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Mesoscopic modeling of cancer photothermal therapy using single-walled carbon nanotubes and near infrared radiation: insights through an off-lattice Monte Carlo approach

Feng Gong\textsuperscript{1}, Zhang Hongyan\textsuperscript{2}, Dimitrios V Papavassiliou\textsuperscript{3,5}, Khoa Bui\textsuperscript{4}, Christina Lim\textsuperscript{1} and Hai M. Duong\textsuperscript{1,5}

\textsuperscript{1} Department of Mechanical Engineering, National University of Singapore, 117576, Singapore
\textsuperscript{2} School of Science, Chang’an University, Xi’an, People’s Republic of China
\textsuperscript{3} School of Chemical, Biological, and Materials Engineering, University of Oklahoma, Norman, Oklahoma, 73019, USA
\textsuperscript{4} Department of Petroleum Engineering, Texas A&M University, College Station, Texas, USA

E-mail: mpedhm@nus.edu.sg and dvpapava@ou.edu

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Abstract

Single-walled carbon nanotubes (SWNTs) are promising heating agents in cancer photothermal therapy when under near infrared radiation, yet few efforts have been focused on the quantitative understanding of the photothermal energy conversion in biological systems. In this article, a mesoscopic study that takes into account SWNT morphologies (diameter and aspect ratio) and dispersions (orientation and concentration), as well as thermal boundary resistance, is performed by means of an off-lattice Monte Carlo simulation. Results indicate that SWNTs with orientation perpendicular to the laser, smaller diameter and better dispersion have higher heating efficiency in cancer photothermal therapy. Thermal boundary resistances greatly inhibit thermal energy transfer away from SWNTs, thereby affecting their heating efficiency. Through appropriate interfacial modification around SWNTs, compared to the surrounding healthy tissue, a higher temperature of the cancer cell can be achieved, resulting in more effective cancer photothermal therapy. These findings promise to bridge the gap between macroscopic and microscopic computational studies of cancer photothermal therapy.

Keywords: cancer photothermal therapy, SWNTs, NIR, thermal boundary resistance, Monte Carlo simulation

(Some figures may appear in colour only in the online journal)

1. Introduction

Cancer photothermal therapy with local heating agents has attracted much research interest in recent years due to its non-invasiveness and gentleness compared with traditional clinical
chemotherapy and radiotherapy [4, 29, 38]. With the presence of local heating agents, thermal energy can be targeted to malignant tumor, while minimizing the damage to healthy tissue [16, 50, 57]. Carbon nanotubes (CNTs) are promising local heating agents due to their strong laser absorbance in the tissue-transparent near infrared irradiation region (NIR: wavelength from 700 to 1100 nm) [24]. When functionalized by appropriate surfactants, CNTs may selectively attach to cancer cells, inducing selective ablation of cancer cells with NIR irradiation [19, 26, 40, 55]. Compared with gold nanoparticles as local heating agents (e.g. nanorods, nanospheres and nanoshells), CNTs require much lower NIR intensity and shorter radiation time in cancer photothermal therapy, which reduces the effect on surrounding healthy tissues [55]. With appropriate functionalization, CNTs could exhibit no cytotoxicity in vivo [58, 59] and be excreted through the kidneys and urinary system [43].

Cancer photothermal therapy using NIR and CNTs has been investigated by experiments both in vitro and in vivo [16, 35, 36, 51]. Kam et al [24] functionalized single-walled carbon nanotubes (SWNTs) using phospholipids (PLs) with polyethylene glycol (PEG) and folic acid (FA) terminal groups. The functionalized SWNTs selectively attached to HeLa cancer cells due to the overexpressed folate receptors on cancer cell membranes. With 808 nm laser radiation focused at 1.4 W cm$^{-2}$ for 2 min, apparent death of cancer cells was achieved without damage to normal cells. Zhou et al [57] investigated the effect of FA-SWNTs on tumor cell death in laser treatment of mouse tumors. With 1 W cm$^{-2}$ laser radiation for 5 min, a surface temperature up to 63 °C was observed with an FA-SWNT concentration of 1 mg kg$^{-1}$, while the temperature only increased to 54 °C without the injection of FA-SWNT into the tumor. Utilizing SWNTs functionalized by IGF1R and HER2 specific antibodies, Shao et al [40] observed only 20% viability of breast cancer cells after applying an 808 nm laser at 0.8 W cm$^{-2}$ for 3 min. By using anti-HER2 IgY antibody functionalized SWNTs, Xiao et al [51] also achieved the selective destruction of breast cancer cells with SWNTs located on cancer cell membranes.

