In silico radiobiology: Have we reached the limit of Monte Carlo simulations?

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Abstract. Monte Carlo radiation transport models are increasingly being used to simulate biological damage. However, such radiation biophysics simulations require realistic molecular models for water, whereas existing Monte Carlo models are limited by their use of atomic cross-sections, which become inadequate for accurately modelling interactions of the very low-energy electrons that are responsible for biological damage. In this study, we borrow theoretical methods commonly employed in molecular dynamics simulations to model the molecular wavefunction of the water molecule as the first step towards deriving new molecular cross-sections. We calculate electron charge distributions for molecular water and find non-negligible differences between the vapor and liquid phases that can be attributed to intermolecular bonding in the condensed phase. We propose that a hybrid Monte Carlo – Molecular Dynamics (MC-MD) approach to modelling radiation biophysics will provide new insights into radiation damage and new opportunities to develop targeted molecular therapy strategies.

1. Introduction
Classical radiobiology has provided a remarkably successful framework for understanding cell killing by ionising radiation and linear-quadratic models, in particular, have proven to be invaluable for quantifying and predicting survival of tumor cells exposed to typical therapeutic doses of radiation [1]. While empirical radiobiological models are now gradually being used to biologically optimise radiotherapy treatment, many Monte Carlo (MC) models continue to be developed to gain further insight into the biophysics of DNA damage inflicted by radiation. Most in silico models focus on direct damage to nuclear DNA [2, 3], rather than the more prevalent indirect damage caused by the free radicals produced by radiolysis. New MC models are also emerging that address non-targeted damage to healthy cells caused by radiation at low-doses [4, 5], where radiobiological models predicting normal tissue complications have had limited success in describing clinically observed normal tissue reactions [6].

A major challenge confronting radiation biophysics simulations is that existing MC models use atomic interaction cross-sections. While this is adequate for high incident energies and tissue-scale dose volumes, the atomic target approximation is inadequate for determining energy and momentum transfer on sub-cellular scales [7]. At the very low energies ($\ll 100\text{eV}$) of the electrons that are ultimately responsible for biological damage, the molecular nature of the target cannot be ignored. Thus, it is necessary to consider the nanoscale dynamics of electrons.
in soft, condensed matter. This requires new models to be developed for molecular interaction cross-sections (see Figure 1).

Several previous studies investigating low-energy electron inelastic scatter in water have used a semi-classical approach, deriving a differential cross-section in terms of the dielectric response function for water [8, 9]. An alternate approach is to derive the differential cross-section using a quantum mechanical approach, which requires an accurate description of the molecular wavefunction for water [10]. Here, we briefly report on our study using this first principles approach and we present preliminary results on the radial distribution of electron charge in molecular water for both the vapor and liquid phases, a key test of the molecular wavefunction.

2. Approach and Methodology

In this study, we used an \textit{ab initio} method based on the Hartree-Fock level of theory for multi-electron systems. We constructed atomic orbitals using the same basis set and contracted gaussian functions as that used by Champion [10]. To calculate the molecular orbitals and construct the water molecule wavefunction, however, we used the linear combination of atomic orbitals approximation, whereas Champion used a single-center partial wave expansion method. All quantum chemistry calculations were performed using the Gaussian 03 program [11]. Calculations for liquid water used the polarizable dielectric continuum model available within Gaussian 03. The radial distribution of electron charge density and the partial atomic charges were calculated to evaluate the derived molecular wavefunction for water in the two distinct thermodynamic phases.
Figure 2. Spherical electron charge density radial distributions for molecular water for the liquid and vapor phases (with origin centred on the oxygen atom). Theoretical results from the present work (open circles) are shown against the analytical prediction of Katase et al. [12] for water vapor (blue circles) and experimental data (stars) from Neuefeind et al. [13].

3. Results and Discussion

3.1. Electron charge density distribution for molecular water

Figure 2 shows the spherical electron charge density distribution $4\pi r^2 \rho(r)$ calculated for molecular water in the vapor and liquid phases. The main peak in the distribution (at $r \simeq 0.1$ a.u.) is governed by the electronic distribution around the oxygen atom. The second peak corresponds to the influence of the hydrogen atoms. Our theoretical results, calculated using contracted gaussian functions for the atomic orbitals, are plotted against the analytical prediction of Katase et al. [12] for water vapor and experimental data for liquid water [13]. Noticeable differences are evident in Fig. 2, particularly before the first peak, between our results for water vapor (black circles) and those of Katase et al. [12]. This can be attributed to the different descriptions of atomic orbitals, since the analytical prediction is based on Slater-type orbitals. Our theoretical results for the liquid phase (red circles) also differ from the corresponding experimental data (stars), especially between the two peaks. This may be attributed to some of the simplifications made in the theoretical model, such as the number of gaussian functions used to approximate the atomic orbitals. On the other hand, the differences in $4\pi r^2 \rho(r)$ between the vapor and liquid phases show a similar trend for our results to that exhibited in the experimental and analytical data. In particular, the liquid phase exhibits a more pronounced peak in charge density near 0.1 a.u. (oxygen atom) compared to the vapor phase,
which reflects the influence of the stronger dipole moment on the valence electron distribution. The enhanced dipolar nature of molecular water in the liquid phase can be attributed to intermolecular hydrogen bonding, which is also responsible for the difference in $4\pi r^2 \rho(r)$ near $r \simeq 0.3 - 0.4$ a.u. between the vapor and liquid phases.

3.2. Surface charge analysis

Figure 3 shows the partial charges of each atom as well as the total surface charge distribution in a water molecule for the vapor and liquid phases. The partial charges were calculated within Gaussian 03 by dividing the total electron distribution according to overlaps of the atomic orbitals. As is evident in Fig. 3, oxygen has a more negative partial charge in a liquid water molecule compared to a vapor molecule, while the hydrogen atoms are more positive. This indicates a stronger polarity of the water molecule in its liquid phase compared to its vapor phase, which can be attributed to the hydrogen bonding with surrounding molecules. This is also reflected in the surface charge density distributions shown in Fig. 3, where red indicates maximum negative charge, while blue indicates minimum negative charge. This supports the interpretation of the differences in the radial charge distribution $\rho(r)$ being due to the intermolecular hydrogen bonds present in liquid water.

4. Conclusion

Our results demonstrate that there are non-negligible differences in the molecular orbitals of water in the vapor and liquid phases that can be attributed to the increase in the dipole moments due to hydrogen bonding. This will in turn affect the cross-section for low-energy electron inelastic scatter in biological tissue. Work is currently in progress to calculate new cross-sections and determine the effect on existing models for low energy electron transport, including track structure. We propose that a hybrid Monte Carlo – Molecular Dynamics (MC-MD) approach will extend the current capability of radiation transport simulations, enabling more realistic simulation of biological damage and hence, the development of new targeted molecular therapy strategies into the future.

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