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ORIGINAL PAPER

Quantitative study of BSA coating silica nanoparticle

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Abstract The loading of biomolecules on nanoparticles might be thought of as a first step to design a cargo in drug delivery system. Here, we study a quantity of bovine serum albumin (BSA) surrounding the silica nanoparticle. The silica nanoparticle is modeled as a perfect sphere whereas the BSA is represented by an ellipsoid. On utilizing a continuous approximation, the electrostatic and van der Waals interactions can be analytically expressed. Further, a number of BSA molecules coating on the nanoparticles of various sizes can be simply determined as a function of the protein ring radius. Our finding is in a good agreement found in experiment and this can be a guide to evaluate the number of protein on other type of spherical nanoparticles.

Keywords Bovine serum albumin · Silica nanoparticle · Lennard-Jones function · Coulombic function

1 Introduction

The integration of nanoparticles with biomolecules may yield novel hybrid nanobiomaterials of combined properties and functions arising from the unique physical and chemical properties of nanoparticles and the unique recognition by cell of biomaterials. There is a growing knowledge that the fundamental interactions of nanoscale

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objects with living substance play a major role in nanomedicine, as well as in terms of nanosafety issue [1]. For this reason the study of the nanoparticles coated by protein as a protein corona might be thought of as a first step to create drug or gene delivery systems.

In biomedical field, silica nanoparticles may serve as a delivery system for drugs and genes [2,3]. For example, DNA can be functionalized on the surface of silica nanoparticles and is transported into animal tissues [4–9]. Moreover, these nanoparticles may bind to drugs and serve as a cargo to deliver such molecules to the targeted cells [3,10–12]. In particular, Schübbe et al. [13] investigated the location of SiO_2 nanoparticles of 32 and 83 nm in diameters in Caco-2 cells as a model of human intestinal cells, and they found that silica of both sizes can enter into the cytoplasm. With increasing incubation time, the particles move towards the nucleus of the cells.

Bovine serum albumin (BSA) has been widely used as a protein model in many applications both in industry and academic research [14]. This protein is essential for the transportation of hormones and fatty acids in mammals. BSA has an isoelectric point at pH 4.75, and carries a negative net charge at pH 7. Wright and Thompson [15] proposed a prolate ellipsoid model for BSA with the dimensions of $2a = 140.4 \pm 4.9$ Å and $2b = 2c = 41.6 \pm 3.6$ Å. According to structure determination by Carter et al. [14,16] using X-ray diffraction, the three-dimensional structure of BSA is proposed as a heart-shaped comprising three homologous domains. Röcker et al. [17] studied a number of BSA coating FePt and CdSe/Zns nanoparticles, and found a thickness of the protein corona of approximately 3.3 nm. In case of the interaction between BSA and silica nanoparticles, Su et al. [18] observed by neutron reflection that a uniform layer of the protein adsorbed at the hydrophilic silica-water interface. They suggested that the layer thickness is always <4 nm.

The mechanics of silica nanoparticle coated with a layer of BSA, in terms of energy calculation, may be determined using a continuous approach. Here one assumes that discrete atomic arrangements can be replaced by a uniform atomic distribution, so that the total interaction energy between two molecules can be evaluated using an integral technique. In the case of interaction energy between nano-structures, Girifalco et al. [19,20] applied the continuous approach to analytically derive the potential energies for various arrangements of a carbon nanotube and a C_{60} fullerene. This continuous approximation can also be used to determine the interaction energy between an organic molecule, C_{60} fullerene, and a biological structure, lipid bilayer, as proposed by Baowan et al. [21] where they studied the location of fullerene penetrating to the DPPC lipid bilayers. Recently, the authors utilized the same method to study the encapsulation of silica nanoparticles in liposomes [22].

By using techniques from applied mathematics, this paper aims at determining a number of protein molecules coating silica nanoparticles of different sizes. We account for electrostatic interactions by a Coulombic term and by the Born equation for the solvation free energy, where they are detailed in Sect. 2. Further, we utilize the Lennard-Jones potential function for the van der Waals interaction. The model formulation for the BSA surrounding the silica nanoparticles is presented in Sect. 3 followed by the numerical results. Finally, the summary is presented in Sect. 5.

