Accelerating the Research in Drug Delivery System; A Challenge of the Earth Simulator to Medical Innovation

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Objectivity of our project is to accelerate the research of drug delivery system through computational scientific method. In FY05, we have developed a quantum chemistry program based on the tight-binding approximation and carried out preliminary calculations. This year we applied our program for a larger realistic system. In addition, density functional method was employed for an understanding of fine-resolution behavior of DNA and polymers in the vicinity of connection. Results of our simulations were positive for a standard scenario which experimental scientists thought of. However, satisfactory calculation of large-scale behavior of DNA system in solution was revealed still beyond our reach in spite of the efforts in this year.

Keywords: drug delivery system, DNA, polymer, molecular orbital method, tight-binding approximation

1. Introduction

Since the end of the last decade nanotechnology has been grown at rapid pace and spread over many different fields out of its birthplace, material science. Now in medical science, nanotechnology is expected to open up the door to the innovative methods of treatments no one can imagine twenty years ago. One of its novel application is drug delivery system (DDS). The main purpose of DDS is to target the seat of a disease and carry drugs there precisely.

Our project aims to accelerate the research of DDS by fully exploiting the amazing computational ability of the Earth Simulator. In FY05, we have developed a quantum chemistry program based on the tight-binding approximation (TBA) and carried out preliminary calculations. This year we applied the program to PEG-DNA system in solution to clarify the condensation mechanism which is the smallest-scale fundamental phenomena take place in DDS process. In addition, DFT was employed for an understanding of local behavior of DNA and PEG in the vicinity of connection.

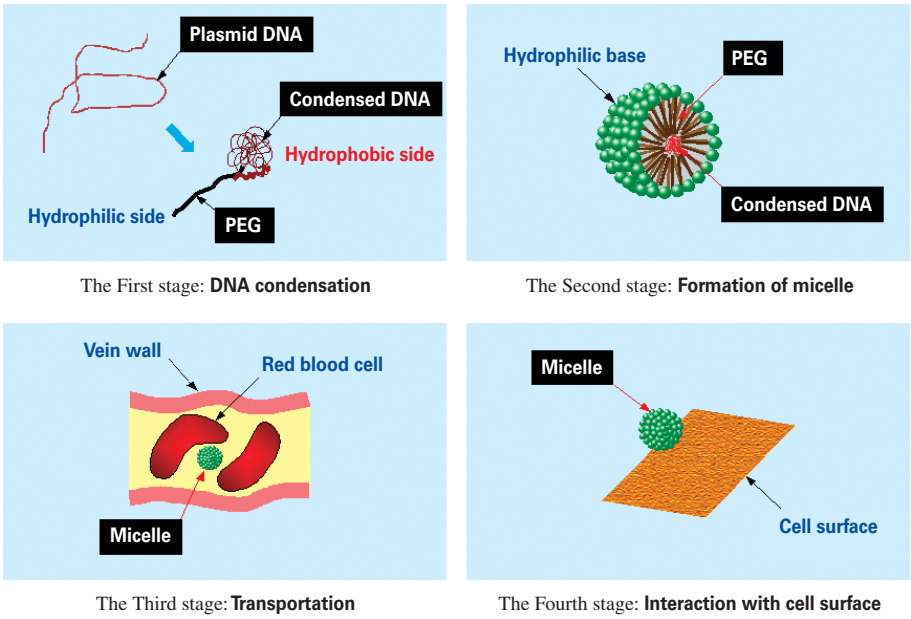
This report is organized as followings. The next section describes the physical aspects of DDS in detail. In the third section, we examine some computational methods. In the fourth section, TBA is explained. Our program is based on that approximation. The fifth section gives computational results. Final section summarizes this report.

2. Drug delivery system

Many kind of DDS technology has been proposed so far. Amongst them, our project pays much attention to the method using nano-sized particle called micelle mainly comprised of poly-ethylene-glycol (PEG). This method is recently developed by Professor Kataoka of the University of Tokyo and expected to be promising in near future because of its relatively low impact on human body [1]. Although the whole process of PEG-motivated DDS is much complicated, we can recognize four characteristic stages in that. See Fig. 1.

In the first stage, relaxed DNA attached to a PEG starts to condense in solution. Shortly after, DNA gets tangled to a small ball. Notice that PEG-DNA complex has a hydrophilic end in PEG and a hydrophobic end in DNA. In other word, it has amphiphathic property. In the next stage, hundreds of those PEG-DNA complexes in the water meet together and spontaneously form sphere called micelle in which each DNA heads for the center and PEG heads for the surface. The driving force of this self-organizing formation is amphipathic property mentioned above. In the third stage, micelles are carried through vein and capillary tube slipping through the blood cells. In the last stage, micelles reached the targeted portion of disease are attracted by the local gradient of ion concentration in the vicinity of the cell surface and then absorbed into it through the carrier or channel protein located at the membrane.

