Protein folding: from simplified models to the design of folding inhibitors.

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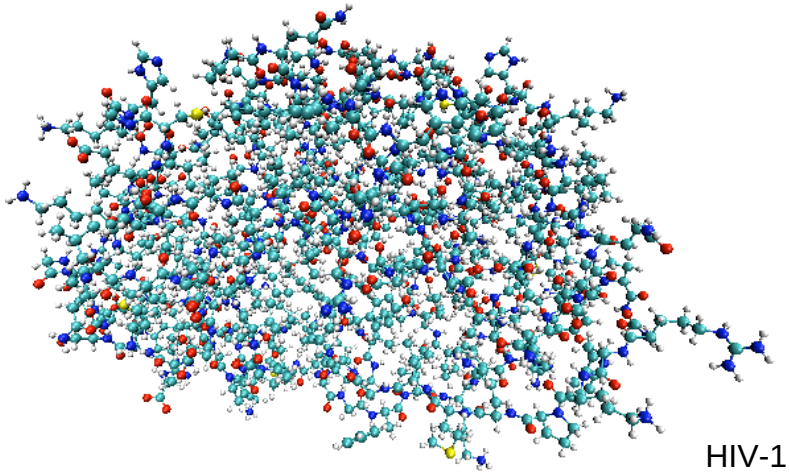

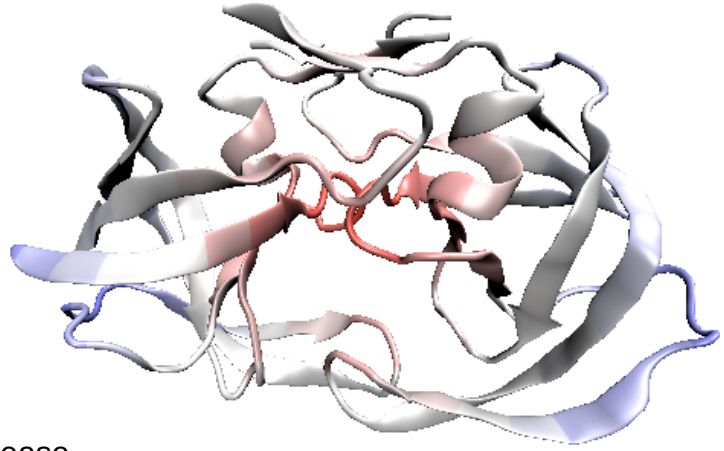

HIV-1 protease

- protein folding
- results from simplified models
- one slide on the computational algorithm

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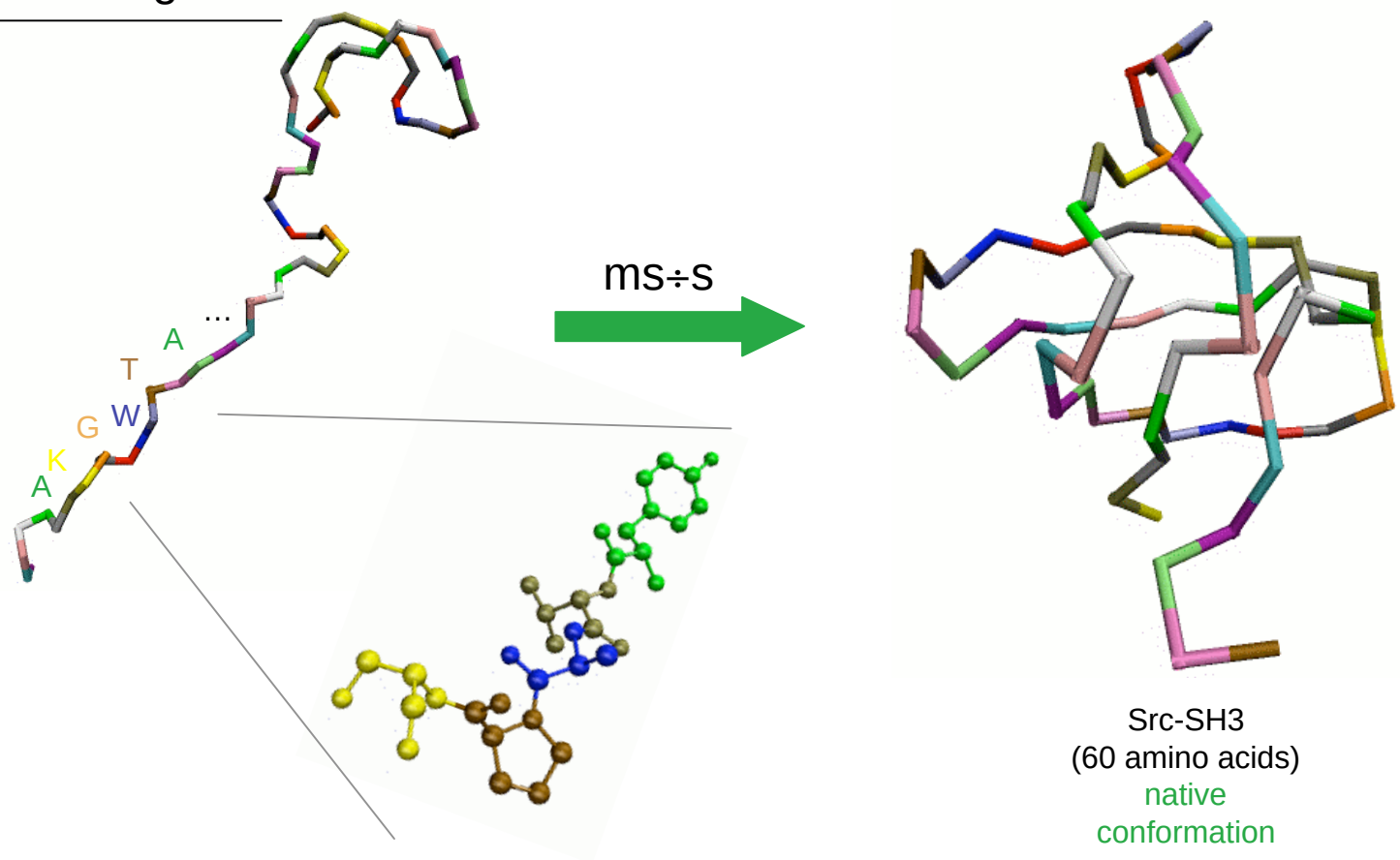
young investigators symposium 2008

