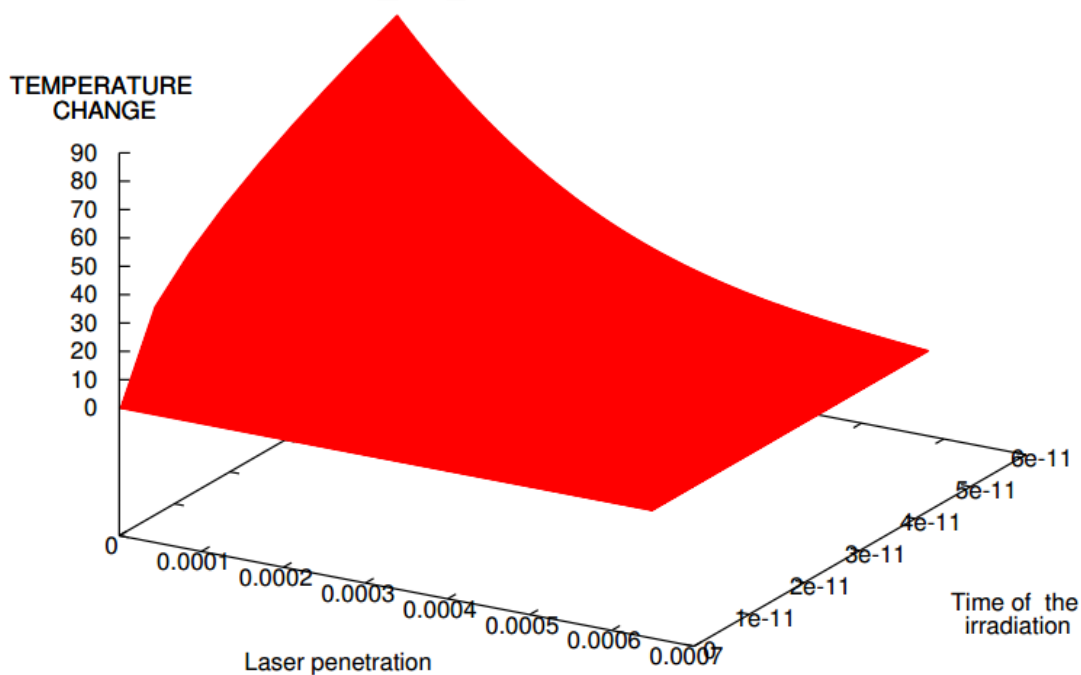
**Figure 2:** Laser heating of the biological tissue for the treatment of the hyperthermia using the dioxide of carbon laser radiation at a wavelength 9900 nm (0,126 eV). The intensity of the luminous flat over a small area is  $6,2 \cdot 10^{10} \text{ W/cm}^2$  and  $t_0 = 5 \cdot 10^{-11} \text{ s}$

This laser is used at a power setting at 1 W and pulse durations sufficient to bring the temperature at the value of 44°C. This corresponds to a moderate rise in temperature resulting in cell death due to changes in enzymatic processes. This figure shows the temperature response for the heated biological tissue under consideration, along the Ox axis. The provision described in this figure can help remedy hyperthermia. Indeed, treatment of this disease is possible for temperatures between 41 °C and 45 °C.

From figure (3), we can infer that, when the intensity of the incident laser increases, the area affected by laser heating also increases. Similarly, the maximum temperature reached by the biological tissue increase, under the same conditions. It should be noted that, in this case, intensity of the laser ray is set to the value,  $2 \cdot 10^{11} \text{ W/cm}^2$  ; whereas, previously, it was chosen to be  $6,2 \cdot 10^{10} \text{ W/cm}^2$  .