Those types of problem are recently interested in many



The First stage: **DNA condensation**

The Second stage: **Formation of micelle**

The Third stage: **Transportation**

The Fourth stage: **Interaction with cell surface**

Fig. 1 Characteristic stages of drug delivery system.

fields and able to be classified as multi-scale and multi-principle phenomena in contrast to single-scale and single-principle phenomena conventional science has dealt with. To simulate such kind of complicated phenomena efficiently we must choose suitable computational methods corresponding to each stage and combine them interactively. However such simulation technique is still on experimental level. So we focus our interest in the first stage, i.e. DNA condensation.

3. Computational methods

In DNA condensation, the electronic structure inside DNA is thought to play an important role. Therefore quantum mechanical consideration is significant to calculate such phenomena. Density functional theory (DFT) is usually preferred for those cases. Although DFT can perform highly accurate calculation and give reliable results, its computational workload is immensely large, sometimes unacceptable. From that reason, DFT has been applied for relatively small systems up to few hundred of atoms even on the current top-rated supercomputers. However as least few thousands of atom are indispensable to simulate condensation of DNA in solution. We anticipate that very high accuracy like DFT offers is unnecessary to figure out the behavior or mechanism of DNA condensation. On the other hand, we suspect that molecular dynamics method based on heuristic potential is insufficient in accuracy since it is unable to take complex configuration of local electrons into account. Taking the middle of those, we adopt TBA as a baseline algorithm. By virtue of its thinner workload, TBA can be expected to handle more than ten thousands of atoms. In addition, it can take local configuration into account to some extent. In addition we also used DFT to see the local behavior of atoms in close distance.

4. Tight binding approximation

Quantum many body problem is one of the most difficult physical problem and many approximation methods were proposed so far. Amongst them, three major methods are molecular orbital (MO) method, Hartree-Fock method and DFT. First we describe MO method since our TBA is related to it to large extent.

Imagine a hydrogen atom, which has single electron going around single ion. In this case, known as two-body problem, the equation of motion of electron can be solved explicitly. From its results, we can see there exists infinite orbitals and the electron is allowed to occupy one of those orbitals. Adding electrons to this system makes the problem extremely difficult. As is well known, even three body problem is analytically intractable as same as classical dynamics. However, if inter-electron interaction is sufficiently weak, we can expect the orbital picture still works for a multi-electron atom as a good building block of approximation. It is called the atomic orbital assumption.

Electrons are considered as independent each other, and orbitals can be calculated from single electron hamiltonian. So far, single ion is in our mind, and now moves to two ions. If those ions locates close each other, they can be looked upon as doubly charged single ion: a fused ion. In this case, there is no doubt to apply atomic orbital assumption for it. Extrapolating this argument, we can assume the existence of molecular orbitals even if ions are separated. The molecular orbitals are calculated from single electron hamiltonian of molecule and expected to be distributed over entire molecule, not to be localized at specific ion. Practically, molecular orbitals are approximated as linear combination of atomic orbitals (LCAO) and their optimal coefficients are deter-

mined by variational principle.

In what follows, computational aspects of our program are described in brief. A main constituent in calculation of variational principle is hamiltonian matrix. Generally hamiltonian matrix has dense elements and turns out to require plenty of arithmetic operations, while TBA restricts this matrix elements to the nearest atoms around each atom [2]. By virtue of this decimation, operational count of TBA becomes significantly smaller than fully banded hamiltonian. In addition, it needs to handle only valence orbitals and electrons. On the other hand, Hartree-Fock method inevitably requires full orbitals and electrons due to totally anti-symmetric property of Slater determinants. Furthermore, tight binding method calculate each matrix element from a few parameters sometimes called Slator-Koster parameters instead of time-consuming exact integration [3]. Using sparse hamiltonian matrix above, energy of electrons can be obtained from the density of states (DOS) of electrons, which is determined by applying spectrum theorem for Green function.

Electron Energy is defined as

$$E_{elec} = \int^{E_f} n_0(E)\, E dE,$$

where E_f denotes Fermi energy. Spectrum theorem assures a following relation

$$n_0(E) = -\frac{1}{\pi} \lim_{\varepsilon \to 0} \mathrm{Im}\, G_{00}(E + i\varepsilon).$$

Green function is defined as a kind of inverted hamiltonian matrix. Problem here is to invert matrix directly requires extremely large workload and usually exhausts majority of computational time.