Protein Folding

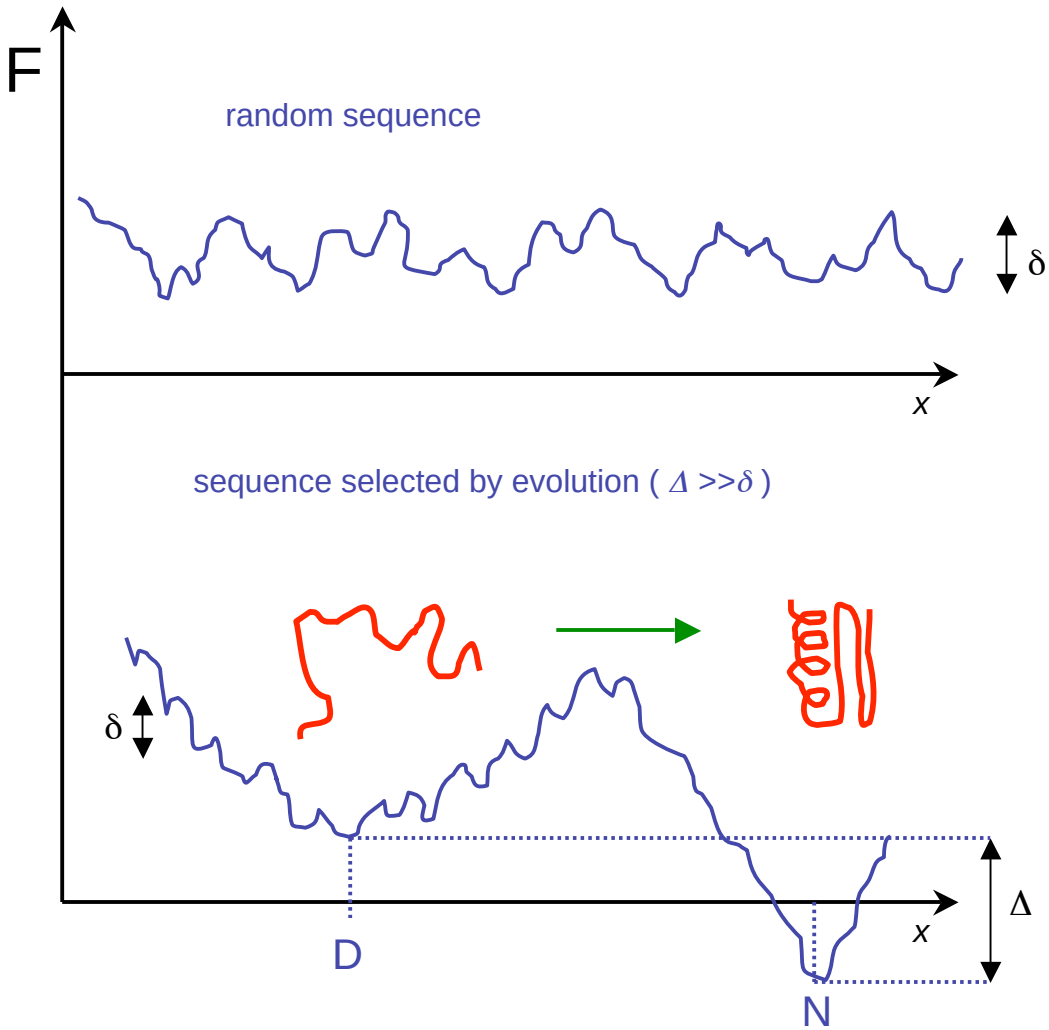


Src-SH3
(60 amino acids)
native
conformation

questions:

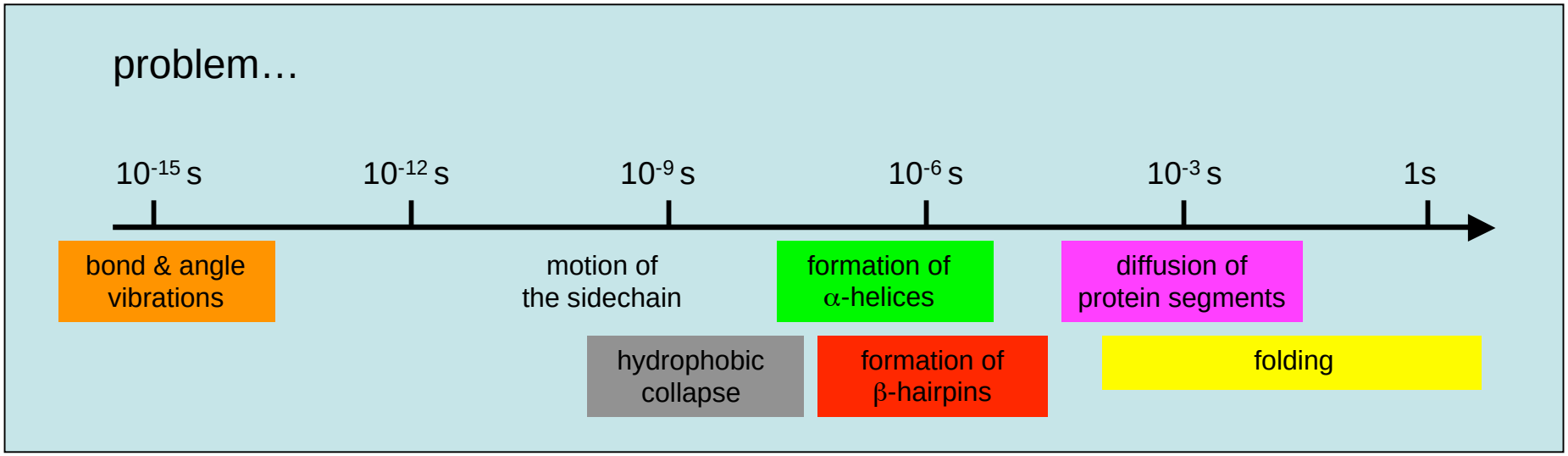
- how can such a complicated system display a unique (S≈0) equilibrium state?
- how can folding be so fast?
- what is the native state of a given sequence?
- what is the effect of mutation? are there other stable conformations? etc…

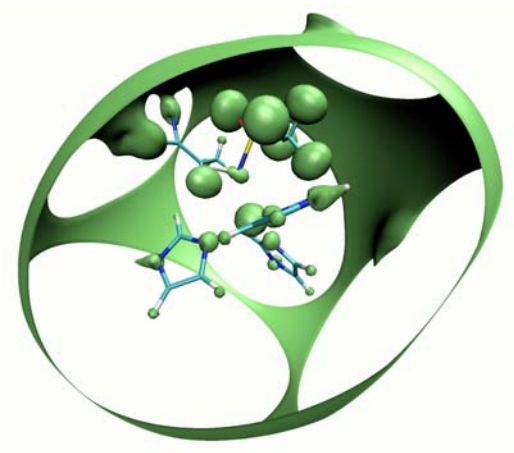
The source of all problems : the interactions within proteins are frustrated



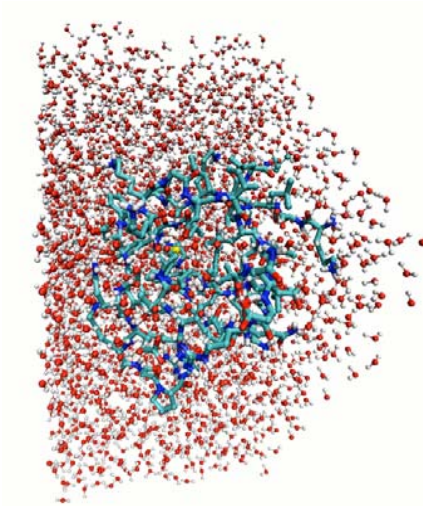
Residual frustration:
- still complicated to predict the N state
- protein marginally stable ($\Delta F \approx 10\ kT_{room}$)
- kinetics easily trapped

Folding simulations

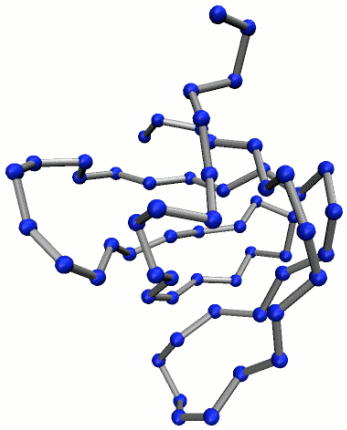




quantum description



classical, all-atom, explicit solvent



simplified

Simplified models

- simplified degrees of freedom
- potential tuned to reproduce some experimental data

$$U = \sum_{i<j} B_{ij} \left[\left(\frac{r_0}{r_{ij}} \right)^{12} - 2 \left(\frac{r_0}{r_{ij}} \right)^{6} \right]$$

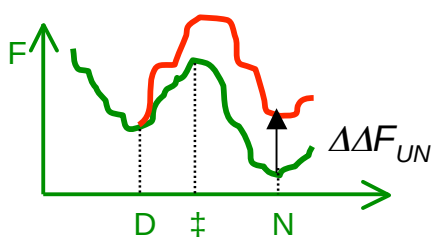
- native state as ground state

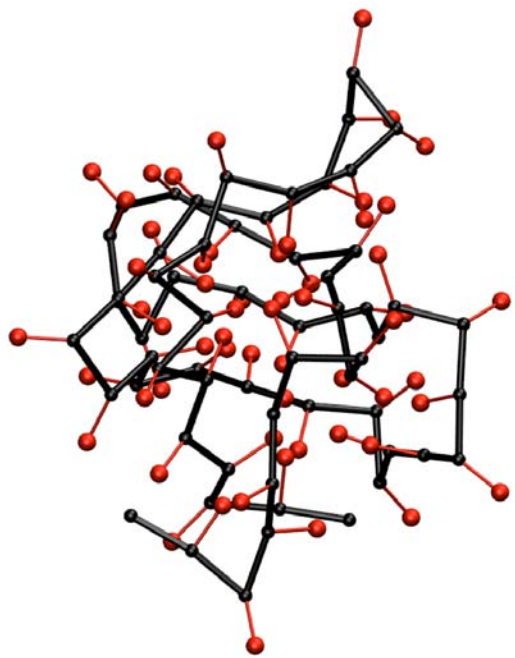
→ $B_{ij} > 0$ only if i and j are close in the native conformation.

