Modeling of protein shape dynamics

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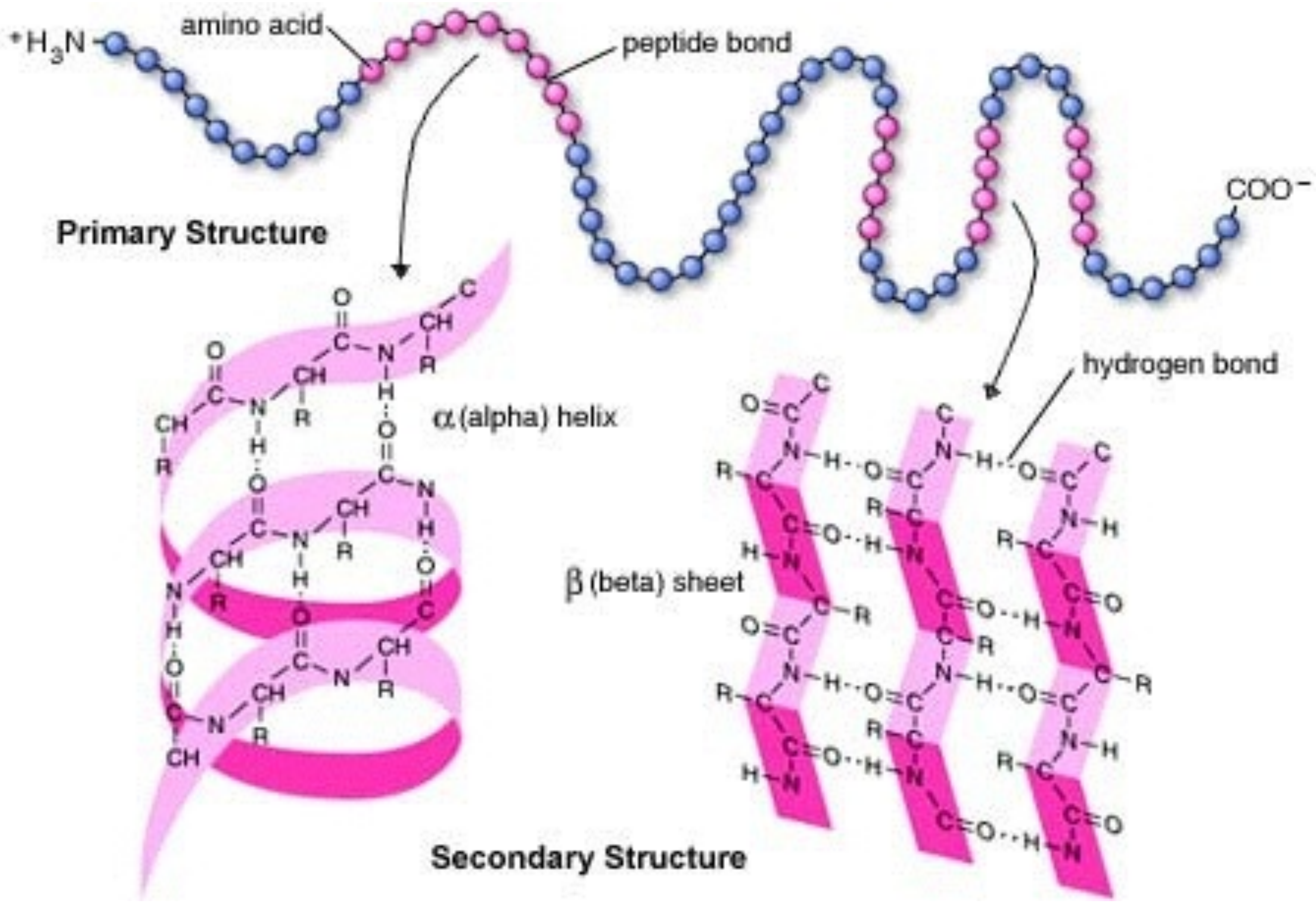
Protein disfunction can lead…

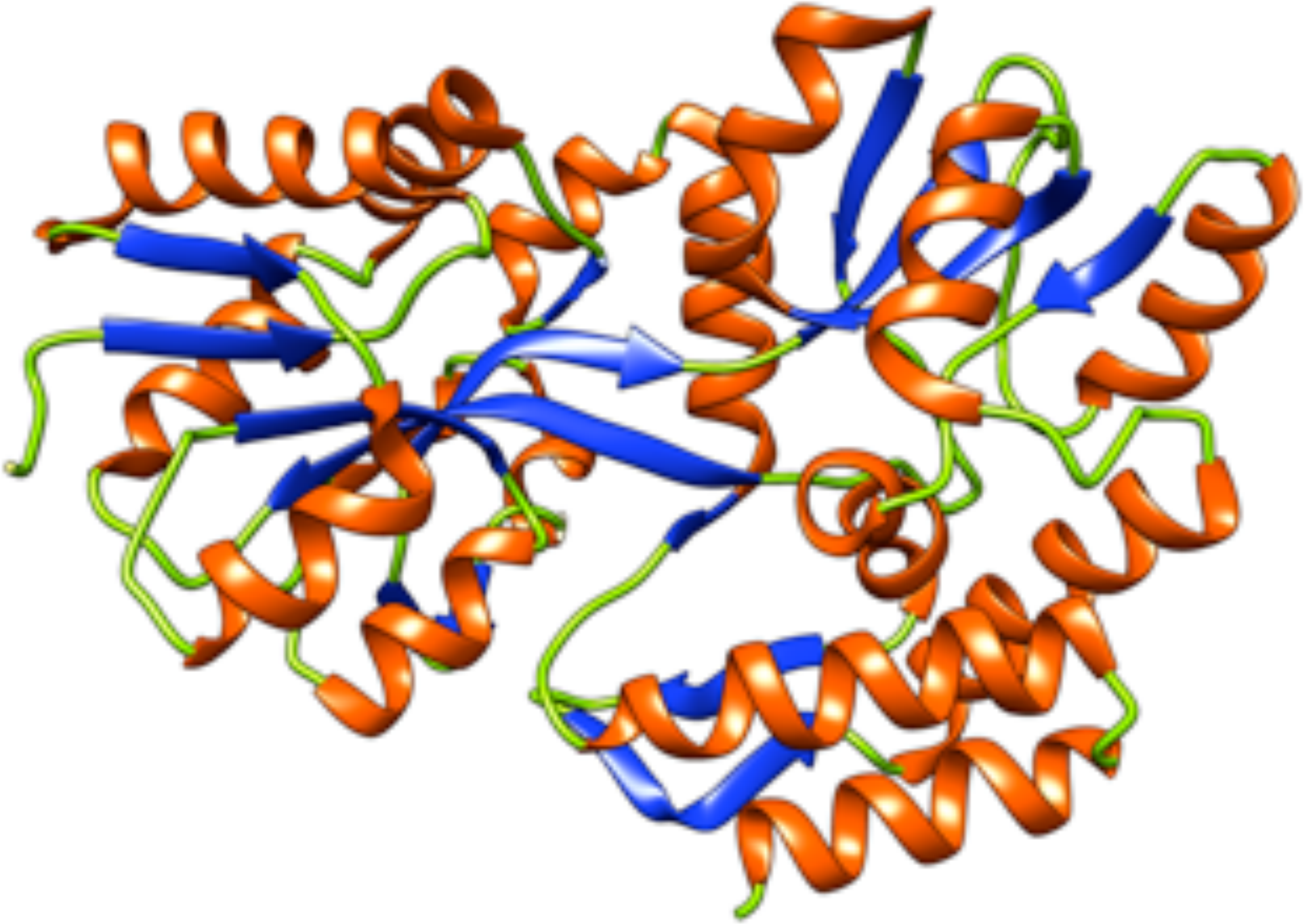
- Amyloidosis: Alzheimer's disease or Parkinson's disease
- Type 2 diabetes
- Cancer

