Form 3

Abstract of Thesis

Name （Bekker, Gert-Jan）	
Title	Complex Structure and Affinity Prediction of a Flexible Protein Receptor and its Inhibitor using Molecular Dynamics Simulations 柔軟なタンパク質受容体とその阻害剤の複合体構造と親和性の予測

Abstract of Thesis

In order to predict the accurate binding pose as well as the binding affinity for a flexible protein receptor and its inhibitor drug, enhanced sampling with multicanonical molecular dynamics (McMD) simulations and thermodynamic integration (TI) were combined as a general drug docking method. Cyclin-dependent kinase 2 (CDK2) is involved in the cell cycle regulation. Malfunctions in CDK2 are thought to cause tumorigenesis, and is thus a potential drug target. Here, a long McMD simulation for docking the inhibitor CS3 to CDK2 starting from the unbound conformation was performed. McMD can explore a wide conformational space without conformational trapping at local minima by applying a bias to the system. This bias enables uniform sampling over a specific energy range, facilitating a random walk within this energy space, where each energetic state is equally probable to be sampled. From the multicanonical ensemble, the canonical, i.e. physically accepted ensemble, can be obtained by the reweighing process. Using McMD, stable binding poses can thus be obtained, while the simulation is not trapped in local energy minima. However, due to the limited amount of unbound structures in the canonical ensemble, the affinity is difficult to determine from the McMD simulations. TI however is very effective at calculating the affinity by measuring the average forces on the ligand along the binding/unbinding pathway, where integration of these forces produces the binding free energy. Using the multicanonical ensemble, the predicted bound complex, a potential binding/unbinding pathway connecting the predicted bound complex with the unbound one, and stable intermediary structures along this pathway were obtained. Subsequently, the forces along this pathway were sampled, starting from these stable intermediary structures. Finally, the binding free energy was readily computed by TI. Using this combination, the correct binding pose of CS3 to CDK2 was predicted, and their affinity coincided well with the experimental value.

様式 7

論文審査の結果の要旨及び担当者

氏　名　（ Gert-Jan Bekker ）			
	（職）		氏　　名
論文審査担当者	主 査	教授	中村　春木
	副 査	教授	難波　啓一
	副 査	教授	中川　敦史
	副 査	教授	高木　淳一

論文審査の結果の要旨

申請者は、分子動力学計算を応用した効率的構造サンプリング（マルチカノニカル分子動力学法）と熱力学的積分法（Thermodynamic Integration）を組み合わせることによって、複合体の構造予測と複合体形成の結合自由エネルギーを算出するオリジナルな手法を考案した。この手法を用いて、Cyclin Dependent Kinase 2にその阻害剤の一つであるCS3が結合した複合体構造と結合自由エネルギーを推定したところ、実験による複合体構造と親和力と良く一致した。この手法は極めて一般的な手法であり、多くの異なる蛋白質に対するリガンド結合に応用でき、薬物開発への応用も期待される。以上から、申請者は学位授与を受けるに値すると考える。