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MODELING THE INTERACTION OF NANOPARTICLES WITH BIOMEMBRANES: A REVIEW

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Review article

Abstract: Nowadays, with a growing number of produced nanoparticles, the question related to human and environmental safety arises. Because of their small dimensions, nanoparticles may overcome biological membranes more easily. The detailed pathway is still not understood well and, therefore, toxic potential of many nanoparticles remains unclear. Although several experimental techniques are able to capture changes in biomembranes, many effects may be effectively studied only using computational modeling. Therefore, in the first part of this article, basic experimental and simulation methods often used in the study of nanoparticle-biomembrane interaction will be shortly introduced, and, in the following part, the most recent relevant modeling studies published since 2008 will be reviewed with an emphasis on key factors playing role in nanoparticle-biomembrane interaction.

Keywords: Molecular dynamics, dissipative particle dynamics, nanoparticle-biomembrane interaction, modeling.

Introduction

Nanotechnology relates the area of production or utilization of materials with very small dimensions (at least one dimension must be smaller than 100 nm). Due to their unusual properties, nanomaterials become more and more produced nowadays and have been succesfully applied in different areas of industry: semiconductors (Pinto et al., 2003; Kočí et al., 2011), magnetic nanomaterials with high storage capacity (Carl and Wassermann, 2002), polymeric nanocomposites for food packaging (Azeredo, 2009), photocatalysts (Liao et al., 2011), optoelectronic devices (Ogawa, 2004), fluorescence probes for imaging (Rodrigues et al., 2014), very hard materials (Brazkin and Lyapin, 2014), drug delivery systems (Oberoi et al., 2013), and many others. The great number of reported applications is associated with emerging safety issues. Although nanomaterials exhibit very interesting properties, they may be also very dangerous. Because of small dimensions, nanomaterials may easier penetrate biological membranes which can lead to undesirable toxic effects. From this reason, study of interaction between nanoparticles (NPs) and biomembranes (BM) becomes the challenging task. Characterization of BM is extremely difficult, because they are dynamic systems dissolved in liquid medium. Therefore, except the experimental observations, modeling of the interaction between nanoparticles and BM has been found useful.

Modeling may be performed on various levels (atomistic, mezoscale, continuum) differing in achievable resolution, length and time scales all at once to satisfactory computational costs. When research requires information about mutual interactions of individual atoms (host-guest interactions in active areas of proteins) atomistic scale should be chosen. However, many changes of BM characteristics evolve in longer times than that available using atomistic modeling. Therefore, usage of mezoscale modeling operating on adequate length and time scales is appropriate for such problems.

At the mezoscale level, two mutually opposite approaches exist. The first one, called “top-down” approach, utilizes continuum equations with empirically derived parameters, but due to the lack of necessary experimental data, the second one, called “bottom up” approach, seems to be more suitable. The main advantage of the “bottom-up” approach is utilizing of parameters that are (or may be) derived from ab-initio calculations. In this case, the transition from atomistic to mezoscale level is very easy.

For study of more than one BM, continuum modeling utilizing hydrodynamic equations may be applied. However, as same as in the top-down approach, limitations in the form of lack of available experimental data need to be overcome prior to its wider usage in the area of modeling NP-BM interactions.

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The aim of this article is to familiarize the reader with some above mentioned modeling techniques used in the study of NP-BM interaction and to give overview of more recent modeling studies related to this interaction.

Materials and methods

Interaction of nanoparticles with biomembranes

Good starting point for the study of interactions between BM and NPs is the interaction between artificial BM called giant vesicles (GV) and NPs. GV are spherical particles with diameters about 10 - 100 μm which are visible under the light microscope and have similar size as the cells (Dimova, 2012). GV (or in the case of lipidic GV - liposomes) are usually prepared by electroformation, which means that liposomes are produced from the solution of lipids placed between two electrodes (Döbereiner, 2000). Because of limited space of this article, the readers more interested in variations of preparatory techniques are referred to (Okumura, 2013). Except liposomes, GV prepared from other amphiphilic molecules with potential applications in drug delivery were also reported (Foster et al., 2010).

