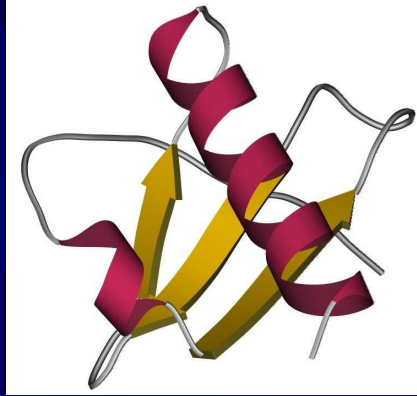


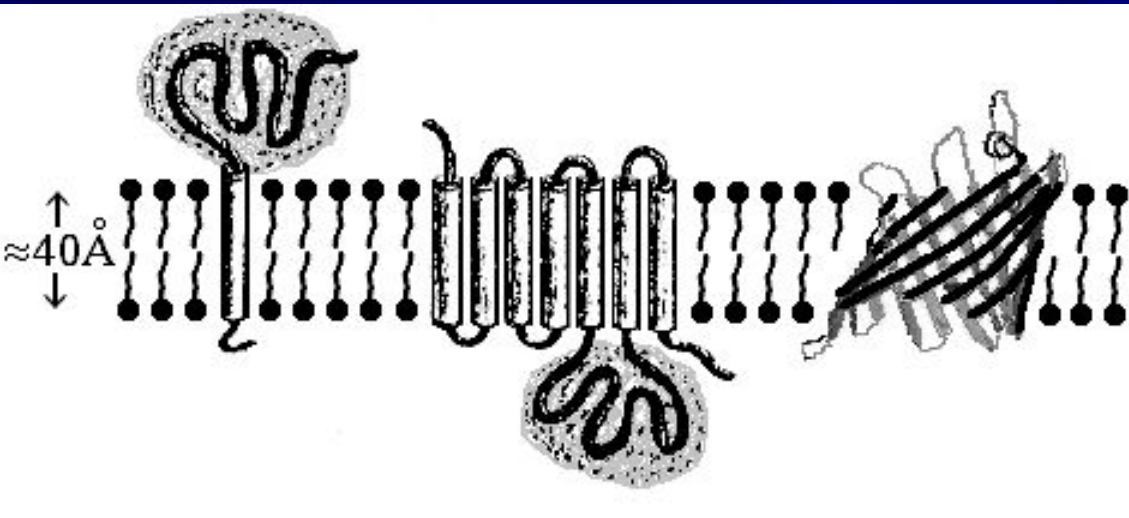
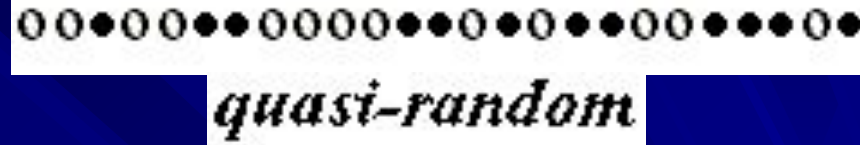
# PROTEIN PHYSICS

## LECTURES 11-12

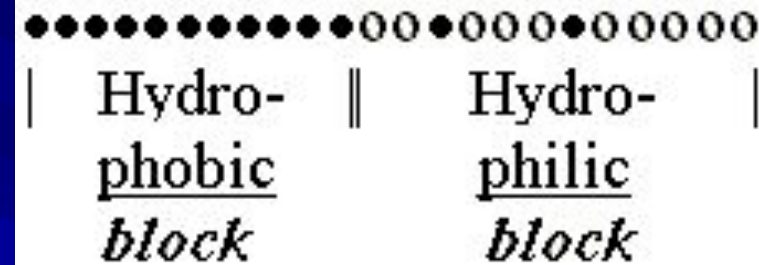
- Fibrous proteins and their functions
- Membrane proteins and their functions
  
- Fibrous proteins: building blocks
- Membrane proteins: transmitters



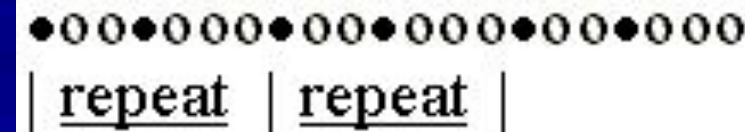
# Globular proteins



# Membrane proteins



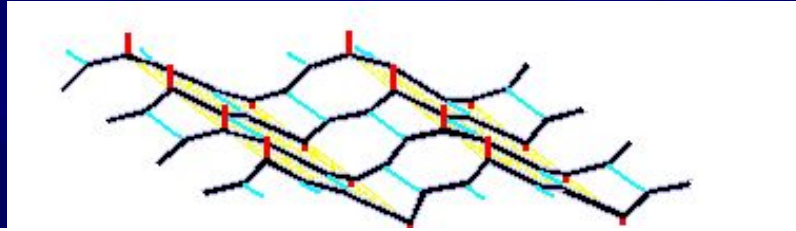
# Fibrous proteins



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

# Fibrous proteins: regular building blocks

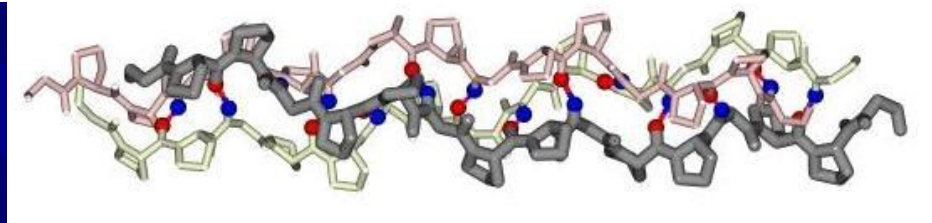
$\beta$



$\alpha$

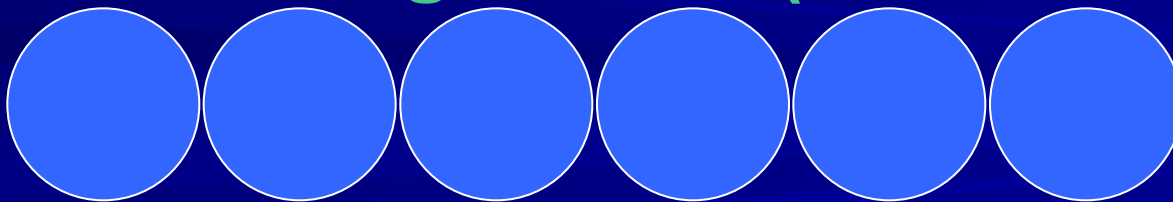


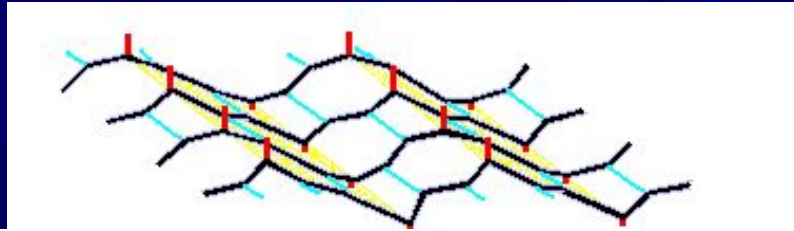
collagen



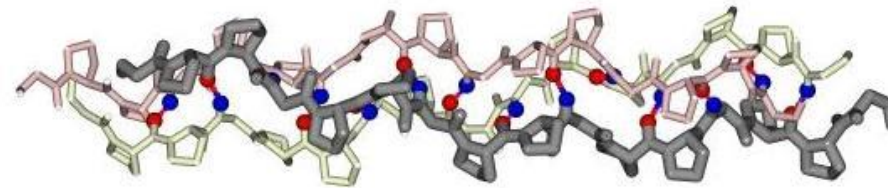
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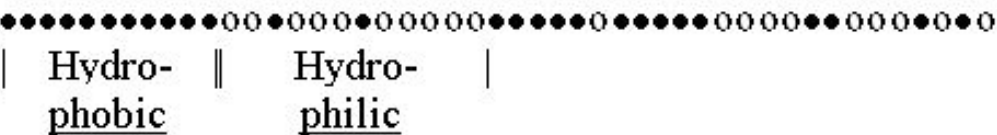
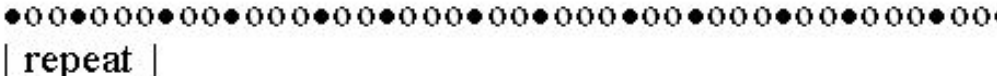
Here, we will not consider fibrous proteins  
made of globules (actin, etc.)



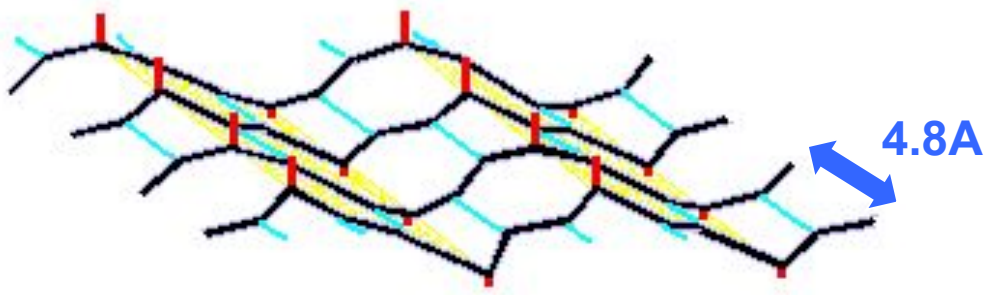
$\beta$  $\alpha$ 

# collagen



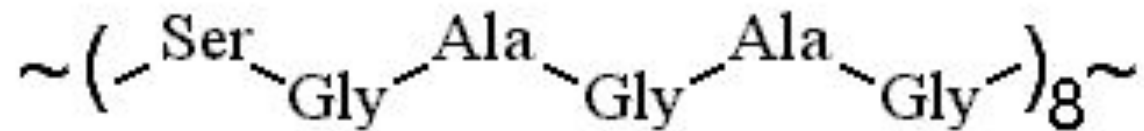
PROTEINS	SEQUENCES	
<u>Globular</u>		<i>quasi-random</i>
<u>Membrane</u>		<i>blocks</i>
<u>Fibrous</u>		<i>repeats</i>



