A high-throughput computational method to generate energy landscape of transmembrane protein association

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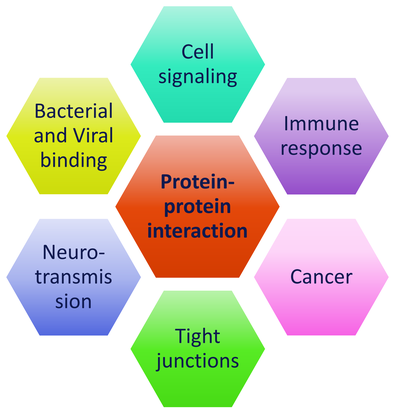
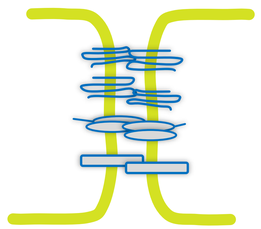
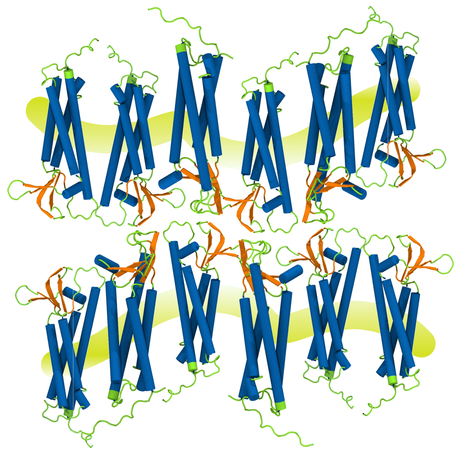
Motivation

Protein-protein interactions are crucial to biological events





Example:
Tight junction protein associations

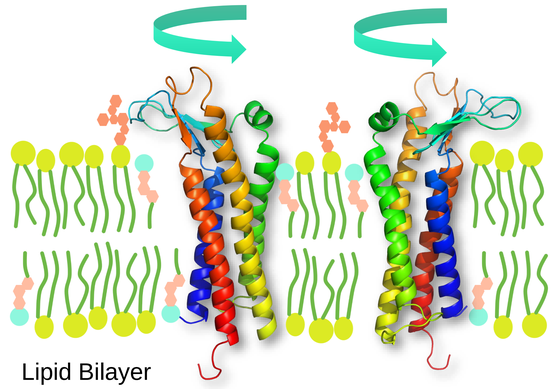


- Orientations of protein association dictate their function
- Mutations in proteins affect protein associations
- Resulting conditions may include autoimmune diseases, neurological disorders and cancer, among several others

Need

- Difficulty in experimental methods
- With available computational methods:
  - difficult to obtain comprehensive data
  - computationally expensive

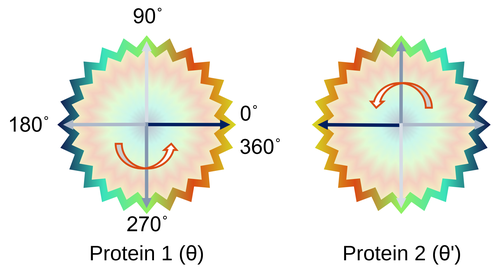
Method



Top view

Goal of this work:

- To explore protein association states exhaustively
- To quantify the association stability
- To achieve this using minimal computational resources



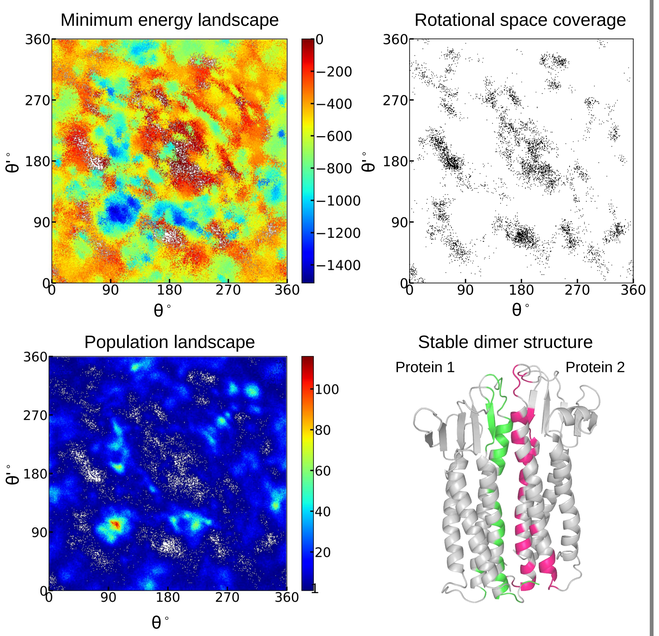
Rotational space schematic

Achieved by:

- Exploring the rotational space
- Quantifying the stability by computing interaction energies (LJ and Coulombic interactions)
- Employing highly parallelized work flow

Results and Conclusions

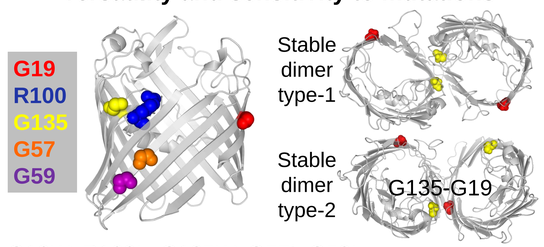
Claudin-5: Dimer – Protein Association Energy Landscape (PANEL)



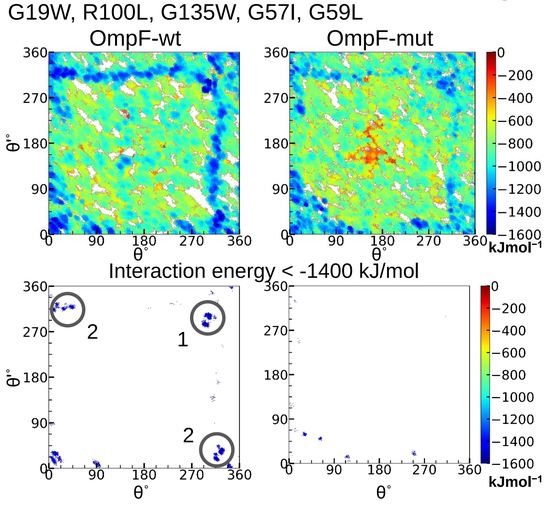
PANEL provides information about the likelihood of formation of dimer orientations anywhere in the rotational space based on their energies of interaction

OmpF: Dimer – PANEL

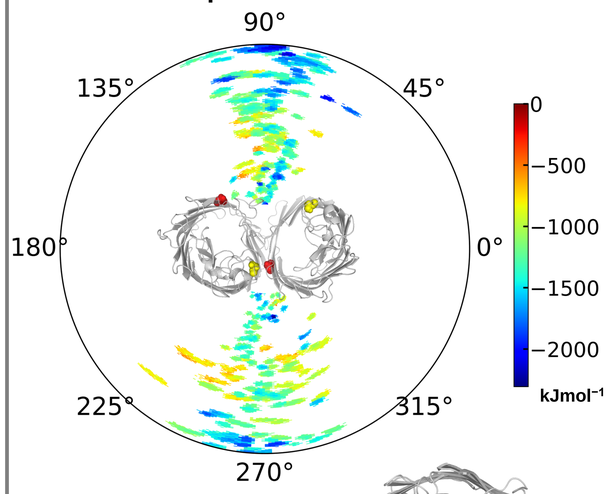
Versatility and sensitivity to mutations



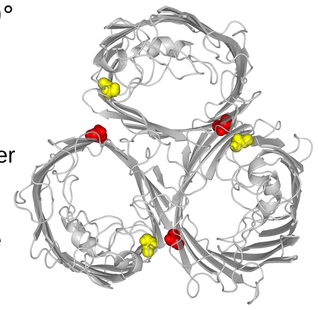
G19W, R100L, G135W, G57I, G59L



OmpF: Trimer – PANEL



- PANEL for OmpF trimer starting from lowest energy asymmetric dimer (G19-G135 interaction)
- Lowest energy trimer structure identical to the crystal structure



System Performance

	Self-assembly	PANEL
Size	50 nm × 50 nm	10 nm × 10nm
Performance	~185 ns/day	~3600 ns/day
Length	~15 μs	~400 ns
# systems	3	3000
# CPU	100	100
Time required	$\frac{15000\ \text{ns}}{185\ \text{ns/day}} = \sim\mathbf{81\ days}$	$\frac{400\ \text{ns} \times 3000}{3600\ \text{ns} \times 100} = \sim\mathbf{3.4\ days}$

Conclusions:

- Provides complete interaction profile for the interacting proteins
- Based on interaction energy – a more reliable metric to determine the stability of orientations
- Applicable to any transmembrane entity
- Robust and versatile to proteins across different species, in different lipid environment
- Highly efficient in predicting and capturing mutations
- Highly parallelized, computationally inexpensive and quick in yielding reliable results
- Transferrable to different force-fields
- Can prove useful in designing peptide based targeted drugs

References

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5. Rajagopal, N., Nangia, S., Comprehensive and Affordable Approach to Obtaining Protein Association Energy Landscape (PANEL) for Integral Membrane Proteins. To be submitted.

Acknowledgement

XSEDE Extreme Science and Engineering Discovery Environment

RESEARCH computing

Syracuse University Research Computing: Academic Virtual Hosting Environment (AVHE)