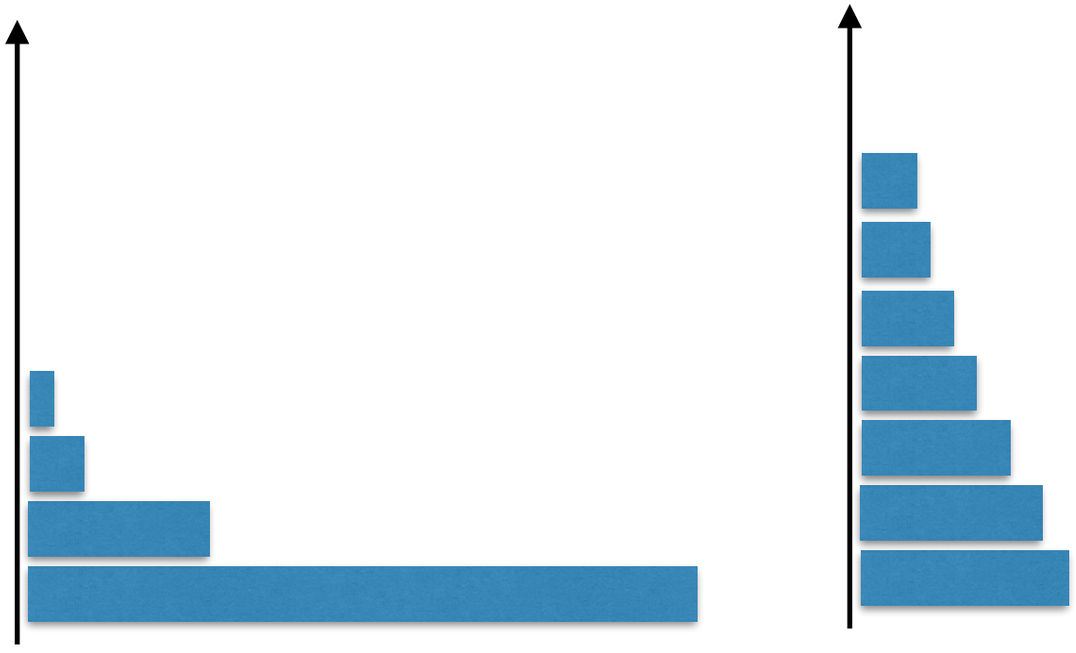
Dinâmica

Lei de distribuição de Boltzmann

$$p_i = \frac{exp\left(-\frac{E_i}{kT}\right)}{Z}$$

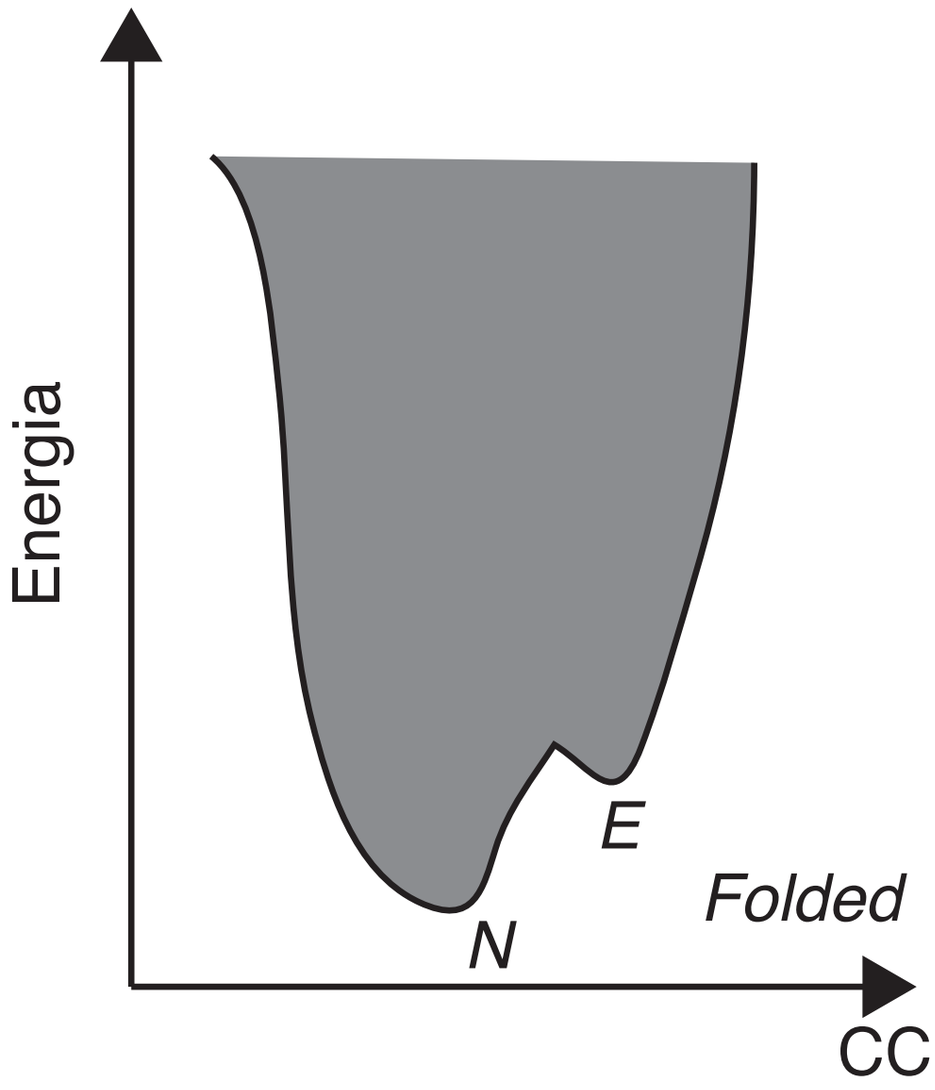
$$Z = \sum_{i=1}^{N} exp\left(-\frac{E_i}{kT}\right)$$



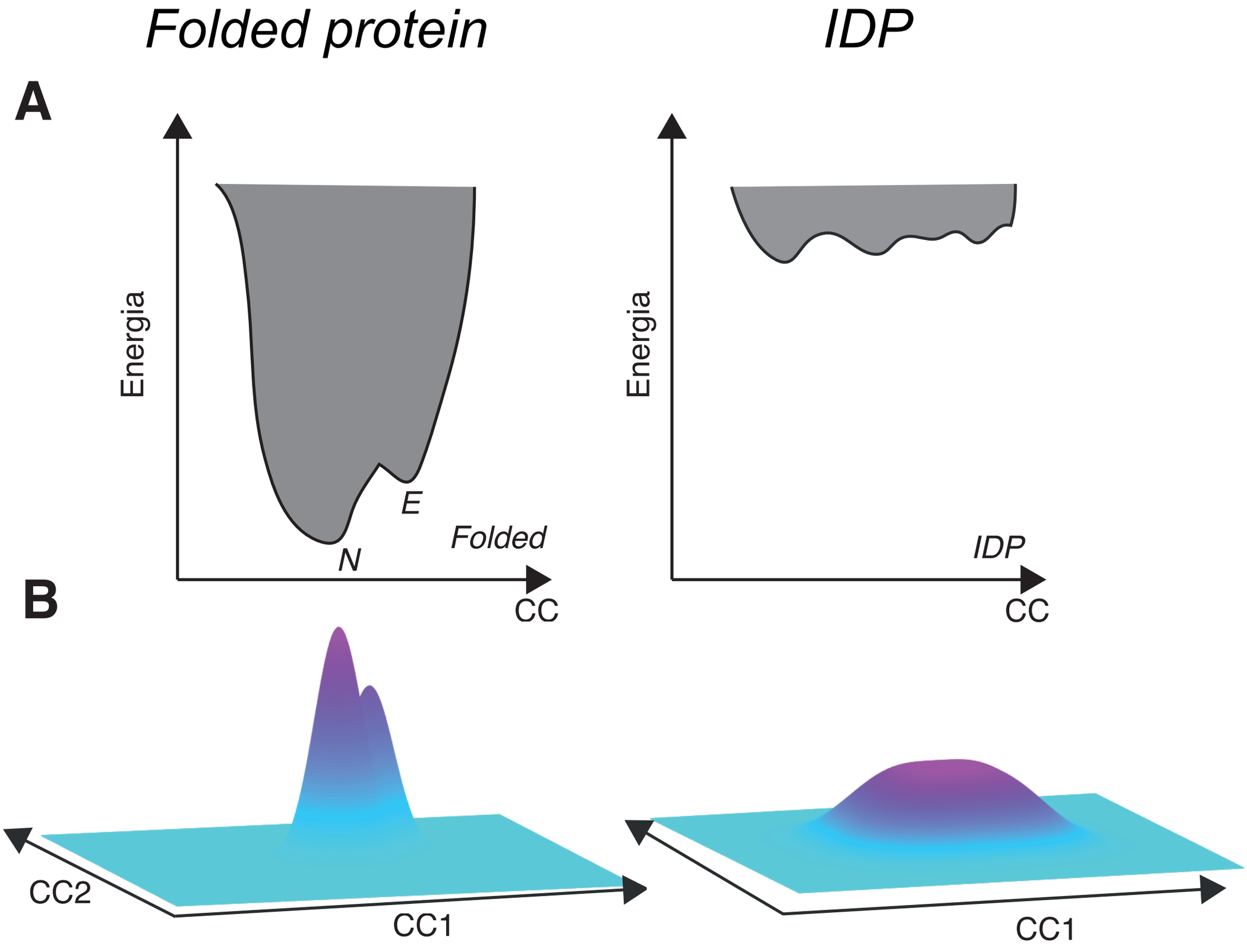
"Conformational energy landscape"

