Sodium Iodide Effects on the Helical Stability of a Mainly Alanine Peptide

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SIGNIFICANCE

- Most diseases are caused by proteins that are defective in function due to a flaw in structure.
- Peptide based drugs may provide a means of treatment for many diseases.
  - Ex. HIV, Cancer
- Knowledge about the stability of protein secondary structure is critical in the development of peptide based drugs.[1]
  - α-helix

[1]C. Drahl, *C&EN.* 86, 18-23 (2008).

INTRODUCTION

- Helical peptides can be stabilized through the addition of salts.
- The stabilization effects specific ions will have on a peptide can be described using the Hofmeister series.

  $H_2PO_4^-$ > SO_4^{2-} > F^- > CH_3COO^- > Cl^- > Br^- > NO_3^- > I^- > ClO_4^- > SCN^-
- UVRR and CD found percholrate ions stabilize AP's helical structure[2].
  - Computationally REMD achieved the same result.

[2] Xiong K., E.K. Asciutto, J.D. Madura, S.A. Asher, In Preperation. 2009.

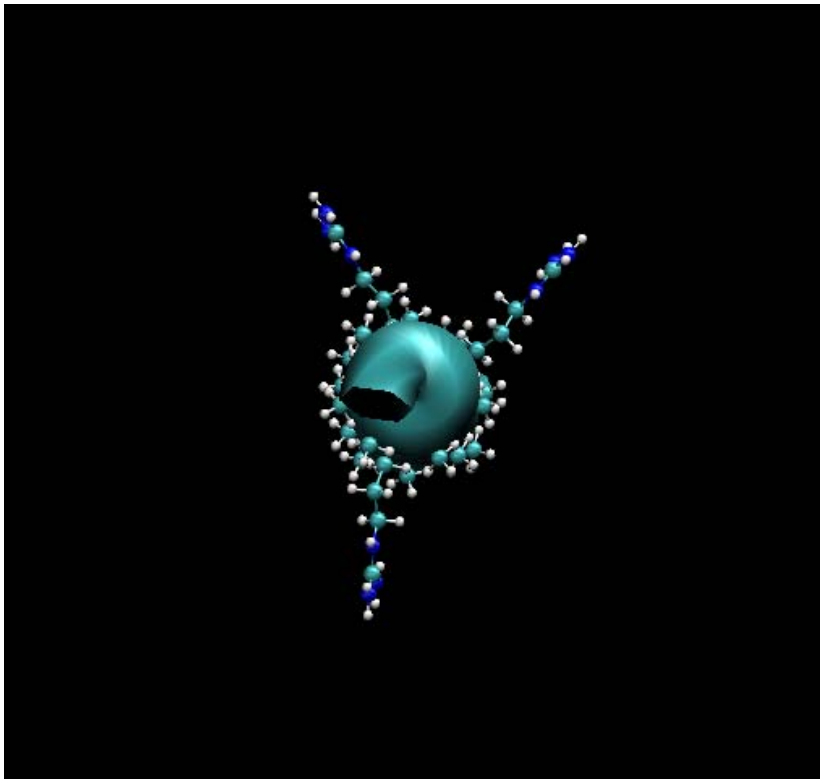
Sodium Iodide

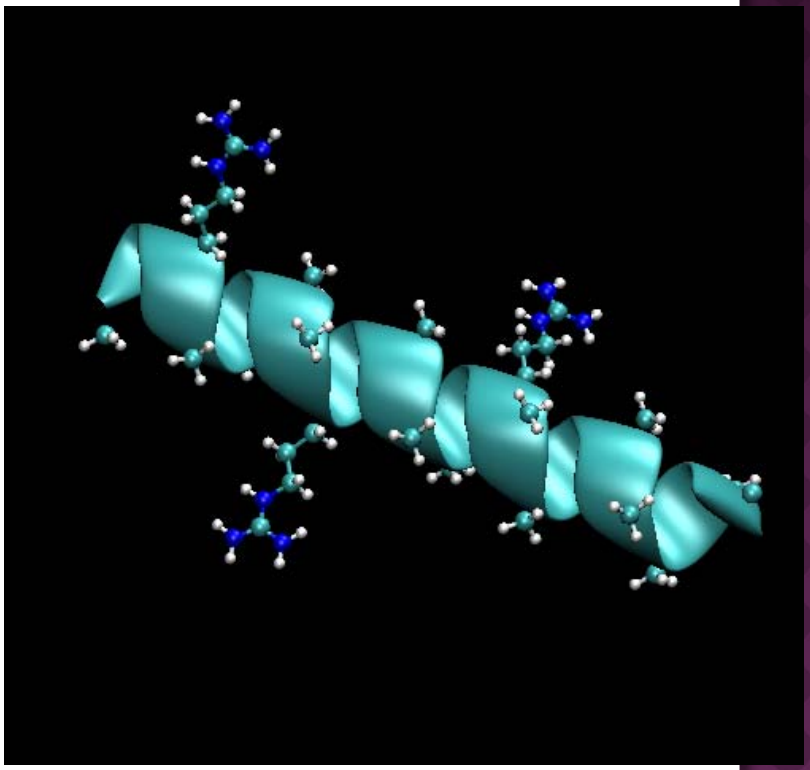
- I^- is a large, low charge density ion
  - Chaotrope
    - Disrupts the structure of water

Wikipedia. Sodium iodide.jpg.
http://en.wikipedia.org/wiki/File:Sodium_iodide.jpg (accessed July 1, 2009).

