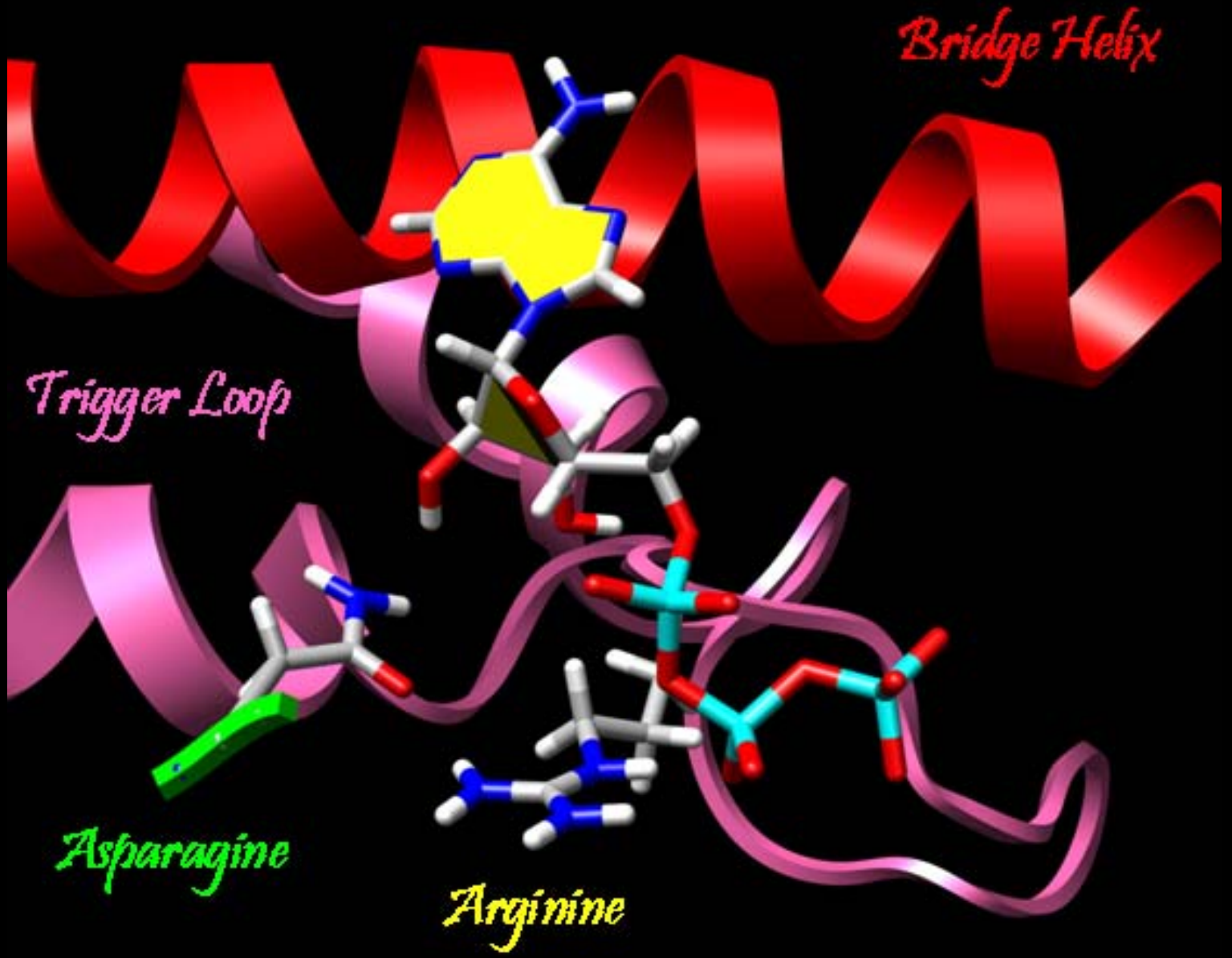
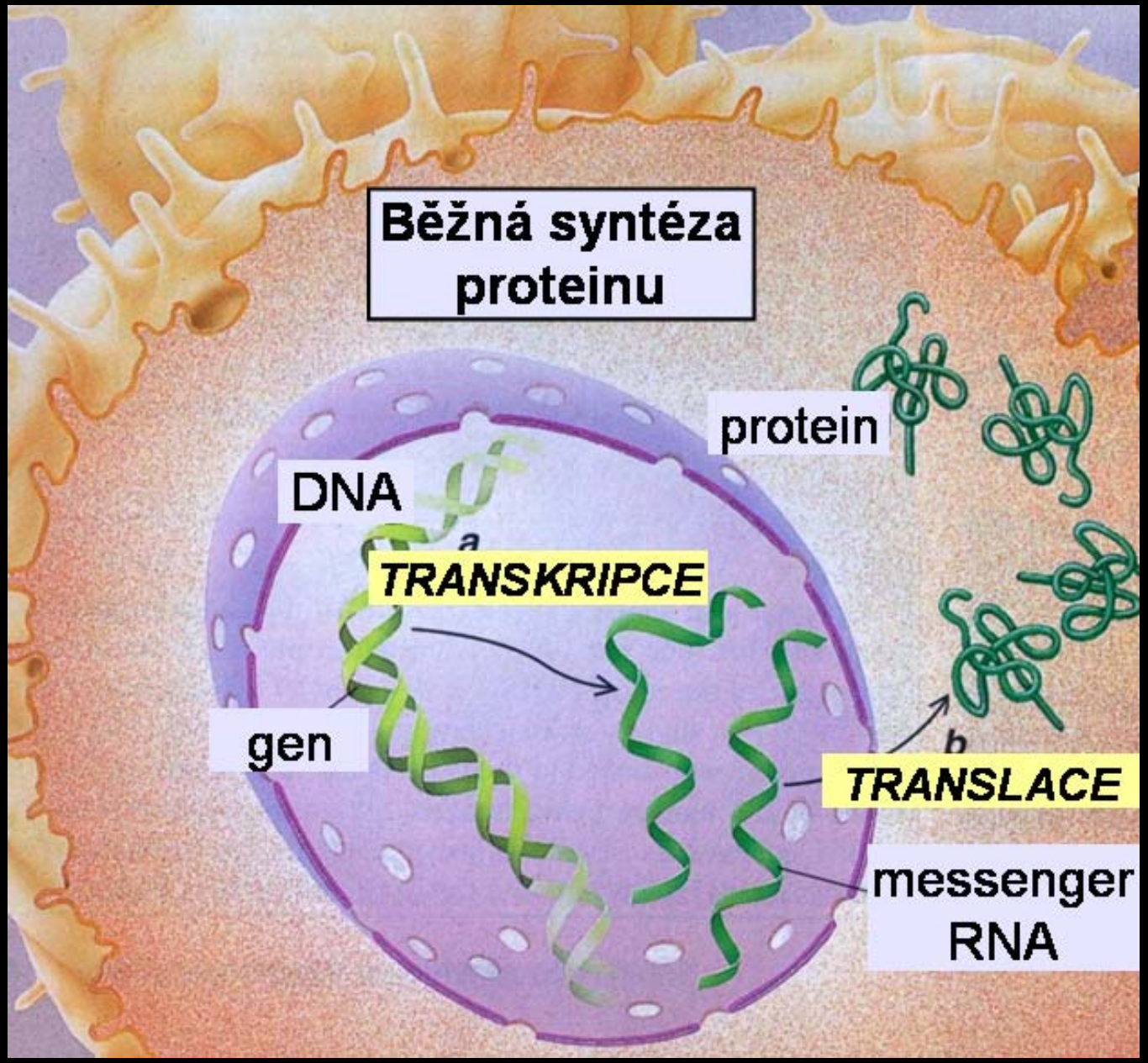
BCM316 Počítačové modelování biomolekul

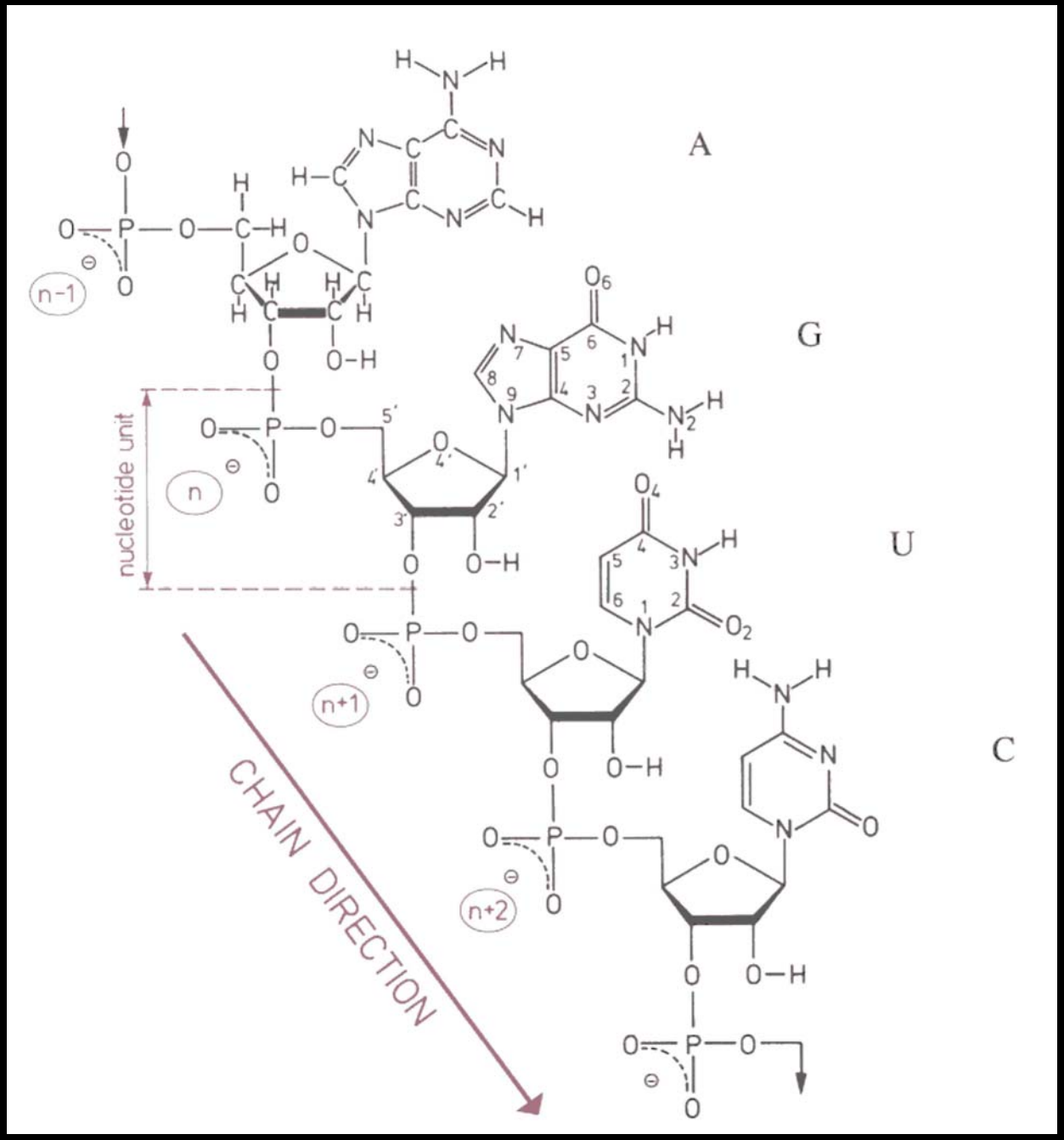
Ivan Barvík (Fyzikální Ústav, MFF UK)

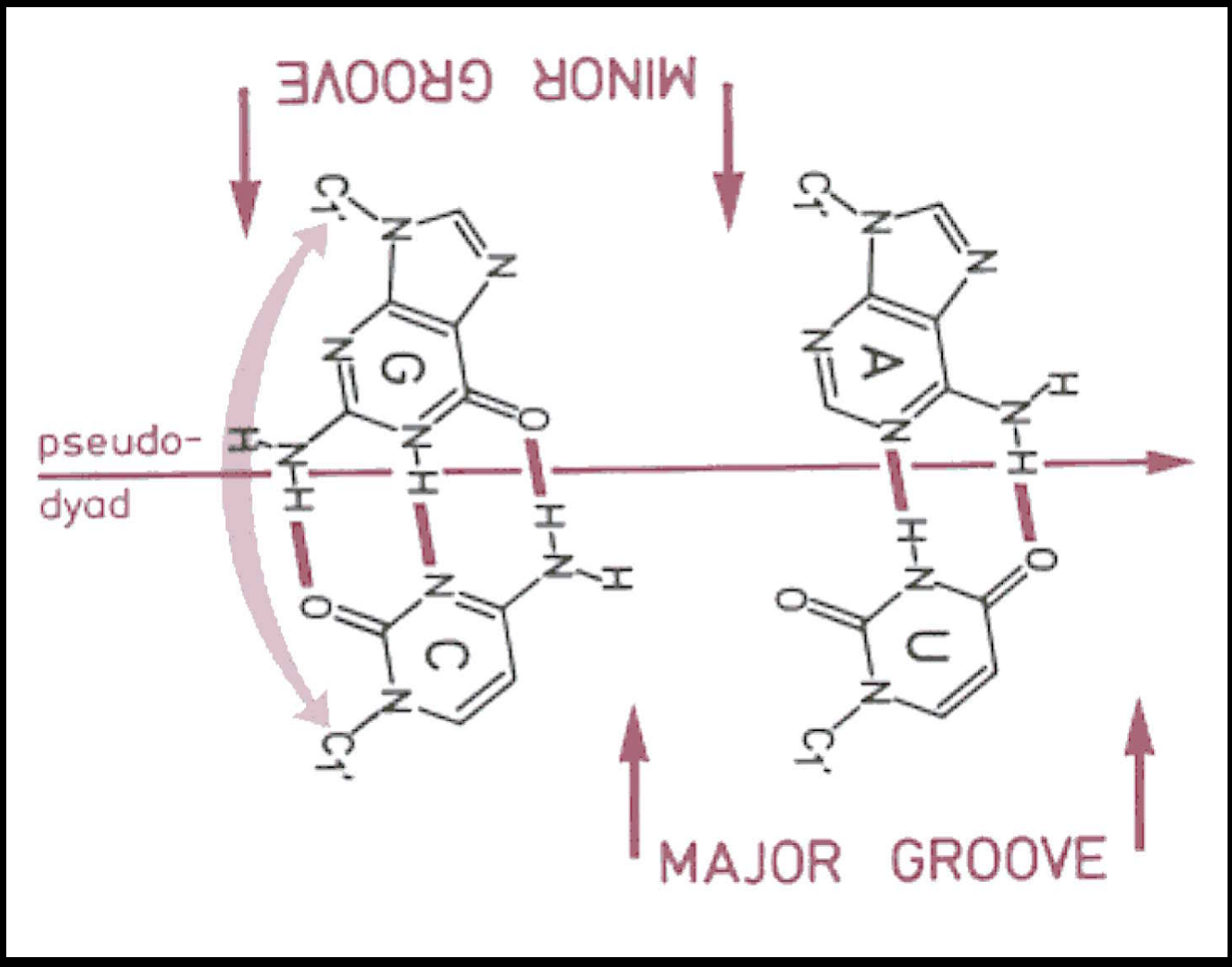


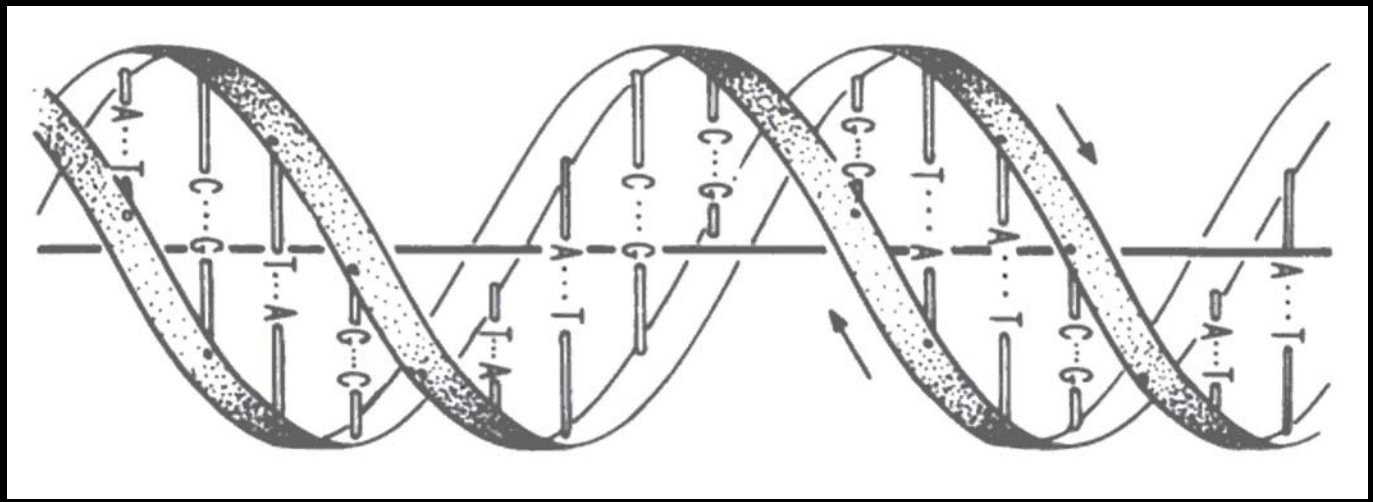
Nukleové kyseliny – Proteiny – Buněčné membrány



Nukleové kyseliny


A
G
U
C
nucleotide unit
n-1
n
n+1
n+2
CHAIN DIRECTION


MINOR GROOVE
pseudo-
dyad
MAJOR GROOVE



Cavendishova laboratoř *(William Lawrence Bragg* *1915 za fyziku + W.H.Bragg)*

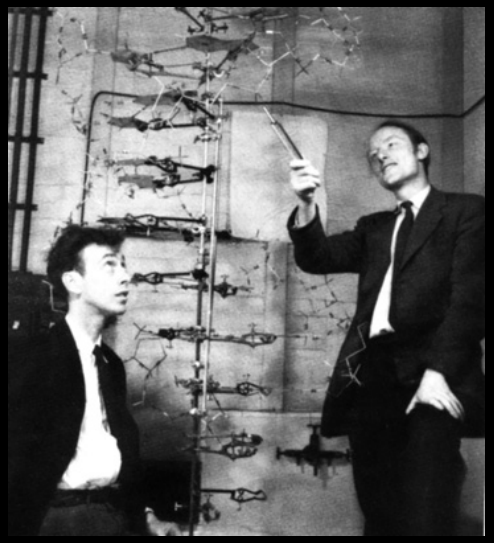
Linus Pauling – trojšroubovice / Petr Pauling

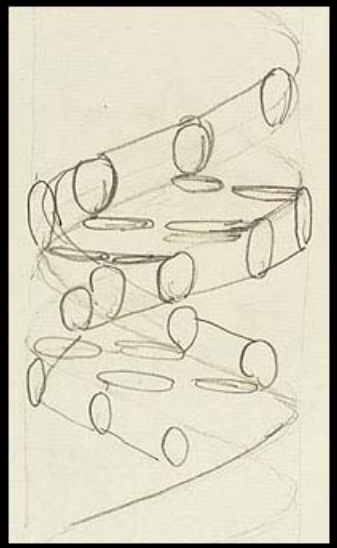
James D. Watson
Francis Crick
1962
za medicínu a fyziologii

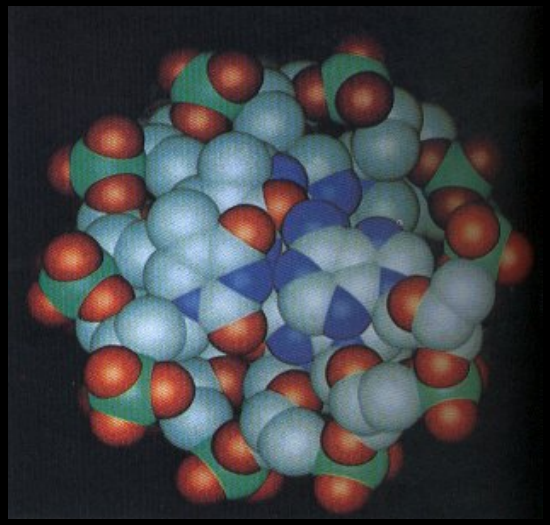
1962
za chemii
Max Perutz
John Kendrew

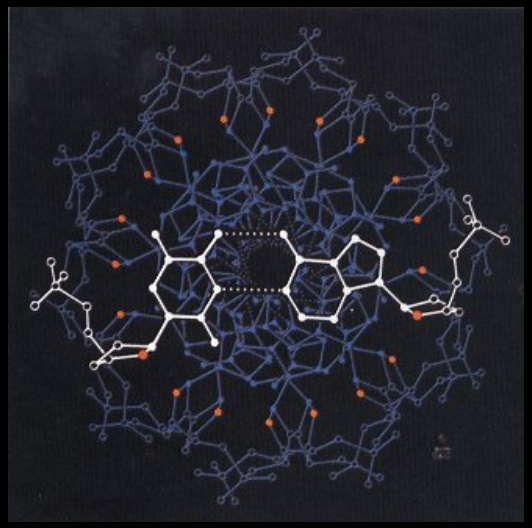
King‘s College v Londýně

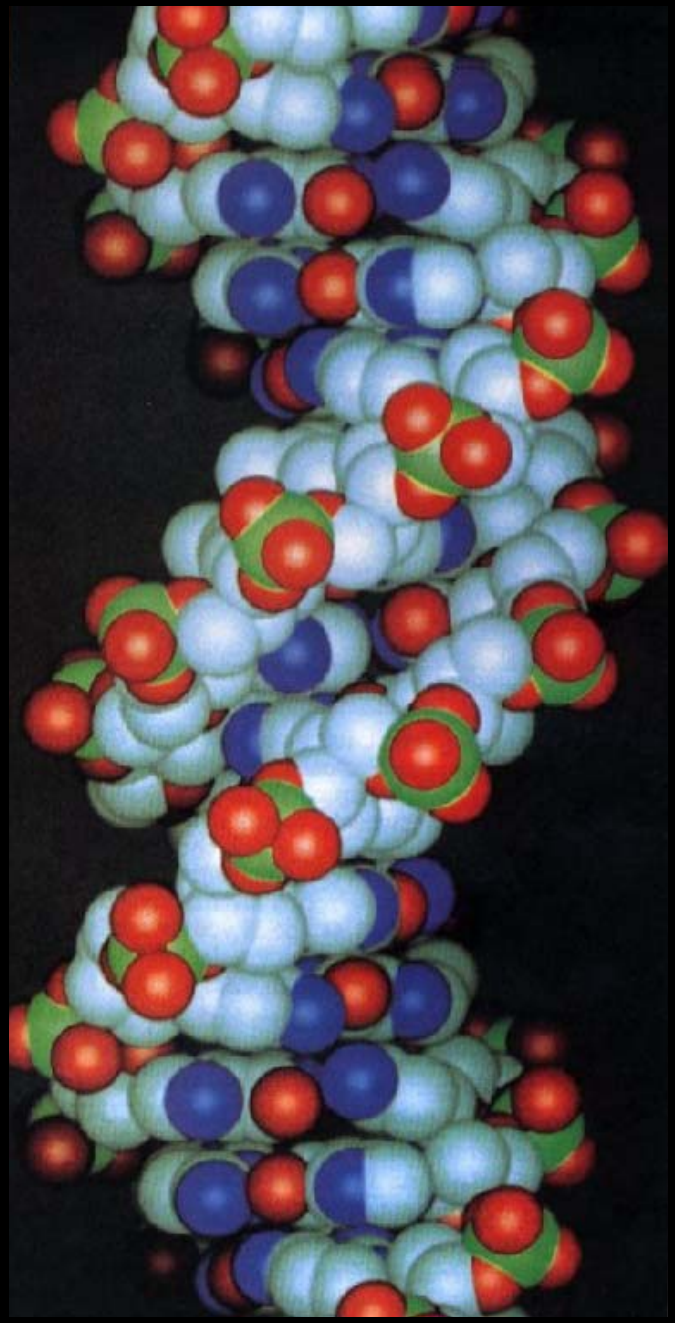
Rosalinda Franklinová
Maurice Wilkins
1962
za medicínu a fyziologii

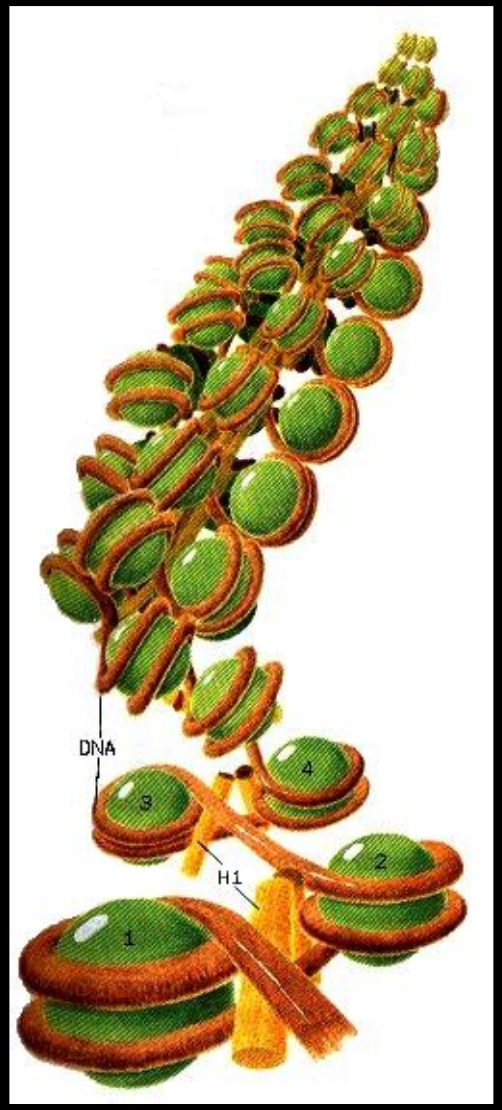


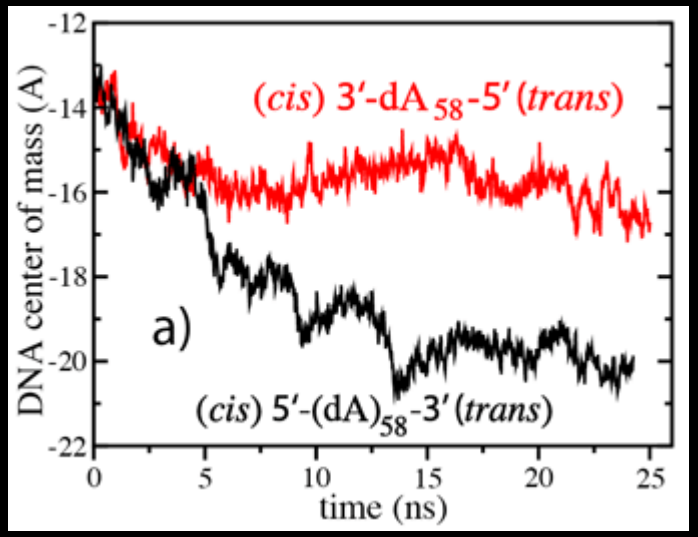


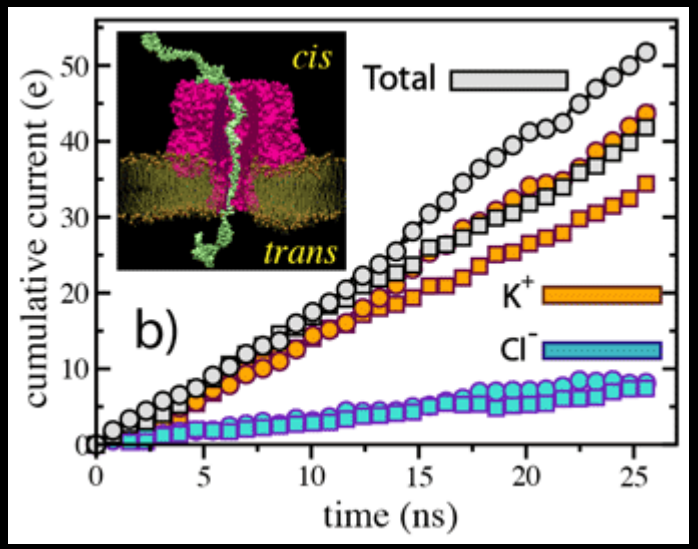


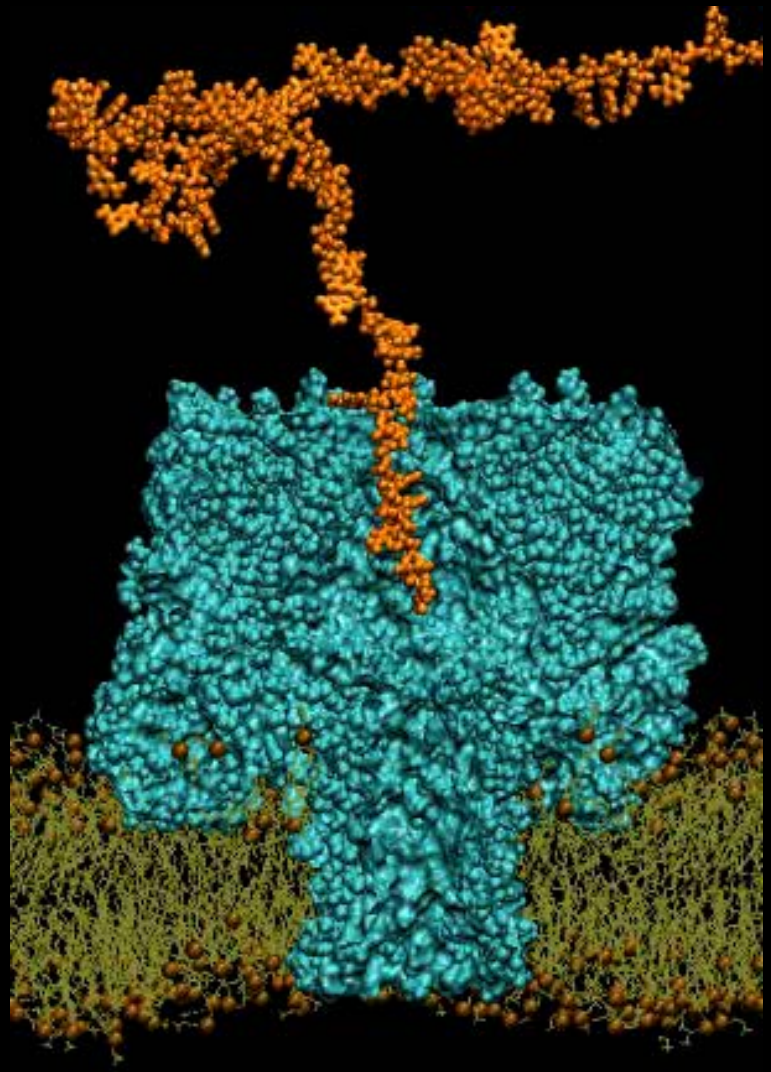




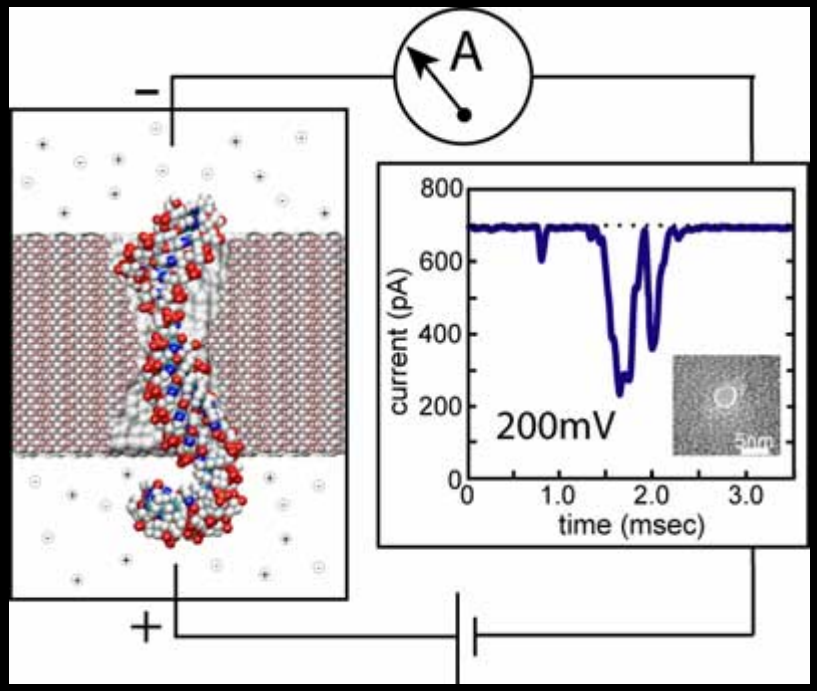

DNA
4
3
2
H1
1

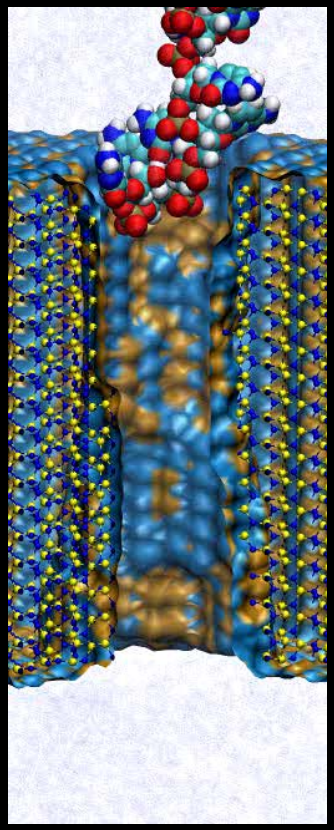

DNA center of mass (A)
-12
-14
-16
-18
-20
-22
0
5
10
15
20
25
time (ns)
(cis) 3′-dA 58-5′ (trans)
a)
(cis) 5′-(dA)58-3′ (trans)

