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REVIEW

# Nanomaterials in biological environment: a review of computer modelling studies

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**Abstract** Nanotechnology is set to impact a vast range of fields, including computer science, materials technology, engineering/manufacturing and medicine. As nanotechnology grows so does exposure to nanostructured materials, thus investigation of the effects of nanomaterials on biological systems is paramount. Computational techniques can allow investigation of these systems at the nanoscale, providing insight into otherwise unexaminable properties, related to both the intentional and unintentional effects of nanomaterials. Herein, we review the current literature involving computational modelling of nanoparticles and biological systems. This literature has highlighted the common modes in which nanostructured materials interact with biological molecules such as membranes, peptides/proteins and DNA. Hydrophobic interactions are the most favoured, with $\pi$-stacking of the aromatic side-chains common when binding to a carbonaceous nanoparticle or surface. van der Waals forces are found to dominate in the insertion process of DNA molecules into carbon nanotubes. Generally, nanoparticles have been observed to disrupt the tertiary structure of proteins due to the curvature and atomic arrangement of the particle surface. Many hydrophobic nanoparticles are found to be able to transverse a lipid membrane, with some nanoparticles even causing mechanical damage to the membrane, thus potentially leading to cytotoxic effects. Current computational techniques have revealed how some nanoparticles interact with biological systems. However, further research is required to determine both useful applications and possible cytotoxic effects that nanoparticles may have on DNA, protein and membrane structure and function within biosystems.

**Keywords** Nanomaterials · Nanoparticles · Nanotoxicology · Molecular simulation · Peptide-decorated nanoparticles · Biological membranes · Proteins · DNA · Water

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## Introduction

Nanotechnology is a fast-growing field set to impact numerous areas of development in science and technology, specifically with applications in materials science, medicine, bioimaging, sensing and electronics (Gu et al. 2007; Gunasekera et al. 2009; Houili et al. 2010; McBain et al. 2008). Some of the more specific applications of nanotechnology in medicine include the use of nanoparticles for drug delivery (McBain et al. 2008; Yang et al. 2007), biological labels (Alivisatos et al. 2005) and imaging (Gunasekera et al. 2009).

While the most immediate near-term benefits expected from the use of nanotechnology arise from the novel properties of nanomaterials due to their unique volume-to-surface ratios, and the ability to prepare and control their properties with greater precision and complexity, there is apprehension that nanoparticles used for medical applications may in fact induce cytotoxic effects, as has already been shown in eukaryotic and prokaryotic cells (Brunner et al. 2006; Deng et al. 2009; Feris et al. 2010; Hanley et al. 2008; Reddy et al. 2007). Moreover, engineered nanoparticles, which are expected to be used increasingly in industry and the manufacture of household goods, can also interact with biological molecules and have potential to damage cells in vivo (Fischer and Chan 2007).

Modification of nanoparticles through functionalisation can allow a greater degree of control to target specific interactions, which enables their use in a broader range of applications, from environmental (Theron et al. 2008), industrial (Barth et al. 2005) to biomedical uses (Salata 2004).

Generally, nanoparticles can be considered to exist in one of three broad categories (Burcham 2010): organic, inorganic and hybrid particles (Fig. 1). Organic particles are those created by simple monomeric building blocks, such as polymer-based nanoparticles. The second and perhaps most well-represented group is that of inorganic nanomaterials, which includes carbon nanotubes, fullerene particles, metallic nanoparticles, including gold and silver nanoparticles, and many metal oxide species. Hybrid nanoparticles are the third group of engineered nanoparticles, consisting of a combination of organic and inorganic nanomaterials, such as peptide- and DNA-functionalised gold nanoparticles (Lin et al. 2009) and DNA–carbon nanotube arrays. This group also includes nanoparticles intended for use as drug delivery vehicles [illustrated in Fig. 2 for membrane-active peptides such as antimicrobial peptides; see Zhang et al. (2010) and references therein].

Nanomaterials are of the same size scale as typical cellular components (Fig. 3) and thus offer an entirely unique point from which to view and manipulate fundamental biological pathways and processes. At the same time, this size commensurability enables interatomic interactions between nanoparticles and biological molecules, therefore there is significant potential to interfere with biological function.

Currently, the relationship between size, shape and surface chemistry of nanostructures and their correlation with

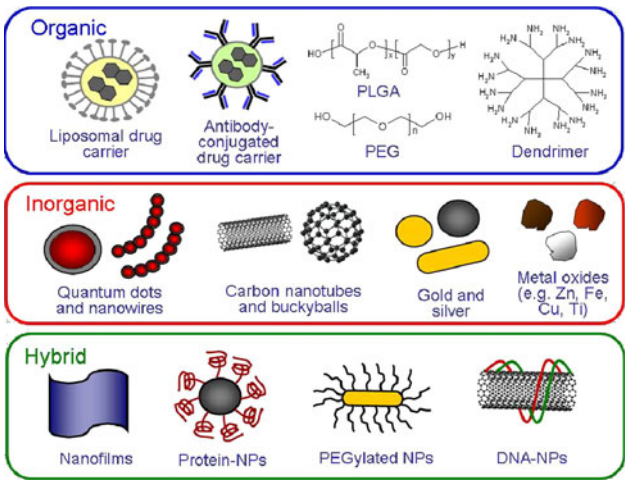


**Fig. 1** Most engineered nanomaterials in current use belong to three broad classes. *PLGA* Poly-lactic-co-glycolicacid, *PEG* polyethylene glycol, *NP* nanoparticle. Reprinted with permission from P. Burcham 2010 (Burcham 2010)

