Keynote Address

The Evolution of Protein Structure Determination: From Column Chromatography to Homology Modeling

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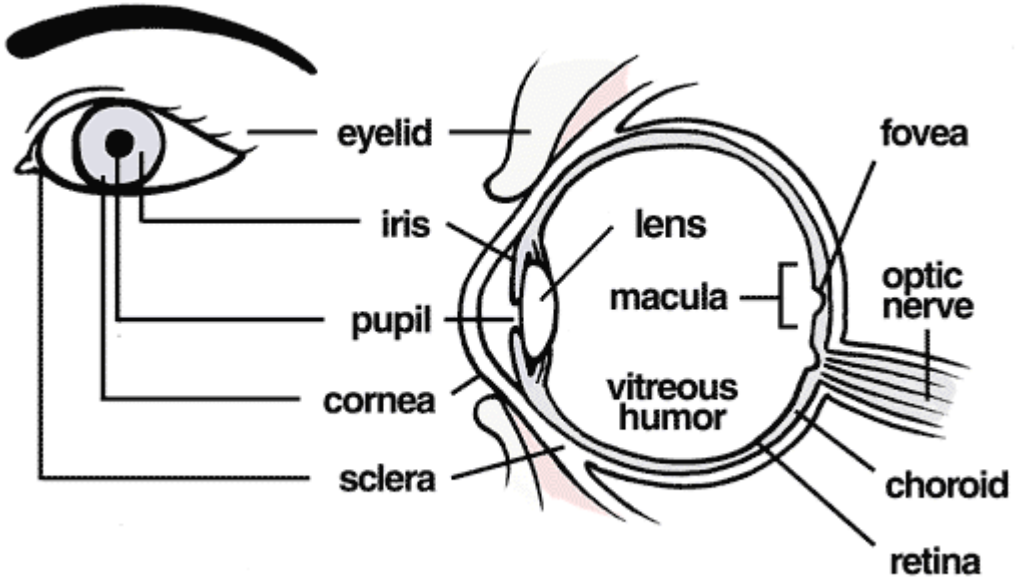
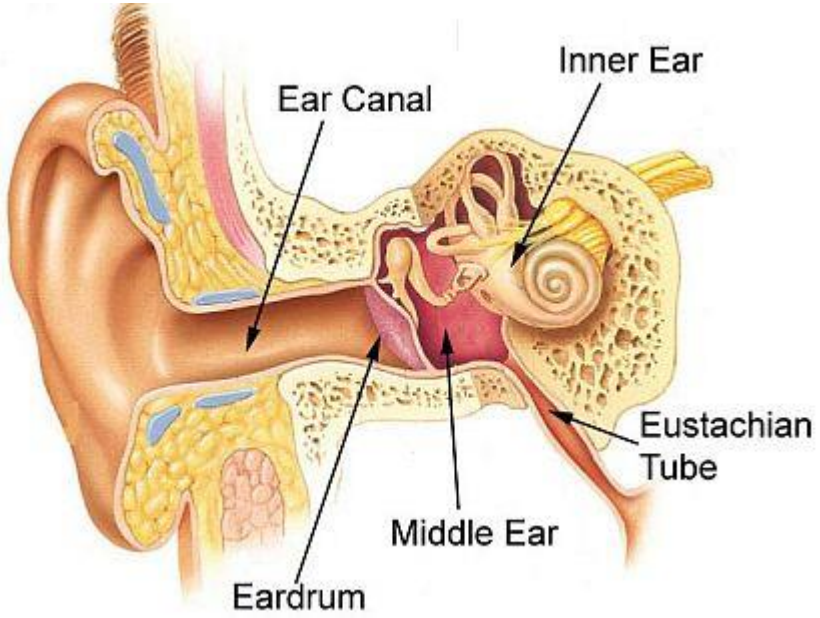
Lebanese International University

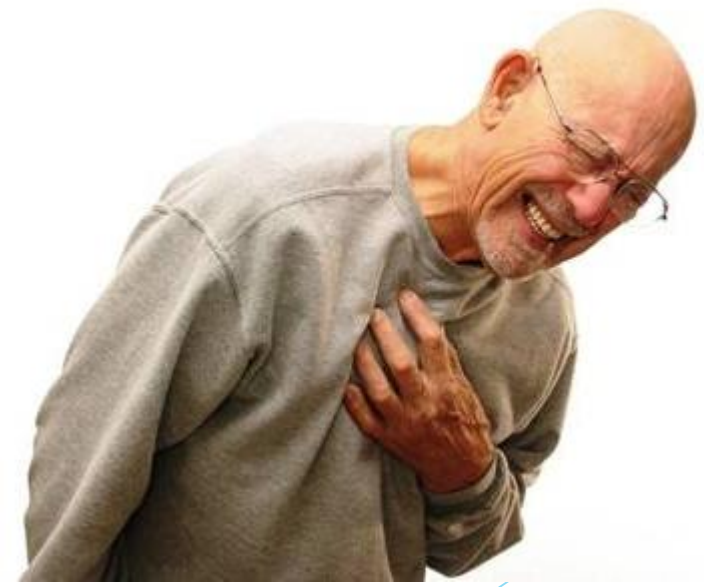
Proteins in Action



www.mvrf.org - illustration based upon information from National Eye Institute / National Institutes of Health



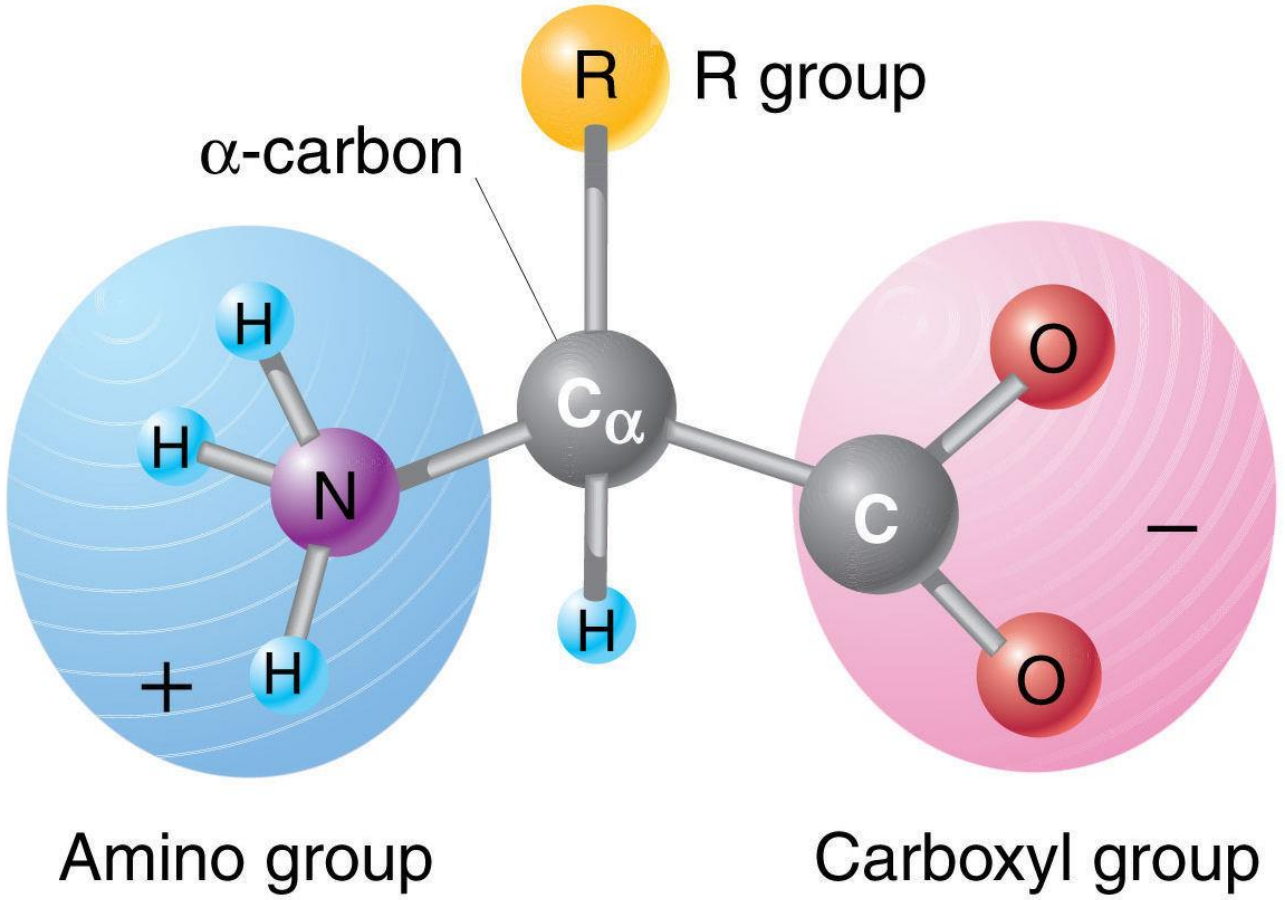
Proteins in Action



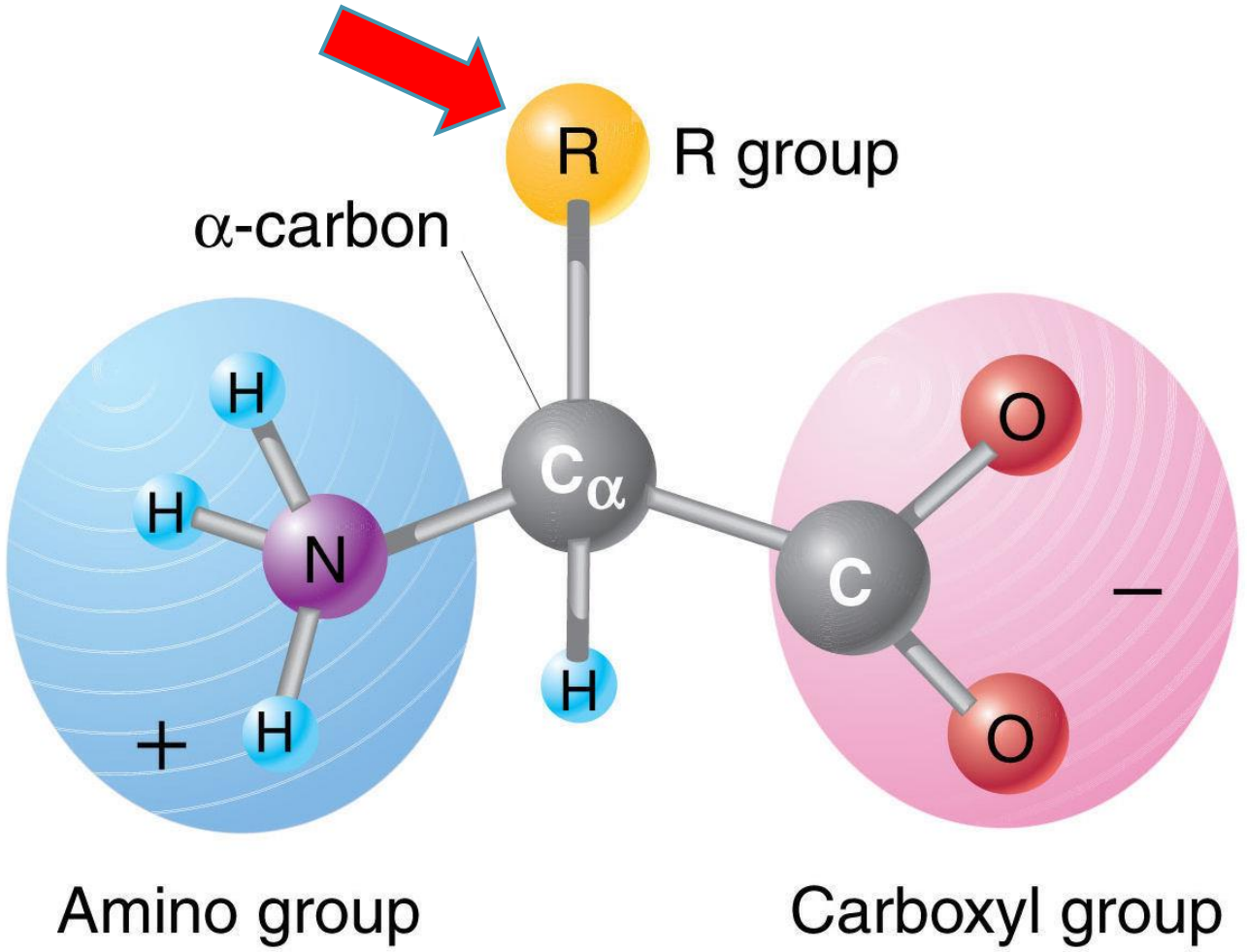
Definition

Macromolecular assemblies composed of basic units (amino acids) connected to each other in a regular format (peptide bond), occupying a specific 3-D shape (fold or structure), which conveys the intended (or faulty) function

