Heating of Nanoshells by Near-infrared Radiation: A rapid and Minimally-invasive method for destroying tumors

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1.0 Executive Summary

The purpose of this project is to model a novel and promising cancer treatment that involves the destruction of tumor cells by the direct injection of biocompatible nanoparticles (gold-silicon nanoshells) and their subsequent heating with near-infrared radiation. The use of near infra-red radiation gives this procedure an advantage over other thermal ablation treatments for cancer since light at this range (700-900 nm) is not significantly absorbed by chromopores in human tissue and can therefore penetrate more deeply (Hirsch et al., 2003). The method is also quick and minimally invasive. Using the simulation software FIDAP, we analyzed the diffusion of the nanoshells into a spherical tumor after being injected into its center. The change in temperature of the tumor due to the exposure of the nanoshells to near-infrared light was also studied. We found out that when 50 microliters of nanoshell solution (concentration of 1.5 e10 nanoshells/ml) is introduced to a 1-cm diameter tumor, it takes 29 hours for the nanoshells to fill up the tumor. At this point, exposure of the tumor with a laser (800 nm, power = 5.6 W/m^2) for 10 min raised the temperature of the entire tumor to at least 45°C, effectively destroying it. Further analysis on the effect of nanoshell distribution on the temperatures obtained showed that it has negligible effect. All distributions tested (0%, 25%, 50%, 75% and 100%) resulted in the entire tumor being heated above 45°C. The laser can therefore be immediately applied to the tumor right after injection. Nanoshell concentration vs. time and temperature vs. time profiles for the tumor for various treatment conditions were also obtained. The results of the mathematical modeling will help further studies of this treatment. Although the method still needs to be refined, it should provide an effective new treatment for the destruction of breast carcinomas and other localized tumors.

2.0 Introduction

Breast cancer is one of the leading causes of death in women. According to the American Cancer Society, approximately 200,000 women will be diagnosed with breast cancer in 2006. Furthermore, the chance of a woman having invasive breast cancer sometime in her life is approximately 1 in 8. The conventional method of treatment is to surgically remove the tumor. Breast cancer that has metastasized requires chemotherapy, which involves successive doses of highly cytotoxic drugs.

An alternative to removing tumors is thermal ablation treatment, a method of heating tumors until they suffer irreversible tissue damage. This technology is minimally invasive and does not cause a systemic reaction. The treatment methods tested to date include laser-induced thermal therapy, microwave and radio-frequency ablation, magnetic thermal ablation, and focused ultrasound. A novel procedure involving a class of nanoparticles called metal nanoshells shows great promise (Hirsch *et al*., 2003).

Nanoshells are tiny glass spheres coated with metal and can be tuned to absorb near-infrared light. The thickness of the metal coating determines the frequency at which they resonate when irradiated. Hirsch *et al*. injected nanoshells into a tumor and heated the tissue via the nanoshells with near-infrared light. The nanoshells were disguised from the immune system by attaching PEG to the outer surfaces. Their results show that the heat generated by the nanoshells destroyed the tumor cells without causing serious damage to surrounding tissue.

In this project we will use FIDAP to model the diffusion of nanoshells injected into a tumor and the temperature increase due to heating the nanoshells with near-infrared radiation.

3.0 Design Objectives:

1. Model how the nanoshells spread throughout the tumor after injection. The tumor is assumed to be spherical with at least a 1cm diameter. The nanoshells are initially injected into the center of the tumor where they diffuse radially outward. We will assume radial symmetry within the tumor so the nanoshell concentration will only be a function of distance from the center at any time. We expect to have a time-concentration profile for the nanoshells inside the tumor.
2. Model the temperature-time profile of the tumor containing the nanoshells during irradiation with near-infrared light. The nanoshells will convert the light energy into heat and increase the temperature of the tumor. This process will be treated as heat transfer with internal generation. We will again assume radial symmetry within the tumor so the temperature will only be a function of distance from the center at any time.
3. Determine the time needed for diffusion and the effect of nanoshell distribution on the heating of the tumor. The nanoshell distribution will be affected by the amount of time that they are allowed to diffuse into the tumor before exposure to near-infrared light.
4. Determine the effect of the intensity of near-infrared light on the temperature-time profile of the tumor during heating.
5. Determine the effect of Nanoshell distribution on the temperature-time profile of the tumor during heating.
6. Determine the conditions that will raise the temperature of the entire tumor to at least 45°C, thereby destroying it.
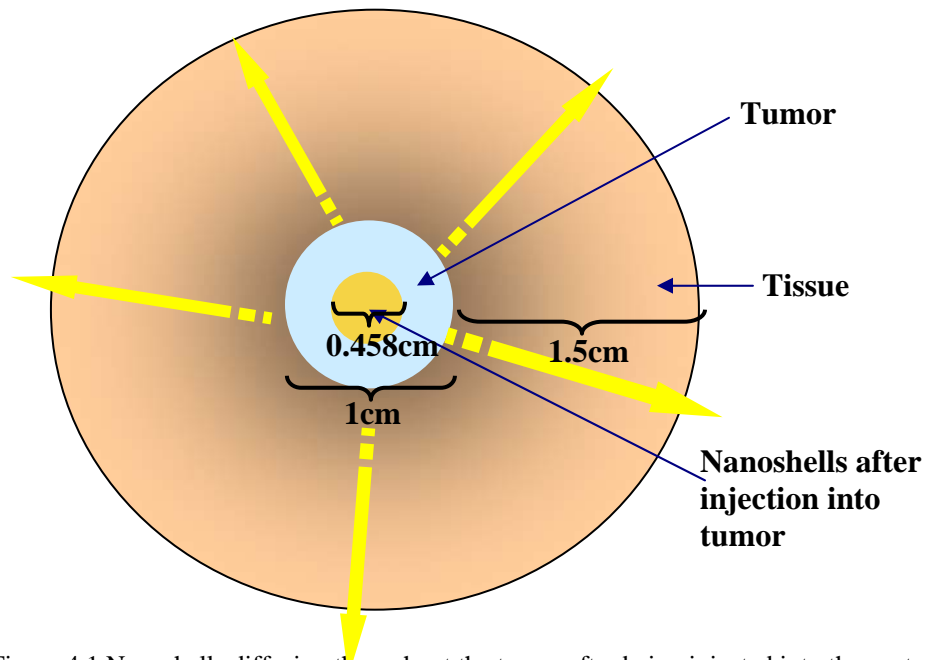
4.0 Schematic

Tumor

Tissue

0.458cm

1.5cm

1cm

Nanoshells after
injection into
tumor

Figure 4.1 Nanoshells diffusing throughout the tumor after being injected into the center:

NIR

Tumor with
nanoshells evenly
spaced throughout

Tissue

1.5cm

1cm

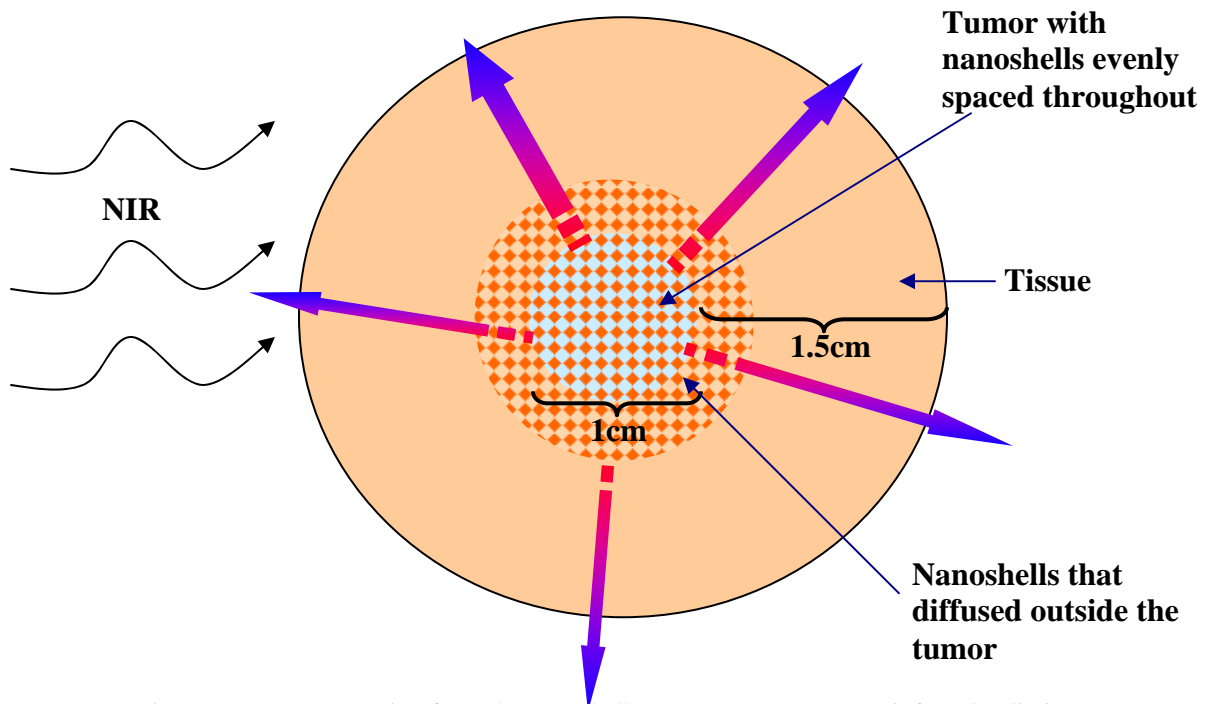Nanoshells that
diffused outside the
tumor