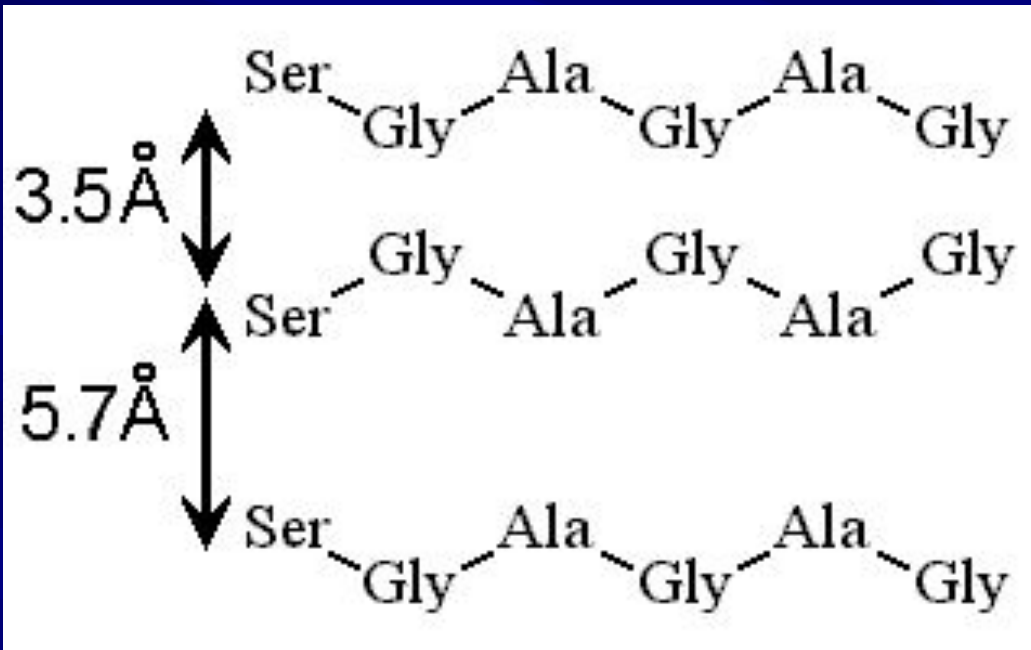


$\beta$

Silk fibroin



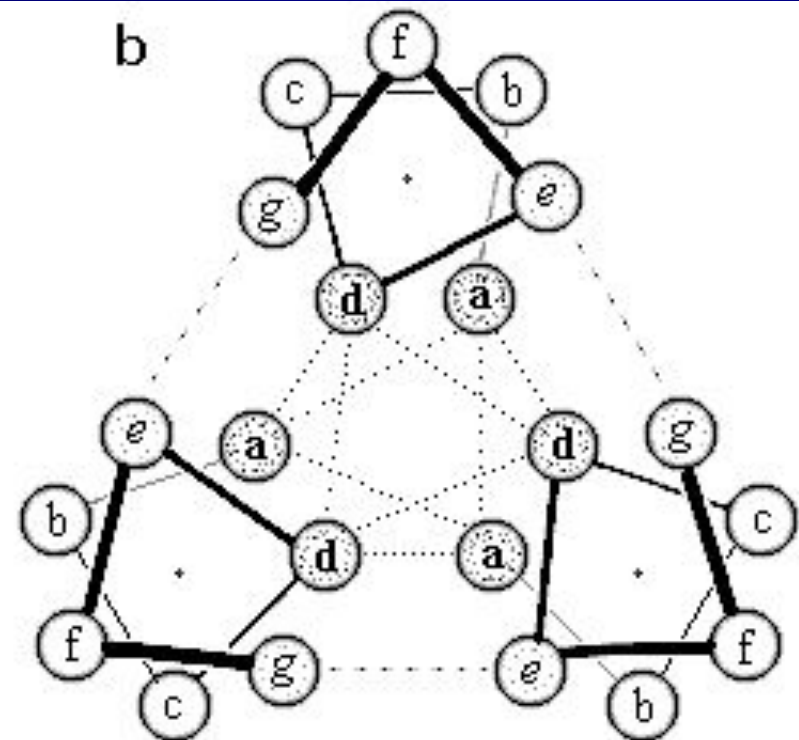
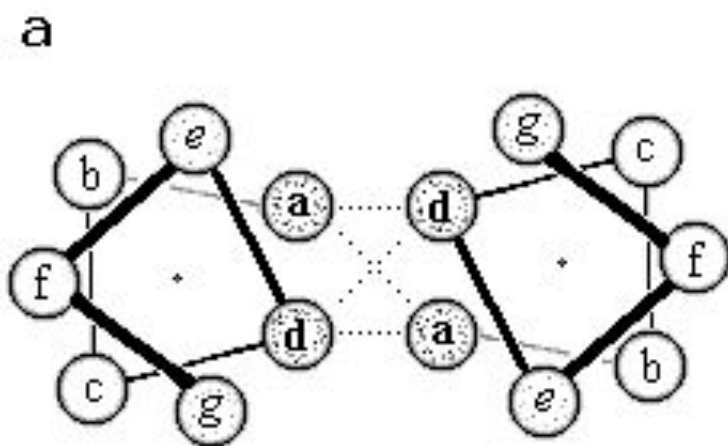
$\times \sim 50$

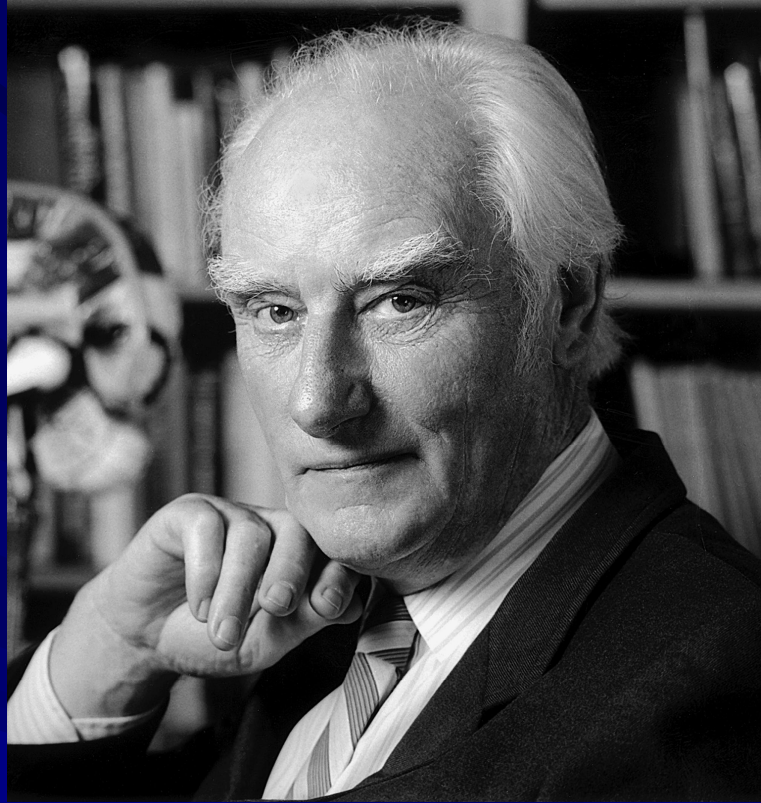




# $\alpha$ -helical coiled- coil

$\dots - \mathbf{a} - \mathbf{b} - \mathbf{c} - \mathbf{d} - e - \mathbf{f} - g - \mathbf{a} - \mathbf{b} - \mathbf{c} - \mathbf{d} - e - \mathbf{f} - g - \mathbf{a} - \mathbf{b} - \mathbf{c} - \mathbf{d} - e - \mathbf{f} - g - \dots$   
 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21





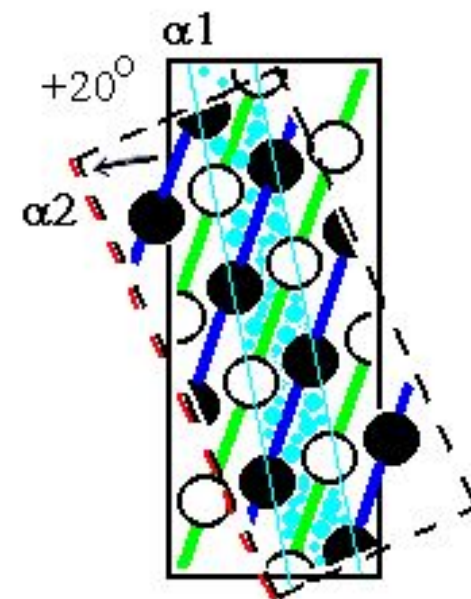
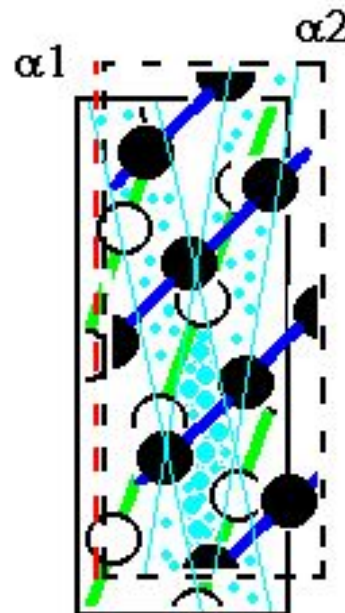
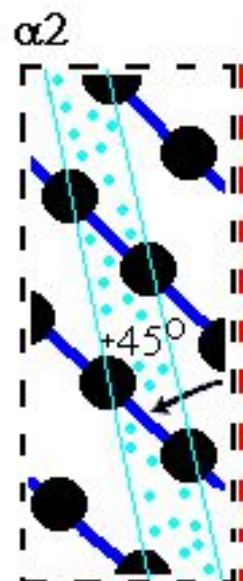
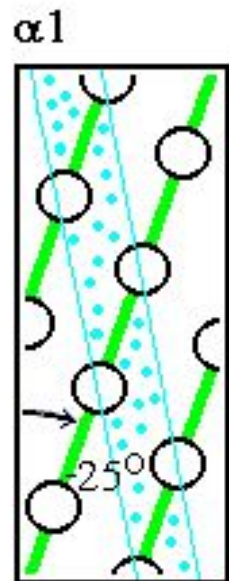
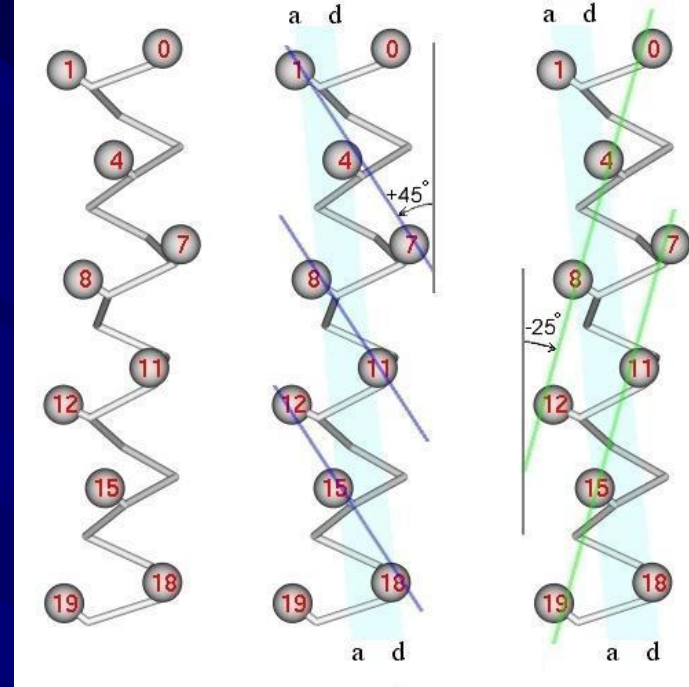
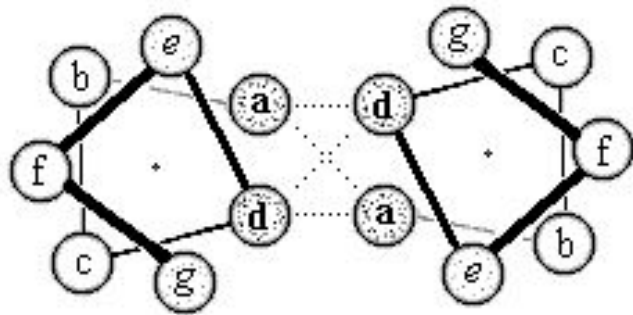
Francis Harry Compton **Crick** (1916 – 2004)  
Nobel Prize 1962  
for **DNA structure, 1953**