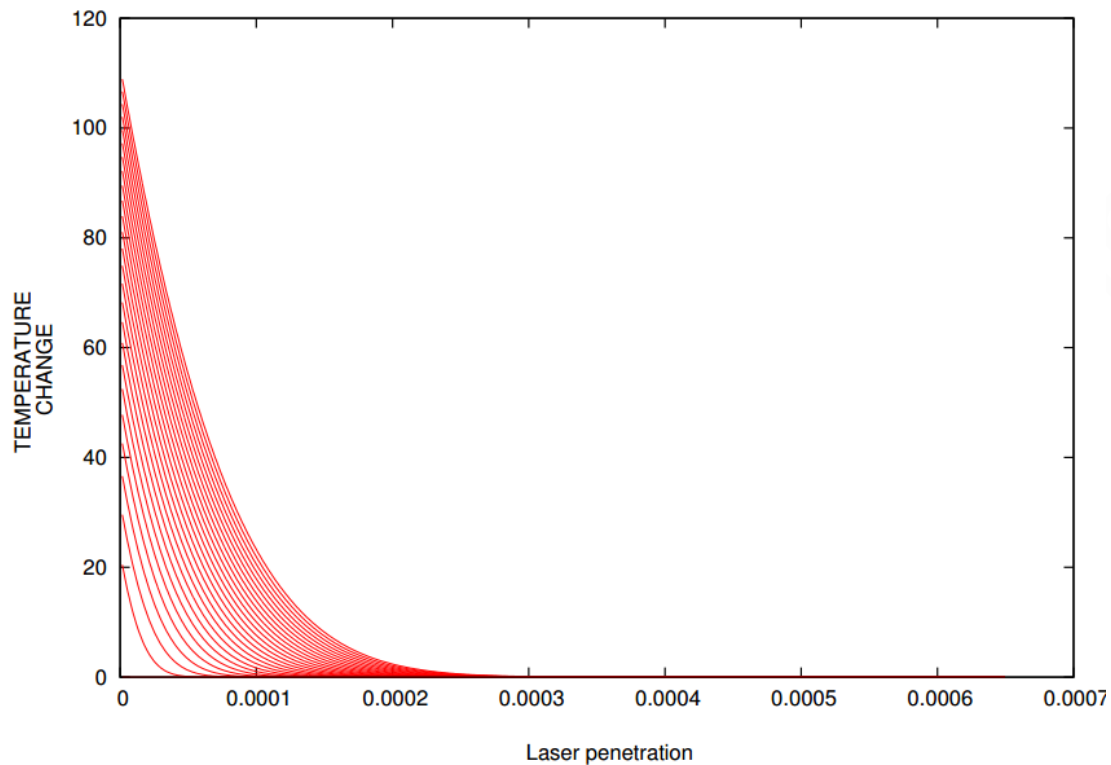
**Figure 3:** We take into account the same considerations as in Fig. 1, except that the intensity of the laser ray over a small area is setting to  $6,2 \cdot 10^{11} \text{ W/cm}^2$ .



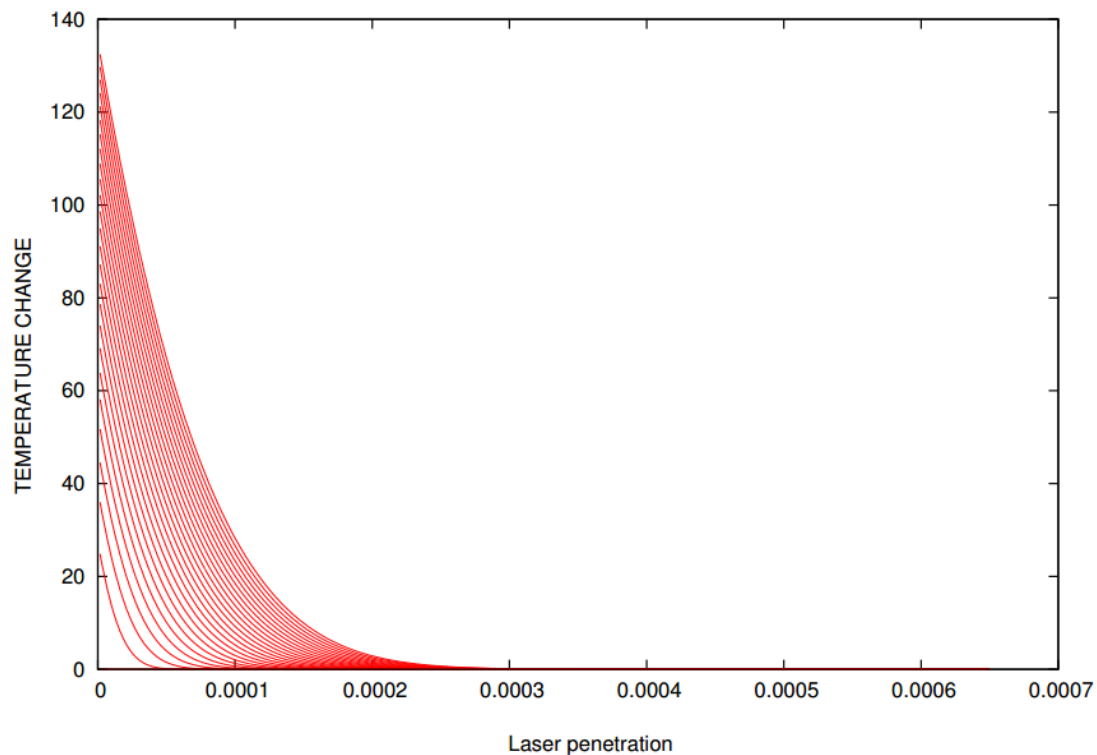
**Figure 4:** Temperature distribution on the biological tissue for different time periods; taking into account the same considerations as in Fig. 1. Here, we have the intensity  $6,2 \cdot 10^{11} \text{ W/cm}^2$ .