Important properties of BM as well as GV are the fluidity and permeability which can be experimentally studied using fluorescence anisotropy measurement (Pottel et al., 1983), dynamic light scattering analysis (Arriaga et al., 2009), video microscopy (Genova et al., 2012; Peterlin, 2012) or differential scanning calorimetry (Chapman et al. 1974; Kapoor et al. 2011). In the presence of external stimuli (electromagnetic field, temperature, interaction with other particles, pH, etc.), these properties may change (Grebowski et al., 2013; Fujimoto et al., 1999). For our purposes most important stimulus is the interaction with other particles, especially NPs, because the resulting effect on the properties of BM (or GV) determines the toxicity of NP. Interaction between NPs and liposomes is mainly electrostatic (Bhai et al., 2012) and, therefore, zeta potential (as the indirect observation of the surface charge) is very important characteristics of GV and NPs, respectively. In the case of BM, zeta potential may be altered especially by varying the lipid composition, pH, and the external environment. Surface charge of NPs is altered by changing the functional groups attached to the NPs surface (Wu et al., 2008), or by changing the coating material (Jiang et al., 2009). The direct measurement of the enthalpy, entropy and free energy of binding between NPs and BM is enabled by isothermal titration calorimetry (Ikonen et al., 2010), while the resulting structure is studied by TEM (Mady et al., 2012) or AFM (Qiu et al., 2012). Useful tool enabling the study of both - i.e. energetical and structural characteristics - is the usage of computer simulations as showed for example in (Kagawa et al., 2013).

Modeling the interactions between nanoparticles and biomembranes

In the area of modeling BM two main simulation regimes dealing with different length scales and modes of accuracy are recognized: atomistic scale and mezoscale. Despite of including all atoms in the simulations performed on the atomistic scale, due to the size of simulated system, BM need to be modeled with the neglect of electronic properties. Two methods differing in the way of generating the statistical ensembles (needed for calculation of properties) are established for this type of problem. In molecular dynamics (MD) approach, system is evolved in time and the final statistical ensemble is obtained as the collection of states in discrete time points. For the time evolution, Newton's equations of motion are utilized. Monte Carlo (MC) technique generates the statistical ensemble in little different way as the big number of different configurations. In each MC cycle randomly generated number u ranging from 0 to 1 is compared to acceptance probability p_{accept} calculated using (Eq. 1),

$$p_{accept} = min\left\{1, \exp\left(\frac{\Delta E}{k_b T}\right)\right\} \qquad \text{Eq. 1}$$

where ΔE denotes energy difference between newly generated and the previous structure, k_b refers to Boltzmann constant and T is the temperature of simulated system. Based on the comparison, generated configuration is either accepted, or rejected. Both methods operating on the atomistic scale utilize the determination of energy. For this purpose, set of potential functions with appropriate parameters called force field is used. Many types of force fields developed over time, differ from each other in the ability of coverage the problems. Some force fields are more general (Mayo et al., 1990; Rappe et al., 1992), but less accurate, while the others are more special. In simulations of BM, on the lipids focused variants of GAFF (Wang et al., 2004), OPLS-AA (Damm et al., 1998), GROMOS (Oostenbrink, 2004), AMBER (Skjevik, 2012) and CHARMM (Klauda, 2010) force fields are often used. Inorganic NPs may not be covered by these force fields. Therefore, one has to use more general force field covering atoms in both BM and NP, or

combination of parameters from more force fields. Not only individual atoms but also the groups of atoms (functional groups, small molecules, etc.) can be described using force field. Modeling which treats groups of atoms as "beads" is called the coarse-grained dynamics (Shih, 2007; Arkhipov, 2008).

Mezoscale simulations utilize little bit different approaches. Dissipative particle dynamics (DPD) represents one type of mezoscale simulation. This method was initially developed by Hoogerbrugge and Koelman (Hoogerbrugge and Koelman, 1992) which used dissipative (F_D), random (F_R) and conservation forces (F_C) for the description of system (Eq. 2).

$$\vec{f}_i = \sum_{j \neq i}^{n} \left(\vec{F}_{ij}^{C} + \vec{F}_{ij}^{D} + \vec{F}_{ij}^{R} \right) = \frac{d^2 \vec{r}_i}{dt^2} \qquad \text{Eq. 2}$$

Due to the improvement of the method by Groot and Warren (Groot and Warren, 1997), which gave the connection between soft interaction potential a_{ij} (needed for the calculation of the conservation force) and Flory-Huggins interaction parameter χ_{ij} (describes the solubility), inputs for mezoscale simulations may be derived directly from the atomistic simulations. Interaction centers are obviously composed from more atoms grouped together into a bead as in the case of coarse-grained dynamics. Such design enables easier calculation of bigger systems, and longer time scales.

