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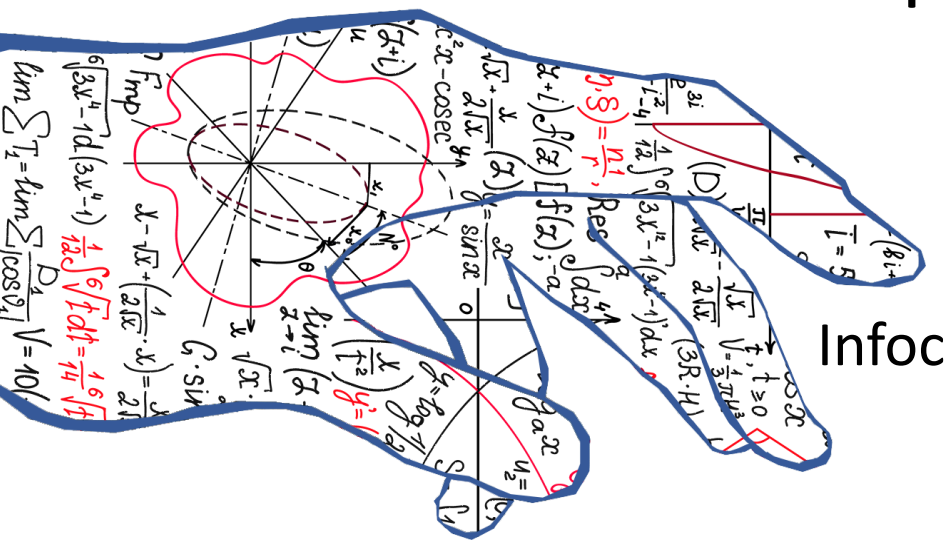
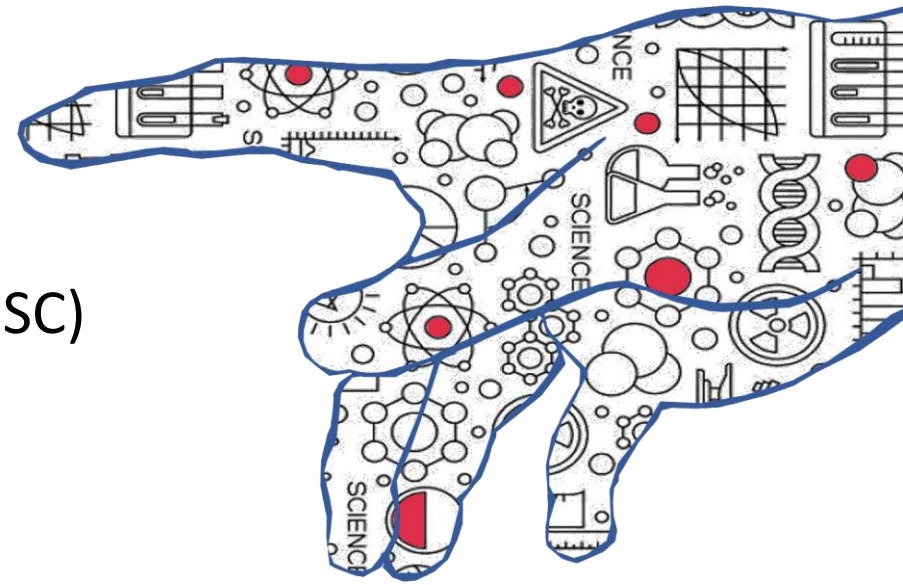
INFOCHEMISTRY SCIENTIFIC CENTER

Cheminformatics and synthetic biology: Molecular Dynamics

Prof. Sergey Shityakov



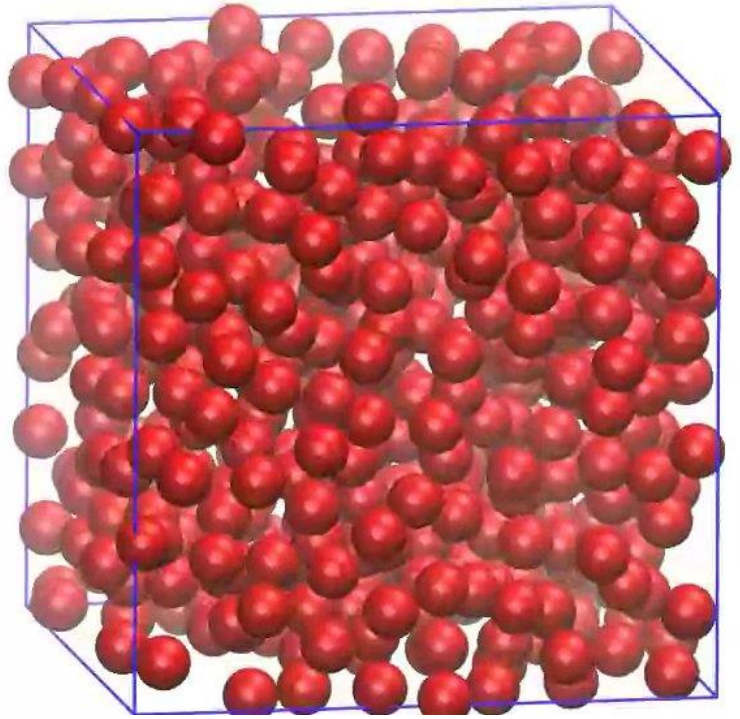
Infochemistry Scientific Center (ISC)
ITMO University
Saint-Petersburg, 2024



Overview

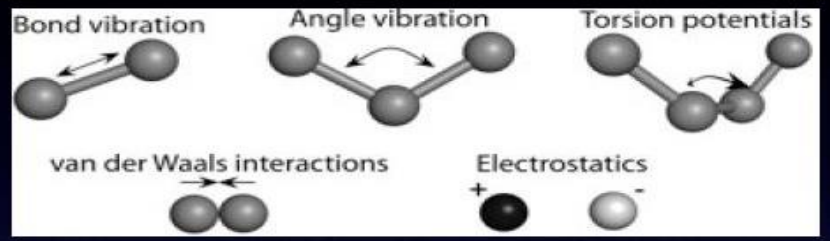
What is molecular dynamics (MD)?

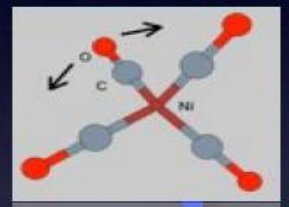
Numerical method for studying many-particle systems such as molecules, clusters, and even macroscopic systems such as gases, liquids and solids

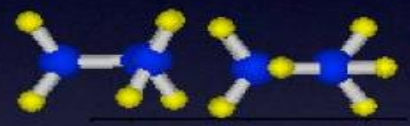


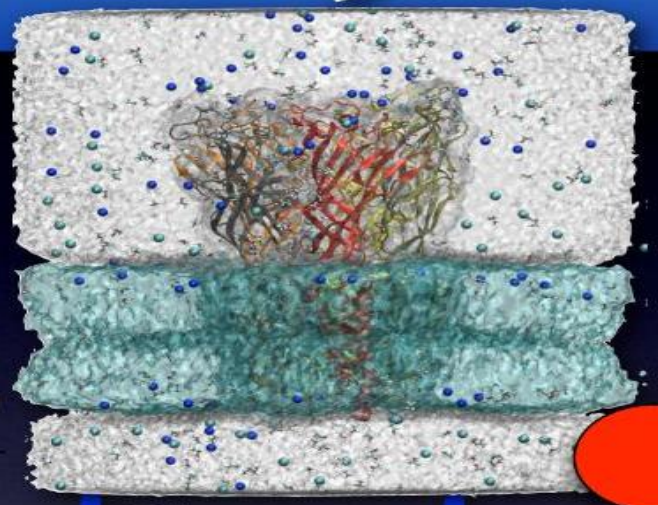
Used extensively in materials science, chemical physics, and biophysics/biochemistry