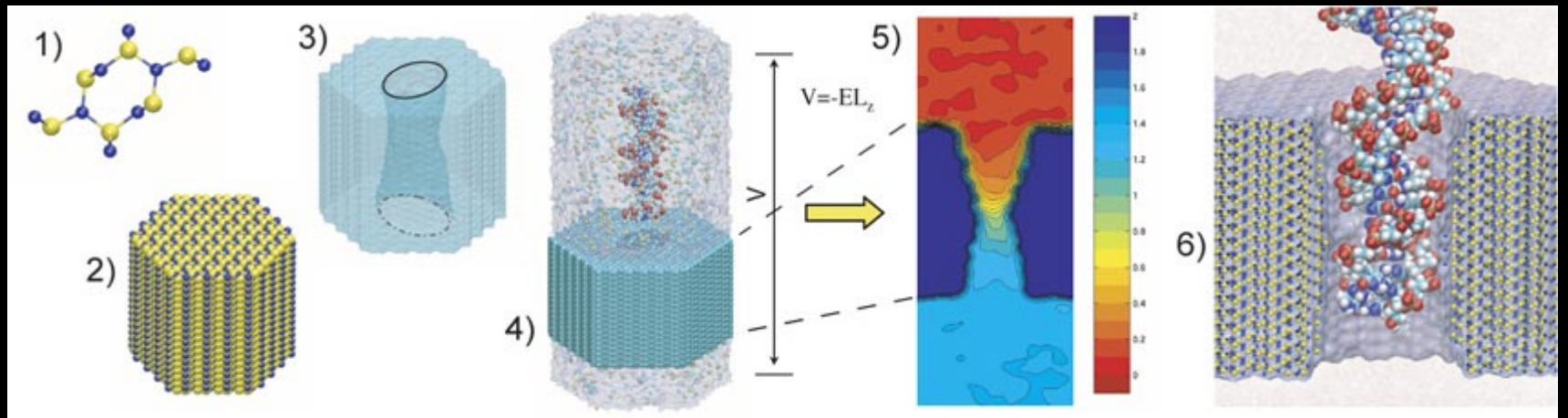

cumulative current (e)
50
40
30
20
10
0
0
5
10
15
20
25
time (ns)
cis
trans
Total
K+
Cl-
b)

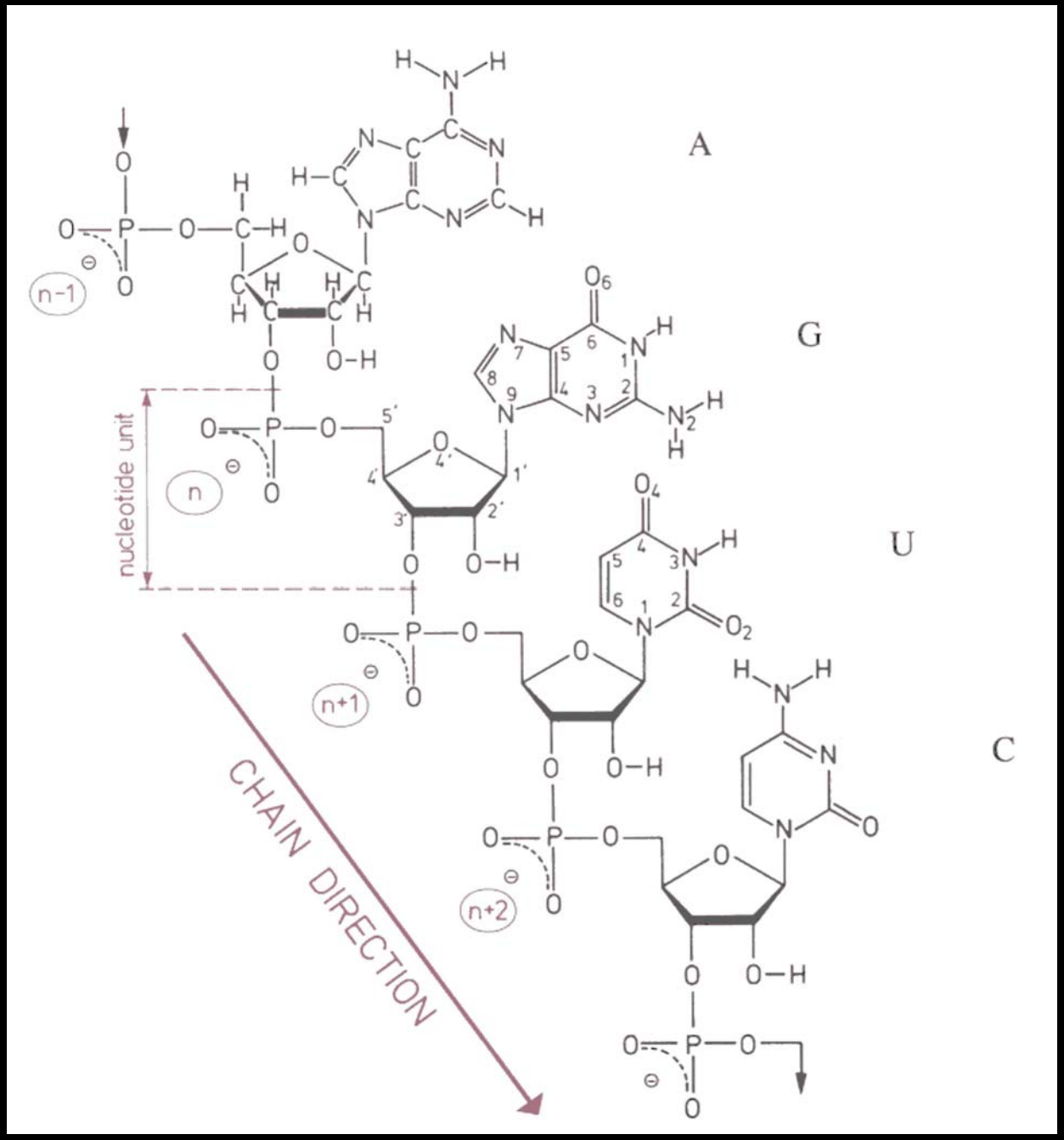


Electric detection of individual DNA molecules with a nanopore

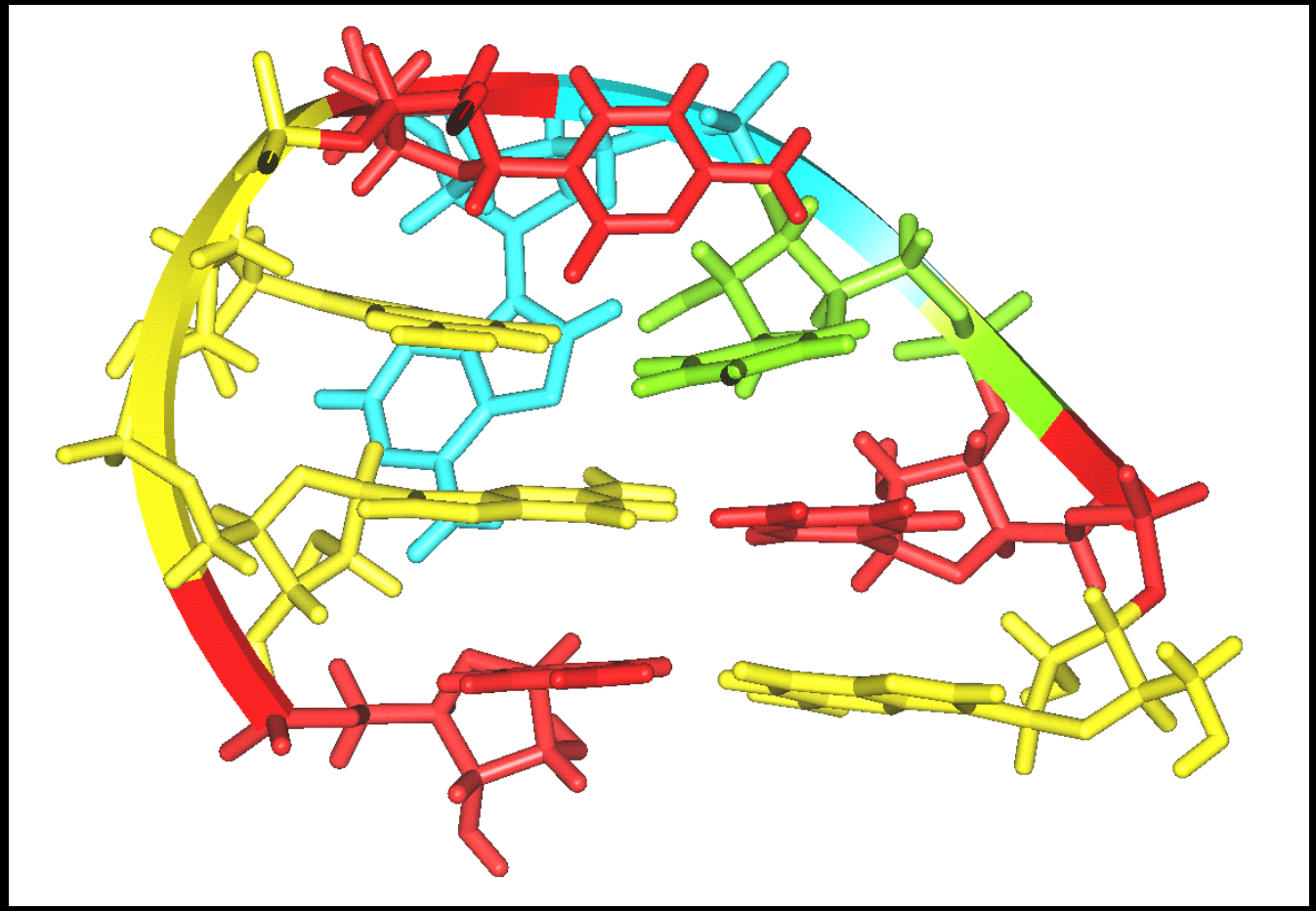




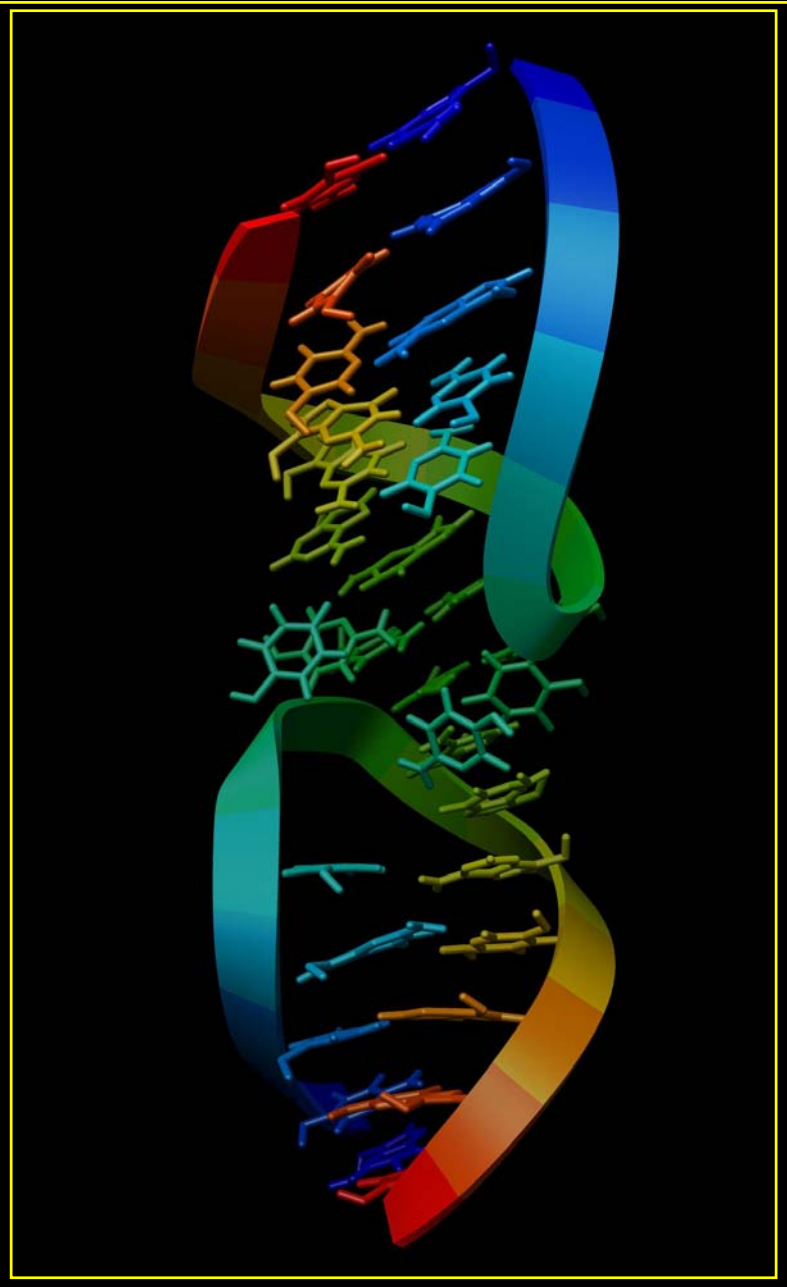


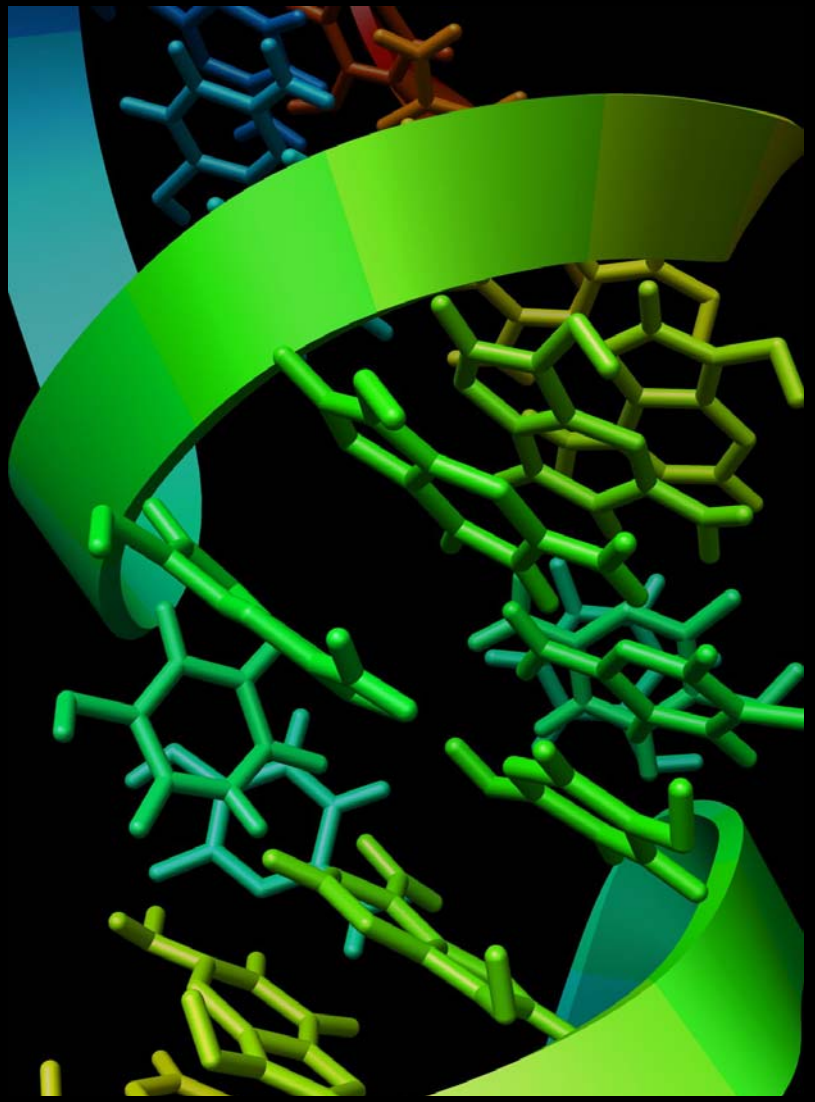

A
G
U
C
nucleotide unit
n-1
n
n+1
n+2
CHAIN DIRECTION

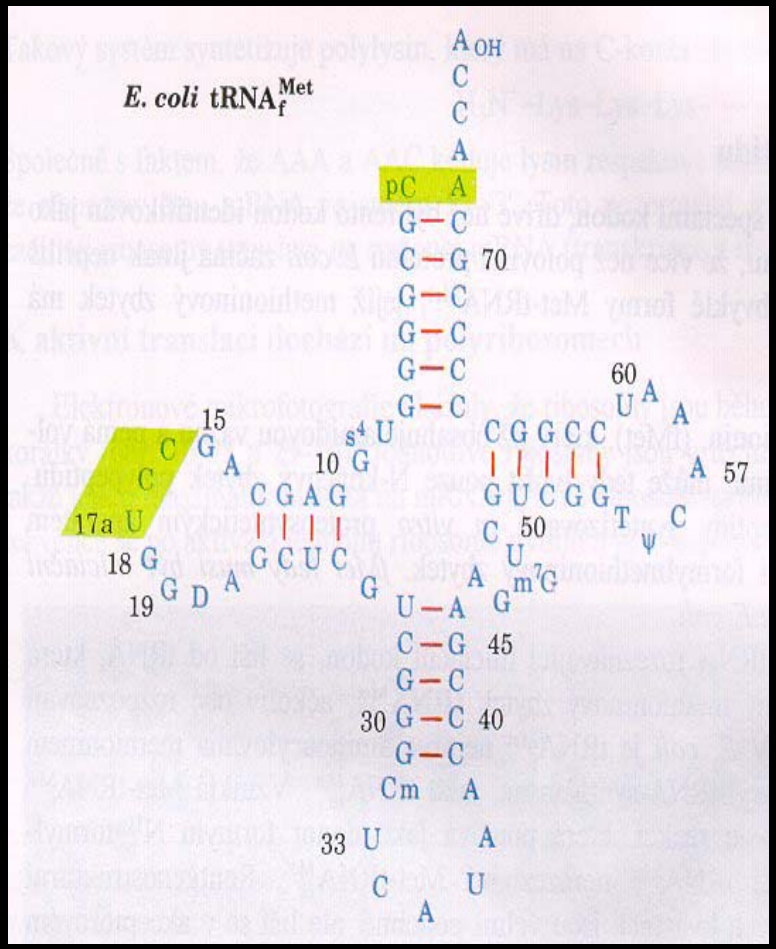
Hairpin loops - Vlásenky

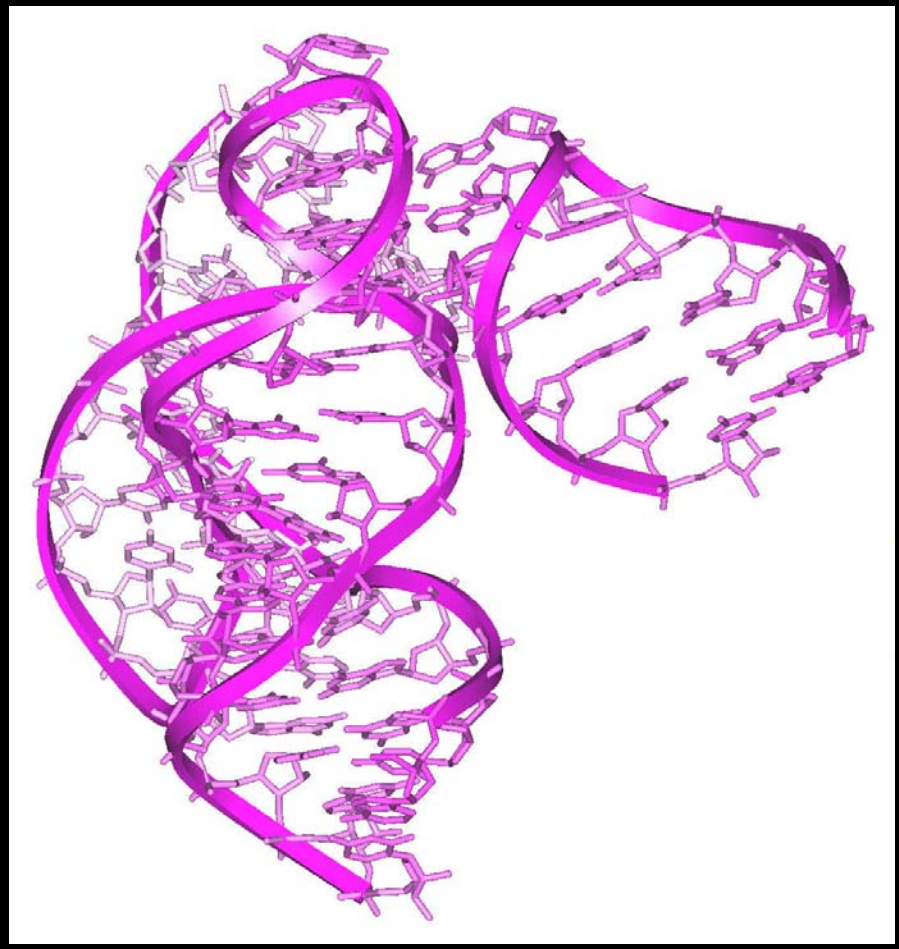


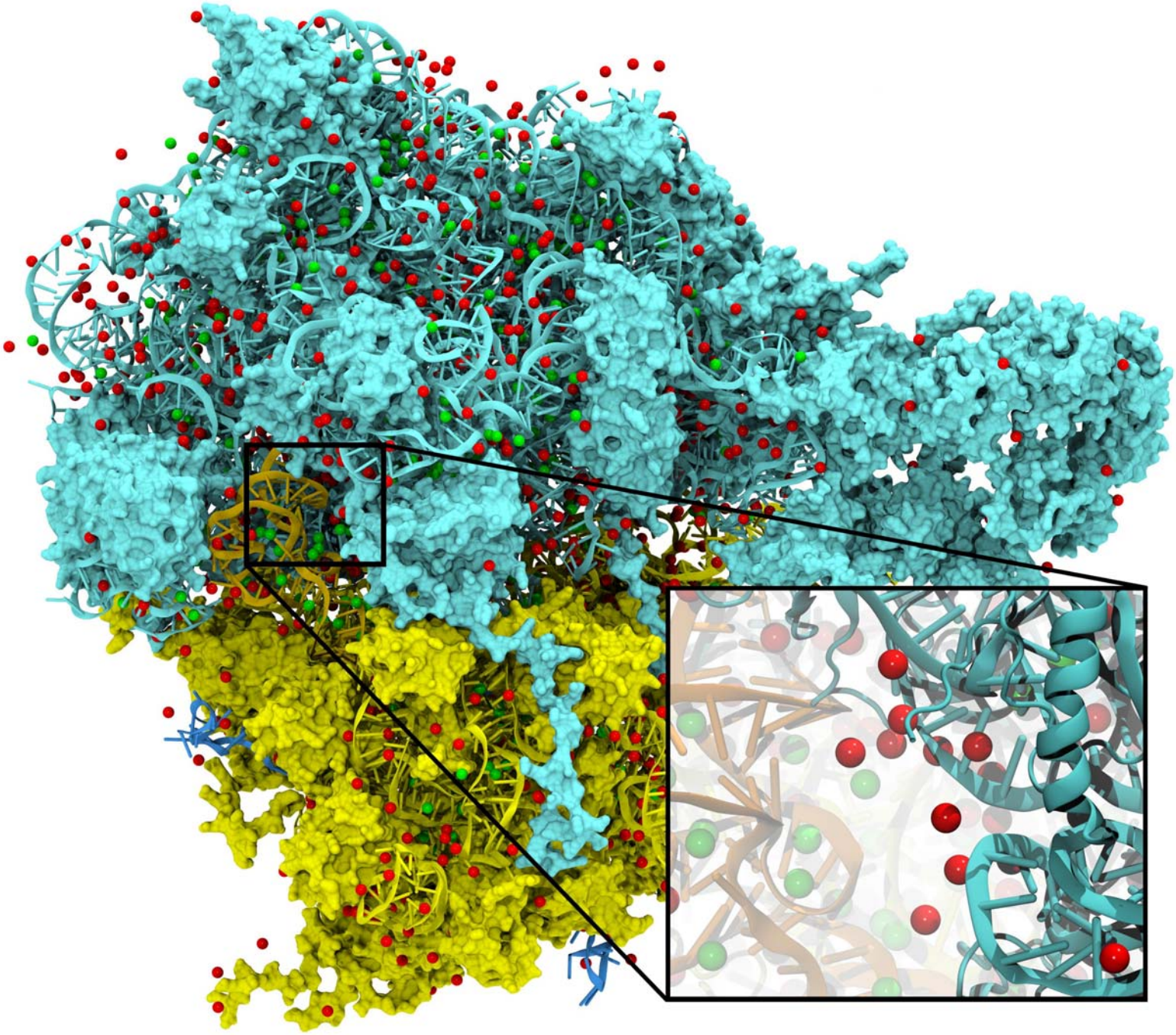
TAR.TAR* kissing komplex



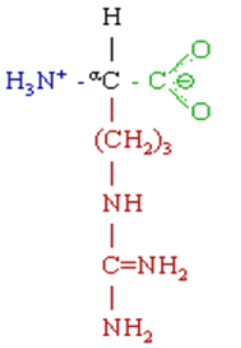


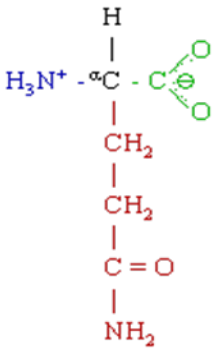

E. coli tRNA$_f^{Met}$
A OH
C
C
A
pC A
G—C
C—G 70
G—C
G—C
G—C
G—C
60
U A A
15
C G
C
17a U
18 G
19 G D A
A
10 G
s^{4}U
C G A G
G C U C
C G G C C
G U C G G
C 50
U
A m^{7}G
A 57
T C
ψ
G
U—A G
C—G 45
G—C
30 G—C 40
G—C
Cm A
33 U A
C U
A

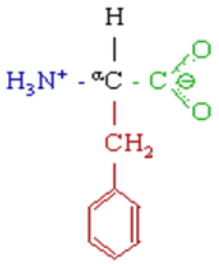


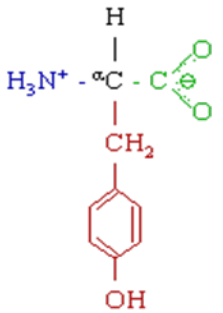


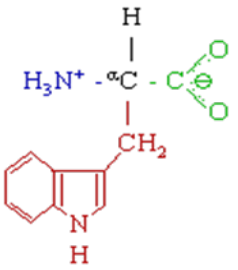
Struktura proteinů

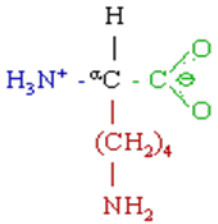

Arginine
(Arg / R)

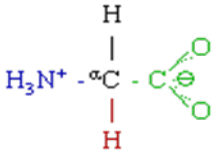

Glutamine
(Gln / Q)

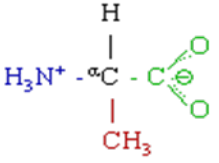

Phenylalanine
(Phe / F)

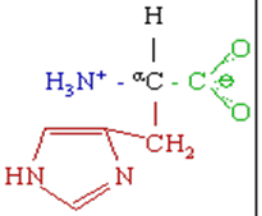

Tyrosine
(Tyr / Y)

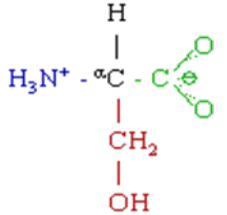

Tryptophan
(Trp, W)

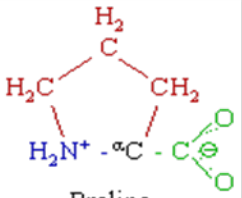

Lysine
(Lys / L)

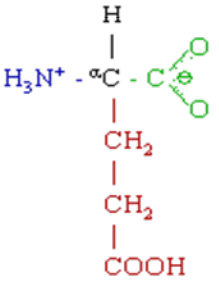

Glycine
(Gly / G)

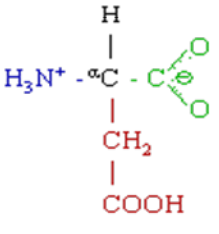

Alanine
(Ala / A)

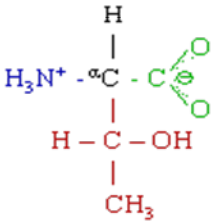

Histidine
(His / H)

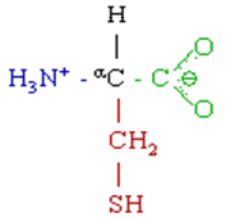

Serine
(Ser / S)

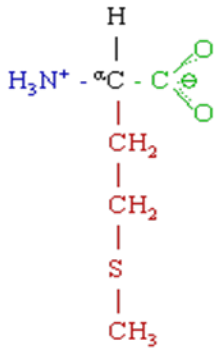

Proline
(Pro / P)

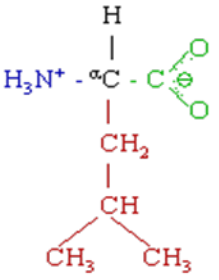

Glutamic Acid
(Glu / E)

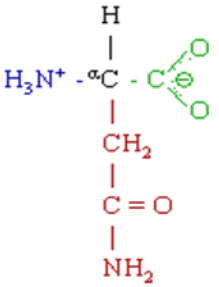

Aspartic Acid
(Asp / D)

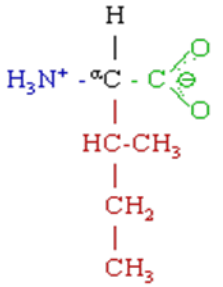

Threonine
(Thr / T)

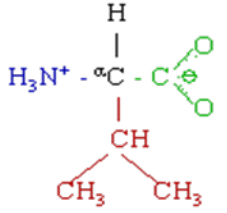

Cysteine
(Cys / C)

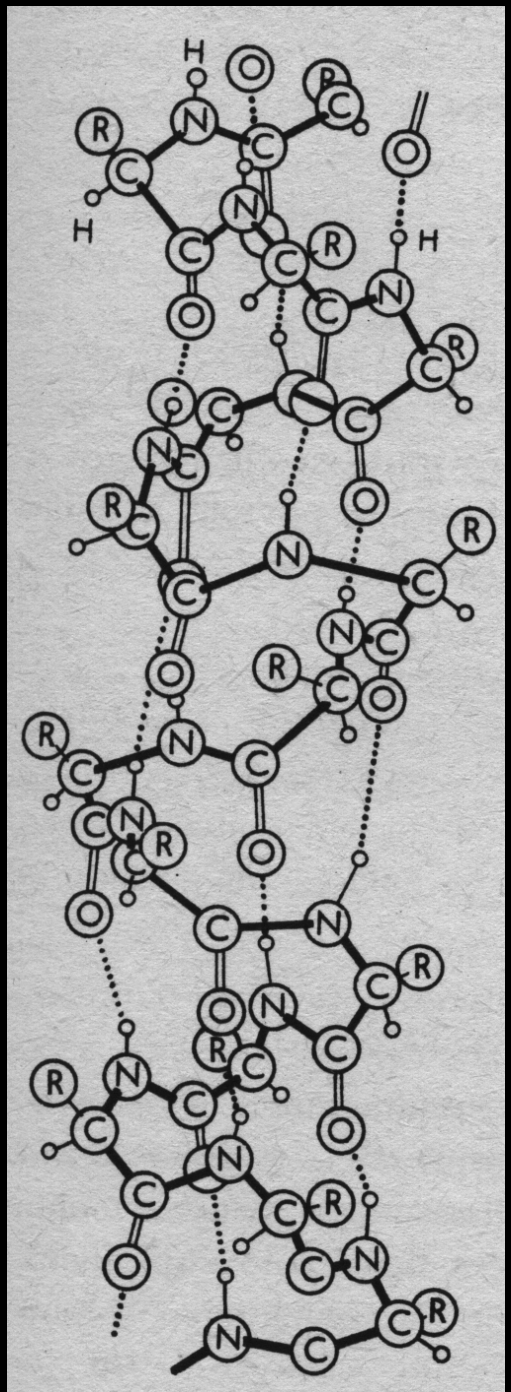

Methionine
(Met / M)

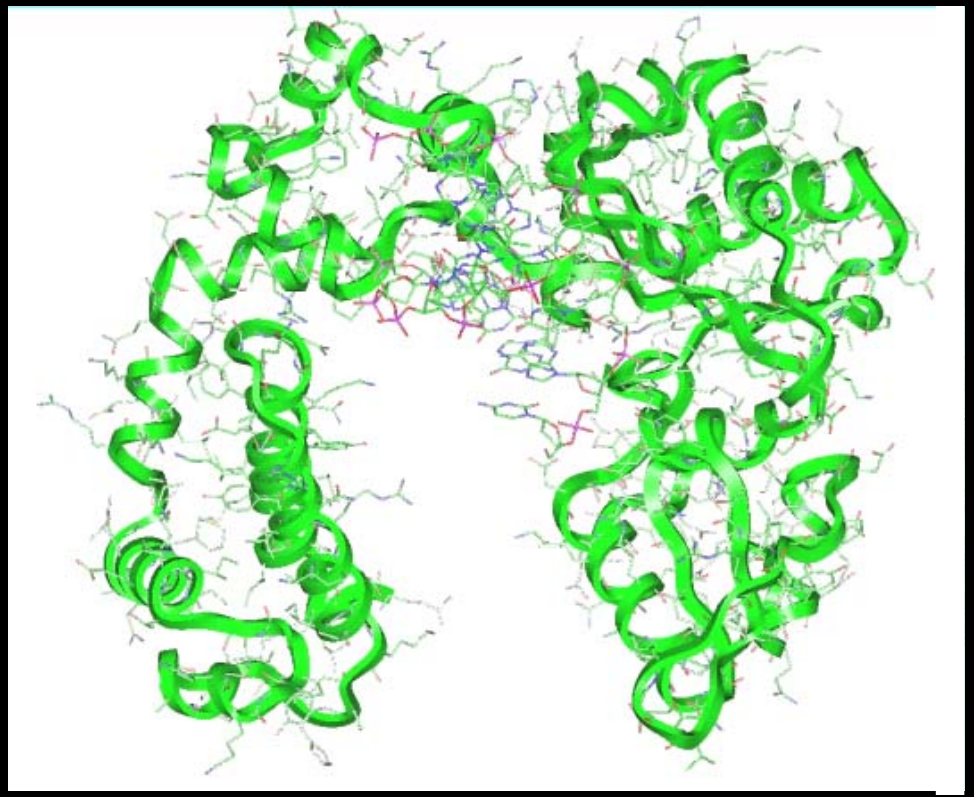

Leucine
(Leu / L)