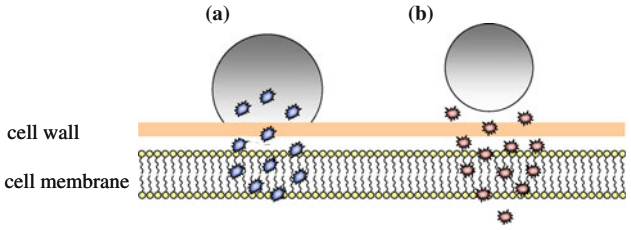


**Fig. 2** Nanoparticles used as carriers of membrane-active peptides in drug delivery: **a** Carried antimicrobial drugs are released across a cell membrane after nanoparticles fuse with the cell wall; **b** Drug molecules can diffuse into the interior of the microorganisms by crossing the cell membrane once the nanoparticles bind to the cell wall

intracellular and in vivo bio-distribution remains ambiguous (Fischer and Chan 2007), as does our understanding of the interactions between nanomaterials and biological matter (Klein 2007). At the same time, it has been demonstrated that nanoparticles could cross the lung, blood and brain barrier, and enter the cardiovascular circulation, thereby reaching many organs (Barlow et al. 2005; Lewinski et al. 2008). Various studies have shown that airborne combustion-generated carbon nanoparticles (<100 nm) are associated with increased pulmonary and cardiovascular mortality (Mills et al. 2005), alerting to potential harm from both intentional (medicinal) and unintentional exposure to carbon nanotubes, fullerenes and their derivatives (Geiser et al. 2005). Remarkably, they fall into a fibrous fine "respirable" dust category, as do asbestos fibres.

It is believed that cytotoxic nanoparticle effects emerge in a dose- and time-dependent manner for carbon-, metal- and semiconductor-based nanoparticles (Lewinski et al. 2008), and oxidative stress is the best developed paradigm to explain the toxic effects of inhaled nanoparticles (Nel et al. 2006). It was also shown that nanoparticles can nucleate protein fibrillation (Linse et al. 2007) and possibly contribute to the development of protein unfolding diseases such as Alzheimer's, Creutzfeld-Jacob disease and dialysis-related amyloidosis (Linse et al. 2007).

In summary, the mechanisms of the interatomic interactions between nanoparticles and biological molecules are not sufficiently understood. While little is known about possible effects of nanoparticles on molecular structure and function of biological molecules, specifically proteins, DNA and biological membranes, numerous nanomaterials are enjoying rapid growth in a number of applications, from industrial to medicinal.

It has become apparent that health and safety aspects associated with the spread of nanomaterials need serious scientific scrutiny so that possible cytotoxic effects can be identified and prevented. Physicochemical mechanisms that nanoparticles undergo to affect biological molecules and complex systems are currently under investigation by

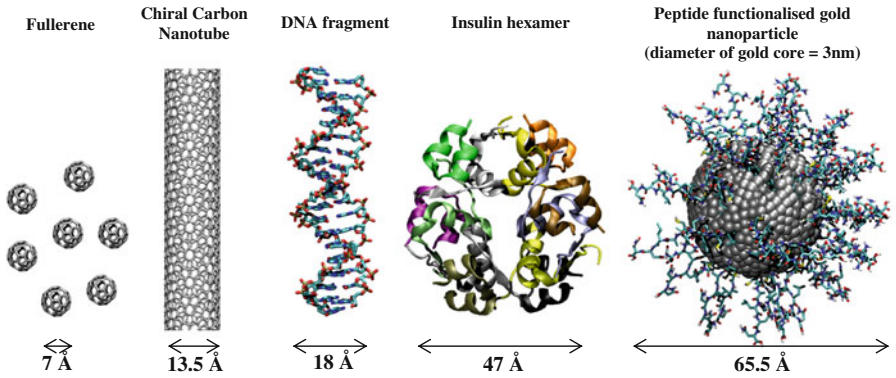


**Fig. 3** Size comparison of some common nanoparticles and biological molecules

experimental and theoretical methods. However, current experimental techniques have limitations (Chang et al. 2008) for the study of nanoparticle interactions with biological environments at the nanoscale. At the same time, the spatial and temporal resolutions that computational techniques currently allow (Dror et al. 2010) enable the investigation of specific interactions and dynamics that nanoparticles induce in biological molecules. This has led to increasing use of computational methods to elucidate the fundamental aspects of inter-molecular interactions within nanoparticle–biomaterial systems.

Current computational techniques include electronic structure methods (Leach 2001; Roman et al. 2006), all-atom Monte Carlo (Carlsson et al. 2004) and molecular dynamics methods (Pei et al. 2008) and coarse-grained methods (Hwang et al. 2009), which have all been used to gain better understanding of the interactions and dynamics of nanoparticles within biological systems.

First-principles electronic structure methods based on density functional theory compute the total energy of molecules as a function of electron density (Leach 2001). These methods can be used to accurately calculate electronic and chemical properties including binding energies and chemical reaction barriers. However, these techniques are very computationally demanding, and their applications are, therefore, limited by the system size (up to a few hundred atoms) and simulation time scales of the order of several picoseconds (for ab initio molecular dynamics simulations).

The most widely applied computational techniques are the classical methods, which enable exploration of the structural evolution and structure–activity relationships in biological systems with atomistic resolution. The all-atom molecular dynamics simulation method is based on Newton's laws of motion: by solving the differential equations embodied in Newton's second law it is possible to obtain a trajectory that describes the atomic positions as they progress over time. All-atom simulations rely on the fundamental forces that govern atomic motion, which are derived from many-body interatomic interaction potentials and are usually mathematically defined and empirically parameterised in the form of a forcefield. These forcefields describe bond stretching, bending and rotation as well as the non-bonded interactions, including electrostatic and van der Waals interactions (Leach 2001). The choice of a forcefield for each simulated system is important, as forcefields are developed with a specific environment/application in mind and ultimately determine the quality of the results (Todorova et al. 2008). Using the classical molecular dynamics method it is currently feasible to investigate systems in solution with explicit representation of up to millions of atoms (Bjelkmar et al. 2009; Dror et al. 2009) over nanoseconds–microseconds time scales. An advantage of this method is the ability to determine the structure and dynamics of complex systems with atomic detail. However, many biological processes occur over longer periods of time and/or require modelling of larger systems, thus more simplistic techniques, such as the coarse-grained methods need to be applied.

