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JAMES RENNIE BEQUEST

REPORT ON EXPEDITION/PROJECT/CONFERENCE

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Expedition/Project/Conference Title: 3DSIG 2009: the 5th Bioinformatics and Computational Biophysics satellite meeting

Travel Dates: 26-28 June 2009 ....

Location: Stockholm International Fairs, Sweden ....

Group Member(s): Wissam Mehio ....

Aims: Present Talk/Poster about my program, STP...

OUTCOME (not less than 300 words):-

Introduction

I went to this conference to present my new algorithm that predicts protein binding sites, to learn about the new advancements in the field, and to meet the international community of computational structural bioinformatics. The outcome of the conference exceeded my expectations by far, as I got into very interesting discussion about the accuracy of the current energy functions to the cons and pros of various simulation and modeling paradigms.

In short, the experience was breathtaking and extremely educational. Two days of continuous talks and surprisingly all of them were exciting and beneficial. My talk was scheduled on the afternoon of the second day, and it was great. I detail below some of the research I had the chance to look at and considered of direct benefit to my study of protein ligand interactions.

Relevant and Interesting Research

A. Site Prediction/ Interaction / Docking

Fiber Dock

FiberDock performs Protein-Protein docking simulations of with the receptor treated as a flexible molecule, simulating sidechain flexibility by rotamers and backbone flexibility by normal mode simulations. It is available online at: http://bioinfo3d.cs.tau.ac.il/FiberDock/.

Atomic Interactions for characterizing protein ligand binding interfaces

Energy simulations have been run to characterize the binding modes and orientations in protein ligand complexes. This study clearly shows that studying one partner is not enough to detail the interaction specifically. The need of thorough studies for both binding partners have been asserted.

Prediction Hot Spot Residues at protein – protein interfaces

This study showed that when trying to detect the best residues with known forcefield parameters for energy simulations, the result attained was not perfect. The authors then attempted to use machine learning (via a support vector machine) to train their computer at calculating new forcefield parameters by learning from existing protein-protein complexes. The surprising result

was that the new parameters attained performed better than the commonly used parameters, though significantly different than what is approved as general forcefield parameters.

Differential geometry to characterize biologically relevant interfaces (RNA/DNA)

This study highlights the difference in surface topology between protein binding sites that bind RNA and those that bind DNA. Differential geometry was used to define peaks, valleys, pockets, ridges, etc… and the result was a clear distinct between the two classes of binding sites.

Protein Binding Pocket Similarity based on comparison of 3D atom Clouds

This program can compare binding pockets and hence predict potential ligands based on the location of the atoms in the binding pocket. It is freely available at: http://cbio.ensmp.fr/paris

Ligand-based Active site alignment

This program, called Ligalign, compares enzyme active side based on the ligands they bind. A set of physiochemical properties is then assigned based on various ligand types. It is freely available at: http://compbio.cs.toronto.edu/

B. Modelling

State of Ab-initio Modeling

Till now, ab-initio modeling paradigm has not been a greatly successful. However, and due to the increase in computational power and the algorithms being publically released, allowing third party improvements, we have reached a stage where ab-initio modeling has become a fact, and a reality.

Structural modelling of protein-protein interactions

This database gives access to a genome-wide protein-protein interaction data including structural models and analysis tools. Available at: http://gwidd.bioinformatics.ku.edu

3D-BLAST

This program uses Spherical Polar Fourier transformations to define the shape of a protein and enables quick comparison between different proteins based on tertiary structure only, without relying on sequence.

TopDomain-web: Protein Domain Decomposition

This is a handy tool for characterizing domains in protein structures, freely available at: http://topdomain.services.came.sbg.ac.at

COPS: workbench for explorations in foldspace

Cops is another databank of protein structures, organized by structural similarities between domains, and allows users access to the classification software to classify their new proteins. Freely available at: http://cops.services.came.sbg.ac.at/

ModLink+: improving fold recognition with protein-protein interactions

This program predicts the fold of a protein using protein-protein interaction information. It surpasses current method of remote homology detection in both coverage and accuracy. Freely available at: http://sbi.imim.es/modlink/

C. The State of computational Molecular Recognition

This discussion took place at the end of day 1 of 3DSig, with presenting all the challenges that face the field of computational molecular recognition. With our inability to conduct molecular dynamics simulations for more than a few microseconds and our uncertainty of the accuracy of our forcefield energy parameters, the questions that would intuitively be asked are:

1. Will computational biology deliver what it promised?
2. How far more can the field advance?
3. Are the energy definitions wrong?
4. Is the computational capacity insufficient?
5. Is the computational accuracy insufficient?

Although there is no definite answer for any of those questions, it was a general consensus that the increase of data available helps create better models. There is definitely something

inaccurate in the definitions of energy interactions, otherwise they would have been much more successful. Finally, everyone looks forward to the new advancements in computing, especially quantum computing which started as a science fiction theory and is slowly becoming a reality. When this technology is attainable, longer simulations will be made possible and computer models will do a better job at predicting molecular recognition.

Conclusion

There is no way to be diplomatic and academic about my impressions. This conference was awesome! The people I've met… their enthusiasm… the new methods I had a look at… the questions I received about my work… Everything made me more excited about going back to Edinburgh to continue on with my PhD, hoping I would meet this group of researchers once again next year. Finally, I would like to thank the JRB for funding this conference trip.