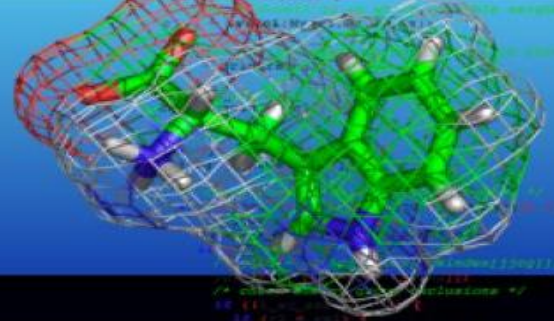
Molecular Dynamics











Experiments

Efficient averaging

Less detail

Where we need to be

Physics — Chemistry — Biology

10^{-15}s 10^{-12}s 10^{-9}s 10^{-6}s 10^{-3}s 10^{0}s 10^{3}s

Simulations

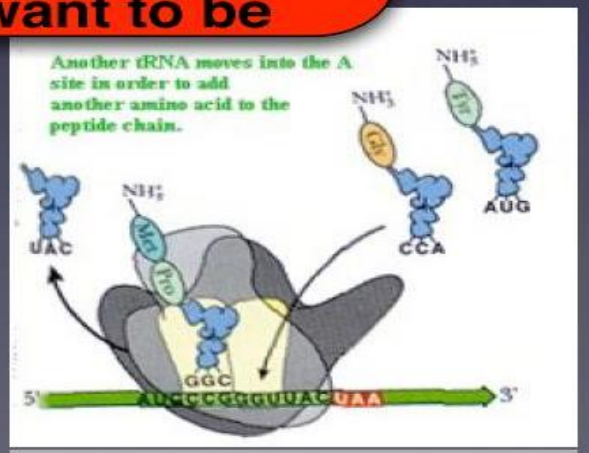
Extreme detail

Sampling issues?

Parameter quality?

Where we are

Where we want to be



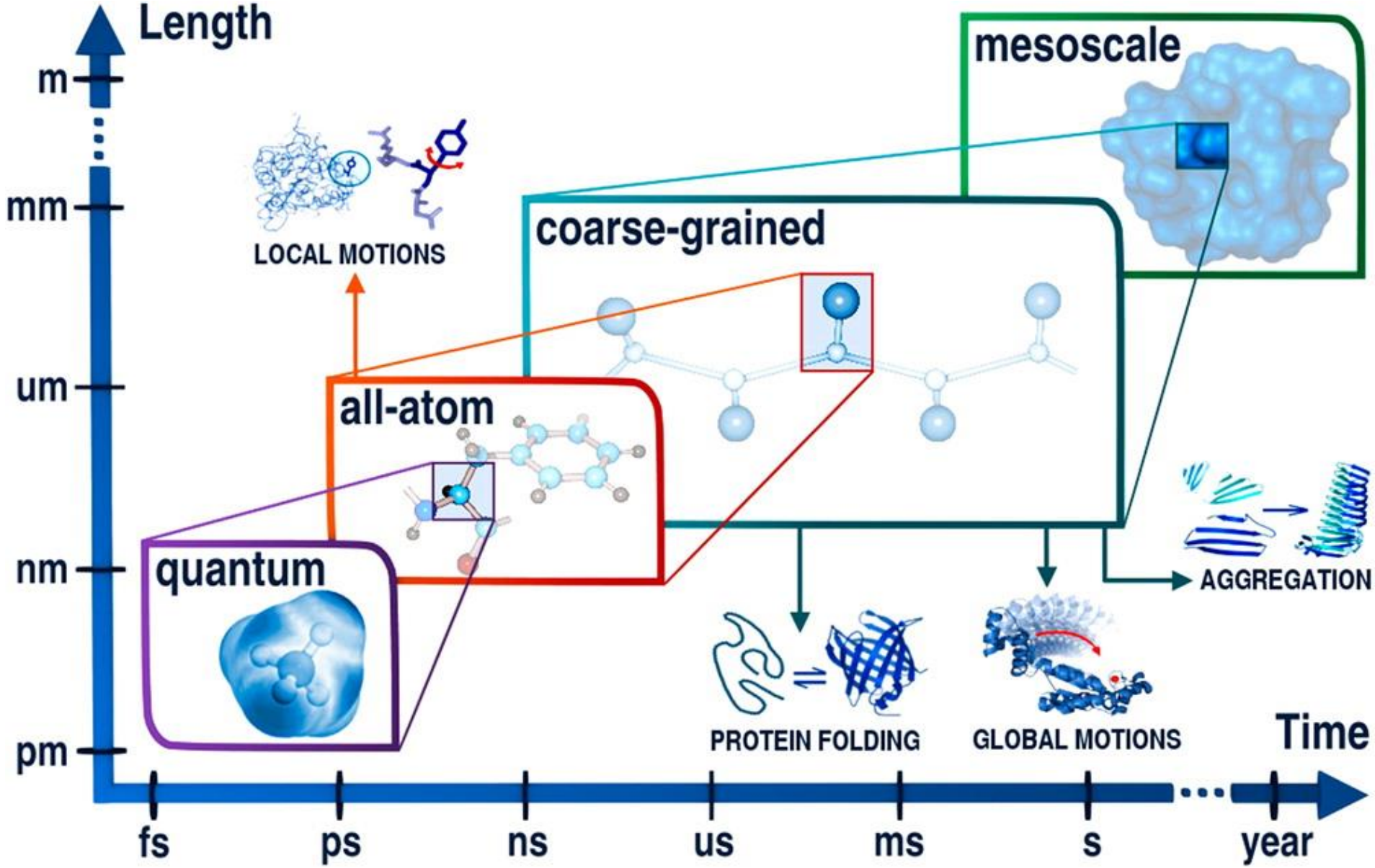
Molecular dynamics

- MD is a computer simulation of physical movements of atoms and molecules in the context of N-body simulation.
- The trajectories of atoms and molecules are determined by numerically solving the Newton's equation of motion for a system of interacting particles, namely:

$$F = m \cdot a$$

- Deterministic method: state of the system at any future can be predicted from its current state
- Acing force on each atom is assumed to be constant during the time interval of simulation
- Forces on the atoms are computed and combined with the current positions and velocities to generate new positions and velocities a short time ahead (from ps to ns/µs)

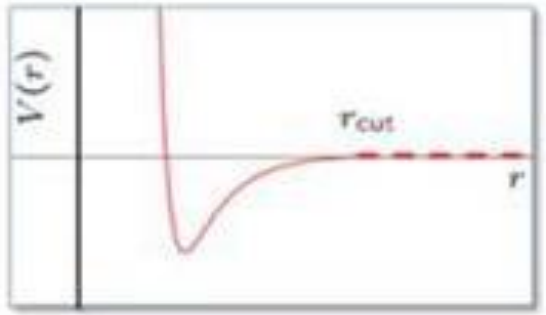
MD limits


Length
m
mm
um
nm
pm
LOCAL MOTIONS
mesoscale
coarse-grained
all-atom
quantum
AGGREGATION
PROTEIN FOLDING
GLOBAL MOTIONS
Time
fs
ps
ns
us
ms
s
year

