Chemotherapy efficiency increase via shock wave interaction with biological membranes: a molecular dynamics study

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Abstract Application of ultrasound to biological tissues has been identified as a promising cancer treatment technique relying on temporal enhancement of biological membrane permeability via shock wave impact. In the present study, the effects of ultrasonic waves on a 1,2-dipalmitoyl-sn-phosphatidylcholine biological membrane are examined through molecular dynamics simulations. Molecular dynamics methods traditionally employ periodic boundary conditions which, however, restrict the total simulation time to the time required for the shock wave crossing the domain, thus limiting the evaluation of the effects of shock waves on the diffusion properties of the membrane. A novel method that allows capturing both the initial shock wave transit as well as the subsequent longer-timescale diffusion phenomena has been successfully developed, validated and verified via convergence studies. Numerical simulations have been carried out with ultrasonic impulses varying from 0.0 to 0.6 mPa s leading to the conclusion that for impulses \( \geq 0.45 \) mPa s, no self-recovery of the bilayer is observed and, hence, ultrasound could be applied to the destruction of localized tumor cells. However, for impulses \( \leq 0.3 \) mPa s, an increase in the transversal diffusivity of the lipids, indicating a consequent enhancement of drug absorption across the membrane, is initially observed followed by a progressive recovery of the initial values, thereby suggesting the advantageous effects of ultrasound on enhancing the chemotherapy efficiency.

Keywords Molecular dynamics · Impulse · Boundary conditions · Shock wave · Cancer · Biological membrane

1 Introduction

Every year, more than 8 million people around the globe die from cancer and more than 12 million are diagnosed for the first time, making cancer one of the leading causes of death in the western world (World Health Organization 2009). Therefore, efforts across the scientific community have been devoted to establishing new methods as well as improving the potency and efficacy of existing ones.

The treatment of cancerous tissue with high-intensity focused ultrasound (HIFU) relies on destruction of cells through conversion of mechanical energy into heat (coagulative necrosis) (Ganzenmüller et al. 2011) and through mechanical damage induced by acoustic cavitation (formation and implosion of microscopic gas bubbles that generate liquid jets toward the cell membrane) (Vogel et al. 1996). The latter could be utilized not only to eliminate localized cancer tumor cells (Ganzenmüller et al. 2011; Brú and Casero 2006) but also in conjunction with chemotherapy in order to temporally increase the chemotherapeutic agents absorption across the membrane (Koshiyama et al. 2006). The basic composition and structure of a biological membrane is often described by the fluid mosaic model (Singer and Nicholson 1972), where the membrane is considered as a two-dimensional fluid along the cell surface composed mainly of a phospholipid bilayer with embedded protein channels that allow the drug to actively penetrate into the cell. As the shock wave, following Ganzenmüller’s definition (Ganzenmüller et al. 2011), impacts the membrane, the lateral diffusion of the...
lipids and protein channels is enhanced and, hence, the probability of the drug to be trapped by these channels is consequently increased.

By utilizing coarse graining techniques (CG), Ganzemüller et al. (2011) concluded that, for gel phase DPPC (Tieleman et al. 1997), there is a critical shock wave velocity beyond which no self-recovery of the membrane is observed leading to cell disruption. The corresponding impulse (Eq. 2) was proved to be the most influential variable (Kodama et al. 2000), and its critical value was estimated in the range (0.39, 0.52) mPa s (Eq. 3).

Koshiyama et al. (2006) used MD to model the interaction of shock waves with biological membranes, specifically with the DPPC in crystalline phase that corresponds to the majority of body cells in nature (Tieleman et al. 1997), for impulses \( I \in (0, 100) \) mPa s. However, the use of periodic boundary conditions (PBC) restricted the total simulation time to the time required for the shock impulse to travel through the computational domain and reach the opposite side of the simulation box (Koshiyama et al. 2006), thus leading to a large disparity between these values and the time required for studying diffusion mechanisms (Tieleman et al. 1997).

The aim of the present study is to investigate the response of a DPPC membrane in crystalline phase subjected to ultrasonic shocks and examine whether there is a critical impulse value for which the membrane can no longer recover, in view of the ultrasound cancer treatment. In order to study long timescales of diffusion phenomena, a method that allows to expand the total MD simulation time has been developed.

### 2 Scientific computing methods

MD employs the Newton equation of motions for each particle \( i \)

\[
m_i \ddot{r}_i = -\frac{\partial V_i}{\partial r_i},
\]

where \( m_i \) is the mass of the atom \( i \), \( r_i \) the position of the mass points, and \( V_i \) stands for the potential energy, which is a sum of semi-empirical analytical functions that model the real interatomic forces.

