Coarse-grained methods for high pressure simulation of proteins

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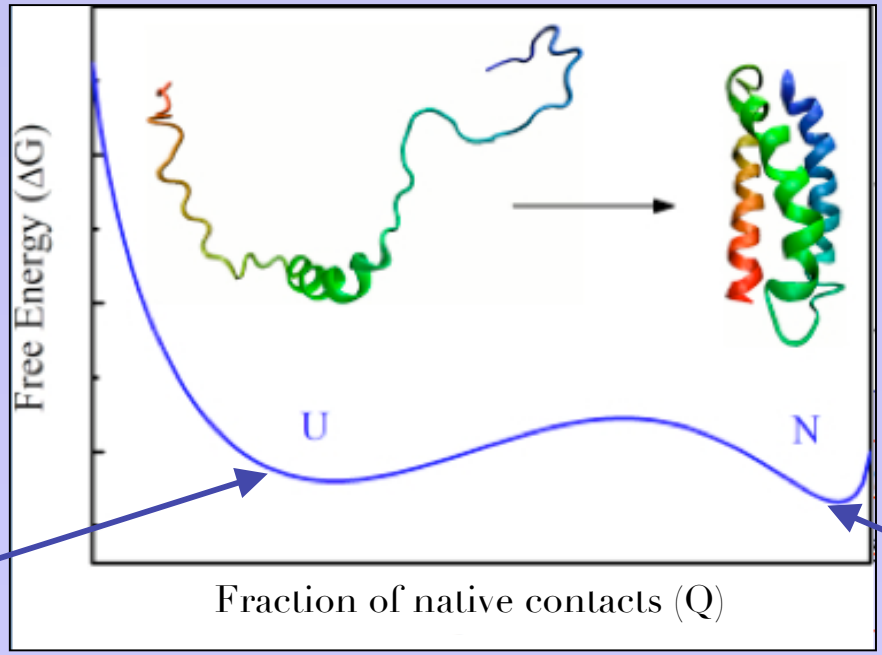
The protein folding questions :

- How can proteins fold in a so short time scale (µs, ms) ?
- What are the driving forces in proteins folding ?



Unfolded states : stabilized by entropy

Folded states : stabilized by enthalpy

Classic free-energy representation for two-states proteins

There are many ways to unfold proteins :

Irreversible methods :

- Urea, GuHCl : chemical denaturation
- pH : acid denaturation

Reversible methods :

- Temperature : heat or cold denaturation
- **Pressure**

The p,T stability phase diagram :

$$d\Delta G = -\Delta S dT + \Delta V dp$$

Taylor expansion up to the second order

Hawley (Biochemistry) 1971

Smeller (BBA) 2002

$$\Delta G = \frac{\Delta\beta}{2}(p-p_0)^2 + \Delta\alpha(p-p_0)(T-T_0) - \Delta C_p\left[\frac{(T-T_0)^2}{T_0}\right] + \Delta V_0(p-p_0) - \Delta S_0(T-T_0) + \Delta G_0$$

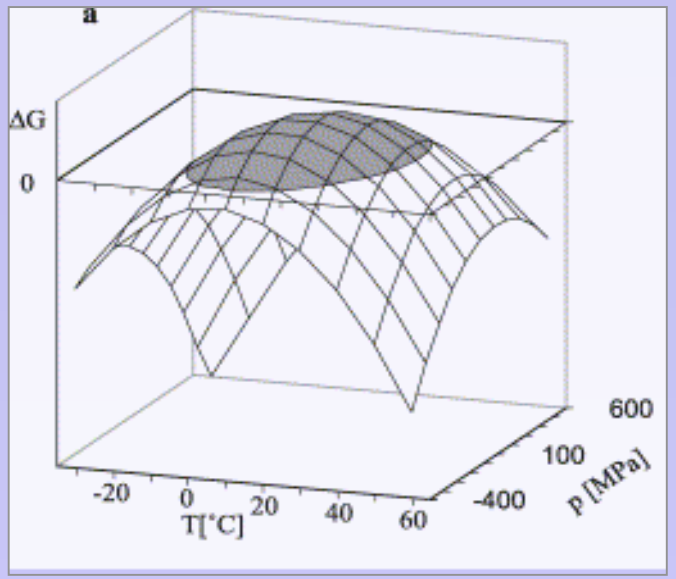
2nd derivatives of ΔG :

$$\Delta\alpha = \frac{1}{V}\left(\frac{\partial\Delta V}{\partial T}\right)_p$$ Thermal expansivity

$$\Delta\beta = -\frac{1}{V}\left(\frac{\partial\Delta V}{\partial p}\right)_T$$ Compressibility