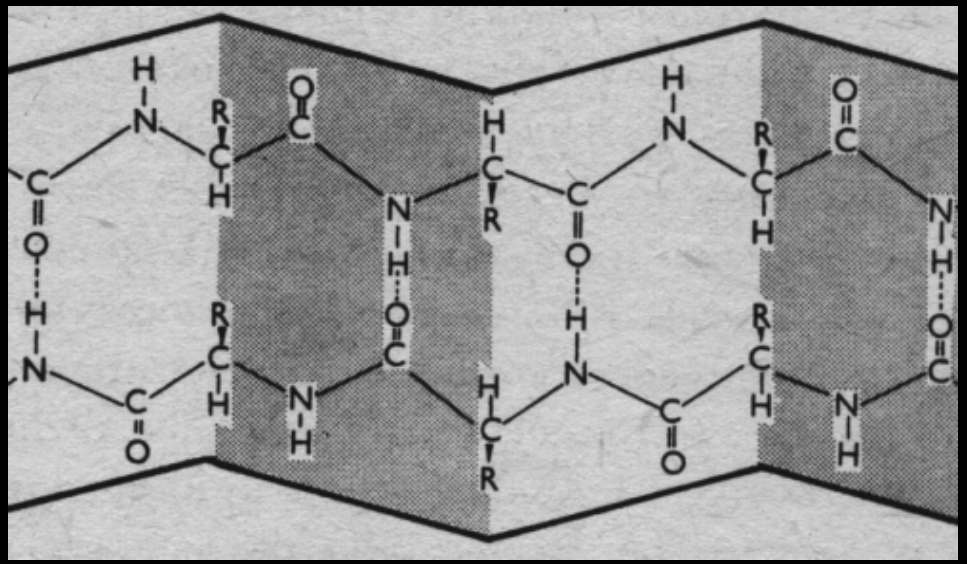

Asparagine
(Asn / N)


Isoleucine
(Ile / I)

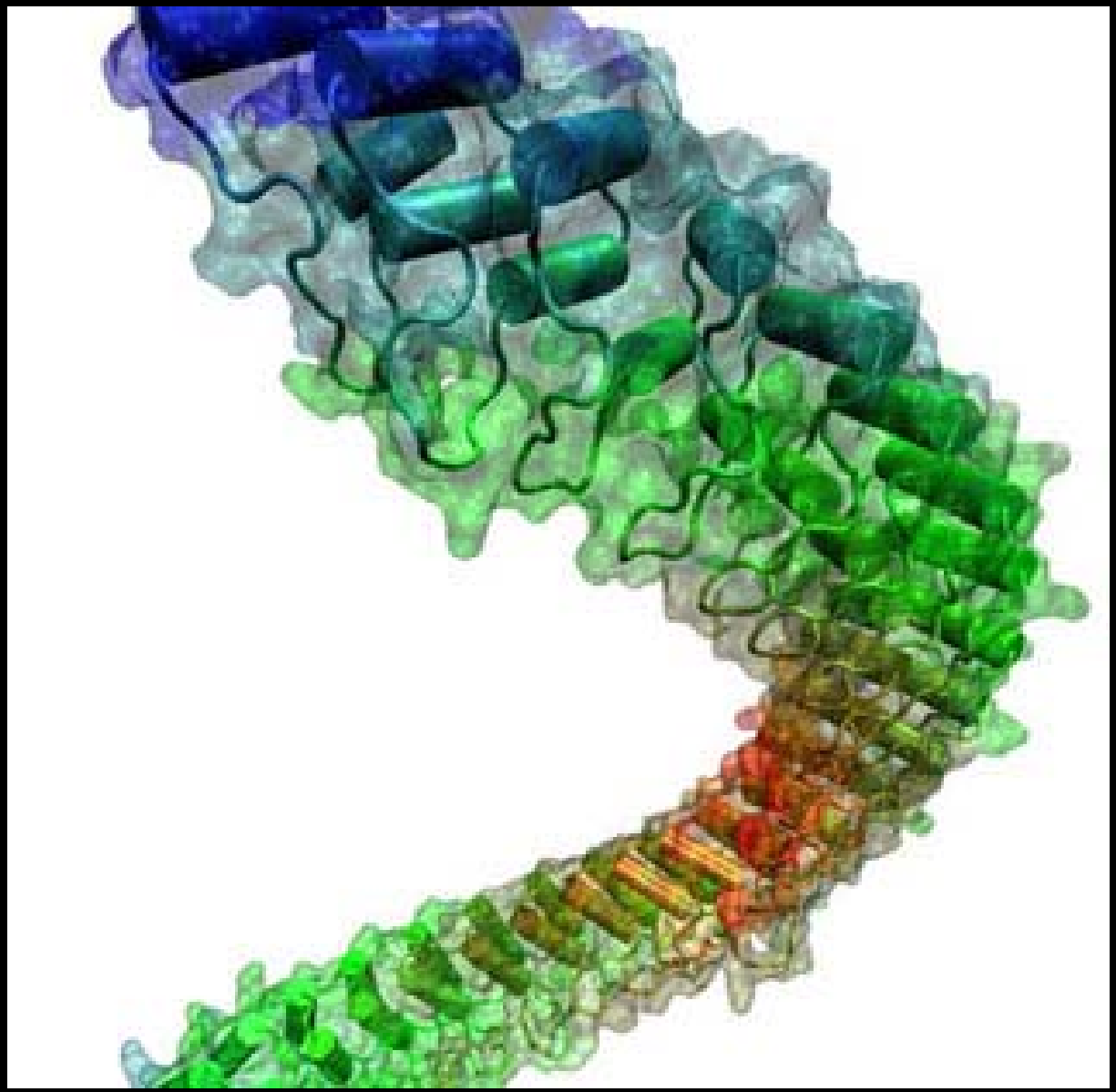

Valine
(Val / V)