Since photothermal therapy with NIR and CNTs is a promising effective cancer treatment, it is quintessentially important to quantitatively understand the photothermal energy conversion in the malignant tumor [27]. However, few studies have been directed to the computational study of heat transfer in photothermal therapy with NIR and CNTs. Macroscopic models of cancer therapy using laser and metal nanoparticles have been developed by solving the heat diffusion equation using the finite element method (FEM) [17, 27, 47]. These models may not be applicable to the study of heat conversion in photothermal therapy when using CNTs, because the optical and thermal properties of CNTs and metal nanoparticles are largely different. The effect of morphology (e.g. diameter and length), dispersion pattern (e.g. orientation and concentration) and interactions of CNTs on cancer photothermal therapy cannot be investigated in depth by using macroscopic models, due to the smaller dimension of CNTs. Moreover, macroscopic models have not taken into account the thermal boundary resistance (also known as Kapitza resistance) around CNTs, which plays a significant role in the heat transfer through systems containing CNTs [2, 53]. Microscopic models may overcome these limitations by taking into consideration the morphology and dispersion of CNTs, as well as the thermal boundary resistance around CNTs [25, 41]. Microscopic models usually apply the molecular dynamics (MD) method to study the interactions between CNTs and cell membranes or subcellular organelles [48, 56]. However, limited by the computational power, the length of CNTs used in microscopic models is usually less than 10 nm, which is much smaller than the real length of CNTs used in the experimental studies (normally longer than 100 nm [24]). The number of CNTs studied in microscopic models is also limited. Therefore, the effect of CNT length and quantity on the temperature increase of cancer cells may be misinterpreted and underestimated.

The contribution of the present study is to break the limitations of macroscopic and microscopic studies, and to develop a mesoscopic model of cancer photothermal therapy using NIR and SWNTs based on an off-lattice Monte Carlo method. Various SWNT morphologies (e.g. diameter and aspect ratio) and dispersion patterns (e.g. orientation and concentration) are simulated, and their effect on the temperature increase of biological systems has been investigated in detail. The role of thermal boundary resistance in the temperature increase of the healthy tissue and the cancer cell are both quantitatively studied. Our findings promise to bridge the gap between macroscopic and microscopic models and to guide the optimization of cancer treatment conditions with NIR and SWNTs.

2. Simulation algorithm

A 3D model is developed with healthy tissue, cancer cells and randomly distributed SWNTs. As shown in figure 1(a), the side of the cube representing healthy tissue is 2 μm and the diameter of the sphere representing a cancer cell is 1 μm. SWNTs are represented as solid cylinders and are randomly distributed over the surface of the cancer cell. The size of SWNTs for base study is 1.2 nm in diameter and 150 nm in length, which is consistent with the experimental study [24]. The system is under the illumination of an 808 nm laser from the top surface. Assuming the laser has a Gaussian distribution in space, the laser density distribution at a location (x, y, z), I(x, y, z), can be expressed as [49].

$$I(x, y, z) = I_0 e^{-(a x^2 + b y^2 + c z^2)}$$

(1)

wherein $I_0$, $\varepsilon$, $\alpha$, $r$ and $h$ are the laser density, the saturated absorption coefficient, the damping coefficient, the radius of the laser beam and the side length of the cubic model in figure 1(a), respectively. The origin of the coordinate system is at the bottom left corner of the model.
In the current work, SWNTs with different orientations are assumed to have the same optical absorption coefficient, $\varepsilon$, due to the negligible effect of SWNT orientation on the optical property of SWNTs under low photon energy irradiation (less than 2 eV) [34].

Owing to the strong NIR absorbance of SWNTs and the high transparence of the healthy tissue and the cancer cell, it can be reasonably assumed that only SWNTs absorb laser energy and instantaneously convert optical energy to thermal energy. Thermal energy is modeled by releasing a large quantity of thermal walkers with the same energy from SWNTs in each small time step. Considering the orientation of SWNTs, the number of thermal walkers released from an SWNT in a time step can be calculated as

$$N = N_{\text{max}} \exp\left(-\alpha(h - z)\right) \exp\left(-\frac{x^2 + y^2}{r^2}\right) \sin \varphi$$  \hspace{1cm} (2)

where $N_{\text{max}}$ is the maximum number of thermal walkers released from an SWNT in a single time step. This value is 10 000 in the current work based on our previous work, in order to balance algorithm accuracy and computational time [14]. The angle between the SWNT orientation and the laser direction is designated by $\varphi$, which is the parameter that accounts for the effect of SWNT orientation. Due to the much smaller size of the SWNTs (1.2 nm diameter) compared to the

\[ (x = 0, \ y = 0 \ \text{and} \ z = 0). \]
radius of the laser beam (3000 nm), the center of each SWNT was used to calculate the number of thermal walkers released from each of them.

