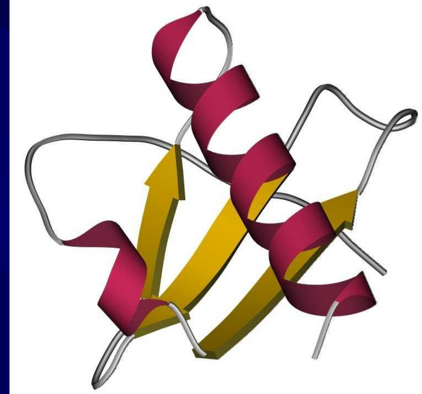
PROTEIN PHYSICS

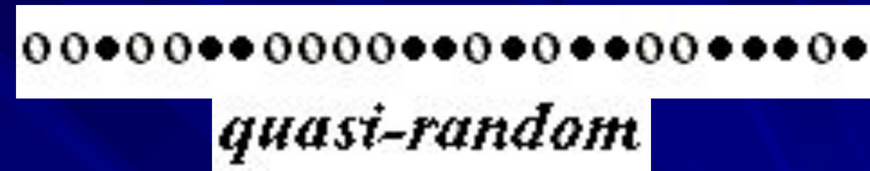
LECTURES 11-12

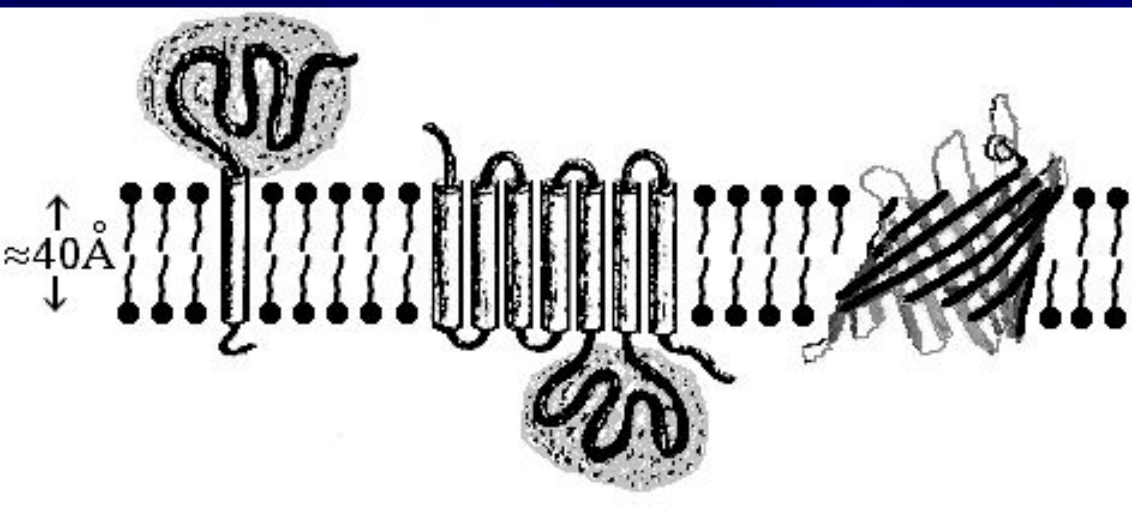
- Fibrous proteins and their functions
- Membrane proteins and their functions

- Fibrous proteins: building blocks
- Membrane proteins: transmitters

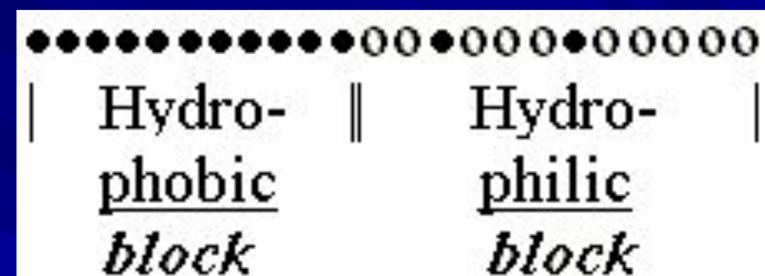


Globular proteins

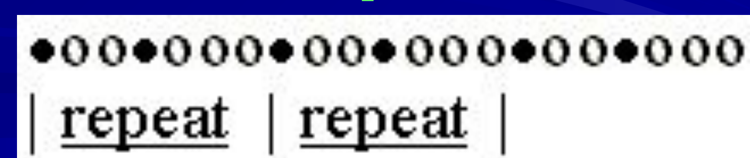




Membrane proteins



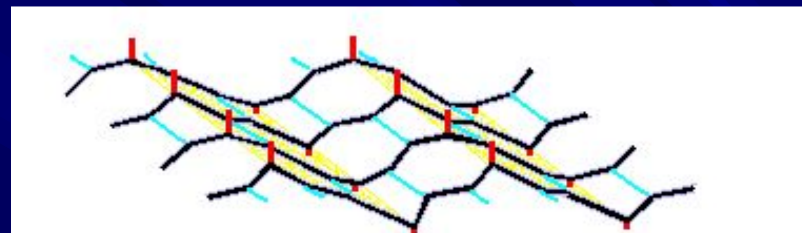
Fibrous proteins



H-bonds (NH:::OC) & hydrophobic forces

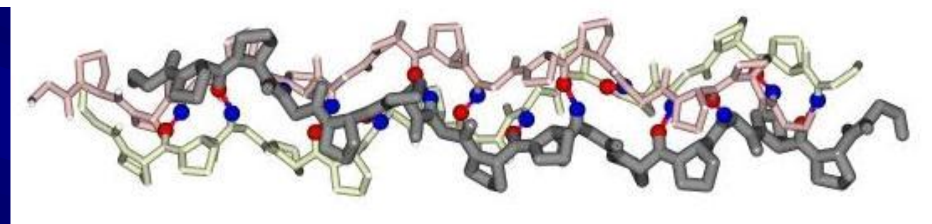
Fibrous proteins: regular building blocks

β

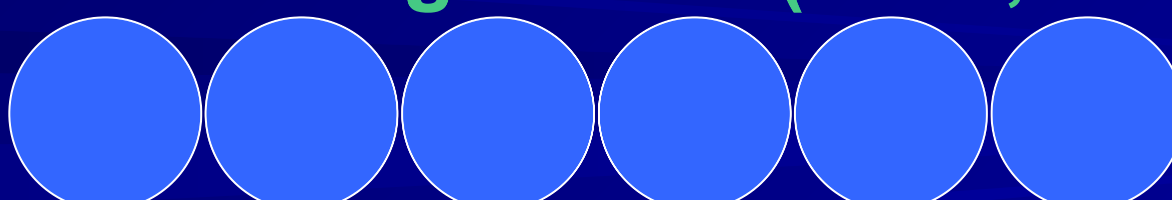


α

collagen

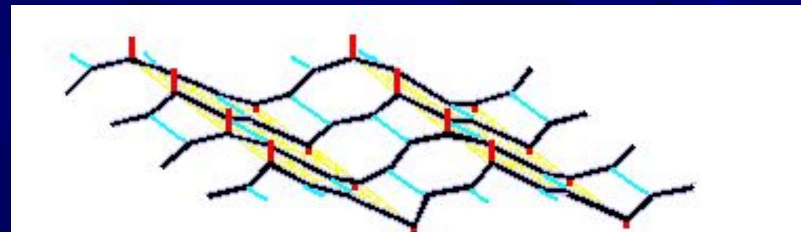


Here, we will not consider fibrous proteins made of globules (actin, etc.)

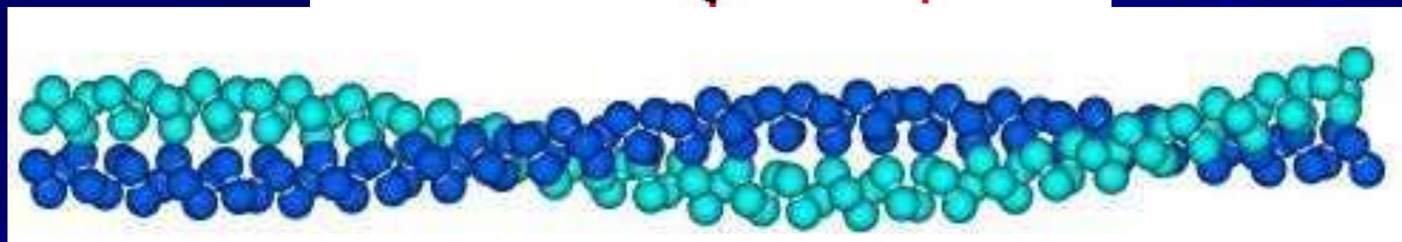


Fibrous proteins: regular building blocks

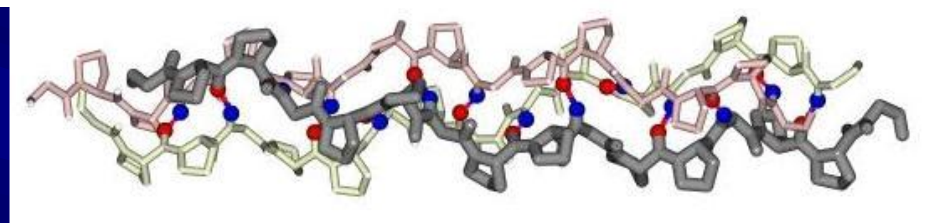
β



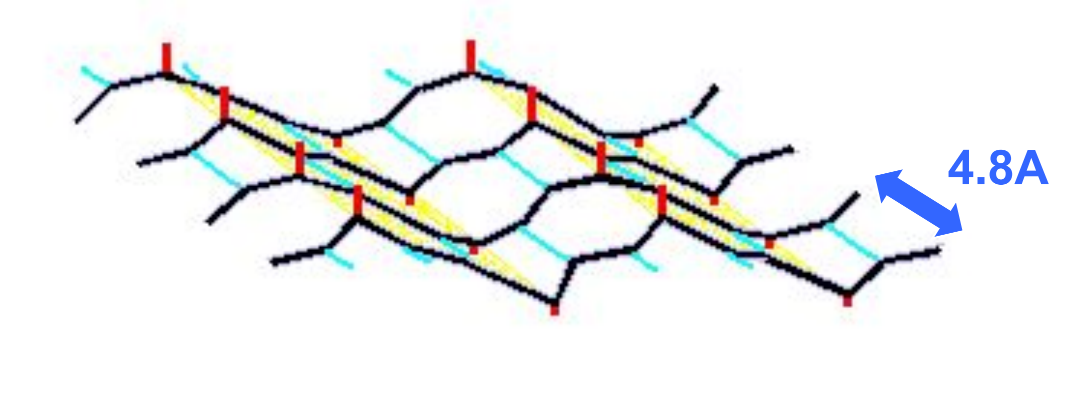
α



collagen



PROTEINS	SEQUENCES	
Globular	○○●○○●●○○●○●●○●○○●○○○●●○●○○●○●○○●●○●○○○○○●○○○●	*quasi-random*
Membrane	●●●●●●●●●●●○○●○○○●○○○○○●●●●●○●●●●●○○○○●●○○○●○●○	*blocks*
	| Hydro-phobic ‖ Hydro-philic |	
Fibrous	●○○●○○○●○○●○○○●○○●○○○●○○●○○○●○○●○○○●○○●○○○●○○●	*repeats*
	| repeat |	