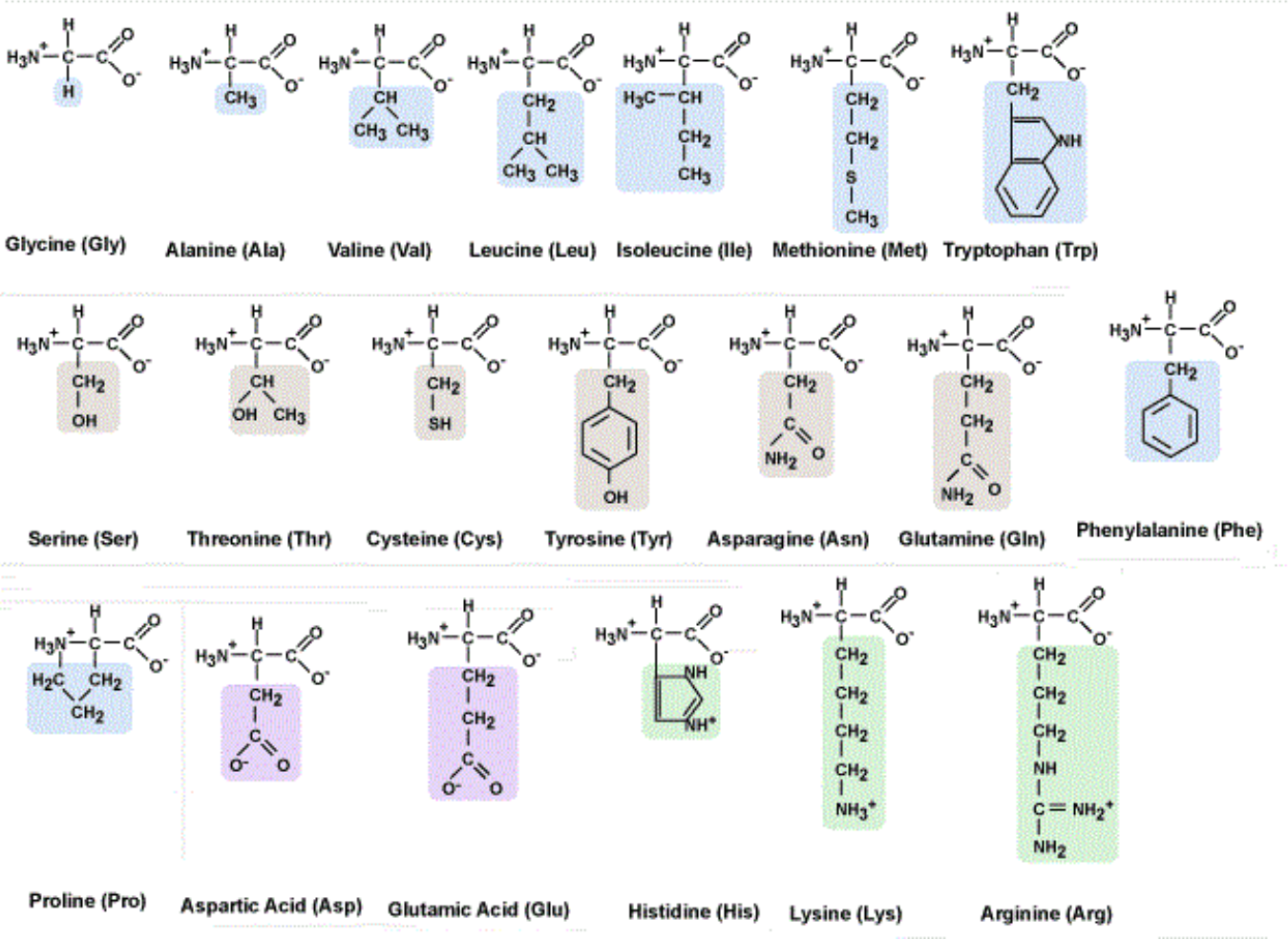
BIOC001 – Biochemistry for Pedestrians



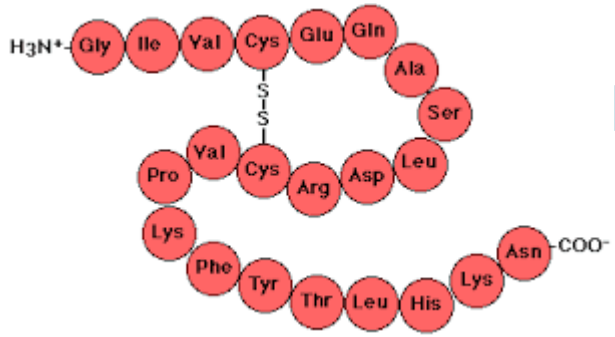
BIOC001 – Biochemistry for Pedestrians

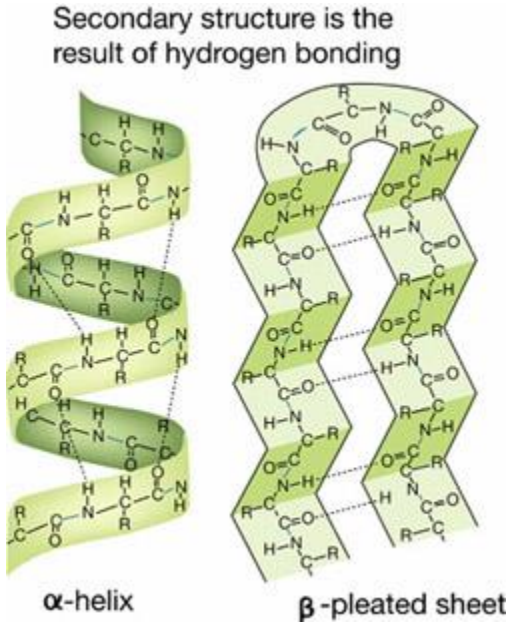


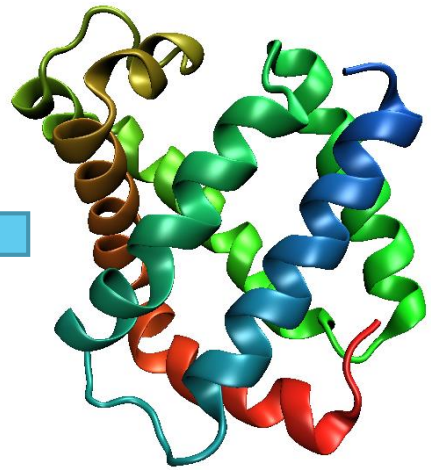
BIOC001 – Biochemistry for Pedestrians

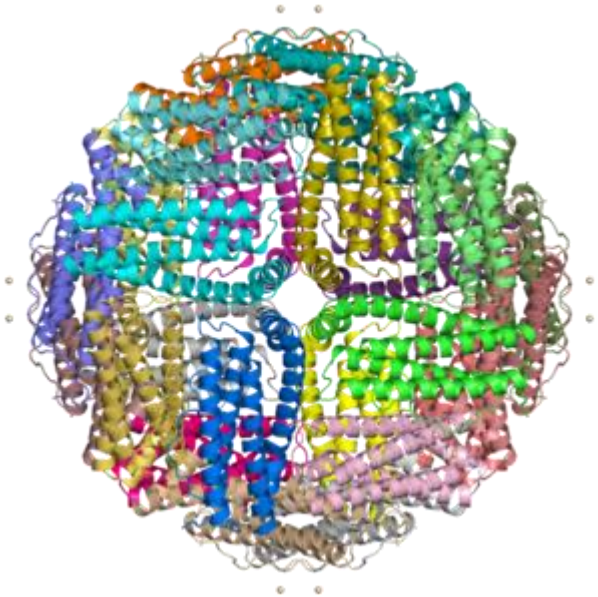


BIOC001 – Biochemistry for Pedestrians

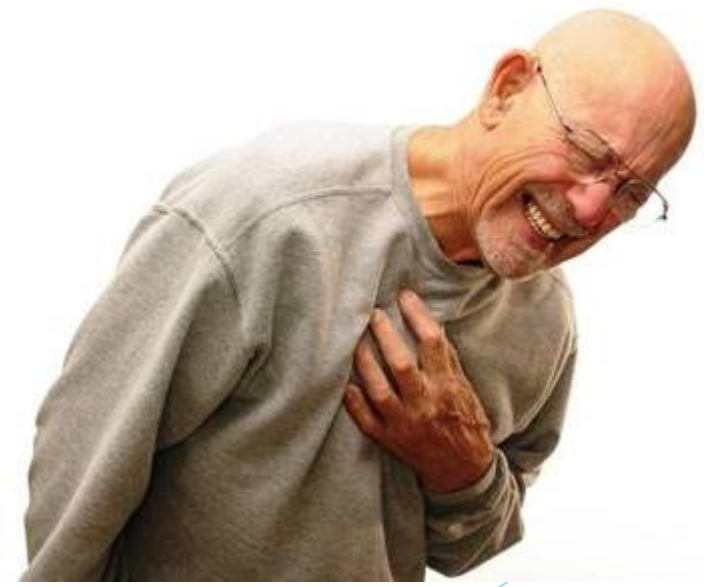






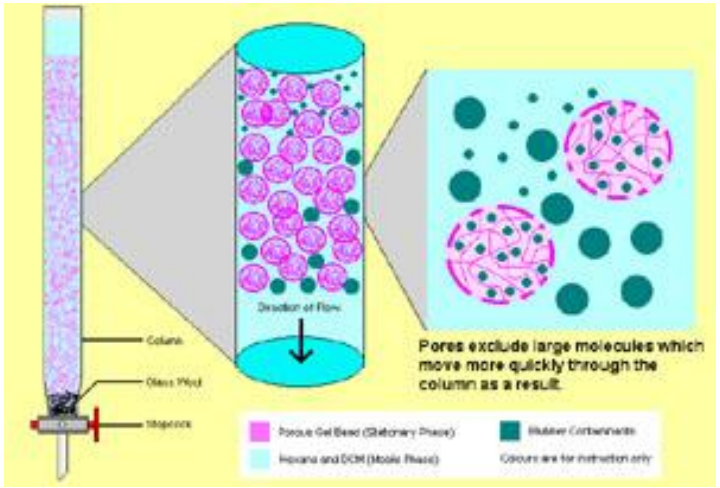


What went wrong?