2 Method

Here, we determine the optimal number of proteins in a monolayer coating a sliica nanoparticle. Instead of using complicated force fields, we employ the continuous approach for modeling the total non-bonded energy. Both van der Waals and electrostatic interactions are taken into account.

The standard 6–12 Lennard-Jones function is given by

$$\Phi = -\frac{A}{\rho^6} + \frac{B}{\rho^{12}} = 4\epsilon\left[-\left(\frac{\sigma}{\rho}\right)^6 + \left(\frac{\sigma}{\rho}\right)^{12}\right],$$

where ρ denotes the distance between two typical points, and A and B are attractive and repulsive Lennard-Jones constants, respectively.

The electrostatic energy for molecules carrying partial charges can be modeled using the sum of Coulombic function and Born equation to account for the solvation energy [23] which is given by

$$U = \frac{q_i q_j}{4\pi\epsilon_0\epsilon_r}\frac{1}{\rho} - \frac{1}{8\pi}\left(\frac{1}{\epsilon_i} - \frac{1}{\epsilon_r}\right)\frac{q_i q_j}{f_{GB}},$$

where ρ denotes the distance between two typical charge centers, q_i and q_j are partial point charges, ϵ_0 denotes the vacuum permittivity of $8.85 \times 10^{-12}\,\mathrm{CV^{-1}m^{-1}}$, and ϵ_i and ϵ_r are relative dielectric constants. The generalized Born equation (f_{BG}) is given by $f_{GB} = \sqrt{\rho^2 + a^2 e^{-\rho^2/(4a^2)}}$ where a is the van der Waals radius of a charged particle, and for $\rho \gg a$ we may approximate $f_{GB} = \rho$. Therefore, the electrostatic term becomes

$$U = \frac{q_i q_j}{4\pi}\left[\frac{1}{\epsilon_r\epsilon_0} - \frac{1}{2}\left(1 - \frac{1}{\epsilon_r}\right)\right]\frac{1}{\rho},$$

where we take $\epsilon_i = 1$.

Using the continuous approach, where the atoms at discrete locations of the molecule are averaged over a surface or a volume, the molecular interatomic energy is obtained by calculating integrals over the surface or the volume of each molecule, which is given by

$$E = \eta_1\eta_2\int_{S_1}\int_{S_2}\left\{\left(-\frac{A}{\rho^6} + \frac{B}{\rho^{12}}\right) + \frac{q_i q_j}{4\pi}\left[\frac{1}{\epsilon_r\epsilon_0} - \frac{1}{2}\left(1 - \frac{1}{\epsilon_r}\right)\right]\frac{1}{\rho}\right\} dS_2 dS_1,$$

where η_1 and η_2 represent the average surface or the average volume density of atoms on each molecule. For convenience, we define

$$I_n = \int_{S_2}\int_{S_1}\rho^{-2n} dS_1 dS_2, \tag{1}$$

where $n = 1/2$, 3 and 6 correspond to the degree of ρ that appears in the above energy equation.

Table 1 Lennard-Jones and Coulombic parameters for silica nanoparticle used in this model

Atom type	ϵ (kJ/mol)	σ (nm)	q (C)	Dangling atom density (nm^{-2})
Si	1.297	0.4295	$+0.3\|e\|$	1.0
O	0.628	0.3500	$-0.3\|e\|$	1.0

Table 2 Lennard-Jones parameters for BSA used in this model

Atom type	ϵ (kJ/mol)	σ (nm)	Number of atoms in one molecule
C	0.0951	0.30275	3,072
H	0.0512	0.28464	4,828
N	0.0774	0.32626	816
O	0.0957	0.30332	928
S	0.3440	0.35903	40