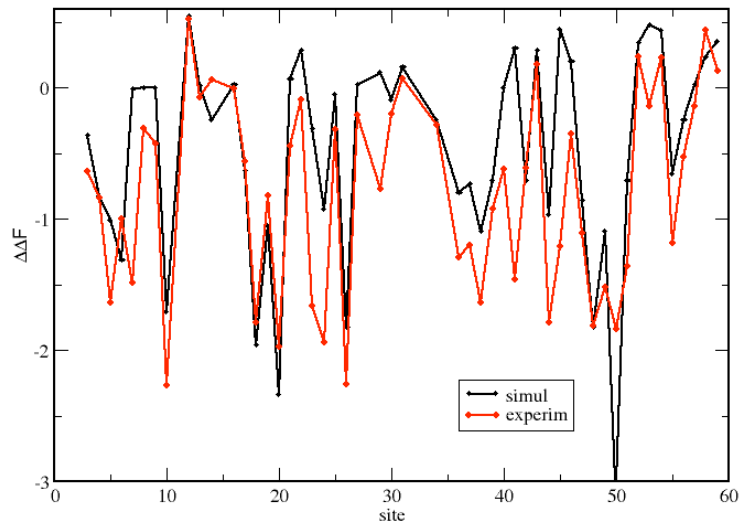
(automatically cooperative transition)

- reproduce effects of mutations on the stability of the native state ($\Delta\Delta F_{UN}$)

→ obtain a set of B_{ij} from the $\Delta\Delta F_{UN}$ tabulated for each site.

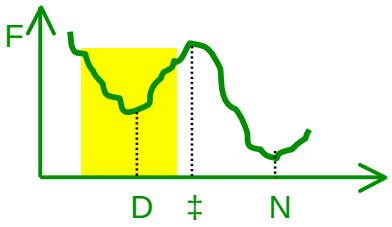






simulation algorithm: metadynamics (at the end...)

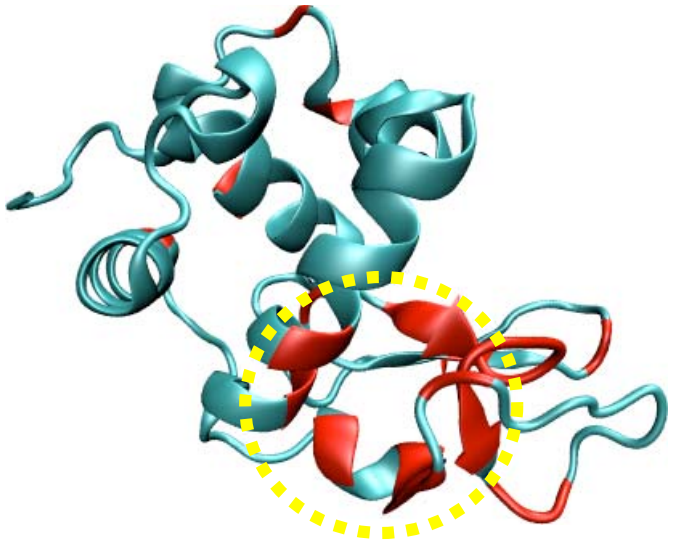
Limelight on the denatured state

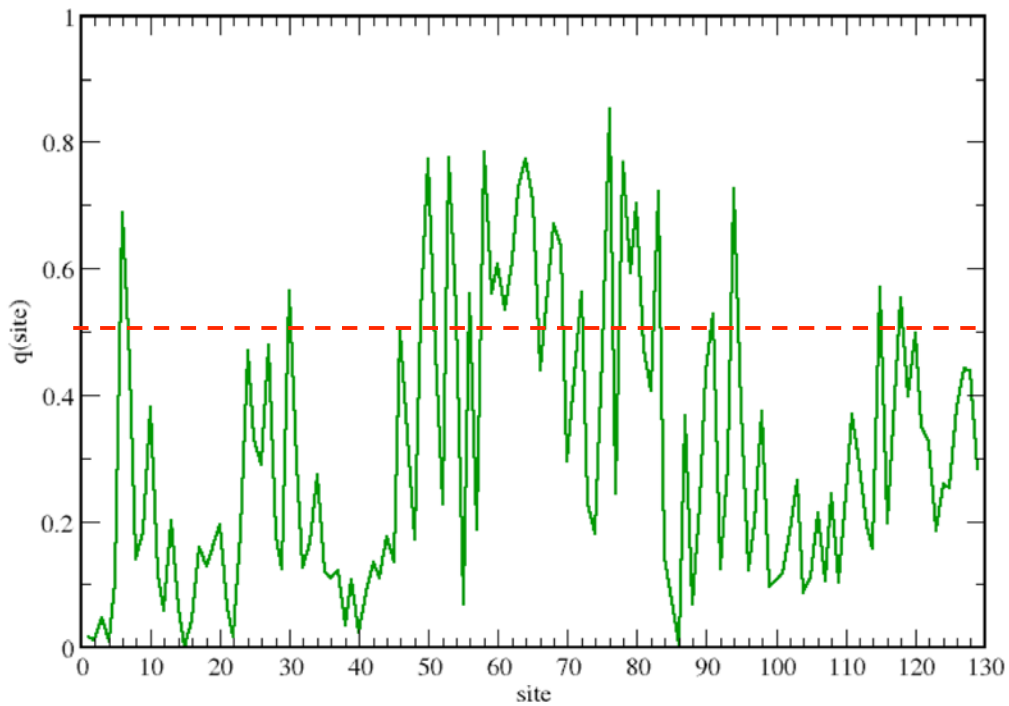


Is the denatured state a random coil?