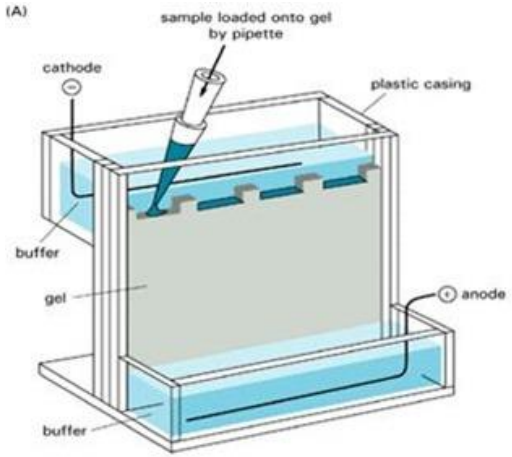
Function ⟺ Structure

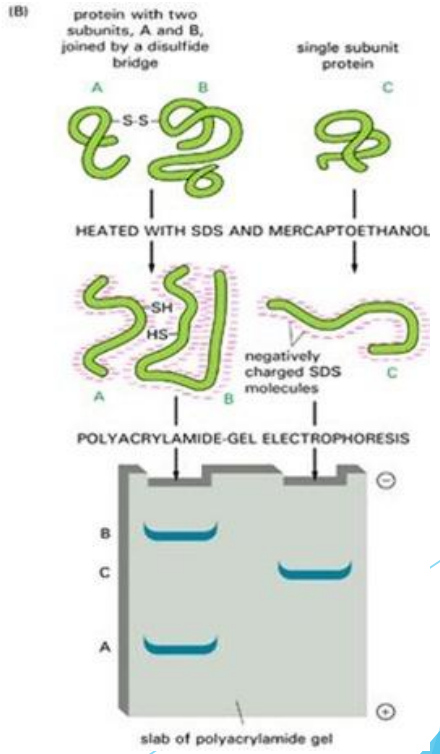
Initial Methods – very limited



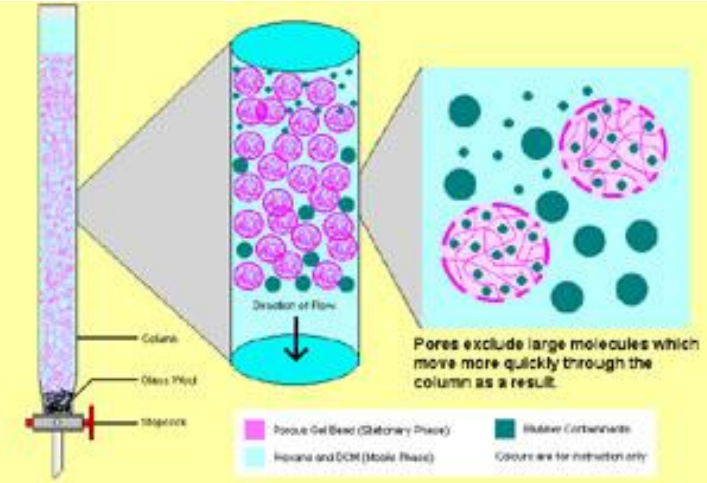
Gel Chromatography

SDS PAGE



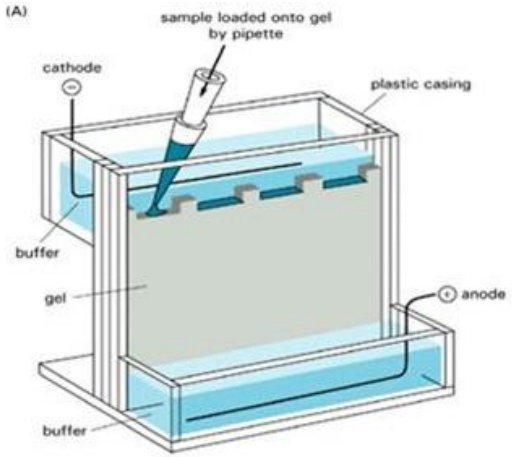


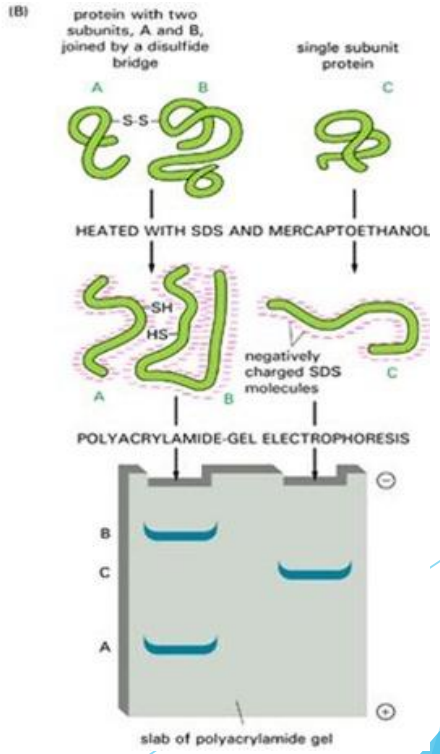
Initial Methods – very limited



Gel Chromatography

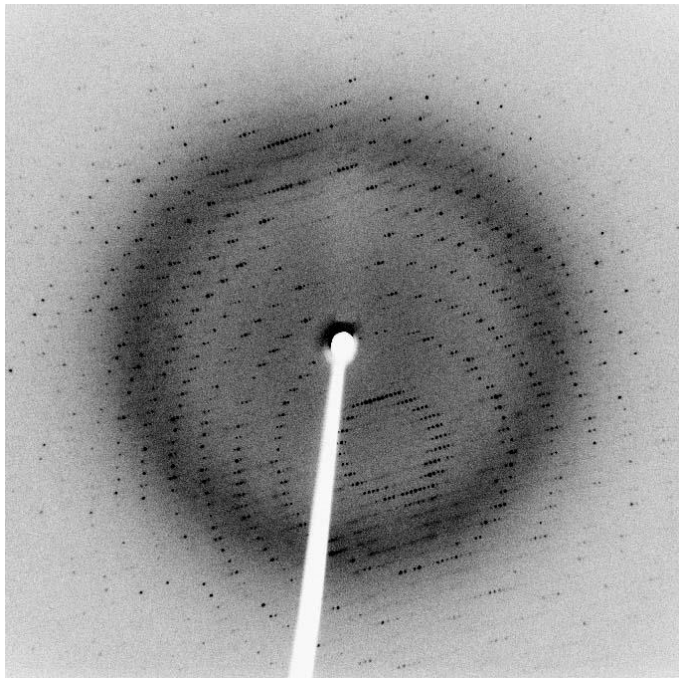
SDS PAGE



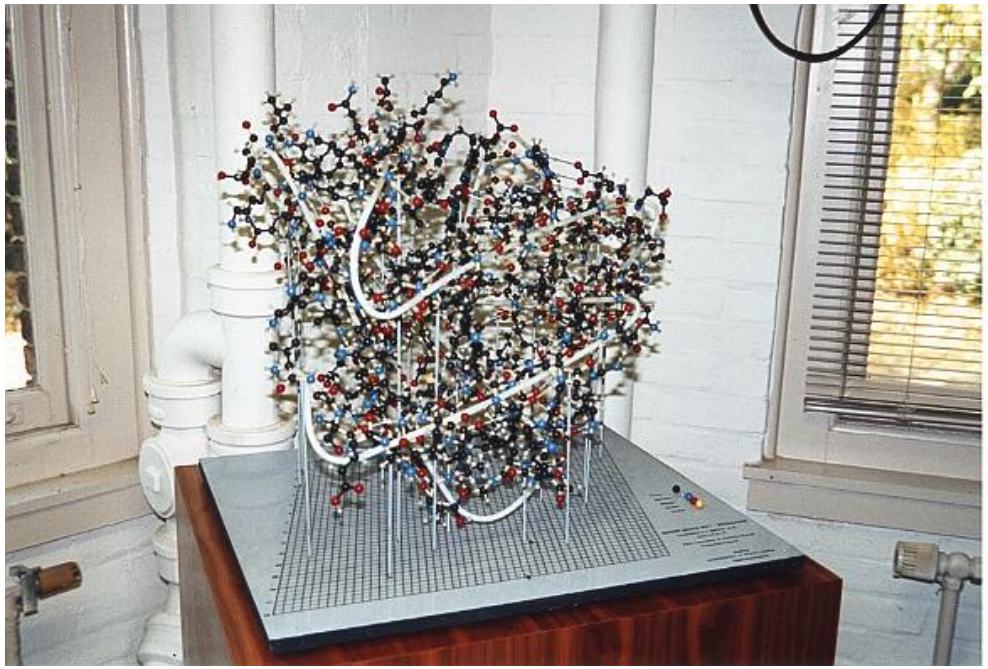


Only SIZE information

The Revolution - 1958



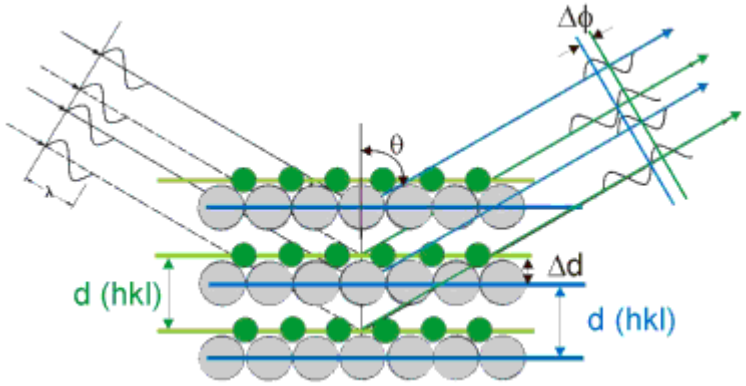
X-ray crystallography



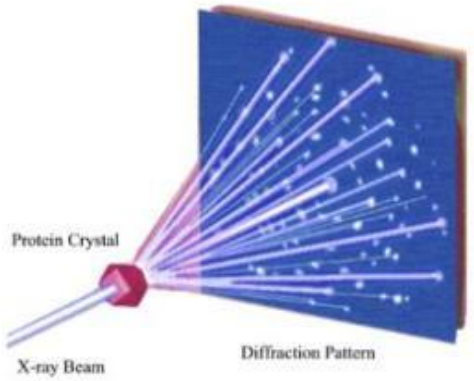
Structure of Myoglobin

1962 – Nobel Prize in Chemistry (Kendrew + Perutz)

