A Review of computer simulation studies of cell membrane interaction with neutral and charged nano-objects. Quasi-zero-dimensional nanoparticles, drugs and fullerenes

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The present paper is an overview of molecular dynamics simulation studies related to the interaction of neutral and charged nano-objects with cell membranes. This research area is of great interest because of possible biomedical applications of nanoparticles and since now computer simulation techniques provide a detailed picture of structure and dynamics of membranes. An attempt is made to "systematize" the results of currently available numerical studies, combining nano-objects into six groups according to their general characteristics, for example, size, shape, fractal dimension, composition. A number of possible mechanisms of the nano-objects impact on the lipid bilayer structure and properties are revealed and discussed.

Keywords: molecular dynamics, cell membrane, lipids, nano-object, charged nanoparticle, computer simulation

1. Introduction

A typical cell membrane is a lipid bilayer, with charged or polar groups on both surfaces, and a lipophilic inner region [1]. The lipid composition of the bilayer and of the integrated membrane complexes determine the properties of the cell membrane such as flexibility, permeability, selectivity, surface electric charge. Depending on their geometry and physical properties, nano-objects and nanoparticles (NPs) can interact with cell membranes in several different ways, they can: (a) be adsorbed on the membrane surface; (b) pass through the cell membrane, e.g., by passive diffusion or by wrapping (*endocytosis*), or (c) get trapped in the bilayer interior thus imposing mechanical stresses and membrane deformation (bending, swelling) and causing changes in the membrane thickness, in the specific surface per lipid, in lipid tail orientation and in the elastic properties and mechanical state of membrane.

Charged and functionalized NPs with organic or inorganic cores are used in a number of biomedical applications [2, 3]. The interaction of charged NPs with the cell membrane may result in the formation of micelles in the bilayer, separation of vesicles, formation of pores and discontinuities in the membrane (so-called cytotoxicity). Moreover, charged NPs can strongly affect intracellular processes by changing the membrane potential [4]. Nanoparticles can be used for intracellular delivery, targeting drugs and genes toward diseased organs and cells. Functionalized magnetic nanoparticles and their clusters can target drugs toward tumors, and can be used in magnetic hyperthermia of cancer as well as be used as contrast agents for magnetic resonance imaging (MRI) [5].

Computer simulations have become an important part of mathematical modeling of many natural systems in physics, chemistry and biology, providing possibility of relatively low cost numerical experiments employing theoretical models. This makes computer simulation popular as a research tool especially in studies of nanoscale processes taking place in complex biophysical systems. In the last decade, numerous papers were published on the interaction of different nano-objects with cell membranes. The process was investigated employing methods of all-atom molecular dynamics (AA MD) and coarse-grained (CG) approach with popular computational techniques like constrained and steered molecular dynamics (SMD) [6], and

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versions of Monte Carlo method [7], which may employ the same force fields.

In the present review, nano-objects can mean: (a) nanoparticles, (b) cluster of nanoparticles, (c) nanoparticle-polymer complex with non-covalent bonds, (d) quasi-one-dimensional nano-objects (carbon nanotubes, bundles of nanotubes, asbestos nanofibers, gold nanowires), (e) two-dimensional nano-objects (graphene nanosheets, sandwich-like nanostructures, layered double hydroxides of metals, aluminum oxyhydroxide, inorganic nanofilms and substrates).

The nano-objects can be divided in six groups:

I. Small molecules and ions.

II. Drugs, peptides, proteins.

III. Pristine and functionalized fullerenes, their aggregates and derivatives.

IV. Medium size and large functionalized nanoparticles (dendrimers, polymers, nanoparticles with inorganic core).

V. One-dimensional nano-objects.

VI. Two-dimensional nano-objects.

In present review, only three (I–III) groups of nano-objects will be considered.