Figure 4.2 Heat generation from the nanoshells upon exposure to near-infrared radiation:
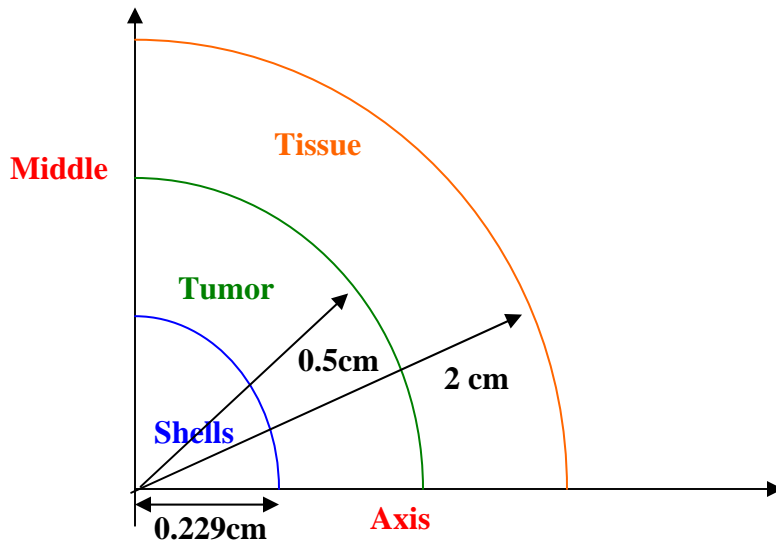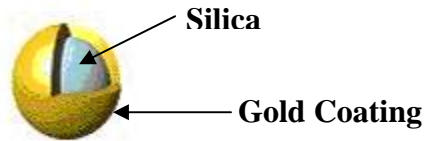
Figure 4.3 Axis-symmetric model:

Figure 4.4 Schematic of a nanoshell (www.nanospectra.com).

5.0 RESULTS AND DISCUSSION

The problem involves two parts: (1) Diffusion of the nanoshells and (2) heating of the nanoshells during exposure to near infrared radiation.

5.1 Non-dimensionalization of governing equations for FIDAP

The governing equation for the mass transfer of the nanoshells is:

$$\frac{\partial c_A}{\partial t} = D[\frac{\partial^2 c_A}{\partial r^2} + \frac{2}{r}\frac{\partial c_A}{\partial r}]$$

There is no value for diffusivity of nanoshells in the literature so we assumed that it would be similar to a large biomolecule. We found that the largest molecular weight species diffusing in a tumor is an antibody with $D = 2e\text{-}11$ m^2/s (Saltzman and Radomsky, 1991). Considering that the nanoshells are bigger than an antibody, we decided to try $D = 1e\text{-}11$ m^2/s for our simulations.

Since the diffusivity is very small, we have to non-dimensionalize the mass transfer equation, using the time variable $\tau = t*D/a^2$ and length variable R = r/a. We chose the 'a' to be

the radius of the initial region with nanoshells, 0.00229 m. The geometry in Gambit would have to be expressed in terms of R. The non-dimensional equation to be used in FIDAP is now:

$$\frac{\partial c_A}{\partial \tau} = D[\frac{\partial^2 c_A}{\partial R^2} + \frac{2}{R}\frac{\partial c_A}{\partial R}] \text{ with } D = 1$$

Since we are using non-dimensional species equation, we also have to modify the energy equation so that it will use the non-dimensional time equation defined above.
FIDAP solves the energy equation in the form:

$$\rho c_p (\frac{\partial T}{\partial t}) = k\left[\frac{\partial^2 T}{\partial r^2} + \frac{2}{r}\frac{\partial T}{\partial r}\right] + Q$$

We have to express this using derivatives of the non-dimensional variables, $\tau = t*D/a^2$ and R = r/a:

$$\frac{D}{a^2}\rho C_p \frac{\partial T}{\partial \tau} = \frac{1}{a^2} k \frac{\partial^2 T}{\partial R^2} + Q$$

Next we divided the equation by D/a^2:

$$\rho C_p \frac{\partial T}{\partial \tau} = \frac{k}{D}\left[\frac{\partial^2 T}{\partial R^2} + \frac{2}{R}\frac{\partial T}{\partial R}\right] + \frac{Q a^2}{D}$$

When specifying the properties in FIDAP, we have to use k/D as the thermal conductivity term and $\frac{Q a^2}{D}$ as the volumetric generation term.

5.2 When to apply the laser

After injection, the nanoshells initially occupy the 'shells' entity and then diffuse into the tumor 'entity'. We initially assumed that the best time to apply the laser is when the nanoshells have completely filled the tumor but have not yet gone to the tissue. We quantified this condition as when the nanoshells concentration at the tumor-tissue boundary has reached 1% of the original concentration of 1 e16 nanoshells/m^3. The diffusion of the nanoshells was run in FIDAP using the non-dimensional species equation (D = 1e-11 m^2/s). Results show that the 1% concentration condition is reached after 29 hours of diffusion. The long diffusion time would mean that the patient will have to come back the next day after injection of the nanoshells for the heat treatment. The relatively large size of the nanoshells (130 nm) would not allow their movement into the capillaries to be carried away from the tumor by blood flow.

5.3 Heat generation of nanoshells due to exposure to near-infrared radiation

After 30 hours, an infrared laser is shone on the tumor and heat is produced by the nanoshells. Tissue that reaches 45°C would be damaged.

5.4 Calculation of volumetric heat generation term

Hirsch et al. reported that when tumors injected with nanoshells were exposed to near infrared light (4 W cm^{-2} power), their temperature rose by 15°C after 1 min. If we assume that at this short time, heat conduction from the region where there is generation is not significant, then the increase in temperature is only due to the heat generation by the nanoshells. If we further assume that 15°C is the average increase in temperature for the region with nanoshells, then we have the following equation for the heat generation:

$$Q \text{ (volumetric heat generation)} = \rho \, C_p \, \Delta T/\Delta t$$

The tumor physical properties are:
$\rho = 1{,}000$ kg m^{-3}
$C_p = 4{,}180$ J kg^{-1} °C^{-1}
$\Delta T = 15$°C
$\Delta t = 60$ s

$Q = (1{,}000$ kg m$^{-3})(4{,}180$ J kg^{-1} °C$^{-1})(15$°C/60 s$) = 1.045$ x 10^6 W m^{-3}

The nanoshells are injected into the tumor at a concentration of 1.5 x 10^{10} nanoshells/ml. Since the nanoshells have a very low diffusivity value (1 x 10^{-11} m^2 s^{-1}), it is reasonable to assume that they have not significantly diffused after 30 minutes which is the time allowed to elapse before they are exposed to near infrared light after injection (Hirsch et al., 2003). We can therefore say that at a concentration of 1.5 x 10^{10} nanoshells/ml, the volumetric heat transfer is the one that we calculated above.

Since we are using non-dimensional energy equation, we have to use k/D as the thermal conductivity term and $\dfrac{Q\,a^2}{D}$ as the volumetric generation term in FIDAP. The values are:

$$\frac{k}{D} = \frac{0.48 \, W/m-°C}{1e-11 \, m^2/s} = 4.8\,e10 \, J/m^3-°C$$

$$\frac{Q\,a^2}{D} = \frac{(1.045 \text{ x } 10^6 \text{ W m}^{-3}) * (0.00229m)^2}{1e-11 \, m^2/s} = 5.48\,e11 \, J/m^3$$

5.5 Testing of Q value in FIDAP

The first run was to check the Q calculation with the assumption that there is no heat conduction away from the region where there is volumetric heat generation. This was achieved by specifying a very small value of k/D. The results gave the mean temperature in the shells entity to be 51.74°C which is 14.74°C higher than the initial temperature of 37°C.

We then tried the simulation with the calculated Q and the actual k/D of 4.8 e10 J m^{-3}°C^{-1}
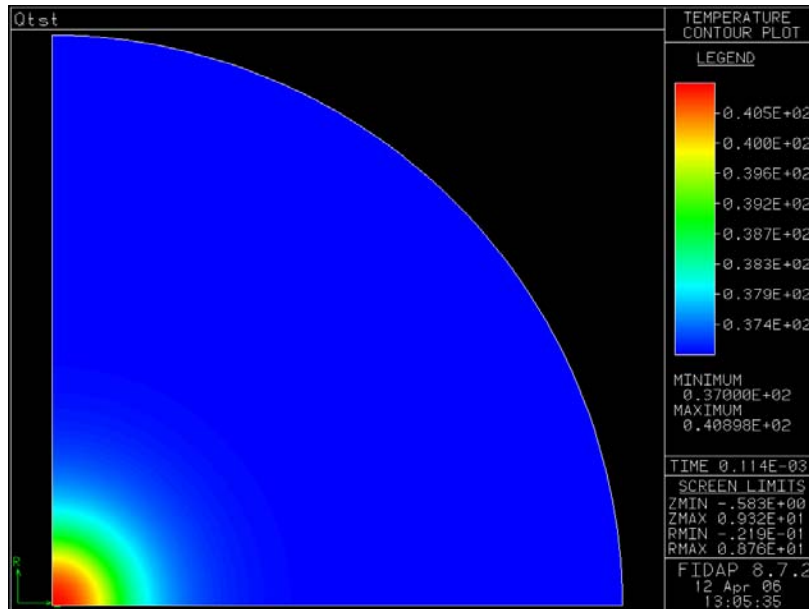
Figure 5.5.2 Temperature contour plot of model with heat added and actual k/D of 4.8 e10 J m^{-3}°C^{-1}.