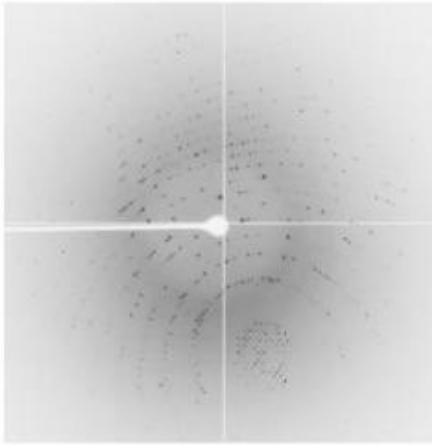
BIOP001 – Biophysics for the Layman



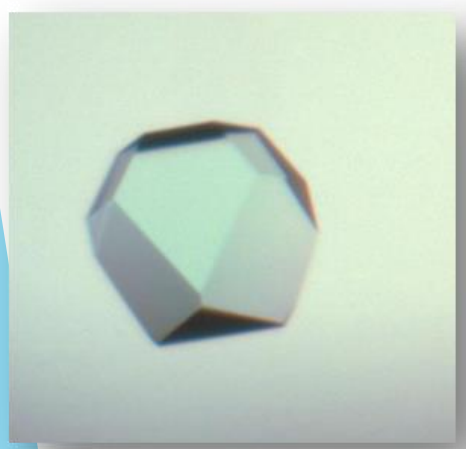
Bragg's Diffraction

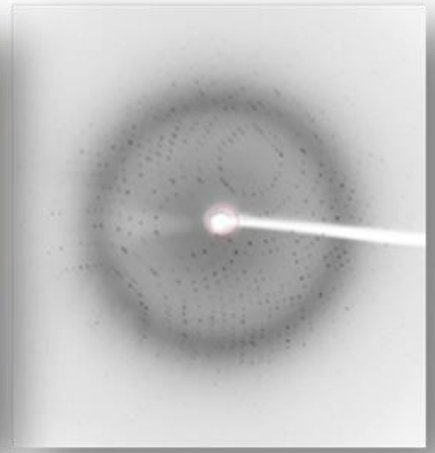


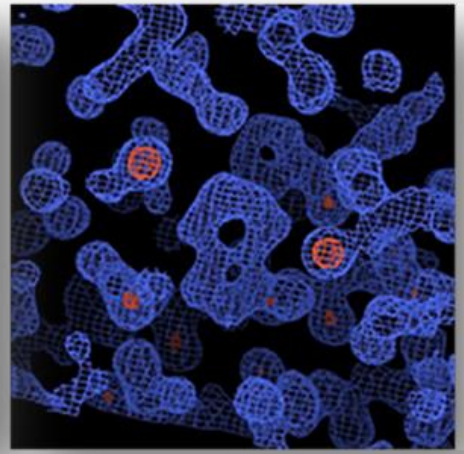
Diffraction Process

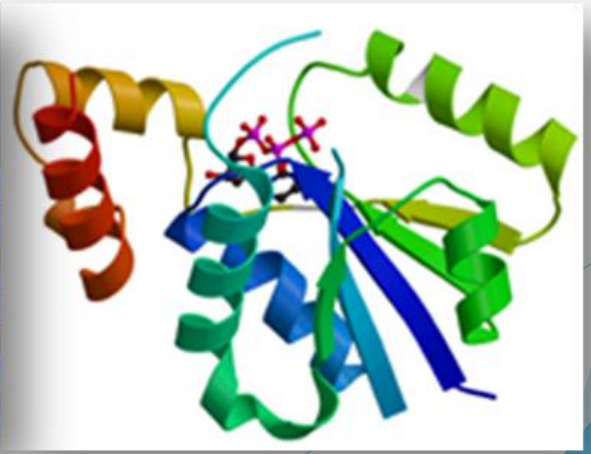


Diffraction Pattern from NSLS

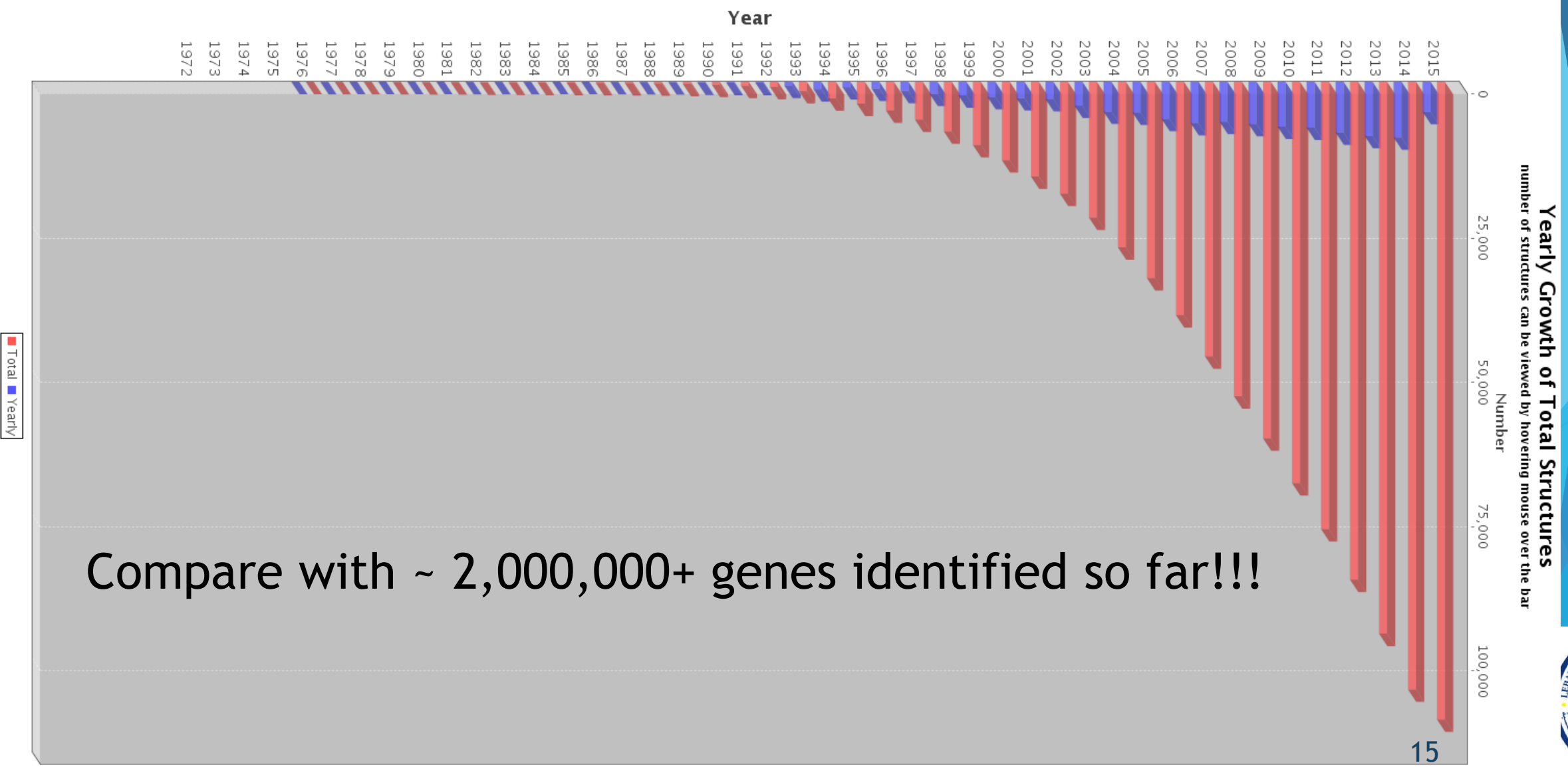








Too many sequences, too few structures



Compare with ~ 2,000,000+ genes identified so far!!!

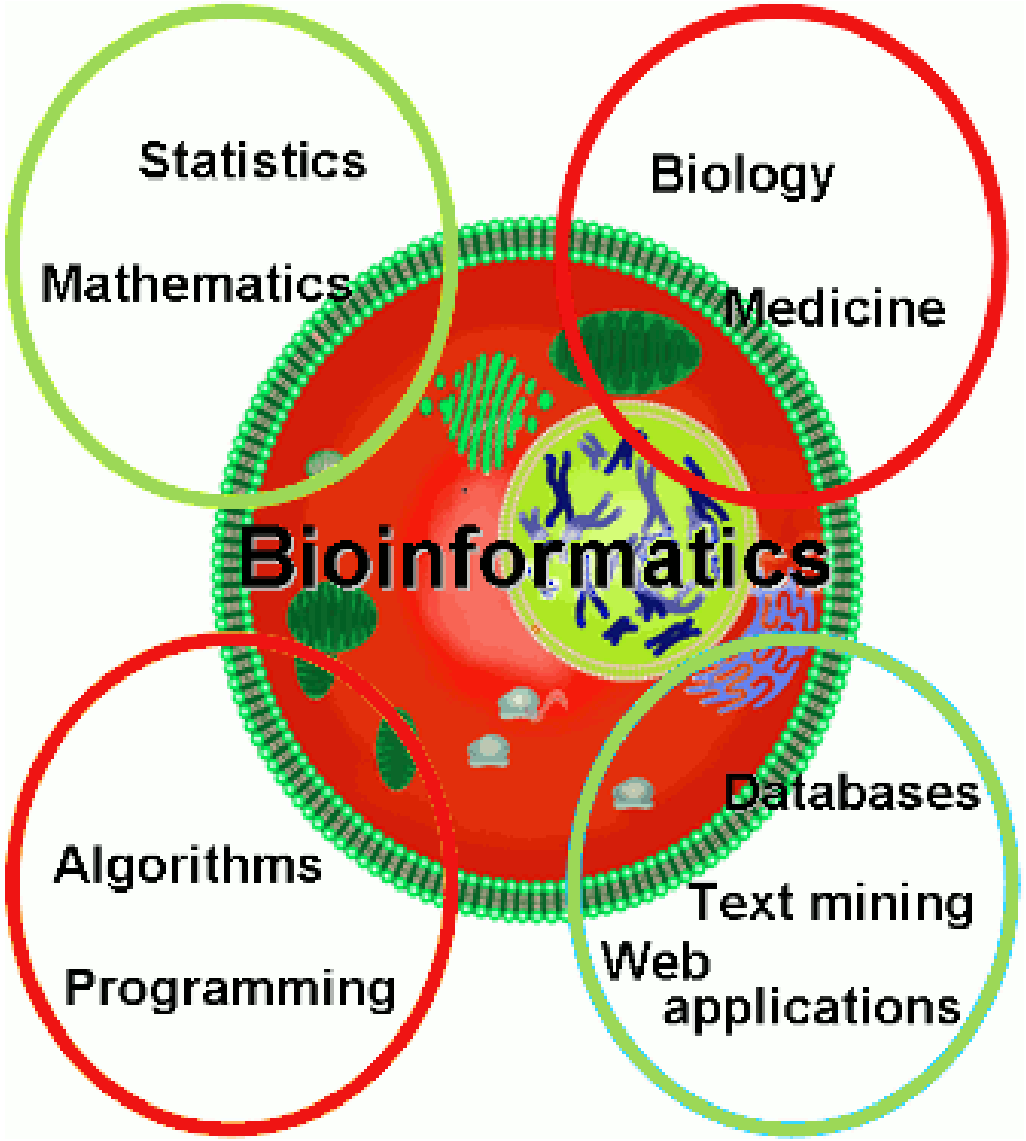
Reasons….technical:

- X-ray crystallography
  - Crystals are ordered systems -> defy the laws of nature
- Structural Electron Microscopy (strEM) - **1983**: Jacque Dubochet
  - Liquid crystals
- Structural Nuclear Magnetic Resonance (strNMR) - ***1978***: Kurth Wüthrich
  - Size limitation
- ..
- ..
- Bioinformatics
  - Still in its infancy

