様式３

論　文　内　容　の　要　旨

氏　名　（　速水　智教　）	
論文題名	A novel algorithm for enhanced conformational sampling and its applications to compute free-energy landscapes of protein-protein and protein-ligand interactions （タンパク質—タンパク質およびタンパク質—リガンド分子の相互作用に関する自由エネルギー地形を計算するための新規の立体構造探索手法の開発と応用）

論文内容の要旨

It is known that there is relationship between protein conformation and function, and various experiments and computer simulations have been used to study the relationship. In recent years, computer-aided conformational sampling is becoming increasingly important to investigate biomolecular phenomena including protein–ligand, protein–protein, and protein–DNA binding processes as well as protein folding. In many cases, generalized-ensemble methods are used to enhance sampling. For example, adaptive umbrella sampling, apply an effective potential, which is derived from temporarily assumed canonical distribution as a function of one or more arbitrarily defined reaction coordinates. However, it is not straightforward to estimate the appropriate canonical distribution, especially for cases applying multiple reaction coordinates. Multidimensional virtual-system coupled canonical molecular dynamics (mD-VcMD), which is one of the generalized-ensemble MD methods does not rely on the form of the canonical distribution. Therefore, it is practically useful to explore a high-dimensional reaction-coordinate space.

In this study, I applied the mD-VcMD method to two types of system to verify its usefulness in the field of bioscience. At first, I performed the method with the simple molecular models consisting of three or four alanine peptides. I confirmed that mD-VcMD efficiently searched 2D and 3D reaction-coordinate spaces defined as inter-peptide distances.

Next, I applied the method to three systems consisting of mSin3B and one of three compounds, sertraline, YN3, and acitretin. Sertraline, YN3, and acitretin are chemical compounds designed to inhibit binding of neural restrictive silencer factor/RE1-silencing transcription factor (NRSF/REST) to a corepressor mSin3B. These compounds can be a drug candidate for neurological diseases, such as Down’s syndrome, medulloblastoma, Huntington disease, cardiomyopathy, and neuropathic pain. The mD-VcMD method produced useful quantities such as the spatial density of the ligand around the receptor, the intermolecular contact patterns, the propensity of molecular orientation, and the ligand flexibility. From these analyses, I showed that only sertraline produces a similar inter-molecular binding mode observed in the REST/NRSF–mSin3B complex.

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論文審査の結果の要旨及び担当者

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	（職）		氏　名
論文審査担当者	主 査	教授	中川　敦史
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論文審査の結果の要旨

速水智教氏は分子シミュレーション計算において高効率な立体構造探索を行うため、仮想系と共役した全原子分子動力学法を多次元に発展させたmD-VcMDと称する計算手法を開発し、単純なモデル分子系において迅速にカノニカル・アンサンブルが生成されることを確認し、その手法の有効性を示した。次に、開発した本手法を応用し、神経特異的転写抑制因子NRSFに結合するコリプレッサー蛋白質mSin3BのPAH1ドメインに結合し髄芽腫細胞の増殖抑制を示すSertralineと、mSin3Bへ結合するが髄芽腫細胞の増殖抑制を示さないYN3およびacitretinの3種の化合物に対して、mSin3BのPAH1ドメインとの複合体形成のシミュレーション計算を実施した。その結果、SertralineとYN3はmSin3Bと強く相互作用し、Sertralineの結合様式が最もNRSFの結合様式に近いことが解明された。これらの研究成果に関して、第１著者として3報の学術論文を発表した。

以上の理由により、博士の学位を授与するに値するものと認める。なお、チェックツール“iThenticate”を使用し、剽窃、引用漏れ、二重投稿等のチェックを終えていることを申し添えます。