



FRIAS

FREIBURG INSTITUTE
FOR ADVANCED STUDIES
ALBERT-LUDWIGS-
UNIVERSITÄT FREIBURG
SCHOOL OF
SOFT MATTER RESEARCH

protein dynamics

introduction for physicists by francesco rao



1

proteins are **necessary** for biological function

selectively regulate ion passage

regulate permeability

cytoskeleton

genetic code
read - modify - activate

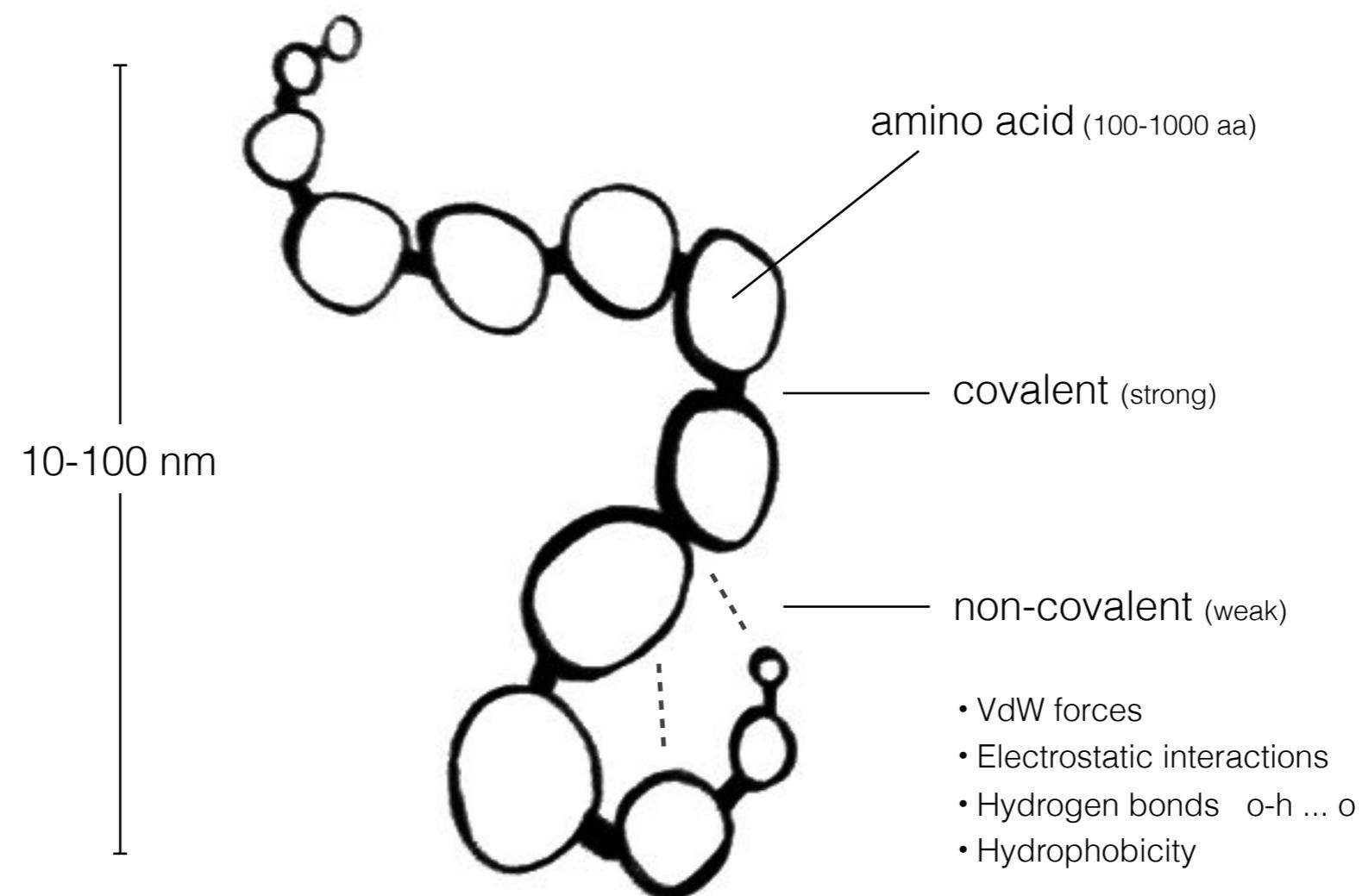
CELL

pump against gradient
(motors)

