ESCOLA GAÚCHA DE BIOINFORMÁTICA

Molecular Dynamics Simulations:

Theory and Applications

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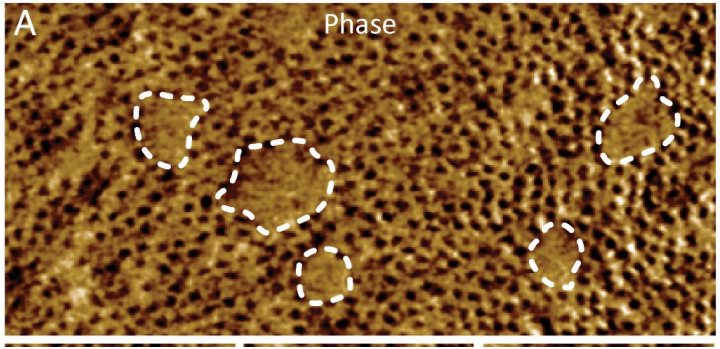
Hedin et al. (2011) J. Proteome Res. 10, 3324-3331

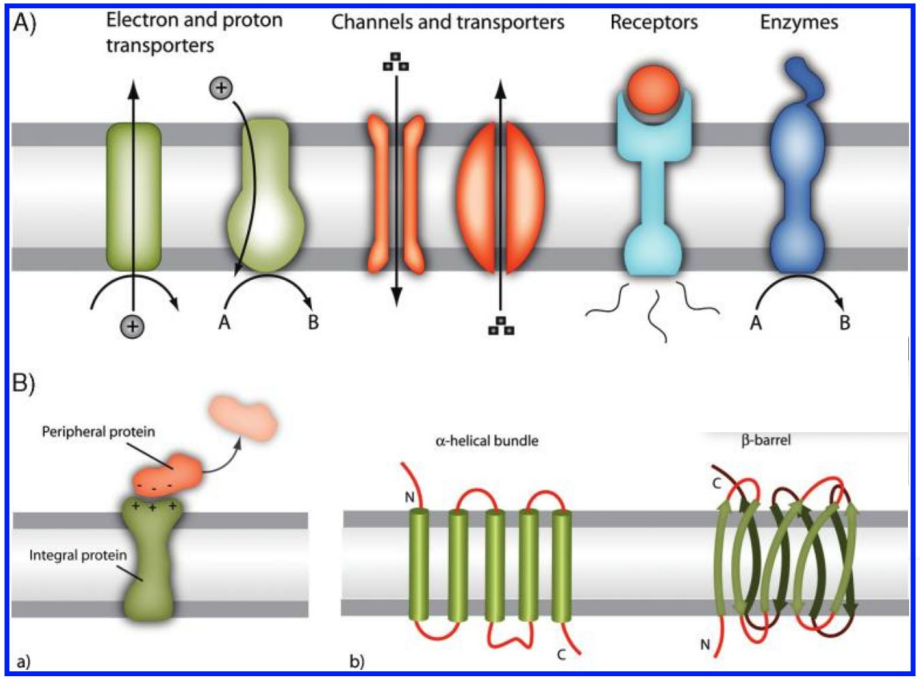
Membrane Proteins

Almost ⅓ of the proteins in the human genome:

- 60% are targets for therapies
- Important functions:
  - Signalling
  - Transportation
  - Integrity and Stability
  - Regulation of biological processes

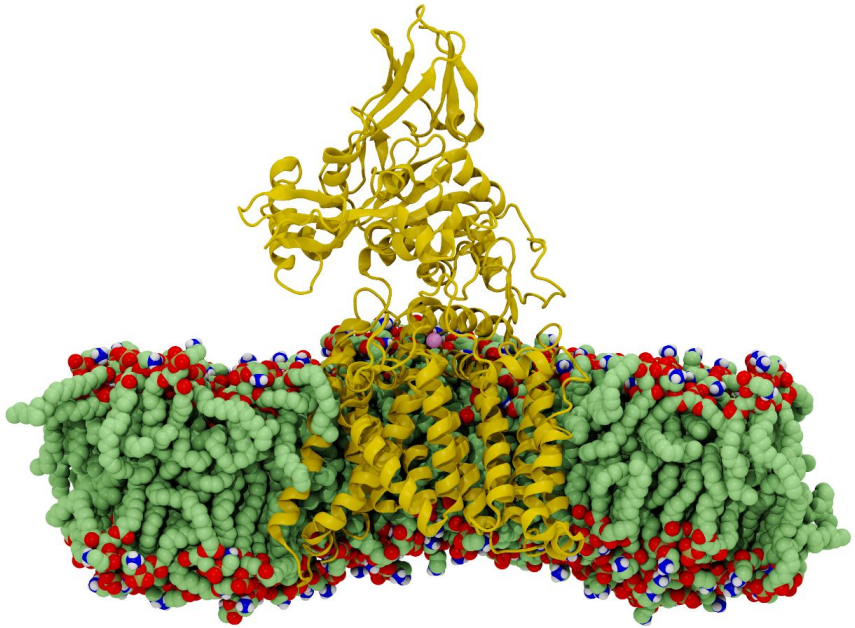


Porins in the outer membrane of E. coli (Benn et al. (2021) PNAS)



