Modeling the interaction of metal ions with proteins and nucleic acids

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March 2, 2018

Metal ions in biology

30%
of all proteins
are metal-binding proteins

40%
of enzymatic reactions
involve metals

Na^+ K^+

Mg^{2+} Ca^{2+} Mn^{2+}

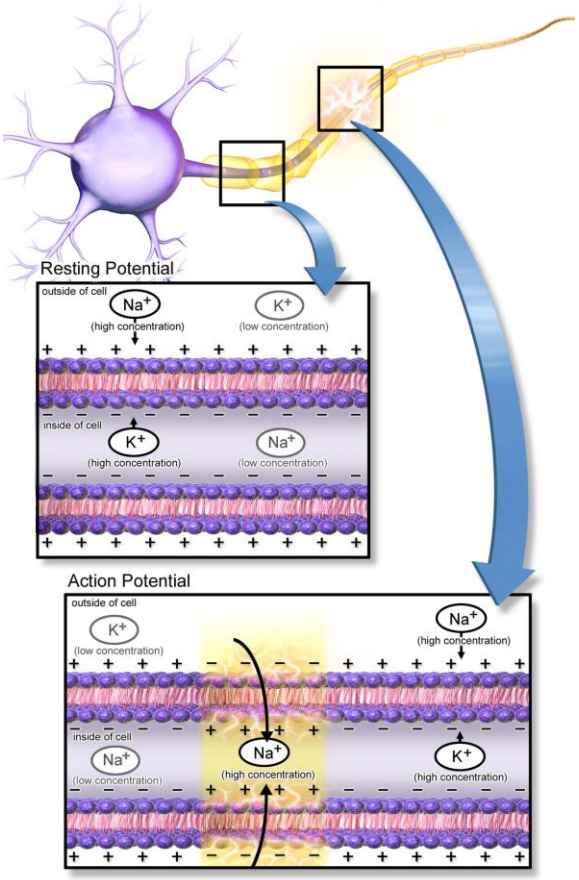
Fe^{2+} Zn^{2+}

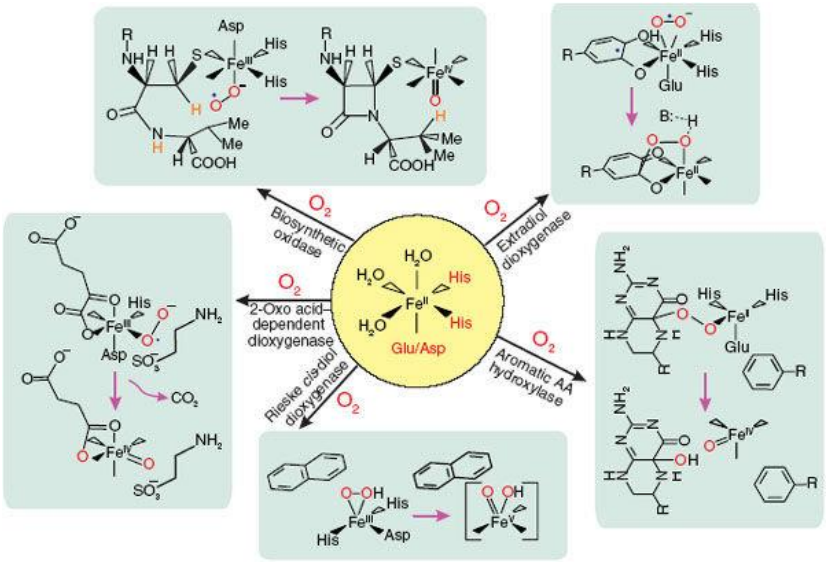
13%
of approved drugs
target ion channels

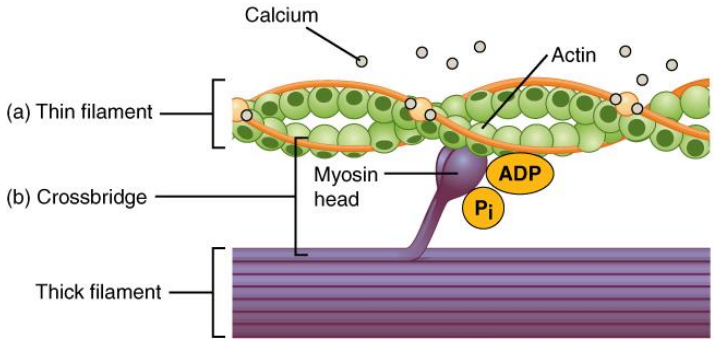
13%
of disease-associated
single nucleotide polymorphism
are related to metal binding sites

E. Monosson. Evolution in a Toxic World
PNAS **2016,** *113* (20), 5472-5474
Human Mutation 2011, 32 (11), 1309-1318.

Metal ions in biology



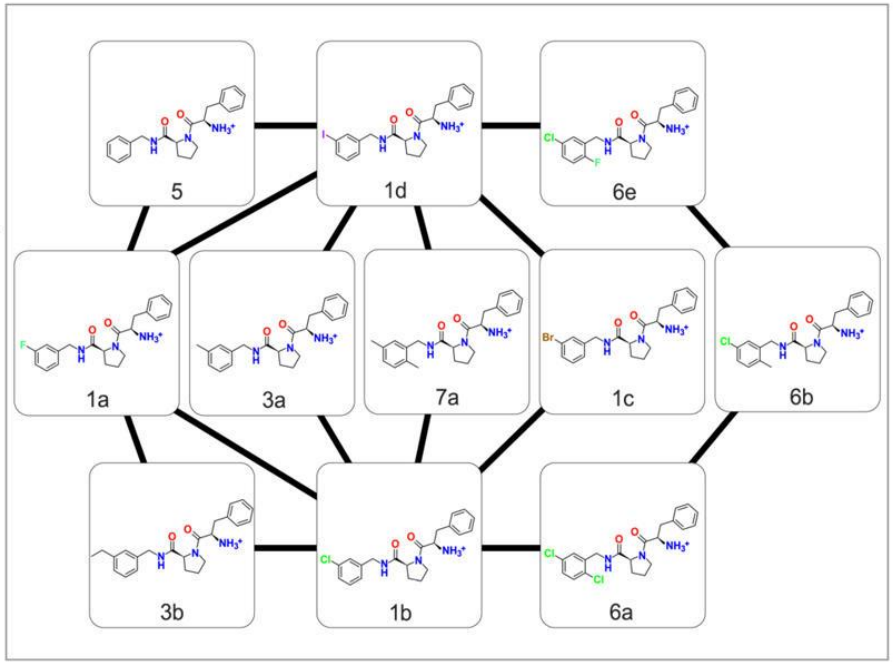


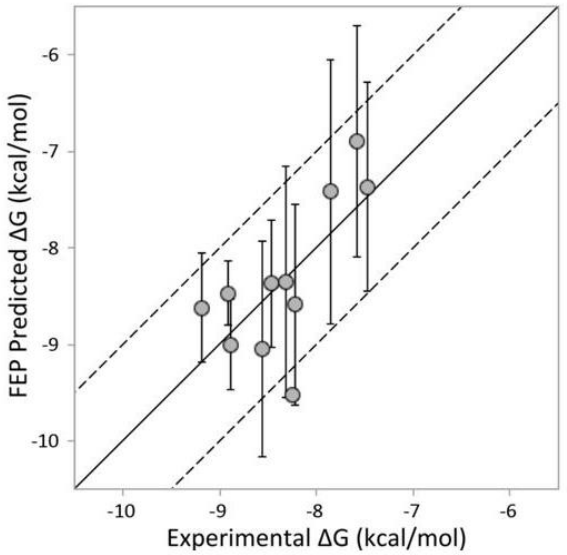


Nature Chemical Biology **4**, 186–193 (2008)
QBI research

Molecular modeling

- Molecular modeling has been valuable for understanding the microscopic mechanisms of biological processes and accelerating drug discovery

