1. SVOJ PROJEKT:

- razmisliti o izboru sustava za svoj projekt koji ćete računati sami, nešto jednostavno, protein bez kofaktora i prostetičkih skupina (može i iznimka, ali je to onda puno teže), potražiti pdb od tog proteina, PITANJE NA KOJE HOĆETE NAĆI ODGOVOR – poslati do nedjelje u ponoć
- pokušajte to započeti slijedeći tjedan dok smo Natalia i ja tu

2. „*JOURNAL CLUB*" U SRIJEDU 25.2. (publikaciju ćete svi dobiti u petak)

3. ISPIT sredina 3. mjeseca? razmisliti – fiksirati na Journal clubu

POLJE SILA

Kolegij:

Strukturna računalna biofizika

2. OSNOVNI PRINCIPI NA KOJIMA SE ZASNIVAJU RAČUNALNE METODE KOJE SE KORISTE ZA ISTRAŽIVANJE BIOPOLIMERA.

Podijela računalnih metoda

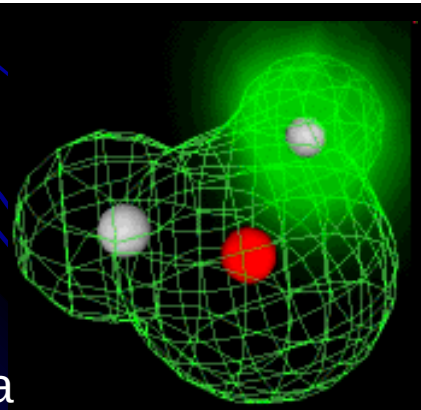
kvantno-mehaničke metode

empirijske metode

$H\Psi=E\Psi$

polyG -$(Gly)_{100}$ – 706 atoma

kvantna mehanika



- cijepanje veza

molekulska mehanika

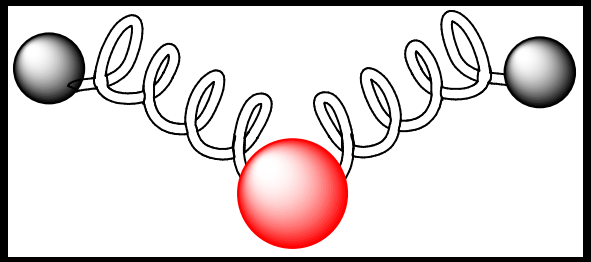


Table 1: Examples of levels of modeling in computational biochemistry and molecular biology.

Methods	Degrees of freedom	Properties, processes	Time scale
quantum dynamics	atoms, nuclei, electrons	excited states, relaxation, reaction dynamics	picoseconds
quantum mechanics (ab initio, density functional, semiempirical, valence bond methods)	atoms, nuclei, electrons	ground and excited states, reaction mechanisms	no time scale
classical statistical mechanics (MD, MC, force fields)	atoms, solvent	ensembles, averages, system properties, folding	nanoseconds
statistical methods (database analysis)	groups of atoms, amino acid residues, bases	structural homology and similarity	no time scale
continuum methods (hydrodynamics and electrostatics)	electrical continuum, velocity continuum etc.	rheological properties	supramolecular
kinetic equations	populations of species	population dynamics, signal transduction	macroscopic

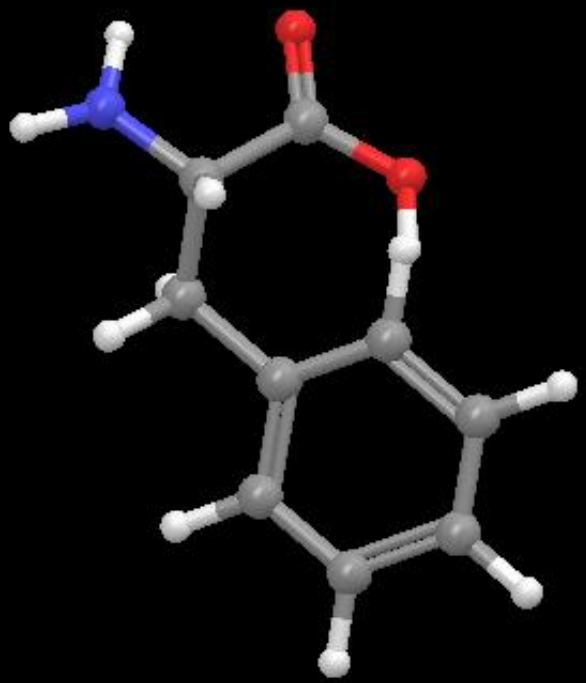
Empirijske metode

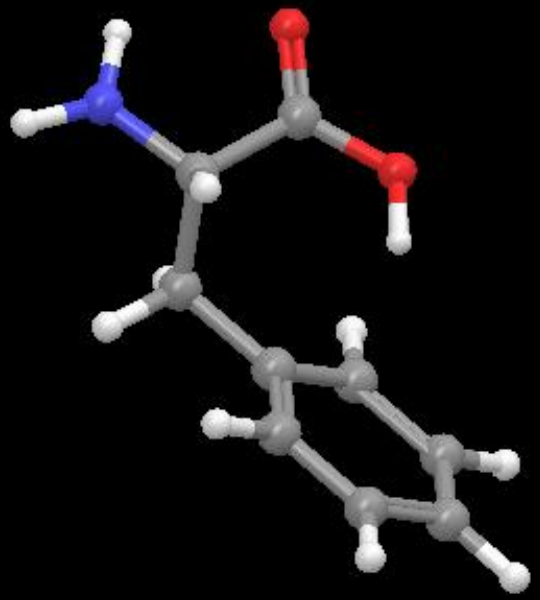
- **računalne metode temeljene na polju sila:**

- molekularna mehanika (MM)
- molekularna dinamika (MD)
- Monte Carlo konformacijska pretraga (MC)
- molekularna dinamika s nasumičnim ubrzanjem (RAMD)
- metadinamika
- QM/MM

EMPIRIJSKE METODE

(METODE TEMELJENE NA POLJU SILA)

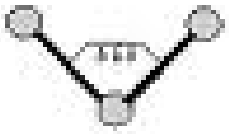




$$E = Estrech + Ebend + Etors + Eoop + Eel + Evdw + \sum Ecross$$

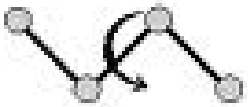
$$Estrech = \frac{k_s}{2}(l - l_0)^2$$

$$Eel = \frac{q_1 q_2}{4\pi\varepsilon r_{12}}$$

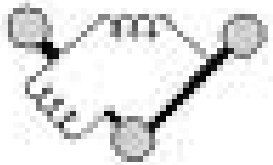


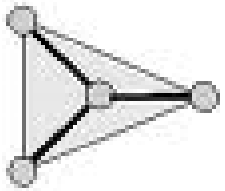
$$Ebend = \frac{k_b}{2}(\theta - \theta_0)^2$$

$$Evdw = \frac{A}{r^{12}} - \frac{C}{r^6}$$



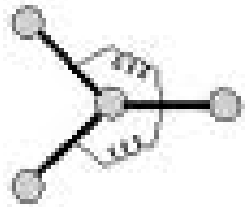
$$Etors = \sum_{n=0}^{N} \frac{V_n}{2}\left[1 + \cos(n\varphi - \gamma)\right]$$





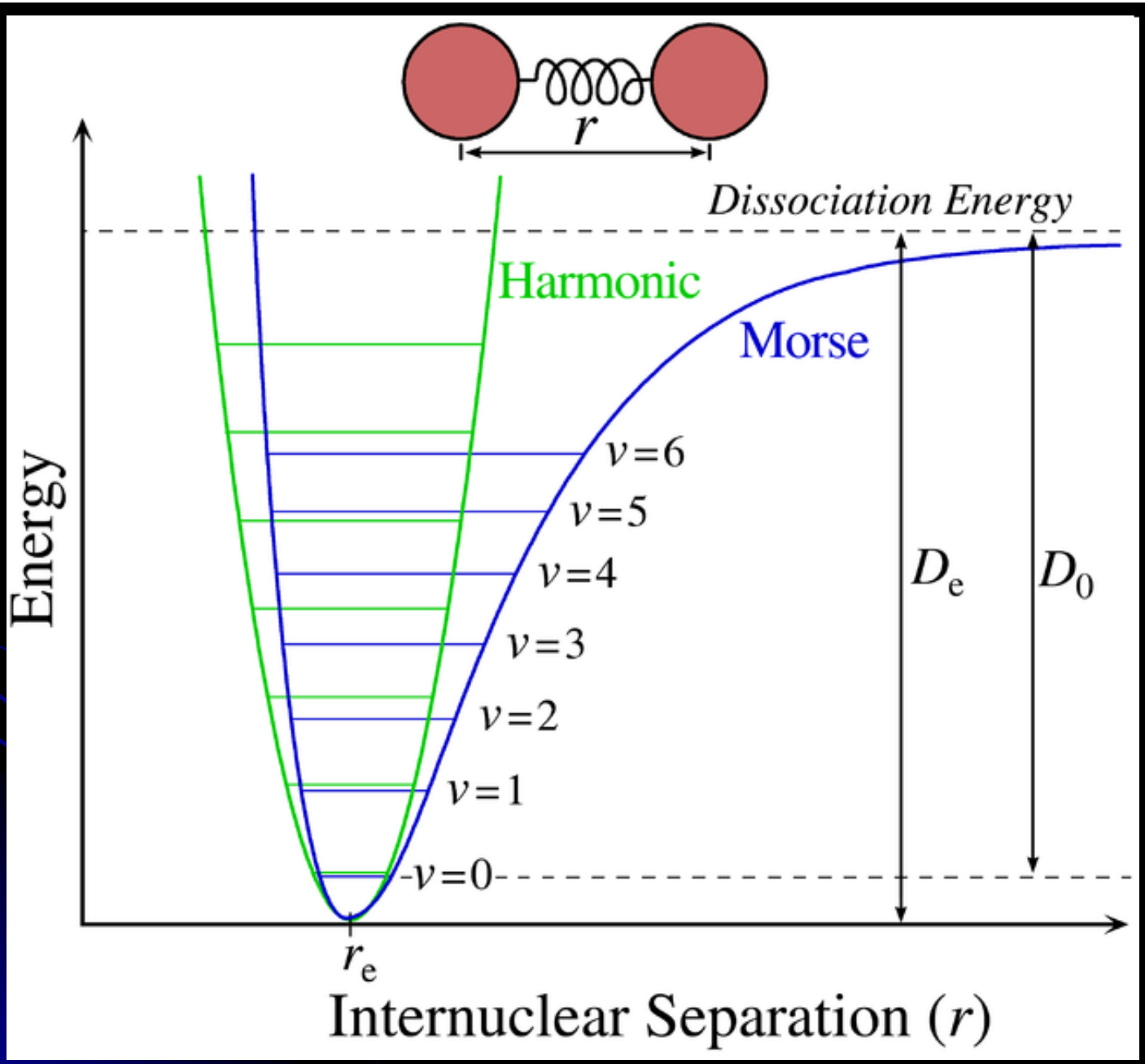
$$Eoop = \frac{1}{2} k_\xi \xi^2$$

$$EcrossS.-B. = \frac{k_{S.B.}}{2}\left[(l_1 - l_{10}) + (l_2 - l_{20})\right](\theta - \theta_0)$$