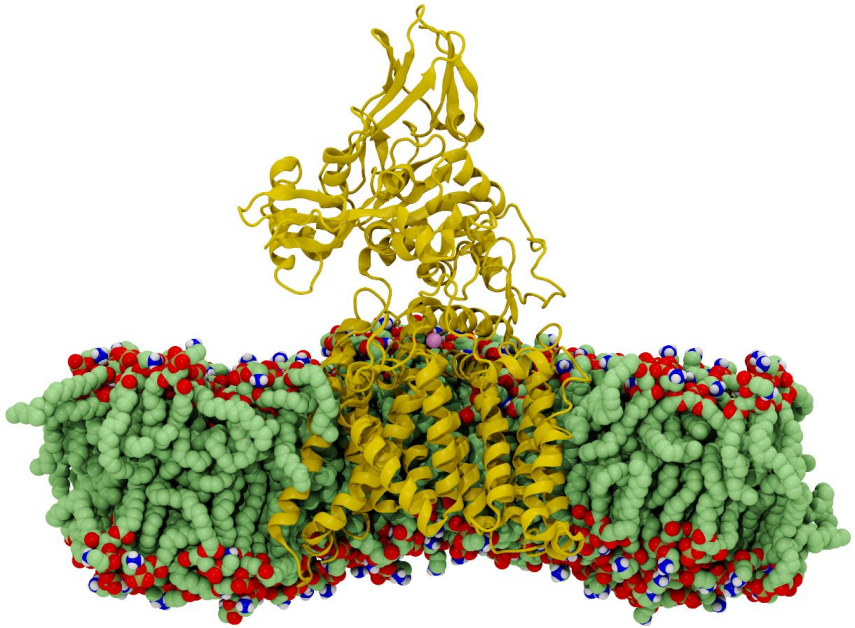
Membrane Proteins

- Important questions to ask yourself before simulating membrane systems:
  - What type of membrane? Planar? Vesicle? Micelle?
  - Phospholipid composition (hydrophobic tail type, polar headgroups)
  - Presence of other molecules: cholesterol? lipid carriers? gangliosides?
  - What is the correct temperature for the simulation of my membrane? (liquid-crystal state)



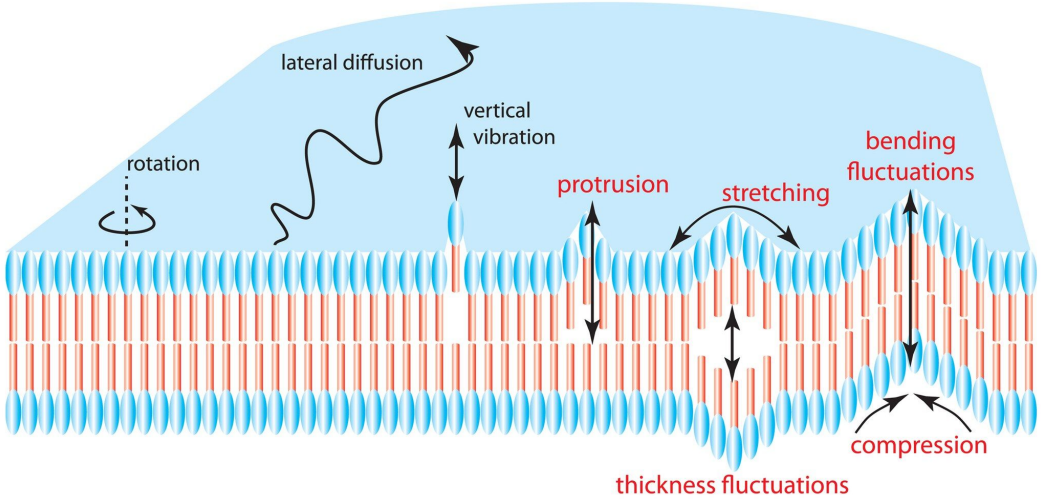
Membrane Proteins

- Membrane insertion:
  - Different ways of doing it => g_membed, InflateGRO, CHARMM-GUI, “craft method”
  - It is important to remove any superimposition of atoms that might blow up the system.
  - Attention to detail:
    - **amino acids at the protein surface at every region of the membrane (polar or hydrophobic?)**;
    - **water in the membrane**
  - Membranes employed in simulations: pre-equilibrated or self-assembled.



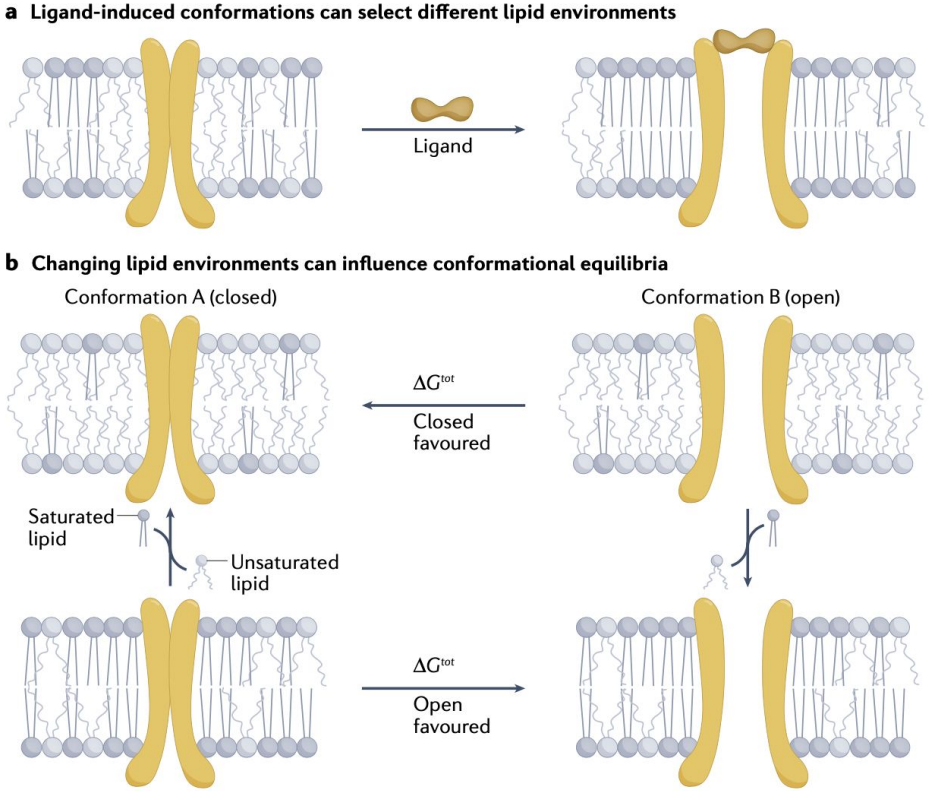
Membrane Proteins

- Equilibration is a crucial factor
  - Membranes could be pre-equilibrated and used subsequently
  - Don’t eliminate the equilibration step after protein insertion
- How to determine if the membrane is properly equilibrated?
  - Relevant properties: APL, thickness, lateral diffusion of lipids



Levental & Lyman. (2023). Nat. Rev. Mol. Cell Biol. 24, 107-122.