Based on our previous work [14], thermal walkers in CNTs are assumed to travel randomly with an infinite speed due to CNTs’ ultrahigh thermal conductivity [1]. In the healthy tissue and the cancer cell, thermal walkers move randomly with Brownian motion [11]. The Brownian motion is described by changes in the position of walkers in each time step. The position changes in each space direction take values from a normal distribution with a zero mean and a standard deviation, $\sigma$, which depends on the thermal diffusivity of the healthy tissue and the cancer cell:

$$\sigma = \sqrt{2D_m\Delta t}$$  \hspace{1cm} (3)

wherein $\Delta t$ is the time increment, and $D_m$ is either the thermal diffusivity of the healthy tissue or the cancer cell in which a thermal walker is travelling.

Thermal boundary resistances (often referred to as Kapitza resistances) at interfaces have been taken into consideration by introducing a probability for the thermal walkers to transmit across an interface, when their random motion makes them jump across an interface. According to the acoustic mismatch theory [45] for the prediction of the thermal boundary resistance, the probability for walkers to jump across the interface between the tissue and SWNTs, $f_{u-CNT}$, is given by

$$f_{u-CNT} = 4/\rho_i C_i V_i R_{u-CNT}$$  \hspace{1cm} (4)

where $\rho_i$, $C_i$, $V_i$ and $R_{u-CNT}$ are the density, specific heat of the healthy tissue, sound velocity in the healthy tissue and the thermal boundary resistance between CNTs and the healthy tissue, respectively.

Once a thermal walker in the healthy tissue reaches the tissue–SWNT interface, it will either jump into the SWNTs with a probability of $f_{u-CNT}$, or stay in the original position with a probability of $1-f_{u-CNT}$. A similar rule governs the motion of thermal walkers in the tissue reaching the interface between the tissue and the cancer cell. Thermal walkers in the cancer cell travel similarly to those in the healthy tissue. Thermal walkers in SWNTs, due to their infinite speed, may reach tissue–SWNT or cancer cell–SWNT interfaces in a single time step. Thermal walkers inside the SWNTs will jump into the healthy tissue with a probability of $f_{CNT-u}$ to travel to the cancer cell with a probability of $f_{CNT-ce}$, or stay in the original SWNT with a probability of $1-f_{CNT-u}-f_{CNT-ce}$. In thermal equilibrium, the average walker density (i.e. the number of walkers per SWNT volume) in SWNTs does not change with time to keep a constant temperature. This means that, within a time step, heat flux entering an SWNT should be equal to that exiting from the SWNT. Owing to their infinite speed, all the walkers in SWNTs may travel into the surrounding healthy tissue in a time step, but for the walkers in the healthy tissue only those around the SWNT’s surface may jump into the SWNT due to the random Brownian motion in the healthy tissue. Therefore, the two probabilities, $f_{CNT-u}$ and $f_{u-CNT}$, are related as

$$V_{CNT}f_{CNT-u} = C_i\sigma A_{CNT}f_{u-CNT}$$  \hspace{1cm} (5)

wherein $V_{CNT}$ and $A_{CNT}$ are the volume and surface area of SWNTs and $C_i$ is a thermal equilibrium factor, which depends on the interfacial area and the geometry of the SWNTs. The relation between $f_{CNT-ce}$ and $f_{u-CNT}$ is similar, but the thermal equilibrium factor is different due to the different interaction areas. The tissue–SWNT and cell–SWNT equilibrium factors are numerically determined to be 0.25 and 0.045, respectively [8]. Since there is a relatively large interfacial area between the healthy tissue and the cancer cell, it is reasonable to assume that the probability of thermal walkers traveling from the tissue to the cell is equal to the probability of walkers jumping back from the cell to the tissue. A detailed description of thermal walker motion can be found in our previous work [14].

The computational box is divided into 200 grids on each side (total of $200 \times 200 \times 200$ computational bins) and the temperature distribution is calculated from the number of walkers in each computational bin. As the initial condition, the body temperature ($37 \, ^\circ C$) is assumed everywhere in the model. The temperature in each bin can be calculated as

$$T = T_i + \Delta T = T_i + \frac{Ne}{\rho V C_p}$$  \hspace{1cm} (6)

wherein $T_i$ and $\Delta T$ are the initial and increased temperature. $N$ and $e$ are the number of thermal walkers and the energy of one thermal walker in a bin. $\rho$, $V$ and $C_p$ are the density, volume and specific heat capacity of the bin, respectively. The thermal properties and parameters used in the simulations can be found in table 1. In this work, constant temperature of the SWNTs was assumed for the determination of the thermal equilibrium factors. This assumption was used to avoid the violation of the second law of thermodynamics, when applying interfacial thermal resistances at the tissue–SWNT and cell–SWNT interfaces at thermal equilibrium. For the simulations of the temperature increase rate in the cancer cell and the tissue, the temperature of the SWNTs changed with time as the whole system was in a transient process during the laser heating.