Results

Two main driven forces lead to the study of NP-membrane interactions. The first is the utilization of NPs as ideal candidates for modern drug delivery systems (Probst, 2013), while the second investigates their risks and possibilities of having toxic effects. Because the second reason is more related to the issue of environmental as well as human safety of NPs, the following section will be especially focused on the most recent topics (since the year 2008) dealing with molecular modeling of NP-BM interactions and studying their impact on BM's properties. Nowadays, one from the biggest producers of nanoparticle pollutants is the combustion. More than 40 % of the number of particles generated by vehicle engines is smaller than 50 nm (Morawska, 2008). Although the composition of nanoparticles may vary, in the first step of nanoparticle generation, carbonaceous nucleus is produced. In order to obtain its structure Atomistic Model for Particle Inception (AMPI) was developed (Violi, 2004). AMPI combines MD with kinetic MC in order to achieve longer time scales while keeping the atomistic resolution of model. The reactive force field AIREBO (Stuart et al., 2000) was used for the energy description and the results were successfully compared with available experimental data of H/C ratio identified in aromatic and aliphatic flames. Two molecular modeling studies investigated the interaction between NPs generated with AMPI and BM. Choe et al. (2008) focused on the interaction of pollutant NP with pulmonary surfactant (PS) - mixture of phospholipids and proteins prepackaged in lamellar bodies in alveolar type II pneumocytes and secreted into the alveolar lumen to reduce surface tension and prevent alveolar collapse during expiration (Chen, 2010). PS modeled as monolayer of 90 dipalmitoylphosphatidylcholine (DPPC) molecules and 2 peptides composed from first 25 amino acids of pulmonary SP-B proteins represents one type of studied system. The second system was prepared by adding pollutant NP to previously described one. Comparison of these two model systems showed that the structure as well as function of PS is altered after the addition of NP, due to repulsion between nanoparticle and peptide. This conclusion is based on the measuring of differences between tilt angles of peptides and the shift of first peak of radial distribution function between centre of mass of N-terminal tail and headgroups of lipids. Potential of mean force (PMF) computations revealed relatively strong incorporation of NP into the PS. The value of potential barrier for its translocation into water phase was higher than the energy of thermal motion. Fiedler and Violi (Fiedler and Violi, 2010) studied the influence of NP's morphology on the permeation through the model membrane composed from mixture of dimyristoylphosphatidylcholine (DMPC)/choline (in molar ratio 3/1). Based on the calculation of free energy profiles of NPs permeation through the membrane using thermodynamic integration (TI) and constraint force approach (CF), they found that three types of NPs with similar size (buckyball, opened buckyball and pollutant NP) show different behavior. Although the free energy minima are located inside the bilayer in all three cases, minimum of pollutant NP is in contrast to two others exactly in the centre of bilayer and the value of its binding energy 145 kJ/mol is nearly two times higher than that of buckyball. Measurement of angle between principal axis of NPs and bilayer norm in dependence on the location of NP along the norm showed little differences in the case of buckyball, while after the entrance into hydrophobic part of bilayer this angle decreased to near zero values in the case of both anisotropical NPs. Interaction of another NP with DMPC bilayer was studied using all-atom molecular dynamic simulations (Fengxian et al., 2013). Spontaneous adhesion of Au NPs on the BM surface as a result of the NP-DMPC

