Mutation and binding-induced fold switching

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Overview

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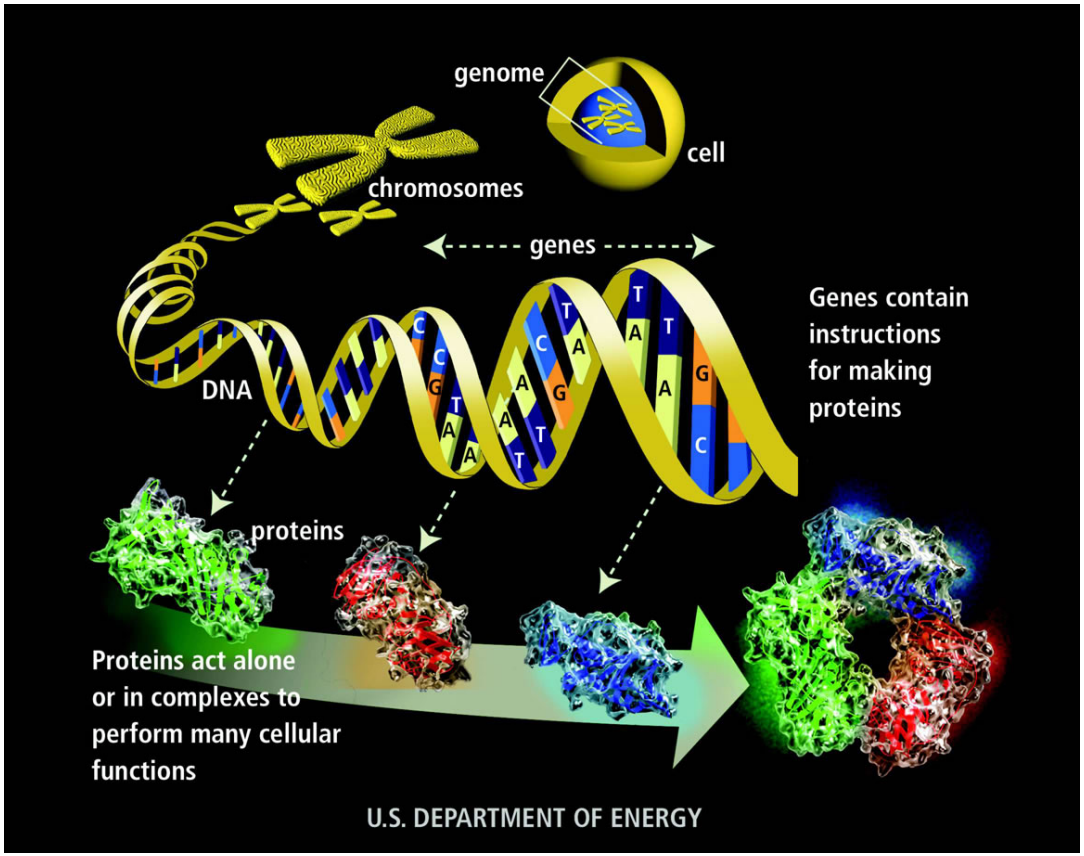
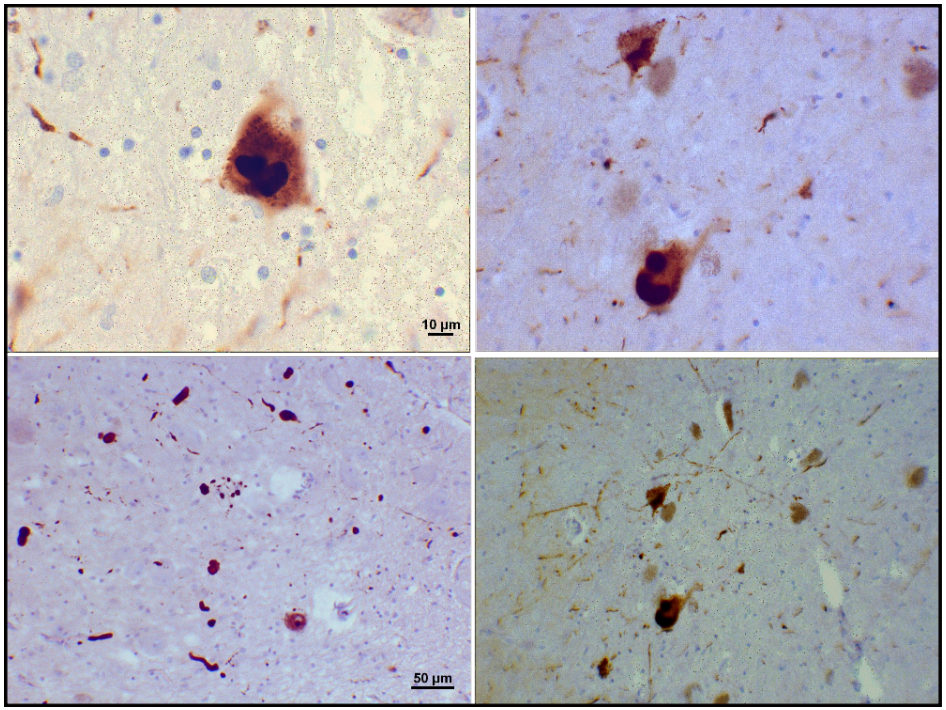
Overview