MAINLY ALANINE PEPTIDE (AP)

- $AAAAA(AAARA)_3A$



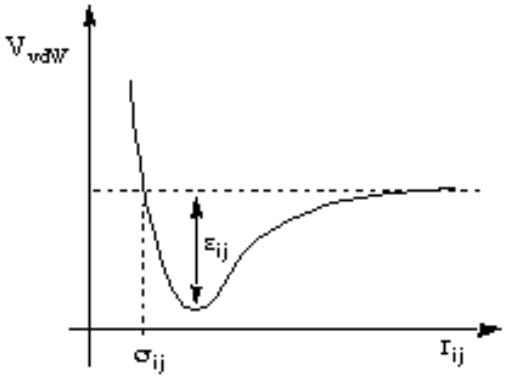


STANDARD MD WATER BOX

- System:
  - 403 I^- (0.2M)
  - 1 AP peptide
  - Water model TIP3P
  - ff99SB force field

Lenard-Jones Potential[3]

$$V_{vdW} = 4\varepsilon_{ij}\left[(\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^{6}\right]$$



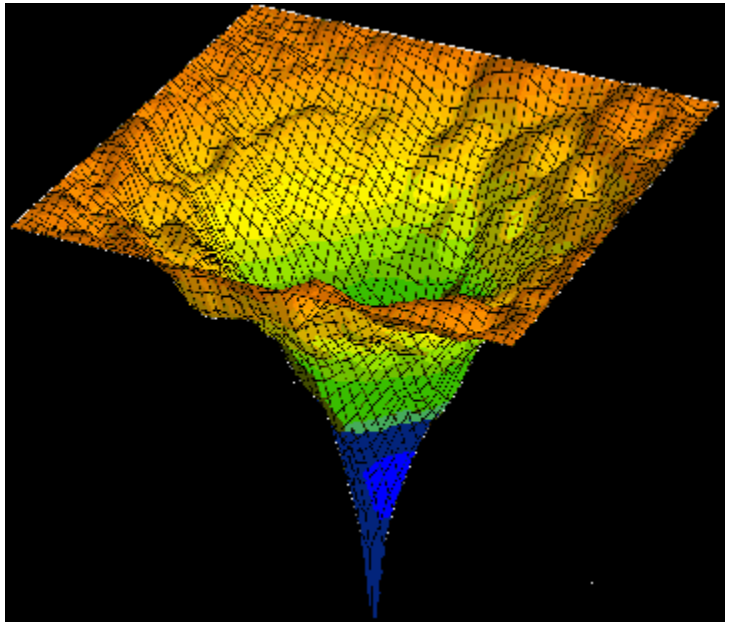
- Lennard-Jones Parameters[4]:
  - I^-
    - $R_{min}/2$ = 2.860 Å
    - ε = 0.0536816 kcal/mol
  - Na+
    - $R_{min}/2$ = 1.369 Å
    - ε = 0.0874393 kcal/mol

[3] Force Field Methods. http://www.cup.uni-muenchen.de/oc/zipse/lv18099/mm1.html (accessed July 29, 2009).

[4] Joung I. S., Cheatham T. E. III. *J. Phys. Chem B.,* **2008**, 112 (30), 9020-9041.

MINIMIZATION

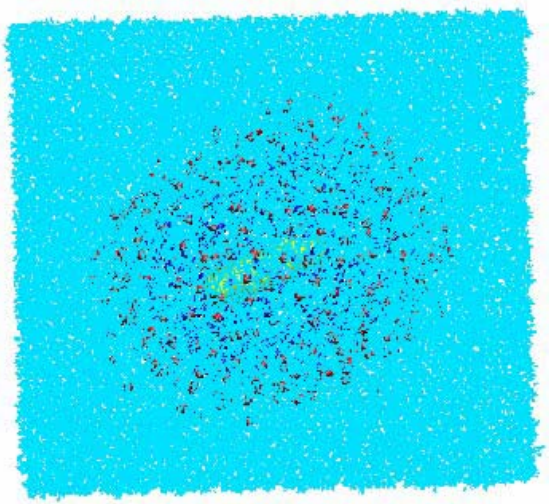
- Minimization is needed to find the equilibrium configuration of the system
  - This corresponds to the global and local minima on the potential energy surface of the system



