بسم الله الرحمن الرحيم

SUDAN UNIVERSITY OF SCIENCE ANDTECHNOLOGY

COLLEGE OF GRADUATE STUDIES

A THESIS SUBMITTED IN PARTIAL FULFILMENT FOR DEGREE OF M.sc IN BIOMEDICAL ENGINEERING

A Study of Optical and Thermal Effectsof Gold Nanoparticles

دراسة التأثيرات الضوئية والحرارية لجزيئات الذهب النانوية

BY

Alsaida Fatima Abd Alati Mohamed

SUPERVISOR

Dr.Fragoon Mohammed Ahmed

January 2018

بسم الله الرحمن الرحيم

﴿قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ﴾

سورة البقرة (الآية 32)

DEDICATION

This work is dedicated to the two most influential and supportive people in my life ***my beloved parents*** *who provided me with endless encouragement that I could achieve anything I put my full effort into.*

For ***myPrecious brothers*** *and* ***my sister****.*

For all ***my friends*** *who palm up their hands praying for me.*

Acknowledgment

In this project I had learned how to search for desired aim. Also I had learned the meaning of patience.

First and foremost, I thank Allah for the completion of this work.

I would like to express about my appreciation to my supervisor Dr. Fragoon Mohammed Ahmed (Department of biomedical engineering), who gave me different ideas to improve the research.

Special thanks to my beloved friends Doaa Hayder and Shahd Mohamed Salih for their help, unconditional love and support.

Also i would like to thank engineer Saddam Saed for his help and support on this project.

And my wholehearted thanks to my family for their generous support they provided me throughout my entire life and particularly through the process of pursuing the master degree.

And all my friends for their advice and prayers, I have the chance to complete this work..

To them all I say THANK YOU AND GOD BLESS YOU.

List of Contents

CHAPTER FIVE: RESULT AND DISCUSSION

Table of Figures:

Abbreviations

GNPs	gold nanoparticles
NPs	nanoparticles
Au	gold
AuNS	gold nanoshell
SPR	surface Plasmon Resonance
HAuCl4	Hydrogen tetrachloroaurate tetrahydrate
PTT	Photothermal Therapy
PPTT	PlasmonicPhotothermal Therapy
OTM	one temperature model
TEM	Transmission Electron Microscope
COMSOL	computer solution
TTM	two temperature model
SPB	urface Plasmon Band
QDs	quantum dots
UV_ Visible	Ultraviolet-Visible
PL	Photoluminescence
emw	Electromagnetic Wave, Frequency Domain
PML	Perfectly Matched Layer
FEM	finite element methods

List of Table

Abstract

The interaction between nanoparticles and radiation holds great interest in Nano medicine. Hyperthermia by laser has been considered as safe cancer treatments methods with lower harmful effects on normal tissues. Using nanoparticles in cancer treatment has improved laser therapy, which is based on a selective cell targeting method to localize cell damages. Metallic nanoparticles such as gold, silver, and copper have been recognized to highly interact with laser beam because of surface plasmon resonance phenomena. i.e. the resonant oscillation of free electrons in the nanoparticles with light. Due to toxicity of silver and copper, gold nanoparticle has received great interest in nanomedicine particularly as a protein denaturizing agent applied to the targeted cells. On the other hand, interaction between laser beam and nanoparticles depends on laser properties, medium and particle characteristics.

This project divided into two steps Firstly focused on simulation optical property of Gold nanoparticles to determining the absorption characteristics of the nanoparticle given the medium, particle, and laser parameters .Secondly the nanoparticle temperature over time numerically determined by solving the heat transfer equation using One temperature model , the effects of different Optical and thermal parameters on the Time Dynamics of Nanoparticle Heating were discussed.

المستخلص

التداخل بين الجزيئات النانوية والاشعاع شغل إهتماما كبيرا في الطب الدقيق. الحراره العالية الناتجة من اشعة الليزر تعتبر من الطرق الآمنه في علاج السرطان بأقل تأثيرات ضارة على الخلايا السليمة المجاورة . إستخدام الجزيئات النانوية في علاج السرطان طور العلاج بالليزر فهو يعتمد على اختيار الخلية المعنية لتركيز الضرر فقط على الخلية السرطانية. الجزيئات النانوية المعدنية مثل الذهب والفضة والنحاس تمتاز بتفاعلها العالي مع اشعة الليزر وذلك بسبب بلازمون تذبذب السطح وهو تذبذب الاللكترونات الحرة للجزيئات النانويه مع الضوء. بسبب سمية الفضة والنحاس شغلت جزيئات الذهب اهتمام كبير في مجال الطب الدقيق خاصة استخدامه كعامل يرتبط بالبروتينات للتركيز في الخلية المعنية.

من جانب آخر, يعتمد التفاعل بين اشعة الليزر وجزيئات الذهب النانوية على خصائص نبضة الليزر و الجزيئ النانوي والوسط المحيط.

هذا البحث ينقسم إلى جزئين , الاول يركز على محاكاة الخصائص الضوئية لجزيئات الذهب النانوية لقياس خصائص امتصاص الجزيئات للضوء باستخدام معاملات خاصةبنبضة الليزر وجزيئات الذهب النانويه و الوسط المحيط.

ثانيا تم قياس حرارة جزيئات الذهب النانوية مع الزمن رياضيا عن طريق حل معادله انتقال الحرارة ,بإستخدم نمذج الحرارة الواحدة. وتمت مناقشة تأثير العوامل الحرارية والضوئية المختلفة على تغيير حرارة جزيئات الذهب النانوية مع الزمن.

CHAPTER ONE
INTRODUCTION

CHAPTER ONE

Introduction

1.1 Overview:

Nanomedicine is currently an active field. This is because new properties emerge when the size of a matter is reduced from bulk to the nanometer scale. These new properties, including optical, magnetic, electronic, and structural properties, make nano-sized particles (generally 1–100 nm) very promising for a wide range of biomedical applications depending on the structure, composite and shape of the nanomaterial. [1]

Noblemetal nanoparticles strongly absorb and scatter specific wavelengths of optical radiation owing to their surface plasmon resonance (SPR) properties SPR is caused by the collective excitation of the conduction electrons, called plasmon oscillation, the SPR frequency is affected by the size and shape of the particle, which provide a unique tunability to the nanoparticle optical properties. Because of their unique optical properties, GNPs have been the subject of intense investigation for a variety of biomedical applications [2]. One particular area is the application of nanoparticles to enhance the diagnostic and treatment methods available for cancer [3].

It has long been known that the power of light plays an important role in multiple biological processes, but overexposure can have serious complications. [4]

Laser use in thermal therapy has long held great promise, but has never been carried out with great success. Tissue penetration, inability to selectively heat the target, and a lack of predictive heat control have prevented its widespread clinical use. Recently, gold nanoparticles (GNPs) have been proposed to enhance the treatment efficacy of Laser-induced thermal therapy. [4]

The use of gold nanoparticles (GNPs) has emerged as a good method to achieve local heat delivery when combined with laser light. GNPs have a Plasmon resonance frequency that can be tuned to absorb strongly where tissue absorption of laser light is minimal, allowing for less tissue heating and better penetration.

For further development of the technique and appropriate clinical translation, it is essential to have a computational method by which the temperature distribution within the tumor and surrounding tissue can be estimated. To understand how photothermal

therapy could be useful, it is important to understand how radiation interacts with nanoparticles.[5]

For biomedical applications especially photo thermal therapy, it is important to tailor the nanoparticle's optical properties to satisfy specific requirements.[1]

1.2 problem Statement:

to study The thermal activation of AuNPsand evaluate a safe and feasible temperature range and treatment parameters in order to destroy the tumor ,need a equipped laboratories provide an environment suitable for the experiment, but All available labs no Provides specifications required for practical experiment.

1.3 Objectives:

1.3.1 General objective:

General objective of this project is to study optical, and temperature dynamics of gold nanoparticles in biological tissue with time.

1.3.2Specific objective: Is to

- Simulation optical properties of GNPs.
- Numerical modelingof thermal activation of gold nanoparticles ,And numerically evaluated the effects of different parameters in the laser beam and particle, to facilitate the accurate controlling of laser-induced hyperthermia process .
- Verify the model to the degree needed for the models intended purpose or applications.

1.4 Thesis layouts:

This research was divided into six chapters:

Chapter one is an introduction include the objective and the general idea of the project, then chapter two shows a theoretical background of the Gold nanoparticles and their optical and thermal properties and theory of using gold nanoparticles in photo thermal therapy, chapter three shows literature reviews, chapter four include the computational modeling for opticaland thermal activation of gold nanoparticles using COMSOL

multyphysics , MiePlot software and Mable software , chapter five shows the results obtained and its discussion, finally chapter six include the conclusion and recommendations.

CHAPTER TWO
THEORETICAL BACKGROUND

Chapter two

Theoretical background

2.1 Introduction:

Nanotechnology is the ability to measure, design, and manipulate at the atomic, molecular and supramolecular levels on a scale of about 1 to 100 nm in an effort to understand, create, and use material structures, devices, and systems with fundamentally new properties and functions attributable to their small structures [6]. The art of nano manufacturing has brought about a revolution in the field of biomedical engineering where the nano -materials and –devices are designed to interact with the body at sub-cellular level.

When the size of a material is reduced to the nanometer length scale (which is the length scale of the electronic motion that determines the material's properties), it's electronic and thus chemical properties change tremendously. In semiconductor nanoparticles, the property change results from quantum confinement of the electronic motion. In metals, the properties of the surface become dominant and give nanoparticles new properties. In noble metals the coherent collective oscillation of electrons in the conduction band induces large surface electric fields which greatly enhance the radiative properties of gold and silver nanoparticles when they interact with resonant electromagnetic radiation. This makes the absorption cross section of these nanoparticles orders of magnitude stronger than the strongest absorbing molecules and the scattered light becomes orders of magnitude more intense than the fluorescence of organic dyes. These unique properties provide great potential for the nanoparticles to be used in many medical applications. [7]

2.2 Gold Nanoparticles and their properties:

Gold plays a special role in nanotechnology as it presents additional advantages, it have been used by man for over 2000 years [7]. The first known usage stems from ancient Indian medicine, where gold nanoparticles, around 60 nm in diameter were a part of a medicinal substance used to treat various diseases [8]. The Romans used gold nanoparticles hundreds of years later to create ornamental stained polychromatic glass

[9]. It took however over 1500 years to realize gold nanoparticles were the actual source of these desired effects, when Michael Faraday observed that colloidal gold solutions have properties differing from bulk gold[10] . He reported the first controlled synthesis of colloidal gold in 1857; Colloidal dispersions of gold were prepared by reducing an aqueous solution of a gold salt HAuCl4 with a solution of phosphorous in carbon disulphide. The most popular method of preparing gold particles in water is the reduction of HAuCl4 in a boiling sodium citrate solution. [7]

The interest in gold nanoparticles arises from their unique physical properties, which enable their use for many diverse applications. Of fundamental importance is the production of gold nanoparticles with finely controlled sizes and shapes[11].It is the most stable noble metal, Therefore designers of any nano-scale objects requiring metallic components preferably use gold instead of other less noble metal that can be altered by oxidation. Then, gold is a far better electron conductor than silicon. The third advantage of gold is that it offers a unique surface chemistry. In fact, gold nanoparticles grafted with organic molecules (usually via the sulfur atom) have the ability to self-assemble into two or three-dimensional ordered structures that can have potential applications in biomedical and chemical detection and optical and microelectronics devices. For the assembling of gold and other metal nanoparticles, the "bottom-up" approach (assembling of single atoms and molecules into larger nanostructures) is most commonly used compared to "top-down" approach (breaking down of large pieces of material to generate the required nanostructures from them).

There are many subtypes of GNPs based on the size, shape and physical properties [7].The earliest studied GNPs are gold nanospheres (although not exactly spherical in a strict sense) .subsequently, nanorods , nanoshell and nanocages have all been reported.

2.2.1 Optical Properties of Gold Nanoparticles:

The Romans are known to be the first using Au NPs (or colloidal gold) to stain glasses. For instance, the Lycurgus Cup (Figure 2.1), a glass embedded with 5 - 60 nm gold/silver alloy particles, changes its color depending on the illumination mode. The color of the glass appears green when it is illuminated from the outside, such as under the daylight. However, the glass appears red, when the illuminated light transmits through the glass. The fascinating colorful property comes from the optical properties of nanoparticles in the stained glass.[12]

Figure 2.1: The Lycurgus Cup

Electron microscopy of the dichroic glass revealed that most of the gold and silver nanoparticles embedded into the glass have spherical shape with diameters ranging from 5 to 60 nm. The shape and size of these nanoparticles will determine its localized surface plasmon resonance in the 400-600 nm range of the electromagnetic wavelengths which correspond to the color from violet to green of the visible spectrum (Figure 2.2) [12].