Several in-depth reviews related to the topic of the present review are worth mentioning. Tieleman summarized results on the modeling of transmembrane transport, considering passive diffusion and electroporation mechanism as well as functioning of membrane proteins such as transporters and channels [8]. Previously Tieleman et al. reviewed MD studies of lipid bilayer systems, including membrane-protein interaction and permeation of small molecules across the membrane [9]. Monticelli et al. published a detailed review on interactions of fullerenes, carbon nanotubes, and combustion-generated carbon nanoparticles with phospholipid bilayers [10]. Lee and Larson reviewed literature data on numerical modeling of polyamidoamine dendrimers in a solvent, near the surface of a lipid membrane and in contact with polyelectrolytes and fragments of a DNA molecule [11]. These studies were performed employing AA MD and CG MD methods, mesoscale models, and Monte Carlo and Brownian dynamics methods. Orsi and Essex reviewed numerical approaches to the estimation of membrane permeability for various compounds and to the modeling of penetration of organic molecules, drugs, and fullerenes through lipid membranes [12]. Loura and Ramalho reviewed MD studies on interactions of fluorescent compounds with lipid membranes [13]. Papers on interaction of pristine and functionalized nanoparticles with biological objects such as cell membranes, proteins, and the double helix were reviewed in [14].

2. Computer simulation

2.1. Small molecules and ions

In this group we consider small inorganic molecules, having molecular weight $M < 100$ amu, and organic compounds with number of carbon atoms $C_N < 20$, except drugs, amino acids and peptides. Numerical studies of the interaction of small molecules with cell membranes mainly deal with estimation of their penetration through the lipid bilayer (the membrane permeability). In most cases, the presence of such NPs near membranes and inside the bilayers only slightly disturbs the membrane structure, as was demonstrated by MD simulations for benzene [15, 16], pyrene [17], dimethyl sulfoxide [18], and hexane [19]. The MD calculations of a lipid membrane in a liquid crystal phase with dissolved benzene were made in [15]. It was shown that these small molecules fail to affect the membrane thickness and that the rate of translational diffusion varies with position within the bilayer and is faster in the center than near the polar head groups. The first estimates of the membrane permeability for water molecules were made in [20, 21]. Marrink and Berendsen studied the penetration of small molecules like molecular oxygen O_2, ammonia NH_3, and SPC water (Simple Point Charge water model) molecules, and also generalized neutral molecules (LJ particles, having Lennard-Jones parameters only) through a lipid bilayer [22]. Jedlovszky and Mezei estimated the profiles of free energy for molecules of water, oxygen, chloroform, and carbon and nitrogen oxides (CO, CO_2, NO) through a lipid membrane [23]. The effect of lipid chain branching [24] and of the length of the hydrocarbon chain [25, 26] on the penetration of these molecules and artificial polar diatomic molecules through the membrane was studied by MD simulations. Computer simulation of the penetration of small molecules such as ethane, methylamine, methanol, acetamide, benzene, methylacetate, and acetic acid through the lipid bilayer was performed in [27, 28]. NMR and MD simulation studies by Hoff et al. [17] showed that pyrene is located preferentially inside the bilayer near the head groups and has no tendency to diffuse from one monolayer of the membrane to another. The results from simulation and NMR studies show that the normal to the molecular plane is aligned nearly perpendicular to the bilayer normal. The long axis of pyrene lies preferentially parallel to the bilayer normal. MacCallum and Tieleman studied the energy distribution of hexane in a lipid membrane [19]. It was found that hexane molecules prefer to reside in the center of the bilayer. The same conclusion can be made regarding the preferential location of benzene in the membrane [29]. In [30] a multiscale model (CG MD for description of lipids and water and AA MD for description of penetrant molecules) was applied to estimate membrane permeability by seven organic compounds and by water molecules. It had been shown that polar penetrants (e.g. acetic acid) can induce the formation of a "water defect" in the lipid bilayer. The penetration of dimethyl sulfoxide (DMSO) molecules through the membrane was investigated in [18, 31]. Studies of the DMSO influence on the structure of phospholipid bilayers in case of a full replacement of water medium by DMSO molecules demonstrate that the P–N vectors linking phos-