headgroup attraction was observed. However, further incorporation into hydrophobic core showed high energetic barrier in the calculated PMF profile. It was also found that inclusion of Au NPs induced local bilayer deformation and significantly slowed fluidity of the lipid molecules in its vicinity. This effect was enhanced as the size of NP increased. Observation of such NP-BM complex (NPs together with lipids) formation provided a clue for exploration of endocytosis mechanism regulating the translocation of Au NPs across the cellular membrane. Song et al. (Song et al., 2012a) performed a series of coarse-grained MD simulations to investigate the water penetration, ion transport, and lipid molecule flip-flop in a protein-free phospholipid bilayer membrane. Effects of ion concentration gradient, pressure differential across BM, NP size, and permeation velocity were examined. Whereas number of water molecules in the interior of BM during the NP permeation increased with the NP size and the pressure differential, it remains unaffected by the NP permeation velocity or the ion concentration gradient. Ion transport was found sensitive to the size of NP as well as the ion concentration gradient between two sides of BM. In the case of small NP permeation no anion/cation selectivity was observed, while larger NPs caused preferential translocation of anions through the BM. Incidence of lipid molecule flip-flop was proportional to the size of NP and ion concentration gradient and inversely proportional to the pressure differential and NP permeation velocity. Ban et al. (Ban et al., 2011) performed simulation of penetration of a hydrophobic NP into a lipid bilayer using constrained MD. Significant changes in BM shape were observed in response to the NP position. Because of timescale associated with these shape changes exceeds the timescale of the translational motion of the NP, non-adiabatic coupling between the NP transport and BM fluctuations needs to be taken into account during analysis of results. Underestimation of using PMF calculated barrier for translocation of fullerene-like NP across a lipid bilayer was found in coarse-grained MD simulation (Kopelevich, 2013). Differences relative to unconstrained MD were eliminated as the BM was restrained to a flat surface. Therefore, in coarse grained MD simulations correct sampling of PMF and the transport rates are ensured by restriction of BM. The previously discussed differences in thermodynamic and permeation values indicate on the importance of NP's morphology as well as composition for the interaction with BM. In order to investigate the toxicity of NP not only the size but also the morphology and composition must be considered.

Although the analysis of important characteristics of NP-BM interaction may be performed on the atomistic scale, some types of simulations need longer time as well as size scales and, therefore, DPD is often utilized. Li et al. (Li et al., 2012) studied the kinetics of receptors containing membrane uptake of ligand-coated NPs with similar volumes but another shapes. They recognized two stages of NP's endocytosis. First stage corresponded to NP's invagination during which the NP rotates in order to maximize its contact area with the membrane receptors while the second stage of endocytosis called wrapping is strongly coupled to energetical requirements on bending of membrane. Further investigation revealed importance of negative surface tension of BM for endocytosis of NP and that its lowering can lead to more frequent occurrence of asymmetric endocytosis. Another study which was focused on the interaction between BM and graphene NP brought similar observation of NP's rotation and consequent wrapping. Guo et al. (Guo et al., 2013) examined three pairs of graphene sheets differing in size and shape. Each pair was built from one square-like and one circle-like particle, respectively, which had the same surface area. Measurement of dihedral angle Θ between graphene surface and the plane parallel to the BM surface was used for characterization of NP's incorporation. In all studied cases shorter time needed for the incorporation was observed for circle-like NPs and, therefore, absence of edges was assumed to accelerate the kinetics. Nevertheless, the influence of particle shape on detailed pathway was found trivial, because of similarity of processes. Detailed pathway seems to be dependent on NPs size. While in the case of smallest NP (side length = 3.5 nm) simple increase and following decrease of angle Θ to near zero value was observed, for larger NP (side length = 7 nm) fluctuation of Θ from positive to negative values was recorded. Based on the comparison of lipid packing order parameters S, larger NP was proposed more toxic than the smaller one as the source of disorder in lipidic membrane. This result differing from the more common assumption of inverse relation between NPs size and toxicity (Kim et al., 2014) is undoubtedly very interesting and is linked to different pathways as well as final structure of incorporated NP. While in the case of smallest NP the product of final stage is sandwiched graphene-membrane superstructure, larger NPs are partly encapsulated. Nevertheless, for distinguishing the impact of membrane bending or sandwiched superstructure on the overall toxicity further investigation should be done. At least particular answer may provide the experimental and theoretical study of toxicity of graphene and graphene oxide nanosheets towards