#### 2.1 Lipid bilayer/water system

The investigation has been carried out for a DPPC membrane (Tieleman et al. 1997), when fixing temperature and/or pressure, at temperature 323.15 K and pressure of 1 atm (Koshiyama et al. 2006; Kucerka et al. 2006; Klauda et al. 2010; Andoh et al. 2012; Sonne et al. 2007) corresponding to the crystalline phase (Tieleman et al. 1997). The temperature coupling methods analyzed are the Berendsen et al. (1984), velocity rescaling (Bussi et al. 2007) and Nosé–Hoover (Nosé 1984; Hoover 1985) thermostats. The Berendsen algorithm mimics weak coupling with first-order kinetics to an external heat bath, suppressing the fluctuations of kinetic energy (Berendsen et al. 1984). The velocity rescaling method affects the external heat flow by scaling the velocities (Bussi et al. 2007). Finally, the Nosé–Hoover thermostat extends the system Hamiltonian by introducing a friction term and a thermal reservoir in the equations of motion (Nosé 1984; Hoover 1985). The pressure coupling methods under study are the Berendsen et al. (1984) and Parrinello-Rahman (1981) barostats. The latter allows variations not only in the volume of the domain as the former, but also in its shape.

The CHARMM 36 force field (FF) (Klauda et al. 2010) and TIP3P model (Hess et al. 2008) have been employed for lipids and water, respectively, along with the particle mesh Ewald (PME) (Ewald 1921) algorithm with cubic interpolation and no constraints, with a time step equal to 1 fs for stability purposes (Hess et al. 2008). The CHARMM 36 FF allows the all-atom simulations of membrane and membrane protein systems without surface tension (Freites et al. 2010) effects; the latter were found to be negligible by Tieleman and Berendsen (1996). The cutoff parameter for the van der Waals and Coulombic interactions is 1.0 nm (Koshiyama et al. 2006). The center of mass is controlled every time step separately for water and lipid molecules in order to avoid any spurious displacements of the system. Other variables, such as temperature, are also controlled separately between the lipids and the water molecules aiming to avoid any undesirable heat up of the lipids while the water is cooled down (Hess et al. 2008).

Furthermore, the leap frog integrator (LFI) is utilized for all ensembles used except for NVE, where LFI is used with the Velocity Verlet and shift techniques for proper energy conservation (Hess et al. 2008). Due to the high velocities arising from the application of the shock wave, the neighbor list is updated every time step instead of every 5 time steps, as in the equilibration phase. The neighbor list search cutoff distance is increased from 1.0 to 2.0 nm in the NVE simulation.

| System | Lipids | Atoms | Height (nm) | \( A_L \) (nm)² |
|--------|--------|-------|-------------|----------------|
| s72    | 72     | 40,020| 17.51       | 0.6247         |
| s128   | 128    | 73,307| 17.51       | 0.6400         |
| s256   | 256    | 146,227| 17.51      | 0.6400         |
| s72s   | 72     | 39,096| 17.00       | 0.6247         |
| s72b   | 72     | 41,152| 18.00       | 0.6247         |

\( A_L \) is the area per lipid.
Initial topologies with 72 [named as s72 (Klauda et al. 2010)], 128 and 256 [named as s128 and s256 (Jo et al. 2007)] lipids have been employed and placed parallel to the x–y plane in the center of the periodic box. The molecular system is solvated until reaching a total height varying from 17 to 18 nm (Koshiyama et al. 2006). The main characteristics of the topologies following solvation are outlined in Table 1. According to Klauda et al. (2010), the cross-section is kept squared for maintaining consistency between the numerical solution and the underlying physical phenomena.

2.2 Shock waves modeling

The jet stream generated from the ultrasound is modeled through a rise in the momentum of the water molecules that lie within the upper layers of the simulation box that are under the effect of the ultrasonic wave. The amount of momentum transferred into the system is determined by the impulse (Kodama et al. 2000):

\[ I = \int_{0}^{t_+} p(t) \, dt, \]  

(2)

where \( t_+ \) is the positive phase duration of a half cycle of the shock wave and \( p \) is the pressure near the cells in water.