Membrane Proteins

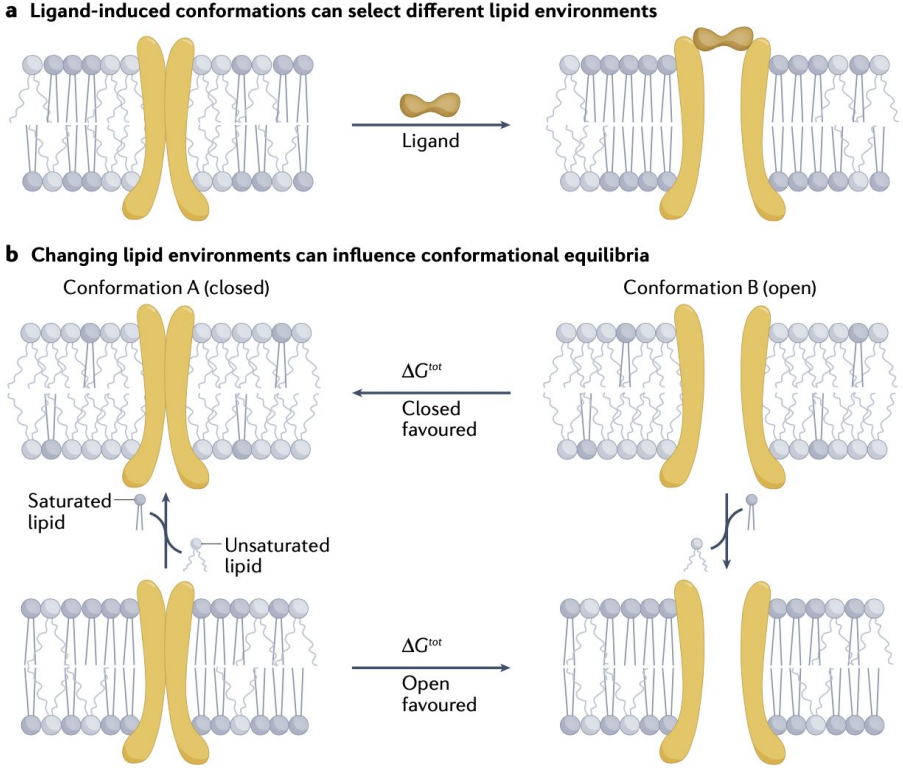


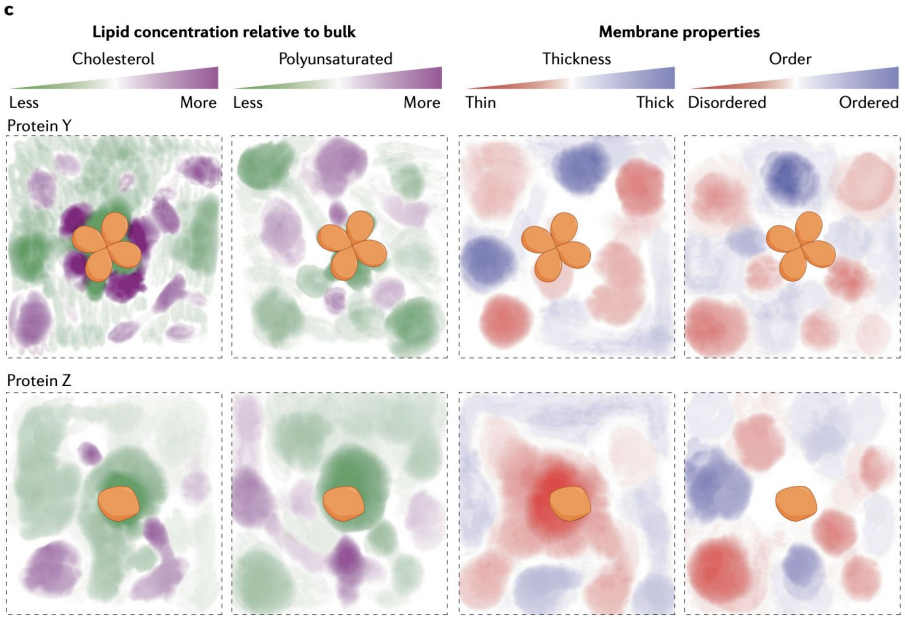
Ligand-induced conformation = different lipid environment

Lipid composition can alter conformational equilibration

Levental & Lyman. (2023). Nat. Rev. Mol. Cell Biol. 24, 107-122.