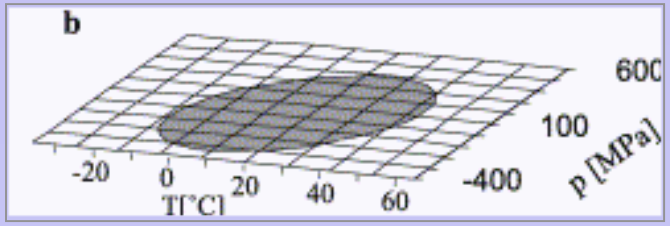
$$\Delta C_p = T\left(\frac{\partial\Delta S}{\partial T}\right)_p = \left(\frac{\partial\Delta H}{\partial T}\right)_p$$ Heat capacity

Diagram representation :

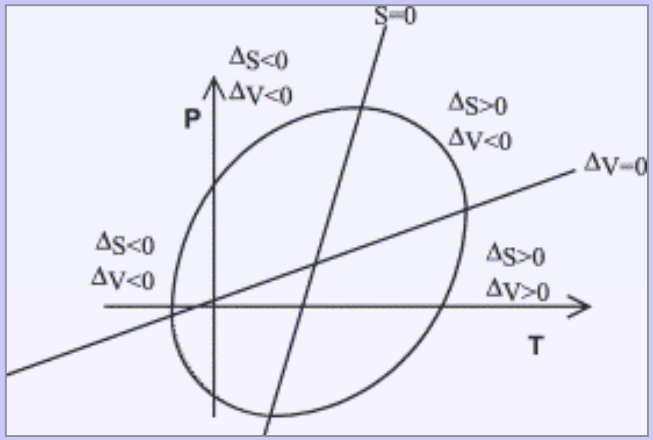


3d representation

Planary section
at ΔG=0



Classic representation

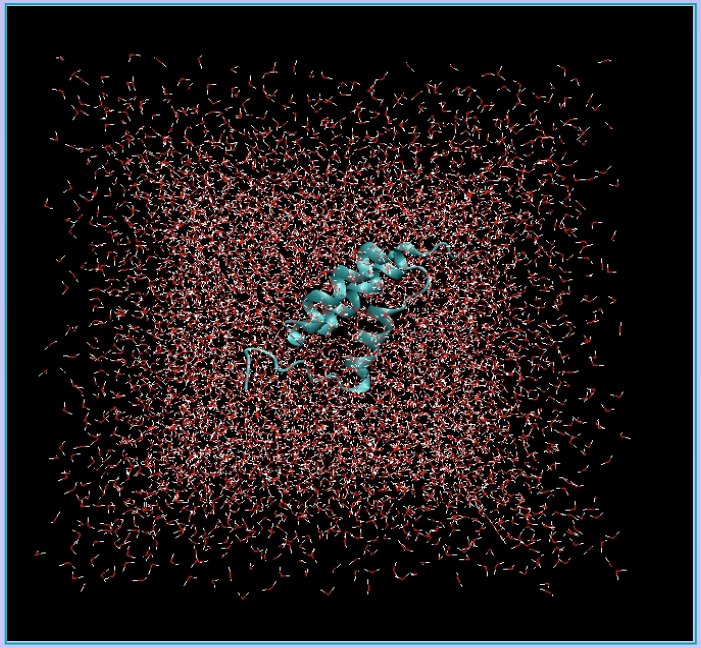


Keeps ellipsity while:

$$\Delta\alpha^2 > (\Delta Cp\,\Delta\beta)/T_0$$

Molecular Dynamics simulations of proteins :

All-atom MD simulation is a usefull method to study folding/unfolding



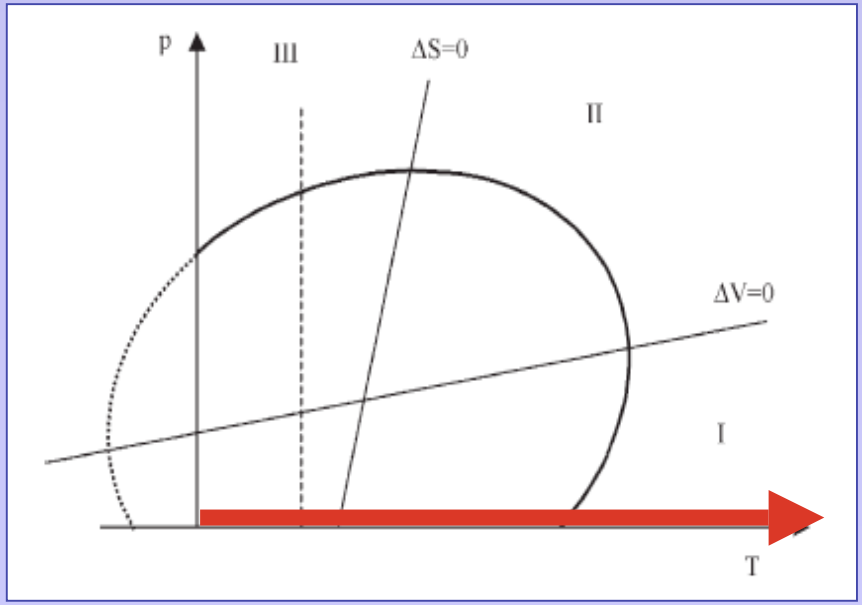
Popular packages :