Medical ultrasound has an oscillatory nature in the MHz range, and thus, its characteristic time is three orders of magnitude longer than the total simulation time. Hence, an average velocity \( v_{UW} \) is added to the thermal velocity due to the ultrasonic wave:

\[ v_{UW} = \frac{I \times A_{UW}}{m_{\text{water}} \cdot N_{UW}} = \frac{I \times A}{\frac{\text{MM}_{\text{water}}}{N_{\text{av}}} N_{UW}}, \]  

(3)

where \( A \) is the transversal area of the computational box, \( \text{MM}_{\text{water}} = 0.0180154 \, \text{kg/mol} \) is the molecular mass of water for the TIP3P model, \( N_{\text{av}} \) is the Avogadro number and \( N_{UW} \) number of water molecules in the water slab dictated by the thickness of the UW impact, \( L_{UW} \). The latter is taken as 4nm as in Koshiyama et al. (2006), being a conservative decision since the impulses considered are one order of magnitude smaller than Koshiyama’s. The ultrasound region is in contact with the zone occupied by the lipids, as in Koshiyama et al. (2006). The impulses employed here are 0.3, 0.45 and 0.6 mPa s corresponding to 74.92, 112.39 and 149.85 m/s, respectively.

2.3 Boundary conditions

During minimization and equilibration, PBC with minimum image convection are employed in all three directions. During and after the shock wave impact, a new
method that allows capturing both the initial shock transit as well as the subsequent longer timescale has been developed. The method is based on surrounding the original system by symmetric ones along the direction of the shock propagation. This is equivalent to utilizing PBC within a system composed of the original system and its symmetric one (Zhao et al. 2006), as illustrated in Fig. 1. In the new system, two shock waves travel to opposite directions away from the center of the box toward the lower and upper boundaries along the z-axis. Once the shock waves arrive at the end of the domain, due to the presence of PBC, the two waves collide and the majority of their momentum is canceled out (Zhao et al. 2006).

The addition of a vacuum between the normal and the symmetric system (Fig. 1) is necessary for avoiding overlapping between water molecules. A vacuum of the same characteristics is added at the periodic boundary, so as for the method to be robust in conjunction with any MD solver. The size of the vacuum region has been selected to be of the order of a water molecule diameter (0.05 nm).

2.4 Non-dimensionalization and further analysis

The potential energy per unit of mass, $\text{pe}$, is given by:

$$\text{pe} = \frac{\text{PE}}{m_{\text{box}}}, \quad \text{pe} \, (\%) = \frac{\text{pe} - \text{pe}_{\text{final}}}{\text{pe}_{\text{initial}} - \text{pe}_{\text{final}}} \cdot 100 \quad (4)$$

where PE is the potential energy and

$$m_{\text{box}} = \frac{N_L \cdot \text{MM}_L + N_W \cdot \text{MM}_W}{N_{av}} \quad (5)$$

$N$ is the number of molecules, $\text{MM}$ is the molecular mass and the subscripts L and W stand for lipid and water, respectively. The dimensionless temperature and pressure are obtained by dividing the dimensional values by the reference ones.

The mass and electron density profiles are calculated by dividing the periodic box in 500 slabs in the longitudinal direction and counting the particles of interest in each region (Hess et al. 2008). The thickness of the membrane is calculated as the distance between the two peaks in the electron density profiles, as per experimental measurements (Tieleman et al. 1997). The position of the peaks of the electron density profiles coincides with those of the phosphate electron density profiles (Andoh et al. 2012); therefore, when applying the shock wave, the latter are utilized.

The deuterium order parameter, $S_{CD}$, is defined as:

$$-S_{CD} = \frac{2}{3} S_{xx} + \frac{1}{3} S_{yy}, \quad S_y = \frac{1}{2} \langle 3 \cos \theta_i \cos \theta_j - \delta_{ij} \rangle \quad (6)$$

where the brackets denote an ensemble average, $\theta_i$ is the angle between the $i$th molecular axis and the bilayer normal, and $\delta_{ij}$ is the Kronecker’s delta. For the $C_n$ methylene group, the $C_{n-1}-C_{n+1}$ direction is taken as $z$ and the $C_{n-1}-C_n-C_{n+1}$ plane is the $yz$ (Tieleman et al. 1997). The order parameters are a measure of the spatial restriction of the motion of a CH vector. The change in length can be characterized by the averaged instantaneous deuterium order parameter (Koshiyama et al. 2006), because the chain length becomes smaller as the disorder of chain bend angles increases.