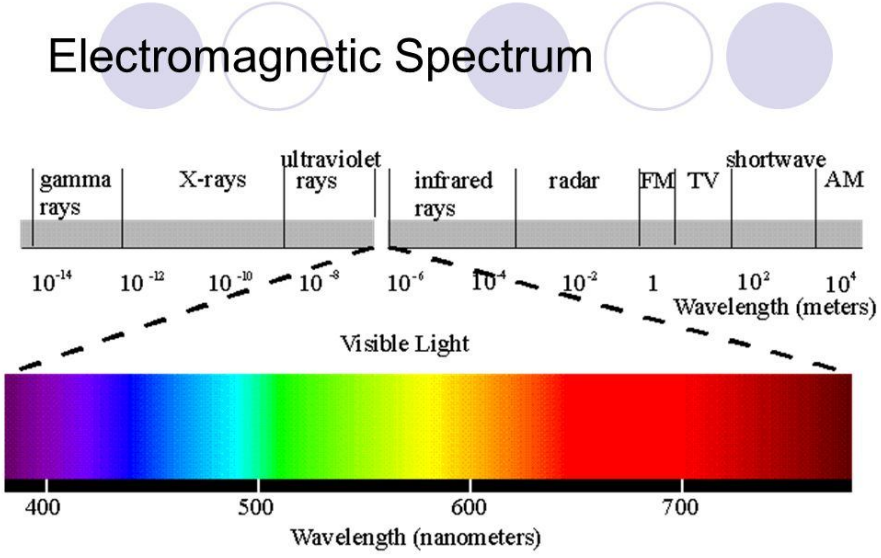

Figure 2.2: The electromagnetic spectrum.

2.2.2 Surface Plasmon Resonance:

The optical properties of nanomaterials have been extensively investigated due to their potential application in molecular-specific imaging, photothermal therapy, chemical and biological sensing, and nano-optical devices and manymore[13].

The energy loss of electromagnetic wave (total light extinction) after passing through a matter results from two contributions: absorption and scattering processes. Light absorption results when the photon energy is dissipated due to inelastic processes. Light scattering occurs when the photon energy causes electron oscillations in the matter which emit photons in the form of scattered light either at the same frequency as the incident light (Rayleigh scattering) or at a shifted frequency (Raman scattering)[1].

Noble metal nanoparticles, such as Gold in particular, are superior light absorbers and scatterers due to their strongly enhanced plasmon resonance located in the visible range [14]. The origin of the localized surface plasmon resonance may be explained as follows. When the size of the nanoparticles are comparable to or smaller than the mean free path of the free electrons in the noble metals, all the interactions with electromagnetic waves take place at the nanoparticle surface. When the wavelengths of the incoming electromagnetic waves are much larger than the nanoparticle sizes, the electron clouds at the nanoparticle surface will synchronize with the incoming optical wave and oscillate in resonance with the optical wave frequency. Figure (2.3) presents the surface charge distribution of nanoparticles at a particular time, and it is observed that the charges are polarized to oppose external electric field. The resonance condition depends on the size and shape of nanoparticles as well as the dielectric constants of materials and surroundings. [14]

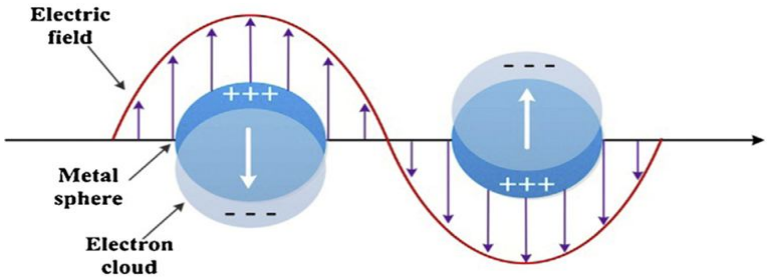

Figure 2.3: Localized surface plasmon resonance induced by external electric field surface plasmon absorption of spherical nanoparticles illustrating the excitation of the dipole surface plasmon oscillation. [15]

This induces a dipolar oscillation of all the electrons in the same phase. When the frequency of the electromagnetic field becomes resonant with the coherent electron motion.

The unique electronic optical property of the gold nanoparticles depends on their shape, size and surface to volume ratio. For instance, changing the shape from sphere to rods the surface Plasmon resonance split into two bands that differ in their sensitivity to the size changes of the GNPs. This optical property is used in experimental detection changes of parameters during the synthesis of GNPs [16].

2.2.3 Theory of Electromagnetic Waves:

2.2.3.1 Introduction to waves:

In optical phenomena such as scattering, diffraction, and interference, many photons of light are involved, not just a single photon. A beam of light with a large number of photons behaves as a wave.

Light is an electromagnetic wave made of electric E and magnetic B fields oscillating perpendicularly to each other.[5]

Propagation of Light: Since different optical phenomena can happen with the light in a medium, such as scattering, refraction, absorption, and dispersion, in general the index of refraction is a complex number, $m = n - ik$ Here, n is the real part, which describes the optical phenomena like scattering and refraction of the light, and k is the imaginary part, which is responsible for absorption of the light in the medium. [5]

2.2.3.2 Analytical Study of the Scattering and Absorption of GNPs:

The phenomena of SPR can be described via classical electrodynamics where the Electromagnetic field, generated by a distribution of electric charges, is postulated by Maxwell's equations, whose differential forms are written as:

$$\nabla \times H = J + \frac{\partial D}{\partial t} \quad 2.1$$

$$\nabla \times E = -\frac{\partial B}{\partial t} \quad 2.2$$

$$\nabla \cdot D = \rho \quad 2.3$$

$$\nabla \cdot B = 0 \quad 2.4$$

$$\nabla \cdot J = -\frac{\partial \rho}{\partial t} \quad 2.5$$

WhereE is the electric field intensity, D is the electric displacement (or flux) density, H is the magnetic field intensity, B is the magnetic flux intensity, ρ is the electric charge density and J current density . The above Maxwell's equations are applicable for general time-varying fields. Equation 2.1 and Equation 2.2 are referred to as Ampere's law and Faraday's law, respectively[17].

Electromagnetic waves scatter when encountering obstacles, e.g. nanoparticles, a part of the scattering comes from the change of propagation direction from original wave direction, and this takes place when the incoming wave interacts with the oscillating free electrons in the nanoparticles. Another part of the scattering comes from the secondary radiation of nanoparticles resulted from the accelerated electrons in the incident electromagnetic field. The accelerated electrons may also absorb a portion of the incident energy in the form of thermal energy. The sum of scattering and absorption is called extinction which represents the total energy loss of incident waves upon interacting with nanoparticles [18]. In order to quantify the energy power that is lost either by scattering or absorption, a physical quantity, called cross-section, is defined as a hypothetical area that describes the probability of light being scattered or absorbed.

2.2.3.3 Lorenz–Mie solution:

An analytical solution of the Maxwell's equation for the spherical particles was found by the Danish physicist Ludwig Lorenz in 1890, and also independently by the German physicist Gustav Mie in 1908, who was working on the problem of explaining the color of colloidal gold particles in water [5].

The Mie theory provides exact values of the far-field extinction, absorption and scattering efficiency and asymmetry factors for a spherical particle suspended in a non-absorbing host medium illuminated by an incident plane wave.

In the most general case, the Lorentz–Mie solutions give the scattering matrix of particle j, $S^j(\theta,\varphi)$ this consists of four complex functions, $S^j(\theta,\varphi)$ (i=1, 2, 3, 4), describing the amplitude and phase of a scattered scalar wave in any direction Forward scattering $(\theta = 0°)$contains the attenuation process of the electromagnetic wave, and for the case of spherical particles, $S_3^j = S_4^j = 0$ Thus, we can limit the description to a single scattering amplitude function

$$S^j = S_1^j(0) = S_2^j(0) = \frac{1}{2}\sum_{l=1}^{\infty}(2l+1)Re\left(a_l^j + b_l^j\right) \qquad 2.6$$

The Mie coefficients a_l and b_l contain the characteristics of the dispersal medium and are calculated through the cylindrical Bessel function of the first kind, $\psi_l(y)$,and the Hankel function of the second kind, $\zeta_l(\rho)$=, both with half-integral indices

$$a_l = \frac{\dot{\psi}_l(y)\psi_l(\rho) - \tilde{m}\psi_l(y)\dot{\psi}_l(\rho)}{\dot{\psi}_l(y)\zeta_l(\rho) - \tilde{m}\psi_l(y)\dot{\zeta}_l(\rho)} \qquad 2.7$$

$$b_l = \frac{\tilde{m}\dot{\psi}_l(y)\psi_l(\rho) - \psi_l(y)\dot{\psi}_l(\rho)}{\tilde{m}\dot{\psi}_l(y)\zeta_l(\rho) - \psi_l(y)\dot{\zeta}_l(\rho)} \qquad 2.8$$

Here, $\tilde{m} = \frac{m_0}{m1}$ is the relative value of the refractive index of the medium;

$m_0 = n_0 - ik_0$, And $m_1 = n_1 - ik_1$ are the complex refractive indices of the particle material and the aqueous suspension, respectively; $\rho = 2\pi r_0/\lambda$ is the Mie parameter; and $y = 2\pi r_0 n_0/\lambda$, $\psi_l(u) = (\pi u/2)^{1/2} J^{(1)}_{l+1/2}$, $\zeta_l(u) = (\pi u/2)^{1/2} H^{(2)}_{l+1/2}$ and $\dot{\psi}_l = d\psi_l(u)/du$ With knowledge of $S^j(0)$, it is possible to calculate the optical properties of the particles (i.e., the dimensionless efficiencies of scattering, $Q^j_{sca}(\rho,\tilde{m}) = \sigma^j_{sca}(\rho,\tilde{m})/\sigma_0$ absorption , $Q^j_{abs}(\rho,\tilde{m}) = \sigma^j_{abs}(\rho,\tilde{m})/\sigma_0$ and extinction , $Q^j_{ext}(\rho,\tilde{m}) = \sigma^j_{ext}(\rho,\tilde{m})/\sigma_0$ of the radiation at a given wavelength) [5].

$$Q^j_{ext}(\rho,\tilde{m}) = \frac{4\pi}{k^2} Re\{S^j(0)\} \qquad 2.9$$

$$Q^j_{sca}(\rho,\tilde{m}) = \frac{2}{\rho^2}\sum_{l=1}^{\infty}(2l+1)\{\left|a^j_l\right|^2 + \left|b^j_l\right| \ \}^2 \qquad 2.10$$

$$Q^j_{abs}(\rho,\tilde{m}) = Q_{ext}(\rho,\tilde{m}) - Q_{sca}(\rho,\tilde{m}) \qquad 2.11$$

2.3 Applications of gold nanoparticles:

- Electronics - Gold nanoparticles are designed for use as conductors from printable inks to electronic chips. Nanoscale gold nanoparticles are being used to connect resistors, conductors, and other elements of an electronic chip.
- Therapeutic Agent Delivery - Therapeutic agents can also be coated onto the surface of gold nanoparticles, The large surface area-to-volume ratio of gold nanoparticles enables their surface to be coated with hundreds of molecules (including therapeutics, targeting agents, and anti-fouling polymers).
- Sensors - Gold nanoparticles are used in a variety of sensors. For example, a colorimetric sensor based on gold nanoparticles can identify if foods are suitable for consumption.

- Probes - Gold nanoparticles also scatter light and can produce an array of interesting colors under dark-field microscopy. The scattered colors of gold nanoparticles are currently used for biological imaging applications.
- Diagnostics - Gold nanoparticles are also used to detect biomarkers in the diagnosis of heart diseases, cancers, and infectious agents.
- Catalysis - Gold nanoparticles are used as catalysts in a number of chemical reactions.
- Photodynamic Therapy - Near-IR absorbing gold nanoparticles (including gold nanosphere, gold nanoshells and nanorods) produce heat when excited by light at wavelengths from 500 to 800 nm. This enables these nanoparticles to eradicate targeted tumors.[19]

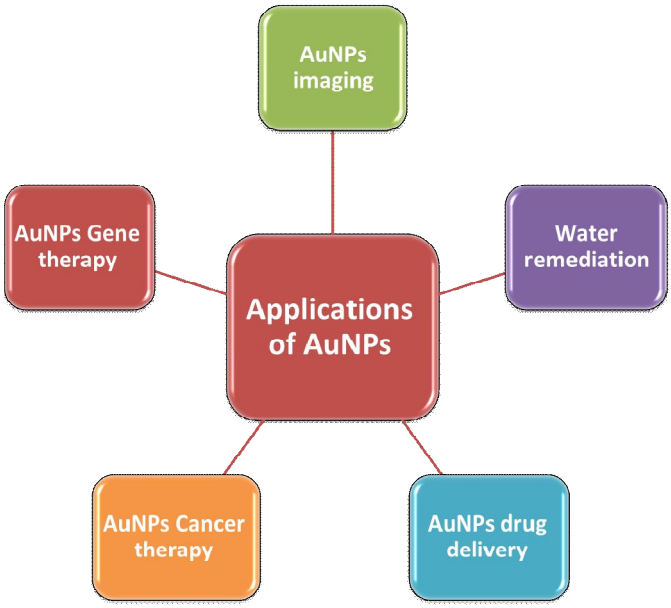

Figure2.4:application of GNPs

2.3.1 Nanotechnology in Cancer Detection and Treatment:

Cancer continues to be among the leading causes of death worldwide. Occupying the second place in developing countries and showing a growing incidence over time. Cancer is a state of abnormal cell growth known as the malignant tumor or malignant neoplasm, with a potential to invade other cells or organs in the body. Cancer is affecting all age groups and is associated with serious medical, psychological, virtually, economic and social insinuations. The most common types of cancers are stomach, lung, breast, colon-rectum, prostate, cervix-uteri, mouth, pharynx, liver and esophagus. Its intricacy relies in being a class or group of combined diseases which makes it extremely challenging to find a single cure and target a specific tissue. Current cancer therapy approaches are based on surgery, radiotherapy and chemotherapy where the latter is the one that shows the greater efficacy for treatment, expressly in advanced stages.