Membrane Proteins



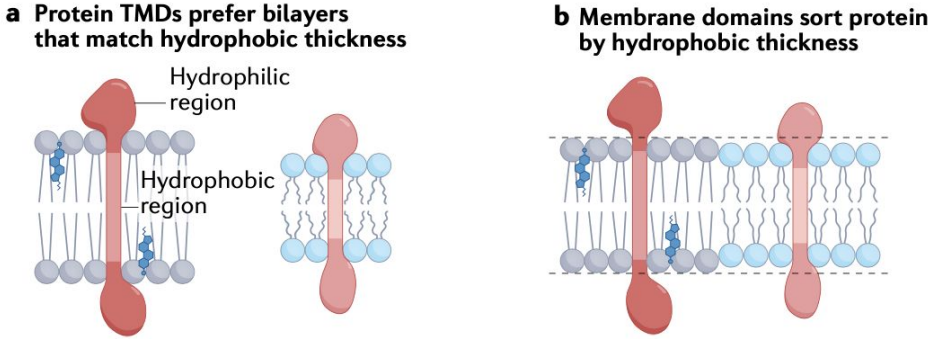


Properties that can be calculated using MD

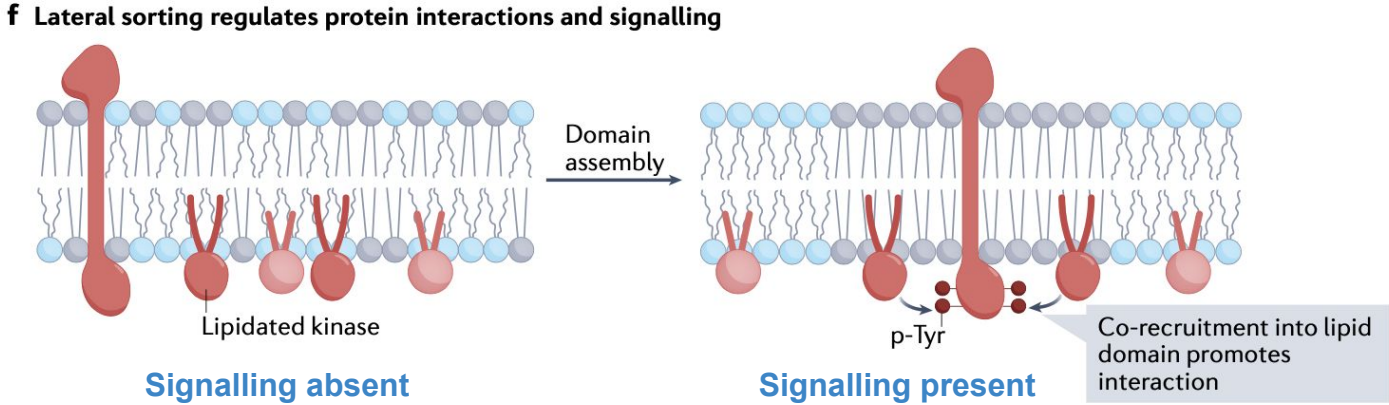
Levental & Lyman. (2023). Nat. Rev. Mol. Cell Biol. 24, 107-122.

Membrane Proteins

TMD domain favours regions which match hydrophobic thickness



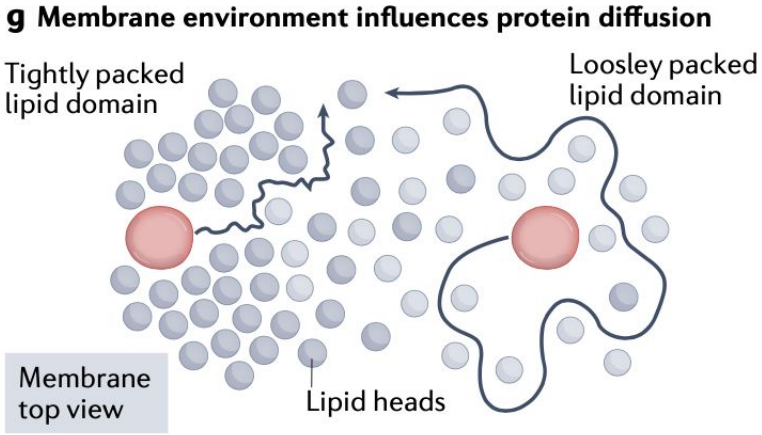
Lateral sorting = interactions and signalling

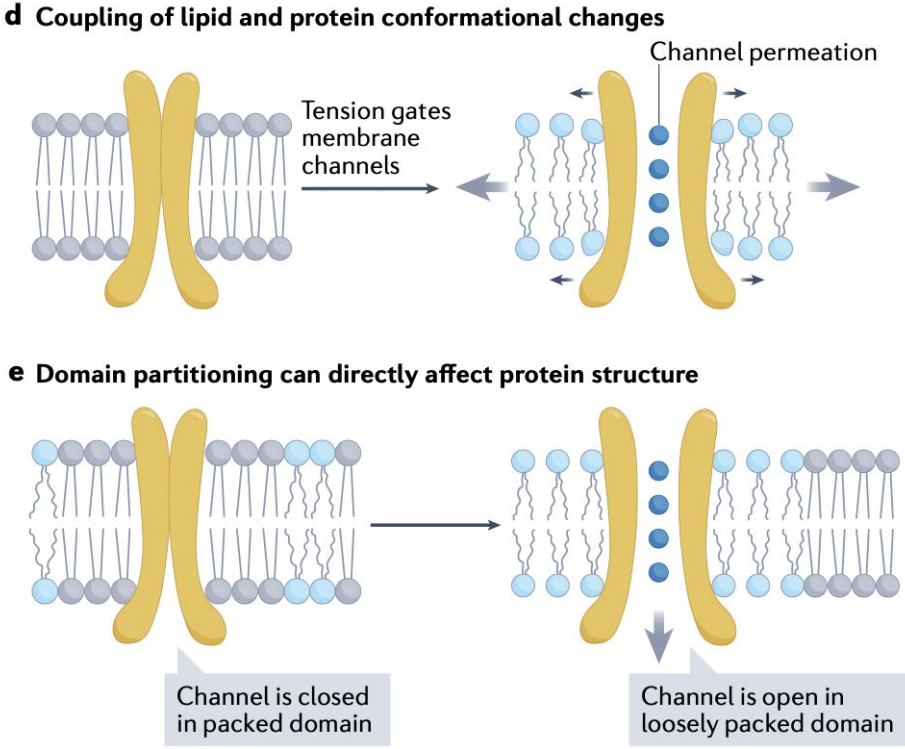


Levental & Lyman. (2023). Nat. Rev. Mol. Cell Biol. 24, 107-122.

