

# Integrated Modelling of PROTEIN Complexes VIA Single Shot Registration using DREAM (IMPROVISeD)

iGem IISc-Software  
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Kotak IISc AI-ML Centre





# Integrated Modelling of Protein Complexes

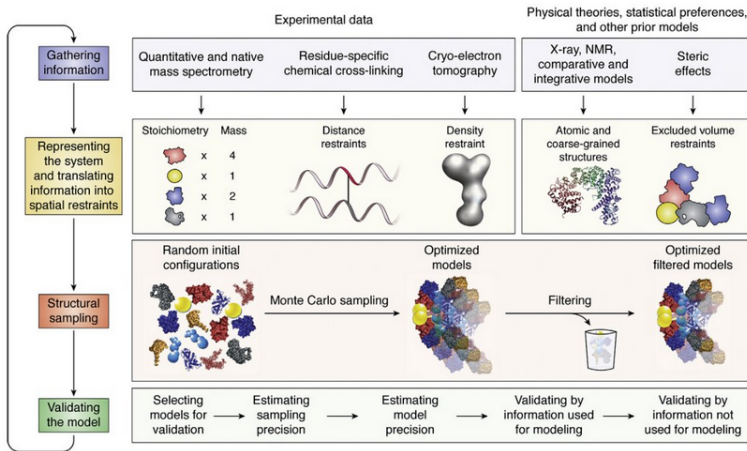
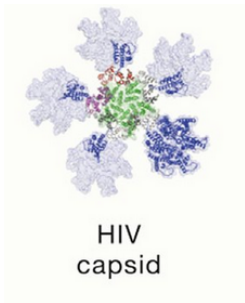
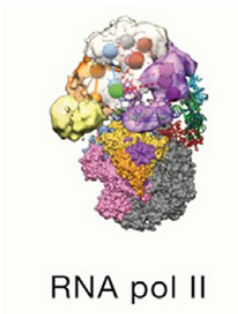


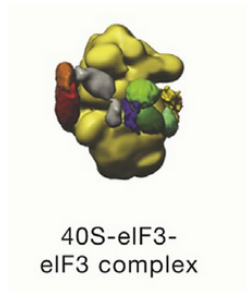
Figure 1: Flowchart representing the IMP



(a) Deshmukh et al., 2013



(b) Murakami et al.,  
2013

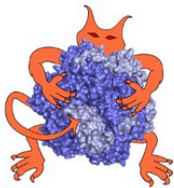


(c) Erzberger et al.,  
2014

# Why Integrated Modelling

- ① Using new information
- ② Maximizing accuracy, precision and completeness
- ③ Planning experiments

