Presenter: Alexey Savelyev

Topic:
Molecular Dynamics IV

Copy of Lecture at:

https://demeler.uleth.ca/biophysics/archive/Savelyev

Last Lectures… (#1, 2, 3)

- **Basic Concepts of the Classical MD Simulations:**
  - Properties of the “particle” (no directions, fixed charge, connected by springs)
  - MD simulation engine (Newton’s eqns.)
  - Integration algorithm (Verlet-type)
  - MD flowchart (structure initialization, minimization, equilibration etc)
  - Periodic Boundary Conditions
  - Molecular Force Field (interaction potentials)

- **Connection to Statistical Mechanics:**
  - Thermodynamic ensembles in MD
  - Ergodicity
  - Computing space and time correlation functions

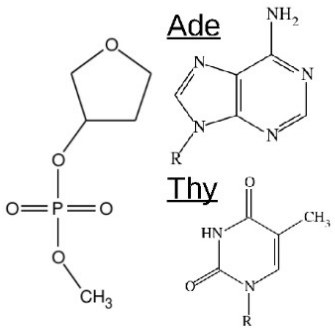
- **Free Energy Methods:**
  - FEP
  - Alchemical Calculations (Thermodynamic Integration)
  - PMF, Umbrella sampling, reaction coordinates (geometric, PCA)

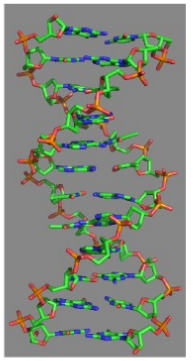
MD Simulations

- **What I did not tell you… (but mentioned & promised to tell)**
  - Multi-scale molecular modeling:
    - Lowering resolution – coarse-graining
    - Increasing resolution/accuracy – polarizable models (“sub-atomic”)
  - Practical Considerations
    - Closer look at .pdb, topology, parameter files
    - MD packages/force fields overview
    - Visualization softwares
  - Historical perspective

MD Simulations

DNA modelling on multiple scales





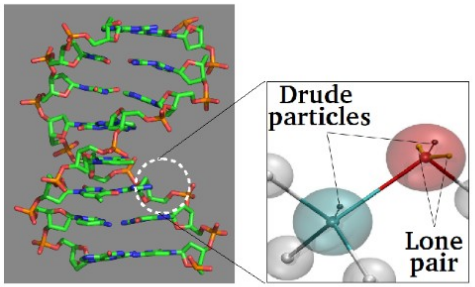
Sub-Atomic
Drude polarizable model

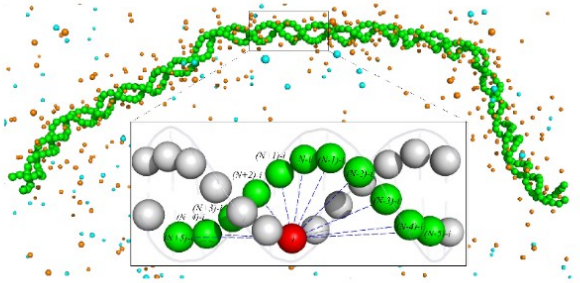
Coarse-Grain
1-bead per residue

Continuum models

QM

All-Atom
Non-polarizable model





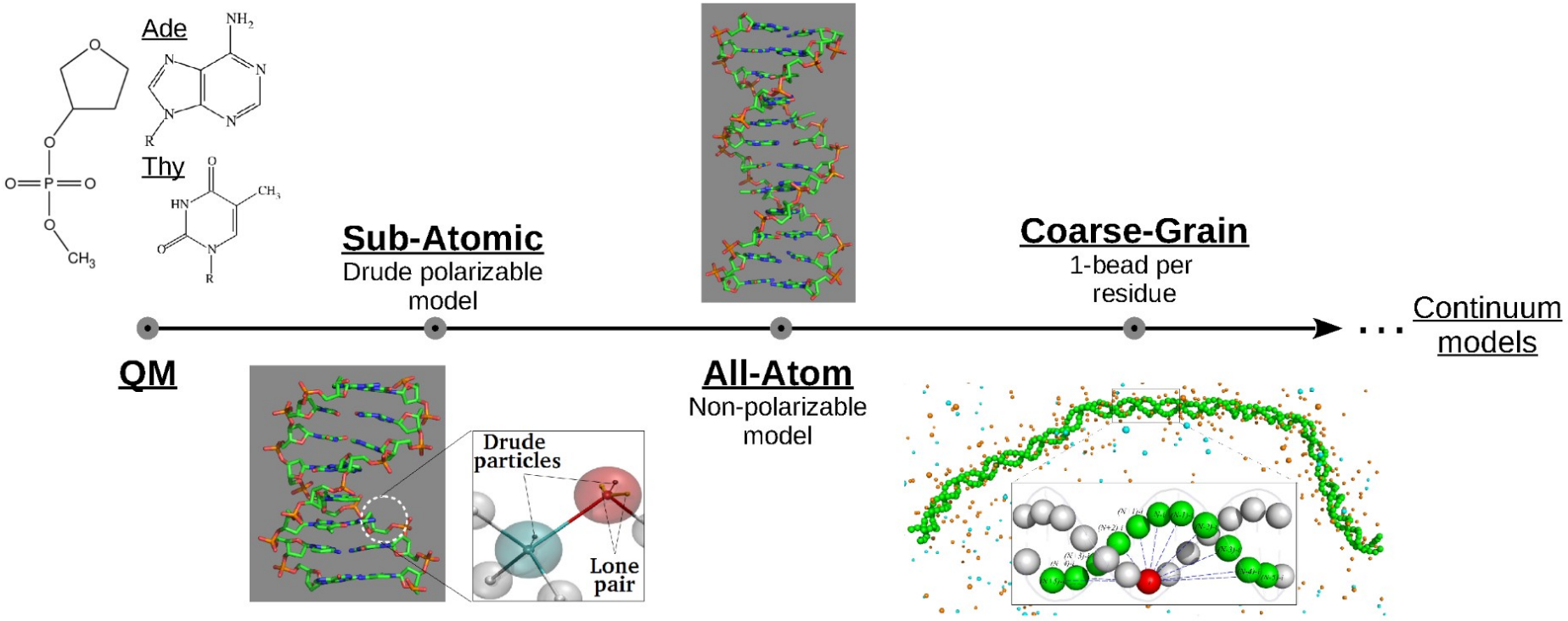
Savelyev & MacKerell, *JCC*, 35, 1219, 2014
Savelyev & MacKerell, *JPC B*, 118, 6742, 2014

Savelyev & Papoian, *Biophys. J*, 96, 4044, 2009
Savelyev & Papoian, *PNAS*, 107, 20340, 2010

Time step:	0.5–1 fs	1–2 fs	10–20 fs
# Particles:	~10^4–10^5	~10^3–10^4	~10^2
Simulation time:	few ~100 ns	Up to ~1 μs	Tens of μs
Resource:	HPC cluster	HPC cluster	Laptop

MD Simulations

DNA modelling on multiple scales

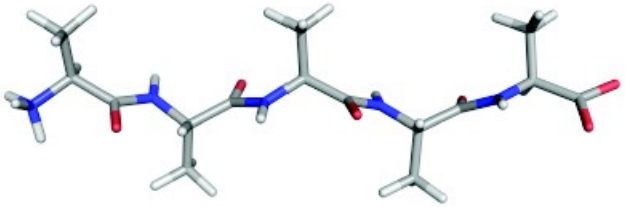


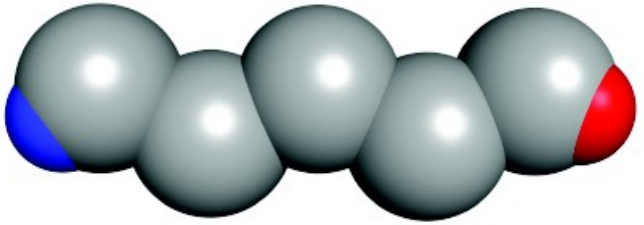
- Studying Ionic atmosphere around DNA
- Studying competitive ionic binding to DNA
- Studying structure of DNA hydration layers
- Identification of the DNA conformational modes
- Numerical calculation of the DNA SAXS profiles
- Studying protein-DNA and DNA-DNA interactions
- Studying interactions of DNA with small molecules
- ……..

- Large scale DNA behavior (persistence length, its dependence on ionic strength)
- Simulating nucleosome core particle and poly-nucleosomal array
- …….

MD Simulations

- **Molecular Coarse-Graining**





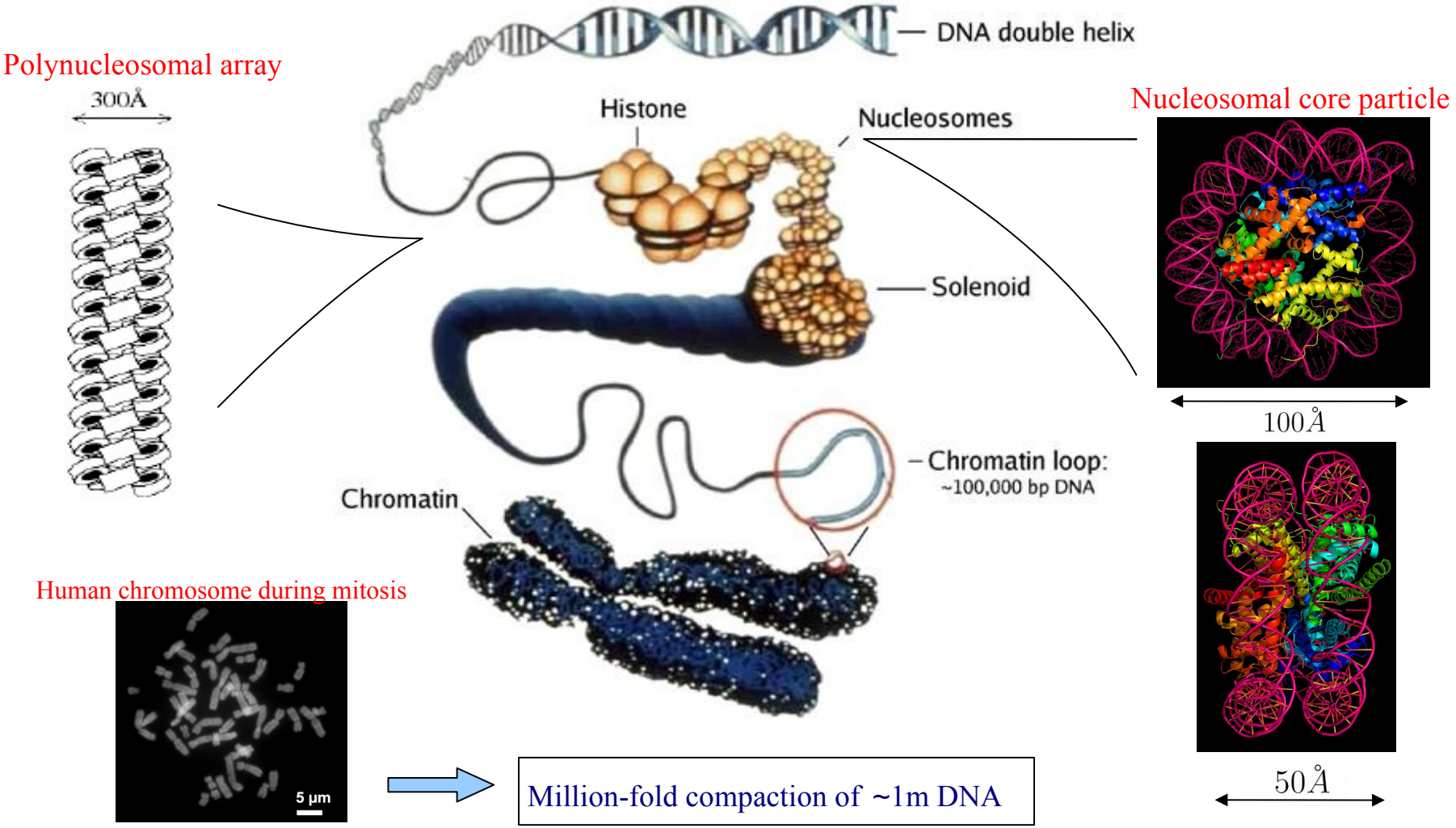
- Despite the inherent differences between the models, it is possible that all of them capture (some of) the essential physics of the system, as required for different scientific endeavors