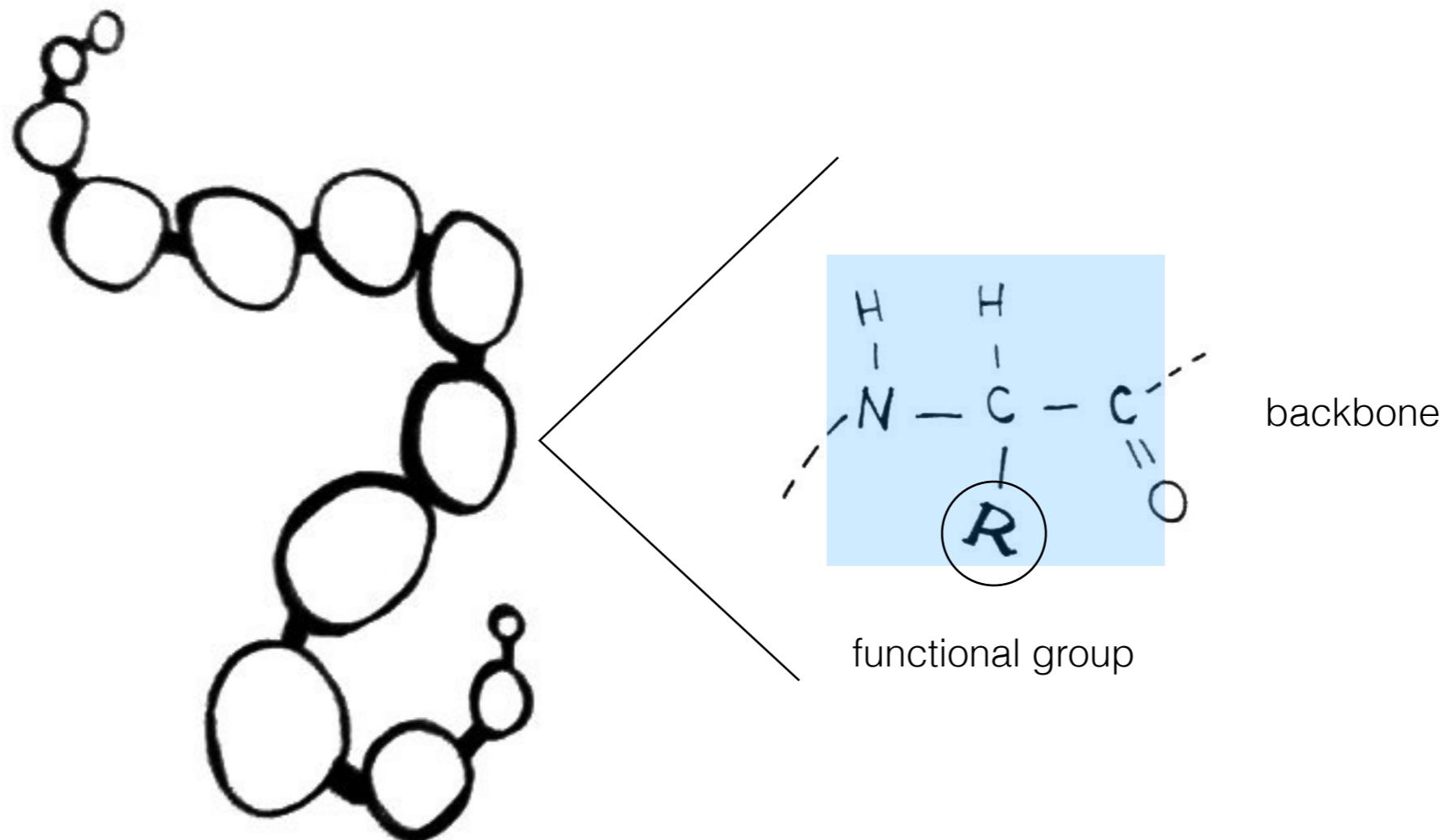
2

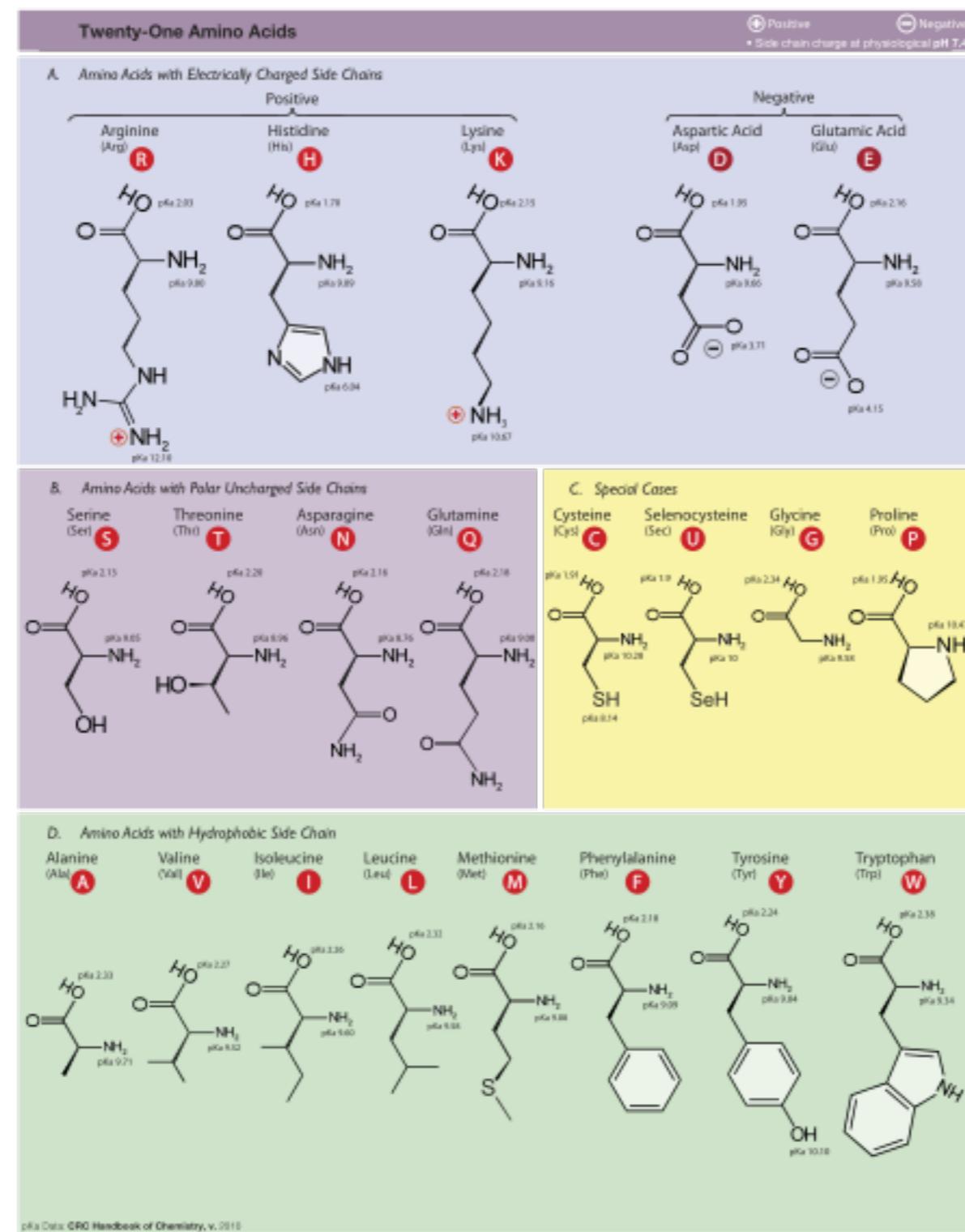
proteins are **biopolymers**

weak bonds determine the structure



amino acids have a complex chemical form





proteins assume a well-defined structure

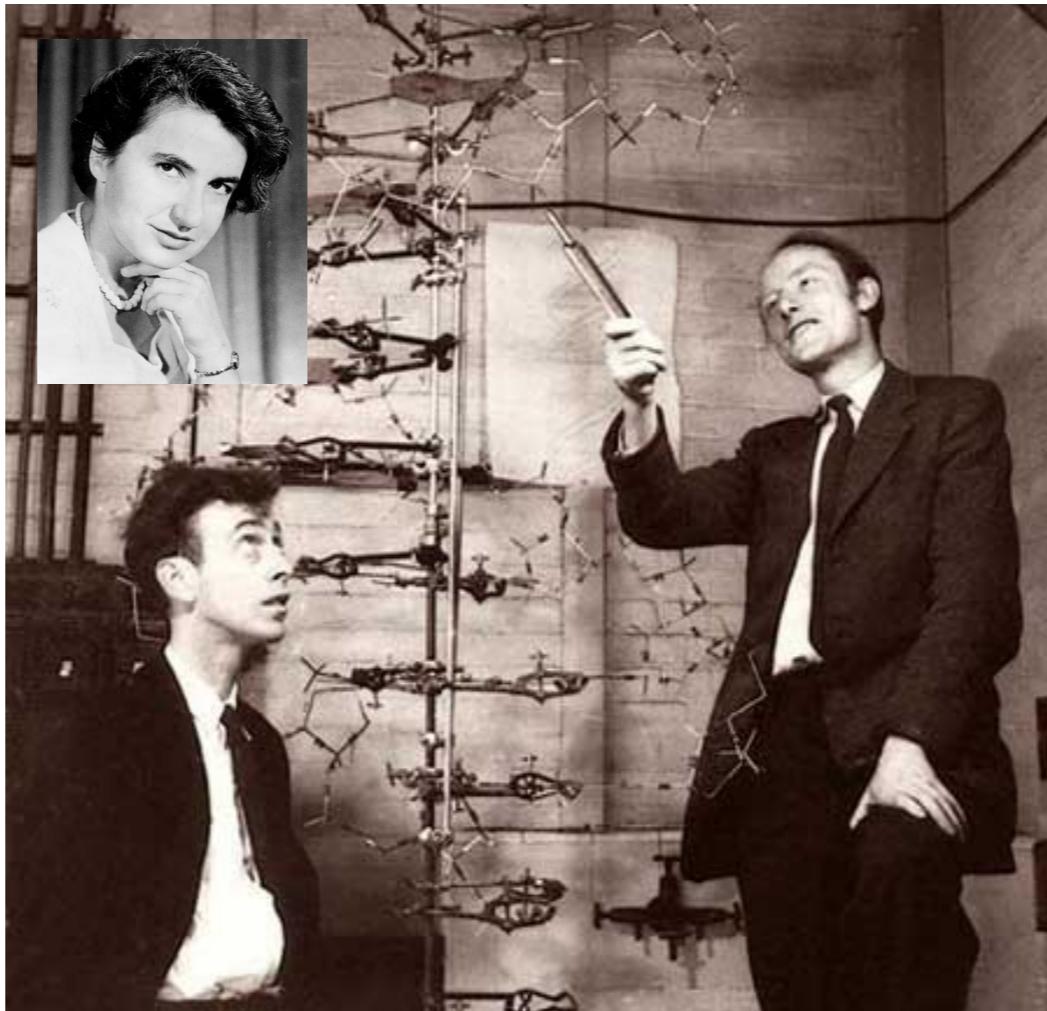
amino acid sequence



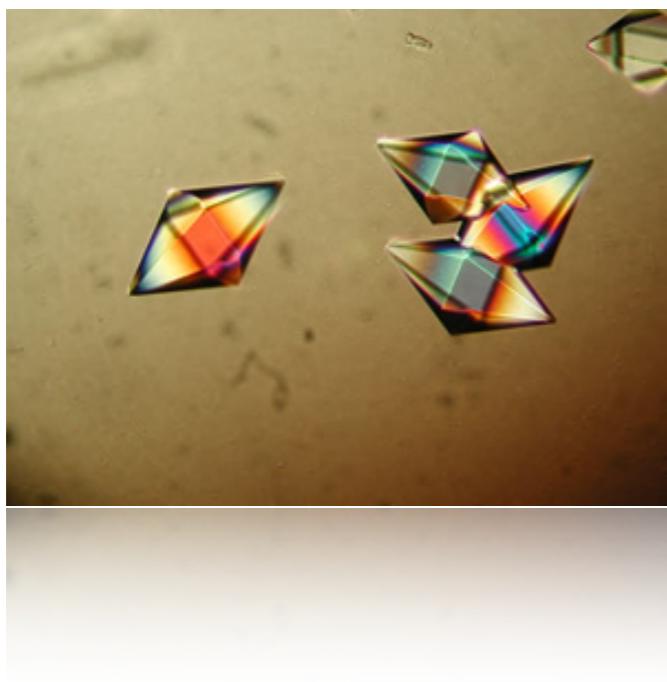
fold or native structure

3

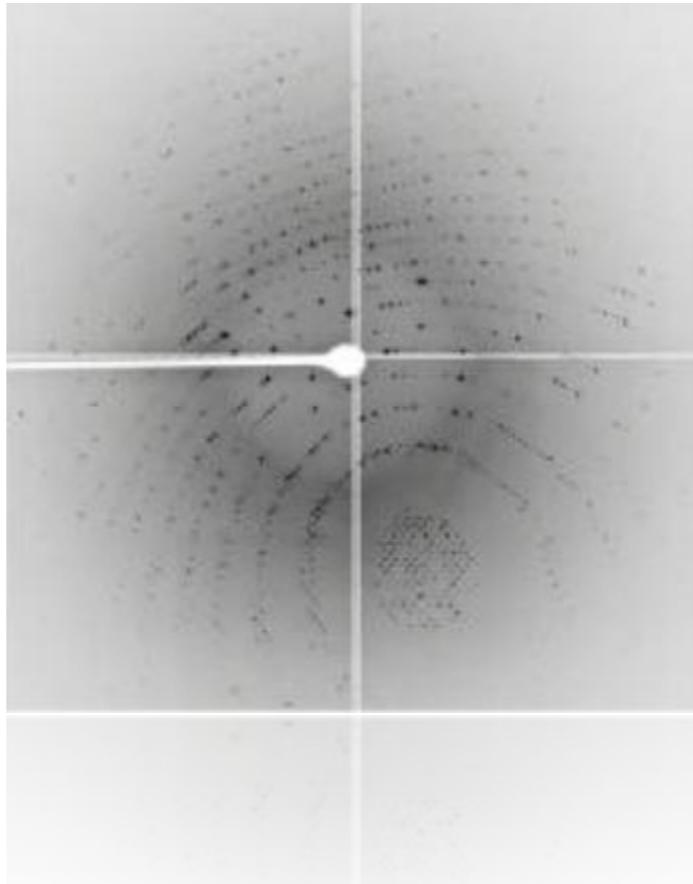
structure determination



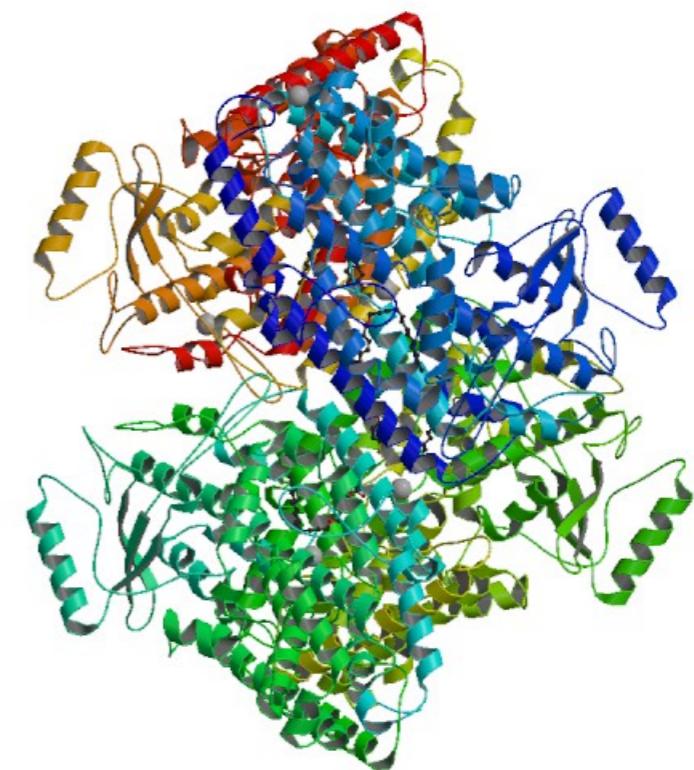
Rosalind Franklin, James D. Watson and Francis Crick were the discoverers of the structure of DNA in 1953