Force Fields

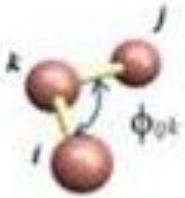
Pairwise interaction:

$$V(r) = \begin{cases} V(|r_j - r_j|), & r \le r_{cut} \\ 0, & r > r_{cut} \end{cases}$$



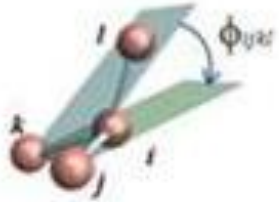
Chemical bond interaction:

bond

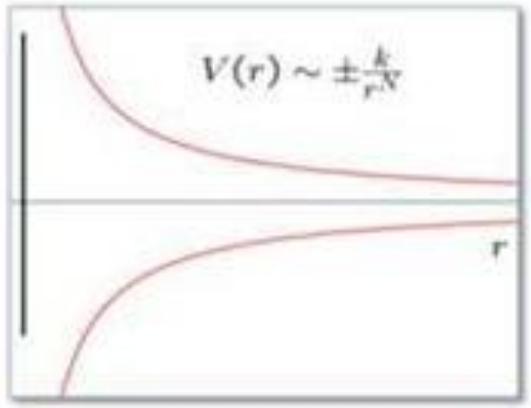


angle

proper dihedral



improper dihedral



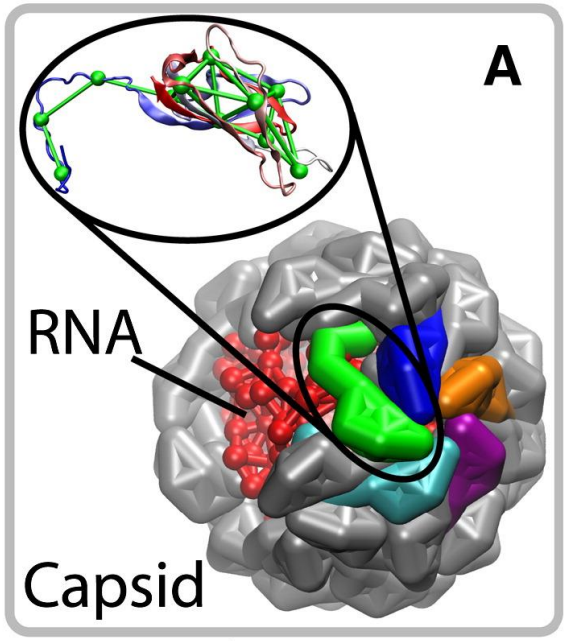
K-space solver:

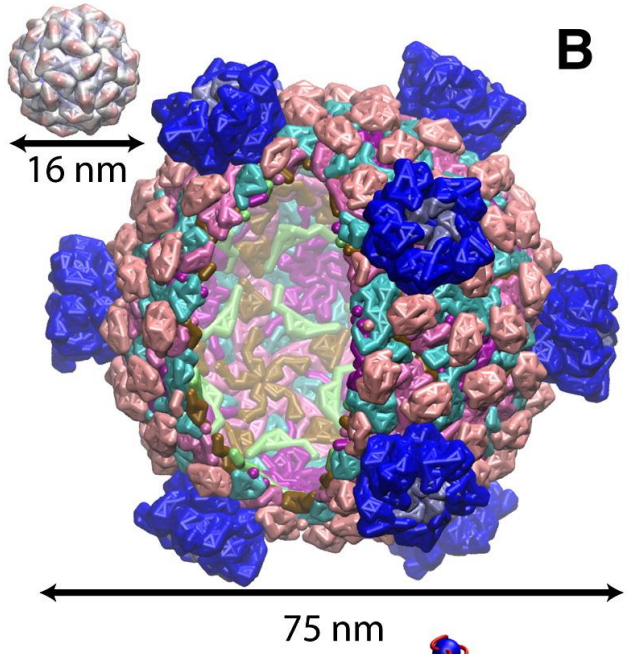
Used in force field with charges, dipoles, etc..

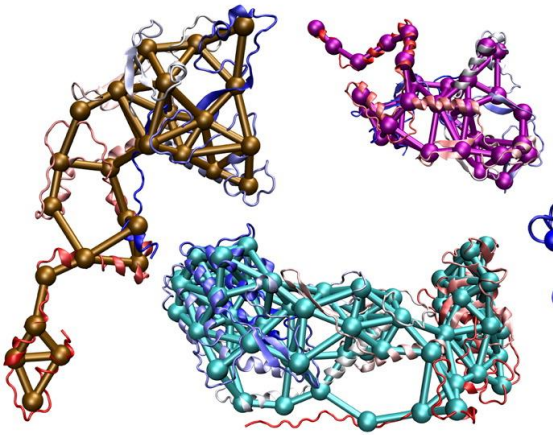
N- radial quantum number (electron state)