It can be seen that the maximum temperature reached is only 40.9°C, giving an increase in temperature below the experimentally observed 15°C. This was expected since the Q was calculated without heat conduction. The actual Q to be used can be determined by increasing the calculated Q and then running in FIDAP to obtain a 15°C rise in temperature after 1 min of heating.

We also allowed the nanoshells to diffuse for 30 minutes before heating since this was done in the experiment. Simulation results show that we get the desired temperature increase for a Q that is 5 times that of the calculated or Q*a2/D = 5*5.48e11 = 2.192e12 (for the non-dimensional energy equation). This corresponds to an actual Q of 5.225 e6 W/m^3 .The temperature contour plot is shown below after 1 min of heating with this Q.

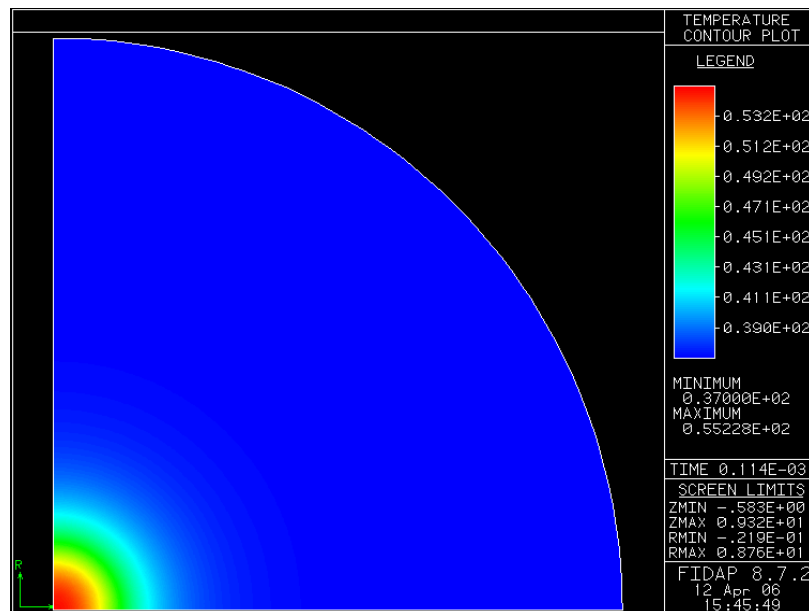
Figure 5.5.3 Temperature contour plot of model after 1 min of heating with Q = 5.225 e6 W/m^3.

5.6 Effect of nanoshell concentration on the volumetric heat generation term

As discussed earlier we are going to allow the nanoshells to fill the entire tumor before application of near-infrared light. Simulation of the diffusion with FIDAP would give the concentration of the nanoshells at the different radial positions in the tumor. Since heat generation is due to the nanoshells, regions with different nanoshell concentrations should give different volumetric heat generation terms. We would therefore need a function that relates Q to nanoshell concentration.

A reasonable relation between Q and nanoshell concentration is that they are directly proportional. With m as the constant of proportionality, and c as nanoshell concentration, we have

$$Q = mc$$

To get mc we use the Q we calculated for $c = 1.5 \times 10^{10}$ nanoshells/ml

$$m = \frac{Q}{c} = \left[\frac{1.045 \, x 10^6 \, W \, m^{-3}}{1.5 \, x \, 10^{10} \, nanoshells \, cm^{-3}} \right] \left[\frac{100 \, cm^{-3}}{1 \, m^{-3}} \right] = 6.97 \, x \, 10^{-11} \, W \ per \ nanoshell$$

The value of m is very small and may cause problems when used in FIDAP so we will use the value 6.97 x 10^{-8} W per kilonanoshells. The relationship between Q and c is now

Q (W m-3) = (6.97 x 10^{-8} W per kilonanoshells) c*

where c* is kilonanoshells/m^3

All concentrations during simulation with heat transfer would be expressed in terms of kilonanoshells/m^3. This is to be implemented in FIDAP by a subroutine for the volumetric heat generation term.

5.7 Solution

The problem we are going to simulate is the case where the nanoshells are allowed to diffuse for 29 hours before heating them with near-infrared light for 6 minutes (the maximum exposure time used in the actual experiment by Hirsch et al, 2003).

The FIDAP simulation results are:
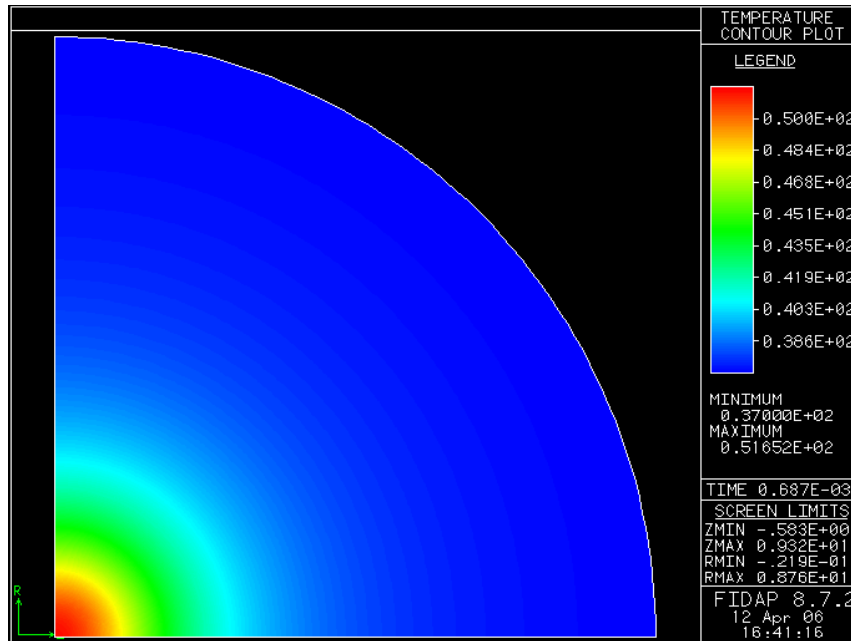
Figure 5.7.1. Temperature contour plot of model after 29 hrs of diffusion and then heating with NIR for 6 minutes.
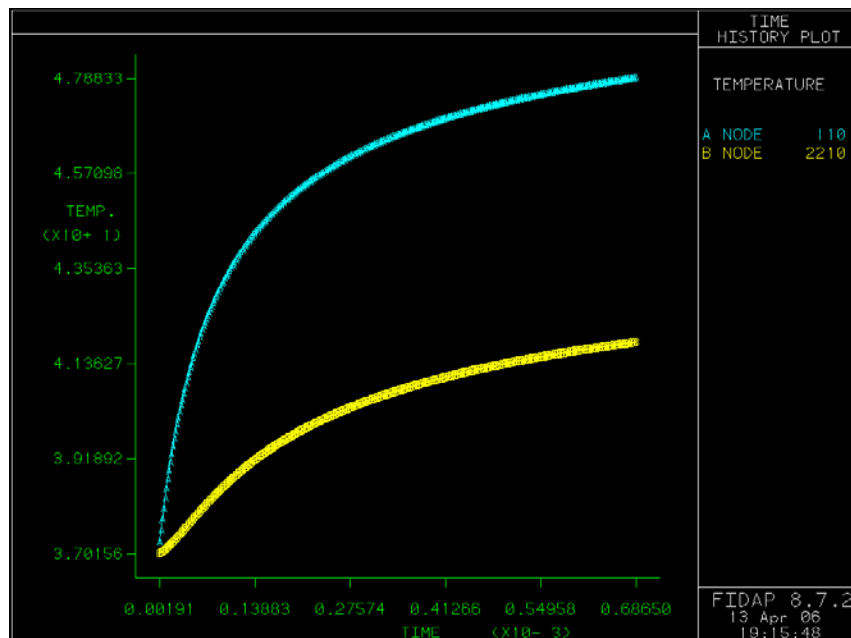
Figure 5.7.2 Temperature vs. Time plot after application of NIR for 6 minutes: Node A (100) is at the shells-tumor boundary, Node B (2200) is at the tumor-tissue boundary

Since our objective is to kill the cancer cells by heating them above 45°C we were interested to determine the temperature ranges for the different entities in our system: (Note that "shells" and "tumor" entities contain cancer cells while "tissue" has healthy cells only)

Shells: 47.9°C to 51.6°C
Tumor: 42°C to 47.9°C
Tissue: 37°C to 40°C

It can be seen that with the parameters used, all the tumors are destroyed in the "shells" entity but not all in the "tumor" entity. We have to see what parameters need to be changed in order to make the "tumor" entity have a minimum temperature of 45°C while still keeping the temperature in the tissue less than this. Possible parameters to change could be the duration of exposure to near-infrared light or the intensity of the laser.