- CHARMM
- AMBER
- GROMACS
- NAMD
- MOSCITO

Actual computational facilities give access to **µs time scale** for all-atom explicit solvent simulations of peptides and small proteins

Heat / pressure effects on kinetics :

- Heat : decrease free energy surface roughness : ↗ speed folding / unfolding (µs)
- Pressure : increase free energy surface roughness : ↘ speed folding / unfolding (ms)



Classic MD simulations can only explore the temperature dimension

Coarse-grained methods for high pressure simulations :

1. Go-model with pressure-dependant PMF

2. Multi-scale coarse graining at high pressure

Go-model with pressure dependant PMF :

First assumption : interactions between natives contacts are the main forces driving proteins folding

No energetical frustration ⟶ Only topological frustration

$$U_{total} = \sum_{bonds} K_r\left(r - r_{eq}\right)^2 + \sum_{angles} K_\theta\left(\theta - \theta_{eq}\right)^2 + \sum_{dihedrals} \frac{V_n}{2}\left[1 + \cos\left(n\phi - \gamma\right)\right] + \sum_{nonbond}\left[w(r)\nu\right]$$

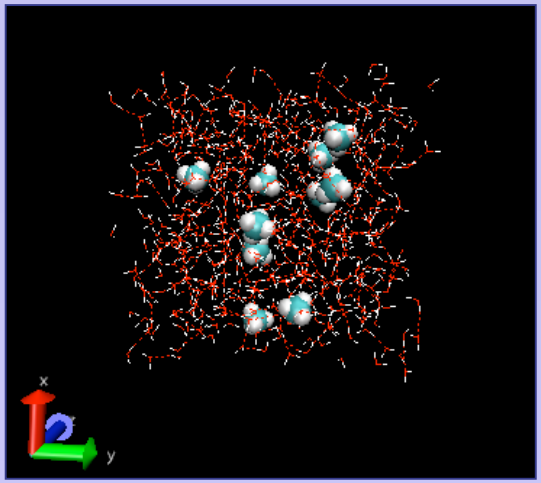
ν=1 if native contact

ν=0 if none native contact

Go-model with pressure dependant PMF :

Second assumption :

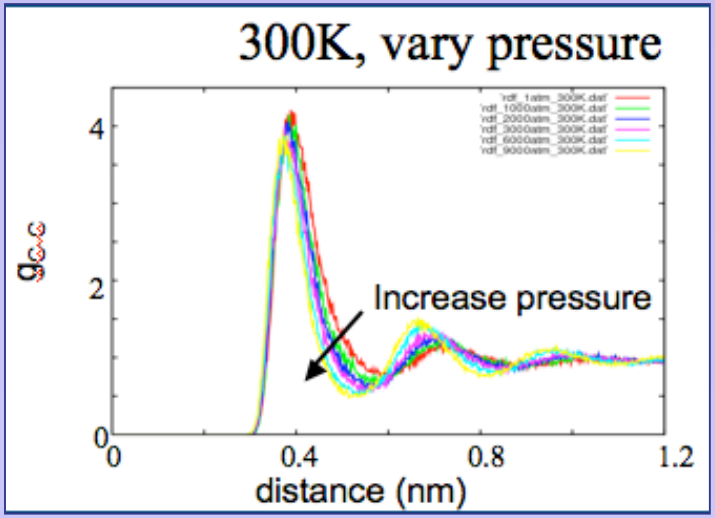
Pressure denaturation is due to water penetration and destabilisation of hydrophobic contacts