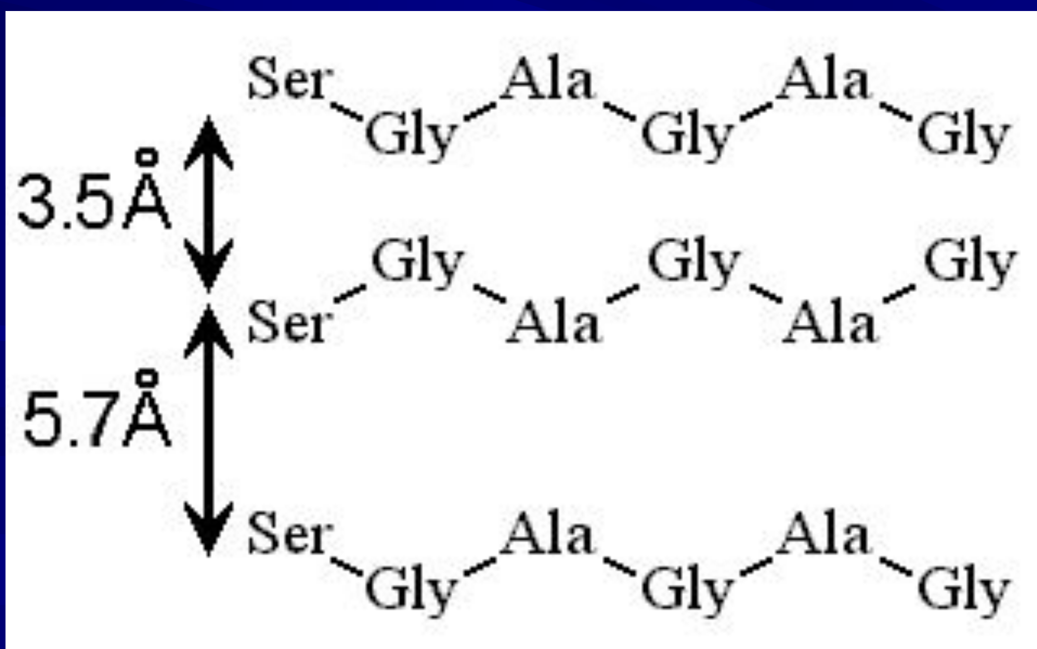


β

Silk fibroin

$$\sim(\text{-Ser-Gly-Ala-Gly-Ala-Gly-})_8\sim$$

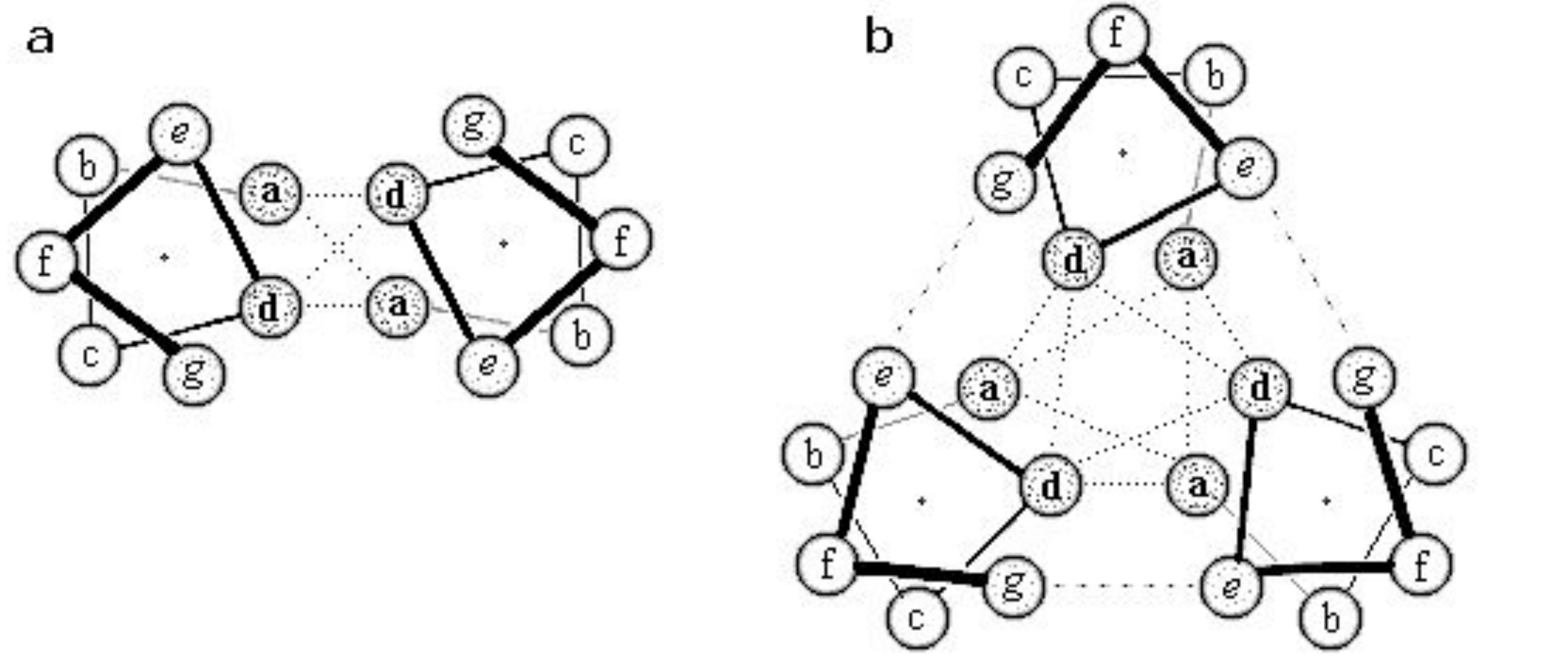
×~50

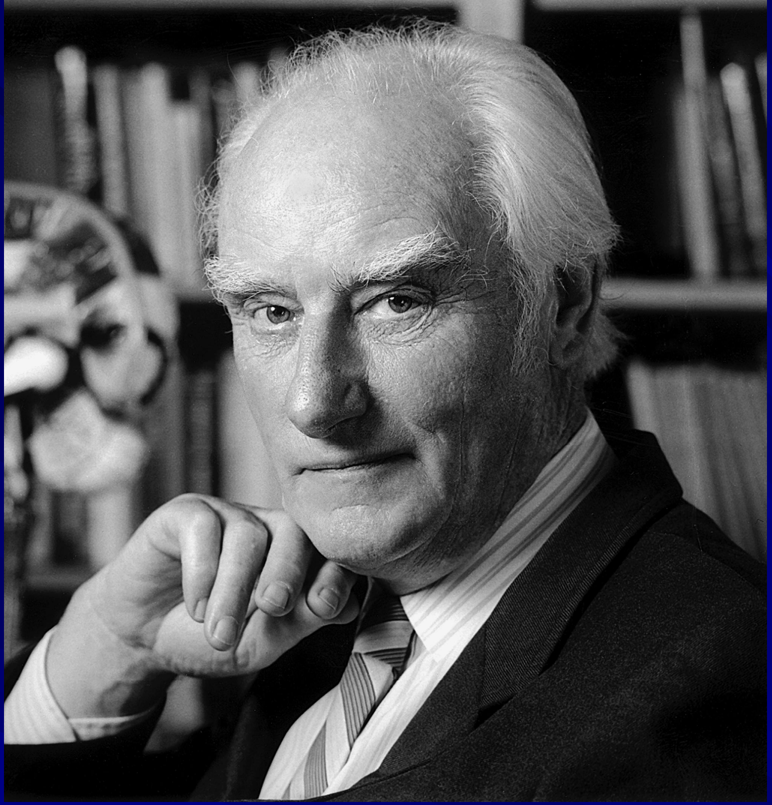


α-helical coiled-coil

... – **a** – b – c – **d** – *e* – f – *g* – **a** – b – c – **d** – *e* – f – *g* – **a** – b – c – **d** – *e* – f – *g* – ...

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

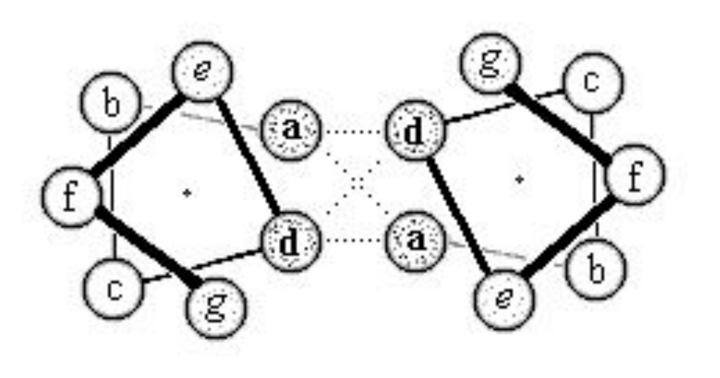


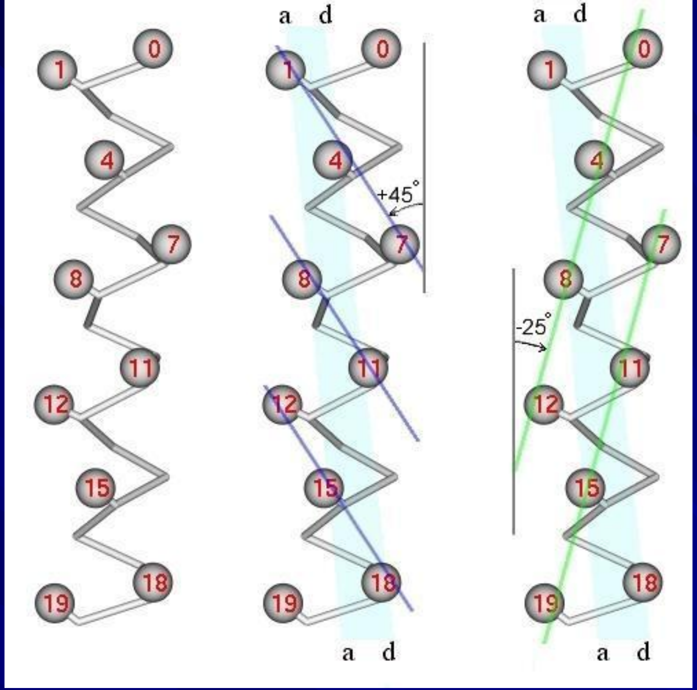


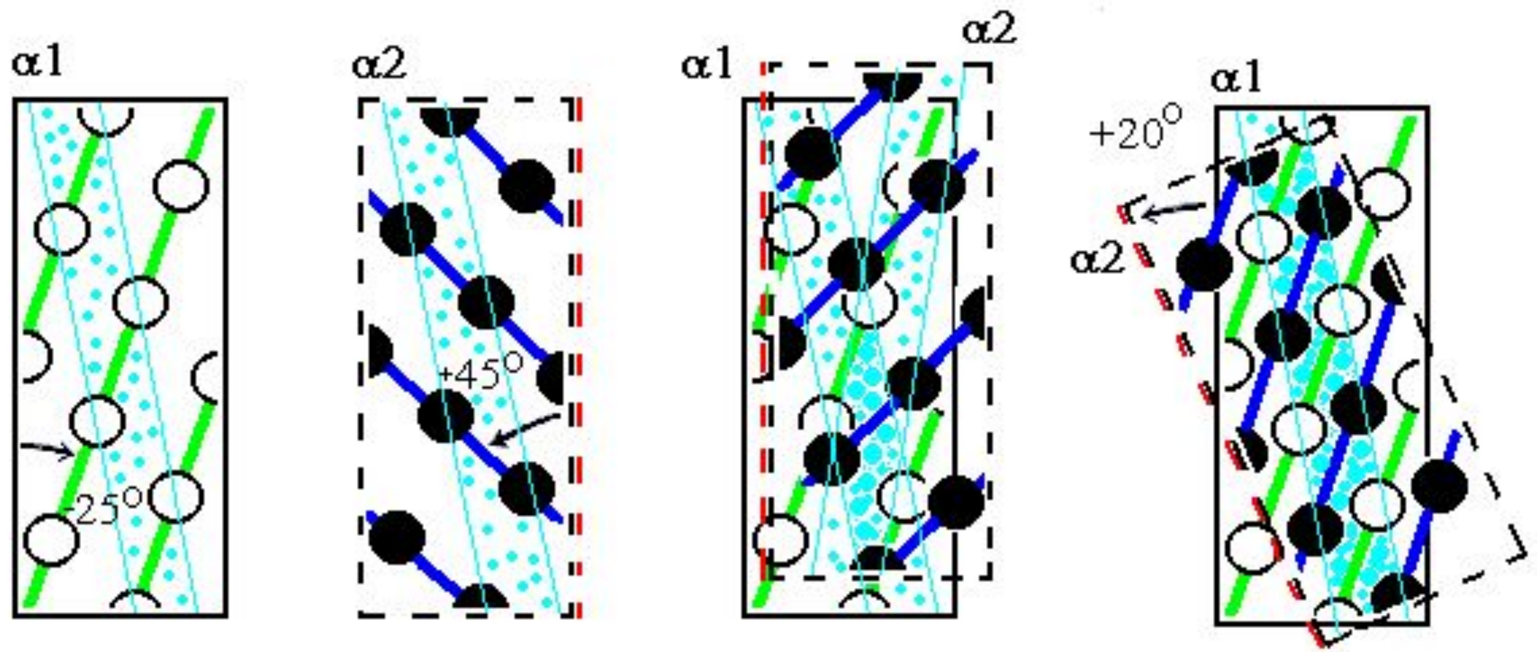
Francis Harry Compton **Crick** (1916 – 2004)
Nobel Prize 1962
for DNA structure, 1953