**Coiled coil structure:** F. **Crick**, 1952

**C. Chothia, M. Levitt, D. Richardson**, 1977

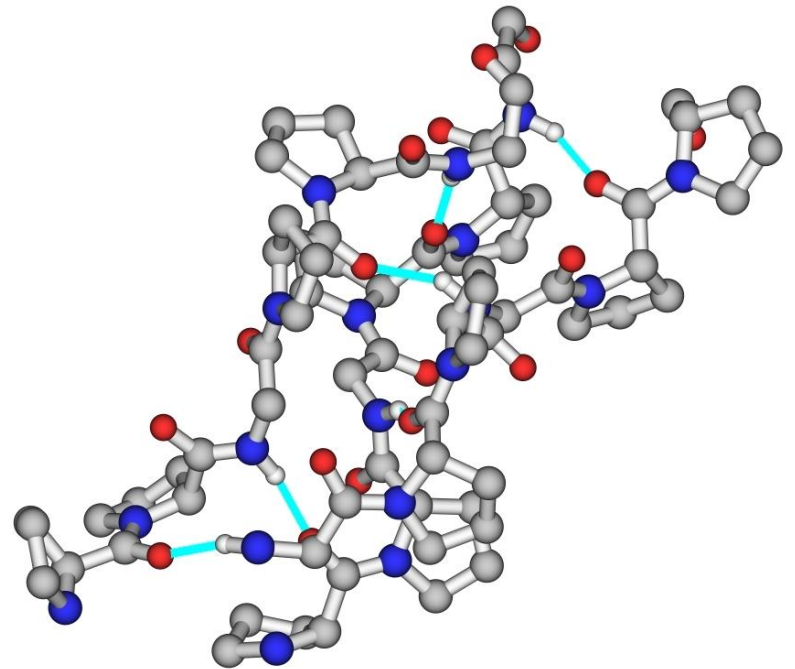
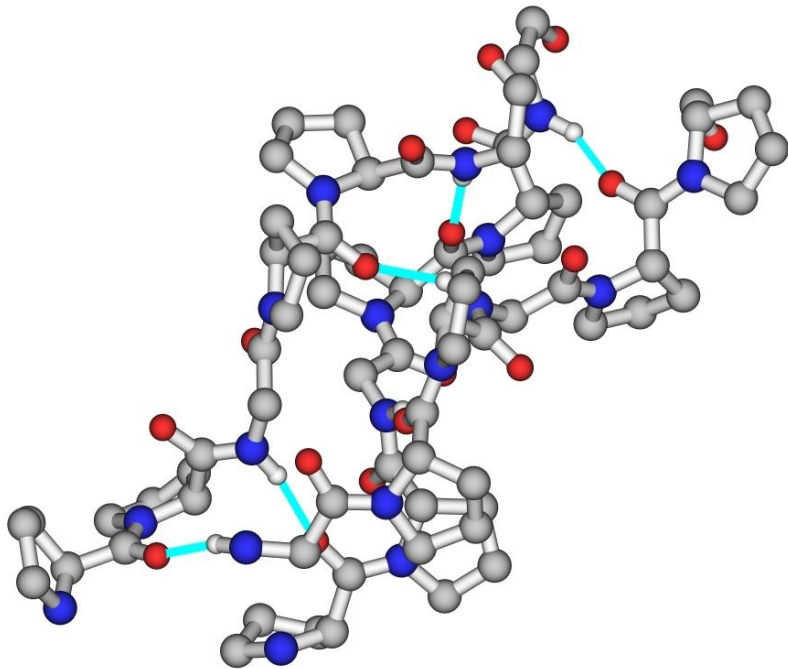
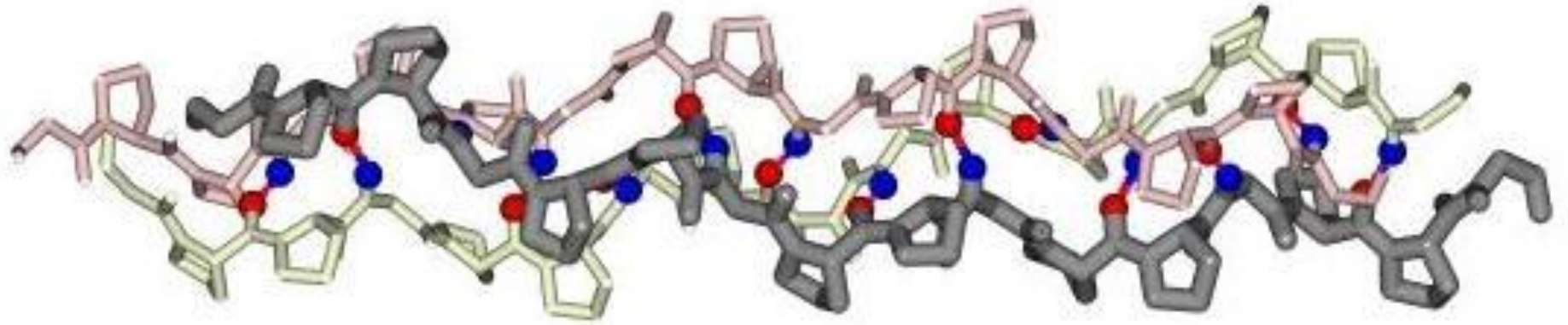


# $\alpha$ -helix packing

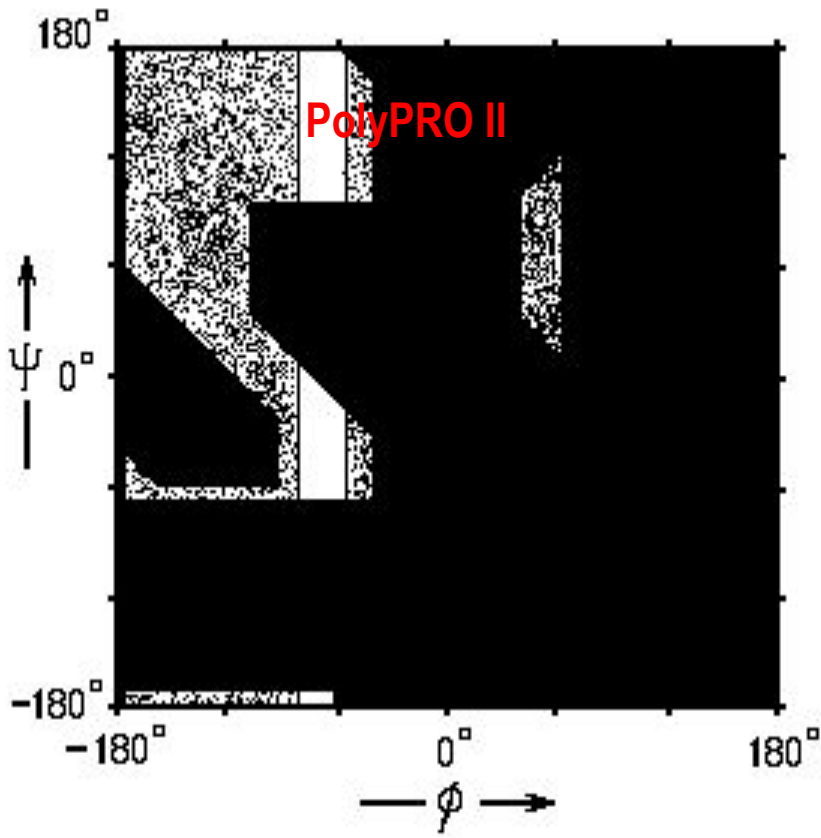
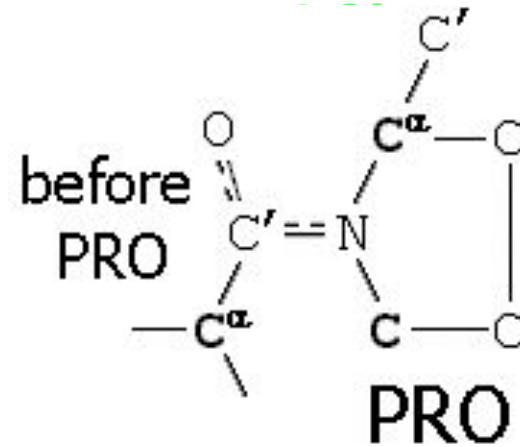




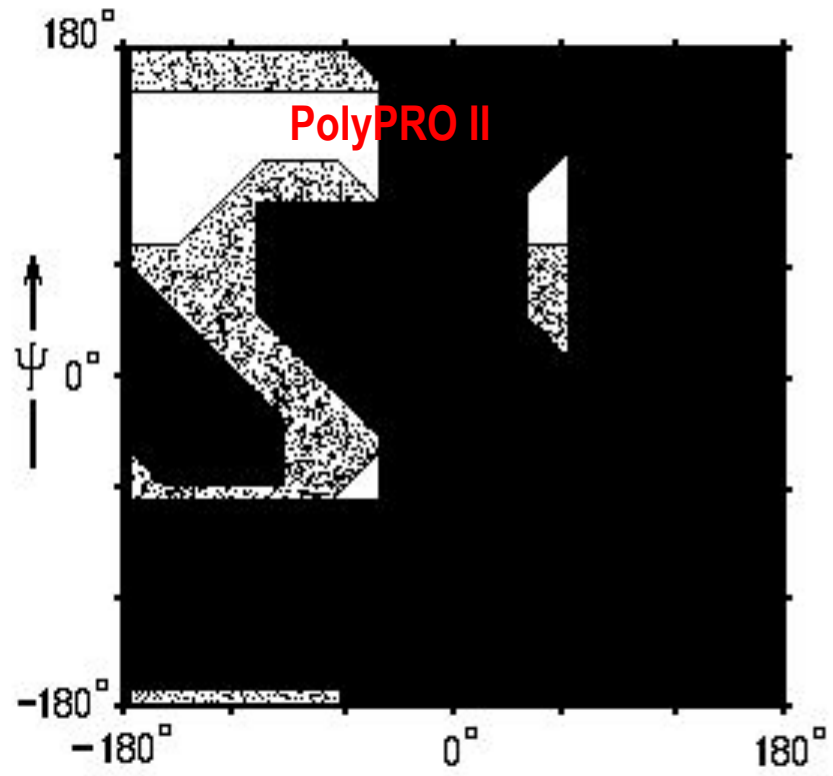
collagen triple helix: 3 chains  $\approx$  [Gly-X-Pro]<sub>~500</sub>