The lateral self-diffusion coefficient of the lipids $(D_{xy})_L$ can be estimated from the slope of the averaged mean-square displacement (MSD) of the center of mass $x(t)$ of single lipids by using the Einstein relation (Bockmann et al. 2003):

$$\langle D_{xy} \rangle_L = \frac{1}{4} \lim_{t \to \infty} \frac{1}{t} \text{MSD} = \frac{1}{4} \lim_{t \to \infty} \langle |x(t_0) - x(t_0 + t)|^2 \rangle \quad (7)$$

Larger slopes of the MSD implies a higher diffusion coefficient. The MSD scales proportionally to the square root of time for the single-file diffusion (SFD), linearly with time for the Fickian diffusion, and proportionally to the square of time for the ballistic diffusion characterized by a higher degree of co-ordination (Striolo 2006).

2.5 Other computational details

The double-precision GROMACS 4.5.5 (Hess et al. 2008) molecular solver has been employed in conjunction with the FTTW 3.3.2 (Frigo and Johnson 2005) C subroutine library. The simulations have been carried out utilizing Cranfield University’s HPC cluster Astral. The system uses the Intel 2012 XE Cluster Suite for compilation (FORTRAN, C, C++) and Message Passing Interface (MPI). The measured maximum performance achieved is 19.9 TFlops, though the theoretical peak processor performance is 22.5 TFlops.

3 Results and discussion

3.1 Minimization

Figure 2 shows the specific potential energy during the minimization stage, for the systems s72, s128 and s256. The attractive sign demonstrates physical consistency, and the potential energy values are in accordance with previously published data (Hess et al. 2008). The results show that the higher the number of lipids is, the smaller the specific potential energy of the converged system becomes; this is due to the fact that the effect of the PBC is diminished when increasing the lipids. The differences are in any case negligible ($\Delta e < 0.7\%$).
3.2 Equilibration

In the equilibration process, consisting of a 100 ps of NVT followed by a 2 ns of NPT, different systems are simulated aiming at verifying the effects of several parameters, such as number of lipids (equivalent to the parallel box size); sampling period, coupling method; characteristic coupling period; isothermal compressibility and perpendicular box size (Tieleman et al. 1997; Hess et al. 2008), and validated the results (target pressure and temperature and area per lipid) against available experimental data (Kucerka et al. 2006; Klauda et al. 2010; Andoh et al. 2012).

3.3 NVT stage

In Fig. 3, the effects of the number of lipids on the temperature as a function of time are presented along with the cumulative time average value and the corresponding variance. As the number of lipids increases, the artifacts induced by the PBC diminish, thus leading to slightly decreased difference (less than 0.01 %) between average and target temperature values. The associated computational cost increases by 27 % for the 128 lipid case over the 72 lipids and 120 % when 256 lipids are employed. Hence, it can be concluded that the 72 lipid case can sufficiently capture the dynamics of the system and provide results.
independent of the box size, an observation that has also been made by Klauda et al. (2010). Therefore, for computational efficiency, the s72 case is utilized for the rest of the study.

Figure 4 shows the effect of the sampling period on the temperature mean and variance. As the sampling period decreases, movements with higher characteristic frequency occur and the root mean squared deviation (RMSD) also increases approaching that obtained when all the time steps are sampled. According to Hess et al. (2008), for lipid systems, the scales of interest are captured with a sampling period $\tau_{\text{samp}} \leq 200$ fs, which is also utilized throughout the present study.

The temperature effects of the coupling method for the three approaches considered are shown in Fig. 5. For a given temperature coupling period ($\tau_T = 0.1$ ps), the Nosé–Hoover method reaches a relative error lower than 0.1 %, which is more than 16 times faster compared to the other cases (Fig. 5). Moreover, even though it produces an oscillatory relaxation, the variance is smaller than 25 % compared to the ones obtained by the alternative methods. The relative error is more than two orders of magnitude smaller compared to other cases and, therefore, this is the

![Figure 6: Effect of the temperature coupling period on the temperature, its cumulative mean and variance, represented by gray, blue and purple respectively, during the NVT equilibration.](image1)

![Figure 7: Effect of the periodic box system height on the temperature, its cumulative mean and variance, represented by gray, blue and purple, respectively, during the NVT equilibration. $\tau_T = 0.3$ ps](image2)

![Figure 8: Effects of the isothermal compressibility and the pressure coupling method on the cumulative mean and variance pressure represented by solid and dotted line, respectively. $\tau_T = 0.3$ ps and $\tau_P = 0.1$ ps](image3)

![Figure 9: Effects of the pressure coupling method and period on the area per lipid, cumulative mean and variance represented by light dotted, thick solid and thick dotted lines, during the NPT equilibration. The validation has been carried out against experimental (Kucerka et al. 2006) and numerical results (Klauda et al. 2010; Andoh et al. 2012; Sonne et al. 2007)](image4)
coupling method used throughout the present study. Figure 6 shows the effect of the temperature coupling period; it can be noticed that the relative error diminishes as the coupling period decreases until it reaches a plateau for $\tau_{T,NH} = 0.3$ ps.