Coiled coil structure: F. **Crick,** 1952
C. **Chothia**, M. **Levitt**, D. **Richardson**, 1977

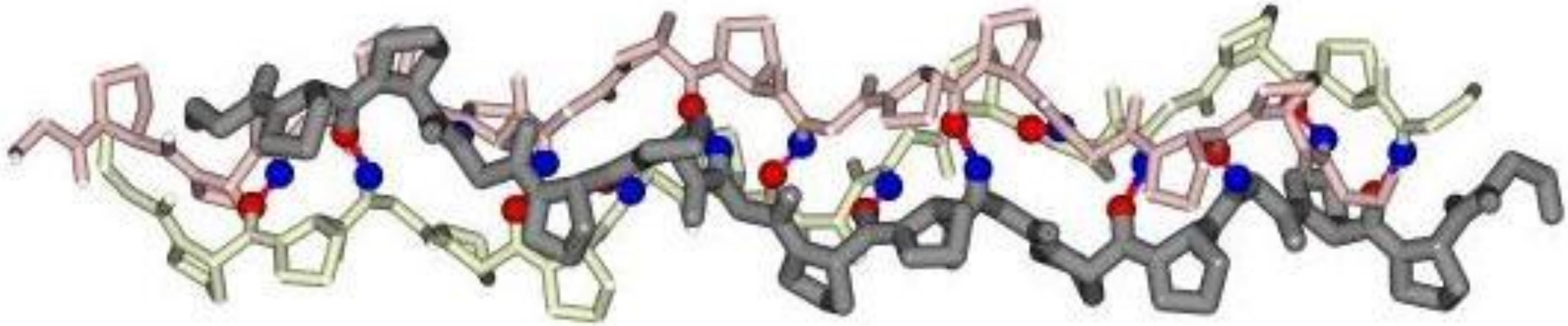
α-helix packing

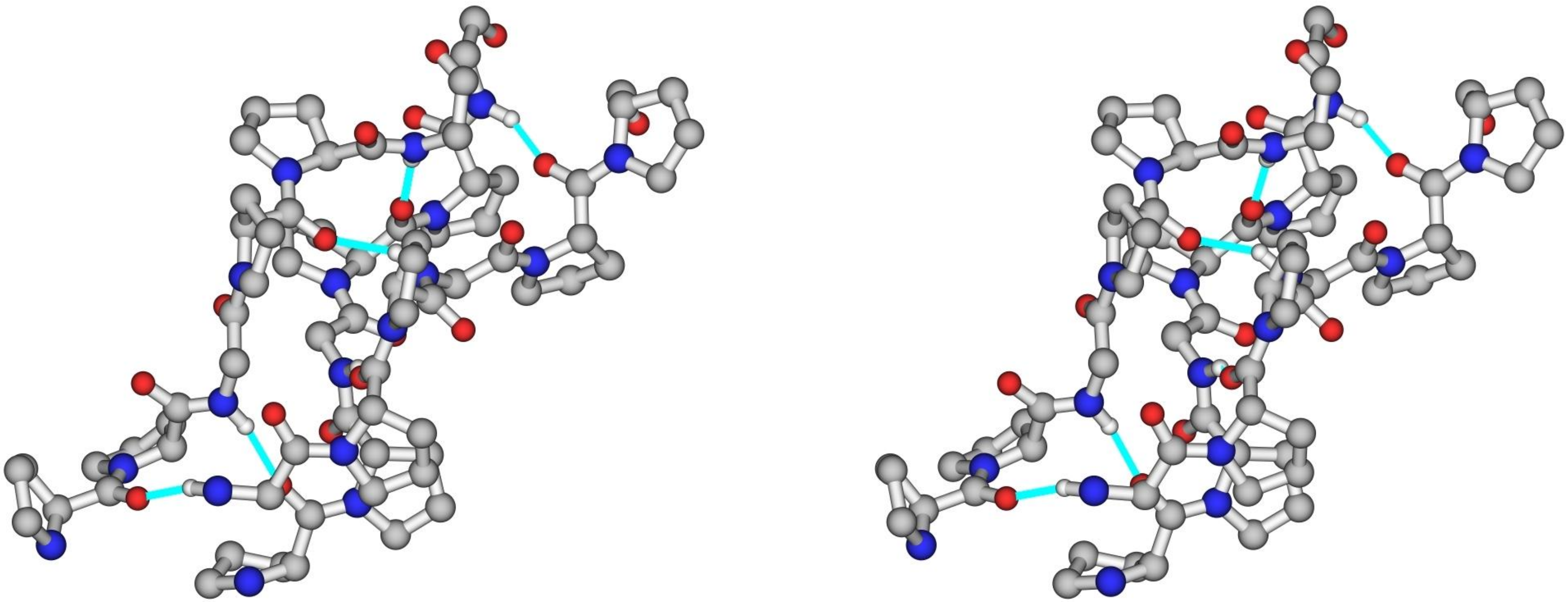




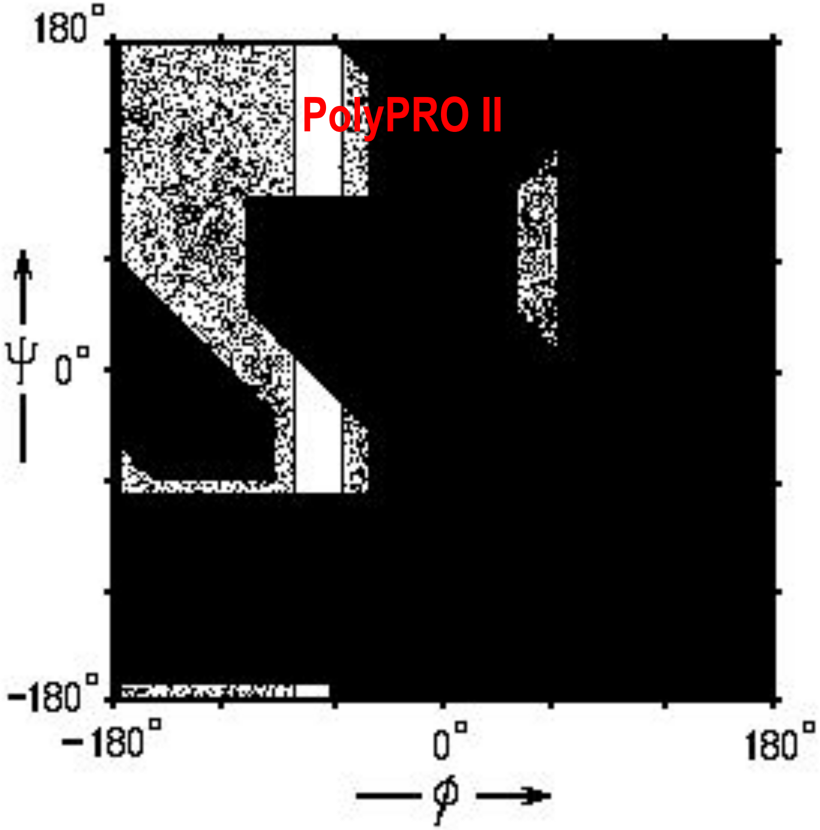


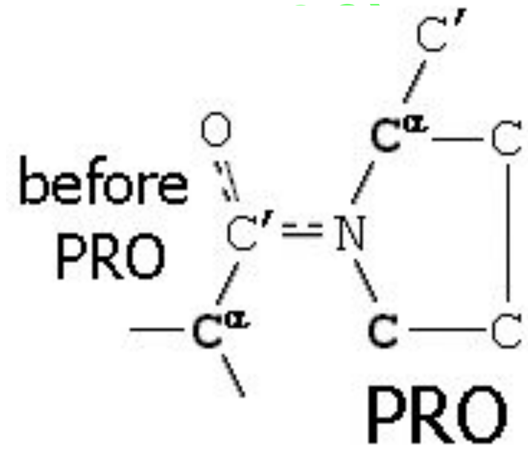
collagen triple helix: **3 chains ≈ [Gly-X-Pro]$_{≈500}$**