Membrane Proteins

Membrane packing influences diffusion and conformational changes

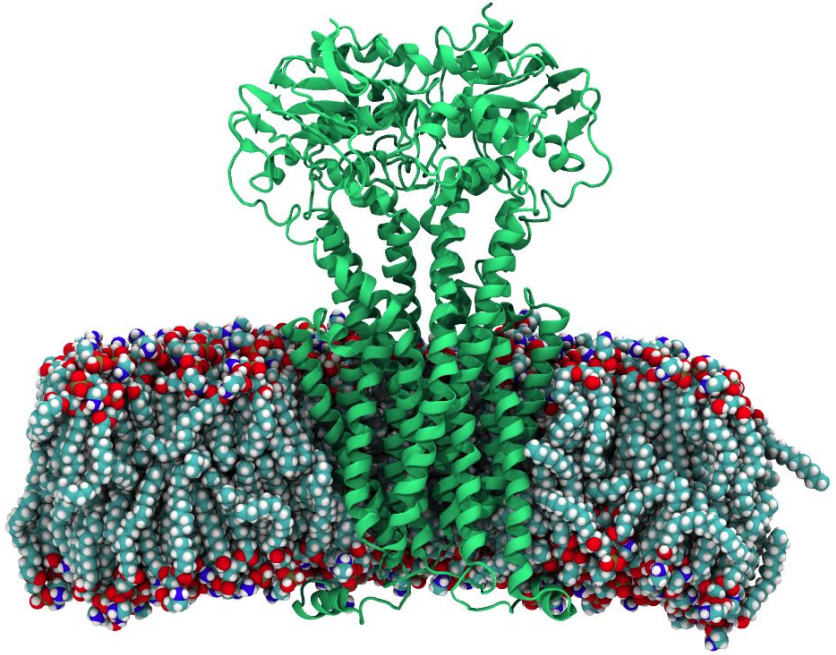




i. e. OM of *E. coli* (outer and inner leaflets)

Membrane Proteins

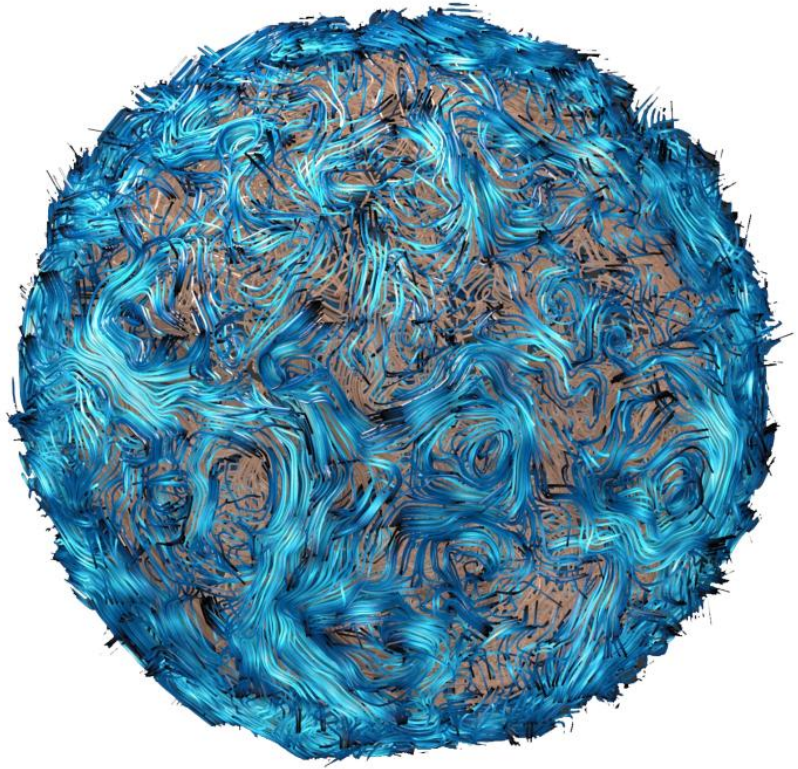
1) Obtain the solute structure for our target
2) Obtain the membrane structure for solute insertion
3) Choose the force field (Are there parameters for all molecules, including membrane and solute?)
4) Build the topology of each component (file containing the force field parameters to be used for that system, allowing the calculation of correct forces)
5) Solvate and neutralize the system
6) Minimize the system energy
7) Equilibrate the simulation box (temperature, pressure, solvation layers and Membrane Parameters)
8) Simulate the unrestrained system (production stage)



Coarse Grained Models

- How to achieve increased sampling, system size and timescales?
  - **All-atom MD** gets prohibitive after a certain point

