Protein-Protein Interactions and Macromolecule Modelling



Juliette Martin Team Modelling Biological Macromolecules

UMR 5086

Molecular Microbiology and Structural Biochemistry, IBCP Lyon

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Who are we?

Team MOBI: Modelling Biological Macromolecules

Team leader



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What do we do?

- Simulation of biological macromolecules : biomembranes, protein-DNA complexes, protein-protein complexes
- Developments in Structural Bioinformatics : protein interface prediction, structural study of non-interacting proteins, tails in protein complexes, protein-protein docking, tools for structural bioinformatics, inference of protein-protein interaction networks

Molecular simulations of biomembranes Luca Monticelli

MARTINI coarse-grained force field development





Biomembranes: interaction with synthetic materials



Lipid droplet biogenesis



Dynamics of protein-DNA recognition

Loic Ethève Richard Lavery Juliette Martin



✓ Time-dependent recognition



SKN-1 (1skn)

✓ Essential features for stability and recognition

Ethève et al NAR 2015 Ethève et al NAR 2016 Ethève et al NAR 2017

Simplified rigid models

Dynamics of protein-protein complexes

Elisa Frezza Juliette Martin Richard Lavery

Allosteric regulation of an adenyly-cyclase by binding of regulatory G-protein

mobile ATP



Human Brain Project

G-protein binding

Frezza et al submitted

ATP locked into active conformation

Structural Bioinformatics

- Protein interface prediction,
- Structural study of non-interacting proteins,
- Tails in protein complexes,
- Protein-protein docking,
- Tools for structural bioinformatics,
- Inference of protein-protein interaction networks

Protein interface prediction

Guillaume Launay Mélanie Garnier Juliette Martin Richard Lavery



Highly localized regions

- Enrichment in experimental interfaces
- Computationally tractable
- Original signal in prediction
- Correct prediction for 70% of the interfaces

25 probes

Martin J, Lavery R: Arbitrary protein-protein docking targets biologically relevant interfaces. *BMC Biophysics* 2012, 5:7.

Martin J: Benchmarking protein–protein interface predictions: Why you should care about protein size. *Proteins* 2014, 82:1444–1452.

Protein interface prediction

Guillaume Launay Mélanie Garnier Juliette Martin



Non-interacting Proteins

Guillaume Launay Nicoletta Ceres Juliette Martin



Interacting proteins

Non-interacting proteins

- ✓ A very common situation
- ✓ Predicted as stable by coarsegrain model
- Major shortcuts in the native network



Launay, Ceres and Martin, Scientific Reports 2017

A new picture of protein-protein interactions

Negative regulation



0.2% Functional interactions

9% pairs with compatible structures

99.8% Negative interactions

Tails in protein-protein complexes

Olivier Martin Guillaume Launay Juliette Martin



 ✓ Terminal residues are strongly rejected at the periphery of interfaces
✓ Terminal residues do not act as charged side chains

Martin et al, PLoS ONE 2016

Protein-protein docking

Guillaume Launay Mélanie Garnier **Juliette Martin**



MEGADOCK docking engine



Masahito Ohue, Tokyo Institute of Technology

Ongoing work....

Tools for structural bioinformatics

Guillaume Launay Mélanie Garnier



Tools for structural bioinformatics



WORKFLOW MANAGMENT SYSTEM

WEB INTERFACE

Tools for structural bioinformatics



GOAL: avoid to run tasks which have already been performed



2) RE-INSTANCE THE IDENTICAL ONE



Inference of protein-protein interactions



Streptoccocus pneumoniae

Pneumococcus, human pathogenic bacterium, major cause of pneumonia.

Work in collaboration with microbiologists of the MMSB lab

Pneumococcus 2030 proteins



PPIs reference set



348 806 interactions http://www.ebi.ac.uk/intact/

25 000 interactions from various organisms obtained by two-hybrid screenings

Guillaume Launay Juliette Martin

Main goal : Identification of molecular targets to block the cellular division of the pathogen.

Strategy: In Silico construction of the complete bacterial interactome.

Pin-point the set of subnetworks responsible of the division process

Divisome

Inference of protein-protein interactions



Inference of protein-protein interactions



Total streptococcus inferred interaction

Filtering the network for seed nodes

Featuring the GO term "cell division"





31 subnetworks part of the "divisome"

Entry	Arnotation score	GENEONTOLOGY Unifying Minkegy	Protein names
Q8CWP9	****	cytoplasm [GO:0005737]; cell cycle [GO:0007049]; cell division [GO:0051301]; regulation of cell shape [GO:0003360]	Cell division protein Dr/IVA
Q8DNV9	***	cell division (GO:0051301); cell septum assembly [GO:0090529); FtsZ-dependent cytokinesis [GO:0043093]; protein polymerization [GO:0051258]	Cell division protein PtsZ
Q82PJ9	मंत्रोतमं	DNA binding [GO:0003677]; chromosome condensation [GO:0030261]; DNA replication [GO:0006260]; sister chromatic cohesion [GO:0007062]	Chromosome partition protein Smc
P67283	¥¥	Integral component of membrane [GO:0016021]; plasma membrane [GO:0005886]; enconuclease activity [GO:0004519]; RNA binding [GO:0000720]; mRNA catabolic process [GO:0006402]	Ribonuclease Y (RNase Y) (EC 3.1)
Q8DNT4	*	DNA binding [GO:0003677]: transcription factor activity, sequence-specific DNA binding [GO:0003700]; transcription, DNA-templated [GO:0006351]	Uncharacterized protein
Q8DP33	×	DNA binding [GO:0003677]; transcription factor activity, sequence-specific DNA binding [GO:0003700]; transcription, DNA-templated [GO:0006351]	Uncharacterized protein

Exemple : first neighbors network of the mapZ protein



Take-home message

The MOBI team at IBCP is interested in:

- ✓ Simulation of biological Macromolecules
 ✓ Structural bioinformatics of
 - Protein-Protein Interactions under various aspects

Acknowledgments

MOBI team

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Human Brain Project