Protein primary structure



picture from Wikipedia

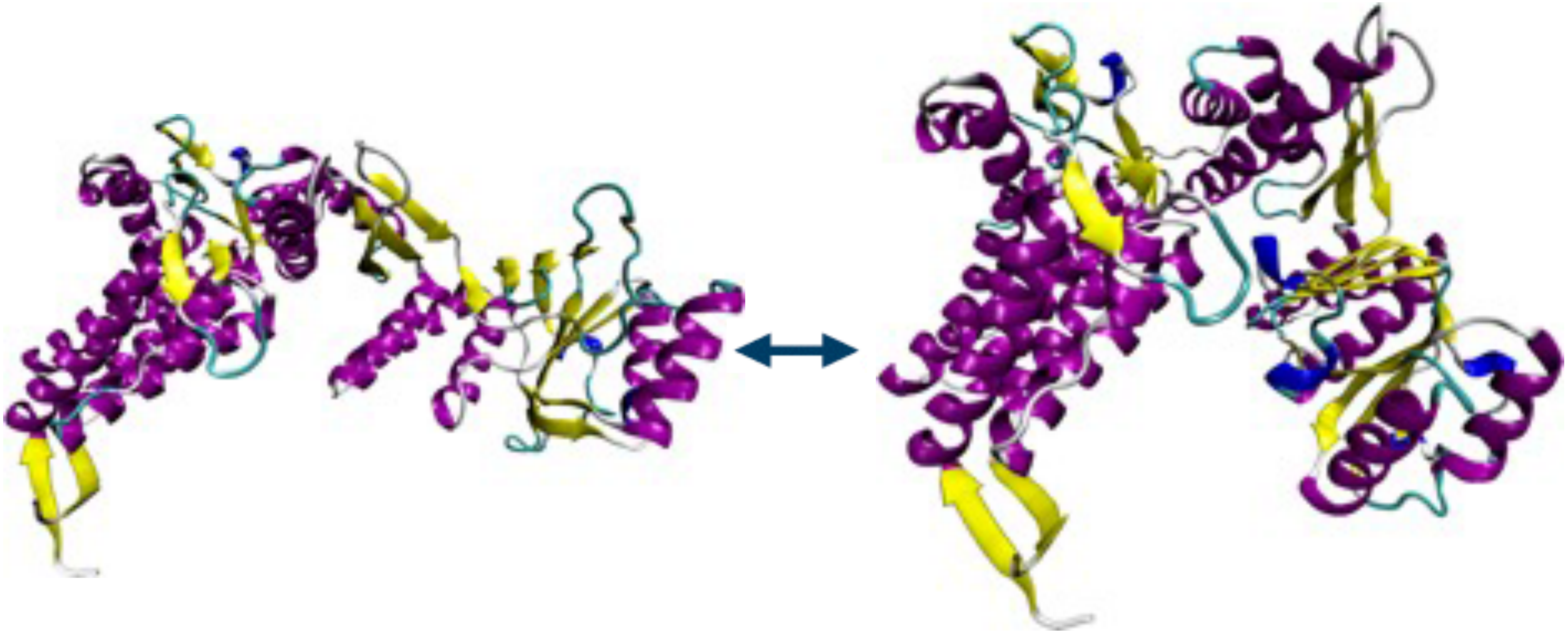
Protein tertiary structure



The picture is adapted from presentation by Dr. Mark Moll

Changes in protein structure

- Drug design
- Protein-protein interactions



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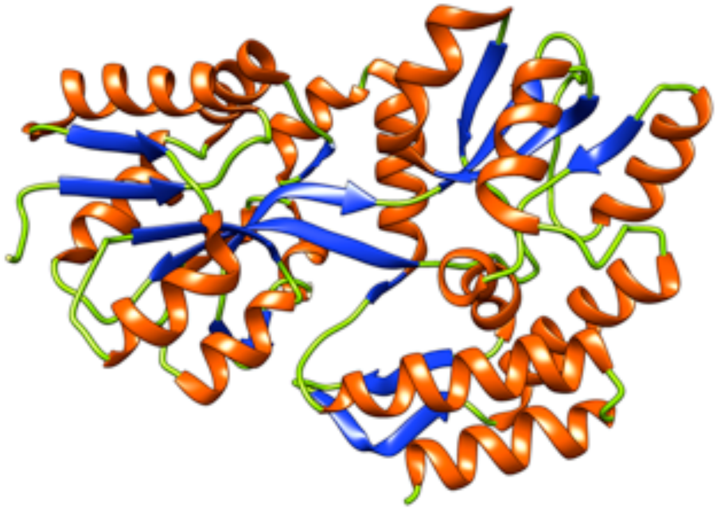
Determining protein structure

