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Cholesterol Interactions with Fatty Acids and DMPC Phospholipids of Liver Membranes

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ABSTRACT

Cholesterol and fatty acids is important subject in liver to different model of regulation for realizing the evolution of vertebrates. The major solubility of cholesterol in bilayers of glycerol-phospholipids is between 65 and 50 mole%, relevant on the bilayer of lipid membrane but they cannot alone form multi layered structures. Livers from the transgenic rat showed increases in mRNAs encoding various enzymes of cholesterol synthesis, the LDL's receptor and fatty acid synthesis. Based on our previous works we have modeled and simulated various molecules of that Cholesterol in binding to membrane. A number of computational chemistry studies carried out to understand of the cholesterol parallel to fatty acid synthesis (FAS) for preventing the fatty liver disease. In this work ELF, LOL, ECP, electrical properties such as electron densities, energy densities, and potential energy densities, eta index for some of the fatty acids have been calculated.

Keyword: Cholesterol, Fatty acid, liver, Nano-biotechnology, drug design.

INTRODUCTION

In contrast to the diversity of phospholipid types, the cells of mammals contain one main sterol, cholesterol, that is exactly required for livability and cell proliferation[1, 2.] Sterols vary from the other membrane bilayer classes, and originally consist of hydrocarbon in the form of a steroid structures. The maximum solubility of cholesterol in bilayers of membranes is between 65 and 50 mole%, relevant on the bilayer of lipid membrane[3,4] but they cannot alone form multi layered structures[5]. Sterols become manifest to have solved for filling the spaces amongst the acyl chains in the membranes[6]

Fatty acid, cholesterol and the primitive lipids synthesized in the liver are a subject to different template of regulation and synthesis. Cholesterol synthesis is great when animals are fed a free diet cholesterol, and it deterioration significantly during of cholesterol feeding. Cholesterol synthesis is also increase when animals consume bile acid–binding resins.

In biological membrane phospholipid bilayers, the length and impregnation of the phospholipids and hydrocarbon also chip in to the different properties of sphingomyelin and phosphatidylcholine's. Generally happening phosphatidylcholine's usually are including two hydrocarbon of approximately similar length.

The attached "acyl" chain to the first carbon of glycerol is generally saturated, while the "acyl" chain esterified to the C2 (next carbon) is normally unsaturated[3-5]. For more understanding of "acyl" chain which basically contains between 1 and 6 double bonds of cis-configuration we simulated our systems. The sphingomyelins in membranes are extremely saturated than naturally phosphatidyl-cholines[6]. In addition, natural sphingomyelin always has very long amide-linked "acyl" chain carbon in the length, while the sphingoid base is most often sphingosine (d-erythro-2amino-trans4-octadecene-1, 3diol).

This will lead to an inconformity in chain length for more natural-sphingomyelins, and such a chain difference has been shown to improve membrane curvature[7, 8].

The chain disparities also enable sphingomyelins to participate in the trans-bilayer hydrocarbon inter-digitation.

The molecular structure of the cholesterols includes a skeleton (tetracyclic fused ring skeleton), with a alone hydroxyl group at carbon three, a double bond between two carbons "five and six" and an isooctyl hydrocarbons side chain at the carbon seventeen.

In Fig. 1 cholesterol bound from human beta2 adrenergic receptor has been shown[9, 10]. The rings of the cholesterol is molten in the trans configuration, which makes the molecule rigid and planar, except for the isooctyl side chain[11-13.]. An important concept on the three dimensional structure of the cholesterol is that the "3b-OH" group, 2 methyl groups and the side chains are all located on the same side of the ring skeleton[4,15].

The hydroxyl group in the cholesterol is important, because it gives another hydrophobic compound (its amphiphilic character) and therefore orients the molecule in phospholipids membrane.

Further, the "OH" group can also interfere the hydrogen bonding of cholesterol by H_2O and possibly with other lipids of cellular membranes[16, 17].