phorus and nitrogen atoms in lipid head groups are reoriented, thus changing the electrostatic potential of the membrane surface with respect to the bilayer center [31, 32]. DMSO molecules, like molecules of water and disaccharides (sucrose and trehalose) [33], have no tendency to penetrate into the lipophilic core of the bilayer. The results of simulations reveal that the interaction of disaccharide molecules with the bilayer occurs at the surface of the bilayer, and it is governed by the formation of multiple hydrogen bonds to specific groups of the lipid. The addition of trehalose or sucrose does not alter the bilayer structure; the interactions between disaccharides and the bilayer occur along the surface of the model membrane, and disaccharide molecules do not penetrate the aliphatic region to any measurable extent. It is shown that DMSO can cause pore formation in the membrane [34]. Gurtovenko and Anwar showed by MD simulations that DMSO at high concentrations can damage the bilayer structure [35] and induce ion leakage through it [36]. It is also noted that the presence of DMSO molecules assists translocation (flip-flop) of phospholipids from one membrane monolayer to another [37]. Patra et al. used AA MD simulations to demonstrate that methanol and ethanol molecules penetrate into the bilayer and reside near head groups, forming hydrogen bonds with lipids; all observed effects were more pronounced for ethanol than for methanol [38]. A negligible influence on the electrostatic potential of membrane due to reorientation of the head group dipoles was also noticed. Vorobyov et al. studied the chloroform partitioning into lipid bilayers using a polarizable model of a $CHCl_3$ molecule [39]. The free energy barriers for penetration of 1,2-dimethoxyethane (DME) and 1,2-dimethoxypropane (DMP) were estimated by MD calculations in [40]. Studies of the interaction of ions with cell membranes were conducted in [41–50]. In particular, using an AA MD model, it was shown that the penetration depth of an anion into the zone of the lipid head groups is defined (at a fixed charge) by the van der Waals radius of the ion [44]. The calculations were performed in TIP3P water and the results demonstrate that the anion hydrophilicity decreases with increasing anion radius. Thus, large anions penetrate deeper into the membrane, resulting in a local increase in bilayer thickness and in dipole reorientation in the head groups. Smondyrev and Berkowitz observed a similar effect (dipole reorientation in head groups) in the case of full replacement of the aqueous medium by DMSO [32].

2.2. Drugs, proteins, peptides

The majority of nano-objects of group II are large molecules with complex topology and charge distribution, often soft and flexible, and this complicates their modelling, in particular employing molecular dynamics methods. Part of the related papers considers the effect of large charged molecules on the membrane, and part of the papers are devoted to estimation of diffusion parameters and permeability of membranes for drugs. Some of the nano-objects, which will be discussed in this section, are represented together with a curved lipid bilayer in Fig. 1. Despite the significant differences in sizes of drugs (Fig. 1, molecules *a*–*e*) and large protein subunits (e.g., Fig. 1, complex *g*), it was decided to consider them in the frames of one group.

According to simulation results [54], diffusion of nifedipine analogue does not depend on its location in the bilayer and does not reveal intermittent motion, unlike small benzene molecules [15]. Nifedipinum is a large organic molecule (Fig. 1, molecule *a*) which blocks the functioning of calcium ion channels. A significant contribution to the be-

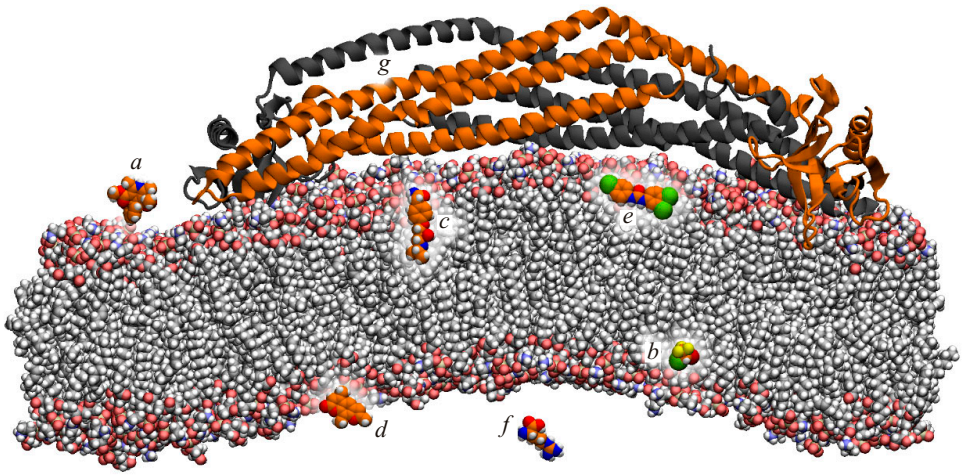

Fig. 1. Schematic illustration of the interaction between nano-objects of group II and the cell membrane: nifedipine (*a*), halothane (*b*), atenolol (*c*), trimethylpsoralen (*d*), triclocarban (*e*), arginine (*f*), and BAR-PH domain in ACAP1 (PDB: 4NSW) (*g*) [51], which controls the membrane curvature. Color code: carbon—grey, hydrogen—white, oxygen—red, nitrogen—blue, phosphorus—goldish, chlorine—green, fluorine—yellow, bromine—brown, carbon in penetrant molecules—orange for contrast. The BAR domain is represented by spirals and leaflets of the secondary protein structure; one monomer—orange, the second—dark grey. The image was constructed using Avogadro [52] and VMD software [53].

havior of drugs inside membranes is an optimization of the hydrogen bonds between a drug molecule and its surrounding, in particular lipid head groups and water [54]. It was also shown that the considered nifedipine analogue does not introduce significant perturbations into the gross properties of the lipid membrane [54].