# Present Landscape



(a) IMP, the integrative modelling platform



(b) rosetta



(c) haddock

Program	Functionality	Web Site	Reference
ISD	Bayesian modeling on the basis of NMR data	N/A	Rieping et al., 2005
IMP	Integrative modeling	<a href="http://integrativemodeling.org">integrativemodeling.org</a>	Russel et al., 2012
Rosetta	Integrative modeling	<a href="http://rosettacommons.org">rosettacommons.org</a>	Das and Baker, 2008
ISDB	Integrative modeling	<a href="http://plumed.org">plumed.org</a>	Bonomi and Camilloni, 2017
pow <sup>er</sup>	Integrative modeling	<a href="http://lbm.epfl.ch/resources/">lbm.epfl.ch/resources/</a>	Degiacomi and Dal Peraro, 2013
cMNXL and Jwalk/MNXL	Integrative modeling	<a href="http://topf-group.ismb.lon.ac.uk/Software">topf-group.ismb.lon.ac.uk/Software</a>	Bullock et al., 2018a; Bullock et al., 2018b
PyRy3D	Integrative modeling	<a href="http://genesilico.pl/pyry3d/">genesilico.pl/pyry3d/</a>	J. M. Kasprzak, M. Dobrychtop, and J. Bujnicki
PGS	Modeling genome structure	<a href="http://github.com/alberlab/PGS">github.com/alberlab/PGS</a>	Hua et al., 2018
TADBit	Modeling genome structure	<a href="http://sgt.cnag.cat/3dg/tadbit/">sgt.cnag.cat/3dg/tadbit/</a>	Serra et al., 2017
MDFF/NAMD	Fitting of molecular models into EM maps using MD simulations	<a href="http://ks.uiuc.edu/Research/mdff">ks.uiuc.edu/Research/mdff</a>	Trabuco et al., 2008
ATSAS	Integrative modeling using SAXS	<a href="http://embl-hamburg.de/biosaxs">embl-hamburg.de/biosaxs</a>	Franke et al., 2017
IFoldRNA	Integrative modeling of RNA	<a href="http://iFoldRNA.dokhlab.org">iFoldRNA.dokhlab.org</a>	Sharma et al., 2008
HADDOCK	Integrative modeling using docking and data derived restraints	<a href="http://haddock.science.uu.nl">haddock.science.uu.nl</a>	Dominguez et al., 2003
ATTRACT-EM	Integrative modeling using docking and EM	<a href="http://attract.ph.tum.de">attract.ph.tum.de</a>	de Vries and Zacharias, 2012
DireX	Flexible fitting of EM maps with data derived distance restraints.	<a href="http://schroderlab.org/software/direx/">schroderlab.org/software/direx/</a>	Wang and Schröder, 2012
MDFit	MD based integrative modeling using EM maps	<a href="http://smog-server.org/SBMextension.html#mdfit">smog-server.org/SBMextension.html#mdfit</a>	Ratje et al., 2010
FPS	Integrative modeling using FRET data	<a href="http://www.mpc.hhu.de/en/software/fps.html">www.mpc.hhu.de/en/software/fps.html</a>	Kalinin et al., 2012
XPLOR-NIH	Structure determination using NMR data	<a href="http://nmr.cit.nih.gov/xplor-nih/">nmr.cit.nih.gov/xplor-nih/</a>	Schwieters et al., 2018
PatchDock	Molecular docking by shape complementarity	<a href="http://bioinfo3d.cs.tau.ac.il/PatchDock/">bioinfo3d.cs.tau.ac.il/PatchDock/</a>	Schneidman-Duhovny et al., 2005
ISPOT	Structure determination using SAS, footprinting and docking	<a href="http://www.theyanglab.org/spot/">www.theyanglab.org/spot/</a>	Hsieh et al., 2017
BCL	Various servers for integrative modeling	<a href="http://meilerlab.org/index.php/servers">meilerlab.org/index.php/servers</a>	Woetzel et al., 2011
ChimeraX	Model visualization	<a href="http://rbvi.ucsf.edu/chimerax">rbvi.ucsf.edu/chimerax</a>	Goddard et al., 2018
VMD	Model visualization	<a href="http://ks.uiuc.edu/research/vmd">ks.uiuc.edu/research/vmd</a>	Humphrey et al., 1996
Protein Model Portal	Portal to atomic models of proteins	<a href="http://proteinmodelportal.org">proteinmodelportal.org</a>	Haas et al., 2013
PDB-Development	Archiving of integrative structures	<a href="http://pdb-dev.wwpdb.org">pdb-dev.wwpdb.org</a>	Burley et al., 2017

# Our Improvement

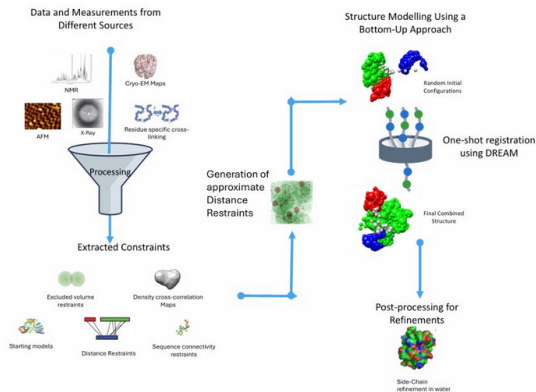


Figure 4: Flow Chart

- 1 Single Shot Registration
- 2 Scalability



## ② Methodology: by Ayush Raina

# Methodology

## Distance Restraints and Energy Assisted Modelling

DREAM algorithm uses distance restraints obtained from NMR data to model the structure of proteins in 3 steps:

- 1 **Construction of Substructures:** We divide the available distance restraints data into dense fragments and model their structure first.