DOE

- Machinery of life
- Encoded in DNA

Why do we want to study proteins?



Wikipedia

- Understanding of biological processes
- Target for drug design

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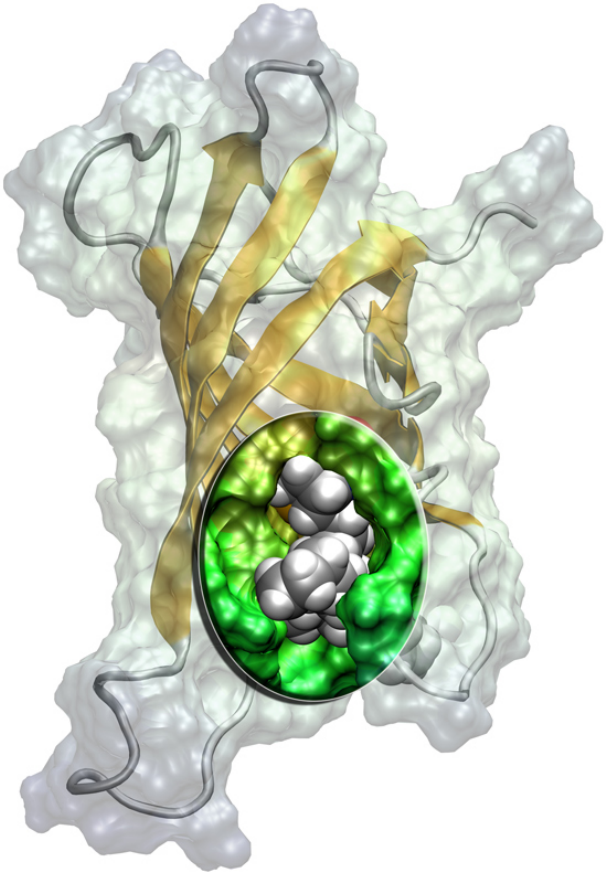
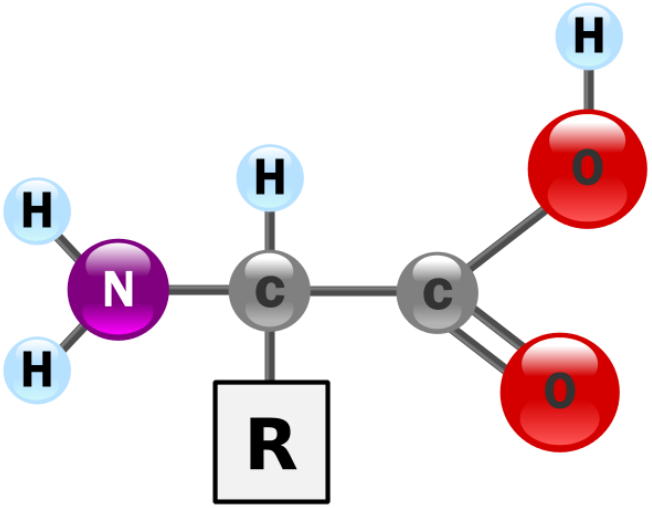
Proteins - From structure to function