The Lennard-Jones and Coulombic constants for silica nanoparticle are taken from the work of Cruz-Chu et al. [24] and are listed in Table 1. Here, SiO_2 is modeled as a perfect spherical molecule where the Si atom is located at the center and the bond length between Si and O is 0.161 nm. Then the average atomic surface density of silica may be obtained as $3/[4\pi(0.161)^2] = 9.325\,\mathrm{nm}^{-2}$, where 3 is the number of atoms in a molecule. Similarly, the average atomic volume density of silica is given by $3/[(4/3)\pi(0.161)^3] = 171.61\,\mathrm{nm}^{-3}$. Further, it is assumed to be comprised at the inside of small overall neutral SiO_2 beads whereas the outer surface of the solvated nanoparticle is partially covered by silanol (–SiOH) groups [24,25]. Following the work of Cruz-Chu et al. [24], the density of the dangling atoms of silicon and oxygen are approximately $1\,\mathrm{nm}^{-2}$. Therefore, to guarantee the neutral charge of the silica nanoparticle, the partial charges for the silicon atoms and hydroxyl groups are taken to be $+0.3|e|$ and $-0.3|e|$, respectively.

We model the BSA protein as an ellipsoid with dimensions of $14 \times 4 \times 4\,\mathrm{nm}$ [15]. This gives a volume of $117.29\,\mathrm{mn}^3$ for one protein molecule. The BSA molecule comprises of 9,684 atoms in total, and therefore the average atomic volume density of the BSA is 82.57 atoms per cubic nanometer. The electrostatic interactions of proteins are mostly due to polar and charged amino acids on the surface. According to the assumed ellipsoidal shape, the surface area of such a BSA molecule is approximately $142.31\,\mathrm{nm}^2$, then the average atomic surface density of the BSA is $68.05\,\mathrm{nm}^{-2}$. Here, we vary the charge of the BSA to represent the pH or ion concentration in an environment. The Lennard-Jones parameters for the atomic components of BSA are taken from the work of Mayo et al. [26], and are presented in Table 2. Mixing rule is employed to study the interaction between two atomic types.

3 Model formulation

According to Röcker et al. [17] and Su et al. [18], BSA forms a monolayer when surrounding nanoparticles. Here, we assume that the protein forms layer of ℓ nm thickness surrounding a spherical nanoparticle of radius a, where ℓ ranges from 4 to 14 nm

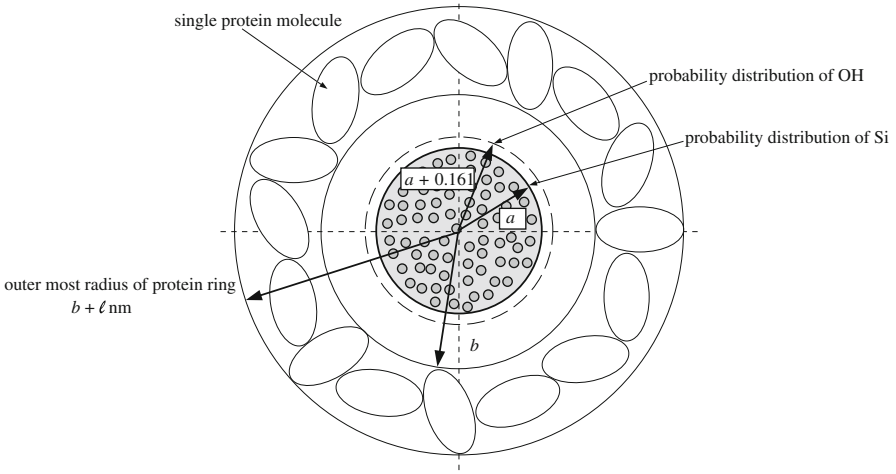

Fig. 1 Model formation for silica nanoparticle coated by BSA where b is the inner most ring radius and ℓ is the thickness of the ring which ranges from 4 to 14 nm

corresponding to the dimensions of a BSA molecule. The silica nanoparticle is assumed to be centered at the origin as shown in Fig. 1. Therefore, the total energy of the system consists of

1. The van der Waals energy between the volume of the spherical protein ring and the volume of the spherical nanoparticle.
2. The electrostatic energy between the surface of the protein ring and the surface of the nanoparticle arising from the silica atoms and hydroxyl groups.