3. Results and discussion

3.1. Model validation

The model is validated with the experimental study carried out by Kam et al [24]. In their study, a biological solution with randomly distributed SWNTs was heated by an 808 nm laser with an intensity of $1.4 \, W \, cm^{-2}$. With an SWNT concentration of $25 \, mg \, l^{-1}$, the biological solution achieved a temperature increase rate of $0.6 \, ^\circ C \, s^{-1}$. A mesoscopic model was built with SWNTs randomly distributed in biological solution. The size (diameter $1.2 \, nm$, length $150 \, nm$) and concentration ($25 \, mg \, l^{-1}$) of SWNTs, as well as the laser intensity ($1.4 \, W \, cm^{-2}$), were identical to the experimental
Table 1. Materials properties and parameters used in the simulations.

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<td>Sound velocity (m s⁻¹)</td>
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<tr>
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<table>
<thead>
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<td>SWNT diameter (nm)</td>
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<tr>
<td>Aspect ratio of CNT, L/D</td>
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<tr>
<td>SWNT concentration (mg l⁻¹)</td>
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<tr>
<td>Laser density (W cm⁻²)</td>
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<tr>
<td>Laser beam radius (μm)</td>
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<tr>
<td>Laser damping coefficient (m⁻¹)</td>
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<tr>
<td>Maximum number of walkers</td>
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<tr>
<td>Time increment (ns)</td>
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<tr>
<td>Cell-SWNT TBR (10⁻⁸ m² K W⁻¹)</td>
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<tr>
<td>Tissue–SWNT TBR (10⁻⁸ m² K W⁻¹)</td>
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<tr>
<td>Tissue–cell TBR (10⁻⁸ m² K W⁻¹)</td>
<td>0.0685–6.85</td>
</tr>
<tr>
<td>Thermal equilibrium factor</td>
<td>f1 = 0.25, f2 = 0.045</td>
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</table>

The thermal boundary resistance was set to be 12 × 10⁻⁸ m² K W⁻¹ between SWNTs and biological solution, which was the average thermal resistance at an SWNT–water interface reported by Maruyama [31]. The laser energy absorbed by each SWNT is calculated in our mesoscopic model. According to equation (1), the saturated absorption coefficient of a single SWNT is indispensable to accurately obtain the laser energy absorbed by each SWNT. Due to the complexity in handling a single SWNT and measuring its absorption coefficient, there is no literature report of the absorption coefficient of a single SWNT. Although some studies have been conducted to characterize the optical properties of CNT films [21, 33], these values may be larger than the value for a single SWNT due to the interaction and bundle effect of CNTs in CNT films. Since nanographene has similar properties to SWNTs, the saturated absorption coefficient of monolayer nanographene may be used for an SWNT. Mark et al [30] have reported the saturated absorbance of monolayer graphene to be 2.3 ± 0.2%. Using this absorbance value for the SWNT, we obtained a temperature increase rate of 0.71 ± 0.07 °C s⁻¹ for the biological solution. This value was the average result of three simulations with different dispersions of SWNTs in the biological solution. The lower limit of the above calculation was slightly higher than the experimental value of 0.6 °C s⁻¹ reported by Kam et al [24]. In experiments, some factors (e.g., interactions between SWNTs, bundle aggregation of SWNTs and other heat losses to the ambient environment) may affect the temperature increase rate of the biological solution. These factors have not been taken into consideration due to the limitation of the current model, which may account for the slightly higher temperature rise than in the experimental study.

3.2. Effect of SWNT optical properties on the temperature increase of the biological solution

As discussed, optical properties of SWNTs significantly affect the temperature increase of the biological solution when heated by an NIR laser. The laser absorbance of SWNTs is related to their molar extinction coefficient, which can be calculated from the absorption cross section of SWNTs. Islam et al [20] first reported the SWNT absorption cross section to be 0.08 × 10⁻¹⁷ cm² per C atom. A larger absorption cross section of 0.7 × 10⁻¹⁷ cm² was later found by Ming et al [32] using DNA-suspended SWNTs. This value is close to that of a monolayer of graphene with an absorbance of 2.3%, which corresponds to an absorption cross section of 0.6 × 10⁻¹⁷ cm². By using Rayleigh scattering, Joh et al [23] measured the absorption cross section of SWNTs to be 2.5 × 10⁻¹⁷ cm². This relatively high value may be ascribed to the strong optical coupling among adjacent SWNTs. Following Joh et al, Schoppler et al determined the absorption cross section to be (1.7 ± 0.4) × 10⁻¹⁷ cm² per C atom by using fluorescence tagging and atomic force microscopy (AFM) images [39]. Using the five different absorption cross sections reported above to calculate the temperature increase rate of the biological solution, we have obtained the temperature increase rates of 0.095, 0.83, 0.71, 2.96 and 2.02 °C s⁻¹, respectively. The larger the value of absorption cross section of SWNTs, the higher the temperature of the biological solution. If the absorption cross section can be modified and increased, the heating efficiency of SWNTs may be enhanced in cancer photothermal therapy. SWNT aggregates and bundles are likely to decrease the absorption cross section of SWNTs in suspensions [7], which can be avoided by using SWNTs functionalized by proper surfactants [6]. With appropriate functionalization of SWNTs, the absorption cross section could be increased, so as to enhance the heating efficiency of SWNTs in photothermal therapy.