- Structure needed to carry out function
- Example: Binding surfaces

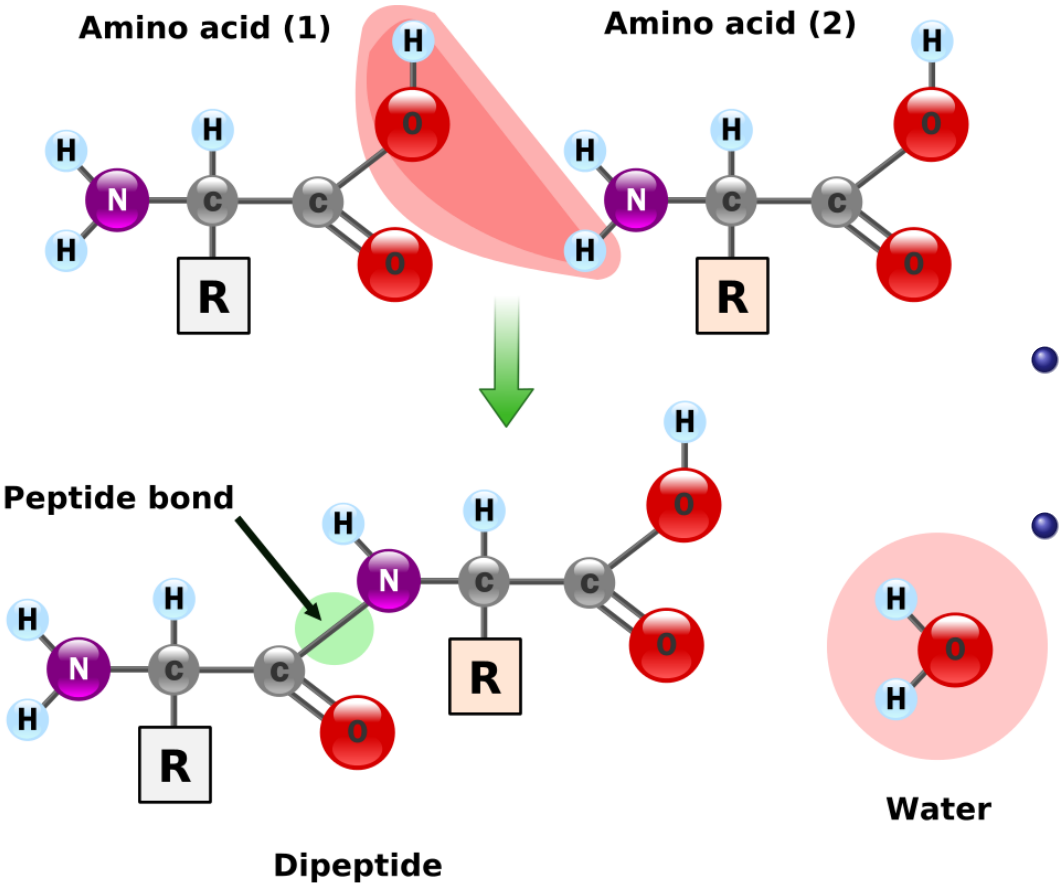
Basic building blocks



macrotomicro.blogspot.com

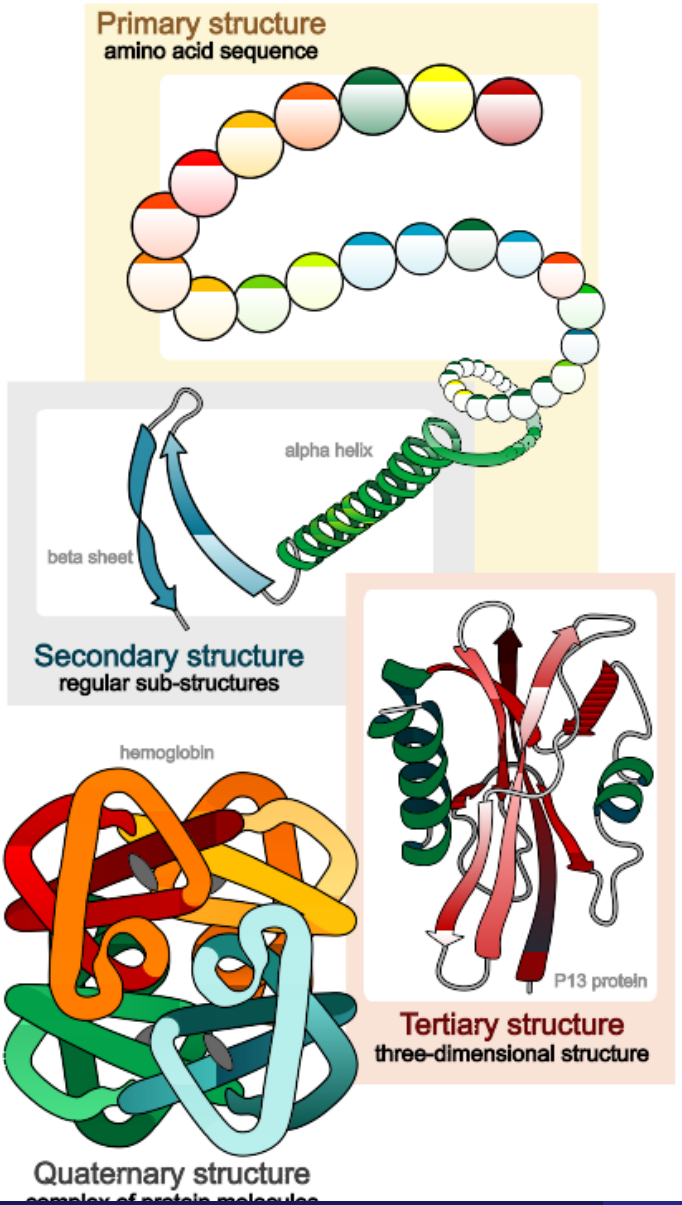
- 20 different amino acids
- 4 different groups

Peptide bonds



- Proteins are long chains of amino acids (often ¿ 200)
- Interactions between amino acids determine structure

