Biological membranes are an essential components of all cells. Their behavior is mainly determined by phospholipids, which due to their amphipathic nature, make the membranes play an important role in many biological and biochemical processes. They participate not only in the compartmentalization of cells and organelles, but also in such processes as intracellular transport or cell division. The membranes in biological systems include a wide variety of components, such as phospholipids, glycolipids, sterols, terpenoids, proteins or peptides. They might be described as a 'fluid mosaic model', where phospholipid template constitutes viscous solvent for proteins [1,2]. The nature of phospholipids building the biological bilayers allows anchoring of transmembrane proteins that can form channels, receptors, pumps and pores. Additionally, as it turns out, the membrane lipid composition affects the activity of such proteins as ATPase or calcium-potassium pump [2,3]. The properties of membranes, such as an integrity and stability are mainly determined by the non-binding interactions: dispersion - between long hydrophobic chains of phospholipids and electrostatic: between their polar heads, in which very important role is played by water molecules (Fig. 1). The biological membranes are disordered structures, where the hydrocarbon chains of the phospholipids may adopt different conformations and exhibit fast rotations of their inbuilt moieties. Due to the limitations of experimental studies (complexity of systems, the resolution - also temporary), a lot of information concerning the behavior of lipid bilayers is drawn from molecular dynamics simulations (MD), which is a method that allows to study model systems with atomic resolution. The MD methods are based on force fields that provide a set of functions and parameters describing the impact of binding and non-binding interactions in modeled systems. So far, the force field parameters have been refined based on experimental studies, Monte Carlo simulations for condensed phase or quantum-mechanical calculations. The main limitation of the MD methods, unrelated to an available computing power, are deficiencies in estimating the force field parameters used in the simulations. The problem is particularly evident for the intra and intermolecular non-binding interactions, for which the parameters are the most difficult to fit and they predominate in the case of such systems as the biological membranes.

This project is focused on improving the parameterization of the OPLS-AA (Optimized Potentials for Liquid Simulations - All Atoms) force field. The OPLS-AA is a generic force fields that is used to simulate small organic molecules, which contain a wide range of different chemical functional groups [5]. This project aims to extend the applicability of the OPLS-AA force field to the phospholipids. The project includes studies on four model molecules: triacetin, dimethyl phosphate, choline and ethanolamine containing moieties present in example in PC and PE, phospholipids constituting main components of animal cells.

The novelty of this project is connected with use of the ab initio MD which by simplified description of electronic wavefunctions allow simulations of condensed phases of model molecules, and thus inclusion of their properties in the procedure of force field OPLS-AA parameters selection. Ab initio MD methods has never been used in the fitting of the force field parameters, therefore test of theses methods will enable us to develop a new procedure of parameterization. The second aspect of innovation of this project is involvement of the triacetin, which, despite access to a wide range of experimental data, was not taken into account as a model molecule in parameterization procedures for systems containing glycerol moiety.

Parameterization of the currently used force fields is geared towards specific biological systems, for example: AMBER, CHARMM - are refined in order to reproduce interactions for protein or nucleic acid models, SlLIPIDS, CHARMM, GROMOS53a6 - are being developed for the simulation of model membranes composed of phospholipids most common in biological systems. However, it should be noted, that force fields development oriented towards reproducing the properties of specific biological systems, often is associated with significant errors in the simulations performed for slightly modified systems. The correct reproduction of the specific experimental properties of a biological membranes with a particular composition (such as the surface and the volume per lipid molecule, disorder parameters, temperatures of phase transitions) may be the consequence of overestimation of one and the underestimation of other parameters, which in turn gives an falsely correct results of classical MD simulations.

Within the project, we will focus on OPLS-AA, which together with GAFF are generic force fields, designed for general purpose [4,5]. According to the philosophy of force field parameterization, we will concentrate on reproducing of the properties of liquid phases (such as enthalpy of vaporization, Gibbs free energy of hydration, density and geometry of hydrogen bonds) for small organic molecules containing chemical groups present in phospholipids, [6], which, as we expect, will expand the applicability, and thus the versatility of the OPLS-AA force field. The studies of gas phases of model molecules (triacetin, dimethyl phosphate, ethanolamine and choline) will be performed using quantum-mechanical methods such as density functional theory methods (DFT) employing B3LYP functional, Möller-Plesset perturbation theory or coupled cluster CCSD (T) methods, the latter in calculations of the electronic energies. Condensed phases of model molecules will be simulated using two ab initio MD methods (Born-Oppenheimer and Car-Parrinello MD) [7].
Our goal is to find a compromise in the form of a set of parameters that will allow reproduction of the properties for both, the gas and condensed phases, with sufficient accuracy, and hence the correct description of intra and intermolecular non-binding interactions in modeled lipid bilayers. Within the refined parameters are mainly: partial charges, the parameters in the Lennard-Jones potential describing van der Waals interactions and coefficients in torsional potential, describing the energy profiles for rotation around chemical bonds. New parameters will be tested performing classical MD simulations for condensed phases of model molecules and bilayers consisting of PC and PE.

Due to the fact that biological membranes are difficult object for the experimental investigation, classical MD simulations of model lipid bilayers are an important source of information about the behavior of the phospholipids, their interactions with each other and with the water molecules, sterols, peptides or transmembrane proteins. Studies dedicated to lipids can not only have chemical, biochemical, biological or biophysical significance but also medical since such systems play an important role in the physiology of organisms and thus have a role in diseases such as atherosclerosis, cancers or Alzheimer [8].
However, it should be borne in mind that correct reproduction of the behavior of the phospholipids in the classical MD simulations is limited by the set of parameters used in the context of the applied force field, and therefore enhancements of the

parametrization procedures through the use of innovative computational methods is very up-to-date.

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