Coarse-grained methods are receiving significant focus at the moment due to their ability to simulate large molecular complexes, such as protein–membrane systems (Shi et al. 2008; Wallace and Sansom 2008; Wong-Ekkabut et al. 2008). In these models a small group of atoms is treated as a single interaction unit, where the interaction is governed by a simplistic forcefield (Marrink et al. 2004, 2007), and then molecular dynamics is applied as in all-atom methods. As a result, larger systems and longer simulation times are possible, however at the expense of losing atomic-level resolution.

Recently there has been an increasing number of computational studies investigating the structure and dynamics of nanoparticles and their interactions with aqueous media (Chiu et al. 2009b; Kuna et al. 2009) and biomolecules, including nucleotides and nucleic acids (Gao et al. 2003; Johnson et al. 2008; Lu et al. 2005; Zhao et al. 2005), peptides and proteins (Chiu et al. 2008, 2009a; Kyani and Goliaei 2009; Noon et al. 2002) and cell membranes (Bedrov et al. 2008; Li et al. 2007; Qiao et al. 2007; Wong-Ekkabut et al. 2008). However, computer simulations in

this field are still at an early stage. Herein, we present a review of recent computational studies investigating effects of nanostructured materials on biological environment and discuss their successes and limitations.

## Effects of nanomaterials on the structure and dynamics of water

First, it is fundamental to understand how nanostructured materials interact with water molecules, since biosystems function in a solvent environment, thus the interactions they have with the solvent, water, are crucial to how they behave. Therefore, the way in which nanoparticles change the structure of the solvent can determine how they affect the surrounding biological molecules.

It was shown using coarse-grained molecular dynamics that the size and thus curvature is crucial in determining the hydrophobic or hydrophilic character of the nanoparticle. This has implications for self-assembly and aggregation of hydrated nanoparticles and colloidal particles (Chiu et al. 2009b). Water-mediated interactions between carbon nanoparticles have shown a similar dependency on the surface curvature of the nanoparticle. A molecular dynamics study by Li et al. (2006) demonstrated that there was a high surface–water dispersion interaction due to the high density of surface atoms. Another work investigating water molecules surrounding gold nanoparticles using molecular dynamics (MD) techniques found the formation of two hydration shells, where the first shell arranged regularly on small nanoparticles (0.8–1.3 nm diameter) and irregularly on larger nanoparticles (>1.3 nm diameter). It was also shown that, on 0.8 nm gold nanoparticles, the first hydration shell arranged in a bulk-like water structure (Chang et al. 2008). Comparably, water was found to form two hydration shells around fullerene (C60) nanoparticles, indicating that the fullerene behaves as a large hydrophobic solute (Weiss et al. 2008). These studies offer a possible explanation for the hydrophobic nature of many nanoparticles where the curvature of the particle plays a crucial role in the degree of hydrophobicity.

A recent MD study revealed that, when a surface has domains similar in size to solvent molecules, the interfacial energy shows non-monotonic trends. Kuna et al. (2009) demonstrated that the solvent behaviour at the interface is controlled by the nanostructured surface (Fig. 4), leading to possible implications for biological processes.

Furthermore, Yiapanis et al. (2007) proposed a methodology to quantify the effects of surface geometry (including atomic roughness) and chemical structure (including hydrophobic/hydrophilic patterns) on interfacial interaction energy in all-atom models.

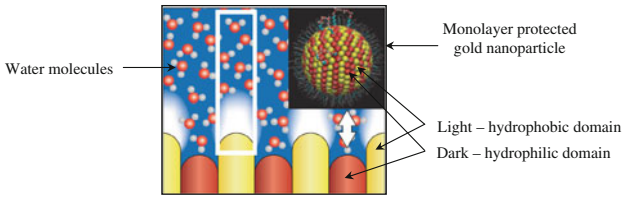


**Fig. 4** Schematic of self-assembled monolayers comprising hydrophobic and hydrophilic domains in contact with idealised water molecules. Reprinted (in part) with permission from Macmillan Publishers Ltd. [Nature Materials] (Kuna et al. 2009), copyright (2009)

## Effects of nanostructured materials on biological membranes

Detailed understanding of the effects of nanoparticles on biological membranes is crucial for the advancement of nanoparticles as drug delivery systems and reduction of possible cytotoxic effects (Verma and Stellacci 2010). Many theoretical studies have been conducted on the interactions of cell membranes and several types of nanoparticles including fullerenes (Bedrov et al. 2008; Li et al. 2007; Qiao et al. 2007; Smith and Bedrov 2007; Wong-Ekkabut et al. 2008), carbon nanotubes (Shi et al. 2008; Wallace and Sansom 2008) and gold nanoparticles (Ghorai and Glotzer 2007). Functionalised nanoparticles have been used to select only particular cellular membranes so that only specific cells are labelled, as well as to improve the uptake of the labelling nanoparticle (Mailander and Landfester 2009). These functionalised nanoparticles have utilised DNA (Zhao et al. 2009) and peptides (Aubin-Tam et al. 2009; Peetla et al. 2009) as receptors for particular cells and in some cases to assist with uptake of encapsulated drugs (Peetla et al. 2009).