Instead of direct inversion, our program adopt Lanczos iteration which can construct Green function very efficiently [4] through continued fraction,

$$G_{00}(E) = \left\langle f_0 \left| \frac{1}{E - H} \right| f_0 \right\rangle = \cfrac{1}{E - a_0 - \cfrac{b_1^2}{E - a_1 - \cfrac{b_2^2}{E - a_2 - \ldots}}},$$

where f_0 denotes a seed state. The coefficients a_n and b_n are obtained through sequential tri-diagonalization of hamiltonian matrix starting from the seed state,

$$a_n = \langle f_n | f_n \rangle,$$
$$b_n = \langle F_n | F_n \rangle,$$
$$|F_n\rangle = H|f_n\rangle - a_n|f_n\rangle - b_n|f_{n-1}\rangle,$$
$$|f_n\rangle = b_n^{-1/2}|F_n\rangle.$$

So far, each ion is fixed under Born-Oppenheimer approximation. However, our physical interest concerns with dynamic behavior of molecules. Thus forces exert on each ion are needed for that purpose. Those forces are obtained by applying Hellmann-Feynman theorem [5].

$$\vec{F} = -\nabla_R E.$$

Finally, second order Verlet method is employed in integration of the equation of motion of ions numerically. Here closes single computational cycle.

The major restriction to TBA is in lack of inter-electron interaction in principle, in other word, no exchange and correlation terms in contrast to Hartree-Fock or DFT. We are certainly aware highly accurate energy calculation is beyond our scope, we concentrate exclusively on the change of configuration or long term behavior of large molecular system which is quantum-mechanically intractable ever. We strongly believe those kind of simulation will come to play a crucial role in future bio-polymer science.

5. Computational results

In terms of DNA condensation, we carried out two types of calculation. One is behavior in large and the other in small. The former calculation is done by our program based on TBA described in the previous section and the latter by a freely distributed DFT program called PWSCF developed by ICTP at Trieste, Italy. Notice that PWSCF we used was modified by us from its original form to utilize vector-pipelined facilities of the Earth simulator. Following subsections describe those results.

5.1 Behavior of DNA in water

Experiments show that DNA condensation is initiated by a polymer comprised of PEG and poly-L-lysin (p(Lys)). Here, Lysin is one of twenty proteins exist in nature and the capital letter L denotes optical isomer. Figure 2 shows a structural formula of PEG-p(Lys) block copolymer. A whole process of DNA condensation takes long duration of nearly

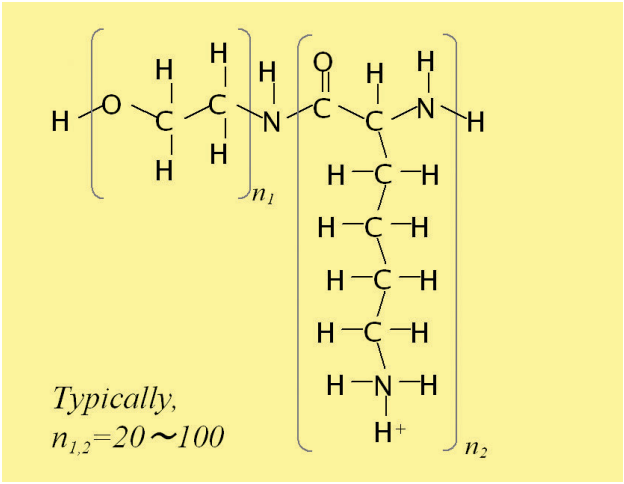


Fig. 2 PEG-p(Lys) block copolymer.

ten seconds. The existence of water molecules is thought to be critical for it. To simulate that process, we prepared DNA of fourteen base-pairs, p(Lys) of four L-lysins and two ethylene-glycol and 260 water molecules in a system. Initially p(Lys) was put near DNA immersed in randomly distributed water molecules. Figure 3 shows the results after 100 femtoseconds calculation. Since computational resource assigned for us was restricted, calculated time was too short to move DNA and p(Lys) significantly. However we proved the possibility of that kind of large-scale calculations. Further calculation was left for future works. Notice that those calculations were done in parallel with eight nodes maximum and their parallel efficiencies recorded over fifty percents. This result means there still exists rooms to be improved.