6.0 Sensitivity analysis

6.1 Effect of increasing heat source and duration of exposure to near-infrared light

We ran simulations using source terms that are 20% and 40% higher than what we used (5.225 e6 W/m^3). These are 6.27 e6 W/m^3 (designated as Q6) and 7.315 e6 W/m^3 (Q7), respectively. The laser was shined on the tumor for 30 minutes to also see how the length of heating affects the temperatures. The results are shown in Fig. 6.1.1
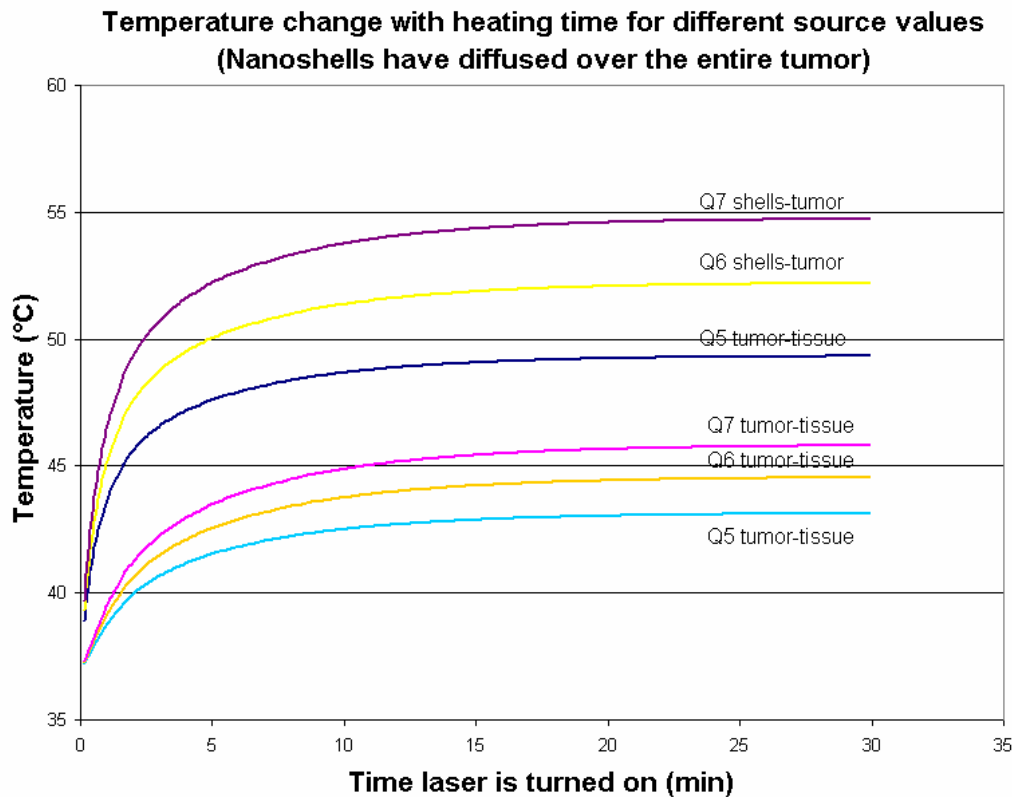
Fig.6.1.1 The effect of changing the source term and the length of heating on the temperatures of the shells-tumor and tumor-tissue boundary.

It can be seen from the graphs that it is only Q7 that gives a temperature greater than 45°C for the tumor-tissue boundary after about 10 minutes of heating. This indicates that for a source term of 7.315 e6 W/m^3, the entire tumor has been heated above 45°C and is therefore destroyed. Since Q7 is 1.4 times greater than the Q calculated based on Hirsch et al. (2003) which used a laser power of 4 W/cm^2, the laser power for Q7 would proportionately be 5.6 W/cm^2. This laser power is below the minimum value for injury to cells of 10 W/cm^2 that was reported by Huang et al. (2006). It should also be noted the temperatures at the "tumor"

boundaries stop increasing after about 20 minutes of heating. This would indicate that a steady-condition has been reached with the rates of heat generation and conduction into the "tumor" becoming equal to the rate of heat removal into the colder "tissue" entity.

Based on our results, a solution to the problem would be to allow the nanoshells to diffuse for 29 h after injection and then heat the tumor by shining a laser with a power of 5.6 W/cm^2 for 10 minutes.

6.2 Effect of changing diffusivity of nanoshells

The time at which near-infrared light is applied depends on how fast the nanoshells can diffuse and fill most of the tumor. We simulated the effect of varying the diffusivity of the nanoshells using FIDAP. The results are shown in the table and graphs below

Time (hours)	Mean concentration in "tumor" entity (kilonanoshells/m^3)				
	0.5e-11 m^2/s	1e-11 m^2/s	2e-11 m^2/s	4e-11 m^2/s	8e-11 m^2/s
10	4.53E+11	6.36E+11	8.47E+11	9.73E+11	8.58E+11
20	6.36E+11	8.48E+11	9.74E+11	8.58E+11	5.56E+11
30	7.61E+11	9.44E+11	9.39E+11	6.90E+11	3.82E+11
40	8.48E+11	9.74E+11	8.58E+11	5.56E+11	2.81E+11

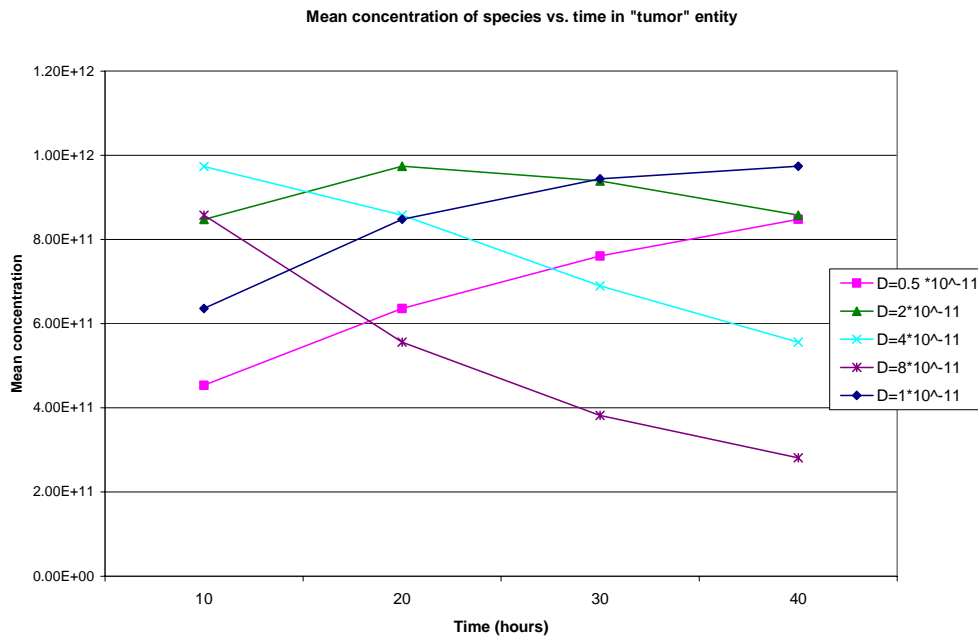Table 6.2.1 Mean concentration in tumor entity for different diffusivities at various times.

Figure 6.2.1 Mean concentration of species in tumor entity for different diffusivities at various times.

It can be seen that if the diffusivity is greater than 2 e-11, there is now nanoshell depletion in the "tumor" region after 30 hrs, indicating that the rate of diffusion out of the tumor into the tissue is greater than the diffusion into the "tumor". We do not want this to happen since this would mean that we have less nanoshells in the tumor and subsequently less heat generation.

It would be useful to know the time when the nanoshell concentration at the tumor-tissue boundary has reached 1% of the original concentration of 1 e13 kilonanoshells/m^3. Simulation with FIDAP gave the following results

Diffusivity (m2/s)	Dimensionless time to reach 1%	time (h)	mean conc. of nanoshells in tumor (kilonanoshells/m^3)	St. Dev
5.00E-12	0.20043	58.39	9.3961E+11	8.51E+11
1.00E-11	0.200586	29.22	9.3972E+11	8.51E+11
2.00E-11	0.200183	14.58	9.3936E+11	8.52E+11

Table 6.2.2 Time required for nanoshell concentration at the tumor-tissue boundary to reach 1% of the original concentration for various diffusivities.

