Generating potential energy landscapes for membrane proteins

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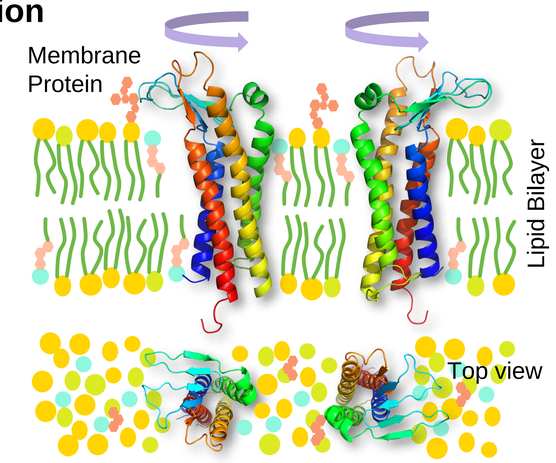
Motivation

- Protein-protein interactions have high clinical significance
- Especially, integral membrane proteins occupy 30-50% of the cell surface area in mammals
- Mutations in proteins affect protein associations
- Resulting pathological conditions include neurodegenerative diseases, cancers, autoimmune diseases, genetic diseases, and many more



Critical need to understand protein interactions

Limitations:

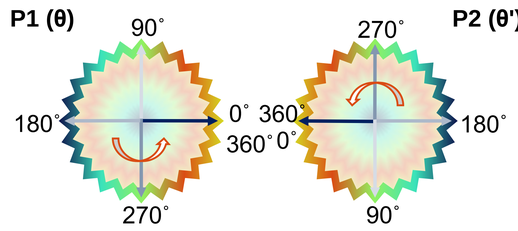
- Experimental methods
  - Resolution
  - Extraction methods for membrane proteins
- Computational methods:
  - Difficult to obtain comprehensive data
  - High computational cost

Methods

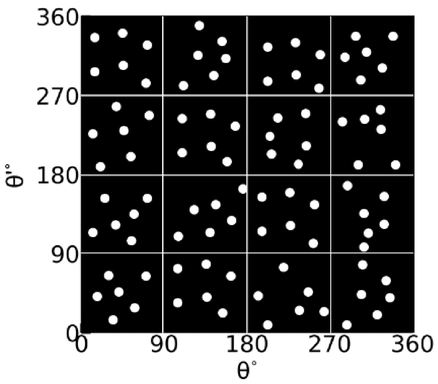
This work:

- Exhaustively explore membrane protein interactions
- Quantify the interaction stability
- Computationally affordable
- Identify key dimers
- Using coarse-grained MD simulations

PANEL
(Protein AssociatioN Energy Landscape)



Rotational space schematic (Proteins as seen from the top view)
Claudin-15 – Representative protein



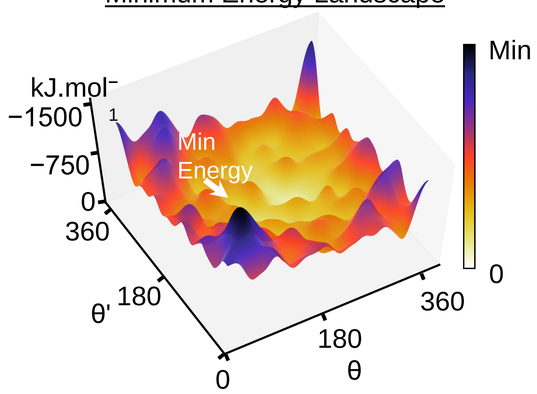
Uniform stochastic distribution of seed geometries (schematic)

Approach:

- *Rotational space*: Defined by axial rotation of an interacting pair of proteins (θ,θ'), in the membrane plane
- *Uniform stochastic distribution*: Rotational space (θ,θ') divided into equal, non-overlapping segments (Ω)—each segment Ω_i comprised of a selected number of random seed configurations.
- *Equilibrium conformations*: Independent and parallel unconstrained MD simulations of seed geometries
- *Non-bonded interaction energy*: Computed between P1 and P2 proteins for each equilibrium conformation
- *PANEL Landscapes*: Minimum energy and Frequency contour plots for each degree rotation of P1 and P2

