

## Monte Carlo simulation of differences in free energies of hydration

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## Contents

- Monte Carlo Method
- Approaches to calculate free energy differences.
- Results
- Conclusion/Summary

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## What is Monte Carlo Technique?

The Monte Carlo method is a numerical method for solving mathematical problems using stochastic sampling.

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## Overview of Molecular Monte Carlo Method

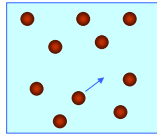
### Objective

Calculation of Macroscopic Properties from Microscopic Properties (intermolecular forces...)

### Averaging Method

Ensemble Averages

*NVT* Ensemble  
*NPT* Ensemble  
 *$\mu$ PT* Ensemble



### Generation of Random Configurations

Use of Random Number  
Importance Sampling  
Markov Chain  
Metropolis Algorithm

### Approximations

Periodic Boundary Condition  
Minimum Image Convention  
Neighborhood List

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## Random Configuration generation

- Use of Random Number
- Importance Sampling
- Markov Chain
- Metropolis Algorithm

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## Averaging Method

- *NVT* Ensemble
- *NPT* Ensemble
- *$\mu$ PT* Ensemble

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## Implementation of MMC in different ensemble

- MMC in different ensembles
  - A very large number of systems for convenient calculation of time average macroscopic properties
  - Common macroscopic attributes
    - $(N, V, E)$  : Microcanonical ensemble
    - $(N, V, T)$  : Canonical ensemble
    - $(N, P, T)$  : NPT ensemble
  - $(\mu, V, T)$  : Grand canonical ensemble
- Microcanonical ensemble cannot be used in MMC because constant-kinetic energy constraint cannot be assumed.
- In thermodynamic limit all ensembles are equivalent and it is also possible to transform between ensembles. The choice of ensemble is completely a matter of convenience.

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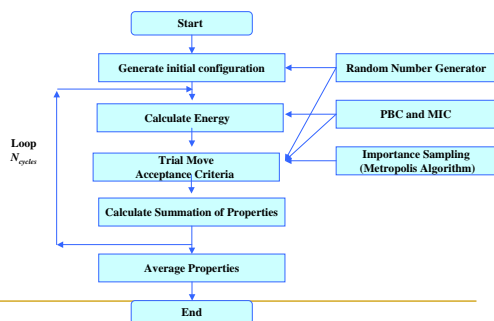
## Approximations

- Periodic Boundary Condition
- Minimum Image Convention
- Neighborhood List

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Theoretical Basis of Molecular Monte Carlo Method

## General MMC Scheme



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## Approaches to compute free energy differences.

- Umbrella sampling
- Perturbation approach

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## Umbrella Sampling

- The procedure was developed by Valleau and coworkers.
- Calculate a distribution function  $g(r)$  that is related to free energy change by  $w(r) = -KT \ln g(r)$ .

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## Perturbation approach

- It centers on the following relationship

$$A_1 - A_0 = -KT \ln \langle \exp[-B(E_1 - E_0)] \rangle_0$$

The equation expresses free energy difference between systems 0 and 1 by an average of function of their energy difference.

- Multiple simulations over intermediate systems between 0 and 1.

- Coupling parameter ( $\lambda$ ) is defined for smooth transition of system 0 to 1.

$$\xi(\lambda) = \xi_0 + \lambda(\xi_1 - \xi_0)$$

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### Perturbation approach

- Application of the approach is in free energy of cavity formation in water, free energy of hydration of methane, studying donor-acceptor complexes, compute free energy change for converting one solute into another in solution.
- Intriguing parallelism to mutagenic experiments in biochemistry.