The energy concentration is noticeable in a very small portion of the tissue when the power increases. So, the more the laser's power increases, the more accurate the operation takes place. This statement is verifiable on the figure (4). This same figure clearly shows that, temperature decreases both with laser penetration and with the time of the biological tissue irradiation.



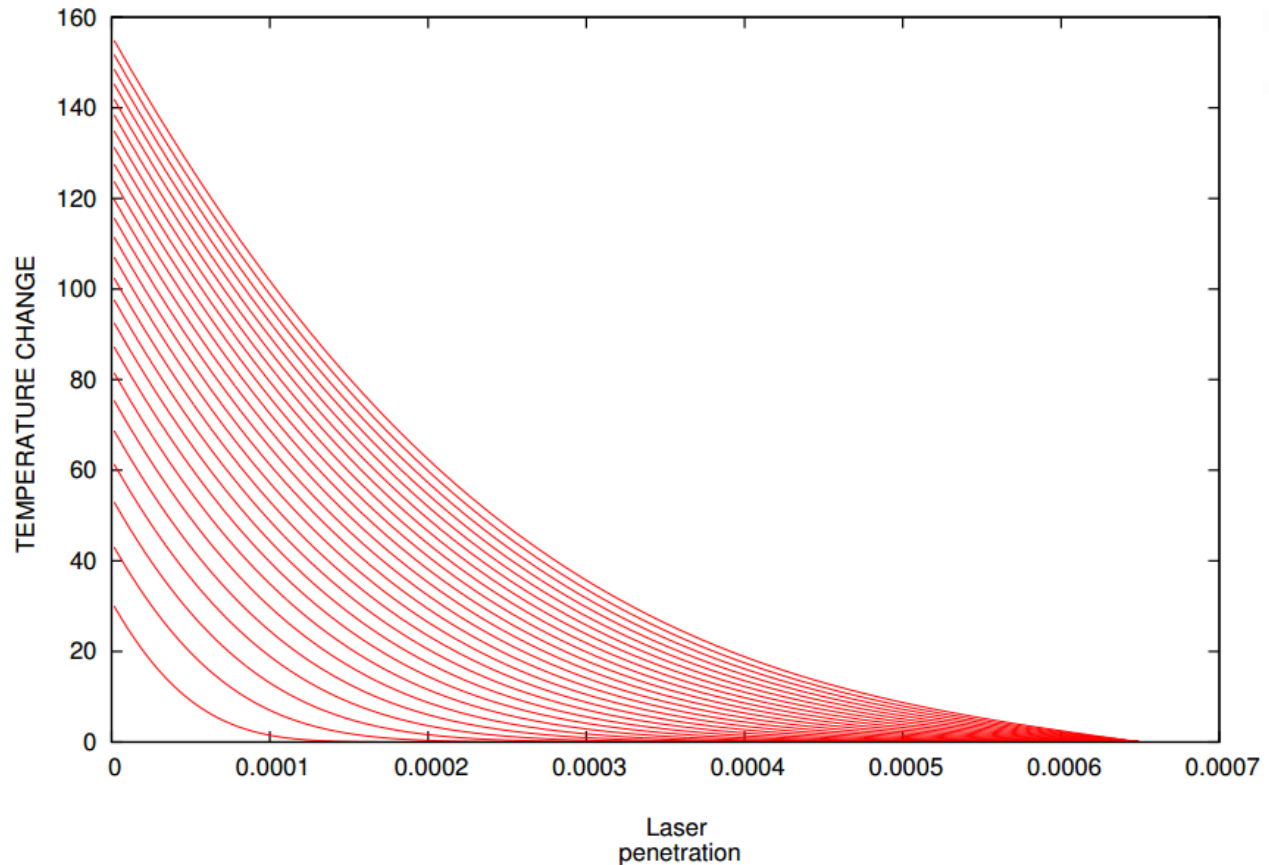
**Figure 5:** Laser heating of the biological tissue for the treatment of tumors of the trachea using the Neodymium-Doped Yttrium Garnet laser radiation (Nd: YAG) at a wavelength 1060 nm (0,585 eV).