calculate the "nativeness" q_i of the sites in the denatured state

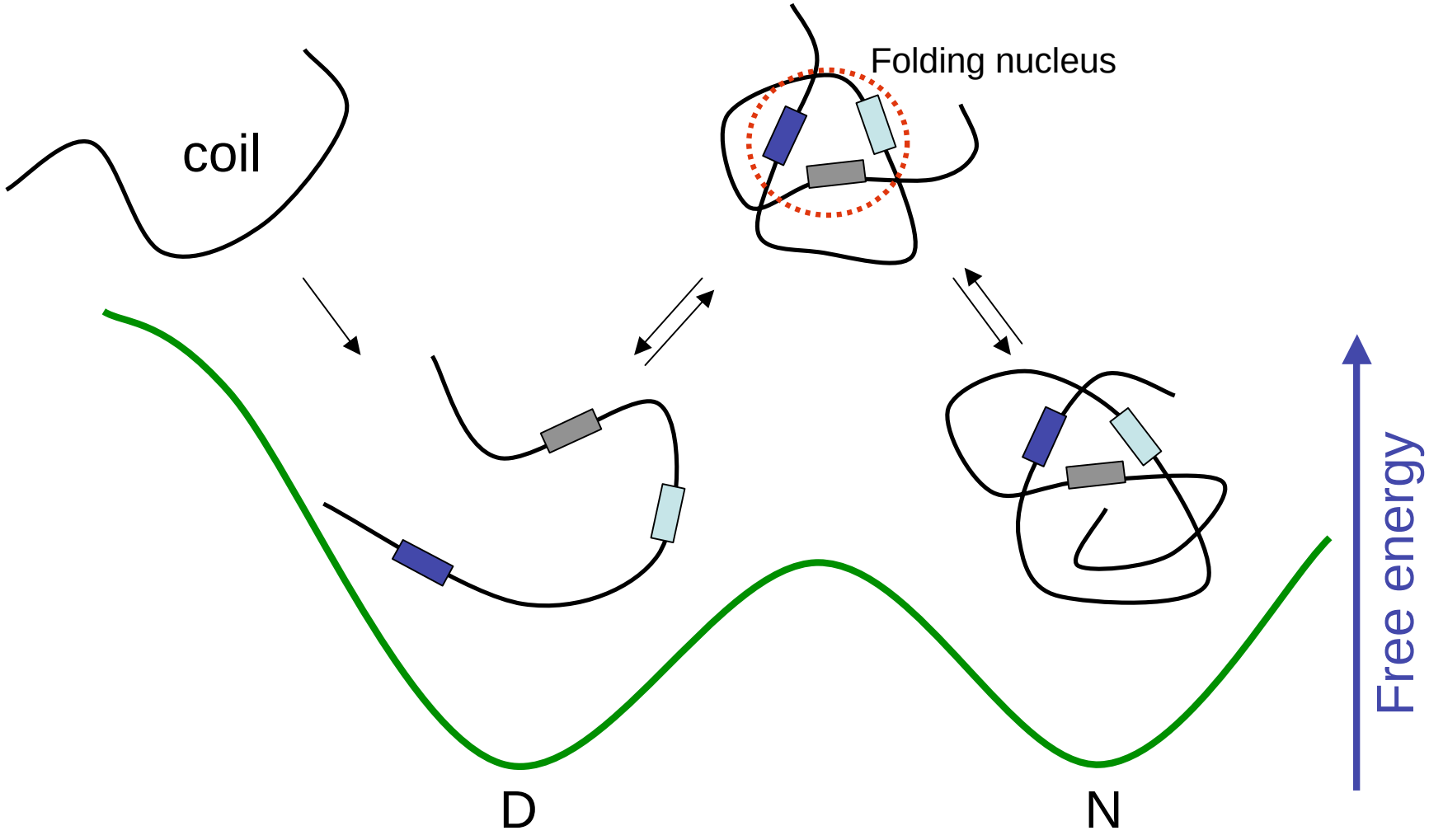
lysozyme





- there is a lot of native structures in the denatured state.
- this agree with recent NMR data (e.g. Klein-Seetharaman et al. Science 2002).
- this stable structures form a nucleus and are related to the transition state.