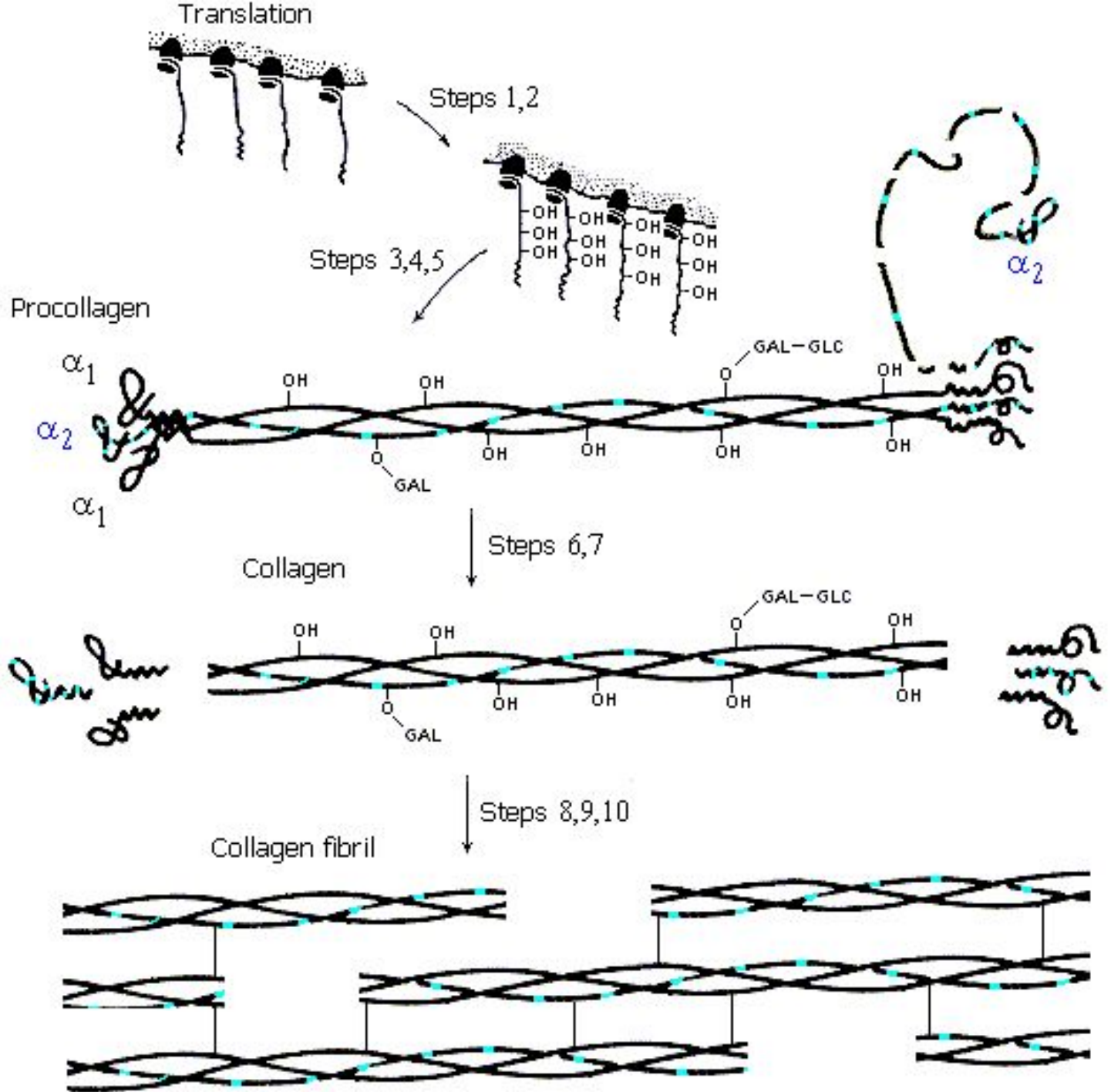
PRO ( $\phi =$



Before PRO



# Collagen: assisted folding

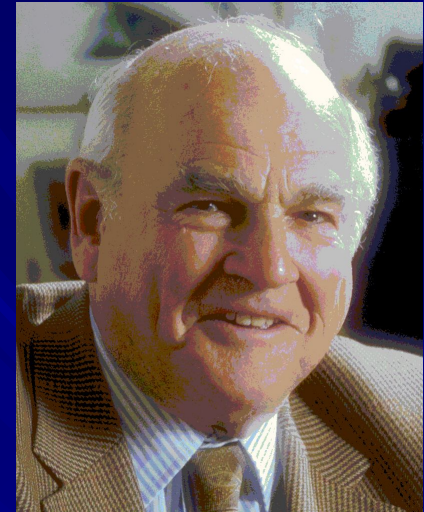






Kuru: a mysterious disease, later demonstrated to be infectious prion disease.

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



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

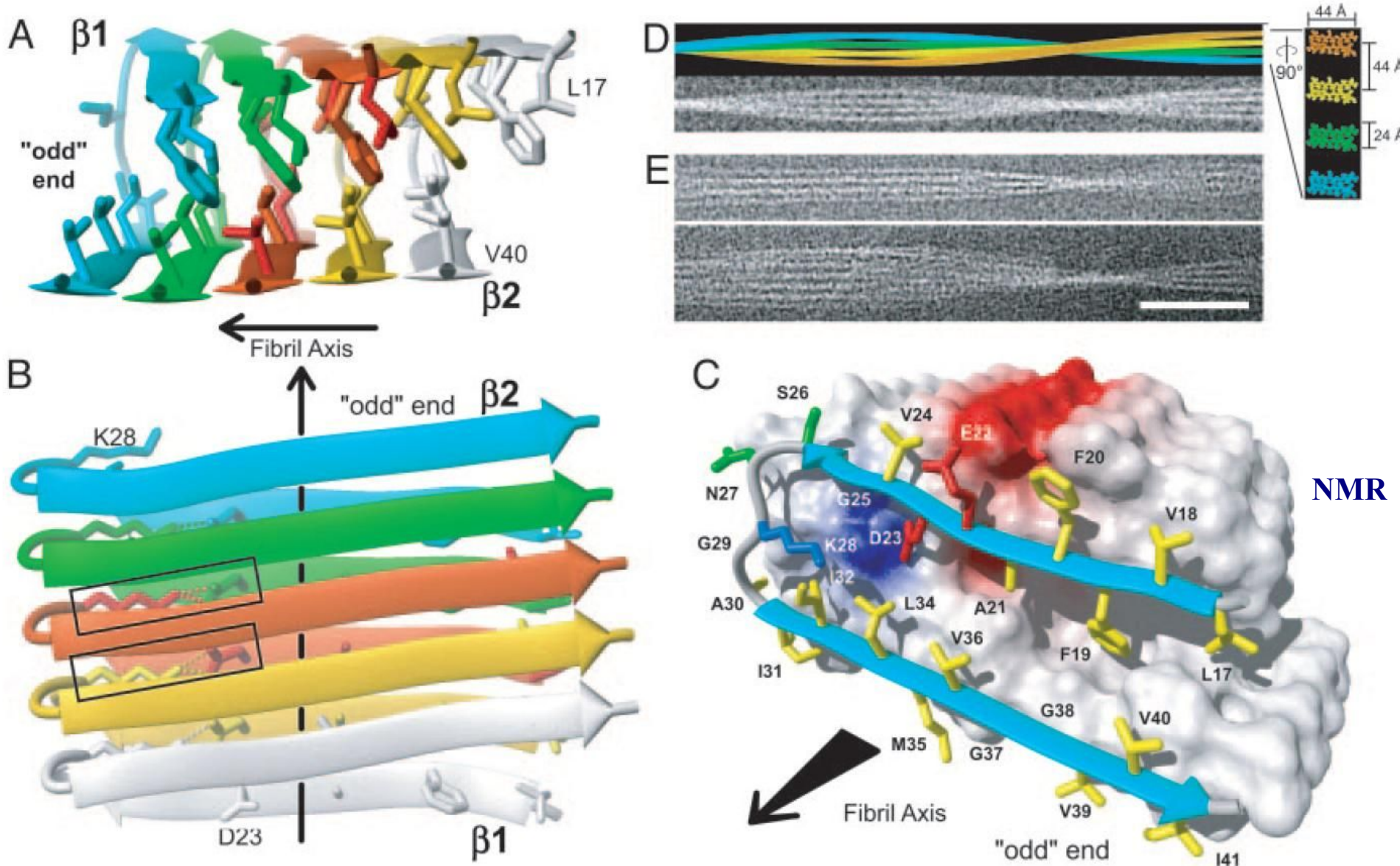
Stanley Benjamin **Prusiner**, 1942  
Nobel Prize 1997