**Figure 6:** The temperature as a function of the laser penetration at different time periods, with the same considerations as in Fig 5. The intensity of the laser ray over a small area being  $6,2 \cdot 10^{12} \text{ W/cm}^2$ .



In the protocol of the treatment of the tracheal tumor from Nd:YAG laser, the laser power is set at the value 90 W. Pulse durations are sufficient to bring the temperature above the value of 100 °C. Treatment, carried out with such laser, comprises firstly a coagulation of the mass of the tumor for temperatures approaching 100 °C, (to ensure complete hemostasis), then a volatilization of the coagulated zone in order to remove the obstruction of the trachea, for temperatures above 100 °C. It is important to notice that with this protocol, the thickness of the area impacted by laser heat is relatively low. High precision is required for small thicknesses. Figs (5) and (6) show that maximal value of attainable temperature increases with the laser intensity.



**Figure 7:** Laser heating of the biological tissue for the treatment of condyloma carried out by volatilization with a dioxide of carbon,  $CO_2$ , laser radiation at a wavelength 9450 nm (0, 0325 eV).

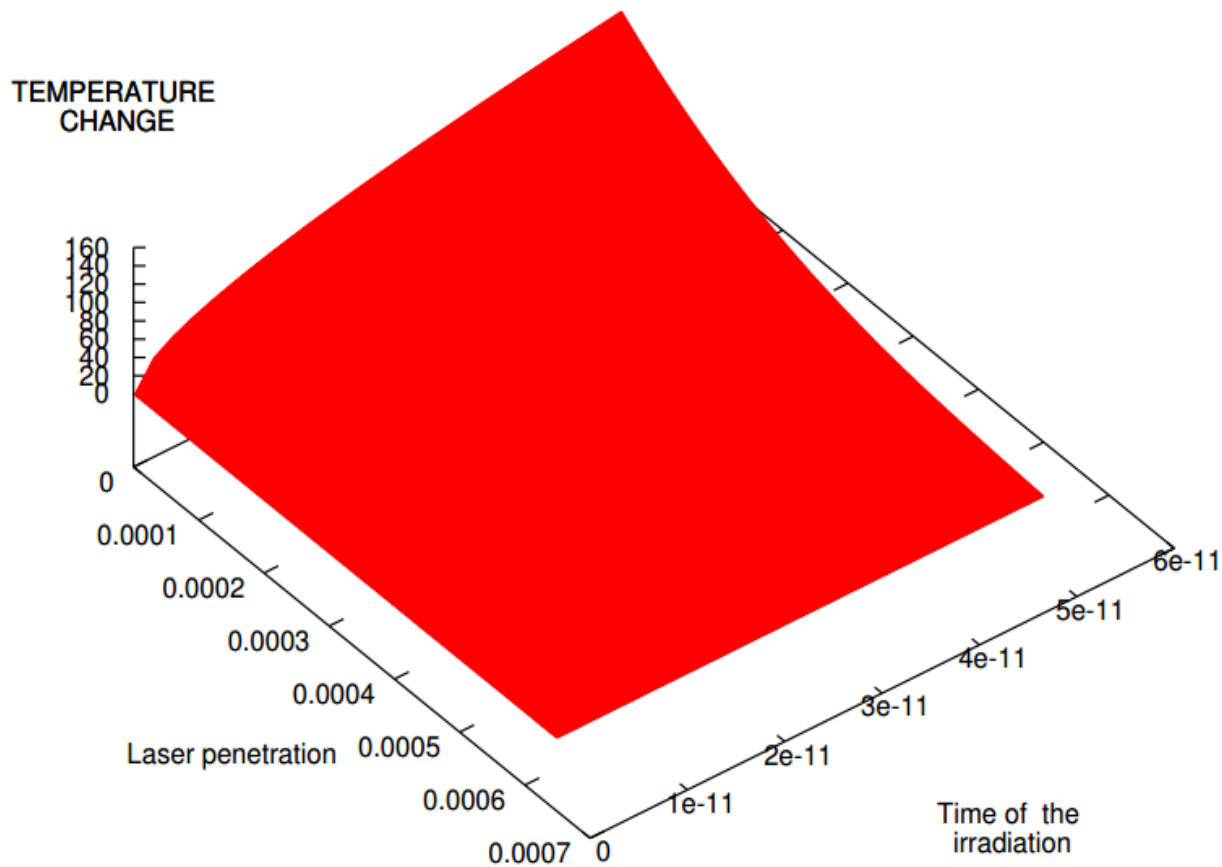
The treatment of condyloma is carried out by volatilization with a  $CO_2$  laser. This laser is used at power and pulse durations sufficient to bring the temperature above the value of 150 °C. Such a treatment leads directly to a volatilization process. Only the altered area of the tissue is concerned. High temperatures, thus obtained, are suitable for volatilization.