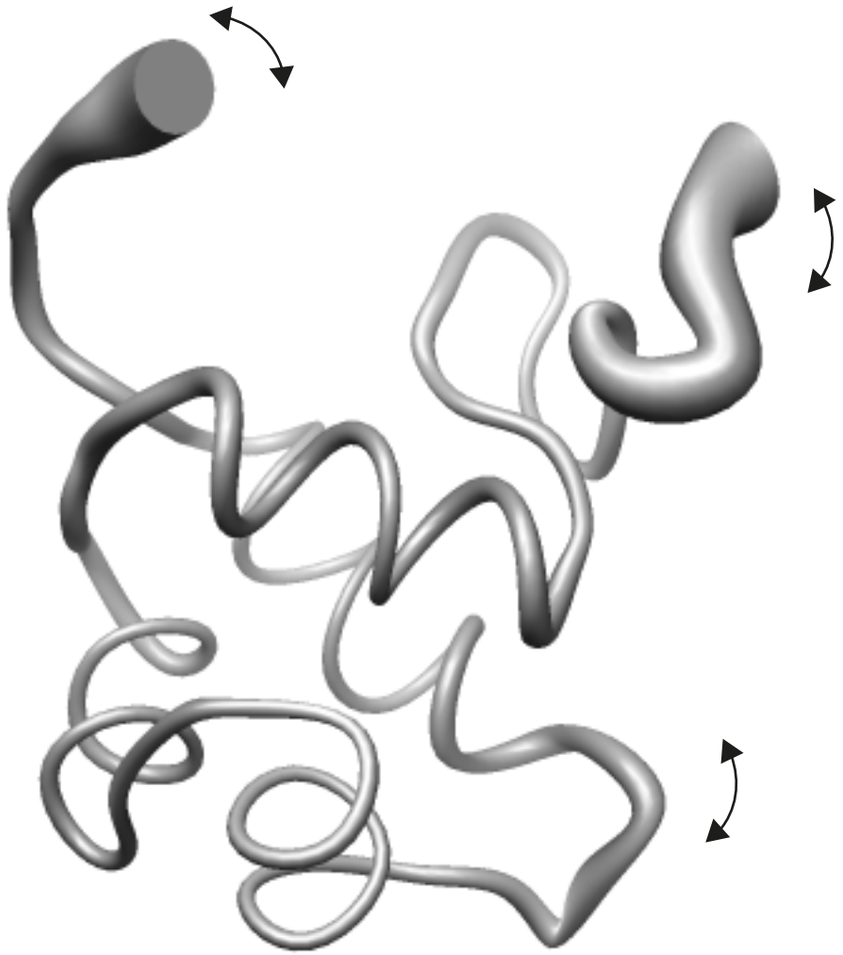
Frauenfelder, Sligar, e Wolynes (1991) The energy landscapes and motions of proteins

Science (1991) 254 1598-603

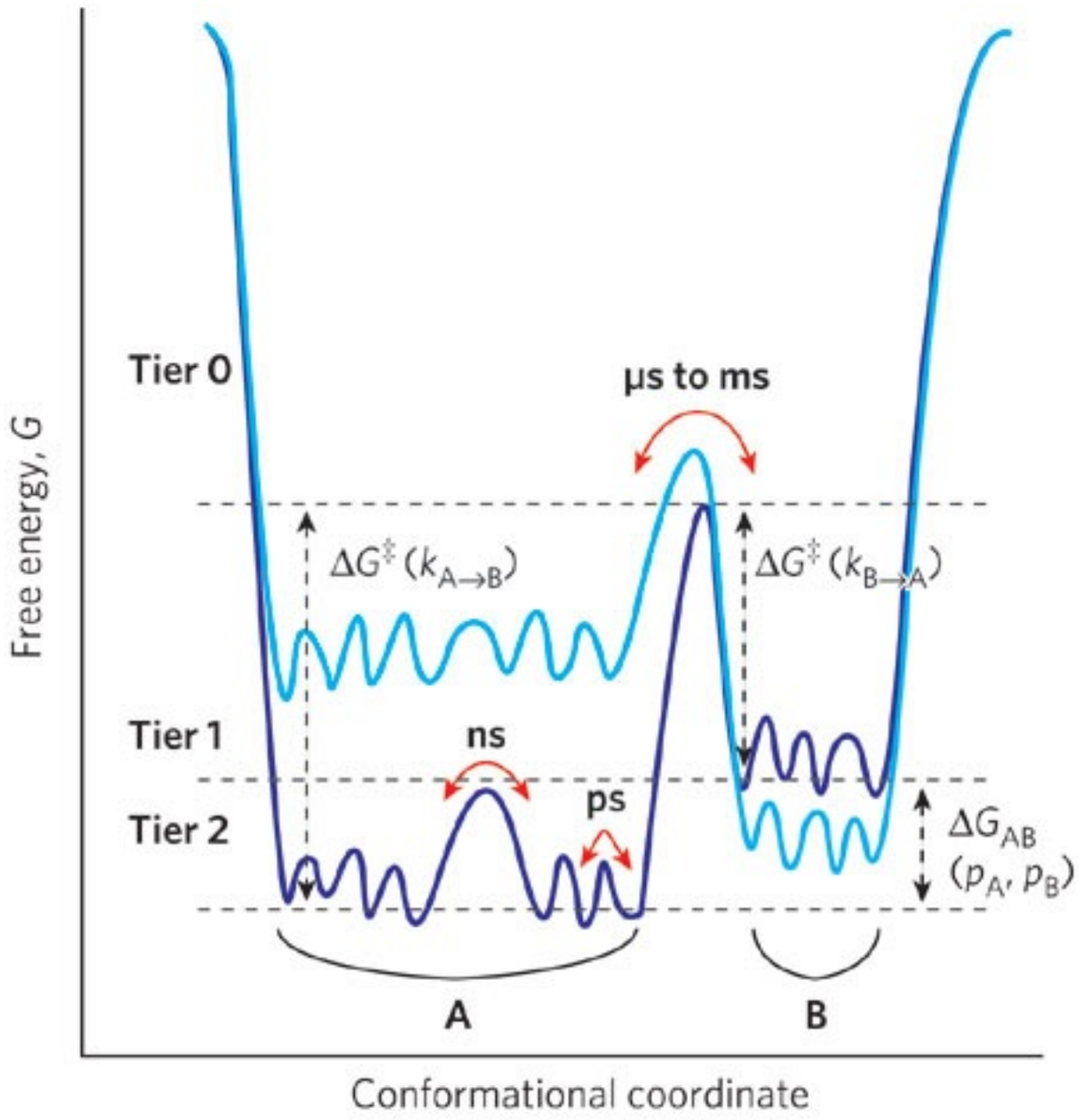


Proteínas visitam diferentes conformações em torno da conformação média de acordo com a energia térmica. Todas as possíveis conformações de uma proteína são populadas de acordo com a sua energia


Folded protein
IDP
A
Energia
E
N
Folded
CC
Energia
IDP
CC
B
CC2
CC1
CC1



PDB 2JVL



Henzler-Wildman, K. and Kern, D. (2007) *Nature* **450**: 964-972

Acúmulo de evidências consolidou a visão de que proteínas são flexíveis

Enzimas exibem dinâmica no sítio ativo

IDPs, IDRs, e condensados

1977: McCammon, Gelin, e Karplus "Dynamics of folded proteins"

Nature (1977) 267 585-590

"The dynamics of a folded globular protein (BPTI) have been studied by solving the equations of motion for the atoms with an empirical potential energy function. The results provide the magnitude, correlations, and decay of fluctuations about the average structure. These suggest that the protein interior is fluid-like in that the local atom motions have a diffusional character"