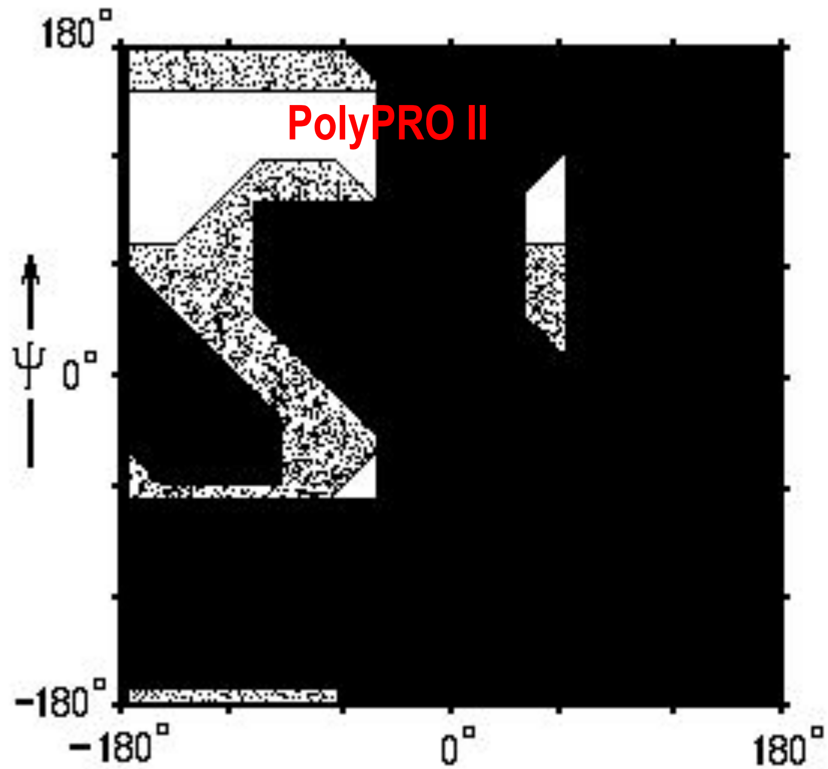




PRO (φ =

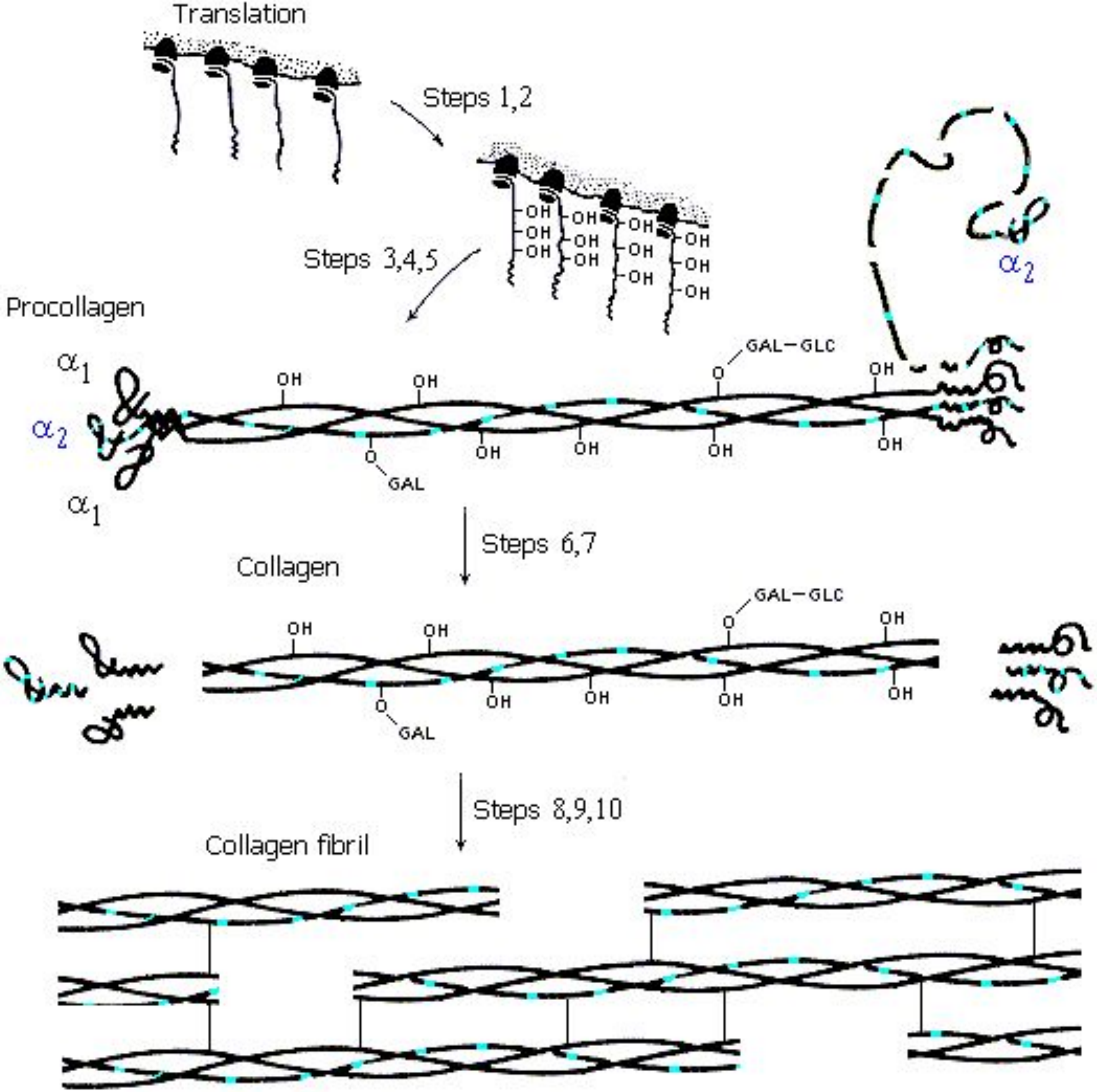






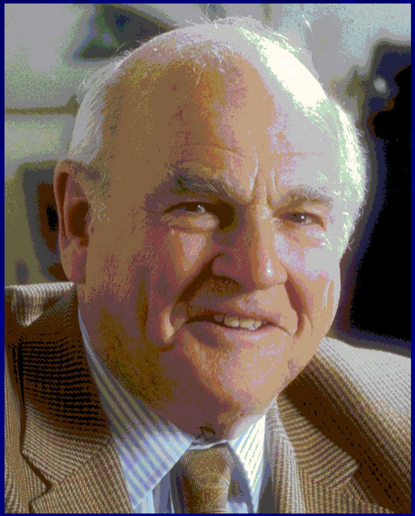
Before PRO

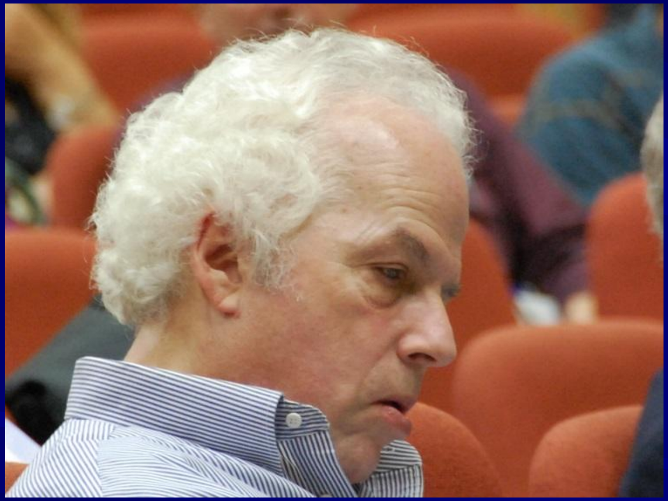
Collagen: assisted folding



Kuru: a mysterious disease, later demonstrated to be infectious prion disease.

Daniel Carleton **Gajdusek** (1923 –2008)
Baruch Samuel **Blumberg** (1925 – 2011)
Nobel Prize 1976



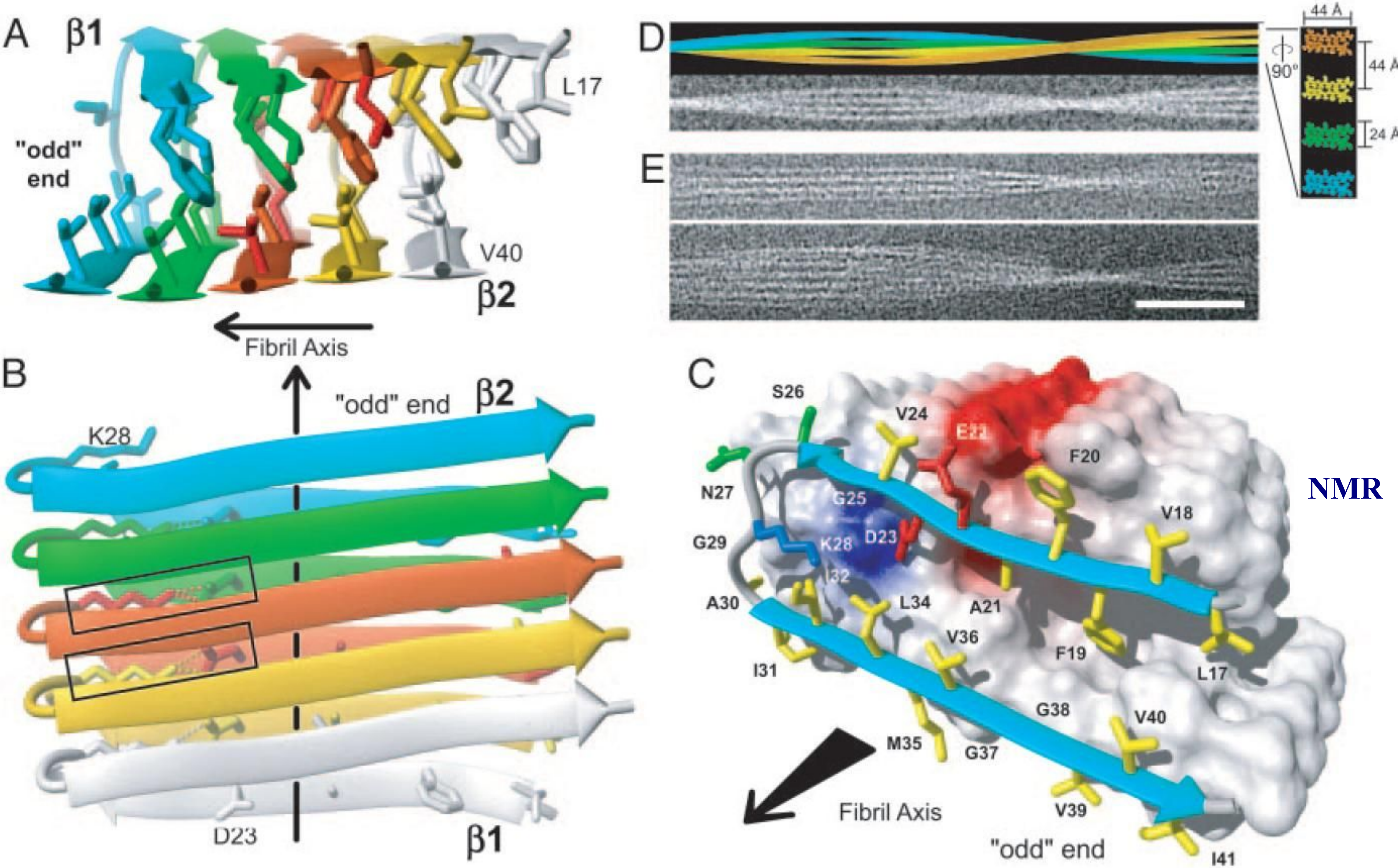


PRION: **PRO***tein* and **In***fection*

Stanley Benjamin **Prusiner**, 1942
Nobel Prize 1997

Studies of amyloid formation

Christopher Martin **Dobson**, 1949
Royal Medal 2009



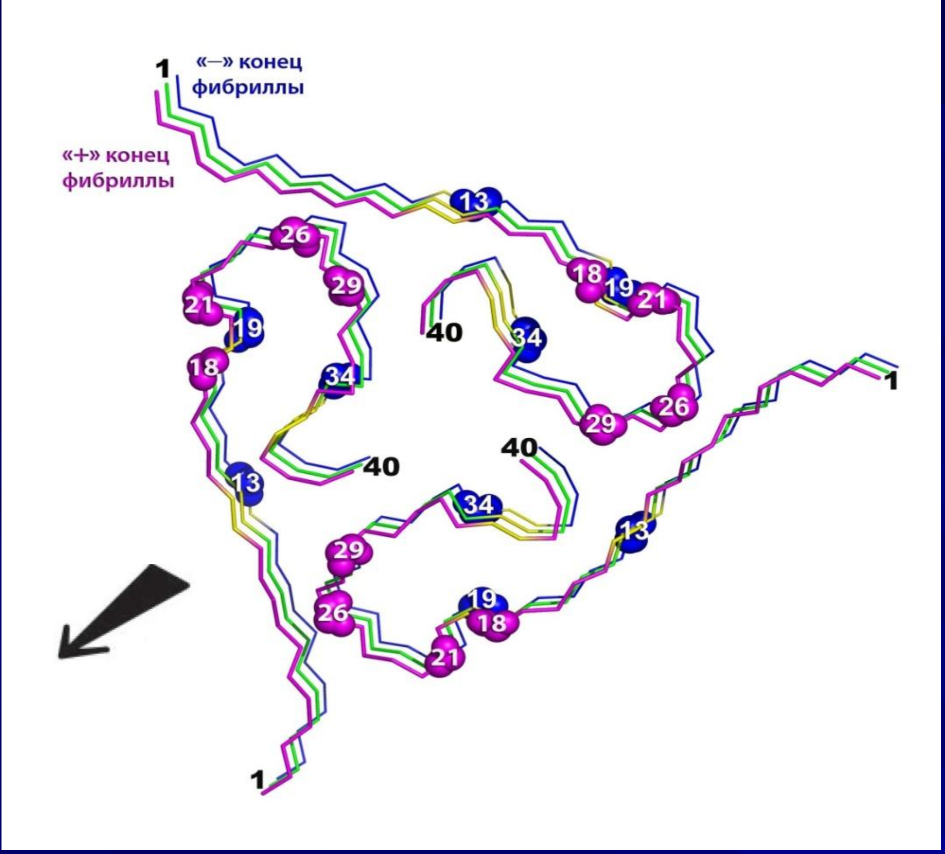
NMR

3D structure of Alzheimer's amyloid-β(1–42) fibrils

T.Lührs, C.Ritter, M.Adrian, D.Riek-Loher, B.Bohrmann, H.Döbeli, D.Schubert, R.Riek. *PNAS* **102**:17342-17347 (2005)