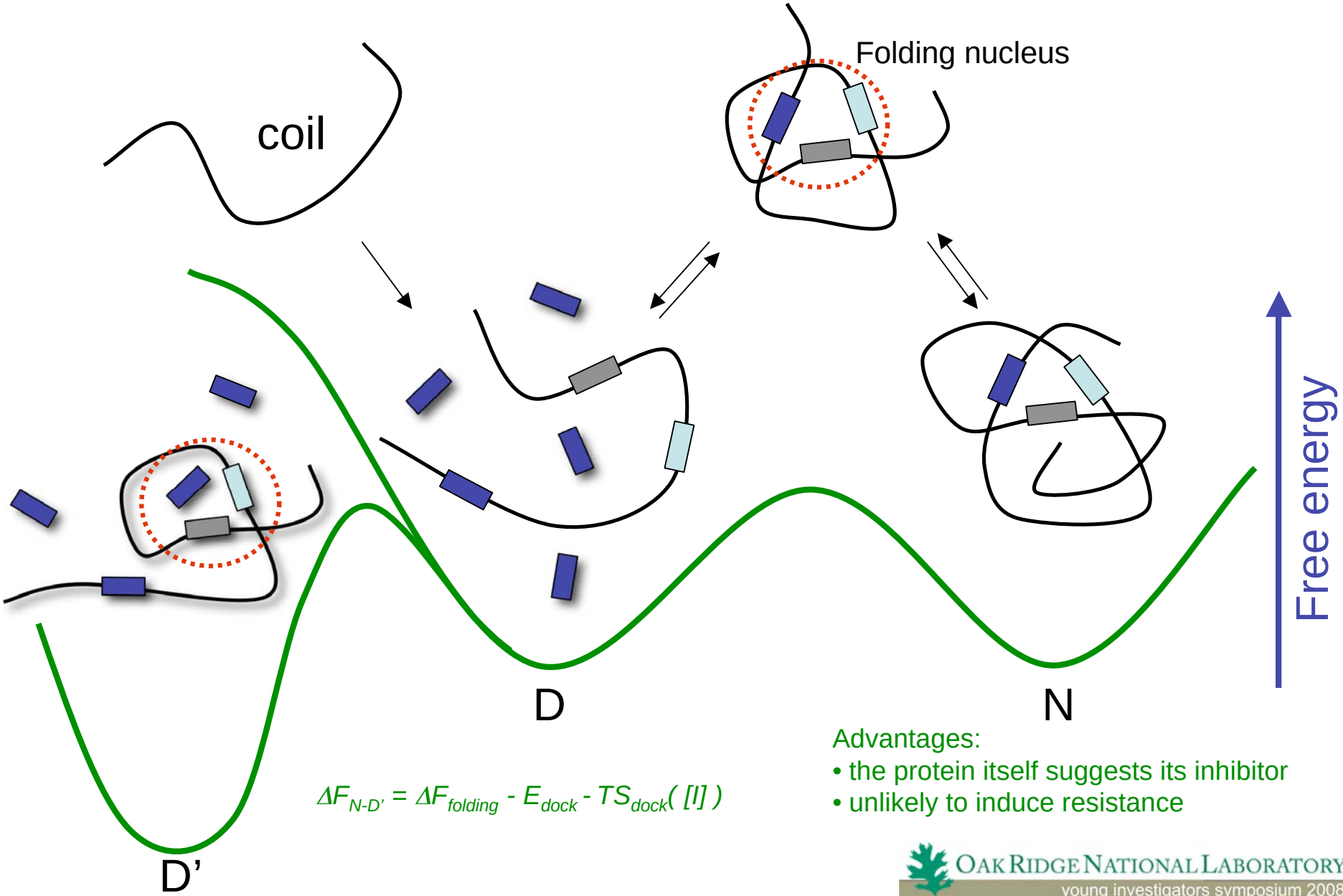
Idea from simple models!



Idea from simple models!

…to inhibit a protein by destabilizing its native state

use a peptide with the same sequence as such critical segments to block the formation of the folding nucleus.



$$\Delta F_{N\text{-}D'} = \Delta F_{folding} - E_{dock} - TS_{dock}([I])$$

Advantages:

- the protein itself suggests its inhibitor
- unlikely to induce resistance

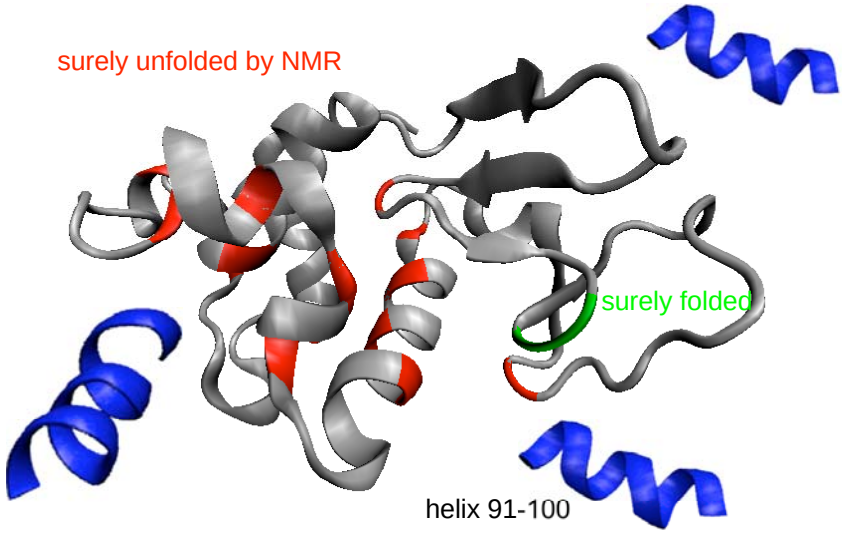
Testing the idea: lysozyme

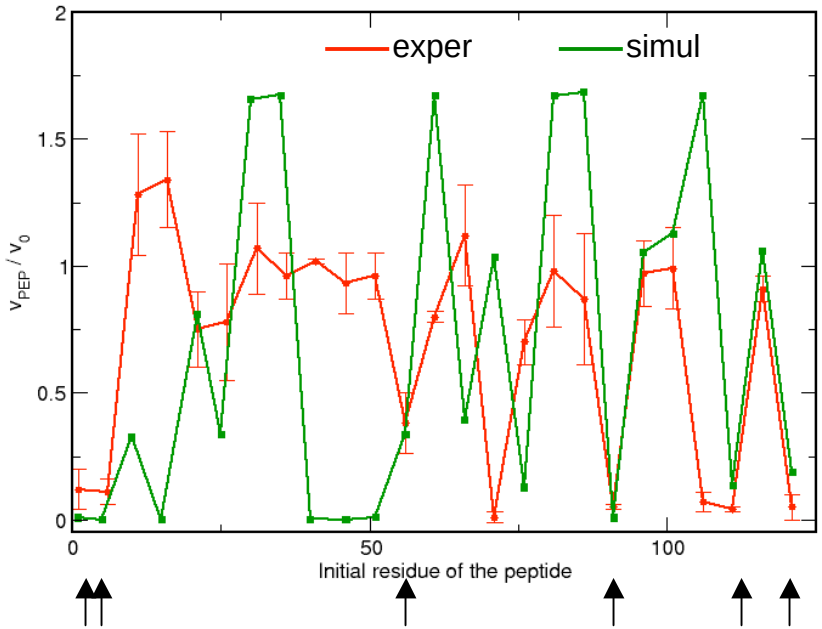
protein sequence : KVFGRCELAAAMKRHGLDNYRGYSLG... ...MKRHGLD

pep 2 (6-15)

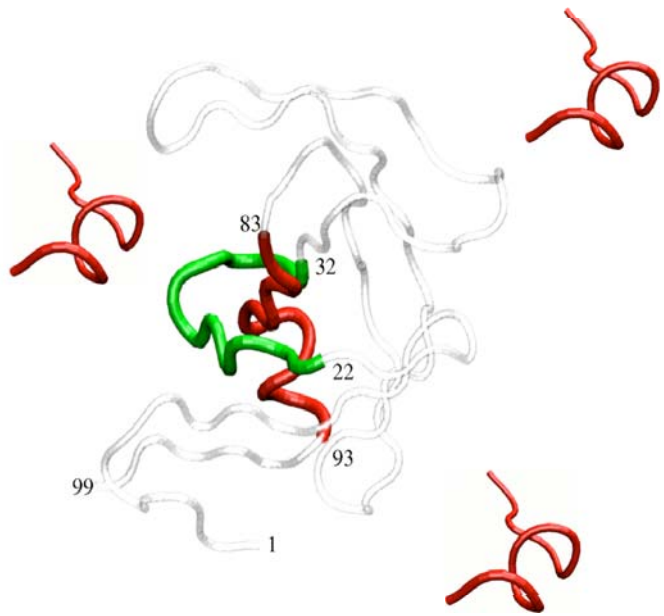
pep 1 (1-10)

pep 25 (121-129)