Carbon-based nanoparticles, such as buckyballs and nanotubes, have shown great potential for application in biomedicine due to their potential ability to permeate a lipid bilayer (Yang et al. 2007). An excellent recent review has been published on the use of both classical molecular dynamics and coarse-grained techniques for carbon nanoparticle–membrane systems (Monticelli et al. 2009). It covers simulations of C60 fullerene nanoparticles and carbon nanotubes translocating across lipid bilayers. It was found that translocation of fullerene particles into a membrane is energetically favourable (Bedrov et al. 2008; Wong-Ekkabut et al. 2008) and that these particles tend to sit off the bilayer centre (Li et al. 2007). Functionalised derivatives of C60 were shown to prohibit translocation of the nanoparticle across the membrane layer, suggesting a method to control transport across a bilayer (D'Rozario et al. 2009; Qiao et al. 2007), while incorporation of charged nanoparticles resulted in membrane breakage (Ginzburg and Balijepailli 2007) due to the formation of

micelle structures. Simulation studies have identified that carbon nanotubes enter a cell membrane either by wrapping into the membrane or by directly piercing through the membrane. A critical nanotube radius exists for the transition between the two modes of entry (Shi et al. 2008). Furthermore, lipids in the bilayer can block the nanotube upon piercing the membrane (Wallace and Sansom 2008). It was suggested that the cylindrical micelle of lipids surrounding the carbon nanotube may be used to solubilise carbon nanotubes (Wallace and Sansom 2009). Surfactant adsorption onto a carbon nanotube was found to be dependent on detergent concentration, while at low concentrations the chirality of the carbon nanotube influenced the wrapping angle and at higher concentrations the detergent molecule rotated away from the nanotube (Wallace and Sansom 2007). Molecular dynamics simulations were also applied to demonstrate that structure and packing of the lipids and peptides in pulmonary surfactant film can be affected by $C_{188}H_{53}$ nanoparticles (Choe et al. 2008).

In addition, recent publications include simulation studies of charged nanoparticles with membrane systems aiming to understand how electrostatics can affect the adsorption and translocation of nanoparticles across a membrane. Using coarse-grained simulations of hydrophobic and semihydrophilic nanoparticles in the presence of a cell membrane, Li et al. found that a hydrophobic nanoparticle can result in inclusion into the bilayer, whereas a semihydrophilic nanoparticle only adsorbs onto the membrane. These results indicated that the surface hydrophobicity can result in different response mechanisms in nanoparticle–biomembrane interactions (Li et al. 2008). Studies of charged nanoparticles on electro-neutral phospholipid bilayers using coarse-grained MD revealed that electrostatic attraction improves the adhesion of a charged nanoparticle to the membrane, where the increase of electrostatic energy resulted in almost full wrapping of the charged nanoparticle by the membrane (Li and Gu 2010). Furthermore, a study by Sachs and Woolf (2003) found that large chaotropic anions penetrate deeply into the interfacial region of lipid bilayers. Using molecular dynamics simulations, they showed that anion size alone can lead to such behaviour, where larger anions are more hydrophobic and hence prefer the bilayer interior, thus accounting for the penetration into the membrane layer. Membrane swelling was also found to occur in the presence of uncharged or hydrophobically modified nanoparticles. Another Monte Carlo investigation of the domain size of monolayers and the diffusion of nanoparticles demonstrated that dipole–dipole interactions could be fundamental in the control of membrane transport (Rueckerl et al. 2008).

Using dissipative particle dynamics (DPD), Yang and Ma found that shape anisotropy and initial orientation of a nanoparticle can play a complicated role in the physical translocation of the particle across a lipid membrane (Yang and Ma 2010). DPD is a coarse-grained technique that groups atoms into beads, which are then subject to conservative, dissipative and random forces as well as obeying Newton's equations of motion. This study highlighted that the volume of nanoparticles had little direct influence on translocation, which suggested that altering the geometry of particles could result in new applications of nanoparticles interacting with membranes (Yang and Ma 2010).

Janus nanoparticles consisting of hydrophobic and hydrophilic portions have been used to form a stable pore in a membrane system using DPD techniques (Alexeev et al. 2008). The results showed that, once a stable pore was formed, small increases in membrane tension readily reopen the pore, thus allowing transport through the membrane. This work also demonstrated that the membrane tension can be altered by changing the temperature or pH (Alexeev et al. 2008).

Gold nanoparticles have been found to repel, adhere to, or penetrate lipid bilayers depending on the density and sign of the surface charge of the nanoparticle (Lin et al. 2010). This coarse-grained simulation study found that gold nanoparticles readily adhere to and penetrate the bilayer, with a hydrophilic pore forming upon penetration of the lipid bilayer. Higher surface charge density was shown to increase membrane disruption, whereas lower surface charge density resulted in increased penetration of the gold nanoparticles. Thus, surface charge density was identified as a possible property that could be controlled to promote gold nanoparticle cellular uptake while minimising toxic effects.

Recent coarse-grained molecular dynamics simulations by Titov et al. (2010) have shown that phospholipid molecules could isolate an embedded graphene layer. It was found that, when a micelle formed around the graphene sheet, it could self-insert into a lipid bilayer and remained stable in the interior of the membrane at room temperature (Fig. 5). Furthermore, stabilisation of composite graphene systems inside a lipid membrane was also suggested to be possible. This study has most relevance to in vitro phospholipid membranes, where graphene-embedded membranes could have applications in biosensing and bioelectronic nanomaterials.

Classical molecular dynamics simulations have revealed that the interactions between single-walled nanotubes and free dipalmitoylphosphatidylcholine (DPPC) lipids are concentration dependent (Wang et al. 2009). At low concentrations of DPPC, the lipid molecules formed a supramolecular two-layer cylindrical structure around the nanotube surface, whereas at higher concentrations the

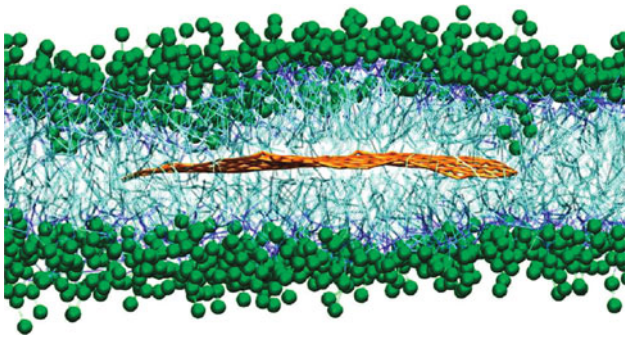

**Fig. 5** Equilibrated superstructure of graphene sheet hosted inside the phospholipid bilayer membrane formed by 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) lipids. Polar heads of the POPC lipids are shown with *green beads*, hydrophobic hydrocarbon chains and the graphene sheet are shown with *thick blue* and *brown lines*, respectively (water beads hidden). Reprinted (in part) with permission from Titov et al. (2010). Copyright 2010 American Chemical Society

DPPC molecules formed multilayered supramolecular structures. The hydrophobic tails of DPPC interacted with the nanotube, while hydrogen bonding between the head groups of DPPC mediated the self-organisation of lipids. Overall, it was found that a membrane-like structure developed on the nanotube, typical of DPPC membranes (Wang et al. 2009).