The application of nanotechnology research in the field of cancer encompasses multi-interdisciplinary approaches integrating medicine, biology, engineering, chemistry, and physics. Many materials have been used in nanotechnology for cancer diagnosis and therapy [16].

2.3.2 Photothermal Therapy:

2.3.2.1 Introduction:

The history of thermal therapy starts more than 3000 years ago. At that time warm baths were used to cure different diseases [20].

Thermal therapy or hyperthermia is a noninvasive approach to cancer treatment, in which tissues are exposed to higher than normal temperatures to promote selective destruction of abnormal cells. Cancer cells are more susceptible to hyperthermia effects than normal cells because of their higher metabolic rates. A marked reduction in tumor size after treatment by localized hyperthermia has been demonstrated by numerous clinical studies. Several methods, including microwave irradiation, RF pulses, and ultrasound, have been used for the delivery of thermal energy. Although they can penetrate deep into tissue, high fluences are required because of their diffusive nature, which produces undesirable hyperthermic effects on surrounding tissues. laser beams can penetrate tissues with sufficient intensity and high spatial precision. However, the

low absorption of NIR light by tumors requires high levels of energy input to produce enough hyperthermic effects [21].

The safety concerns associated with laser at such high energy levels discourage its clinical considerations. To make this treatment clinically safe and viable, the hyperthermic effect has to be intensified and highly localized, which makes it necessary to enhance the light absorption and energy conversion in the tumors. In this sense, localized hyperthermia with gold nanoparticles is being developed as an alternative to the conventional hyperthermia methods [21].

Several clinical trials have demonstrated that hyperthermia provides significant improvements in clinical outcomes for a variety of tumors, especially when combined with radiotherapy. However, its routine clinical application is still not optimal and major improvements are needed. The temperature distributions achieved are far from satisfactory and improved temperature control and monitoring are still in need of further development [22].

2.3.2.2 Photothermal therapy using gold nanoparticles:

Recent studies of optical properties of gold nanoparticles have provided motivation for new type of targeted thermal therapy. The tunable optical resonance and strong absorbance of light in the visible and infrared spectrum by gold nanoparticles makes them suitable for heat dose delivery to a tumor region [23, 24, 25].

Studies have shown that coating the surface of nanoparticles with a specific protein (a "targeting agent," normally an antibody) will induce the nanoparticles to bind to a complementary protein such as found on a cancer cell. After the nanoparticles are bound to the cancerous cells, they can be heated with electromagnetic radiation, inducing a variety of effects around the particles. The heated particle can cause the cell to experience hyperthermia, resulting in denaturing of surface proteins and changing of membrane permeability. Alternatively, the nanoparticles themselves can heat to the point of melting, evaporation, or explosion, causing further damage to cells. These effects can be used to increase the sensitivity of photoacoustic diagnosis or aid in therapy, such as selective photothermolysis, by selective thermal killing of tumor cells (figure 2.5) [3].

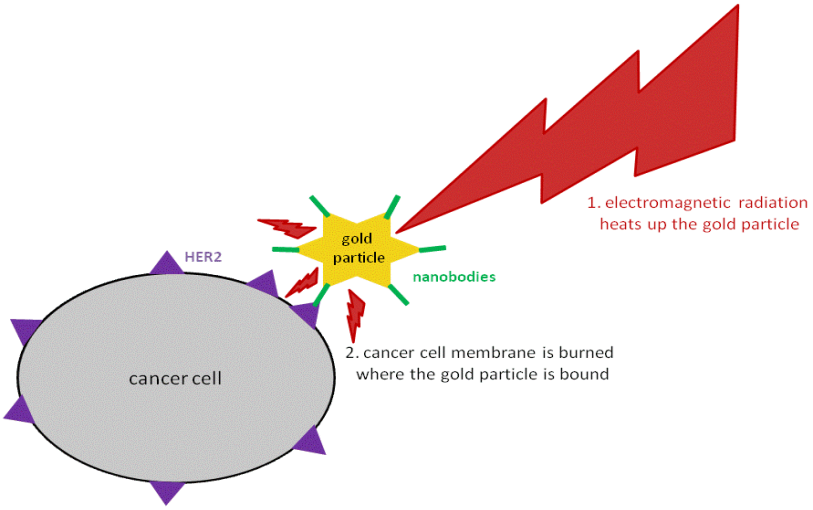

Figure 2.5: photothermal therapy

The potential advantages of these new photothermal sensitizers heated with laser pulses may include:

1. Selective cancer cell targeting by means of conjugation of absorbing particles (e.g., gold nanospheres, nanoshells, or nanorods) with specific antibodies;
2. Localized tumor damage without harmful effects on surrounding healthy tissue.
3. Absorption at longer wavelengths in the transparency window of most biotissues.
4. No undesired side effects (e.g., cytotoxicity or cutaneous photosensitivity), and
5. Relatively fast treatment involving potentially just one or several laser pulses.

Progress toward the development of selective nanophotothermolysis technology requires the investigation of new physical concepts and new approaches to the study of short laser pulse interactions with biological systems containing nanostructures. The extent of the particle heating depends on many factors and parameters [3].

2.3.2.3 Phenomenological parameters and properties of laser–nanoparticle-tissue interactions:

Optimization of different NP types is based on the investigation of the influence of different parameters of NP itself, laser pulses, and ambient media on efficiency of NP applications for laser diagnostics and therapy of cancer. The NPs have two basic geometries: spherical and cylindrical with various compositions including spherical homogeneous and core shell two-layered NPs and gold nanorods [26].

Different parameters of laser radiation, NPs, and ambiences can influence on thermo-optical properties of absorbing NPs and determine the achievement of maximal efficacy of transformation of absorbed energy into photothermal phenomena among these parameters; we can note the next ones:

- **Laser radiation**

(a) Pulse duration

(b) Wavelength

(c) Energy density E (andintensity I0)

- **Nanoparticle**

(a) Material of NP with values of density, heat capacity, and optical properties

(b) Size

(c) Concentration of NPs in medium

(d) Shape (spherical and cylindrical)

(e) Structure (homogeneous and core–shell)

- **Ambient medium**

(a) Coefficient of thermal conductivity, density, and heat capacity

(b) Coefficient of absorption, scattering, and extinction [26].

2.3.2.4 Thermodynamics of Nanoparticles:

2.3.2.4.1 Time Dynamic Model:

The main mechanism of heating a nanoparticle by radiation is the inverse bremsstrahlung absorption of photons by free electrons, followed by heat transferred from the electron gas into the material lattice and further to the surrounding medium. These processes do not occur instantaneously: time must be allowed for the cooling of the electrons and the heating of the lattice producing a difference between electron (T_e) and phonon (T_s) subsystem temperatures. The electron–phonon coupling process has several characteristic time scales electron thermalization timeτ_e, electron cooling time τ_c., lattice heating time τ_i, and duration of the laser pulse τ_p. The relationship between them defines three different regimes of the laser–particle interaction—femtosecond, picosecond, and nanosecond modes of heating.

- The femtosecond mode of heating is realized when the laser pulse duration is shorter than the electron thermalization and cooling times$\tau_p \ll \tau_e, \tau_c$.

- The picosecond mode of heating is observed when the laser pulse duration is comparable to the lattice heating time, $\tau_p \sim \tau_i$
- The nanosecond mode of heating is applied when the laser pulse duration exceeds the electron–phonon coupling time ,$\tau_p > \tau_e, \tau_c, \tau_i$.

Two models are studied to describe the laser pulse interaction with nanoparticles in the femtosecond, picosecond, and nanosecond regimes , The first is a one-temperature model utilizing a heat diffusion equation for the phonon subsystem and applying a uniform heating approximation

Throughout the particle volume. The second is a two-temperature model using two coupled diffusion equations, one describing the heat conduction of electrons and the other that of the lattice [5].

OTM is an appropriate approximation for nanoparticle heating in the femtosecond, picosecond, and nanosecond regimes, thus providing an effective modeling method for further nanomedicine research to explore.

Even with the many factors involved in an experimental setup that contribute to the individual heating characteristics of a nanoparticle, several factors stay relatively constant across many experimental situations. Specifically, spherical gold nanoparticles are commonly used because they are relatively easy to fabricate, nontoxic, easily conjugated to antibodies, and strong absorbers. Nanosecond pulse-width lasers with pulse-firing frequencies of 10 Hz are often used because they are widely available and cheaper than Pico and femtosecond lasers or lasers with higher firing frequencies. Additionally, water or a phosphate buffered saline solution is employed as a surrounding medium due to large similarities to a biological cell [27].

2.3.2.4.2 One-Temperature Model:

During the interaction of a laser pulse of intensity I_0 and pulse duration τ_p with a metal nanoparticle of radius r_0, the laser energy is absorbed by free electrons and then transferred from the electron gas into the material lattice. In the one-temperature model (OTM), it is assumed that the electron heat transfer into the phonon subsystem is very fast, i.e., the electron and lattice temperatures are equal, Te=Ts, at any instant in time [27].

The equation which describes the kinetics of laser heating of the nanoparticle can be written as

$$\frac{\partial T_s}{\partial t} = \frac{3I_0 f(t) Q_{abs}}{4r_0 \rho_s C_s(T_s)} - \frac{3\mu_\infty T_\infty r_0}{(\alpha+1) r_0^2}\left[\left(\frac{T_s}{T_\infty}\right)^{\alpha+1} - 1\right] + \frac{3L}{4r_0 C_s(T_s)}\frac{dr_0}{dt} \qquad 2.12$$

This is called the one-temperature model (OTM) which is derived from heat transfer equation. This model will be used to evaluate the temperatures reached inside the nanoparticle as a function of time. Here, the first term on the right side of the equation describes the heat generation into the nanoparticle due to radiation energy absorption by the nanoparticle. The second term describes the energy losses from the surface of the particle into the surrounding medium due to the heat diffusion process. The lastterm describes the energy losses due to the evaporation of the particle. This evaporation depends on the laser pulse characteristics and particle properties, andit can be realized in five different regimes: free molecular, convective, diffusive, gas dynamic, and explosive modes of evaporation.If the heating of the nanoparticle occurs below the temperature of the phase transition in the particle material, the third term on the right side of equation (2.12) can be neglected [27].

The OTM is an appropriate approximation for pulse durations greatly exceeding the electron–phonon coupling time. This approximation is reasonable for particles sizes not much larger than the laser wavelength, which is completely applicable for the heating of nanoparticles.

The variables that described by OTM listed in table 2.1 [5].

Table2.1 one temperature model variables:

Q_{abs}	Absorption efficiency of NP
I0 [W/cm2]	Intensity of laser pulse
f(t)	Pulse shape
r_0	Radius of gold nanoparticles
C(T)	Specific heat of GNP
ρ_s	Density of NP
μ_∞	Heat conductivity of surrounding medium
T_s	Final temperature of GNP
α	Exponential power
T_∞	Initial temperature of NP
L	Latent heat
dt	Time step

For laser heating of metal nanoparticles in the nanosecond regime, the characteristic lattice heating time $\tau_i$is much smaller than the laser pulse duration: τ_p » τ_i . This means that the temperature inside the nanoparticle is nearly uniform over the whole particle on the time scale of the laser pulse durationτ_p. In this case, the electron and lattice temperatures are equal (Te=Ts), so that thehomogeneous heating of the particle and quasi-steady heat exchange with the surrounding medium can be described by just OTM. The characteristic lattice heating time τi required for the formation of a quasi-stationary temperature profile across the nanoparticle can be estimated from the formula$\tau_i = {r_0}^2/4\chi$. where r0 isthe particle radius and χ the thermal diffusivity of the particle material. For a gold nanoparticle ($\chi = 1.18 \times 10^{-4}\, m^2/s$) ,with radius r0=20–30 nm, the lattice heat diffusion time is $\tau_i \sim 2 \times 10^{-12} s \ll \tau_p \sim 10^{-8} s$.

CHAPTER THREE

LITERATURE REVIEW

CHAPTER THREE

LITERATURE REVIEW

3.1Review ofApplication of Gold Nanoparticles:

Nagender Reddy Panyala, Eladia Mara Pena-Mendez , Josef Havel developed study about "Gold and nano-gold in medicine: overview, toxicology andperspectives"[28].
Nano-technology has entered the field of medicine in recent decades and many of the nanomaterials developed have already had a high impact on health care. Among nanomaterials, gold nanoparticles (GNPs) and gold quantum dots (QDs) (Quantum dots are semi-conducting nanocrystals which have quantum optical properties due to the confinement of their excitons in all three spatial dimensions. These non-fluorescent compounds develop intense, long-lasting colors excitable by UV and visible light-emitting diodes, lasers, etc.) are receiving significant attention because their unique physical, chemical and biological properties are quite different from the bulk of their counterparts. In this article, after a brief historical overview, the use of gold and nano-gold in medicine is reviewed, analyzed, and discussed. The review particularly deals with the use of GNPs and bio-conjugated GNPs in cancer treatment, drug or gene delivery, DNA detection, biomedical imaging including that of brain activity, enhancement of gene regulation, the detection of toxic metals, immuno-assays, disease detection and diagnostics, therapy and also the toxicity of gold and GNPs, etc.