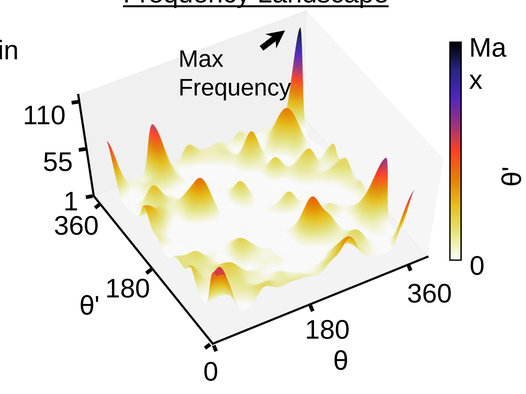
Results & Analysis

Minimum Energy Landscape



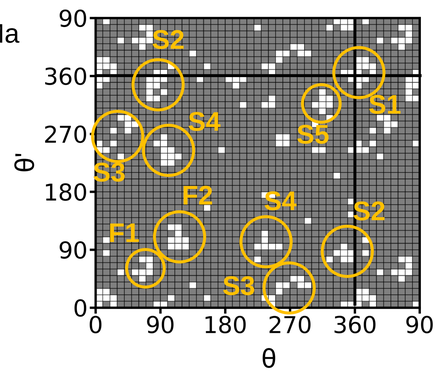
- Protein LJ+Coulombic interaction energies for 360×360 rotational states
- Relative thermodynamic stabilities

Frequency Landscape

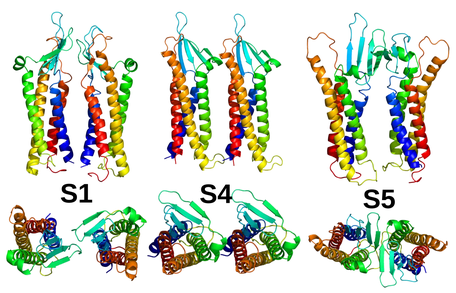


- Visiting frequency of 360×360 rotational states
- Relative kinetic stabilities

Funnels and Saucers

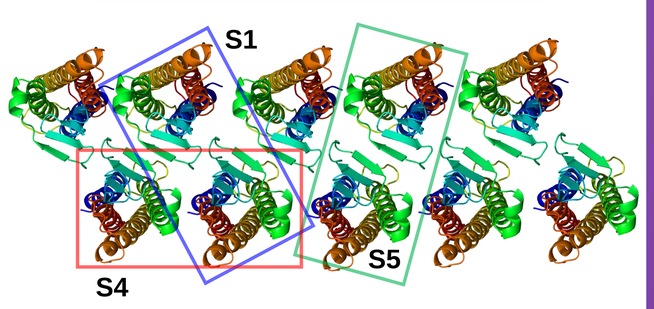


Key dimer orientations

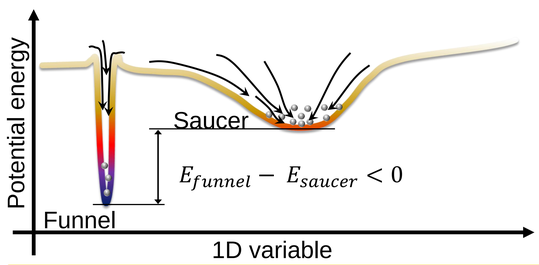


- Significant dimer regions—Grids retaining seed geometries greater than initial value throughout the MD simulation

Crystal lattice-based claudin-15 strand



- **S4:** Crystal lattice protomeric unit
- **S1 and S5:** Dimer orientations across antiparallel strand assembly
- Role of other *Saucers* need to be explored.

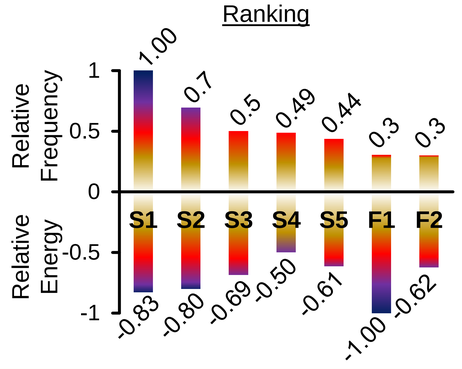


Funnels and Saucers

Often due to local landscape features, energy and frequency landscapes exhibit mismatch in dimer favorability.

- "***Funnels***"— thermodynamically favored states
- "***Saucers***"— kinetically favored states

Ranking



Conclusions

- Comprehensive, robust and versatile method to generate potential energy and frequency landscapes
- Highly parallelized workflow
- Computationally inexpensive short simulations—high throughput.
- Validated for dimer and trimer interactions
- Enabled Identification physiologically relevant key dimer interfaces
- Enabled identification of aggregation patterns
- Applicable to any membrane protein

References

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Acknowledgements

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XSEDE Extreme Science and Engineering Discovery Environment

RESEARCH computing

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