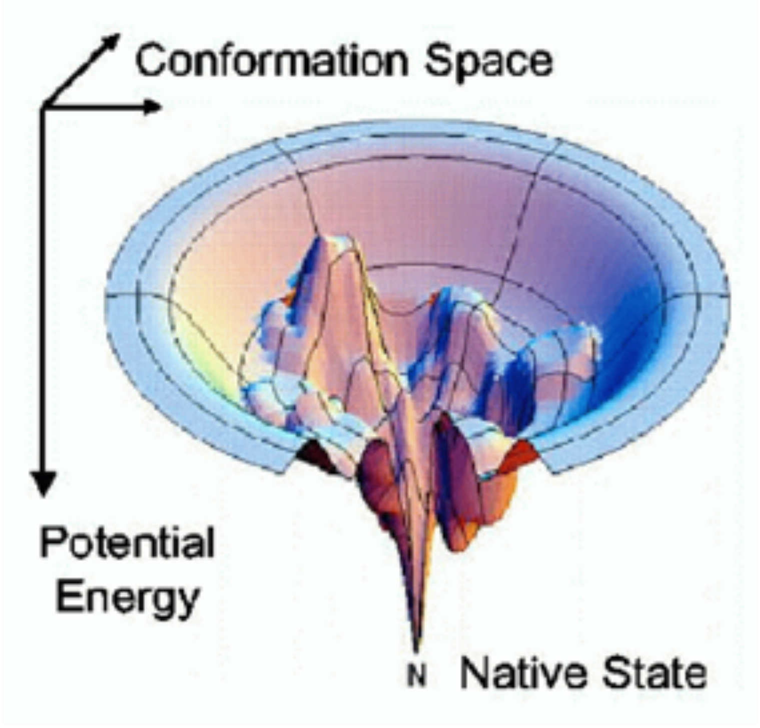
1. Experimentally:

- X-ray microscopy; Nuclear Magnetic Resonance (NMR); Cryo-electro microscopy (cryo-EM)