Cancer nanotechnology is an interdisciplinary area with broad potential applications in fighting cancer, including molecular imaging, molecular diagnosis, targeted therapy, and bioinformatics.Over the last decade, there have been Many researches about this topic.
One of this researches “Applications of gold nanoparticles in cancer Nanotechnology” done by Weibo Cai1, Ting Gao Hao Hong1 Jiangtao Sun1 in USA .[29]

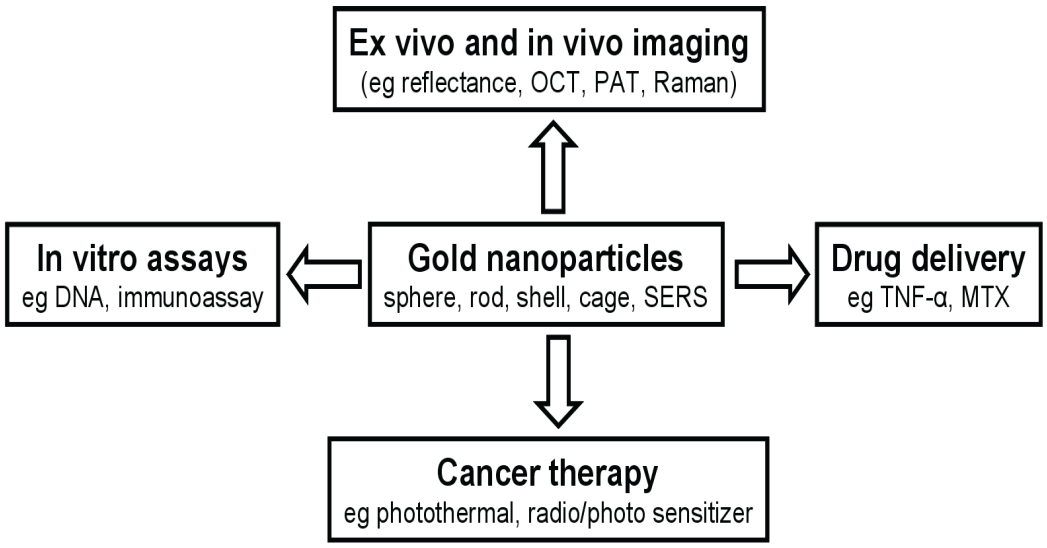

Figure3.1: The versatile properties of gold nanoparticles have been employed for biomedical applications in many areas.

Very few nanoparticle-based agents are in clinical testing or commercialized for cancer diagnosis or treatment.

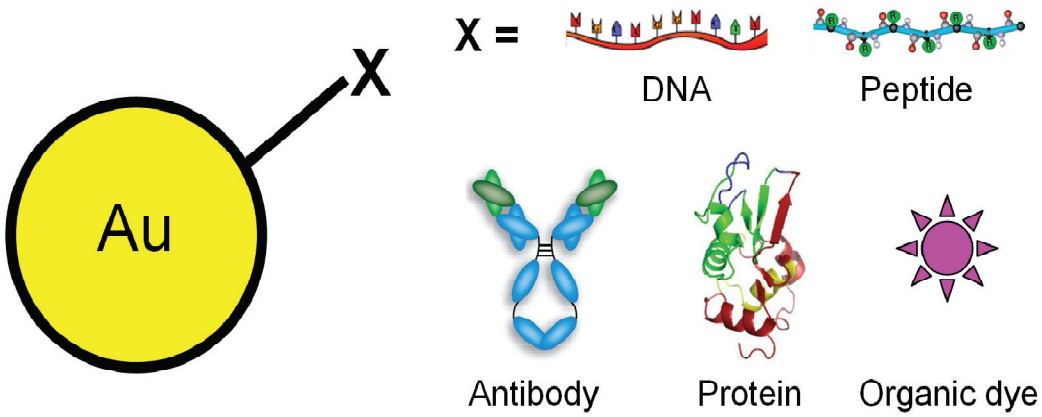

Figure 3.2 : Gold nanoparticles have been modified with various molecules for in vitro assays.

Due to their unique properties, gold nanoparticles can be used to treat cancer .most studies of gold nanoparticle-based cancer therapy have used photothermal therapy for the destruction of cancer cells or tumor tissue. When irradiated with focused laser pulses of suitable wavelength, targeted gold nanospheres, nanorods, nanoshells, and nanocages can kill bacteria and cancer cells [30] .it was estimated that 70–80 °C was achieved through light absorption by the gold nanoparticles.

3.2 Review of optical and Thermal properties of Gold nanoparticle:

Mohamed Anwar K Abdelhalim, Mohsen M. Mady and Magdy M. Ghannam, King Saud University, College of Science, Department of Physics and Astronomy, Riyadh, Saudi Arabia, developed study about " Physical Properties of Different Gold Nanoparticles: Ultraviolet-Visible and Fluorescence Measurements"

This study evaluated the absorption and fluorescence spectra for solutions of GNPs at different concentrations.

In this study the mean sizes of GNPs were calculated from Transmission Electron Microscope (TEM) images, which were also used to study the morphology of the GNPs. UV–Visible and fluorescence measurements, were made from 250-700 nm using 1 cm quartz cuvettes.

They found that When the GNP size changed from 10 nm to 50 nm, the maximum extinction of the Surface Plasmon Band (SPB) shifted from 517 nm to 532 nm in the visible region which may be attributed to the surface plasmon oscillation of free electrons. At constant GNP size, the absorbance was found to be proportional to the concentration of gold; this is because an increased number of GNPs also increases the total surface for surface plasmon resonance. The Photoluminescence (PL) band center appears at 423 nm. An increase in fluorescence intensity with increase in GNP size was observed. At a fixed GNP size of 10 nm, and with increasing GNP concentration, the intensity of the emission band increased, which was consistent with the changes observed for the surface plasmon band of GNPs.

They concluded that the absorption intensity and maxima are particle size dependent. The surface plasmon resonance of the gold particles is red shifted (from 517 to 532 nm) with increasing particle size. These results indicate that the fluorescence intensity and the absorption band of GNPs were concentration and particle size dependent [31].

3.3 Review of Modeling of Gold Nanoparticles:

Renat R. Letfullin, Thomas F. George, Galen C. Duree, and Brett M. Bollinger developed study about: "Ultra short Laser Pulse Heating of Nanoparticles: Comparison of Theoretical Approaches"

In this article two models are studied to describe the laser pulse interaction with nanoparticles in the femtosecond, picosecond, and nanosecond regimes. The first is a

two-temperature model using two coupled diffusion equations: one describing the heat conduction of electrons, and the other that of the lattice. The second model is a one-temperature model utilizing a heat diffusion equation for the phonon subsystem and applying a uniform heating approximation throughout the particle volume. A comparison of the two modeling strategies shows that the two-temperature model gives a good approximation for the femtosecond mode, but fails to accurately describe the laser heating for longer pulses.

On the contrary, the simpler one-temperature model provides an adequate description of the laser heating of nanoparticles in the femtosecond, picosecond, and nanosecond modes.[27]

Ali Hatef, Simon Fortin and Michel Meunier in Laser Processing and Plasmonics Laboratory, Department of Engineering Physics, developed study about :

"Simulation of nanosecond laser-induced thermal dynamics of hollow gold nanoshells for hyperthermia therapy"

In this report, they investigate numerically the thermodynamics of hollow gold nanoshell (AuNS) irritated by nearinfrared light. Simulations are performed for the AuNS in aqueous medium. The nanostructure is illuminated by a nanosecond pulsed laser at plasmonic resonance.They consider a system consisting of AuNS with an exterior and interior diameter of 43 and 38 nm, respectively, immersed in water (Figure 3.3). The core material is considered to be water.

Figure 3.3 (a) shows the absorption, scattering and extinction cross sections as a function of wavelength calculated by FEM numerical solutions of Maxwell's equations for an AuNS with the given dimensions. As seen in this figure, at LSPR wavelength λmax = 784 nm, the absorption (1.75×104 nm2) is the dominant optical phenomenon rather than scattering. This means that for an AuNS with these dimensions, almost all of the laser energy is being converted to heat where the LSPR wavelength lies in the range of therapeutic window or NIR.

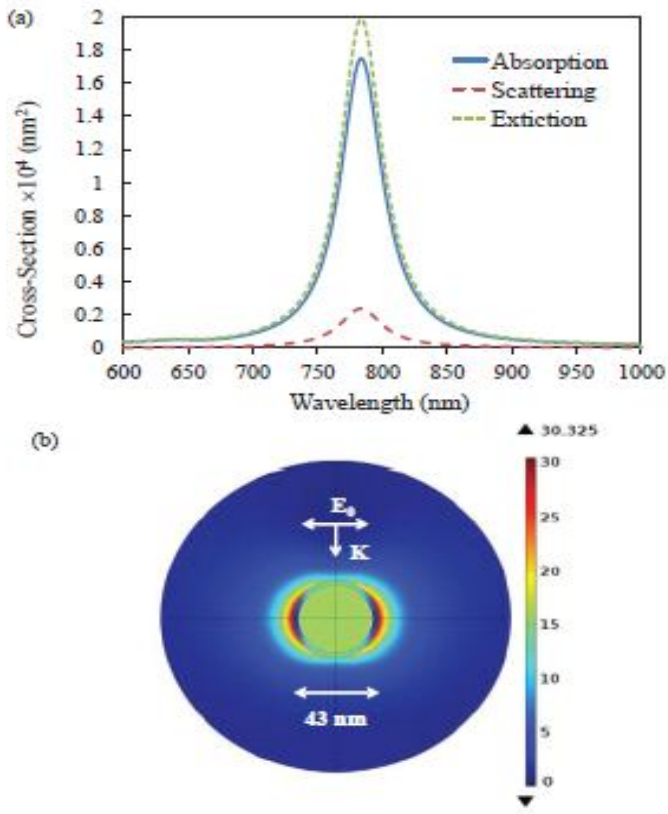

Figure (3.3): (a) FEM calculation of scattering, absorption and extinction as a function of the incident laser wavelength. The maximum field absorption occurs on λmax=784 nm. (b) Cross-section of the near-field enhancement distribution in and around aAuNS, at λmax.

The spatiotemporal evolution of the temperature profile inside and outside the AuNS is computed using a numerical framework based on the finite element method (FEM). In particular, they show how the temperature varies with the laser fluence and pulse duration. The aim of this study is to provide a description of the physics of heat release of AuNSs and useful insights for the development of these nanostructures for biomedical applications such as drug delivery, photothermal cancer therapy and optoporation of cells. [32]

E Sassaroli, K C P Li and B E O'Neill, in Department of Radiology, the Methodist Hospital Research Institutedeveloped study about:"Numerical investigation of heating of a goldnanoparticle and the surrounding microenvironment by nanosecond laser pulses for nanomedicineapplications"

In this study They have modeled, by finite element analysis, the process of heating of aspherical gold nanoparticle by nanosecond laser pulses and of heat transfer between the particle and the surrounding medium, with no mass transfer. In theanalysis, they have included thermal conductivity changes, vapor formation, and changes of the dielectric properties as a function of temperature. They have shown that such changes significantly affect the temperature reached by the particle and surrounding microenvironment and therefore the thermal and dielectric properties of the medium need to be known for a correct determination of the temperature elevation. They have shown that for sufficiently low intensity and long pulses, it is possible to establish a quasi-steady temperature profile in the medium with no vapor formation. As the intensity is increased, a phase-change with vapor formation takes place around the gold nanoparticle. As phase transition starts, an additional increase in the intensity does not significantly increase the temperature of the gold nanoparticle and surrounding environment.

The temperature starts to rise again above a given intensity threshold which is particle and environment dependent. The aim of this study is to provide useful insights for the development of molecular targeting of gold nanoparticles for applications such as remote drug release of therapeutics and photothermal cancer therapy. [2]

F. Rossi, F. Ratto1, and R. Pini, in Institute of Applied Physics "NelloCarrara", Italian National Research Councildeveloped study about:

"Laser Activated Gold Nanorods for the Photothermal Treatment of Cancer"

Photothermal therapy through Gold Nanorods (GNRs) is a new approach for the minimally invasive treatment of cancerous tissue. In order to design the proper settings, it is important to study the thermal effects that are induced close to the nanoparticle (nanoscale model), in the close vicinity and in the cancerous tissue (microscale model). COMSOL Multiphysics 4.2a was used to indicate diode laser irradiation parameters and treatment time in the design of a new concept for hyperthermia of tumor tissue.