## Effects of nanomaterials on the structure and dynamics of proteins

The study of protein interactions with various surfaces can serve as a precursor to understanding behaviour of proteins in the proximity of nanomaterials. Proteins have been studied in the presence of a vast array of surfaces. Studies of graphite, silicon and mica surfaces have all been used to gain understanding of the interactions that can occur between hydrophobic/hydrophilic, neutral/charged surfaces and biological systems. Early work by Yarovsky et al. (1997) used all-atom MD and Monte Carlo simulations to reveal detail of peptide interactions with *n*-alkyl-modified silica ($SiO_2$) surface, which was used as reverse-phase support for high-performance liquid chromatography columns.

Recently, Kubiak and Mulheran (2009) performed molecular dynamics studies of hen egg white lysozyme (HEWL) adsorption on negatively charged, hydrophilic, $SiO_2$ surface (mimicking a mica surface). Their simulations showed that conformational alterations are required for HEWL adsorption, and that upon adsorption the protein lost some α-helical content. The main force governing adsorption was believed to be electrostatic attraction between parts of the protein and the surface. Further studies involving HEWL adsorption to mica surfaces showed that lysozyme clusters diffuse across the substrate at a rate that varies inversely with size, suggesting that molecular-scale mechanisms are responsible for the mobility of the proteins on the substrate (Pellenc et al. 2008). Monte Carlo simulations were applied to investigate lysozyme adsorption to charged surfaces at different protein concentrations, protein net charges, ionic strengths and surface charge densities (Carlsson et al. 2004). Although the method used was quite simplistic (protein represented as hard sphere, and charged surface described by a hard wall), the results compared favourably with experimental findings. The protein adsorption was favoured by high protein concentration, high protein net charge, low ionic strength and high surface charge density. Interestingly, adsorption appeared possible for a weakly negatively charged protein to the negatively charged surface as a result of an electrostatically favourable protein reorientation at the surface (Carlsson et al. 2004).

Graphene surfaces have also been studied extensively because of its many uses in ultra-fast and ultra-low-noise biological sensors (Ohno et al. 2009; Patil et al. 2009; Shan et al. 2009). Density functional theory investigations of adsorption of amino acids, glycine, histidine, cysteine and phenylalanine on the surface of carbon nanotubes and graphite surfaces showed that the zwitterionic form of amino acids adsorbs more strongly than the non-ionic form (Roman et al. 2006). Binding was found to be strongest through the C-terminal end of the amino acid, and the curvature of the surface had a profound effect on the adsorption strength (Roman et al. 2006). Human insulin was used as a protein model in an MD study to investigate the conformational changes in the presence of free and fixed graphene surfaces (Liang et al. 2009). The α-helices of insulin had selective protection from the free graphene surface as a consequence of the flexibility of the graphene surface, which resulted in greater stability of the protein. This selective protection could improve the stability of proteins on biosensors or biomaterials. However, it was shown that the tertiary structure of the protein was partially destroyed when adsorbed to the graphene surface (Liang et al. 2009). Similarly, further MD studies of graphene have revealed that the initial adsorption of fibronectin type I module can result in local rearrangements of the strands that were in contact with the surface, although the overall molecular structure did not change in the initial stages of adsorption. As the simulation progressed the molecule spread along the graphene surface to maximise the surface coverage, and thus interaction energy (Raffaini and Ganazzoli 2004). Overall, these studies point out that hydrophobic surfaces can induce tertiary and in cases secondary structure loss by proteins adsorbed to these surfaces. It has been suggested that the rearrangement of protein on surfaces is dependent on the

hydrophobicity, crystallinity and smoothness of the surface.

We have recently performed MD simulations using both classical and coarse-grained approaches to study the effects of surface hydrophobicity and nanostructuring on protein absorption (Hung et al. 2011). We have modelled monolayer-protected gold nanoparticles (MPMNs), a newly discovered class of nanoparticles whose surface is composed of well-ordered, parallel alternating stripes which circumscribe a metal core (Jackson et al. 2004). Their surface structures can be readily manipulated by altering the relative composition of the self-assembled hydrophobic (octanethiol, OT) and hydrophilic (mercaptohexanol, MH) ligands, rendering them uniquely suited to systematic studies of the role of surface nanometre structure in biomolecule adsorption (Kuna et al. 2009).

Interactions of cytochrome C with MPMN surfaces were studied using experimental protein assays and molecular dynamics simulations. Experimental microBCA assays revealed that cyt C exhibited increased adsorption with increasing %MH, suggesting that cyt C–surface interactions are largely hydrophilic. Protein–surface adsorption enthalpies calculated from simulations indicated increased adsorption with increasing %MH, in agreement with experiments. The simulations identified energetically favourable protein binding orientations on MPMNs and the major contributing residues (Fig. 6). The strength of cyt C binding to mixed-ligand surfaces was directly related to the number of contacts between protein and surface, the intimacy and specificity of these contacts, the extent of registry between polar and non-polar regions of the protein binding site, and the corresponding surface nanostructures. Simulations identified that the amphipathic nature of the lysine side-chain enables it to form simultaneous persistent contacts with both OT and MH at boundaries of phase-separated nanodomains.

Overall, with an understanding of how the nanostructuring of surfaces influences protein dynamics, control of their bound states can be achieved. This may give rise to an array of newly tailored materials/surface coatings for use as biosensors, hybrid materials, nanotechnology and biocompatible surfaces.