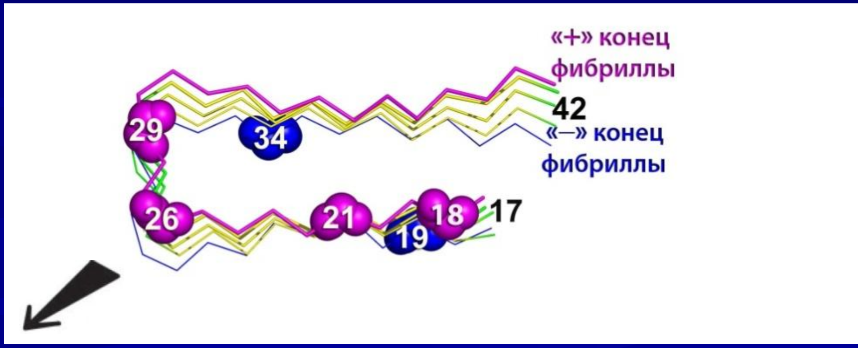
β

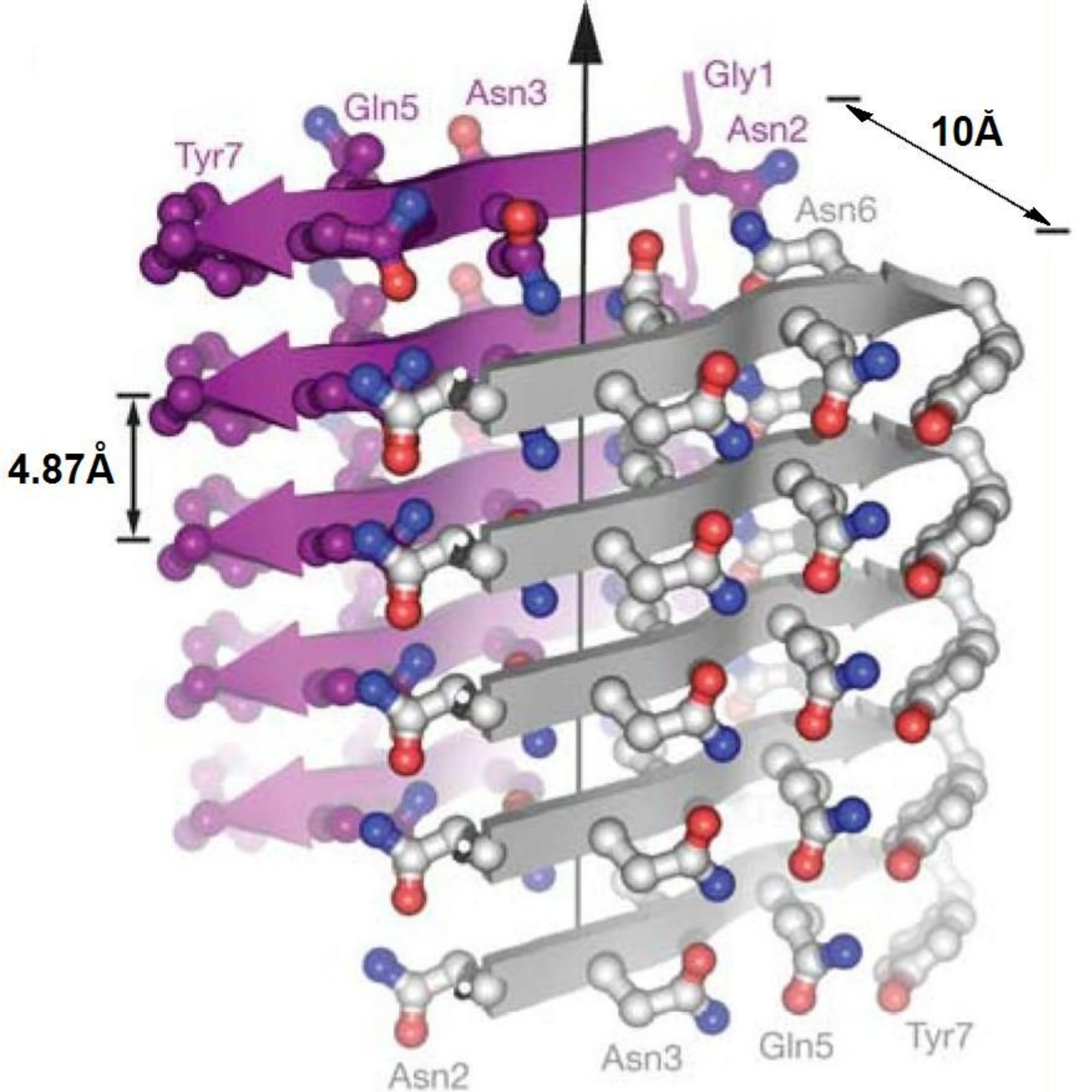
VARIABILITY OF STRUCTURES



Lu J.X., Qiang W., Yau W.M., Schwieters C.D., Meredith S.C., Tycko R.
Molecular structure of β-amyloid fibrils in Alzheimer's disease **brain tissue**.
Cell 154:1257-1268 (2013) .

Lührs T., Ritter C., Adrian M., Riek-Loher D., Bohrmann B., Döbeli H., Schubert D., Riek R.
3D structure of Alzheimer's amyloid-beta(1-42) fibrils.
PNAS 102:17342-17347 (2005) .





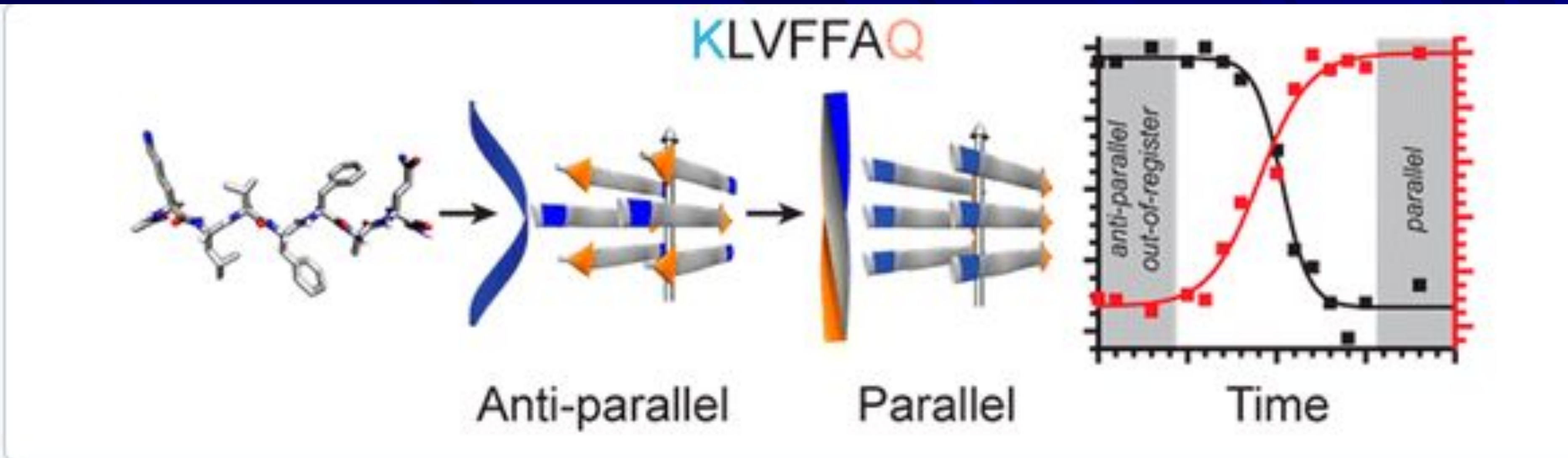
Structure of the cross-β spine of amyloid-like fibrils

R.Nelson, M.R.Sawaya, M.Balbirnie, A.Ø.Madsen, C.Riekel, R.Grothe, D.Eisenberg

Nature **435**:773-778 (2005)

X-RAY

β



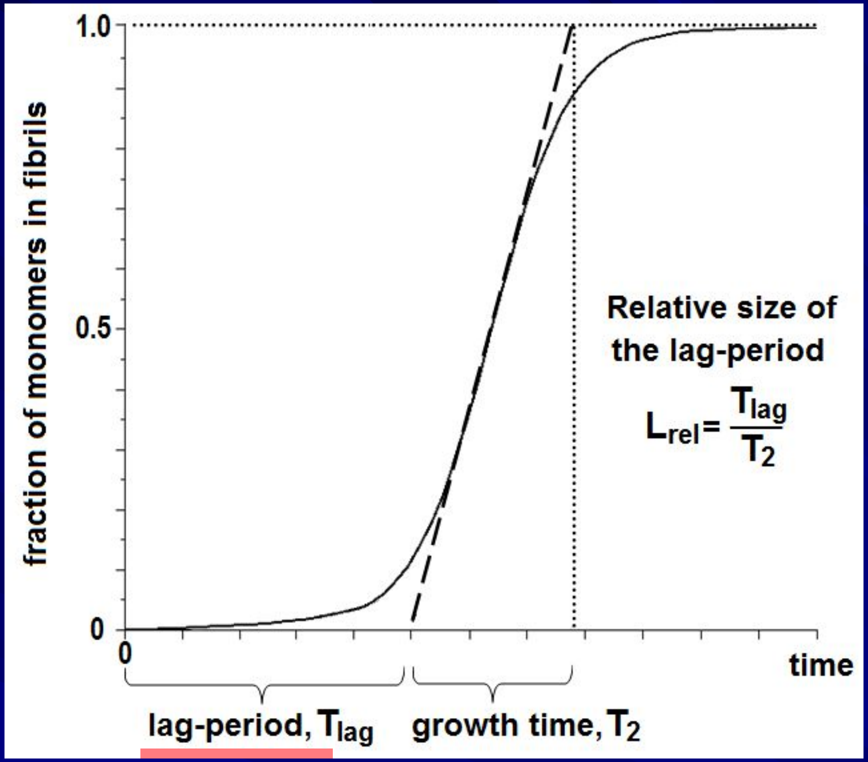
In contrast to an expected Ostwald-like ripening of amyloid assemblies, the nucleating core of the Dutch mutant of the Aβ peptide of Alzheimer's disease assembles through a series of conformational transitions. Structural characterization of the intermediate assemblies by isotope-edited IR and solid-state NMR reveals unexpected strand orientation intermediates and suggests new nucleation mechanisms in a progressive assembly pathway.

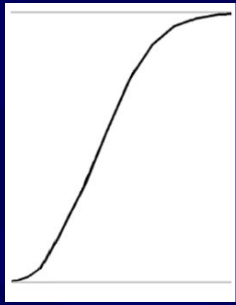
JACS Volume 136, Issue 43 October 29, 2014

Kinetic Intermediates in Amyloid Assembly

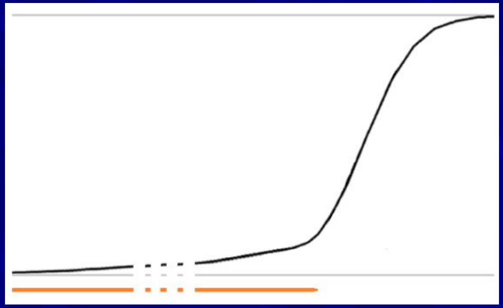
Chen Liang, Rong Ni, Jillian E. Smith, W. Seth Childers, Anil K. Mehta, and David G. Lynn