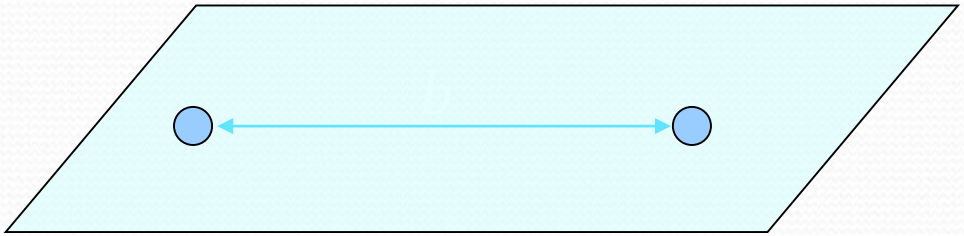


$$Estrech = \frac{k_s}{2}\left(l - l_0\right)^2$$

$$Estrech = D_e\left(e^{[-a(l-l_0)]} - 1\right)^2 - D_e$$

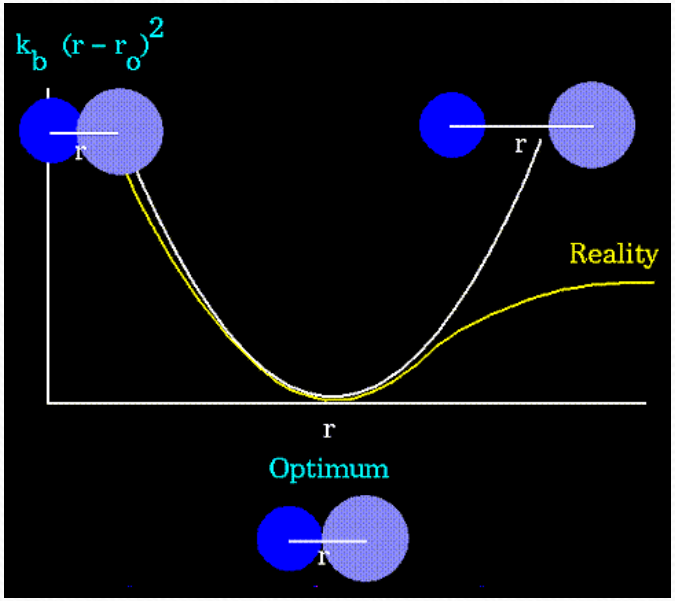


Istezanje veza *(bond potential)*

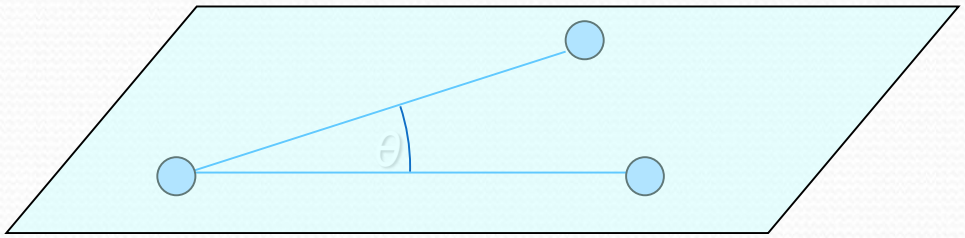


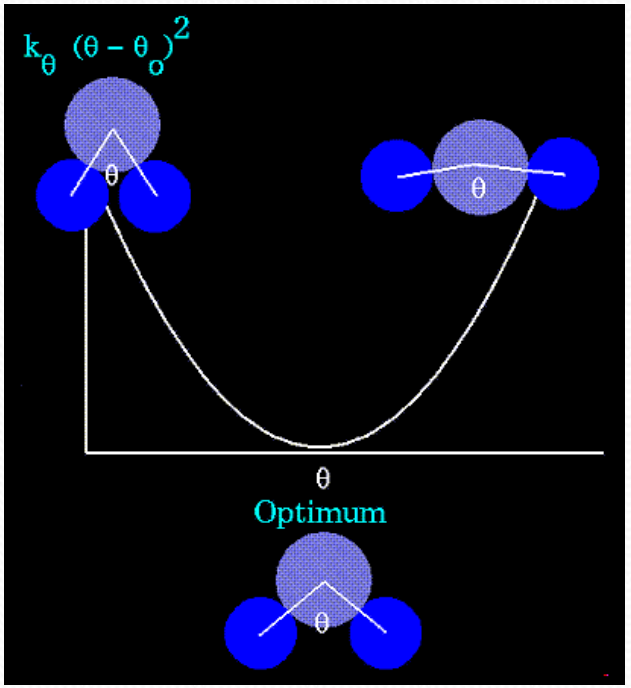
- Morseov potencijal
- $V_{bond} = \sum D_e(e^{-2\alpha(b-b_0)} - 2e^{-\alpha(b-b_0)})$

- HP
- $V_{bond} = \sum k_b (b - b_0)^2$



Savijanje kutova *(valence angle potential function)*

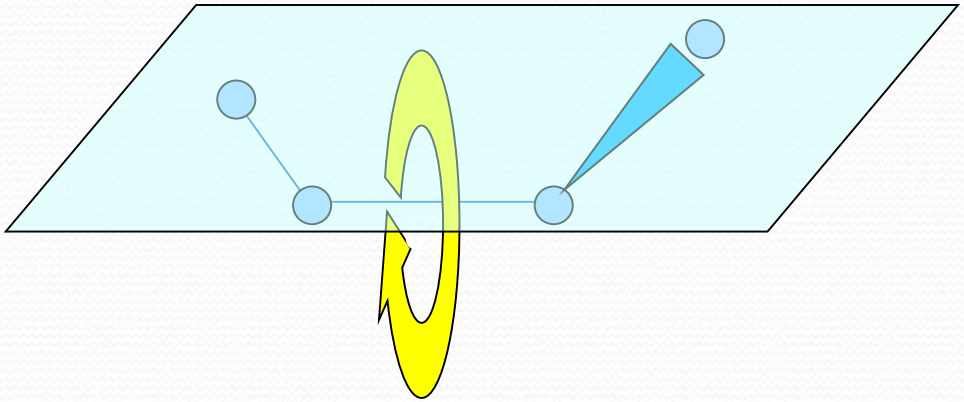


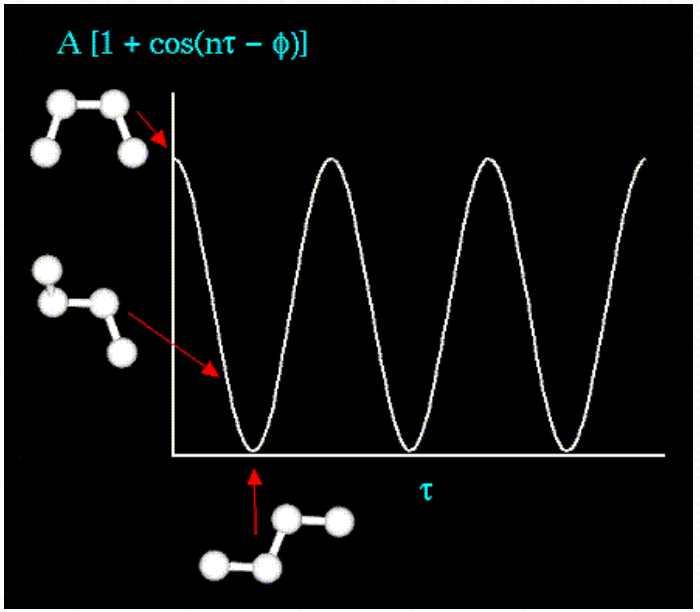


- $V_{va} = \frac{1}{2} \sum k_\theta (\theta - \theta_0)^2$

Torzijski kutovi, odnosno rotacija oko jednostruke veze

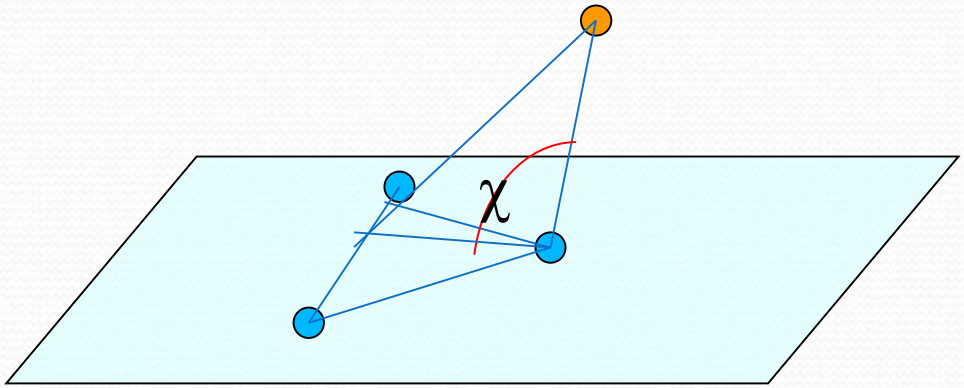
- $V_{ta} = \frac{1}{2} \sum V_{\varphi} (1 \pm \cos n\varphi)$





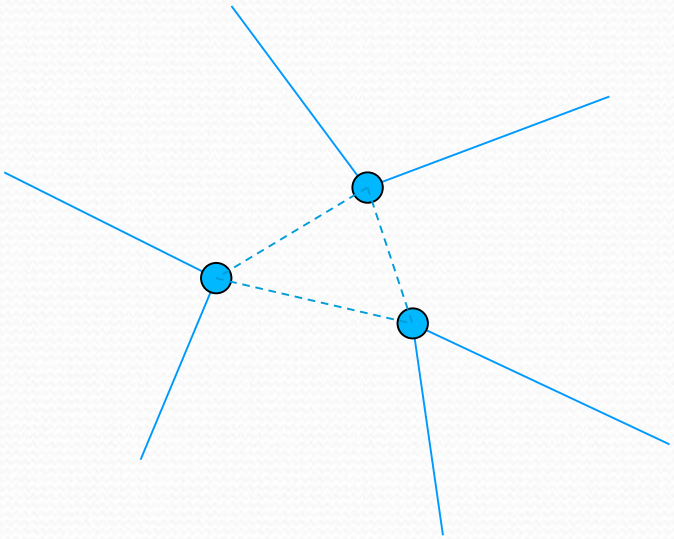
Planarnost sustava (*out of plane potential*)

