How Is a Protein Molecule Nearsighted? *

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The effect range of a local change of a protein molecule is calculated using a cluster method developed in this work based on the Gaussian software. This range is found to be about 8 Å, which gives a concrete estimation on the "nearsightedness" by Kohn for protein molecules. The cluster method can be applied to calculation of the electronic density of a large molecule such as a motor protein and can provide a basis for the dynamical analysis of a single protein molecule.

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Investigation of the dynamical behaviour of a single protein such as a molecular motor is one of the most active fields of biophysics. To answer the questions such as how the force is generated on a molecular motor[1−4] asked by biologists, we must know the charge distribution of the molecule since the electric interaction is the most important one in this regime. Therefore, finding a simple and effective way for the calculation of charge distribution of a large molecule becomes more urgent in this field. Owing to the hardware limitation, the quantum chemical software such as Gaussian[5] can not be applied directly, thus various cluster methods have been developed.[6] The main idea for these methods is to divide the large molecule into small parts and to calculate the concerned quantities for these small parts individually and then to combine the results together to give the quantities for the whole molecule. Lastly, one must cut a small part out of the large molecule and this brings about a problem concerning the boundary conditions for the small part. Apparently it is almost impossible to write down a boundary condition that could give a genuine description of the effect of the environment on the small part. A frequently used way for the treatment of this problem is to set up a buffer region for the small part and to attribute approximately the effect of the whole environment to this buffer region. Then the key quantity is the size of the buffer region, which can be used to characterize the "nearsightedness"[7] of the molecule under consideration. In this Letter, we present a practical method for setting up a buffer region and make a quantitative calculation on the basis of Gaussian03[5] for the nearsightedness of a special motor protein called 3Kin.[8]

Ten years ago, Kohn first clearly presented the nearsightedness principle that provides the basis for the existence of computational methods scaling linearly with the number of atoms.[7] For systems without long distance electric fields it can be expressed as follows: Let $F(\boldsymbol{r}_1, \boldsymbol{r}_2, \cdots, \boldsymbol{r}_v)$ be a static property depending on v coordinates $\boldsymbol{r}_1, \boldsymbol{r}_2, \cdots, \boldsymbol{r}_v$, all within a restricted volume ω of linear dimension $\sim \lambda$, a typical de Broglie wavelength of the ground state wave function. Here the centre of mass is denoted by $\boldsymbol{r}_c$. Then, at fixed chemical potential μ, a change of the external potential $\Delta v(\boldsymbol{r}')$, no matter how large, has a small effect on F, only provided that $\Delta v(\boldsymbol{r}')$ is limited to a distant region, in the sense that for all $\boldsymbol{r}'$, $|\boldsymbol{r}' - \boldsymbol{r}_c| \gg l$. Thus F does not "see" $\Delta v(\boldsymbol{r}')$ if $\boldsymbol{r}'$ is far. Now, what we are concerned with is just how nearsighted a typical protein such as kinesin is when calculating the local electronic density of the molecule. This is quantitatively described by the buffer radius introduced in the following.

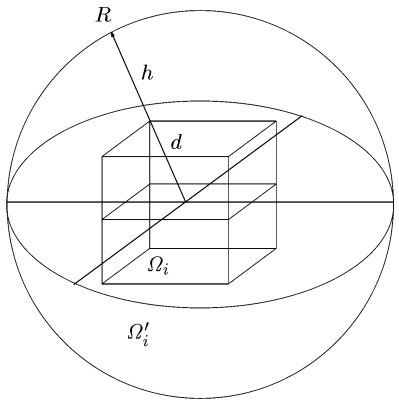


Fig. 1. The cube calculated and its buffer region.

We divide the physical space Ω occupied by the molecule into smaller cubes Ω_i. To calculate the local electronic density $\rho(\boldsymbol{r})$ in Ω_i, we enclose Ω_i by a ball Ω_i' with radius R, as shown in Fig. 1. According to the nearsightedness principle, we can cut away all but Ω_i' and enclose it in a hard wall boundary to calculate

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$\rho_i(\boldsymbol{r})$ in Ω_i. The dimension of Ω_i is characterized by d, which is the distance from the centre of the cube to one of its corner point. The region outside the cube and inside the ball is called the buffer region. The size of the buffer region is described by h, which is called the buffer radius, as shown in Fig. 1.

The relation connecting the buffer radius h and the size of the cube d is

$$h = R - d. \tag{1}$$

The calculation of $\rho_i(\boldsymbol{r})$ is realized by applying the Gaussian software,[5] which is a famous quantum chemical computing software. We first calculate the electronic density inside Ω_i' and then take the value inside Ω_i as $\rho_i(\boldsymbol{r})$. The electronic density of the total molecule is obtained by adding the local ones:

$$\rho = \sum_{i=1}^{N} \rho_i, \tag{2}$$

where $\rho_i(\boldsymbol{r})$ vanishes outside Ω_i. Whether we can obtain a reliable result using this method depends on whether the values of electronic density calculated independently for two adjacent cubes could be connected smoothly on the common boundary surface, meaning that both the values of electronic density and their derivatives must be continuous on the common boundary surface. This smooth connection is mainly determined by the proper choice of the buffer radius. The smallest radius with which the smooth connection can be obtained is the right quantity that characterizes the nearsightedness of the molecule under consideration.