- **Main concepts are the same:**
  - Unit is CG “particle”
  - CG particle has radius (defined by interaction potentials)
  - Particles connected by bonds
  - Particles have partial charges
  - Dynamic and thermodynamic properties are driven by CG force field

“Everything should be made as simple as possible, but no simpler.” A. Einstein

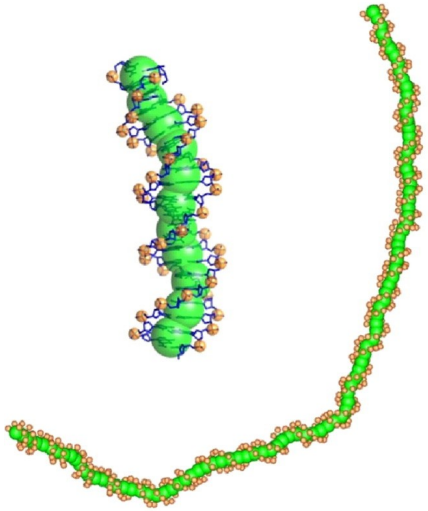
MD Simulations

- **Molecular Coarse-Graining: nucleosomal array examples**
  - Organization of eukaryotic chromatin

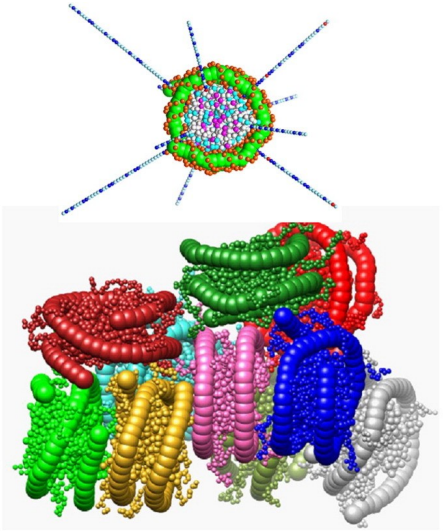


MD Simulations

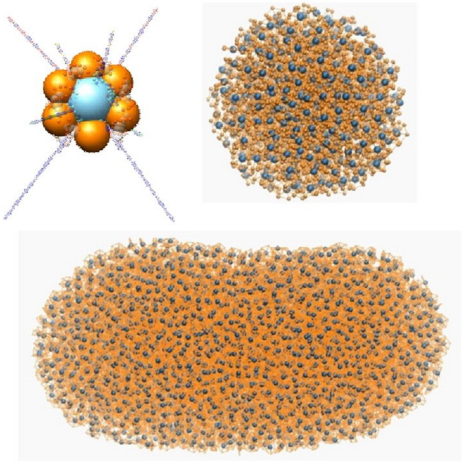
- **Molecular Coarse-Graining: nucleosomal array examples**



coarse-grained DNA model



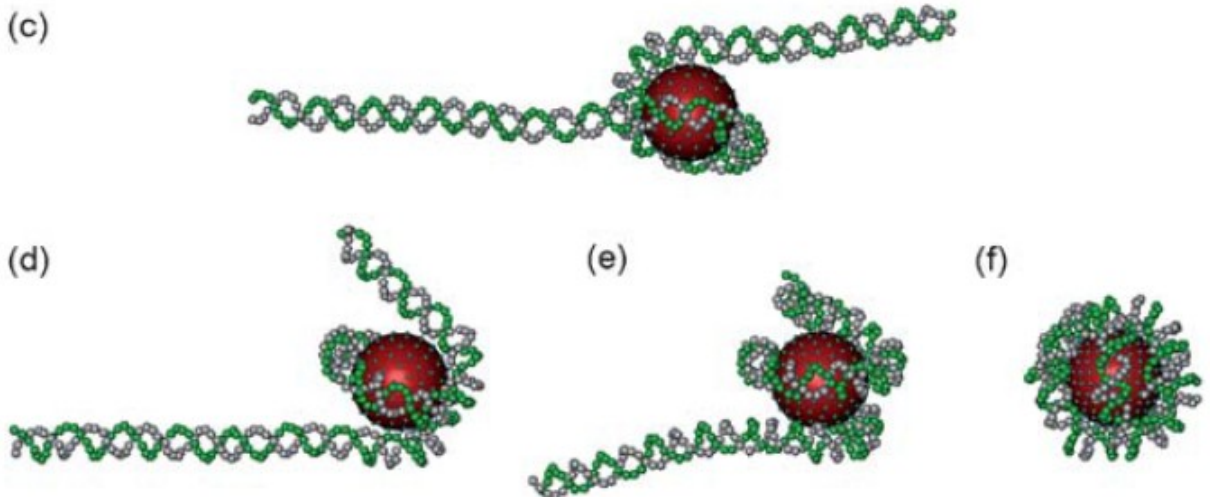
nucleosome-nucleosome stacking



super coarse-grained nucleosome model and nucleosome aggregation

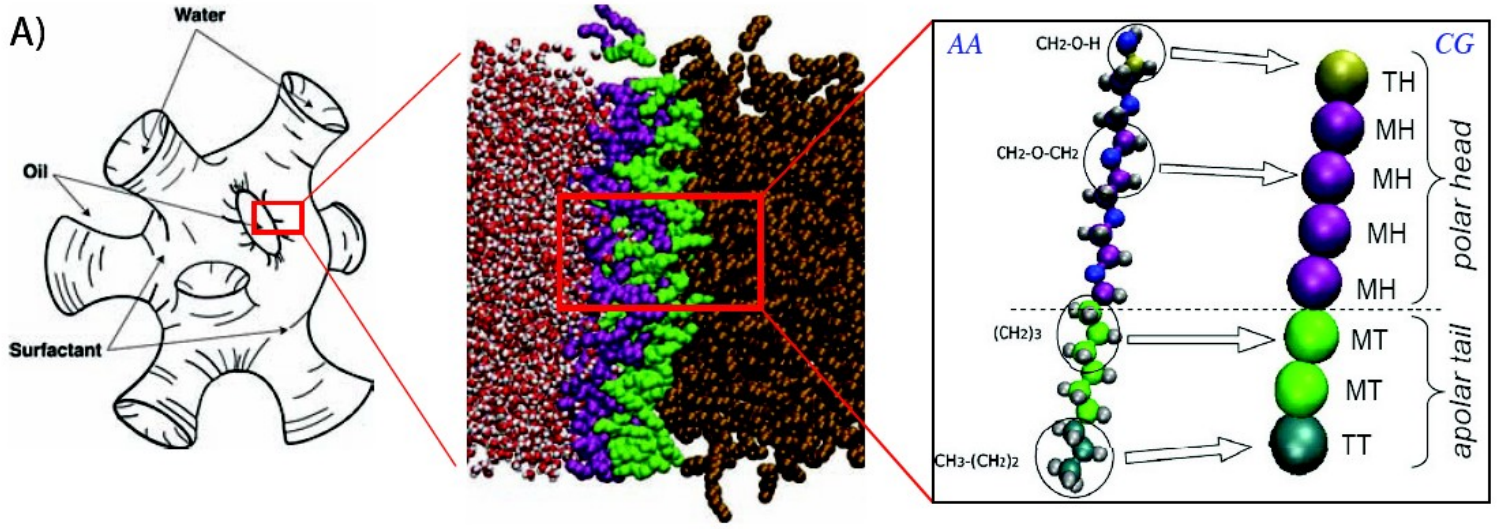
Korolev et al, Advances in Colloid and Interface Science, 232, 2016

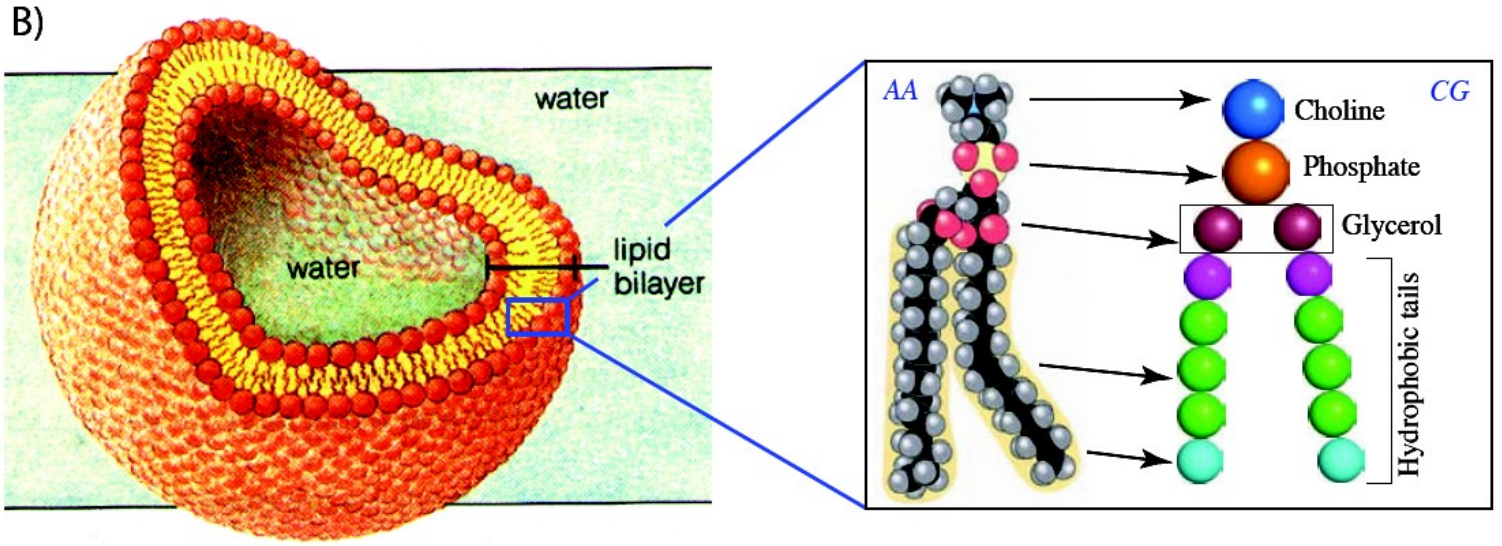
Savelyev et al, PNAS, 2010
J. Chem. Phys., 2014
Soft Matter, 2011
Soft Matter, 2014