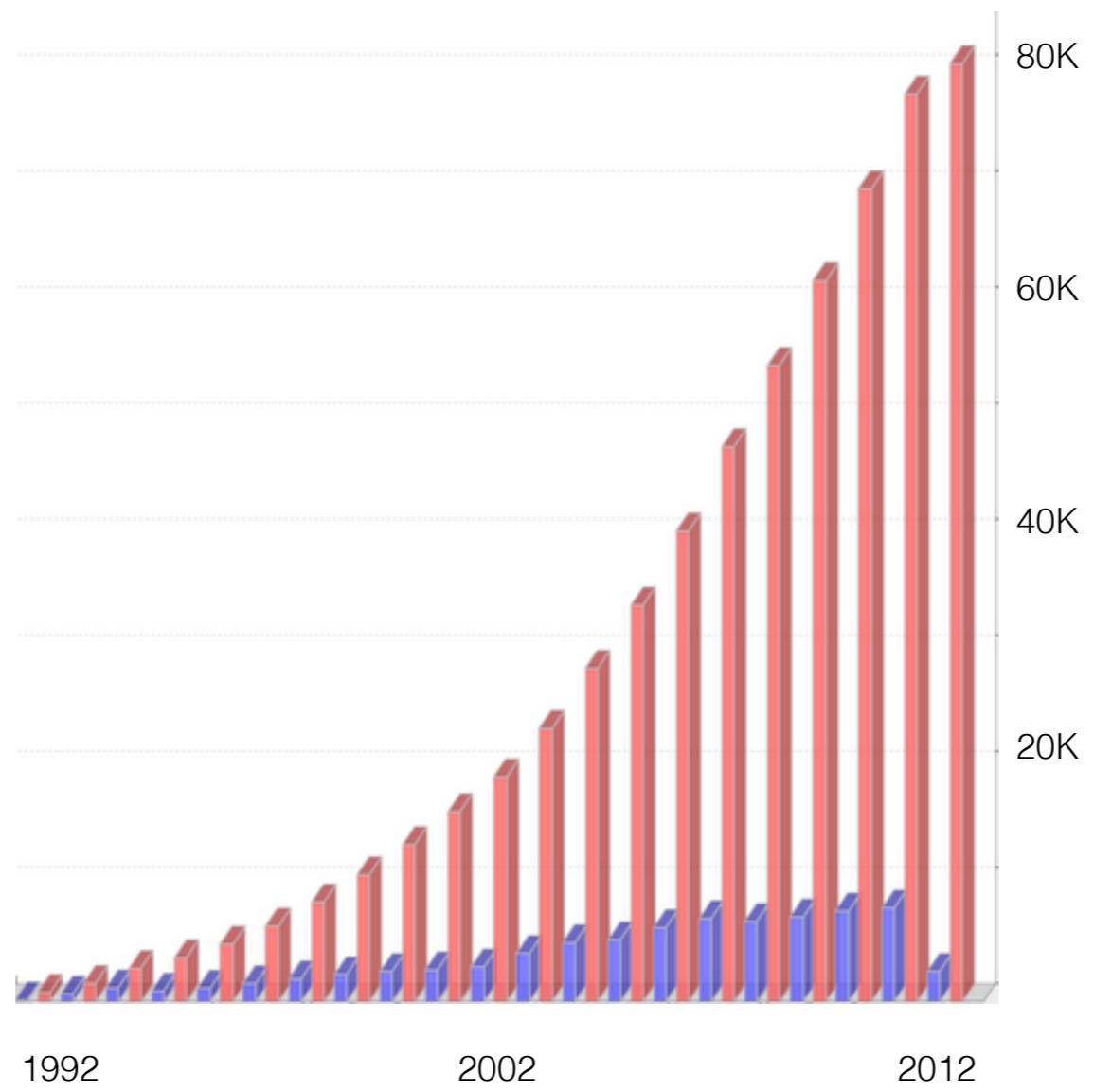
crystal



diffraction

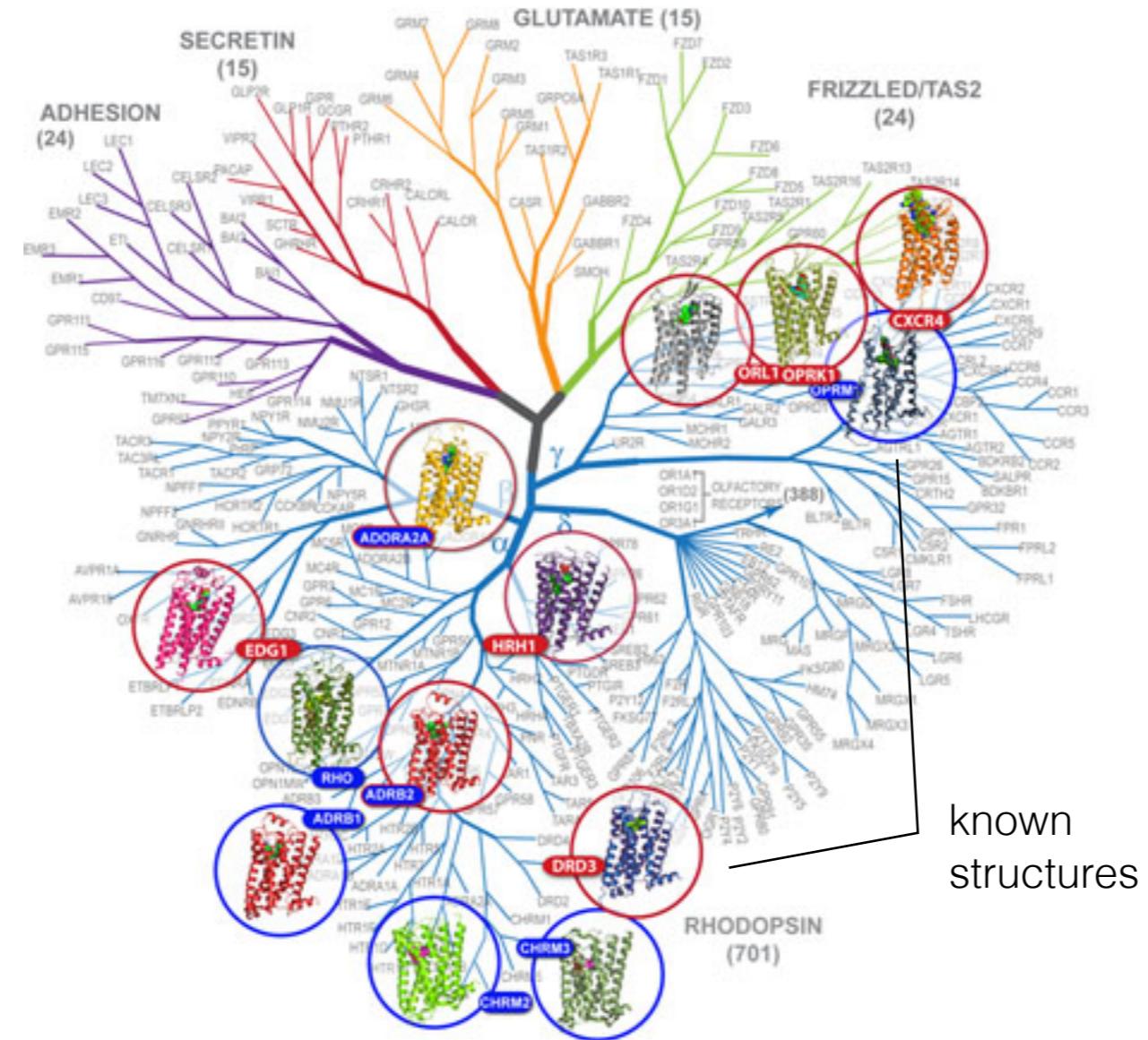


molecular structure



Cumulative number of deposited structures.

It is not just a question of brute force. Many experimental problems limit the number of solved structures.

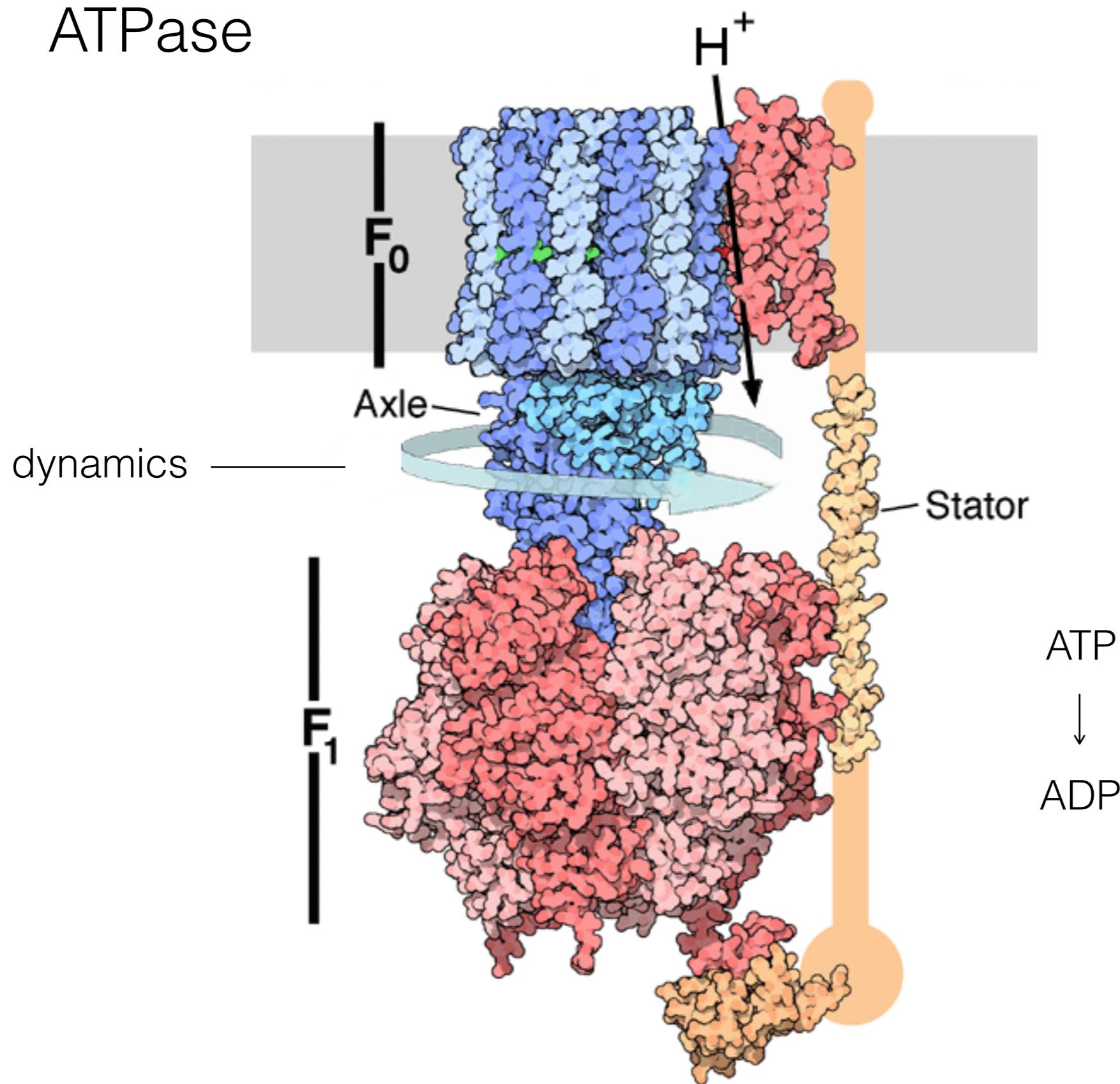


G Protein-Coupled Receptors represent important targets for therapeutic intervention , being at the center of signaling pathways that control all manner of essential processes.