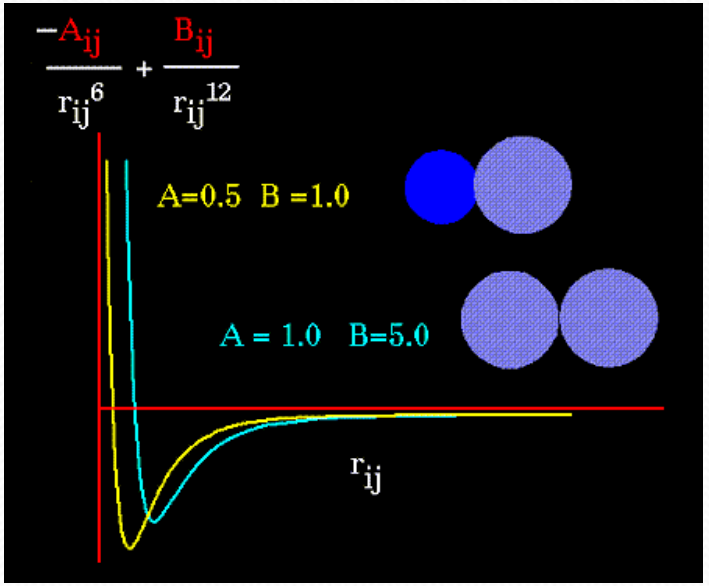
- $V_{\text{oop.}} = ½ \sum k_\chi \chi^2$



Van der Waalsove interakcije

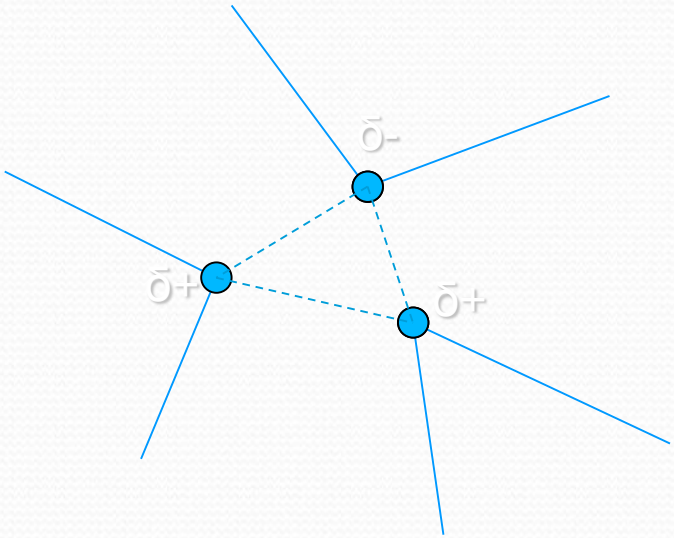
- $V_{\text{van der Waals}} = \sum_{i<j} (A_i A_j r_{ij}^{-12} - B_i B_j r_{ij}^{-6})$





Elektrostatske interakcije

- $V_{\mathrm{el}} \propto \sum_{l<m} q_l q_m r_{lm}^{-1}$



```
PARM99 for DNA,RNA,AA, organic molecules, TIP3P wat. Polariz.& LP incl.02/04/99
C  12.01          0.616  !            sp2 C carbonyl group
CA 12.01          0.360               sp2 C pure aromatic (benzene)
CB 12.01          0.360               sp2 aromatic C, 5&6 membered ring junction
CC 12.01          0.360               sp2 aromatic C, 5 memb. ring HIS
CD 12.01          0.360               sp2 C atom in the middle of: C=CD-CD=C
CK 12.01          0.360               sp2 C 5 memb.ring in purines
CM 12.01          0.360               sp2 C  pyrimidines in pos. 5 & 6
CN 12.01          0.360               sp2 C aromatic 5&6 memb.ring junct.(TRP)
CQ 12.01          0.360               sp2 C in 5 mem.ring of purines between 2 N
CR 12.01          0.360               sp2 arom as CQ but in HIS
CT 12.01          0.878               sp3 aliphatic C
CV 12.01          0.360               sp2 arom. 5 memb.ring w/1 N and 1 H (HIS)
CW 12.01          0.360               sp2 arom. 5 memb.ring w/1 N-H and 1 H (HIS)
C* 12.01          0.360               sp2 arom. 5 memb.ring w/1 subst. (TRP)
CY 12.01          0.360               nitrile C (Howard et al.JCC,16,243,1995)
CZ 12.01          0.360               sp C (Howard et al.JCC,16,243,1995)
C0 40.08                              calcium
H  1.008          0.161               H bonded to nitrogen atoms
HC 1.008          0.135               H aliph. bond. to C without electrwd.group
H1 1.008          0.135               H aliph. bond. to C with 1 electrwd. group
H2 1.008          0.135               H aliph. bond. to C with 2 electrwd.groups
H3 1.008          0.135               H aliph. bond. to C with 3 eletrwd.groups
HA 1.008          0.167               H arom. bond. to C without elctrwd. groups
H4 1.008          0.167               H arom. bond. to C with 1 electrwd. group
H5 1.008          0.167               H arom.at C with 2 elctrwd. gr,+HCOO group
HO 1.008          0.135               hydroxyl group
HS 1.008          0.135               hydrogen bonded to sulphur (pol?)
HW 1.008          0.000               H in TIP3P water
HP 1.008          0.135               H bonded to C next to positively charged gr
HZ 1.008          0.161               H bond sp C (Howard et al.JCC,16,243,1995)
F  19.00          0.320               fluorine
Cl 35.45          1.910               chlorine  (Applequist)
Br 79.90          2.880               bromine  (Applequist)
I  126.9          4.690               iodine   (Applequist)
IM 35.45          3.235               assumed to be Cl- (ion minus)
IB 131.0                              'big ion w/ waters' for vacuum (Na+, 6H2O)
MG 24.305         0.120               magnesium
N  14.01          0.530               sp2 nitrogen in amide groups
NA 14.01          0.530               sp2 N in 5 memb.ring w/H atom (HIS)
NB 14.01          0.530               sp2 N in 5 memb.ring w/LP (HIS,ADE,GUA)
NC 14.01          0.530               sp2 N in 6 memb.ring w/LP (ADE,GUA)
N2 14.01          0.530               sp2 N in amino groups
N3 14.01          0.530               sp3 N for charged amino groups (Lys, etc)
```

tip atoma

```
C   H    HO  N    NA  NB  NC  N2  NT  N2  N3  N*  O    OH  OS  P    O2
OW-HW  553.0    0.9572    ! TIP3P water
HW-HW  553.0    1.5136      TIP3P water
C -C   310.0    1.525       Junmei et al, 1999
C -CA  469.0    1.409       JCC,7,(1986),230; (not used any more in TYR)
C -CB  447.0    1.419       JCC,7,(1986),230; GUA
C -CM  410.0    1.444       JCC,7,(1986),230; THY,URA
C -CT  317.0    1.522       JCC,7,(1986),230; AA
C -N   490.0    1.335       JCC,7,(1986),230; AA
C -N*  424.0    1.383       JCC,7,(1986),230; CYT,URA
C -NA  418.0    1.388       JCC,7,(1986),230; GUA,URA
C -NC  457.0    1.358       JCC,7,(1986),230; CYT
C -O   570.0    1.229       JCC,7,(1986),230; AA,CYT,GUA,THY,URA
C -O2  656.0    1.250       JCC,7,(1986),230; GLU,ASP
C -OH  450.0    1.364       JCC,7,(1986),230; (not used any more for TYR)
C -OS  450.0    1.323       Junmei et al, 1999
C -H4  367.0    1.080       Junmei et al, 1999
C -H5  367.0    1.080       Junmei et al, 1999
CA-CA  469.0    1.400       JCC,7,(1986),230; BENZENE,PHE,TRP,TYR
CA-CB  469.0    1.404       JCC,7,(1986),230; ADE,TRP
CA-CM  427.0    1.433       JCC,7,(1986),230; CYT
CA-CN  469.0    1.400       JCC,7,(1986),230; TRP
CA-CT  317.0    1.510       JCC,7,(1986),230; PHE,TYR
CA-HA  367.0    1.080       changed from 340. bsd on C6H6 nmodes; PHE,TRP,TYR
CA-H4  367.0    1.080       changed from 340. bsd on C6H6 nmodes; no assigned
CA-N2  481.0    1.340       JCC,7,(1986),230; ARG,CYT,GUA
CA-NA  427.0    1.381       JCC,7,(1986),230; GUA
CA-NC  483.0    1.339       JCC,7,(1986),230; ADE,CYT,GUA
CA-OH  450.0    1.364       substituted for C-OH in tyr
CB-CB  520.0    1.370       JCC,7,(1986),230; ADE,GUA
CB-N*  436.0    1.374       JCC,7,(1986),230; ADE,GUA
CB-NB  414.0    1.391       JCC,7,(1986),230; ADE,GUA
CB-NC  461.0    1.354       JCC,7,(1986),230; ADE,GUA
CD-HA  367.0    1.080       Junmei et al, 1999
CD-CD  469.0    1.400       Junmei et al, 1999
CD-CM  549.0    1.350       Junmei et al, 1999
CD-CT  317.0    1.510       Junmei et al, 1999
CK-H5  367.0    1.080       changed from 340. bsd on C6H6 nmodes; ADE,GUA
CK-N*  440.0    1.371       JCC,7,(1986),230; ADE,GUA
CK-NB  529.0    1.304       JCC,7,(1986),230; ADE,GUA
CM-CM  549.0    1.350       JCC,7,(1986),230; CYT,THY,URA
CM-CT  317.0    1.510       JCC,7,(1986),230; THY
CM-HA  367.0    1.080       changed from 340. bsd on C6H6 nmodes; CYT,URA
```

$$Estrech = \frac{k_s}{2}(l - l_0)^2$$

```
HW-OW-HW    100.       104.52    TIP3P water
HW-HW-OW      0.       127.74    (found in crystallographic water with 3 bonds)
C -C -O      80.0      120.00    Junmei et al, 1999 acrolein
C -C -OH     80.0      120.00    Junmei et al, 1999
CA-C -CA     63.0      120.00    changed from 85.0  bsd on C6H6 nmodes; AA
CA-C -OH     70.0      120.00    AA (not used in tyr)
CB-C -NA     70.0      111.30    NA
CB-C -O      80.0      128.80
CM-C -NA     70.0      114.10
CM-C -O      80.0      125.30
CT-C -O      80.0      120.40
CT-C -O2     70.0      117.00
CT-C -N      70.0      116.60    AA general
CT-C -CT     63.0      117.00    Junmei et al, 1999
CT-C -OS     80.0      115.00    Junmei et al, 1999
CT-C -OH     80.0      110.00    Junmei et al, 1999
N*-C -NA     70.0      115.40
N*-C -NC     70.0      118.60
N*-C -O      80.0      120.90
NA-C -O      80.0      120.60
NC-C -O      80.0      122.50
N -C -O      80.0      122.90    AA general
O -C -O      80.0      126.00    AA COO- terminal residues
O -C -OH     80.0      120.00    (check with Junmei for: theta0:120.0?)
O -C -OS     80.0      125.00    Junmei et al, 1999
O2-C -O2     80.0      126.00    AA GLU            (SCH JPC 79,2379)
H4-C -C      50.0      120.00    Junmei et al, 1999
H4-C -CM     50.0      115.00    Junmei et al, 1999
H4-C -CT     50.0      115.00    Junmei et al, 1999
H4-C -O      50.0      120.00    Junmei et al, 1999
H4-C -OH     50.0      120.00    Junmei et al, 1999
H5-C -N      50.0      120.00    Junmei et al, 1999
H5-C -O      50.0      119.00    Junmei et al, 1999
H5-C -OH     50.0      107.00    Junmei et al, 1999
H5-C -OS     50.0      107.00    Junmei et al, 1999
C -CA-CA     63.0      120.00    changed from 85.0  bsd on C6H6 nmodes
C -CA-HA     50.0      120.00    AA (not used in tyr)
CA-CA-CA     63.0      120.00    changed from 85.0  bsd on C6H6 nmodes
CA-CA-CB     63.0      120.00    changed from 85.0  bsd on C6H6 nmodes
CA-CA-CT     70.0      120.00
CA-CA-HA     50.0      120.00
CA-CA-H4     50.0      120.00
CA-CA-OH     70.0      120.00    replacement in tyr
```