3.3. Effect of SWNT orientation and concentration on the temperature increase rate of the biological solution

SWNT orientation plays a significant role in the thermal properties of SWNT–polymer composites [10] and SWNT nanofluids [9]. In order to study the effect of SWNT orientation on the temperature increase of biological solution, models with different SWNT orientations were built, as shown in figures 1(b)–(d). The temperature increase rates of the biological solutions with different SWNT orientations are presented in figure 2. With the same SWNT concentration,
SWNTs with orientation perpendicular to the laser beam produced the highest temperature increase rate of the biological solution, while SWNTs with parallel orientation resulted in the lowest. The effect of SWNT orientation on the temperature increase rate of the biological solution is closely related to the effective absorption area of SWNTs to laser. At the same laser intensity, larger absorption area of SWNTs can absorb more laser energy and hence induce a higher temperature. Perpendicularly orientated SWNTs have the largest effective absorption area, followed by randomly orientated SWNTs, and finally parallel orientated SWNTs. It can be concluded that the heating efficiency of the SWNTs in photothermal therapy could be strengthened by controlling the SWNT orientation relative to the laser direction, which may be achieved by applying a magnetic field [42].

As shown in figure 2, the temperature of the biological solution increases with the rise of SWNT concentration. This result is consistent with the experimental findings of Ghosh et al, in which an increase in CNT concentration resulted in an apparent increase of the temperature rise of the tumor [13]. At higher SWNT concentration, more SWNTs are present as heating agents, resulting in a higher temperature of the biological solution. High concentration of SWNTs benefits cancer photothermal therapy. However, higher concentration of SWNTs may induce higher cytotoxicity in the biological solution. Therefore, the concentration of SWNTs used in in vivo photothermal therapy should be well controlled in order to avoid possible cytotoxicity.

3.4. Effect of SWNT morphology on the temperature increase rate of the biological solution

The morphology of SWNTs (diameter and aspect ratio) was varied to study their effect on the heating efficiency of SWNTs in photothermal therapy. Figure 3(a) is a presentation of the temperature increase rate of the biological solution with the same SWNT concentration but different SWNT diameters. The temperature increase rate decreases with increasing SWNT diameter, indicating that smaller SWNTs have higher heating efficiency. This may be ascribed to the specific larger surface area of smaller SWNTs. At the same SWNT concentration, SWNTs with smaller diameter have larger surface area per volume than those with bigger diameter. The larger surface area could result in a larger absorption area of SWNTs for NIR, as well as a larger interfacial area with the surrounding solution, enhancing the heat transfer from SWNTs to the biological solution [22]. The aspect ratio of SWNTs (i.e. the ratio of length to diameter, $L/D$) seems not to have a significant effect on the temperature increase rate of the biological solution, as shown in figure 3(b). This may be ascribed to the method of varying the aspect ratio in the current study. The aspect ratio of the
SWNTs varied with constant diameter and therefore the length of the SWNTs was altered. At the same concentration of SWNTs, varying length does not significantly affect their surface area and thereby induces negligible effect on the temperature of the biological solution compared to SWNT diameter.

3.5. Effect of thermal boundary resistances on the temperature increase rate

Thermal boundary resistance is the resistance to heat flow at an interface [3], which plays a significant role in the heat transfer of systems containing SWNTs due to their specific surface area [2]. The effect of thermal boundary resistances on the temperature increase rates has been investigated by introducing a probability for phonon transmission at interfaces according to the acoustic mismatch theory [45]. Figure 4 is a presentation of the effect of the thermal boundary resistance between SWNTs and the biological solution on the temperature increase rate of the biological solution. With different dispersions of SWNTs, the temperature increase rates of biological solution all decrease with the rise of the thermal boundary resistance between SWNTs and the biological solution. According to the acoustic mismatch theory, the probability for phonon transmission from SWNTs to surrounding biological solution is inversely proportional to the thermal boundary resistance. Therefore, higher thermal boundary resistance between SWNTs and biological solution greatly inhibits thermal energy transfer from the interior of the SWNTs to the exterior system, inducing a lower temperature in the surrounding biological solution.