The dimensionless time to reach 1% is similar same for the different diffusivities tested. The final mean concentration of nanoshells in tumor and the standard deviations are almost equal for the different diffusivities, indicating that the nanoshell concentration profile within the tumor region are similar. A plot to the time in hours to reach 1% for different diffusivities is shown below

Time to reach 1% at tumor-tissue boundary for different diffusivities
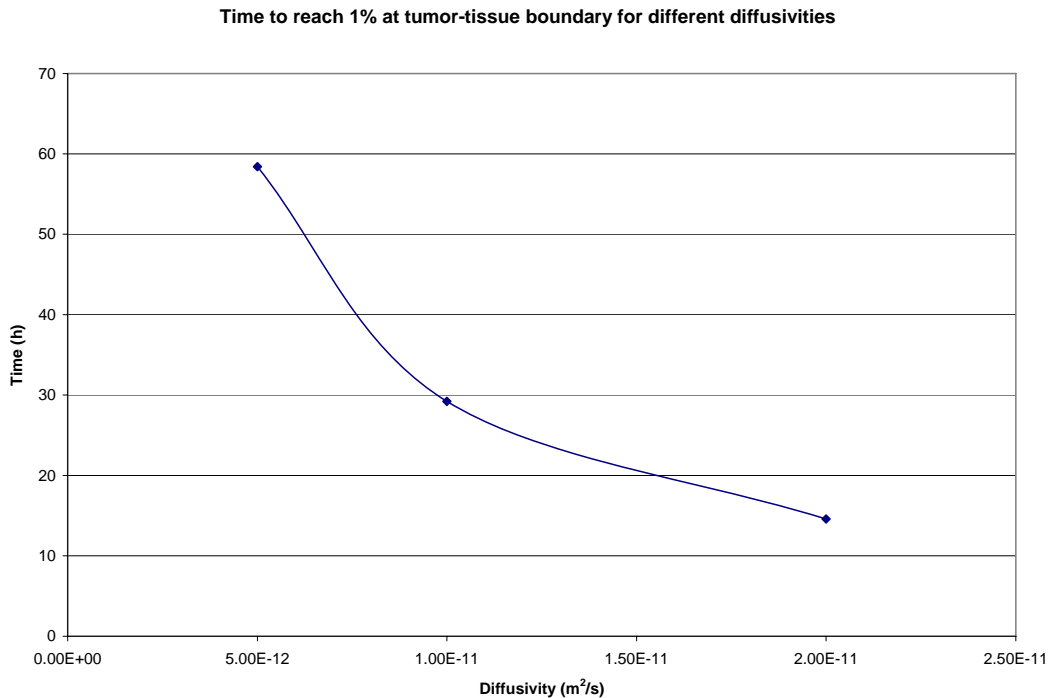

Figure 6.2.2 Time to reach 1% of original nanoshell concentration at the tumor-tissue boundary for different diffusivities.

From the values in the table and the graph above, it would seem that the time to reach 1% has an inverse relationship with the diffusivity. In equation form, we have

Diffusivity*time to reach 1% (h) = constant

From the three diffusivities tested, the average value of the constant is 2.9192e-10. This relationship should allow us to get the time to reach 1% for other diffusivity values.

6.3 Effect of nanoshell distribution in 'tumor' entity

Recall that we apply heat only after the nanoshell concentration at the tumor-tissue boundary is 1% of the initial concentration. This condition corresponds to a 100% distribution of nanoshells into the 'tumor' entity and requires 29 hrs. We decided to test the effect of nanoshell distribution on the tumor temperature by considering nanoshell distributions of 0% (no time is allowed for diffusion, laser is applied immediately), 25%, 50%, and 75% in the 'tumor' entity. These are shown schematically in Fig. 6.3.1
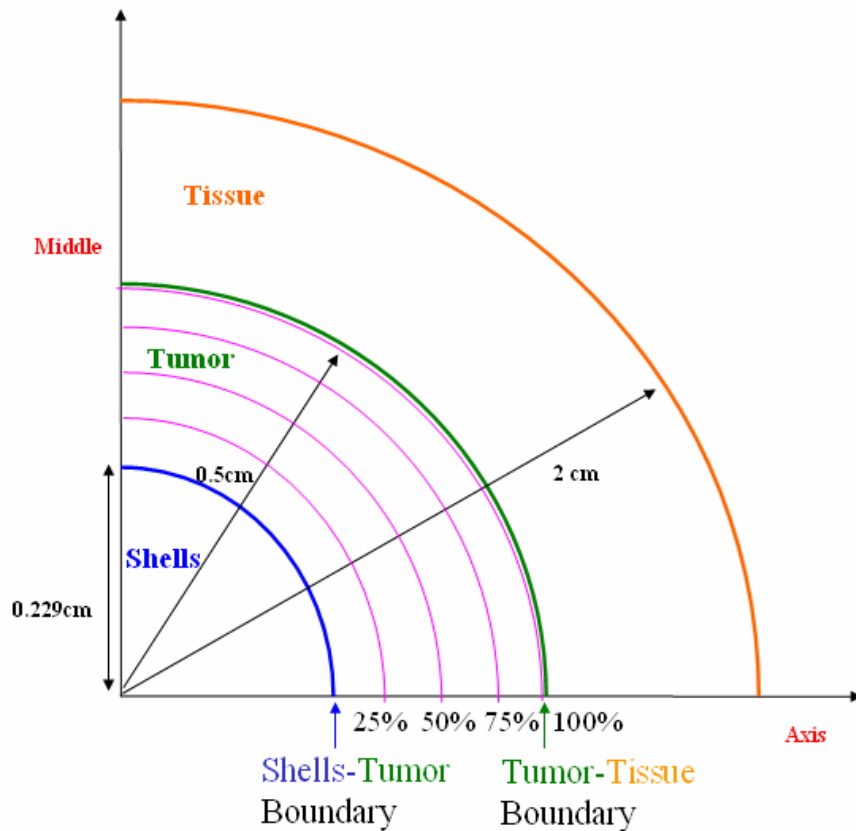

Figure 6.3.1 Schematic of nanoshell distributions considered within 'tumor' entity.

These were implemented in FIDAP by finding nodes that corresponded to the distributions and determining when the nanoshell concentration in these nodes have reached 1% of the initial concentration. The results from the simulations are shown in Fig. 6.3.2.
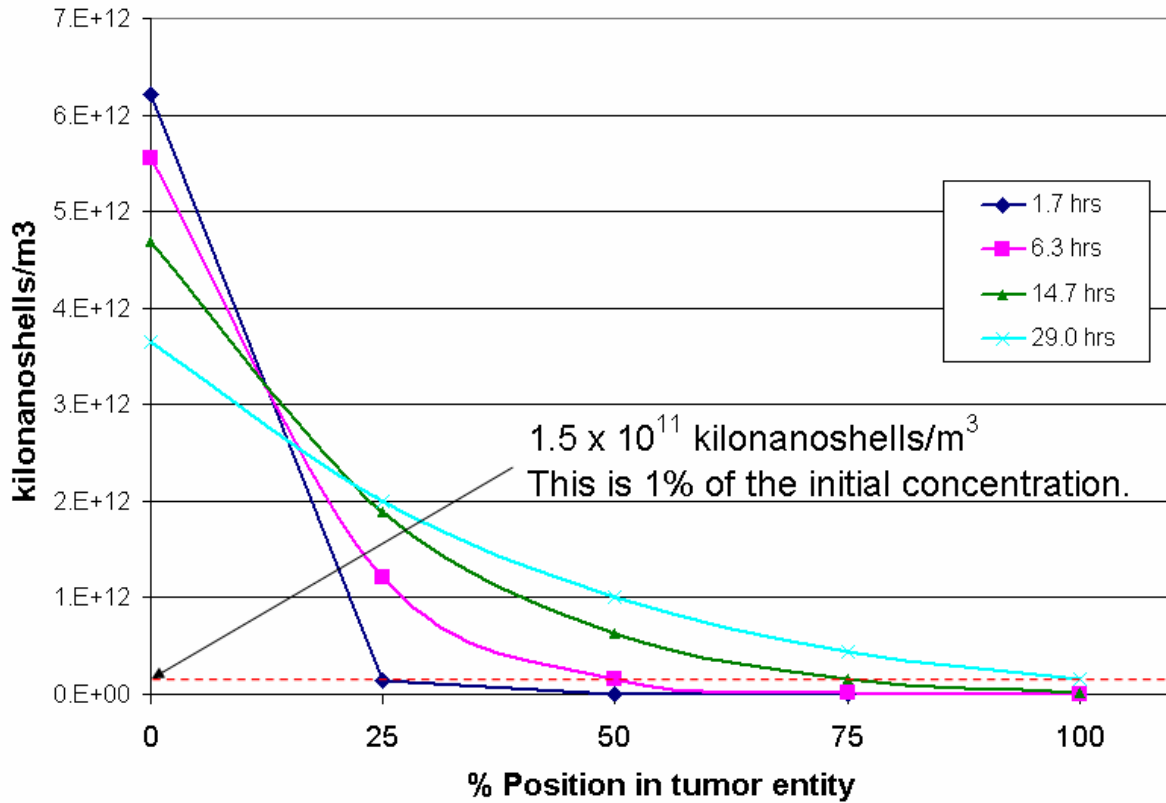
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Figure 6.3.2 Different nanoshell distributions within 'tumor' entity.

The figure also shows the diffusion time required to achieve the different distributions. These are summarized in Table 6.3.1. We can see that the nanoshell concentration profile becomes more flat with increasing time of diffusion. This is expected since as the nanoshells diffuse, the concentration within the tumor becomes more uniform.

Table 6.3.1 Diffusion time required to reach different nanoshell distributions at 'tumor' entity.