Further research has also been conducted in an attempt to elucidate possible nanotoxic effects by investigation of the effects of various nanostructures and nanoparticles on peptide/protein structure and dynamics. Aggregation of peptides and proteins is a common precursor to some neurological diseases, thus investigations of the possible link between nanoparticles and aggregation are underway.

One such study was conducted using discontinuous molecular dynamics (DMD) on a nanoparticle-catalysed peptide to determine how nanoparticles may facilitate the peptide's aggregation (Auer et al. 2009). DMD is a technique used as a faster and computationally simpler alternative to standard molecular dynamics. DMD systems evolve on a collision-by-collision basis, and require the calculation of the collision dynamics and the search for the next collision. Auer et al. (2009) used a modified version of the tube model, where residues are represented by their $C_\alpha$ atoms connected in a chain with a distance of $3.8 \pm 0.2$ Å between neighbouring atoms. It was suggested by Auer and co-workers that the process of aggregation can be sped up by the presence of factors capable of increasing the local concentration of proteins, such as high-surface-area nanoparticles, thus promoting further formation of disordered oligomers.

We performed explicit solvent all-atom molecular dynamics simulations to investigate the effects of several carbonaceous nanoparticles on the structure and dynamics of amyloidogenic apoC-II(60–70) peptide (Todorova et al. in preparation). The nanoparticles investigated were fullerene (C60), single-walled carbon nanotube and graphene sheet. We identified the conformational changes in the peptide due to nanoparticle–peptide interactions and the effect of surface curvature on the self-assembly of apoC-II(60–70) peptide. Persistent $\pi$–$\pi$ interactions between the aromatic residues of the peptide and the carbon surfaces (Fig. 7) have been observed.

Similarly, the MD study by Noon et al. (2002) showed significant hydrophobic interactions at the binding site of an antibody with a desolvated fullerene. These interactions included extensive $\pi$-stacking of the aromatic side-chains with the carbon rings of the fullerene particle, suggesting that $\pi$-stackings are very efficient and common modes of biological recognition of $\pi$-electron-rich carbon nanoparticles. Furthermore, the results demonstrated that an ordinary protein binding site can readily bind to a carbon nanoparticle with high affinity and specificity through

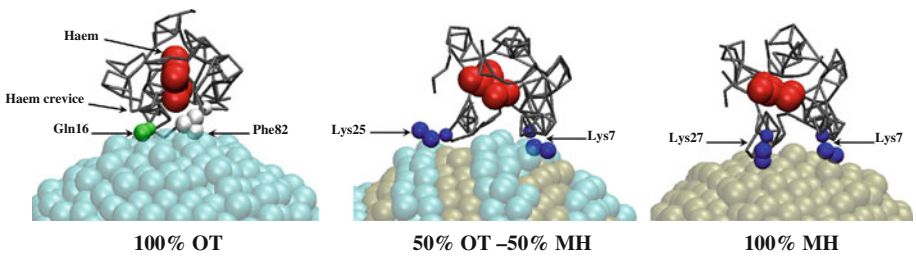


**Fig. 6** Lowest-energy binding conformations for cyt C–MPMN systems with varying MH-to-OT ratio, highlighting the tightly bound residues (*small spheres*) and the haem (*large spheres*)

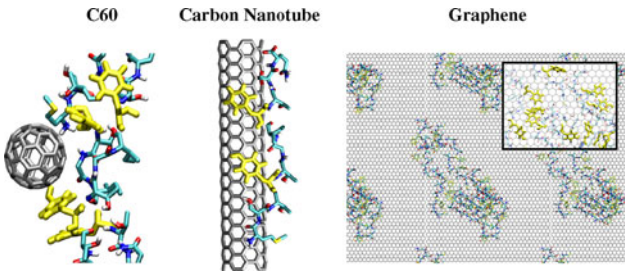


**Fig. 7** MD snapshots of carbonaceous nanomaterials in the proximity of apolipoprotein C-II(60–70) peptide. Dimers of apoC-II(60–70) were shown to $\pi$-stack (shown as *yellow* residues) on the carbon surface at equilibrium (in preparation)

recognition modes that are common in protein–ligand recognition (Noon et al. 2002). In general, carbon–carbon interactions are not considered specific, however these interactions have become more specific due to the nano-structuring of the particle, allowing ordinary protein binding sites to be occupied by carbon nanoparticles.

Adsorption of human serum albumin on the surface of carbon nanotubes (Shen et al. 2008a) was investigated by MD simulations to understand possible conformational changes that the carbon nanotube may induce on the protein structure. It was found that the overall $\alpha$-helical secondary structure of the protein was largely unchanged, whereas the random coils connecting these $\alpha$-helices were strongly affected. This resulted in tertiary structure changes in the protein, mostly due to the orientational and conformational changes of the protein structure to fit the arrangement of carbon atoms on the nanotube surface. Similarly to the studies presented by Noon et al. (2002), adsorbed aromatic rings possessed the most favourable interactions between the protein and carbon nanotube surface (Shen et al. 2008a). It appears that nanoparticles can affect the overall structure and function of proteins by hydrophobic interactions and $\pi$-stacking between the aromatic residues and hexagonal carbon arrangement on some carbonaceous nanoparticles.