The volume of the protein ring around the nanoparticle V_{layer} is given by

$$V_{layer} = \frac{4}{3}\pi\left[(b+\ell)^3 - b^3\right],$$

where b denotes an inner most radius of the protein ring which needs to be determined as a solution of the problem. It can be shown that a volume of an ellipsoid of dimensions $2a \times 2b \times 2b$ is approximately two thirds of a volume of a cylinder with the height of $2a$ and the diameter of $2b$. Accordingly, the amount of the protein molecule in the spherical protein ring is approximately $2V_{layer}/3$. Therefore, the number of BSA molecules coating the silica nanoparticle can be determined by

$$N_p = \frac{2V_{layer}}{3V_p} = \frac{2[(b+\ell)^3 - b^3]}{3(2)(2)(7)} = \frac{(b+\ell)^3 - b^3}{42}, \tag{2}$$

where V_p is the volume of one BSA molecule.

The schematic models for the van der Waals and the electrostatic interactions are depicted in Fig. 2. We firstly determine the molecular interaction between a surface or a volume of a sphere and a single atom as shown in Fig. 2a. Then, the single atom is assumed to be located on the other spherical surface, and either volume or

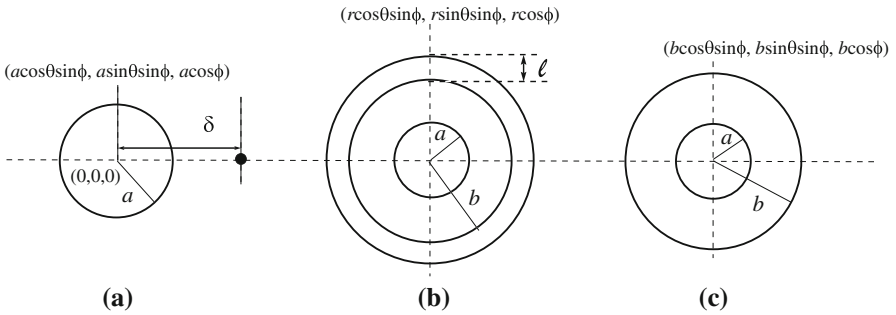

Fig. 2 Schematic structures for **a** a sphere interacting with a single atom, **b** concentric spheres for the outer volume integral, and **c** concentric spheres for the outer surface integral

surface integral is applied to determine the total energy of the system. Mathematical derivations for the van der Waals and the electrostatic interactions using in this model are presented in Sects. 3.1 and 3.2, respectively.

3.1 Van der Waals interaction

We begin by considering the integral I_n defined by (1) for $n = 3, 6$ and for a spherical molecule of radius a centered at the origin and a point located at $(0, 0, \delta)$, as shown in Fig. 2a. The distance from a typical element of the sphere to the atom is given by $\rho^2 = (r\cos\theta\sin\phi)^2 + (r\sin\theta\sin\phi)^2 + (r\cos\phi - \delta)^2$, $r \in [0, a]$. Following the work by Baowan and Thamwattana [27], it is convenient to express the volume integral I_3 and I_6 in terms of J_n which is defined by $J_n = 1/(\delta^2 - a^2)^n$ where n is a positive integer corresponding to the power of the polynomials appearing in I_3 and I_6 defined by (3) and (4), respectively. This gives

$$I_3[J_n] = \frac{4}{3}\pi a^3 J_3, \tag{3}$$

$$I_6[J_n] = \frac{2}{45}\pi a^3 \left(30J_6 + 216a^2 J_7 + 432a^4 J_8 + 256a^6 J_9\right). \tag{4}$$

