Exploring conformational switching in proteins with coarse-grained molecular simulations

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Stefan Wallin

Department of Physics and Physical Oceanography
St John’s, Newfoundland
Sequence-structure relationship in proteins

Proteins are:

• mutationally robust
• under selective pressure to maintain function and thus structure

…how do new folds arise in evolution?

Growth of experimentally determined structures/folds

Protein Data Bank: http://www.rcsb.org
Conformational switching in proteins:

1) Fold switching of “metamorphic” proteins
   - Triggered by ligand binding, change in pH, temperature, etc.

   Cyanobacterial circadian clock:
   ![KaiB fold switching](image1)
   ![KaiB fold switching](image2)
   Li Wang et al. Science 349 2015

2) Coupled folding-binding of intrinsically disordered proteins (IDPs)
   - Especially common in signaling and regulatory proteins.
   ![pKID binding to the KIX domain of CREB, folding in the process](image3)

3) Regulated unfolding

4) Misfolding and aggregation
   - Involved in disease (Alzheimer’s, Parkinson’s, …)
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   - Triggered by ligand binding, change in pH, temperature, etc.

2) **Coupled folding-binding of intrinsically disordered proteins (IDPs)**
   - IDPs common in signaling, regulation.

3) **Regulated unfolding**

4) **Misfolding and aggregation**
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Computational challenges in protein simulations

Ordered protein

\[ \langle O \rangle \approx O_{\text{native}} \]

Disordered protein

\[ \langle O \rangle = \int_{X} O(X)P_{B}(X)dX \]

1. Algorithms for efficient conformational sampling.

2. **Coarse-grained models.** Computationally convenient yet accurate enough to predict functional and structural properties.
Protein simulations at different resolution levels

~1 bead per amino acid, on/off-lattice, Go-type (structure-based) models.

level of detail (≠ precision)

intermediate-level coarse-graining

All-atom explicit water (forcefields e.g. AMBER, CHARMM)

Our approach:

• Intermediate-to-detailed protein geometry but no explicit water
• Monte Carlo sampling techniques
• Parametrization by “top-down” procedure: Require a test set of protein sequences to fold robustly into states with correct structures.
All-atom model, solvent-free  

(lrbäck et al. PMC Biophysics 2 2009)

Open source package (PROFASI): http://cbbp.thep.lu.se/activities/profasi/

• Current test set: ≈20 sequences with 10-65 amino acids and structurally diverse native states

• Effective energy function

\[ E = E_{\text{local}} + E_{\text{exvol}} + E_{\text{hbond}} + E_{\text{sc}} \]

CBβ-model, solvent-free  

(Bhattacherjee and Wallin, Biophys J 102 2012)

• Sidechain single bead (enlarged Cβ-atom)

• 3 amino acid types: hydrophobic (h), polar (p), turn (t)

• Simple effective energy function:
  — Pairwise hh-attraction  
  — Mainchain-mainchain h-bonding
Monte Carlo folding simulation of Top7 (92 amino acids)

Mohanty et al. Proteins 81 2013
Metamorphic proteins and fold switching

- Start point: $G_A$ and $G_B$ (different folds, no sequence similarity)
- Mutational pathway with abrupt fold switch

Possible mechanism for the evolution of new folds.

- How common is fold switching along mutational pathways between folds?
- What are the biophysical properties of protein sequences in the “border lands” between folds?
Cβ-model as a biophysical basis for the sequence-structure relationship

all-α

α+β

all-β

(Bhattacherjee and Wallin, Biophys J 102 2012)
Is there a mutational pathway with a switch in fold?

Fold A

Fold B

$p$p$p$p$h$p$h$p$p$t$t$p$p$h$p$p$

$p$p$p$p$h$p$h$p$h$p$p$p$p$p$h$h$p$p$

Differ in 10 of 16 positions

⇒ Total number of sequences: $3^{16} = 4,304,672$
⇒ Number of combinations for the 10 positions: $3^{10} = 59,049$
⇒ Size of “binary” sequence space: $2^{10} = 1,024$
Several mutational pathways connect folds A and B

Fold switches abrupt, completed in 1-2 mutational steps
Why is protein fold switching so abrupt?

Free energy of fold switching $\Delta F_{AB}$:

$\Delta F_{AB} > 0$  Fold A stable
$\Delta F_{AB} < 0$  Fold B stable

Dissect into energetic and entropic terms:

$$\Delta F_{AB} = \Delta E_{AB} - T \Delta S_{AB}$$

energetic contribution  (chain) entropy contribution
Stability is not everything:
How does functional abilities change along mutational pathway?

- The character of structural and functional transitions differ.
- Smooth functional gradients in sequence space may drive structural fold changes in proteins.
- Switch between folds do not coincide with switch in preferred binding partner.
Binding-induced protein fold switching
Biological benefit of intrinsic disorder?

- Coupled folding-binding as allostERIC transition

- Promote binding diversity
  
  (Staneva et al. PLOS Comp Biol 8, 2012)

- Increased binding rate through a “fly-casting” mechanism?
  
  (Bhattacherjee and Wallin, Biophys J 102 2012)

What are the biophysical properties of coupled folding-binding?

How do they relate to biological function?
Disordered peptides can have multiple binding partners

- p53 and TRTK12
- Similar monomer behaviors

“one-to-many” binding

“many-to-one” binding
Comparison simulated/experimental structures

PDZ domains

S100B

→ Binding mechanism?
→ Mechanism of molecular recognition?
p53 and TRKT12 are structurally heterogeneous after binding

Conformational disorder persists after binding.

Phe385 (p53) and W7 (TRTK12) act as “anchor residues”

Do S100B-IDP binding lead to a “dynamic complexes”?

- A central F/W/L is a conserved feature
- TRTK12 binding mutation-tolerant on most positions except W7. (Makhatadze et al. Biochemistry 52, 2013)
- Computational studies. (Chen et al. JMB 425, 2013)
Summary/Outlook

- Conformational switching in proteins, including disorder-order transitions, are important for function and evolution.
- Anchor residues may play a role in molecular recognition of IDPs.

- Unbiased mutations, coupled with smooth gradients in function, may drive the evolution of new folds.

Thank you for your attention!