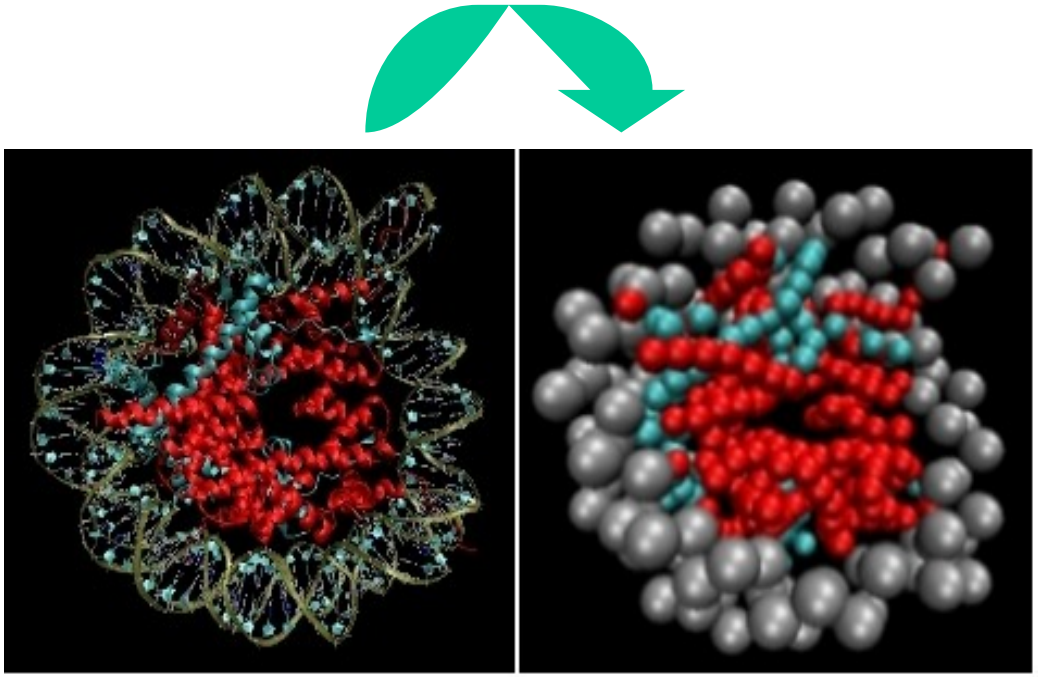
MD Simulations

- **Molecular Coarse-Graining: more examples**



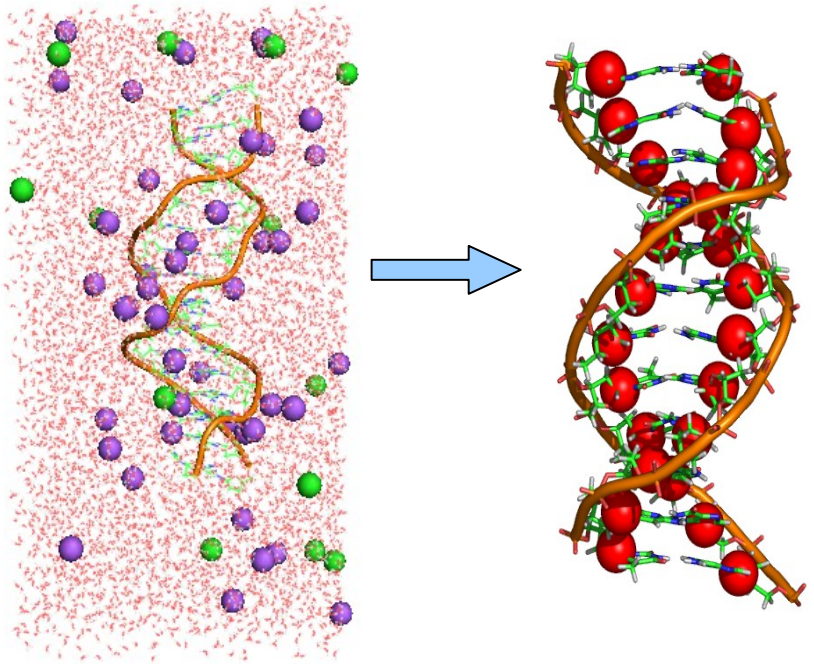


Coarse-grained (CG) Models of the Nucleosome and the Linker DNA from the All-Atom MD Simulations: Bottom Up Approach



~1200 protein residues and ~ 160 base pairs of DNA

Materese C., Savelyev A. and Papoian G. JACS (2009) 131



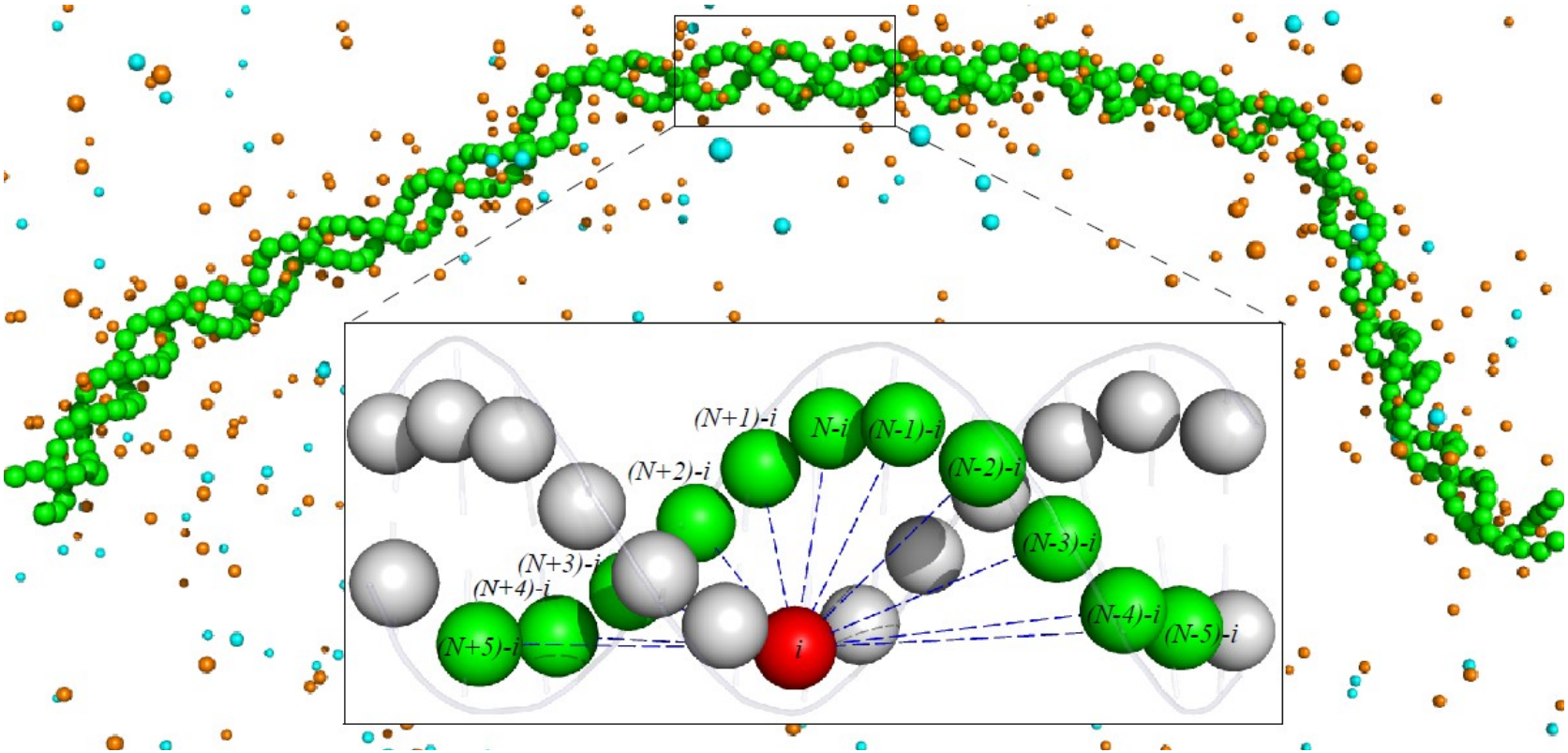
~0 - 80 base pairs of linker DNA

Savelyev A. and Papoian G. JACS (2006) 128

How to get CG force-field ?

All-atom MD simulations of smaller parts

MRG-CG Model for the DNA with Explicit Mobile Ions



- ***Effective Hamiltonian***

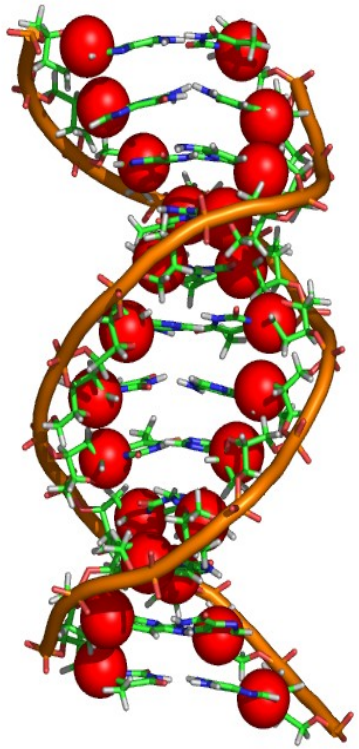
$$\mathcal{H} = \underbrace{\mathcal{U}_{\text{bond}} + \mathcal{U}_{\text{ang}}}_{\textit{Intra}\text{-strand DNA}} + \underbrace{\mathcal{U}_{\text{fan}}}_{\textit{Inter}\text{-strand DNA}} + \underbrace{\mathcal{U}_{\text{el}}}_{\text{Non-bonded [inter-ionic; ion-DNA; DNA-DNA]}}$$

Savelyev A. and Papoian G. PNAS, 2010

MRG-CG Model for DNA with Explicit Mobile Ions

- ***Polymeric DNA distributions***

Potentials of mean force (PMF) as initial effective interactions



$$P^{\mathrm{UA}}_{\mathrm{bond}}(L,T)=\frac{B_{\mathrm{bond}}}{L^2}\int d\Gamma\,\exp[-\beta U^{\mathrm{UA}}(\Gamma)]\sum_i \delta(L_i-L)$$

$$U^{\mathrm{CG}}_{\mathrm{bond}}(L,T)=-\frac{1}{\beta}\ln P^{\mathrm{UA}}_{\mathrm{bond}}(L,T)+A_{\mathrm{bond}}$$

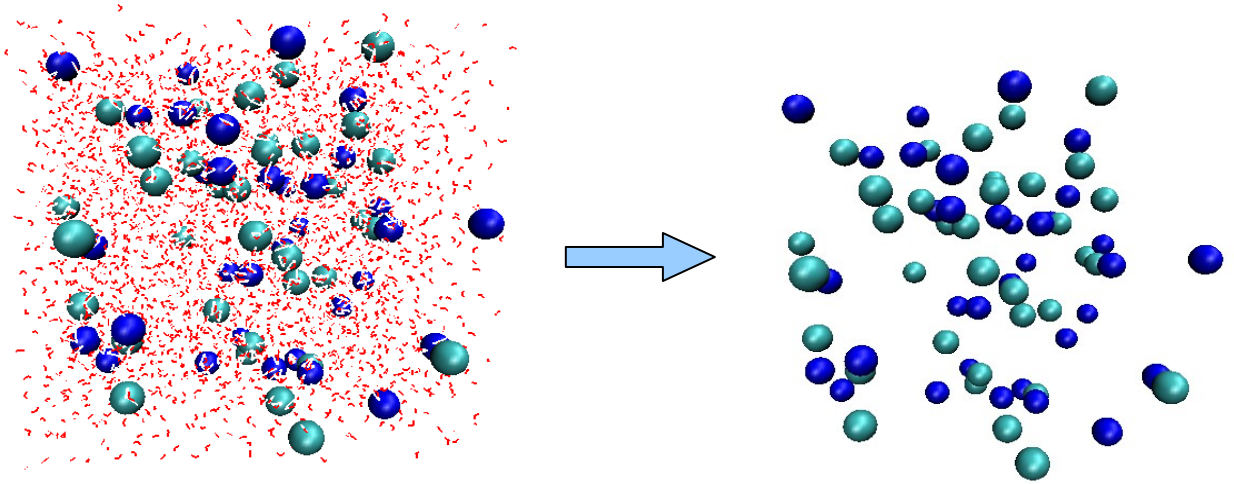
$$P^{\mathrm{UA}}_{\mathrm{ang}}(\Theta,T)=\frac{B_{\mathrm{ang}}}{\sin\Theta}\int d\Gamma\,\exp(-\beta U^{\mathrm{UA}}(\Gamma))\times\sum_i \delta(\Theta_i-\Theta)$$

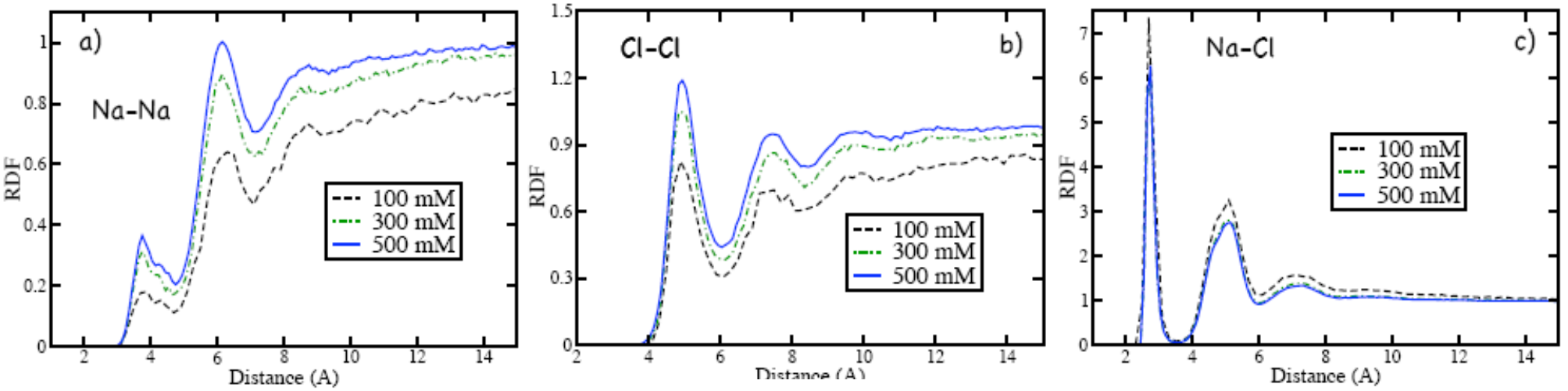
$$U^{\mathrm{CG}}_{\mathrm{ang}}(\Theta,T)=-\frac{1}{\beta}\ln P^{\mathrm{UA}}_{\mathrm{ang}}(\Theta,T)+A_{\mathrm{ang}}$$