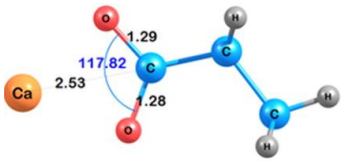


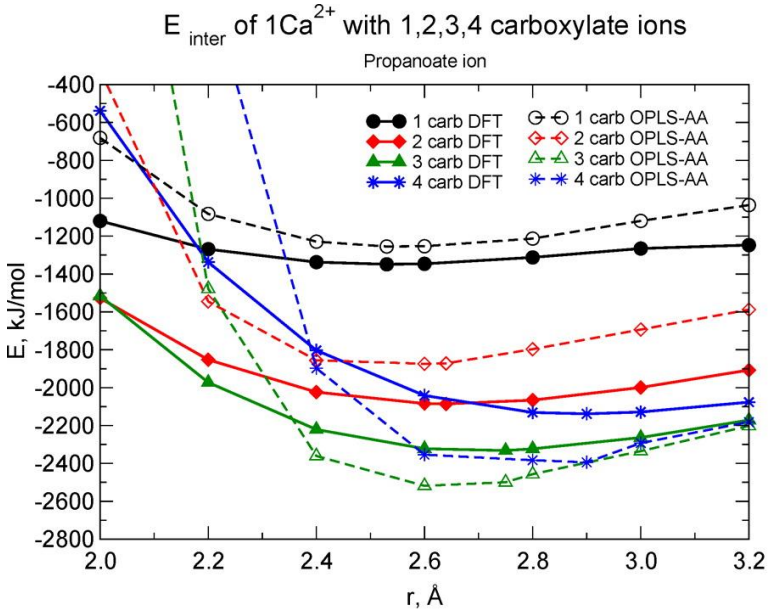


Prediction of thrombin-ligand binding affinity using FEP

Molecular modeling

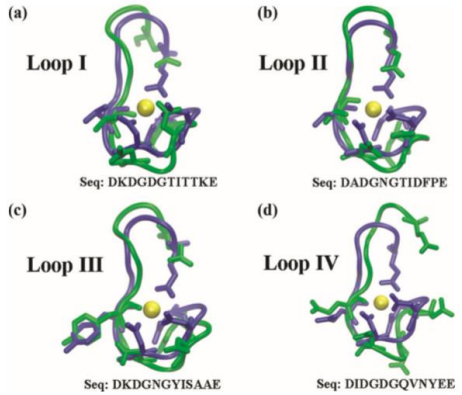
- Molecular modeling suffers from poor accuracy for metal ions

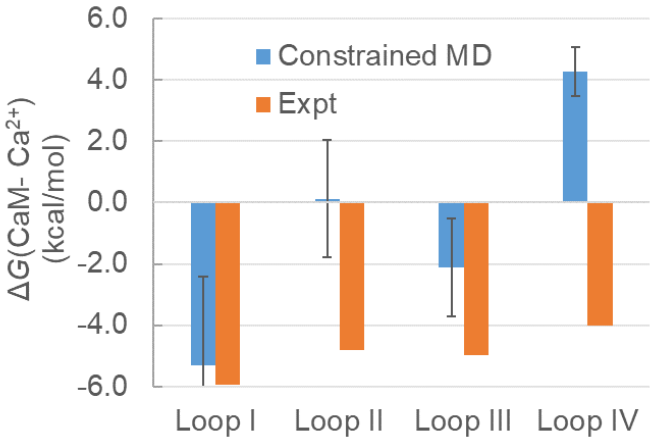




Gas-phase interaction energy

Error ~ 100-200 kJ/mol





Binding free energy

Error ~ 5 kcal/mol

J. Phys. Chem. A, **2015**, *119* (40), pp 10195–10203

Phys. Rev. E 87, 062705 (2013)

Specific Aim 1

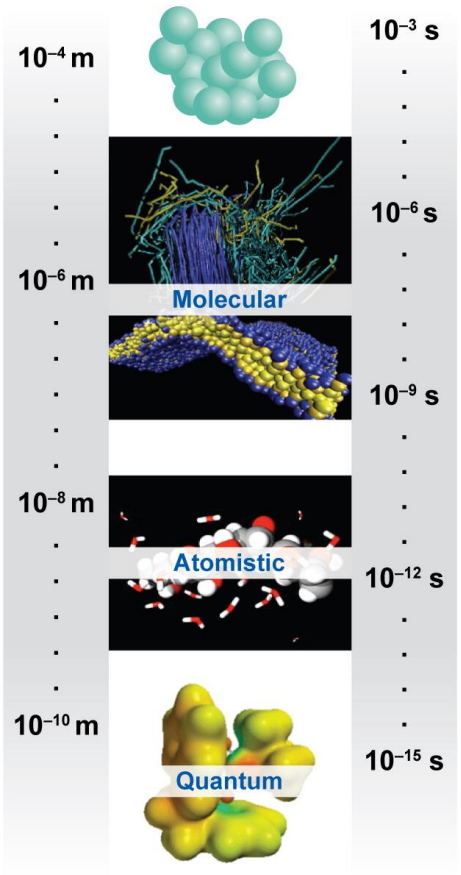
Refine the AMOEBA polarizable force field for divalent metal ions and develop efficient algorithms for free energy calculations

Challenges for molecular modeling

- Accuracy vs. efficiency

Classical fixed-charge force field
Inaccurate for metal ions

Quantum mechanics
Too expensive for conformational sampling



MACRO
Finite-element calculations
Continuum hydrodynamics
Dissipative particle dynamics
MD-MC-Lattice Boltzmann

MESO
MC statics/dynamics
MD, NEMD

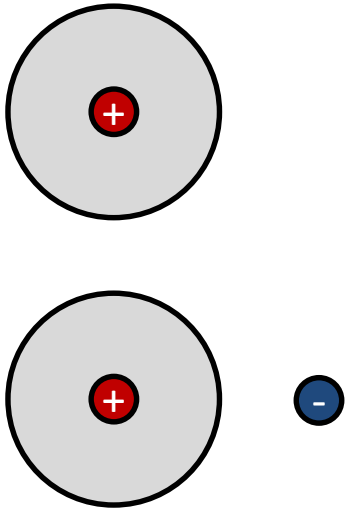
MICRO
Classical force field MD, MC
Embedded atomistic-quantum methods
Car-Parrinello MD
Quantum MC
Quantum chemical methods