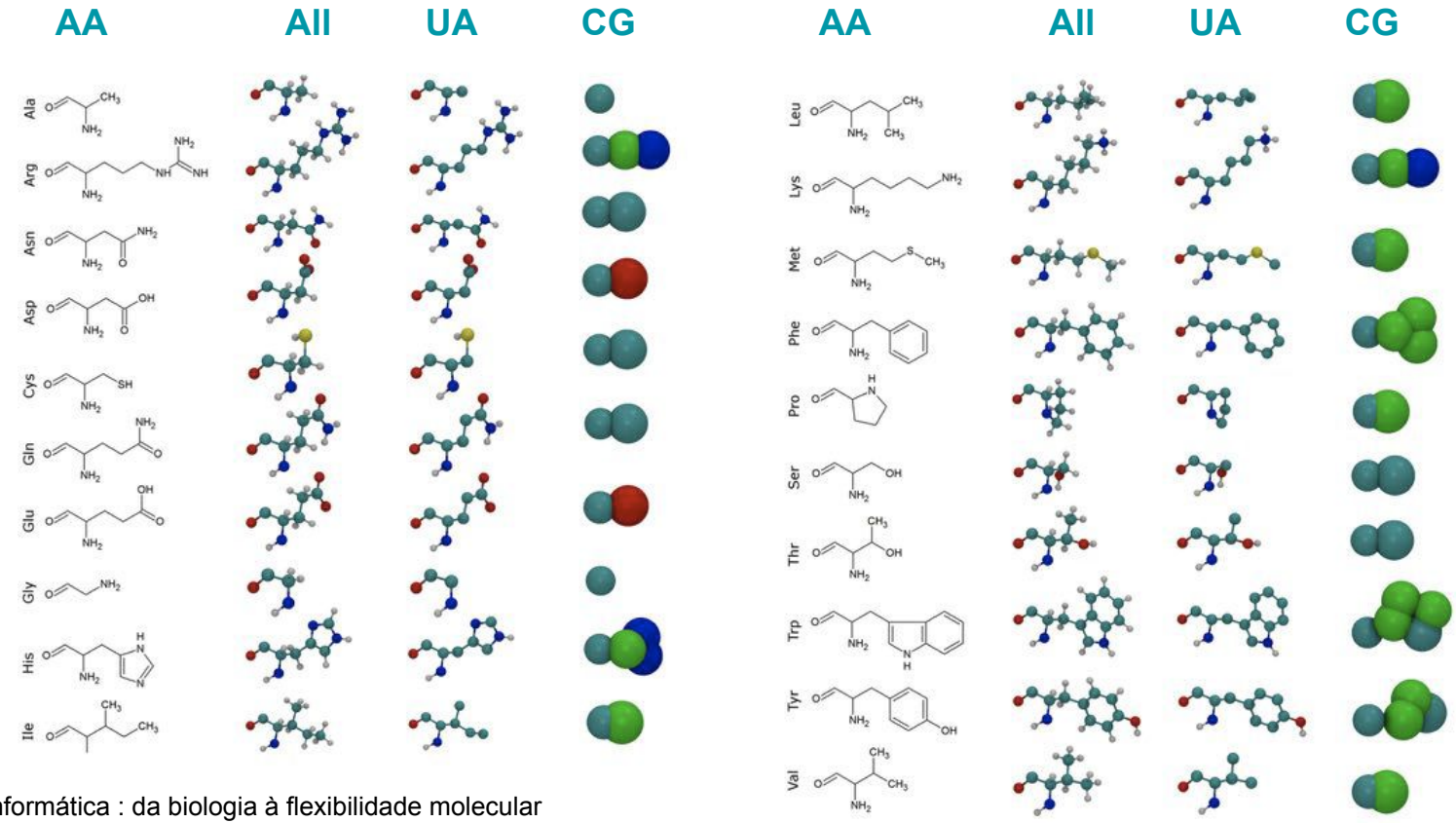
- We can reduce the resolution of our system of interest!
  - **Coarse Grained Models** try to adequately represent, with less degrees of freedom, the relevant physical and chemical properties of a molecular system



Coarse Grained Models

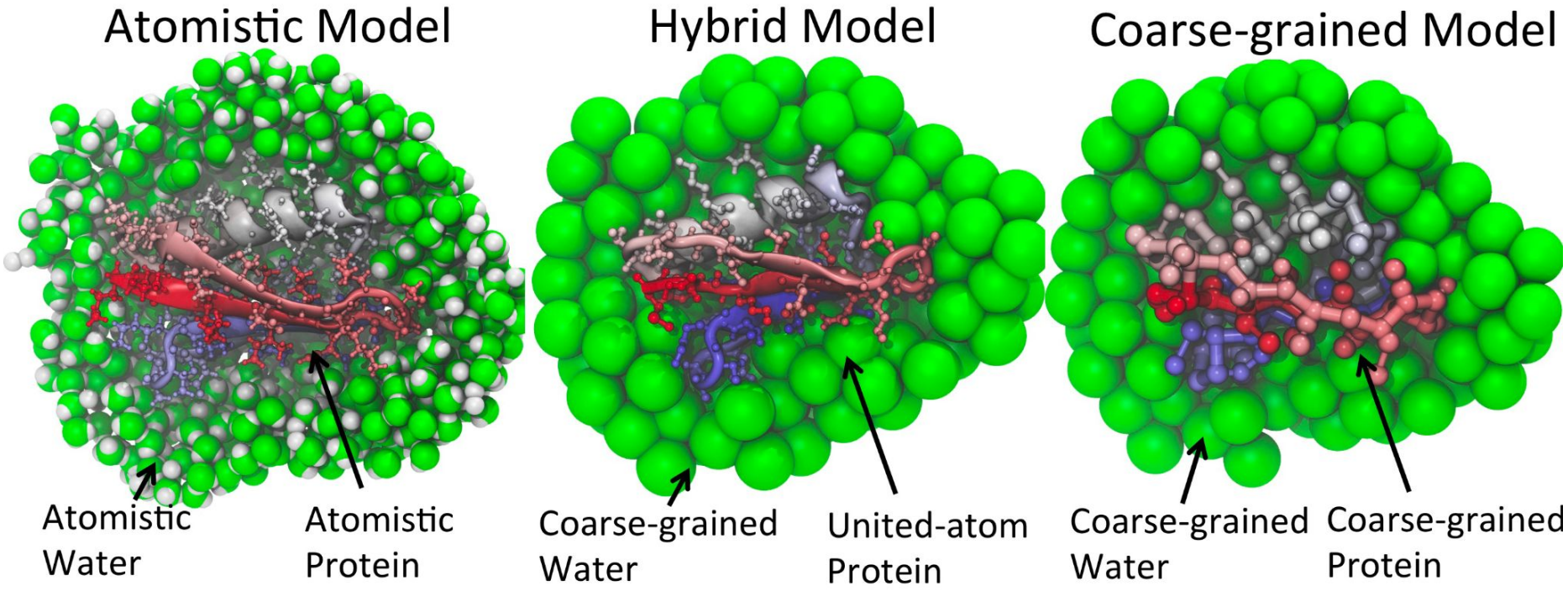
Each bead corresponds to a group of atoms