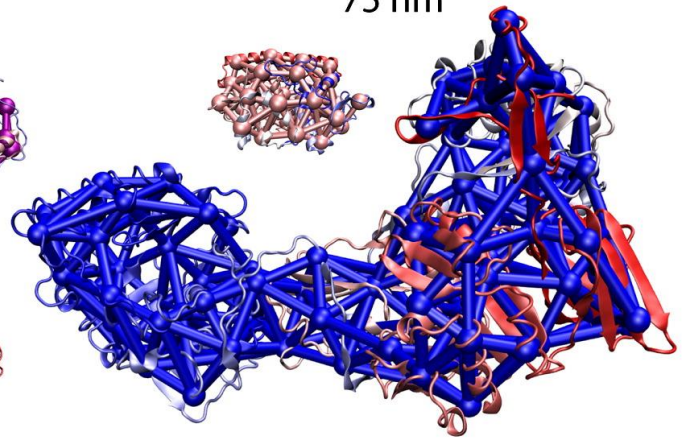
k- Coulomb's constant

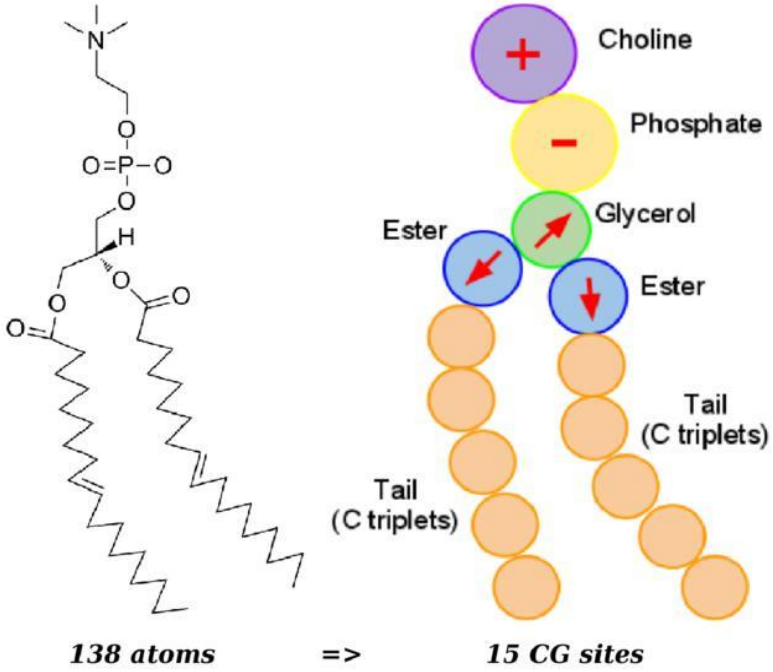
Force Fields

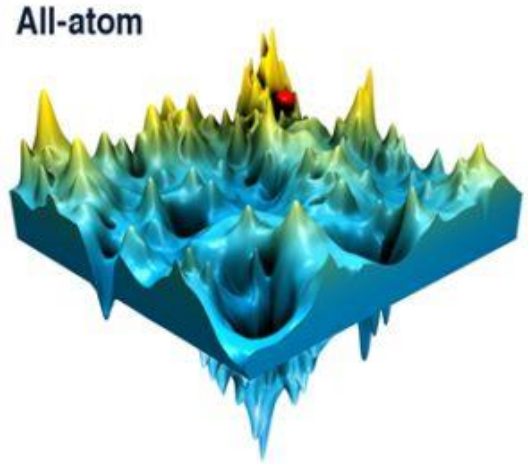


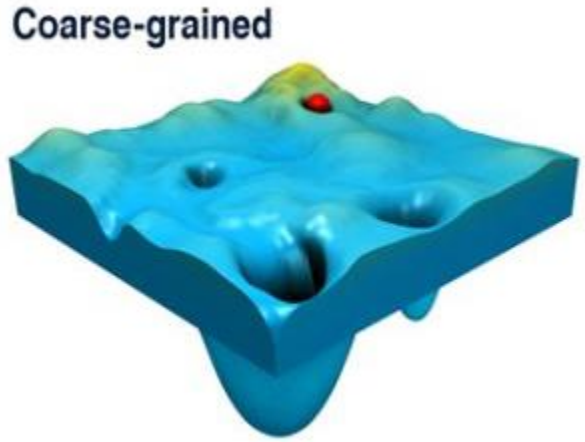


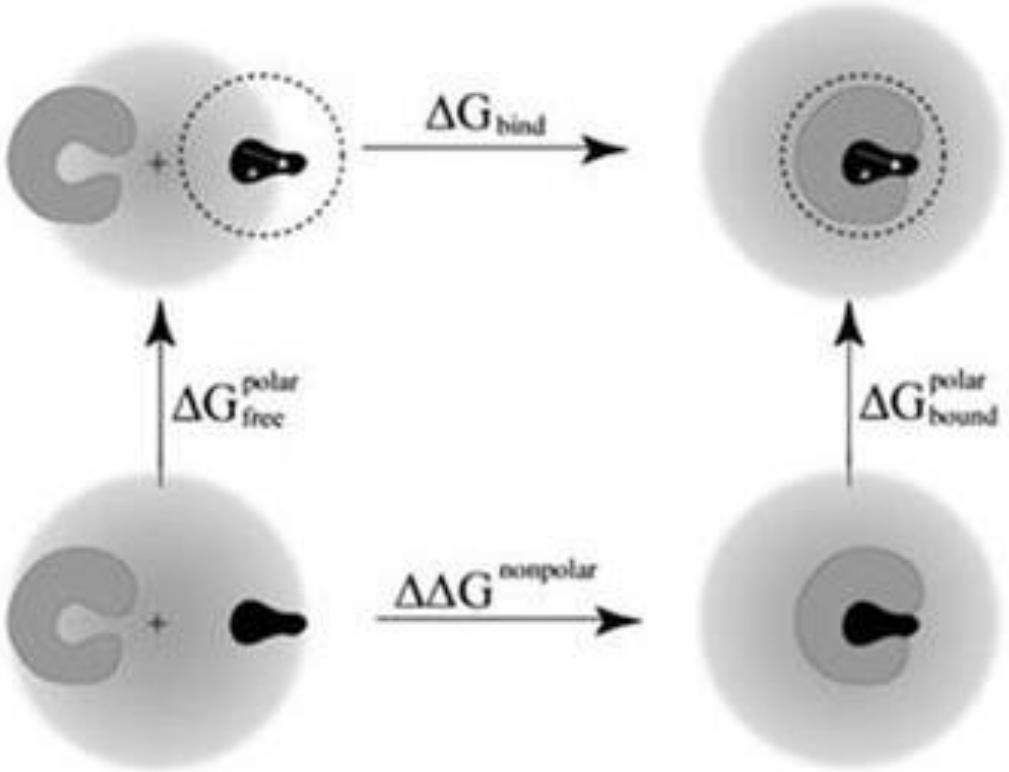








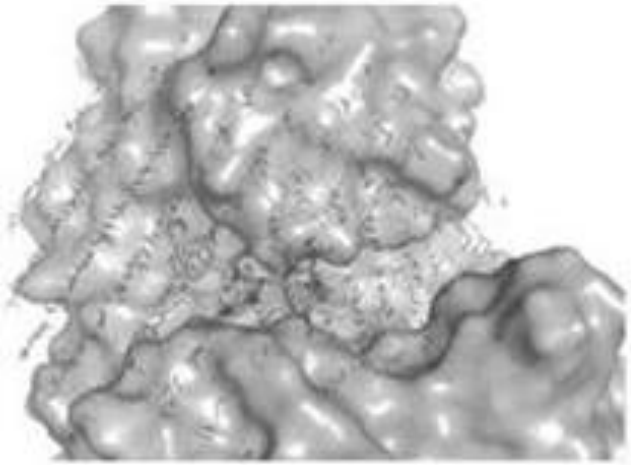


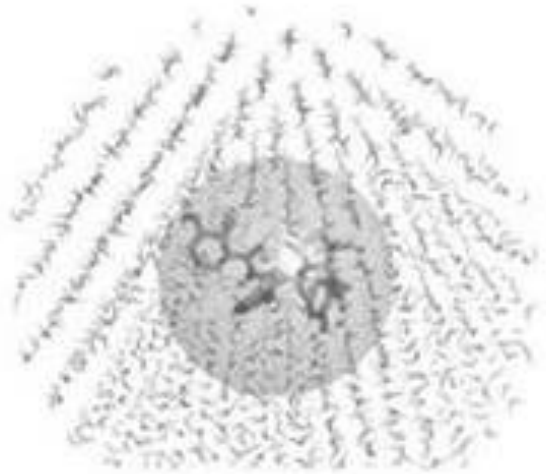


$$\Delta G_{\text{bind}} = (\Delta G^{\text{polar}}_{\text{bound}} - \Delta G^{\text{polar}}_{\text{free}}) + \Delta\Delta G^{\text{nonpolar}}_{\text{bind}}$$

$$= \Delta\Delta G^{\text{polar}}_{\text{bind}} + \Delta\Delta G^{\text{nonpolar}}_{\text{bind}}$$

$$\Delta G_{bind} = \alpha\left(V_{LJ}^{p-l} - V_{LJ}^{w-l}\right) + \beta\left(V_{Coul}^{p-l} - V_{Coul}^{w-l}\right)$$





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Molecular dynamics software

- GROMACS (GROningen Machine for Chemical Simulations) (The Netherlands, University of Groningen, 1991)
- AMBER (Assisted Model Building with Energy Refinement) (USA, University of California and San Francisco, 2002)
- NAMD (Nanoscale Molecular Dynamics Program) (USA, University of Illinois at Urbana-Champaign, 1995)
- Desmond (USA, D. E. Shaw Research, 2007)
- CHARMM (Chemistry at HARvard Macromolecular Mechanics) (USA, Harvard University, 1983)