Studies of amyloid formation

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



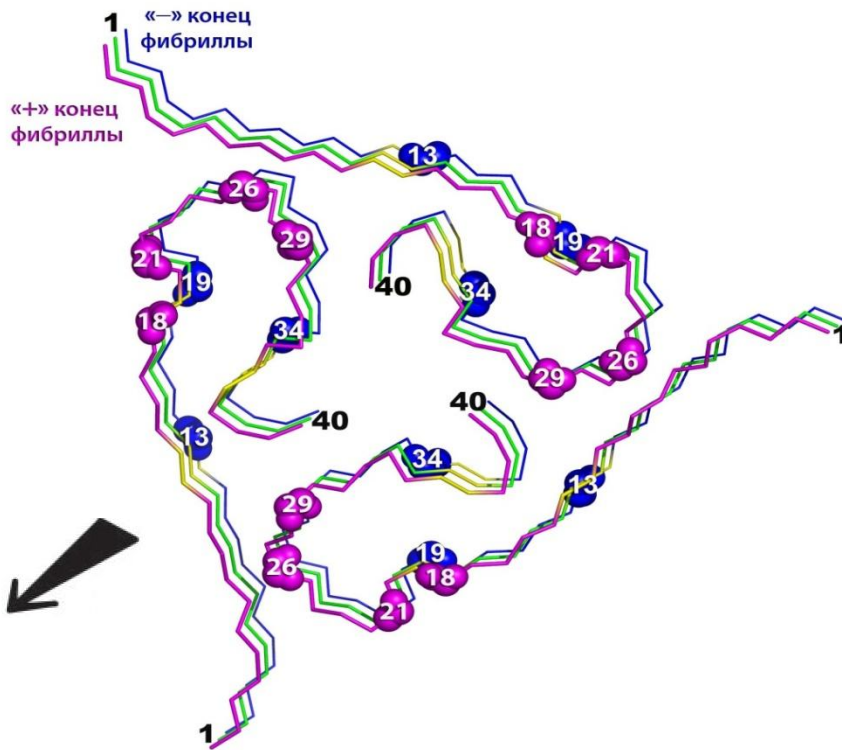


## 3D structure of Alzheimer's amyloid- $\beta$ (1–42) fibrils

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

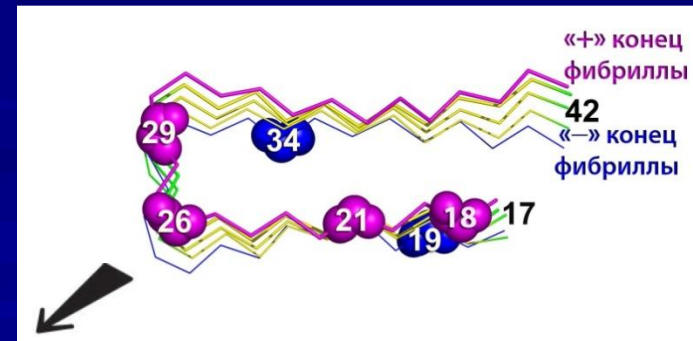


# VARIABILITY OF STRUCTURES

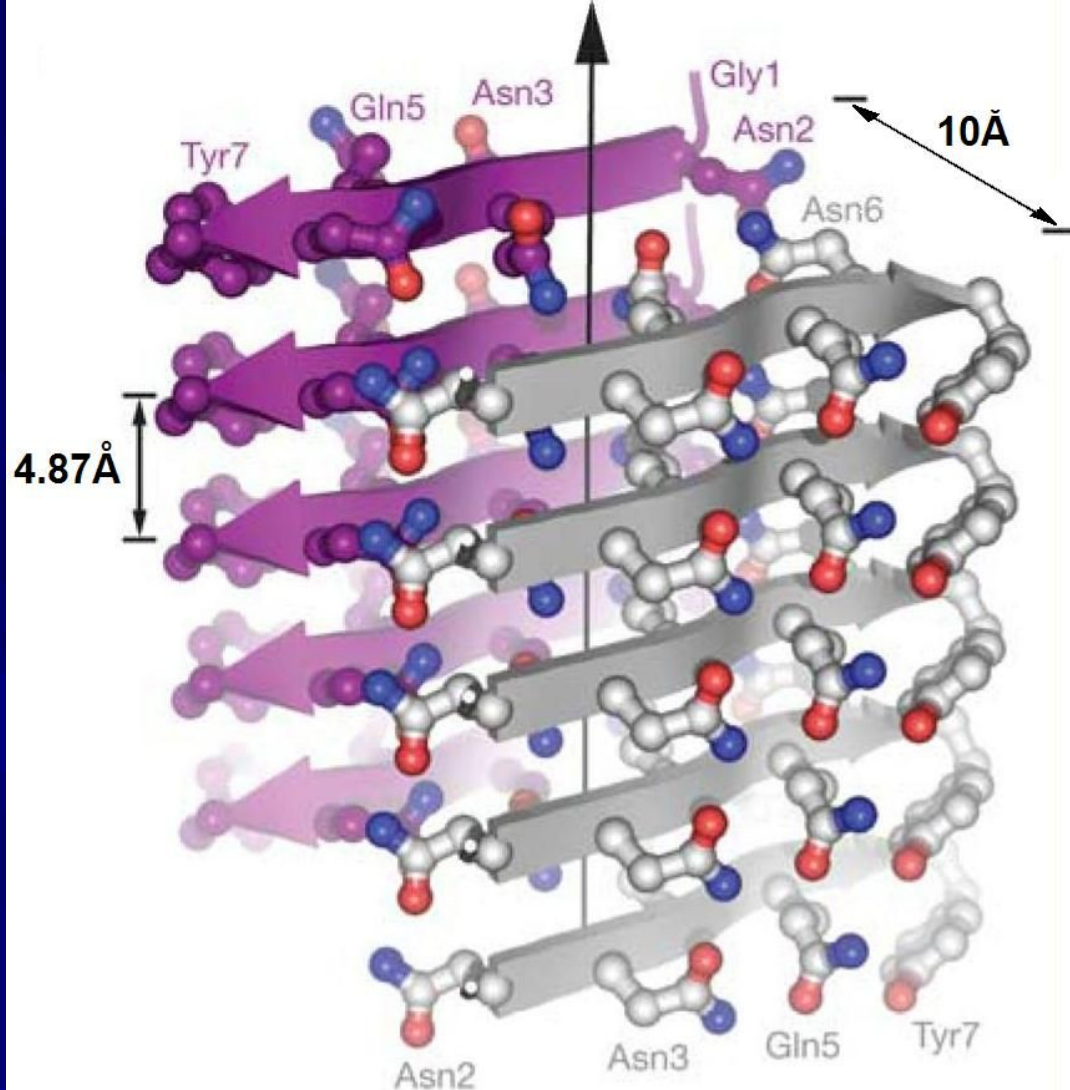


Lu J.X., Qiang W., Yau W.M., Schwieters C.D., Meredith S.C., Tycko R.  
Molecular structure of  $\beta$ -amyloid fibrils in Alzheimer's disease **brain tissue**.  
Cell 154:1257-1268 (2013) .

Lühns 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) .



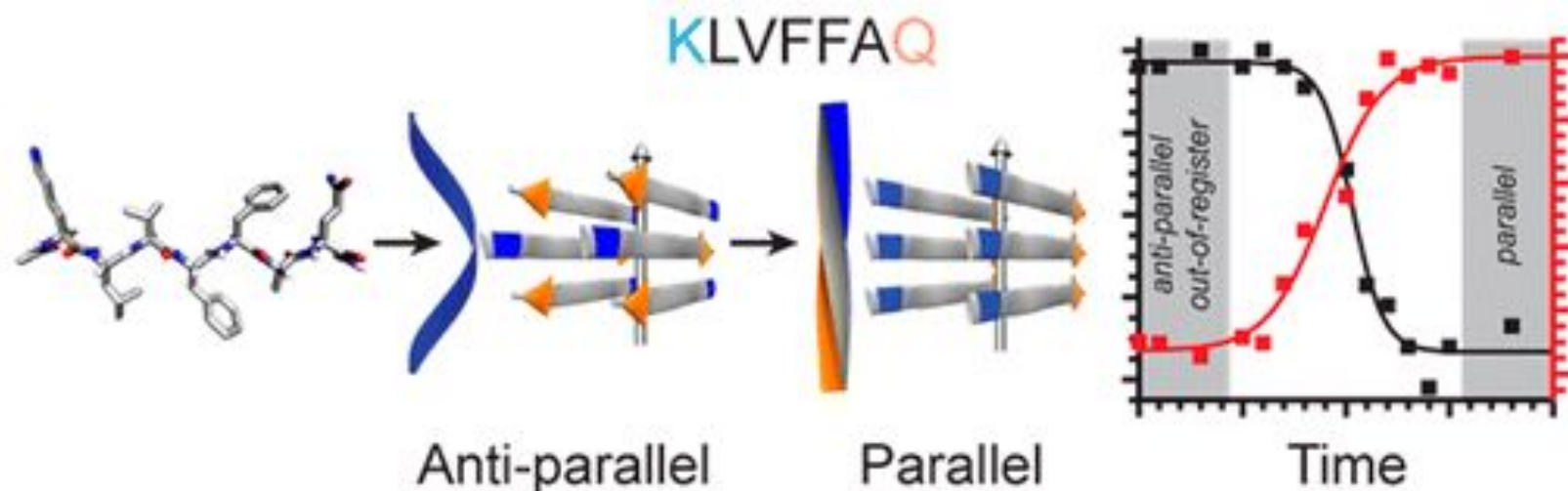




X-RAY

## Structure of the cross- $\beta$ spine of amyloid-like fibrils

R.Nelson, M.R.Sawaya, M.Balbirnie,  
A.Ø.Madsen, C.Riek, R.Grothe, D.Eisenberg  
*Nature* **435**:773-778 (2005)



In contrast to an expected Ostwald-like ripening of amyloid assemblies, the nucleating core of the Dutch mutant of the A $\beta$  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.

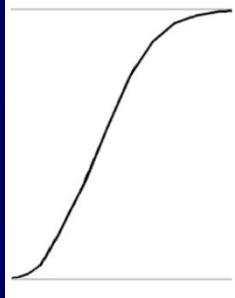
**JACS** → [Volume 136, Issue 43](#) → **October 29, 2014**¶

**Kinetic Intermediates in Amyloid Assembly**¶

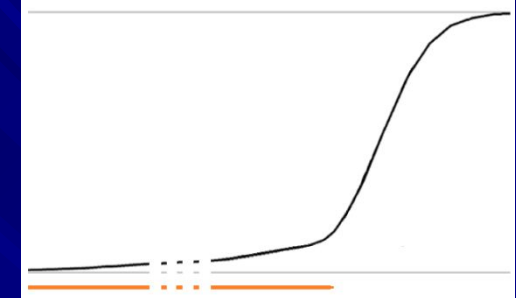
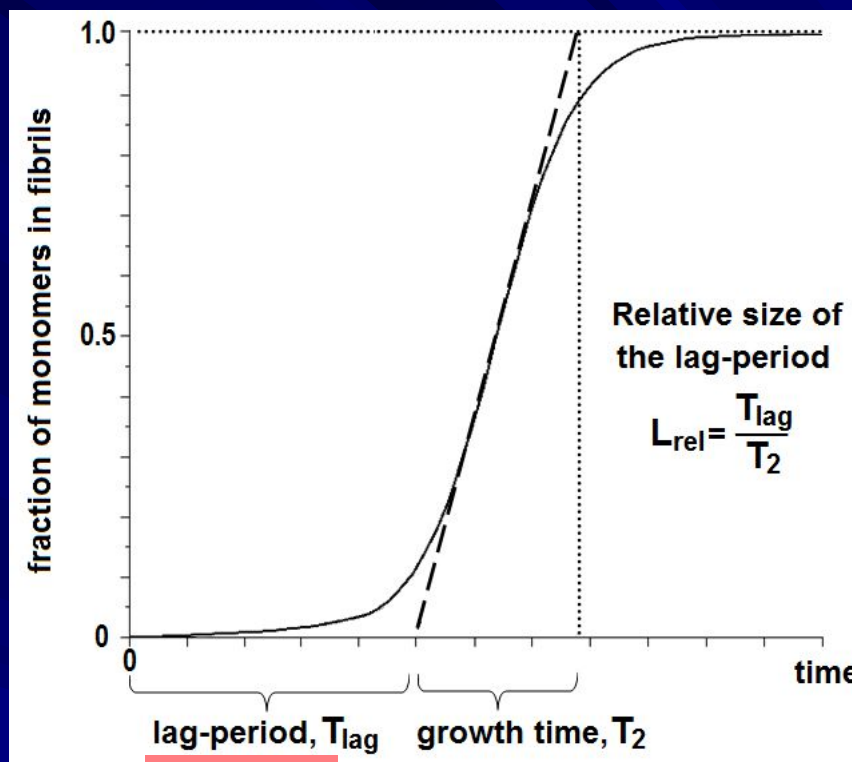
Chen Liang, Rong Ni, Jillian E. Smith, W. Seth Childers, Anil K. Mehta, and David G. Lynn