Figure 7 shows the effect of the perpendicular box size on the temperature cumulative mean and variance. It is noticed that in the range of system height under study, 17–18 nm, the effects are negligible, i.e., $\Delta e < 0.0001\%$.

3.4 NPT stage:

Figures 8 and 9 show the effect of isothermal compressibility, pressure coupling method and coupling period on the values of pressure and area per lipid, respectively. It is observed that the pressure coupling method does not affect significantly the relative error ($\Delta e \leq 0.5\%$); however, the RMSD obtained with Berendsen is 10% lower on average due to the fact that the exponential relation is much faster than the oscillatory one when the initial pressure value is relative far from the target one. Regarding the pressure coupling period (Fig. 9), the relative error obtained with $\tau_p = 1$ ps is 4 times smaller than that obtained with $\tau_p = 5$ ps.

The pressure coupling method allows calibration via the isothermal compressibility of the membrane (Fig. 8), and the isothermal compressibility of pure water has been employed leading to minimum error for the Berendsen method and $\tau_p = 1$ ps. This is physically consistent since the thickness of the water bilayer has been increased so as to implement the shock wave and, hence, the system is closer to pure water than to a membrane with an embedded protein.

As a conclusion, larger sampling periods ($\tau_T = 0.3$ or 0.5 ps and $\tau_p = 5$ ps) tend to significantly overestimate pressure and result in an underestimated area per lipid, while smaller coupling periods ($\tau_T = 0.1$ ps and $\tau_p = 1$ ps) tend

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**Fig. 10** Water density profiles for $I = 0.3$ mPa s and the NVE ensemble for time step 0.01 fs. The system is made of the original system (left) and the symmetric system (right). The hydrophobic region of the membrane in each subdomain corresponds to the region which has less than a 3% water density at $t = 0$ fs when compared to pure water.
to slightly underestimate pressure, thus resulting in a more accurate area per lipid. The effect of the temperature coupling period is more important. When utilizing the Berendsen pressure coupling method with $\tau_{T,NH} = 0.1$ ps and $\tau_{P} = 1$ ps, an error lower than 1.25 % is achieved, suggesting an improvement in the computationally accuracy compared to the most relevant published papers (Klauda et al. 2010; Andoh et al. 2012; Sonne et al. 2007) (Fig. 9).

**4 Shock wave**

4.1 Before the shock reaches the end of the domain

The verification of the ultrasound cancer treatment in short timescales was carried out by Koshiyama et al. (2006), who concluded that the number of lipids used in the simulation model does not significantly affect the results. Although only a qualitative comparison with Koshiyama’s result is possible, due to the difference between the impulse values used in the present study and Koshiyama’s, the most relevant effects associated with the collapse and rebound of bilayers and the water penetration into the hydrophobic region are observed in both studies (Fig. 9).

![Fig. 11 Effects of the ensemble on the electron density profiles and membrane thickness. Validation has been obtained against an experimental structural model (SDP) (Kucerka et al. 2008) and numerical results from Klauda et al. (2010) and Andoh et al. (2012); $z = 0$ nm corresponds to the center of the membrane. Groups description can be found in Klauda et al. (2010)](image)

During the NVE integration, the time step employed should be of the order of 0.01fs. Therefore, for simulating a few tens of nanosecond, $10^9$ time steps are required corresponding roughly to 14 years of simulations based on the available computing resources, the size of the problem and the scalability of the solver used. According to Zhao et al. (2006), once the shock is canceled out, the simulation could be continued by using any of the commonly used ensembles. The effect of the ensemble on the results is estimated by studying the case that corresponds to $I = 0$ mPa s where experimental data for validation are available. In Figs. 11 and 12, the results in the long timescales are verified and validated in terms of electron density profile, thickness, diffusion coefficients and deuterium order parameters through comparisons with available experimental and numerical data (Klauda et al. 2010; Andoh et al. 2012; Kucerka et al. 2008; Seelig and Seelig 1974, 1975; Klauda et al. 2008; Douliez et al. 1995). From the analysis carried out, it is concluded that the NPT ensemble is the recommended choice due to the following reasons:

- The computational performance is ten times faster than the one obtained from the NVE ensemble.
- It is quantitatively closer to the experimental and numerical results, achieving excellent accuracy (error $<1\%$) on the prediction of the membrane thickness, which is crucial for understanding whether or not the membrane will be disintegrated.