Dinâmica molecular de BPTI por 8.8 ps

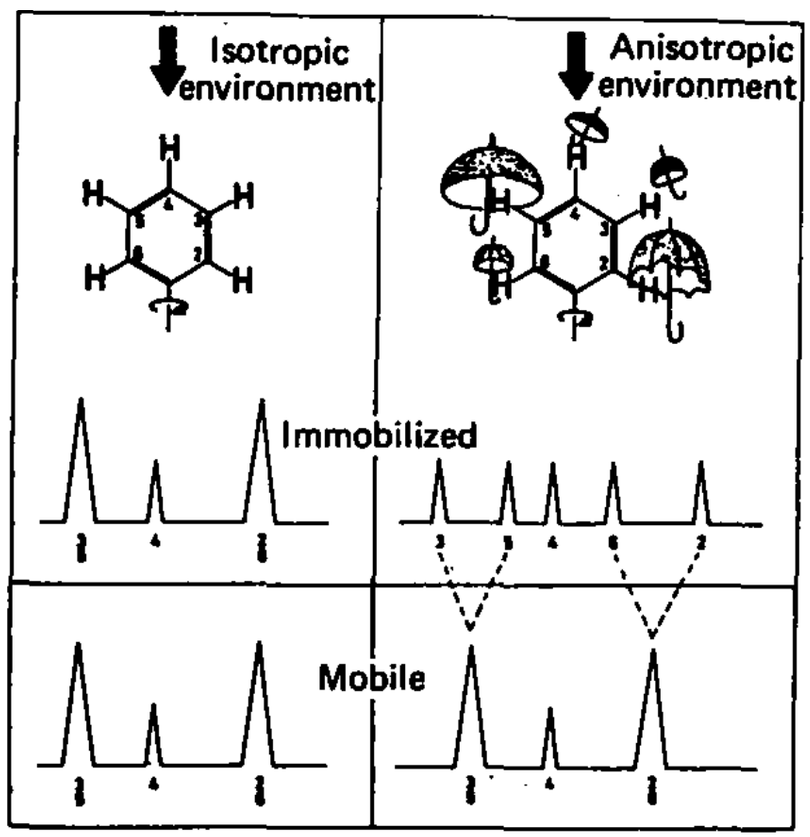
1978: Wüthrich e Wagner "Internal motion in globular proteins"

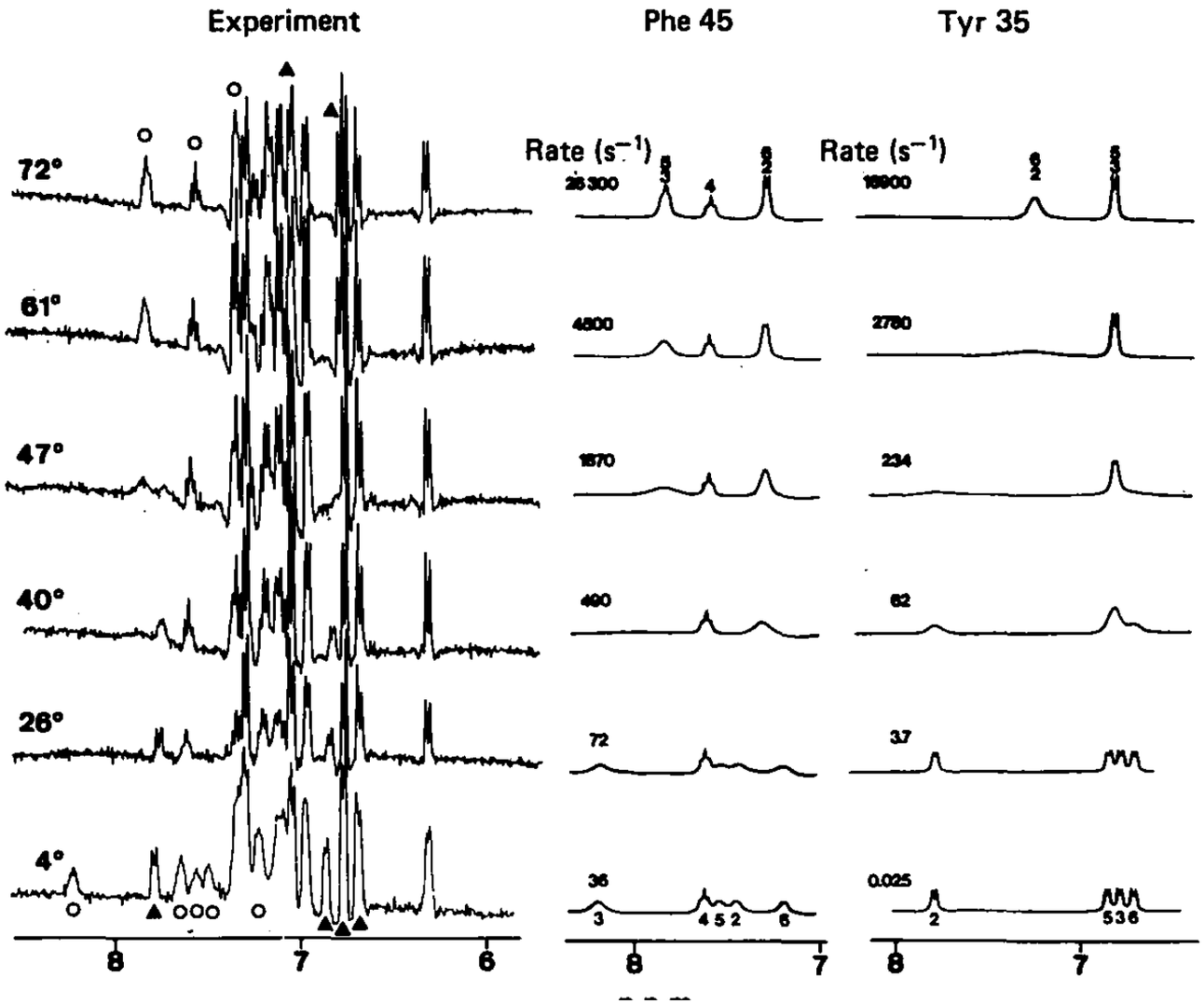
Internal motion in globular proteins

Kurt Wüthrich and Gerhard Wagner

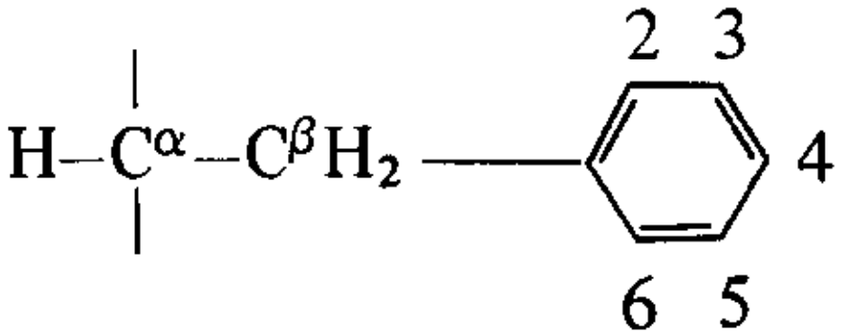
High resolution nuclear magnetic resonance provides insight into the dynamic ensembles which constitute the conformations of globular proteins in solution.