Another interesting consequence of the cleavage of lipids bilayers by phospholipases is that the lateral organization of membrane bilayers may be drastically altered during the enzymatic activity. It has been confirmed where the characterizing effects of cholesterol on the line tension of solid DMPC domains vanishes rapidly after the phospholipase activity sets in. This is an instance of the tight coupling between enzyme activity and membrane bilayers structure alterations. People are worried about eating cholesterol due to a relationship to coronary heart disease.

Dietary restrictions of cholesterol intact do not solve this problem, since we make most of the cholesterol in our bodies (~70% on average). We need cholesterol: it maintains membrane fluidity and forms the basic skeleton for steroids and hormones. From the looks of it, you may think (it seems) that this must come from a lot of different carbon skeletons. The Biosynthesis of Cholesterol has been drawn in Fig. 2

It is most important for understanding the natural & pharmaceutical-based Regulation of Sterol / Cholesterol. Production is based on cholesterol synthesis is an energy-expensive complex process in the cell membrane. Thus it is heavily regulated. The major committed, rate-limiting step of sterol production is the formation of Mevalonate from βHydroxy-βmethylglutarylCoA by the enzyme "HMGCoA" reductase. Therefore, popular target of many drugs, called statins. Statins and all derivatives of fungal natural products Fig 3.

Livers from the transgenic rat showed increases in mRNAs encoding various enzymes of cholesterol synthesis, the LDL's receptor and fatty acid synthesis. The elevations in mRNA for 3hydroxy-3methylglutaryl coenzyme "A (HMG CoA)" synthase and "HMG CoA" reductase were especially marked.

Theoretical background
Density and energy

The density of electron can be defined as

$$\rho(r) = \eta_i \, |\varphi_i(r)|^2 = \sum_i \eta_i \, |\sum_l C_{l,i} \, \chi_i(r)|^2$$

(1).[18-20] Where η_i is "occupation" number of orbital (*i*), φ is wave function orbital, c is the basis function and *C* is the coefficient matrix, the element of row "i_{th}" and column "j_{th}" corresponds to the expansion coefficient of orbital "*j*" respect to basis function "*i*". Atomic unit for density of electron can be explicitly written as e/Bohr³.

$$\nabla\rho(r) = [(\frac{\partial\rho(r)}{\partial(x)})^2 + (\frac{\partial\rho(r)}{\partial(y)})^2 + (\frac{\partial\rho(r)}{\partial(z)})^2]^{\frac{1}{2}}$$

...(2)

$$\nabla^2\rho(r) = \frac{\partial^2\rho(r)}{\partial x^2} + \frac{\partial^2\rho(r)}{\partial y^2} + \frac{\partial^2\rho(r)}{\partial z^2}$$

...(3)[18-20].

The positive and negative value of this function correspond to electron density is locally concentrated and depleted respectively. The relationships between $\nabla^2\rho$ and VSEPR (valence shell electron pair repulsion) model, electron localization, chemical bond type and chemical reactivity have been investigated by Bader .

The kinetic energy density is not individually defined, since the expected amount of kinetic energy operator $< \varphi \, |-(\frac{1}{2})\nabla^2| \, \varphi >$ (4) must be recovered by integrating of kinetic energy density from the alternative definitions.

One of important used definition is:

$$k(r) = -\frac{1}{2}\sum_i \eta_i \varphi_i^*(r)\nabla^2\varphi_i(r)$$

...(5)

Relative to *K*(r), the local kinetic energy definition given below guarantee positivizes everywhere; hence the physical meaning is clearer and is more commonly used.

The G(r) "Lagrangian" of kinetic energy density is also known as the positive definite energy density.

$$G(r) = \frac{1}{2}\sum_i \eta_i \, |\nabla(\varphi_i|^2 = \frac{1}{2}\sum_i \eta_i \{ [(\frac{\partial\varphi_i(r)}{\partial(x)})^2$$
$$+ (\frac{\partial\varphi_i(r)}{\partial(y)})^2 \, (\frac{\partial\varphi_i(r)}{\partial(z)})^2] \}$$

...(6).