Growth of amyloids

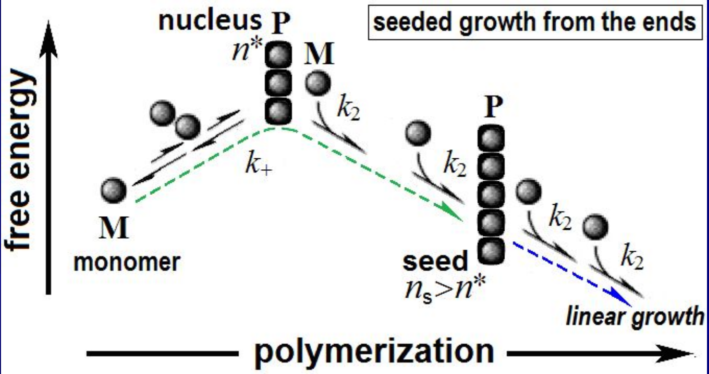




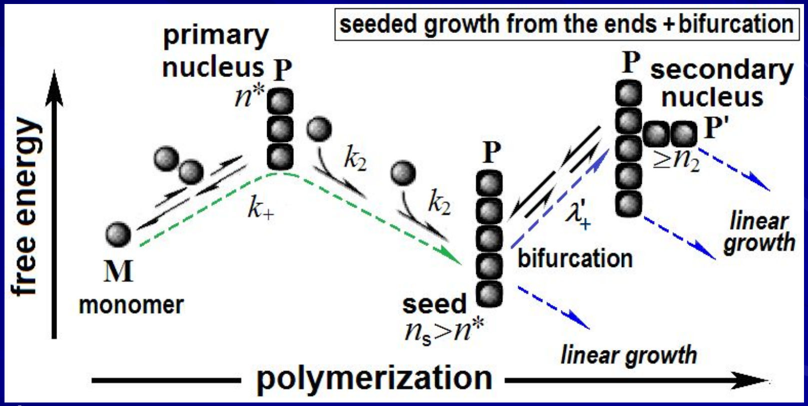
LINEAR GROWTH
NO LAG



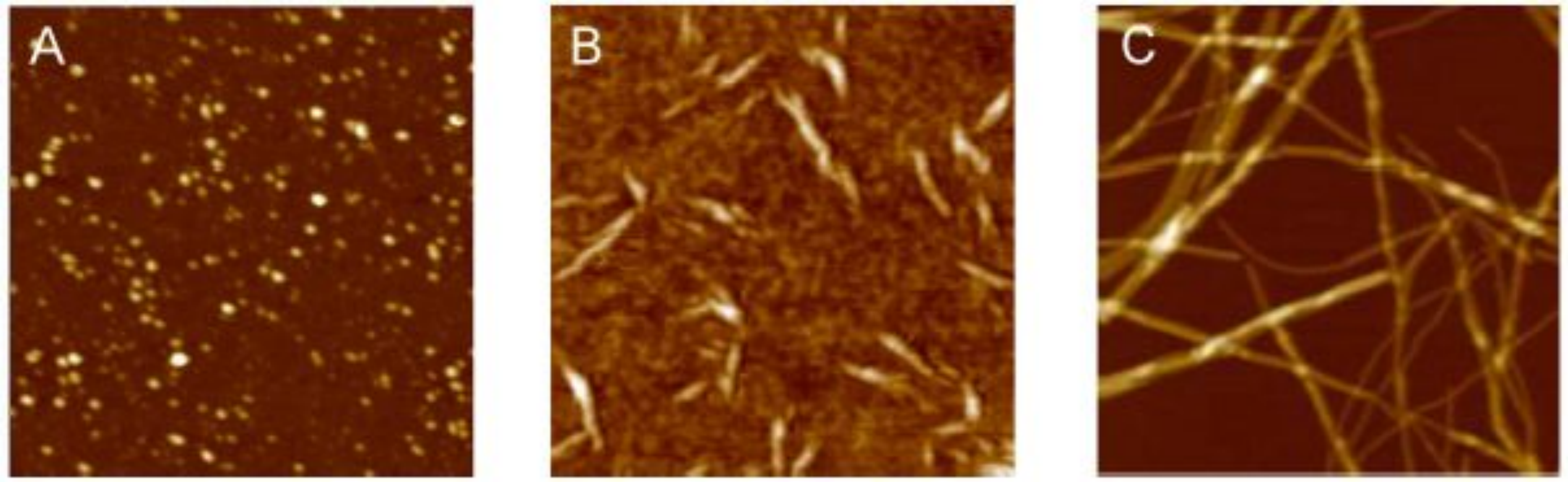
EXPONENTIAL GROWTH
VERY LARGE LAG



Different relative lag-period



Dovidchenko N.V., Finkelstein A.V., Galzitskaya O.V. 2014.
How to determine the size of folding nuclei of protofibrils from the concentration dependence of the rate and lag-time of aggregation. I. Modeling the amyloid photofibril formation.
J. Phys. Chem. B,, 118:1189-1197.



Oligomers Protofibrils Mature amyloid fibrils

Atomic force microscopy

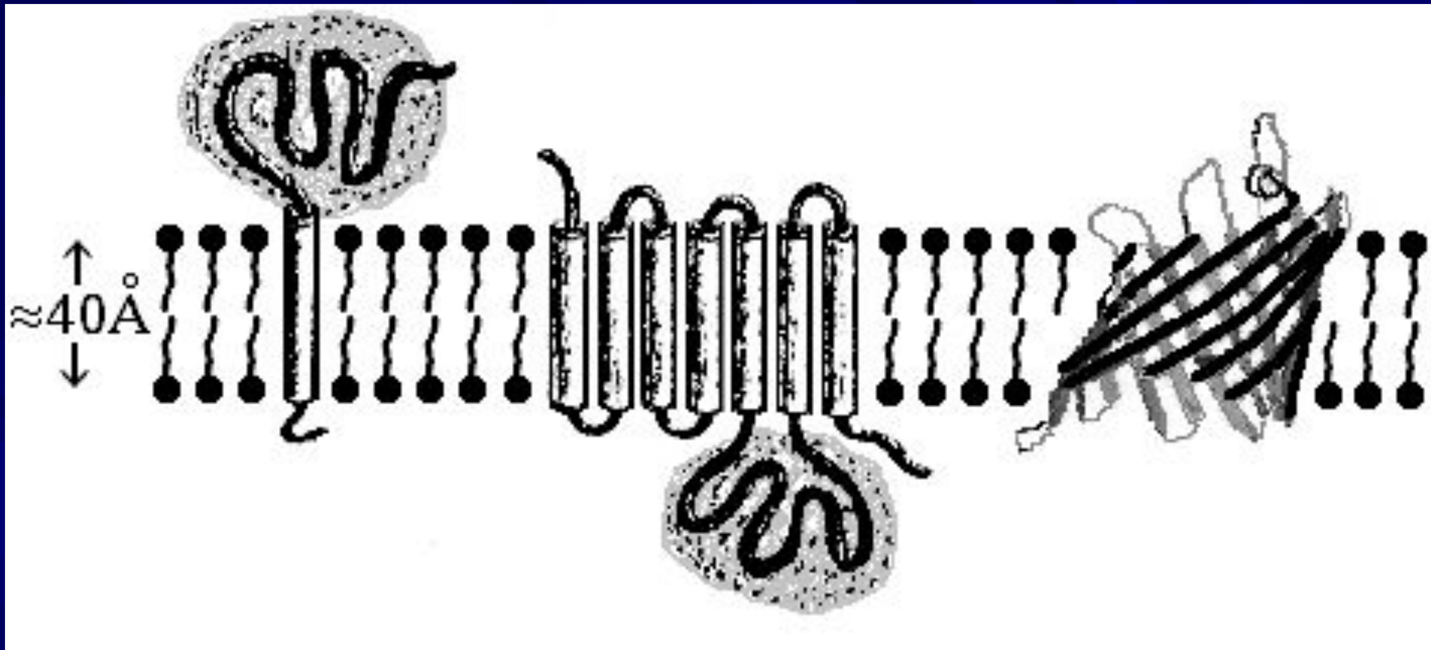
Relini A., Marano N., Gliozzi A. 2014.
Misfolding of amyloidogenic proteins and their interactions with membranes
Biomolecules, 4, 20-55 .

Natively non-structured fibrous proteins:

Elastin:

Matrix protein.
Short repeats.
Poor secondary structure.
Chains are linked by chemically modified Lys residues.
Like in rubber.

Membrane proteins: transmitters

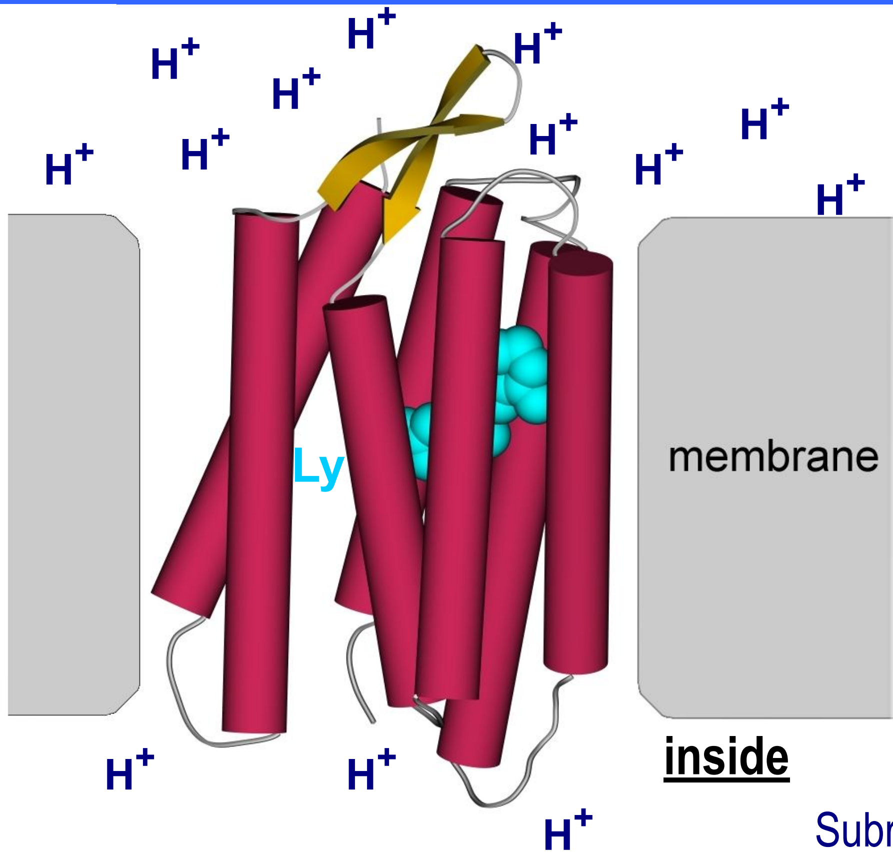


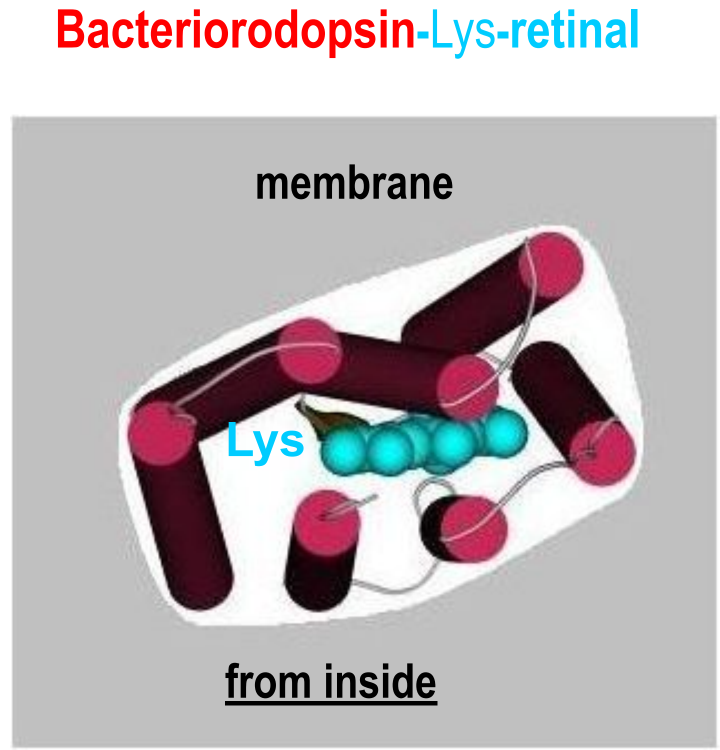
heads (polar)
tails
tails
heads (polar)

H-bonds & hydrophobics

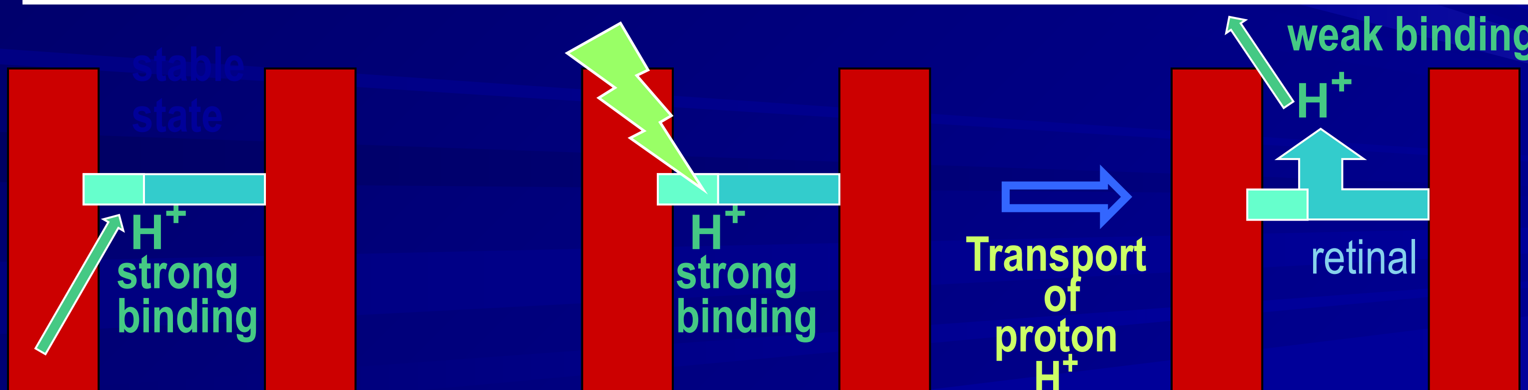
PROTEINS	SEQUENCES	
Globular	○○●○○●●○○○●○●●○●○○○●○○○●●○●○○●○●○○○●●○●○○○○○○●○○○○●	*quasi-random*
Membrane	●●●●●●●●●●●○○●○○○●○○○○○●●●●●○●●●●●○○○○●●○○○○●○●○ | Hydro- phobic ‖ Hydro- philic |	*blocks*
Fibrous	●○○●○○○●○○○●○○○●○○○●○○○●○○●○○○●○○●○○○●○○●○○○●○○● | repeat |	*repeats*