static

a protein at work

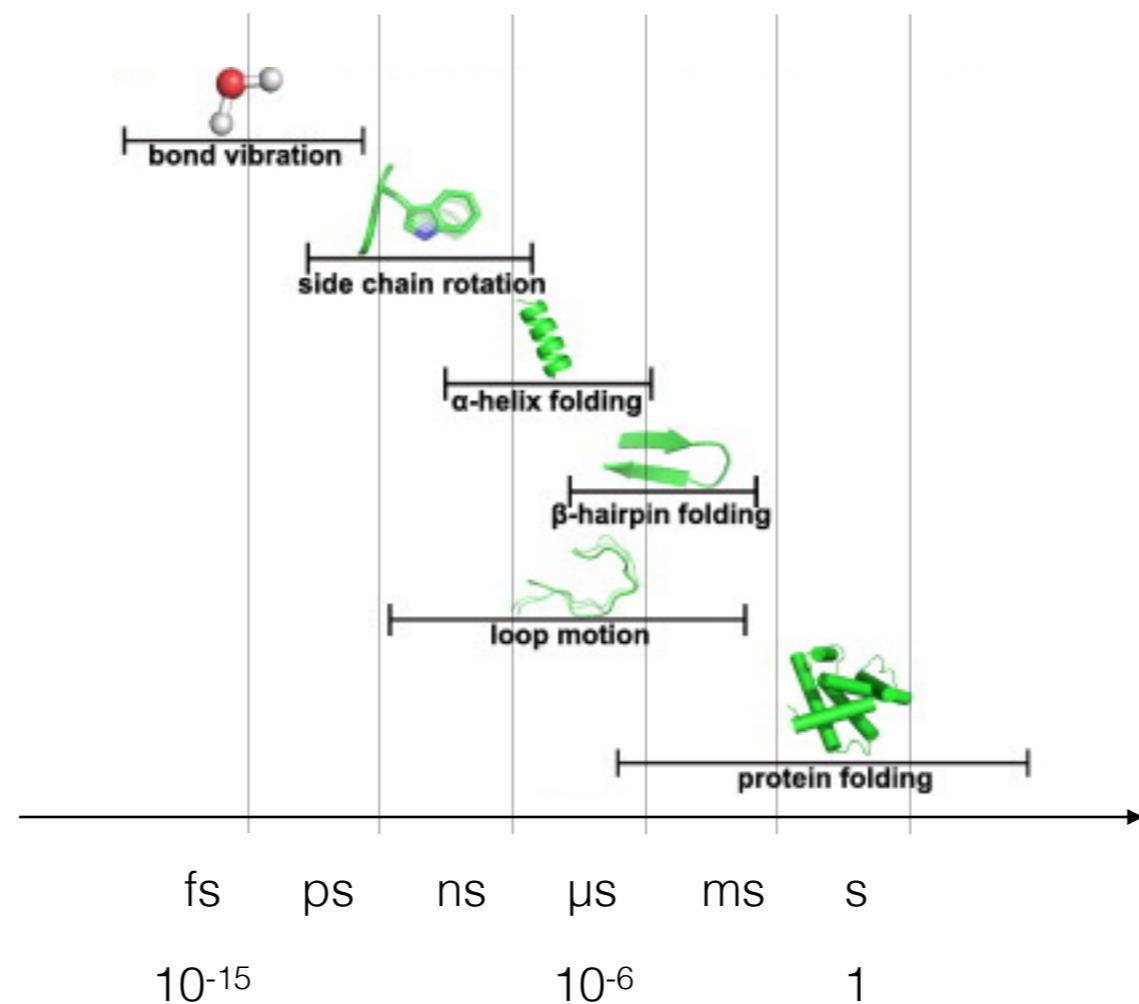
ATPase

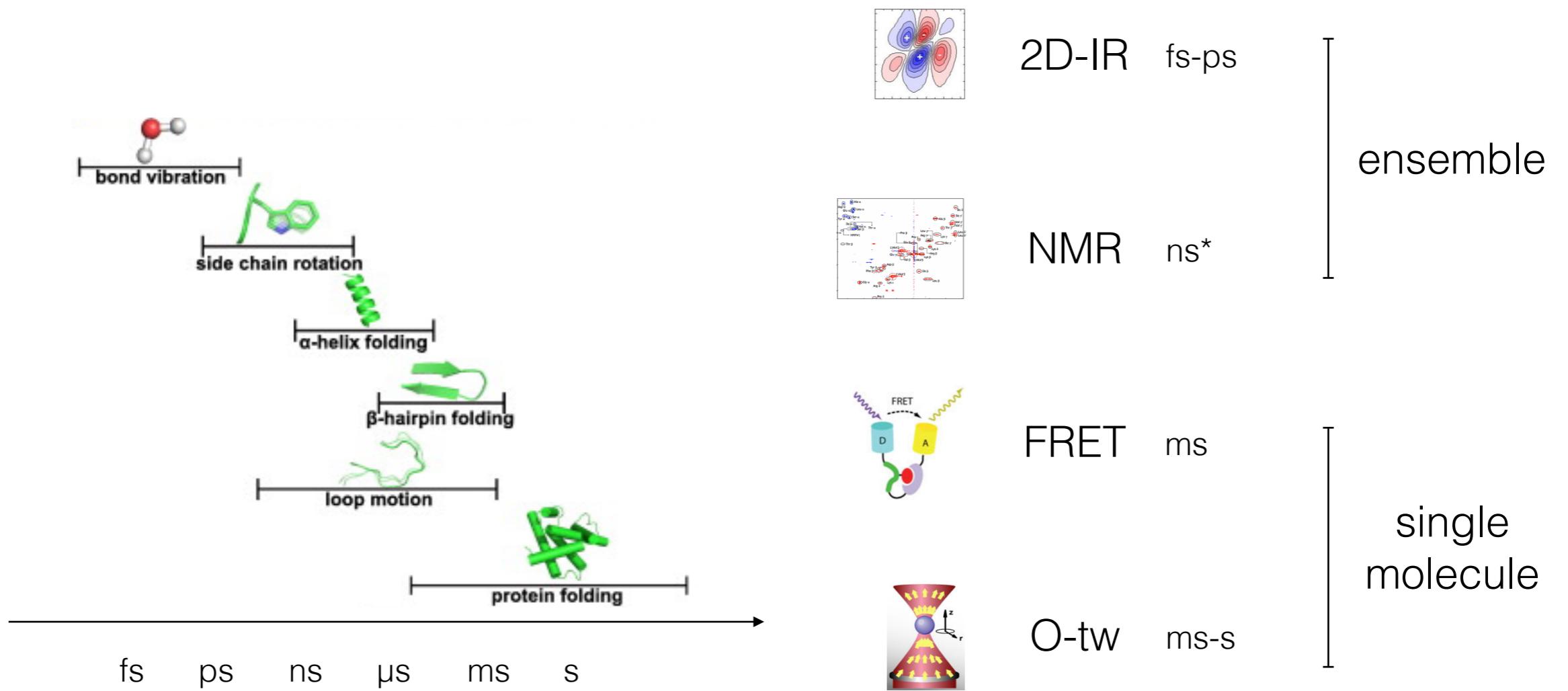


4

dynamical characterization is hard

protein dynamics is heterogeneous





information is limited

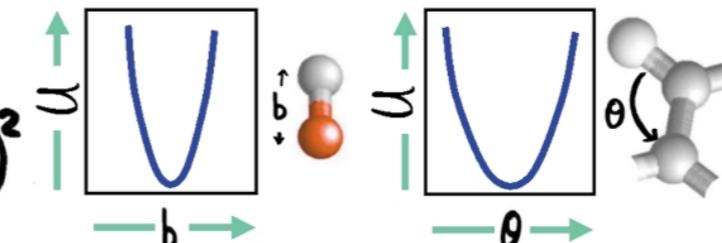
	2D-IR	NMR	FRET	O-tw
site-specific relaxations	●	●	-	-
correlations	●	-	-	-
distance populations	-	-	●	-
distance time series	-	-	-	●

5

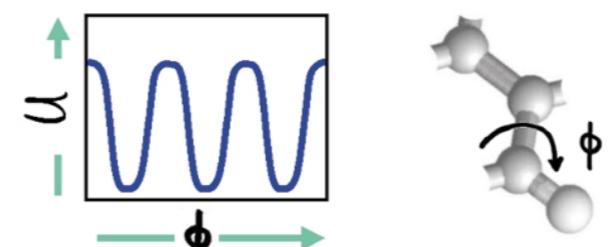
molecular simulations for atomic details

the force field

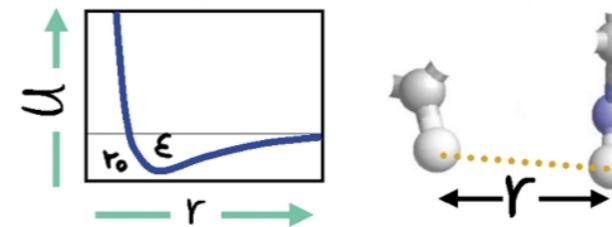
$$U = \sum_{\text{All Bonds}} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\text{All Angles}} \frac{1}{2} K_\theta (\theta - \theta_0)^2$$



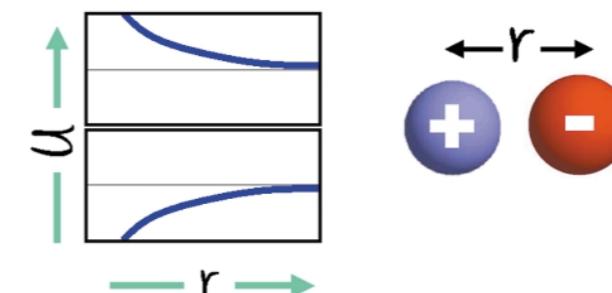
$$+ \sum_{\text{All Torsion Angles}} K_\phi [1 - \cos(n\phi + \delta)]$$



$$+ \sum_{\text{All nonbonded pairs}} \epsilon \left[\left(\frac{r_0}{r} \right)^{12} - 2 \left(\frac{r_0}{r} \right)^6 \right]$$

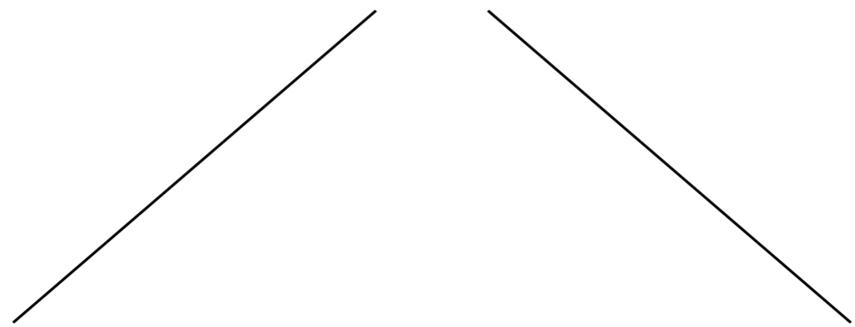


$$+ \sum_{\text{All partial charges}} 332 q_i q_j / r$$



the force field

parameters



comparison with
experiments

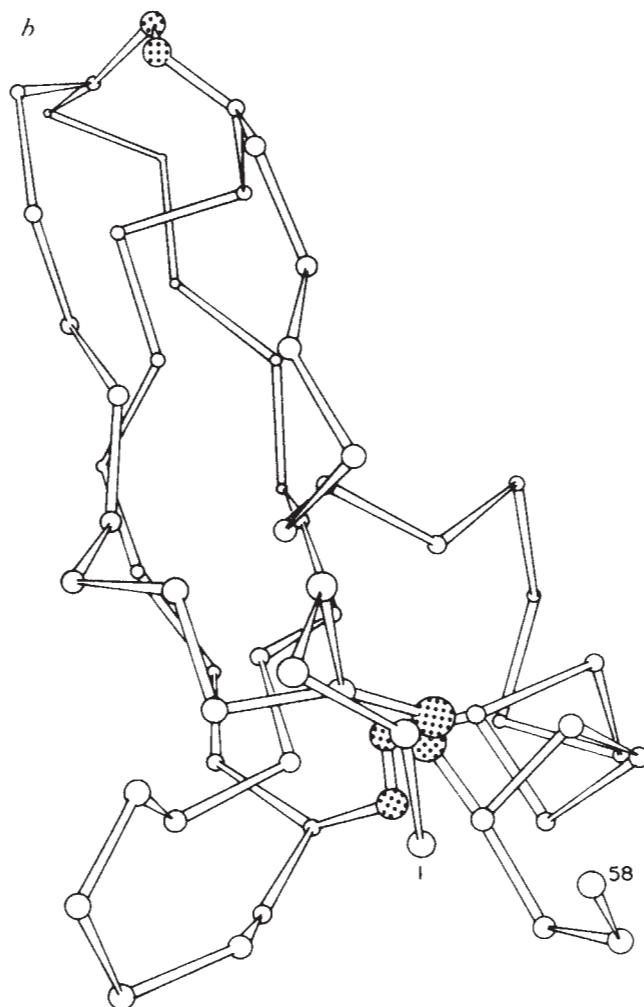
evaluation of
ab-initio (quantum)
potentials

Nature Vol. 267 16 June 1977

Dynamics of folded proteins

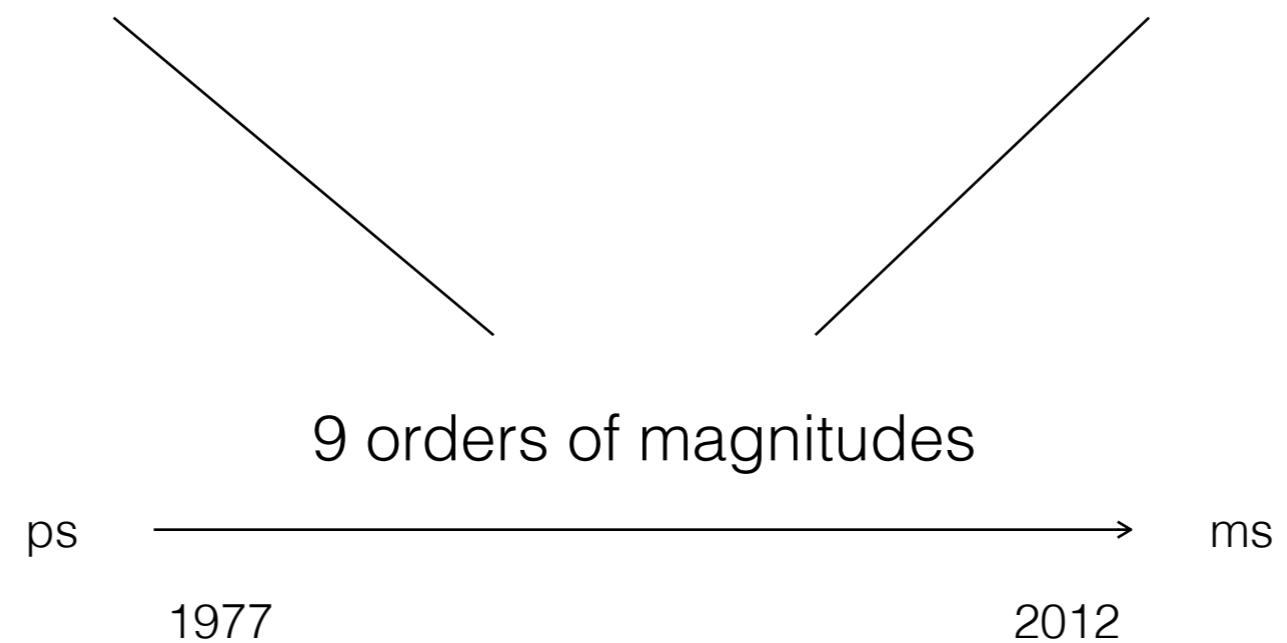
J. Andrew McCammon, Bruce R. Gelin & Martin Karplus