Escherichia coli (Tu et al., 2013). In accordance to previously discussed investigation, transmission electron microscopy showed three rough stages of degradation of the inner and outer cell membranes and MD simulations revealed the atomistic details of the process. Because of strong dispersion interactions, graphene NPs penetrate into BM and extraction of large amounts of phospholipids lead to the destruction of BM. Another study investigated the role of NP's shape (spheres, ellipsoids, rods, discs and pushpin-like particles) and volume on physical translocation processes (Yang, 2010) lead to similar findings. While shape anisotropy and initial orientation are crucial factors for penetration capability, volume affects translocation indirectly. More precisely, contact area and the local curvature of NP at the contact point are the key features for efficiency of transport rate. Therefore, particle rotation can complicate the penetration process. In accordance with previous studies, Ding et al. (Ding et al., 2012) observed enhancement of penetration efficiency and translocation time for NPs with asymmetrical shape or surface decoration. They also found that NP's transport may be further increased by BM asymmetry. Not only the morphology or BM characteristics are involved in the NP-BM interaction and, therefore, also influence of NP composition should be more deeply explored. While Song et al. (Song et al., 2012b) studied (using comparison of bare and coated NPs) role of surface ligands in permeation through BM, Liu et al. (Liu et al., 2013) investigated penetration of nanoprobe through a lipid bilayer. In order to design optimal probe with minimum destructive potential, impact of various types of nanoprobe on bilayer destruction was observed. While clearly hydrophobic or hydrophilic probes cause the reorganization of near lipid molecules and disruption of BM, the incorporation of NP may be improved by combination of hydrophobic and hydrophilic sites on the NP. Three different alignments and various molar ratios were tested in order to find the best design. Results based on the analyses of BM structure and variations in NP's free energy showed the less negative effects for the axially, or randomly patterned NPs with the relative amount of hydrophilic sites equal to 0.5. Noteworthy the value may be slightly different for other types of NPs and seems to be dependent on the strength of hydrophobic/hydrophilic sites. Although investigation of single NP permeation may provide useful findings, it is not unreasonable to assume that synergic effect of many NPs may cause different interaction with BM. In order to study the self-assembly of pattern charged NPs with five different surface charged patterns and NP size on BM DPD simulations were performed (Li et al., 2013). Dependently on NP size, various charged patterns lead to significant differences in the self-assembled structures. Dendritic structures, clusters, linear structures and flaky structures with different connections were formed according to NP size and charge. No NP self-assembly was observed when the surface charge of NP didn't exceed a minimum effective charged area. However, assembled structures of uncharged NPs were also reported. Translocation of fullerene clusters through a model lipid membrane and the effect of NPs concentrations on membrane properties was studied by Wong-Ekkabut et al. (Wong-Ekkabut et al., 2008). NPs exhibited rapid aggregation in water and successive disaggregation in the membrane interior. Therefore, in this case the thermodynamically favored permeation into the lipid bilayer occuring on the microsecond timescale required the formation of a solid-like fullerene aggregate. Although high concentrations of NPs induced structural and elastic changes, these were not large enough to mechanically damage the membrane. Induction of changes in BM structure upon interaction with NPs was apparent also in the following study where, membrane mediated interaction between neighboring anisotropic rod-like NPs showed orientation- and wrapping-dependent behavior (Yue et al., 2013). While in the case of weak NP-BM adhesion wrapping of NPs occured at a slow rate and interaction between NPs resulted from non-homogeneous distribution of BM curvature induced by anisotropic adsorption, in the case of strong adhesion rapid wrapping rate and extensive wrapping caused different responses of upper and lower leaflets leading to enter of NPs the hydrophobic part and formation of inverted micelles surrounding NPs. As a consequence, asymmetrical wrapping induced orientation-dependent NP interaction, which showed a short-range repulsion, intermediate-range attraction and long-range repulsion for rod-like NPs.

Conclusion

Growing research interest is dedicated to interaction between NPs and BM because of prospective usage of NPs in drug delivery and due to unexplored cytotoxic effects. As shown in the first part of this article, the interaction between NP and BM may be experimentally studied using GV as a membrane's model. However, not all features are captured within such research design and, therefore, computer simulations were found useful as complementary characterization as well as design tool. Basics of mostly used modeling techniques (MD, MC, and DPD) were shortly mentioned in the second section.

The following part of this paper was focused on recently performed computational studies which showed that large scale of parameters (i.e. size of NP, shape of NP, charges, coating, surface tension of BM, concentration of NPs, composition of NP and BM, etc.) can be studied using molecular modeling. All these parameters affect the NP-BM interaction and, therefore, molecular modeling is a very efficient tool for its study. Moreover, not only pristine BM but also the additional proteins can be taken into account in models. There are many studies focused on how size and shape of NP of one type only (i.e. gold, carbon, etc.) influences the interaction with BM. However, comparative studies dealing with the same shape of NPs made from various materials has not been reported yet, although it would be of high importance. The relatively low number of articles (in order of tens) published since 2008 and reporting the usage of atomistic and bottom-up mezoscale modeling of NP-BM interaction reveals that this area of research is on the beginning. Moreover, only few published studies combine atomistic and mezoscale approach. Studies are focused either on the atomistic or mezoscale approach and the combination of both is thus an open field for further research. Therefore, in order to better understand the interaction mechanism and evaluate the potential of NP's toxicity, further simulations and experimental investigations need to be done.

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