Levels of structure



- Secondary: Alpha Helices and beta sheets
- Tertiary: 3D arrangement or fold

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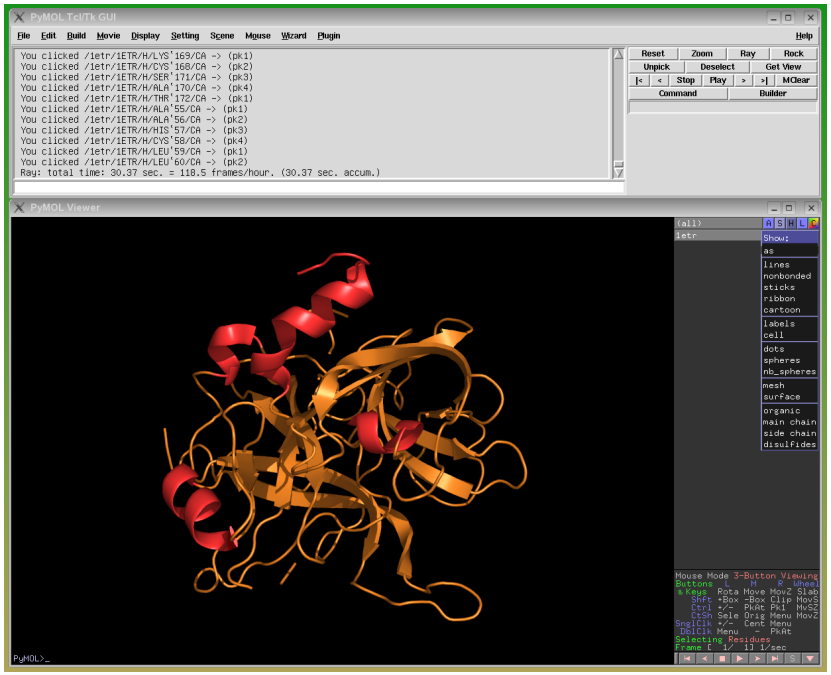
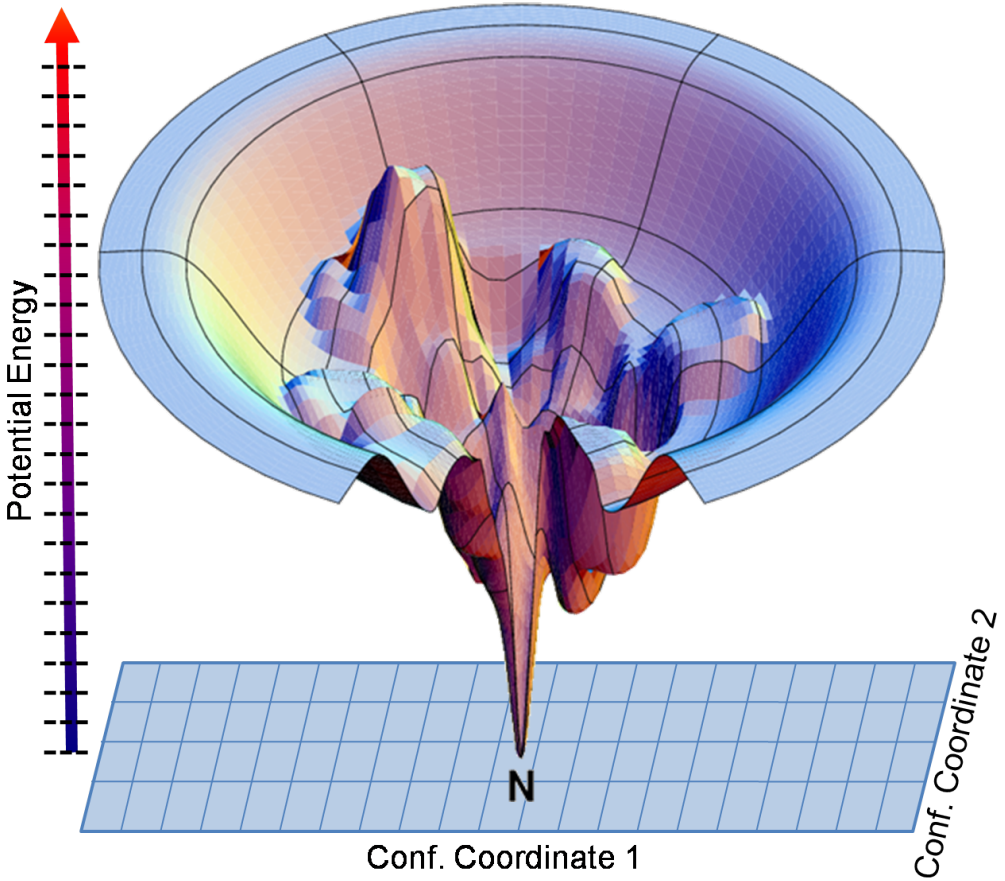
Why computer simulations?



Wikipedia

- Refine experimental data
- Find mechanisms by which proteins fold and interact