Annu. Rev. Phys. Chem. **59**, 545-571 (2008)

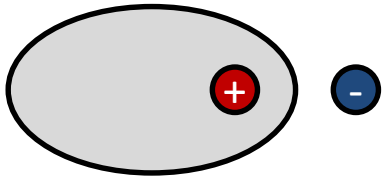
Polarizable force field

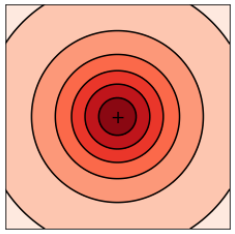
- Classical fixed-point-charge force field does not explicitly account for polarization and atomic multipole

Fixed charge

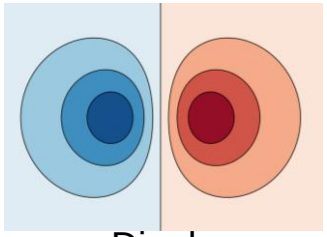


Polarization

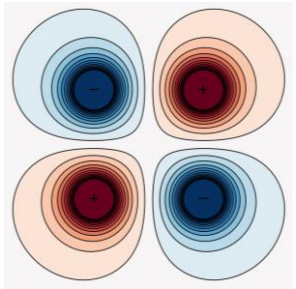




Point charge



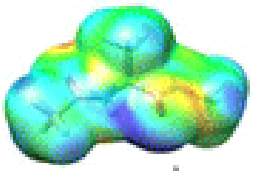
Dipole



Quadrupole



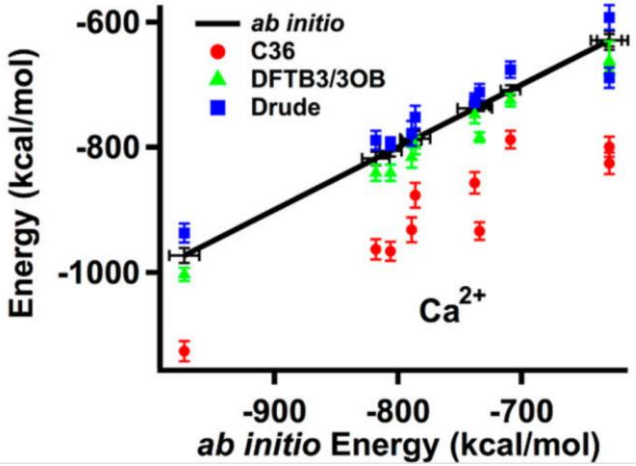
Atomic charges



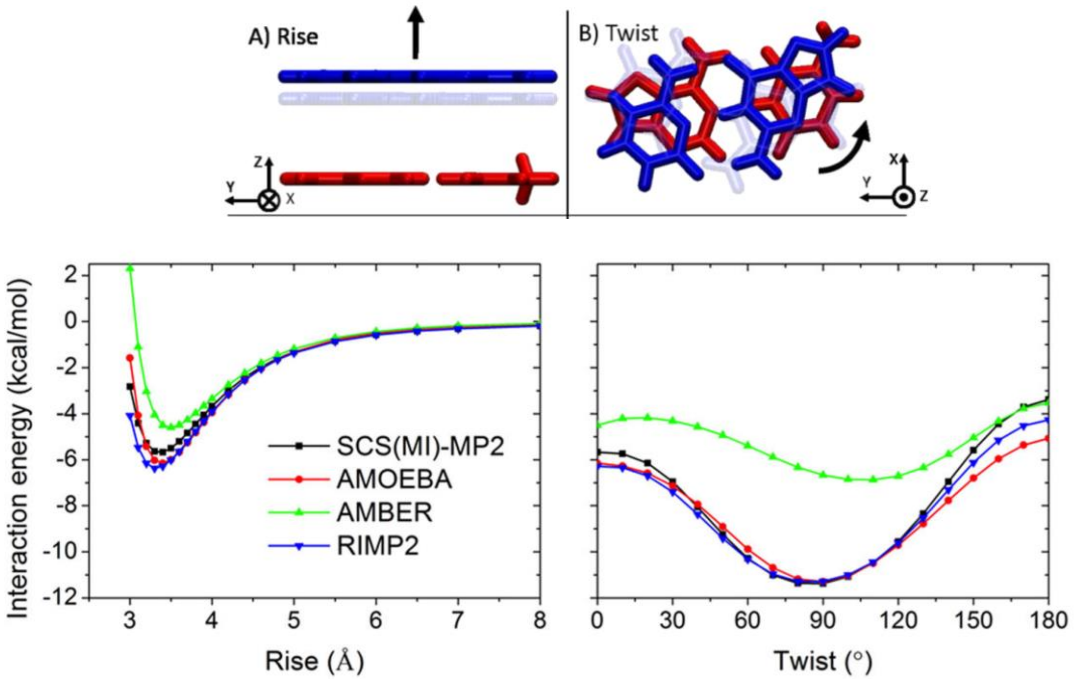
Atomic charges + multipoles

Polarizable force field

- Including polarization and atomic multipole significantly improves the accuracy of force field



