Intrinsically Disordered Proteins and Heterogeneous Complexes

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Presented by Sindhu Raghunandan
# Outline

<table>
<thead>
<tr>
<th>Extension of software: flexible proteins</th>
<th><img src="image1.png" alt="Image" /></th>
<th><img src="image2.png" alt="Image" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical data v. experimental data</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Extension of software: heterogeneous complexes</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Protein Structure

• Importance
• Protein Basics
• DNA/RNA

PURINES

Adenine (A)

Guanine (G)

PYRIMIDINES

Uracil (U)

Thymine (T)

Cytosine (C)
Intrinsically Disordered Proteins

- Definition
- Importance
- Functional Aspects
- Structure

http://DisProt.wsu.edu
Small Angle Neutron Scattering
SASSIE

- Dihedral Structure Generator
- Cryson (SAS Calculator)
- Chi-square filtering
- Density Plot
Generating Structures

\[ V \approx V(\text{VDW}) + V(\text{Dihedral}) \]

\[ V(\text{Dihedral}) = K_1(1 + \cos(n_1\Theta - \Delta_1)) + K_2(1 + \cos(n_2\Theta - \Delta_2)) \]

1 protein, 65 residues, >100,000 configurations

113 proteins, 84719 residues

SASSIE dihedral angle sampling represents experimental data
Dihedral Structure Generator Algorithm

1000s X

Get PDB file
Randomize angles
Energetics sample
Overlap check
Save coordinates
Gag: Motivation and Methods

Immature
Lipid Bilayer
RNA

Mature
Matrix (MA)
Capsid (CA)

Sample
incident beam

scattered beam

2D neutron detector

200 Å ~1100 Å
Full Gag

BEST: 
Rg: ~35
X^2: 0.85

WORST: 
Rg: ~59
X^2: 17
Pieces of Gag

- **MA-NTD**
  - MA Residues 1-122
  - Linker Residues 123-144
  - 27,444 structures
- **NTD-CTD**
  - NTD Residues 1-133
  - CTD Residues 140-209
  - Linker Residues 134-139
  - 19,943 structures
- **NTD-CTD-NC**
  - P2+NC Residues: 210-287
  - Linker Residues: 134-139
  - 117,550 structures
**MA-NTD**

- Best: $R_g = 29.470$, $X^2 = 0.655$
- Worst: $R_g = 19.410$, $X^2 = 9.189$

The diagram shows the scattering intensity $I(q)$ (cm$^{-1}$) against $q$ (angstroms$^{-1}$) with $R_g$ (angstroms) on the x-axis. The graph compares the best and worst fits to the experimental data ($R_g$ EXP).
NTD-CTD

Best
Rg: 22.860
$X^2: 0.2498$

Worst
Rg EXP
Rg: 17.240
$X^2: 5.33$
NTD-CTD-NC

Rg (angstroms):
- Best: Rg = 35.00, $X^2 = 2.822$
- Worst: Rg = 22.530, $X^2 = 17.39$

$I(q)$ (cm$^{-1}$) vs. $R_g$ (angstroms)
Types of Systems

- Homogenous or Heterogeneous

Gag Dimer
Identifying Interactions

- 3D plotting
- Representative Atoms
- Distance measurements
- Cutoff
SASSIE: Complex Dihedral Generate

- Algorithm
- Changes in code
  - Types of overlap
  - Align

1000s X

- Get PDB file
- ID segments
- ID interaction
- Randomize angles
- Energetics check
- Overlap check
- Align
- Save coordinates
HIV-1 Gag Dimer

- Best: $R_g \approx 47$, $X^2 : 1.3$
- Worst: $R_g \approx 64$, $X^2 : 49$
Gag Dimer Assembly: Revisited
Applications:

- Minichromosome maintenance (MCM) proteins
- HIV Integrase

Best MCM structures with old algorithm
Acknowledgements

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UMD-CP
### Gag

<table>
<thead>
<tr>
<th>SANS</th>
<th>Sedimentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>a = b = 13Å</td>
<td>a = b = 13.5Å</td>
</tr>
<tr>
<td>c = 100Å</td>
<td>c = 114 Å</td>
</tr>
</tbody>
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</tr>
<tr>
<td>c = 5Å</td>
</tr>
<tr>
<td>(thickness)</td>
</tr>
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Best Rg: 29.470 X2: 0.655

Worst Rg: 19.410 X2: 9.189

Best Rg: 22 X2: 0.2

Worst Rg: 17.240 X2: 5.13

Best Rg: 17 X2: 0.2

Worst Rg: 17 X2: 5