Simulation of 10 methanes in ≈ 500 H_2O

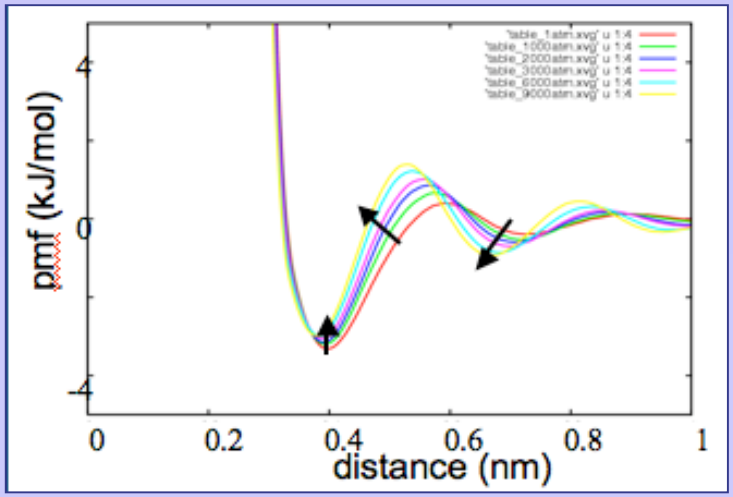
Radial distribution fonction

$$g_{C-C}(r) = \frac{V}{N}\frac{\langle \Delta N(r) \rangle}{4\pi r^2 \Delta r}$$



Potential of mean force

$$w(r) = -k_B T \ln\left(g_{C-C}(r)\right)$$

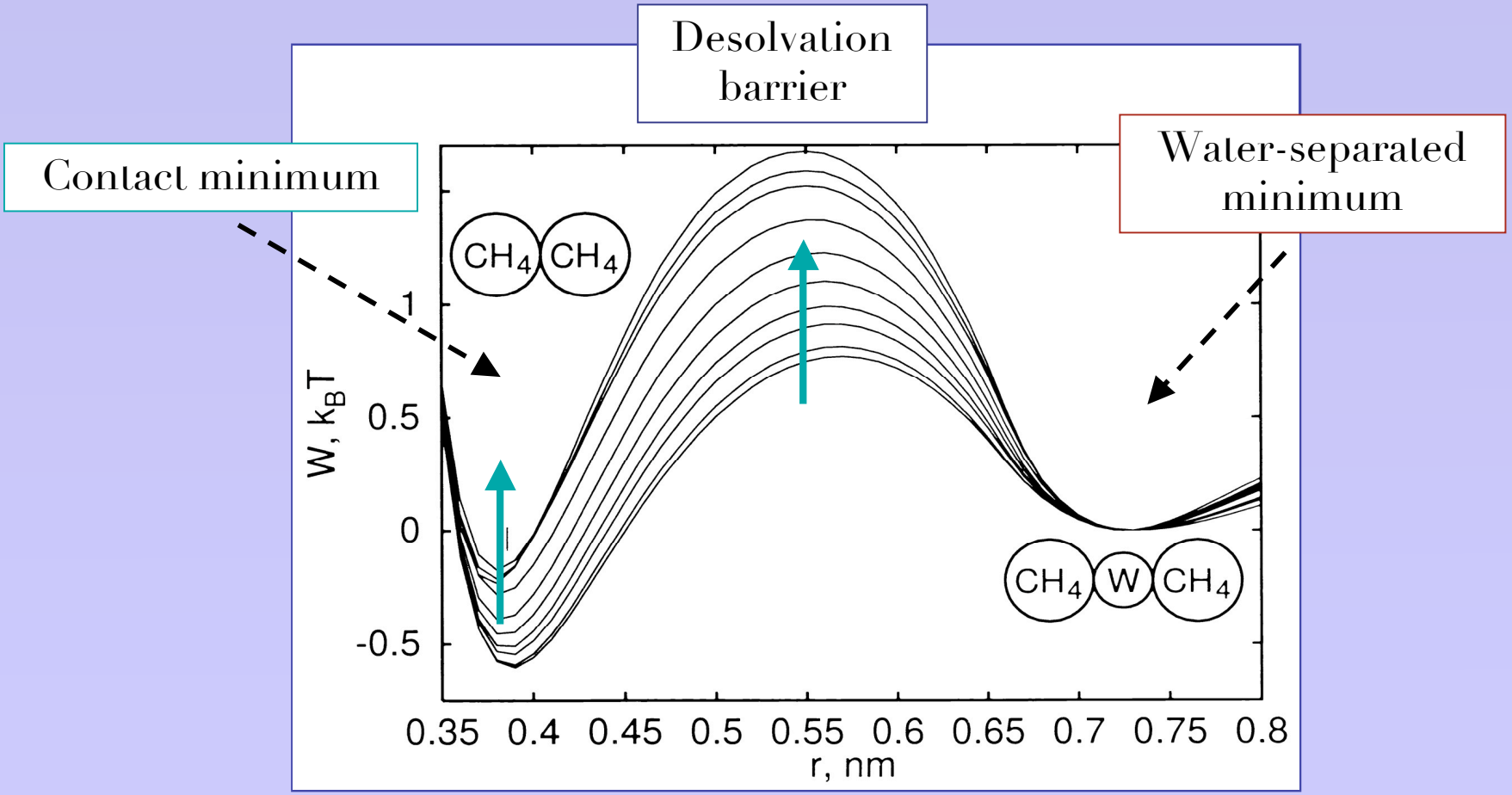


Go-model with pressure dependant PMF :