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138



tremendous
improvement of
computer power

systematic
development
of software

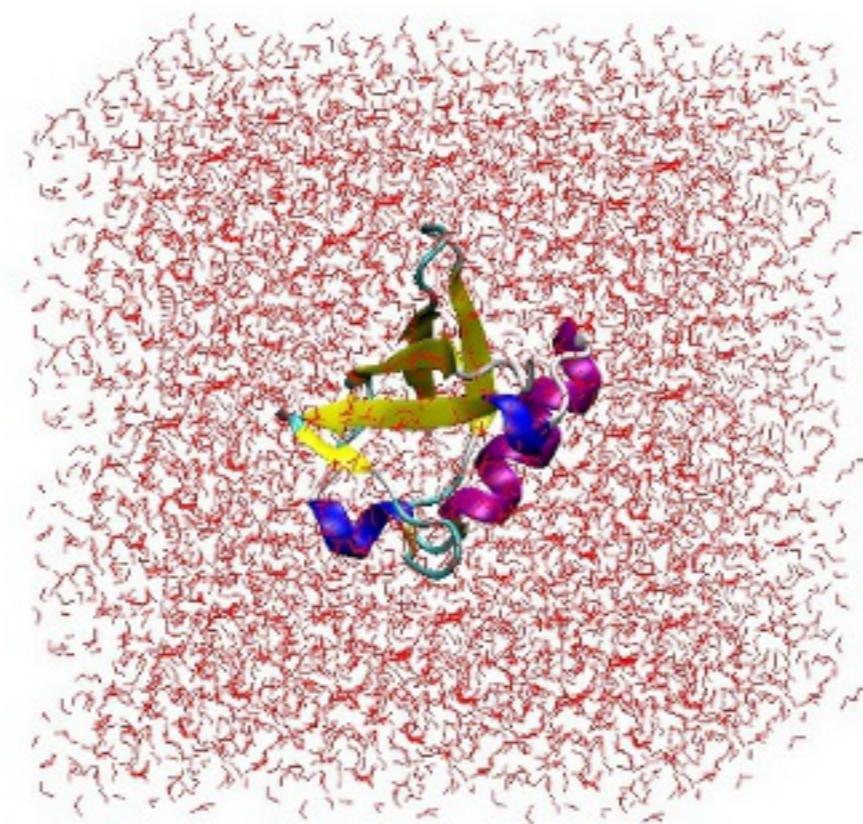


6

the role of water

biological processes take place in water

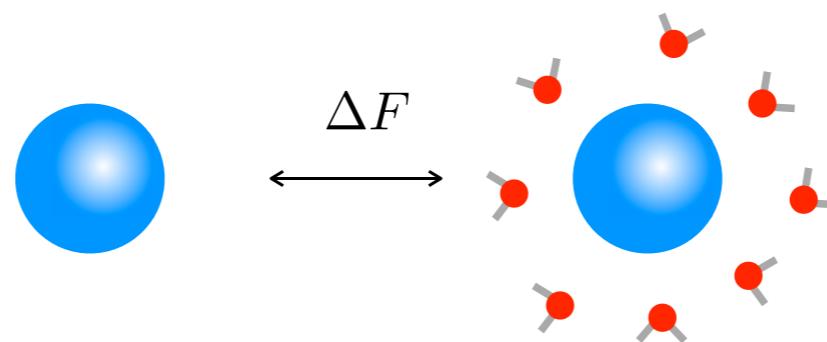
5K + 20K



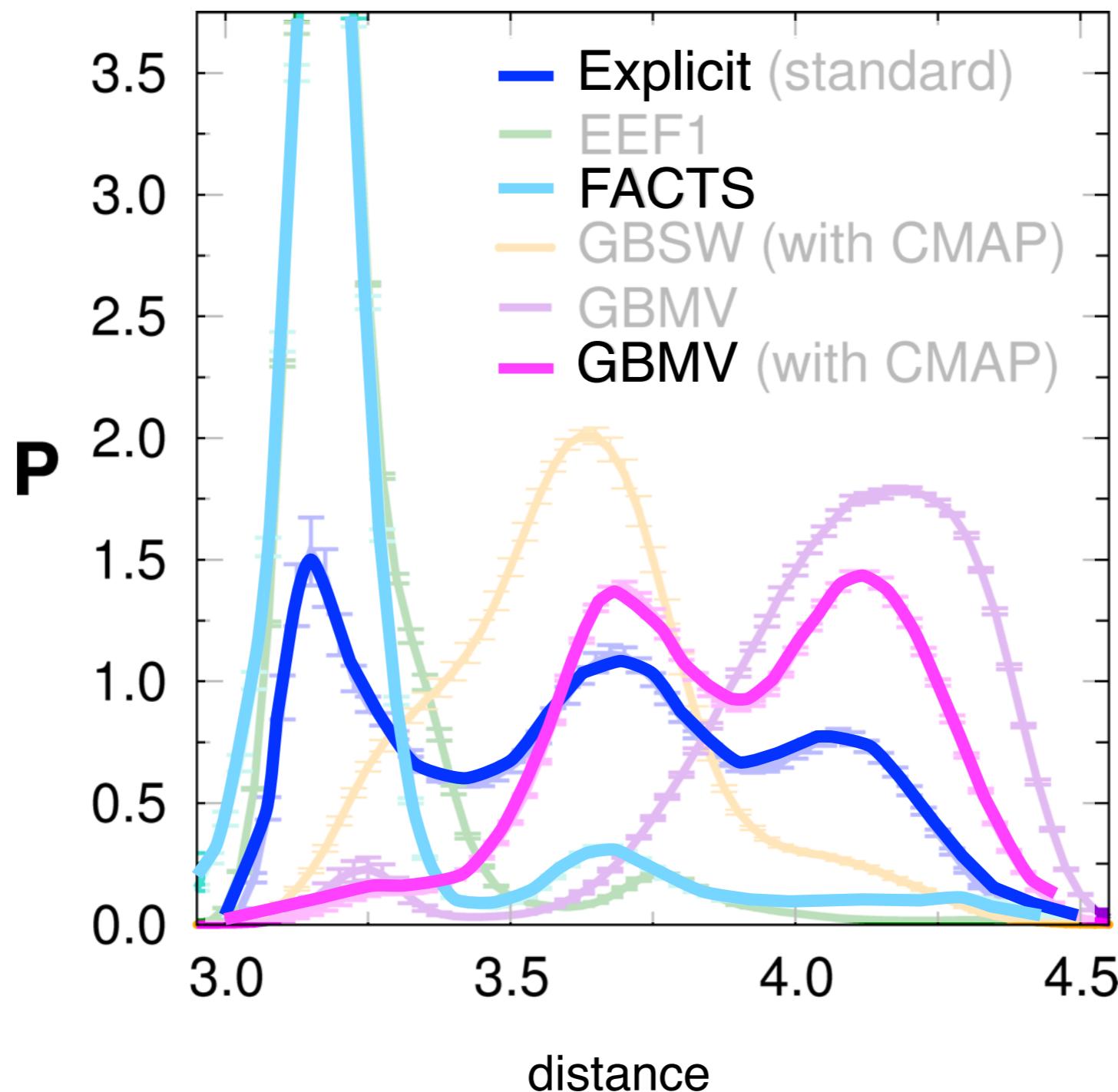
implicit solvents reproduce the free-energy of solvation

100 times speedup

	explicit	FACTS	GBSW	GBMV
Ala-Ser	-2.46	-2.99	-2.06	-2.78
Val-Thr	-2.44	-1.41	-2.03	-2.12
Leu-Asn	-6.10	-1.26	-6.99	-6.47
Phe-Tyr	-4.72	-3.10	-4.80	-3.93
Val-Ala	-0.97	-1.80	-0.68	-0.49
Thr-Ser	-1.29	-3.38	-1.34	-0.52
Phe-Ala	0.01	-2.11	-0.08	0.20
Tyr-Ser	2.46	-2.00	1.94	2.07
rmsd ^b		2.67	0.51	0.41



