Laser Activated Gold Nanorods for the Photothermal Treatment of Cancer

F. Rossi*[1], F. Ratto[1], and R. Pini[1]
[1]Institute of Applied Physics "Nello Carrara", Italian National Research Council
*Corresponding author: Via Madonna del Piano 10 – 50019 Sesto Fiorentino (FI) - Italy, f.rossi@ifac.cnr.it

Abstract: 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 effect that are induced close to the nanoparticle (nanoscale model), in the close vicinity and in the cancerous tissue (microscale model). A temperature dependent 2D-model of this particular light-matter interaction was designed. The expected absorption cross section 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.

Keywords: gold nanorod, cancer treatment, hyperthermia, bioheat equation, laser thermal effect.

1. Introduction

Laser induced photothermal effects are at the basis of new minimally invasive therapeutic and diagnostic approaches in different medical fields (from Ophthalmology to Dermatology, Neurosurgery, Oncology, etc.). Modulation of the laser source settings (wavelength, emission regime, dimensions of the spot, treatment time) and selection of the proper target may induce different degrees of thermal effects in biological tissues, ranging from hyperthermia (43-50°C), to denaturation of proteins and collagen (55-75°C), to vaporization and carbonization (temperatures equal to or higher than 100°C). [1,2]

Nowadays new concepts are emerging, based on the activation of photothermal effects through nanoparticles, in particular in the diagnosis and therapy of cancer. The diagnosis of cancer may be pursued by the intravenous injection and selective accumulation of gold nanoparticles (GNPs) inside the malignant cells. Then the GNPs may be used as highly effective contrast agents in a photo-detection arrangement. Interestingly the same GNP may be used to induce the apoptosis of the malignant cells by a photothermal or photoacoustic microsurgery, as well as by the association of cytotoxic drugs. [3]

In this work we designed a new approach based on the use of gold nanorods, that selectively absorb near infrared laser light. The intended photothermal effect is hyperthermia of cancerous tissue. COMSOL Multiphysics 4.2a software was used to design the correct settings of the laser in order to induce effective temperature values in the biological tissue, avoiding to induce thermal damage at the nanoscale level to the GNR.

2. Materials and Methods

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).

2.1 The gold nanorods

GNRs were designed and produced in our labs, in order to maximize the intended photothermal effects in a biological cancerous tissue. Their size may affect parameters such as their cellular uptake, diffusion, cytotoxicity and efficiency of

the photothermal transduction. Their shape (in particular their ratio of the length to the diameter) mainly governs the stability and position of the plasmon resonances, and therefore their optical response. [4] The prepared GNRs had an average shape and size so that their optical absorption is maximized in the NIR region (around 800 nm). A GNR is a cylinder with dimensions 40 x 10 nm (axis x diameter). The temperature threshold of thermal damage is presumably below 250°C. [5]
The optical behavior of a realistic colloidal suspensions of gold particles was measured by the use of a portable spectrometer (Mod. EPP200 by Stellarnet Inc., USA). The absorption cross section C_{abs} of the GNRs was valued using Gans Theory and was dependent on geometrical properties of the GNRs. In our study we had C_{abs} = 2000 nm^2
The thermal parameters of the GNPs were found in literature, where it is reported also their temperature dependence. [6]

2.2 The laser source

Near infrared laser are usually selected for biological application because of their low absorption in a biotissue. In particular the absorption around 800 nm due to natural endogenous chromophores is quite low and the laser light can penetrate in the deep tissue.[7] The light source used in the design of this new concept is a diode laser emitting at 810 nm. The light is delivered through an optical fiber with 600 µm inner core diameter. The emission mode was a continuous wave. Optimal power density delivered to the GNR and duration time of the treatment were found by analyzing the post-processing results of the FEM model.

3. The COMSOL model

Aim of the study was the analysis of the temperature range induced by the diode laser in the GNR and the environment close to it and in the biological tumor tissue. In order to do this, we developed two different models, the first one describing the nano- scale of the problem and the second one the micro- scale of the same problem.

In both the models, the problem has a spherical symmetry, so we decided to study a bi-dimensional geometry. We studied a time dependent problem.

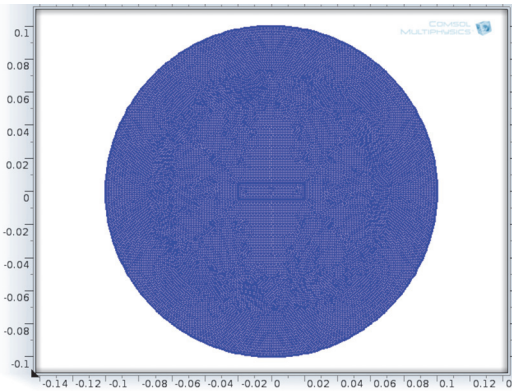

Figure 1. Bidimensional model of a GNR (the rectangular shape in the center of the draw) inside a biocompatible biopolymer circular shell. Dimensions are in micrometers.