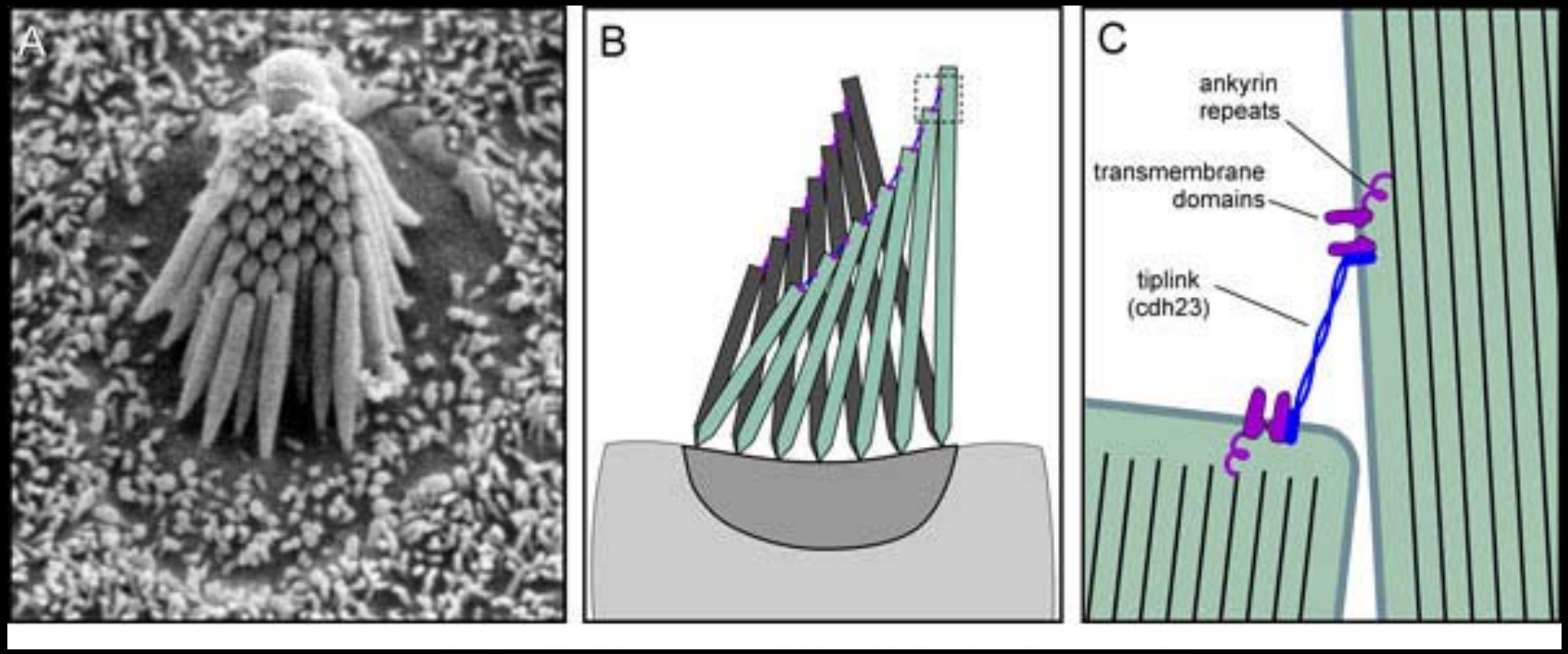




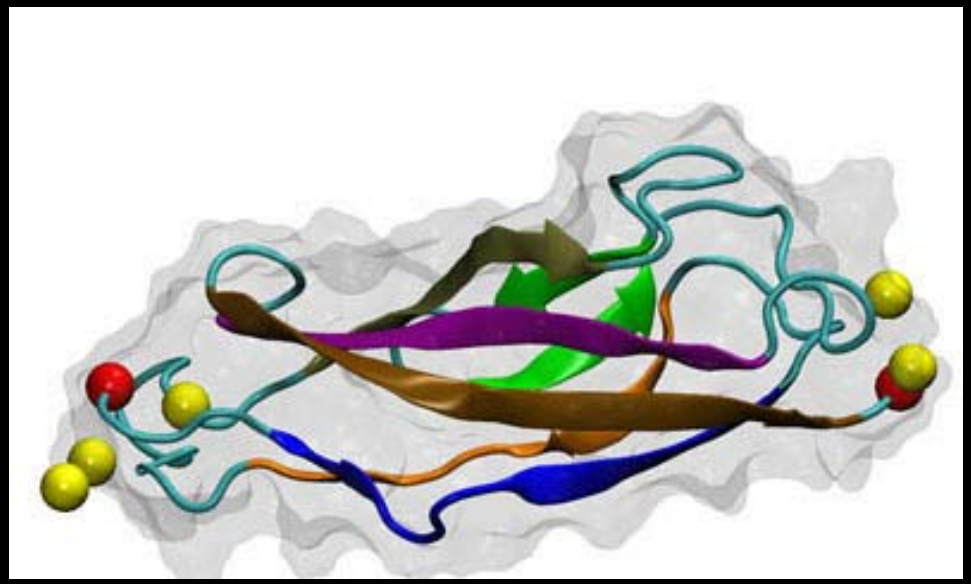
Molecular basis of hearing

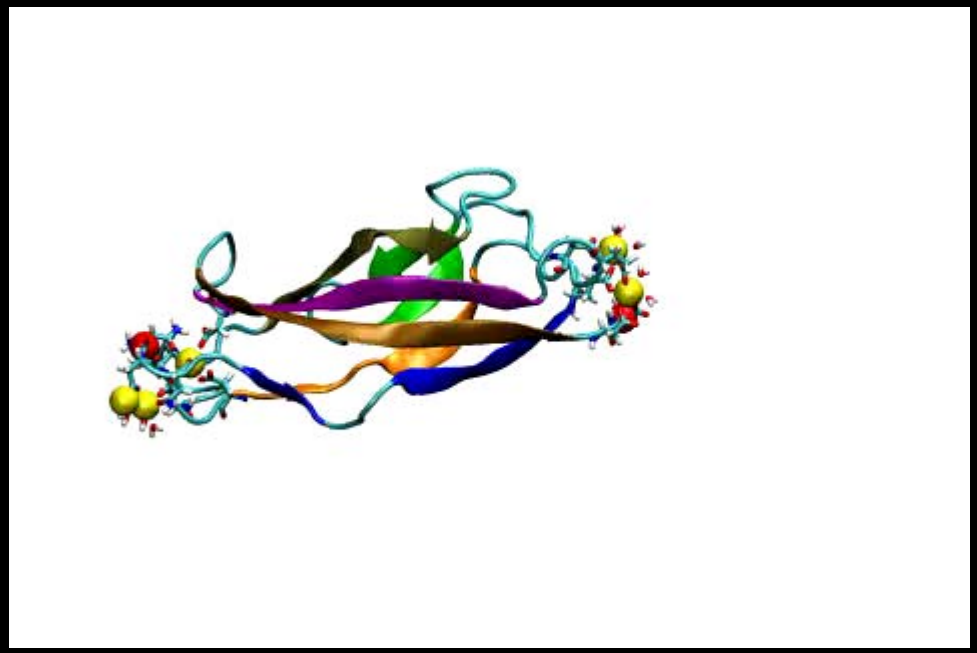


Molecular basis of hearing

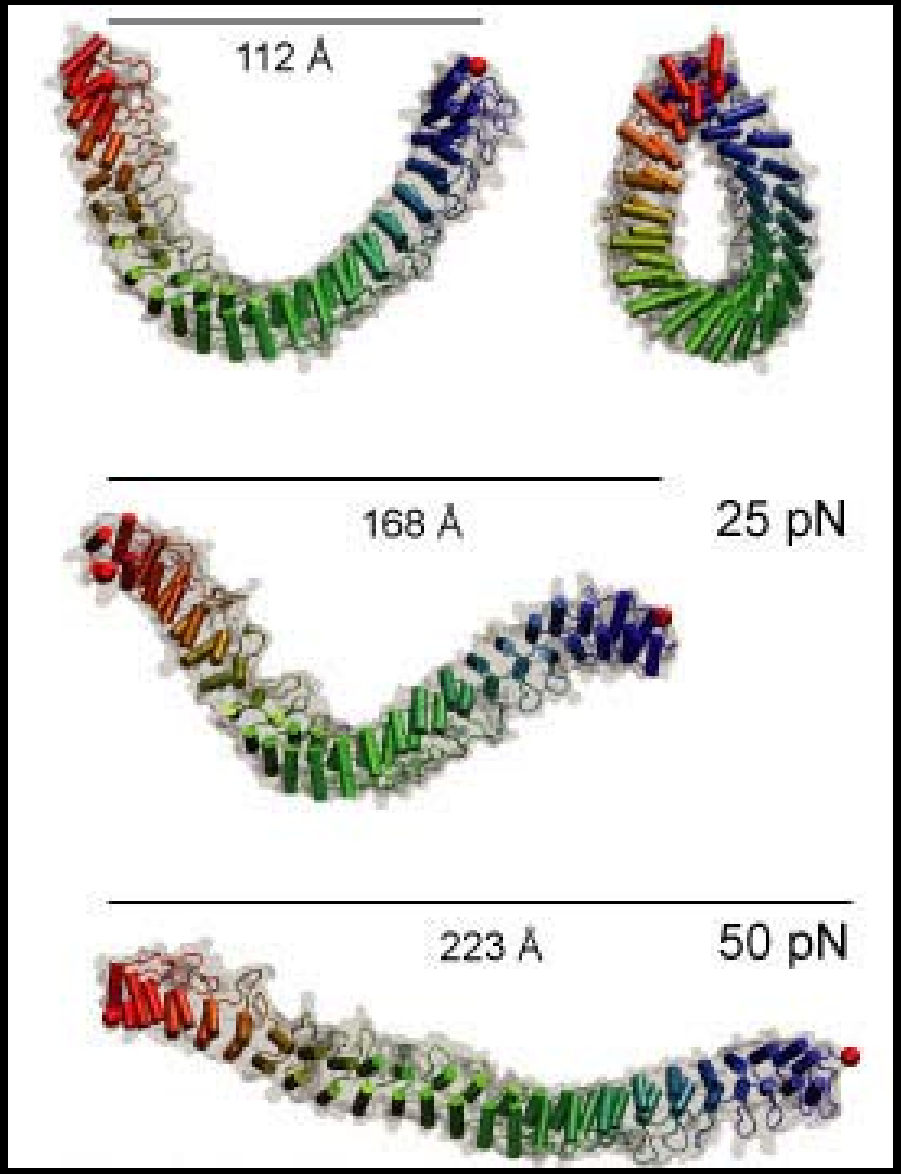


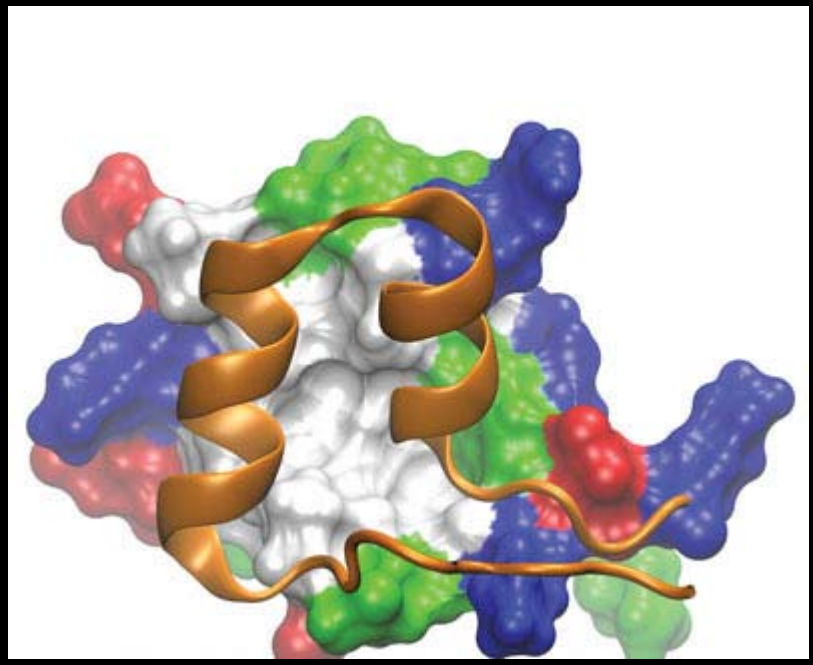
Cadherin: The Stiff Spring



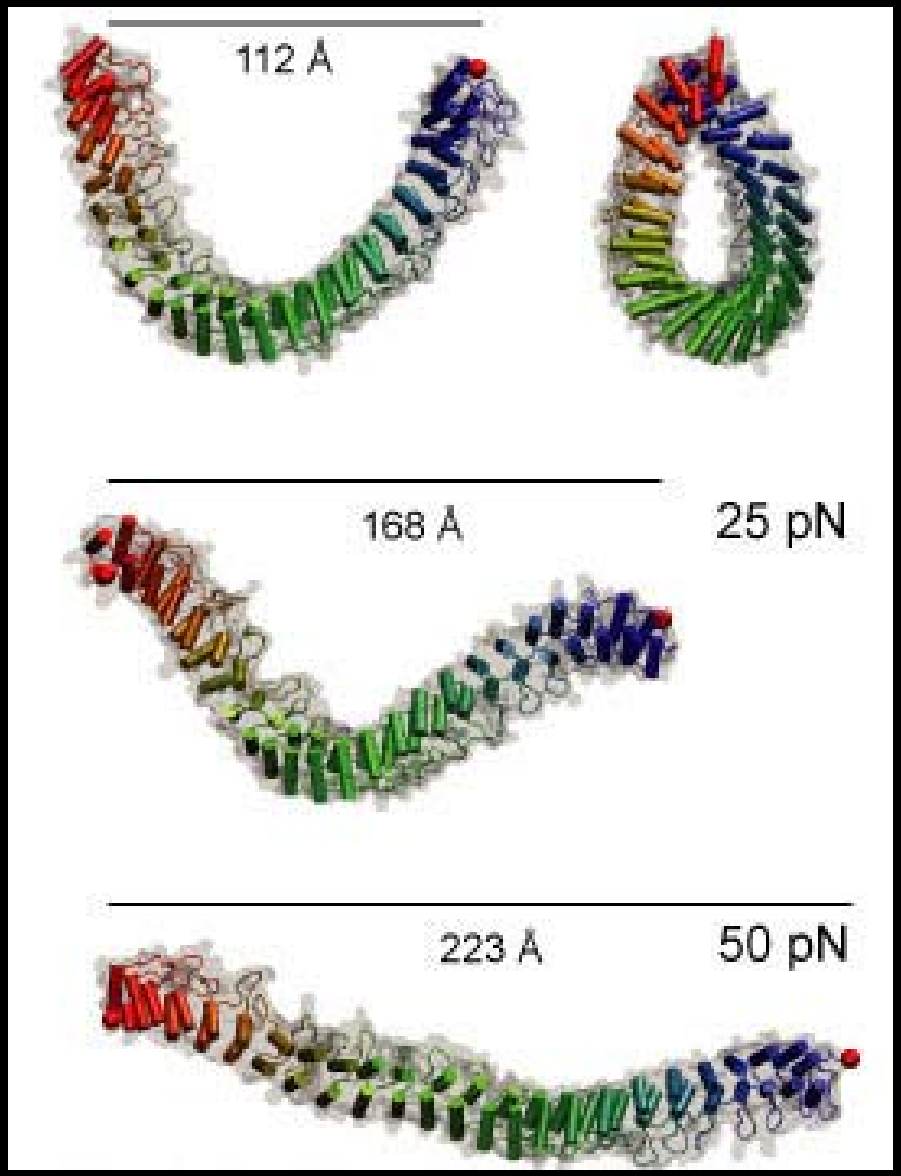


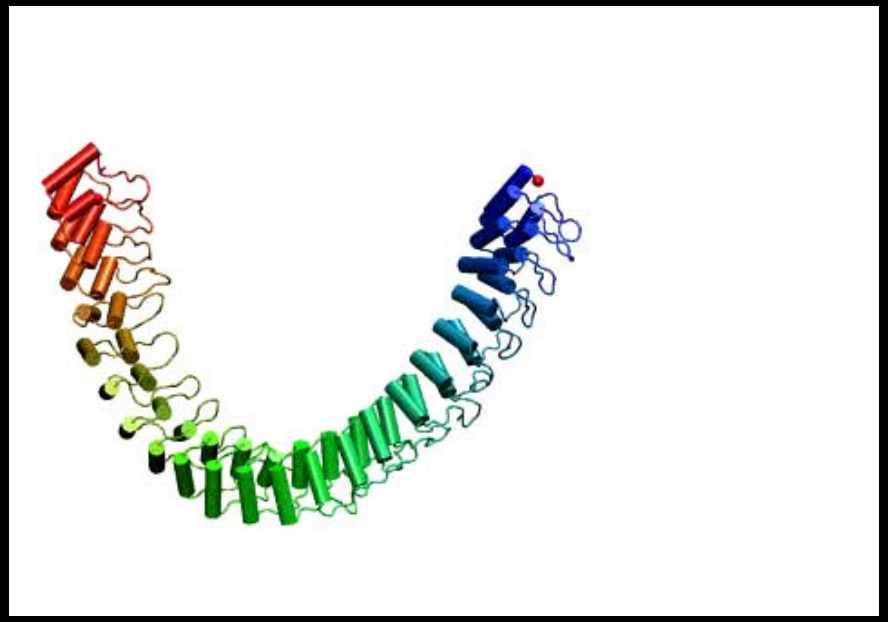
Ankyrin: The Soft Spring



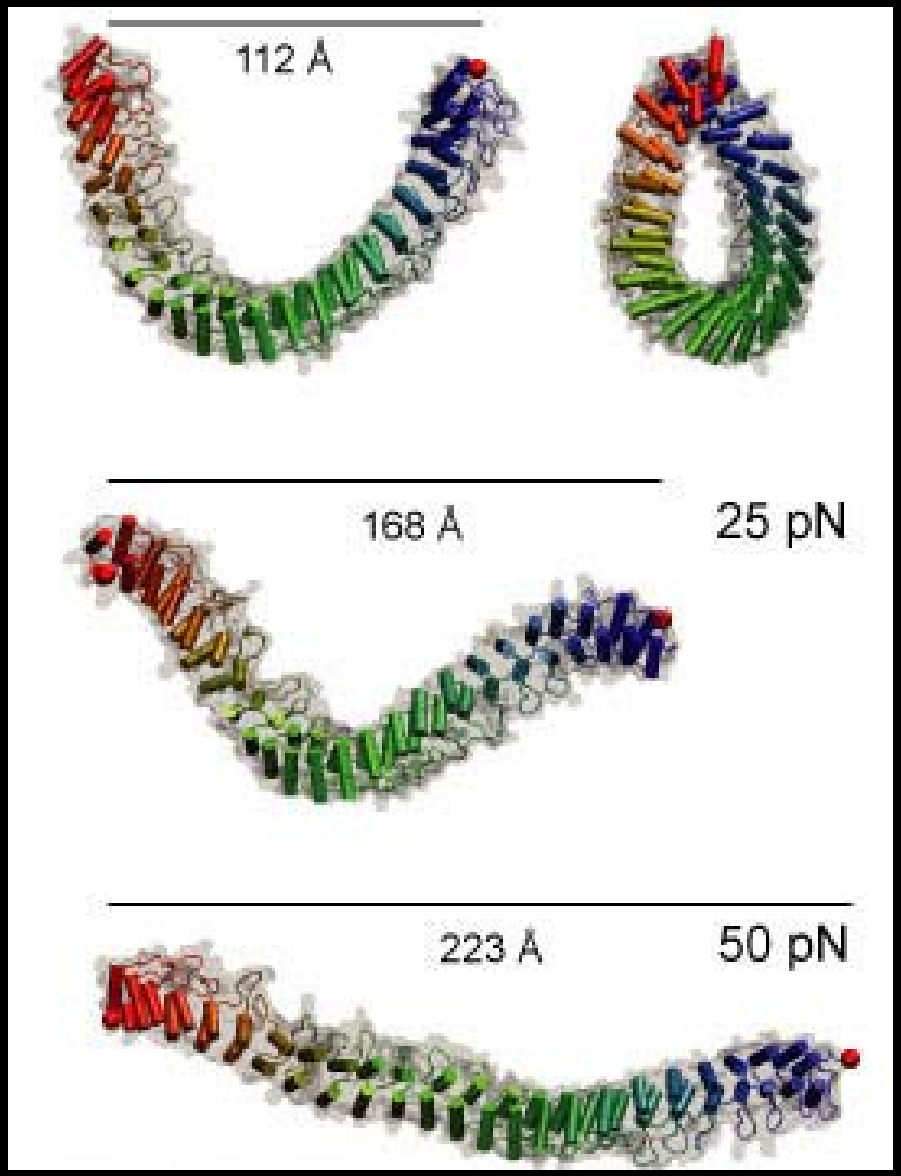


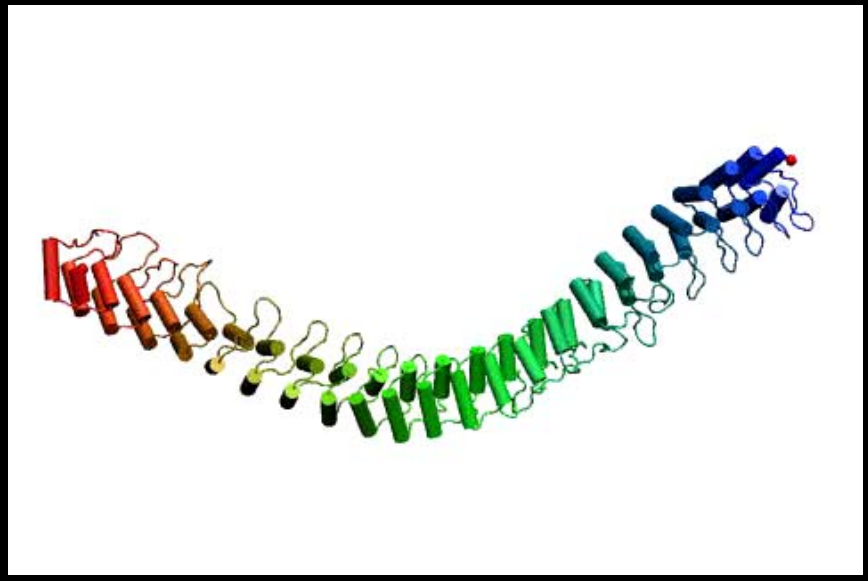
Ankyrin: The Soft Spring



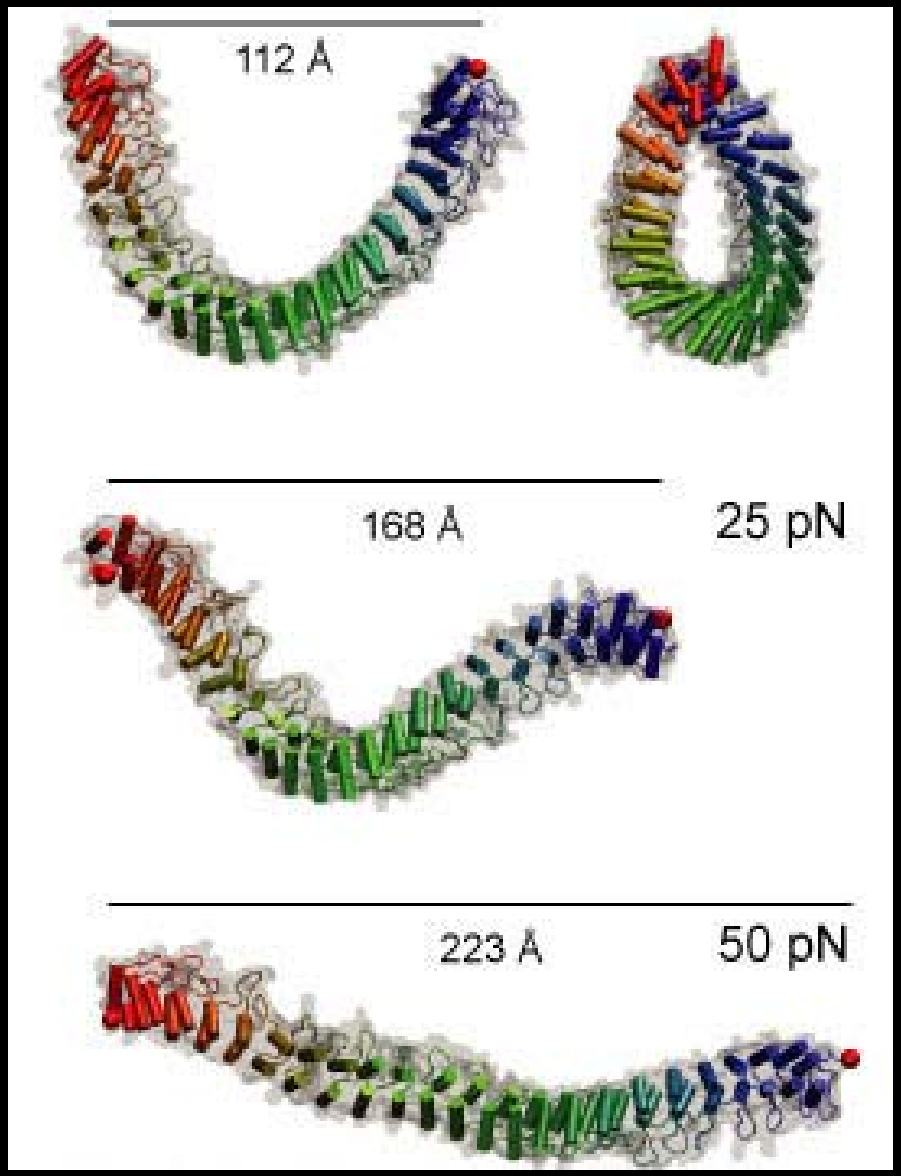


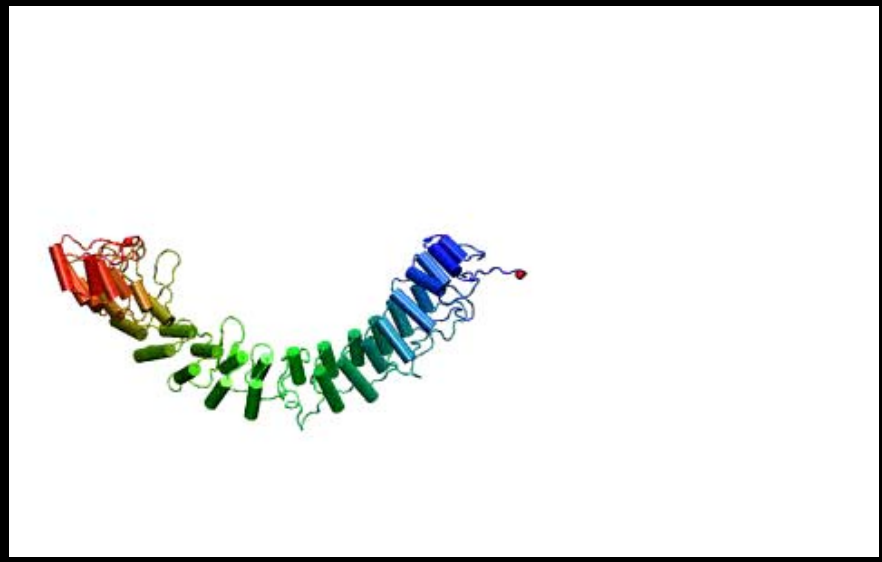
Ankyrin: The Soft Spring



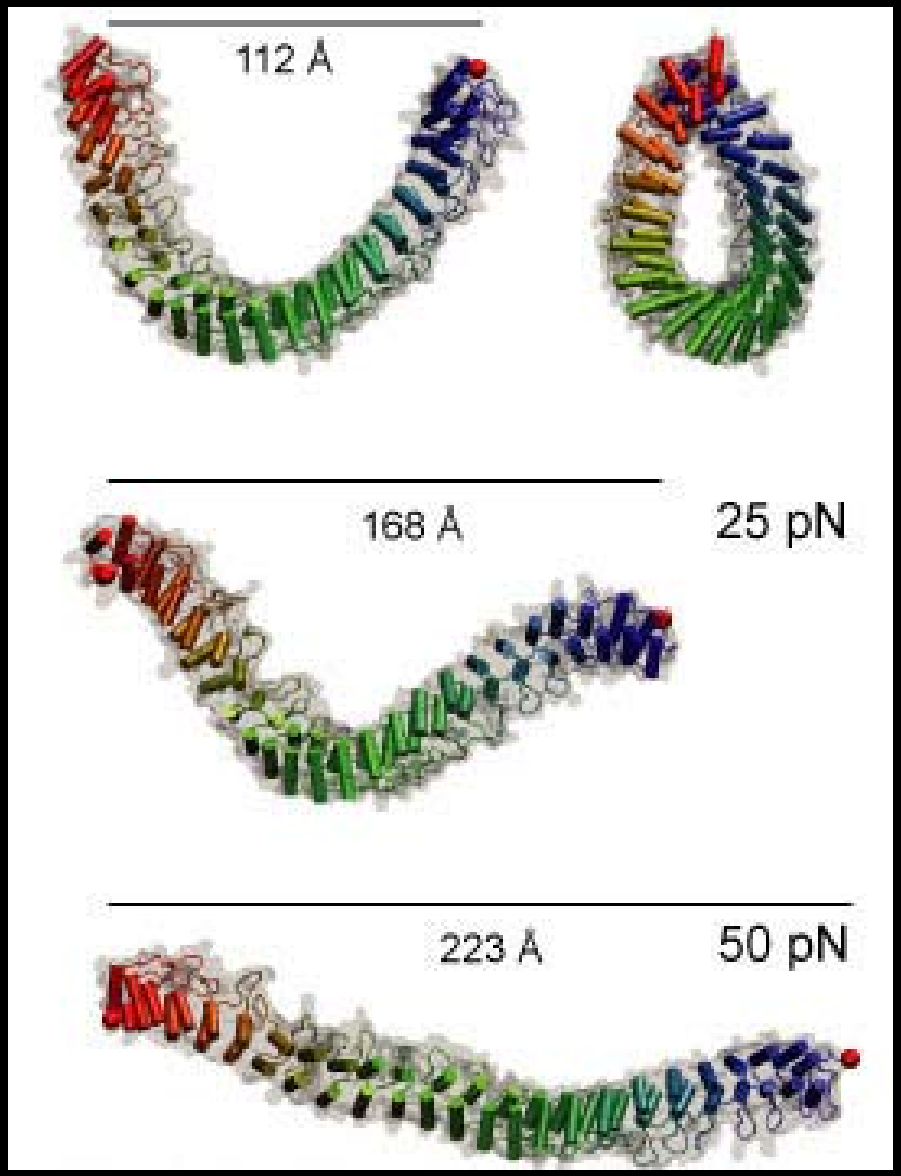


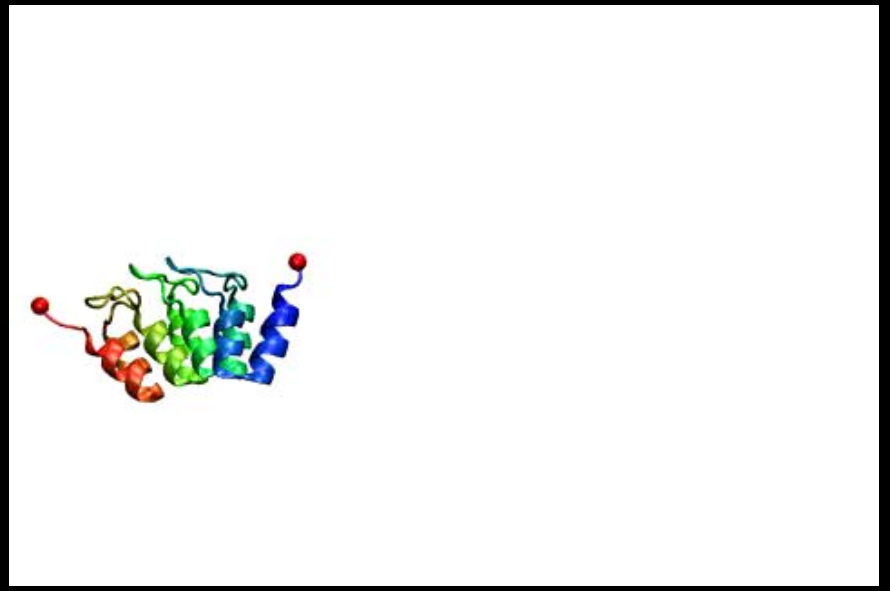
Ankyrin: The Soft Spring



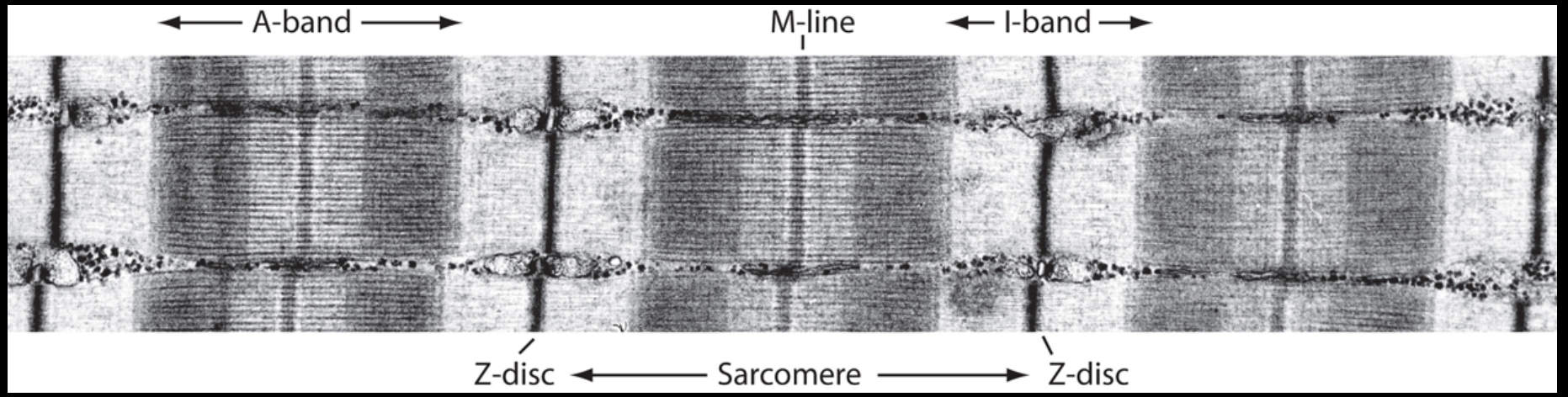


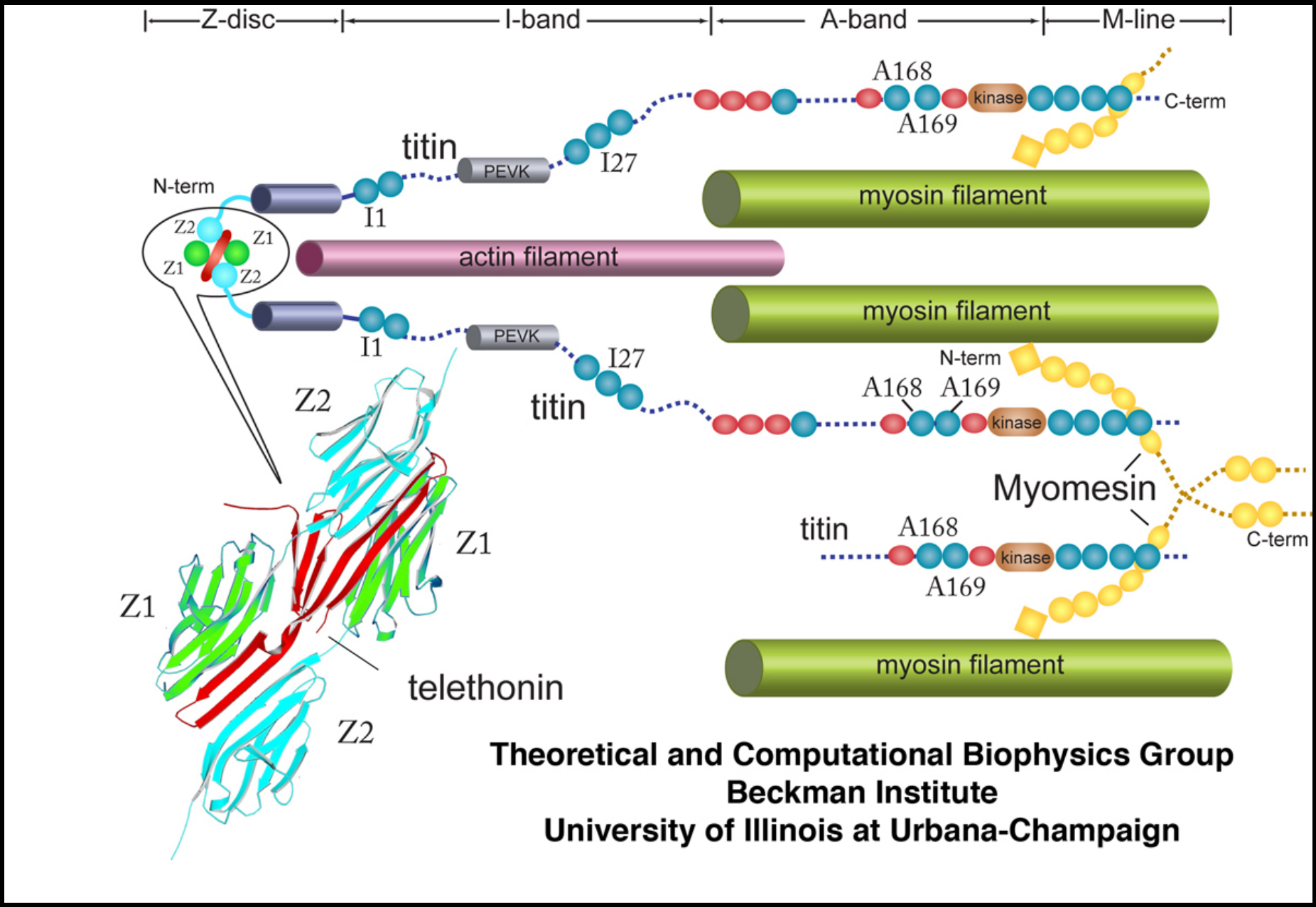
Ankyrin: The Soft Spring





The Titin/Telethonin Complex




Z-disc
I-band
A-band
M-line
titin
N-term
I1
PEVK
I27
A168
A169
kinase
C-term
myosin filament
actin filament
Z2
Z1
Z1
Z2
myosin filament
I1
PEVK
I27
titin
N-term
A168
A169
kinase
Myomesin
C-term
titin
A168
kinase
A169
myosin filament
Z2
Z1
Z1
telethonin
Z2
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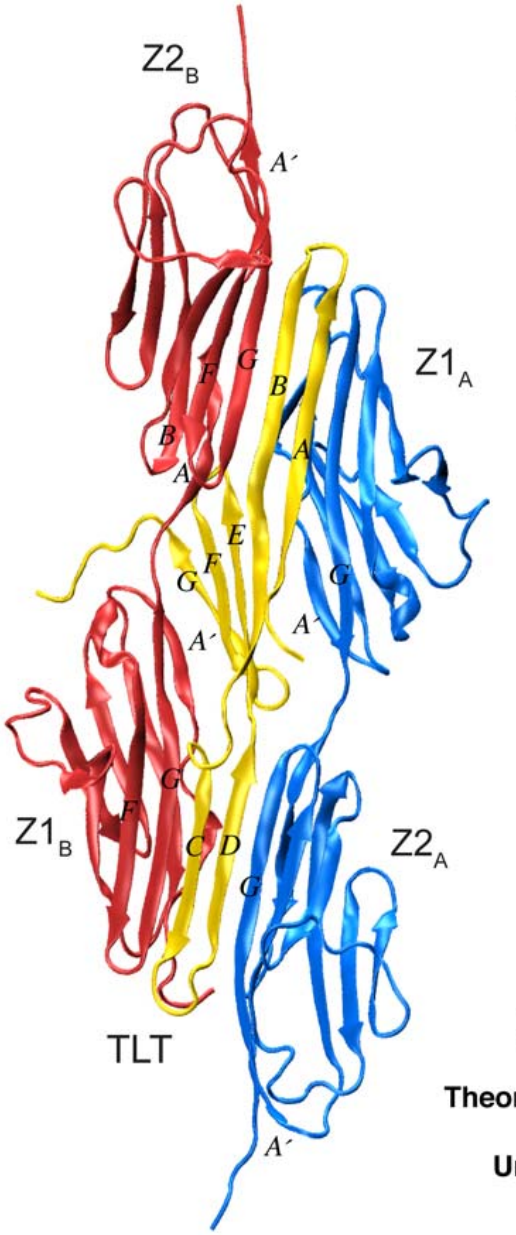
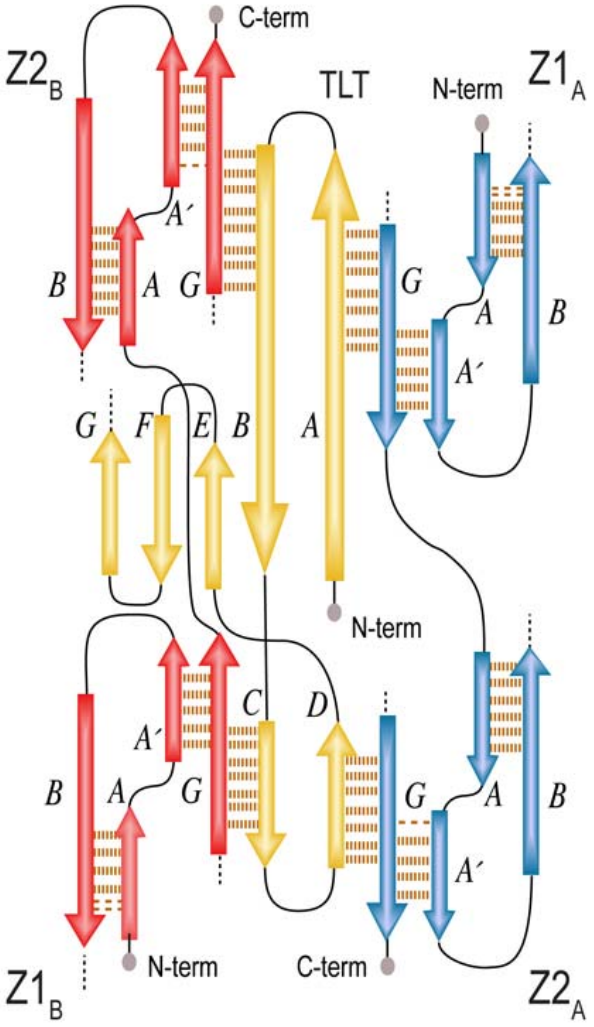
University of Illinois at Urbana-Champaign





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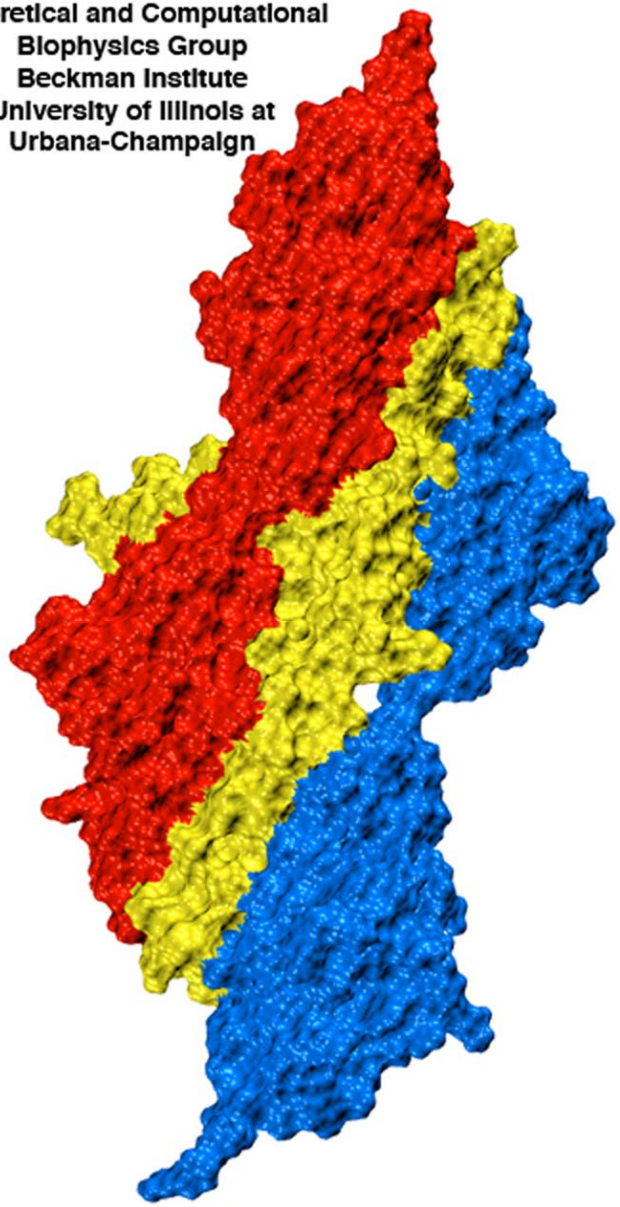
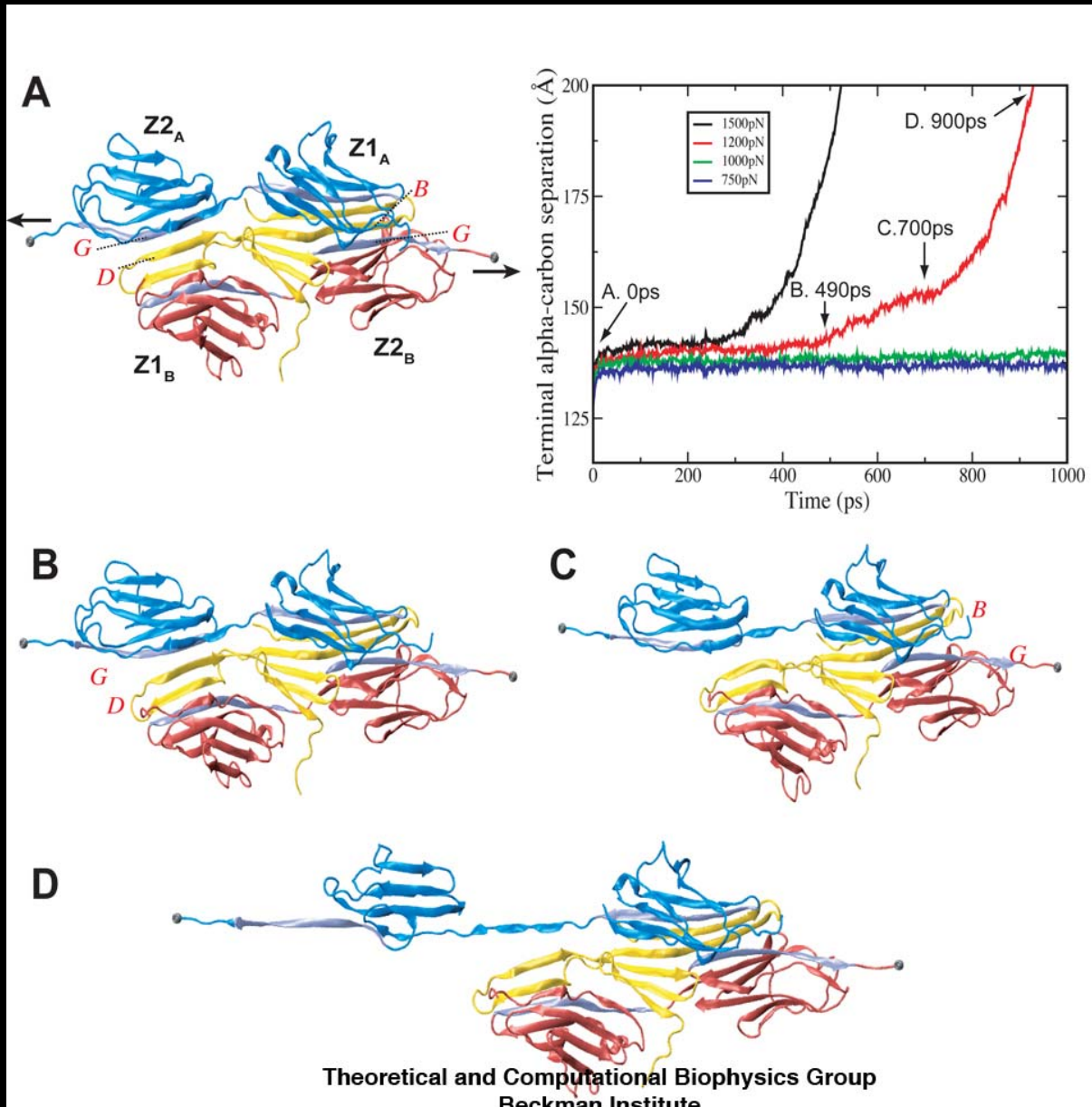
Biophysics Group
Beckman Institute
University of Illinois at
Urbana-Champaign





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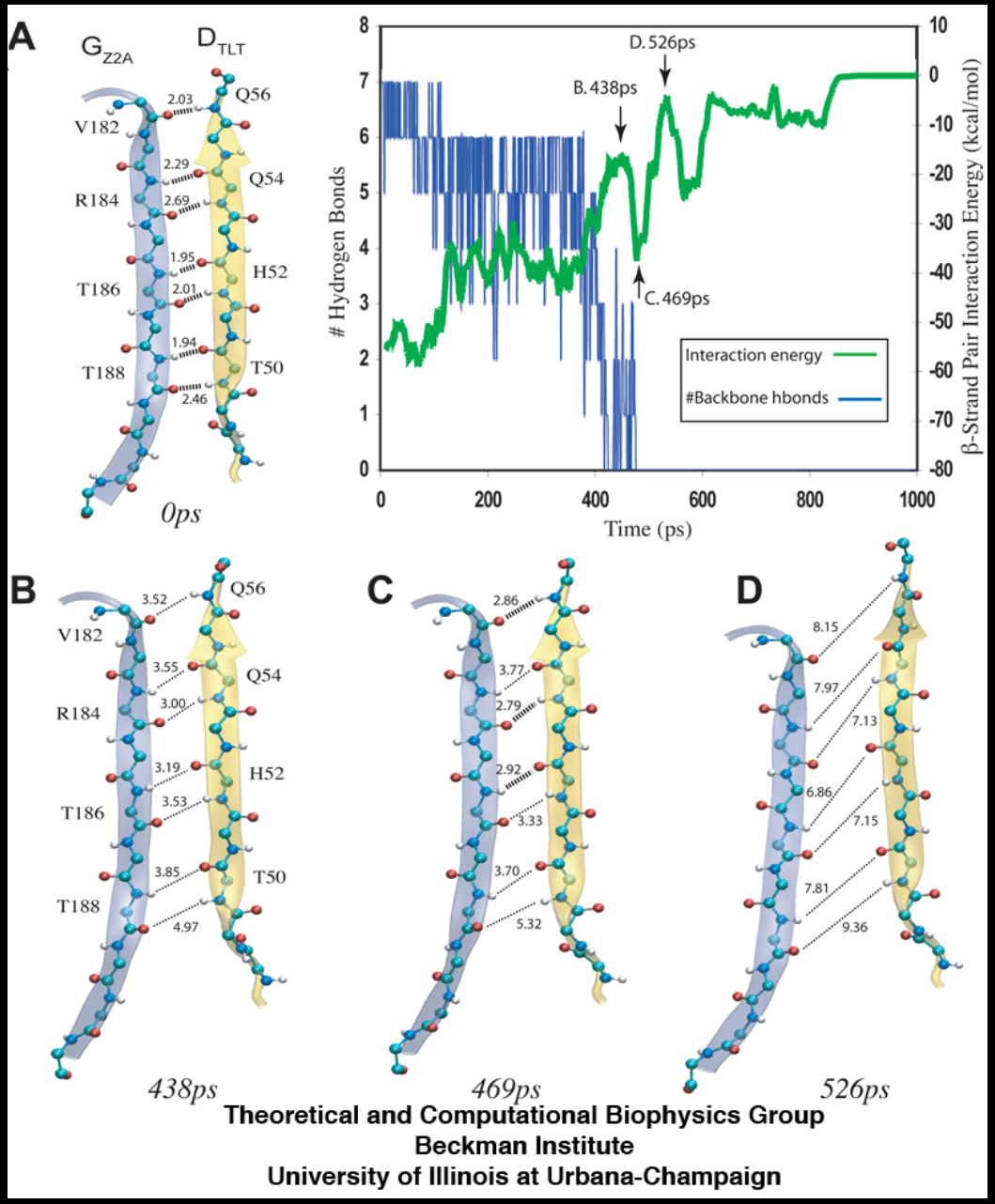
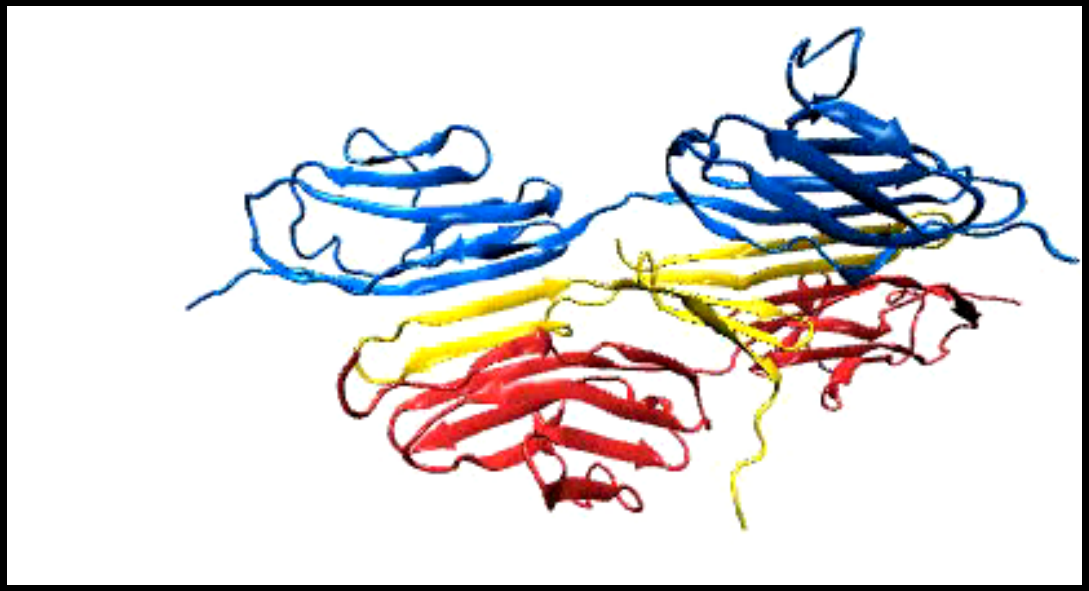
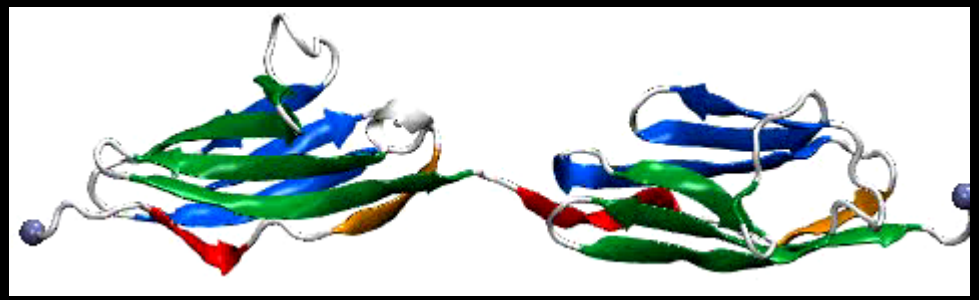
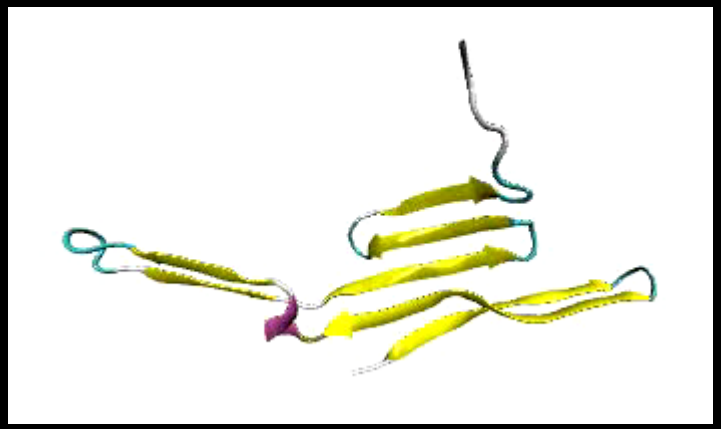
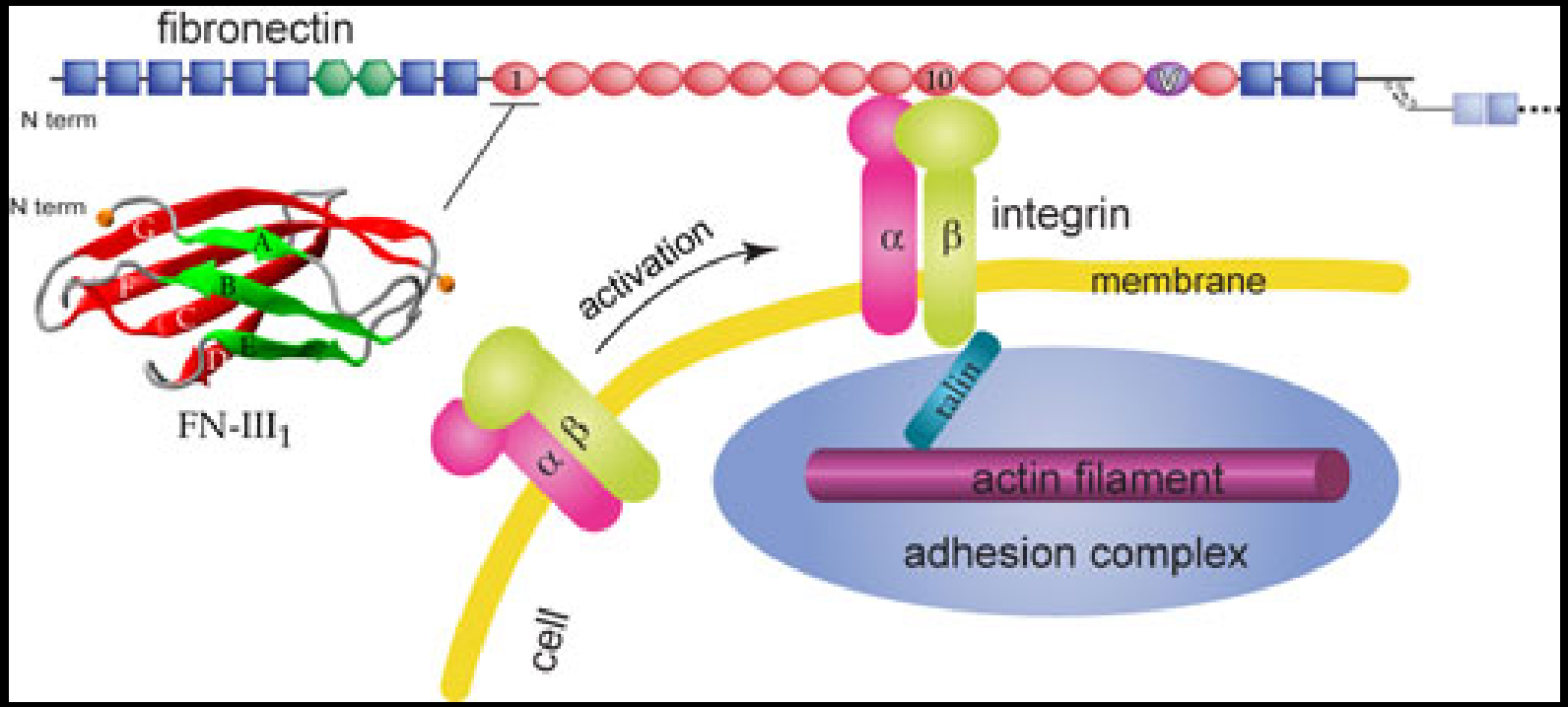