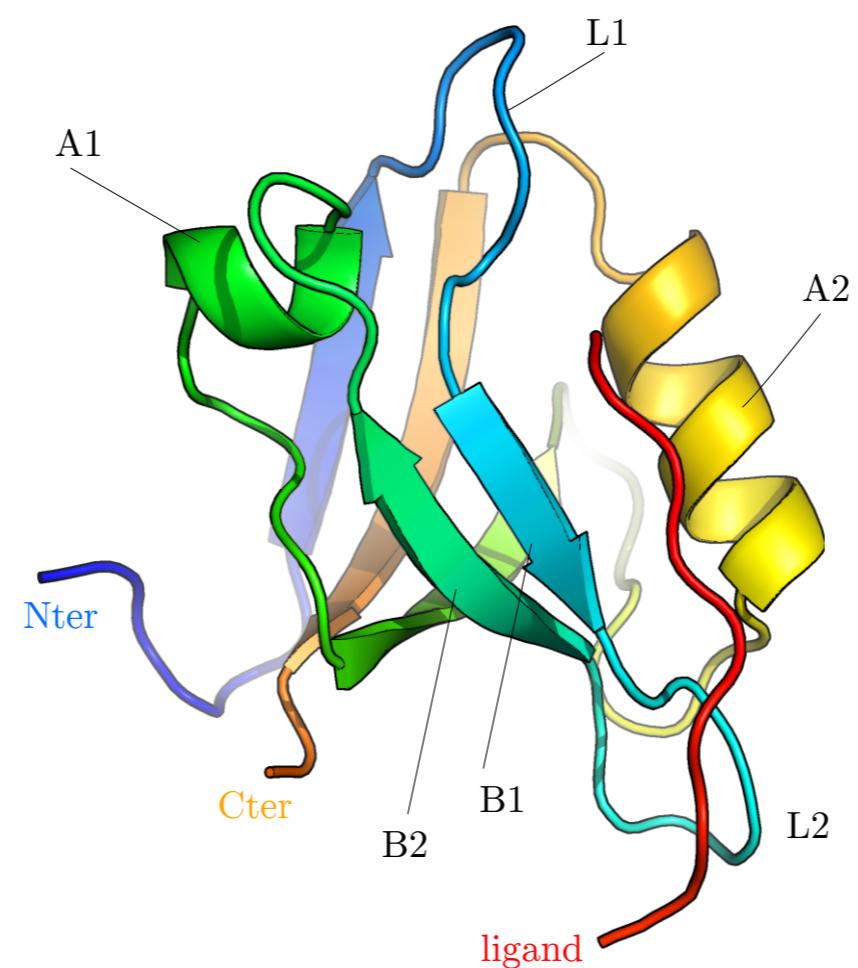
cooperative effects of water are lost



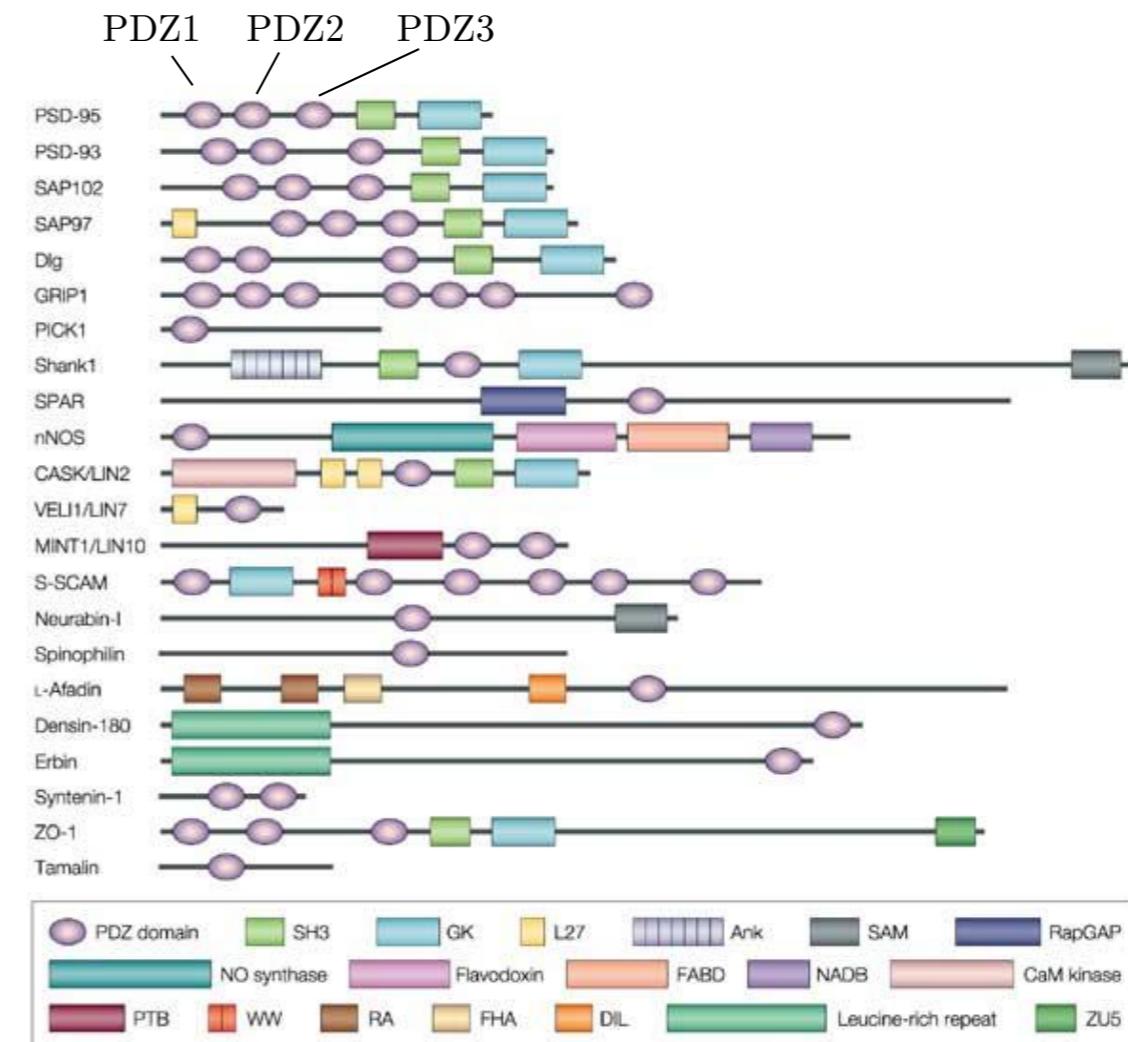
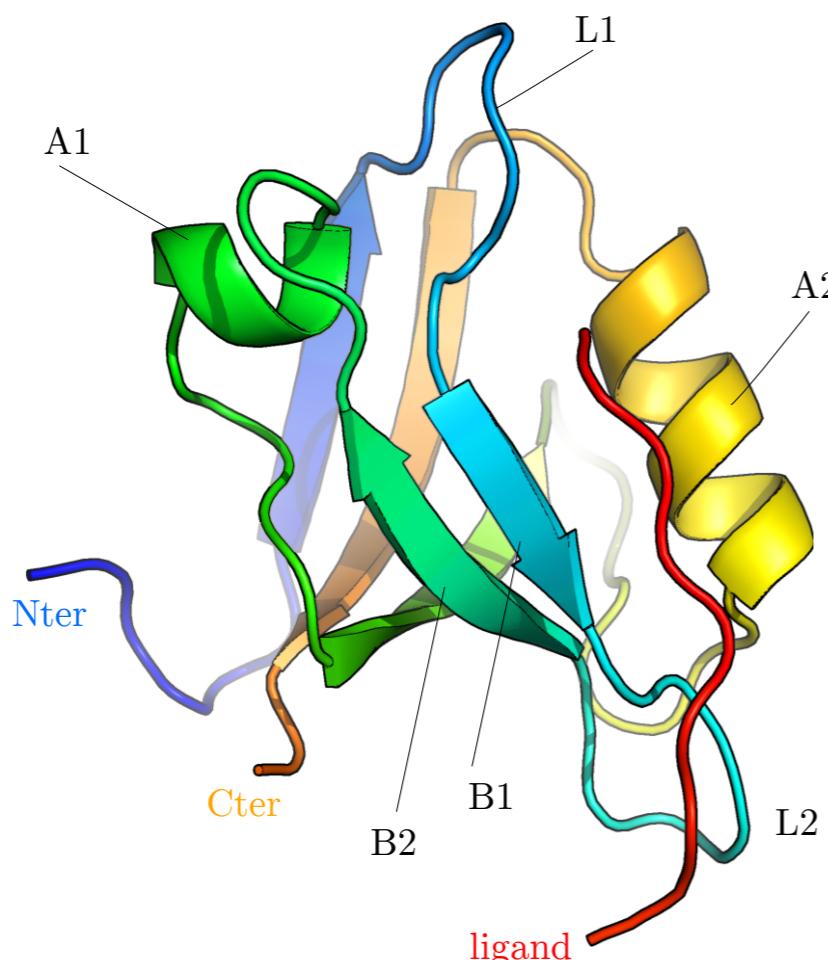
7

an **illustrative** MD study

PDZ domain



more than 250 in humans



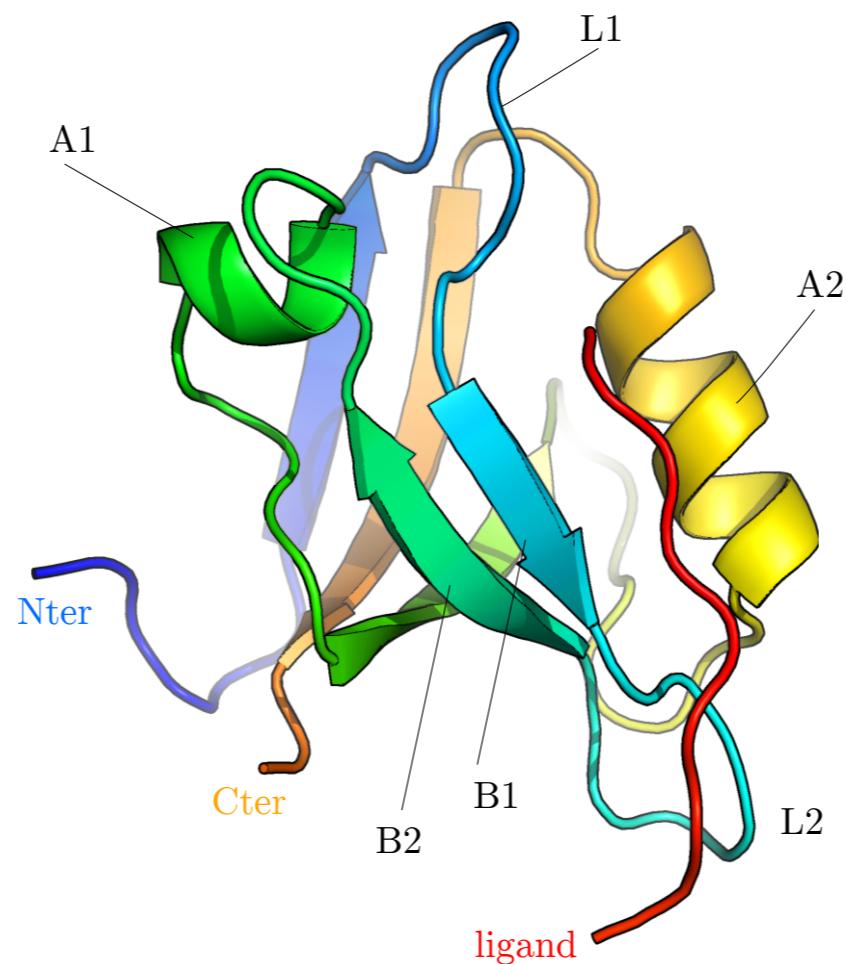
Kim *et al.* Nature review neuroscience 2004