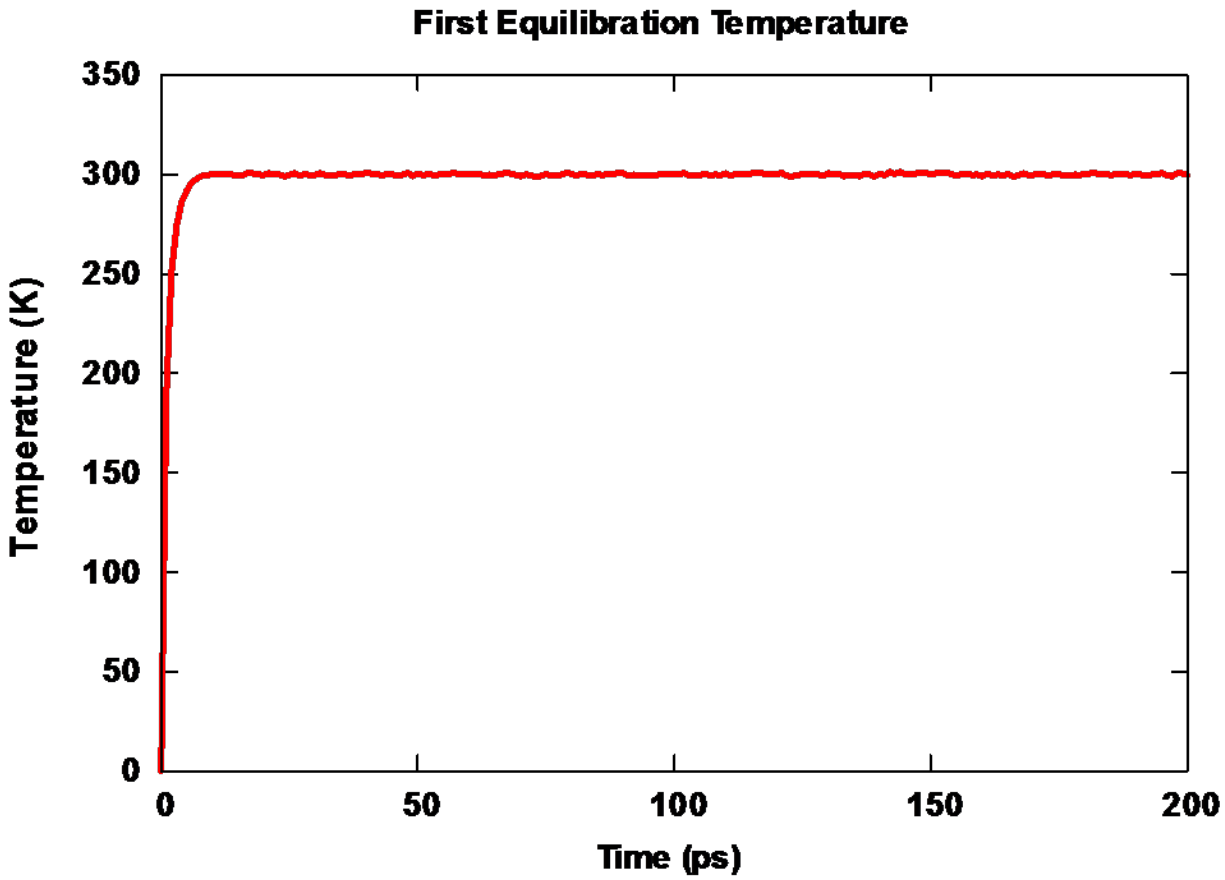
Water Structures and Science. Protein Folding and Denaturing: Protein Folding. http://www.lsbu.ac.uk/water/protein2.html (accessed July 1, 2009).