5.2 Behavior in the vicinity of connection

In water environment, amino-basis in p(Lys) is ionized negatively while phospho-basis in the backbone of DNA positively. Therefore electric force exerts on both bases and attracts each other. It is widely recognized among experimental researchers as standard scenario that such attractive force gets p(Lys) attached to DNA at the onset of condensation. However it is not yet confirmed theoretically. We carried out calculations with a DFT program to prove that scenario numerically. DNA fragment of 139 atoms and p(Lys) of 97 atoms were considered. Water molecules were omitted because of the restriction of computational resources. It took 400 hours for 200 computational steps on the Earth simulator with thirteen nodes. Degree of parallelism larger than 50 is required for larger and longer calculation in the future. Figure 4 shows the results. Nitrogen and oxygen are negatively ionized while phosphate and hydrogen positively. Consequently, attractive force exerts phosphate and nitrogen. In the same way oxygen and hydrogen attract each other. Repulsive force also exerts on nitrogen and oxygen, phosphate and hydrogen in the same time. However animated pictures revealed that attraction slightly prevail over repulsion.

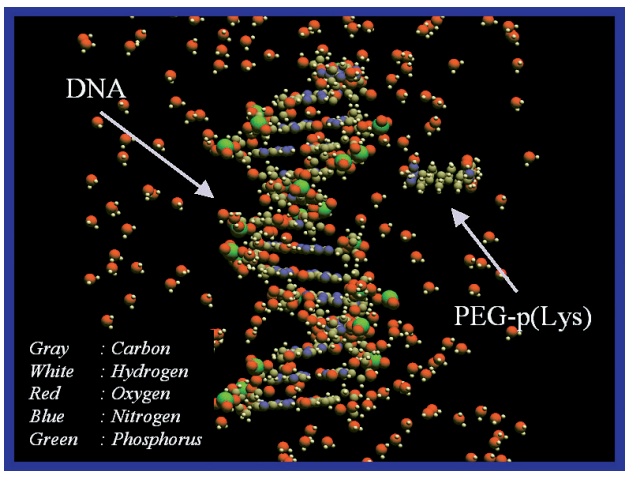


Fig. 3 DNA(14bp) and PEG-p(Lys) in 260 waters.

6. Summary

To make DDS to be realized as early as possible, we try to accelerate it by using computational scientific method. This year we applied our TBA program for a realistic system comprised of DNA, p(Lys) and water molecules. In addition, DFT was employed for an understanding of fine-resolution behavior of DNA and p(Lys) in the vicinity of connection. TBA calculation of large-scale behavior of DNA in solution was revealed still unsatisfactory in spite of our efforts. However the results of DFT calculations found that the standard scenario which experimental scientists thought of were reasonable. Toward further reliable calculation, we will try to make parallel performance better in the next year.

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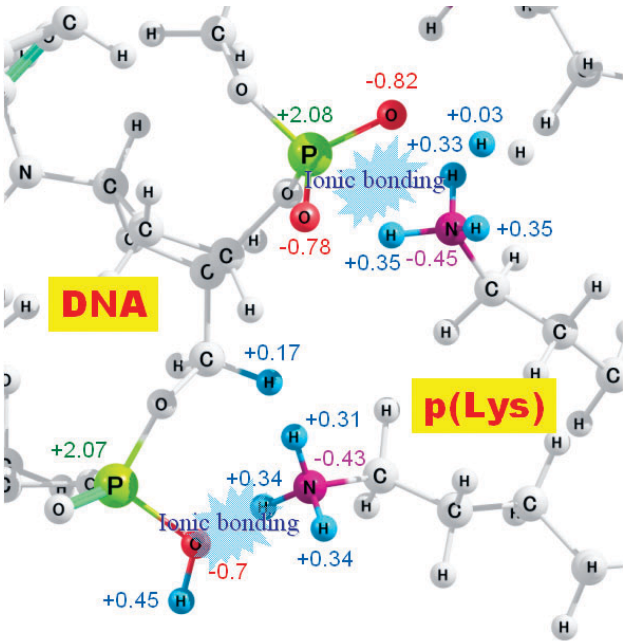

Fig. 4 Charge density of atoms in the vicinity of connection.

地球シミュレータを利用したドラッグデリバリシステムの研究：革新的医療への挑戦

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我々の目的は計算科学的手法を通してドラッグデリバリシステムの研究を加速することにある。昨年度には強束縛近似による多原子種に対応した量子化学プログラムを開発した。本年度はこのプログラムを現実的な系に適用した。また、DNAと高分子の結合部における詳細な振る舞いを理解するために密度汎関数法プログラムを用いた。シミュレーションは実験家に受け入れられている標準的なシナリオを支持する結果となった。しかし水溶液中のDNAの振る舞いを大規模計算によって理解するには昨年度の成果では未だ十分ではないことも明らかとなった。

キーワード：ドラッグデリバリシステム, DNA, 高分子, 分子軌道法, 強束縛近似