Bacteriorodopsin (α) with retinal:
the simplest transporter machine with a light-induced conformational change

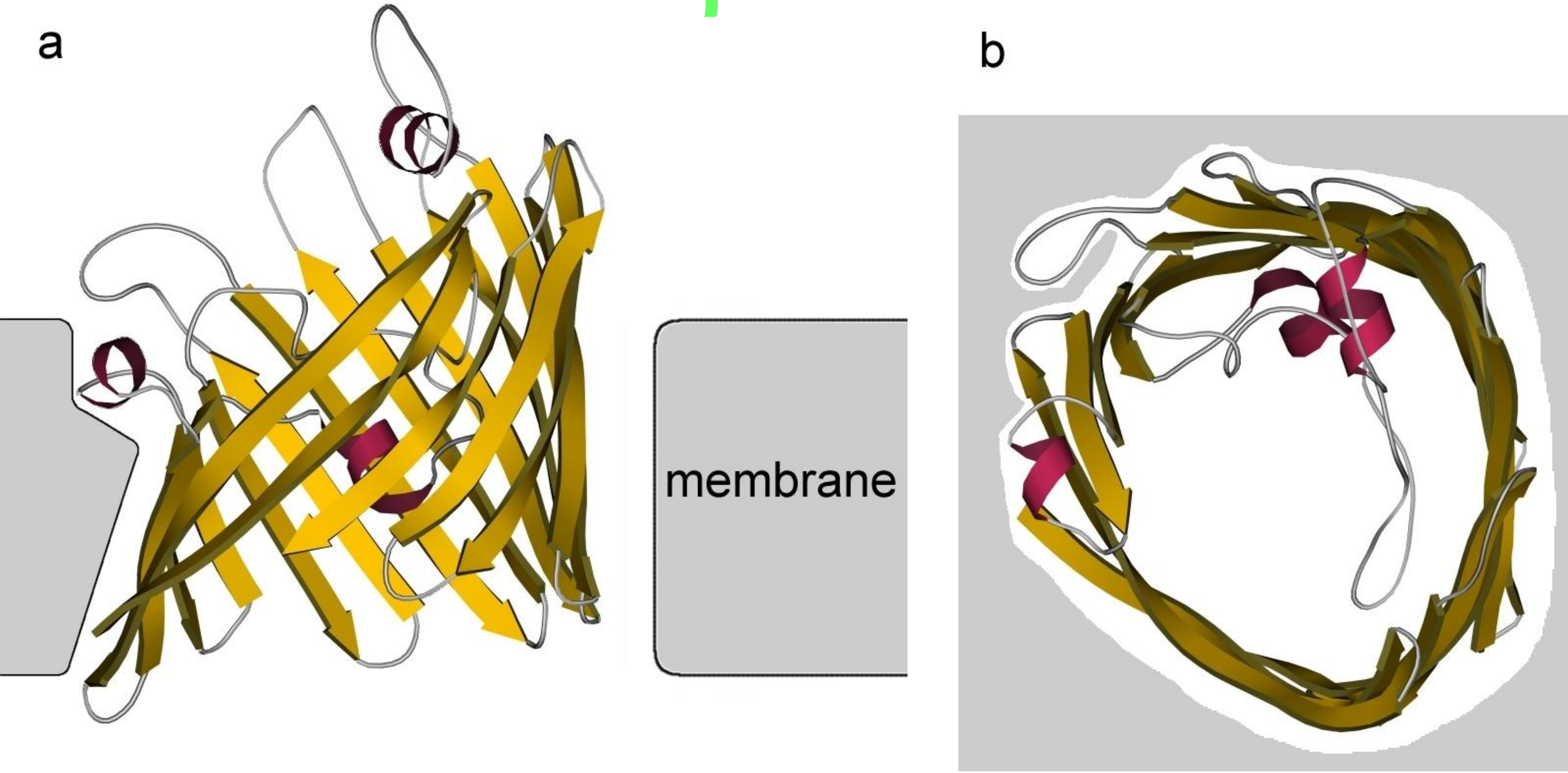




Subramaniam & Henderson, Nature 406, 653 (2000)



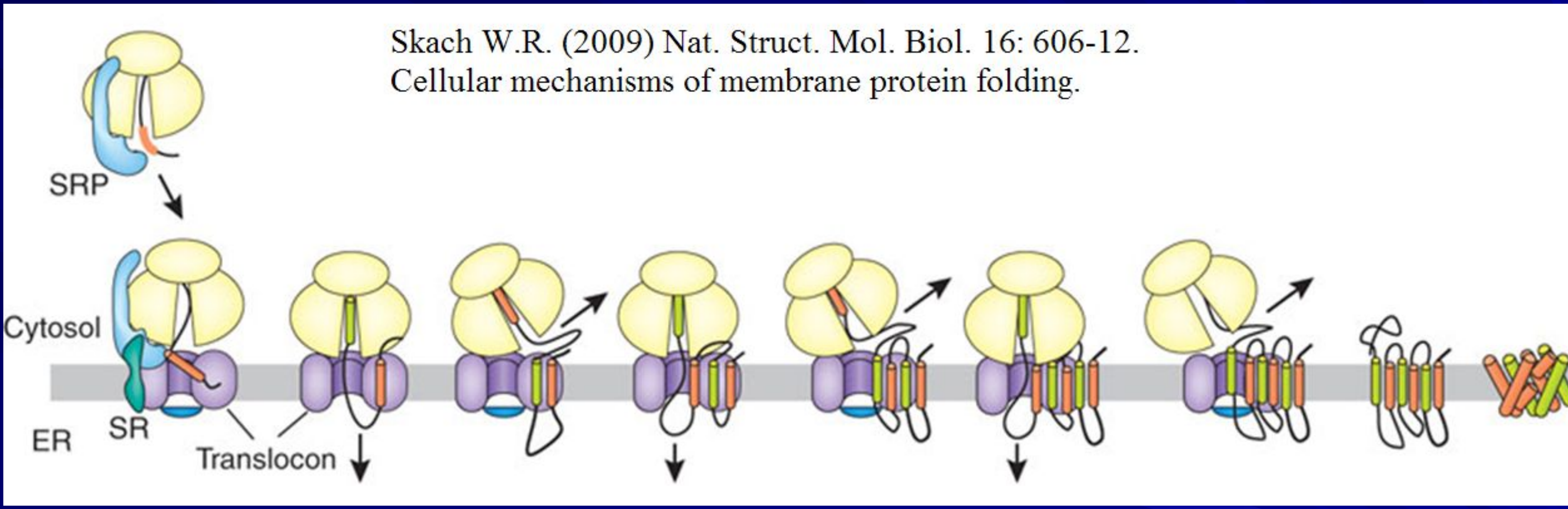
β



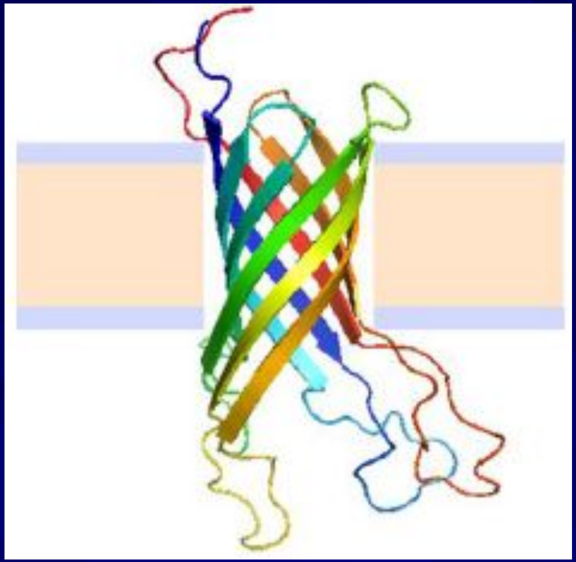
Porin

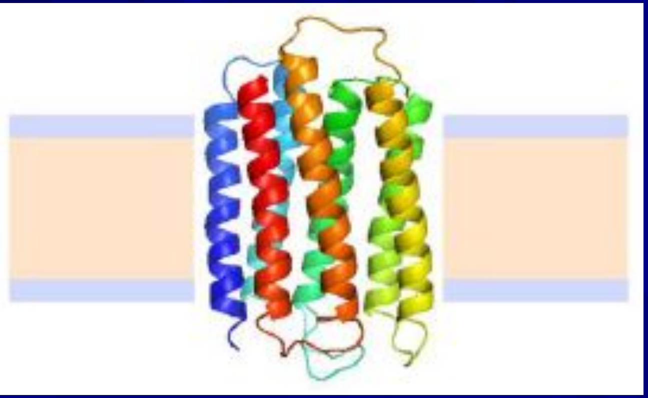
Transport of polar molecules

Membrane protein *in vivo*:
Folding is assisted by “directing factors” - chaperones



MANY OF **SIMPLE** MEMBRANE PROTEINS REFOLD ***IN VITRO*** IN THE PRESENCE OF PHOSPHOLIPID VESICLES OR SURFACTANT MICELLES

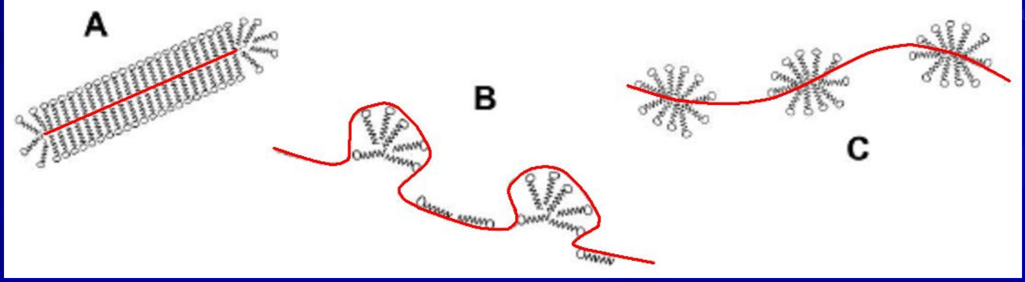


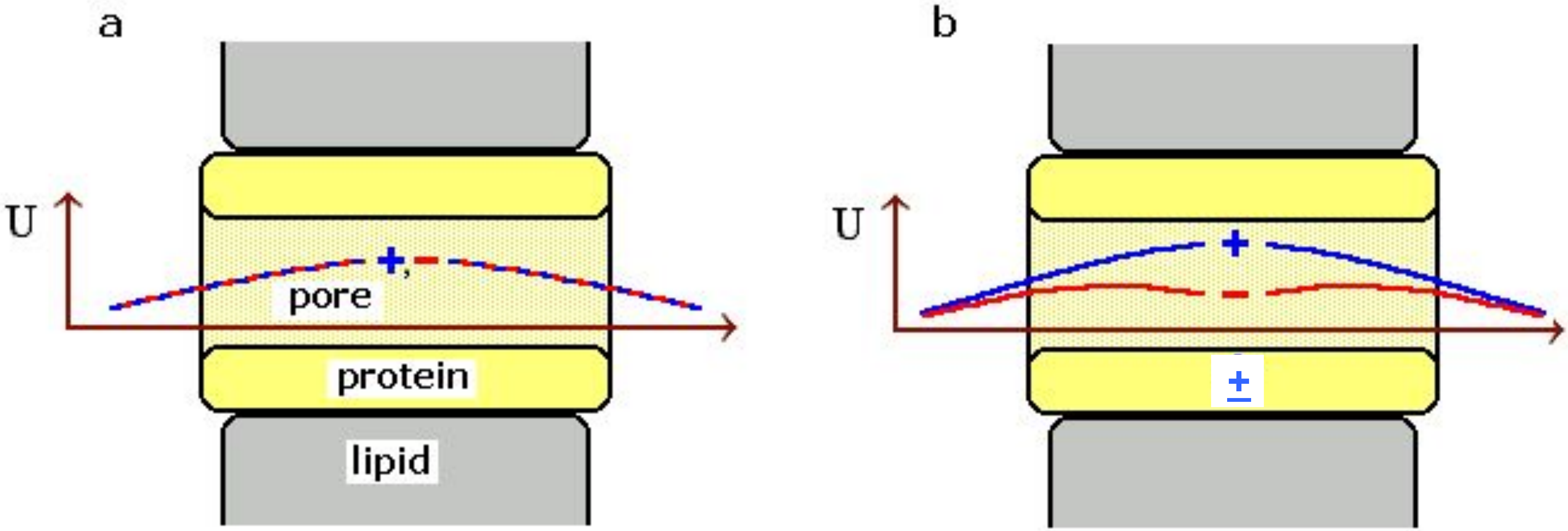


COLLAPSED STATE: MIX OF COIL, α, β
⇓
ASSOSIATES WITH **LIPID VESICLES**, β
⇓
DEEPER PENETRATION INTO LIPIDS
⇓
FULLY FOLDED