Already used as model for protein folding simulations :

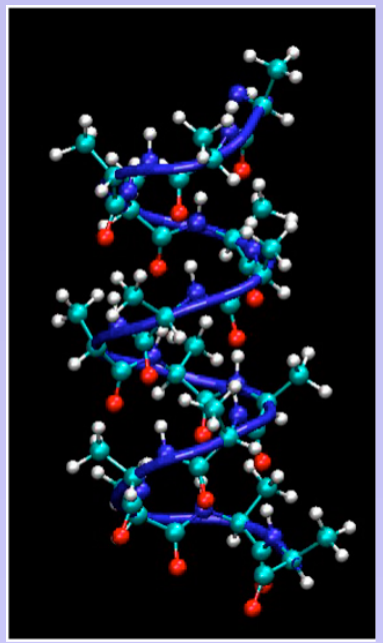
-Hillson et al. PNAS (1999)

- Cheung et al. PNAS (2002)



Multi-scale coarse-graining :

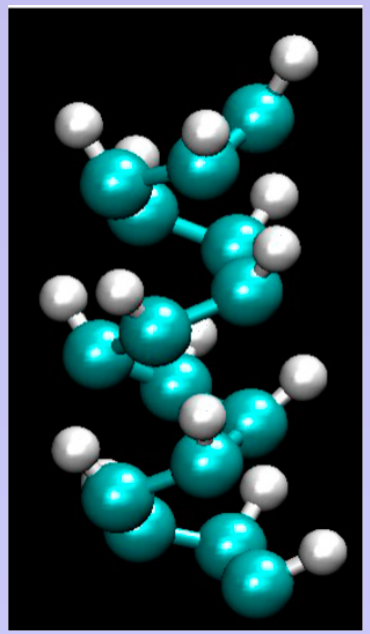
No assumption !



i atomic sites

M_R^N

Mapping operator



I CG sites

Variationnal principles used to determine the optimal approximation of the multi-body PMF

→ Set of Φ_D parameters that minimize the χ^2_{MS} fonction

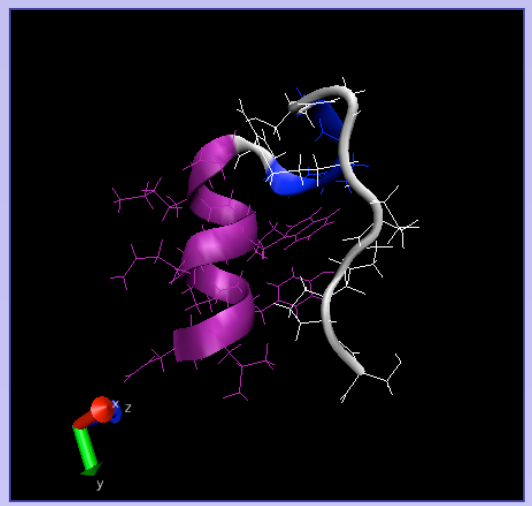
$$\chi^2_{\mathrm{MS}}(\phi) = \frac{1}{3n_t N}\sum_{t=1}^{n_t}\sum_{I=1}^{N}\left|\tilde{\mathbf{f}}_I(\mathbf{r}_t^n) - \sum_{D=1}^{N_D}\phi_D \mathcal{G}_{I;D}(\mathbf{M}_{\mathbf{R}}^N(\mathbf{r}_t^n))\right|^2$$

Projection of the atomic force field to CG site

Set of CG force fields construct from basis functions

Multi-scale coarse-graining :

Trp-cage : smallest protein model



Fully equilibrated simulation at 1 atm

Fully equilibrated simulation at 3000 atm

$\phi_{LP} \mathrm{G}_{\mathrm{LP}}(M_R^N(r_t^n))$

$\phi_{HP} \mathrm{G}_{\mathrm{HP}}(M_R^N(r_t^n))$

Low pressure coarse-grained force field

High pressure coarse-grained force field

Direct comparison of pressure effects *(hopfully…)*

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