Lervik et al [28] reported that the thermal conductance at the protein–water interface was within the range of 100–270 MW K\(^{-1}\) m\(^{-2}\), which corresponds to a thermal boundary resistance of 0.37–1.0 \(\times 10^{-8}\) m\(^2\) K W\(^{-1}\). Since the cell membrane consists of various proteins while healthy tissue is mainly composed of water [44], there might be thermal boundary resistance at the tissue–cancer cell interface due to the interactions between proteins from the cancer cell membrane and water from the healthy tissue. Thermal boundary resistance was assumed to exist at the cell–tissue interface in the current work, and to be of the order of 0.5 \(\times 10^{-8}\) m\(^2\) K W\(^{-1}\) [28].

Systems were built with the cancer cell inside the healthy tissue and SWNTs located on the cell membrane. A larger diameter of SWNTs (6 nm) was applied considering the functionalization of SWNTs. The thermal boundary resistances at cell–SWNT, tissue–SWNT and tissue–cell interfaces were quantified to investigate their effect on the temperature increase rates of the tissue and the cancer cell. As shown in figure 5(a), the temperature increase rate of the cancer cell decreases with increasing thermal boundary resistance at the cell–SWNT interface \(R_{\text{cu-cNT}}\). In contrast, the temperature increase rate of the healthy tissue increases with increasing \(R_{\text{cu-cNT}}\). Higher thermal boundary resistance between the cancer cell and SWNTs more significantly hinders thermal energy transfer from SWNTs to the cancer cell, meaning that fewer thermal walkers can travel to the cancer cell from SWNTs. The smaller number of thermal walkers in the cancer cell accounts for the lower temperature increase rate of the cancer cell. However, owing to the much blocked thermal energy in SWNTs, more energy may transfer to the healthy tissue, inducing a higher temperature of the tissue. Figure 5(b) is a plot of the effect of thermal boundary resistance between the healthy tissue and the SWNTs on the temperature increase rate of the tissue and the cancer cell. Higher thermal boundary resistance at the tissue–SWNT interface \(R_{\text{t-cNT}}\) generates a higher temperature increase rate of the cancer cell but a lower rate of the healthy tissue. With high \(R_{\text{t-cNT}}\), thermal energy transfer is greatly impeded from SWNTs to the healthy tissue, which results in a low temperature increase rate of the healthy tissue. Conversely, a large amount of heat from inside SWNTs will alternatively transfer to the cancer cell through SWNT–cell interfaces, hence leading to a high temperature increase rate of the cancer cell. Similarly, the effect of thermal boundary resistance between the healthy tissue and the cancer cell \(R_{\text{t-c}}\) is shown in figure 5(c). The temperature increase rate of the cancer cell increases with increasing \(R_{\text{t-c}}\), while the temperature increase rate of the tissue decreases with the elevation of \(R_{\text{t-c}}\). Since the cancer cell has higher temperature than the healthy tissue, higher thermal boundary resistance at the tissue–cell interface will prohibit more effectively the thermal energy transfer from the cancer cell to the surrounding tissue. Owing to the larger interfacial area between the tissue and the cancer cell, the effect of \(R_{\text{t-c}}\) is more significant than those of \(R_{\text{cu-cNT}}\) and \(R_{\text{t-cNT}}\). As noted in figure 5, the cancer cell has a higher temperature increase rate than the healthy tissue in the current work. This may be ascribed to the smaller mass and specific heat capacity of the cancer cell, as well as the presence of SWNTs as heat sources located on the cell membrane.

![Figure 4. Effect of thermal boundary resistance (TBR) between SWNTs and biological solution on the temperature increase rate of biological solution: the TBR values are varied in the range of 1.2–120 m² KW⁻¹ [31].](image-url)
As discussed above, thermal boundary resistance around SWNTs significantly affects the heating efficiency of SWNTs in photothermal therapy. The thermal boundary resistance can be modified by appropriate functionalization of SWNTs [5, 46]. In biological systems containing cancer cells and SWNTs, through appropriate interfacial modification around SWNTs, the ratio of $R_{ce-CNT}$ to $R_{ti-CNT}$ ($R_{ce-CNT}/R_{ti-CNT}$) can be adjusted to enhance the heating efficiency of SWNTs. Simulations have been carried out to investigate the relation between the temperature increase rate and the ratio of $R_{ce-CNT}$ to $R_{ti-CNT}$. Figure 6, we present the temperature increase rate of the cancer cell and the tissue using different ratios of $R_{ce-CNT}$ to $R_{ti-CNT}$. By fitting the temperature rate of the cancer cell, the following equation can be obtained:

$$T_{ce} = 1 / \left(16.5 + 305 r_t^{0.8}\right) + 0.4249 \quad (7)$$

wherein $T_{ce}$ and $r_t$ are the temperature increase rate of the cancer cell and the ratio of $R_{ce-CNT}$ to $R_{ti-CNT}$. The coefficient $R^2$ has a value of 0.9982 for the curve fit, indicating a good agreement between the equation and the simulation results. Similarly, the effect of the ratio of $R_{ce-CNT}$ to $R_{ti-CNT}$ on the temperature increase rate of the tissue can be obtained and expressed as follows:

$$T_{ti} = 0.0024 / \left[1 + (r_t/0.0586)^{0.8}\right] + 0.183 \quad (8)$$

wherein $T_{ti}$ is the temperature rate of healthy tissue. The coefficient $R^2$ is 0.9806 for the curve fit. As shown in figure 6 and equations (7) and (8), changes in the ratio of $R_{ce-CNT}$ to $R_{ti-CNT}$ lead to opposite effects on the temperature increase rate of the cancer cell and of the healthy tissue.

4. Conclusions

To summarize, we have successfully developed a mesoscopic model of cancer photothermal therapy using SWNTs and NIR through an off-lattice Monte Carlo method. The complex morphology (diameter and aspect ratio) and dispersion pattern (orientation and concentration) of SWNTs have been taken into account. It was found that higher heating efficiency of SWNTs could be achieved by utilizing SWNTs perpendicular to the direction of the NIR beam and SWNTs of smaller diameter because of the induced larger effective absorption area of SWNTs to NIR. Better dispersion of SWNTs in biological systems resulted in enhanced absorption cross section of a single SWNT, thus leading to a higher heating efficiency of SWNTs. The biological systems (healthy tissue and cancer cell) obtained higher temperature with higher concentration of SWNTs, however, which should be well controlled in the case of cytotoxicity at high concentration of SWNTs.

Thermal boundary resistances were investigated by introducing a probability for phonon transmission at interfaces. The temperature of the cancer cell increased with the rise of thermal boundary resistance at tissue–SWNTs and tissue–cell interfaces. In contrast, the temperature of the healthy tissue decreased with the rise of these two resistances. Lower thermal resistance at the cell–SWNT interface induced
a higher temperature of the cancer cell but a lower temperature of the healthy tissue. Higher cancer cell temperature compared to healthy tissue might be achieved by adjusting the thermal boundary resistances around SWNTs through appropriate interfacial modification. These findings may be beneficial for optimization of cancer photothermal therapy using NIR and SWNTs.