CG force fields work with bead types instead of atom types



Verli, H (org). (2014). Bioinformática : da biologia à flexibilidade molecular

Coarse Grained Models

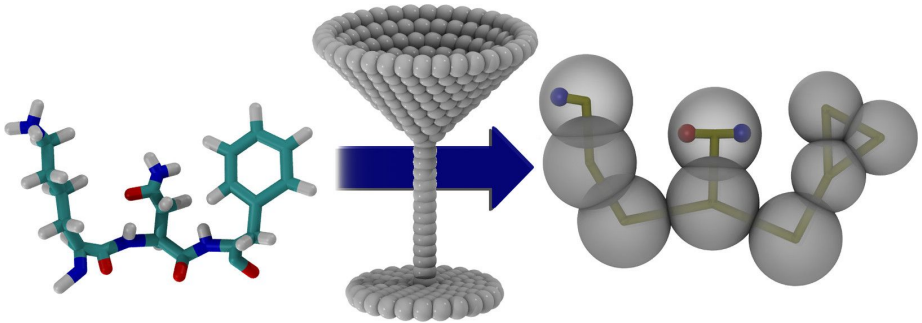


http://www.ks.uiuc.edu/Research/cgfolding/

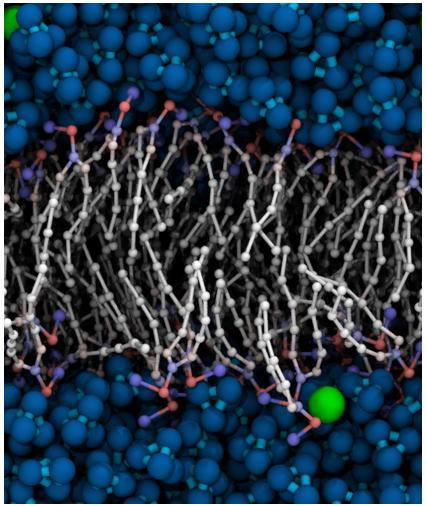
Coarse Grained Models

- Different approaches to transform atoms in CG particles:
  - “**Bottom-up**” = based in high-level complex structures (obtained from MD simulation data, for example - distances distribution, average forces, potentials of mean force)
  - “**Top-down**” = based in energetic and structural experimental data (adjust the force field parameters - charges, potentials, constants - to better reproduce experimental data)

MARTINI



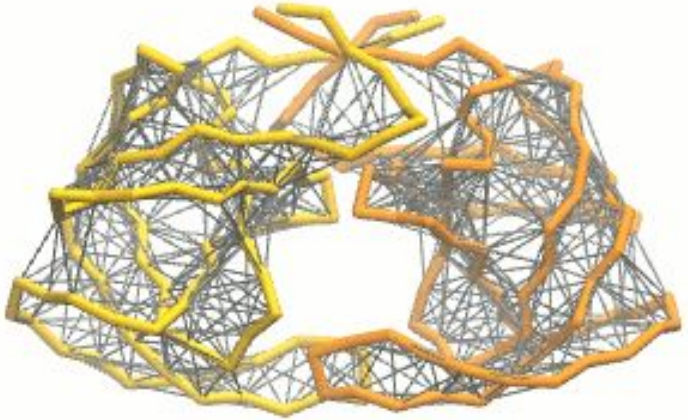
SIRAH



Coarse Grained Models

- Different approaches to transform atoms in CG particles:
  - Elastic networks models:
    - Martini, ElNeDyn, CABS

Tertiary structure conservation



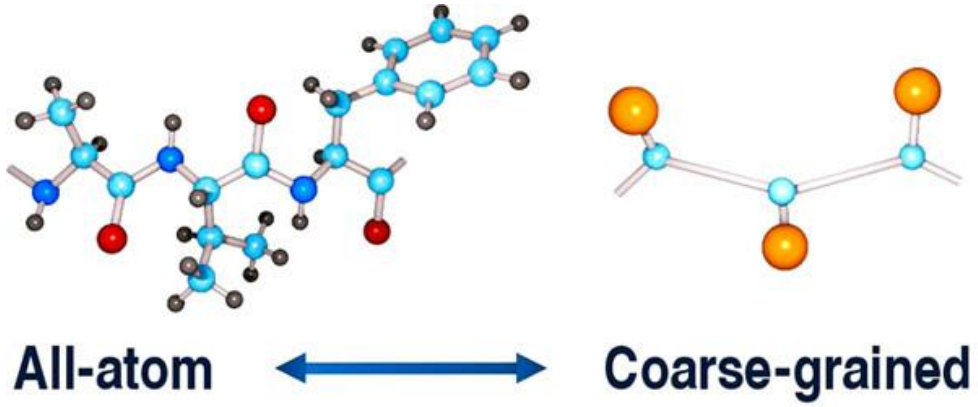
Coarse Grained Models

- Pros:
  - Total system particles reduction
  - Increased integration time step for the simulations (speed ↑↑↑)
  - Simplified energy surface = much faster sampling!
  - Allow the observation of phenomena which require longer timescales

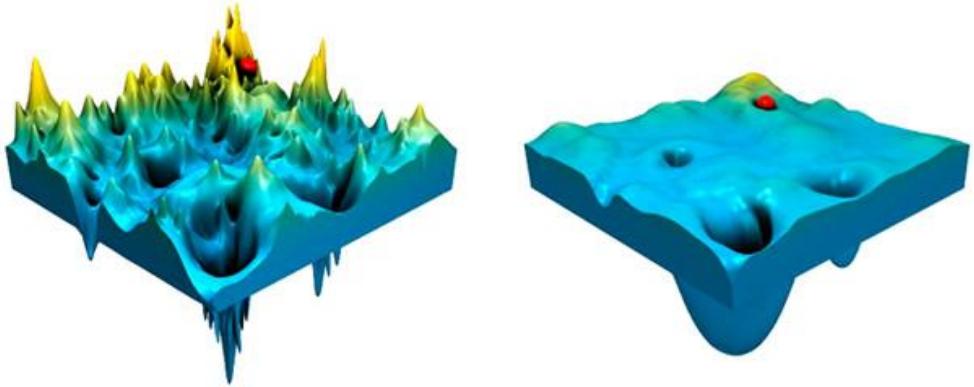
- Cons:
  - Coarse representation = resolution loss
  - Protein Structure - No changes in secondary structure, only tertiary (and restrained by the elastic networks)