Nonpolarizable (C36) vs. polarizable (Drude) force field for Ca^{2+} complexes

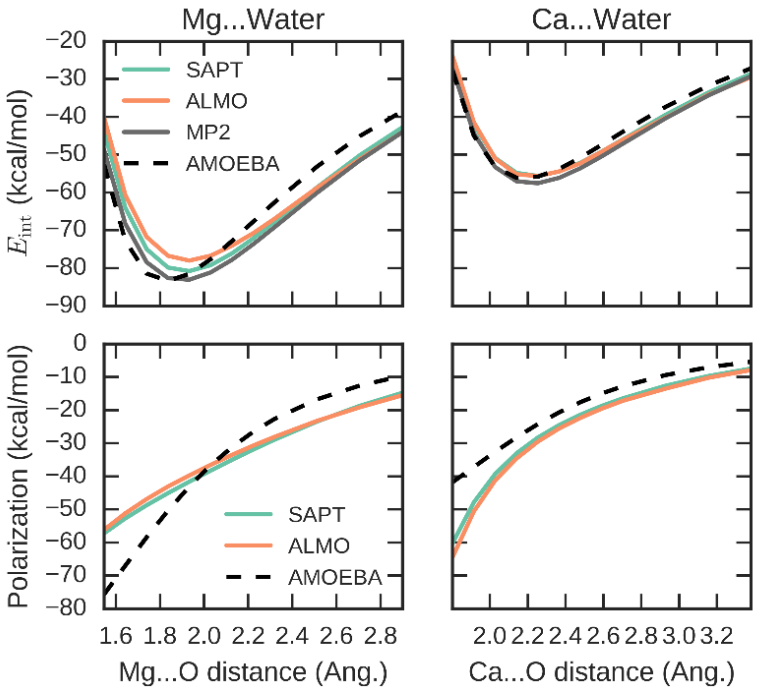


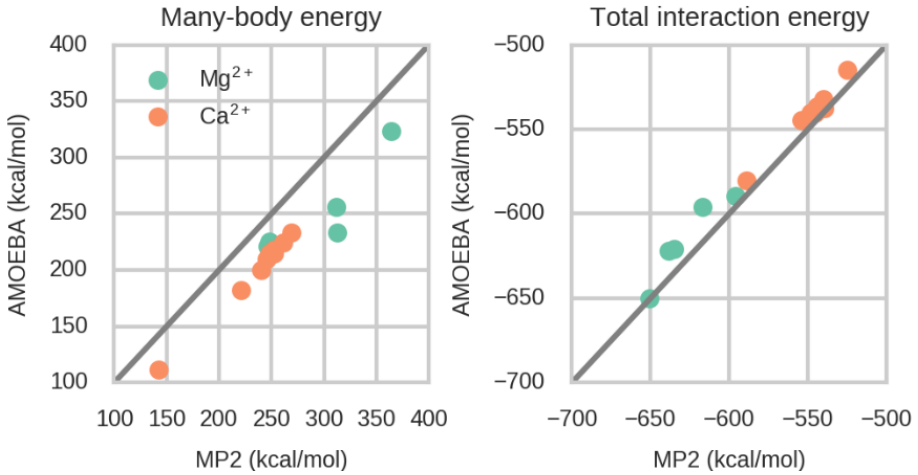
Nonpolarizable (AMBER) vs. polarizable atomic multipole (AMOEBA) force field for G-U base pair stacking

J. Chem. Theory Comput., **2015**, *11* (10), 4992–5001
J. Chem. Theory Comput. **2017**, 13, 666−678

Refined AMOEBA force field for Ca^{2+} and Mg^{2+}

- Energy components, total interaction energy and many-body energy in AMOEBA match QM results





Improve metal ion parameters for nucleic acid simulations

- Refine AMOEBA force field for metal ion-nucleic acid interactions based on QM calculations

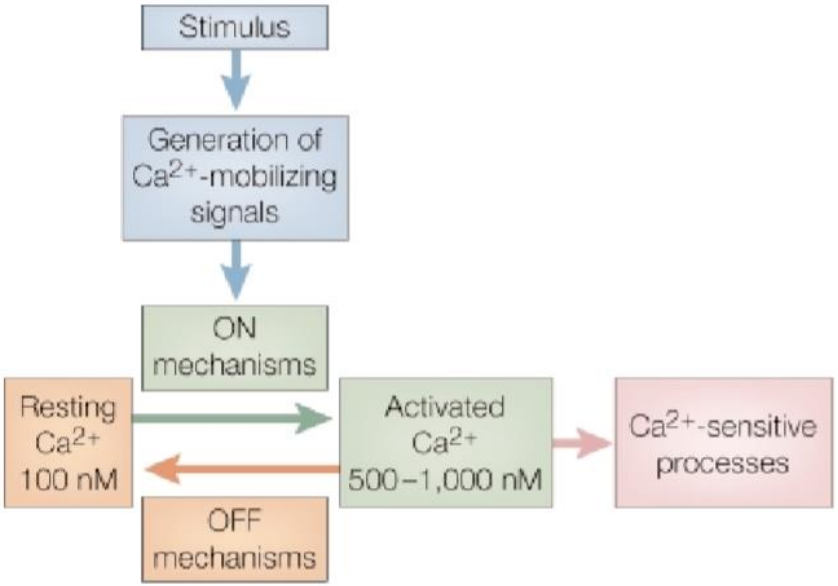
- Refine ion parameters at high concentration based on experimental osmotic pressure/activity coefficient

Specific Aim 2

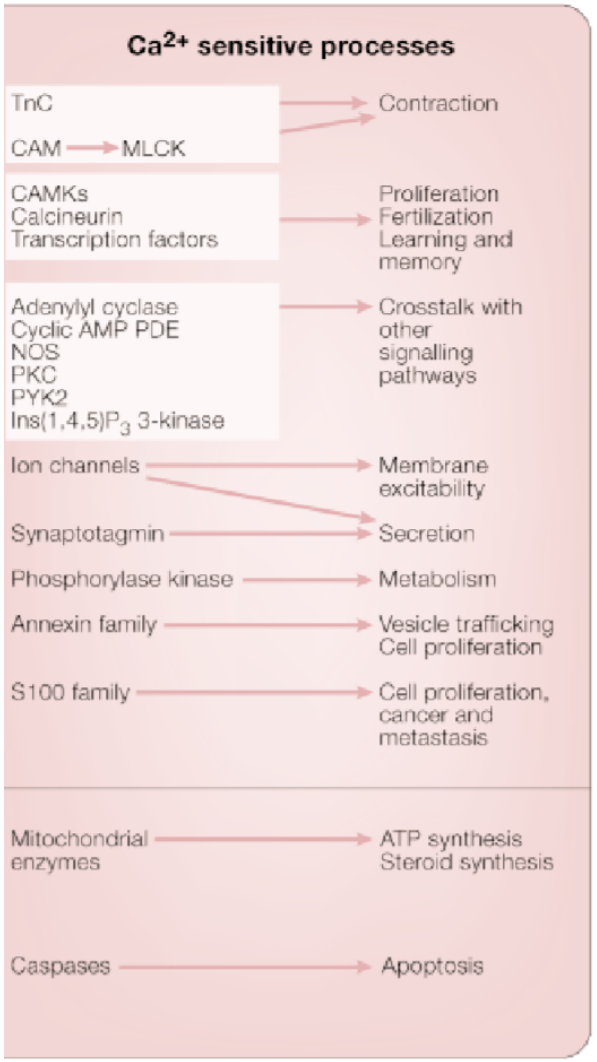
Understand the specificity for Ca^{2+} over Mg^{2+} in calcium-binding proteins

Role of calcium in cell signaling

- Calcium is a versatile messenger

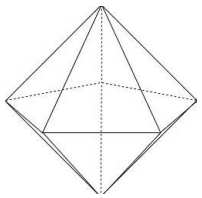


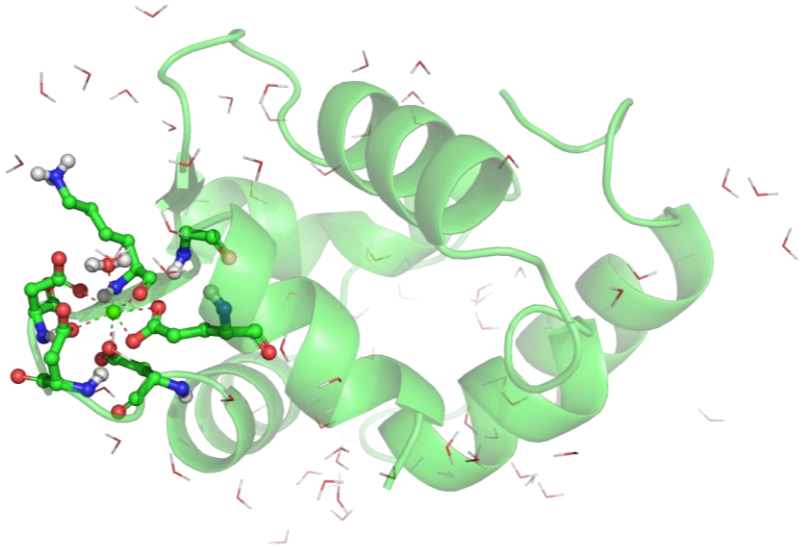
| The four units of the Ca^{2+} signalling network. Stimuli act by generating Ca^{2+}-mobilizing signals that act on various ON mechanisms to trigger an increase in the intracellular concentration of Ca^{2+}. The increased level of Ca^{2+} stimulates various Ca^{2+}-sensitive processes to trigger many different cellular pathways. The response is terminated by OFF mechanisms that restore Ca^{2+} to its resting level. Details