Interaction potentials and forces:

- interaction between atoms and molecules results from electronic structure: not a classical problem, **requires quantum** physics

- two different ways to proceed, leading to two different classes of molecular dynamics simulations, classical MD and ab-initio MD

Classical molecular dynamics

- Interactions are approximated by classical **model potentials** constructed by comparison with experiment (empirical potentials)
- Leads to simulation of purely classical many-particle problem
- Works well for simple particles (such as noble gases) that interact via isotropic pair potentials
- Poor for covalent atoms (directional bonding) and metals (electrons form Fermi gas)
- Simulations **fast**, permit **large particle numbers**

Ab-initio molecular dynamics

- Performs a full quantum calculation of the electronic structure at every time step (for every configuration of the atomic nuclei),

  ab-initio = from first principles

- Forces are found the dependence of the energy on the particle positions

- Much higher accuracy than classical MD, but much higher numerical effort (restricts number of particles and simulation time)

CPU/GPU

Design of biologics

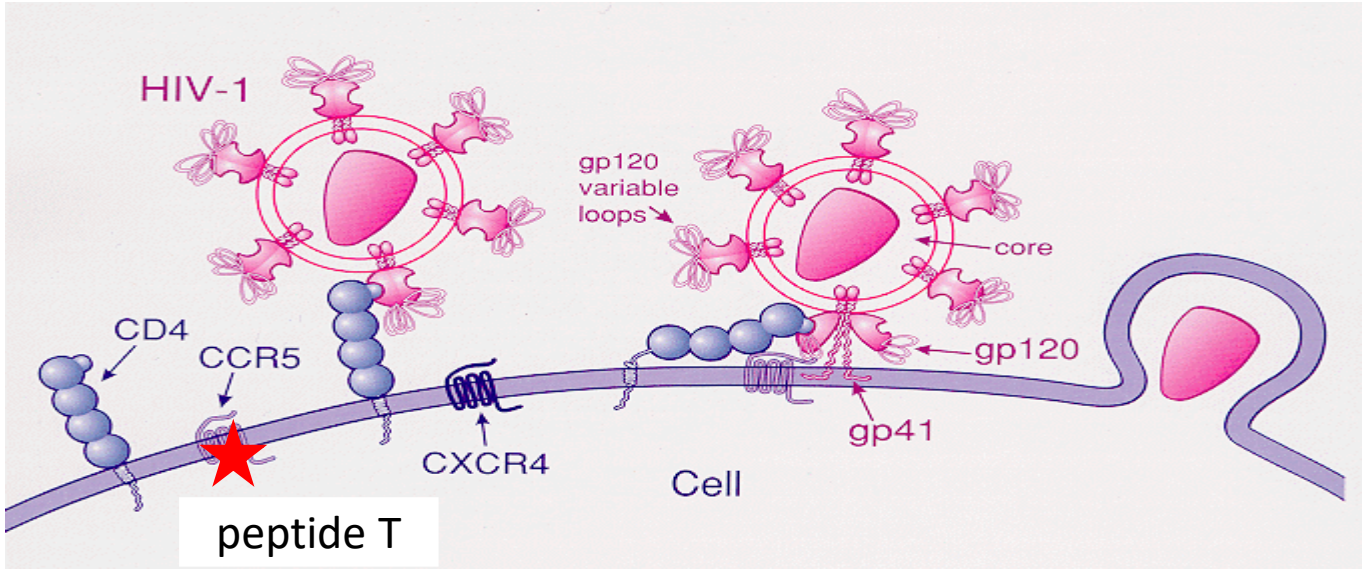
Molecular dynamics simulation of the T peptide as an HIV-1 entry inhibitor:

1) Peptide T (synthetic) is discovered in 1986 at the NIH.

2) Peptide T derivative (DAPTA) is a drug in clinical trials, which blocks binding and infection of viral strains via binding to the CCR5 receptor.

3) Peptide T showed several positive affects related to HIV disease and Neuro-AIDS.

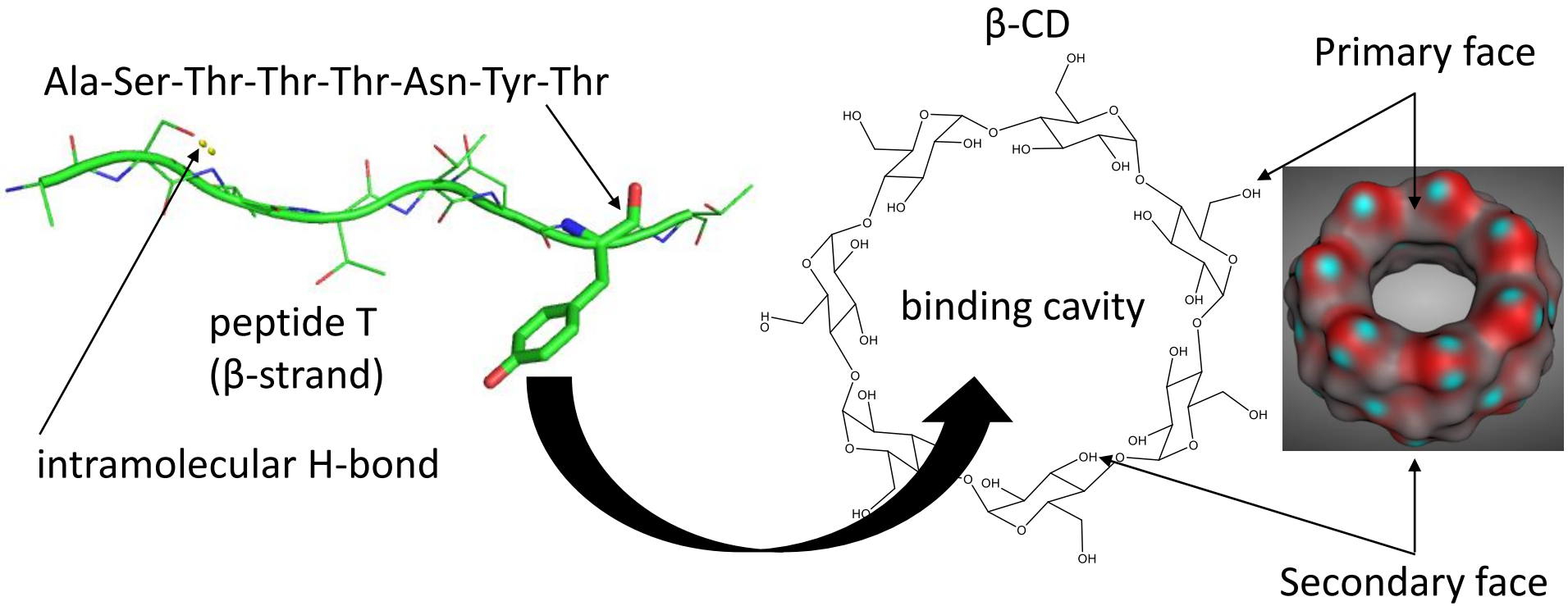
4) Peptide T was associated with improved performance in the HIV/AIDS patients suffered from the severe cognitive impairments.



Peptide-cyclodextrin formulation

1) Cyclodextrins (CDs) are oligosaccharides used to improve drug PK/PD properties (solubility, stability, drug release, etc).

