A Molecular Dynamics Study of the Heat Transfer Phenomena in the Bio-tissue

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Abstract— **The purpose of this study is to obtain the heat transfer phenomena of bio-tissue by the external heating. The molecular dynamics (MD) algorithm and the GROMACS protein data bank are used to analyze the bio-heat transfer characteristics of Alanine molecules in the micro-scale. The simulations focus specifically on the temperature evolution and thermal conductivity of the Alanine molecules under different kinds of thermal boundary conditions. The thermal conductivity of the Alanine molecule is calculated via the autocorrelation function of the Green-Kubo formalism. Overall, the results presented in this study provide a useful source of reference for improving the efficacy of thermal ablation and the phenomena of the micro-scale hyperthermia.***

Index Terms— **Molecular dynamics, GROMACS protein data bank, Alanine, Bio-tissue, Green-Kubo formalism**

I . INTRODUCTION

In recent, cancerous cells can be destroyed by the thermal ablation effectively. Research has shown that the hyperthermia effects induced during thermal ablation result in significant cell death [1]. Therefore, thermal ablation techniques have been widely applied in a variety of disease treatment and cosmetology applications in recent years. It is essential that the heat transfer characteristics of bio-tissues be well understood at the micro-scale. Unfortunately, such detailed information is not available in the literature, and thus further work is required to clarify the temperature profile and dynamic transport properties of bio-tissues at the molecular scale such that the efficacy of clinical thermal ablation techniques can be enhanced.

In general, molecular dynamics (MD) simulations have a fine temporal resolution and therefore enable the rapid variations inherent in natural molecular systems to be accurately reproduced. Furthermore, the elevation of the protein's force field is the key process in MD. As a result, MD simulation is one of the most powerful techniques available for acquiring detailed insights into the basic phenomena of protein systems. Developing such insights is essential to bio-chemical researchers in compiling a robust description of the roles played by various protein materials in common bio-medical problems. The knowledge gained by these researchers is typically compiled within protein data banks maintained in the public domain such that the information is available to all. Increasingly, these data banks have been used as the basis for MD studies aimed at exploring the basic properties and phenomena of bio-molecules. For example, EI-Bastawissy *et al.* [2] employed an MD approach to investigate the mutation behavior of prion protein at both normal and elevated temperatures. Yamashita *et al.* [3] investigated the respective sampling efficiencies of MD simulations and the Monte Carlo method in analyzing the behavior of proteins. Komeiji *et al.* [4] demonstrated the power of parallel computing in performing MD simulations of proteins.

Continuous advances in the nanotechnology have led to the development of many new materials and applications. Various researchers have investigated the dynamic transport properties of such materials in order to extend the principles of thermal science to the nanoscale domain. For example, Maruyama [5] found that the thermal conductivity of single-walled nanotubes (SWNTs) varies as a function of their scale. In investigating the dynamic transport properties of materials in the nanoscale, the thermal conductivity and thermal diffusivity are generally calculated using the Green-Kubo (G-K) formalism [6-10]. For the reason of speedup calculations, the parallel computation method is used to combine molecular dynamics to model and analysis the more complex problem [11].

As discussed above, when performing clinical thermal ablation, it is essential that the applied heat flux be appropriately controlled so as to avoid damaging healthy tissue cells. However, the heat

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transfer phenomena in micro-cavities containing biological cells are not well explained in the literature. Accordingly, the current study employs a hybrid numerical approach combining a MD algorithm and the GROMACS protein data bank to investigate the heat transfer properties of Alanine cells under various thermal boundary conditions. The results obtained for the temperature evolution and thermal conductivity of the Alanine cells provide a useful source of reference for improving the performance of thermal ablation and intense pulsed-laser (IPL) techniques used for clinical purposes.

The remainder of this paper is organized as follows. Section 2 provides a high-level overview of the current simulation system and introduces the relevant mathematical formulations. Section 3 describes the detailed steps involved in the simulation procedure and gives the relevant simulation parameters. Section 4 presents the results of the numerical simulations. Finally, Section 5 summarizes the overall contributions and findings of the study and indicates the intended direction of future research.

Ⅱ. MATHEMATICAL MODEL

The simulations conducted in this study aim to clarify the bio-heat transfer characteristics of Alanine (NHC_2H_4CO) macromolecules. The simulations are performed using the model shown in Fig. 1, and focus specifically on the variation of the temperature and thermal conductivity of the Alanine molecules under the imposition of various external heating conditions. The numerical solutions are obtained using a hybrid iterative scheme comprising a MD algorithm based on the leap-frog method and the GROMACS protein data bank. The effects of the thermal boundary conditions on the molecules are modeled using the Andersen thermobath method [12].