$$Ebend = \frac{k_b}{2}(\theta - \theta_0)^2$$

X -C -C -X	4	14.50	180.0	2.	Junmei et al, 1999
X -C -CA-X	4	14.50	180.0	2.	intrpol.bsd.on C6H6
X -C -CB-X	4	12.00	180.0	2.	intrpol.bsd.on C6H6
X -C -CM-X	4	8.70	180.0	2.	intrpol.bsd.on C6H6
X -C -CT-X	6	0.00	0.0	2.	JCC,7,(1986),230
X -C -N -X	4	10.00	180.0	2.	AA,NMA
X -C -N*-X	4	5.80	180.0	2.	JCC,7,(1986),230
X -C -NA-X	4	5.40	180.0	2.	JCC,7,(1986),230
X -C -NC-X	2	8.00	180.0	2.	JCC,7,(1986),230
X -C -O -X	4	11.20	180.0	2.	Junmei et al, 1999
X -C -OH-X	2	4.60	180.0	2.	Junmei et al, 1999
X -C -OS-X	2	5.40	180.0	2.	Junmei et al, 1999
X -CA-CA-X	4	14.50	180.0	2.	intrpol.bsd.on C6H6
X -CA-CB-X	4	14.00	180.0	2.	intrpol.bsd.on C6H6
X -CA-CM-X	4	10.20	180.0	2.	intrpol.bsd.on C6H6
X -CA-CN-X	4	14.50	180.0	2.	reinterpolated 93'
X -CA-CT-X	6	0.00	0.0	2.	JCC,7,(1986),230
X -CA-N2-X	4	9.60	180.0	2.	reinterpolated 93'
X -CA-NA-X	4	6.00	180.0	2.	JCC,7,(1986),230
X -CA-NC-X	2	9.60	180.0	2.	JCC,7,(1986),230
X -CA-OH-X	2	1.80	180.0	2.	Junmei et al, 99
X -CB-CB-X	4	21.80	180.0	2.	intrpol.bsd.on C6H6
X -CB-CN-X	4	12.00	180.0	2.	reinterpolated 93'
X -CB-N*-X	4	6.60	180.0	2.	JCC,7,(1986),230
X -CB-NB-X	2	5.10	180.0	2.	JCC,7,(1986),230
X -CB-NC-X	2	8.30	180.0	2.	JCC,7,(1986),230
X -CC-CT-X	6	0.00	0.0	2.	JCC,7,(1986),230
X -CC-CV-X	4	20.60	180.0	2.	intrpol.bsd.on C6H6
X -CC-CW-X	4	21.50	180.0	2.	intrpol.bsd.on C6H6
X -CC-NA-X	4	5.60	180.0	2.	JCC,7,(1986),230
X -CC-NB-X	2	4.80	180.0	2.	JCC,7,(1986),230
X -CD-CD-X	4	4.00	180.0	2.	Junmei et al, 1999
X -CD-CT-X	6	0.00	0.0	2.	Junmei et al, 1999
X -CD-CM-X	4	26.60	180.0	2.	Junmei et al, 1999
X -CK-N*-X	4	6.80	180.0	2.	JCC,7,(1986),230
X -CK-NB-X	2	20.00	180.0	2.	JCC,7,(1986),230
X -CM-CM-X	4	26.60	180.0	2.	intrpol.bsd.on C6H6
X -CM-CT-X	6	0.00	0.0	3.	JCC,7,(1986),230
X -CM-N*-X	4	7.40	180.0	2.	JCC,7,(1986),230
X -CM-OS-X	2	2.10	180.0	2.	Junmei et al, 1999
X -CN-NA-X	4	6.10	180.0	2.	reinterpolated 93'
X -CQ-NC-X	2	13.60	180.0	2.	JCC,7,(1986),230
X -CT-CT-X	9	1.40	0.0	3.	JCC,7,(1986),230

$$Etors = \sum_{n=0}^{N} \frac{V_n}{2}\left[1+\cos\left(n\varphi-\gamma\right)\right]$$

H	0.6000	0.0157	!Ferguson base pair geom.
HO	0.0000	0.0000	OPLS Jorgensen, JACS,110,(1988),1657
HS	0.6000	0.0157	W. Cornell CH3SH --> CH3OH FEP
HC	1.4870	0.0157	OPLS
H1	1.3870	0.0157	Veenstra et al JCC,8,(1992),963
H2	1.2870	0.0157	Veenstra et al JCC,8,(1992),963
H3	1.1870	0.0157	Veenstra et al JCC,8,(1992),963
HP	1.1000	0.0157	Veenstra et al JCC,8,(1992),963
HA	1.4590	0.0150	Spellmeyer
H4	1.4090	0.0150	Spellmeyer, one electrowithdr. neighbor
H5	1.3590	0.0150	Spellmeyer, two electrowithdr. neighbor
HW	0.0000	0.0000	TIP3P water model
HZ	1.4590	0.0150	H bonded to sp C (Howard et al JCC 16)
O	1.6612	0.2100	OPLS
O2	1.6612	0.2100	OPLS
OW	1.7683	0.1520	TIP3P water model
OH	1.7210	0.2104	OPLS
OS	1.6837	0.1700	OPLS ether
C*	1.9080	0.0860	Spellmeyer
CT	1.9080	0.1094	Spellmeyer
C	1.9080	0.0860	OPLS
N	1.8240	0.1700	OPLS
N3	1.8240	0.1700	OPLS
NY	1.8240	0.1700	N in nitrile
S	2.0000	0.2500	W. Cornell CH3SH and CH3SCH3 FEP's
SH	2.0000	0.2500	W. Cornell CH3SH and CH3SCH3 FEP's
P	2.1000	0.2000	JCC,7,(1986),230;
IM	2.47	0.1	Cl- Smith & Dang, JCP 1994,100:5,3757
Li	1.1370	0.0183	Li+ Aqvist JPC 1990,94,8021. (adapted)
IP	1.8680	0.00277	Na+ Aqvist JPC 1990,94,8021. (adapted)
Na	1.8680	0.00277	Na+ Aqvist JPC 1990,94,8021. (adapted)
K	2.6580	0.000328	K+ Aqvist JPC 1990,94,8021. (adapted)
Rb	2.9560	0.00017	Rb+ Aqvist JPC 1990,94,8021. (adapted)
Cs	3.3950	0.0000806	Cs+ Aqvist JPC 1990,94,8021. (adapted)
MG	0.7926	0.8947	Mg2+ Aqvist JPC 1990,94,8021.(adapted)
C0	1.7131	0.459789	Ca2+ Aqvist JPC 1990,94,8021.(adapted)
Zn	1.10	0.0125	Zn2+, Merz,PAK, JACS,113,8262,(1991)
F	1.75	0.061	Gough et al. JCC 13,(1992),963.
Cl	1.948	0.265	Fox, JPCB,102,8070,(98),flex.mdl CHCl3
Br	2.22	0.320	Junmei(?)
I	2.35	0.40	JCC,7,(1986),230;
IB	5.0	0.1	solvated ion for vacuum approximation

$$V(r) = \varepsilon\left[\left(\frac{r_m}{r}\right)^{12} - 2\left(\frac{r_m}{r}\right)^{6}\right]$$

```
!!index array str
 "GLU"
!entry.GLU.unit.atoms table  str name  str type  int typex  int resx  int flags  int seq  int elmnt  dbl chg
 "N" "N" 0 1 131072 1 7 -0.516300
 "H" "H" 0 1 131072 2 1 0.293600
 "CA" "CT" 0 1 131072 3 6 0.039700
 "HA" "H1" 0 1 131072 4 1 0.110500
 "CB" "CT" 0 1 131072 5 6 0.056000
 "HB2" "HC" 0 1 131072 6 1 -0.017300
 "HB3" "HC" 0 1 131072 7 1 -0.017300
 "CG" "CT" 0 1 131072 8 6 0.013600
 "HG2" "HC" 0 1 131072 9 1 -0.042500
 "HG3" "HC" 0 1 131072 10 1 -0.042500
 "CD" "C" 0 1 131072 11 6 0.805400
 "OE1" "O2" 0 1 131072 12 8 -0.818800
 "OE2" "O2" 0 1 131072 13 8 -0.818800
 "C" "C" 0 1 131072 14 6 0.536600
 "O" "O" 0 1 131072 15 8 -0.581900
!entry.GLU.unit.atomspertinfo table  str pname  str ptype  int ptypex  int pelmnt  dbl pchg
 "N" "N" 0 -1 0.0
 "H" "H" 0 -1 0.0
 "CA" "CT" 0 -1 0.0
 "HA" "H1" 0 -1 0.0
 "CB" "CT" 0 -1 0.0
 "HB2" "HC" 0 -1 0.0
 "HB3" "HC" 0 -1 0.0
 "CG" "CT" 0 -1 0.0
 "HG2" "HC" 0 -1 0.0
 "HG3" "HC" 0 -1 0.0
 "CD" "C" 0 -1 0.0
 "OE1" "O2" 0 -1 0.0
 "OE2" "O2" 0 -1 0.0
 "C" "C" 0 -1 0.0
 "O" "O" 0 -1 0.0
!entry.GLU.unit.boundbox array dbl
 -1.000000
 0.0
 0.0
 0.0
 0.0
!entry.GLU.unit.childsequence single int
 2
!entry.GLU.unit.connect array int
 1
```

$$Eel = \frac{q_1 q_2}{4\pi\varepsilon r_{12}}$$

POLJE SILA

FUNKCIONAL

KOJI OMOGUĆAVA RAČUNANJE “STERIČKE” ENERGIJE KONFORMACIJE MOLEKULE

+

PARAMETRI

KONSTANTE I “OPTIMALNE” (RAVNOTEŽNE) VRIJEDNOSTI VARIJABLI

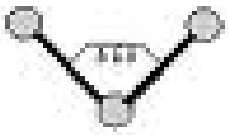
=

POLJE SILA

$$E = Estrech + Ebend + Etors + Eoop + Eel + Evdw + \sum Ecross$$

$$Estrech = \frac{k_s}{2}(l - l_0)^2$$

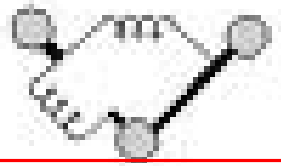
$$Eel = \frac{q_1 q_2}{4\pi\varepsilon r_{12}}$$

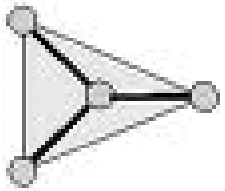


$$Ebend = \frac{k_b}{2}(\theta - \theta_0)^2$$

$$Evdw = \frac{A}{r^{12}} - \frac{C}{r^6}$$

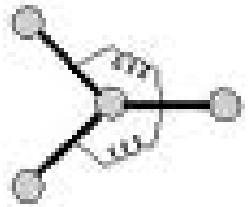
$$Etors = \sum_{n=0}^{N} \frac{V_n}{2}[1 + \cos(n\varphi - \gamma)]$$