INDEPENDENT α-HELICES
⇓
ASSEMBLE IN LIPID TO FULLY FOLDED

DIFFICULT TO STUDY:
DENATURED STATES OF MEMBRANE PROTEINS ARE **DIVERSE & COMPLICATED**





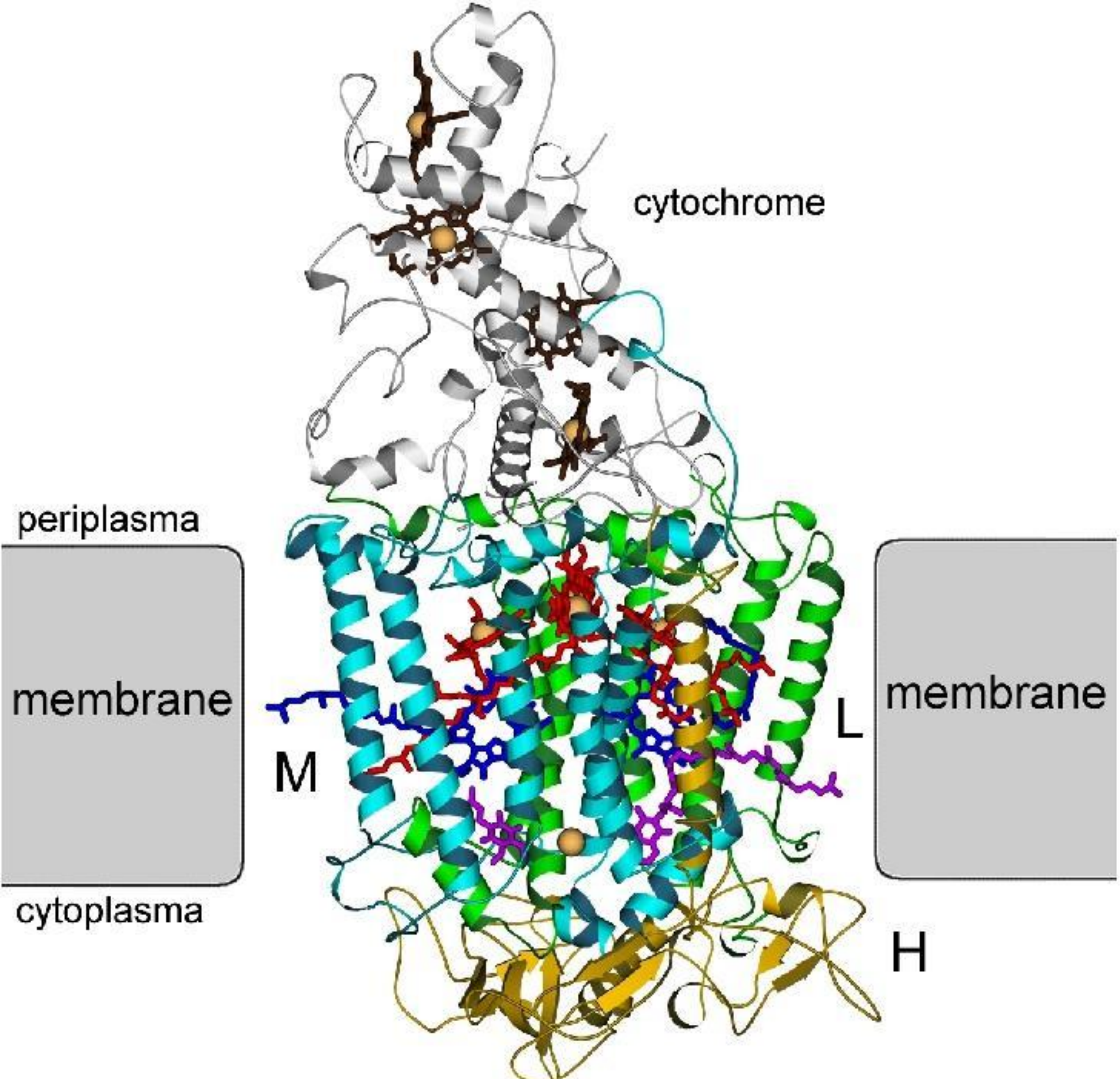
Pore in membrane: SELECTIVITY

Free energy of a charge in the non-charged non-polar pore:

$$\sim q^2 / [(\varepsilon_{MEMBR}\ \varepsilon_{WATER})^{1/2}\ r_{PORE}] \sim$$

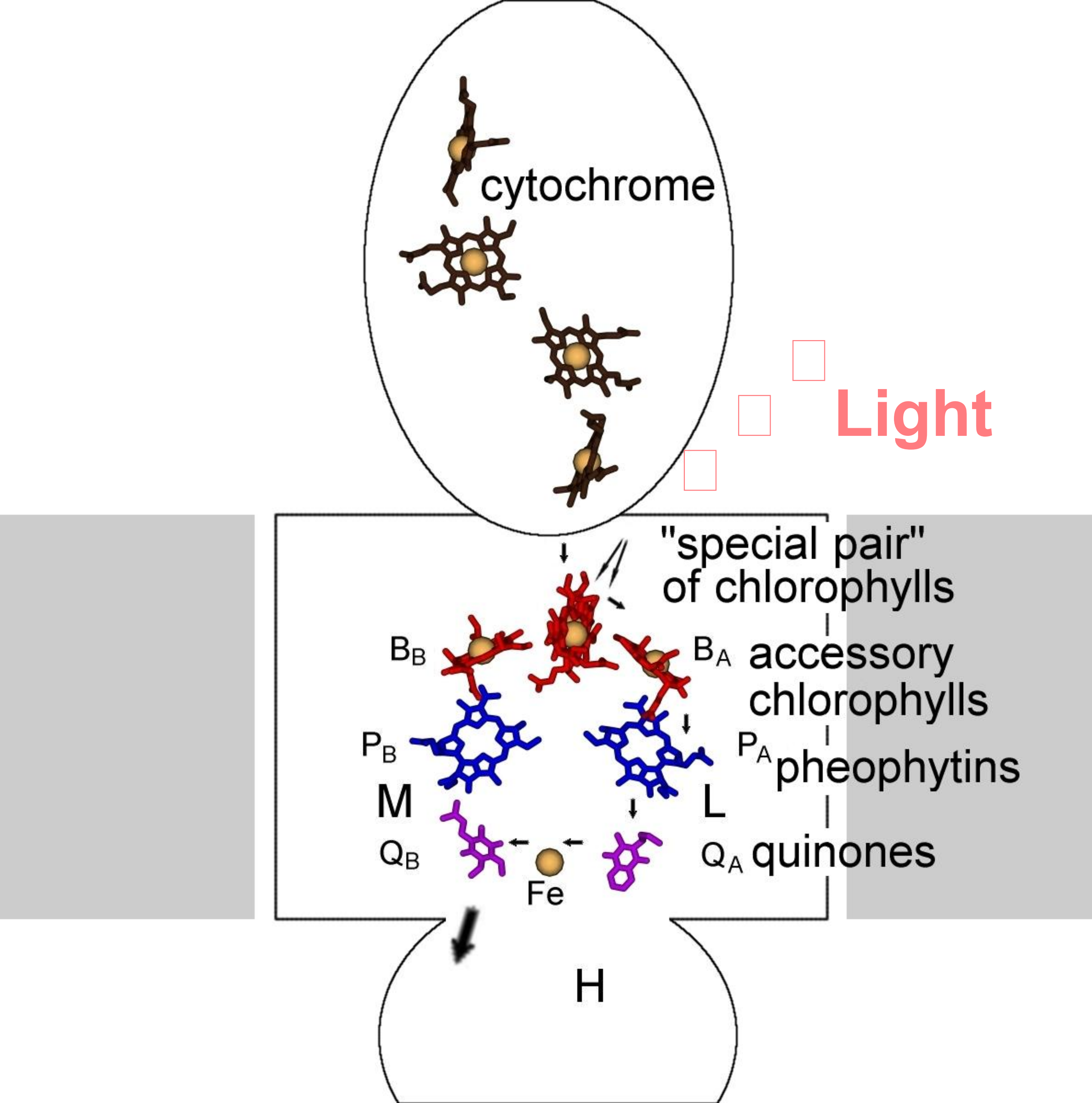
$$\sim 20\ \text{kcal/mol} / r_{PORE}(\text{Å})$$

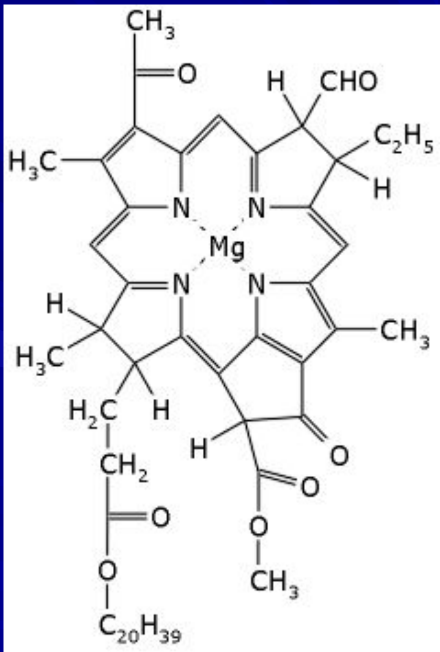
Photo-synthetic center



Robert **Huber**, 1937.
Nobel prize 1988

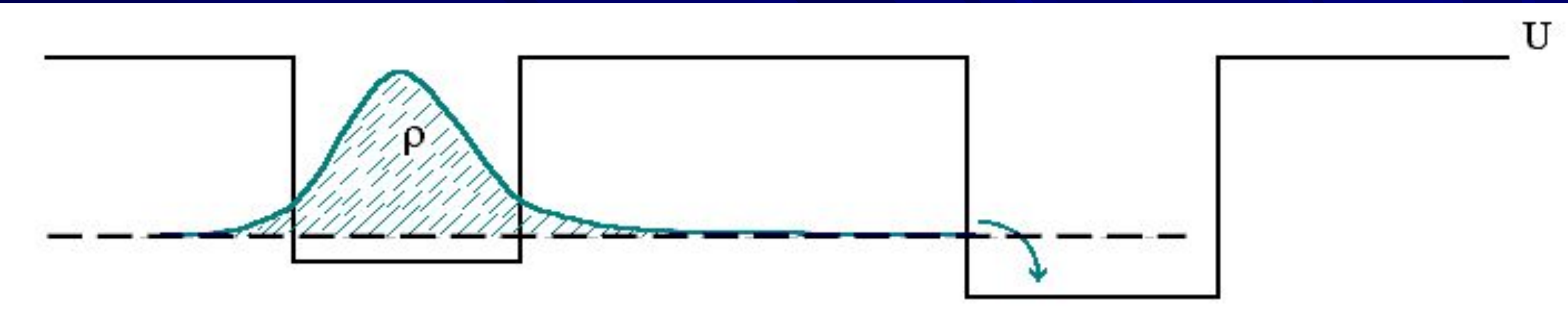
Pigments in photo-synthetic center: Electron transfer





chlorophyll

Tunneling



Atom ≈ 1Å ⇒ Attenuation of electron density: $P(X) \sim 10^{-X(Å)}$

T-independent

Frequency of vibrations (attacks): $f \sim 10^{15}$/sec

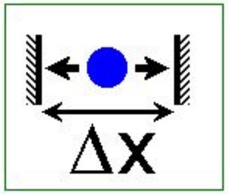
Successful attacks: $f_{succs.}(x) \sim P(x) \cdot f$, e.g.:

$f_{succs.}(5Å) \sim 10^{-5+15} \sim$

$\sim 10^{10}$/sec

Heisenberg's uncertainty:

$$\Delta(mv) \cdot \Delta x \cong \hbar \quad \textit{Planck's const}$$



V = ±|V|

Energy of localization in Δx:

$$E = mv^2/2 \sim (\hbar^2/m)/(\Delta x^2)$$

DELOCALIZATION LEADS TO MORE STABLE STATE OF e