Ca/Mg selectivity

- Typical Ca-binding pockets (e.g. EF hand) are highly charged
  - Pentagonal bipyramid coordination
  - 3-4 Asp/Glu side chains
- Calcium-binding proteins have ~10^3 higher affinity for Ca^{2+} than Mg^{2+}



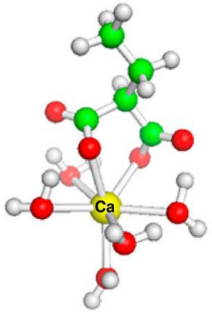


The high selectivity for Ca2+ is contrary to the intuition that Mg2+ is a better charge acceptor

Parvalbumin. PDB: 5CPV

Previous studies on Mg/Ca selectivity

- Solvation penalty
  - Mg has larger solvation penalty
- Geometry
  - The pentagonal bipyramid geometry in EF hand binding site is favorable for Ca
- Geometric constraint
  - For specific proteins (Gla)



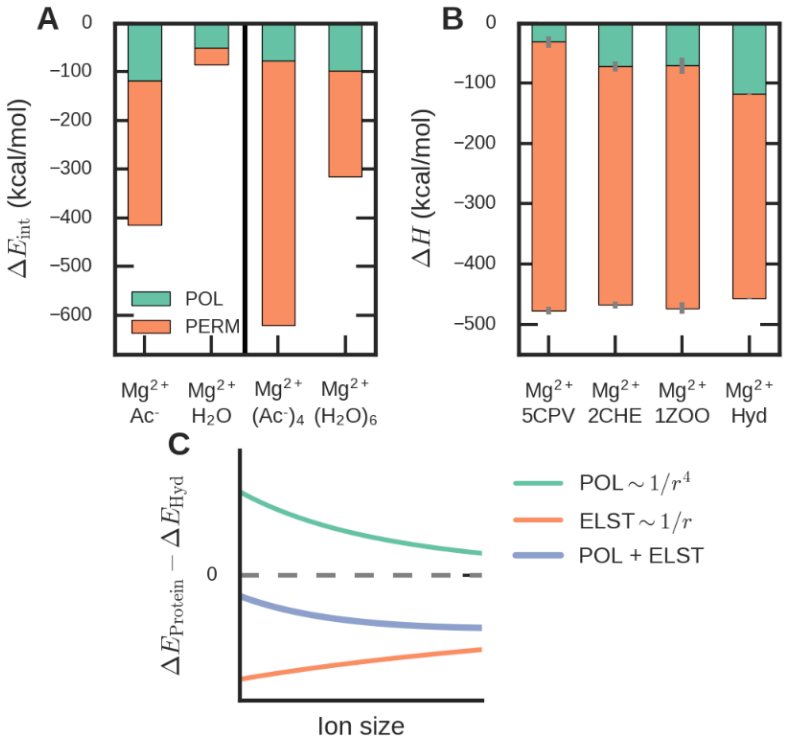
Gla-Ca binding

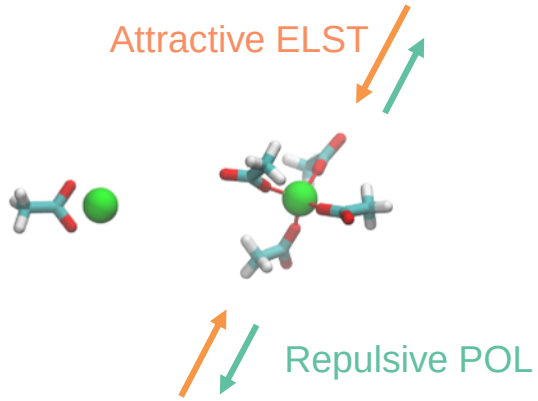
The general selectivity of many proteins for Ca is still unexplained

Biochemical Journal **2007**, 405 (2), 199-221.
Chem Rev **2014,** *114* (1), 538-56

Many-body effect in ion binding

- Favorable electrostatics interaction is largely compensated by less favorable many-body polarization
- Polarization is more sensitive to ion size
- The ion selectivity is determined by many-body polarization



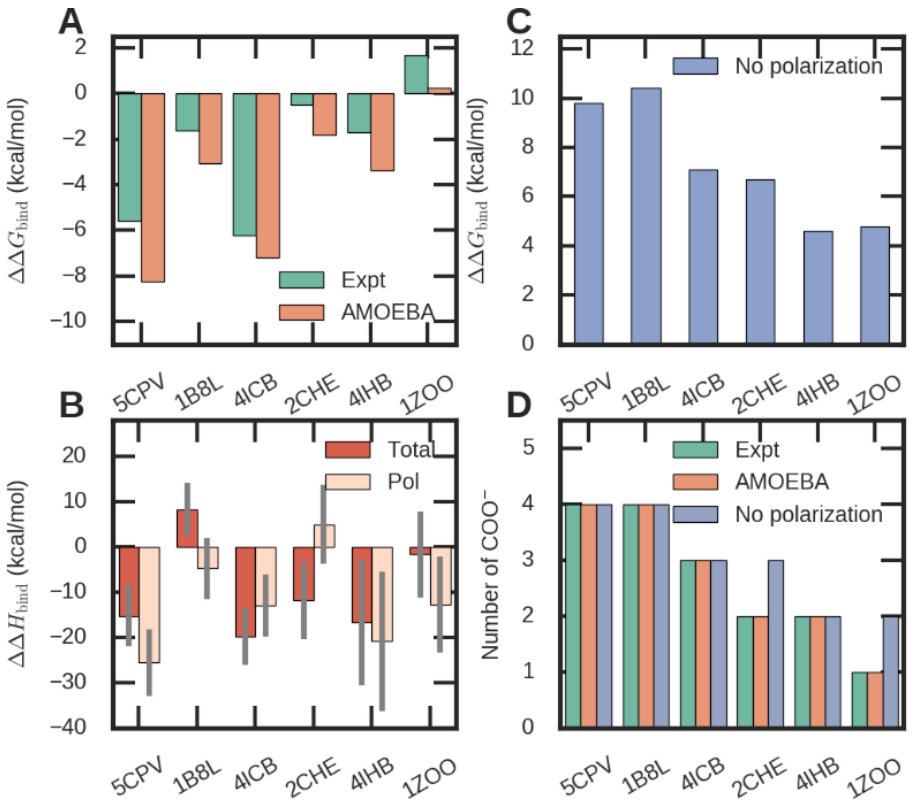


(A-B) Polarization (POL) and permanent energies/enthalpies (PERM) for clusters and protein-ion complexes.
(C) Distance dependence of POL and electrostatics (ELST) energy