TIBS (1978) 227-230

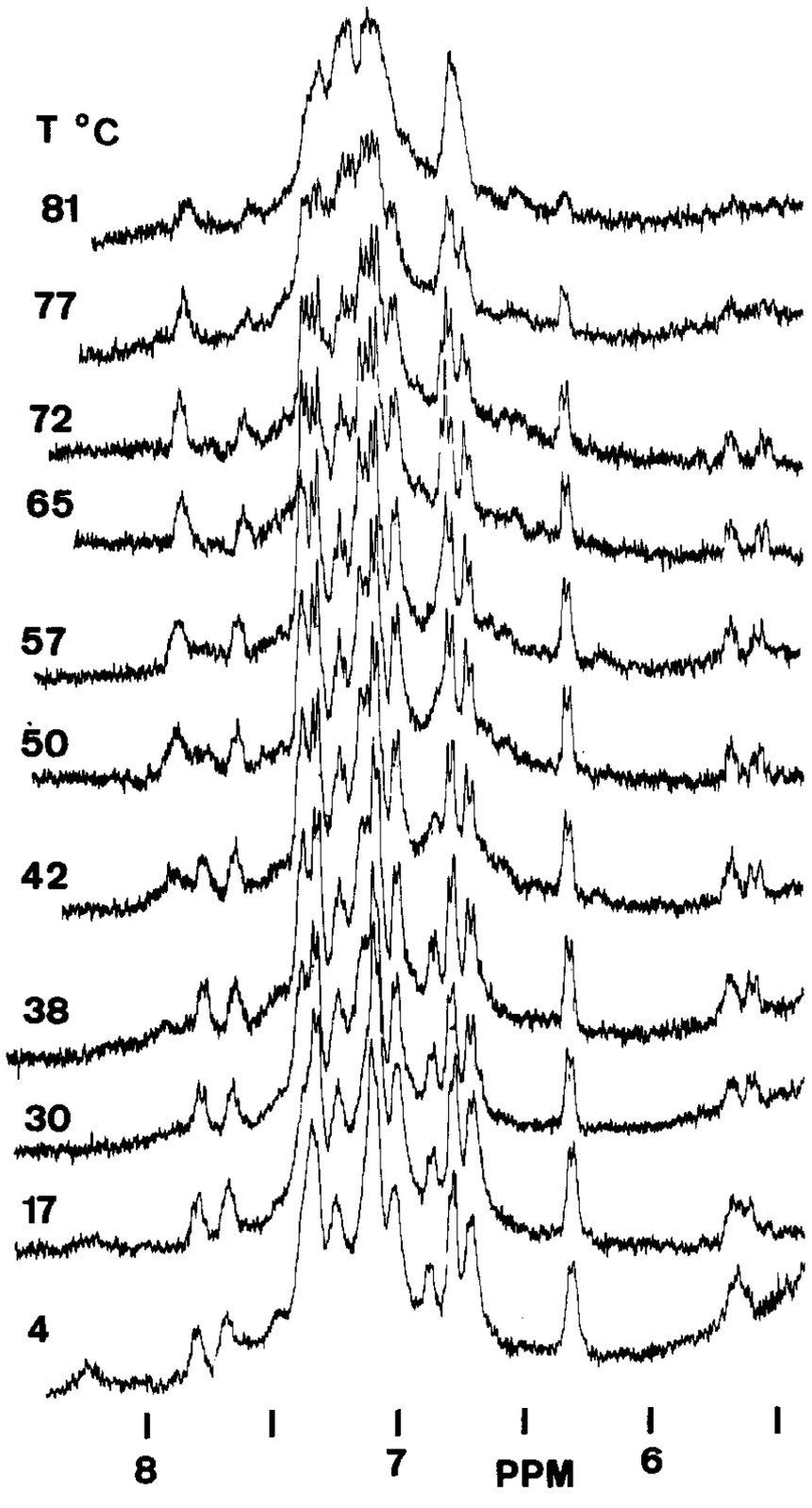




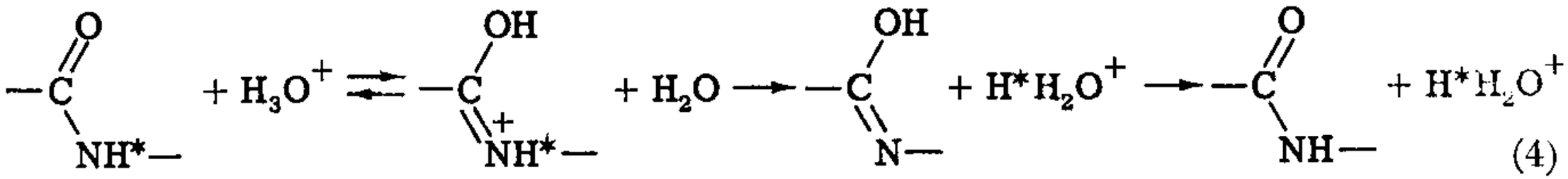
“Flipping” de anéis aromáticos



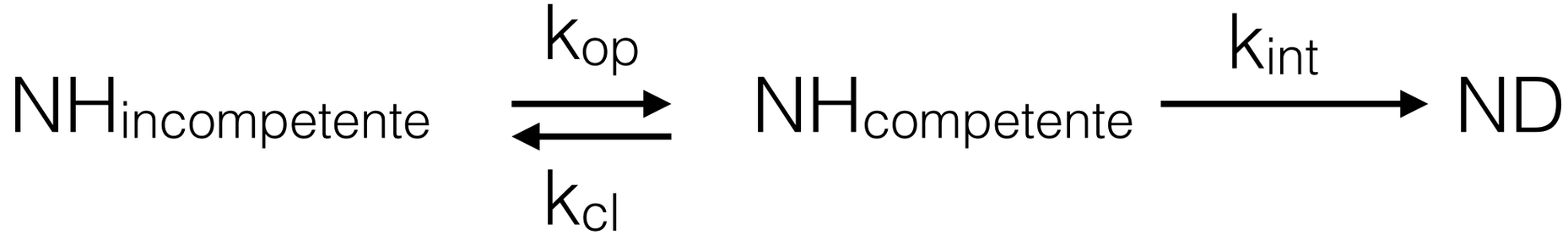
Wüthrich e Wagner (1975)



Medidas da cinética de troca H/D (HDX) em proteínas



Hvidt e Nielsen (1966)



EX1: $k_{obs} = k_{op}$

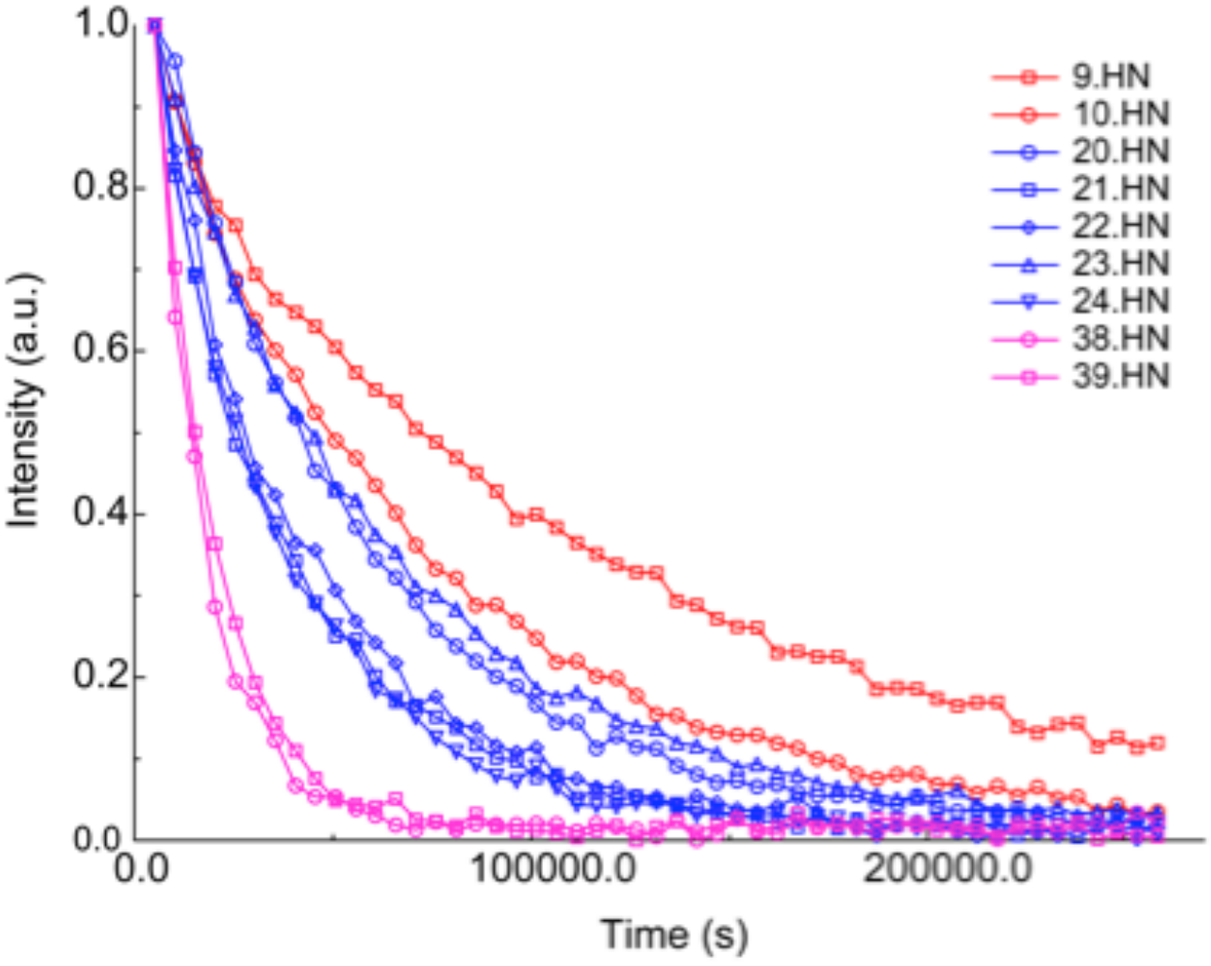
EX2: $k_{obs} = k_{int}\ (k_{op}/k_{cl})$