Nanoshell distribution in 'tumor' entity (%)	Time to reach 1% of initial concentration at specified position (hrs)
25	1.7
50	6.3
75	14.7
100	29.0

It is interesting to note how much the time of diffusion is reduced if the nanoshell distribution is lowered. If the other nanoshell distributions can heat the entire tumor to 45°C, time that the patient needs to wait before the laser treatment would become considerably less. The temperatures were obtained for the different distributions by simulation ('Restart' FIDAP after the corresponding diffusion time). Figure 6.3.2 shows the temperatures at the boundaries of the 'tumor' entity.
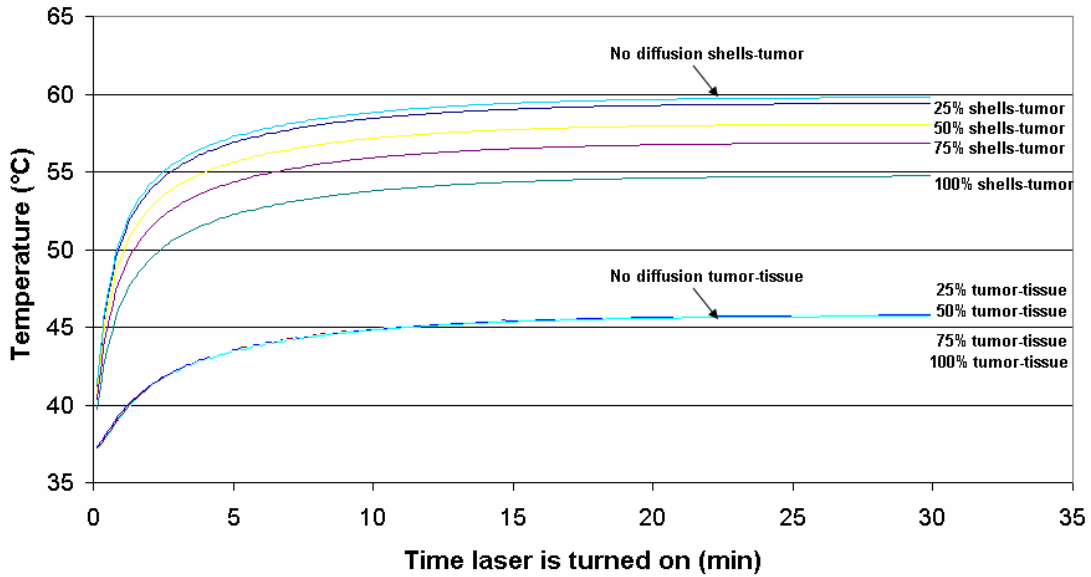
Figure 6.3.2 Temperature profiles at the shells-tumor and tumor-tissue boundaries for different nanoshell distributions (volumetric source is 7.315 x 10^6 W/m^3 ~ laser power of 5.6 W/cm^2).

It can be seen that at the 'shells-tumor' boundary, the temperature decreases as the nanoshells become more distributed within the 'tumor' entity. This is because at low distributions, the nanoshells are still concentrated within the 'shells' entity and heat generation is focused here. At higher distributions the nanoshells are farther into the 'tumor' entity and heat generation is over a bigger volume. The results show that the 'tumor-tissue' boundary temperature are not sensitive to the nanoshells distribution. All distributions give a temperature here that is greater than 45°C after about 10 minutes of heating. This tells us that whatever the nanoshell distribution, the entire tumor is heated above 45°C and is destroyed. We can therefore heat the tumor immediately after injection! (No diffusion case in the Fig. 6.3.2). The FIPOST temperature contour plot for the no diffusion case at steady-state is shown in Fig. 6.3.3.
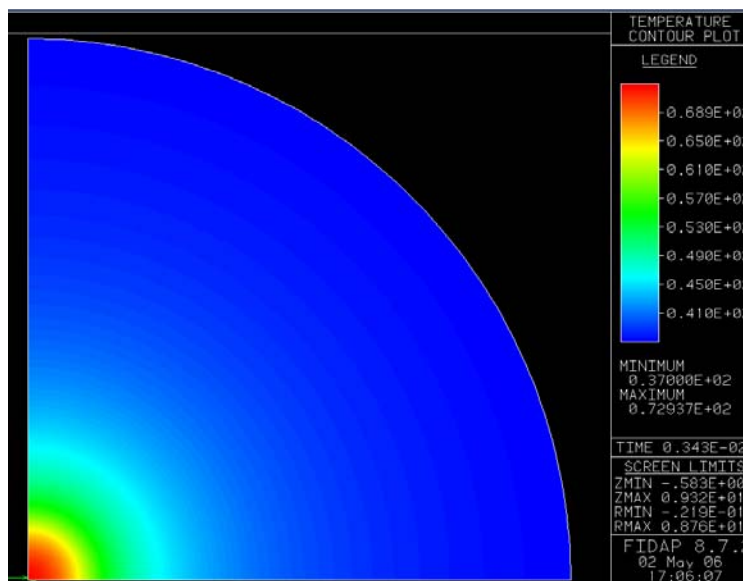

Figure 6.3.3 Temperature contours for no diffusion case at steady-state

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To check if the tissue temperature will increase after heating is stopped, a 'Restart' simulation was done without heat source and using the temperature contour in Fig. 6.3.3 as initial conditions. The results show that the temperatures decreased rapidly and were almost 37°C after 10 minutes.

7.0 Conclusions and Design Recommendations

A model for cancer treatment that involves the destruction of tumor cells by the direct injection of biocompatible nanoparticles (gold-silicon nanoshells) and their subsequent heating with near-infrared radiation was constructed. Simulation results using FIDAP showed that the time required for the nanoshells to fill up a 1-cm tumor after injecting 50 uL nanoshell solution at its center (1.5 e10 nanoshells/ml) is 29 hours. At this point, exposure of the tumor with a laser (800 nm, power = 5.6 W/m^2) for 10 min raised the temperature of the entire tumor to at least 45°C, effectively destroying it. Further analysis on the effect of nanoshell distribution on the temperatures obtained showed that it has negligible effect. All distributions tested (0%, 25%, 50%, 75% and 100%) resulted in the entire tumor being heated above 45°C. The laser can therefore be immediately applied to the tumor right after injection.

7.1 Realistic Constraints

While the nanoshell thermal ablation treatment process shows great promise, there are certain design constraints that must be considered. Our main focus was on economic and health and safety constraints.

Conventional methods of treatment include radiation therapy, chemotherapy and invasive surgical procedures to remove the tumor. Because the nanoshell treatment method is minimally invasive, it provides a cost effective method of treating cancer. Nanoshells are composed of a silica core and coated with a thin gold shell. According to Sigma Aldrich, a 5mL vial of 5% suspension colloidal microparticles costs $20.70. Gold coating of the silica particles could be achieved using a sputter coater. The cost of a SPI model sputter coated is $5,839. However, the cost to coat the small amount of particles required per surgery (~50μL) would not be a significant increase to the cost of the silica particles. Furthermore, because this procedure is minimally invasive, the process could likely be conducted on a hospital out-patient basis and the patient could go home the same day that the procedure was conducted which would significantly decrease hospitalization costs.

The health and safety constraints that must be considered include the biocompatibility of nanoparticles and the risk and long term effects associated with the thermal ablation procedure. Because of the inherent biocompatible nature of gold colloid, nanoshells are acceptable for internal use. Furthermore, because the only invasive aspect of the thermal ablation method is the syringe injection, this process places the patient at minimal risk. Studies show that non-tumor tissue does not absorb near infrared light and thus the tissue surrounding the tumor would be minimally affected. Moreover, from our analysis we discovered that when the laser is turned off after heating the nanoshells, the temperature in the surrounding tissue does not increase.

8.0 Literature cited

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9.0 Special Conditions

Our problem consisted of two parts: diffusion of the nanoshells throughout the tumor region followed by laser heating to destroy the tumor. While we were investigating the problem specifications, we realized that our heat generation term (Q) is a function of nanoshell concentration. In order to account for this, we needed to write our own subroutine using Fortran. Since we were not aware of any debugger, and the compiler was not very strict, it took many days to determine the syntax and logical errors in the code. In order to make the diffusion and heating problems easier to manage, we employed a FIDAP restart.

Appendix A

Governing equations:
Species Mass Conservation Equation in Spherical Coordinates
For mass diffusion of nanoshells into the tissue
Subscript A is used for the nanoshells.
Assuming no momentum (v = 0), and no reaction ($r_A = 0$)

$$\frac{\partial c_A}{\partial t} = D[\frac{\partial^2 c_A}{\partial r^2} + \frac{2}{r}\frac{\partial c_A}{\partial r}]$$

Energy Conservation Equation in Spherical Coordinates
For heat transfer from the nanoshells to the surrounding tissue during application of near-infrared radiation:

$$\rho c_p (\frac{\partial T}{\partial t}) = k\left[\frac{\partial^2 T}{\partial r^2} + \frac{2}{r}\frac{\partial T}{\partial r}\right] + Q$$

where Q represents the heat generated by both the nanoshells and tissue.

Boundary conditions:

During mass transfer:
At the curve boundary, c_A (r = 2 cm) = 0
At the middle boundary, flux = 0
At the axis, flux = 0

During heat transfer:
At the curve boundary, $T=T_0= 37^0C$
At the middle boundary, flux = 0
At the axis, flux = 0

Initial conditions:
Fifty microliters of the nanoshell solution (1.5×10^{10} nanoshells/mL) will be injected into the tumor. Assuming that it will occupy a spherical region concentric with the tumor, the radius occupied by the nanoshell solution is calculated as follows:

$(50 \times 10^{-6}$ L$)$ $(1000$ cm^3/L$)$ = $(4/3)\pi r^3$
r = 0.229 cm

Mass transfer:
At $0 \leq r \leq 0.229 cm$, c_A = 1.5×10^{10} nanoshells/mL
At $0.229\ cm < r \leq 2\ cm$, c_A = 0.

Heat transfer:
T = 37^0C at all r.