The interaction of anesthetics (halothane) molecules with a cell membrane was considered in [55–59]. In particular, it was shown that halothane prefers to reside in the upper zone of lipid acyl chains (Fig. 1, molecule *b*). As a result the membrane expands laterally, its thickness decreases, and the P–N vectors of lipid head groups are reoriented according to the difference of electric potential in the middle of the bilayer and a point in the vicinity of the membrane surface, indicating that the behavior of the bilayer interior is not absolutely hydrophobic for such a molecule. The indoles prefer to reside within an environment containing acyl chains, lipid head groups and water molecules [60]. Norman and Nymeyer compared the behavior of the indole and small molecule of benzene in the lipid bilayer [29]. The MD results showed that indole molecules prefer to reside near the glycerol groups of lipids, whereas, entirely hydrophobic benzene has the most stable position in the hydrocarbon core of the bilayer.

The interaction of a valproic acid and its anionic conjugate base valproate with lipid membrane was studied using MD in [61]. The valproic acid molecule is an amphiphilic compound, used as an anticonvulsant drug. It had been shown that the carboxyl group of valproic acid forms hydrogen bonds with lipid head groups. The lipid–valproic acid interactions lead to a local bilayer deformation that results in the formation of finger-shaped "water defects". Such water defect allows the penetrant molecule to be partly hydrated up to depth about 0.7 nm from the bilayer center. The increasing with depth nonpolar interaction between the lipid tail groups and hydrophobic alkyl chains of valproic acid partly counterbalance the desolvation energy penalty of the amphiphilic penetrant [61]. Charged valproate experiences more significant resistance while it penetrates the bilayer. The anionic valproate permeation coefficient is several orders of magnitude smaller than that of the neutral valproic acid without taking into account possible protonation of the anion. The valproate molecule in the charged state may retain its first hydration shell even while residing in the hydrophobic core of the membrane [61].

A research on the behavior of a synthetic hydrophilic molecule, having a linear shape with a length close to the bilayer thickness and initially residing in the membrane center, showed that within 2 ns the molecule turns from membrane-parallel position to transmembrane orientation, anchoring by end groups in the hydrophilic headgroup zones [62]. The same preferred orientation state was found for molecules of three β-blockers: alprenolol, atenolol (Fig. 1, molecule *c*), and pindolol [63]. It is shown that large and small drugs molecules, despite their different sizes, after permeation into the bilayer tend to arrange their major axes parallel to the normal to the membrane plane. It is noted that an important role in absorption of drugs by the membrane belongs to the formation of hydrogen bonds between lipids and a drug molecule governed by the structure and orientation of the molecule. Bemporad et al. demonstrated that polar groups of the β-blockers (as well as of the small polar organic compounds) were preferentially oriented toward headgroup region, where they can form the H-bonds [63].

Dos Santos and Eriksson studied the spatial distribution and translocation of five psoralen derivatives (Fig. 1, molecule *d*) inside two types of the lipid membranes [64]. Psoralen and its derivatives belong to a family of photochemically active compounds—furocoumarins. Using MD simulations, the estimations of transversion free energy barriers and transverse diffusion coefficients for these compounds were obtained [64]. The results demonstrate a strong photodynamic drug accumulation in the lipid headgroup region. It is also observed that furocoumarins have a very high number of contacts between their photochemically active bonds and unsaturated carbon atoms of the lipids.