2) β-CD is widely used in the formulations of various pharmaceutical substances. It has 7 glycoside units with lipophilic binding cavity and hydrophilic exterior.



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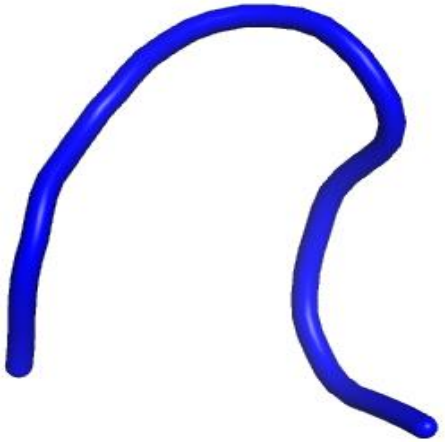
Peptide and CD-peptide complex stability

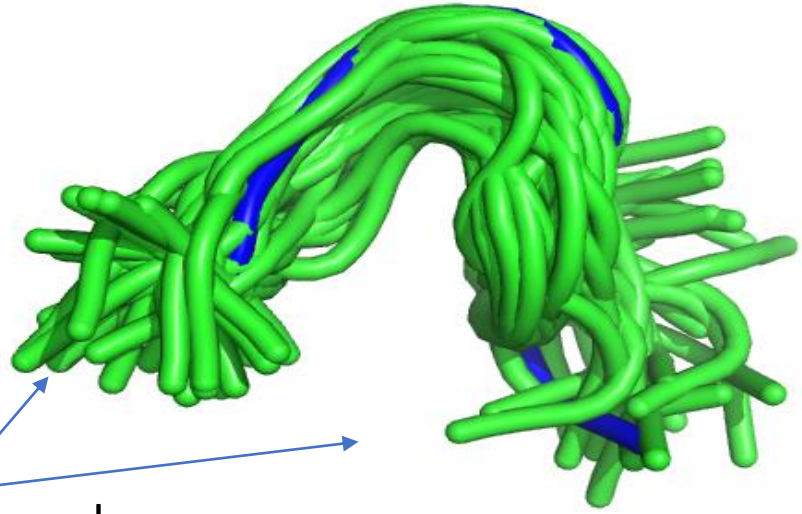
RMSD – root-mean-square deviation to measure dynamic stability of peptide T alone and in the complex by least-square fitting the peptide to the reference molecule using the following equation:

$$RMSD = \sqrt{\frac{1}{M}\sum_i m_i \|r_{i,t} - r_{i,t0}\|^2}$$

where *M* is the mass of the peptide, m_i is the mass of atom *i*, $r_i(t)$ is the coordinate of atom *i* of conformation at time *t*, $r_{i,t}$ is the coordinate of atom *i* at initial state *t0* (native conformation).

saddle-like conformation





highly flexible ends

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Equilibrium constants

RMSD – root-mean-square deviation to measure dynamic stability of the BB-3497 inhibitor alone and in the complex by least-square fitting this compound to the reference using the following equation:

$$RMSD = \sqrt{\frac{1}{M}\sum_i m_i (r_{i.t} - r_{i.t0})^2}$$

where M is the mass of the protein, m_i is the mass of atom i, $r_i(t)$ is the coordinate of atom i of conformation at time t, $r_{i.t}$ is the coordinate of atom i at initial state $t0$ (native conformation).

Equilibrium: E + I ⇔EI

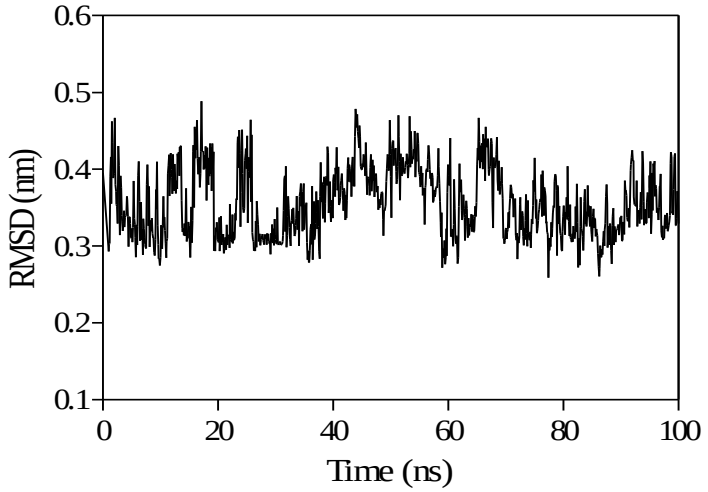
Binding: E + I => EI, K(binding), Kb

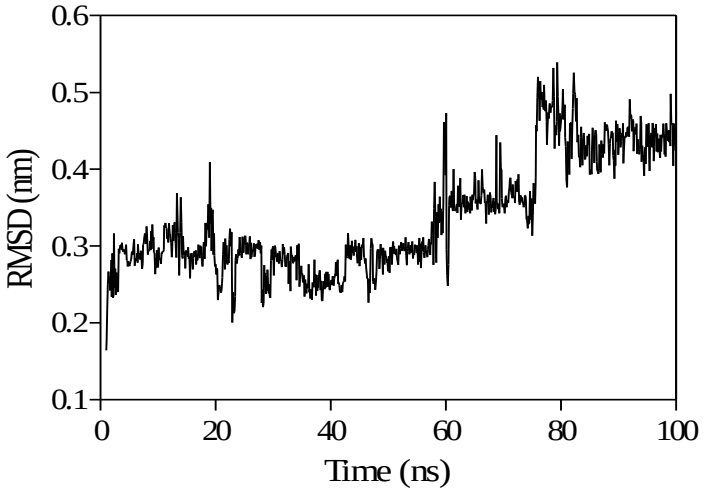
Dissociation: E + I <= EI, K(dissociation), Kd or Ki

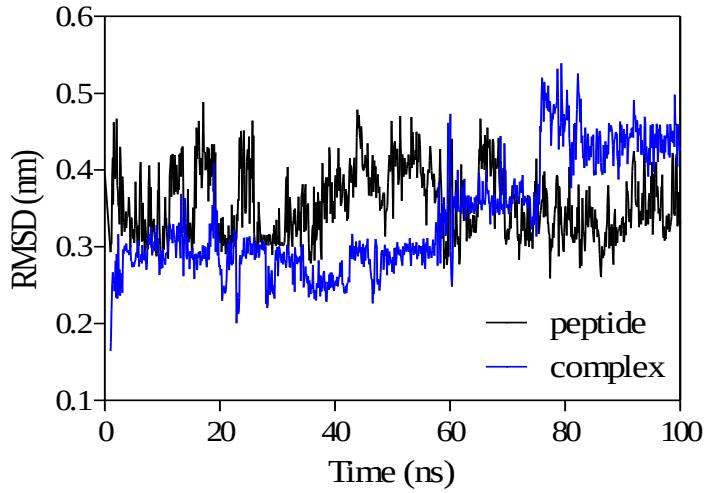
$Kb = \frac{1}{Kd}$, where $lnKb = -lnKd$, $Ki = \frac{[E][I]}{[EI]}$, $\Delta G = -RT * lnKb = RT * lnKi$,