Savelyev A. and Papoian G. Biophys. J, 2009

MRG-CG Model for DNA with Explicit Mobile Ions

- ***Coarse-graining of electrolyte solutions***





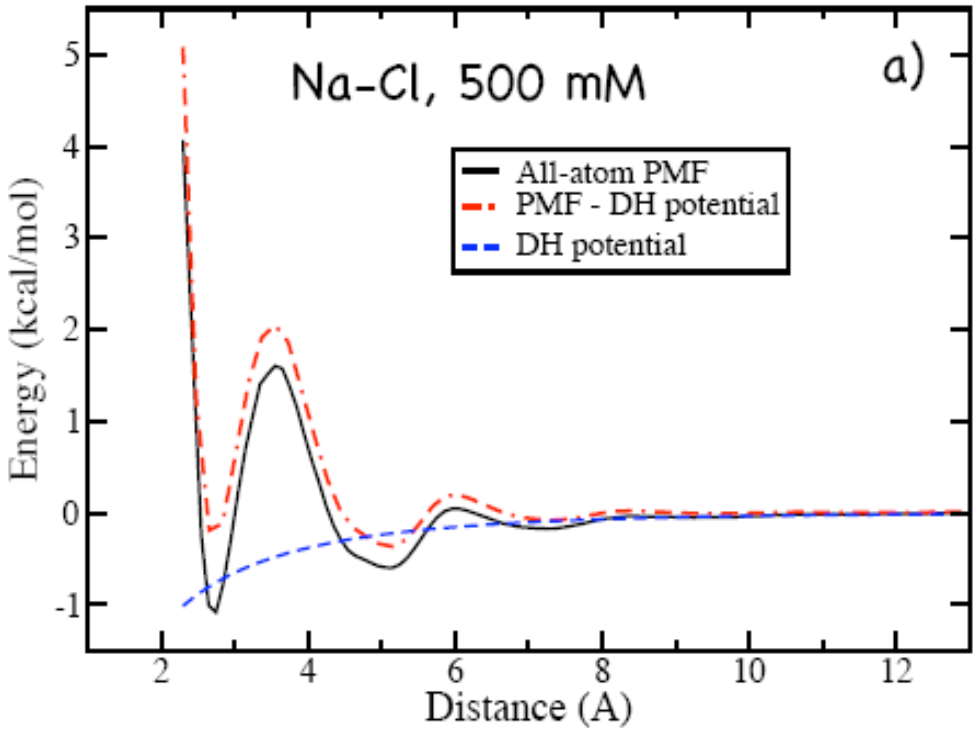
$$U_{\mathrm{PMF}} = -k_{\mathrm{B}}T \ln g(r).$$

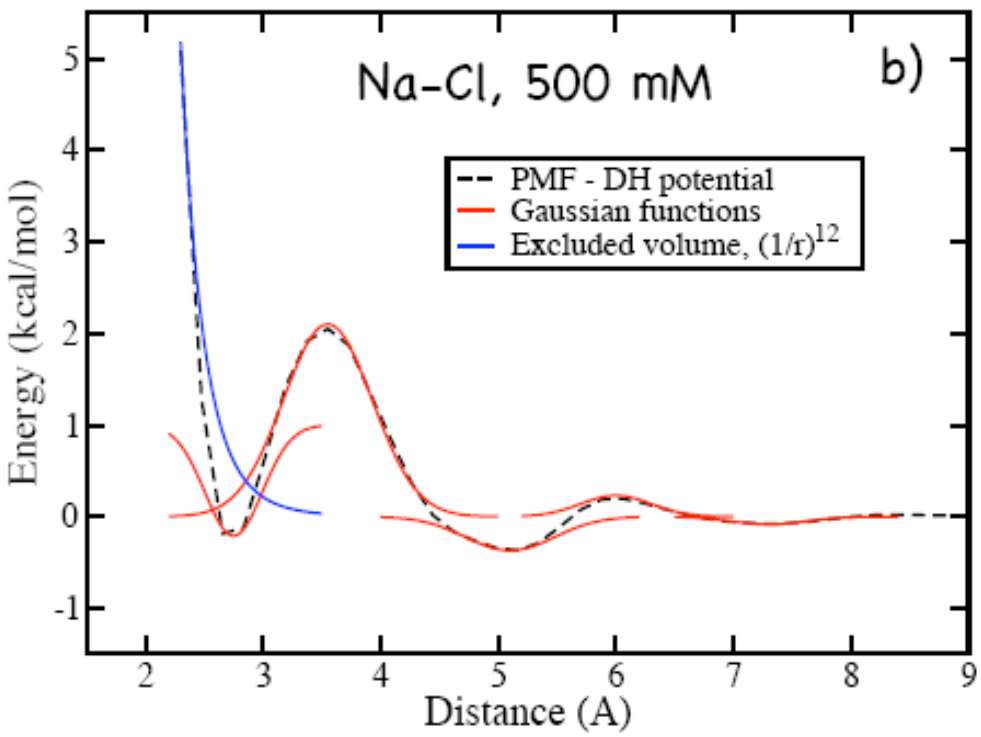
$$\mathscr{H} = \mathscr{U}_{\mathrm{ex}} + \mathscr{U}_{\mathrm{hyd}} + \mathscr{U}_{\mathrm{el}}.$$

Savelyev A. & Papoian G. J Phys Chem B (2009) 113, 7785

MRG-CG Model for DNA with Explicit Mobile Ions

- ***Inter-ionic CG potentials***





$$U_{\mathrm{PMF}} = -k_{\mathrm{B}}T \ln g(r).$$

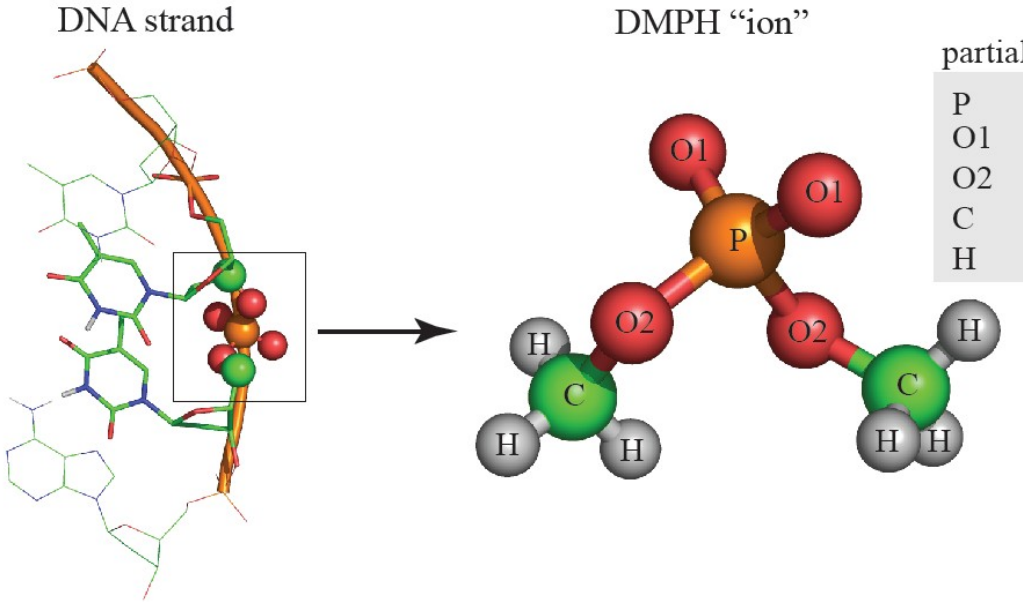
$$\mathscr{H} = \sum_{i>j} \left[\frac{A}{r_{ij}^{12}} + \sum_{k=1}^{5} B^{(k)} \mathrm{e}^{-C^{(k)}\left[r_{ij}-R^{(k)}\right]^2} + \frac{q_i q_j}{4\pi\varepsilon_0 \varepsilon r_{ij}} \right]$$

Savelyev A. and Papoian G. J Phys Chem B, 2009, 113, 7785

MRG-CG Model for DNA with Explicit Mobile Ions

- ***CG Interactions among DNA beads and Na+, Cl- ions***

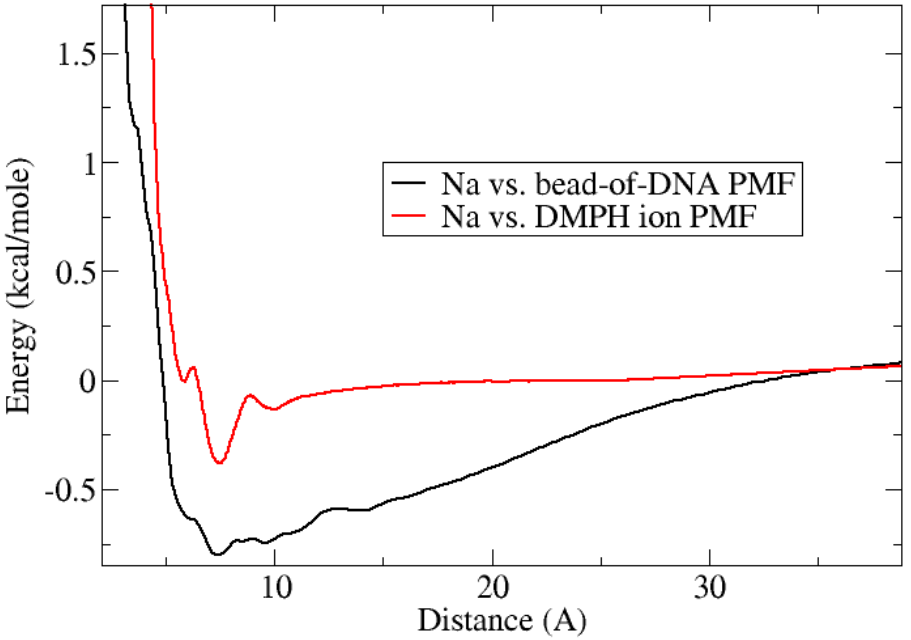
To guess the functional form of ion-DNA interactions, we cut DNA into **"monomers"**



partial charges

P	+1.1659
O1	-0.7761
O2	-0.4954
C	-0.0069
H	0.06515

$$\varphi(r) = \frac{A}{r_{ij}^6} + \sum_{k=1}^{3} B^{(k)} \mathrm{e}^{-C^{(k)}\left[r_{ij}-R^{(k)}\right]^2} + \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon r_{ij}}$$



Savelyev A. and Papoian G. PNAS, 2010, 113, 7785

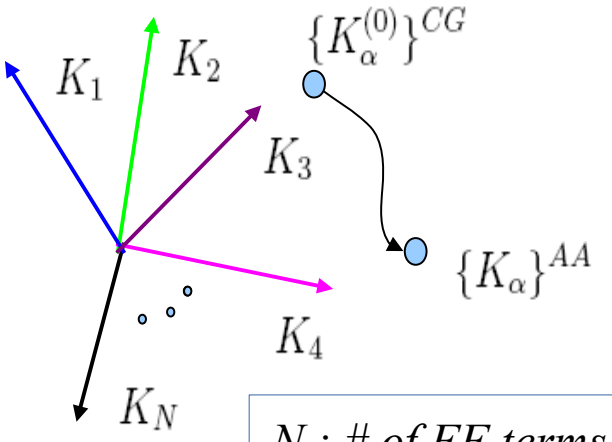
- ***Reshaping the effective Hamiltonian: DNA interactions***

$$H = \sum_{\alpha} K_\alpha S_\alpha = K_1 \underbrace{\sum_{i,j} (r_{ij} - r_0)^2}_{S_1^{\text{bond}}} + K_2 \underbrace{\sum_{i,j} (r_{ij} - r_0)^3}_{S_2^{\text{bond}}} + K_3 \underbrace{\sum_{i,j} (r_{ij} - r_0)^4}_{S_3^{\text{bond}}}$$

$$+ K_4 \underbrace{\sum_{i,j,k} (\theta_{ijk} - \theta_0)^2}_{S_1^{\text{angle}}} + K_5 \underbrace{\sum_{i,j,k} (\theta_{ijk} - \theta_0)^3}_{S_2^{\text{angle}}} + K_6 \underbrace{\sum_{i,j,k} (\theta_{ijk} - \theta_0)^4}_{S_3^{\text{angle}}} + \ldots.$$