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References

transport in the cross-plane direction of superlattices Phys.
Rev. B 57 14958–73
nanoparticles for highly effective in vivo near-infrared
photothermal therapy of cancer ACS Nano 6 5605–13
modification effects on thermal conductivity of carbon
nanotube composites Polymer 47 5990–6
containing a sulfuric group with a (5,5) carbon nanotube
J. Phys. Chem. C 114 17249–56
heterogeneities of aqueous single-wall carbon nanotube
suspensions J. Am. Chem. Soc. 129 8058–9
[8] Duong H M, Papavassiliou D V, Mullen K J and Maruyama S
2008 Computational modeling of the thermal conductivity of
single-walled carbon nanotube–polymer composites
Nanotechnology 19 065702
[9] Duong H M, Papavassiliou D V, Mullen K J, Wardle B L and
Maruyama S 2008 Calculated thermal properties of single-
walled carbon nanotube suspensions J. Phys. Chem. C 112
19860–5
[10] Duong H M, Yamamoto N, Papavassiliou D V, Maruyama S
and Wardle B L 2009 Inter-carbon nanotube contact in thermal transport of controlled-morphology
polymer nanocomposites Nanotechnology 20 155702
Phys., NY 17 891–921
structure, mechanical and vibrational properties of single-
walled carbon nanotubes Nanotechnology 9 184–91
Guthold M and Gmeiner W H 2009 Increased heating
efficiency and selective thermal ablation of malignant tissue
with DNA-encased multiwalled carbon nanotubes ACS
Nano 3 2667–73
Monte Carlo simulation of heat transfer through carbon
nanotube multiphase systems taking into account thermal
65 1023–43
functionalized carbon nanotubes in chemical and biological
environments ACS Nano 4 2615–26
2013 Spatially controlled photothermal heating of bladder
tissue through single-walled carbon nanohorns delivered with a fiberoptic microneedle device Lasers Med. Sci. 28
1143–50
Determination of the minimum temperature required for
selective photothermal destruction of cancer cells with the
use of immunotargeted gold nanoparticles Photochem.
Photobiol. 82 412–7
nanotube suspensions Nat. Mater. 2 731–4
[19] Iancu C and Mocan L 2011 Advances in cancer therapy
through the use of carbon nanotube-mediated targeted
hyperthermia Int. J. Nanomedicine 6 1675–84
[20] Islam M F, Milkie D E, Kane C L, Yodh A G and
Kikukawa J M 2004 Direct measurement of the polarized
optical absorption cross section of single-wall carbon
nanotubes Phys. Rev. Lett. 93 037404
[21] Ikitis M E, Niyogi S, Meng M E, Hamon M A, Hu H and
Haddon R C 2002 Spectroscopic study of the Fermi level
electronic structure of single-walled carbon nanotubes Nano
Lett. 2 155–9
[22] Jiang W T, Ding G L and Peng H 2009 Measurement and
model on thermal conductivities of carbon nanotube
nanorefrigerants Int. J. Thermal Sci. 48 1108–15
[23] Joh D Y, Kinder J, Herman L H, Ju S Y, Segal M A,
carbon nanotubes as exciogenic optical wires Nat.
Nanotechnol. 6 51–6
Carbon nanotubes as multifunctional biological transports
and near-infrared agents for selective cancer cell destruction
[26] Kostarelos K, Bianco A and Prato M 2009 Promises, facts and
challenges for carbon nanotubes in imaging and therapeutics
Nat. Nanotechnol. 4 627–33
[27] Lal S, Clare S E and Halas N J 2008 Nanoshell-enabled
photothermal cancer therapy: impending clinical impact Acc.
Chem. Res. 41 1842–51
[28] Lervik A, Bresme F, Kjelstrup S, Bedeaux D and Rubi J M
Chem. Phys. 12 1610–7
[29] Liu H Y, Chen D, Li L L, Liu T L, Tan L F, Wu X L and
Tang F Q 2011 Multifunctional gold nanoshells on silica
nanorattles: a platform for the combination of photothermal
therapy and chemotherapy with low systemic toxicity
Angewandte Chemie-Int. Edn. 50 891–5
Heinz T F 2008 Measurement of the optical conductivity of
graphene Phys. Rev. Lett. 101 196405
Anisotropic heat transfer of single-walled carbon nanotubes
[32] Ming Z and Diner B A 2004 Solution redox chemistry of
carbon nanotubes J. Am. Chem. Soc. 126 15490–4
[33] Mohite A, Chakraborty S, Gopinath P, Sumanasekera G U and
Alphnaeus B W 2005 Displacement current detection of
photocouduction in carbon nanotubes Appl. Phys. Lett. 86
061114
[34] Murakami Y, Einarsson E, Edamura T and Maruyama S 2005
Polarization dependent optical absorption properties of
single-walled carbon nanotubes and methodology for the
evaluation of their morphology Carbon 43 2664–76
[35] Neves L F F, Krais J J, Rite B D V, Ramesh R,
Ronces D E and Harrison R G 2013 Targeting single-
walled carbon nanotubes for the treatment of breast cancer
using photothermal therapy Nanotechnology 24 375104
Programmable self-assembly of carbon nanotubes assisted
by reversible denaturation of a protein Nanotechnology
23 465605
[37] Patel H A, Garde S and Keblinski P 2005 Thermal resistance of
nanoscopic liquid-liquid interfaces: Dependence on
chemistry and molecular architecture Nano Lett. 5 2225–31
[38] Robinson J T, Tabakman S M, Liang Y Y, Wang H L,
Casalongue H S, Vinh D and Dai H J 2011 Ultrasmall
reduced graphene oxide with high near-infrared absorbance
for photothermal therapy J. Am. Chem. Soc. 133 6825–31
[39] Schoppler F, Mann C, Hain T C, Neubauer F M, Privitera G,
Bonaccorso F, Chu D P, Ferrari A C and Hertel T 2011
Molar extinction coefficient of single-wall carbon nanotubes
[40] Shao N, Lu S, Wickstrom E and Panchapakesan B 2007
Integrated molecular targeting of IGF1R and HER2 surface
receptors and destruction of breast cancer cells using single wall carbon nanotubes Nanotechnology 18 315101


[42] Singh R and Nalwa H S 2011 Medical applications of nanoparticles in biological imaging, cell labeling, antimicrobial agents, and anticancer nanodrugs J. Biomed. Nanotechnol. 7 489–503


[51] Xiao Y et al 2009 Anti-HER2 IgY antibody-functionalized single-walled carbon nanotubes for detection and selective destruction of breast cancer cells Bmc Cancer 9 351


[56] Yang K and Ma Y Q 2010 Computer simulation of the translocation of nanoparticles with different shapes across a lipid bilayer Nat. Nanotechnol. 5 579–83