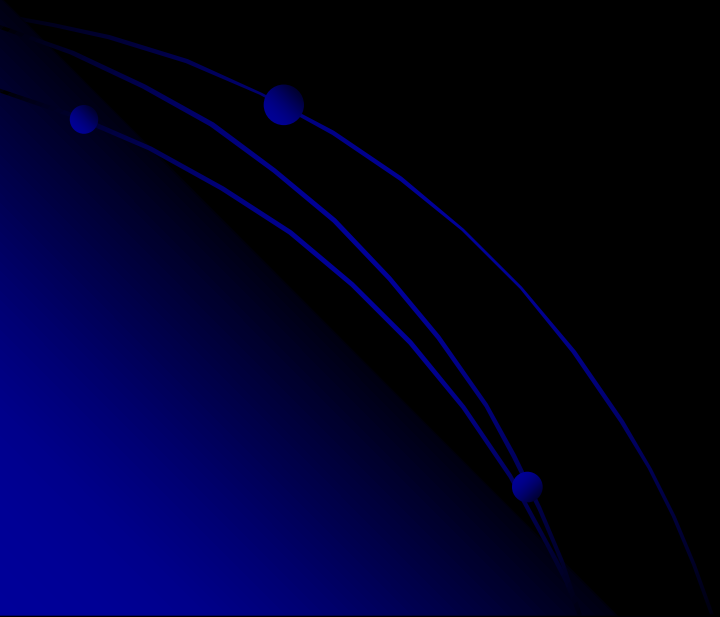


$$Eoop = \frac{1}{2} k_\xi \xi^2$$

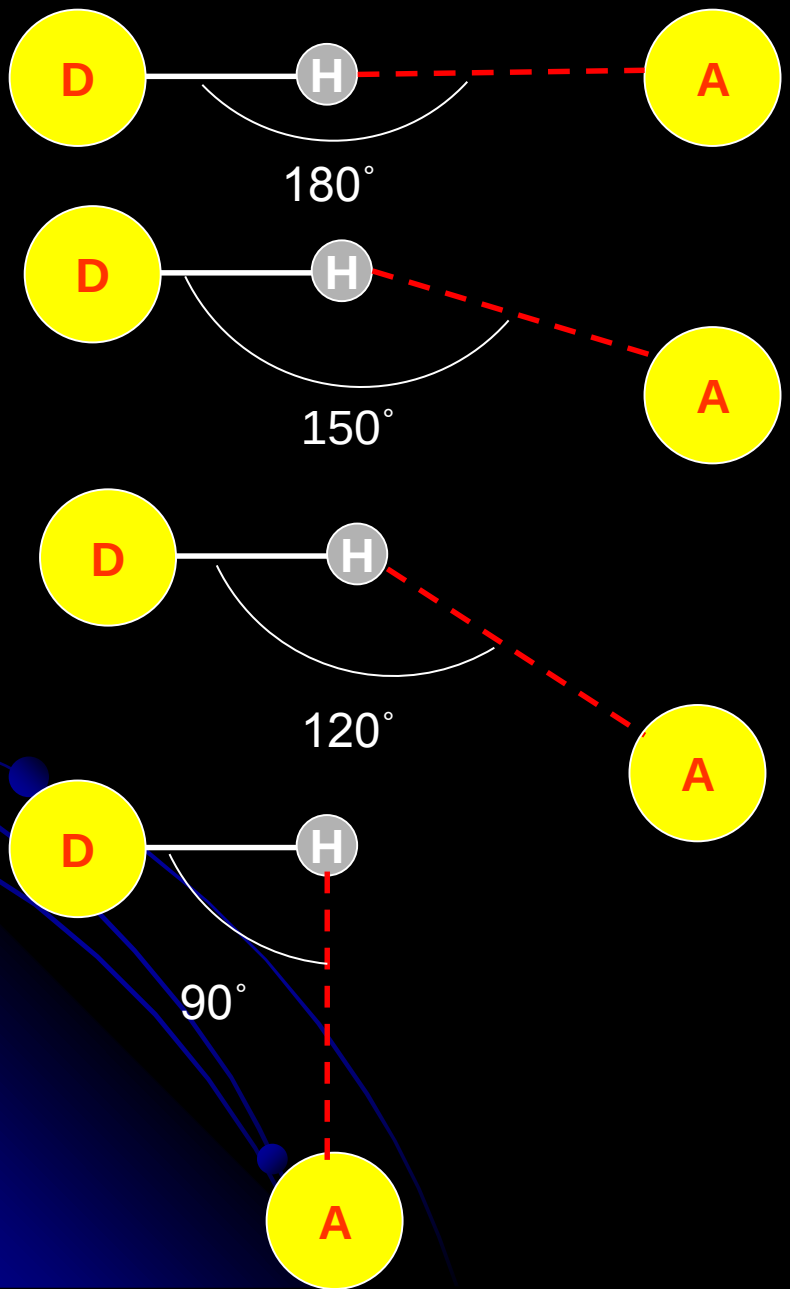
$$EcrossS.-B. = \frac{k_{S.B.}}{2}[(l_1 - l_{10}) + (l_2 - l_{20})](\theta - \theta_0)$$



Koje važne nekovalentne interakcije nismo spomenuli?



VODIKOVE VEZE :



$$E = \left(\frac{C}{d^6} - \frac{D}{d^4} \right) \cdot \cos^4 \phi$$

POLJE SILA

- nekovalentne interakcije (vdw i ele.) se računaju samo za atome odvojene s 4 ili više kovalentnih veza
- upravo nekovalentne interakcije su najvažnije za biofizičke sustave, a istodobno i daleko najteže za parametrizirati!

Četiri problema s kojima se empirijske (***FF***) metode susreću:

Table 2: Four basic problems of biomolecular modeling.

1. force-field problem	A) very small (free) energy differences, many interactions
	B) entropic effects
	C) variety of atoms and molecules
2. search problem	A) convergence
	B) alleviating factors
	C) aggravating factors
3. ensemble problem	A) entropy
	B) averaging
	C) nonlinear averaging
4. experimental problem	A) averaging
	B) insufficient number of data
	C) insufficient accuracy of data

- problem eksperimentalnih podataka – vrlo je mali broj eksp. podataka dobivenih mikroskopskim promatranjem sustava, većina eksperimentalnih observabli su **makroskopska** svojstva

POLJE SILA

1. male razlike u energiji između dva stanja biofizičkog sustava (npr. dvije konformacije) nastaju kao posljedica razlika u velikom broju nekovalentnih interakcija

- npr. sustav od 1000 atoma ima ukupno 500 000 parova nekovalentnih interakcija
- kako bi mogli izračunati male razlike u energiji, potrebno je imati jako dobru parametrizaciju tih interakcija i njih precizno izračunati

2. uključivanje entropijskog efekta

- većina biofizičkih procesa zasniva se upravo na entropijskom efektu!
- entropijski efekt je u polja sila uključen indirektno kroz parametrizaciju
- $\Delta G = \Delta H - T\Delta S$

3. transferabilnost parametara

- važno je da su parametri prenosivi između sustava, u protivnom bi imali enormno velik broj parametara
- u cilju postizanja prenosivosti, parametri se uzimaju iz malih molekula, nastoje se držati čim jednostavnijim *(Zašto ne eksp. vrijednosti iz. proteina?)*

POLJE SILA

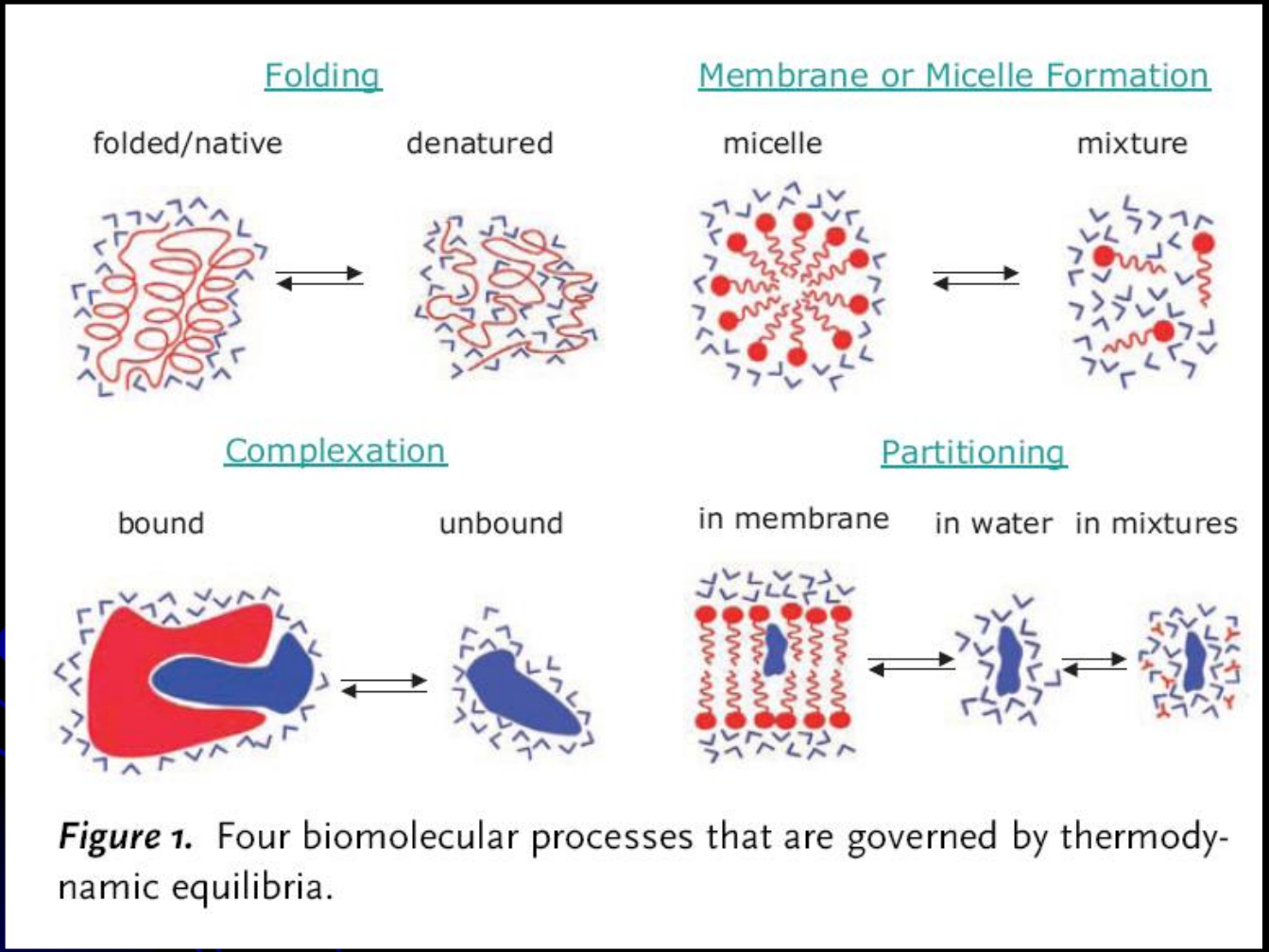


Figure 1. Four biomolecular processes that are governed by thermodynamic equilibria.