The simulations commence by performing an equibration process in which Eq. (1) is used to adjust the velocities of the molecules when the system is maintained to be a particular temperature.

$$T_a^* = \frac{1}{3N}\left\langle \sum_i v_i^{*2} \right\rangle, \quad v_i^{*,new} = v_i^* \sqrt{\frac{T_s^*}{T_a^*}}, \qquad (1)$$

where N is the number of molecules in the specified region, T_a^* is the instantaneous dimensionless temperature of the specified region following completion of all the collision processes at each time step, T_s^* is the initial dimensionless temperature of the specified region, v_i^* is the dimensionless velocity of the i -th molecule following collision with another molecule at each time step, and $v_i^{*,new}$ is the dimensionless corrected molecular velocity of the i -th molecule.

In accordance with basic statistical thermodynamics principles, it is known that the initial velocities of the molecules in an equilibrium system are distributed in accordance with a Maxwell-Boltzmann velocity distribution provided that the temperature of the isolated system remains constant. In addition, the net momentum of the system must be equal to zero in order to ensure that the system does not move under the effects of an external force.

In the Green-Kubo method, the thermal conductivity, k , is defined as a integral of the autocorrelation function of heat current [13], i.e.

$$k = \frac{1}{k_B V T^2} \int_0^\infty \langle J_x(0) J_x(t) \rangle dt \qquad (2)$$

where k_B , V and T are the Boltzmann constant, the system volume and the temperature, respectively, while J is the heat current and is given by

$$J = \frac{1}{2}\left(\sum_{i=1}^{N} m v_i^2 \vec{v}_i + \sum_{i=1}^{N}\sum_{j\neq i}^{N}\left(\phi(r_{ij})\vec{v}_i - w(r_{ij})\frac{\vec{r}_{ij}}{r_{ij}}\vec{v}_i \cdot \frac{\vec{r}_{ij}}{r_{ij}} \right) \right) \qquad (3)$$

where $\phi(r_{ij})$ is the potential between molecules i and j and $w(r_{ij})$ is the pair virial function, defined as

$$w(r_{ij}) = r_{ij}\frac{d\phi(r_{ij})}{dr_{ij}} \qquad (4)$$

Ⅲ. SIMULATION DETAILS

As shown in Fig.1, the simulation domain measures $700nm \times 700nm \times 700nm$ and extends from $-X \sim 0$, $-Y/2 \sim Y/2$ and $-Z/2 \sim Z/2$. The control volume contains approximately 345 Alanine macromolecules of diameter $\sim 100nm$, and thus the global density (ρ) is $1000\left(N/\mu m^3\right)$. The present simulations consider two external heat boundary

temperatures (T_b), i.e. $353K$ and $373K$, respectively, and four different applied heat fluxes (q_w), i.e. $150kw/m^2$, $200kw/m^2$, $250kw/m^2$ and $250\cos(wt)kw/m^2$, respectively, where w is assumed to be 10^{10} s^{-1}. The temperature and heat flux boundary conditions are imposed at the right wall of the simulation system by thermal bath condition and flux boundary condition [14] separately, while periodic boundary conditions (PBCs) are imposed at all the other boundaries.

The complicated potential interactions between the Alanine macromolecules are modeled using the GROMACS protein data bank [15]. In the solution procedure, GROMACS computes the position, velocity and acceleration of each Alanine molecule and exports the results to the MD algorithm, which then calculates the new position and velocity of each molecule using the leap-frog algorithm. In general, the accuracy of the results obtained from MD simulations is dependent on the truncation distance applied when modeling the interactions between the molecules. In accordance with the recommendations of Allen and Tildesley [16], the current simulations impose a truncation distance of $r_c = l/2$, where l is the length of the model, in order to ensure that the simulation results reflect the effects of long-range interactions. Note that a detailed description of the numerical method is presented by the current author in [17].

The simulation procedure commences by performing an equilibration process in which the velocities of the molecules are adjusted such that they conform to a Maxwell velocity distribution. The total number of time steps in each simulation (excluding those of the equilibration process) is specified as 2.5×10^7, with each time step having a duration of 0.1 fs. The initial temperature and pressure of the simulation system are specified as $T = 309.15K$ and $P = 1atm$, respectively. The parameter values applied in the current simulations are summarized in Table 1. The thermal conductivity is computed using 10000 independent autocorrelation functions. The typical CPU time of each simulation is approximately 80 hours when run on an Intel Pentium D 945 3.4G, 4G RAM, Linux system.

The major steps in the simulation procedure can be summarized as follows:

Step 1. The initial model is constructed using the GROMACS protein data bank. The initial positions of the molecules are assigned in such a way as to construct a regular triangular grid. Having constructed the initial model, the system is relaxed using the equilibration process described in Steps 2 to 5 below such that it approaches the specified temperature condition.

A. Equilibration process

Step 2. The acceleration between two Alanine molecules, $\vec{a}_i$, is computed by GROMACS in order to represent the interaction between them.

Step 3. At each time step, GROMACS exports an output file to the MD simulation algorithm indicating the position, velocity and acceleration of each Alanine molecule. Using the information contained within this file, the MD algorithm computes the updated position and velocity of each molecule using the leap-frog algorithm.