K(r) and *G*(r) are straightly defined by Laplacian of electron density

$$\frac{1}{4}\nabla^2\rho(r) = G(r) - K(r)$$

...(7)

Edgecombe and Becke, noted that averaged like spin conditional (pair probability) has direct relation with the "Fermi hole" and then suggested ELF (electron localization function) [18-20].

$$\text{ELF}(r) = \frac{1}{1 + [D(r)/D_{0(r)}]^2}$$

(8) where,

$$D(r) = \frac{1}{2}\sum_i \eta_i \, |\nabla\varphi_i|^2 - \frac{1}{8}[\frac{|\nabla\rho_\alpha|^2}{\rho_\alpha(r)} + \frac{|\nabla\rho_\beta|^2}{\beta(r)}]$$

...(9)

and

$$D_{0(r)} = \frac{3}{10}(6\pi^2)^{\frac{2}{3}}[\rho_\alpha(r)^{\frac{5}{3}} + \rho_\beta(r)^{\frac{5}{3}}]$$

...(10)

for close-shell system, since

$$\rho_\alpha(r) = \rho_\beta(r) = \frac{1}{2}\rho$$,

D and *D*0 terms can be simplified as

$$D(r) = \frac{1}{2}\sum_i \eta_i \, |\nabla\varphi_i|^2 - \frac{1}{8}[\frac{|\nabla\rho|^2}{\rho(r)}]$$

...(11),

$$D_{0(r)} = \frac{3}{10}(3\pi^2)^{\frac{2}{3}}\rho(r)^{\frac{5}{3}}$$

...(12).

Savin has reinterpreted "ELF" in the viewpoint of kinetic energy[20] which makes "ELF" also meaningful for "Kohn-Sham" DFT wave-function or even post-HF wave-function[20]. They indicated which "*D*(r)" reveals the excess kinetic density caused through Pauli repulsion, while $D_0(r)$ can be evaluated as "Thomas-Fermi" kinetic energy density[19,20].

LOL or Localized orbital locator is the other function for locating high localization regions as the same "ELF", defined by Becke and Schmider.

$$LOL(r) = \frac{\tau(r)}{1+\tau(r)}$$

...(13),

where:

$$(r) = \frac{D_0(r)}{\frac{1}{2}\sum_i \eta_i \, |\nabla\varphi_i|^2}$$

...(14)

Computational details

Calculations were accomplished by Gaussian package. In present work, we have looked at for getting the results from "DFT" methods such as m062x, m06L, and m06 for the molecular reaction that are monotonous via the comparison between different situations.

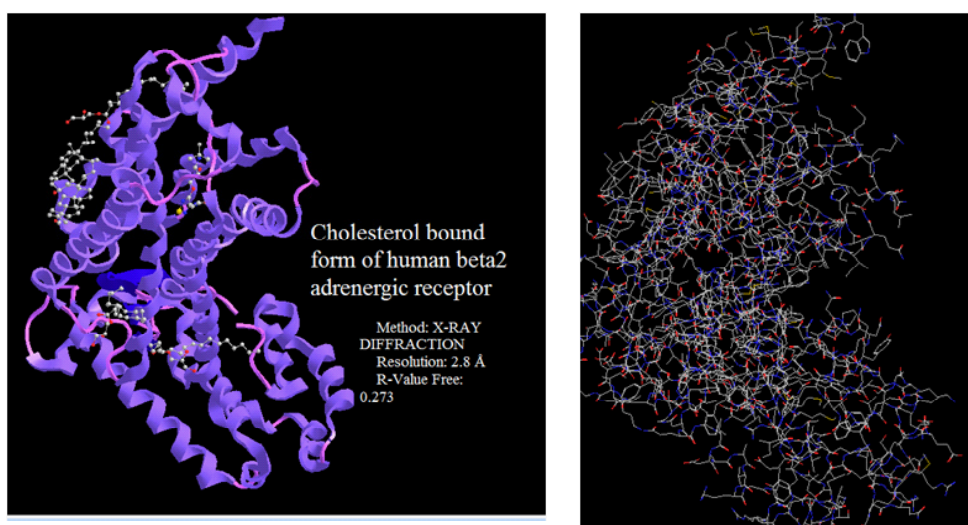The m062x, m06L, and "m06HF" are new approach in DFT with a good correspondence in

