Title	スタッキング相互作用における非加算性寄与に見いだされる不整合な第一原理予見に関する研究
Author(s)	秦，肯
Citation	
Issue Date	2020-03-25
Type	Thesis or Dissertation
Text version	ETD
URL	http://hdl.handle.net/10119/16647
Rights	
Description	Supervisor:前園　涼，先端科学技術研究科，博士

氏名	QIN, Ken			
学位の種類	博士(情報科学)			
学位記番号	博情第 426 号			
学位授与年月日	令和 2 年 3 月 25 日			
論文題目	Inconsistencies in ab initio evaluations of non-additive contributions of DNA stacking energies			
論文審査委員	主査	前園涼	北陸先端科学技術大学院大学	教授
		東条敏	同	教授
		本郷研太	同	准教授
		大島義文	同	教授
		小口多美夫	大阪大学産業科学研究所	教授

論文の内容の要旨

The main research methods on biomolecules are experiments at present. As with other materials science studies, experimental methods are difficult to describe the microscopic details of biomolecules, including molecular-level dynamics and basic functional states. For drug development, such as cancer-targeted drugs, precise matching of biological targets is required. Generally, screening of target compounds requires high-throughput experiments, but this is costly. Therefore, computer simulation plays an important role in understanding and studying the structure and biological function of biomolecules compared to traditional experimental methods. In many-body systems, the empirical force field based on pairwise method cannot consider the non-additivity beyond force field superposition. Unlike classical mechanics, the force field superposition of quantum systems cannot be added by the instantaneous polarization. Therefore, the non-additivity in the interactions is expected in inter-molecular bindings due to the induced polarization by quantum fluctuations, such as van der Waals (vdW) forces.

The description and reproduce of the bonding itself, due to intermolecular forces, is a huge challenge for *ab initio* methods. Non-additivity is a more difficult subject that has long been far from the mainstream research field and has not been well analyzed yet. The *ab initio* quantum chemistry theory is a good description of the natural stacking energy, which allows reliable energy to be found on any base structure. Calculations, in any case, need to be done at a sufficient theoretical level. For example, standard Density Functional Theory (DFT), Hartree-Fock (HF), and semi-empirical methods all fail in the description of base stacking because they cannot correctly capture the dispersion effect. Of course, the high-precision method coupled-cluster with singles, doubles, and perturbative triples with complete basis set correction (CCSD(T)/CBS) is a widely used method called "gold standard" for quantum chemistry. It is impossible to calculates large systems due to its exponential growth computational cost. Recent advances in accurate calculation methods, especially through Quantum Monte Carlo (QMC) calculations, make it possible to handle larger systems. However, some work applied to systems consisting of weakly constrained subsystems shows that non-additivity is much larger than we expected. Although there is non-additivity in larger molecules, if the non-additive contribution is positive, then there is no research significance. If so, it will only make minor corrections to the C_6 (the coefficient of $1/R^6$ deciation interactions) force without any qualitative impact.

DNA molecules are the basis of biological, genetic variation. The most typical ten kinds of B-DNA molecular structures are composed of two kinds of purines and pyrimidines. For DNA molecules, the number of atoms is around 10, and the weak force between many-body molecules itself is the challenge in the quantum chemistry. We evaluated the non-additive contribution of the inter-molecular interactions in B-DNA stacking by using Fixed-Node Diffusion Monte Carlo (FNDMC) methods. In the previous calculation methods, the sign of the non-additive contribution is positive and tiny. Recent studies have shown that in the calculation using FNDMC method, and negative values appear in the results of non-additive contributions. First of all, the evaluation result in dispersion interaction by the standard SCF methods was proved failed due to the lack of dispersion term. Second, even the CCSD(T) method still evaluates dispersion interaction as the SCF-level, because of the practical handling of CBS at the feasible level with second order Møller–Plesset perturbation theory (MP2). Finally, although the calculation is trustworthy for the DMC method itself, the FN method cannot be ruled out to cancel the approximation error when the sign problem occurs, because we still divide the system according to the H-bond in the non-additive evaluation. While the SCF-level non-additivity is mostly positive, the non-additive contributions described by FNDMC are both positive and negative signs. The negative sign is found to be reasonable, which might be supported by a simple model analysis based on the London theory. It would, however, be premature to draw a conclusion that the FNDMC non-additivity reveals the truth. This is because the Watson-Crick base-pair involves the charge transfer caused by the H-bonds, but we could not verify if the error cancellations of the FN errors were successful for the H-bonds, as in the case of complexation energies. However, we cannot ignore the FN approximation which is used to solve the QMC sign problem. We analyzed the possible errors in this approach and discussed it.

Keywords: B-DNA, Stacking energy, Non-additivity, Quantum Monte Carlo, *ab initio* methods

論文審査の結果の要旨

タンパク質のダイナミクス解析などを代表例とした「分子間相互作用が支配する大規模系」は、シミュレーション科学の一つの地平となっている。分子間相互作用、特に量子ゆらぎに起因する分散力相互作用は、従前の古典的力場モデルによる表現が正当化されづらい記述対象であり、「2 体相互作用の重ね合わせ」で表現できない非加算性寄与の存在は代表格といえる。量子モンテカルロ法電子状態計算は、こうした量子効果を正確に取り扱う事のできる較正法として有用で、量子化学分野での従前手法では、本研究が対象とした DNA 塩基スタッキング系のシステムサイズは適用が難しい問題である。本研究は、「量子モンテカルロ法電子状態計算のみが、他の従前手法と定性的に異なる非加算性寄与の予見を与える」というインパクトのある事実を明らかにした。なぜ、此のような結果が得られるのかについて、科学的/多角的な議論を展開し、当該系を典型例とする大規模分子間結合系に一般に見いだされ得る新たな物性機構に関する知見を提供した研究である。特に、数多くの従前手法との予見比較を、「非加算性寄与の符号反転」という観点でまとめ上げ、その正当化可否を、モデル理論やデータインフォマティクス的な定理発見的アプローチで議論展開した手腕は評価に値するものである。本論文に関わる研究成果の一部は既に、申請者を主著者とする査読付原著論文成果[K.S. Qin, T. Ichibha, K. Hongo, and R. Maezono, Chem. Phys. 529, 110554 (2020)]に発表されており、当該コミュニティにおいて一定の評価を獲得している。

以上、本論文は、大規模分子間結合系に一般に見いだされ得る「相互作用の非加算性寄与」に関する機構を明確に洗い出し、最先端の大規模シミュレーションを駆使した系統的な研究調査により、バイオ系シミュレーション科学の地平拡大に大きく貢献する新たな知見を提供した業績として学術的に貢献するところを認め、よって博士(情報科学)の学位論文として十分価値あるものと判断した。