- Guide experimental search for protein design

The protein energy landscape



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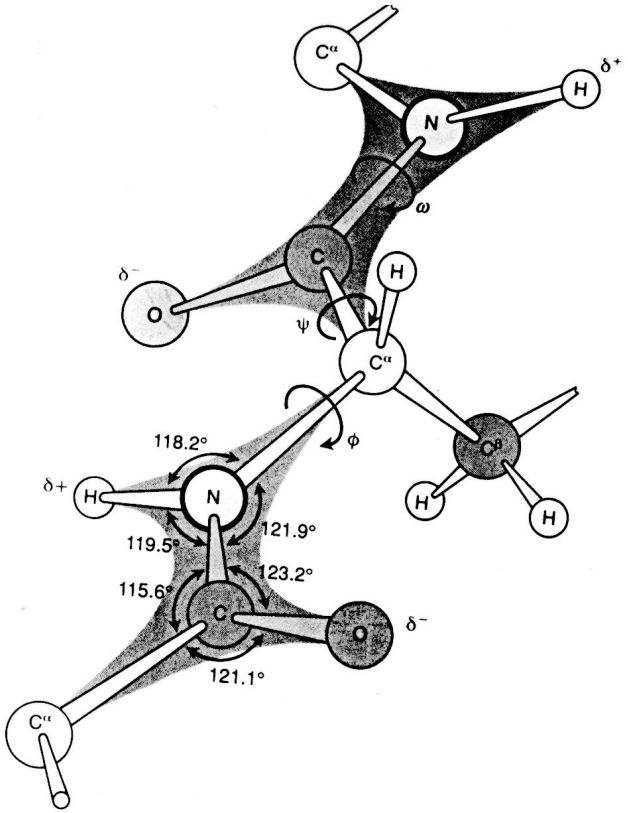
- Structure of a protein is hard to tell from sequence
- Energy landscape determined by interactions between amino acids
- Levinthal Paradox