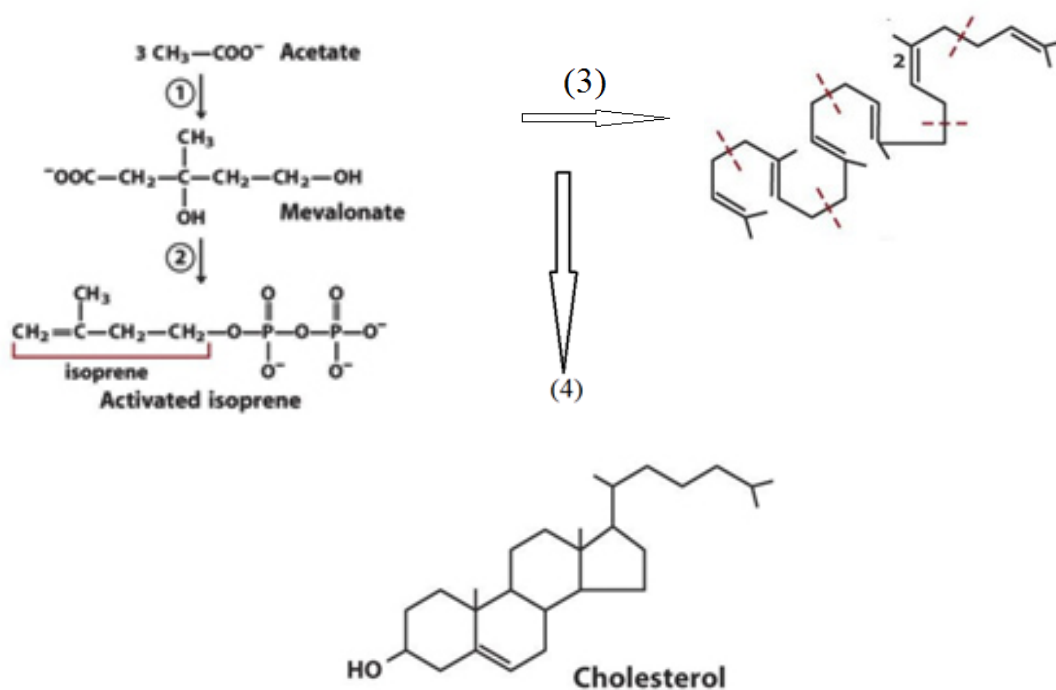**Fig.1: Cholesterol bound from human beta2 adrenergic receptor**

Fig.2 Biosynthesis of Cholesterol

reaction calculation and are useful for the energy between two fragments in cholesterol with binding to a membrane.

We employed DFT theory to model the exchange correlation energies for our systems. The double ζ-basis sets with a polarization orbital (DZP) were used for the phospholipids atoms while single ζ-basis set with a polarization orbital (SZP) were employed for the fatty acids in the membrane layers, respectively.
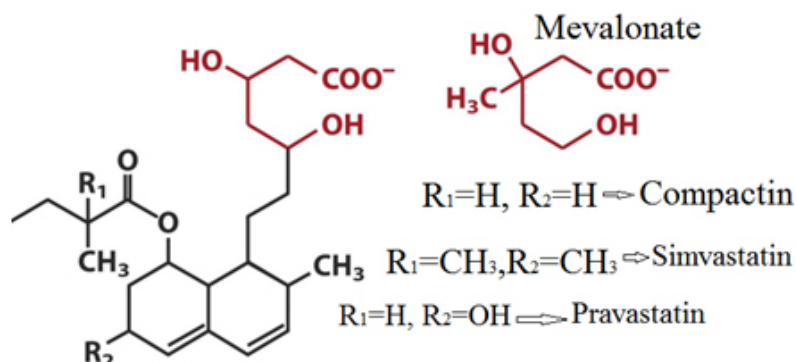