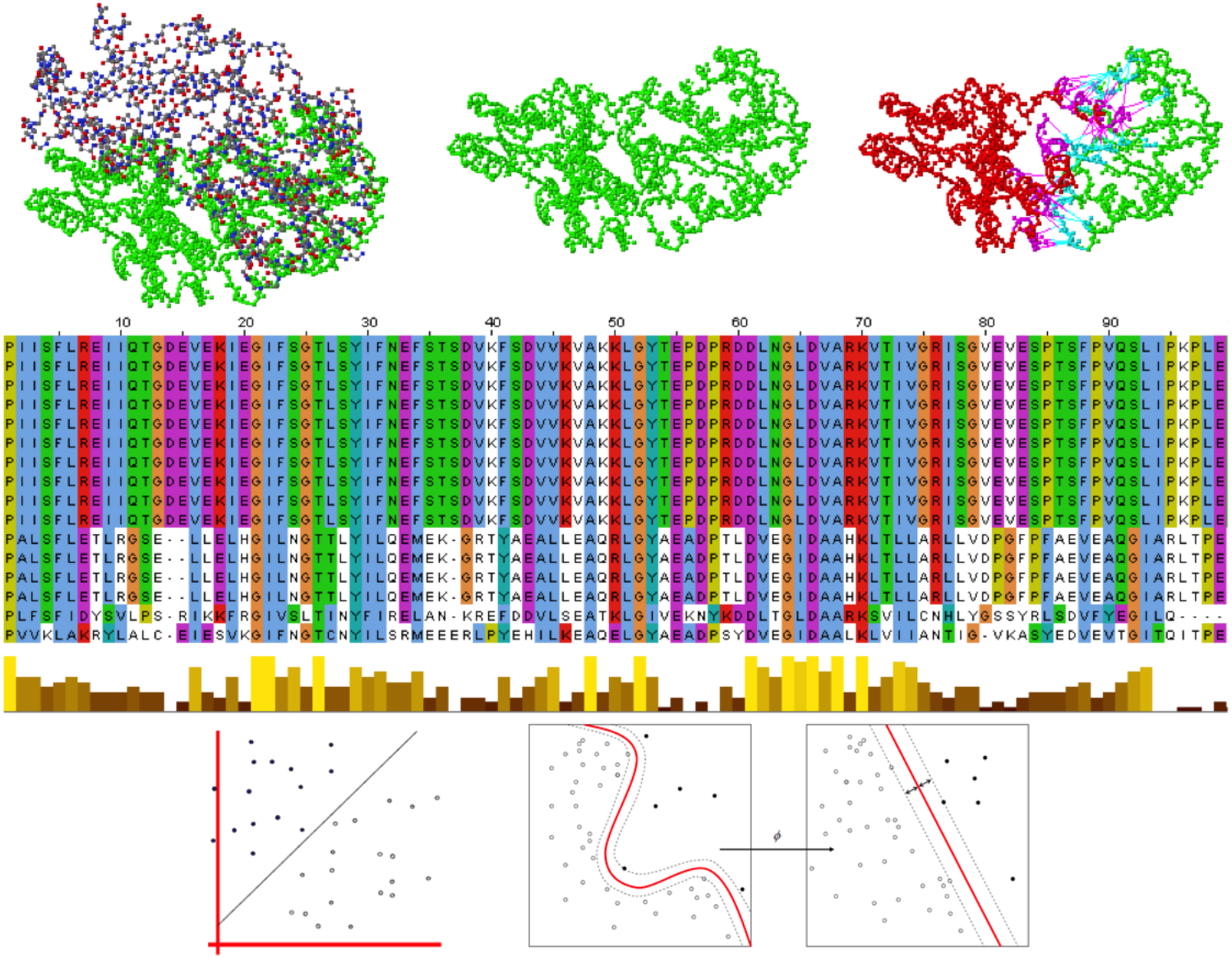
Bioinformatics

- ***1976***: Robert Langridge, credited for developing the first programs to visualize protein structures on a computer screen
- Advancement in the computer and network technology
- Success stories in other fields