Coarse Grained Models

Type of model

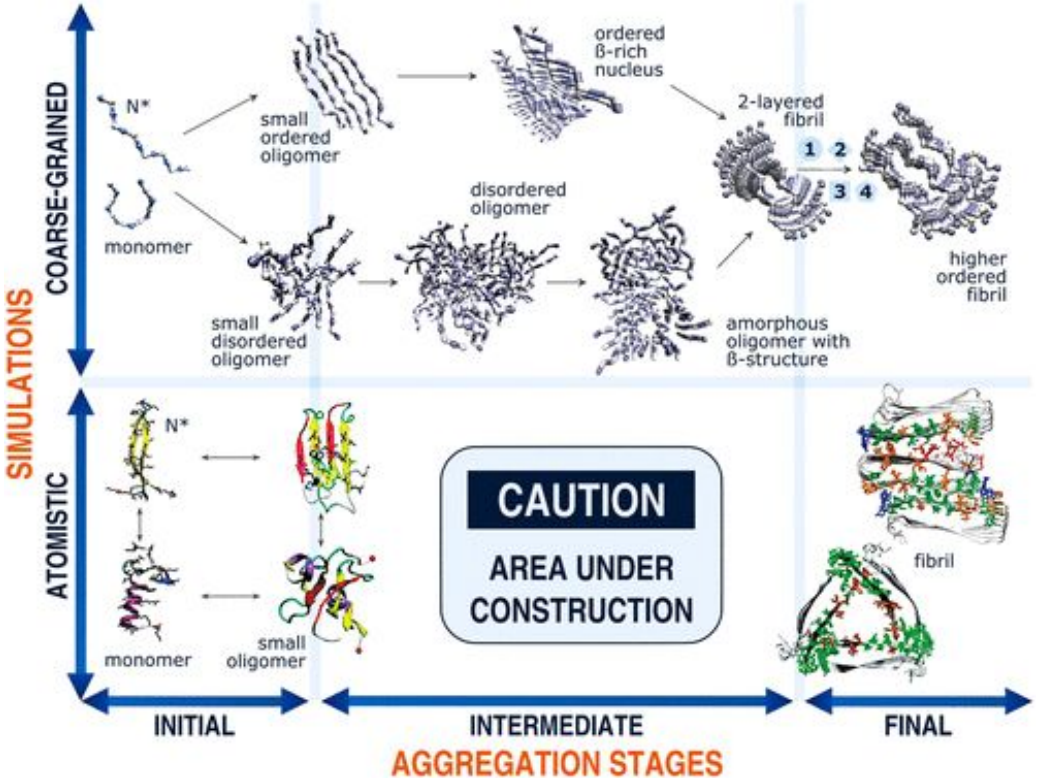


Energy surface



Kmiecik et al. Chem. Rev. 2016, 116, 14, 7898–7936

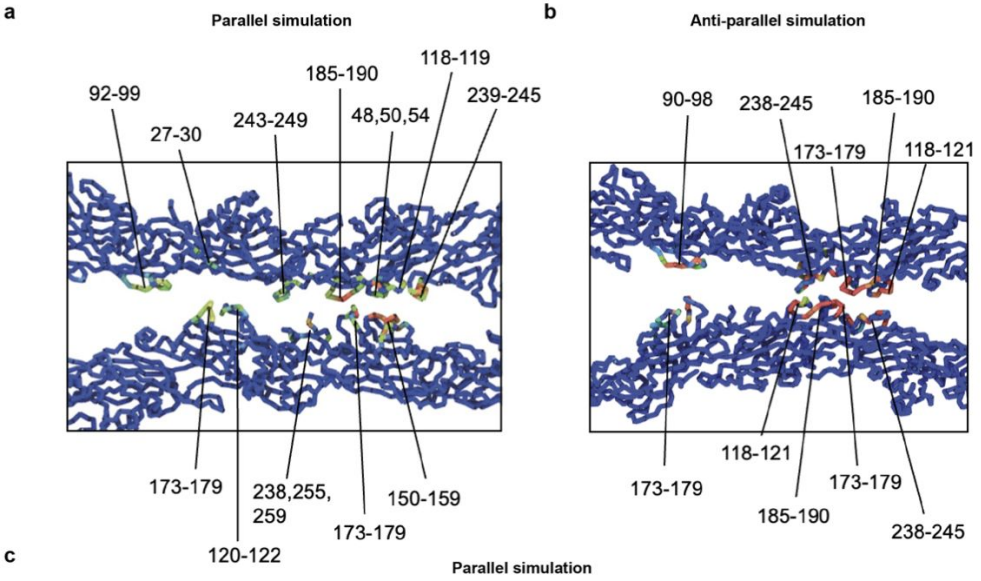
Coarse Grained Models



Folding events, global motions and protein-protein interactions

Kmiecik et al. Chem. Rev. 2016, 116, 14, 7898–7936

Coarse Grained Models



Böhning et al. (2022). Nat. Commun., 13, 7082

Coarse Grained Models

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2) Choose the force field (do we have parameters for all the solute molecules?)
3) Build the solute topology (file containing the force field parameters to be used for that system, allowing the calculation of correct forces). Decide if using Elastic Networks or not.
4) Solvate and neutralize the system
5) Minimize the system energy
6) Equilibrate the simulation box (temperature, pressure, solvation layers)
7) Simulate the unrestrained system (production stage)
8) Back-mapping - Transform the system back to atomistic