# Growth of amyloids

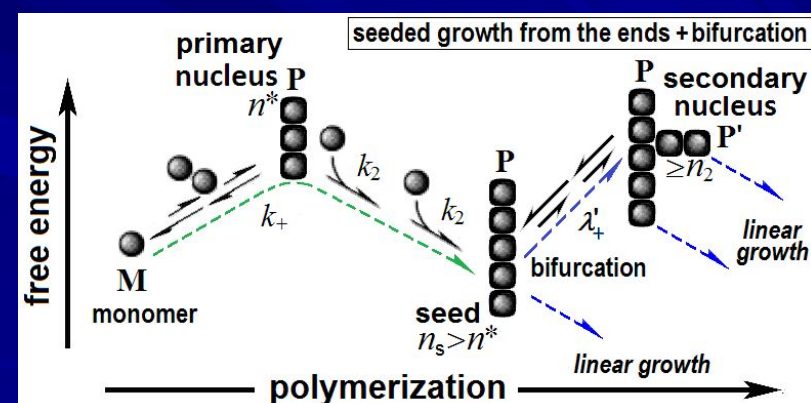
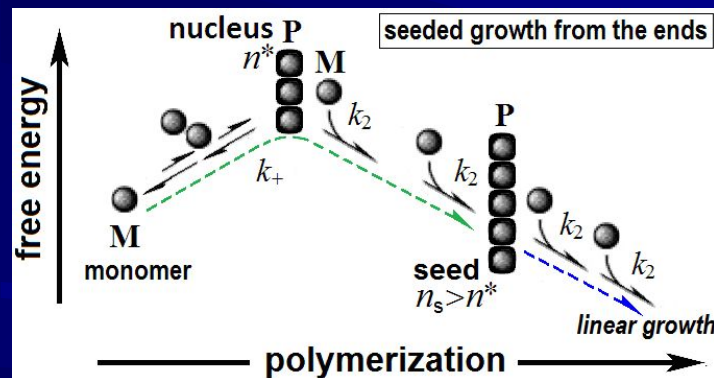


**LINEAR  
GROWTH  
NO LAG**

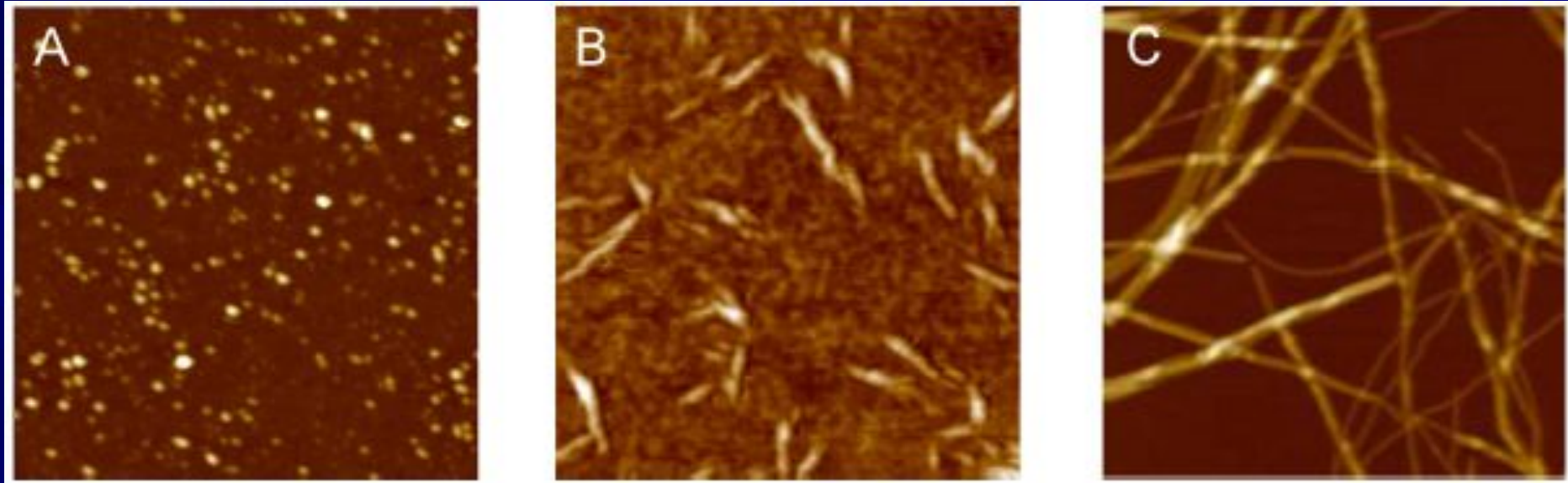


**EXPONENTIAL  
GROWTH  
VERY LARGE LAG**

**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 protofibril 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.

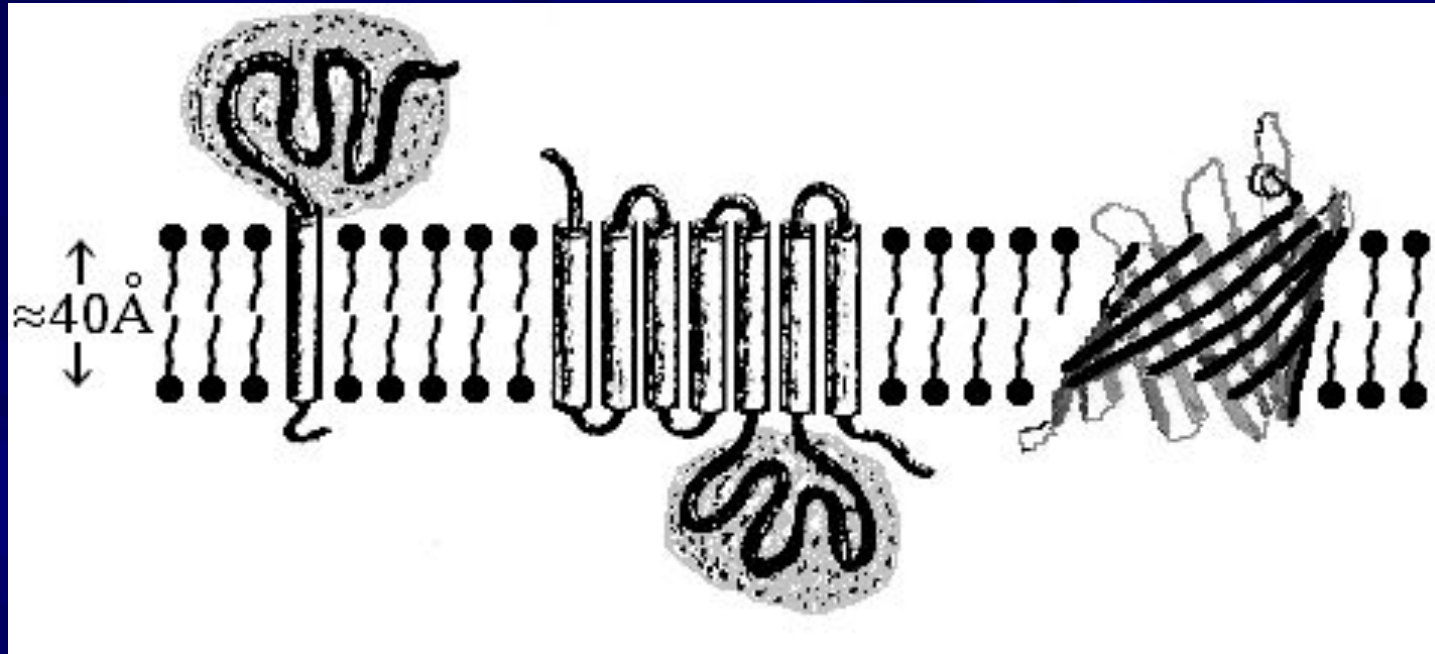
Short repeats.

Poor secondary structure.

Chains are linked by chemically  
modified Lys residues.

Like in rubber.

# Membrane proteins: transmitters



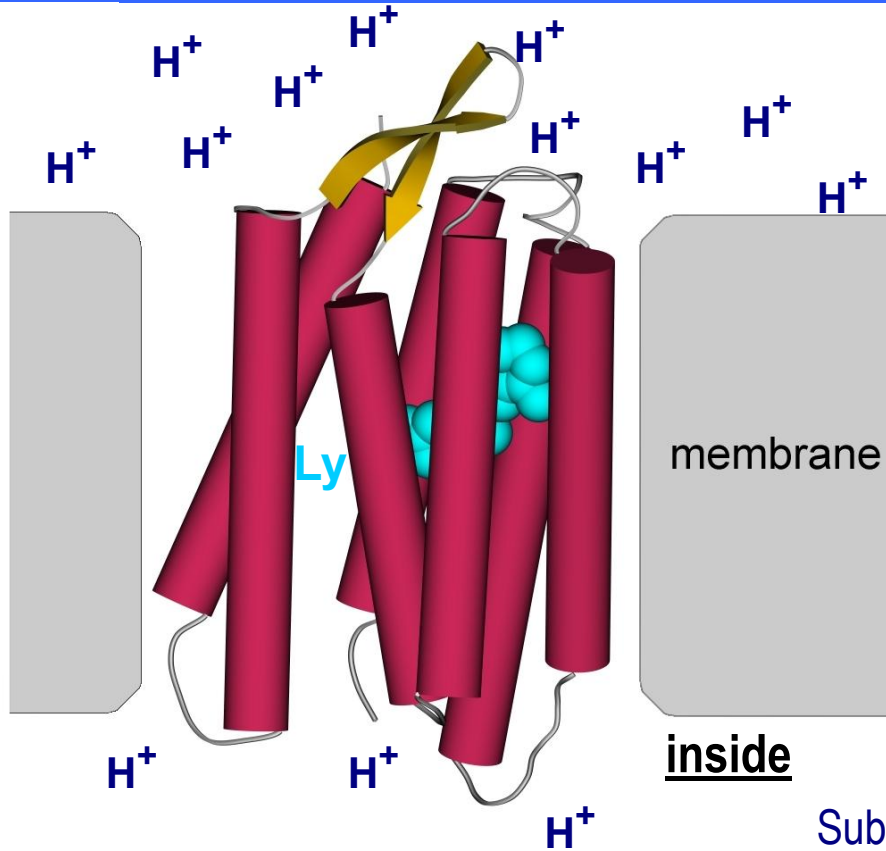
heads (polar)  
tails  
tails  
heads (polar)

# H-bonds & hydrophobics

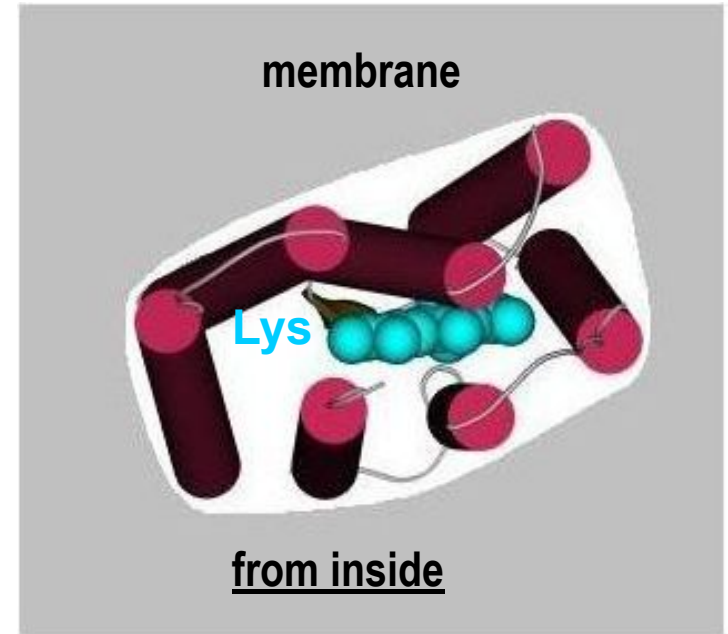
PROTEINS	SEQUENCES	
<u>Globular</u>	oo	<i>quasi-random</i>
<u>Membrane</u>	.....ooo.....   Hydro-    Hydro-   phobic       philic <hr style="width: 10%; margin-left: 0;"/>	<i>blocks</i>
<u>Fibrous</u>	oooooooooooooooooooooooooooooooooooooo   repeat	<i>repeats</i>