A temperature dependent 2D-model of this particular light matter interaction was designed. The expected absorption cross sections of the GNRs were used to calculate the optical absorption of the GNR. The bioheat equation then enabled to describe the photothermal effect within the GNRs and the environment. The postprocessing results may be used to evaluate a safe and feasible temperature range and treatment time, in order to destroy the tumor volume.

The concept of the new approach for the laser induced hyperthermic treatment of cancerous tissue is based on the use of GNRs, located close to the external membrane or eventually inside a tumor cell. The laser light emitted by a NIR diode laser (@810 nm) is delivered through an optical fiber to the tumor site where the GNRs are located. The laser light is selectively absorbed by the GNR and then converted into thermal energy. If the GNRs are properly attached to the tumor tissue, a correct balance of the concentration of GNRs in the tumor volume and of the laser parameters can induce hyperthermia and so destruction of the cancer. Aim of the modeling study is to evaluate the photothermal conversion efficiency, in dependence of the settings parameters, in order to find reasonable parameter values prior than any experimental investigation (ex vivo or in vivo).

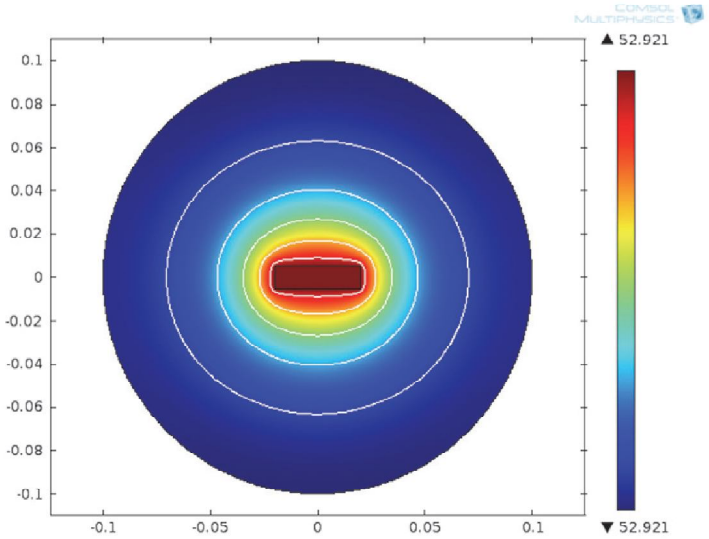

Figure 3.4. Bidimensional model of a GNR (the rectangular shape in the center of the draw) inside a biocompatible biopolymer circular shell. Dimensions are in micrometers. Temperature map after 2s irradiation with a 0.5 mW/cm2 diode laser.

They considered different intensities of the laser light, in order to find the optimized value to induce hyperthermia in the tumor tissue without destroying the GNR and its biopolymeric shell.

Also they varied the treatment time, and found that 0.5 mW/cm^2 and a treatment time of around 2s are a good compromise to induce optimal values around the GNR. The GNR immediately thermalizes with the external shell. The induced temperature value is around 53°C, well above the hyperthermic range. By using a value higher than the recommended 42°C, they obtain a good thermal distribution around the intended value in the surrounding tissue.

CHAPTER FOUR

METHODOLOGY

CHAPTER FOUR

Methodology

In this chapter an electromagnetic and thermodynamic study of the optical property and heating of GNPs is modeled.

The procedure consists primarily of two stages:

(1) **Stage one:** modeling optical property of GNPs and determining the absorption and scattering characteristics of the nanoparticle (given the medium, particle, and laser parameters).

(2) **Stage two**: numerically solving the heat transfer equation using one temperature model to determine the nanoparticle temperature over time.

4.1 Stage one:

4.1.1 Simulation Optical properties of gold nanoparticles:

4.1.1.1 Simulation by COMSOL multyphysics:

COMSOL multyphysics is finite element analysis and solver software for various physics and engineering applications.

To simulate optical and thermal property of gold nanoparticles with COMSOL multiphysics we must follow all steps in the modeling process as in the figure 4.1 below

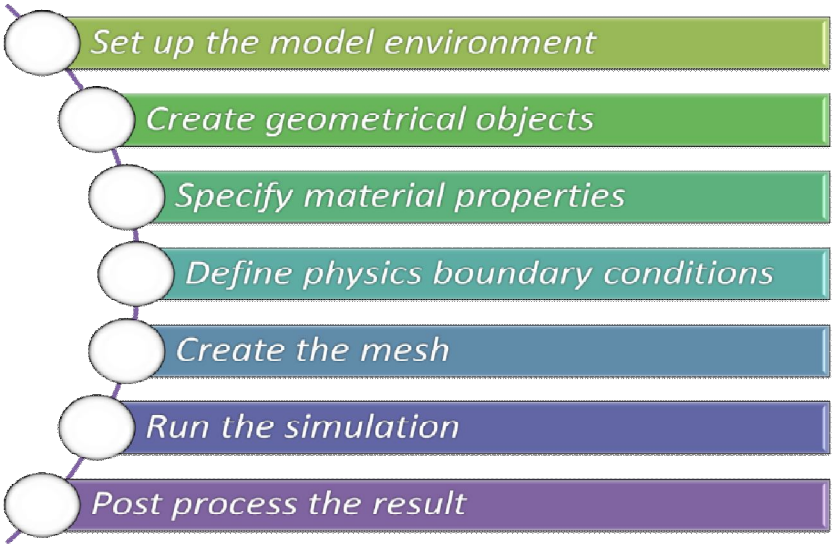

Figure 4.1: COMSOL workflow

Simulation of optical field of a gold nanoparticle in x-y plane by COMSOL 5.2 the interface must use was Electromagnetic Wave, Frequency Domain (emw) under the module Radio Frequency. Study in 3D under frequency domain.

4.1.1.1.1 Model Definition:

Consider a system consisting of gold sphere with 100nm diameter, (Figure 4.2). The core material considered to be water(The biological soft tissues and cells mostly consist of water up to 60–70% of the total content) . The free space wavelength range from 400 nm to 700 nm is simulated.

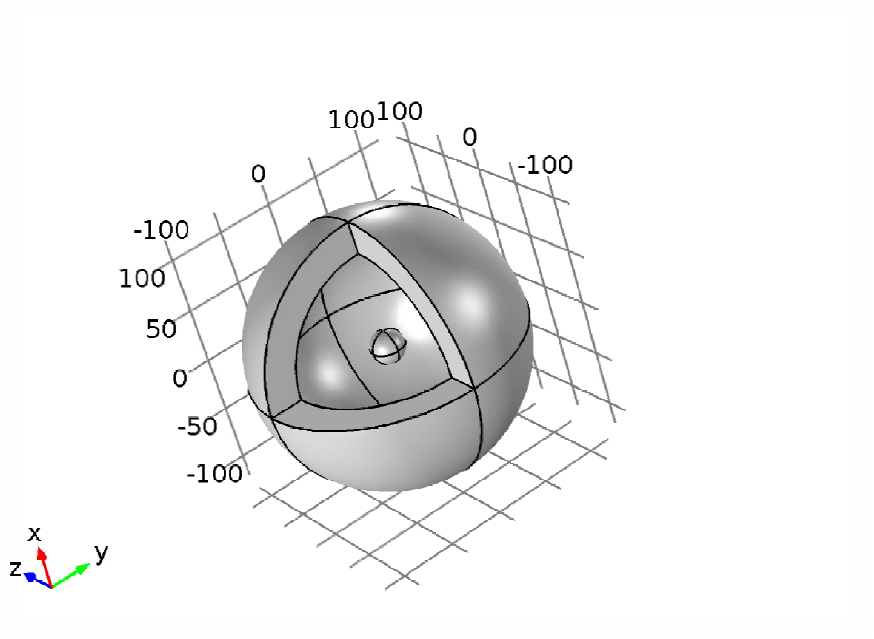

Figure 4.2: 3D model of Gold sphere

Parameters were defined as shown in Table 4.1.

Parameters:

Table 4.1 parameters of optical scattering of GNP

Name	Expression	Value	Description
r0	100[nm]	1.0000E-7 m	Sphere radius
lda	532[nm]	5.3200E-7 m	Wavelength
t_water	1000[nm]	1.0000E-6 m	Water medium radius
t_pml	200[nm]	2.6600E-7 m	Thickness of PML
h_max	lda/6	8.8667E-8 m	Maximum element size
E0	1e8[V/m]	1E8 V/m	
S_in	E0^2/2*Z0_const	10.000 Hz	

After the model was constructed and materials were applied to appropriate domains, the Perfectly Matched Layer (PML) (In COMSOL's users guide it is stated that PMLs are used for simulation of infinite domains. It further tells us that one has to stretch the virtual domains surrounding the physical region of interest into the complex plane by creating perfectly matched layers in order to absorb outgoing waves of a frequency-domain problem), and *Scattering Boundary Condition* was defined .

To solve the model for the scattered field, we need to provide background electric field (E-field) information.

The electromagnetic response of AuNPs is calculated using three-dimensional (3D) full-wave time-harmonic. Assuming time-harmonic electric field, the electric field distribution $\bar{E}(r,t)$ is computed using the Helmholtz equation :

$$\nabla \times \mu_r^{-1}(\nabla \times E) - {k_0}^2 \left(\varepsilon_r - \frac{j\sigma}{\omega\, \varepsilon_0}\right) E = 0 \qquad 4.1$$

Where: $\varepsilon_r$is the relative complex permittivity, $\mu_r$is relative permeability, $k_0$is the wave number and ω is the angular frequency.

The meshing quality of the computational domain plays an important role in FEM. In order to obtain the correct solution, at least 10 linear elements per wavelength were used during meshing of the geometries with even more fine refinement of the nanoparticle's mesh.

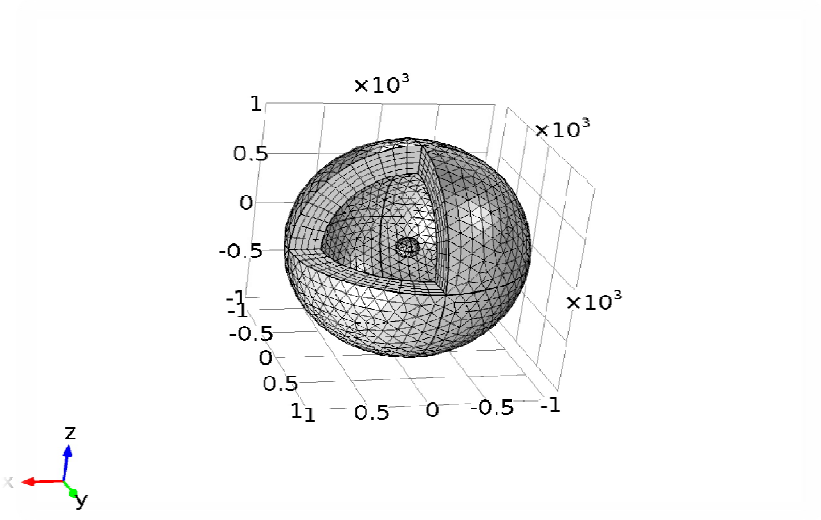

Figure 4.3: GNP mesh

4.1.1.2 Mie Simulations of the Absorption and Scattering Spectrum of GNPs :

Using Lorenz–Mie solutions to find the optical properties of a spherically symmetric particle. These solutions characterize absorption and scattering for incoming light of a given wavelength in terms of the nanoparticle size and the electromagnetic properties of the nanoparticle and surrounding media. Starting in general terms with the electric permittivity ε and the magnetic permeability μ the solutions utilize an assumption that the material is nonmagnetic, and thus $\mu \approx 1$ and $\varepsilon = m^2$. Therefore, absorption and scattering efficiencies of the nanoparticle exposed to incoming light of wavelength λ can be calculated with only three input parameters:

• Nanoparticle radiusr_0;

• Complex refractive index m_0 of the sphere;

• Complex refractive index m_1 of the surrounding medium.

The nanoparticle radius is a parameter that can be engineered to modify the light absorption properties of a particle. The complex refractive indices of the nanoparticle

material and surrounding medium, however, are dependent upon the physical situation under investigation. The refractive index of the surrounding medium (water) equal 1.336384.