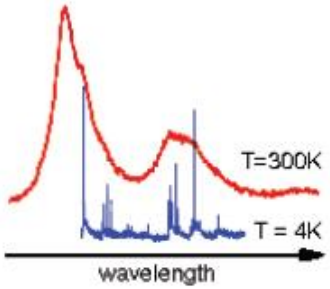
- većina fundamentalnih biofizičkih procesa zasnivaju se na entropijskom efektu!

PARAMETRIZACIJA

Type of data	Type of system	Phase	Type of properties	Force-field parameter
structural data (exptl)	small molecules	crystalline solid phase	molecular geometry: bond lengths, bond angles	b_0, θ_0, ξ_0
spectroscopic data (exptl)	small molecules	gas phase	molecular vibrations: force constants	K_b, K_θ, K_ξ
thermodynamic data (exptl)	small molecules, mixtures, solutions	condensed phase	heat of vaporization, density, partition coefficient, free energy of solvation	van der Waals: $C_{12}(i,j)$, $C_6(i,j)$, q_i(final)
dielectric data (exptl)	small molecules	condensed phase	dielectric permittivity, relaxation	charges q_i
transport data (exptl)	small molecules	condensed phase	diffusion and viscosity coefficients	$C_{12}(i,j)$, $C_6(i,j)$, q_i
electron densities (theor.)	small molecules	gas phase	quantum-chemical calculation of atom charges	charges q_i(initial)
energy profiles (theor.)	small molecules	gas phase	quantum-chemical calculation of torsional-angle rotational profiles	K_ϕ, δ, m

PARAMETRIZACIJA

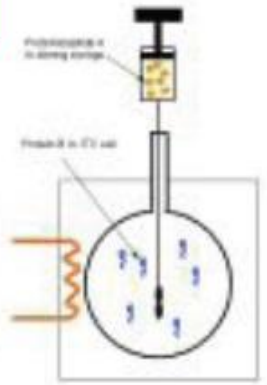
Quantum mechanical calculations
(e.g. partial charges, bond properties…)



Spectroscopy
(e.g. bond, angle properties…)

force field parameters

X-ray, NMR structures



Thermodynamic data
(e.g. free energies of hydration)

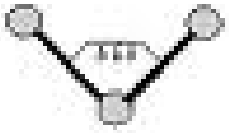
PARAMETRIZACIJA

SVOJSTVA

EKSP. PODACI

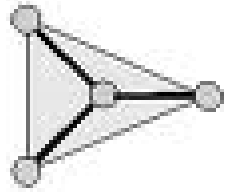
$$Estrech = \frac{k_s}{2}\left(l - l_0\right)^2$$

kristalografija, IR spetroskopija



$$Ebend = \frac{k_b}{2}\left(\theta - \theta_0\right)^2$$

kristalografija, IR spetroskopija



$$Eoop = \frac{1}{2}k_\xi \xi^2$$

kristalografija, IR spetroskopija

$$Etors = \sum_{n=0}^{N} \frac{V_n}{2}\left[1 + \cos\left(n\varphi - \gamma\right)\right]$$

QM računi, kristalografija, UGAĐANJE *(FITANJE)*

$$Evdw = \frac{A}{r^{12}} - \frac{C}{r^6}$$

procijena na temelju difuzijskih koeficjenata, entalpija isparavanja, energija solvatacije, particijskih koeficjenata, UGAĐANJE *(FITANJE)*

$$Eel = \frac{q_1 q_2}{4\pi\varepsilon r_{12}}$$

QM računi, UGAĐANJE *(FITANJE)*

PARAMETRIZACIJA

- početni skup parametara se procijeni na temelju dostupnih eksperimentalnih podataka

- najveći problem su parametri za nevezne interakcije koje se pokušava procijeniti na temelju: difuzijski koeficijenata, entalpija isparavanja, energija solvatacije, particijskih koeficijenta, …

- inicijalni skup parametara se zatim **ugađa (fita)** iterativnim postupkom u kojem se valjanost seta parametara vrednuje predviđanjem eksperimentalno određenih svojstava sustava (TERMODINAMIČKI PODATCI, RAVNOTEŽNE KONFORMACIJE, VIBRACIJSKE FREKVENCIJE, GIBBSOVA ENREGIJA SOLVATACIJE, …)

- polje sila se vrednuje predikcijom eksperimentalno određenih svojstava !

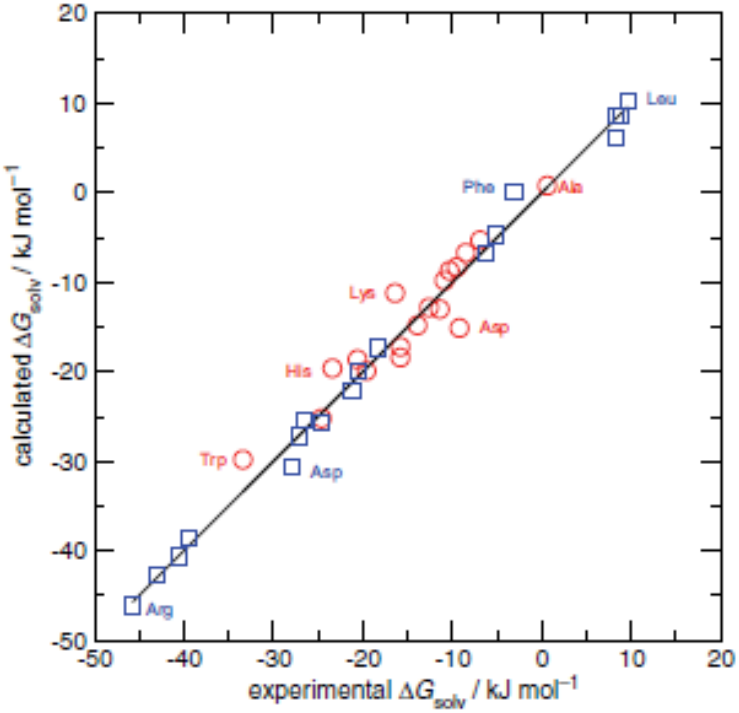


Figure 5. Comparison of the calculated (MD simulation using the GROMOS 53A6 force field) and experimental Gibbs free energies of solvation in cyclohexane (circles) and in water (squares) of 18 amino acid analogues (no Gly and Pro).[7]

PARAMETRIZACIJA

- primjer validacije polja sila usporedbom s eksp. podatcima:

- konformacije polipeptida - crveno – određene NMR-om ili kristalografijom, plavo – dobivene na temelju MD simulacija

- polje sila je unaprijeđeno na način da se reparametrizirano kako bi bolje računalo vrijednosti energija solvatacije polarnih amino kiselina

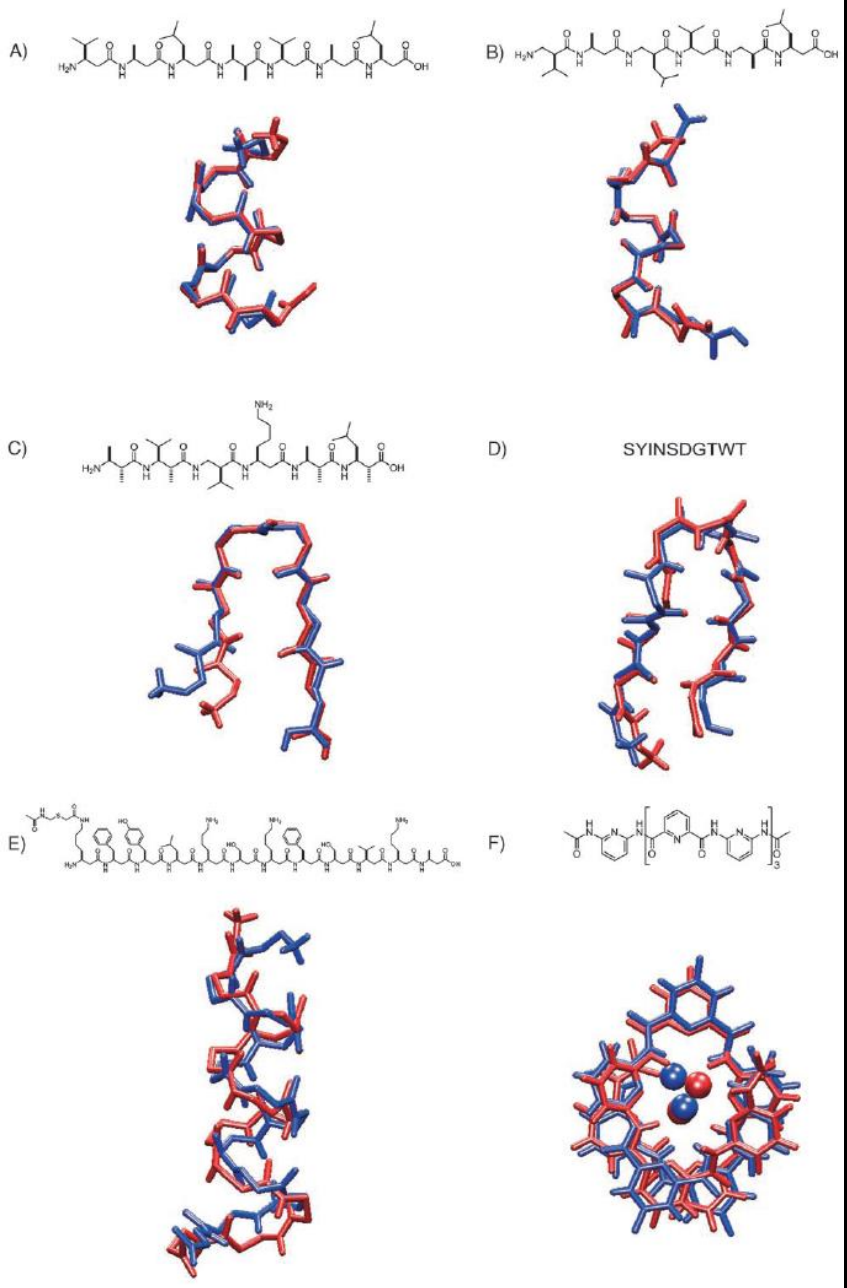


Figure 7. Folding of different polypeptides and peptoides into different folds in different solvents by MD simulation. The folded structure (red), modeled from the available NMR or X-ray experimental data, is superimposed on a folded structure (blue) representing the most populated conformation from the MD simulations of the folding/unfolding equilibrium.[32–37] The solvents are methanol (A–C, E), water (D), and water or chloroform (F). The versions of the GROMOS force field used are: 43A1 (A–D), 45A3 (F), and 53A6 (F).