Many-body effect in ion binding

- Free energy calculation using FEP/BAR
- AMOEBA polarizable force field reproduces the binding free energy between Mg/Ca and various proteins

PDB	Protein
5CPV	Carp parvalbumin
1B8L	D51A/E101D/F102W mutant of 5CPV
4ICB	Bovine calbindin D9k
2CHE	Response regulator protein CheY
4IHB	C2A domain from human dysferlin
1ZOO	I domain from the CD11a integrin



Molecular determinants of Mg/Ca selectivity

- Further study how mutations in the binding site affect the many-body polarization and metal ion selectivity

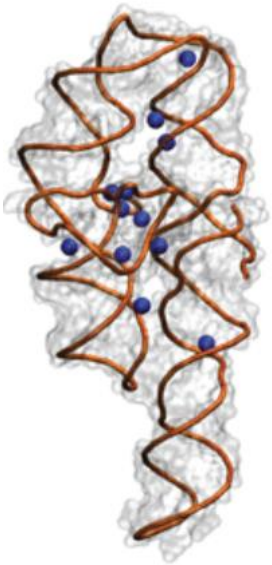
- Positive cooperativity of Ca^{2+} binding

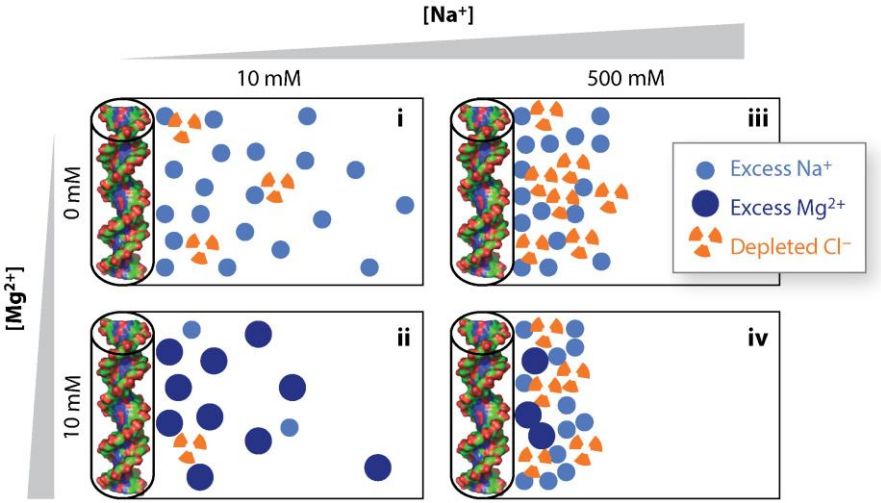
Specific Aim 3

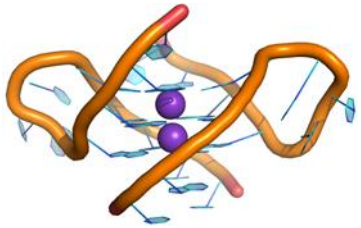
Investigate the ion distribution around DNA/RNA and the effect of ions on their structure and stability

Nucleic acids and metal ions

- Metal ions have profound impact on NA folding/condensation and NA-protein binding





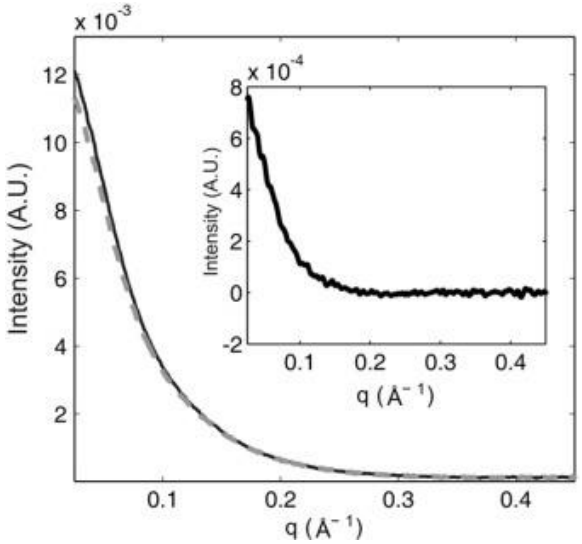


Metal ions both directly bind to NA and form an ion atmosphere

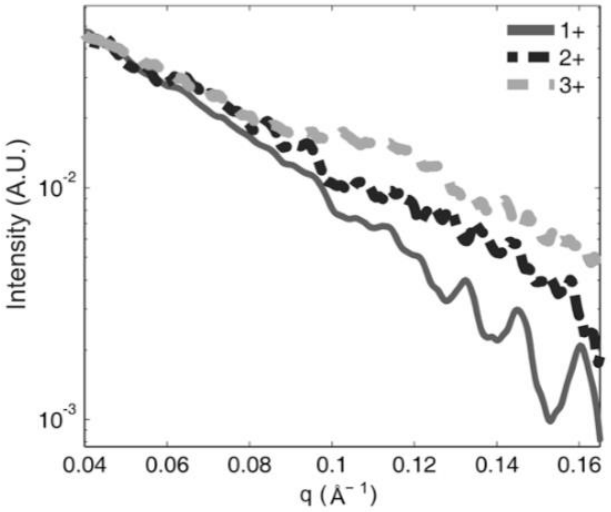
G-quadruplexes are stabilized by metal ion coordination

Ion distribution around DNA/RNA

- Experiments cannot resolve detailed structures of the ion atmosphere
- Ion distribution can be inferred from ASAXS



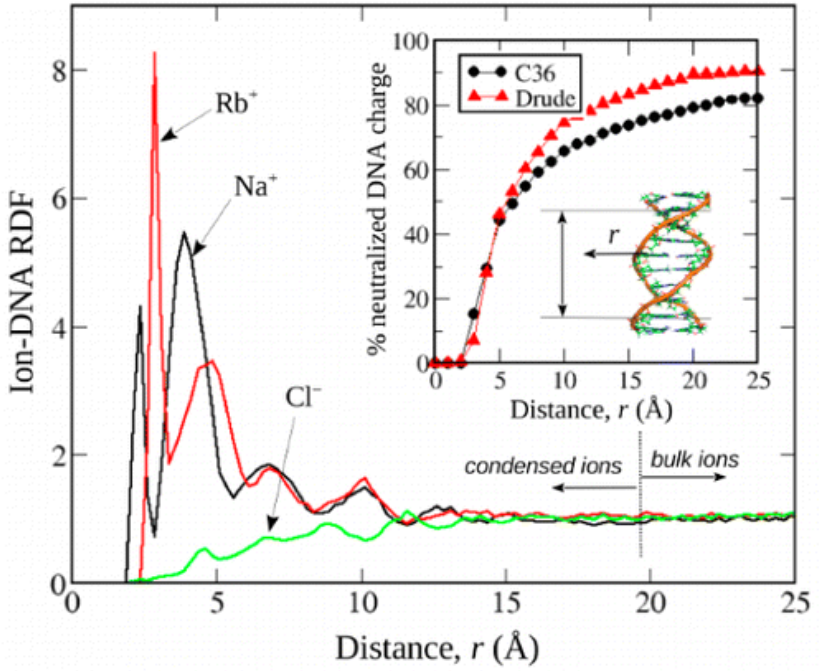
Anomalous small angle X-ray scattering



ASAXS profiles for mono-, di- and tri-valent ions

Ion distribution around DNA/RNA

- MD simulations can provide microscopic structure and thermodynamic information
- Polarization is important for ion distribution and DNA structures