Fig. 3: Mevalonate, Compactin, Simvastatin and Pravastatin structures
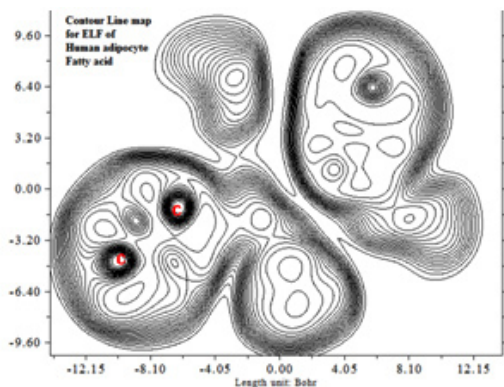

Fig. 4: Contour line map for Human adipocyte fatty acid

For an accurate DFT calculation; "B3LYP" is not able to describe correlation systems by interaction. The disability of B3LYP and other popular functional to correctly describe of correlation and exchange limits their applicability for the two parts. Recently, studies have shown that inexactitude for the exchange energy leads to the large systematic error for the prediction of chemical physics properties for the molecules.

Electronic structure calculations and geometry optimization for our systems have been performed using the "Kohn-Sham" equation of the
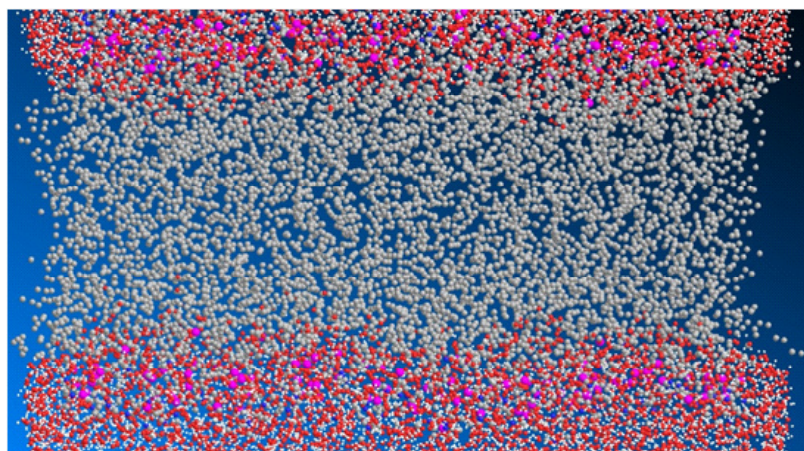

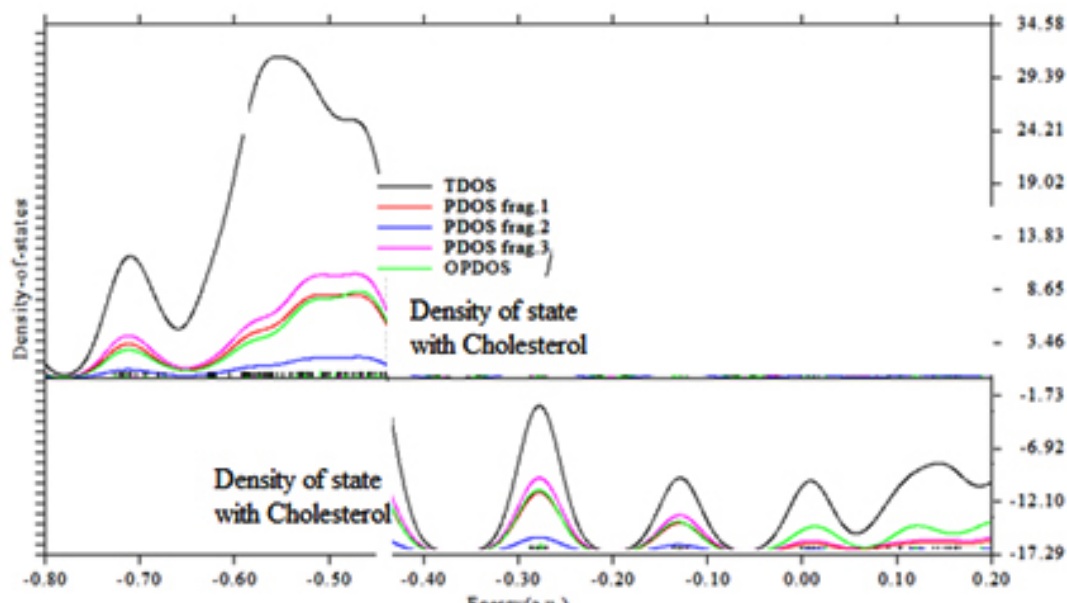**Fig. 5: Cholesterol among 60 domain of DMPC membrane in leaver**

