Weekly Report – Yan Lu (Feb 12, 2012)

0.1 Addition of Methyl Group

Charge information was downloaded from http://ozone3.chem.wayne.edu which was got from ab initial calculations[1], where the tests showed that the results are consistent with Amber94 parameters[2].

To investigate the role of methylation on a wide range of sequences, I did simulations on all the CG hexmer, which is NNNCGN with CGCG flank on the two ends for both methylated and unmethylated sequences. Totally there are 512 trajectories. Now 300 of them are running and the other 212 jobs are in queue.

0.2 Paper

Zou[3] et al from UIUC demonstrated that CpG methylation enhanced the binding of methyl-CpG binding domain protein and methylated DNA (MBD-mDNA), and the dinucleotide were recognized by two Arginines by using molecular dynamics and quantum chemical calculations. The results showed that methylated cytosine renders the stair motif more stable than non-methylated cytosine by increasing contact areas and number of hydrogen bonds.

4 wild type simulations were performed: MBD1-mDNA (PDB ID: 1IG4, human, crystal), MBD2-mDNA (PDB ID: 2KY8, chicken, NMR), Meep2-mDNA (PDB ID: 3C3I, X-ray), and MBD1-nDNA(The same as MBD1-mDNA with cytosine non-methylated). 5 mutational simulations were performed: V20A, R22A, Y34A, R44A and S45A. The main results were got by comparing the results of MBD1-mCpG and MBD1-CpG. There were about 5000∼6000 atoms in each system which simulated for 30 ns (100 ns for MBD1-mDNA).

The molecular dynamics simulations were performed by using NAMD software with CHARMM27 force field for DNA and CHARMM22 force field for protein. Quantum chemical calculations, specifically, FEP calculations were used for the calculation of interaction energy. Binding strength was estimated by contact area which was defined by $\delta(t) = \frac{1}{2}(S_{prot}(t) + S_{DNA}(t)) - S_{prot+DNA}(t))$, where S are the solvent accessible surface area for protein, DNA and protein-DNA respectively.

Sequence alignment of human and mouse MBD family proteins showed that two Argine amino acids (ARG22 and ARG44) involved in stair motifs (CYT ∨ ARG ∨ GUA) formation were strictly conserved, suggesting the important role of Arginine.

In the three methylated systems there were hydrogen bonds between Arg and Gua but not in other systems, neither in MBD1-nDNA nor in the mutational systems.

References