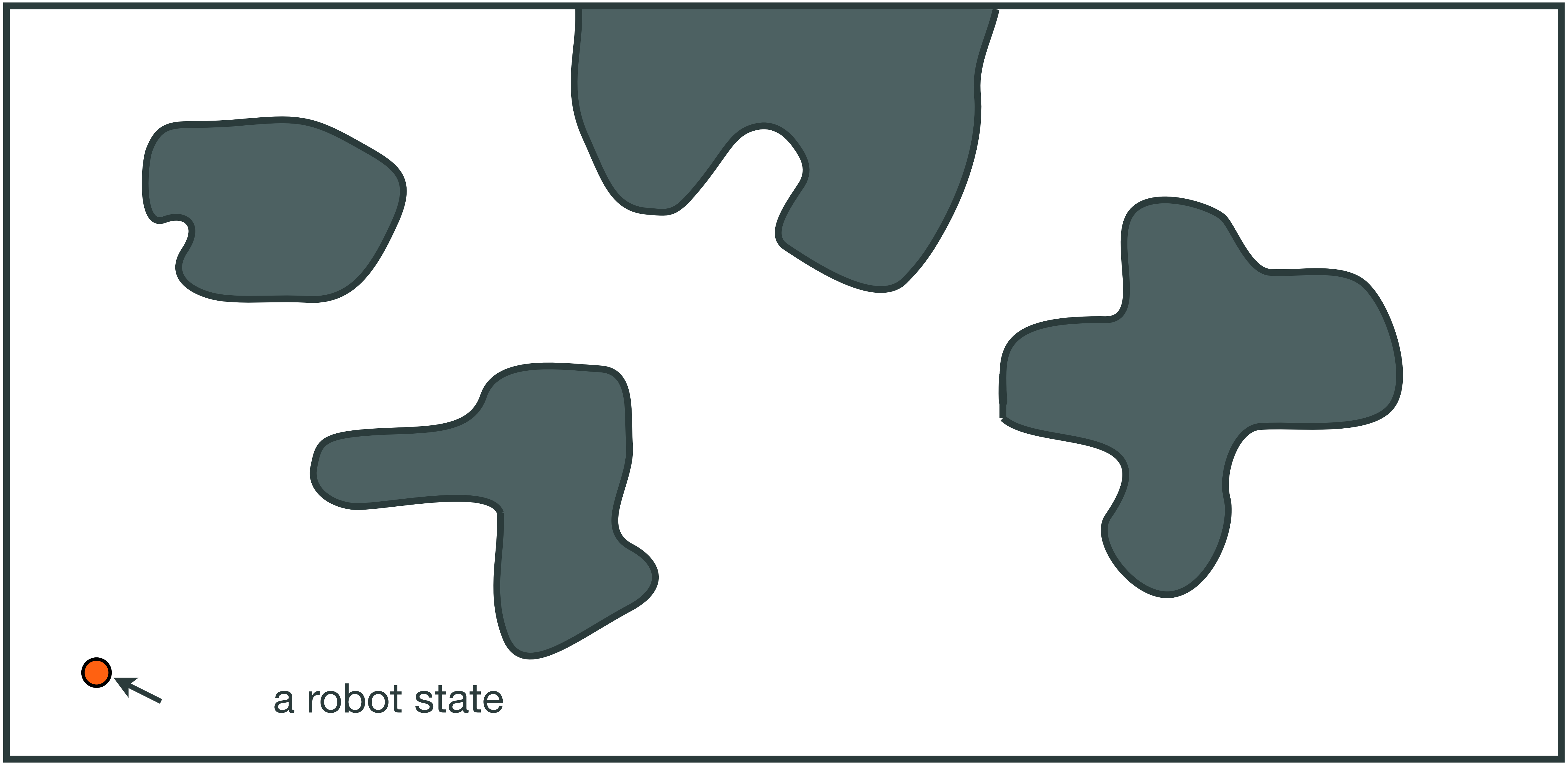


2. Computationally:

- Molecular Dynamics
- Probabilistic Methods

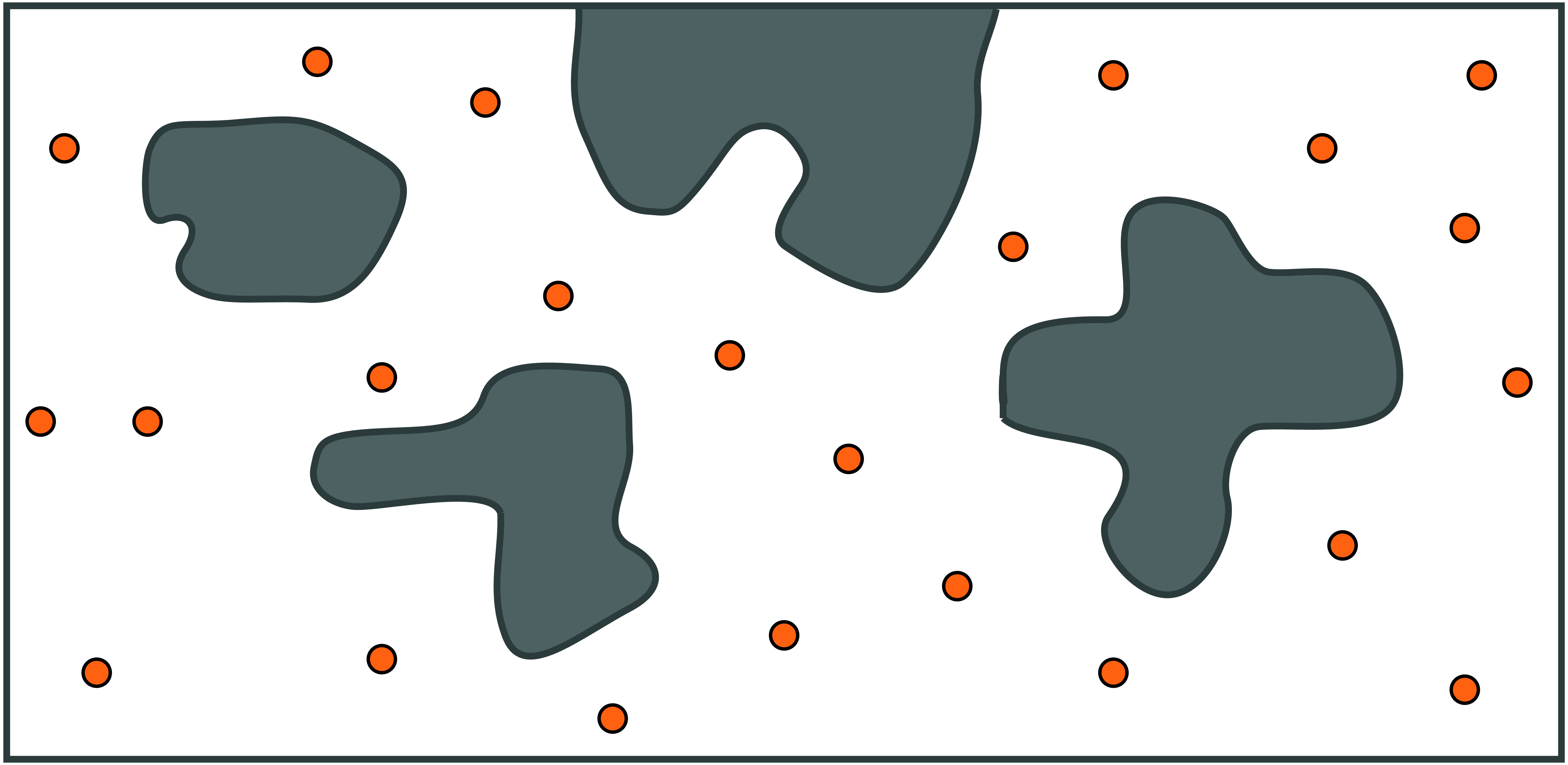


Sampling-based motion planning technique



Kavraki, Svestka, Overmars and Latombe