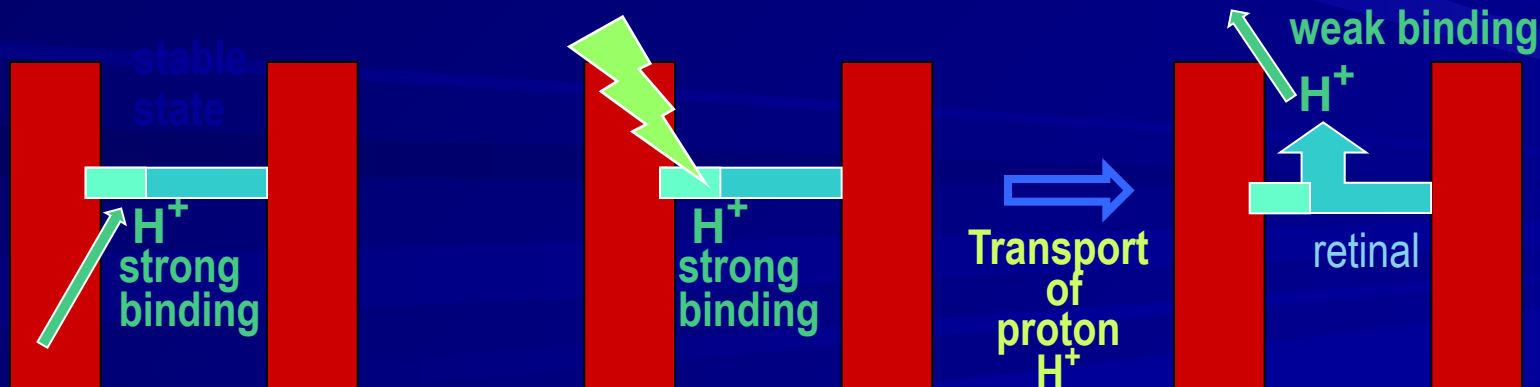
# Bacteriorhodopsin ( $\alpha$ ) with retinal: the simplest transporter machine with a light-induced conformational change



## Bacteriorhodopsin-Lys-retinal

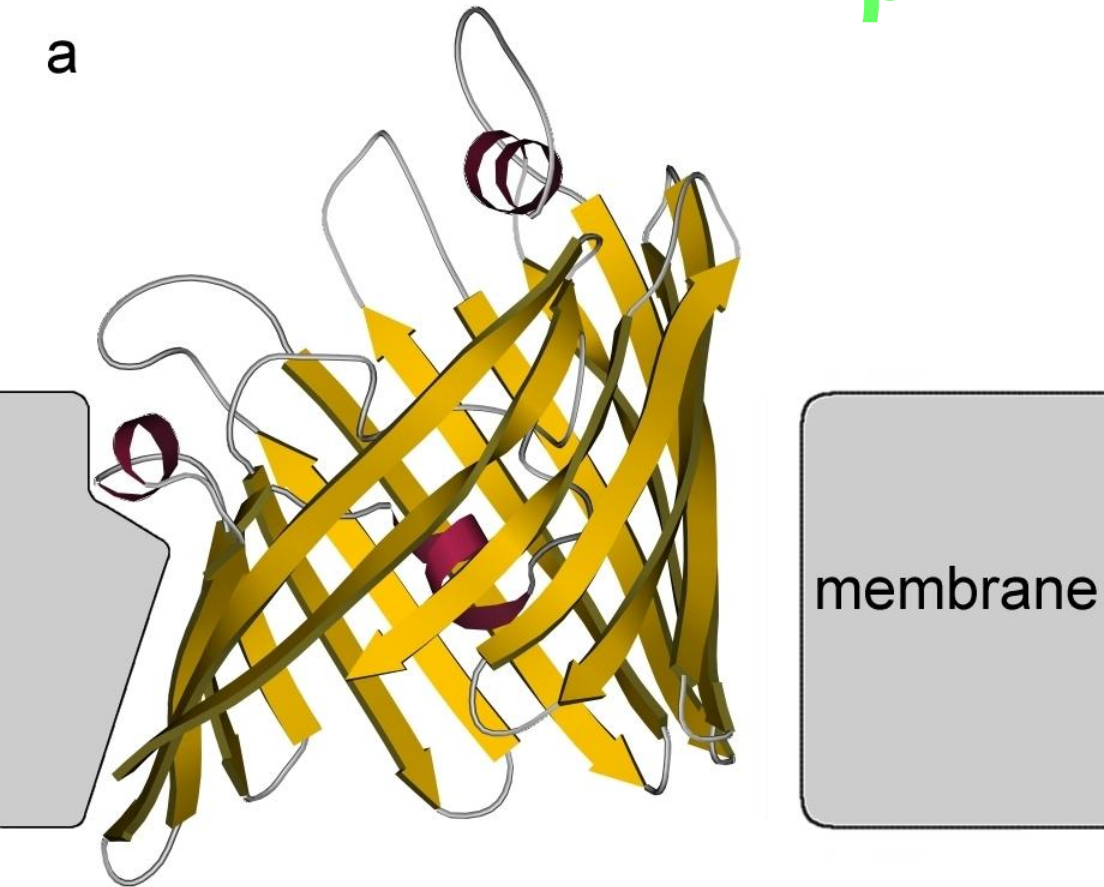


Subramaniam & Henderson, Nature 406, 653 (2000)



$\beta$

a



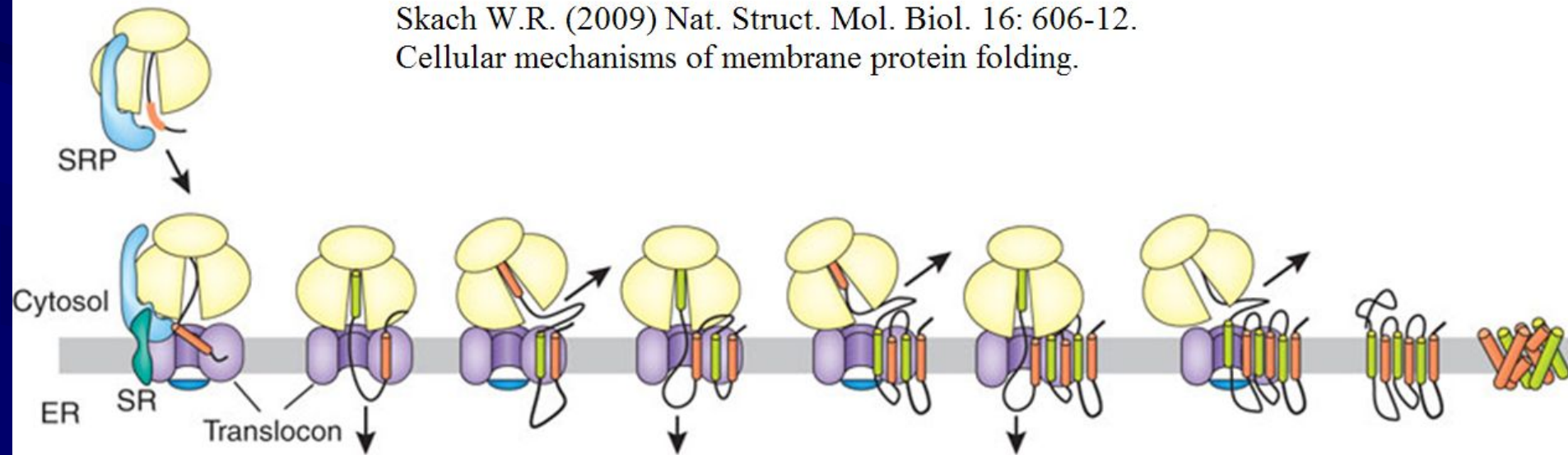
b



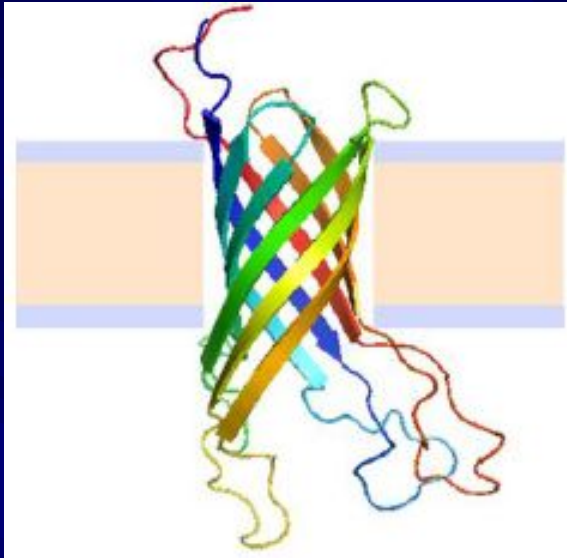
**Porin**  
**Transport of polar molecules**

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

Skach W.R. (2009) Nat. Struct. Mol. Biol. 16: 606-12.  
Cellular mechanisms of membrane protein folding.