Metropolis Monte Carlo



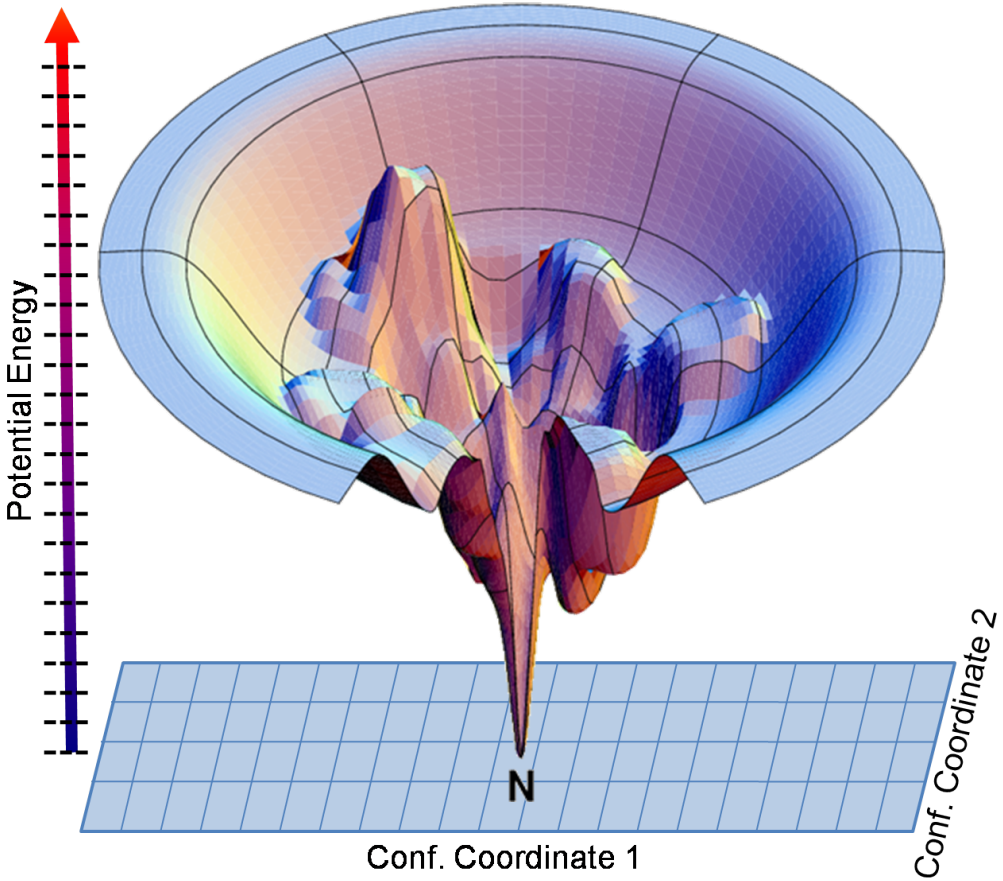
cmgm.stanford.edu

- Make a trial move for a degree of freedom of the chain
- Calculate new energy ΔE
- Accept new configuration with probability $e^{-\beta \Delta E}$

Metropolis Monte Carlo, Results

- Samples according to Boltzmann distribution: $\frac{\sum_E e^{-\beta E} O(E)}{\sum_E e^{-\beta E}}$
- Get interesting quantities like average energy, heat capacity, etc.