A
G_{Z2A}
D_{TLT}
Q56
Q54
H52
T50
V182
R184
T186
T188
2.03
2.29
2.69
1.95
2.01
1.94
2.46
0ps
D. 526ps
B. 438ps
C. 469ps
Hydrogen Bonds
β-Strand Pair Interaction Energy (kcal/mol)
Interaction energy
#Backbone hbonds
Time (ps)
0
200
400
600
800
1000
B
3.52
3.55
3.00
3.19
3.53
3.85
4.97
438ps
C
2.86
3.77
2.79
2.92
3.33
3.70
5.32
469ps
D
8.15
7.97
7.13
6.86
7.15
7.81
9.36
526ps
Theoretical and Computational Biophysics Group
Beckman Institute
University of Illinois at Urbana-Champaign

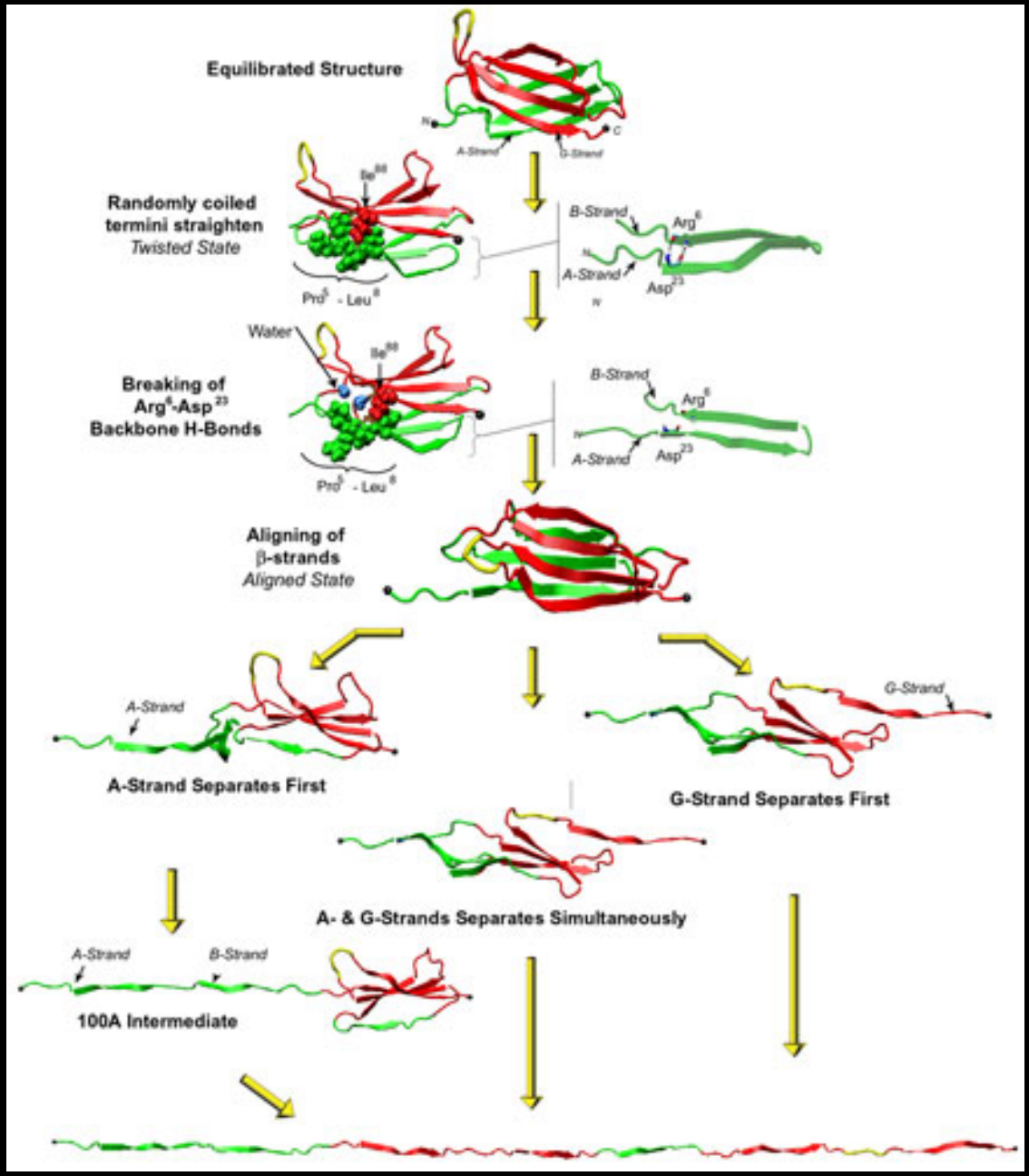




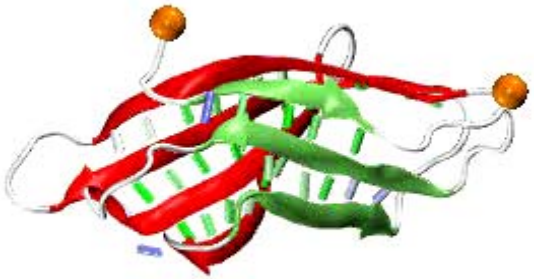


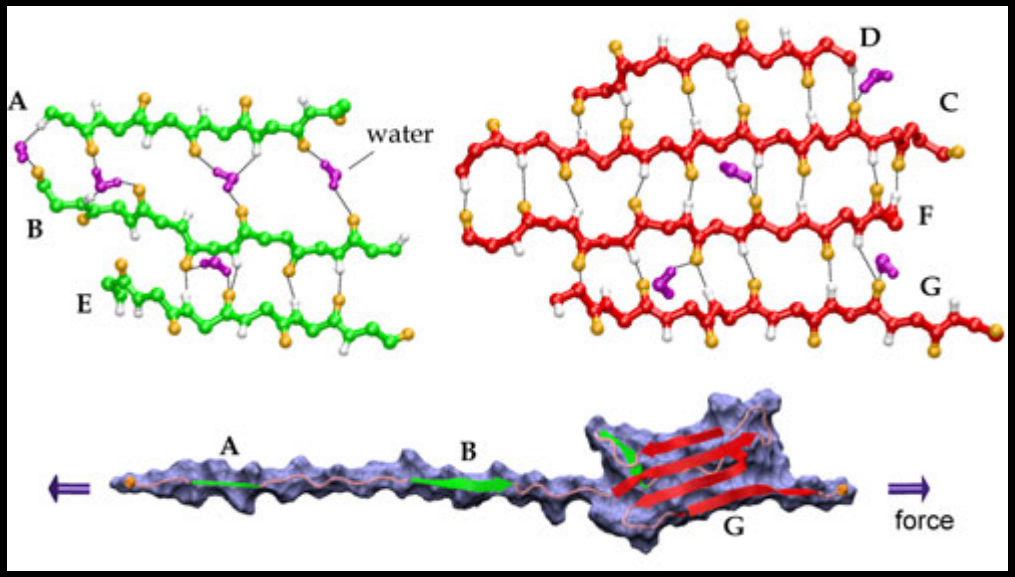
Fibronectin and integrin




Equilibrated Structure
N
C
A-Strand
G-Strand
Randomly coiled
termini straighten
Twisted State
Ile88
Pro5 - Leu8
B-Strand
Arg6
N
A-Strand
Asp23
N
Water
Breaking of
Arg6-Asp23
Backbone H-Bonds
Ile88
Pro5 - Leu8
B-Strand
Arg6
N
A-Strand
Asp23
Aligning of
β-strands
Aligned State
A-Strand
A-Strand Separates First
G-Strand
G-Strand Separates First
A- & G-Strands Separates Simultaneously
A-Strand
B-Strand
100A Intermediate

Fibronectin

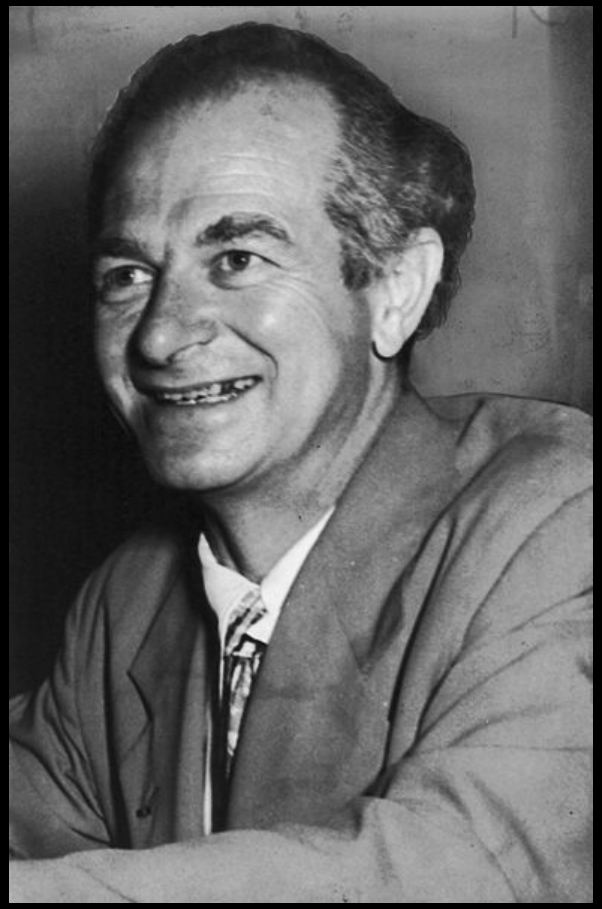


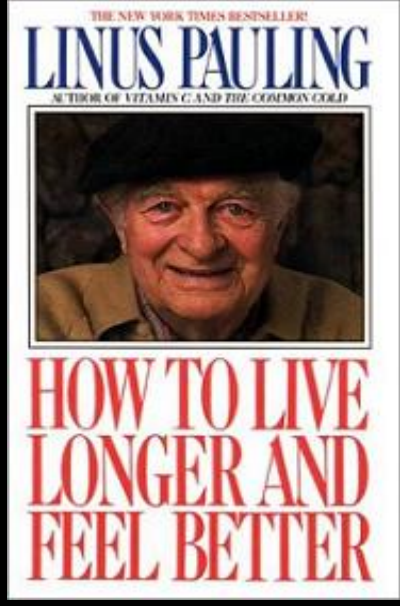


Linus Pauling 1901-1994

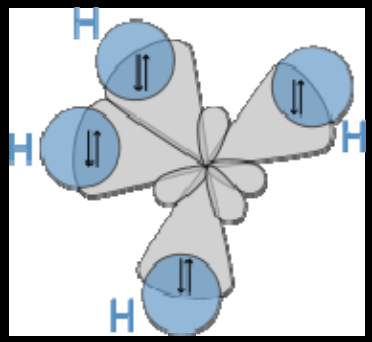
1954 za chemii

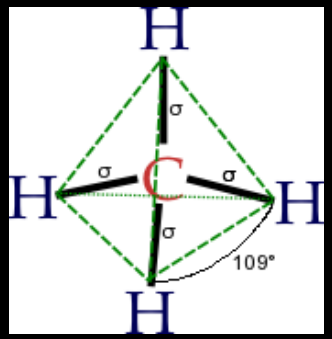
1962 za mír

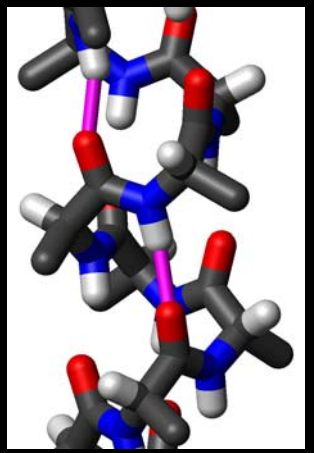


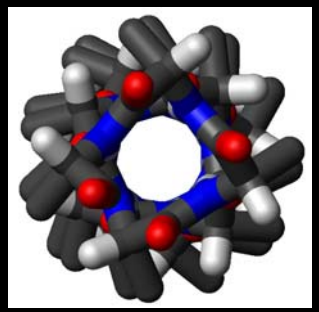


[Guggenheim Fellowship]
German physicist [Arnold Sommerfeld] in [Munich],
Danish physicist [Niels Bohr] in [Copenhagen],
Austrian physicist [Erwin Schrödinger] in [Zürich].









α – helix

Cavendishova laboratoř *(William Lawrence Bragg* *1915 za fyziku + W.H.Bragg)*

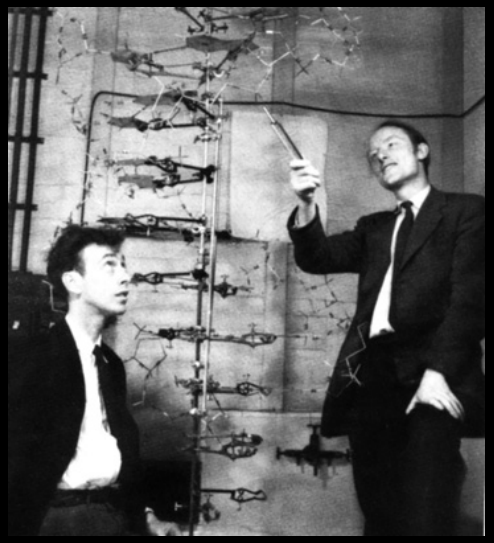
Linus Pauling – trojšroubovice / Petr Pauling

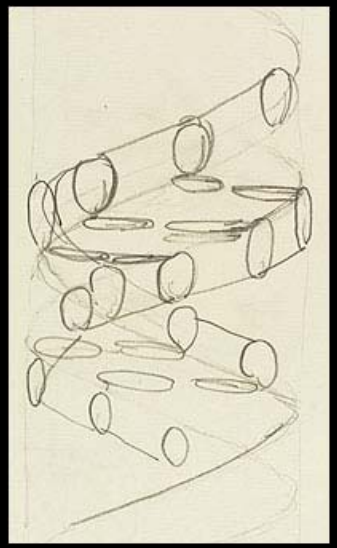
James D. Watson
Francis Crick
1962
za medicínu a fyziologii

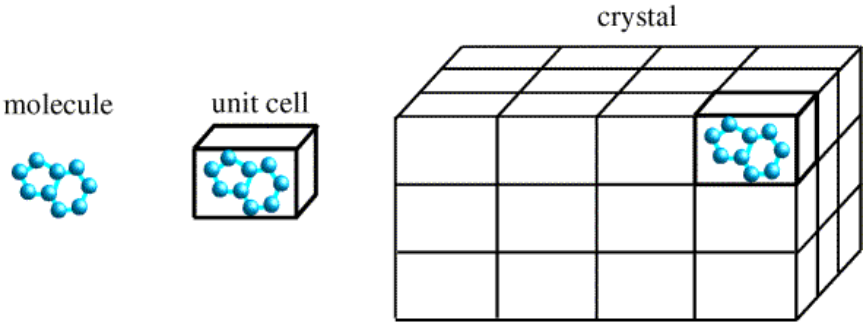
1962
za chemii
Max Perutz
John Kendrew

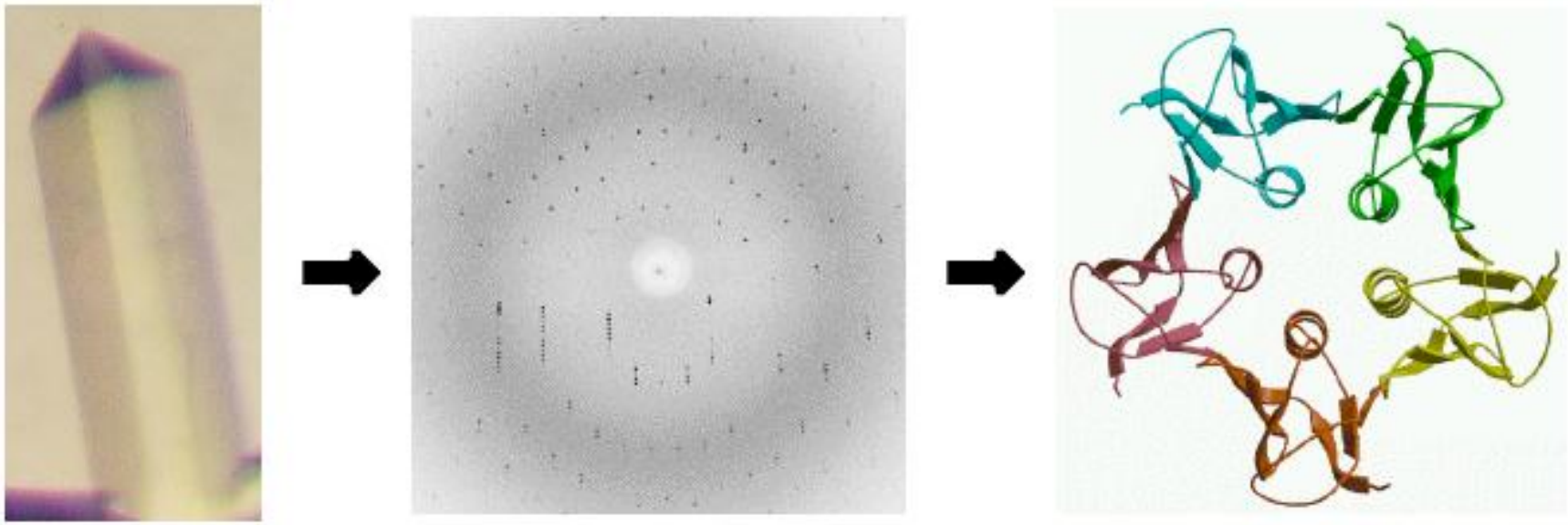
King‘s College v Londýně

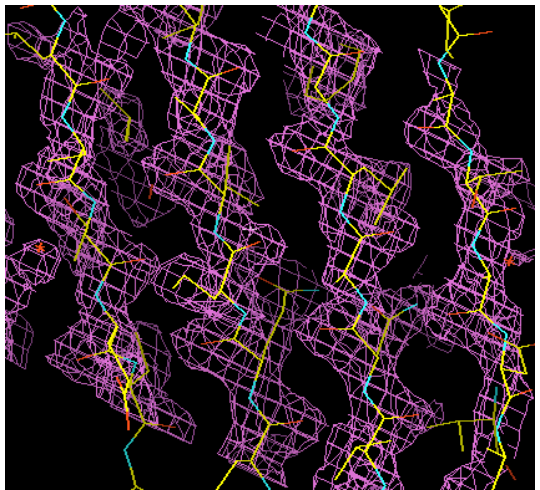
Rosalinda Franklinová
Maurice Wilkins
1962
za medicínu a fyziologii



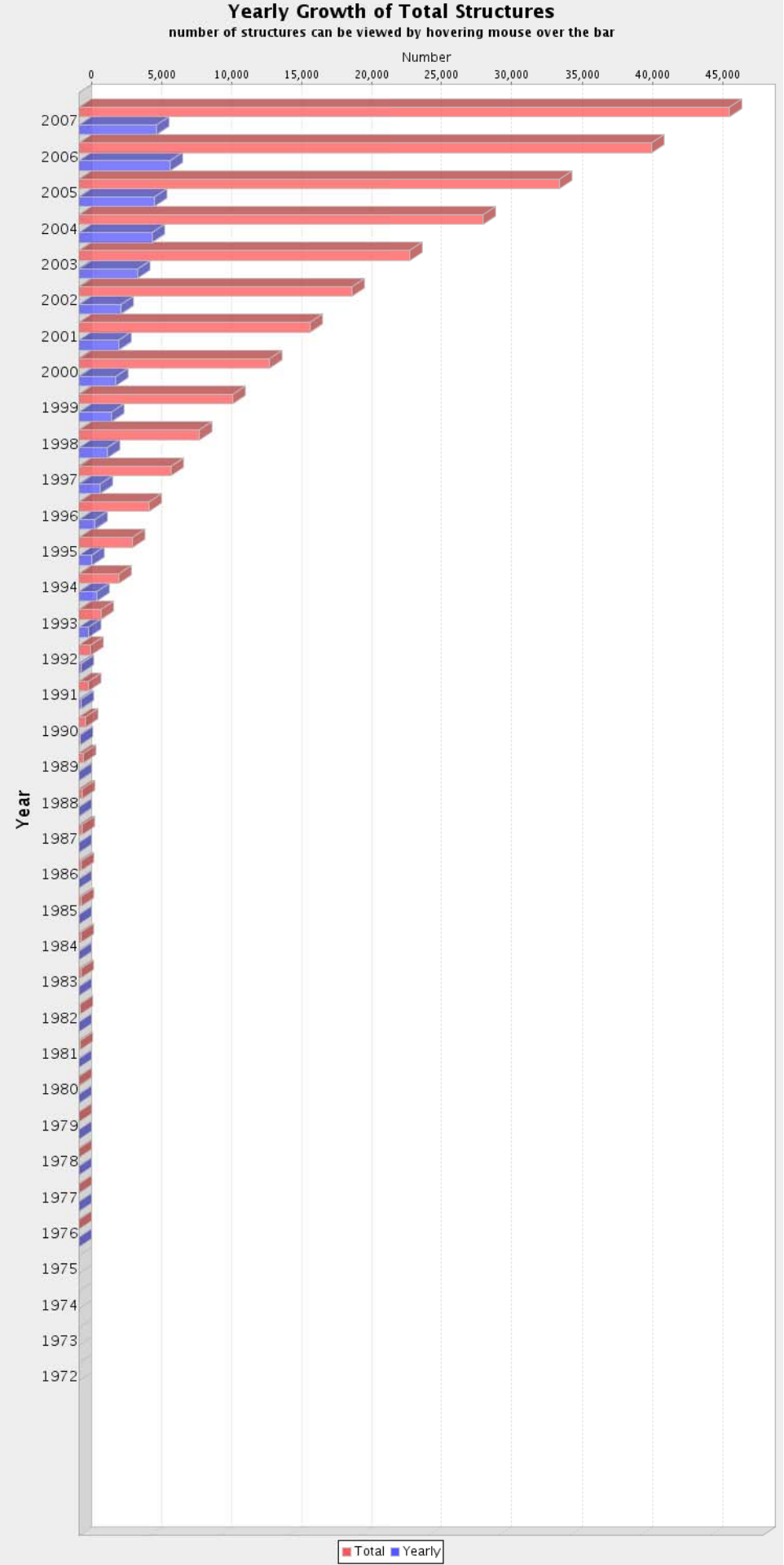




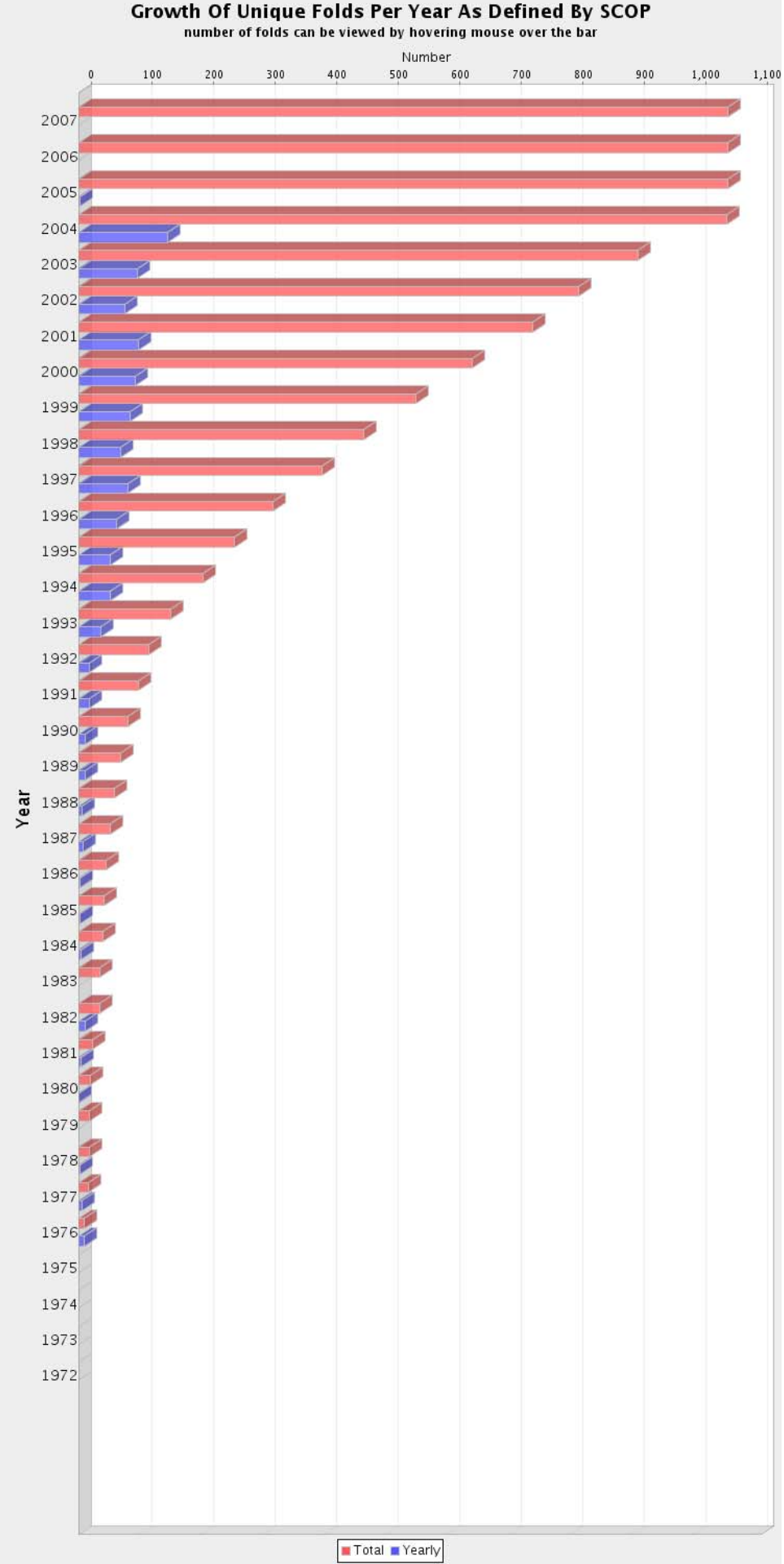




RCSB PDB
PROTEIN DATA BANK



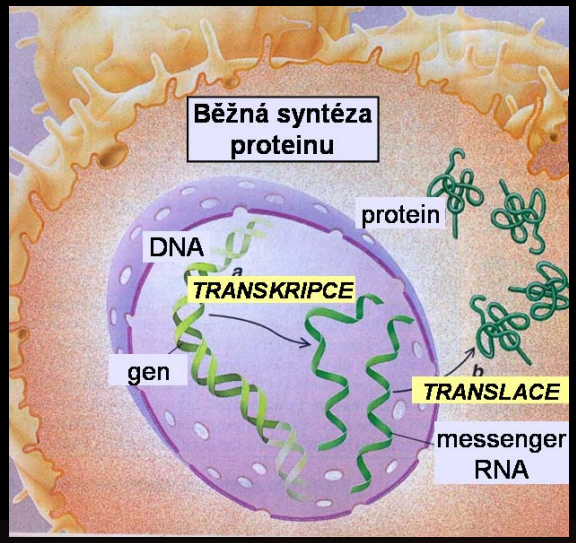
PDB
PROTEIN DATA BANK
RCSB

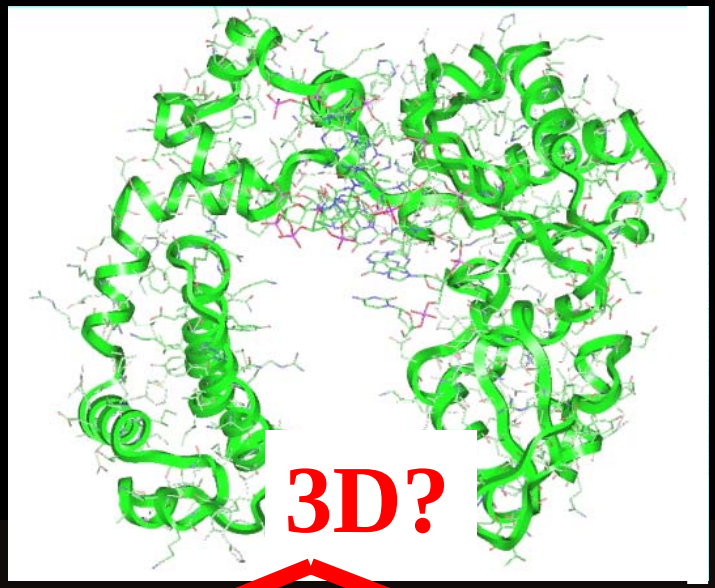


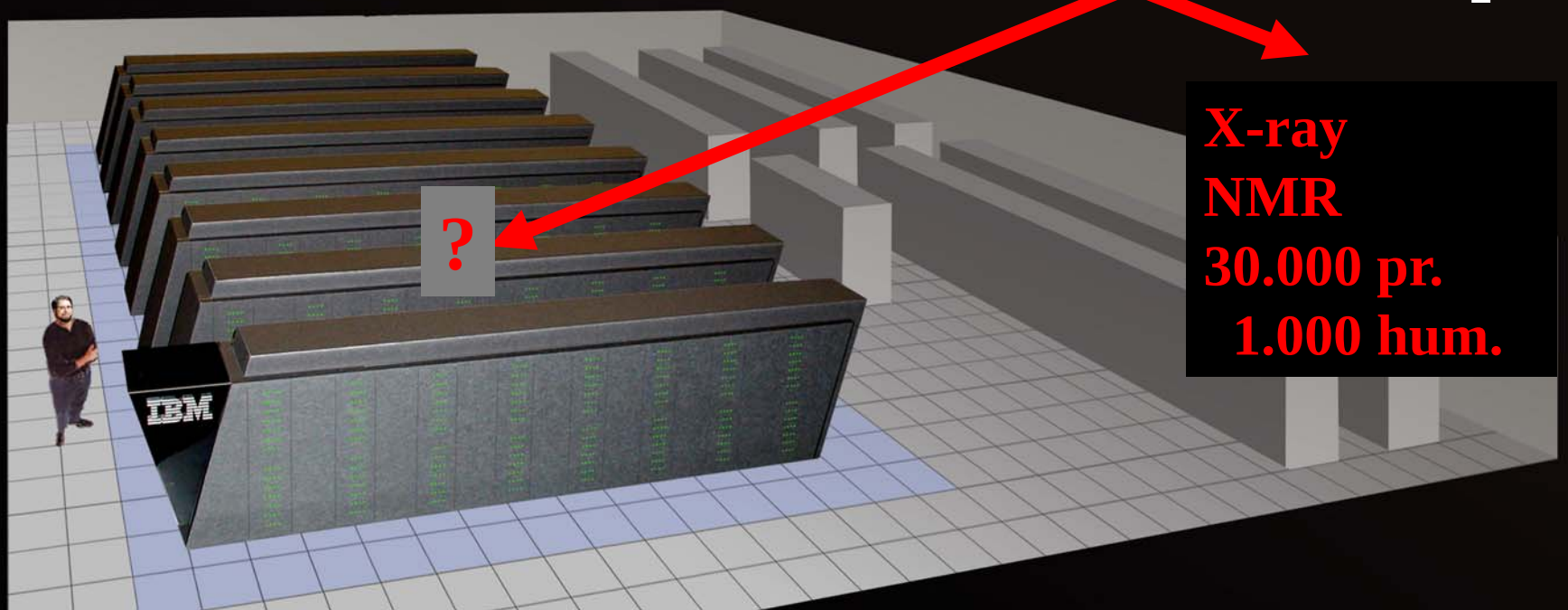
PDB
PROTEIN DATA BANK
RCSB

DNA **Protein** …Arg-Lys-His-Trp-Tyr-Glu-Asp…

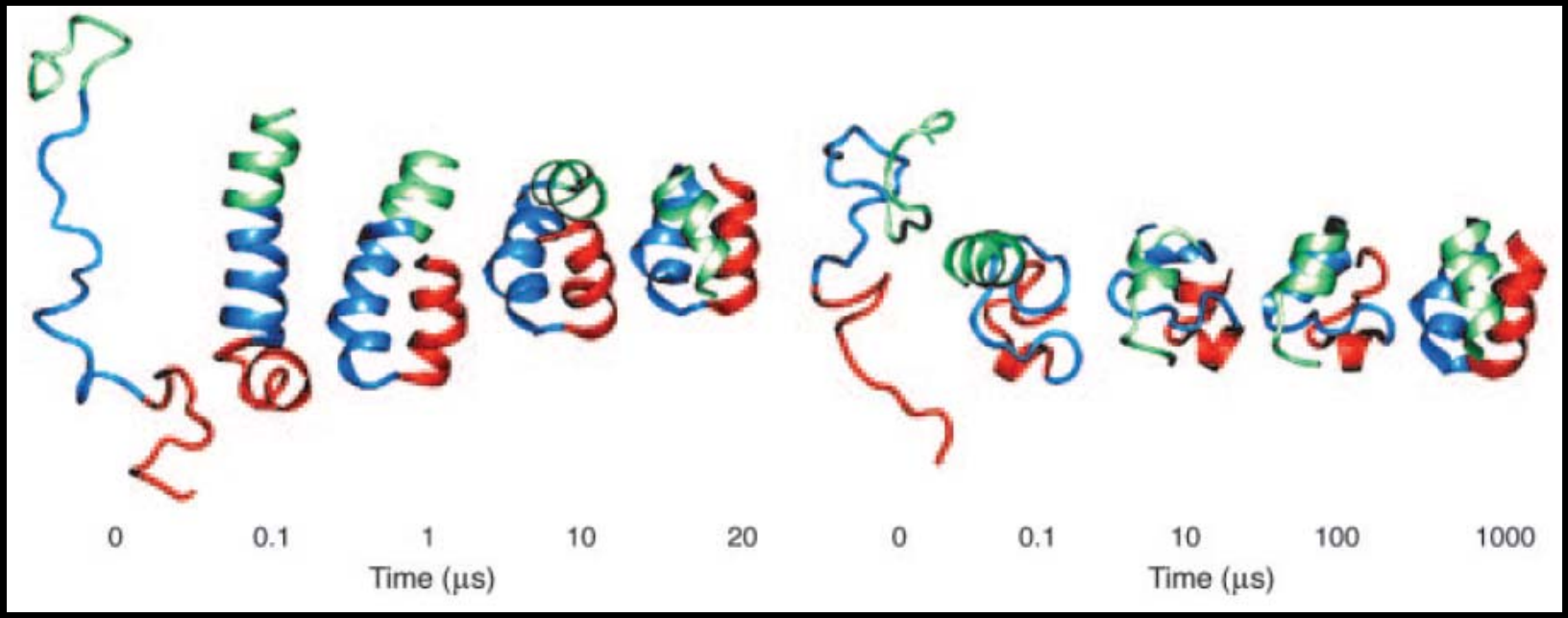
…
A-T
G-C
C-G
T-A
T-A
G-C
…

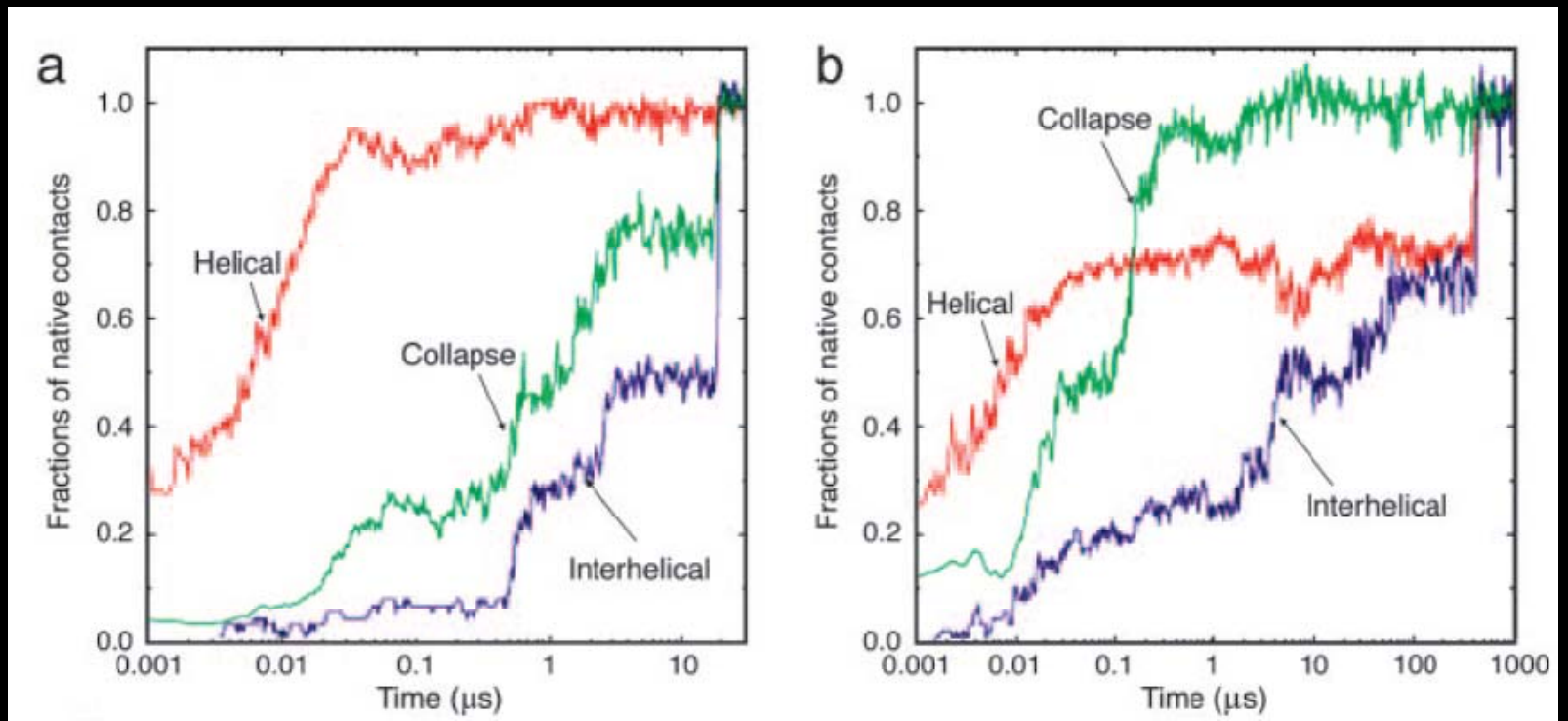






X-ray
NMR
30.000 pr.
1.000 hum.