1ST EQUILIBRATION

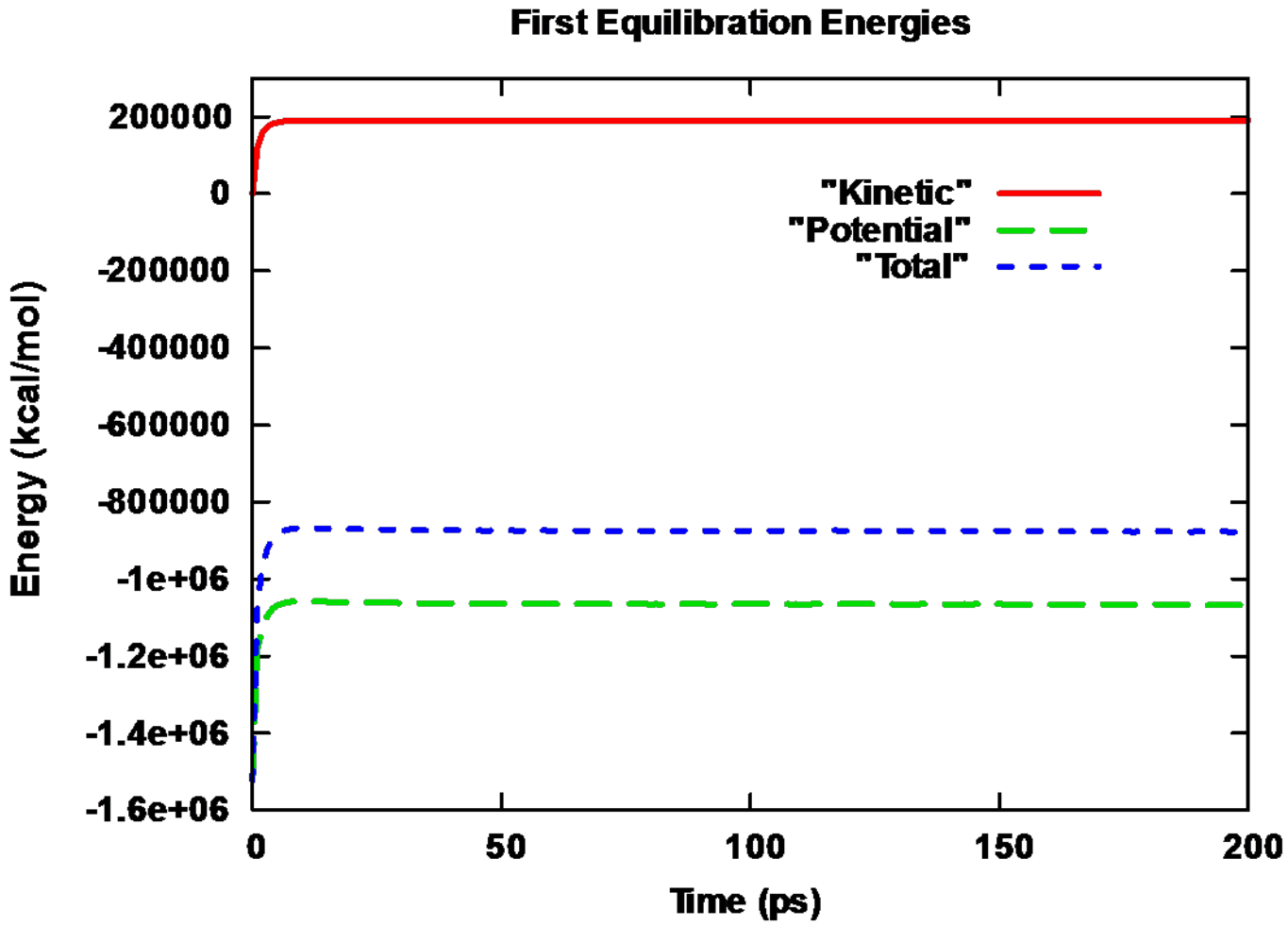
- Peptide Fixed
- Temperature increased from 0 to 300K
- 200ps



1ST EQUILIBRATION LARGE BOX



1ST EQUILIBRATION LARGE BOX



REMD (REPLICA-EXCHANGE MOLECULAR DYNAMICS)

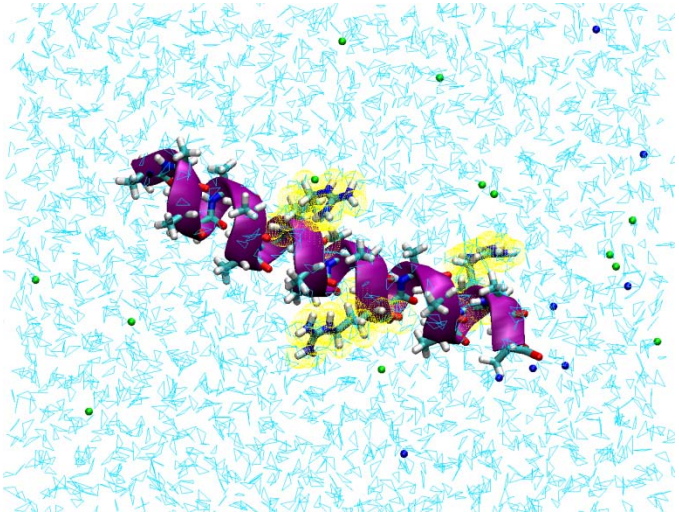
- Many replicas of a system are simulated simultaneously at different temperatures.
- Replicas “switch” temperatures allowing escape from local energy minima.
- When compared to standard MD the replica exchange method is more efficient.