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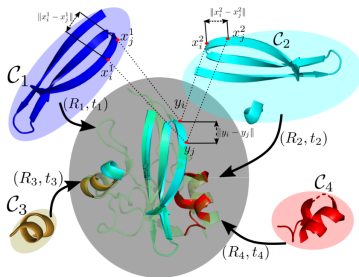
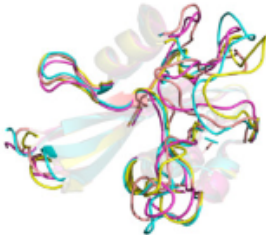


Figure 6: One Shot Registration

Here  $(R, t)$  denotes the rotation and translation of the substructure.

# DREAM

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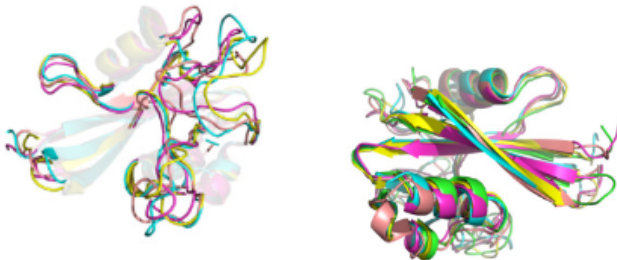


Figure 7: Gap Filling



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- Uses divide and conquer approach which increases robustness and scalability.
- Reduces numerical instabilities because of the use of dense fragments.
- In sequential registration, the error keeps on accumulating which is not the case in one shot registration.

# Sequential vs One Shot Registration

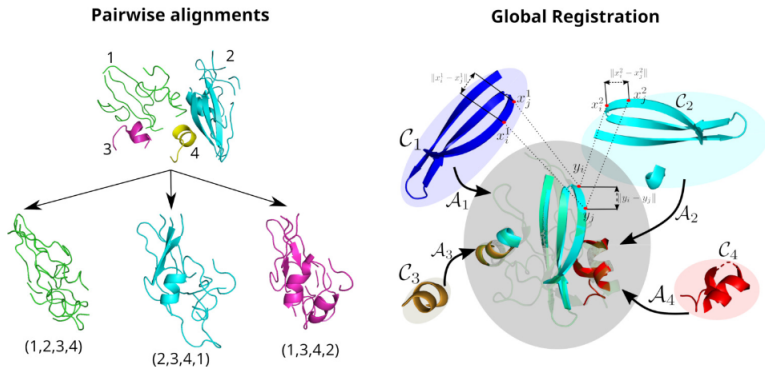


Figure 8: Sequential vs One shot registration

# Integrative Modelling Platform

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We wish to replace the computationally expensive sampling techniques to paradigms used in DREAM:

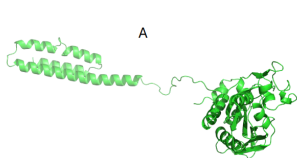
- Orientate the structures of subunits based on experimental evidence which is similar to substructure computation in DREAM
- Register the subunits in one shot while respecting the experimental evidence. (an enhancement of DREAM's registration)

# How will this happen ?

- Our substructures in this case are different kinds of proteins.
- We have cross-links data available these proteins.

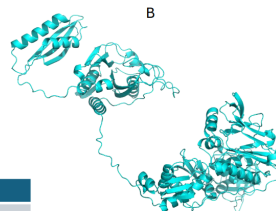
Given this information, we need to do one shot registration of these proteins to model the structure of complex.

# Inputs



Coordinates	
75	CA
85	CA
181	CA
237	CA
321	CA
342	CA

Crosslinks			
78	A	650	B
85	A	650	B
87	A	679	B
321	A	502	B
342	A	610	B
181	A	593	B
75	A	650	B
237	A	502	B