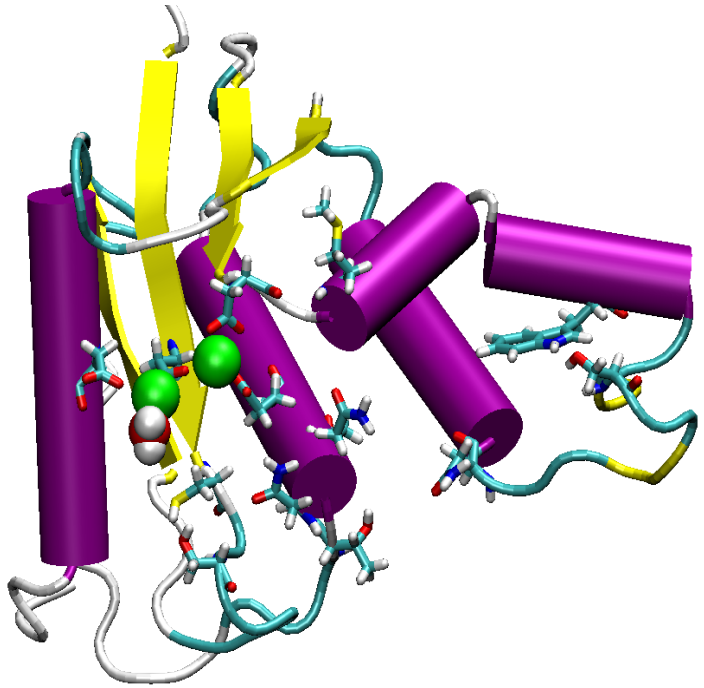

0
0.1
1
10
20
Time (μs)
0
0.1
10
100
1000
Time (μs)

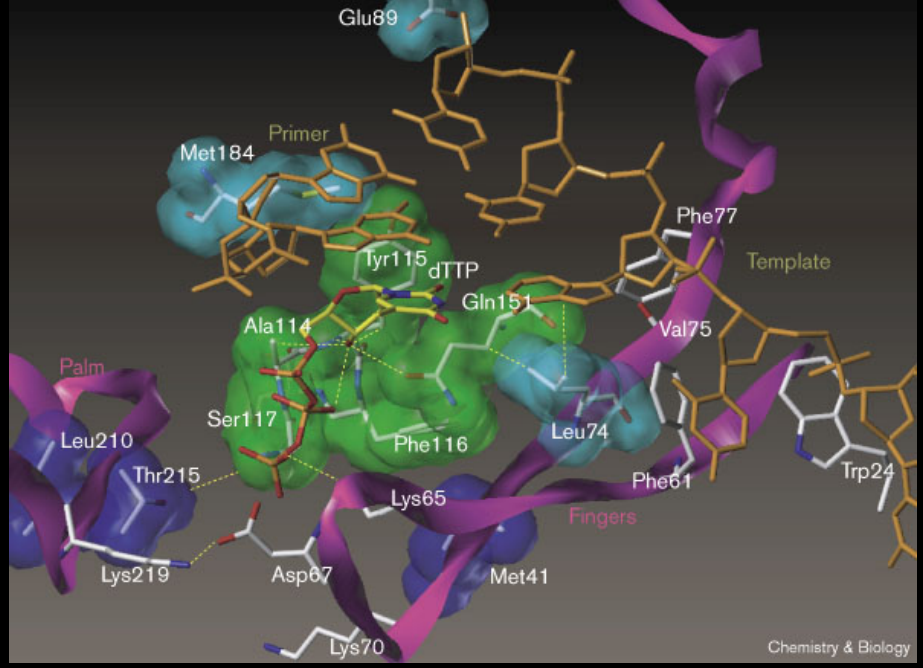

a
Fractions of native contacts
1.0
0.8
0.6
0.4
0.2
0.0
Helical
Collapse
Interhelical
0.001
0.01
0.1
1
10
Time (μs)
b
Fractions of native contacts
1.0
0.8
0.6
0.4
0.2
0.0
Collapse
Helical
Interhelical
0.001
0.01
0.1
1
10
100
1000
Time (μs)

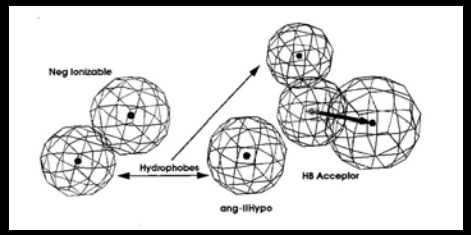
Homologní modelování

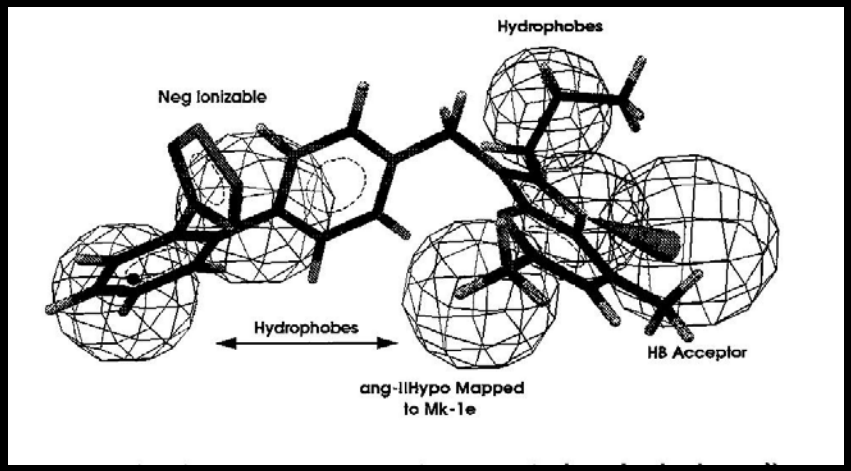
```
 _aln.pos          10         20         30         40          51        60
Ecoli      -7KQVEIFTDGSCLGNPGPGGYGAILRYRGREKTFSAGYT---RTTNNRMELMAAIVALEALK--EHA
human      MGDFVVVYTDGCCSSNGRRRPRAGIGVYWGPGHPLNVGIRLPGRQTNQRAEIHAACKAIEQAKTQNIN
 _consrvd       *    * * *   *          *   * *         *      * ** * *   **   * *   *

 _aln.p    70     75  80         90         100        110        120        130
Ecoli      EVILSTDSQYVRQGITQWIHNWKKRGWKTADKKPVKNVDLWQRLDAALGQHQIKWEWVKGHAGHPENE
human      KLVLYTDSMFTINGITNWVQGWKKNGWKTSAGKEVINKEDFVALERLTQGMDIQWMHVPGHSGFIGNE
 _consrvd     * ***      *** *    *** ****    * * *        *          * *   * ** *    **

 _aln.pos  139        150
Ecoli      RADELARAAAMNPTLEDTGYQVE
human      EADRLAREGAKQSED--------
 _consrvd   **  ***   *
```

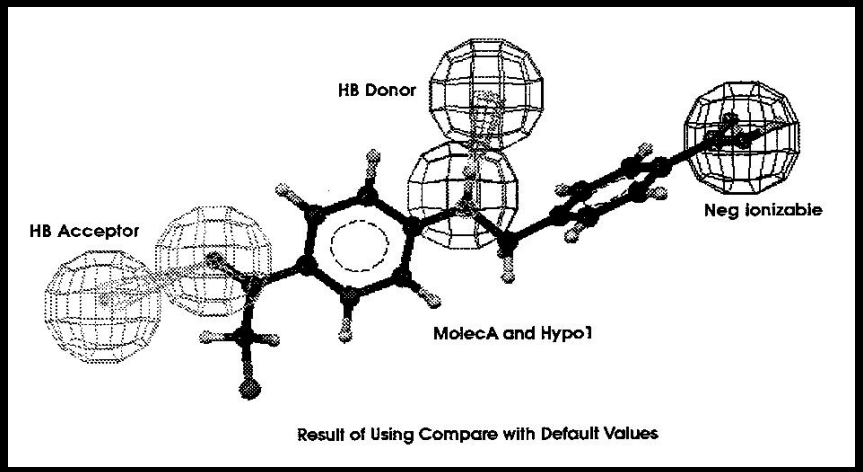
```
A  5
R -2  9
N -1  0  8
D -1 -1  2  9
C -2 -3 -2 -2 16
Q  0  2  1 -1 -4  8
E -1 -1 -1  2 -2  2  7
G  1 -3  0 -2 -3 -2 -3  8
H -2  0  1  0 -4  0  0 -2 13
I -1 -3 -2 -4 -4 -3 -4 -4 -3  6
L -2 -2 -3 -3 -2 -2 -2 -4 -2  2  6
K -1  3  0  0 -3  1  1 -2 -1 -3 -2  6
M -1 -1 -2 -3 -3 -1 -2 -2  1  1  3 -1  7
F -3 -2 -3 -4 -2 -4 -3 -3 -2  1  2 -3  0  9
P -2 -3 -2 -2 -5 -2  0 -1 -2 -2 -4 -1 -2 -4 11
S  1 -1  1  0 -1  1  0  0 -1 -2 -3  0 -2 -2 -1  5
T  0 -2  0 -1 -1 -1 -1 -2 -2 -1 -1  0 -1 -1  0  2  6
W -3 -2 -4 -5 -6 -1 -2 -2 -5 -3 -1 -2 -2  1 -4 -5 -4 19
Y -2 -1 -2 -3 -4 -1 -2 -3  2  0  0 -1  1  4 -3 -2 -1  3  9
V  0 -2 -3 -3 -2 -3 -3 -4 -4  4  2 -2  1  0 -3 -1  1 -3 -1  5
B -1 -1  4  6 -2  0  1 -1  0 -3 -3  0 -3 -3 -2  0  0 -4 -3 -3  5
Z -1  0  0  1 -3  4  5 -2  0 -4 -2  1 -2 -4 -1  0 -1 -2 -2 -3  2  5
X  0 -1 -1 -1 -2 -1 -1 -1 -1 -1 -1 -1  0 -1 -2  0  0 -2 -1 -1 -1 -1 -1
   A  R  N  D  C  Q  E  G  H  I  L  K  M  F  P  S  T  W  Y  V  B  Z  X
```

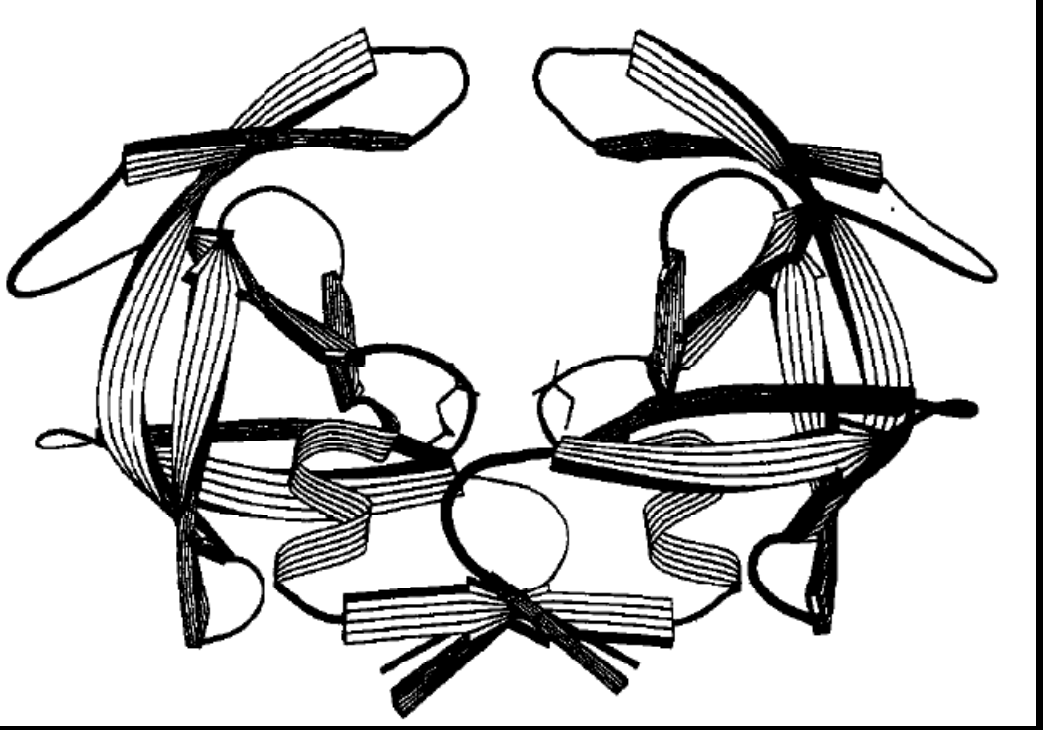


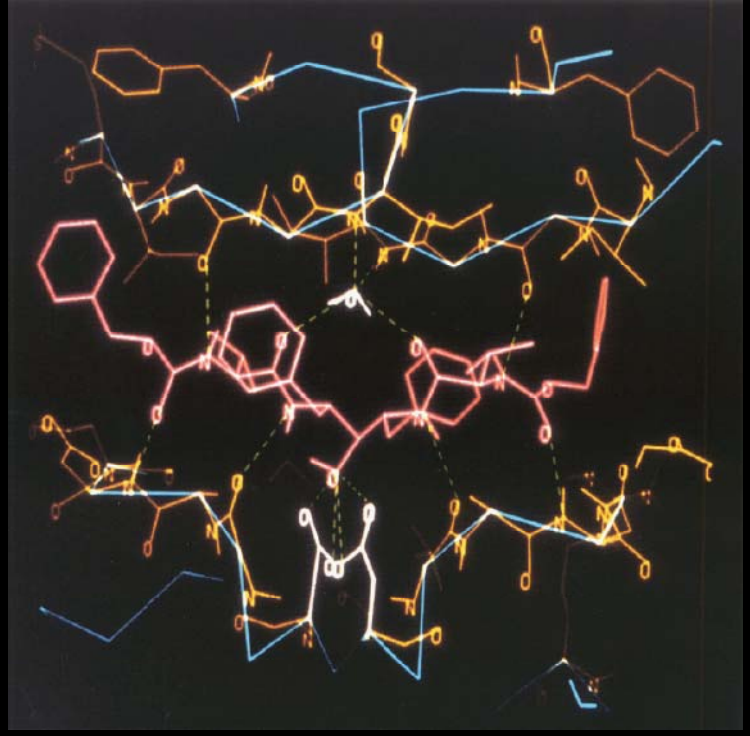

Glu89
Primer
Met184
Phe77
Template
Tyr115
dTTP
Gln151
Ala114
Val75
Palm
Ser117
Leu210
Phe116
Leu74
Thr215
Trp24
Phe61
Lys65
Fingers
Lys219
Asp67
Met41
Lys70
Chemistry & Biology


Neg Ionizable
Hydrophobes
HB Acceptor
ang-IIHypo

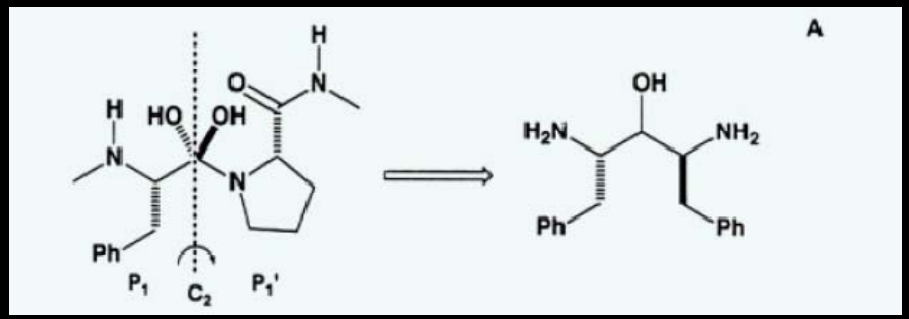

Hydrophobes
Neg Ionizable
Hydrophobes
HB Acceptor
ang-IIHypo Mapped
to Mk-1e


HB Donor
Neg Ionizable
HB Acceptor
MolecA and Hypo1
Result of Using Compare with Default Values