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



COLLAPSED STATE: MIX OF COIL,  $\alpha$ ,  $\beta$



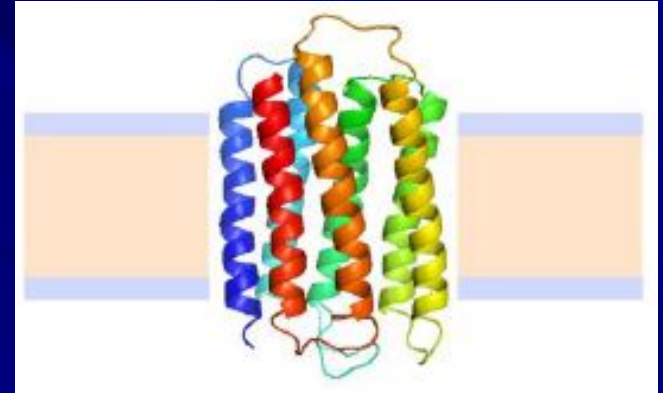
ASSOCIATES WITH **LIPID VESICLES**,  $\beta$



DEEPER PENETRATION INTO LIPIDS



FULLY FOLDED



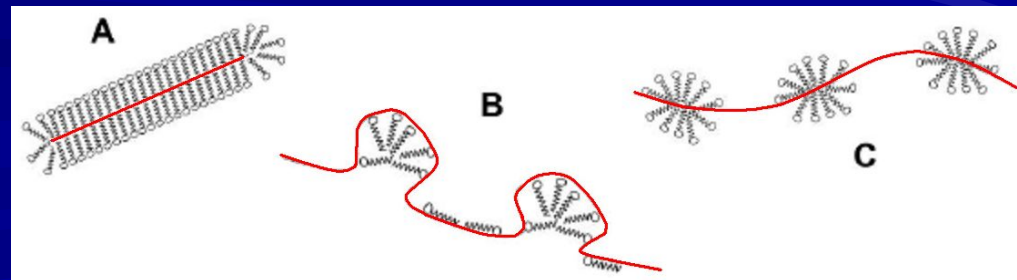
INDEPENDENT  $\alpha$ -HELICES



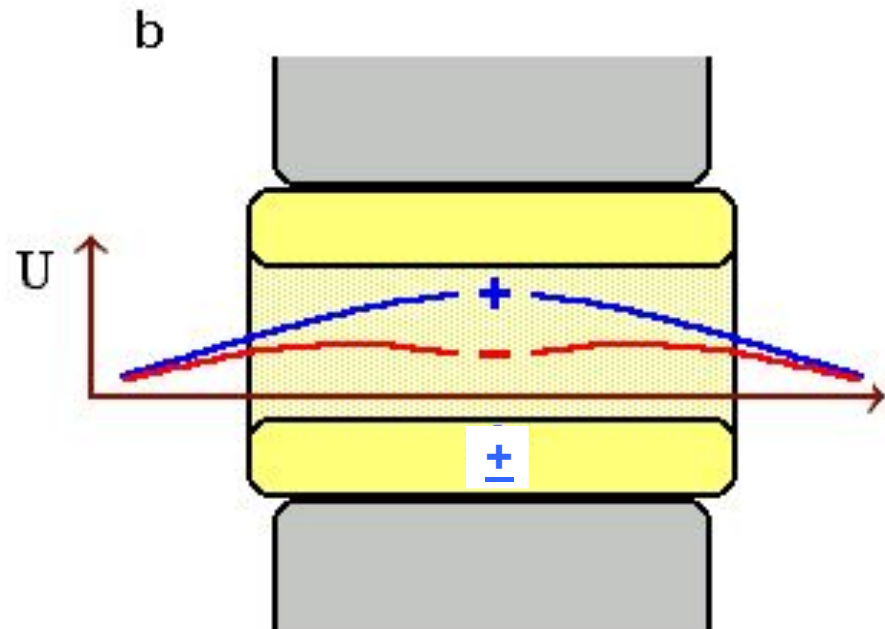
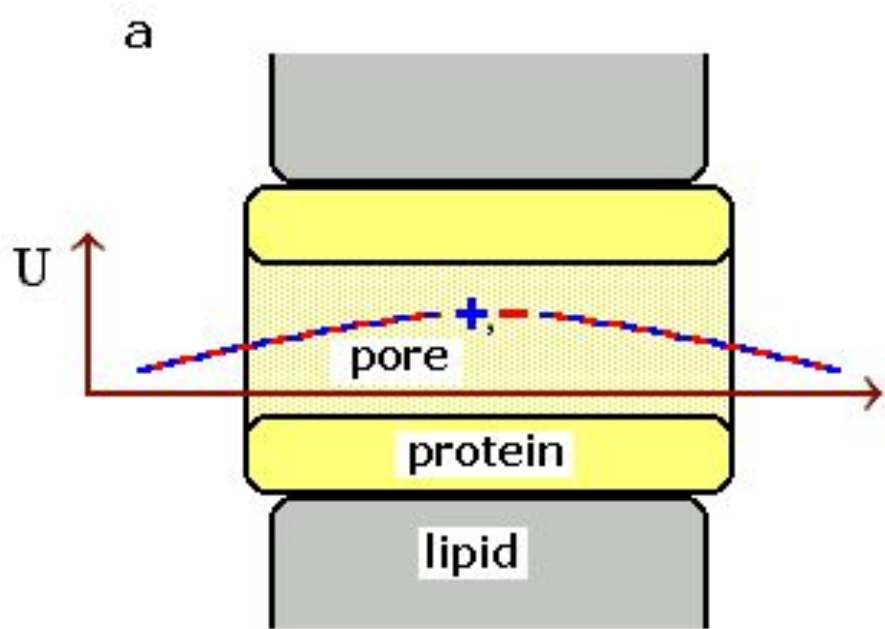
ASSEMBLE IN LIPID TO FULLY FOLDED

**DIFFICULT TO STUDY:**

DENATURED STATES OF MEMBRANE  
PROTEINS ARE **DIVERSE & COMPLICATED**







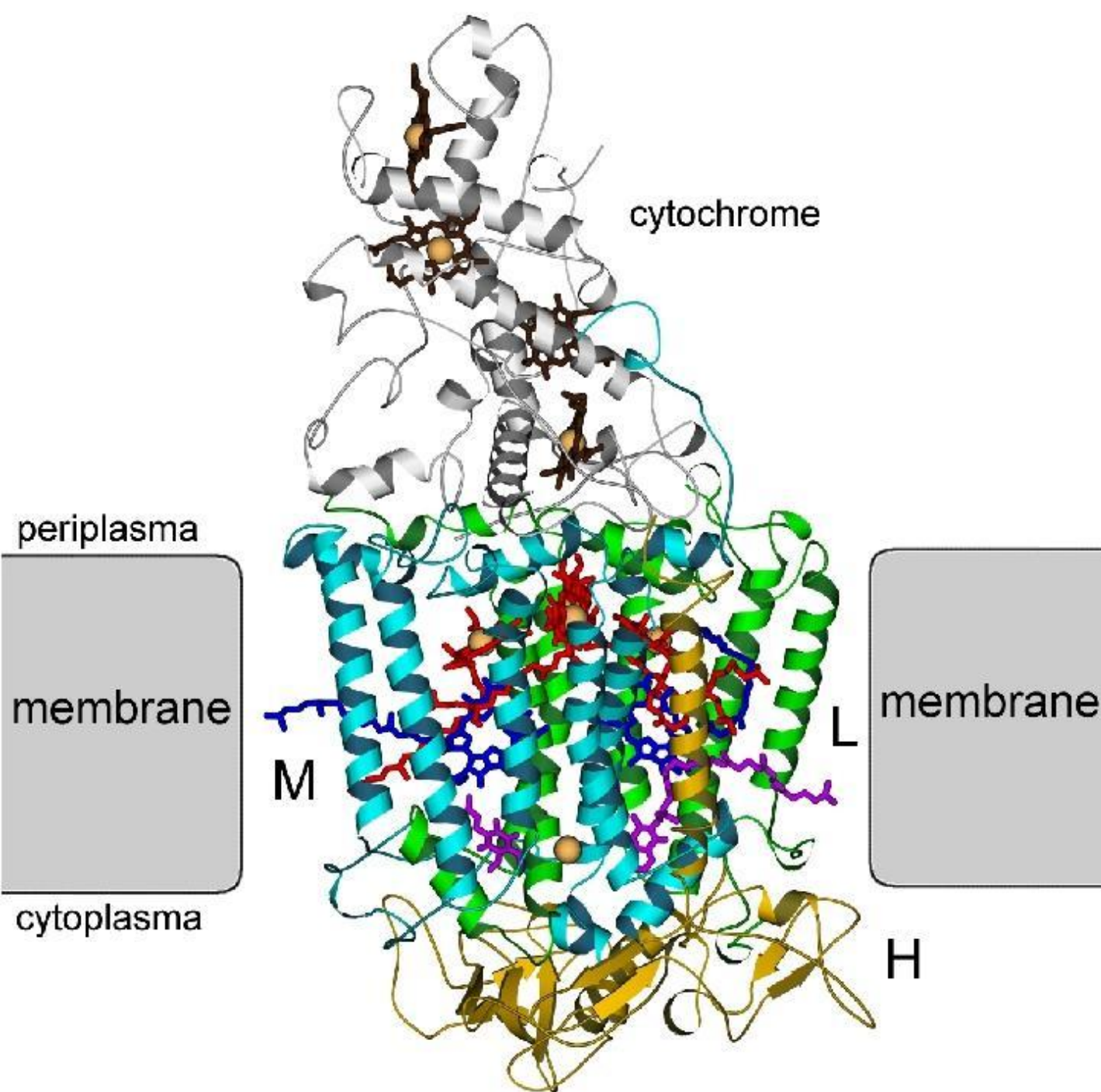
## Pore in membrane: SELECTIVITY

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

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

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

# Photo-synthetic center

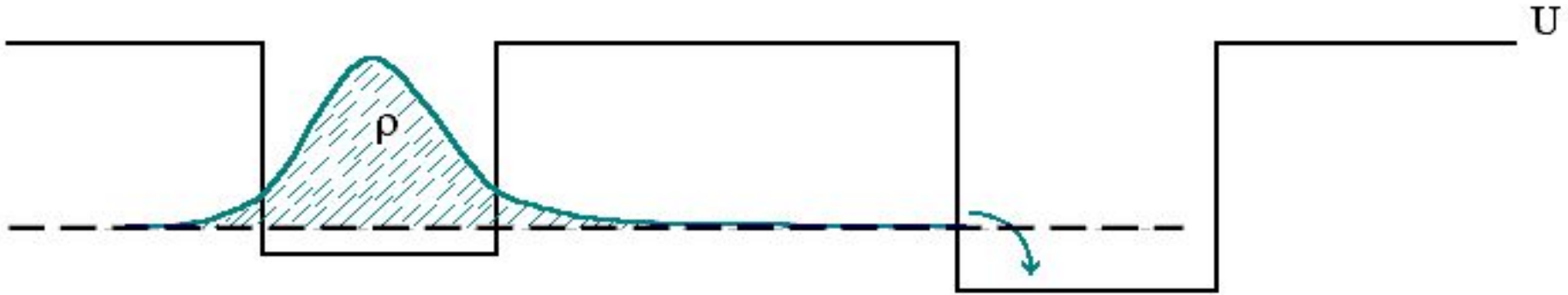


**Robert Huber,**  
1937.  
Nobel prize 1988

# chlorophyll



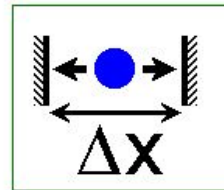
# Tunneling



**Atom  $\approx 1\text{\AA}$   $\Rightarrow$  Attenuation of electron density:  $P(X) \sim 10^{-X(\text{\AA})}$**

Heisenberg's uncertainty:

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



$$V = \pm |V|$$

Energy of localization in  $\Delta x$ :

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

**DELOCALIZATION LEADS TO MORE STABLE STATE OF  $e$**

**T-independent**

**Frequency of vibrations (attacks):**

$$f \sim 10^{15}/\text{sec}$$

**Successful attacks:**

$$f_{\text{SUCCS.}}(x) \sim P(x) \cdot f, \text{ e.g.:}$$

$$f_{\text{SUCCS.}}(5\text{\AA}) \sim 10^{-5+15} \sim 10^{10}/\text{sec}$$