Properties
The tumor physical properties are: ρ = 1,000 kg m^{-3}, C_p = 4,180 J kg^{-1} °C^{-1} (Datta, 2004)
κ = 0.48 W m^{-1} K^{-1} (Ng, E.Y. K. and N. M. Sudharsan, 2001)
ΔT = 15°C, Δt = 60 s (Hirsch, *et al.*, 2003)
Size of tumor: Sphere with radius of 0.5 cm

Appendix B

a) Problem statement keywords

Geometry type	2-D Axis-symmetric	Modeled nanoshells, tumor, and tissue as projected sphere quadrant
Flow regime	Incompressible	Contents are incompressible
Simulation type	Transient	The concentration and heating depends on time.
Flow type	Momentum turned off	No fluid flow
Convective term	Linear	There is no convection
Fluid type	Newtonian	The system behaves in a Newtonian manner.
Momentum equation	No momentum	No momentum in the tumor or tissue.
Temperature dependence	Energy	For FIDAP restart, there will be laser heating.
Surface type	Fixed	The surface is fixed.
Structural solver	No structural	There is no structural solver.
Elasticity remeshing	No remeshing	No remeshing occurs.
Number of phases	Single phase	All matter is in one phase.
Species dependence	Species = 1	Non-reactive species (nanoshells).

b) Solution statement keywords

S.S. = 50	Successive substitution
VELCONV = 0.001	Velocity convergence tolerance
RESCONV = 0.01	Residual vector convergence tolerance
SCHANGE = 0	Default percentage change in solution magnitude
ACCF = 0	Acceleration (relaxation) factor

c) Time integration statement keywords

	Diffusion	Restart (Source subroutine)	
Time integration	Backward	Backward	Method for transient analysis
No. time steps	1500	200	Max # discrete time integration steps
Starting time	0	0	Starting time is 0
Ending time	0.1988	3.43E-03	Ending time (D*t/L^2)
Time increment	1.99E-04	1.72E-05	Time increment (D*t/L^2)
Time stepping algorithm	Fixed	Fixed	The time increment is fixed

d) Mesh Evaluation

Before solving the problem it is necessary to see if the mesh affects the result since if it does it means that the mesh is not fine enough. We tested 4 different meshes and compared the mean concentration in tumor entity after 30 hrs of nanoshell diffusion. The results are shown in the table below and a plot of this was made. The % change in the mean concentration as the mesh was successively refined is also shown in figure 2.

Mesh	Divisions per side	Mean Concentration in tumor entity (kilonanoshells/m^3)
A	1327	8.72E+11
B	3509	9.26E+11
C	7235	9.44E+11
D	12254	9.54E+11
E	18702	9.60E+11
F	26021	9.64E+11

Table A.1. Effect of mesh refinement on mean concentration in tumor entity
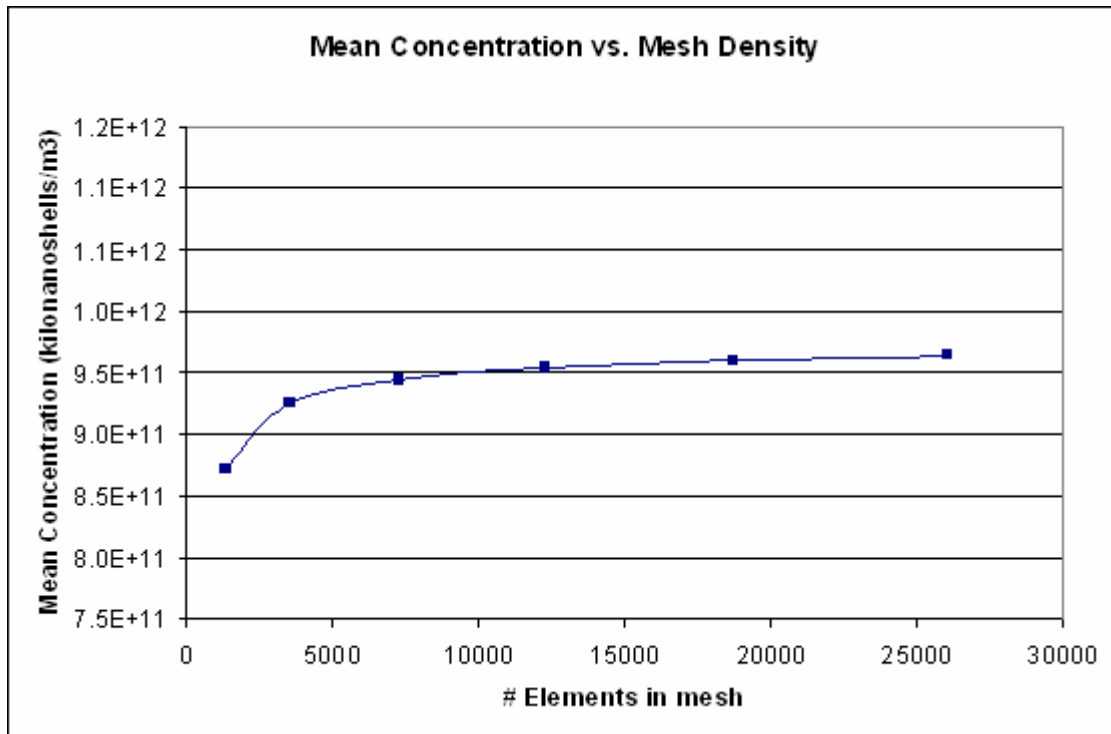
Figure A.1. Change in mean concentration in tumor as mesh is made finer
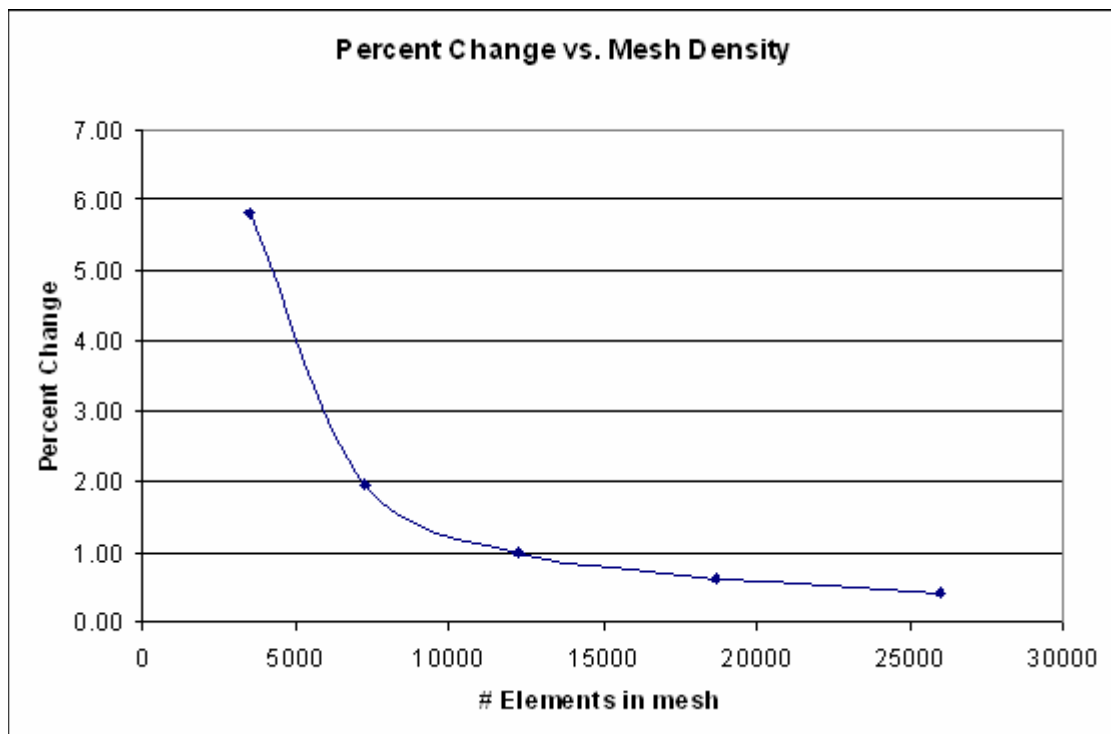