Nanoparticles and in particular nanotubes have been highlighted as having a huge range of applications from field-effect transistors to biological application, such as drug delivery vehicles. However, dispersion of nanotubes within aqueous environments is problematic due to their high affinity for one another. As a result, peptides have been identified as possible nanotube dispersion mediators. One such designed peptide is nano-1 (Chiu et al. 2008), an amphiphilic helical peptide which has been simulated using MD techniques in varying environments including water/oil, water/graphite and water/single-walled carbon nanotube (SWNT) interfaces (Chiu et al. 2008). Additional simulations conducted by Chiu et al. showed that nano-1 has reduced amphiphilic character at the water/oil interface and exhibited partial unfolding of the $\alpha$-helix when adsorbed to graphite surface. In contrast, the peptide was observed to curve on the SWNT external surface and retained its $\alpha$-helix structure by maintaining hydrophobic contacts with the SWNT and hydrogen bonds with water (Chiu et al. 2009a). Their results also showed that the inter-peptide hydrogen bonding through the peptide's lysine and glutamate residues help to stabilise the peptide-wrapped carbon nanotube. The peptides were found to collectively tilt along the nanotube surface, resulting in peptide–peptide interactions that completely shield the nanotube from contact with water. All hydrophobic residues of the peptide interacted with the nanotube, which allowed hydrogen bonding with water molecules to stabilise the multipeptide–SWNT complex (Chiu et al. 2009a).

Reversible cyclic peptides (RCP) have also been investigated for use as carbon nanotube dispersion mediators (Chiu et al. 2010; Friling et al. 2010). Using free energy calculations and molecular dynamics simulations, Chiu et al. showed that SWNT association is thermodynamically favourable with reversible cyclic peptides' preference to form antiparallel $\beta$-sheet-like structure. These $\beta$-sheet-like ring stacks form through peptide backbone hydrogen bonding along the SWNT surface. These structures can lead to the formation of tubular peptide stacks encasing the SWNT, which was also found to be a thermodynamically favourable process (Chiu et al. 2010). The limited diameter selectivity in carbon nanotube solubilisation is due to intra-peptide and inter-peptide disulphide bonds and not a result of single peptide wrapping (Friling et al. 2010).

As mentioned previously, carbon nanotubes have been considered as ideal drug delivery systems (De Jong and Borm 2008; Yang et al. 2007), and work has been extended to study peptide encapsulation. Steered and classical molecular dynamics simulations were used to demonstrate the ability of carbon nanotubes to encapsulate peptides or proteins (Chen et al. 2009). It was found that van der Waals attractive forces were the driving force for the encapsulation of a peptide within the carbon nanotube. Furthermore, Chen et al. found that longer nanotubes provide a broader area to trap peptides, while nanotubes with smaller diameter were able to encapsulate the peptide with deeper interaction energy well. Thus, balancing the diameter and length of carbon nanotubes is important for their possible role as drug delivery devices (Chen et al. 2009).

Hydroxyapatite (HAP) is the main component of bones and teeth (Dong et al. 2007; Shen et al. 2008b); synthetic HAP has medical applications as a bioinert coating (Kilpadi et al. 2001) as well as a tool to investigate bone growth and formation (Suzuki et al. 2006). As a result, investigations of the effects of HAP on the structure and function of fibronectin have been conducted. Steered MD and classical

MD studies revealed that the charged C- and N-terminals interacted most strongly with the surface (Shen et al. 2008b). Charged guanido groups, neutral amino groups and hydroxyl groups also have considerable interactions with the surface (Shen et al. 2008b). Other studies of hydroxyapatite (HAP) crystal and protein molecules (BMP-2) have also used steered molecular dynamics (Dong et al. 2007). The results agree with previous work which suggested that the –OH and the C- and N-terminals are the three groups through which the protein molecule BMP-2 interacts with HAP. It was also found that, along with the Coulombic force, the water-bridged hydrogen bond is important in the adsorption process (Dong et al. 2007).

## Effects of nanomaterials on DNA structure

DNA molecules contain the genetic instructions used in the development and functioning of all known living organisms and are a fundamental component of life, thus it is important we have in-depth understanding of the effects of various nanoparticles on DNA structure and function. More recently, increasing numbers of studies have considered DNA molecules as a potential avenue for nanoparticle functionalisation. Investigation of nucleotides in the presence of carbon-based nanoparticles such as nanotubes and buckyballs has been extensive, as these nanoparticles are considered ideal for targeted drug delivery (De Jong and Borm 2008; Yang et al. 2007). This possible application has resulted in many simulation studies considering translocation of DNA through carbon nanotubes. Gao et al. (2003) suggested that van der Waals and hydrophobic forces were the most important interactions in the insertion process of DNA into a carbon nanotube, with the former dominating the interaction between the DNA and carbon nanotube. Several studies have investigated the effects of external fields on translocation of oligonucleotides through a carbon nanotube. These molecular dynamics simulation studies have shown that gravitational (Pei et al. 2008) and electric fields (Xie et al. 2007) can promote translocation through the carbon tube. It was concluded that translocation is tube size dependent and that a critical field strength existed for which no translocation occurred (Xie et al. 2007). Furthermore, an energy barrier was found for an oligonucleotide passing from a (14, 14) tube into the (10, 10) tube, suggesting that translocation of DNA within a carbon nanotube channel is quite different from that of DNA translocation from the outside into a carbon nanotube (Fig. 8) (Pei et al. 2008).

Initial investigations into the effects of nanoparticles on DNA structure and function have also been conducted; for example, Johnson et al. investigated DNA–carbon nanotube hybrids using MD techniques to study the

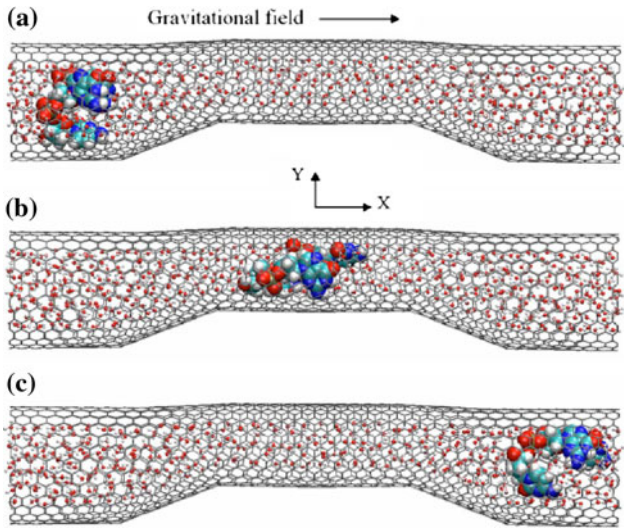


**Fig. 8** Snapshots of DNA oligonucleotide translocation through a (10, 10)–(14, 14) carbon nanotube under a gravitational field of $a_g = 2.6 \times 10^{13}$ m/s$^2$ at (**a**) time = 0 ps, (**b**) time = 330 ps and (**c**) time = 600 ps. Reprinted with permission from Q. X. Pei, C. G. Lim, Y. Cheng and Huajian Gao, *The Journal of Chemical Physics*, Vol. 129, Page 125101–4, (2008). Copyright [2008], American Institute of Physics