PARAMETRIZACIJA

- za nepolarne polipeptide se raspodjela konformacija tijekom simulacije nije promijenila (donja slika), za **polarne** se značajno promijenila (gornja slika)

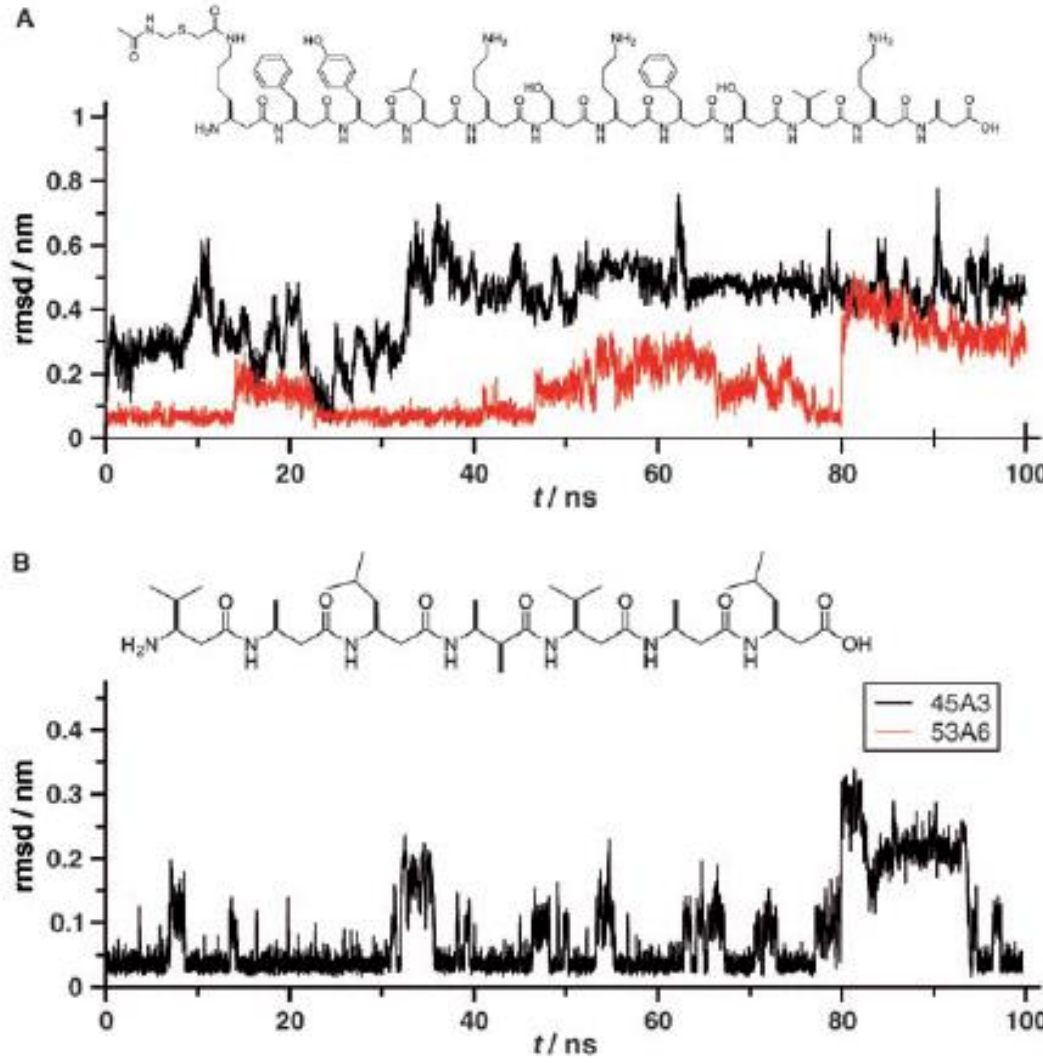


Figure 8. Root-mean-square deviation (rmsd) of the positions of bac bone atoms in MD trajectory structures from the helical model structures derived from NMR data for two β-peptides in methanol. A) The peptide containing polar side chains only shows the experime tal fold with the newer force-field parameter set 53A6.[36] B) The othe peptide is equally well folded by using the old (45A3) and the new (53A6) force fields, and only data for the former are shown.

POLJA SILA

AMBER
CHARMM
GROMOS
OPLS

→ BIOPOLIMERI (PROTEINI, DNA, RNA)

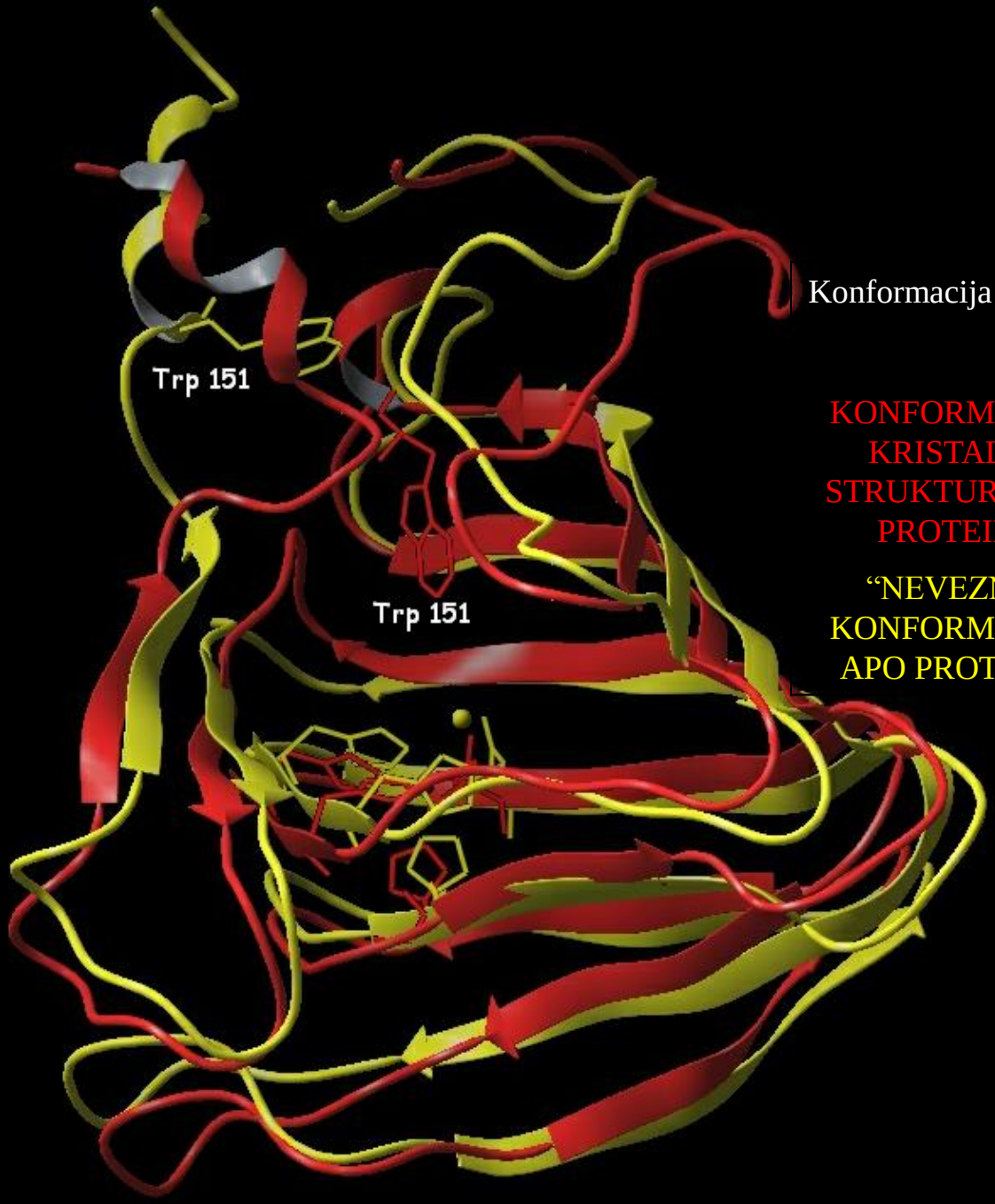
MM2
MM3
CVFF
CFF
Tripos

→ ORGANSKE MOLEKULE

MMFF
COMPASS
ESFF
UFF

→ OPĆENITA POLJA SILA

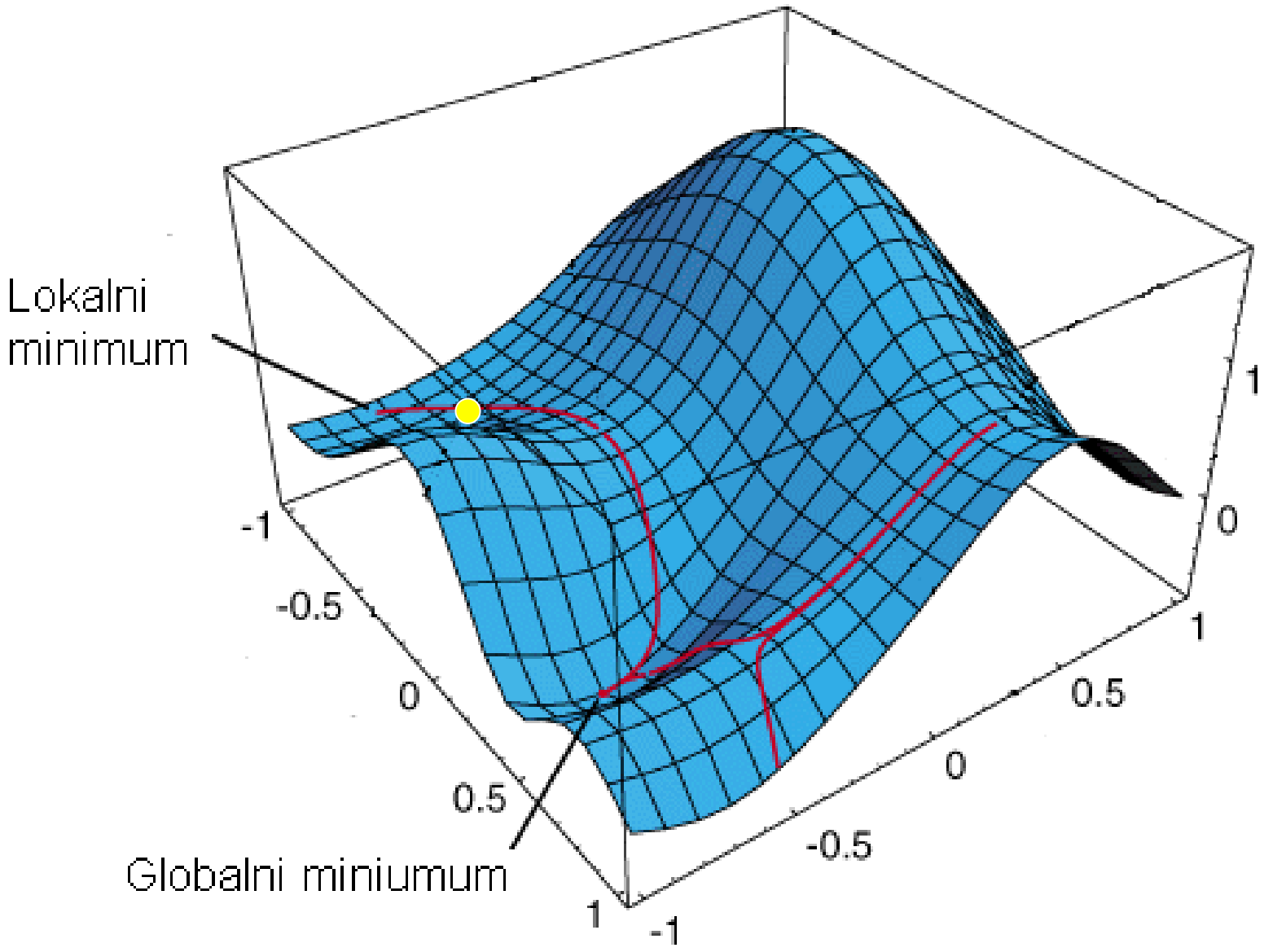
YETI – POLJE SILA ZA KOMPLEKSNE SPOJEVE



Konformacija	Energija / $kcal \cdot mol^{-1}$	Gradijent / $kcal \cdot mol^{-1} \cdot Å^{-1}$
KONFORMACIJA KRISTALNE STRUKTURE APO PROTEINA	$-7{,}36 \cdot 10^{6}$	$9{,}59 \cdot 10^{-2}$
"NEVEZNA" KONFORMACIJA APO PROTEINA	$-7{,}84 \cdot 10^{6}$	$9{,}87 \cdot 10^{-2}$