Determining the Number of Replicas and Temperatures

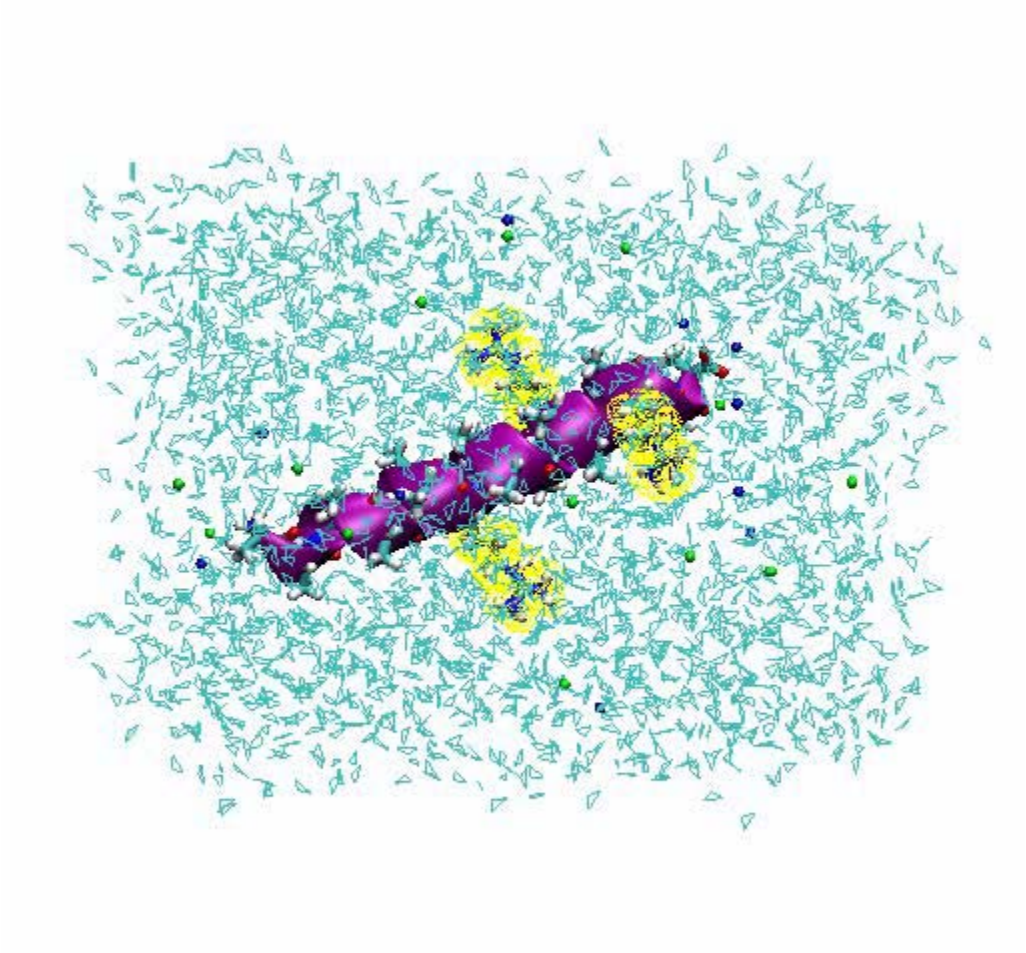
- Number of replicas
  - Related to the square root of the total number of atoms in system
    - 48 replicas
- Temperatures
  - Geometric function:
    - $270[1+(273.7-270)/270]^{replica-1}$
      - 270K-511.9K

REMD WATER BOX

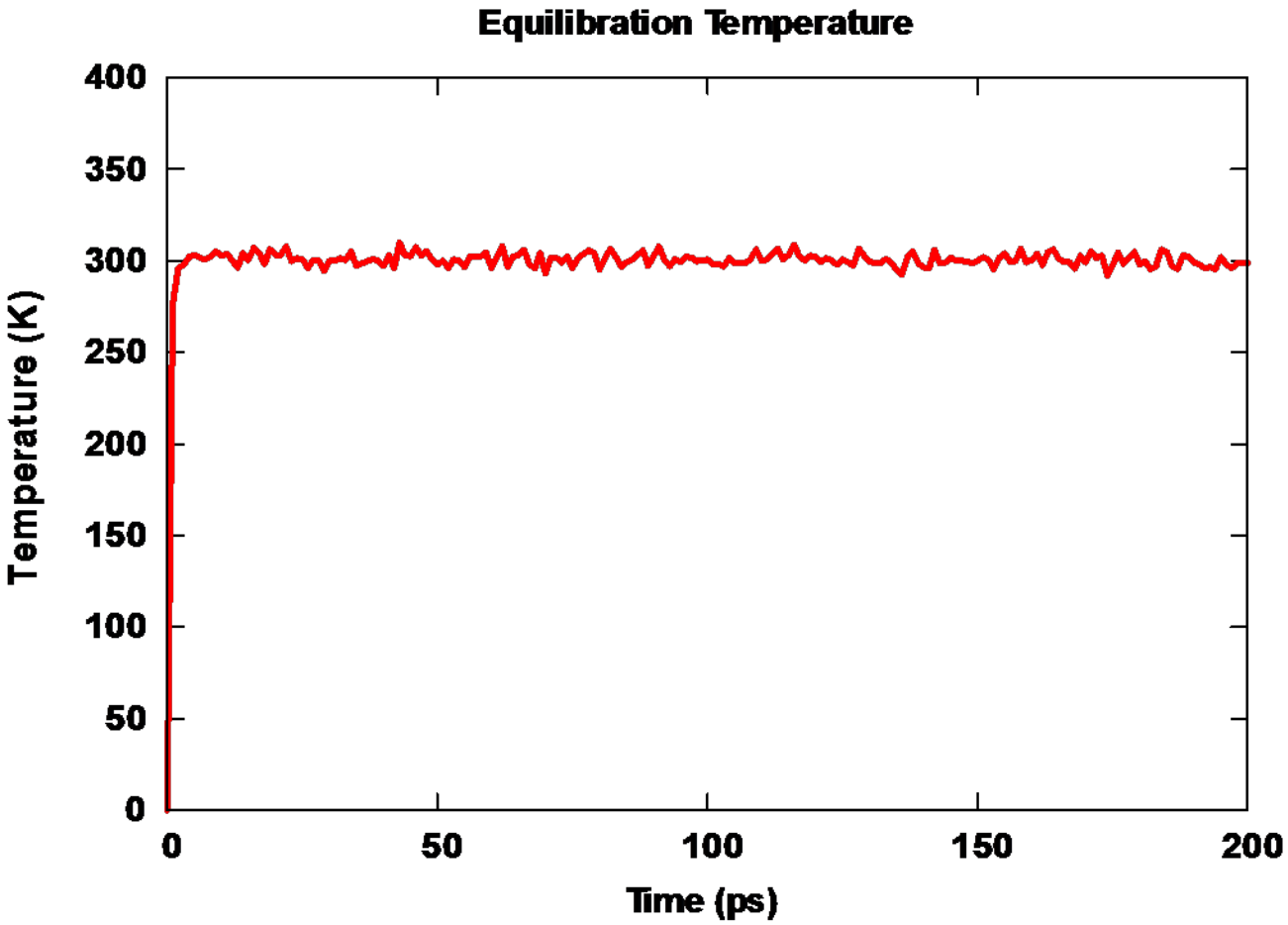
- Construction
  - 1 Peptide
  - 13 I^- (0.2M)
  - 56.21Å X 43.77Å X 44.50Å
  - Volume = 109486.824 $Å^3$
  - Density = 0.719 g/cc
- Minimization