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### Jorgensen et al Procedure

- Series of Monte Carlo simulations were carried out for the interconversion of methanol and ethane in dilute aqueous solution.
- A coupling parameter  $\lambda$  was used to smoothly transform methanol ( $\lambda = 0$ ) to ethane ( $\lambda = 1$ ).
- Simulations were run for  $\lambda_i = 0.0, 0.125, 0.25, 0.50, 0.75, 1.0$ .
- Double ended sampling - Simulations were run in both directions to check the self consistency.  
 $\lambda_i \rightarrow \lambda_{i+1}$  and  $\lambda_{i+1} \rightarrow \lambda_i$

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### Continuation of Jorgensen et al Procedure

- The simulations were run in NPT ensemble at **25 degrees C** and **1 atm** using standard procedures including periodic boundary conditions.
- The system had **125 water molecules** plus solute in a cube.
- Metropolis sampling
- An attempt made to move solute on every 50<sup>th</sup> configuration and change in volume was tried on every 600<sup>th</sup> configuration.

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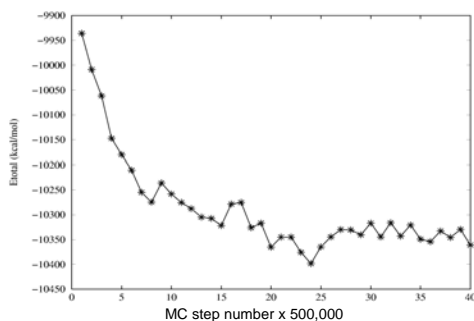
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## Continuation of Jorgensen et al Procedure

- Ranges for attempted moves were the same in each simulation and provided ~40% acceptance probability for new configurations.
- Each simulation consisted of equilibrium phase for  $0.5 \times 10^6$  configurations, which was followed by averaging for properties over  $1.5 \times 10^6$  configurations.

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## Convergence of Total Energy



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## Continuation of Jorgensen et al Procedure

- The interaction energy between monomers was determined by Coulomb and Lennard-Jones interactions between all intermolecular pairs of sites.

TABLE I. Parameters for the intermolecular potential functions.

Molecule	Group	q	$\sigma$ (Å)	$\epsilon$ (kcal/mol)
CH <sub>3</sub> OH	CH <sub>3</sub>	0.265	3.775	0.207
CH <sub>3</sub> OH	O	-0.700	3.070	0.170
CH <sub>3</sub> OH	H	0.435	0.0	0.0
CH <sub>3</sub> CH <sub>3</sub>	CH <sub>3</sub>	0.0	3.775	0.207
H <sub>2</sub> O	O	0.0	3.1536	0.155 04
H <sub>2</sub> O	H	0.52	0.0	0.0
H <sub>2</sub> O	M <sup>a</sup>	-1.04	0.0	0.0

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## Continuation of Jorgensen et al Procedure

- Standard geometries for monomers for ethane ,  $r(\text{CC}) = 1.53$  Angstrom, for methanol  $r(\text{CO}) = 1.43$  Angstrom.
- The bond length gradually increases from 1.43 to 1.53 Angstrom.
- Smooth interconversion of geometries of the two systems.

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## Hydration of Methanol

- $2\text{CH}_3\text{OH} \leftrightarrow \text{C}_2\text{H}_6 + 2(\text{OH})$
- Carbon in yellow, Oxygen in blue(United atom model).



- Note the bond length gradually increases from 1.43 to 1.53 Angstrom.

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## Results

- Thermodynamics
- Energy Distributions
- Radial distribution Functions

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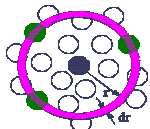
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## Radial distribution Functions

- The *rdf* addresses the question, "given that I have one atom at some position, how many atoms can I expect to find at a distance  $r$  away from it?"—more precisely, we ask for the number of atoms at a distance between  $r$  to  $r + dr$ . The idea is demonstrated in this figure.



- The darkened atom at the center is the reference atom, and the circles around it represent the other atoms. A ring centered on the reference is drawn with radius  $r$  and thickness  $dr$ , and in this example three other atoms are positioned within this ring and highlighted.