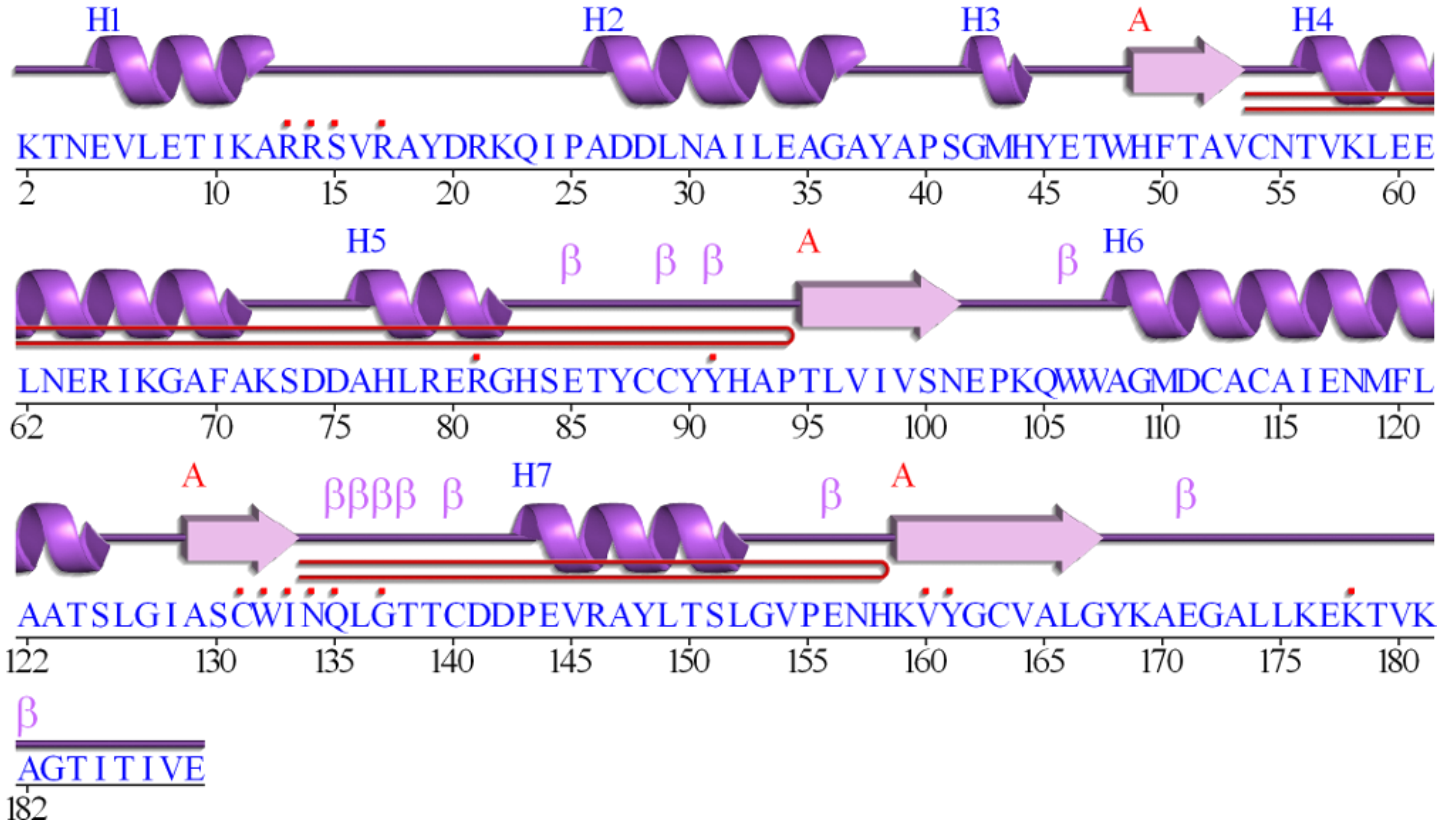
Bioinformatics



Bioinformatics



Bioinformatics – Stat at its best

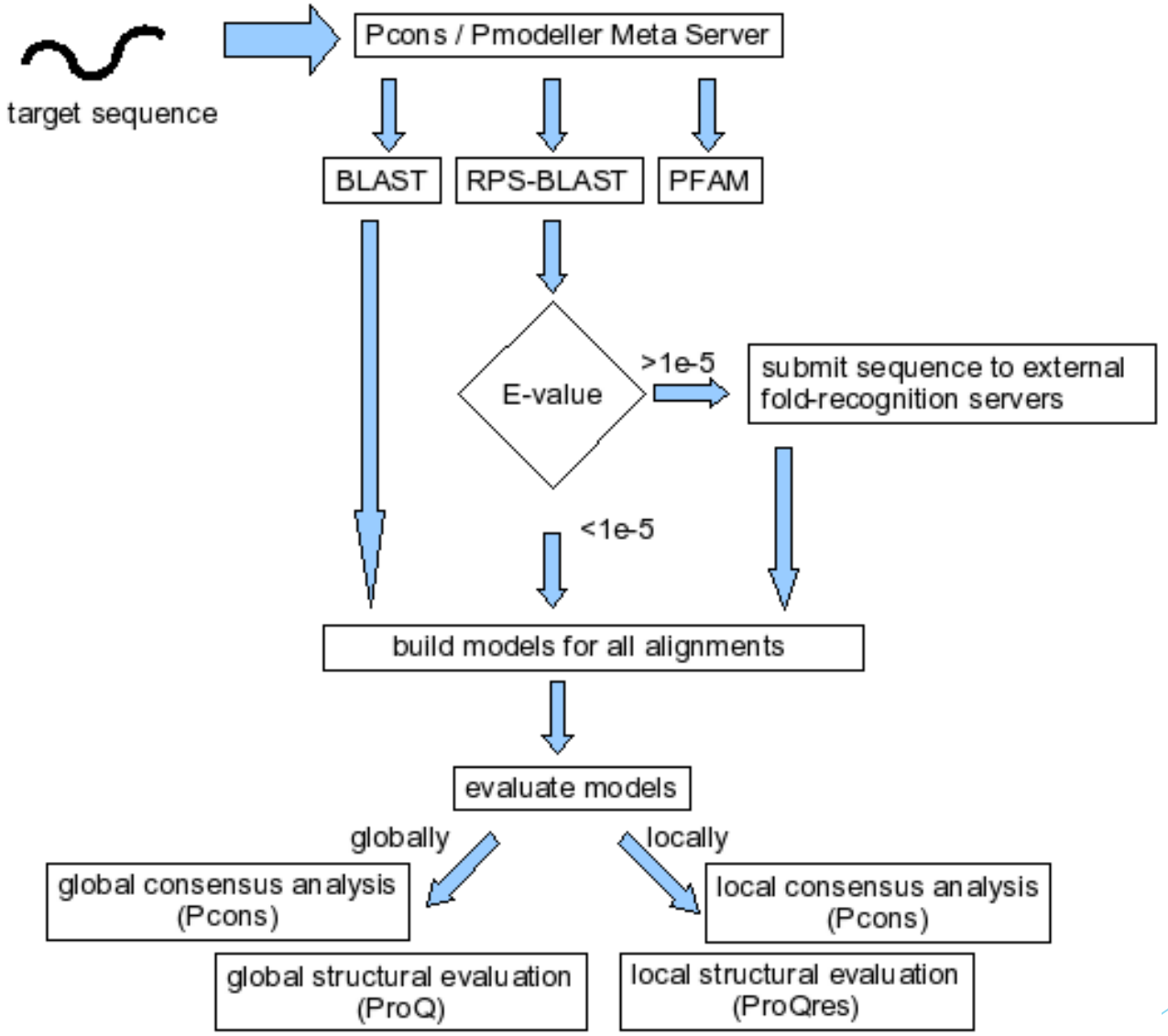


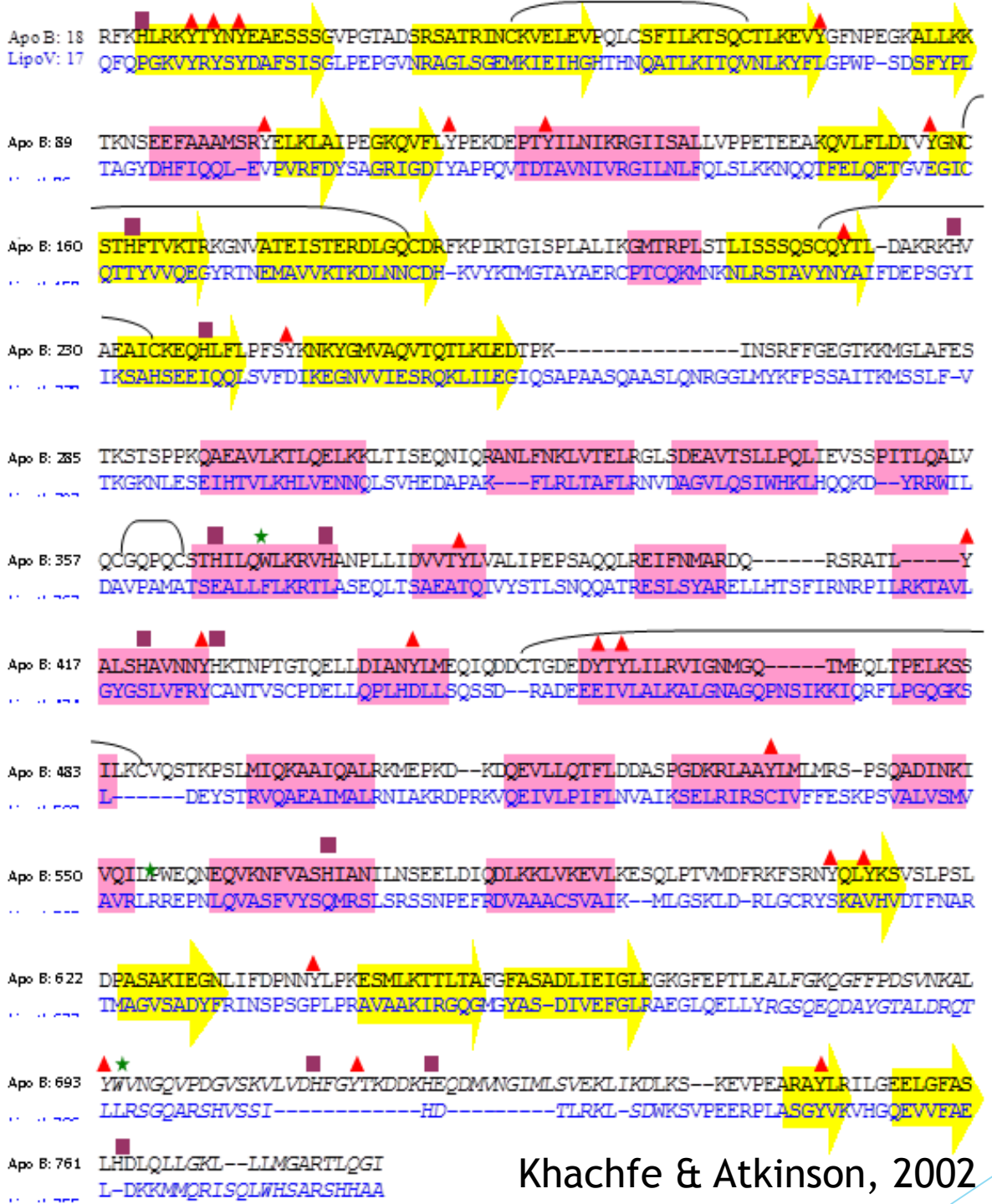
Excellent prediction of Secondary Structural elements

Bioinformatics – 3D Structure?

- Homology Modeling
- Ab initio
  - Molecular Dynamics
  - Genetic algorithms

Bioinformatics – Homology Modeling



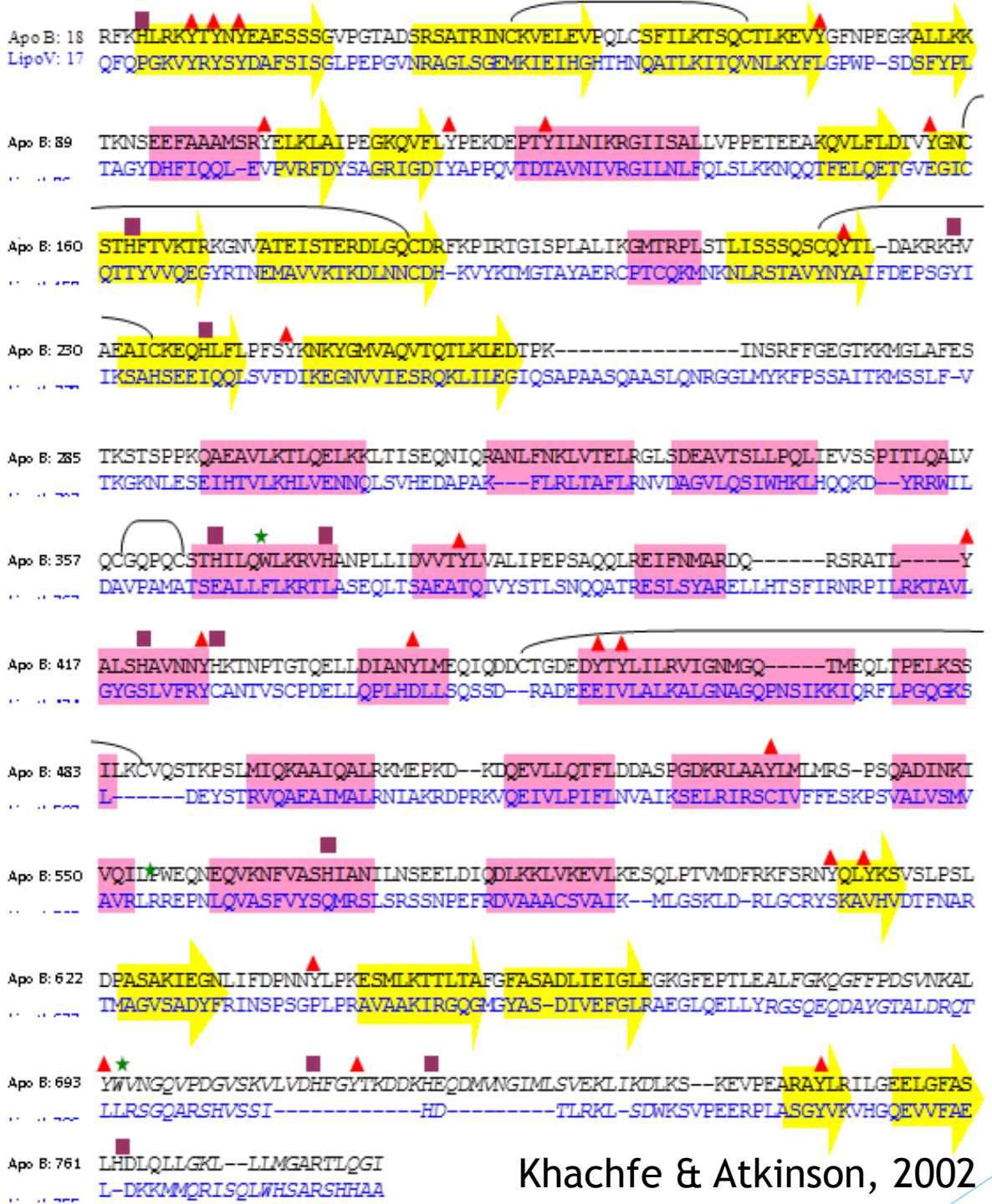


Khachfe & Atkinson, 2002

Bioinformatics – Needleman Wunsch alg.

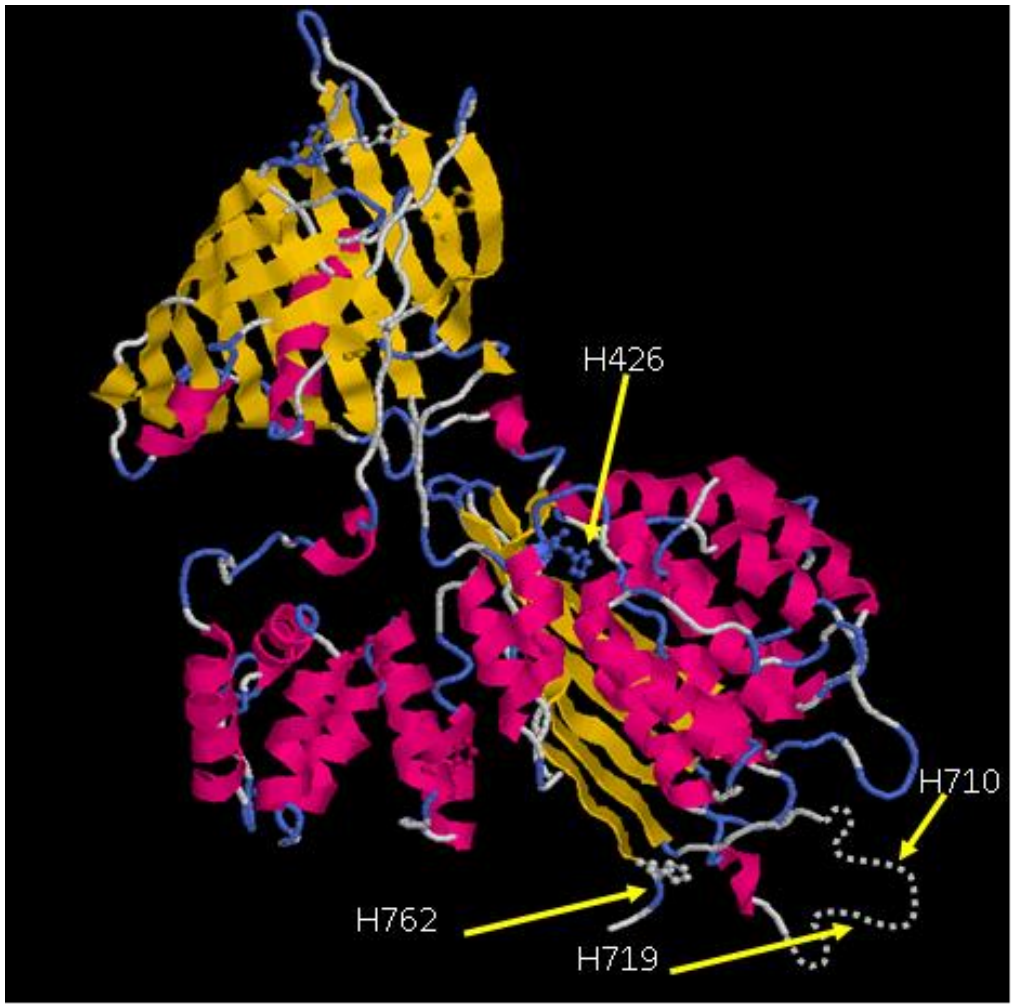
$$S_{ij} = max \begin{cases} S(a_i, b_j) + S_{i-1,j-1} \\ \delta + S_{i,j-1} \\ \delta + S_{i-1,j} \end{cases}$$

-	-	A	T	C	G	A	C
-	0	-4	-8	-12	-16	-20	-24
C	-4	-3	-7	-3	-7	-11	-15
A	-8	1	-3	-7	-6	-2	-6
T	-12	-3	6	2	-2	-6	-5
A	-16	-7	2	3	-1	3	-1
C	-20	-11	-2	-1	0	-1	8