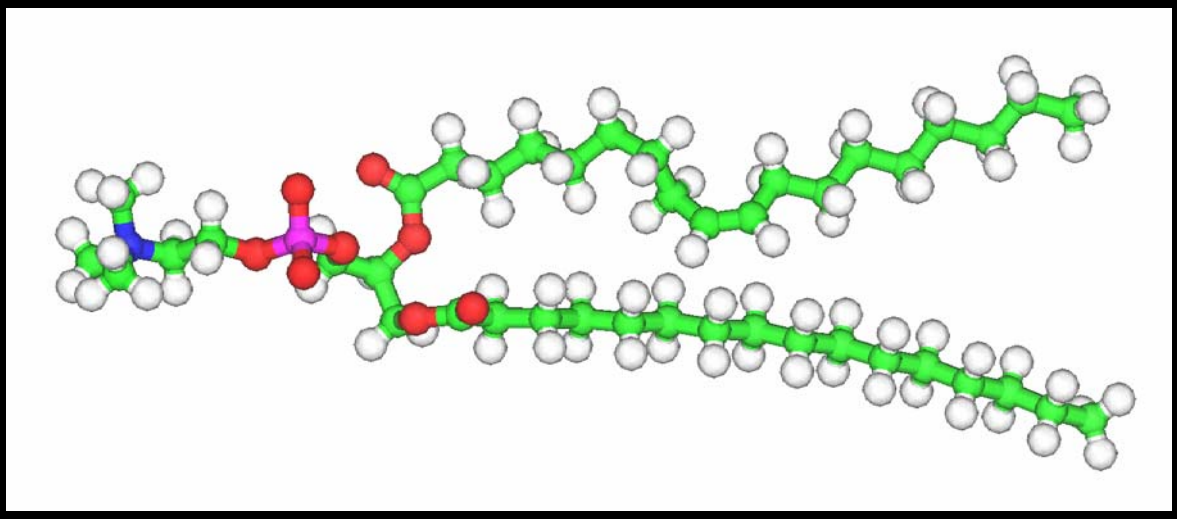


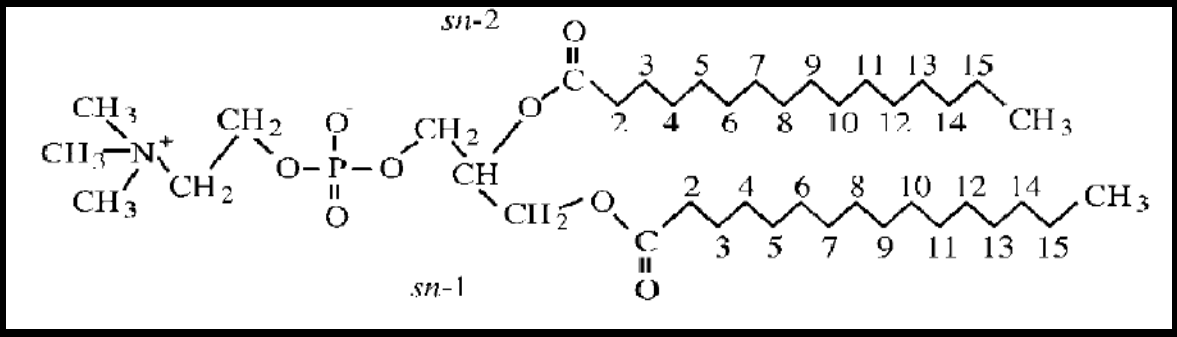


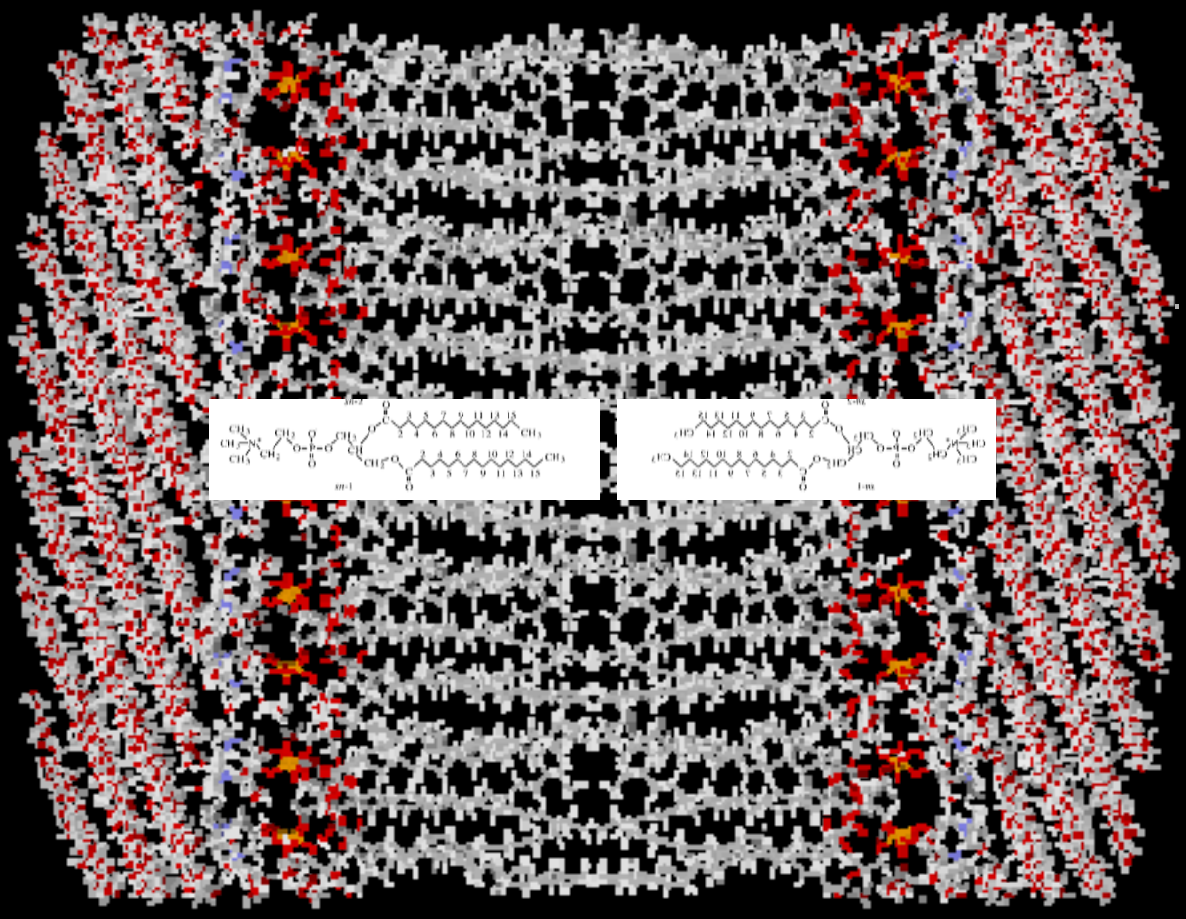
HIV proteáza

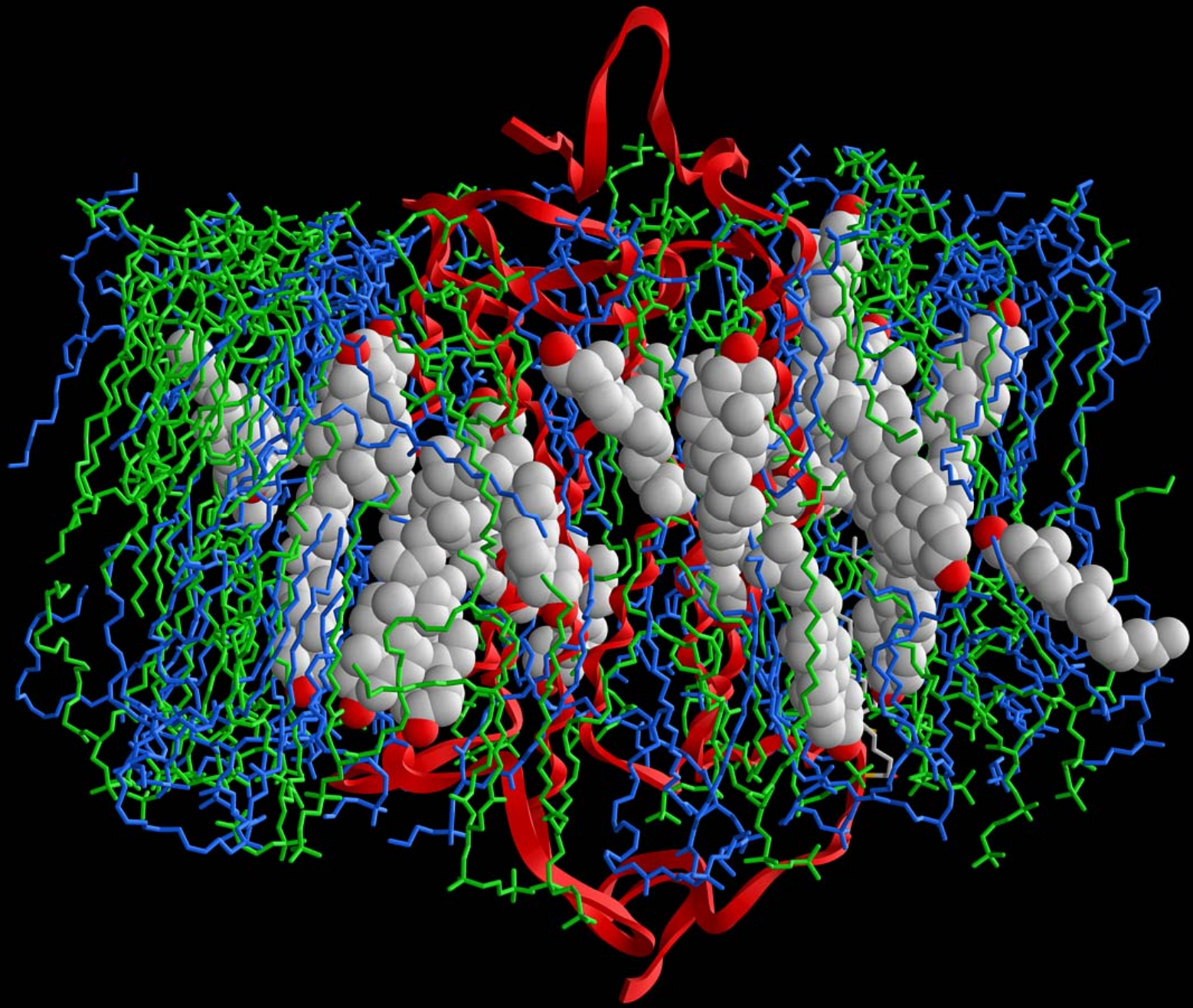


Buněčné membrány

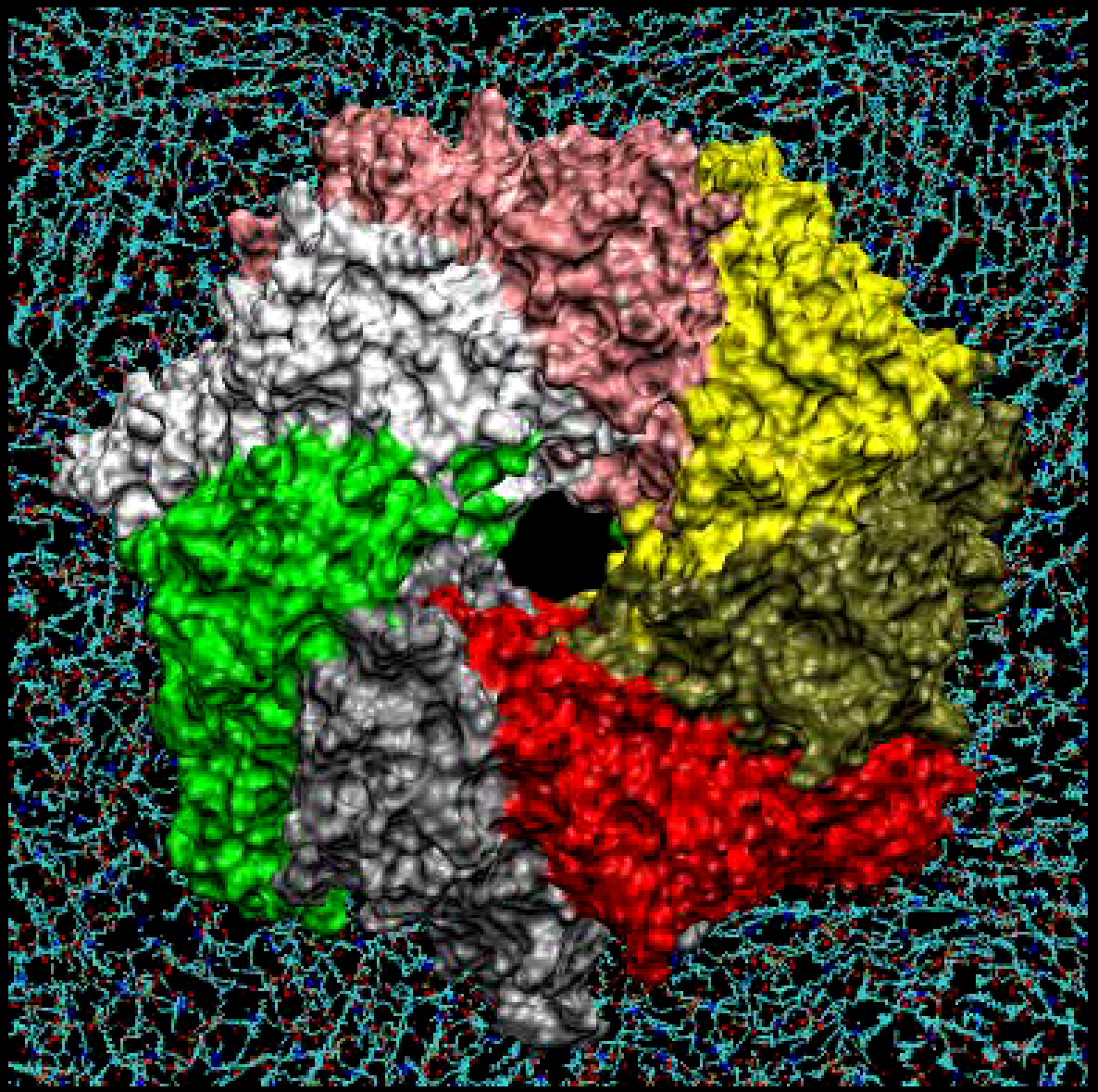


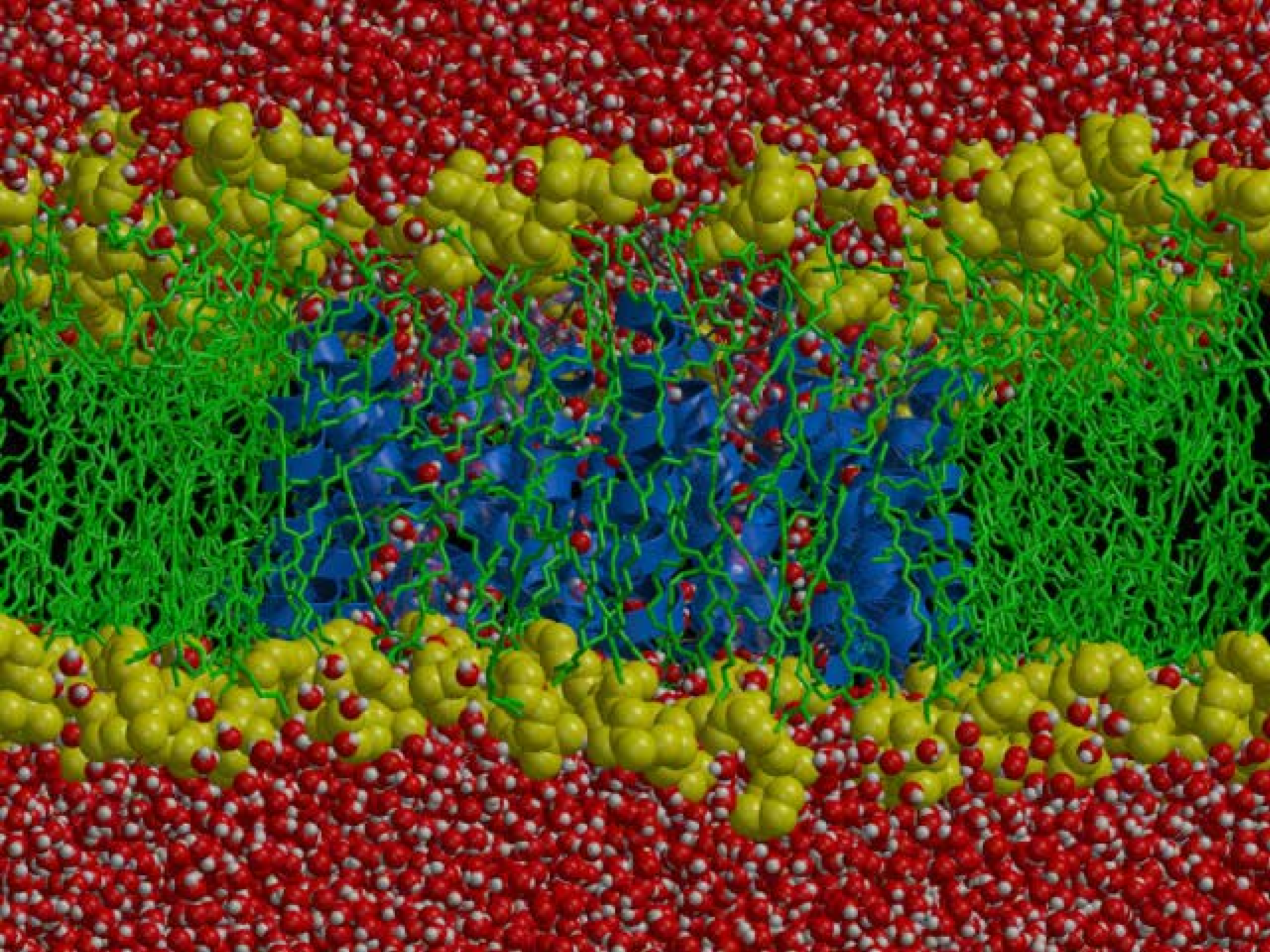

sn-2
sn-1



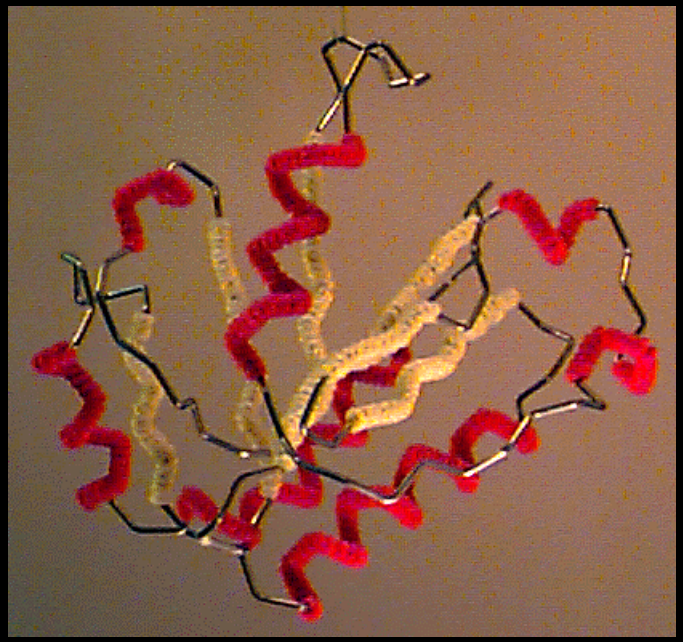


Hemolysin



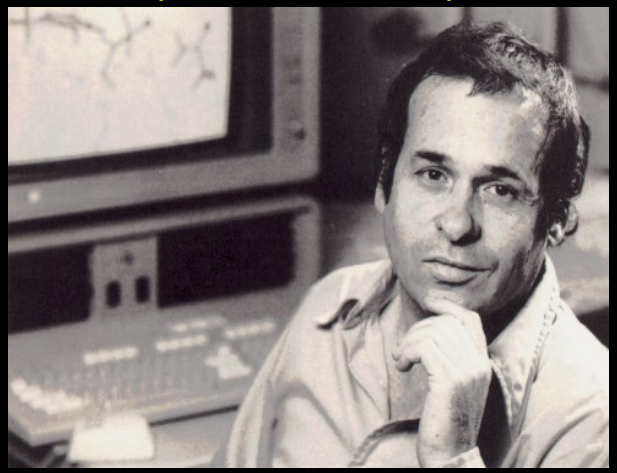


Počítačové modelování biomolekul



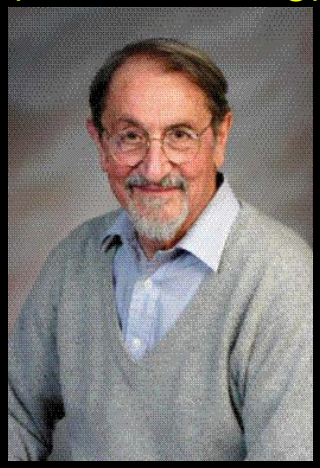

DIGITAL EQUIPMENT CORPORATION

Arieh Warshel
(Sneior Lifson)



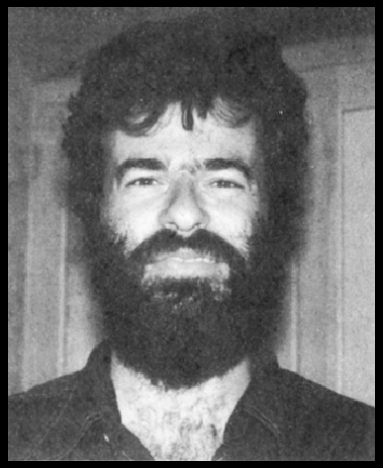
CFF (1967)
Consistent Force Field

Martin Karplus
(Linus Pauling)



CHARMM

Peter Kollman



AMBER (1981)

Klaus Schulten

NAMD

Michael Levitt
(John Kendrew)

Andy McCammon

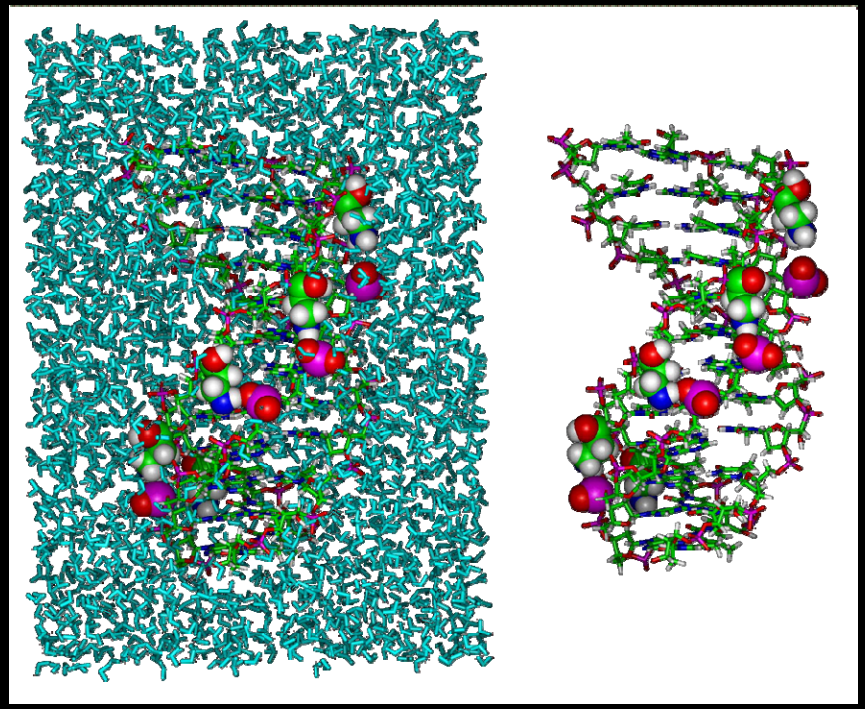
Bruce Gellin

WEIZAC
GOLEM

BPTI (1977)

MD - numerické řešení
Newtonových pohybových rovnic
s použitím empirických silových polí

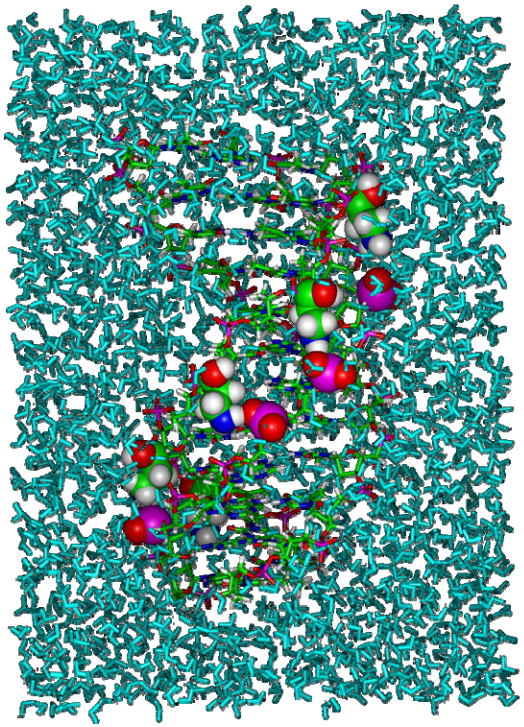
$$\frac{\mathrm{d}^2\vec{r}}{\mathrm{d}t^2} = \frac{1}{m}\vec{F}(\vec{r},\vec{v},t)$$

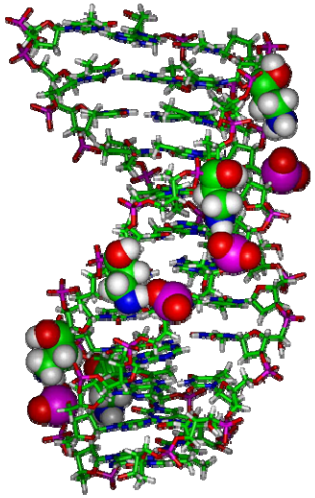


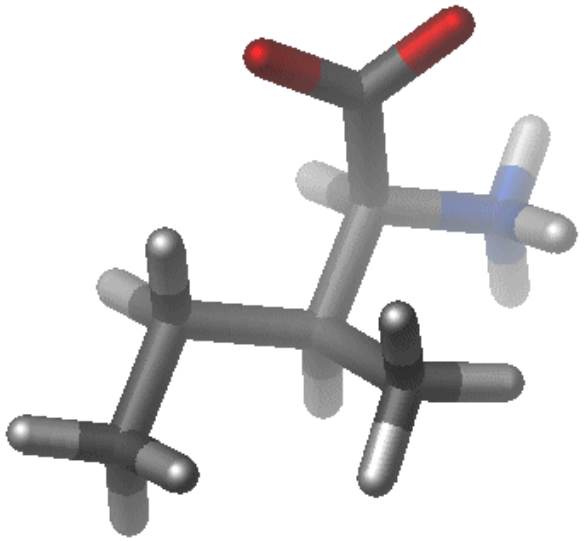
Leap-frog algoritmus

$$\vec{r}(t+\Delta t) = \vec{r}(t) + \vec{v}(t+\frac{1}{2}\Delta t)\Delta t + \frac{1}{2m}\vec{F}(t)(\Delta t)^2$$

$$\vec{v}(t+\frac{3}{2}\Delta t) = \vec{v}(t+\frac{1}{2}\Delta t) + \frac{1}{m}\vec{F}(t+\Delta t)\Delta t.$$







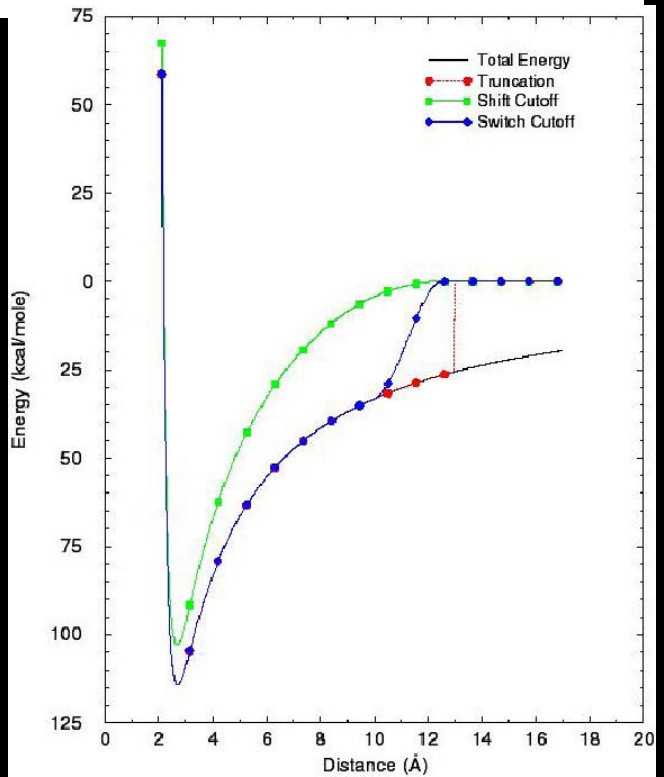
$$U(\mathbf{R}) = \sum_{bonds} K_r(r - r_{eq})^2 \qquad bond$$

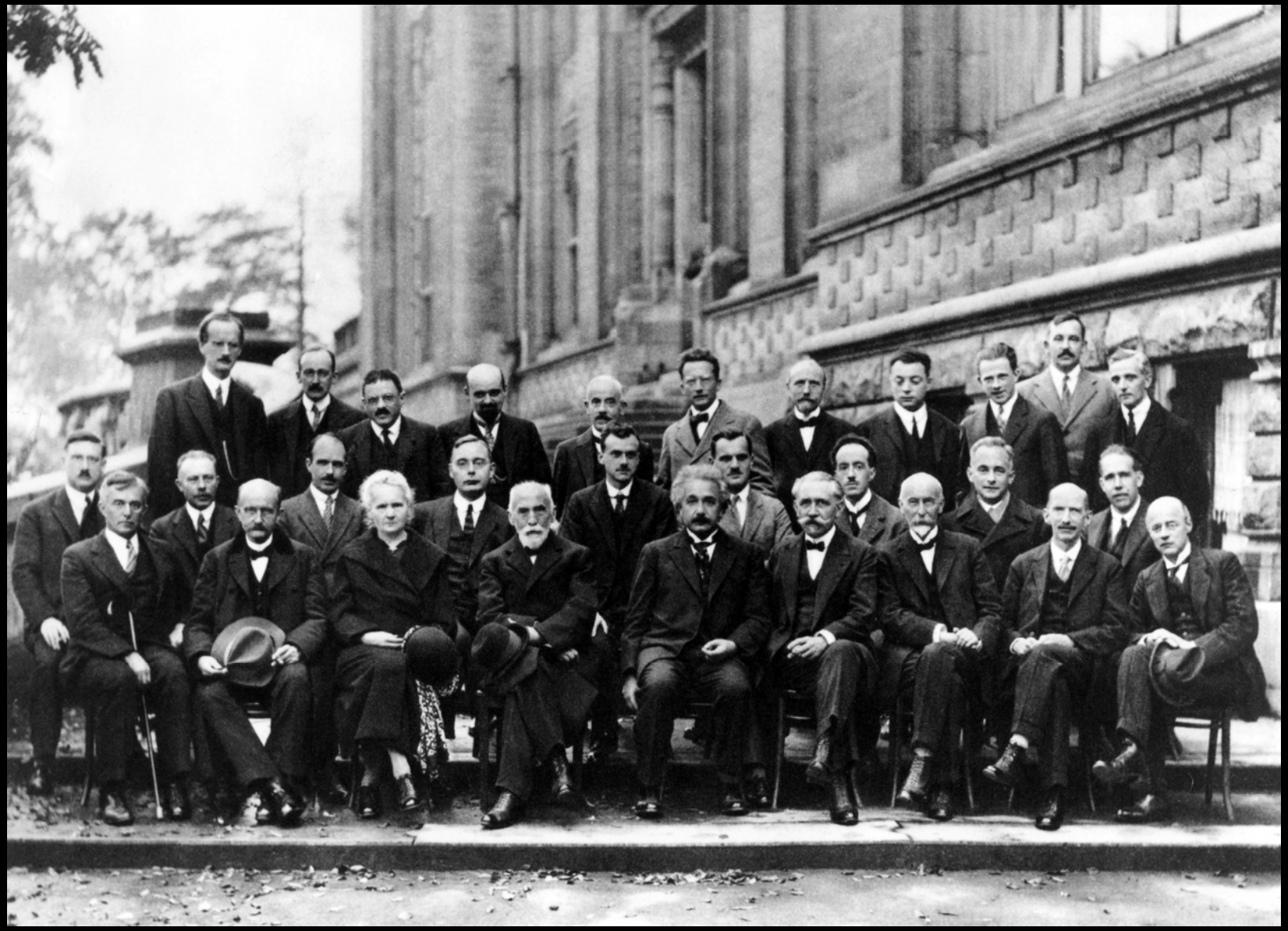
$$+ \sum_{angles} K_\theta(\theta - \theta_{eq})^2 \qquad angle$$

$$+ \sum_{dihedrals} \frac{V_n}{2}(1 + \cos[n\phi - \gamma]) \qquad dihedral$$

$$+ \sum_{i<j}^{atoms} \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} \qquad Van\ der\ Waals$$

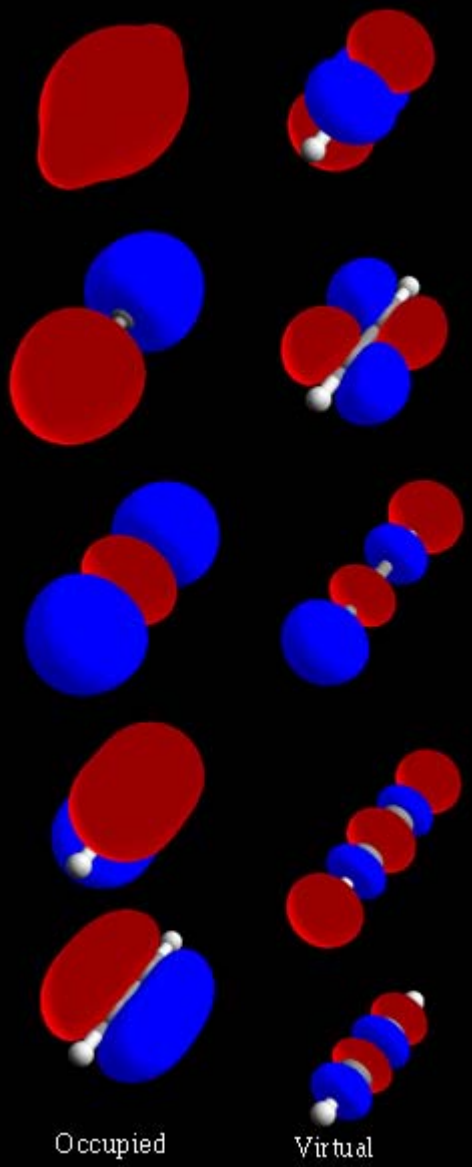
$$+ \sum_{i<j}^{atoms} \frac{q_i q_f}{\epsilon R_{ij}} \qquad electrostatic$$





A. Piccard, E. Henriot, P. Ehrenfest, , Th. De Donder, E. Schrödinger, J.E. Verschaffelt, W. Pauli, W. Heisenberg, R.H. Fowler, L. Brillouin, P. Debye, M. Knudsen, W.L. Bragg, H.A. Kramers, P.A.M. Dirac, A.H. Compton, L. de Broglie, M. Born, N. Bohr, I. Langmuir, M. Planck, Mme. Curie, H.A. Lorentz, A. Einstein, P. Langevin, , C.T.R. Wilson, O.W. Richardson

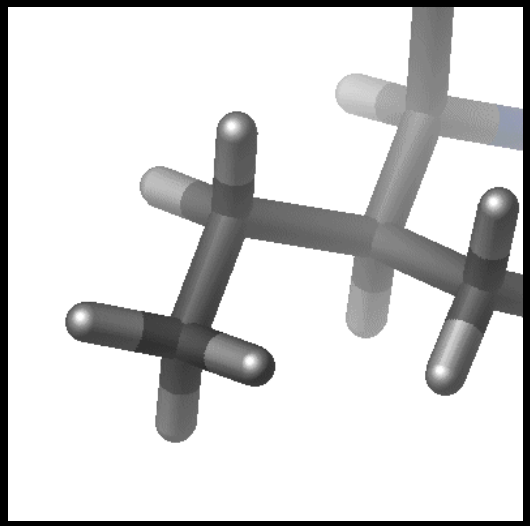
John A. Pople  1998 za chemii  Walter Kohn

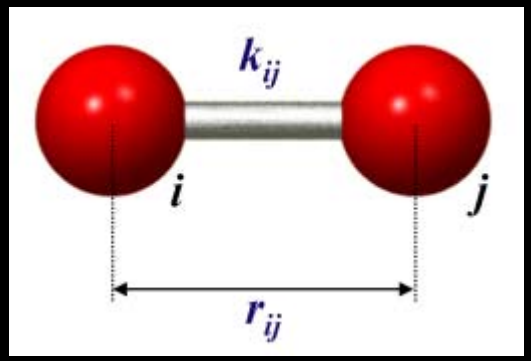


Gaussian 70

DFT

Ab initio výpočty – parametrizace silových polí pro MD





$$E_{stretch} = \sum_{\substack{bonds \\ AB}} \tfrac{1}{2} k_{AB} \left(r_{AB} - r_{AB}^{0} \right)^2$$

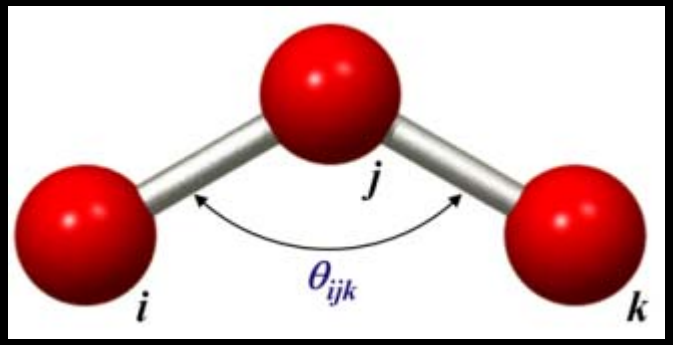
parameter:
force constant

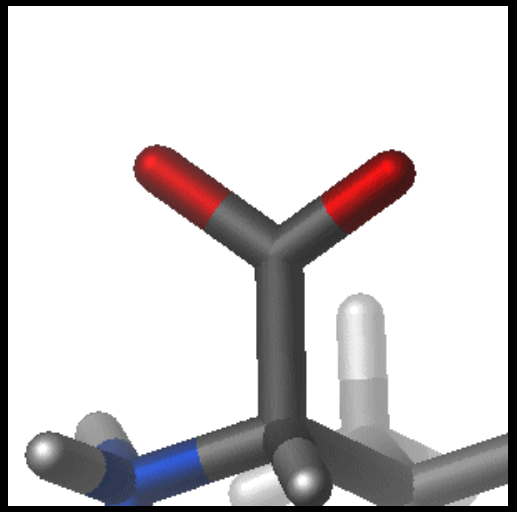
steepness

parameter:
natural bond length

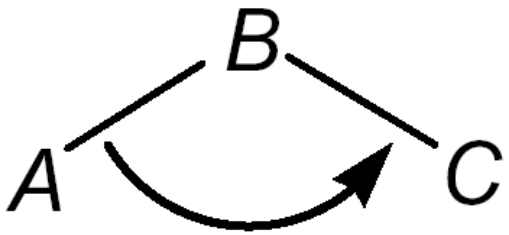
r_{AB}^{0}

Ab initio výpočty – parametrizace silových polí pro MD



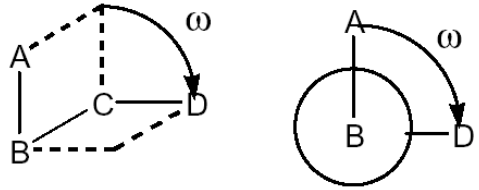


$$E_{bend} = \sum_{\substack{bonds \\ ABC}} \frac{1}{2} k_{ABC} \left(\theta_{ABC} - \theta^0_{ABC} \right)^2$$

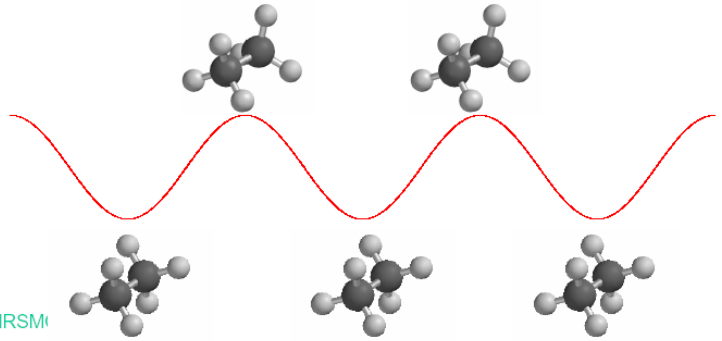


Ab initio výpočty – parametrizace silových polí pro MD

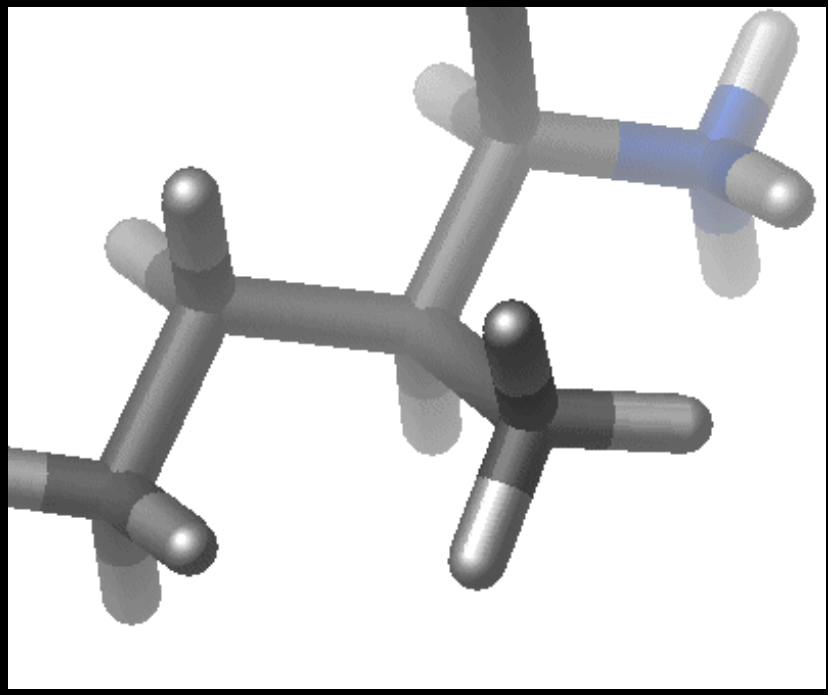
- torsion angle
  =dihedral angle

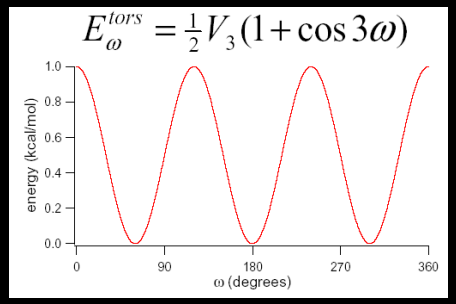


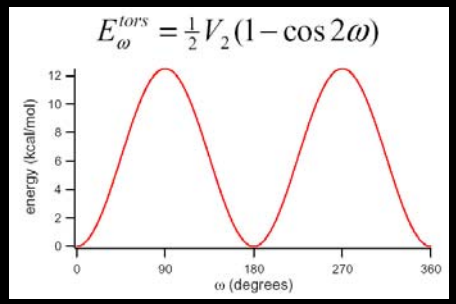
- related to barriers of rotation

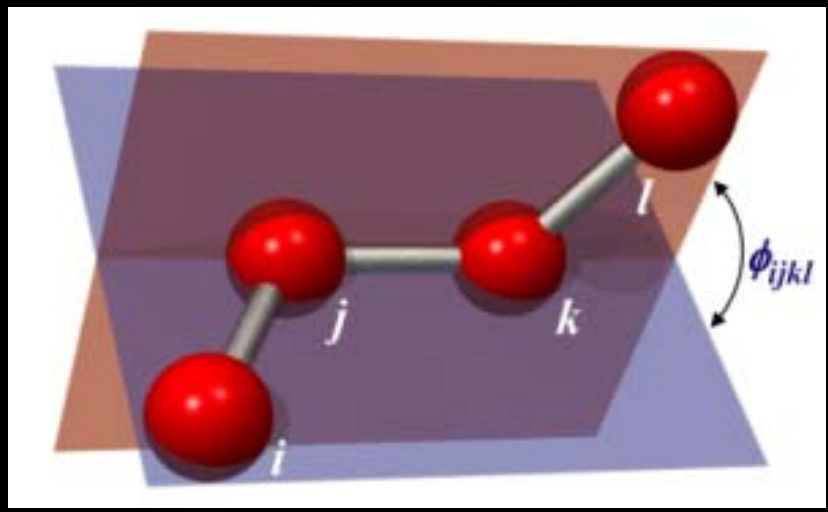


MM MolMech HRSM

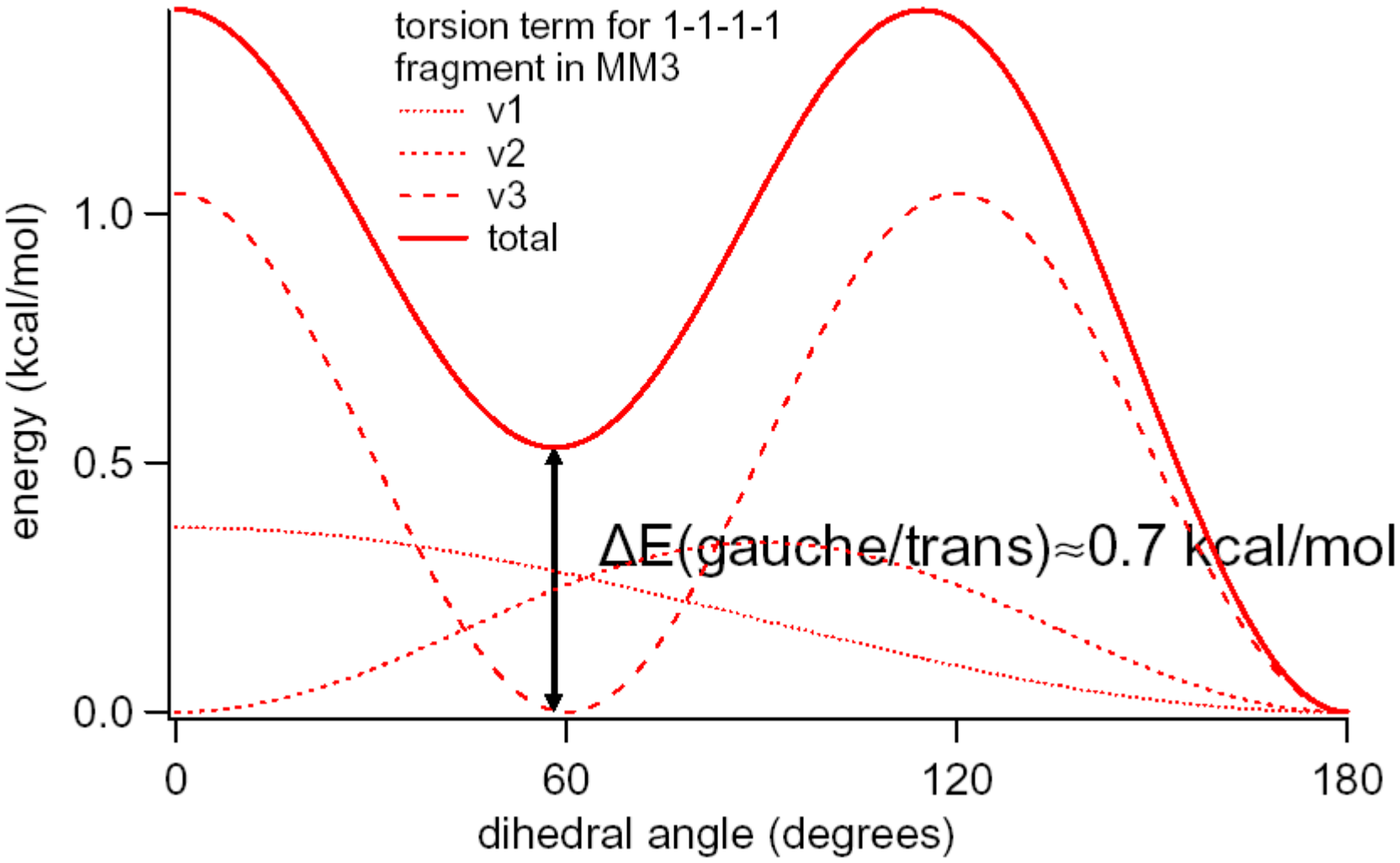




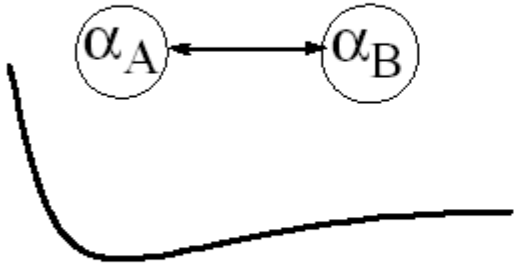




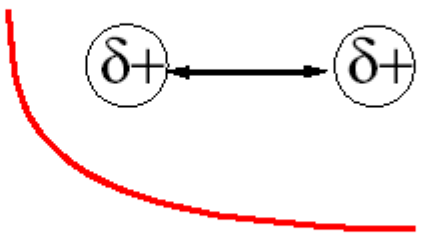
- C-C-C-C (e.g. butane)

