学 位 論 文 内 容 の 要 旨

博士の専攻分野の名称　博士（情報科学）　氏名　RATNAYAKE MUDIYANSELAGE Sangeetha Udani Ratnayake

学 位 論 文 題 名

Enhancing Precision in Antibody-Antigen Complex Structure Prediction Through Parametric Optimization of RosettaAb Docking Scoring Function
（RosettaAb Docking スコアリング関数のパラメータ最適化を通じた抗体-抗原複合体構造予測の精度向上）

Understanding the structure of antibody-antigen (Ab-Ag) interactions is crucial for various scientific applications. Computational methods have emerged as efficient tools for studying these interactions, offering advantages over traditional methods. However, existing computational docking methods face challenges in accurately predicting Ab-Ag structures. One key limitation is the scoring function, designed for rigid and well-characterized protein structures, which often falls short in practice despite optimizations for Ab-Ag in programs. Rosetta is a widely used program for Ab-Ag docking.

To address this issue, a proposed solution involves using decoy distribution as a valuable indicator for assessing the goodness of fitting in docking simulations. A decoy, representing an alternative binding pose or conformation, is plotted on a distribution graph that showcases energy scores versus Root Mean Square Deviation (RMSD) values. This decoy distribution becomes crucial for evaluating existing scoring functions and seeking more optimized parameters, essential for accurately predicting Ab-Ag structures.

The thesis comprises four chapters. The first chapter provides background information, while the second chapter evaluates specific parameters within Rosetta-derived scoring functions, focusing on the energy landscape of generated structures. The third chapter develops models within the Rosetta framework to optimize scoring function parameters, using quantitative evaluations of decoy distributions to refine parameters for each Ab-Ag complex. This chapter introduces a novel approach to customizing scoring functions, potentially advancing drug discovery and deepening our understanding of molecular-level antibody-antigen interactions. The fourth chapter summarizes key findings, discusses further applications, and suggests areas for future investigation.

The application of the decoy distribution revealed that the default Rosetta approach proved ineffectual in 88 out of 100 cases, showcasing the influence of particular amino acids within antibody binding sites on its performance. The removal of solvation parameters slightly improved Rosetta's performance, but not to a sufficient extent. A new method was developed to optimize scoring function parameters for each Ab-Ag complex, resulting in significantly reduced RMSD values and the identification of parameters effective for most complexes.

The research outcomes hold implications for drug development, protein engineering, and computational biology. This work serves as a catalyst for innovation in medical research and therapeutic development, shedding light on the complexities of Ab-Ag interactions at the molecular level.