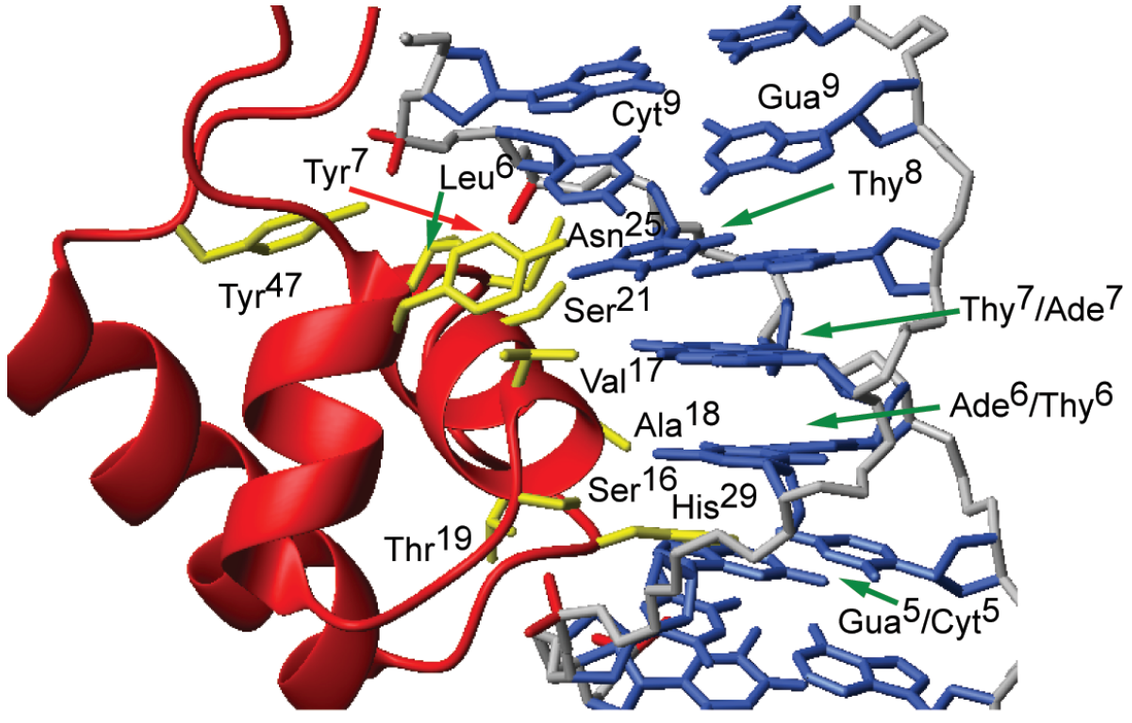
$\Delta G_{op} = -RT \ln(k_{op}/k_{cl}) = - RT \ln(k_{obs}/k_{int})$

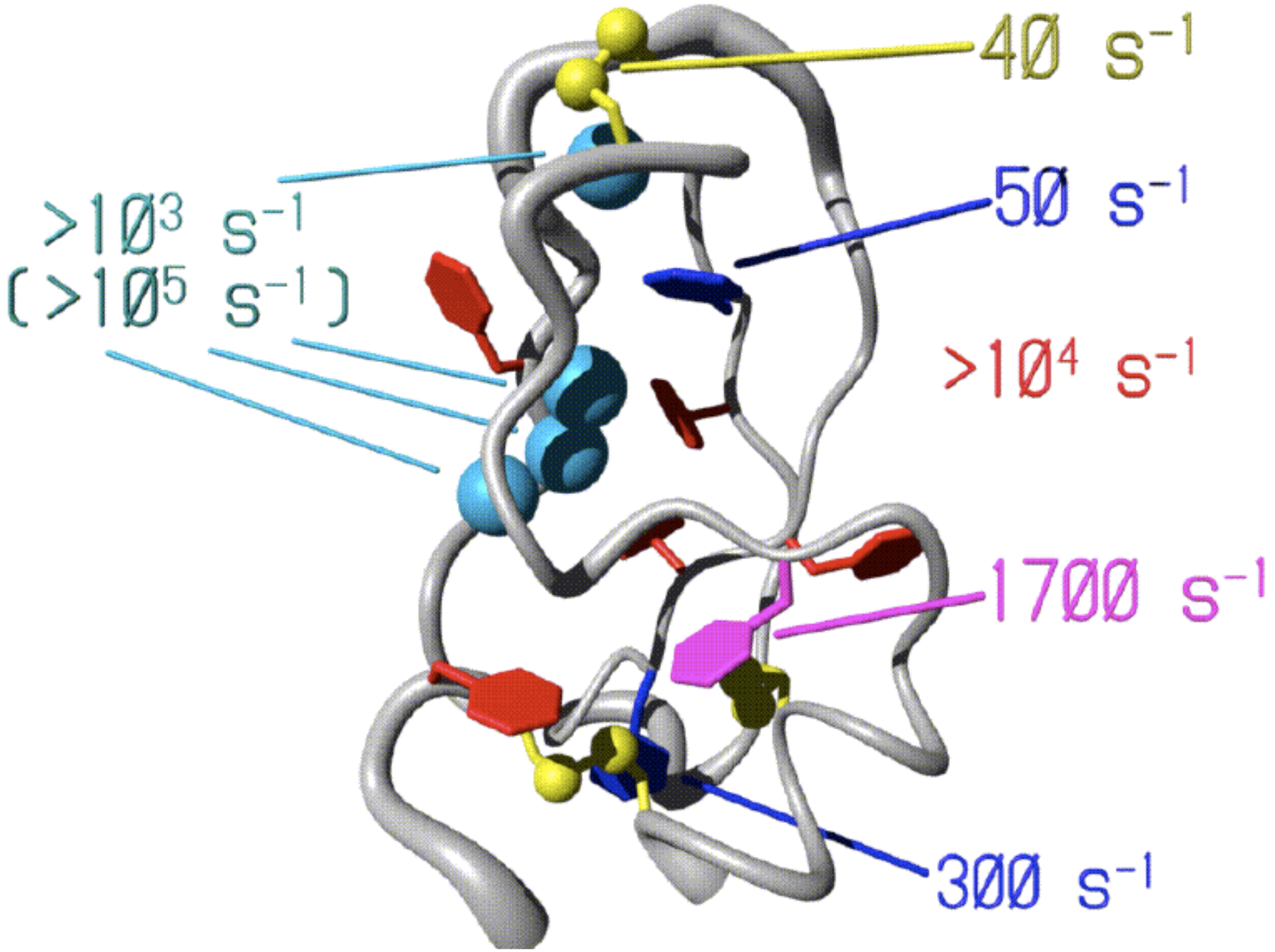
Experimentos de cinética de troca H/D (HDX) usando RMN

$$k_{obs} = Kk_{int}$$

log(P) P=kobs/kint







Wüthrich, K. (2003) *Angew. Chem. Int. Ed.* **42**: 3340-3363.

Múltiplos tipos de movimento

- Bond vibration (fs)
- Loop motions (ns - μs)
- CH_3 motion (ps - ns)
- Aromatic ring flipping (ps - ms)
- Domain motions (μs - ms)