Radial distribution of ions around DNA from MD simulations with nonpolarizable (C36) vs polarizable force field (Drude)

Drude force field represents electrostatics by point charges, which is inaccurate for base stacking

There is no study of divalent/trivalent ions or RNA by polarizable force field

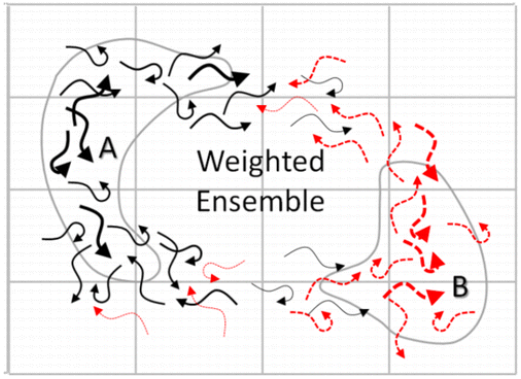
Ion distribution around DNA/RNA

- Simulate the ion distribution of mono-, di- and trivalent ions around DNA/RNA by AMOEBA force field
  - monovalent ions around DNA for validation
  - di- and trivalent ions around DNA/RNA
    - Polarization effect on NA-ion binding, ion correlation and water structure
    - Sequence-specific effect on ion distribution
    - Difference between DNA and RNA

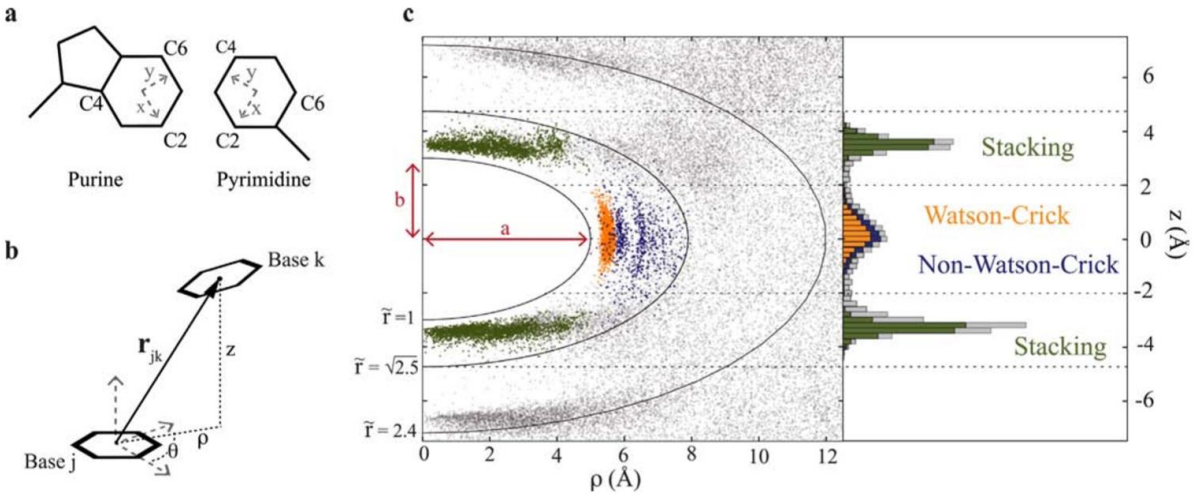
- Ion concentration and specific ion effect on DNA/RNA structure, conformation and stability
  - Persistence length of DNA/RNA
  - Stability of B-DNA
  - Stability of Z-DNA and specific ion effect

Conformational sampling of NA

- Weighed ensemble/Markov state model
  - Statistically optimal distribution of simulation trajectories



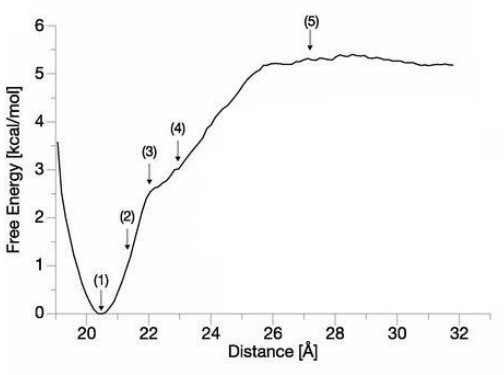
- eRMSD-based reaction coordinate
  - A set of essential coordinates for characterizing NA conformations

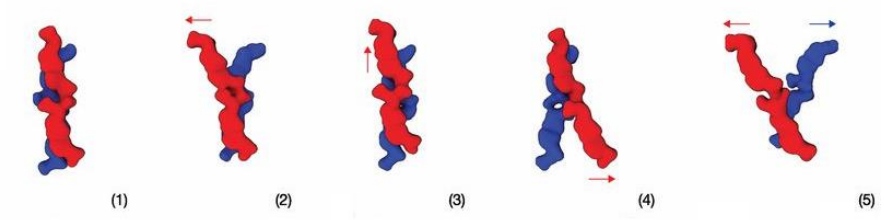


Nucleic Acids Research, 2014, Vol. 42, No. 21
J. Chem. Theory Comput., **2014**, *10* (7), pp 2658–2667