Coordinates	
502	CA
593	CA
610	CA
650	CA
679	CA

Figure 9: Example of 2 proteins with cross-links data



# Problem

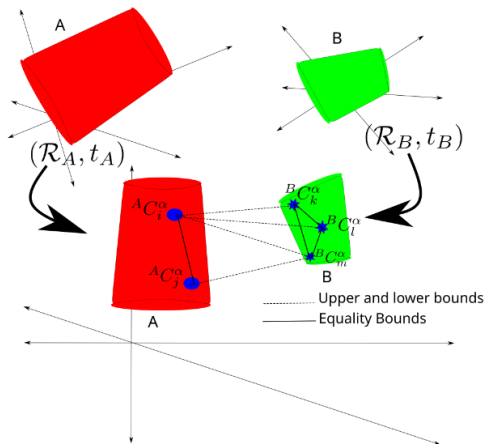
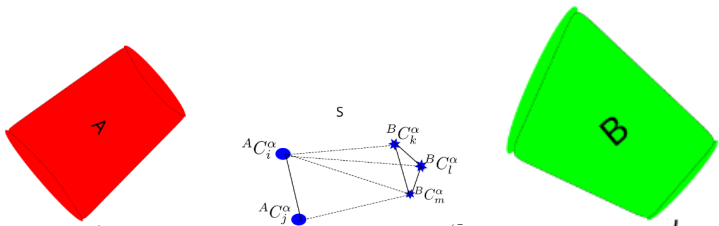


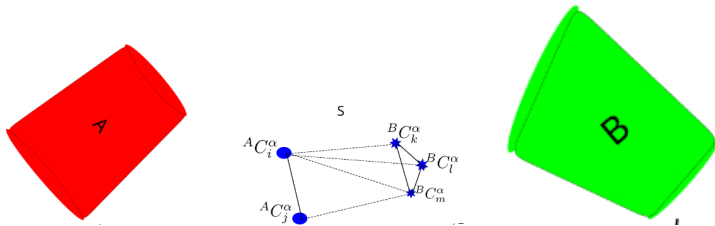
Figure 10: Consider A,B as proteins and the lines as cross-links

# Solution



Consider S as hypothetical framework.

# Solution



Consider S as hypothetical framework. Then we can do one shot registration of A, S and B

# Solution

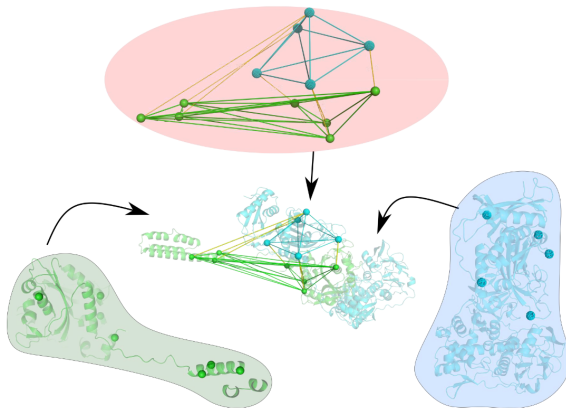


Figure 11: One shot registration

# Some Observations

1. In the hypothetical framework, we have all pairs of distances between C-alpha atoms in each protein.

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1. In the hypothetical framework, we have all pairs of distances between C-alpha atoms in each protein.
2. For registering  $n$  proteins, only 1 hypothetical fragment is needed. So registration of  $n + 1$  proteins is done.

### ③ Human Practices: by Trishna Singh

# Human Practices

## The 3R's

- Reflection
- Responsibility
- Responsiveness

Our stakeholders:

- Professors
- Research Students
- Protein Modelling Companies



# Education

- 1 Demonstrations
- 2 Computational Biology Solvathons
- 3 Structural Biology workshops for iGEMers
- 4 Talks by people in industry, academia

# Our Mentors



(a) Dr. Shruthi(NCBS)



(b) Prof Debnath Pal  
(Dept for  
Computational and  
Data Sciences)

# To Summarize

Content to be added

# Thank You!

# Thank You!

Here are some references:

- 1 DREAMweb,  
<https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/pmic.202300379?af=R>
- 2 Improved NMR-data-compliant protein structure modeling captures context-dependent variations and expands the scope of functional inference, [https://onlinelibrary.wiley.com/doi/full/10.1002/prot.26439?\\_gl=1\\*1f1t0yi\\*\\_gc1\\_au\\*MjcyNjE4Nzc0LjE3MTg5MDgxOTg](https://onlinelibrary.wiley.com/doi/full/10.1002/prot.26439?_gl=1*1f1t0yi*_gc1_au*MjcyNjE4Nzc0LjE3MTg5MDgxOTg).