The COMSOL modules were in both cases the same, the Heat Transfer Module, and in particular we used Heat Transfer in Solids and Bioheat Transfer. Here in the followings we describe the problem in details.

3.1 Model at the nanoscale

We supposed that the GNRs are distant, so that interaction effects among particles can be neglected. In this problem we thus considered only one GNR. We also supposed that the GNR is enclosed in a biocompatible biopolymeric shell, whose thermal characteristics are close to water.
The geometrical model (depicted in Figure 1) was meshed with an extremely fine triangular mesh. The Heat Transfer in Solids module was used, imposing an outflow at the external boundary of the biopolymer (the circle in Figure 1). The heat source Q_{ext} was localized in the GNR, absorbing the laser light, and it was set as reported in literature: [6]

$$Q_{ext} = \frac{C_{abs} I}{v_p}$$

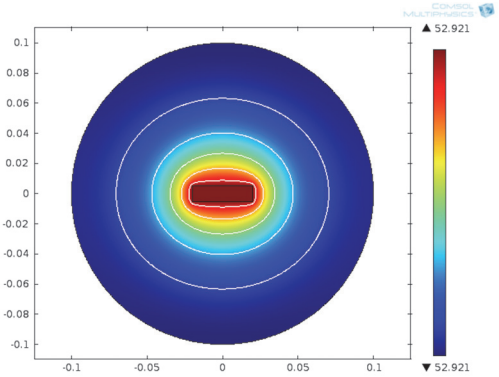

Figure 2. Bidimensional model of a GNR (the rectangular shape in the center of the draw) inside a biocompatible biopolymer circular shell. Dimensions are in micrometers. Temperature map after 2s irradiation with a 0.5 mW/cm^2 diode laser.

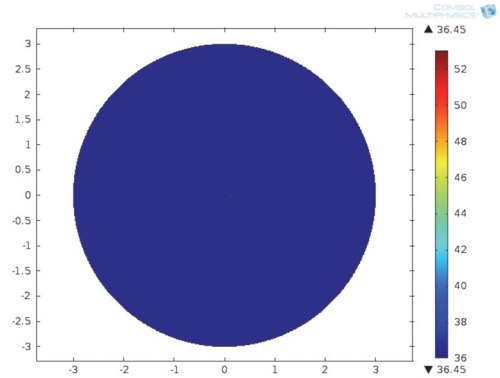

Figure 3. Bidimensional model of a tumor tissue (spherical symmetry), with a GNR (and its biopolymeric shell) located at its center. Dimensions are in millimeters. Temperature map after 2s irradiation with a 0.5 mW/cm^2 diode laser.

where C_{abs} [nm^2] is the absorption cross section of the GNR, I [W/cm^2] is the intensity of the laser light, v_p [nm^3] is the volume of the GNR. We supposed that the GNR and the biopolymeric shell where in thermal equilibrium and at the body temperature (35-38°C) and we set this value as the initial temperature value.

3.2 Model at the microscale

We supposed that the GNR enclosed in the biopolymeric shell was inside a pancreas tumor. As reported in literature, the shape of such a tumor is quite spherical, with a mean volume of around 50 mm^3 after 1 week. [8]
The problem was thus considered a bidimensional geometry (spherical symmetry), with the GNR located at the center of the tumor mass. We used the Bioheat Transfer module to describe the thermal history in the tumor and the heat Transfer in Solids module in the GNR and biopolymeric shell.
We supposed that the heat source was confined in the GNR and that the tumor is optically transparent to the laser light. Extra fine user controlled triangular mesh was used.
Flow exchange was imposed at the biopolymeric/tumor tissue interface.
The physical parameter of the tumor tissue were found in literature. [9] In particular it was evidenced that the heat perfusion rate of a biological tissue is not constant with temperature. Moreover, in the special case of a tumor tissue the heat perfusion rate decreases with increasing temperature, especially in the hyperthermic temperature range (around 43°C).
In the model we thus used this non-constant value of the heat perfusion rate coefficient.
As initial temperature value we set 35°C (close to the body temperature) and we supposed that all the domains were at thermal equilibrium.

4. Results

4.1 Model at the nanoscale

We 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. We also varied the treatment time.
We 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.