Khachfe & Atkinson, 2002

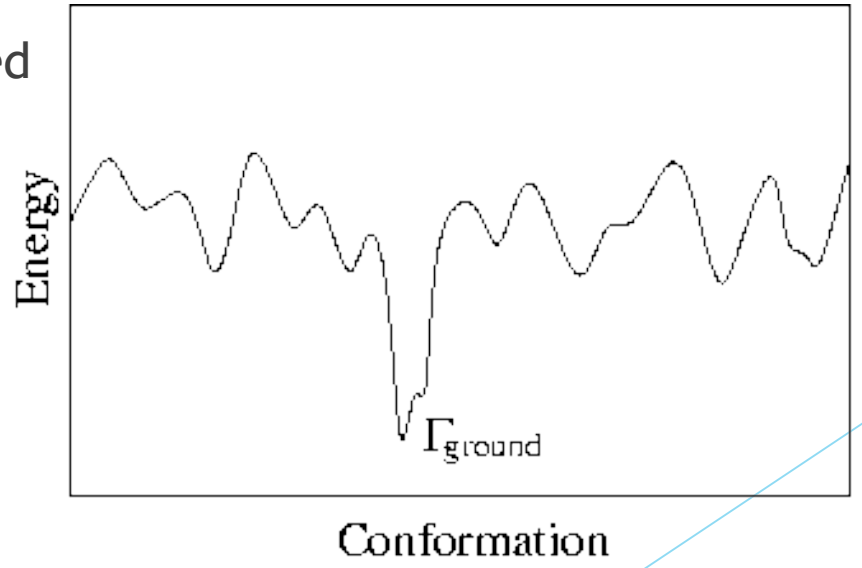
Bioinformatics – Homology Modeling

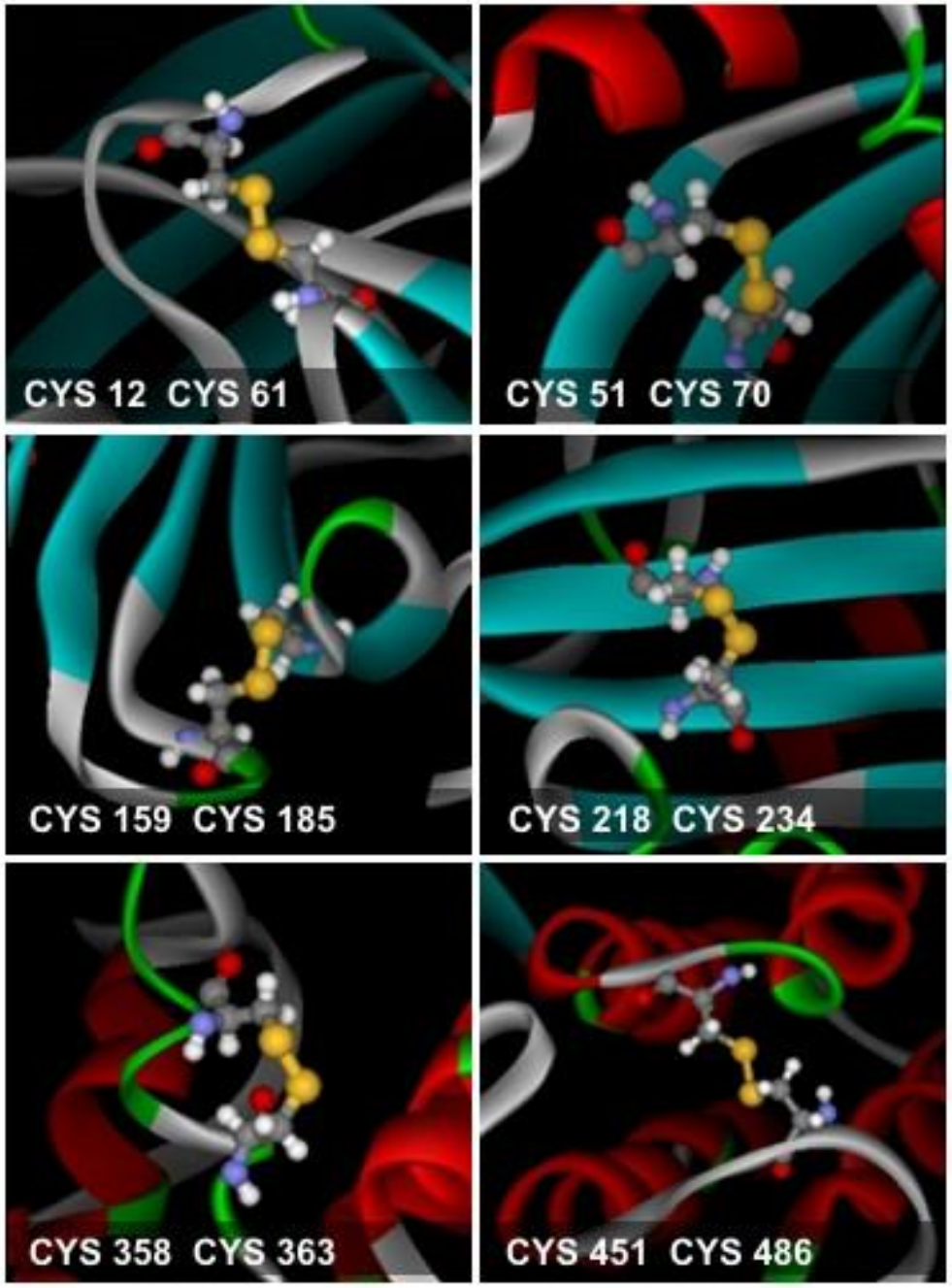


Al-Ali & Khachfe, 2007

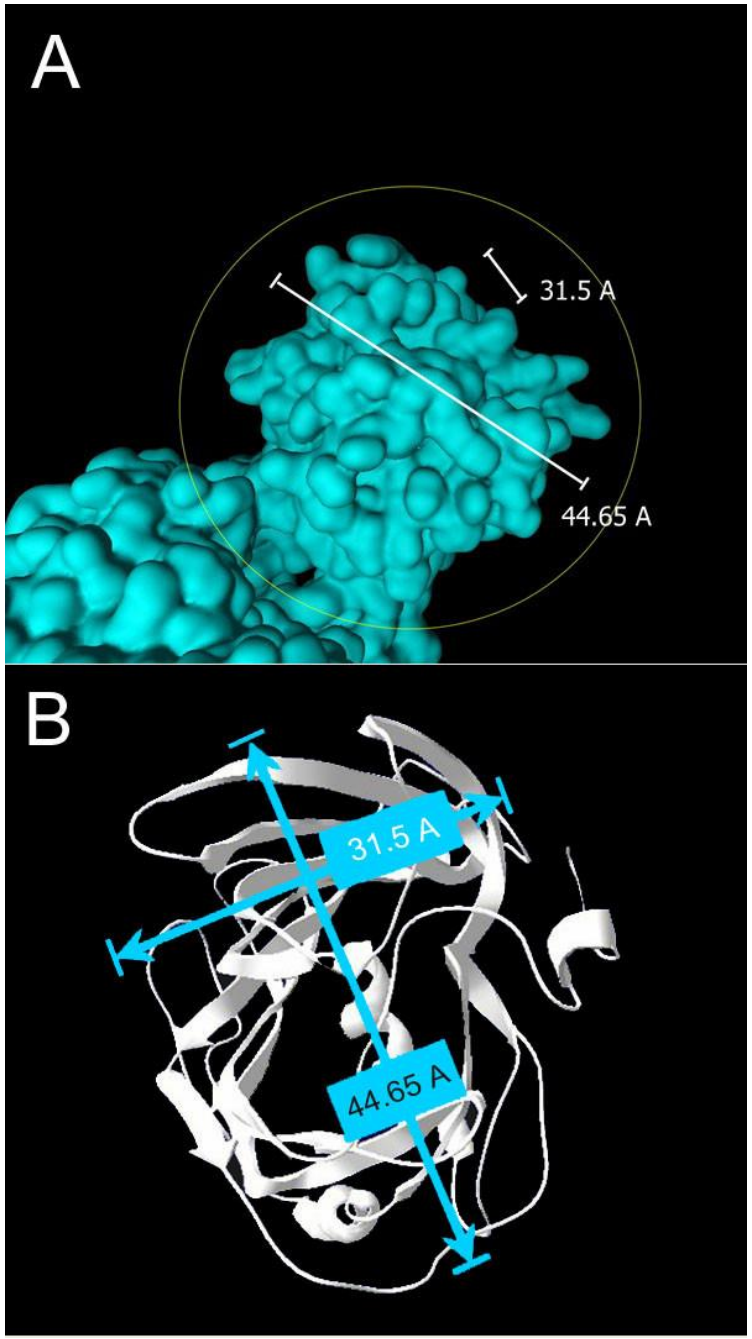
Bioinformatics – Energy minimization

- Energies are calculated by:
- $E_{bonded} = E_{bond} + E_{angle} + E_{dihedral}$
- $E_{nonbonded} = E_{electrostatic} + E_{van\ der\ Waals}$
- $E_{total} = E_{bonded} + E_{nonbonded}$