The MiePlot software offers an easy-to-use interface providing graphs of intensity vs. scattering angle, wavelength, radius, and refractive index

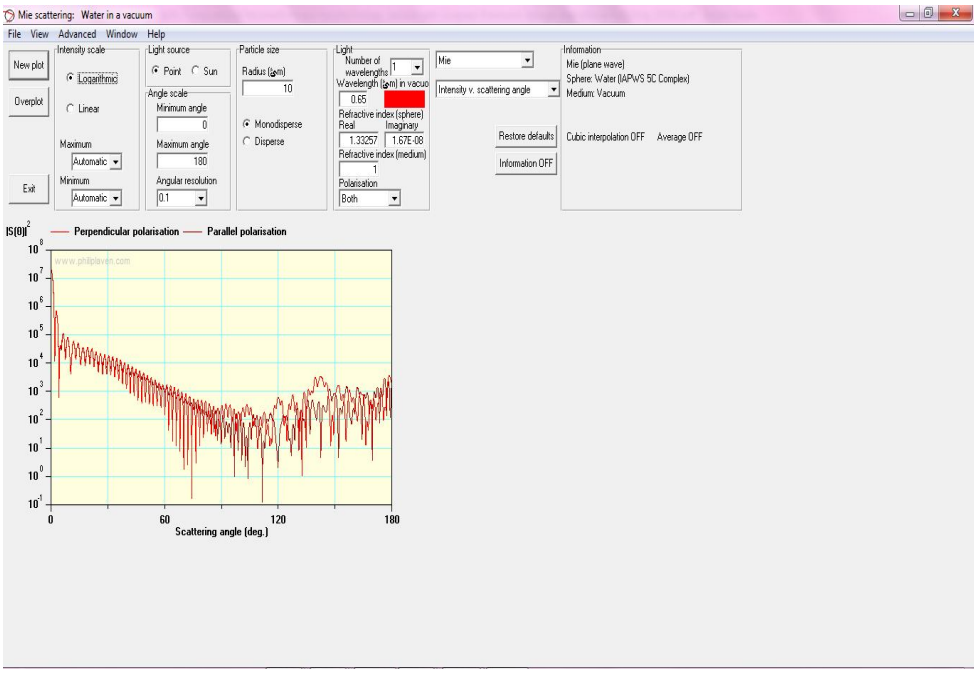

Figure 4.4: Interface of MiePlot

4.1.1.2.1 Simulation of the extinction Qext, scattering Qsca and absorption Qabs efficiencies vs. the particle radius:

To run the simulations for absorption, scattering, and extinction efficiencies vs. the particle radius for a given wavelength of the radiation ,selects the index of refraction for the surrounding water medium which is 1.336384 and the wavelength 530[nm] , the index of refraction for a gold nanoparticle/sphere is equal to 0.558235+i2.202579.

I choose a radius range for the sphere/particle from 1 to 100nm.

4.1.1.2.2 Simulation of the absorption and scattering spectrum of the nanoparticle vs. the wavelength of radiation:

The radius of the particle selected from absorption, scattering, and extinction efficiencies vs. the particle radius spectrum. the maximum absorption of the gold nanoparticle for 530 nm light is observed for a gold nanoparticle radius of 35 nm. Then

setting range for the wavelength of radiation. most simulations were run in the optical range of spectrum from 200 up to 1000 nm.

The optimal range of nanoparticle sizes and optimal wavelength of radiation for effective activating/heating of nanoparticles in biological medium can be calculated.

4.2 Stage two:

In this step heat-mass transfer equation is used to model the time evolution of thermal fields in gold nanoparticle. Using Maplesoft 2016

By solving one-temperature model in the form:

$$\frac{\partial T_s}{\partial t} = \frac{3I_0 f(t) Q_{abs}}{4r_0 \rho_s C_s(T_s)} - \frac{3\mu_\infty T_\infty r_0}{(\alpha+1) r_0^2}\left[\left(\frac{T_s}{T_\infty}\right)^{\alpha+1} - 1\right] \qquad 4.2$$

The temperature dependences of the electron heat capacity for gold and specific heat and thermal conductivity for water were obtained by interpolating the experimental data available in the literature.

The heating kinetics of the nanoparticles is sensitive to the time structure of the radiation delivery described by the function f(t) in the first term on the right side of OTM equation , where f(t) determines the pulse shape, In OTM simulations, I use a Gaussian profile ,Thus, a single pulse can be described by a Gaussian-like curve

$$f(t) = e^{-(bt-d)^2}$$

Where b and d are constants defining the pulse duration. The input data for OTM simulations are listed in Table 4.3

4.2.2 input data:

Thermophysical characteristics of the gold nanoparticle and surrounding medium as well as the additional input parameters used in the Maplesoft are listed in table 4.3 :

Table 4.3 input parameters used in the Maplesoft:

Gold Particle	
absorption efficiency	4.376
Specific heat (J/kg K)	129
Density (kg/cm3)	0.0193
Initial temperature (K)	300
Laser	
Energy density (J/cm2)	Varied with trial (0.15_0.25)
pulse duration(ns)	Varied with trial (3_8_9_30)
Laser Intensity (W/cm^2)	Energy density /pulse duration
Water medium	
Thermal conductivity (W/cm.K)	0.591
Specific heat (J/kg.K)	4190
Exponential power	1

As a case for analyses of different nonstationary laser–nanoparticle interactions in a single pulse mode of heating, calculations performed to determine how changing pulse duration, particles size and the energy density would change the time required to reach the nanoparticle maximum temperature, and the magnitude of the maximum temperature.

CHAPTER FIVE

RESULT AND DISCUSSION

CHAPTER FIVE

Results and Discussion

5.1 Modeling of Optical properties of GNPs:

As shown in chapter four the following results were obtain using COMSOL Multiphysics v5.2 and Mieplot v.4611 .

5.1.1 normalized electric-field:

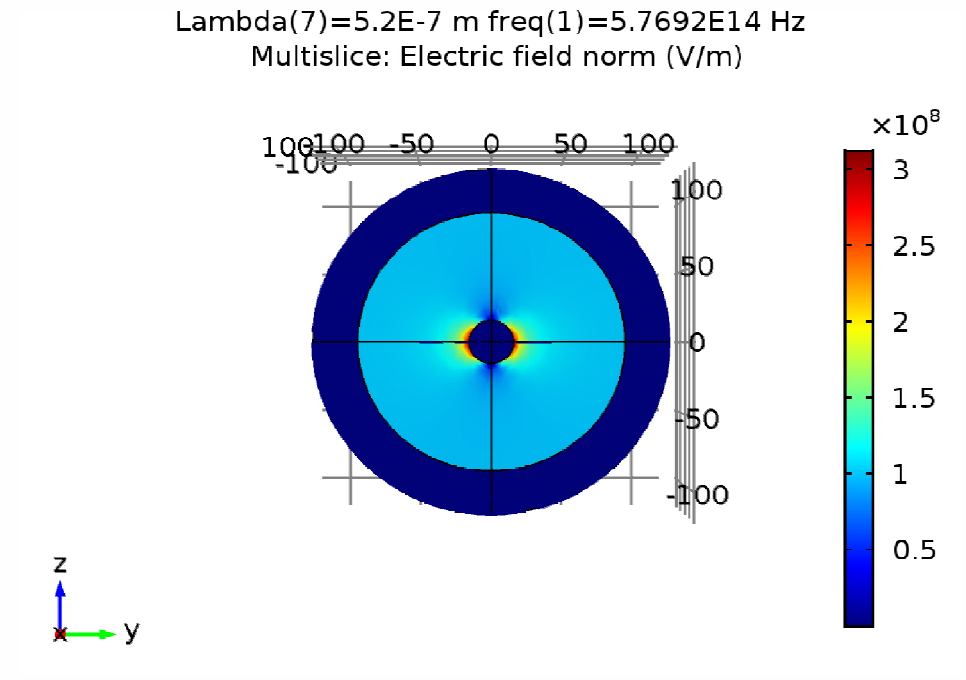

Figure5.1: The generated normalized electric-field map generated using the finite element method of COMSOL. The sphere particle is with 100nm diameter placed in a laser field

The simulated optical field of a gold nanoparticle in z-y plane is shown in Figure (5.1). The background light was set as$E_b = e^{-jkz}\,\hat{y}$, that is, the waves propagate in the z direction and polarize in the y direction. The software solved the in-plane vector of the scattered electric field. It is observed that the optical field is polarized in the y direction, which agrees with the polarization of the incident plane wave. As explained before, this phenomenon is due to the collective oscillation of conductive electrons and incident photons.

The optimal wavelength of laser radiation and the optimal size range of nanoparticles for effective laser killing of cancer cell by using Lorenz–Mie diffraction theory at the single-scattering approximation described

5.1.2 Extinction Qext, scattering Qsca and absorption Qabs efficiencies vs. the gold nanoparticle radius:

The radius of the particle selected from absorption, scattering, and extinction efficiencies vs. the particle radius spectrum using Mieplot .

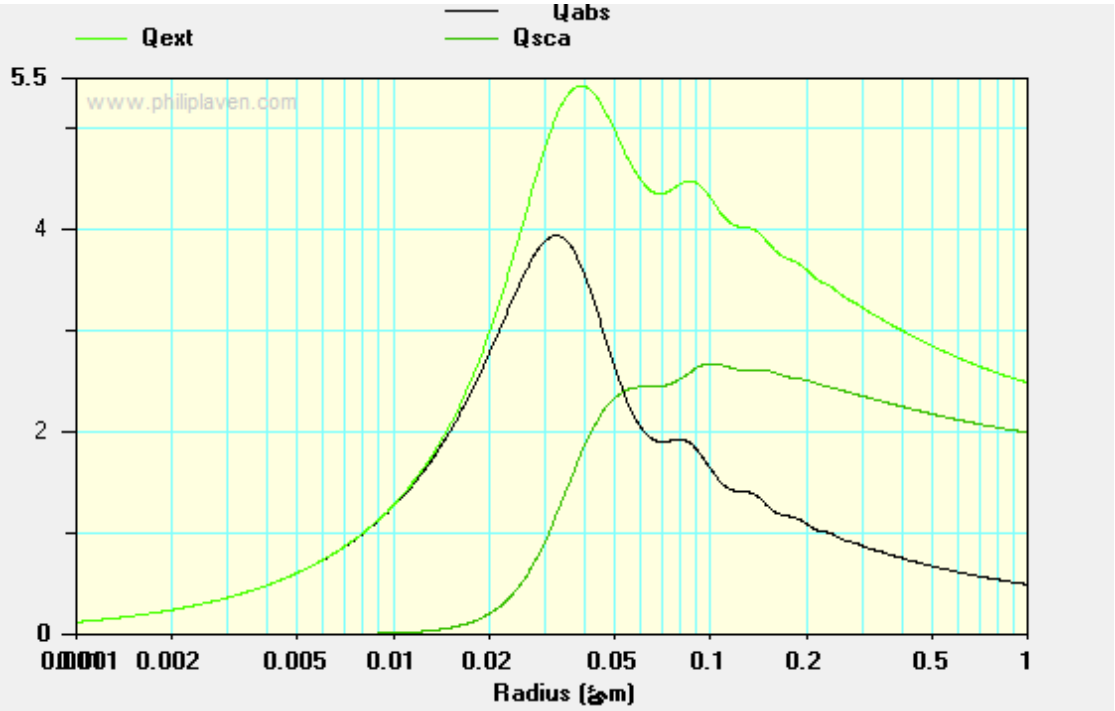

Figure 5.2: Extinction Qext, scattering Qsca and absorption Qabs efficiencies vs. the gold nanoparticle radius.

The results of the simulations for the extinction Qext (light green curve), scattering Qsca (green curve), and absorption Qabs (black curve) efficiencies vs. the particle radius are shown in Figure (5.3).

Reduction in the size of the spherical nanoparticles lowers the absorption efficiency, as seen when comparing a 30-nm gold nanoparticle to a 5-nm Au nanoparticle, where Qabs loses an entire order of magnitude.

From these curve we can determine the optimal radius of the nanoparticle of a given material for therapeutic or diagnostic applications. This optimal radius for the therapeutic uses corresponds to the maximum absorption point. The Optimal radius range for diagnostic applications is determined by the region where the scattering efficiency Qsca (green curve) dominates over the absorption efficiency Qabs (black curve).

For particles with radii (r) in the range of 1–45 nm, Qabs is considerably greater than Qsca, i.e., the efficiency of laser heating of nanoparticles in this size range is high. Thus, the optimal nanoparticle size range for effective laser activating/heating of gold nanoparticles for therapy of tumor cells is 10–45 nm, where Qabs>1 and Qabs>Qsca.

5.1.3 Absorption, scattering, and extinction efficiencies of the gold nanoparticle vs. the wavelength of the radiation:

Simulates the absorption and scattering spectrum of the nanoparticle vs. the wavelength of radiation to perform Mie simulations of the particle's optical properties vs. wavelength of radiation and to find an optimal wavelength.

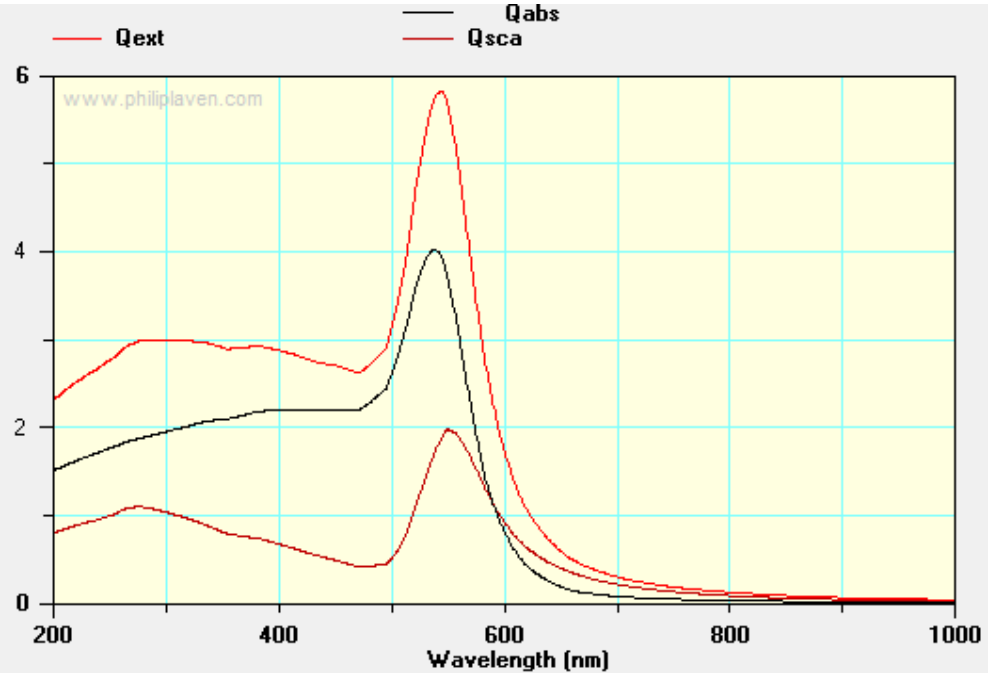

Figure 5.3: Absorption, scattering, and extinction efficiencies of the gold nanoparticle vs. the wavelength of the radiation.