Simulated Tempering



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- Want to jump out of local minima
- Allow change of temperature with probability $e^{-(\Delta\beta E+\Delta g)}$
- Optimize g parameters to visit all temperatures equally

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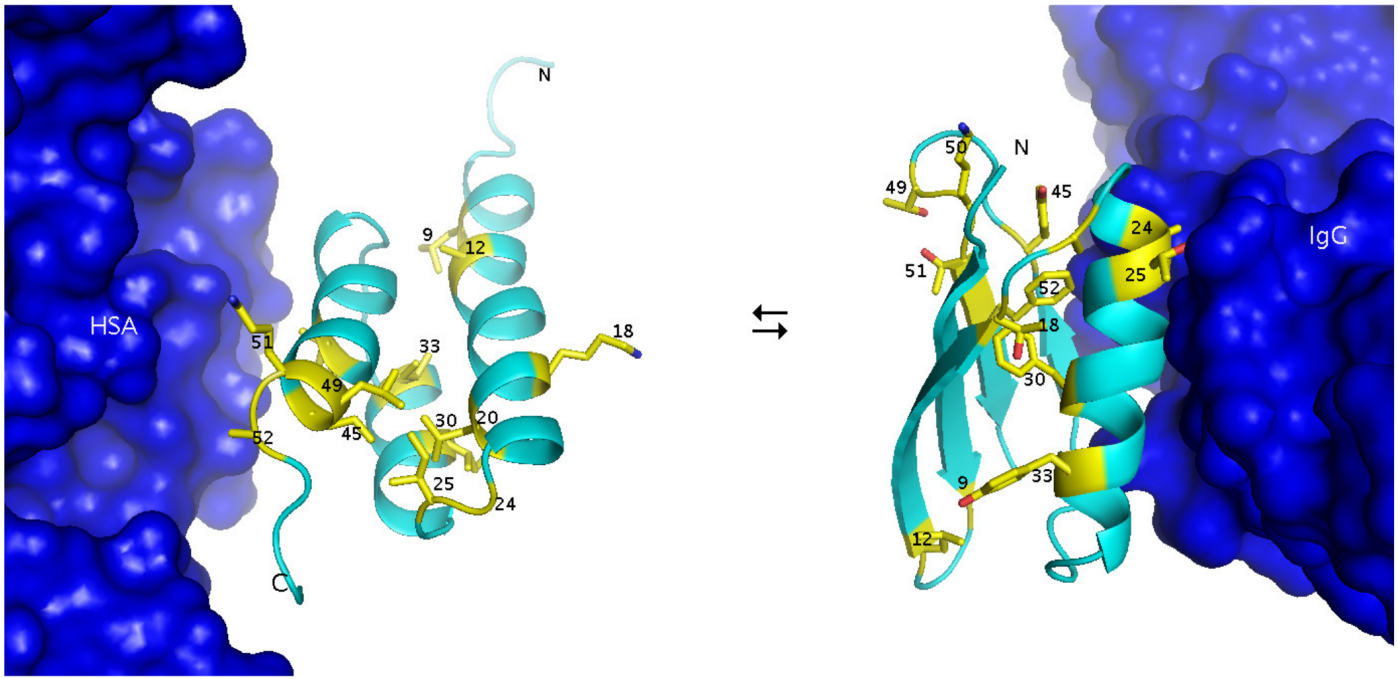
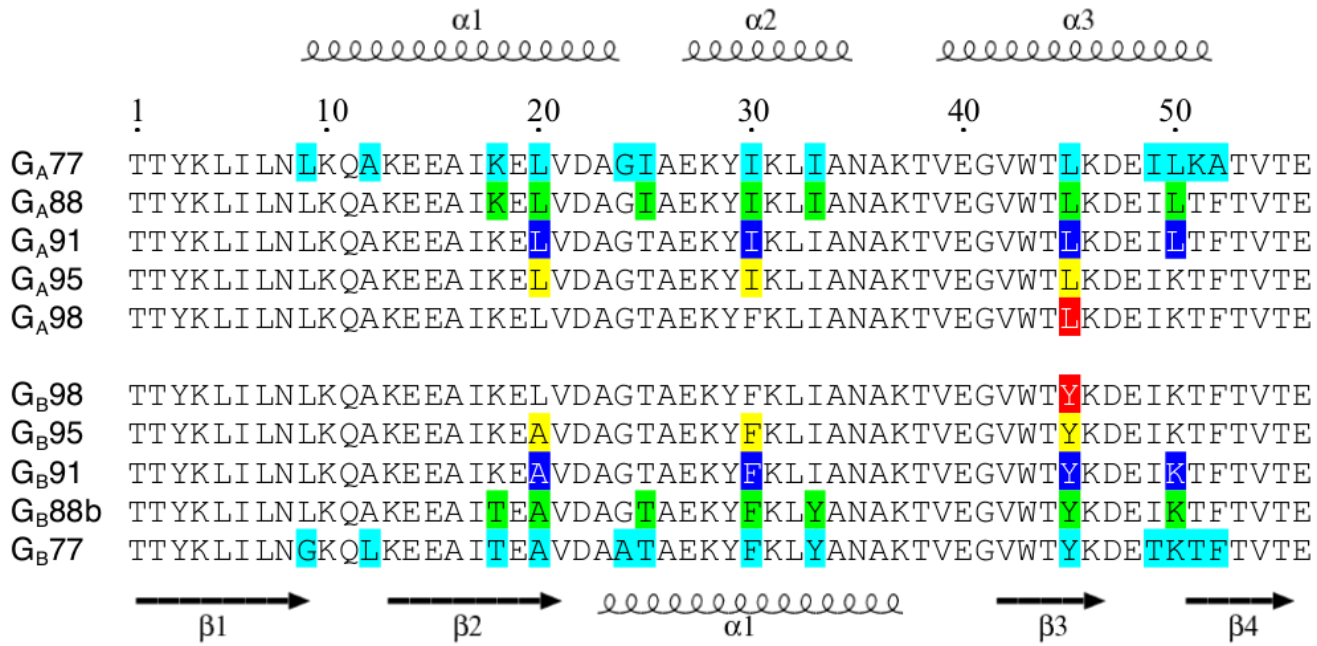
Experimental background: Protein GA and GB