self-assembly mechanisms, structure and energetic properties of these nanocomplexes. Their work showed that single-walled carbon nanotubes induce single-stranded DNA bases to undergo a spontaneous conformational change that enables the hybrid to self-assemble via $\pi$–$\pi$ stacking interactions between the DNA bases and carbon nanotube walls (Fig. 9). Spontaneous wrapping about the carbon nanotube was also observed, with the wrapping driven by electrostatic and torsional interactions within the sugar-phosphate backbone (Johnson et al. 2008).

The replica exchange molecular dynamics (REMD) method was applied to determine the free-energy landscape of a DNA–carbon nanotube hybrid (Johnson et al. 2009). The

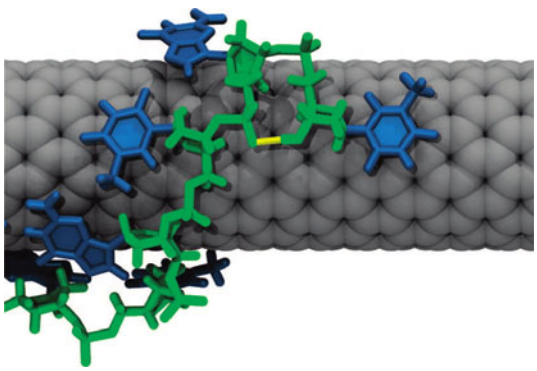

**Fig. 9** Hydrogen bond (*yellow*) at 3′ end resulting in bending of the terminal nucleotide. A similar configuration occurs at the 5′ end. Reprinted (in part) with permission from (Johnson et al. 2009). Copyright 2009 American Chemical Society

global minimum was found to be a nonhelical loop structure of the single-strand DNA. Base adsorption was limited to steric effects; however, upon adsorption, nucleotides displayed considerable conformational disorder (Johnson et al. 2009). Similar work was conducted by Martin et al. (2008) with some discrepancies in the simulated structures, which was suggested to be due to differences in the computational setup of the REMD method. This finding highlights the importance of proper conformational sampling.

Research has also focused on C60 buckyballs in the presence of single- and double-stranded DNA molecules (Zhao et al. 2005). The results of this MD study demonstrated high binding energies between the fullerene and nucleotides, which were attributed to hydrophobic forces that dominate the interactions between the molecules. In this study, C60 was shown to be able to penetrate the double helix of double-stranded DNA to form stable hybrids which frustrated the hydrogen bonds between end-group base pairs of the DNA molecule (Zhao et al. 2005). Thus, cytotoxic effects could be induced if DNA replication is impacted by the stable complexes formed between the nanoparticles and DNA molecules.

Molecular dynamics simulations and ab initio calculations were used to investigate the effects of DNA–carbon nanotube arrays on the electronic structure of the combined system (Lu et al. 2005). This study revealed that the array of carbon nanotubes arranged to fit into the major groove of the DNA is semiconducting and that the bands on either end of the gap were derived exclusively from either the DNA or nanotubes. This work has implications and possible applications in devices using electron switching and possibly for ultrafast DNA sequencing.

Functionalised nanoparticles have many applications, including in drug discovery (Debouck and Goodfellow 1999), biosensing (Shan et al. 2009) and sequencing (Duggan et al. 1999). Thus, research has been conducted on the effect of DNA functionalisation on a flat gold surface (Lee and Schatz 2009a) and a gold nanoparticle (Lee and Schatz 2009b) using MD simulations. These studies showed that both base stacking and non-Watson–Crick hydrogen bond formation are involved in the interactions between DNA molecules on the gold surface, whereas no significant hydrogen bonding occurs on the gold nanoparticle surface. It was found that on both surfaces an increase in sodium concentration occurs, which is consistent with an observed increase in melting temperature of DNA (Lee and Schatz 2009a, b).

## Conclusions

Recent computational literature has highlighted the common modes in which nanoparticles and surfaces interact with biological systems. Hydrophobic interactions are the most favoured, with $\pi$-stacking of the aromatic side-chains common when binding to a carbonaceous nanoparticle or surface. The binding of nanoparticles to DNA and protein molecules resulted in changes of their structure. van der Waals forces were found to dominate the insertion of DNA molecules into carbon nanotubes. Fullerene particles were found to frustrate DNA pairs and bind to a location disrupting the structure of the DNA molecule. This nanoparticle was also able to adhere to the binding site in an antibody molecule, thus potentially preventing its activity. Nanomaterials have been shown to induce conformational changes that favour aggregation of peptides/proteins, possibly leading to amyloidogenic formations as well as disrupting the tertiary structure of proteins due to the curvature and arrangement of the nanoparticle surface. Furthermore, many hydrophobic nanoparticles were able to transverse a lipid membrane. Some nanoparticles even caused mechanical damage to the membrane, thus potentially leading to cytotoxic effects. At the same time, current literature suggests many useful applications for nanoparticles, with nanoparticles able to encapsulate DNA and protein molecules, such as membrane-active peptides, and then penetrate a membrane layer to deliver drug molecules (e.g. antimicrobial peptides). Current computational techniques are only starting to reveal how nanoparticles interact with biological systems. Further research is required to determine further useful applications as well possible cytotoxic effects that nanostructured materials may have on DNA, protein and membrane structure in solution.

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