Fig. 6: Density of state with and without cholesterol for DMPC

DFT theory for a plane wave basis set with the projector augmented wave pseudo potentials.

The PBU (Perdew-Burke-Ernzerh) of XC (exchange-correlation) functional of the GGA (generalized gradient approximation) is adopted. The optimization of the lattice constant and the atomic coordinate are made by the minimization of the total energy. Except for the band determination, the partial occupancy was treated using the tetrahedron methodology with Blöchl correction.

The charge transfer and electrostatic potential-derived charge was also calculated using the Merz-Kollman-Singh, chelp, or chelpG .

For the charge calculation, based on molecular MESP (electrostatic potential) fitting are not well suited for treating a large system where some of the atoms are located far away from the points at which the "MESP" is computed. In this condition, variation of those atomic charges will not lead to significant changes of the outset atoms for the molecule. In other words, the accurate values for the innermost atomic charges are not well-determined via MESP of the molecule.

The representative atomic charge for our molecules should be computed as average value over several phospholipid molecules. We have also extracted the charge densities proûles from ûrst principles calculations via an averaging process described. Based on our previous works[21-46] the system of cholesterol in binding to DMPC has been simulated. The result has shown that the mechanism of fatty acid synthesis (FAS) enhanced due to cholesterol increases extremely.

RESULT AND DISCUSSION

Monte Carlo simulation always detect the so called "important phase-space" regions which are of a low energy. Because of defect of the force field, those lowest energies basin usually does not correspond to a native state in most cases. So the rank of the native structures in those decoys has produced through the force fields it selves are poor. In this study difference in force field is illustrated by comparing the energies and physical properties calculated by using molecular mechanic force fields such as MM+, Amber, and OPLS.

This study has investigated mainly on the electron density of cholesterol in a binding system

Table 1:(LOL), from nuclear charge and from electron charge for Phosphor in DMPC with%5 to 20% cholesterol