Optimization scheme algorithm:

1. Collect all boxed values from AA MD; these are exact <S>*;
2. Run CG MD with trial set of $K^{(0)}$;
3. Collect boxed values, $S^{(0)}$, from CG simulation driven by $K^{(0)}$; find $\triangle S^{(0)}$
4. Collect all (cross-)correlators from CG simulation;
5. Correct set of K in a CG Hamiltonian;
6. Repeat steps 2-5 until corrections to K become statistically irrelevant



N : # *of FF terms*

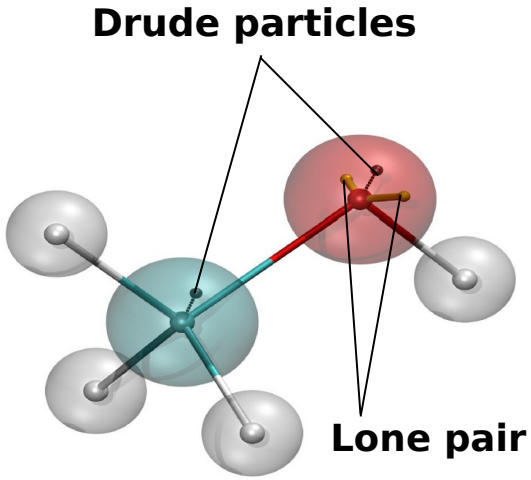
Savelyev A. and Papoian G. Biophys. J, 2009, 96, 4044
Savelyev A. and Papoian G. PNAS, 2010

MD Simulations: Polarizable Models

- **Going to "sub-atomic" regime: Polarizable Models**
  - Induced Dipole Model
  - Fluctuating Charge Model
  - **Classical Drude Oscillator Model**
    - Very fast (for polarizable model): up to 1fs
    - Only 4-fold overhead compared to non-polarizable AA model
    - The only polarizable model framework having comprehensive set of biomolecular force fields for large molecules:
      - Proteins
      - Nucleic Acids (DNA & 1st gen. RNA)
      - Lipids (membranes)
      - Carbohydrates

Savelyev, A.; B. Roux; Mackerell A. D. "*Explicit Inclusion of Induced Polarization Effects in Atomistic Force Fields Based on the Classical Drude Oscillator Model*", Book Chapter for "Many-Body Effects and Electrostatics in Biomolecules" ed. by Q. Cui, P. Ren, and M. Meuwly, Pan Stanford **2016** Print ISBN: 978-981-4613-92-7

MD Simulations: Drude Polarizable Model



$$q(A) = q_c(A) + q_D(A)$$

$$\alpha(A) = q_D^2(A)/k_D$$

$$U_{elec} = \sum_{A<B}^{N} \frac{q_c(A)\cdot q_c(B)}{|\mathbf{r}(A) - \mathbf{r}(B)|} + \sum_{A<B}^{N,N_D} \frac{q_D(A)\cdot q_c(B)}{|\mathbf{r}_D(A) - \mathbf{r}(B)|} + \sum_{A<B}^{N_D} \frac{q_D(A)\cdot q_D(B)}{|\mathbf{r}_D(A) - \mathbf{r}_D(B)|} + \frac{1}{2}\sum_{A}^{N_D} k_D|\mathbf{r}_D(A) - \mathbf{r}(A)|^2$$

Drude model extensions:

- Anisotropic polarizability:

$$U_{self}(\mathbf{d}) = \frac{1}{2}\mathbf{d}\cdot\mathbf{K}^D\cdot\mathbf{d} = \frac{1}{2}\left(K_{11}^D d_1^2 + K_{22}^D d_2^2 + K_{33}^D d_3^2\right)$$

- Atom-based Thole screening:

$$S_{ij}(r_{ij}) = 1 - \left(1 + \frac{(t_i + t_j)r_{ij}}{2(\alpha_i\alpha_j)^{1/6}}\right) e^{-(t_i+t_j)r_{ij}/2(\alpha_i\alpha_j)^{1/6}}$$

- Atom-based NBFIX correction (LJ tuning)
- HardWall feature (overpolarization problem, increased time-step)

MD is based on use of the extended Lagrangian method:

Drude and real particles are used on equal footing, *dynamically*

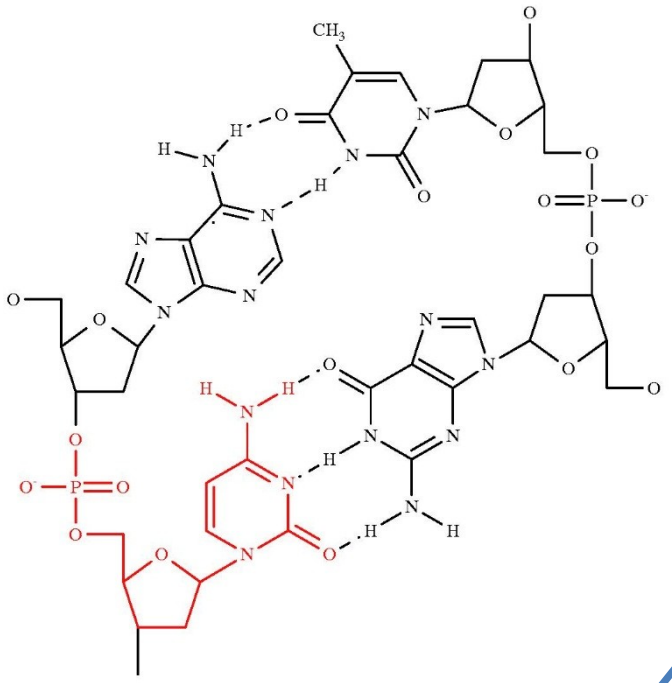
Drude and real particles are coupled to *separate thermostates* to remain in the SCF regime

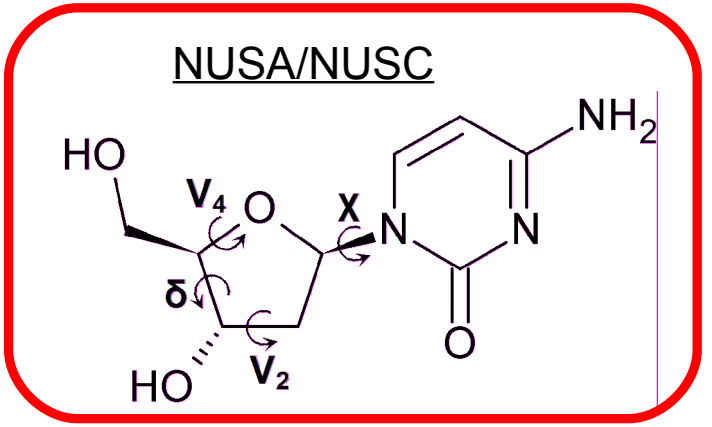
Lamoureux & B. Roux, J. Chem. Phys. 2003

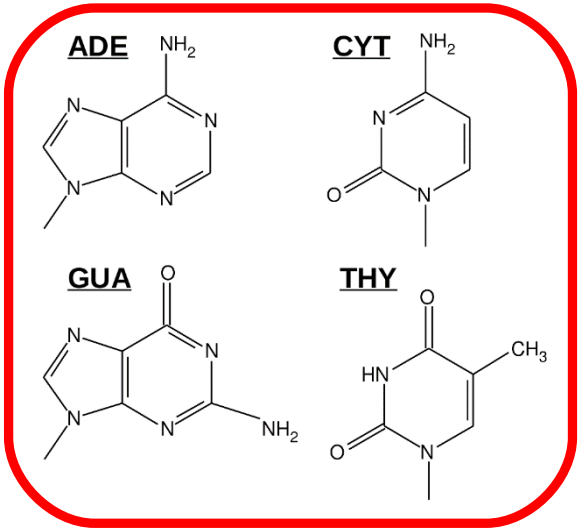
Jiang et al, **JPC Letters**, 2, 87–92: 2011.

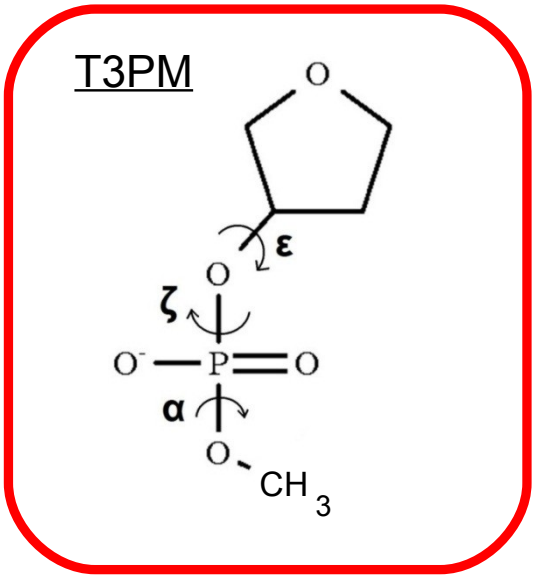
Drude Polarizable model for DNA: Building Blocks

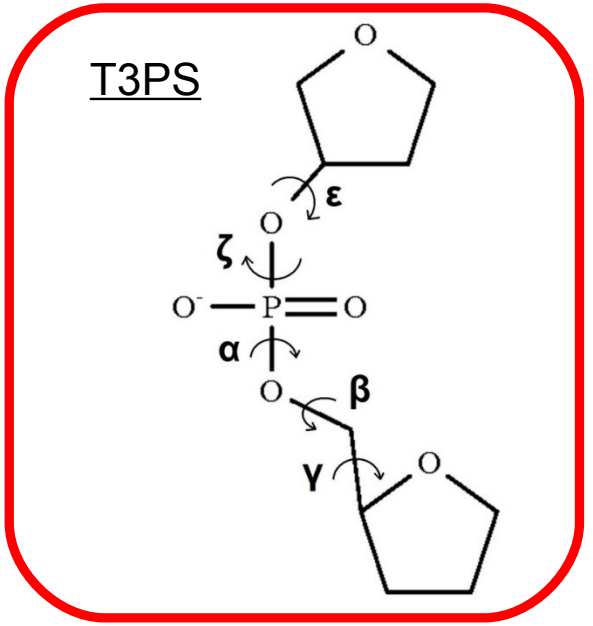
- Begin with molecule analogues constructed from smaller model compounds