Algumas proteínas são naturalmente desenoveladas

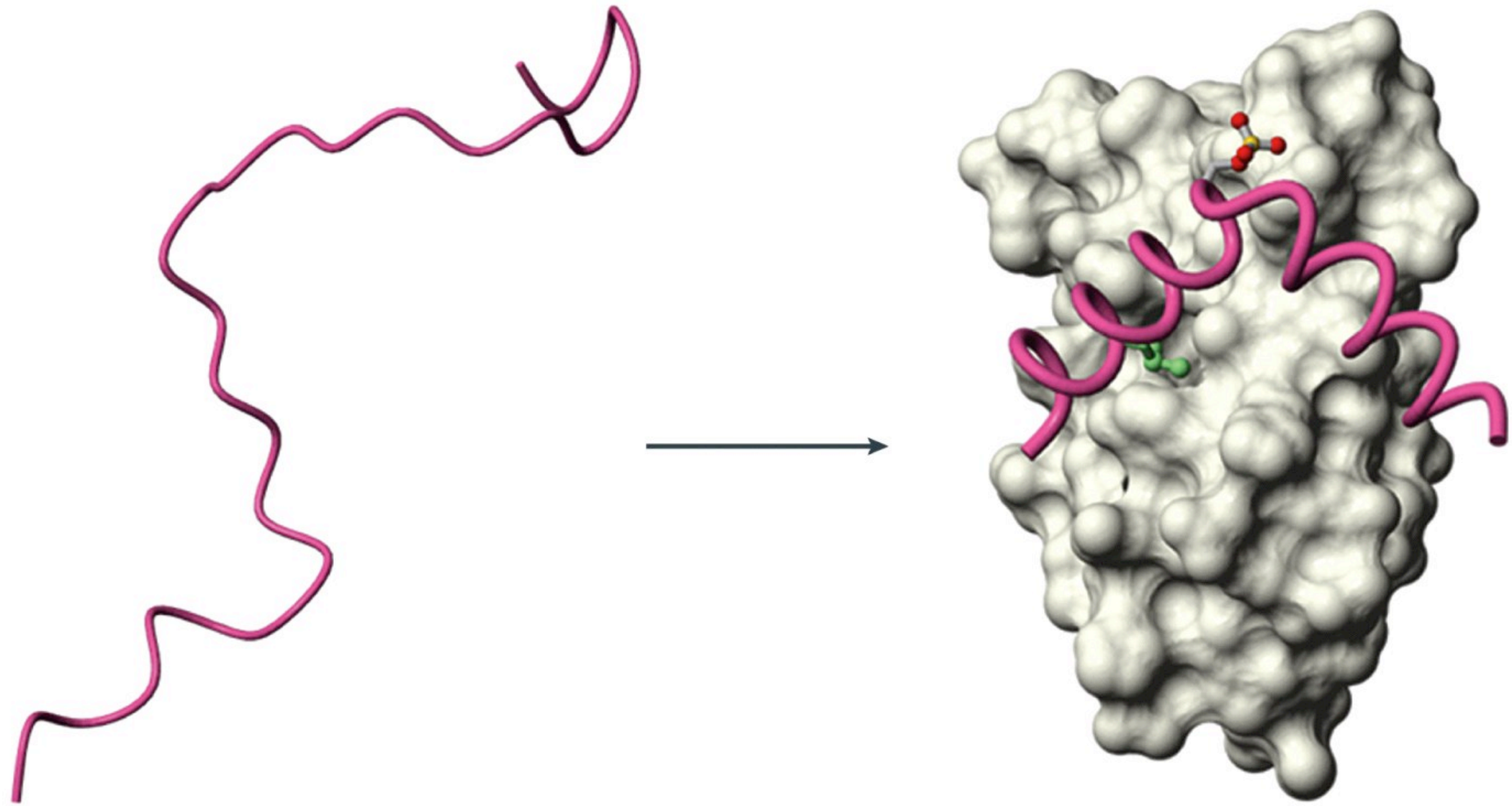
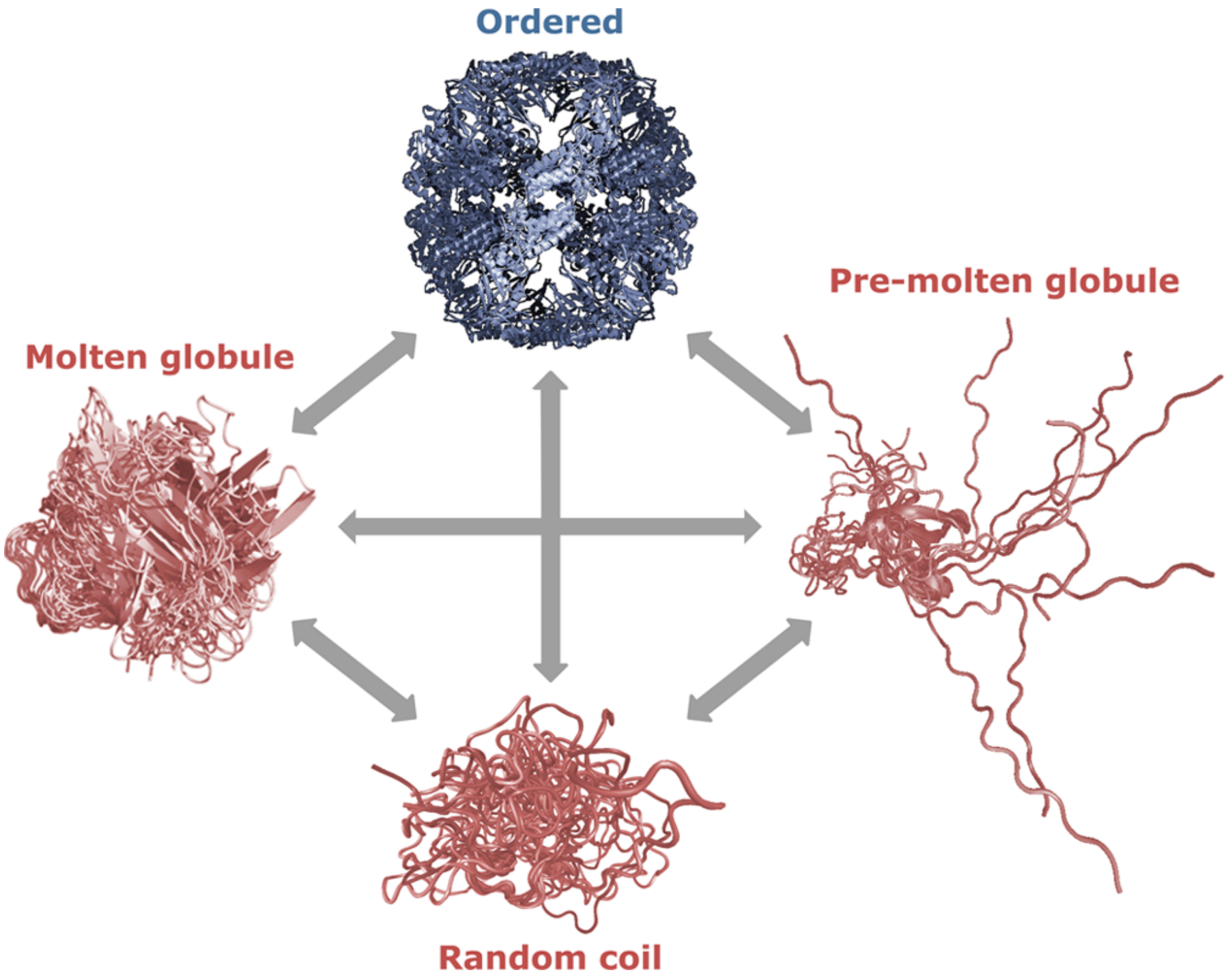


Figure 9-8

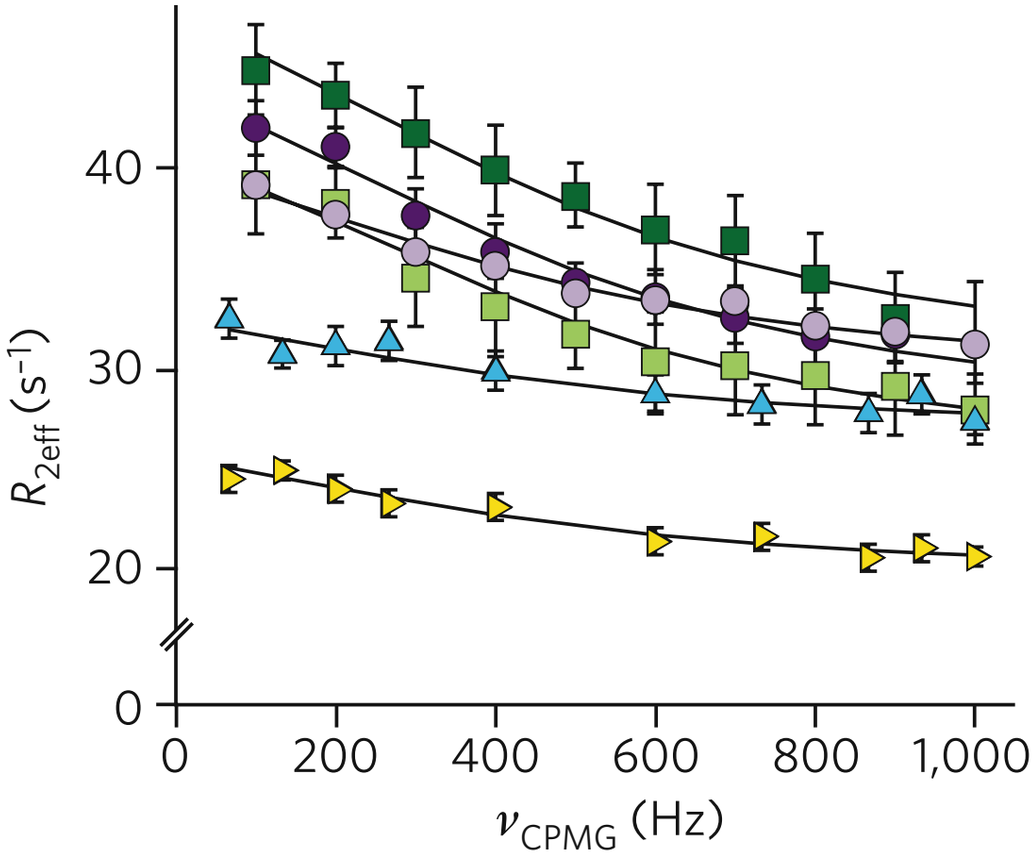
Voet&Voet 4a edição pág. 283

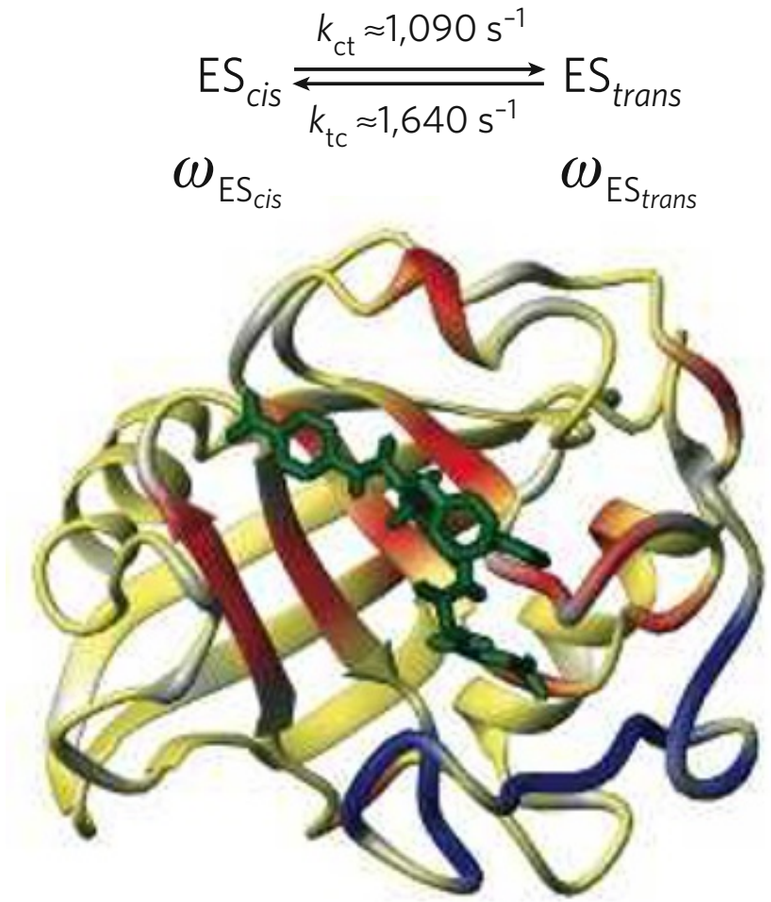
Intrinsically Disordered Proteins (IDPs) e Intrinsically Disordered Regions (IDRs) apresentam diferentes graus de desordem