Sampling-based motion planning technique



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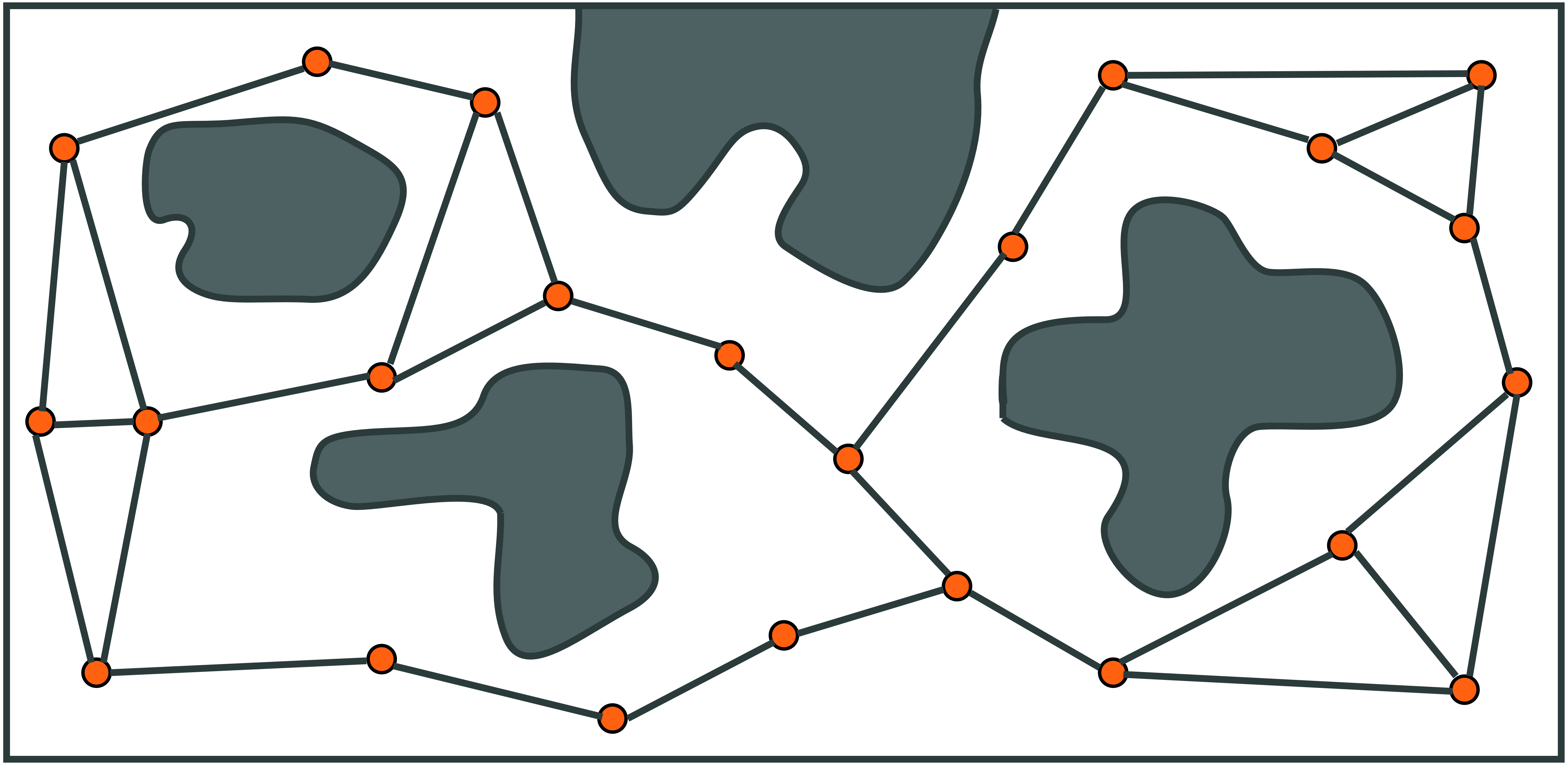

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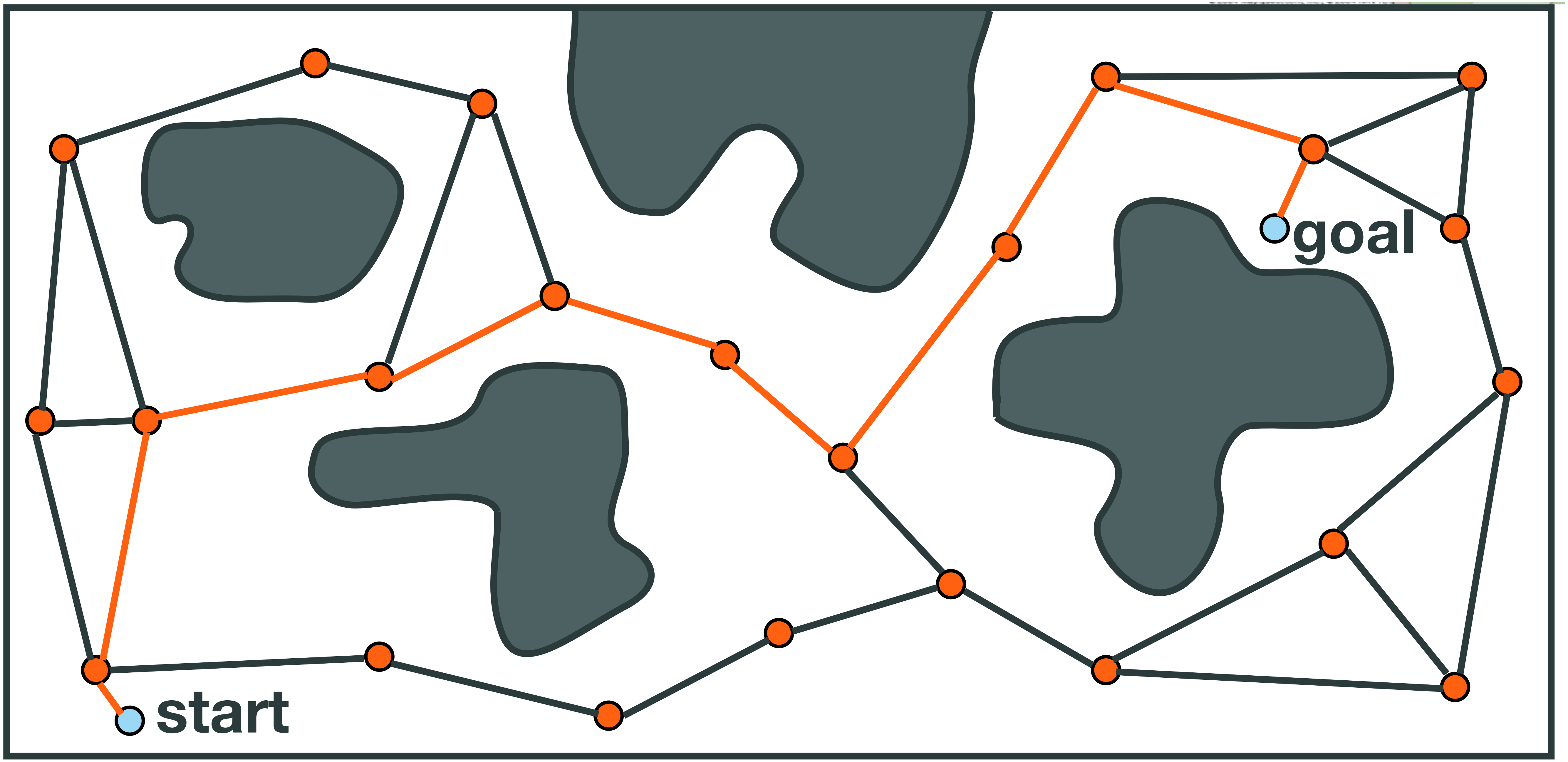