EQUILIBRATION



EQUILIBRATION SMALL BOX REPLICA 9, 301.1K



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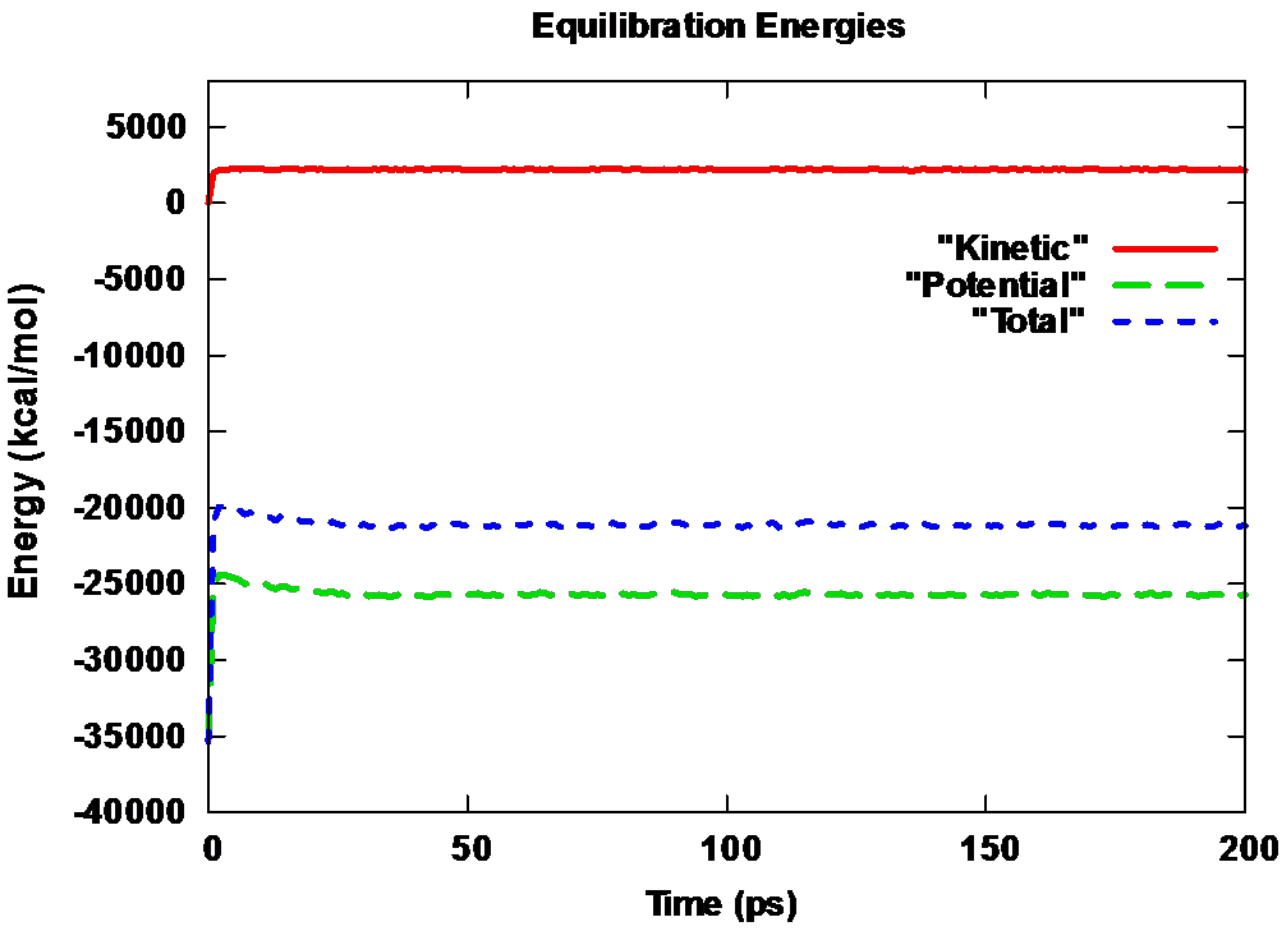