As an example, we calculate the electronic density for some sensitive parts of a typical kinesin motor, 3Kin.[8] It should be pointed out that the crystal structure of this motor protein has been analysed. Therefore we do not need to perform the conformation optimization when doing Gaussian computation. This saves us a great amount of computing time. We take out two adjacent cubes from 3Kin each sized $5 \times 5 \times 5$ Å^3 (Fig. 2) and surrounded by a buffer region with radius $h = 8$ Å.

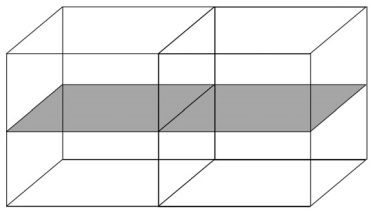


Fig. 2. Two adjacent cubes cut out of 3Kin. Each cube has the size $5 \times 5 \times 5$ Å^3. The shaded plane is a typical section plane with a common boundary in the middle.

In Fig. 3 we depict the contour diagrams of the electronic density and its derivative for a section plane of the two adjacent cubes (the shaded plane in Fig. 2). The values of the upper and lower parts come from two independent calculations for the two cubes. It is seen that the electronic density and its derivative both are continuous on the common boundary.

The smooth connection shown in Fig. 3 is obtained at the 6–31 g level with the buffer radius $h = 8$ Å. For buffer radii less than 8 Å, the smooth connection is ruined. We depict a contour diagram with buffer radius $h = 6$ Å, as shown in Fig. 4. It can be seen that the continuity of the contour along the boundary line is broken.

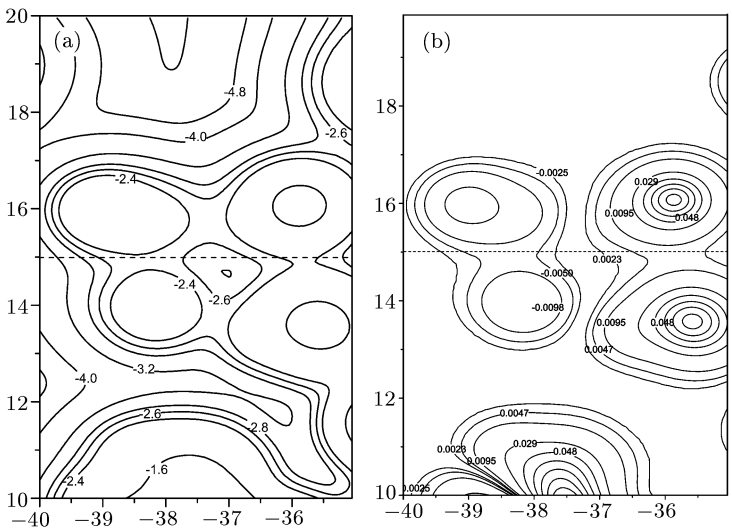


Fig. 3. The contour diagrams of the electronic density (a) and its derivative (b) for a section plane of the two adjacent cubes with buffer radius $h = 8$ Å.

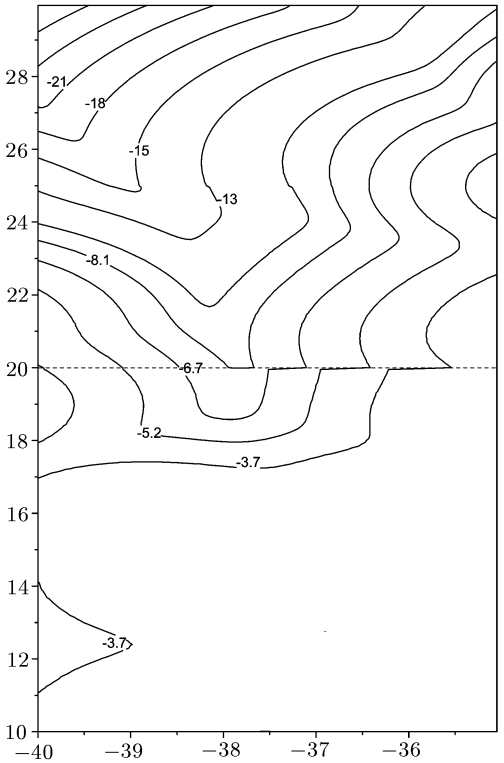


Fig. 4. The contour diagrams of the electronic density for a section plane of the two adjacent cubes with buffer radius $h = 6$ Å.

The value of the buffer radius, i.e. the nearsightedness of the molecule, depends on several factors including the type of the molecule, the choice of the Gaussian basis, etc. The result we give here, i.e. $h = 8$ Å, is obtained by many trial computations with different radii and the Gaussian basis. We believe that this is a relatively conservative value for protein molecules. It should be pointed out that the amino acids are assumed to be uncharged in our calculation. Otherwise, the long distance electric interaction would exist and the nearsightedness principle could not be applied directly.

The computing time in our method is largely determined by the size of the cube and the buffer radius. The values of the two parameters given here just adapt for the computing capacity of current personal computers. Thus the method presented here is simple and practical enough for the calculation of electronic density and other related quantities on an ordinary personal computer. In addition, this method allows a parallel computation since the calculation for each cube is independent of the others.

The concept of nearsightedness may bring some deeper insight into the biological properties of proteins. For example, biologists have performed several experiments to identify the influence of a single amino acid on the properties of the whole kinesin motor.[9,10]. They found that many amino acids (about 130) that are far away from the microtubule-binding site could be replaced without reducing the microtubule affinity of kinesin. By checking the positions of these amino acids we found that their average distance from the microtubule-binding site is more than 1 nm, so the microtubule-binding site can not see the effect of them. This is consistent with the result obtained at present.

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