Kavraki, Svestka, Overmars and Latombe

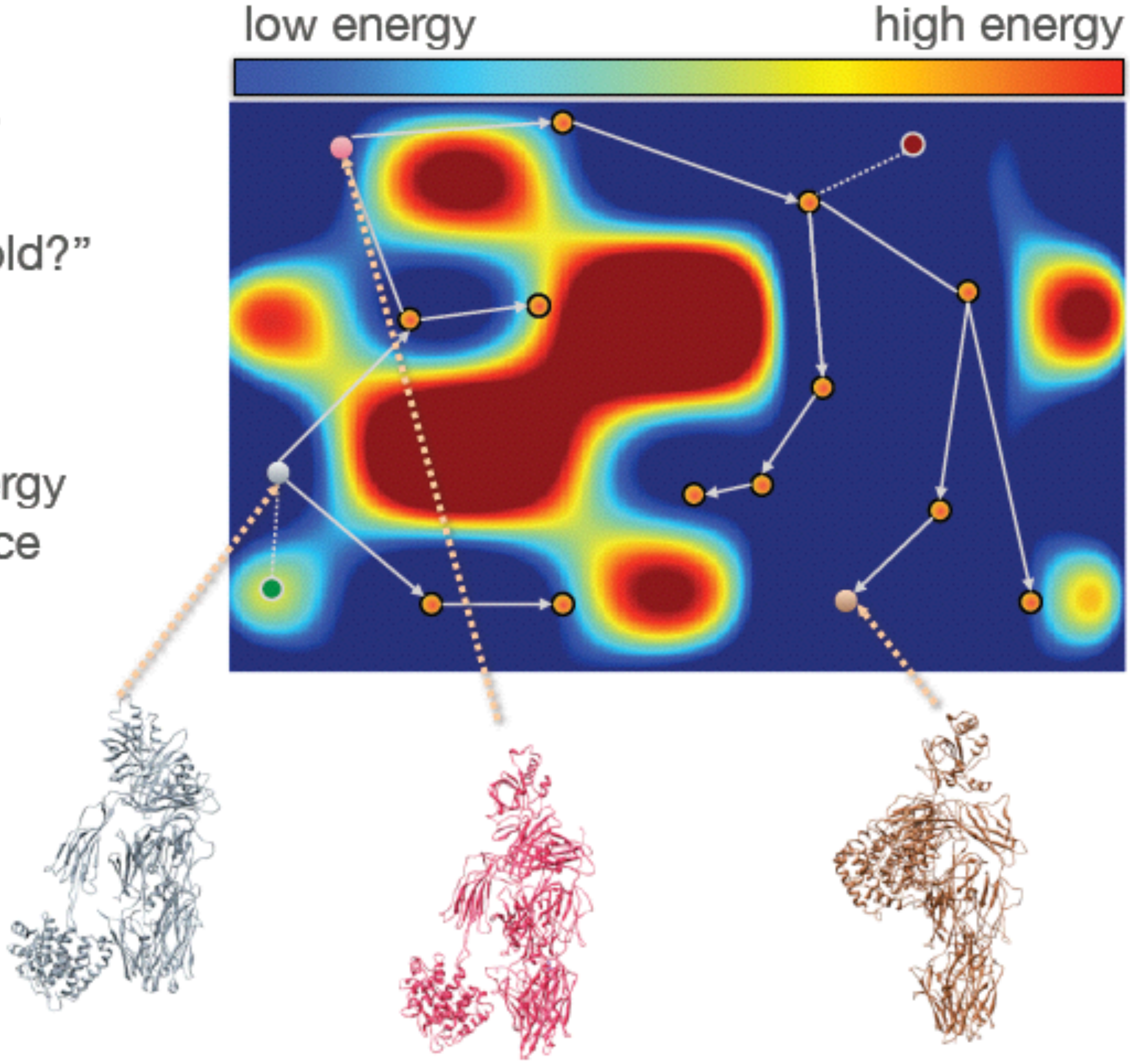
Motion planning approach

"is state valid?"

=

"is energy < threshold?"

Many different energy functions and force fields exist.