The results of the simulations for the extinction Qext (light green curve), scattering Qsca (green curve), and absorption Qabs (black curve) efficiencies of the gold particle

in water medium, vs. the wavelength of radiation are shown in Figure (5.4) . From these simulations we can determine the optimal wavelength of radiation for a given nanoparticle which best suits therapeutic or diagnostic applications. The optimal wavelength of light for therapeutics uses corresponds to the maximum absorption point.
The optimal wavelength range for diagnostic applications is determined by the region where the scattering efficiency Qsca (green curve) dominates over the absorption efficiency Qabs (black curve).
Absorption of gold nanoparticles dominates over the scattering with a maximum efficiency Qabs=4.02 corresponding to the wavelength λ=538.3 nm (Figure 5.4). Thus, the laser radiation with the wavelength λ=538.3 nm is optimal for therapeutic applications for activating and heating the gold nanoparticles.

5.2 Time Dynamics of gold nanoparticle heating:

The impulse of electromagnetic radiation to a particle results in the heating of the particle as well as the surrounding medium over time. This simulation studies the time dependence of the temperature of a gold nanoparticle when irradiated by a single short laser pulse,To analyze the effects due to varying the characteristics of the experiments.

5.2.1 Effect of the pulse duration on the Time Dynamics of Nanoparticle Heating:

The most substantial change within single-pulse heating is the effect of pulse duration on the time dynamics of particle heating and cooling as shown in figure (5.6).

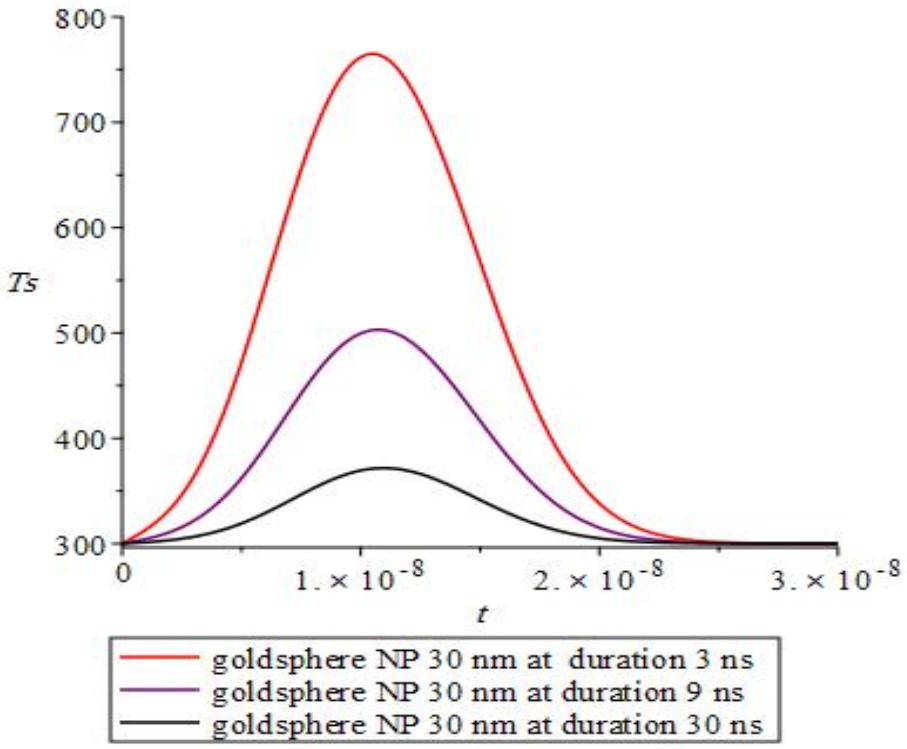

Figure 5.4 Time–temperature profiles for three different pulse durations used in single-pulse mode heating. Of 30nm gold sphere, 3 ns pulse (red), 9 ns pulse (purple) and 30 ns pulse (black).

Simulations show that by increasing the pulse duration, the maximum nanoparticle temperature decreases, but heating and cooling both take longer and allow for a longer time period when the nanoparticles are above the denaturing temperature of 433 K. This increased duration of high particle temperature could prove beneficial to assure cellular damage. .

Also at the instance when the laser pulse stops, the cooling rate reaches almost the same values as the heating rate due to the large surface area of the nanoparticle and high thermal conductivity of the surrounding aqueous medium.

The time for a particle to reach the maximum temperature is longer than the laser pulse duration because the heating kinetics involves first the transfer of energy from the irradiating source to the electron subsystem, and then further to the phonon subsystem. This creates a time delay in reaching the maximum temperature by the particle.

5.2.2 Effect of the Particle Size on the Time Dynamics of Nanoparticle Heating:

Changing a particle size alters the peak absorption wavelengths and the respective coefficients of absorption becausethe heat generation in the nanoparticle volume is due to laser energy absorption by the nanoparticle.

Effect of the particle size on the time dynamics of Nanoparticle heating shown in figure (5.7) below.

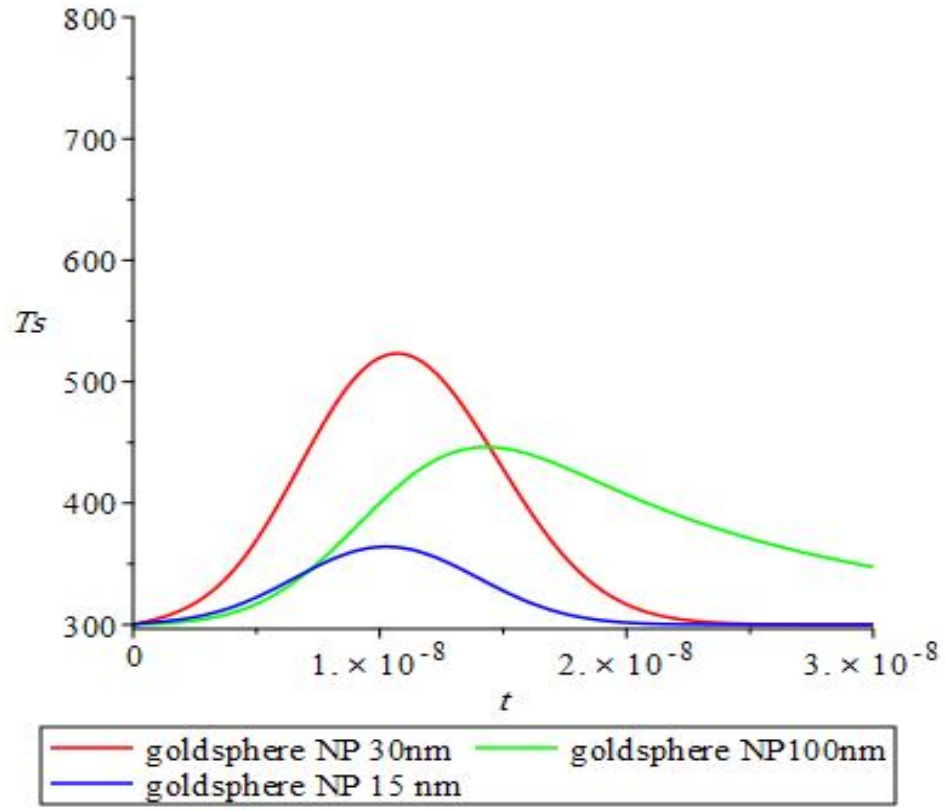

Figure 5.5: Time–temperature profiles for 30-nm diameter (red) ,100 nm diameter (green) and 15 nm gold particles in water irradiated by a 8-ns, 0.15 J/cm2 pulse at 532 nm wavelength.

It is interesting to investigate the effect of the particle's radius on the temperature dynamics of the nanoparticle heated by the nanosecond laser radiation in the biological surroundings, there are two competitive factors here.On one hand, according to the Mie diffraction theory, the absorption efficiency of the gold nanoparticle drops with

decreasing size of the particle. On the other hand, the heating rate increases for smaller particles.

figure (5.7) shows the time–temperature profiles for 30-nm diameter (red), 100 nm diameter (green) and 15nm gold particles in water irradiated by a 8-ns, 0.15 J/cm2 pulse at 532 nm wavelength ,we can see that the gold particle in 30 nm radius which have an absorption efficiency around 4.376 when irradiated with 532-nm light have maximum temperature comparing with gold particle in 100 nm (Q_{abs}~1.6105) and gold particle in 15 nm (Q_{abs}~1.9949).

As shown in the Figure 5.7, particles are heated even after 10ns when pulse is over. Temperature reaches to its maximum value and then particles start getting cooled which result in the transfer of heat to the surrounding medium. The maximum temperature increases by the increased particle size.

5.2.3 Effect of the Energy density on the Time Dynamics of Nanoparticle Heating:

The magnitude of the temperature is directly related to and greatly dependent on the energy density of the laser. Figure (5.8) demonstrates this with two time–temperature profiles: a 30-nm diameter gold sphere irradiated by a 0.15 J/cm2 pulse (black curve) and 0.25 J/cm2 pulse (red curve),

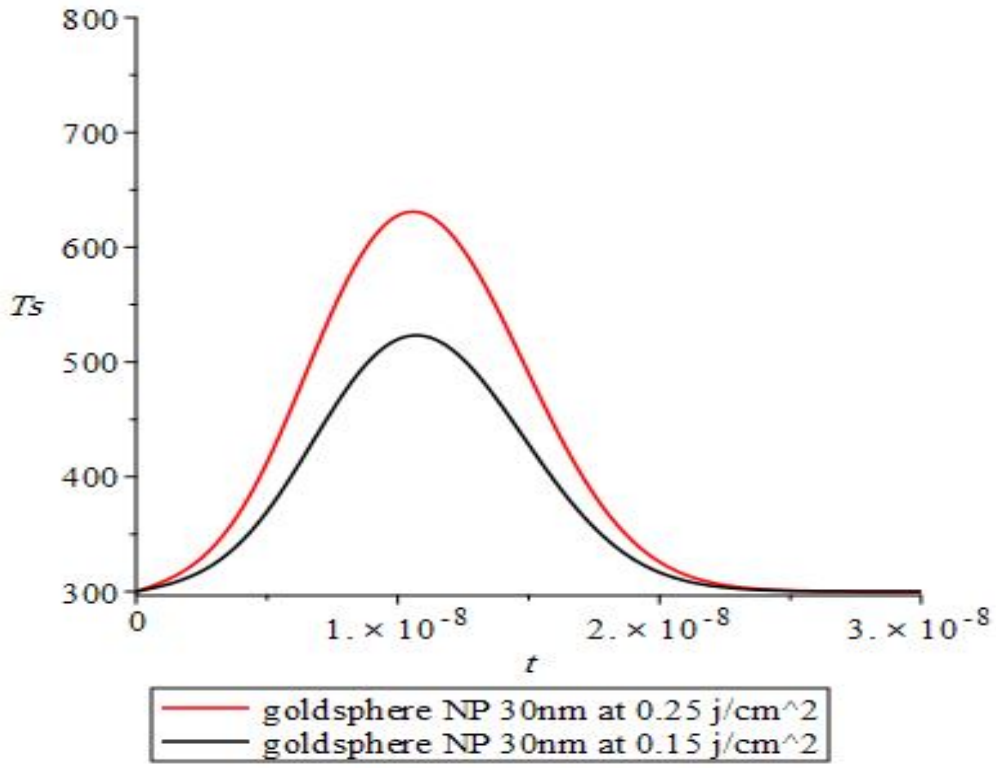

Figure 5.6: Time–temperature profiles for 30-nm diameter gold particles in water irradiated by a 8-ns, 0.15 J/cm2 (black curve) pulse ,and 0.25 J/cm2(red curve), at 532 nm wavelength.

From figure(5.8) we can see that changing the energy density in the chosen range has a very small or no effect on the time it takes for the particle to heat to the maximum temperature. This is due to the fast transfer of energy from the irradiating source to the electron lattice, and further to the phonon system which has a picosecond time scale, and is much shorter than the nanosecond duration of the laser pulse. The time for electron– phonon thermalization is more dependent on the specific heat of the electron and particle structures, rather than the energy density.Though it does affect the magnitude of temperature reached.