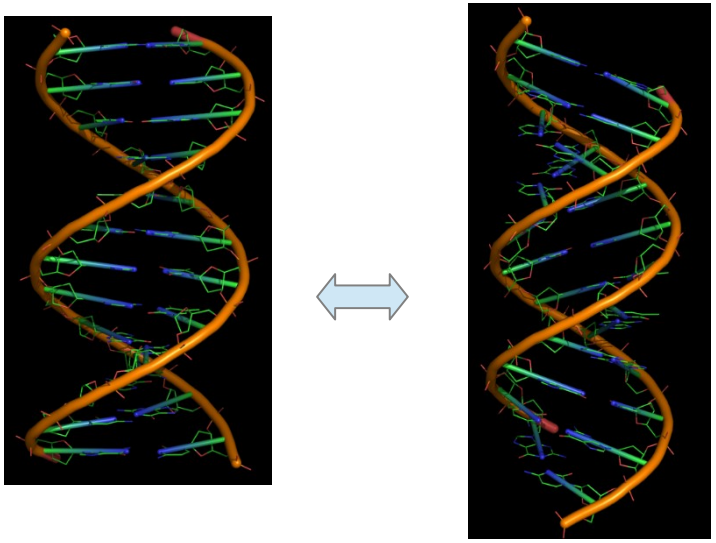


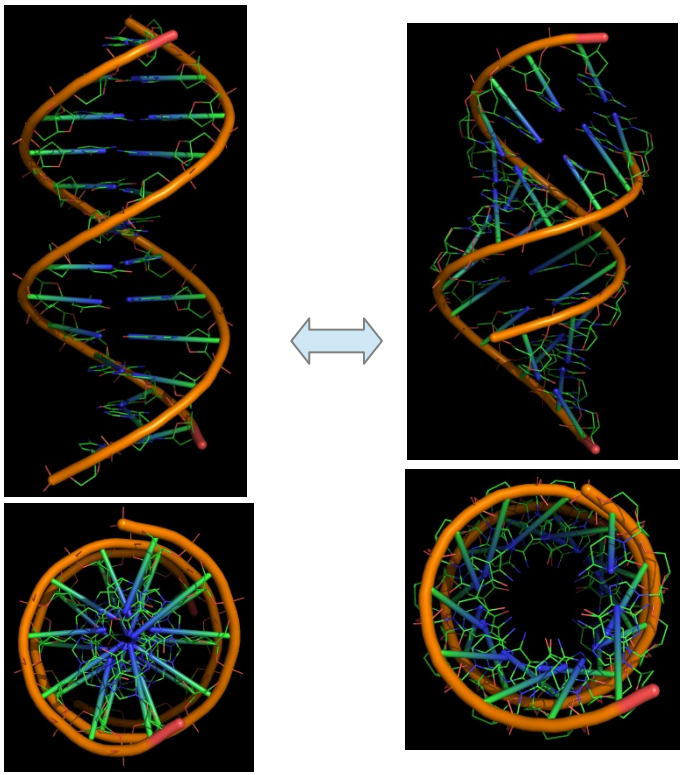






Optimization of the CHARMM Drude polarizable FF for DNA





- **QM/MM data:**
  - 1D and 2D (eps vs. zeta) energy profiles (T3PS, T3PM)
  - relative energies of the *North* and *South* sugar conformations
- **Crystal/NMR surveys:**
  - data for backbone/sugar bending/dihedral angles and sugar P angle
  - survey for DNA helicoidal parameters (roll, twist etc.)
- **NMR experiments:**
  - dynamics of sugar repuckering/BI-to-BII transitions in B DNA:
  - S^2 order parameters for some atoms in phosphodiester backbone and bases
  - Sequence dependence of BII sampling for Ecor1/Junfos
- **Proper balance of the interactions among ions, water & DNA:**
  - Hydration and osmotic properties of relevant ions and their solutions
  - ionic distributions around DNA (CC theory predictions)

DNA stable on **500ns+ time scale**
[several sequences]

Savelyev & MacKerell, *JCC*, 35, 1219, 2014
Savelyev & MacKerell, *JPC B*, 118, 6742, 2014
Savelyev & MacKerell, *JPC Lett*, 6, 212, 2014
Lemkul, Savelyev & MacKerell, *JPC Lett*, 5, 2014
Savelyev & MacKerell, *JPC B*, 119, 4428, 2015
Savelyev & MacKerell, *JCTC*, 11, 4473, 2015

MD Simulations: Drude Polarizable Model

- DNA electrostatics:
  - Counter-ion condensation (theory, ~75% of DNA charge neutralization)
  - Competitive ionic binding (Na+ vs K+, comparison to exp.)
- DNA base flipping (free energy, comparison to exp.)
- SAXS DNA profiles (in Na+, comparison to exp.)
- Differential effect of different ions on DNA conformational properties (prediction)

These comparative studies demonstrated that inclusion of polarization effects provides far more realistic representation of DNA conformational dynamics, electrostatic effects, interactions between DNA and surrounding mobile ions and other biomolecules compared to the non-polarizable DNA models (currently a mainstream in all-atom MD simulations).

MD Simulations: Drude Prepper in CHARMM-GUI

CHARMM-GUI
Effective Simulation Input Generator and More

CHARMM is a versatile program for atomic-level simulation of many-particle systems, particularly macromolecules of biological interest. - M. Karplus

Some lectures and job postings are now available. See upload log for update history and giving for donation. Contact info is given below.

Input Generator
- PDB Reader
- Glycan Reader & Modeler
- Ligand Reader & Modeler
- Glycolipid Modeler
- LPS Modeler
- Multicomponent Assembler
- Solvator
- Quick MD Simulator
- Drude Prepper
- Membrane Builder
- Martini Maker
- PACE CG Builder
- Boundary Potential Utilizer
- PBEQ Solver
- Implicit Solvent Modeller
- Free Energy Calculator
- NMR Structure Calculator
- MAP Utilizer
- GCMC/BD Ion Simulator
- DEER Facilitator

Drude Prepper

Tutorial

Drude Prepper generates a series of CHARMM PSF, coordinate, and input files from an identical system equilibrated with the CHARMM36 non-polarizable additive force fields to a system compatible with the Drude polarizable force fields.

Please note that

- The Drude polarizable force field is currently available for water, ions, protein, DNA, hexapyranose monosaccharides, polyalcohols, and the DLPC/DMPC/DPPC/POPC/DOPC/DPPE/POPE/DOPE lipids. Additional molecules will be made accessible upon publication.
- The Drude Prepper is only compatible with the additive CHARMM C36 (protein, lipid, DNA, hexapyranose monosaccharide and polyalcohol) force field. If necessary, use CHARMM-GUI PDB Reader to regenerate the additive CHARMM and XPLOR PSF files.
- Both CHARMM and NAMD minimization (step3) and production (step4) inputs are provided. The NAMD inputs are under the "namd" directory.
- **The NAMD inputs are optimized for NAMD 2.12 or higher. The user who is using lower version of NAMD needs to comment out "ioformat extended" in toppar_drude/toppar_drude_master_protein_2013e.str.**
- The current Drude FF only supports the following chemical modifications: terminal pathches, disulfide bonds and protonation (GLUP and ASPP). Any phosphorylation is not supported at this moment.
- For small molecules the residue name and the atom names should match with those in the corresponding Drude model compound.

Reference for Drude Prepper:
S. Jo, T. Kim, V.G. Iyer, and W. Im (2008)
CHARMM-GUI: A Web-based Graphical User Interface for CHARMM. *J. Comput. Chem. 29:1859-1865*

Upload PSF File:
Browse... No file selected.
PSF File Format: CHARMM X-PLOR

Upload Coord. File:
Browse... No file selected.
Coordinate File Format: PDB CHARMM NAMD

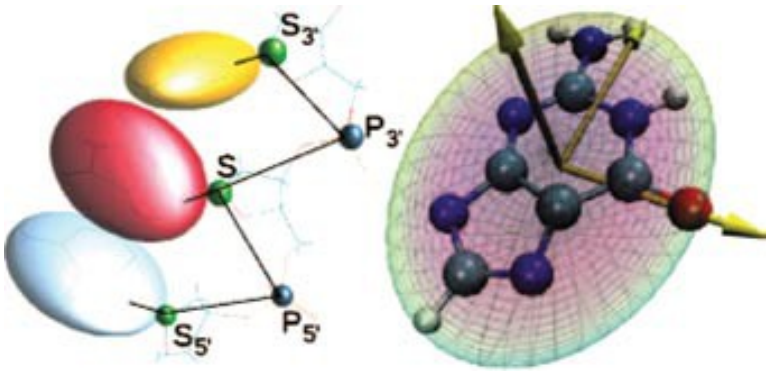
Setup PBC:
Select Box Type: Cubic
X: Å

References for the Drude Force Fields:
G. Lamoureux, E. Harder, I.V. Vorobyov, B. Roux and A.D. MacKerell, Jr. (2006)
A polarizable model of water for molecular dynamics simulations of biomolecules. *Chem. Phys. Lett. 418: 245-249*
H. Yu, T.W. Whitfield, E. Harder, G. Lamoureux, I. Vorobyov, V.M. Anisimov, A.D. MacKerell, Jr. and B. Roux (2010)
Simulating Monovalent and Divalent Ions in Aqueous Solution Using a Drude Polarizable Force Field. *J. Chem. Theory. Comput. 6: 774–786*
W. Jiang, D. Hardy, J. Phillips, A. D. MacKerell, Jr., K. Schulten and B. Roux (2011)
High-performance Scalable Molecular Dynamics Simulations of a Polarizable Force Field Based on Classical Drude Oscillators in NAMD. *J. Phys. Chem. Lett. 2:87-92*
J. Chowdhary, E. Harder, P.E.M. Lopes, L. Huang, A.D. MacKerell , Jr. and B. Roux (2013)
A Polarizable Force Field of Dipalmitoylphosphatidylcholine Based on the Classical Drude Model for Molecular Dynamics Simulations of Lipids. *J. Phys. Chem. B. 117:9142-9160*
He, X., Lopes, P.E.M., and A.D. MacKerell, Jr. (2013)
Polarizable Empirical Force Field for Acyclic Poly-Alcohols Based on the Classical Drude Oscillator. *Biopolymers, 99:724-738*
P.E.M. Lopes, J. Huang, J. Shim, Y. Luo, H. Li, B. Roux and A.D. MacKerell, Jr. (2013)
Polarizable Force Field for Peptides and Proteins based on the Classical Drude Oscillator. *J. Chem. Theory. Comput. 9:5430–5449*
D.S. Patel, X. He, and A.D. MacKerell, Jr. (2014)
Polarizable Empirical Force Field for Hexopyranose Monosaccharides based on the Classical Drude Oscillator. *J. Phys. Chem. B. Article ASAP*
A. Savelyev and A.D. MacKerell, Jr. (2014)
All-Atom Polarizable Force Field for DNA Based on the Classical Drude Oscillator Model. *J Comput Chem. 35(16):1219-39*

MD Simulations

- **Other Concepts: MD engines & particle shapes**
  - **Discrete MD (DMD)** N. Dokholyan, S. Buldyrev, E. Stanley, E. Shakhnovich, Folding & Design, 1998
    - Uses discrete PE function
    - Trajectory – sequence of atomic collisions
    - Forces are not computed (faster than Newtonian MD)
    - Atoms are moved with constant velocities (rather than with constant accel.)
    - This regime is also referred as “ballistic” mechanics
    - Solvation: implicit
  - **CG models with anisotropic shapes of functional groups**
    - Non-isotropic PE functional forms
    - More accurate geomentry
    - Slower (than analogous CG models)

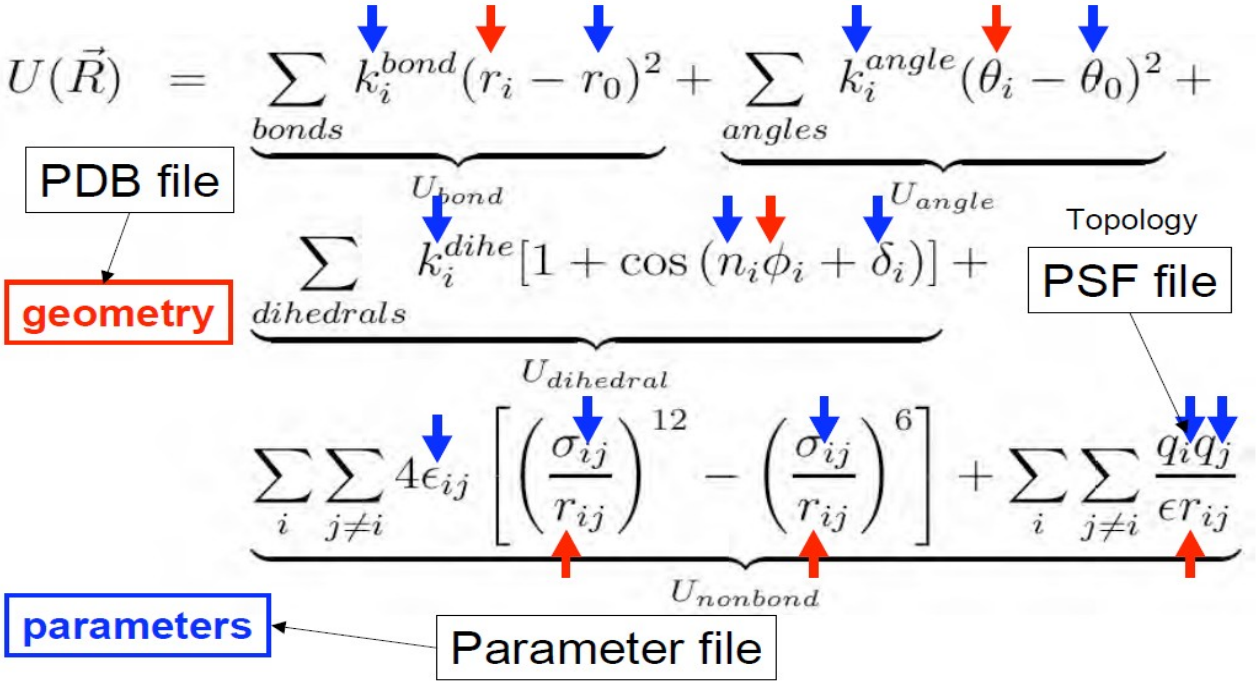
Plotkin et al, J Chem Phys 2010, 132: 035105–035122
Potoyan, Savelyev, Papoian, WIREs Comput. Mol. Sci., 2012



Schematic representation of three nucleotides, with **ellipsoidal beads** corresponding to bases and the beads labeled as S and P to sugars and phosphate groups, respectively.