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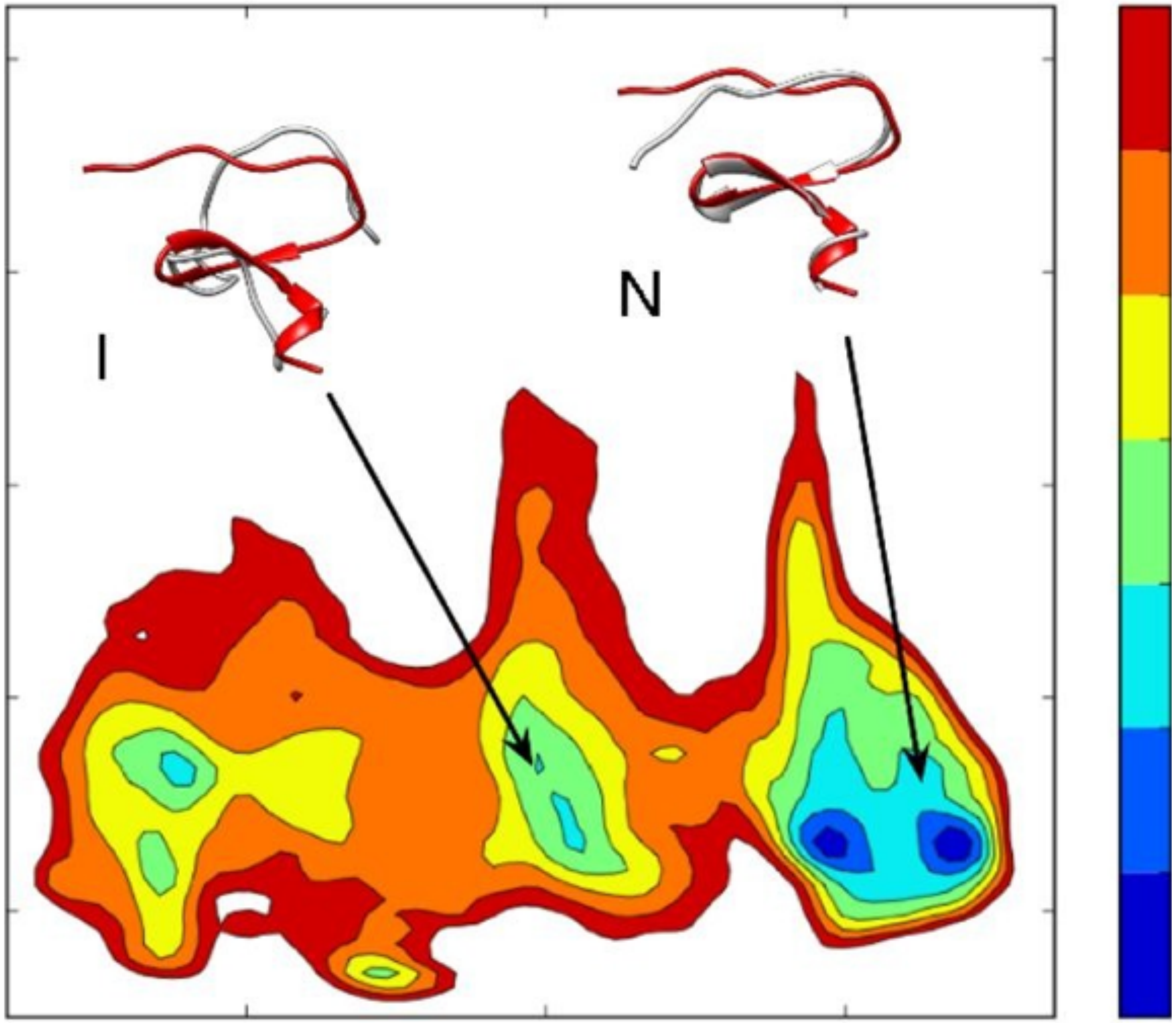
Challenges



- Extremely high-dimensional
- The majority of the states are high-energy

image is adapted from Prof. A. Barducci

Generating low-energy states

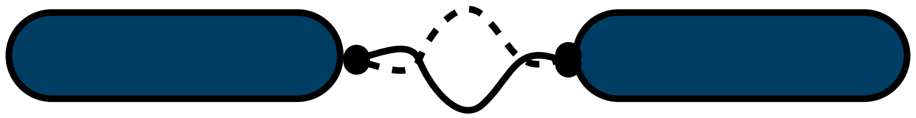
- Pick good state from already generated graph