![Graph showing the evolution in time of the water density profiles for $I = 0.3$ mPa s when utilizing the NVE ensemble. The shock wave produces a high-density water that induces the shrinkage of the hydrophobic region. Initially, the upper layer is pushed downward, while the lower layer remains intact (Fig. 10b). The minimum thickness is reached when the excess of momentum is transferred to the lower layer, which is also pushed downward (Fig. 10c). At that time, the force pushing the upper layer down becomes weaker, and the rebound stage sets in. The rebound stage is more important for water penetration than the collapse stage, as it was also observed by Koshiyama et al. (2006) (Fig. 10d–f).](image)

When the two shock waves reach the boundary, the majority of the momentum is canceled out; following that, two shock waves of reduced intensity and speed propagate toward the axis of symmetry (Fig. 10g–l). The efficiency of the method is defined as the fraction of impulse that it is canceled out, which can be estimated as follows:

$$\text{Efficiency} = \frac{I_1 - I_2}{I_1} \times 100 \approx \frac{N_{W,1v_{s,1}} - N_{W,2v_{s,2}}}{N_{W,1v_{s,1}}} \times 100 \approx 98\%$$

For the present study, the efficiency of the double shocks method is around 98 %, improving those of previous studies in solids (Zhao et al. 2006).

4.2 After the shock reaches the end of the domain

![Figures showing the results in the long timescales are verified and validated in terms of electron density profile, thickness, diffusion coefficients and deuterium order parameters through comparisons with available experimental and numerical data (Klauda et al. 2010; Andoh et al. 2012; Kucerka et al. 2008; Seelig and Seelig 1974, 1975; Klauda et al. 2008; Douliez et al. 1995).](image)
As the volume is not fixed, spurious effects such as the occurrence of small densities in the center of the box are avoided and the membrane behavior obtained corresponds to the physical one.

Finally, the effect of the impulse on the long timescales has been investigated by selecting values closer to the critical value estimated in Ganzenmüller et al. (2011).

Following the implementation of the shock, NPT simulations with impulses 0.3 and 0.45 mPa s and time steps of 1 fs and 0.5 fs, respectively, are carried out, increasing the pressure coupling period to 5 ps for stability.

Figures 13 and 14 show the mean-square displacement of the lipids in the membrane as function of time and the electron density profiles for different shock impulses. For impulses \( \geq 0.45 \text{ mPa s} \) no self-recovery of the bilayer is observed, whereas for impulses \( \leq 0.3 \text{ mPa s} \), the increase in the transversal diffusivity of the lipids (ballistic motion) and consequent enhancement of drug absorption across the membrane are followed by a progressive recovery of the initial values.

5 Concluding remarks

The short- and long-timescale effects of ultrasonic shock waves through DPPC lipid bilayers were investigated using MD. In respect of the long-timescale effects, a new method that utilizes symmetric systems has been developed, validated and verified. The new method exhibits an efficiency better than other MD transmitting boundary conditions previously utilized for solids (Zhao et al. 2006).

From the analysis of the long timescales, it can be concluded that for impulses \( \geq 0.45 \text{ mPa s} \) no self-recovery of the bilayer is observed. However, for impulses \( \leq 0.3 \text{ mPa s} \), an increase in the transversal diffusivity of the lipids (ballistic motion), and consequent enhancement of drug absorption across the membrane, is noticed followed by a progressive recovery of the initial equilibrium values.
Therefore, if the ultrasound method is utilized for HIFU applications, attention should be drawn to cases where \( I \geq 0.45 \) mPa s, whereas if the purpose of the cancer treatment is to increasing the efficiency of chemotherapy, attention should focus on the range \( I \leq 0.3 \) mPa s. Furthermore, the research project proves numerically the efficacy of the ultrasound technique to cancer treatment.

The analysis of the response of more complex membrane models that include embedded proteins will further contribute to a better understanding of the mechanisms involved as well as optimizing the drug delivery and absorption. Furthermore, the success of the method developed has opened up the possibility of reaching timescales of medical interest that could be explored in future studies.

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