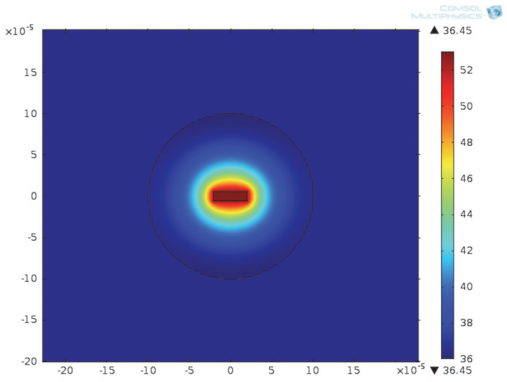

Figure 4. Enlargement of Figure 3, showing the GNR with its biopolymeric shell inside the tumor tissue. Dimensions are in millimeters. Temperature map after 2s irradiation with a 0.5 mW/cm^2 diode laser.

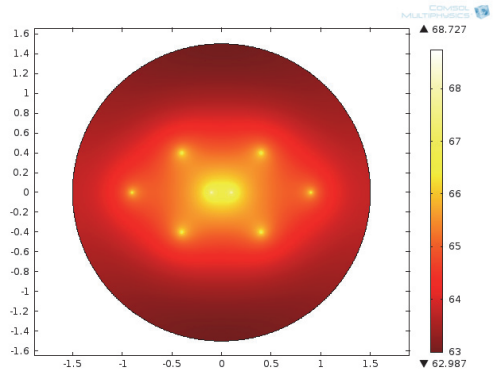

Figure 5. Tumor tissue with 8 heat point sources (GNRs clusters). Temperature map after 2s irradiation with a 0.5 mW/cm^2 diode laser.

By using a value higher than the recommended 42°C, we obtain a good thermal distribution around the intended value in the surrounding tissue.
Results after 2 s treatment time are reported in Figure 2.

4.2 Model at the microscale

The results of the nanoscale problem were confirmed also at the microscale. The main problem is that the thermal effect is strictly localized in the GNR surroundings (see Figure 3 and Figure 4). In order to induce an homogeneous thermal effect in the whole volume, we should use some clusters of GNRs as heat point sources in the whole tumor mass (see Figure 5).

5. Discussion and Conclusion

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. The preliminary results will be useful when designing the experimental measurements in cells.

8. References

1. Niemz, M.H., *Laser Tissue Interactions*, pp.77-80, Springer-Verlag, Berlin (1996).
2. Thomsen, S., Pathologic analysis of photothermal and photomechanical effects of laser-tissue interactions, *Photochem Photobiol*, **53**, 825-35 (1991)
3. F. Ratto, P. Matteini, S. Centi, F. Rossi, and R. Pini, Goldnanorods as new nanochromophores for photothermal therapies, *J.Biophoton*, 1–10(2010)/DOI10.1002/jbio.201000002.
4. F. Ratto, P. Matteini, F. Rossi, R. Pini, Size and shape control in the overgrowth of gold nanorods *J. Nanopart. Res.* **12**(6), 2029-2036 (2010).
5. F. Ratto, P. Matteini, A. Cini, S. Centi, F. Rossi, F. Fusi, R. Pini. CW laser-induced photothermal conversion and shape transformation of gold nanodogbones in hydrated chitosan films, *J Nanopart Res* **13**:4337–4348DOI10.1007/s11051-011-0380-5 (2011).
6. E. Sassaroli, KCP Li and BE O'Neill, Numerical investigation of heating of a gold nanoparticle and the surrounding microenvironment by nanosecond laser pulses for nanomedicine applications. *Phys. Med. Biol.* **54**, 5541–5560 (2009).
7. J. Mobley, T. Vo-Dinh, Optical Properties of Tissue, in *Biomedical Optics Handbook*, pp 2-54, T. Vo-Dinh Ed, CRC Press, Boca Raton FL-USA (2003).

8. AS Huynh, DF Abrahams, MS Torres, MK Baldwin, RJ Gillies, et al., Development of an Orthotopic Human Pancreatic Cancer Xenograft Model Using Ultrasound Guided Injection of Cells, *PLoSONE* **6**(5): e20330. doi: 10.1371/ journal.pone.0020330 (2011).
9. Lang et al., Impact of non linear heat transfer on temperature control. *IEEE Transactions On Biomedical Engineering*, **46**(9):1129-37, 1999.

9. Acknowledgements

The authors wish to acknowledge the "IPERNANO" Project of the Tuscany Region (POR CREO FESR 2007 – 2013) for supporting this study.