Molecular dynamics simulations of doxorubicin in phospholipid membranes

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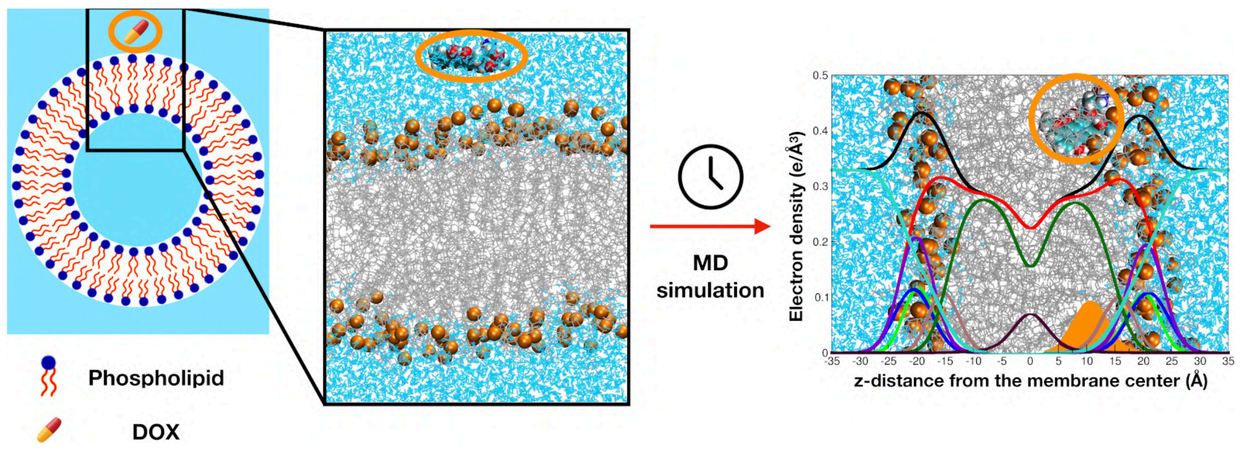
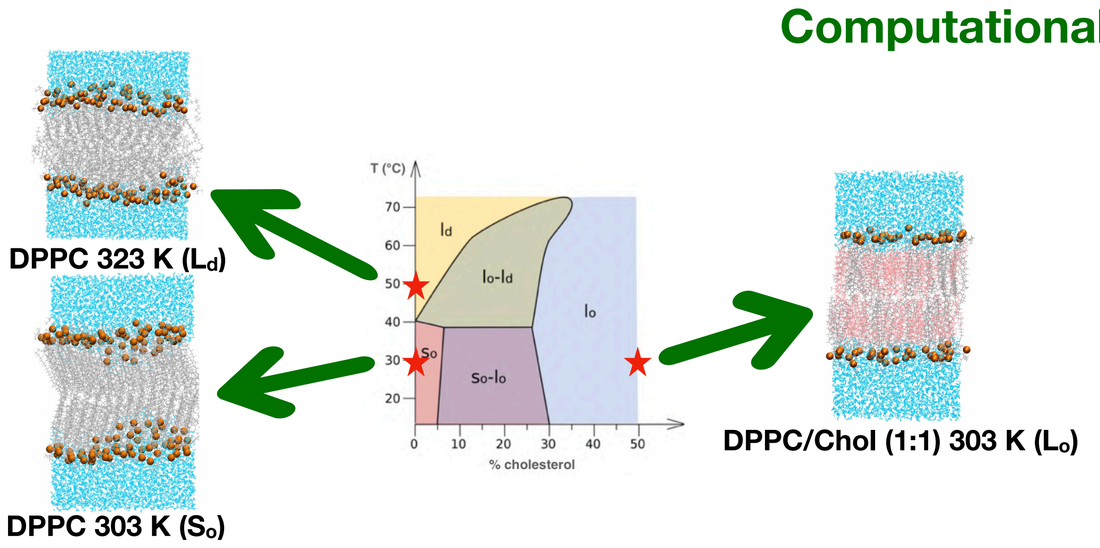
Introduction

Doxorubicin (DOX) is a chemotherapy drug intercalating between the double helix of DNA in tumor cells and causing its damage, which inhibits the cell growth and replication. However, the cytotoxicity of DOX is nonspecific and normal cells, such as those of the heart tissue, are also affected [1]. One way to overcome this limitation is to design **lipid-based carriers** to improve the targeting and efficacy of DOX, thus reducing its cardiotoxicity. These carriers, known as **liposomes**, have **phospholipids and cholesterol** as their most fundamental structural components. Incorporating antitumoral drugs such as DOX into liposome vesicles would increase their pharmacokinetics and clinical efficacy [2]. Hence, a molecular understanding of the **drug-membrane interactions** and the **drug partitioning** into lipid bilayer models is of the utmost importance. Numerical **molecular dynamics (MD) simulations** offer useful tools to accomplish this aim, providing relevant information at an atomistic resolution level. Here, we present a systematic and comparative study on the location of a protonated DOX molecule (DOX^+) in distinct DPPC and PSM lipid phases in the presence or absence of cholesterol by means of force-field MD simulations [3].