POLJA SILA

- Pridruživanje određenih parametara atomima u molekuli omogućava računanje potencijala koji vlada u molekuli ovisno o njezinoj konformaciji, odnosno o vrijednostima: dužina veza, torzijskih i valentnih kutova, te neveznih udaljenosti.
- Upravo računanje energije pojedinih konformacija molekule i jest glavna zadaća metoda koje se baziraju na polju sila.
- Naime, vrijednost potencijalne energije molekule izračunata s pomoću polja sila nema direktno fizikalno značenje. Upotrebom različitih polja sila dobit će se različite vrijednosti potencijalne energije iste konformacije, tako da računi ostvareni različitim poljima sila nisu međusobno usporedivi.
- Međutim vrijednosti energija dobivenih za različite konformacije molekule korištenjem istog polja sila jesu međusobno usporedive. Konformacijska analiza primarna je zadaća empirijskih metoda.



Ploha potencijalne energije molekule u 3D presjeku
(prikazana je ovisnost energije o dvije interne koordinate)

2. OSNOVNI PRINCIPI NA KOJIMA SE ZASNIVAJU RAČUNALNE METODE KOJE SE KORISTE ZA ISTRAŽIVANJE BIOPOLIMERA.

- **EMPIRIJSKE METODE**
- **MODEL “KUGLICA I OPRUGA”, POLJE SILA**
- **JEDNOSTAVNOST ~ PRIMJENJIVOST** (S OBZIROM NA SLOŽENOST SUSTAVA)

POLJA SILA

Perspektive u poboljšanju parametrizacije polja sila:

1. vdw parametri i naboji dobiveni na temelju slobodne energije solvatacije

- vrlo je teško precizno eksperimentalno izmjeriti vrijednosti energije solvatacije, a teško ih je i precizno izračunati

2. parametrizacija smjesa otapala (npr. DMSO/voda)

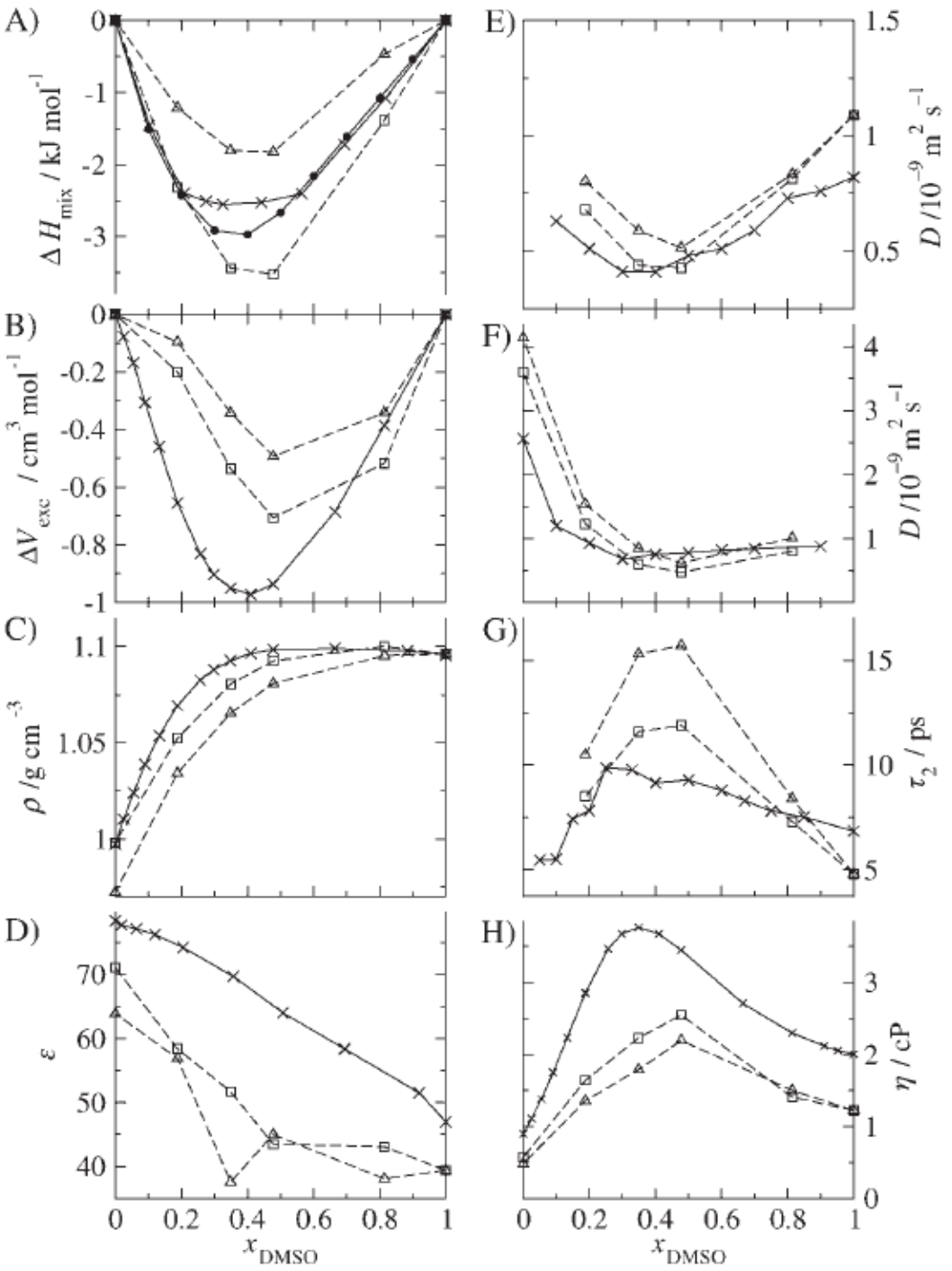
- vrlo je teško precizno izračunati gustoću takvih smjesa otapala ovisno o udjelu pojedine komponente
- važno je uključiti i entropiju i entalpiju miješanja

3. uvođenje polarizibilnosti

- vrlo važan aspekt, ali znatno povećava zahtjevnost računa!

POLJA SILA

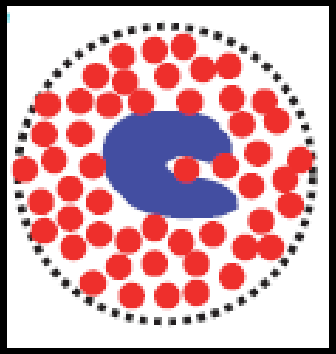
- različita svojstva tekuće smjese voda/DMSO ovisno o molarnom udjelu DMSO (x) izračunata MD simulacijama uz različite tipove molekula vode (SPC –□, SPC/L – Δ, eksperimentalno – x i ●)



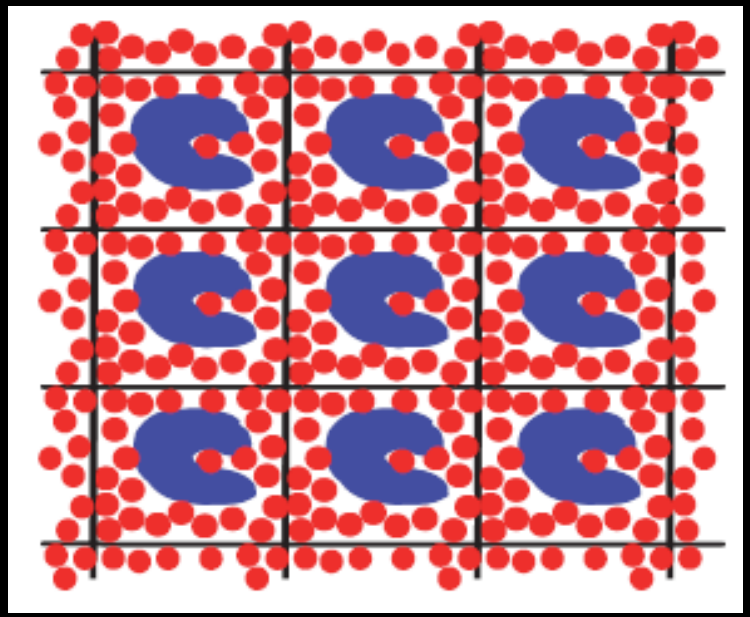
MODELIRANJE OTAPALA

- otapalo, rubni uvjeti

implicitni model



model kapi

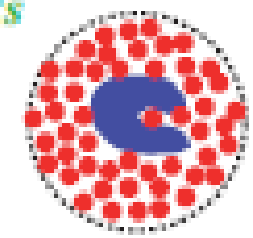


periodični rubni uvjeti

Vacuum

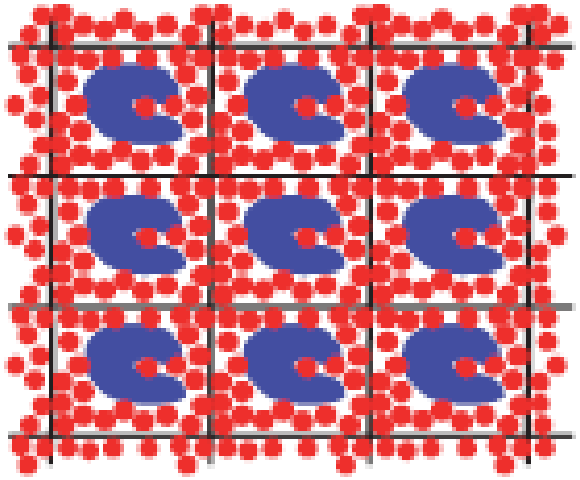
- Surface effects (surface tension)
- No dielectric screening

Droplets



- Still surface effects (at water – vacuum interface)
- Only partial dielectric screening
- Evaporation of the solvent

Periodic: system is surrounded by copies of itself



Advantage:

- No surface effects

Disadvantage:

- Artificial periodicity
- High effective concentration

Figure 3. Three types of spatial boundary conditions used in molecular simulation.