The temperature profile, exhibited in figure 8, clearly shows the temperature distribution on the sick portion at regular time intervals. Temperatures are high enough to trigger the process of volatilization. As it can be seen in all these figures, laser parameters and pulse duration determine how the deposited thermal energy propagates through the tissue.

The main principle is as follows:

- (i) The doctor must diagnose the disease and estimate its range of extension.
- (ii) Based on these preliminary results, a treatment protocol is setup including
- (iii) Laser power, Intensity
- (vi) Duration of laser beam application

By so doing, temperature rise induced in biological tissue by pulsed focused lasers (Nd:YAG,  $CO_2$ ) should be under control. Thanks to this control of the temperature evolution, we could avoid destroying healthy cells located near the defective area.



**Figure 8:** Temperature distributions for the biological tissue under consideration along the Ox axis for different temporal periods of the computation. Considerations are the same as in Fig 25, except that temperatures are very high in this context.

#### 4. CONCLUSION

The fundamental principle of the process developed in this contribution is summarized as follows: biological tissue is irradiated by a laser ray. Then, one observes multiple effects like coagulation, vaporization, carbonization or melting. We use laser heating of the biological tissue for the treatment of three types of diseases, namely angioma, condyloma and the tumor of the trachea affecting living tissue. These laser-based techniques lead to necrosis and then to the elimination of the infected site and thus to the potential eradication of the infection.

It should be noticed that in some cases, the patient may not tolerate other treatment methods. Because of his medical notebook, he can realize that he is not eligible for an ordinary surgery, for instance. Not being a good candidate for surgery, the only option available to him can be reduced to lasers treatment.

The use of lasers in medicine requires special attention. Use of continuous lasers leads to unwanted collateral damage on the human body which needs to be controlled or eliminated. This has prompted the use of pulsed wave lasers in medical imaging and therapy applications. The effectiveness of the process is dictated by the doctor's ability to limit the collateral damage caused by the laser pulse on healthy cells. In this sense, very précised computations have to be achieved to minimize the risk of error. This is why the DOPRI5 fourth-and-fifth-order Runge-Kutta variable step integrator was chosen in this context: A high resolution technique. This technique helps us in optimizing the reliability of the computational results for a more effective treatment with minimum damage to surrounding tissues. A correct set of physical parameters of the considered laser as well as the exact time period of laser application are the keys of the process.

In this vein, we propose a theoretical model to simulate the laser heat impact on biological tissue. As we mentioned earlier, these effects depend on the nature of the laser; its peak power, its wavelength and also on the duration of heating. Other primary information to be gathered also concerns the physical parameters of the biological tissue being treated. The thermal effects of lasers on biological tissue can be presented in three main stages: conversion of light to heat, heat transfer to the defective or undesirable portion of tissue and the tissue reaction.

We have obtained that, maximum temperatures are reached, instantly, after the triggering of the heating process. Then, this temperature gradually decreases as the distance increases. The duration of laser application, as well as the intensity of the incident laser, impacted seriously the size of the tissue affected by heating and the maximum temperature attainable during the process.

Knowledge of laser-tissue interaction, via the spatial distribution of heat through the tissue can help doctors to selecting the appropriate laser for their therapy. The results presented in this paper can be used to control the laser treatment parameters and to optimize the treatment outcome.

Finally, we hope that the computational results presented in this contribution should facilitate a better characterization of the parameters of laser ablation. We hope that this should help Physicians in optimizing the laser ablation process for a more effective treatment with minimum damage to surrounding tissues.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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