DMPC Percent of Cholesterol	ΔEs(eV)	ALIE* LIE		ELF* LOL† ESp#		α°±n β°±m γ°±k		Electron Density* a.u. Energy Density H(r)†(eV)	
(%=5)	0		P_{1+}	1.05 (E-04)* 1.32 (E-02)† 1.13 (E+01)#	P_{1+}	110.3° 111.6° 116.2°	P_{1+}	3.29 (E-03)* 2.89 (E-01)†	P_{1+}
(%=10)	+1.21	P_{1+} = - 0.16 P_{1-} = - 0.12	P_{1+} : P_{1-}	1.25: 2.16 (E-04)* 1.35: 2.01 (E-02)† -3.6:- 4.2 (E+01)#	P_{1+} : P_{1-}	112.0:112.3 111.2:110.3 123.1:101.5	P_{1+} : P_{1-}	4.19:4.07 (E-03)* 3.06:3.16 (E-01)†	P_{1+} : P_{1-}
$1_+, 1_-$ $2_+, 2_-$ (%=15)	1.37	P_{1+} =-0.06 P_{1-} =-0.09 P_{2+} =-0.07	P_{1+} : P_{1-} P_{1+} : P_{2-}	1.25: 1.36 (E-04)* 1.15: 1.24 (E-02)† -31:- 6.3 (E+01)# 1.19:1.21 (E-04)* 1.02:1.18) E-02)† -4.03:-5.90 (E+01)#	P_{1+} : P_{1-} P_{1+} : P_{2-}	110.0:112.1 102.3:112.8 111.4:111.4 104.3:112.6 102.5:113.3 102.1:121.9	P_{1+} : P_{1-} P_{1+} : P_{2-}	3.09:3.45 (E-03)* 2.81:4.16 (E-01)† 3.29: 3.25 (E-03)* 2.11:3.29(E-01)†	P_{1+} : P_{1-} P_{1+} : P_{2-}
$1_+, 1_-$ $2_+, 2_-$ $3_+, 3_-$ $4_+, 4_-$ $5_+, 5_-$ ((%=20))	0.9	P_{2-} =-0.08 P_{3+} =-0.04 P_{3-} =-0.08 P_{4+} =-0.04 P_{4-} =-0.05	P_{2+} : P_{2-} P_{3+} : P_{3-} P_{4+} : P_{4-} P_{5+} : P_{5-}	1.15: 1.25 (E-04)* 1.21: 1.23 (E-02)† -3.14:- 6.7 (E+01)# 1.41:1.31 (E-04)* 1.32:1.48) E-02)† -3.3:-5.10 (E+01)# 1.07:1.15 (E-04)* 1.22:1.04) E-02)† -4.12:-6.4 (E+01)# 1.09:1.05 (E-04)* 1.12:1.08) E-02)† -3.01:-4.24 (E+01)# 2.17:2.25 (E-04)* 1.06:1.67) E-02)† -31:-4.6 (E+01)#	P_{1+} : P_{1-} P_{2+} : P_{2-} P_{3+} : P_{3-} P_{4+} : P_{4-} P_{5+} : P_{5-}	102.1:103.4 112.5:111.8 111.7:102.8 101.0:108.2 112.5:101.9 110.6:114.9 114.1:116.2 113.2:114.2 113.5:115.3 113.3:114.2 113.1:115.5 114.2:113.8 115.1:114.1 113.3:113.8 114.4:113.5	P_{1+} : P_{1-} P_{2+} : P_{2-} P_{3+} : P_{3-} P_{4+} : P_{4-} P_{5+} : P_{5-}	4.12:4.10 (E-03)* 4.23:4.28 (E-01)† 3.11: 4.15 (E-03)* 4.14: 4.34 (E-01)† 3.09: 3.13 (E-03)* 4.12: 4.15(E-01)† 3.07:3.16 (E-03)* 4.12: 3.11(E-01)† 3.26: 3.26 (E-03)* 4.19: 4.51(E-01)†	P_{1+} : P_{1-} P_{2+} : P_{2-} P_{3+} : P_{3-} P_{4+} : P_{4-} P_{5+} : P_{5-}

with DMPC membrane. The binding details are shown in figs1-6. As it has been indicated in table1, the electrical and magnetically properties can be obtained via changes in the binding interaction.

Electron densities such as energy density, Potential energy density, eta index, "ELF", "LOL", electron density, and ECP for cholesterol were calculated for each simulation.

According to the equation 10- 14 the largest ELF is located on atoms which are bonded to phosphor of phospholipids which in those atoms the electron motion is more likely to be confined within that region. If an electron is completely localized in such atoms, they can be distinguished from the other ones. As it has been shown in the tables 2 & 3 the largest ELF is close to the bonded atoms to phosphors. The regions with large ELF need to have large magnitudes of Fermi-hole integration which would lead those atoms towards "superparamagnetic" phenomenon. The "Fermi hole" is a six-dimension function and as a result, it is difficult to be studied visually[12-14].

Based on equations 10-14, Edgecombe and Becke have noted that the "Fermi hole" is a spherical average of spin which is in a good agreement with our results.

"ELF" indicates that it is a relative localization and must be accounted within the range of [0-1]. A large amount of ELF value corresponds to a large localized electron which indicates that a lone pair or inner shells of the atom are involved[12-14]. According to equation 14, "LOL" can be interpreted similar to the ELF in terms of a kinetic energy, though; "LOL" can also be interpreted in terms of localized orbitals. Large (small) LOL value usually appears in the boundary (inner) region of the localized orbitals due to the small (large) gradient of orbital wave function in this area. The value range of "LOL" is identical to "ELF", namely [0, 1].

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