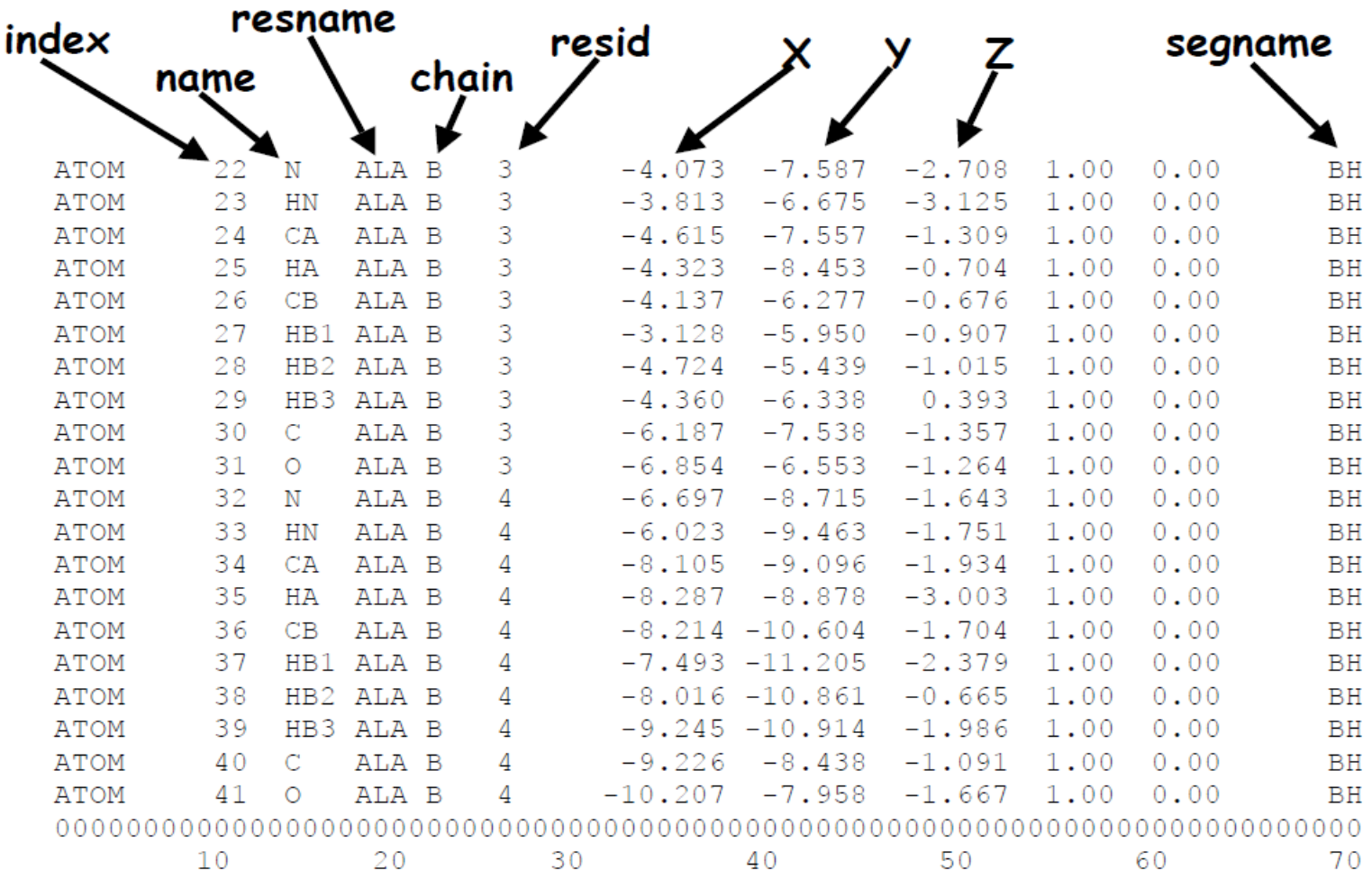
MD Simulations

- **Minimum Input for MD simulations:**
  - PDB file (structure)
  - Topology file (connection information)
  - Parameter file (force field)
  - PSF file (protein structure file)



MD Simulations

- **Minimum Input for MD simulations:**
  - PDB file (structure)



>>> It is an ascii, fixed-format file <<<

"No connectivity information"

MD Simulations

- **Minimum Input for MD simulations:**
  - Topology file (connectivity, residue structure, partial charges)

From top_all22_model.inp

```
RESI PHEN        0.00   ! phenol, adm jr.
GROUP
ATOM CG   CA    -0.115  !
ATOM HG   HP     0.115  !          HD1   HE1
GROUP                   !           |     |
ATOM CD1  CA    -0.115  !          CD1--CE1
ATOM HD1  HP     0.115  !          //     \\
GROUP                   !     HG--CG       CZ--OH
ATOM CD2  CA    -0.115  !          \       /     \
ATOM HD2  HP     0.115  !          CD2==CE2     HH
GROUP                   !           |     |
ATOM CE1  CA    -0.115  !          HD2   HE2
ATOM HE1  HP     0.115
GROUP
ATOM CE2  CA    -0.115
ATOM HE2  HP     0.115
GROUP
ATOM CZ   CA     0.110
ATOM OH   OH1   -0.540
ATOM HH   H      0.430
BOND CD2 CG CE1 CD1 CZ CE2 CG HG CD1 HD1
BOND CD2 HD2 CE1 HE1 CE2 HE2 CZ OH OH HH
DOUBLE CD1 CG CE2 CD2  CZ CE1
```

Atom types

Partial charges

connectivity

MD Simulations

- **Minimum Input for MD simulations:**
  - Topology file (masses)

Masses are specified for atom types

```
……..
MASS   31 H     1.00800 ! polar H
MASS   32 HC    1.00800 ! N-ter H
MASS   33 HA    1.00800 ! nonpolar H
MASS   34 HP    1.00800 ! aromatic H
MASS   35 HB1   1.00800 ! backbone H
MASS   36 HB2   1.00800 ! aliphatic backbone H, to CT2
MASS   37 HR1   1.00800 ! his he1, (+) his HG,HD2
MASS   38 HR2   1.00800 ! (+) his HE1
MASS   39 HR3   1.00800 ! neutral his HG, HD2
MASS   40 HS    1.00800 ! thiol hydrogen
MASS   41 HE1   1.00800 ! for alkene; RHC=CR
MASS   42 HE2   1.00800 ! for alkene; H2C=CR
MASS   43 HA1   1.00800 ! alkane, CH, new LJ params (see toppar_all22_prot_aliphatic_c27.str)
MASS   44 HA2   1.00800 ! alkane, CH2, new LJ params (see toppar_all22_prot_aliphatic_c27.str)
MASS   45 HA3   1.00800 ! alkane, CH3, new LJ params (see toppar_all22_prot_aliphatic_c27.str)
MASS   46 C    12.01100 ! carbonyl C, peptide backbone
MASS   47 CA   12.01100 ! aromatic C
MASS   48 CT   12.01100 ! aliphatic sp3 C, new LJ params, no hydrogens
MASS   49 CT1  12.01100 ! aliphatic sp3 C for CH
MASS   50 CT2  12.01100 ! aliphatic sp3 C for CH2
MASS   51 CT2A 12.01100 ! from CT2 (asp, glu, hsp chi1/chi2 fitting)
MASS   52 CT3  12.01100 ! aliphatic sp3 C for CH3
MASS   53 CPH1 12.01100 ! his CG and CD2 carbons
MASS   54 CPH2 12.01100 ! his CE1 carbon
MASS   55 CPT  12.01100 ! trp C between rings
MASS   56 CY   12.01100 ! TRP C in pyrrole ring
MASS   57 CP1  12.01100 ! tetrahedral C (proline CA)
MASS   58 CP2  12.01100 ! tetrahedral C (proline CB/CG)
MASS   59 CP3  12.01100 ! tetrahedral C (proline CD)
MASS   60 CC   12.01100 ! carbonyl C, asn,asp,gln,glu,cter,ct2
MASS   61 CD   12.01100 ! carbonyl C, pres aspp,glup,ct1
MASS   62 CS   12.01100 ! thiolate carbon
MASS   63 CE1  12.01100 ! for alkene; RHC=CR
MASS   64 CE2  12.01100 ! for alkene; H2C=CR
MASS   65 CAI  12.01100 ! aromatic C next to CPT in trp
MASS   66 N    14.00700 ! proline N
MASS   67 NR1  14.00700 ! neutral his protonated ring nitrogen
……
```

MD Simulations

- **Minimum Input for MD simulations:**
  - Parameter file (molecular FF)

```
BONDS
!
!V(bond) = Kb(b - b0)**2
!
!Kb: kcal/mole/A**2
!b0: A
!
!atom type Kb          b0
!
NH2  CT1   240.000     1.4550 ! From LSN NH2-CT2
!
!Indole/Tryptophan
CA   CAI   305.000     1.3750 ! from CA CA
CAI  CAI   305.000     1.3750 ! atm, methylindole, fit CCDSS
CPT  CA    300.000     1.3600 ! atm, methylindole, fit CCDSS
CPT  CAI   300.000     1.3600 ! atm, methylindole, fit CCDSS
CPT  CPT   360.000     1.3850 ! atm, methylindole, fit CCDSS
CY   CA    350.000     1.3650 ! trj, adm jr., 5/08/91, indole CCDB structure search
CY   CAI   350.000     1.3650 ! from CY CA
CY   CPT   350.000     1.4300 ! atm, methylindole, fit CDS data
CY   CT3   375.000     1.4920 ! atm, methylindole, fit CDS data
CY   CT2   375.000     1.4920 ! atm, methylindole, fit CDS data
HP   CAI   340.000     1.0800 ! from HP CA
HP   CY    350.000     1.0800 ! trp, adm jr., 12/30/91
NY   CA    270.000     1.3700 ! trp, adm jr., 12/30/91
NY   CPT   270.000     1.3700 ! atm, methylindole, from CCDS 1/17/04
NY   H     537.500     0.9760 ! atm, methylindole, 1/17/04
CA   CA    305.000     1.3750 ! ALLOW   ARO
            ! benzene, JES 8/25/89
CE1  CE1   440.000     1.3400   !
```

```
ANGLES
!
!V(angle) = Ktheta(Theta - Theta0)**2
!
!V(Urey-Bradley) = Kub(S - S0)**2
!
!Ktheta: kcal/mole/rad**2
!Theta0: degrees
!Kub: kcal/mole/A**2 (Urey-Bradley)
!S0: A
!
!atom types     Ktheta    Theta0   Kub     S0
!
H    NH2  CT1   50.000    111.00           ! From LSN HC-NH2-CT2
H    NH2  CT2   50.000    111.00           ! From LSN HC-NH2-CT2, Neutral Gly Nterminus
NH2  CT1  CT1   67.700    110.00           ! From LSN NH2-CT2-CT2
NH2  CT1  CT2   67.700    110.00           ! From LSN NH2-CT2-CT2
NH2  CT1  CT3   67.700    110.00           ! From LSN NH2-CT2-CT2
CT1  CD   OH1   55.000    110.50           ! From ASPP CT2-CD-OH1
CT3  CT1  CD    52.000    108.00           ! Ala cter
NH2  CT1  HB1   38.000    109.50   50.00   2.1400 ! From LSN NH2-CT2-HA
NH2  CT1  C     50.000    107.00           ! From ALA Dipep. NH1-CT2-C
NH2  CT2  C     50.000    107.00           ! From ALA Dipep. NH1-CT2-C, Neutral Gly Nterminus
```

MD Simulations

- **Minimum Input for MD simulations:**
  - PSF (protein structure file)

    Generated based on topology & parameter force field files for specific system of interest:
    - Example: d(CCGGTTAACCG) DNA oligomer in 150mM NaCl and explicit solvent (water)
      - topology information is pulled out for cytosine, guanine, adenine, thymine, Na+, Cl-, water (e.g. TIP3 model)
      - All type of (cross-) interactions are pulled out from parameter file (all DNA bonded interaction terms, non-bonded for DNA-Na+, DNA-Cl-, DNA-water, Na-Na, Na-Cl, Cl-Cl, Na-water,….)