van der Lee et al. (2014) *Chemical Reviews* doi: dx.doi.org/10.1021/cr400525m

Enzimas exibem dinâmica no sítio ativo: A cadeia principal de resíduos no sítio ativo de uma peptidil-prolil-isomerase experimenta movimentos na mesma escala de tempo que o turn-over (a escala de tempo importa)





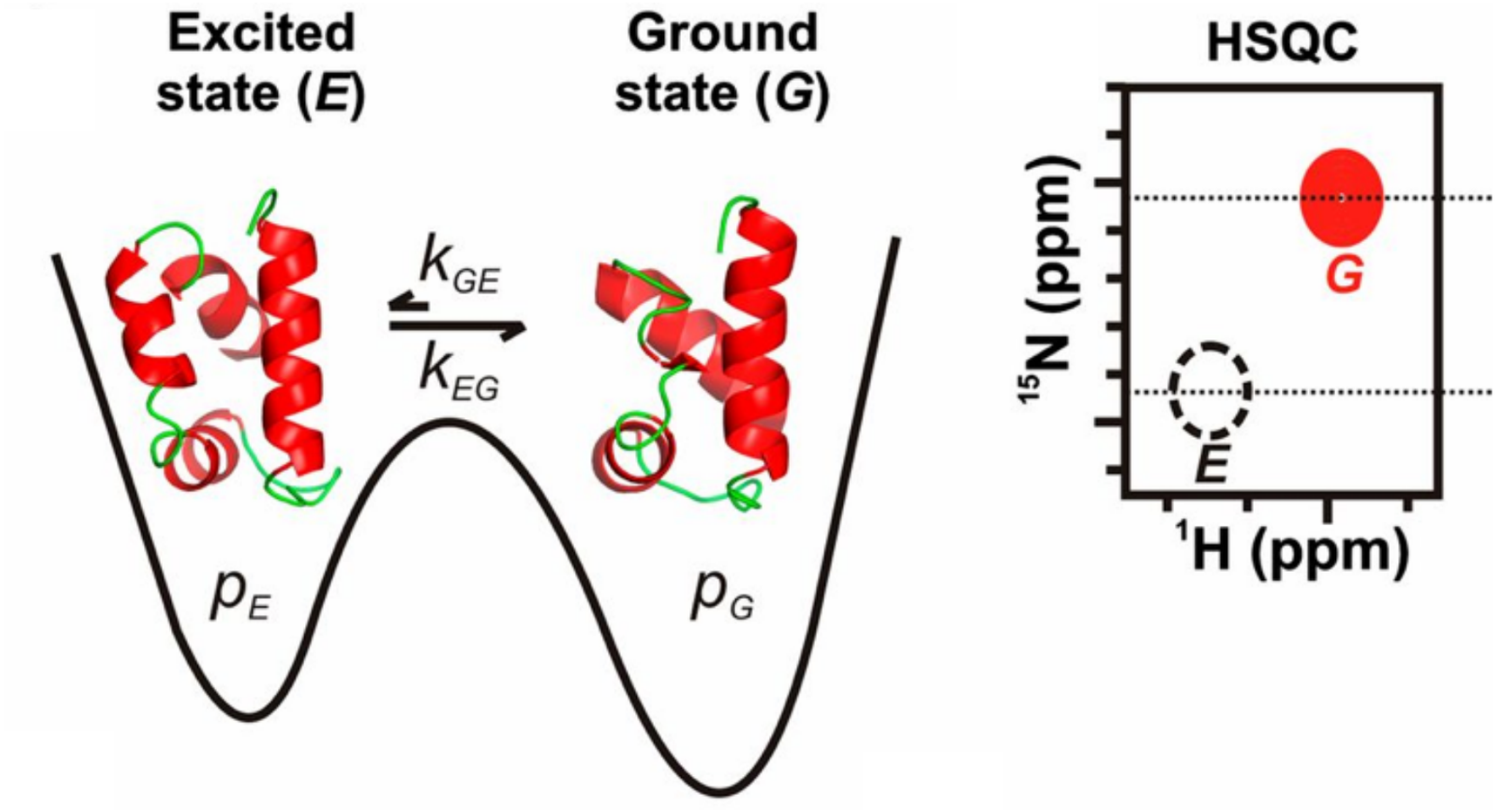
(vermelho) resíduos que experimentam $k_{ex} \sim k_{ct} + k_{tc}$

(azul) resíduos que experimentam movimentos mais rápidos

Eisenmesser et al. (2005) *Nature* doi:10.1038/nature04105
Henzler-Wildman, K. and Kern, D. (2007) *Nature* 450: 964-972