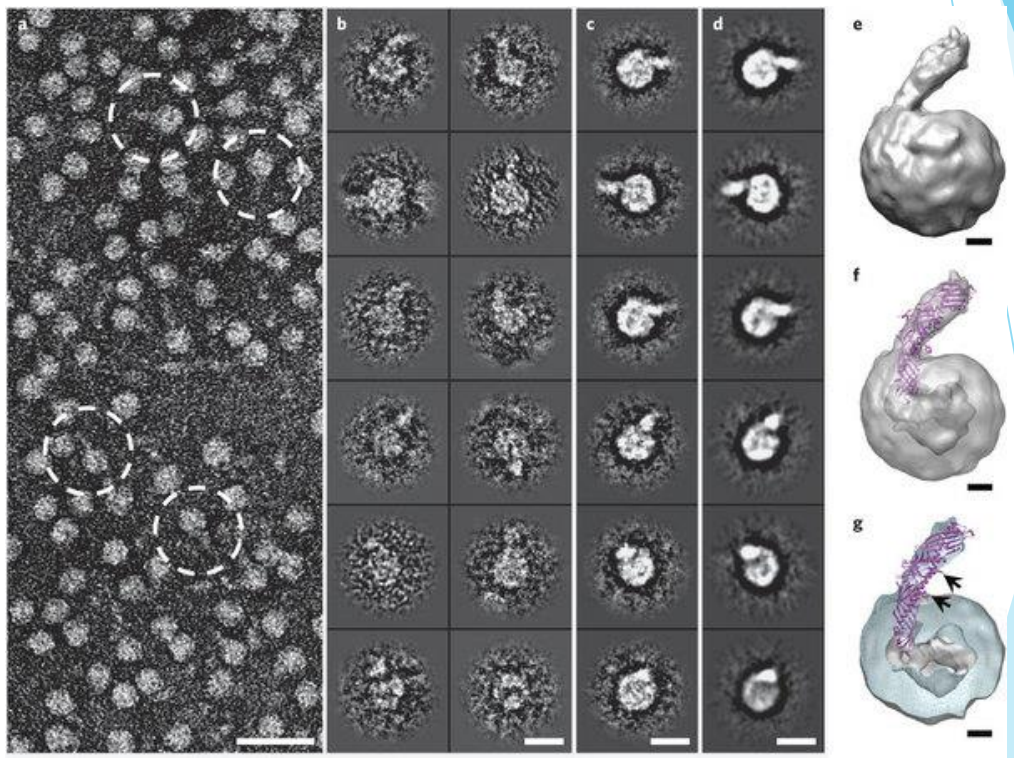




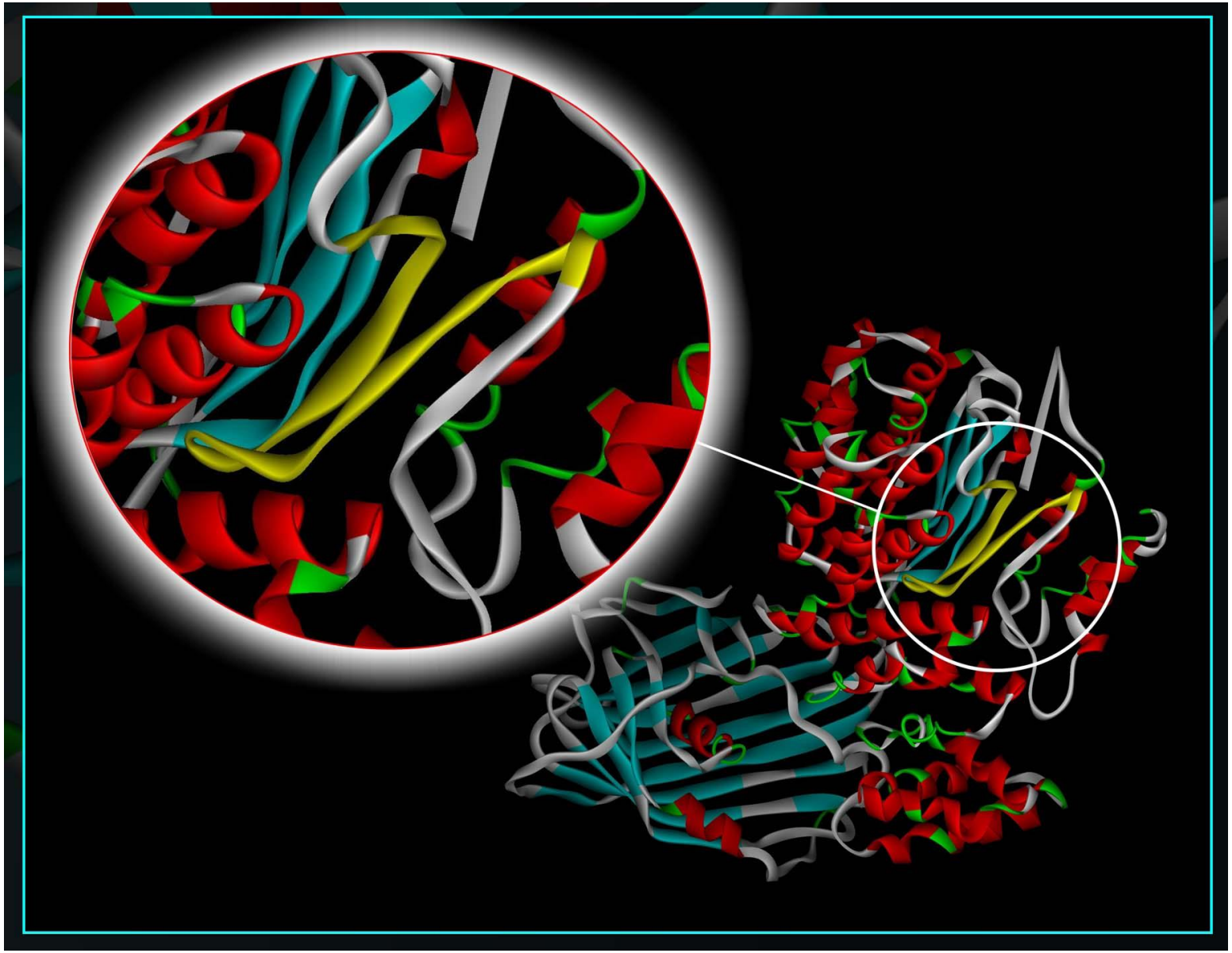
Al-Ali & Khachfe, 2007



Al-Ali & Khachfe, 2007

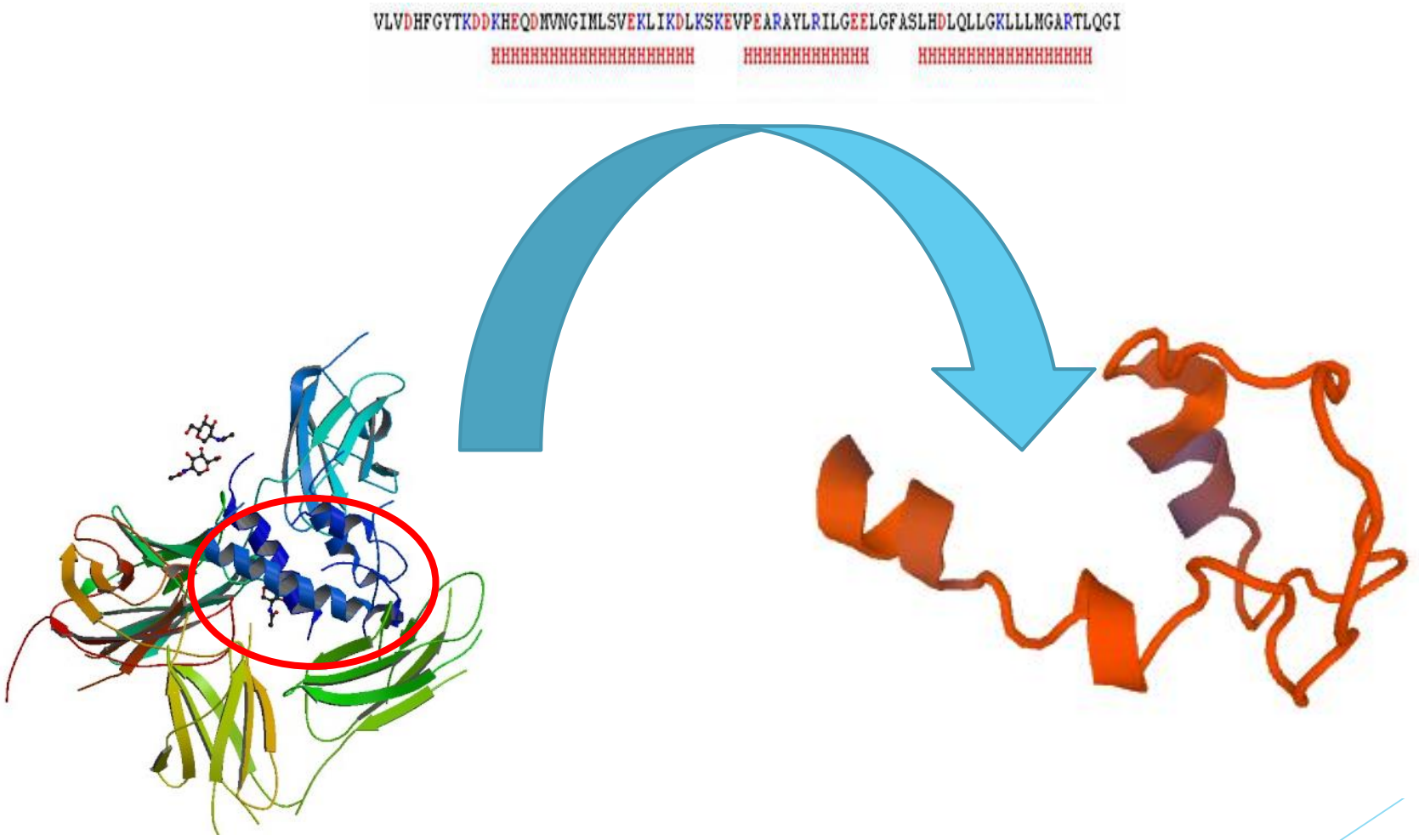


Poulos, 2001



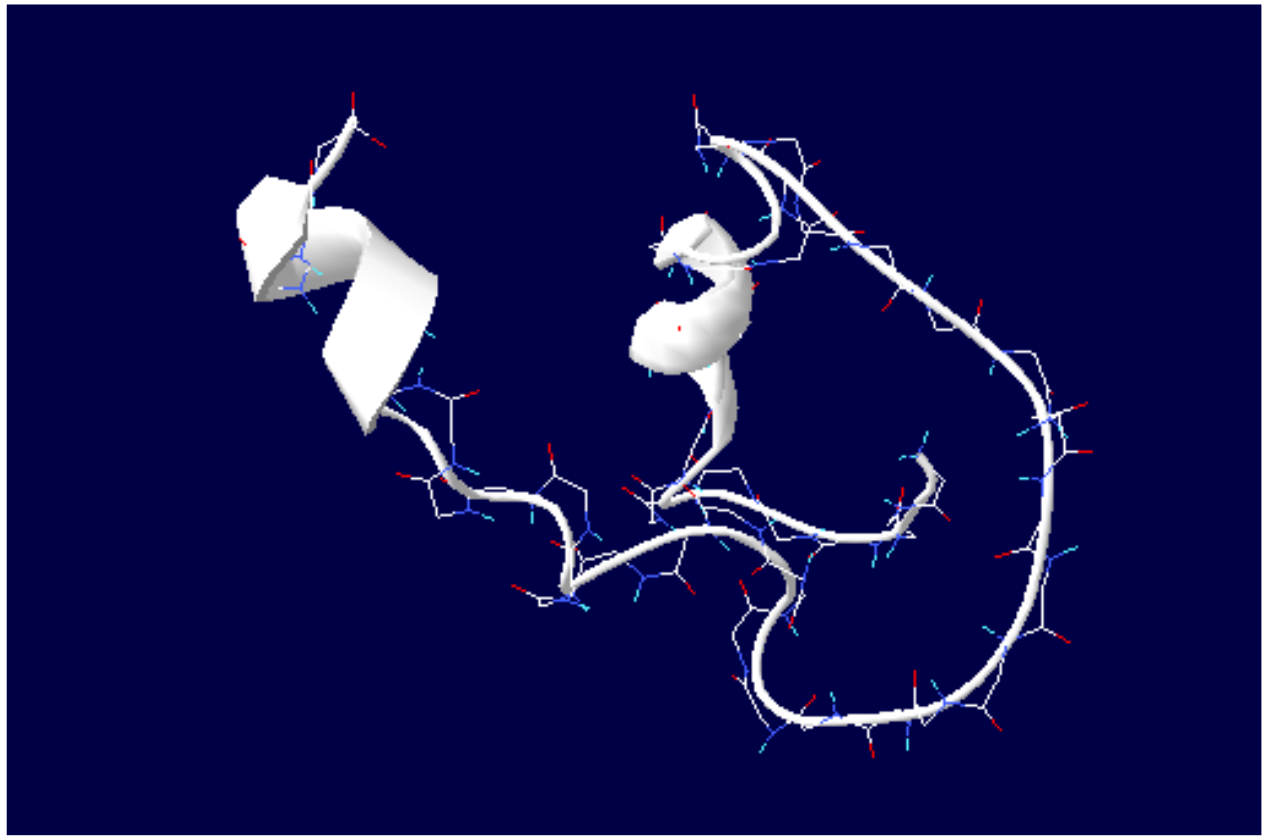
Al-Ali & Khachfe, 2007

Bioinformatics – RPS Blast



Challita & Khachfe, 2015

Bioinformatics – Success story



- Total energy before minimization is 205.602 KJ/mol
- Total energy after minimization is -327.502

Challita & Khachfe, 2015


рахмат
danke
謝謝
ngiyabonga
spas
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
kiitos
dankie
thank you
gracias
хвала
nanni
nandri
dhanyavad
maururu
köszönöm
asante
manana
bedankt
hvala
gràcie
bayarlalaa
akun
dankon
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rahmet
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তোমাকে ধন্যবাদ
감사합니다
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