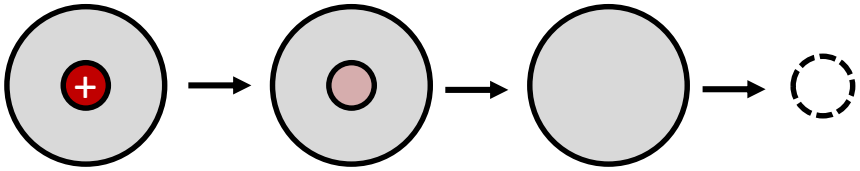
Methods for studying NA stability

- Pulling simulation

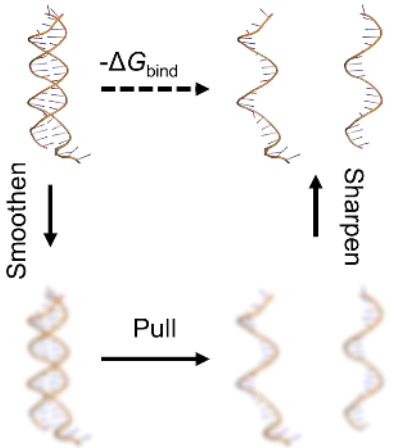




- Alchemical transition pathway



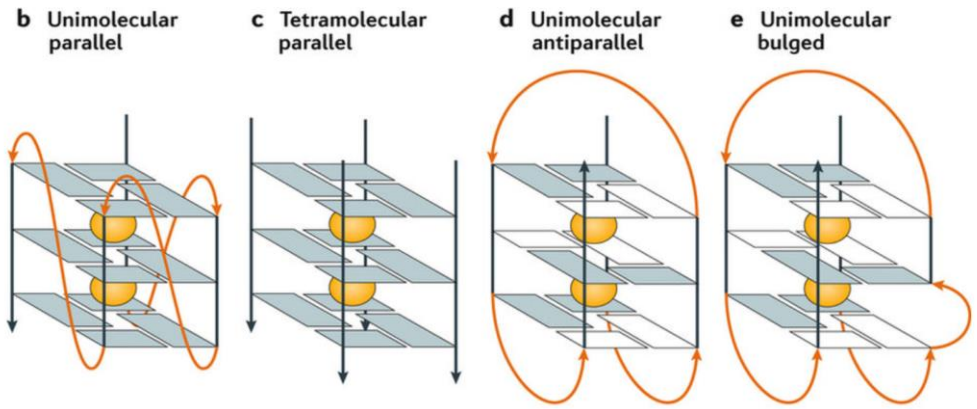
- Hybrid approach: Smoothening and pulling



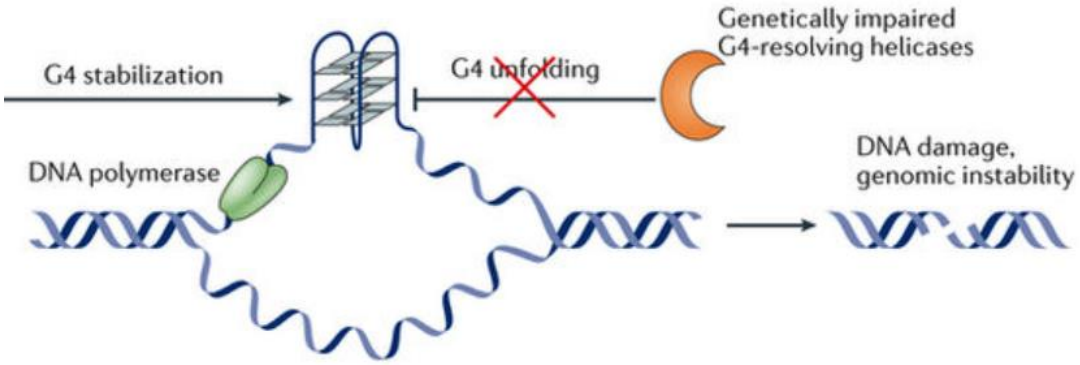
- Characterizing stability by fluctuations of order parameters

Science, **2016**: Vol. 353, Issue 6304, aaf5508
J. Chem. Theory Comput., **2016**, *12* (6), pp 2489–2492

G-quadruplex



- G-quadruplexes have functions in the regulation of transcription and genome stability
- Therapeutic potential for treatment of cancer

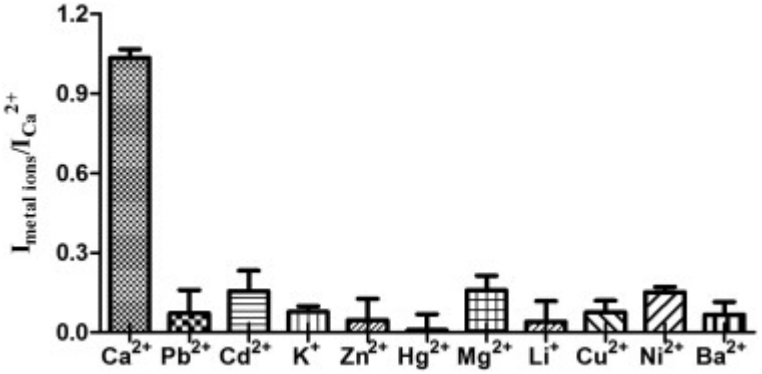


Nature Reviews Molecular Cell Biology **18**, 279–284 (2017)

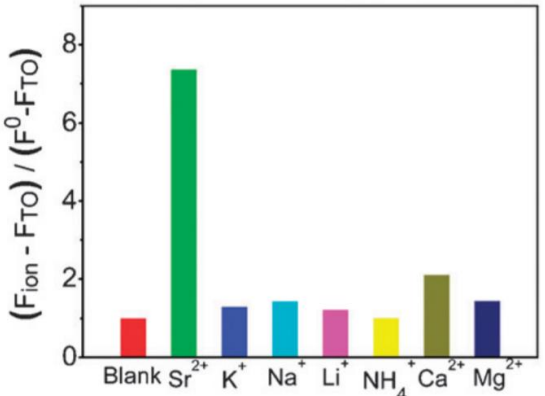
Ion specificity of G-quadruplex

- G-quadruplexes have high specificity for different ions depending on the structure and sequence

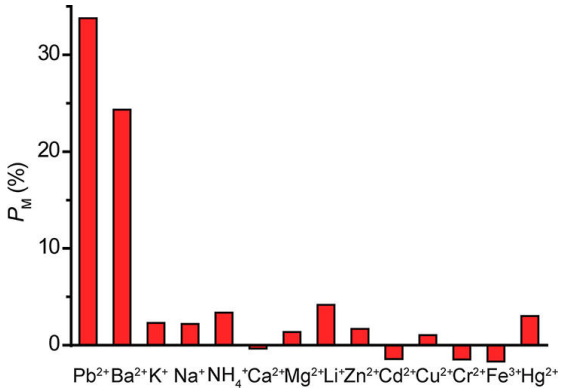
DNA G-quadruplex based probes



Methods **64** (2013) 212–217



Mol. BioSyst., **2012**, 8, 779–782



Anal. Chem., **2013**, *85* (15), 7302

Ion specificity of G-quadruplex

- Effect of mono- and di-valent ions on the conformation of G-quadruplex
  - Use the conformational sampling method described in Aim 3.1

- Effect of ions on G-quadruplex stability
  - Relative free energy calculations using FEP/BAR
  - Polarization, entropy, hydration

Summary

- Develop accurate models based on the AMOEBA force field and efficient algorithms to enable the study of metal ions through MD simulations

- Preliminary results have shown the critical effect of polarization on Ca^{2+}/Mg^{2+} selectivity in proteins; future work will try to elucidate its detailed molecular determinants.

- Interaction with metal ions is crucial for the structure and function of nucleic acids. Polarization and advanced electrostatics models are important for nucleic acid interactions. I will study the effect of ions on the structures and stability of double-strand DNA/RNA and G-quadruplexes by polarizable force field