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RESEARCH PAPER

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.

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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

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