Next, we need to evaluate the volume integral for the outer spherical ring where the schematic model is shown in Fig. 2b. The distance δ from the center of the first sphere to a typical point on the spherical ring is given by $\delta = r$ and, therefore we may deduce

$$\begin{aligned} L_n^{LJ} &= \int_V J_n dS = \int_{-\pi}^{\pi}\int_b^{b+\ell}\int_0^{\pi} \frac{r^2\sin\phi}{(r^2-a^2)^n} d\phi dr d\theta \\ &= \frac{4\pi(-1)^n}{a^{2n-3}} \int_{\sin^{-1}(b/a)}^{\sin^{-1}[(b+\ell)/a]} \left[\frac{1}{\cos^{2n-1}(t)} - \frac{1}{\cos^{2n-3}(t)}\right] dt, \end{aligned} \tag{5}$$

where ℓ is the thickness of the ring, and for any given value of n, an analytic expression of L_n^{LJ} can be obtained. The total van der Waals interaction between the sphere and the

spherical ring of thickness ℓ can be obtained by substituting L_n^{LJ} defined by (5) into I_3 and I_6 defined by (3) and (4), respectively. Therefore, the van der Waals interaction between the spherical molecule of radius a and the spherical ring of thickness ℓ is given by

$$P_{1-2} = \eta_1\eta_2\left\{-A_{1-2}\left(\frac{4}{3}\pi a^3 L_3^{LJ}\right) + B_{1-2}\left[\frac{2}{45}\pi a^3\left(30L_6^{LJ} + 216a^2L_7^{LJ} + 432a^4L_8^{LJ} + 256a^6L_9^{LJ}\right)\right]\right\}, \tag{6}$$

where η_1 and η_2 represent the average atomic volume densities of the sphere and the protein ring, respectively, and A_{1-2} and B_{1-2} are the Lennard-Jones attractive and repulsive constants, respectively.

Hence, the total van der Waals interaction between the spherical silica nanoparticle and the ring of the BSA with thickness ℓ is given by

$$\begin{aligned} E_{vdW} = {} & \left(\frac{1}{3}\right)\left[\left(\frac{3072}{9684}\right)P_{Si-C} + \left(\frac{4828}{9684}\right)P_{Si-H} + \left(\frac{816}{9684}\right)P_{Si-N} \right. \\ & \left. + \left(\frac{928}{9684}\right)P_{Si-O} + \left(\frac{40}{9684}\right)P_{Si-S}\right] \\ & + \left(\frac{2}{3}\right)\left[\left(\frac{3072}{9684}\right)P_{O-C} + \left(\frac{4828}{9684}\right)P_{O-H} + \left(\frac{816}{9684}\right)P_{O-N} \right. \\ & \left. + \left(\frac{928}{9684}\right)P_{O-O} + \left(\frac{40}{9684}\right)P_{O-S}\right], \end{aligned} \tag{7}$$

where P_{1-2} is defined by (6). The rational coefficients come from the proportional content of 1/3 silicon and 2/3 oxygen atoms in the silica nanoparticle. By the same consideration the atomic proportions for the BSA can be obtained, this yields the value of 9684 in the denominator.

3.2 Electrostatic interaction

For this we consider the integral I_n defined in Eq. (1) with $n = 1/2$. In the case of a spherical surface interacting with a single atom, as depicted in Fig. 2a, we may deduce

$$\begin{aligned} I_{1/2} &= \int_s \frac{1}{\rho}dS = \int_{-\pi}^{\pi}\int_0^{\pi} \frac{a^2\sin\phi}{(a^2+\delta^2-2a\delta\cos\phi)^{1/2}}d\phi d\theta \\ &= \frac{\pi a}{\delta}\int_{(\delta-a)^2}^{(\delta+a)^2}\frac{1}{\sqrt{t}}dt \\ &= 4\pi a^2\frac{1}{\delta}, \end{aligned} \tag{8}$$

where δ is the distance from the center of the sphere to the atom.