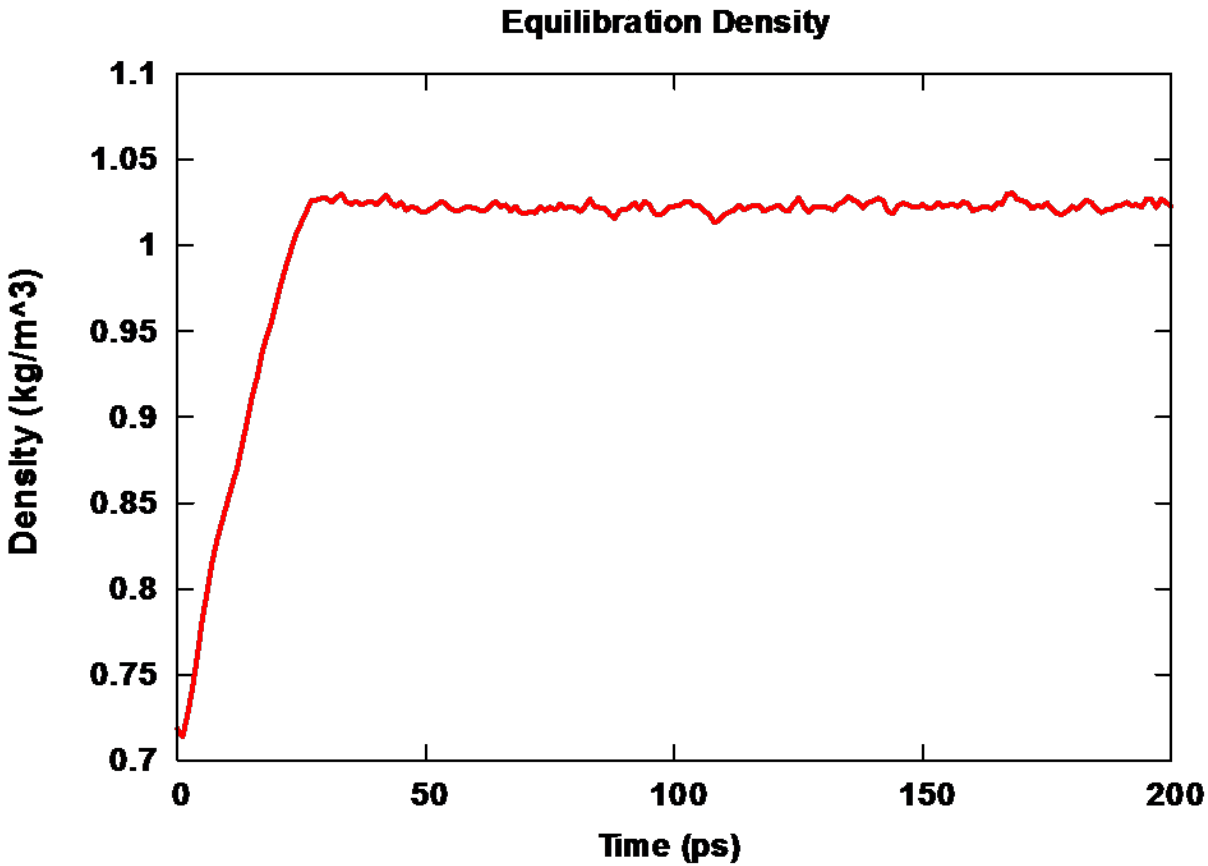


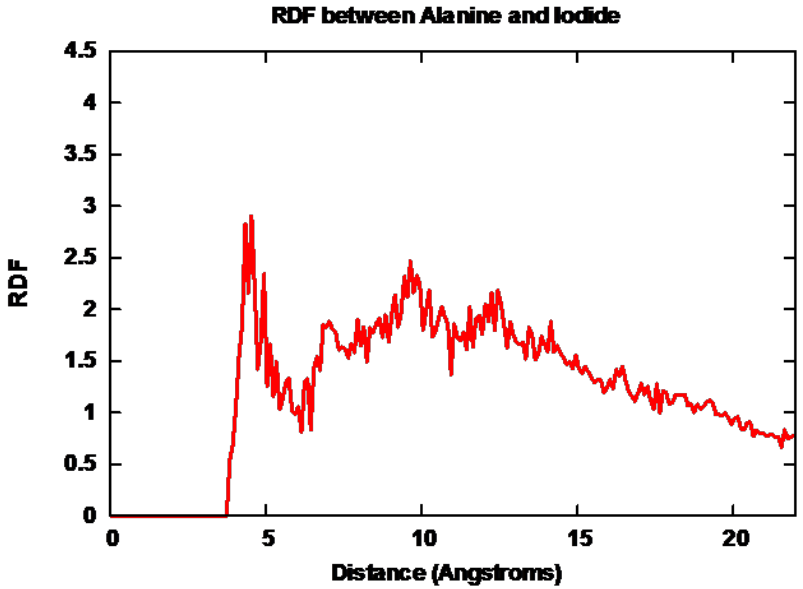
EQUILIBRATION SMALL BOX REPLICA 9, 301.1K