Nature Reviews | Neuroscience

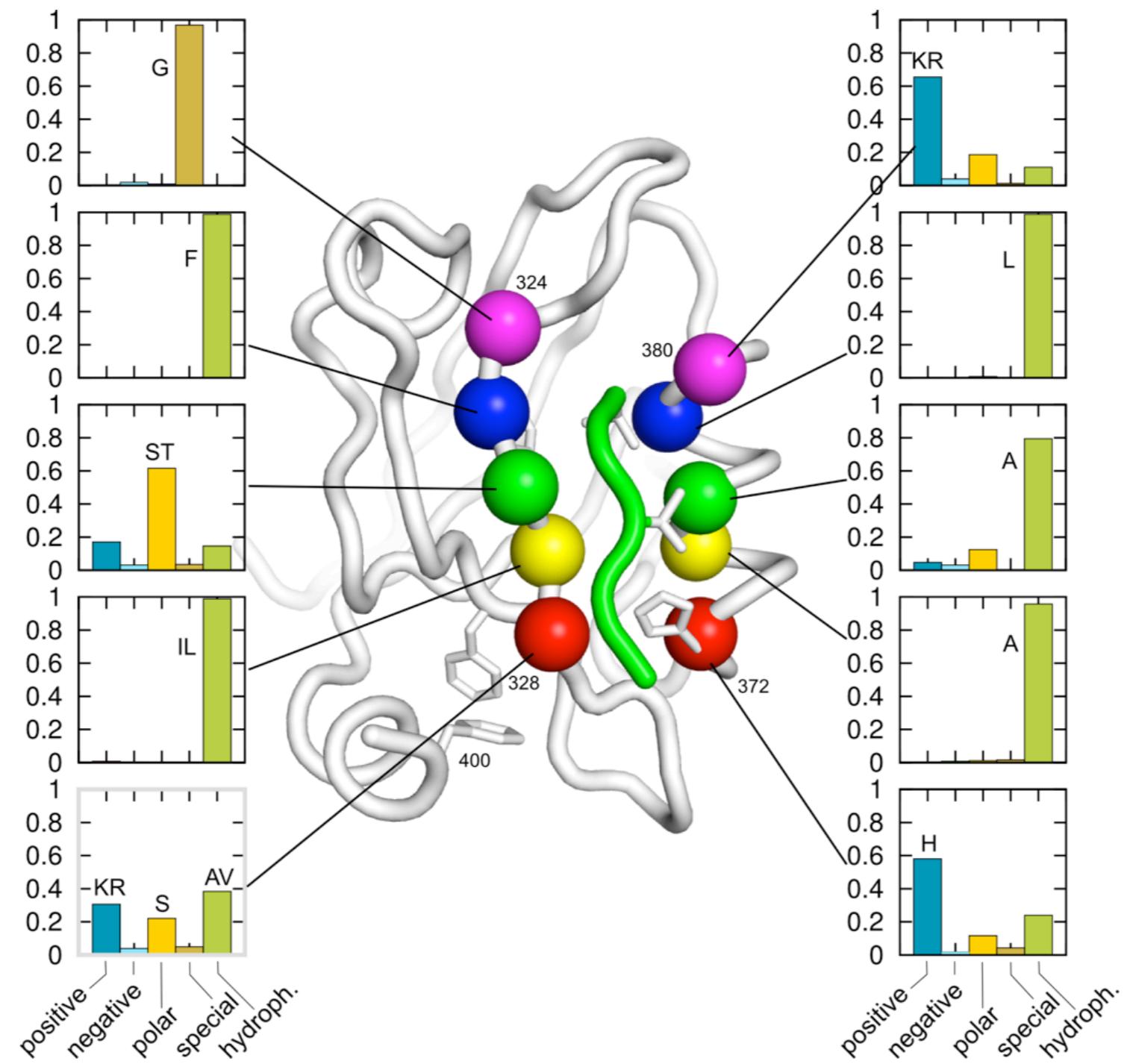
it binds to other proteins



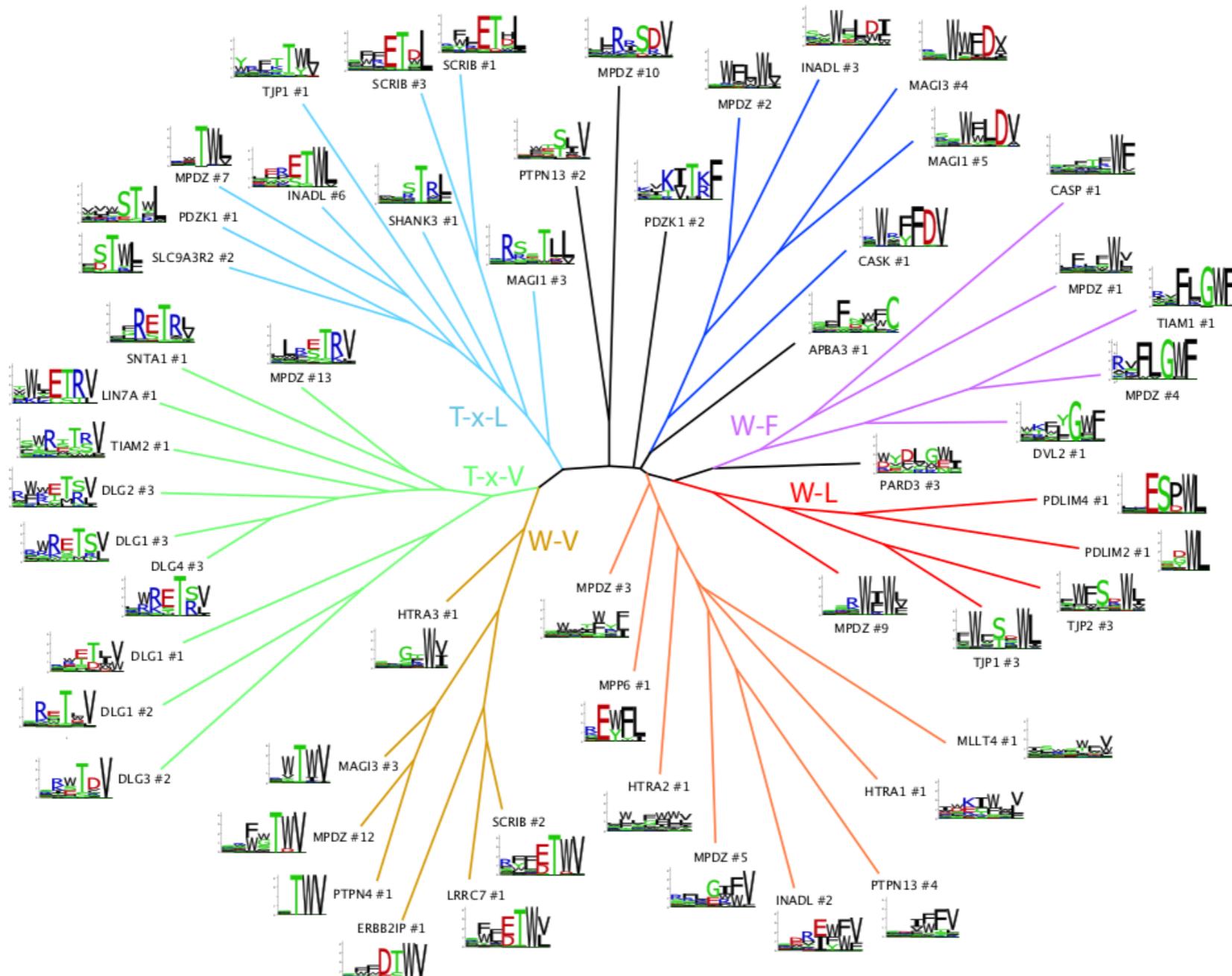
signaling processes



the binding site is highly conserved



heterogeneous selectivity



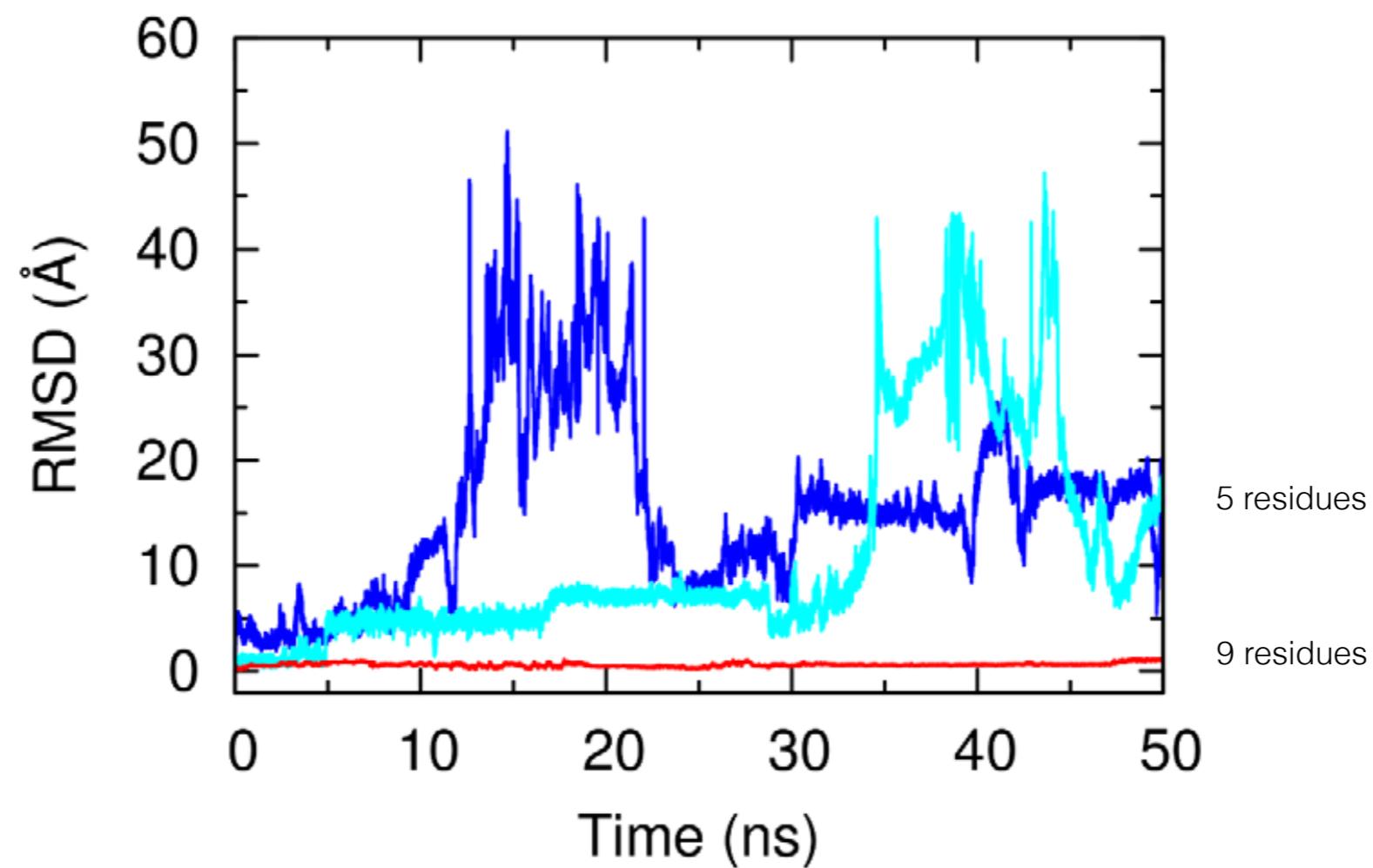
phage display experiments, courtesy of D. Gfeller

molecular dynamics simulation from the crystal structure

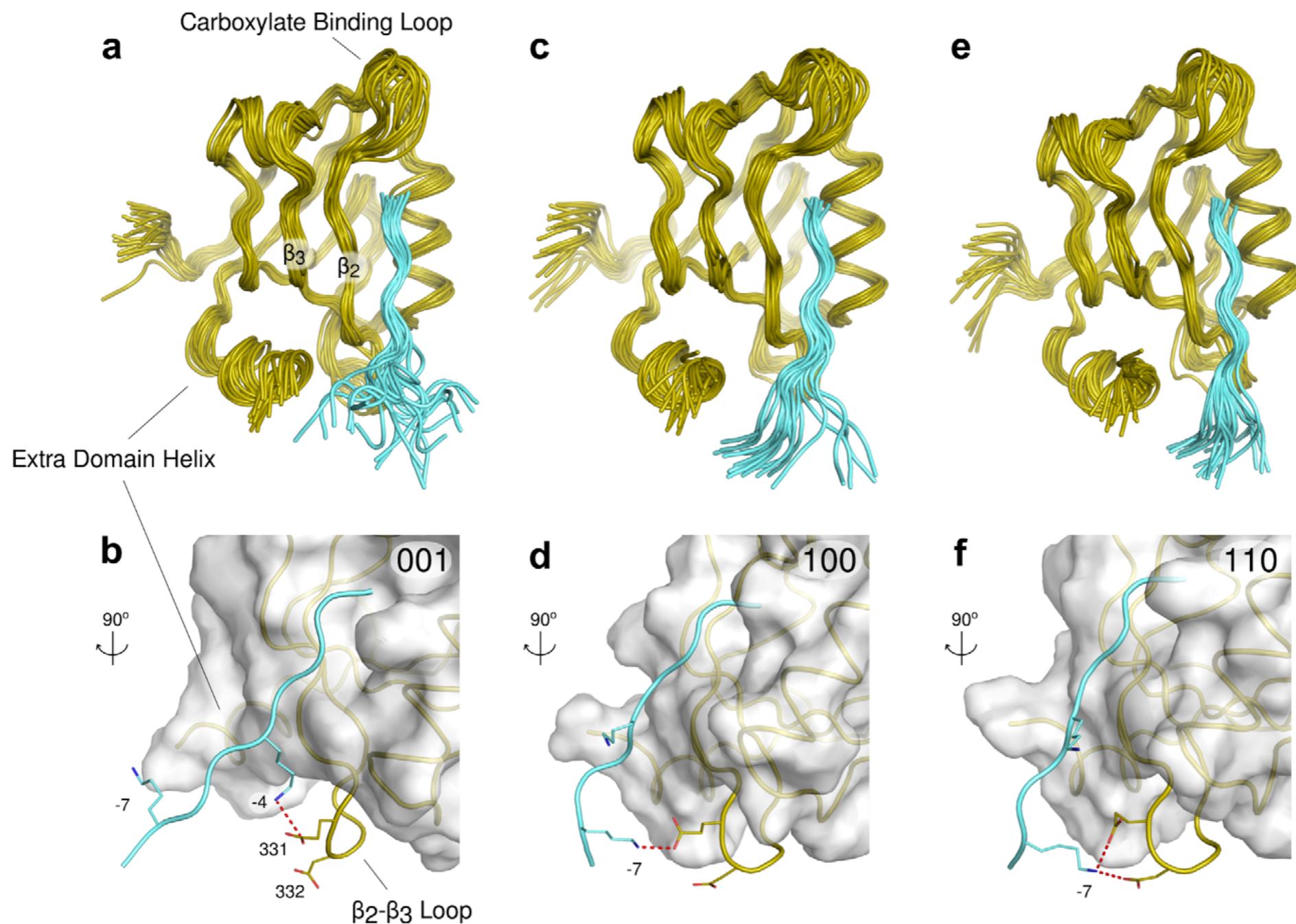
PSD95



rapid dissociation of the peptide



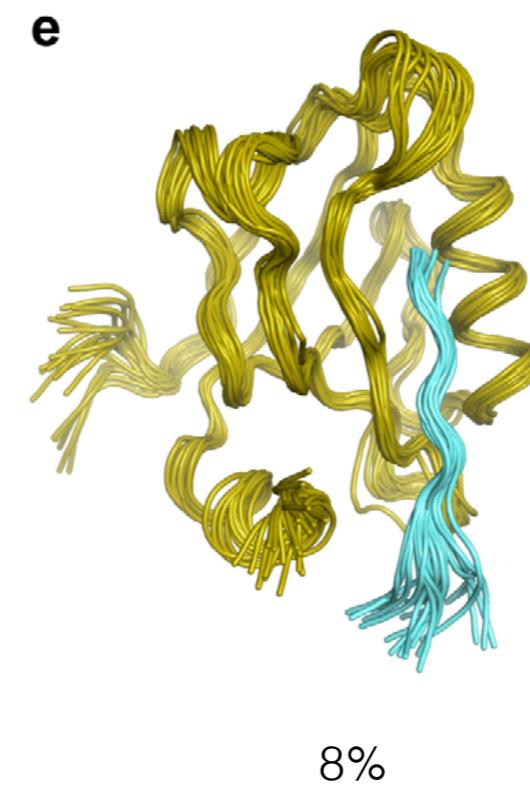
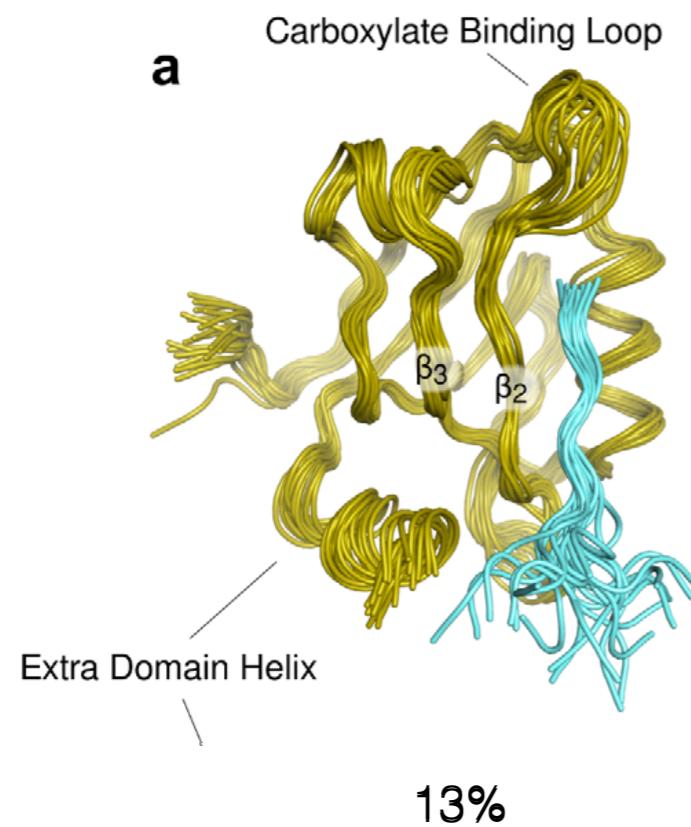
interactions beyond the binding site