- Slightly perturb DOFs

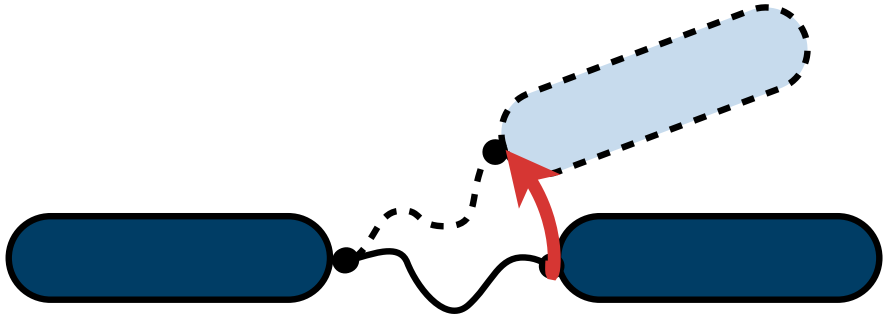
Generating low-energy states

Special moves

- Loop sampling

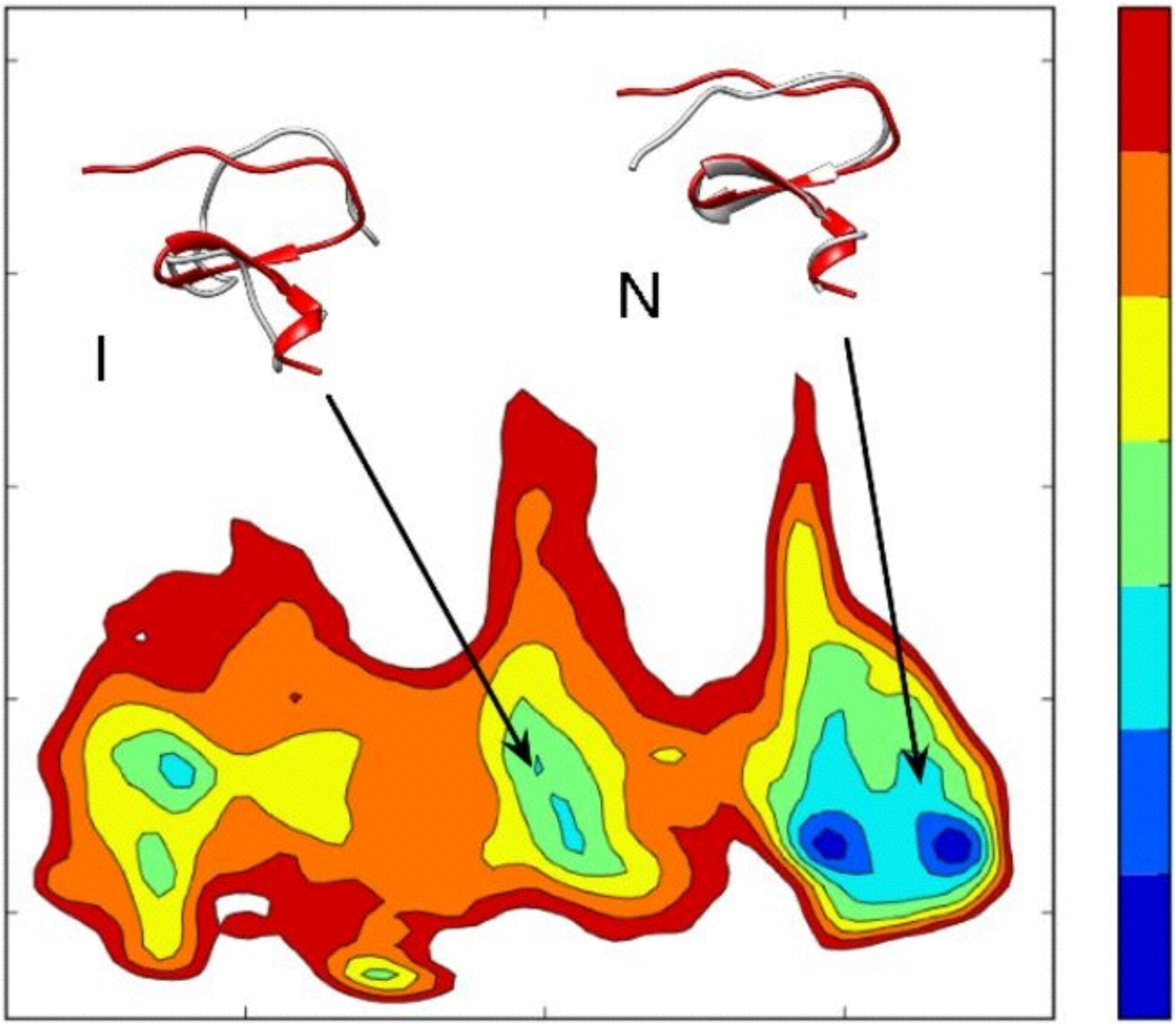


- Rigid body moves



- Random dihedral angle sampling (needed for probabilistic completeness)
- Energy minimization (needed to “fix up” structures)

The algorithm still fails



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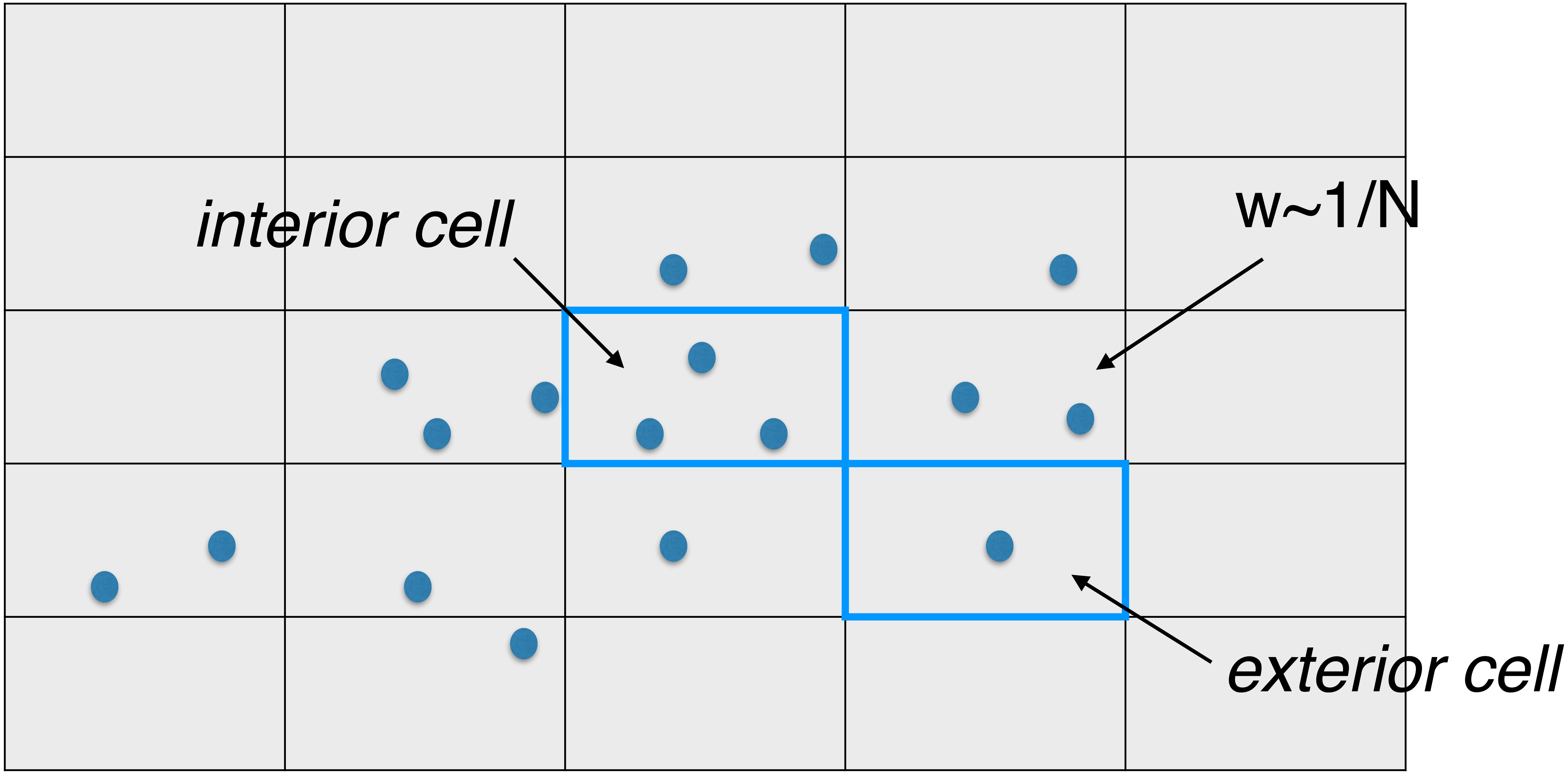
Directing the exploration



- Use low-dimensional projection
- Pick states mostly from the *exterior* grid cell

Summary

For very high-dimensional, very constrained systems (such as proteins) new challenges arise:

- Need to pick degrees of freedom carefully
- Need to sample configurations intelligently
- Need a good way to keep track of exploration progress