Next we aim to integrate $1/\delta$ over another concentric spherical structure. As shown in Fig. 2c, we have $\delta = b$, and we may deduce

$$L^{Q}_{1/2}(a,b) = 4\pi a^2 \int_S \frac{1}{\delta} dS = 4\pi a^2 \int_{-\pi}^{\pi}\int_0^{\pi} \frac{b^2 \sin\phi}{b} d\phi d\theta = 16\pi^2 a^2 b. \quad (9)$$

Then the electrostatic interaction between two concentric spheres is given by

$$Q_{1-2} = 4\pi \eta_1^* \eta_2^* q_1 q_2 \left[\frac{1}{\epsilon_r \epsilon_0} - \frac{1}{2}\left(1 - \frac{1}{\epsilon_r}\right)\right] a^2 b, \quad (10)$$

where in this case η_1^* and η_2^* are the average atomic surface densities of the nanoparticle and the protein molecule, respectively. Hence, the total electrostatic interaction between the ring of BSA and the surface of the silica nanoparticle arising from the two layers of silica atoms and hydroxyl groups can be deduced

$$E_{elec} = 4\pi \eta_1^* \eta_2^* q_2 \left[\frac{1}{\epsilon_r \epsilon_0} - \frac{1}{2}\left(1 - \frac{1}{\epsilon_r}\right)\right] \left[0.3|e|a^2 b - 0.3|e|(a + 0.161)^2 b\right], \quad (11)$$

where q_2 denotes the total charge of the BSA. Here, the probability distribution of silica atoms is assumed to be on the spherical surface of radius a and the probability distribution of hydroxyl group is assumed to be on the spherical surface of radius $a + 0.161$ nm.

4 Numerical results and discussion

Due to the unknown BSA charge q_2, here we assume three possible negative charge values which are $-0.1|e|$, $-0.3|e|$ and $-0.5|e|$. This is from the fact that BSA carries a negative net charge at pH 7. The dielectric constant ϵ_r is taken to be 80 as the relative permittivity of water. We note that the value of ϵ_r does not effect the physical behaviour of the system [22]. The electrostatic energy profiles for the three negative charge values are shown in Fig. 3. We found that increasing the magnitude of the charge increases the magnitude of the electrostatic energy in the system. The positive total energy comes from the repulsion between the assumed negative charge of the protein and the negative charge of the hydroxy group. Further, we found that the value of the electrostatic energy has three orders of magnitude lower than the value of the van der Waals energy. Therefore, only the van der Waals interaction is needed in order to determine the optimum ring radius b.

The summation of the van der Waals and the electrostatic energies given in (7) and (11) gives rise to the total energy of the system. Figure 4 shows an energy profile for the specific value of the silica nanoparticle radius $a = 15$ nm at the isoelectric point. We obtained the optimum radius of the inner ring at $b = 15.37$ nm. The other sizes of silica nanoparticles give the same energy behaviors, and they are not shown here.

A number of BSA molecules surrounding the silica nanoparticle can be calculated by the relation given by (2). The radius of the protein ring b is determined at the

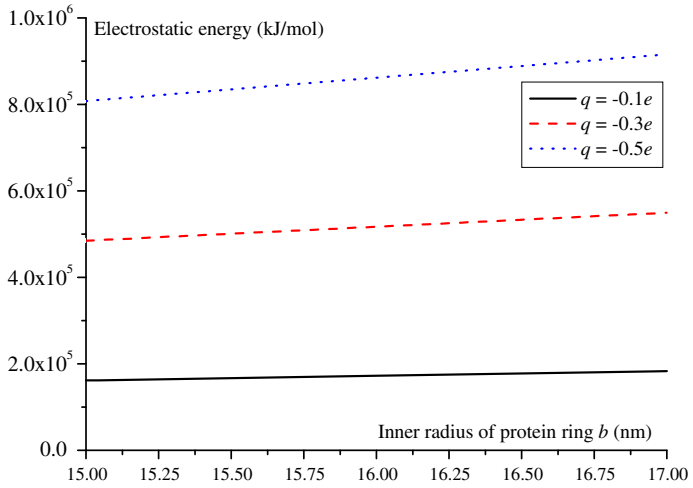

Fig. 3 Electrostatic energy for three different negative charge values on BSA for silica nanoparticle of radius 15 nm coated by BSA