Fig.A.2 Percent change in mean concentration as mesh is made denser

It can be seen that the mean concentration increases as the divisions per boundary goes up. However, the change in the mean concentration (slope) decreases as the divisions per

boundary increases. The change observed from 80 to 100 divisions is small compared to that for 40 to 60. We would ideally choose the 120 mesh but since in our problem solution we need to use a subroutine that reads the concentration at every mesh node and then calculates the heat generation there, the simulation time would be long for such a fine mesh. We therefore decided to use the 80 mesh since the % change between this mesh and the 100 is less than 1 %. It also gave simulation results within a reasonable time (about 1 hour).
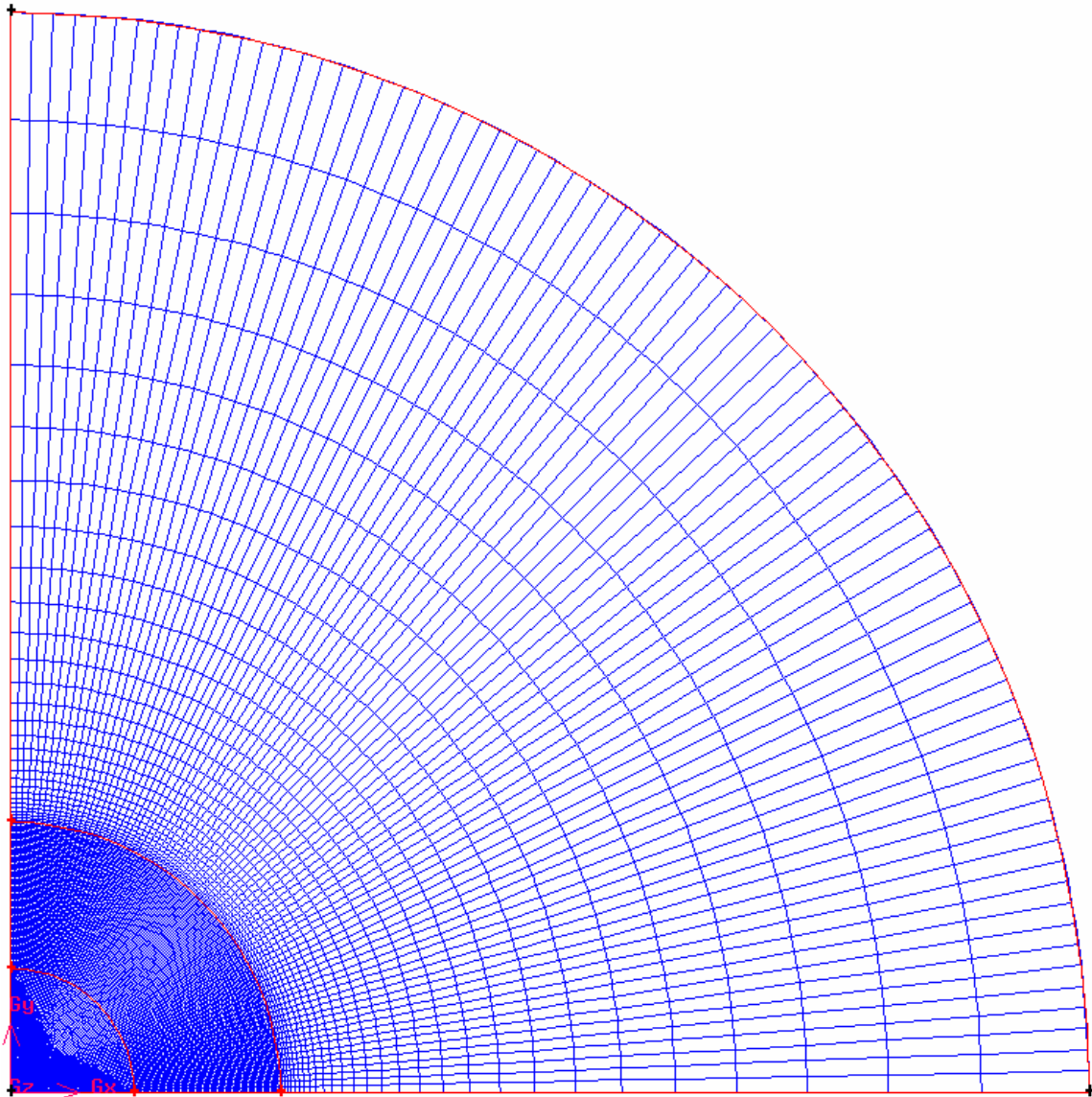

Fig.A.3 The mesh used (12,254 elements) for all FIDAP solutions. The inner shells and tumor regions had a uniform 80 subdivision each, while the outer tissue region was graded.

Appendix C

Input file

```
FIPREP
 PROB (AXI-, ENER, NOMO, TRAN, LINE, FIXE, NEWT, INCO, SPEC = 1.0)
 PRES (MIXE = 0.100000000000E-08, DISC)
 EXEC (NEWJ)
 SOLU (S.S. = 50, VELC = 0.100000000000E-02, RESC = 0.100000000000E-01,
       SCHA = 0.000000000000E+00, ACCF = 0.000000000000E+00)
 TIME (BACK, FIXE, TSTA = 0.000000000000E+00, TEND = 0.1988,
       DT = 0.198800000000E-03, NSTE = 1500)
 OPTI (SIDE)
 DATA (CONT)
 PRIN (NONE)
 POST (RESU)
 SCAL (VALU = 436.68122)
 ENTI (NAME = "shells", SOLI, PROP = "mat1", SPEC = 1.0, MDIF = "C1_shells")
 ENTI (NAME = "tumor", SOLI, PROP = "mat1", SPEC = 1.0, MDIF = "C1_tumor")
 ENTI (NAME = "tissue", SOLI, PROP = "mat1", SPEC = 1.0, MDIF = "C1_tissue")
 ENTI (NAME = "shellsleft", PLOT)
 ENTI (NAME = "shellsaxis", PLOT)
 ENTI (NAME = "tumoraxis", PLOT)
 ENTI (NAME = "tumorleft", PLOT)
 ENTI (NAME = "tissueaxis", PLOT)
 ENTI (NAME = "tissueleft", PLOT)
 ENTI (NAME = "tissuearc", PLOT)
 ENTI (NAME = "tumorarc", PLOT)
 ENTI (NAME = "shellsarc", PLOT)
 DENS (SET = "mat1", CONS = 1000.0)
 SPEC (SET = "mat1", CONS = 4180.0)
 COND (SET = "mat1", CONS = 48000000000.0)
 DIFF (SET = "C1_shells", CONS = 1.0)
 DIFF (SET = "C1_tumor", CONS = 1.0)
 DIFF (SET = "C1_tissue", CONS = 1.0)
 BCNO (TEMP, CONS = 37.0, ENTI = "tissuearc")
 BCFL (HEAT, CONS = 0.000000000000E+00, ENTI = "shellsleft")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "shellsleft")
 BCFL (HEAT, CONS = 0.000000000000E+00, ENTI = "tumorleft")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "tumorleft")
 BCFL (HEAT, CONS = 0.000000000000E+00, ENTI = "tissueleft")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "tissueleft")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "tissuearc")
 ICNO (TEMP, CONS = 37.0, ENTI = "shells")
 ICNO (SPEC = 1.0, CONS = 0.150000000000E+14, ENTI = "shells")
 ICNO (TEMP, CONS = 37.0, ENTI = "tumor")
 ICNO (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "tumor")
 ICNO (TEMP, CONS = 37.0, ENTI = "tissue")
 ICNO (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "tissue")
 EXTR (ON, AFTE = 5, EVER = 5, ORDE = 3, NOKE, NOFR)
END
/  *** of FIPREP Commands
CREATE(FIPREP,DELE)
CREATE(FISOLV)
PARAMETER(LIST)
```

Subroutine for Q as a function of nanoshell concentration

```fortran
      SUBROUTINE USRSRC (NELT,NE,NG,SORCE,VARI,DVARI,NDFCD,LDOFU,SHP,
     1                   DSDX,XYZL,deter,PROP,TIME,NPTS,ndp,MNDP,IERR,
     2                   IOPT)
C
C     USER DEFINED SOURCE FOR ENERGY OR SPECIES EQUATIONS
C
C     NELT  = GLOBAL ELEMENT NUMBER
C     NE    = LOCAL ELEMENT NUMBER
C     NG    = GROUP NUMBER
C     SORCE = HEAT OR SPECIES SOURCE (RETURNED VALUES)
C     VARI  = ARRAY OF SOLUTION VARIBLES AT INTEGRATION POINTS
C     DVARI = GRADIENTS OF SOLUTION VARIABLES AT INTEGRATION POINTS
C     LDOFU = pointer array for accessing vari and dvari information
C     XYZL  = X,Y,Z COORDINATES
C     DETER = the value of the transformation determinant at
C             each of the npts points.  For axi-symmetric problem it is
C             R*determinant
C     SHP   = ELEMENT SHAPE FUNCTIONS
C     DSDX  = SHAPE FUNCTION DERIVATIVES IN THE X,Y,Z DIRECTION
C     PROP  = USER DEFINED PARAMETERS
C     MNDP  = FIRST DIMENSION OF SHAPE FUNCTION MATRICES
C     TIME  = TIME
C     NPTS  = NUMBER OF POINTS
C     IOPT = 0   ENERGY EQUATION
C     IOPT = N   TRANSPORT EQUATION FOR SPECIES N (0<N<16)
C
#include "IMPLCT.COM"
#include "PARUSR.COM"
C     Modified USRSRC by Brendan Holt
C     i = loop indexer
C     TLASER = time when laser is turned on
C     FACTOR = for non-dimensionalizing Q
C            = a^2/D
C     EFFICIENCY = constant for converting concentration to Q
C          in W per kilonanoshells
C     VARI(...) accesses the concentration
      INTEGER i
      DIMENSION SORCE(NPTS)
      DIMENSION SHP(NPTS,MNDP),DSDX(NPTS,NDFCD,MNDP),XYZL(NPTS,NDFCD)
      DIMENSION PROP(*),VARI(NPTS,*),DVARI(NPTS,NDFCD,*),LDOFU(*)
      DIMENSION DETER(NPTS)
      ZRO = 0.D0
      IF (IOPT.EQ.0) THEN
         DO i = 1, NPTS
            SORCE(i) = 0.03655*VARI(i,LDOFU(kds+1))*7
         ENDDO
      ENDIF
      RETURN
      END
```