Step 4. The velocity of each molecule is adjusted in accordance with Eq. (1) such that the system temperature approaches the specified value.

Step 5. If the velocity distribution satisfies the Maxwell-Botlzmann velocity distribution, the equilibration process is terminated; otherwise the computations return to Step 2.

B. Start simulation

Step 6. Step 2 is repeated to obtain the acceleration of each Alanine molecule.

Step 7. Step 3 is repeated to obtain the new position and velocity of each molecule under the specified thermal boundary condition.

Step 8. At each time step, the Andersen thermobath model and the energy conservation principle are applied to correct the position and velocity of each molecule in accordance with the thermal boundary condition.

Step 9. To maintain the wall temperature at the required value and to ensure momentum conservation within the system, the velocity of each wall molecule is further corrected using Eq. (1) subject to the constraint that each molecule and all of the molecules obey the principle of momentum conservation.

Step 10. If the specified number of simulation time steps has been completed, the GROMACS / MD simulation process terminates; else the computational procedure returns to Step 6.

Ⅳ. RESULTS AND DISCUSSIONS

In this study, the power of the proposed method for estimating the temperature profiles and dynamic transport properties in bio-heat problems was demonstrated by performing MD simulations under different heating effects. The simulations considered various values of q_w and estimated the temperature

profiles of the thermal bio-system.

Fig. 2 illustrates the evolution of the temperature of the bio-tissue surface ($x = 0nm$) over the course of the simulation for applied heat fluxes of $q_w = 150kw/m^2$, $200kw/m^2$ and $250kw/m^2$, respectively. Note that the temperature at a specified time (t_j) is calculated from the average kinetic energy of the Alanine molecules over the temporal domain $t_j \pm 1000 \cdot \Delta t$ and spatial domain ($x \pm 25nm$). From inspection, the difference in the tissue temperature at time $t = 1000ps$ under applied heat fluxes of $150kw/m^2$ and $200kw/m^2$, respectively, is found to be approximately $1K$, while the temperature difference at time $t = 2500ps$ is of the order of $1.5K$. Similar temperatures differences are observed at the same simulation times for the applied heat fluxes of $200kw/m^2$ and $250kw/m^2$, respectively. Hence, it can be inferred that while the intensity of the applied heat flux has a direct effect on the absolute value of the temperature attained within the cell tissue, it has a negligible effect on the heating rate during the mid- to late-stages of the heating process.

In practice, the heating effect generated by blood perfusion as the human pulse beats has a sinusoidal form. Fig. 3 reproduces this effect by illustrating the temperature profile at the Alanine tissue surface ($x = 0nm$) for an applied heat flux of $q_w = 250\cos(wt)kw/m^2$. From inspection, the temperature profile is found to have a period of $628ps$ and an amplitude of approximately $\pm 2K$. Although the sinusoidal form of the heating effect is clear, the profile is severely contaminated by noise arising as a result of the application of statistical techniques to the huge volume of data involved in the simulation procedure.

Fig. 4 illustrates the evolution of the thermal conductivity of the Alanine macromolecules at boundary temperatures of $T = 353K$ and $373K$, respectively. It is observed that at both temperatures, the thermal conductivity converges to a stable value of approximately $0.4W/(m \cdot K)$ after a time of $t = 150ps$. This value is consistent with that of bulk Alanine protein [18]. The small absolute value of the thermal conductivity and its relative insensitivity to the magnitude of the boundary temperature indicate that Alanine molecules are poor conductors of heat. This property is advantageous when performing clinical thermal ablation since it reduces the level of damage caused to healthy cells compared to that caused by traditional chemotherapy or surgical techniques.

V. CONCLUSION

This study has applied a numerical method comprising a MD algorithm and the GROMACS protein data bank to investigate the temperature profile and thermal conductivity characteristics of Alanine macromolecules under various thermal boundary conditions. In general, the results have shown that the heating rate of the bio-tissue is insensitive to the magnitude of the applied heat flux. However, the absolute value of the tissue temperature increases slightly as the applied heating intensity is increased. The results have confirmed the ability of the proposed numerical scheme to reproduce the sinusoidal heating effect induced via blood perfusion in response to the human pulse activity. Finally, it has been shown that Alanine macromolecules are poor conductors of heat and have a thermal conductivity similar to that of bulk Alanine protein.

The simulation results presented in this study provide useful insights into the thermal behavior of Alanine macromolecules under specific thermal boundary conditions. In general, the results provide a useful source of reference for future initiatives aimed at improving the efficacy and safety of thermal ablation techniques. However, the current numerical results are essentially qualitative in nature. Accordingly, a future study will aim to perform a precise quantitative analysis of the temperature profile evolution in Alanine bio-tissue in order to provide a more detailed understanding of the thermal phenomena at work during clinical thermal ablation therapy.

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BIOGRAPHIES

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