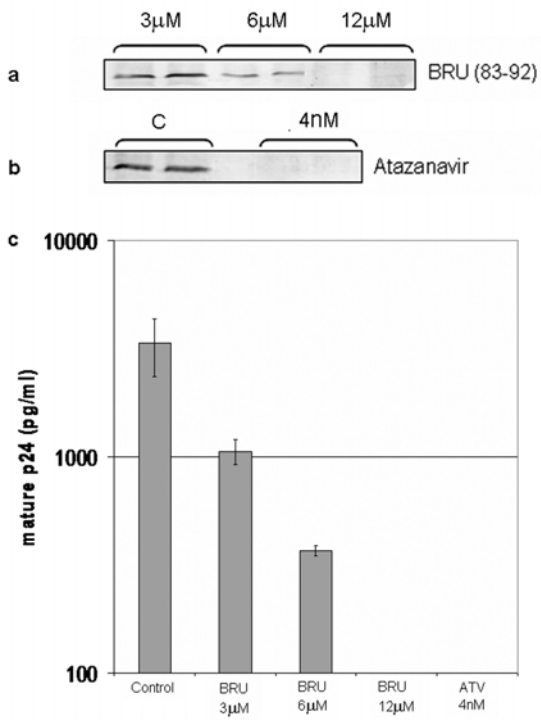
A more interesing case: HIV-1 protease



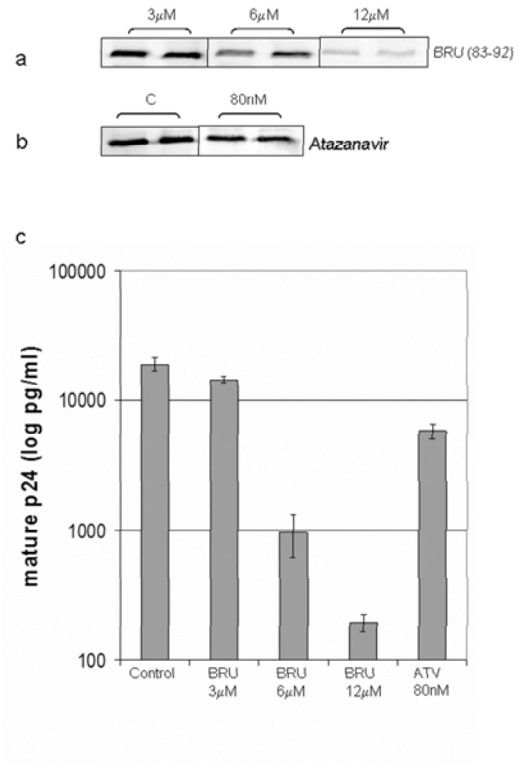
peptide 83-93

k_I=2.58±0.7 μM

wild-type infected cells



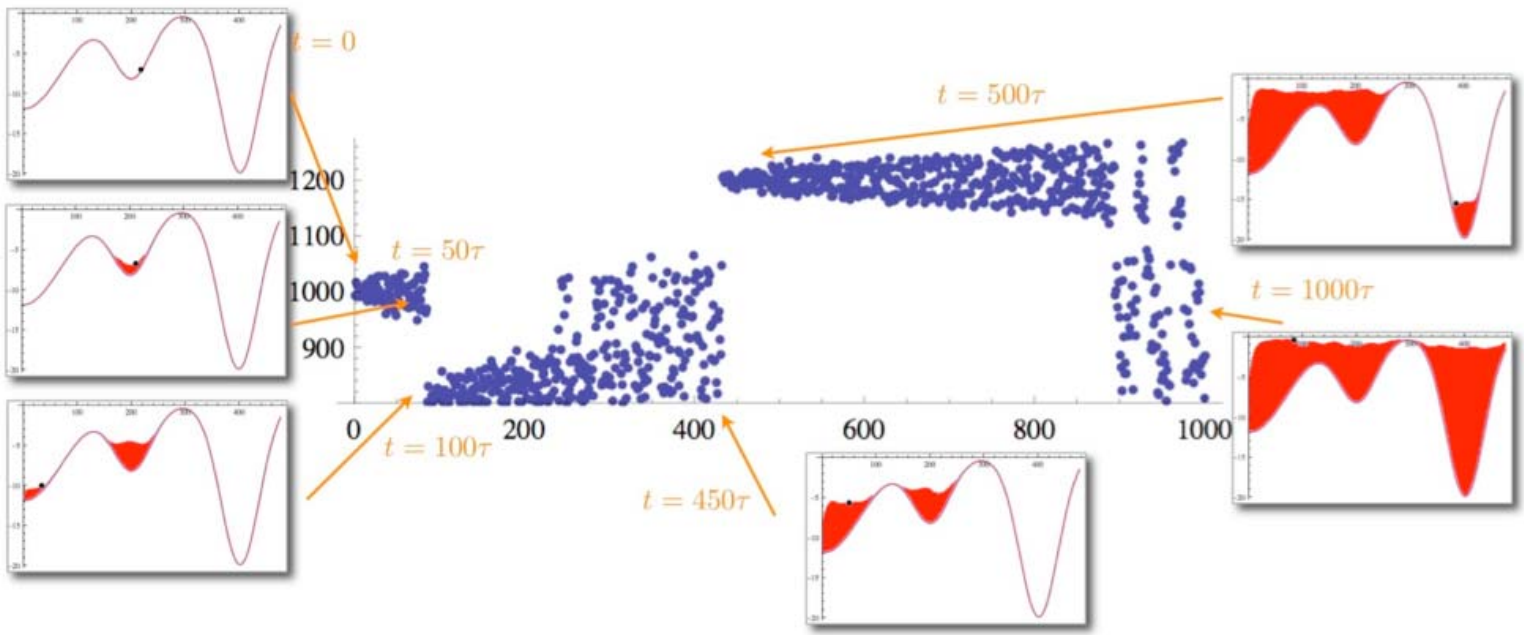
multi-resistant infected cells

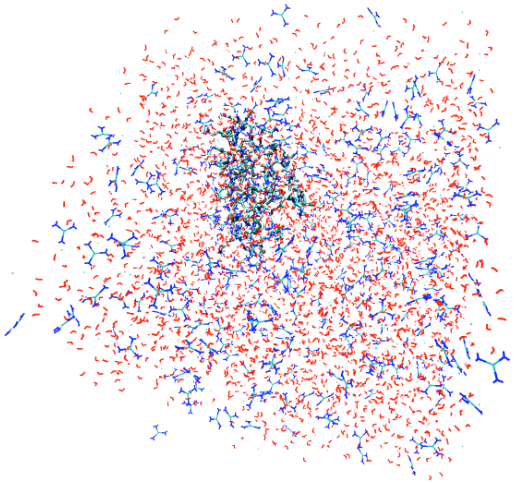


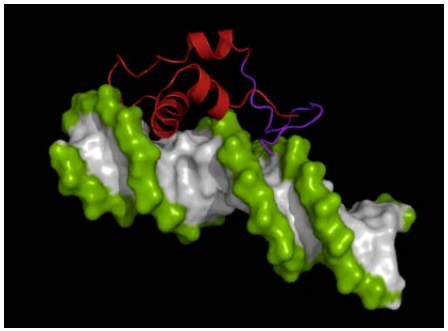
Metadynamics

Laio and Parrinello, *Escaping free-energy minima*, PNAS 2002
Camilloni, Provasi, Tiana and Broglia, *Exploring the protein G..*, Proteins 2008.
Tiana, *Estimation of microscopic averages from metadynamics*, Eur. Phys. J. B, 2008

- select few slow-varying “collective variables” of the system.
- add a non-Markovian term to the Hamiltonian which disfavours the sampling of regions already visited.







Thanks....

Who did the job...

experiment

Martina Caldarini
Francesca Vasile

theory

Ludovico Sutto

Carlo Camilloni

Davide Provasi

(now at Mount Sinai University, NYC)

Franz Marini

Ricardo A. Broglia

GT