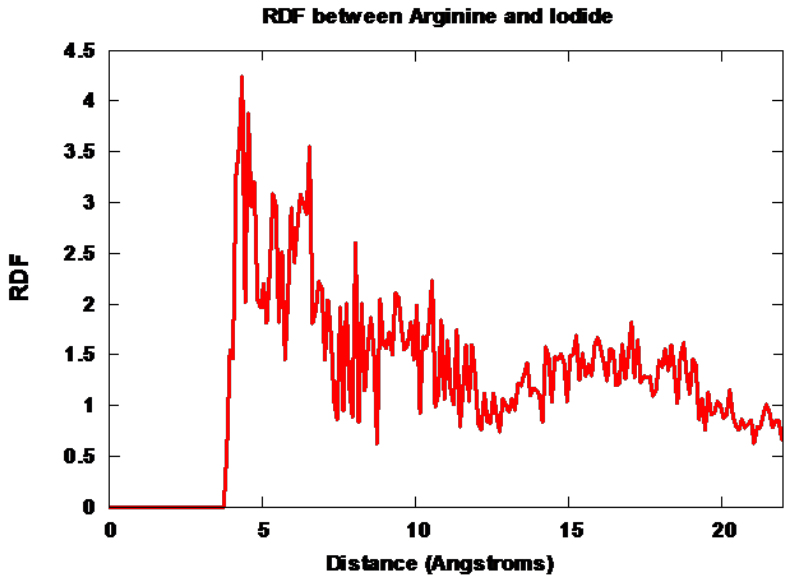
Experimental Density[5]: 1.019442-1.020056
REMD Density:1.0228

[5] MacInnes, D.A.; Dayoff, M. O., J. Am. Chem. Soc. 1952, 74, 1017-20.

DISTRIBUTION OF IODIDE AROUND ALANINE AND ARGININE

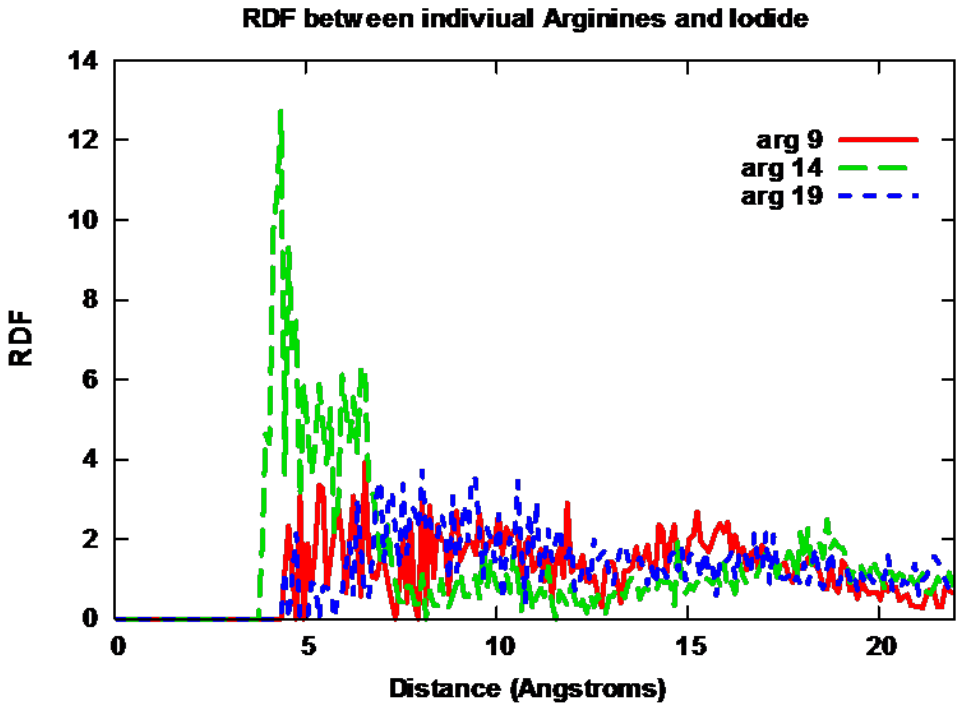


Alanine



Arginine

DISTRIBUTION OF IODIDE AROUND INDIVIDUAL ARGININE RESIDUES



WHAT'S NEXT…

- REMD Simulation
- 2nd Equilibration of Large Box
  - Total energy, density, temperature, and pressure are to be analyzed from 2nd equilibration.
  - Should all values be satisfactory the system can be submitted for molecular dynamics simulation.

THANK YOU

- BBSI
- Dr. Madura
- Eliana Asciutto
- Kat
  - And her notebook
- NIH/NSF