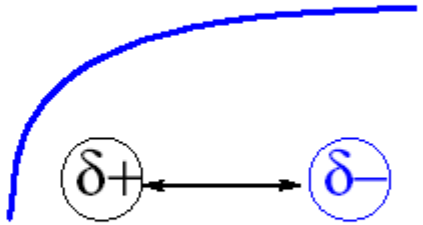


Nonbonding Interactions

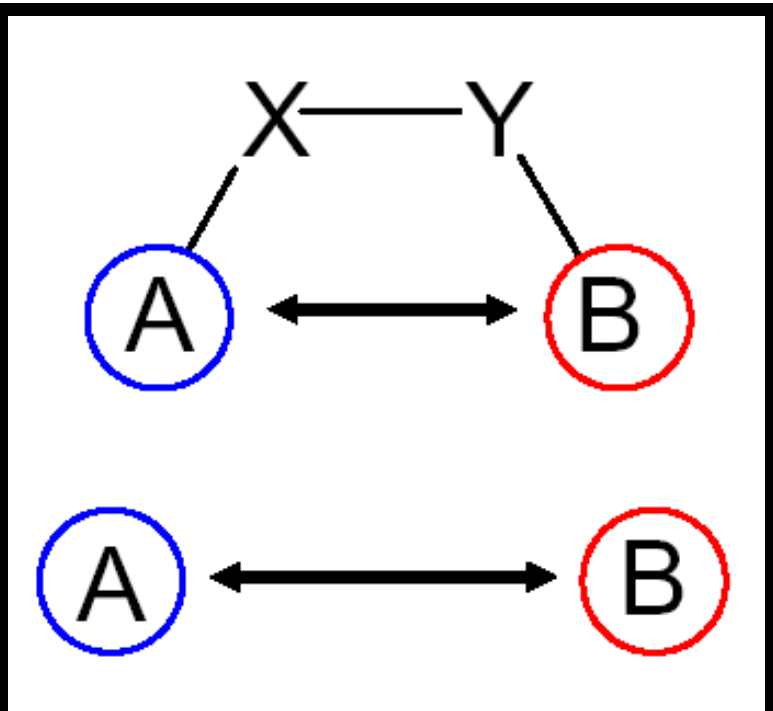


van der Waals interaction



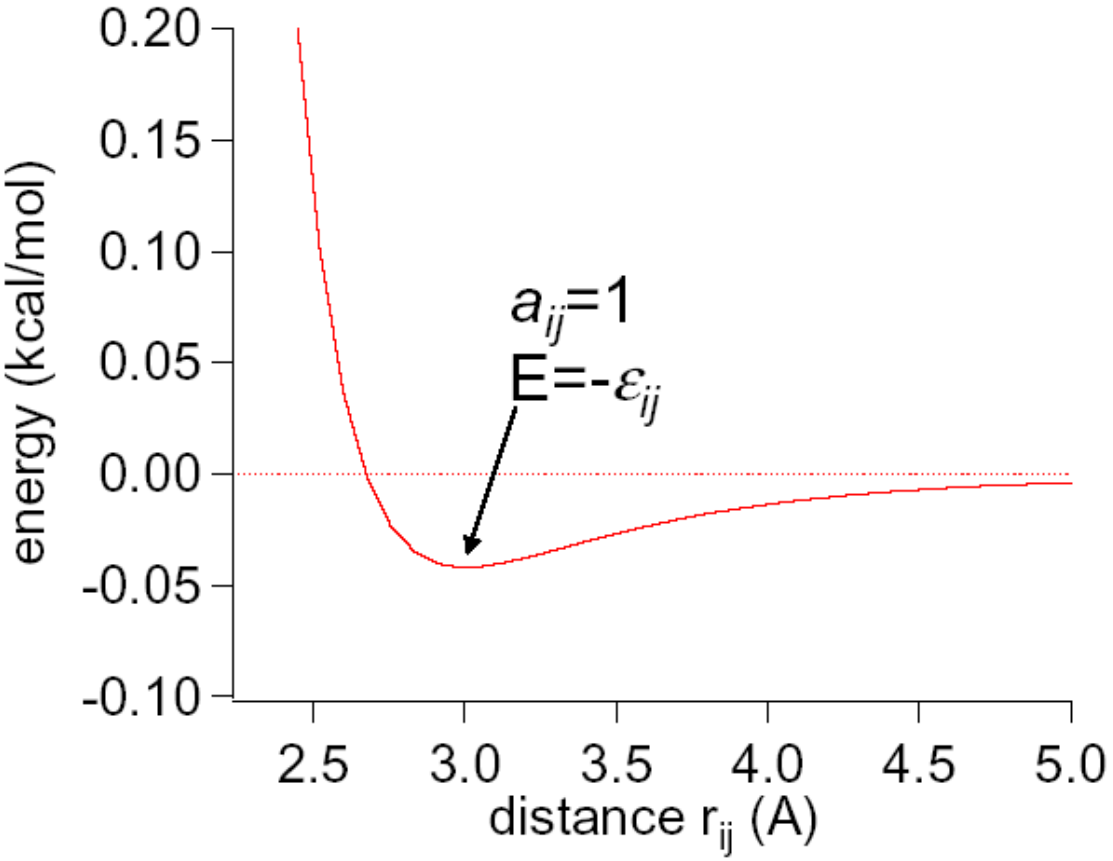


electrostatic interaction



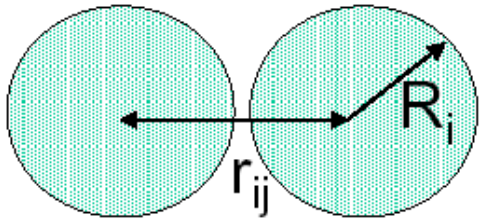
van der Waals interaction

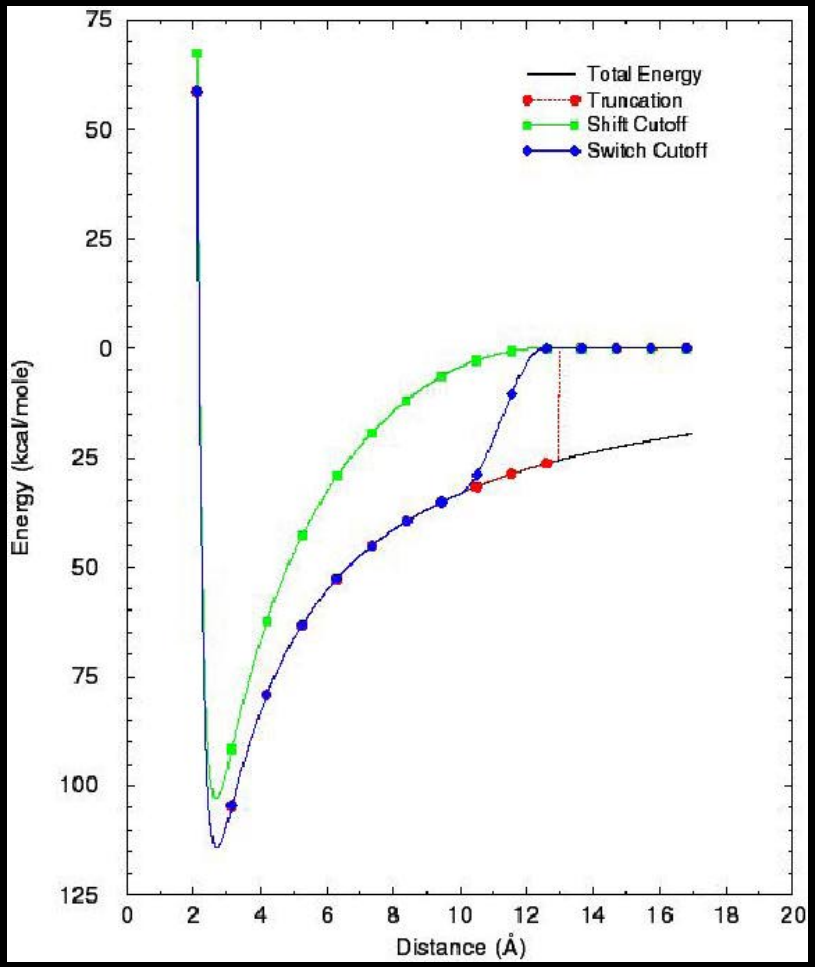
Lennard-Jones potential $E_{vdW} = \sum_{\substack{non-bonded \\ atom\_pairs}} \varepsilon_{ij}(a_{ij}^{-12} - 2a_{ij}^{-6})$



$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$$

$$a_{ij} = \frac{r_{ij}}{R_i + R_j}$$





TRUNCATION: the interactions are simply set to zero for interatomic distances greater than the cutoff distance. This method can lead to large fluctuations in the energy. This method is not often used.

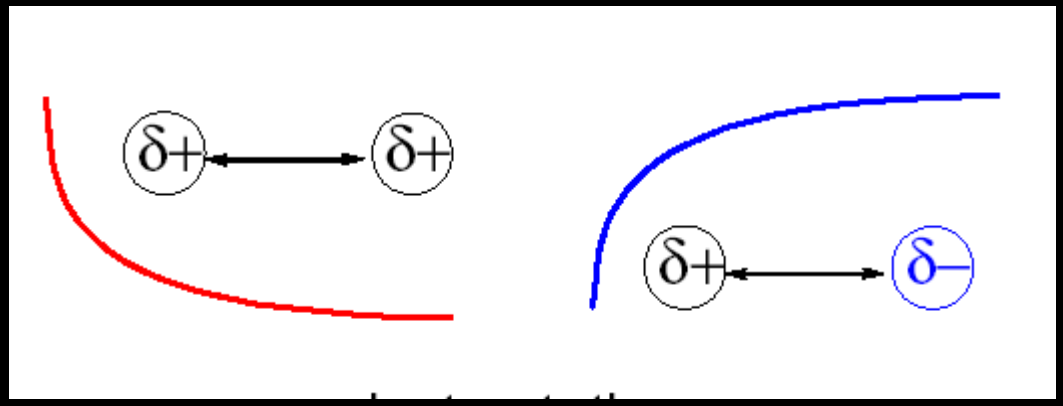
The **SHIFT** cutoff method: this method modifies the entire potential energy surface such that at the cutoff distance the interaction potential is zero. The drawback of this method is that equilibrium distances are slightly decreased.

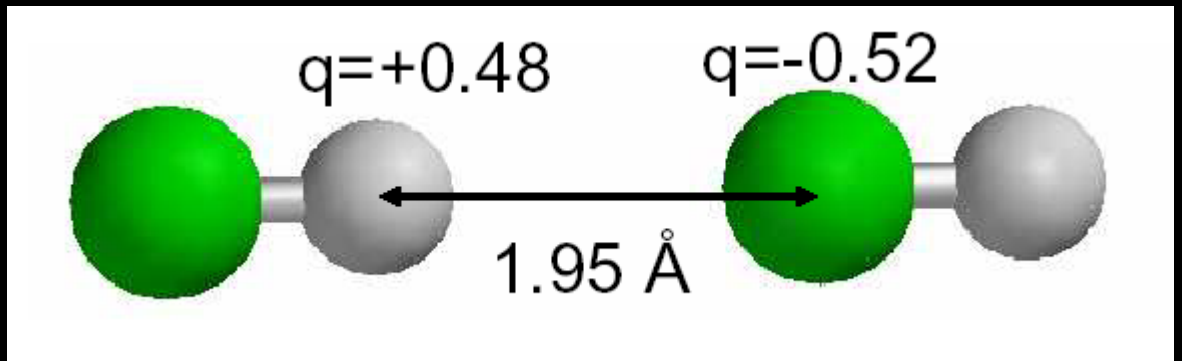
The **SWITCH** cutoff method: This method tapers the interaction potential over a predefined range of distances. The potential takes its usual value up to the first cutoff and is then switched to zero between the first and last cutoff. This model suffers from strong forces in the switching region which can slightly perturb the equilibrium structure. The SWITCH function is not recommended when using short cutoff regions.

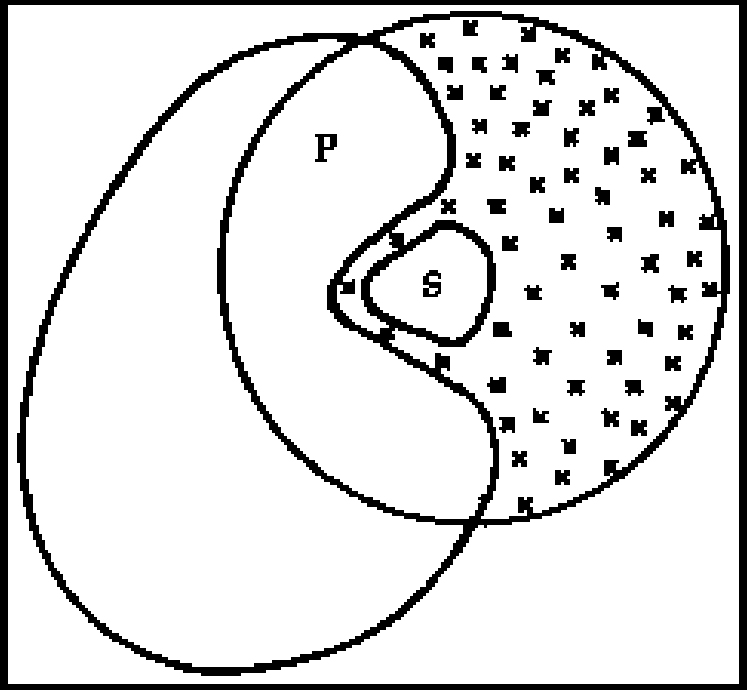
Electrostatic Interactions

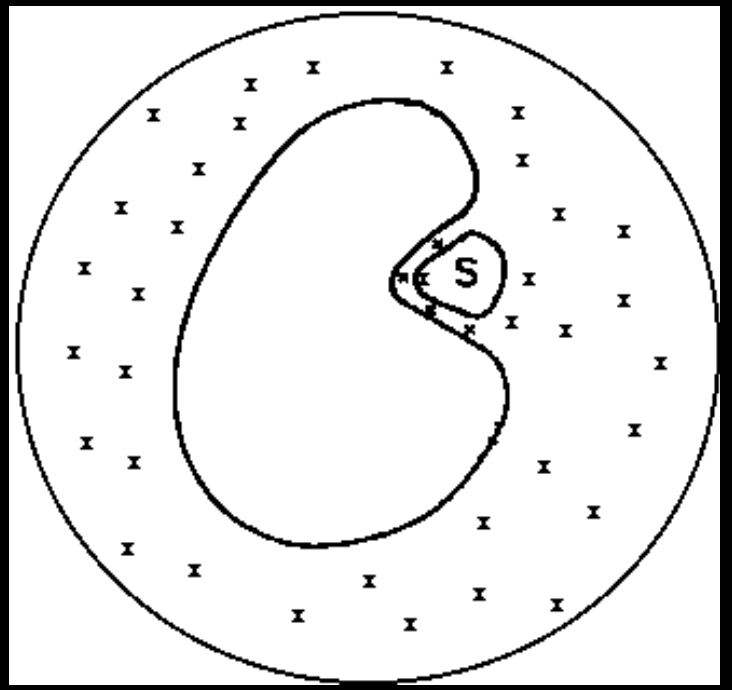
- standard approach: Coulomb's Law

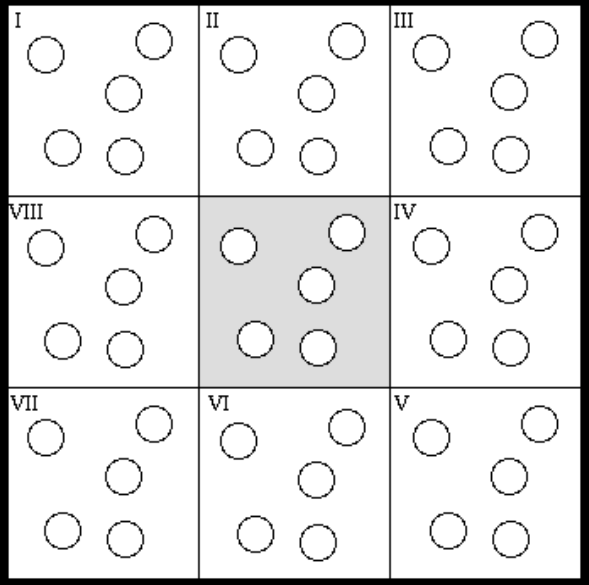
$$E_{electrostatic} = 332.1 \sum_{\substack{atom\ pairs \\ i,j}} \frac{q_i q_j}{\varepsilon_{ij} r_{ij}} \quad \text{(kcal/mol)}$$






P
S

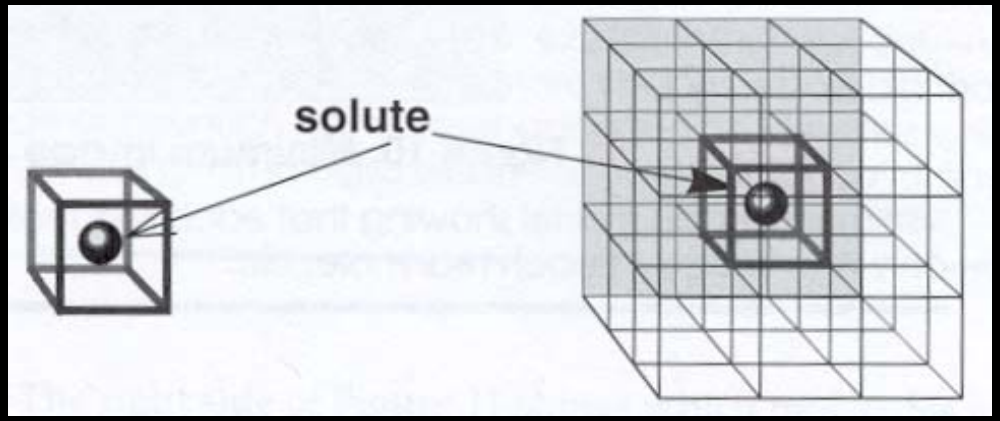

S


I
II
III
VIII
IV
VII
VI
V

$$E_{non-bonded} = E_{van-der-Waals} + E_{electrostatic}$$

$$E_{van-der-Waals} = \sum_{\substack{nonbonded \\ pairs}} \left(\frac{A_{ik}}{r_{ik}^{12}} - \frac{C_{ik}}{r_{ik}^{6}} \right)$$

$$E_{electrostatic} = \sum_{\substack{nonbonded \\ pairs}} \frac{q_i q_k}{D r_{ik}}$$



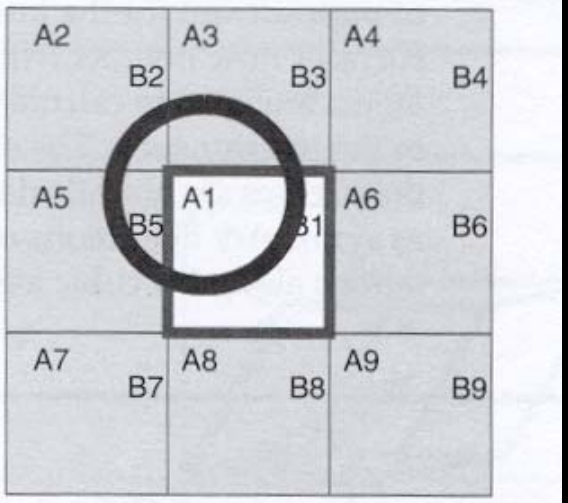
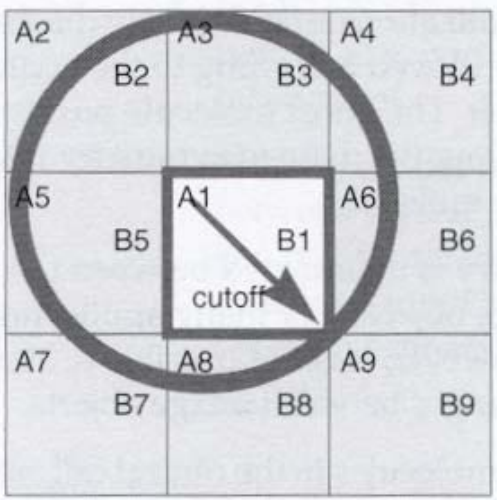


Figure 10. Minimum image model



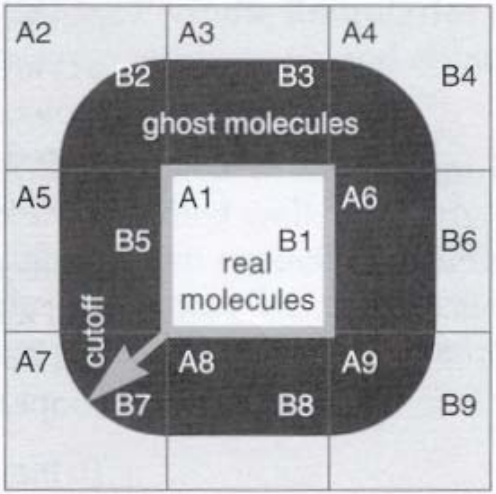
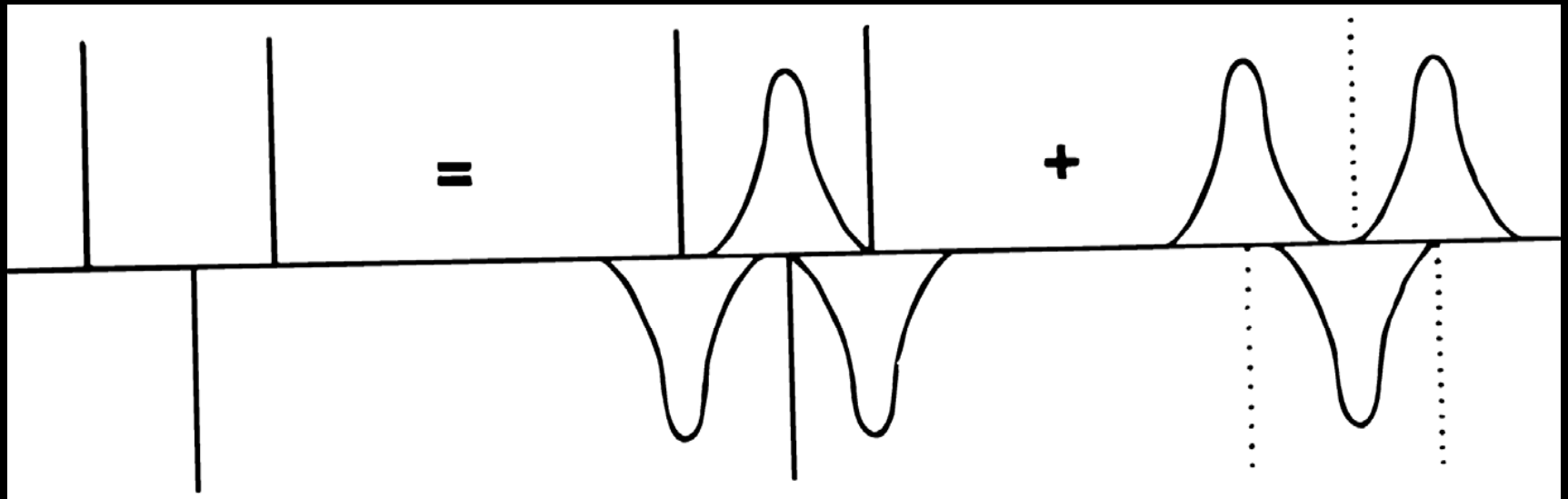
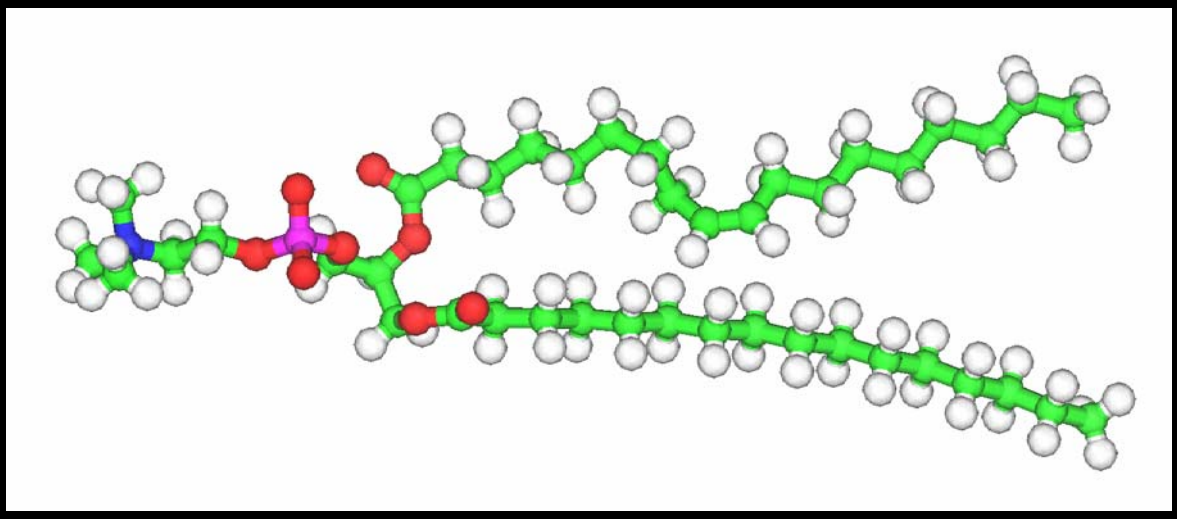


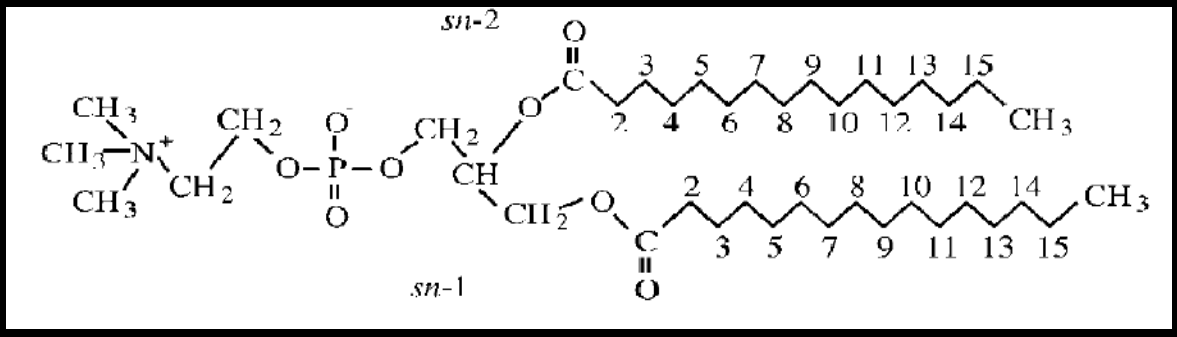
Figure 11. Explicit image model

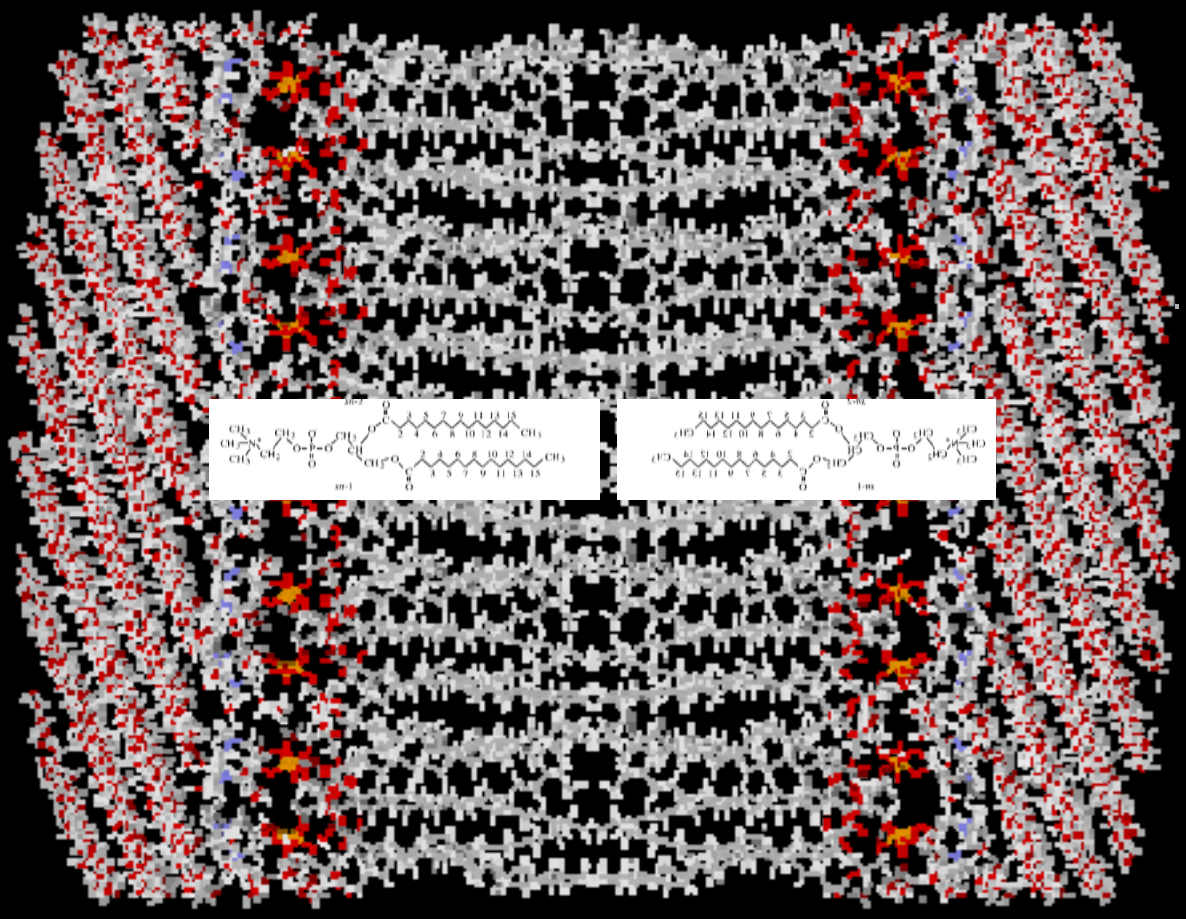
$$S_m = \frac{1}{2}\sum_{L,\,i,\,j}\frac{A_{ij}}{\left|\mathbf{r}_i - \mathbf{r}_j - \mathbf{R}_L\right|^m}$$



$$S_m = \frac{1}{2}\sum_{L,\,i,\,j}\frac{A_{ij}\phi_m\left(\left|\mathbf{r}_i - \mathbf{r}_j - \mathbf{R}_L\right|\right)}{\left|\mathbf{r}_i - \mathbf{r}_j - \mathbf{R}_L\right|^m} + \frac{1}{2}\sum_{L,\,i,\,j}\frac{A_{ij}\left(1 - \phi_m\left(\left|\mathbf{r}_i - \mathbf{r}_j - \mathbf{R}_L\right|\right)\right)}{\left|\mathbf{r}_i - \mathbf{r}_j - \mathbf{R}_L\right|^m}$$




sn-2
sn-1



Molecular Dynamics Simulations of Lipid Bilayers: Major Artifacts Due to Truncating Electrostatic Interactions

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