- Two domains of protein G from Streptococcus
- Bind to proteins in blood serum
- Might allow bacteria to camouflage

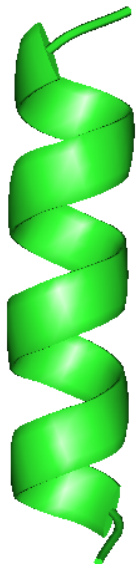
The mutational pathway



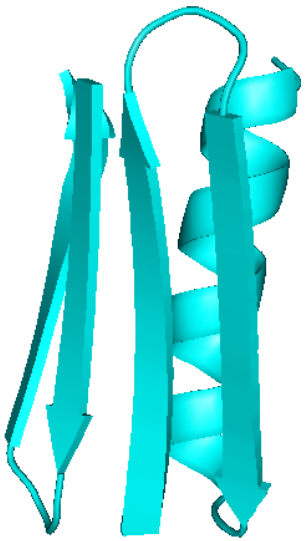
Alexander, *PNAS* 2009 106 (50) 21149-21154

Cbeta model, coarse grained

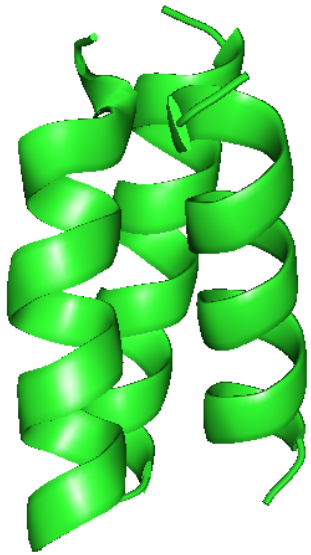
- Only three types of amino acids, represented by spheres
- Basic MC and Simulated Tempering
- Fold switch achieved



Cbeta model, binding



- How do the binding properties vary along the mutational path?
- Does the fold of a sequence switch upon binding?



Summary

- MC simulations useful tool to elucidate protein folding and binding
- GA and GB exhibit mutation and binding-induced fold switching
- Sequence-Structure space can be mapped using coarse grained models