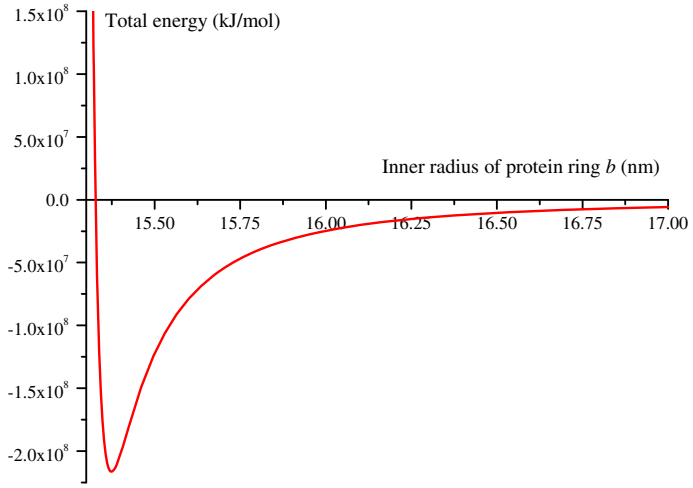

Fig. 4 Total energy at an isoelectric point of silica nanoparticle of radius 15 nm coated by BSA

equilibrium position, and their values for five different sizes of silica nanoparticles are given in Table 3. We assume three values for the ring thickness ℓ arising from the maximum, average and minimum dimensions of a BSA molecule, which are 14, 7.33 and 4 nm, respectively. We found that the number of protein molecules coating the nanoparticles is independent of the charge values on BSA. Moreover when ℓ is assumed to be 4 nm, our result for the case of $a = 5.6$ nm is in a good agreement with the number given by Röcker et al. [17] where we predict that there are 21 BSA molecules surrounding the nanoparticle and they obtained 23 molecules coating the nanoparticle. Further, 4 nm is also represented the protein thickness surrounding the silica nanoparticle as proposed by Su et al. [18].

Table 3 Numerical results for the inner most radius b of BSA and a number of proteins N_p coating silica nanoparticle

a (nm)	Inner most radius b (nm)	Number of proteins N_p		
		$\ell = 14$ nm	$\ell = 7.33$ nm	$\ell = 4$ nm
5.6	5.974	187	54	21
10	10.374	331	119	57
15	15.374	560	235	130
20	20.374	866	406	244
25	25.374	1,259	638	409

The main result of this paper is the derivation of an analytical expression for the total energy of the system as a function of a spherical core radius. The silica nanoparticle is introduced here as a model particle to illustrate the physical properties such as size and charge. Once the particle type is replaced by another material, only the parameters and constants need to be changed, but the mathematical expressions derived here remain the same. Similarly, the type of a protein molecule can be changed and only the proportion of atomic species are needed to be adjusted. Furthermore, the calculation of a number of protein molecules loading on the nanoparticle can be easily modified utilizing different geometries of the protein molecules.

5 Summary

A quantitative determination of BSA monolayer coating on a silica nanoparticle surface is studied here, which might be thought of as a delivery process of biomolecules on the nanoparticle as a targeted drug cargo. Both van der Waals and electrostatic interaction energies are taken into account utilizing the Lennard-Jones potential and the Coulombic potential including Born equation. The continuous approach, where the atoms in a molecule are assumed to be uniformly distributed over a surface or a volume of the molecule, is employed to determine the total energy of the system. Then the surface and the volume integral techniques are utilized to analytically express the model calculations. In this study, we assume that the silica nanoparticle can be modeled as a perfect sphere whereas the BSA can be represented by an ellipsoid.

Due to an unknown charge on the protein molecule, we assume three possible negative charge values which are $-0.1|e|$, $-0.3|e|$ and $-0.5|e|$. The total interaction energy for the silica nanoparticle coated by BSA is obtained as a function of the nanoparticle size and the charge of the protein. The solution of the problem is the inner most radius of the protein ring which will be used to determine the quantity of the protein surrounding the nanoparticle. Three values of ring thickness ℓ are assumed. Further, we found that the number of protein molecules on the silica nanoparticle cannot be explained by charge effects and Coulomb interaction, it depends on the van der Waals interaction alone. Moreover, the results obtained here are comparable with the ones obtained in experiments. Our work thus could be viewed as a first step toward designing cargo to load the biomolecules on the organic nanoparticle.

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