MacCallum et al. using MD estimated the free energy of partitioning of the amino acids side chains from bulk water to interfacial region and from water into the center of the bilayer [65, 66]. In particular, regions of preferential location for different groups of amino acids inside the bilayer were determined. It is found that there is a large difference between the free energy profiles for positively (Arg, Lys) and negatively (Asp, Glu) charged residues as well as for the aliphatic (Ala, Val, Leu, Ile) and polar (Asn, Gln, Ser, Thr) ones. The MD results showed that the polar and ionizable residues in a charged state are capable to form a large stable water defect in the bilayer structure, which accompanies the penetrant partitioning into the lipophilic core. In the case of polar amino acid side chain such as asparagine, the water defect is observed up to 0.4 nm from the bilayer center, being 0.3 nm deeper than in the case of valproic acid [61]. Moreover, charged arginine, initially placed at the center of undisturbed bilayer, forms stable water defect within the few nanoseconds [66]. The arginine residue is schematically represented near the membrane surface in Fig. 1, as molecule *f*. MacCallum et al. found out that the energy of penetration of several arginine residues through the bilayer is only slightly different the energy of the penetration of a single arginine molecule [67]. This can be explained by the formation of the water-filled defect in the membrane behind the first arginine. The presence of the hydrated pore facilitates penetration of next residues, lowering free energy barrier of transfer from bulk water into the bilayer interior [67].

The two-scale MD approach used earlier [30] was applied to simulate the interaction of a cell membrane with antimicrobial agents: triclocarban (TCC) and triclosan (TCS) [68]. The translocation free energy profiles were estimated for both agents. It was found that molecules pre-

fer to reside at the interface between the polar and the apolar lipid and prefer to be oriented parallel to the membrane plane (Fig. 1, molecule *e*). At high concentrations of the antimicrobials (33 mol %) the significant decrease was observed in the magnitude of the lateral pressure in the lipid headgroup region. This is a consequence of the fact that TCC and TCS behave as surfactants, lowering the surface tension at the polar–apolar interface. It was also noted that increasing concentrations of antimicrobials in the bilayer (especially TCS) facilitates the potential destabilization of the bilayer toward a non-bilayer inverse (having negative curvature) phase. This means that the drugs can cause spontaneous bilayer curvature and even produce single-layer structures. Orsi et al. found that TCC leads to decrease of the electrostatic potential difference between the bilayer center and the water from ~0.5 V to 0.1 V [68].

The penetration of boronic acid derivatives (benzothiophene-2-boronic acid, BZB), which are inhibitors for β-lactamase-enzyme produced by bacteria to counteract antibiotics, was studied in [69]. It was shown that the BZB derivatives while penetrating through the membrane can be accompanied by a monomolecular channel of several water molecules which form bonds with the polar groups of BZB.

Cramariuc et al. studied the mechanism of a ciprofloxacin (CPFX) translocation across a lipid membrane [70]. The ciprofloxacin is a representative of fluoroquinolone antibiotics, in which molecules coexist in neutral and zwitterionic forms at physiological pH conditions. The mechanism of CPFX transfer was proposed according to which the zwitterionic ciprofloxacin molecules approach the membrane in stacks, then due to intramolecular proton transfer between adjacent zwitterions, CPFX penetrates the lipid bilayer in the neutral form of molecule. According to the MD results, the zwitterionic CPFX, residing near the bilayer center, can form two deep water defects on the both sides of the membrane simultaneously [70].

The interactions of α-helical transmembrane peptides with the bilayer were investigated in [71–73]. In particular, Saiz et al. [71] determined possible effects of a homopentameric bundle of α-helical M2 segments of the nAChR glycoprotein on the membrane lipid bilayer properties such as: (i) local increase of a bilayer thickness from 3.5 nm to 3.8 nm; (ii) increase of the orientational order parameter for all carbons of lipid acyl chains; (iii) decrease of the angle between the bilayer normal and P-N vectors of the lipid head groups, resulting in increase of positive surface charge of membrane. The free energy of transmembrane WALP23 dimer association in three types of lipid membranes was estimated in [73]. Estimations were made to assess the influence of WALP23 in single and parallel dimer configuration on the bilayer structure. It is shown that the membrane partial density is perturbed up to a distance of 1 nm from a single immersed WALP23 peptide; the order parameter of lipid acyl chains is perturbed up to ~2 nm and the membrane thickness perturbation extends to about 2.5 nm. It is noted that the lipid ordering is the most sensitive parameter to the presence of the transmembrane protein subunits [73].