$\Delta G = \Delta H - \Delta TS$

Peptide and CD-peptide complex stability







RMSD (peptide) = 0.36 nm

RMSD (complex) = 0.33 nm

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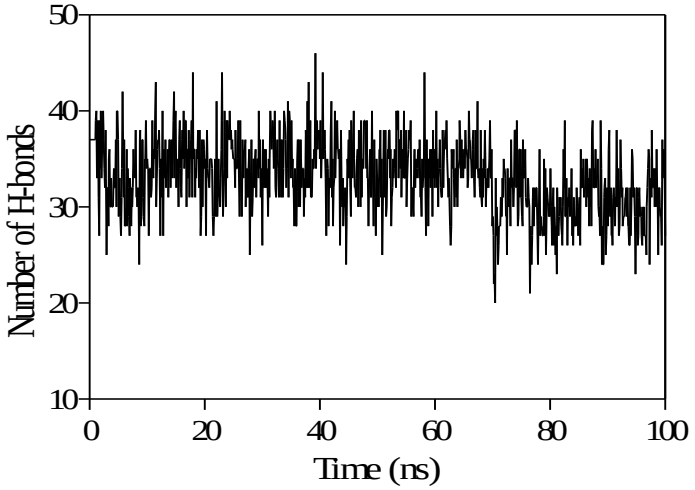
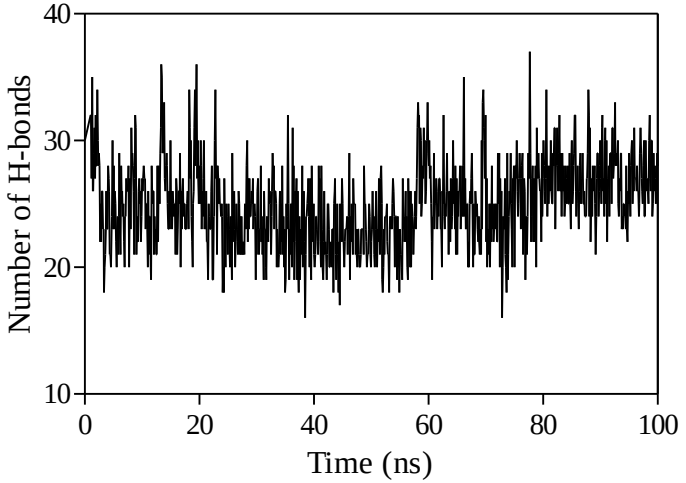
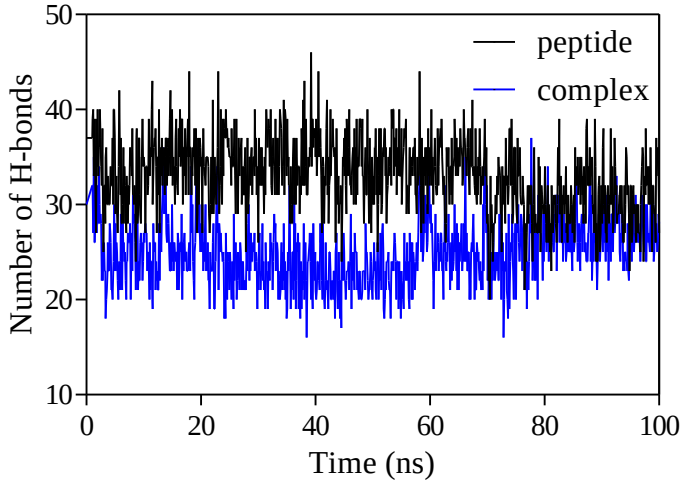
Peptide and CD-peptide complex stability







#H-bond$_{mean}$ (peptide) = 33

#H-bond$_{mean}$ (complex) = 25

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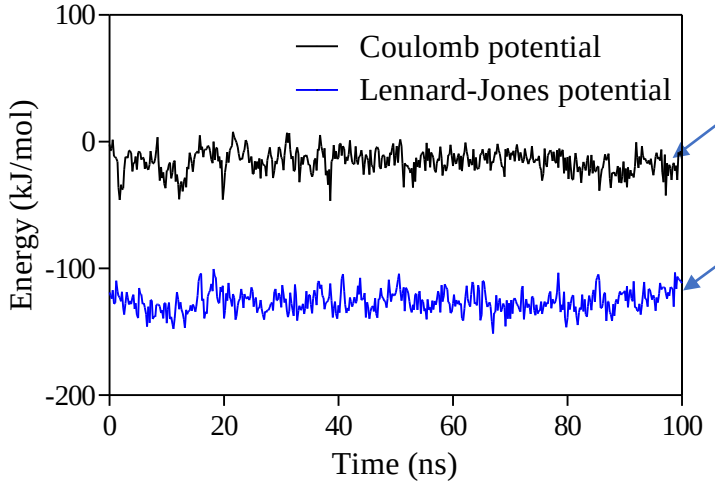
CD-peptide complex stability



Electrostatic force
(Coulomb potential)

Van der Waals force
(Lennard-Jones potential)