Computational methods and models

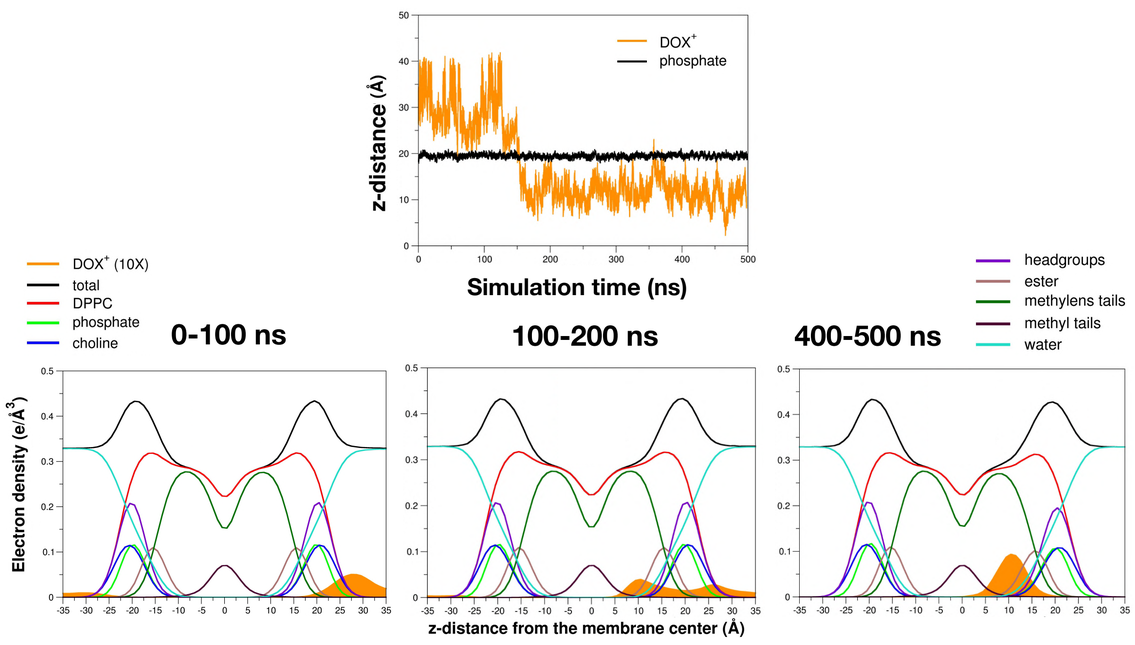


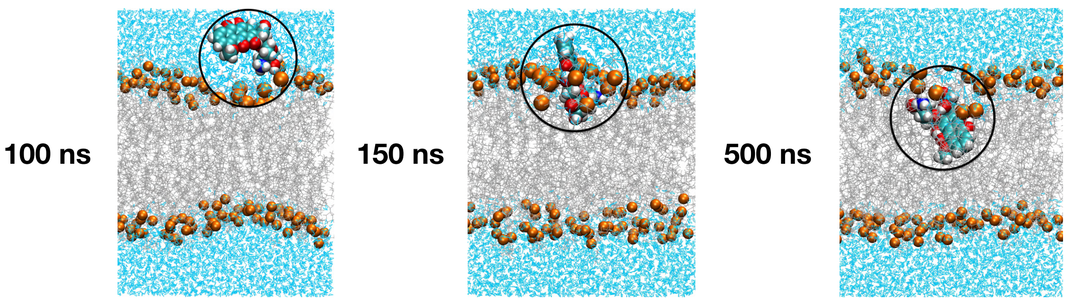
- Classical MD simulations (NAMD2.13 code [4] with GPU interface)
- CHARMM36FF [5] and CGenFF [6] force fields
- CHARMM TIP3P water model
- Free energy calculations based on ABF and TI methods
- DPPC, DPPC/cholesterol, PSM and PSM/cholesterol membrane models (So, Ld and Lo lipid phases)