It is worthy to mention the family of BAR domains. These domains represent comparatively large dimeric complexes which participate in various cellular processes involving rearrangement and geometrical change of the membrane (Fig. 1, dimer *g*). A vivid example of such processes is a cell division. The interaction of BAR domains with lipid membranes and the mechanism of membrane binding and bending were investigated by simulation in numerous studies [74–82]. Arkhipov et al. conducted a series of numerical experiments on the interaction of BAR domains with the membrane [74]. Levtsova et al. studied the I-BAR interaction with neutral and negatively charged membranes [80]. It is shown that the BAR domain, due to the presence of positively charged groups on the surface, interacts with anionic lipids and causes membrane bending with clustering of anionic lipids on the membrane surface at the points of its contact with protein. Freddolino et al. developed four models using approaches with different degrees of refinement: AA MD, residue-based CG MD (RBCG), shape-based CG MD (SBCG) [83], and description of the membrane by a continuum medium. Calculations were performed for a single domain and for six domains with estimation of membrane curvature parameters.

2.3. Pristine and functionalized fullerenes, their derivatives and aggregates

Pristine fullerenes are hydrophobic molecules, and hence they are aggregated in an aqueous solution, forming nano- and microclusters stabilized by hydrophobic interactions and van der Waals forces. The term functionalized means that nanoparticles possess polar or charged (hydrophilic) groups (ligands). The functionalized groups can be linked to molecules by covalent or non-covalent bonds.

The interaction of pristine fullerene C_{60} and its derivative hydroxide $C_{60}(OH)_{20}$ with a cell membrane was studied using a MD model in [84]. It was shown that pristine fullerene easily penetrates into the bilayer, while fullerene hydroxide prefers to interact with lipid head groups without penetration into the membrane. Li et al. demonstrated that fullerenes C_{60} prefer to reside inside the bilayer at a distance of 0.6–0.7 nm from its center and that the formation of the aggregate of C_{60} pair in the bilayer is energetically unfavorable [85]. Molecules of C_{60} inside the bilayer are shown schematically in Fig. 2, molecules *a*. Bedrov et al. studied the penetration of pristine fullerene C_{60} through the bilayer [86]. It was found that the lipid membrane permeability for C_{60} is higher than the permeability for many other compounds. This fact can be explained by a non-classical hydrophobic effect with a considerable energy contribution by dispersion forces (van der Waals) of close-packed atoms on the fullerene surface [86].

The penetration of a C_{60} cluster through a lipid membrane and the effect of high fullerene concentrations inside bilayer on the membrane properties were studied in [87]. It

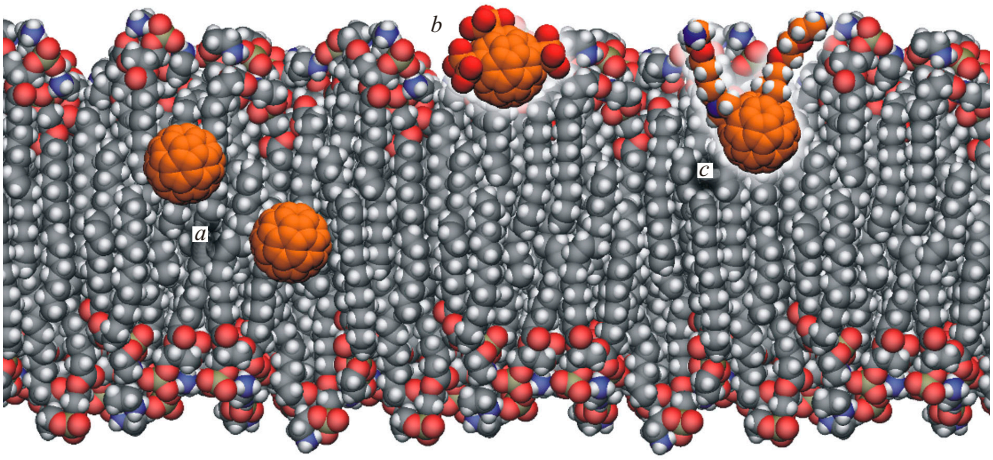

Fig. 2. Schematic illustration of pristine fullerenes C_{60} and functionalized tris-malonyl-C_{60} and C_{60}-(amino-derivative)$_2$ inside and on the surface of a cell membrane. The color code is the same as in Fig. 1. The image was constructed using Avogadro and VMD software.

is shown that fullerene aggregates penetrate into the membrane and are accumulated there; the penetrated clusters decompose into separate fullerene molecules inside the bilayer due to the lipophilic surrounding of the membrane core. It is noted that high fullerene concentrations inside the membrane changes the membrane structure and elastic properties**,** but this effect is not so high to cause mechanical damage of the membrane [87]. Using a MD model, it was demonstrated that functionalized fullerenes $C_{60}(OH)_N$ can penetrate into the bilayer if $N < 10$, otherwise the fullerene hydroxide prefers the water surrounding [88]. Chang and Lee studied the interaction of a cluster of pristine fullerenes C_{60} with the cell membrane using all-atom MD [89]. It was found that the dynamics of C_{60} inside the bilayer is more intensive than in the water surrounding and that increasing the fullerene concentration in the membrane leads to increase the membrane thickness, and as a result fullerenes C_{60} inside the bilayer have more freedom.