$E_{int} = \langle E_{LJ} \rangle + \langle E_{Coul} \rangle$

$\langle E_{Coul} \rangle = -15.48$ kJ/mol

$\langle E_{LJ} \rangle = -126$ kJ/mol

$E_{int} = -141.48$ kJ/mol

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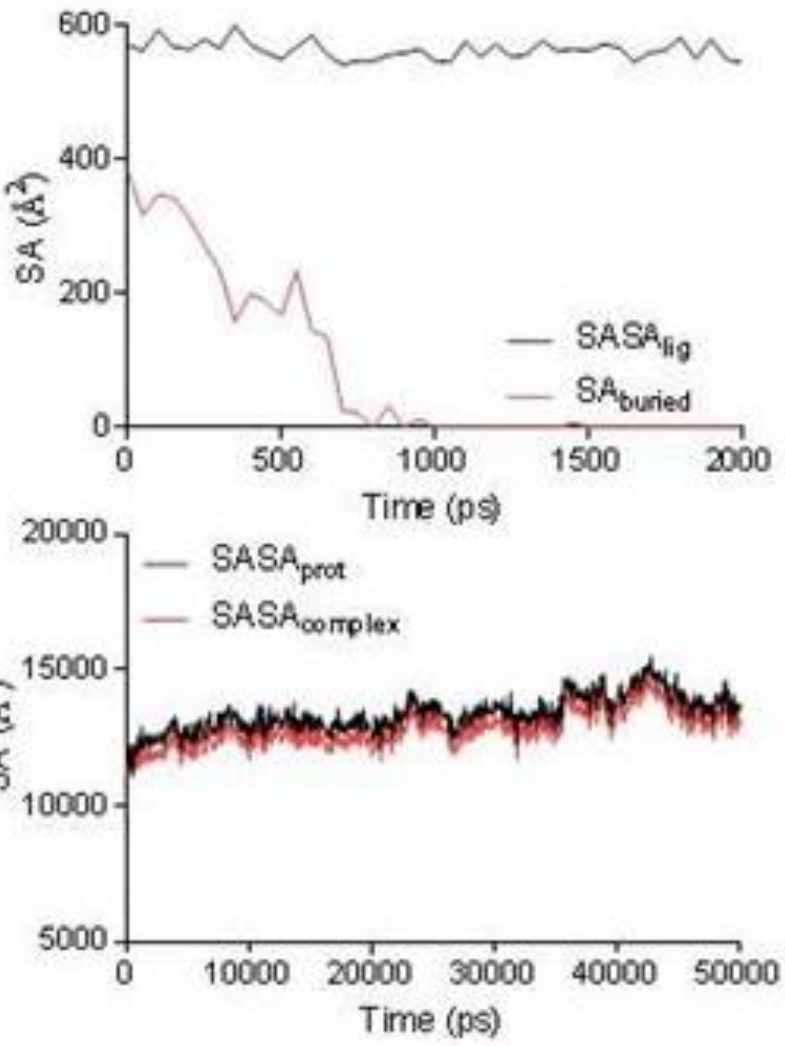
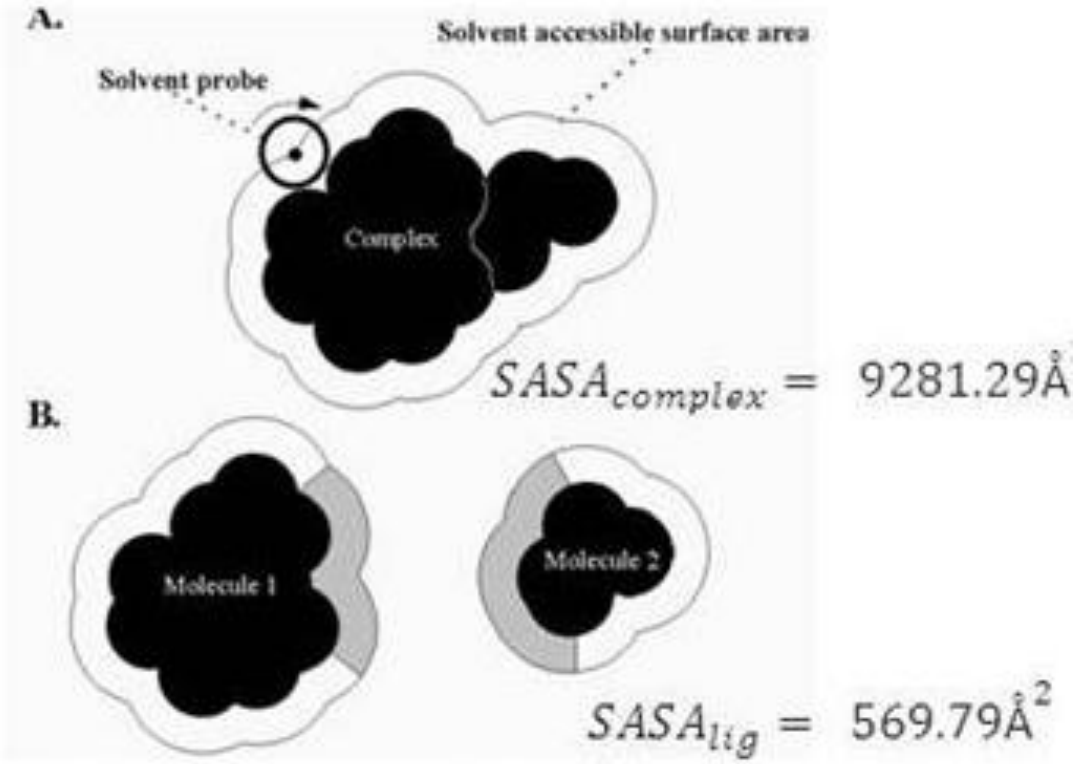
Buried surface area

$$SA_{buried} = \frac{SASA_{prot} + SASA_{lig} - SASA_{complex}}{2}$$





$SASA_{complex} = 9281.29Å$

$SASA_{lig} = 569.79Å^2$

$SASA_{prot} = 9478.15Å^2$

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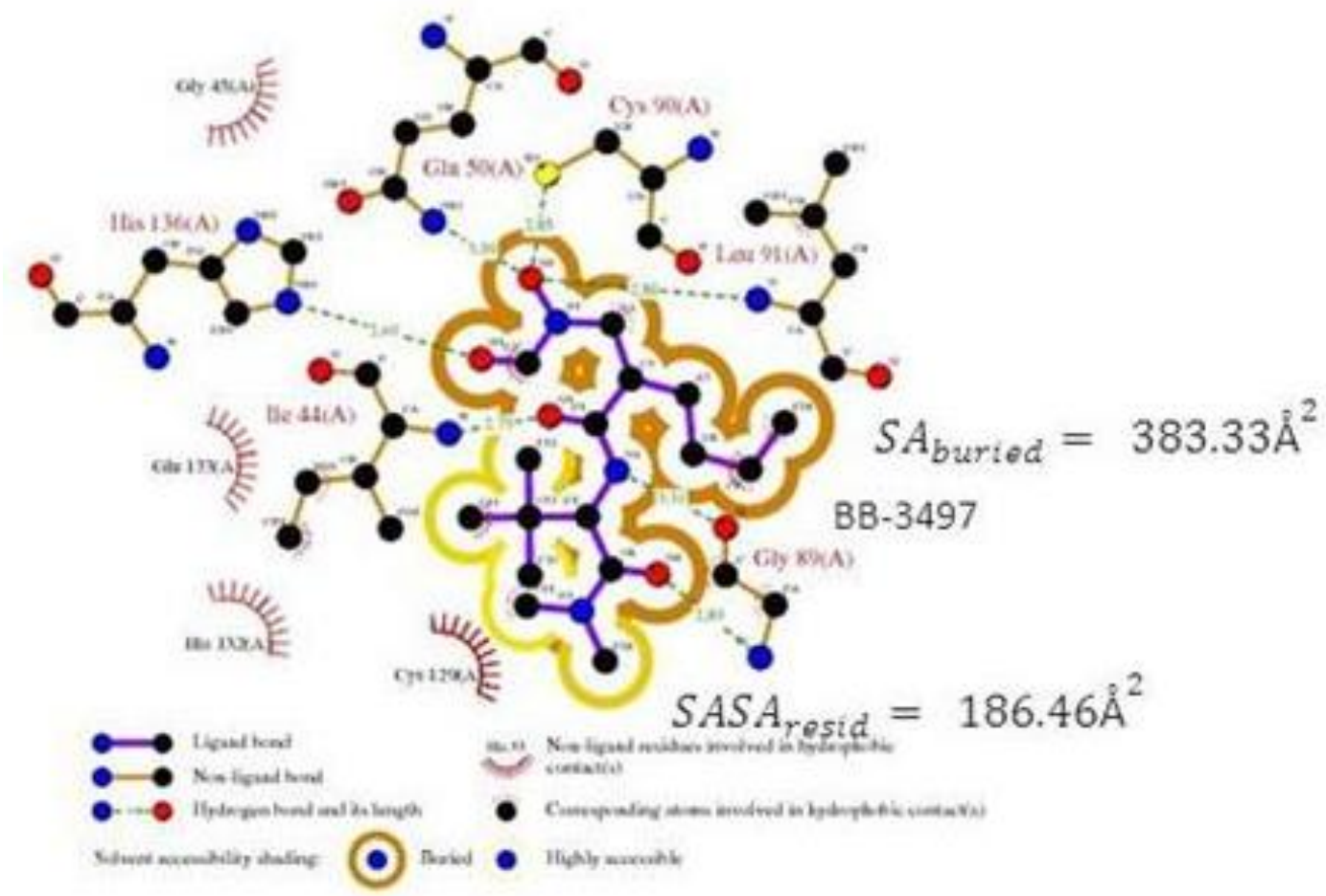
Buried surface area



$SA_{buried} = 383.33 Å^2$

BB-3497

$SASA_{resid} = 186.46 Å^2$

$$SASA_{lig} = SA_{lig} = SASA_{resid} + SA_{buried}$$

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Thank you for your attention