these interactions are entropic in nature

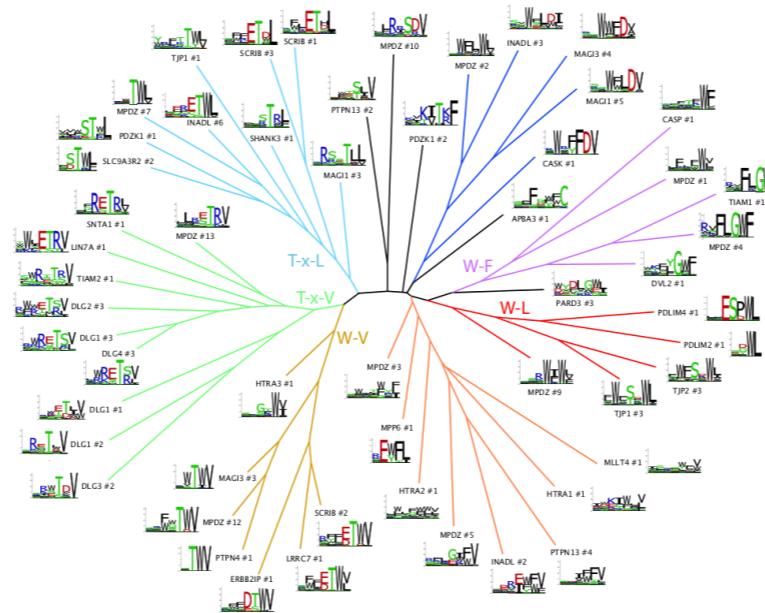


blind to crystallography



cumulative 44%

the binding loop is not conserved



suggesting specificity due to
regions away from the binding site



FRIAS
FREIBURG INSTITUTE
FOR ADVANCED STUDIES
ALBERT-LUDWIGS-
UNIVERSITÄT FREIBURG
SCHOOL OF
SOFT MATTER RESEARCH

acknowledgements

Stefano Mostarda
Diego Prada-Gracia
Roman Shevchuk
Ganna Berezovska

David Gfeller EPFL
Lausanne

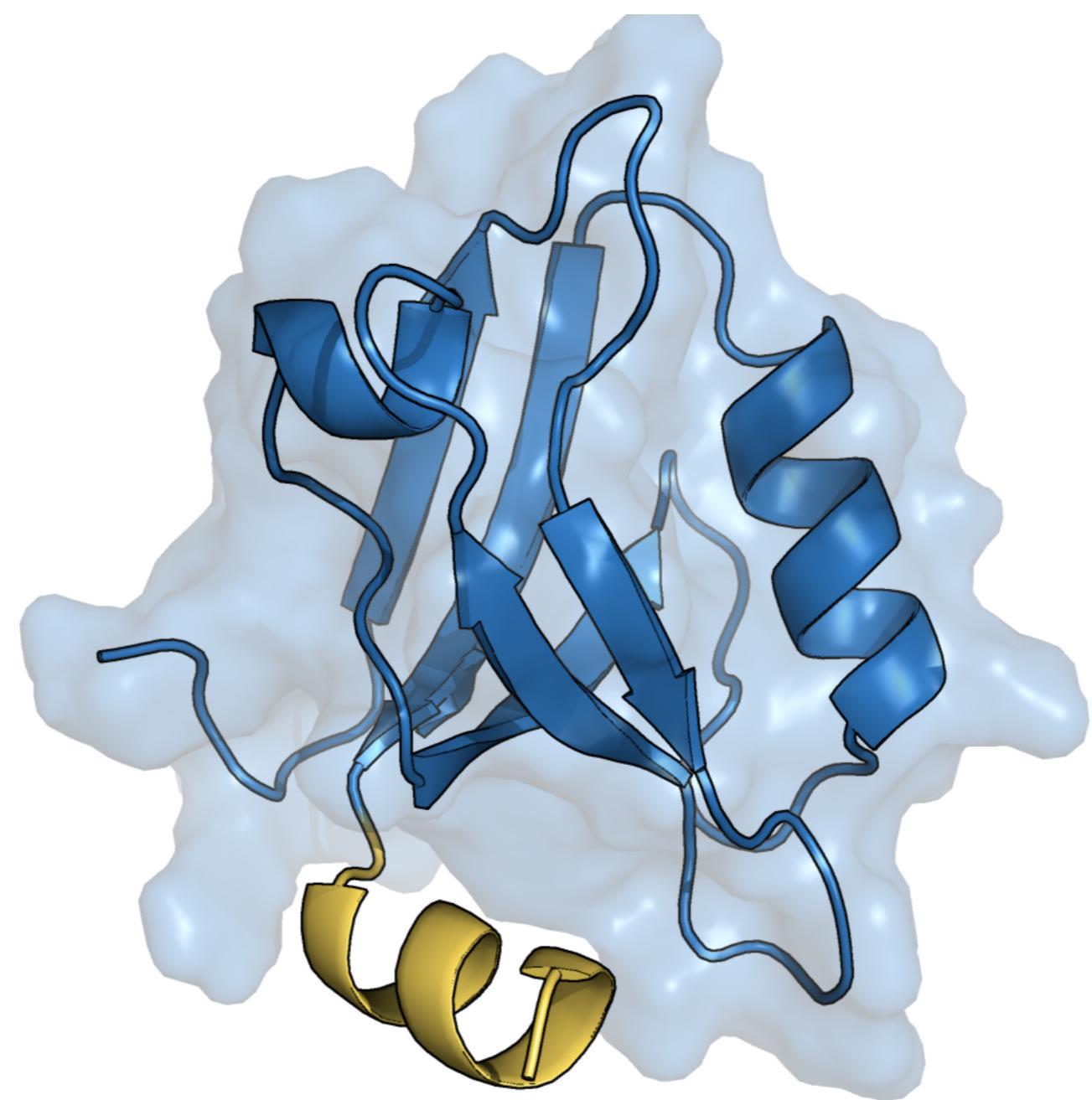
Martin Spichty ENSL
Lyon

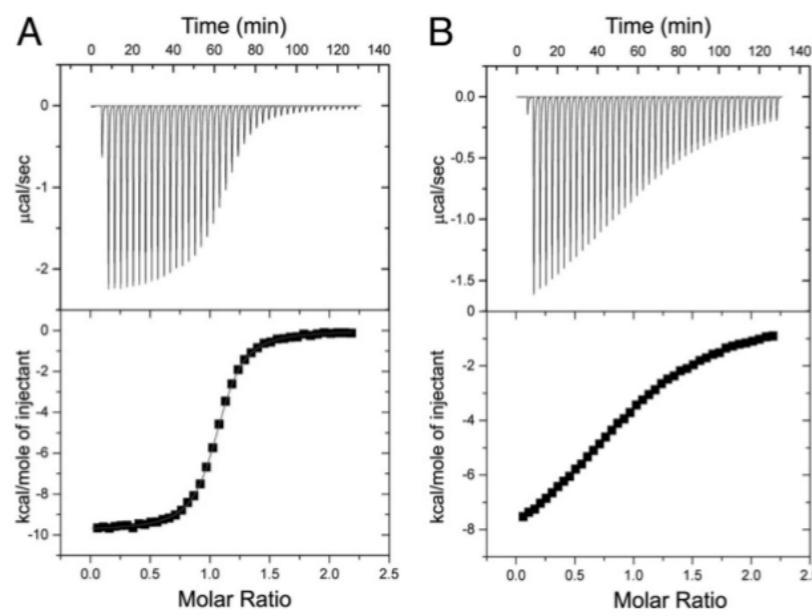
Felice Frankel MIT
Boston



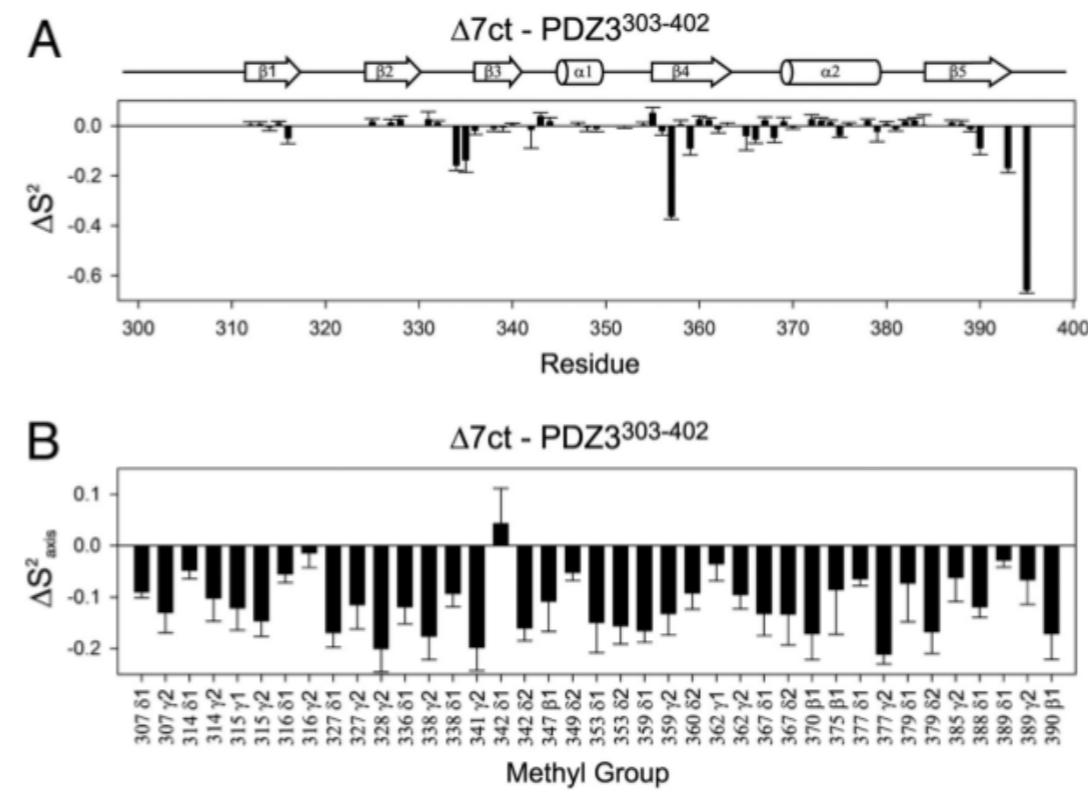
interpretation of NMR data

PSD95-PDZ3





DLG4-PDZ3



Hidden dynamic allostery in a PDZ domain, Petit *et al.* PNAS 2009