NAMD Scalable Molecular Dynamics

Results

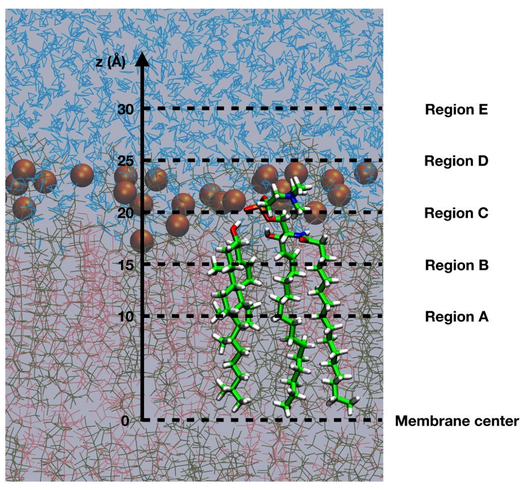
Structural parameters



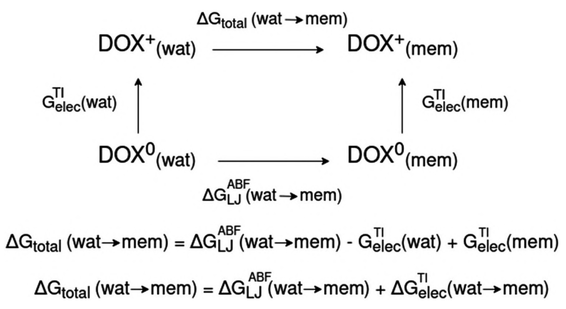


z-distance of DOX^+ c.o.m. and phosphate groups as a function of the simulation time; DOX^+/membrane electron density profiles and snapshots from the MD simulations at different times for a DPPC Ld membrane.

Thermodynamic parameters



Graphical representation of the membrane regions (A-E) adopted to evaluate the free energies of DOX^+ partitioning in PSM^{So} and PSM^{Lo}/cholesterol (1:1) bilayers.



$$\Delta G_{total}\,(wat\rightarrow mem) = \Delta G^{ABF}_{LJ}\,(wat\rightarrow mem) - G^{TI}_{elec}(wat) + G^{TI}_{elec}(mem)$$

$$\Delta G_{total}\,(wat\rightarrow mem) = \Delta G^{ABF}_{LJ}\,(wat\rightarrow mem) + \Delta G^{TI}_{elec}(wat\rightarrow mem)$$

Thermodynamic cycle adopted in this work to estimate the total free energy of DOX^+ partitioning in PSM bilayers. DOX^0 stands for the "uncharged" DOX molecule whereas DOX^+ represents its "fully-charged" state.

Free energies of DOX^+ partitioning in pure PSM^{So} bilayer.

(kcal/mol)	Region A	Region B	Region C	Region D	Region E
$\Delta G_{wat\rightarrow mem}^{LJ}$	−12.2 (±2.3)	−4.7 (±2.4)	6.0 (±2.4)	5.7 (±2.6)	0.5 (±2.6)
$\Delta G_{wat\rightarrow mem}^{elec}$	5.7 (±2.5)	5.1 (±1.5)	1.6 (±1.8)	−4.1 (±3.0)	−8.2 (±3.4)
$\Delta G_{wat\rightarrow mem}^{total}$	−6.5 (±3.4)	0.4 (±2.8)	7.6 (±3.0)	1.6 (±4.0)	−7.7 (±4.3)

Free energies of DOX^+ partitioning in PSM^{Lo}/cholesterol (1:1) bilayer.

(kcal/mol)	Region A	Region B	Region C	Region D	Region E
$\Delta G_{wat\rightarrow mem}^{LJ}$	−6.8 (± 2.8)	−4.5 (± 2.8)	0.8 (± 3.0)	0.3 (± 3.1)	0.4 (± 3.2)
$\Delta G_{wat\rightarrow mem}^{elec}$	26.9 (± 3.6)	7.2 (± 1.2)	−7.7 (± 1.7)	−8.8 (± 2.8)	−8.0 (± 1.1)
$\Delta G_{wat\rightarrow mem}^{total}$	20.1 (± 4.6)	2.7 (± 3.0)	−6.9 (± 3.5)	−8.5 (± 4.2)	−7.6 (± 3.4)

Conclusions

- DOX^+ diffusion in the membrane is dependent on its lipid composition and phase
- DOX^+ permeation is favored in less ordered lipid phases and its location is driven by its vdW interactions with the lipids hydrophobic moieties
- DOX^+ partitioning is spontaneous over a broader hydrophilic region in PSM/cholesterol membrane

Acknowledgements

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