From these simulations modifications to the laser energy density or wavelength can be used to change the maximum particle temperature. And such laser parameter modifications could allow for an easier and more refined treatment than modification of particle size or shape.

CHAPTER SIX

CONCLUSION AND RECOMMENDATION

CHAPTER SIX

Conclusion and recommendation

6.1 Conclusion:

The interaction between nanoparticles and radiation holds great interest in nanomedicine. Many studies have shown that gold nanoparticles are highly effective agents for conversion of laser light into heat. Thermal therapy that utilizes this effect is called Plasmonic Photothermal Therapy (PPTT), where light absorption by photothermal agents (plasmon-resonant gold nanoparticles) causes kinetic energy to increase, resulting in heating of the area surrounding the agent and using in killing Cancer cell.

Due to the limitations of current equipment for nanoparticle characterization, numerical methods and computational models are widely used to understand the physics at the nanoscale.

The project models the light absorption properties of spherical gold nanoparticles, To find the optimal wavelength of radiation and optimal size range of nanoparticles for effective heating/activating of the nanoparticles . To achieve sufficient heating with pulses of lower energy densities, it is important to find absorption efficiency peaks. These peaks occur due to the Plasmon resonance of the nanoparticle at that particular wavelength. Using extended Lorentz–Mie theory, taking into account the Plasmon-resonance absorption effect observed in gold nanoparticles.

Reduction in the size of the spherical nanoparticles lowers the absorption Efficiency.

From results found that Gold nanoparticles are effective absorbers of radiation ($Q_{abs}>1$, Q_{sca}) over a wide range of the spectrum, 400–580 nm, with a maximum efficiency $Q_{abs}=4.02$ at the wavelength $\lambda=538.3$ nm in the surrounding water medium. The optimal nanoparticle size range for effective radiation heating of nanoparticles is 10–45 nm, where $Q_{abs}>1$ and $Q_{abs}>Q_{sca}$ in water.

The project also performed time-dependent simulations and detailed analyses of different nonstationary laser–nanoparticle interactions in a single pulse mode of heating, using one temperature model. Analysis of the heating of gold nanoparticles in a water environment shows that alterations to the particle size have effects on the magnitude of

the maximum particle temperature. Also modifications to the laser energy density , pulse duration or wavelength can be used to change the maximum particle temperature. Such laser parameter modifications could allow for an easier and more refined treatment than modification of particle size or shape.
Both the thermal and optical properties affect the behavior of the thermal field.

Despite the increasing number of publications on gold-nanoparticle-assisted cancer detection and therapy over the last few years, there is still a lot of work to be done before this technique is clinically applicable

6.2 Recommendation:

There are still several directions to take the next step with this project.

- trying the same simulations with different metal cores of the NPs
- trying the same simulations by altering the shape of the NPs
- Simulation and study the effect of hyperthermia heating process using GNPs on the healthy tissue and tumor.
- Effective modeling of nanoparticle heating in the femtosecond and picosecond, regimes.
- Solving heat transfer equation using two temperature model (TTM) to determine the nanoparticle temperature over time. And compare between one temperature model and two temperature model.
- Simulation of 3D temperature distribution of GNP in tumor with different parameters.
- Once these studies have been completed and depending on the results the project could move in to animal studies to look at specific tissues in the animals after being given NPs. Animal models are imperative to developing a technique that will be taken further towards clinical application.

References:

1. XiaohuaHuang ,Mostafa A. El-Sayed, Gold nanoparticles: Optical properties and implementations in cancer diagnosis and photothermal therapy, Journal of Advanced Research, 13–28.
2. E Sassaroli, K C P Li and B E O'Neill, Numerical investigation of heating of a gold nanoparticle and the surrounding microenvironment by nanosecond laser pulses for nanomedicine application, physics in medicine and biology **,** 2009 5541–5560.
3. Renat R. Letfullin, Christian B. Iversen, Thomas F. George, Modeling nanophotothermal therapy: kinetics of thermal ablation of healthy and cancerous cell organelles and gold nanoparticles, Nanomedicine: Nanotechnology, Biology, and Medicine, 2010, 137–145.
4. Rudolf Steiner, Laser-Tissue Interactions, Researchgate, October 2011, 10.1007/978-3-642-03438-1.
5. Renat R. Letfullin, Thomas F. George, Computational Nanomedicine and Nanotechnology, Springer International Publishing,2016, 978-3-319-43577-0 .
6. Malsch, N.H.ed, Biomedical nanotechnology, 2005.
7. Xiaohua Huang ,Gold Nanoparticles Used in Cancer Cell Diagnostics, Selective Photothermal Therapy and Catalysis of NADH Oxidation Reaction, Georgia Institute of Technology, May, 2006.
8. Bhattacharya R, Mukherjee P. Biological properties of naked metal nanoparticles. Advanced Drug Delivery Reviews 2008, 60 (11), 1289 1306.
9. Ghosh SK, Nath S, Kundu S, Esumi K, Pal T. Solvent and ligand effects on the localized surface plasmon resonance (lspr) of gold colloids. Journal of Physical Chemistry B 2004, 108 (37), 13963–13971.
10. Hayat M: Colloidal gold: principles, methods, and applications Academic Press 1989.
11. Enustun BV, Turkevich J. Coagulation of colloidal gold. Journal of the American Chemical Society 1963, 3317–3328.
12. Maier S.A. Plasmonics: fundamentals and applications, Springer, 2007.
13. P. K. Jain and M. A. El-Sayed, Universal scaling of Plasmon coupling in metal nanostructures: extension from particle pairs to nanoshells, *Nano Letters*, 2007, pp. 2854.
14. U. Kreibig and M. Vollmer, Optical properties of metal clusters, Springer, 1995.

15. J. L. Hammond, Localized surface plasmon resonance as a biosensing platform for developing countries, *Biosensor*, 2014, pp. 172.
16. HeyamSaad Ali, Samrein Ahmed and GazalaAfreen Khan, gold nanoparticles in cancer therapy and diagnostics,European journal of pharmaceutical and medical research, 2016, 54-67.
17. Jackson J.D. Classical electrodynamics, 3rd ed. John Wiley Sons, Inc, 1999.
18. S.Yushanov, J. S. Crompton, and K. C. Koppenhoefer, Mie scattering of electromagnetic waves, AltaSim Technologies.
19. Liuen Liang, gold nanoparticles: synthesis, growth kinetics and optical properties, The University of New South Wales ,August 2012.
20. Chiche A., Skowronek J., Kubaszewska M., and Kanikowski M. Hyperthermia - description of a method and a review of clinical applications. Reports of Practical Oncology and Radiotherapy, 2007, 267-275 .
21. Jing-Liang Li and Min Gu, Gold-Nanoparticle-Enhanced Cancer Photothermal Therapy, IEEE journal of selected topics in quantum electronics, july/august 2010, 16, no. 4,
22. Francisco J. Reynoso, modeling of near infrared laser-mediated plasmonic heating with optically tunable gold nanoparticles for thermal therapy, November 11, 2011.
23. Jain P.K., Huang X., El-Sayed I.H., and El-Sayed M.A. Noble metals on the nanoscale: Optical and photothermal properties and some applications in imaging, sensing, biology, and medicine. Accounts of Chemical Research, 2008, 1578-1586.
24. Zhang J.Z. and Noguez C. Plasmonic optical properties and applications of metal nanostructures. Plasmonics, 2008, 127-150.
25. Huang X., Jain P.K., El-Sayed I.H., and El-Sayed M.A. Gold nanoparticles: Interesting optical properties and recent applications in cancer diagnostics and therapy, Nanomedicine, 681-693.
26. Victor K. Pustovalov ,L. G. Astafyeva , E. Galanzha and V. P. Zharov ,Thermo-optical analysis and selection of the properties Of absorbing nanoparticles for laser applications in cancer nanotechnology , Cancer Nano ,2010, 1:35–46.
27. Renat R. Letfullin, Thomas F. George,Galen C. Duree and Brett M. Bollinger, Ultrashort Laser Pulse Heating of Nanoparticles: Comparison of Theoretical Approaches, Advances in Optical Technologies,2008, 251718.

28. Nagender Reddy Panyala1, Eladia Mara Pena-Méndez, Josef Havel, Gold and nano-gold in medicine: overview, toxicology and Perspectives, Journal of applied biomedicine, 2009, 75–91.
29. Weibo Cai, Ting Gao , Hao Hong, Jiang tao , Applications of gold nanoparticles in cancer Nanotechnology, Nanotechnology, Science and Applications 2008,1 17–32 .
30. Everts M, Saini V, Leddon JL, Kok RJ, Stoff-Khalili M, Preuss MA, Millican CL, Perkins G, Brown JM, Bagaria H, Nikles DE, Johnson DT, Zharov VP, Curiel , Covalently linked Au nanoparticles to a viral vector: potential for combined photothermal and gene cancer therapy ,2006 ,587-91
31. Mohamed Anwar K Abdelhalim, Mohsen M. Mady and Magdy M. Ghanna , Physical Properties of Different Gold Nanoparticles: Ultraviolet-Visible and Fluorescence Measurements , Journal of Nanomedicine & Nanotechnology, 2012, 2157-7439.
32. Ali Hatef, Simon Fortin-Deschênes and Michel Meunier, Simulation of nanosecond laser-induced thermal dynamicsof hollow gold nanoshells for hyperthermia therapy, electronic photonic plasmonicphononicand magnatic properties of nanomaterials ,2014,105-110.
33. F. Rossi, F. Ratto, and R. Pini,, Laser Activated Gold Nanorods for the Photothermal Treatment of Cancer, 2012.

Appendix (A):

Equations:

1. $\nabla \times \mu_r^{-1}(\nabla \times E) - k_0^{\,2}\left(\varepsilon_r - \frac{j\sigma}{\omega\,\varepsilon_0}\right)E = 0$
2. $Q_{ext}^{j}(\rho, \tilde{m}) = \frac{4\pi}{k^2}\mathrm{Re}\{S^j(0)\}$
3. $Q_{sca}^{j}(\rho, \tilde{m}) = \frac{2}{\rho^2}\sum_{l=1}^{\infty}(2l+1)\{\left|a_l^j\right|^2 + \left|b_l^j\right|\ \}^2$
4. $Q_{abs}^{j}(\rho, \tilde{m}) = Q_{ext}(\rho, \tilde{m}) - Q_{sca}(\rho, \tilde{m})$
5. $\rho_f c_f \frac{\partial T_f}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \mu_f \frac{\partial T_f}{\partial r}\right) + q_{gen}$
6. $\frac{\partial T_s}{\partial t} = \frac{3I_0 f(t) Q_{abs}}{4r_0 \rho_s C_s(T_s)} - \frac{3\mu_\infty T_\infty r_0}{(\alpha+1){r_0}^2}\left[\left(\frac{T_s}{T_\infty}\right)^{\alpha+1} - 1\right]$
7. $f(t) = e^{-(bt-d)^2}$

Appendix (B):

Code and method

```
>restart;
>with(plots) :
>with(DEtools) :
>f := exp(-(t·2·10^8 − 2)^2);
```

$$f := e^{-(200000000\,t-2)^2}$$

```
>plot(f, t = 0..25·10^-9);
>C[W] := 4190;
```

$$C_W := 4190$$

```
>r[goldsphr] := 30·10^-7;
```

$$r_{goldsphr} := \frac{3}{1000000}$$

```
>Q[goldsphr] := 4.376;
```

$$Q_{goldsphr} := 4.376$$

```
>T[0] := 300;
```

$$T_0 := 300$$

```
>τ := 8·10^-9;
```

$$\tau := \frac{1}{125000000}$$

```
>E := 0.15;
```

$$E := 0.15$$

```
>I0 := E/τ;
```

$$I0 := 1.875000000\,10^7$$

```
>α := 1;
```

$$\alpha := 1$$

```
>ρ[goldsphr] := 0.0193;
```

$$\rho_{goldsphr} := 0.0193$$

```
>μ[medium] := 0.591;
```

$$\mu_{medium} := 0.591$$

```
> DE[goldsphr] := diff(Ts(t), t) = (3·Q[goldsphr]·I0)·f/(4·r[goldsphr]·C[W]·ρ[goldsphr])
    − μ[medium]·T[0]/((α + 1)·r[goldsphr]^2·C[W]·ρ[goldsphr])·((Ts(t)/T[0])^(1 + α) − 1);
```

$$DE_{goldsphr} := \frac{d}{dt}Ts(t) = 2.536572397\,10^{11}\,e^{-(200000000\,t-2)^2} - 1.353388211\,10^6\,Ts(t)^2 + 1.218049390\,10^{11}$$

```
>soln[goldsphr] := dsolve({DE[goldsphr], Ts(0) = 300}, Ts(t), numeric);
```

$$soln_{goldsphr} := \mathbf{proc}(x\_rkf45)\ \ldots\ \mathbf{end\ proc}$$

```
>for z from 0 to 50 do zz[z] := soln[goldsphr](z·10^-11);od:
> p[goldsphr] := odeplot( soln[goldsphr], [t, Ts(t)], 0 ..30/10^9, view = [0 ..30/10^9, 300 ..800],
      numpoints = 1000, legend = "goldsphere NP", color = red);
```