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http://www.charmm-gui.org/

- CHARMM-GUI provides a web-based graphical user interface to generate various molecular simulation systems and input files to facilitate and standardize the usage of common and advanced simulation techniques. Currently, CHARMM-GUI supports CHARMM, NAMD, GROMACS, AMBER, GENESIS, LAMMPS, Desmond, OpenMM, and CHARMM/OpenMM simulation programs mostly based on the CHARMM force fields.

MD Simulation softwares: All-atom models

Package name	supported force fields
• CHARMM www.charmm.org	CHARMM (E / I; AA / UA), Amber
• Amber amber.scripps.edu	Amber (E / I ; AA)
• GROMOS www.igc.ethz.ch/GROMOS	Gromos (E / vacuum ; UA)
• Gromacs www.gromacs.org	Amber, Gromos, OPLS - (all E)
• NAMD www.ks.uiuc.edu/Research/namd	CHARMM, Amber, Gromos, ...

+ Drude polarizable FF (from ~2005)

E = explicit solvent	AA = all atom
I = implicit solvent	UA = united atom (apolar H omitted)

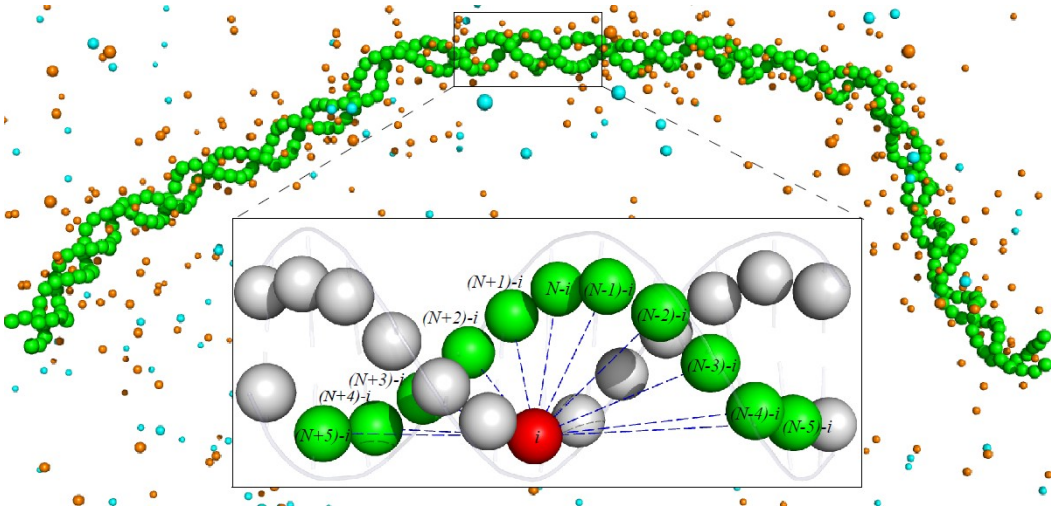
MD Simulation softwares: multi-scale models

- **LAMMPS** https://lammps.sandia.gov/

LAMMPS is a classical molecular dynamics code with a focus on materials modeling. It's an acronym for Large-scale Atomic/Molecular Massively Parallel Simulator.

LAMMPS has potentials (force-fields) for:

- solid-state materials (metals, semiconductors)
- soft matter (biomolecules, polymers)
- It can be used to model atoms or, more generically, as a parallel particle simulator at the atomic, meso-, or continuum scale.



- All non-standard CG interaction potentials can be integrated into LAMMPS (open source)

$$\mathscr{H} = \sum_{i>j}\left[\frac{A}{r_{ij}^{12}} + \sum_{k=1}^{5} B^{(k)} \mathrm{e}^{-C^{(k)}\left[r_{ij}-R^{(k)}\right]^2} + \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon r_{ij}}\right]$$

MD Visualization softwares

https://en.wikipedia.org/wiki/List_of_molecular_graphics_systems

- Standalone
  - Chimera
  - BALLView
  - **PyMol**
  - RasMol
  - **VMD**
- Web-bases
  - JSMol

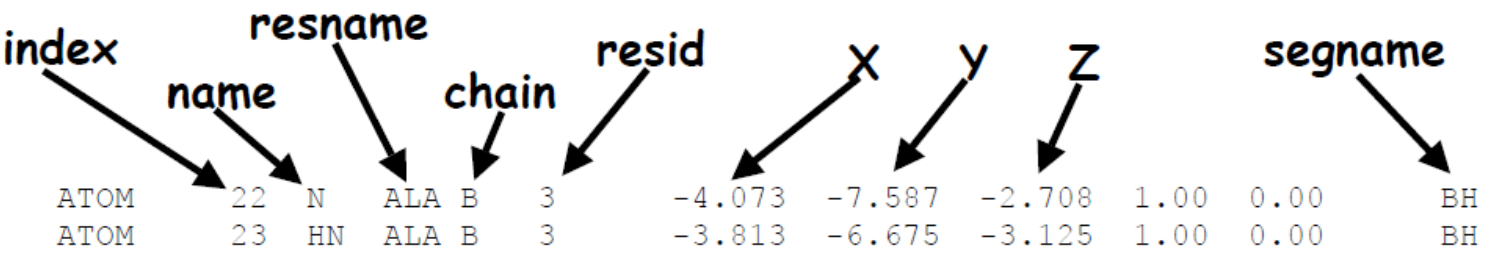
Provide visualization of 3D static and dynamic structures, simulation trajectories, various molecule representations, surface and charge density plots etc.

PyMol: According to the author, almost 1/4 of all published images of 3D protein structures in the scientific literature were made via PyMOL. Has console capabilities.

VMD: Besides visualization (including making movies!), it's also designed for modeling and basic analysis of MD simulation trajectories. Can be used to prepare PSF files (as alternative to CHARMM-GUI or other platforms).. Has its own console language..

MD Visualization softwares

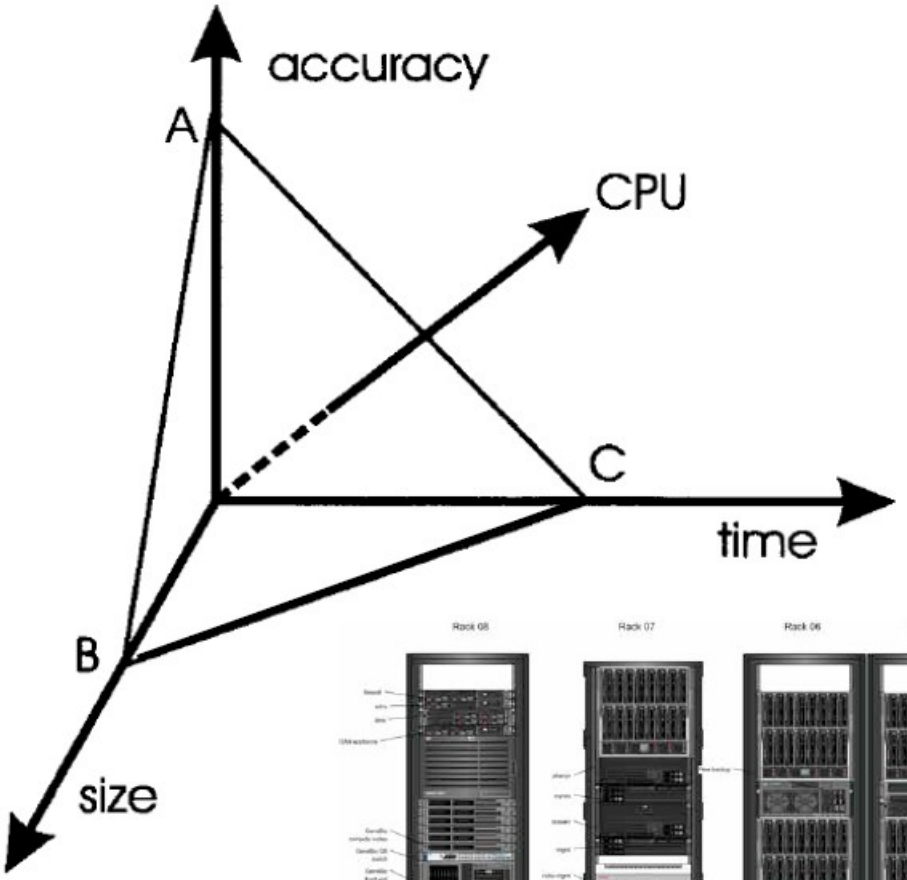
- **VMD selection commands**

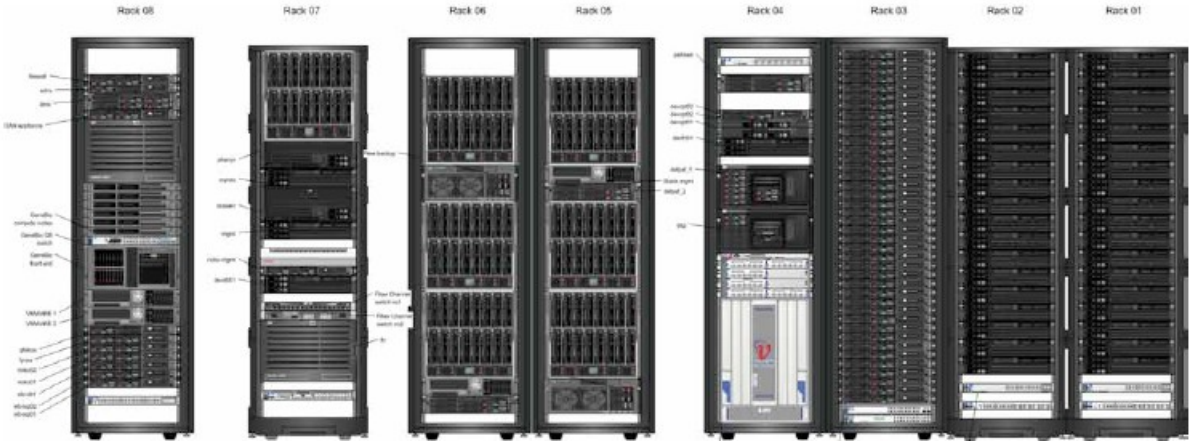



```
(name CA CB) and (resid 1 to 4) and (segname BH)

protein and resname LYS ARG GLU ASP

water and within 5 of (protein and resid 62 and name CA)

water and within 3 of (protein and name O and z < 10)
```

MD simulations of different resolution systems

- **Trade-off between accuracy, size and simulation time**





MD Simulations: Historical Perspective

- **Theoretical Milestones**

Newton (1643-1727):	Classical equations of motion: $F(t)=m\,a(t)$
Euler-Lagrange (1750s):	Euler-Lagrange formulation of mechanics
Boltzmann(1844-1906):	Foundations of statistical mechanics
Schrödinger (1887-1961):	Quantum mechanical eq. of motion: $-ih\,\partial t\,\Psi(t)=H(t)\,\Psi(t)$

- **MD/MM Milestones**

Alder (1957):	First Molecular Dynamics (MD) simulation of a liquid (hard spheres)
Rahman (1964):	First MD simulation with Lennard-Jones potential (first realistic potential for liquid Argon)
Stillinger & Rahman(1974):	MD simulation of liquid water
Karplus (1977) & McCammon (1977)	First MD simulation of proteins (bovine pancreatic trypsin inhibitor)
Karplus (1983):	The CHARMM general purpose FF & MD program
Kollman(1984):	The AMBER general purpose FF & MD program

References

- Alder, B. J. and Wainwright, T. E. J. Chem. Phys. 27, 1208 (1957)
- Alder, B. J. and Wainwright, T. E. J. Chem. Phys. 31, 459 (1959)
- Rahman, A. Phys. Rev. A136, 405 (1964)
- Stillinger, F. H. and Rahman, A. J. Chem. Phys. 60, 1545 (1974)
- McCammon, J. A., Gelin, B. R., and Karplus, M. Nature (Lond.) 267, 585 (1977)