Kraszewski et al. studied the influence of fullerenes C_{60} on a cell membrane and three types of potassium channels: KcsA, MthK, and Kv1.2 [90]. It was found that fullerene tends to occupy a position near external hydrophobic loops of KcsA which links S6 segments with P helices. In the case of a more complex Kv1.2 channel, fullerenes also tend to bind the external loops, which link the S1-S2 helices, S3-S4 and S5-S6. In some cases binding of C_{60} with top of S3-S4 causes significant conformational movements in the voltage sensor domain. It was also shown that C_{60} can be tied to the entry of the cavities of MthK and Kv1.2 channels *via* intracellular regions, resulting in considerable conformational changes in M2, S6 helices and in narrowing of possible paths for ion transport through the channel. Kraszewski et al. studied also the interaction of the membrane with fullerenes functionalized by short amino derivatives [91]. It was shown that a single amino derivative (without C_{60}) fails to penetrate into the bilayer. Functionalized fullerene C_{60} penetrates into the bilayer but is anchored by the ends of its amino derivative to the hydrophilic headgroup zone of the membrane. This case is schematically shown in Fig. 2, molecule *c*. Fullerene can continue its penetration into the bilayer only after deprotonation of all functional groups. A similar result was obtained for short single-walled carbon nanotubes [92].

A MD study of the absorption of fullerenes C_{60}, C_{180}, and C_{540} by the membrane reveals that the bilayer structure is disturbed depending on the fullerene concentration [93]. It was shown that for all cases considered, the penetration of fullerenes into the bilayer is thermodynamically favorable. A strong correlation was found between the position of C_{540} clusters in the *xy*-plane and membrane curvature. Simulations of the membrane and potassium channel Kv1.2 in the presence of gallic acid (GA), fullerenes C_{70}, and both GA and C_{70} were performed in [94]. On the time microscale, the presence of C_{70} in the membrane little affects the protein conformation. Some effects are observed for S3 and S4 helices which are the part of the voltage sensor domain. It was pointed out that both direct contact of fullerene with protein and indirect influence *via* changes in physical properties of the membrane can affect the equilibrium conformation of the ion channels [94]. The fullerene C_{60} self-organization and its effect on the cell membrane with detailed characterization of different fullerene assemblies into a nanocluster were considered in [95]. It was revealed that fullerene clusters while penetrating produce considerable local disturbances in the membrane structure. In particular, cluster of C_{60} can form a nanopore in the lipid head group region and cause local deformation of the lipid bilayer.

A CG MD simulation was performed to study the influence of the size of pristine fullerenes (C_{20}, C_{60}, C_{180}) and their concentrations on the membrane [96]. In particular, it

is shown that the presence of C_{60}, C_{180} in the membrane increases mechanical strength of the bilayer and that the increase of fullerene concentration leads to the increase of the critical rupture tension of the membrane. For C_{20} and smaller molecules, the effect is reverse: the membrane strength decreases. It is also demonstrated that the effect depends on the surface density of atoms in a fullerene molecule and on the length of lipid tail groups. The interior of a lipid membrane as a hydrophobic solvent for carbon nanoparticles was considered in [97]. It is shown that the solvent density and perturbed interaction of solvent molecules play a decisive role in dissolution of fullerene aggregates inside the bilayer.

Bozdaganyan et al. studied the interaction of fullerene C_{60}, cluster of pristine C_{60}, and two isomers tris-malonyl-C_{60} with a lipid membrane [98]. Pristine fullerene and cluster of ten C_{60} molecules penetrate into the membrane and accumulate at a distance of 0.7–0.8 nm from the bilayer center. The significant deformation and bending of the membrane were observed, in contrast with the case of amphiphilic C_{60} derivatives C_3-tris-malonic-fullerene and D_3-tris-malonyl-fullerene, which fail to penetrate inside the bilayer but can be adsorbed by the bilayer surface. The tris-malonic derivatives accumulated on the extracellular side of the cell membrane surface (Fig. 2, *b*) can trap *inimical* reactive oxygen species and provide cell protection.