NMR & Structural biology

EXCITED STATES



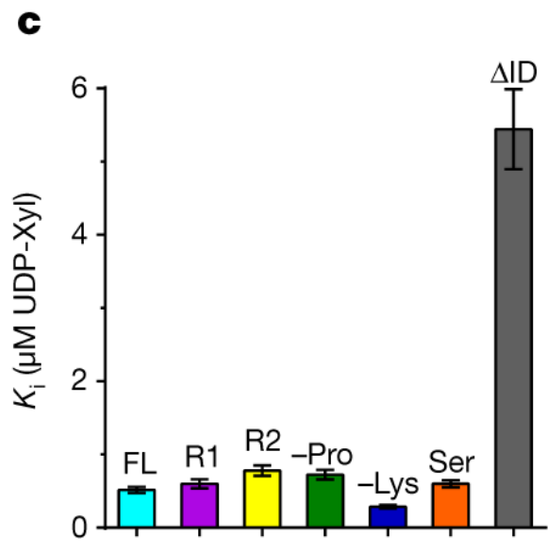
Shekhar & Kay PNAS 2013

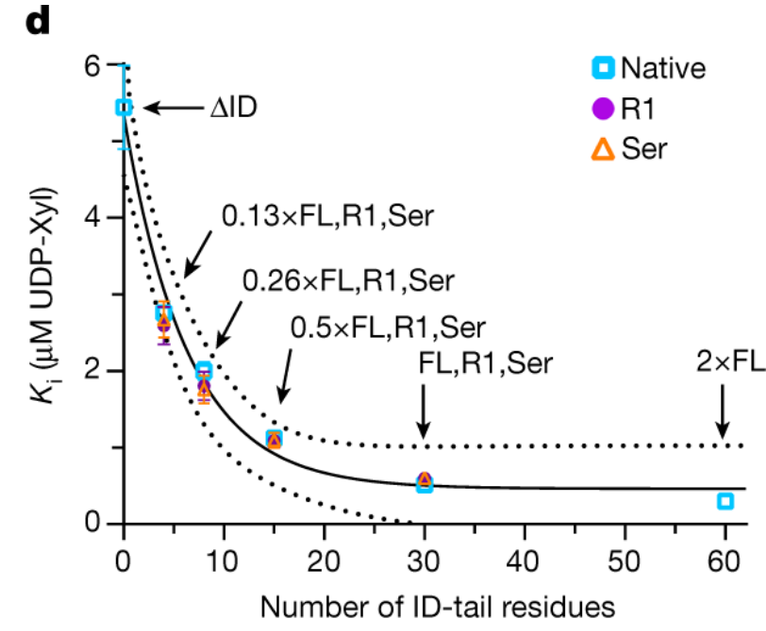
Classes de IDPs

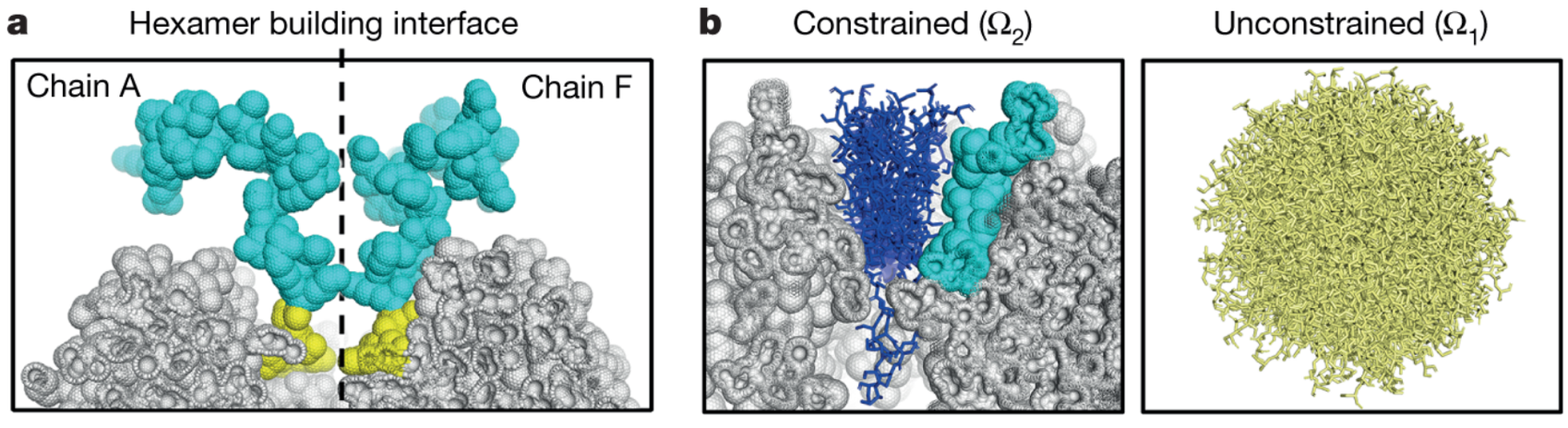
Como dinâmica poderia ser importante para a função biológica de uma proteína?

The entropic force generated by intrinsically disordered segments tunes protein function.

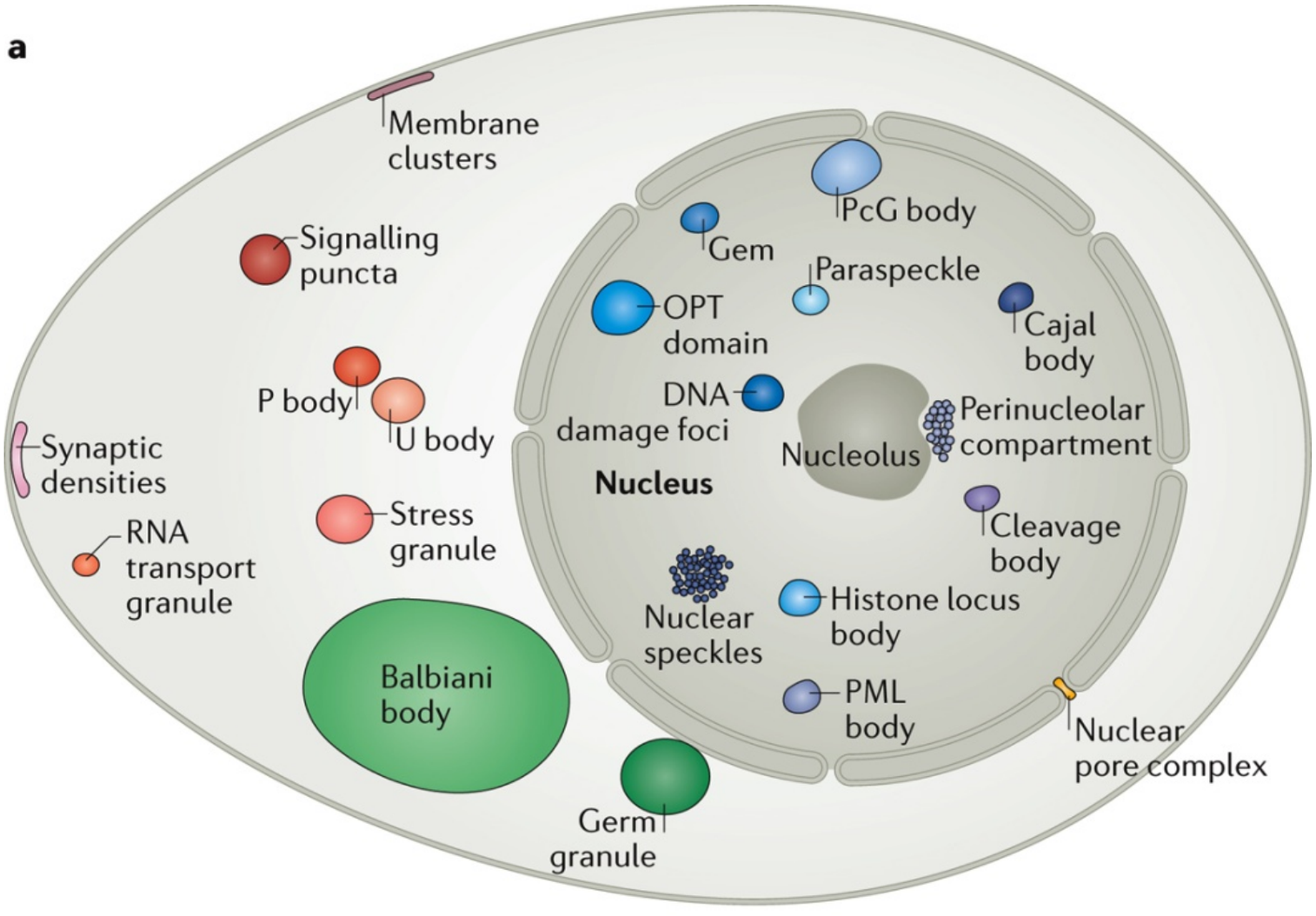
Keul, N.D., Oruganty, K., Schaper Bergman, E.T. et al. Nature **563**, 584–588 (2018).



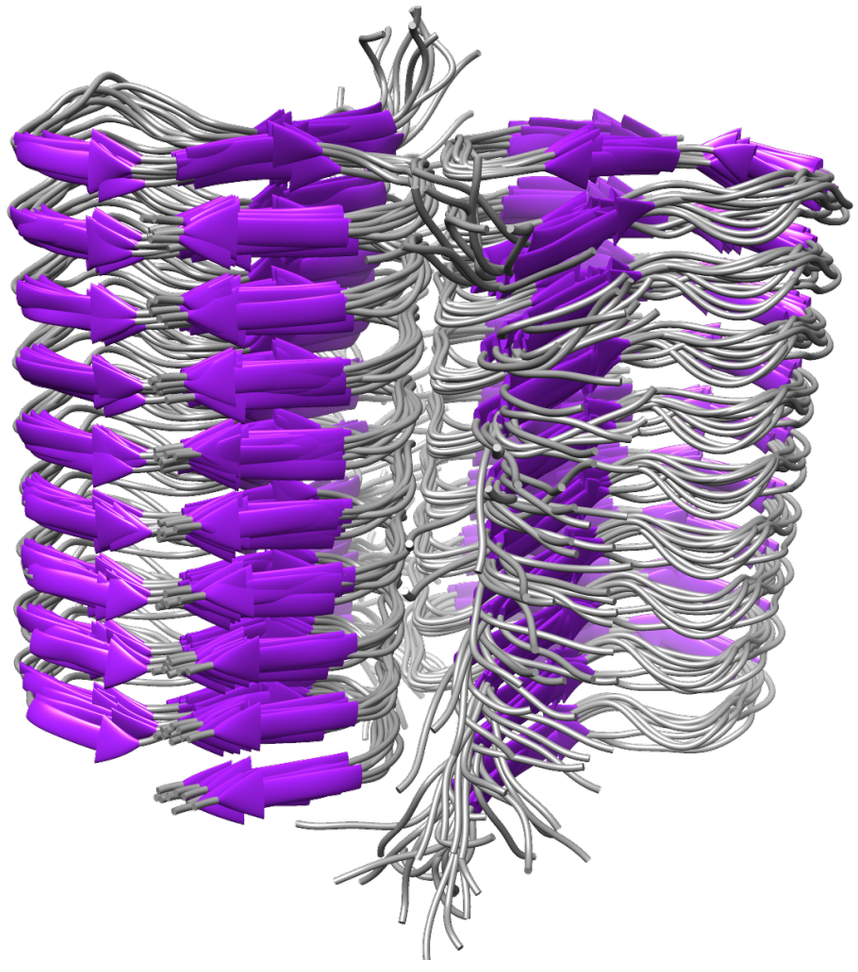




IPDs podem formar condensados por separação de fase líquido-líquido…



IDPs podem formar estruturas mais organizadas como fibras amilóide (Abeta42)



Banani, S., Lee, H., Hyman, A. *et al.* (2017) *Nat Rev Mol Cell Biol* **18,** 285–298

Robert Griffin and co-workers (2016) *J Am Chem Soc* **138**, 9663-9674