It is also worthy to mention several papers devoted to simulation of the interaction between lipid membranes and arbitrarily shaped hydrophobic carbon nanoparticles, including combustion-generated ones [99, 100]. Such NPs can resemble fullerene or graphene fragments in structure and behave similarly interacting with membranes.

3. Conclusions

The most characteristic features in the behavior of charged nano-objects of group I are their interaction with the hydrophilic lipid head groups, adsorption on the membrane surface, the avoidance of the internal lipophilic zone of the bilayer, and the absence of any noticeable damage of the membrane structure. Penetration of a polar molecules into the membrane may cause the formation of a short-lived channel and a small several molecules long water tail behind the penetrant [30]. At high concentrations, molecules like DMSO can cause pore formation in the membrane [34, 35]. It should be emphasized that the observed perturbations of the lipid bilayer electrostatic potential in MD models at high concentrations of polar molecules and ions [32, 44, 45, 48] can be essential for the functioning of membrane proteins sensitive to membrane polarization. The same effect can be produced by a chemically induced ion flow through the bilayer in the presence of DMSO [36]. As for neutral molecules of group I, they can easily penetrate into the lipophilic zone of the membrane and remain there due to hydrophobic interactions, not damaging the lipid bilayer structure. Thus, for hydrophobic molecules, the bilayer interior acts more like a trap rather than a barrier [22]. Hydrophilic molecules possess high resistance to penetration into the lipophilic membrane core, suggesting that the membrane behaves like a filter providing selectivity of the membrane to penetrating species [22].

In most of the cases considered, NPs of group II exert an appreciable effect on the biomembranes. Polar and amphiphilic drug molecules, as a rule, interact with lipid head groups and are accumulated either at the interface of water and head groups or at the interface of polar/apolar lipid groups [56, 58, 60, 64, 68]. These processes, according to [68], may influence the elastic stress of the bilayer and result in bending and then delamination of the bilayer. Membrane thickness may be affected as well [56, 71, 73]. The curvature of the bilayer may be controlled also by the bonds formation between a nano-object and membrane surface, as is the case with BAR proteins [76, 80]. Another finding is the influence on the dipole electrostatic potential of the membrane, which may be crucial for a membrane proteins functioning [56, 59, 68, 71]. Highly polar, zwitterionic or charged nanoparticles of group II, when penetrating in charged state, can be hydrated even in the lipophilic core of bilayer and/or form water channel of few water molecules behind or stable deep “water defect” in the membrane [61, 66, 67, 69, 70].

Neutral representatives of the group III as the pristine fullerenes and their clusters, like hydrophobic NPs of groups I and II, can penetrate into the cell membrane, accumulating in the hydrophobic core of the bilayer [84, 87, 88]. At high concentrations, large-size fullerenes can significantly disturb the membrane structure [93, 95, 98]. The presence of fullerenes $C_{60–180}$ in bilayer with lipid-to-fullerene ratio about 1/1 may increase a mechanical strength of the membrane [96]. Pristine fullerenes may exert influence on ion channels, e.g., block them, when being tied to the entry of a potassium channel *via* intracellular regions [90, 94]. Functionalized fullerenes tend to bind their charged groups with a hydrophilic part of lipids [84, 88] and can be attached to regions near the lipid–water interface or near the interface between lipid head and tail groups, depending on the properties and topology of the ligands [91, 98].

Cell membrane interactions with three groups of nano-objects were analyzed in present review employing molecular dynamics methods. Interaction of cell membranes with large globular nano-particles, quasi-one-dimensional and two-dimensional nano-objects will be reported separately.

Three-dimensional models of lipid membranes (POPC and POPE/POPG) used for illustrations were prepared with LAMMPS package (Sandia National Laboratory) [101, 102] (see also http://lammps.sandia.gov/index.html) and VMD software [53] (see also http://www.ks.uiuc.edu/Research/vmd). Short-time calculations were performed using CHARMM 27 force field [103] and resources of Chebyshev cluster of the Supercomputing Center of Lomonosov Moscow State University (http://www.srcc.msu.su/nivc/index_engl.htm) [104].

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