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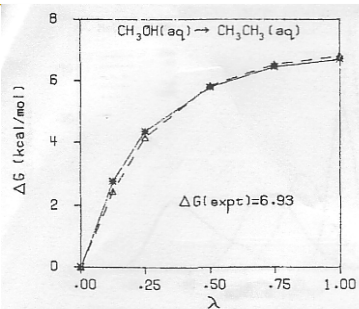


FIG. 1. Computed free energy changes for the interconversion of methanol ( $\lambda = 0$ ) and ethane ( $\lambda = 1$ ) in water. The solid and dashed lines correspond to the forward ( $\lambda = 0 \rightarrow 1$ ) and reverse ( $\lambda = 1 \rightarrow 0$ ) processes, respectively.

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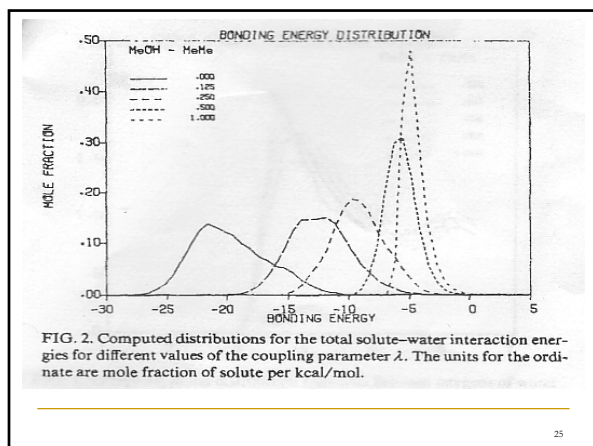
TABLE II. Free energy change for the interconversion of methanol and ethane in water.

$\lambda_i$	$\lambda_j$	$\Delta G$ (kcal/mol)	
		$i \rightarrow j$	$j \rightarrow i$
0.000	0.125	$2.77 \pm 0.10$	$-2.45 \pm 0.06$
0.125	0.250	$1.58 \pm 0.07$	$-1.70 \pm 0.08$
0.250	0.500	$1.44 \pm 0.14$	$-1.69 \pm 0.10$
0.500	0.750	$0.67 \pm 0.08$	$-0.70 \pm 0.08$
0.750	1.000	$0.24 \pm 0.05$	$-0.27 \pm 0.05$
Total		$6.69 \pm 0.21$	$-6.81 \pm 0.17$
Exptl. <sup>a</sup>		6.93	-6.93

<sup>a</sup> Reference 28.

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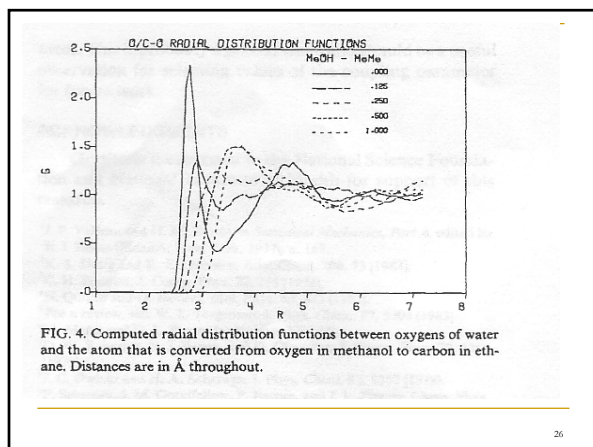
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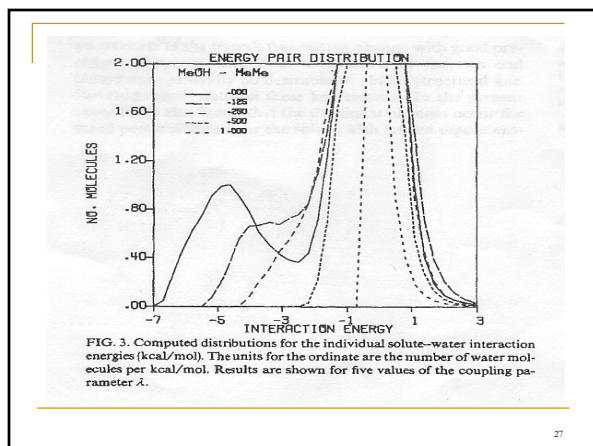
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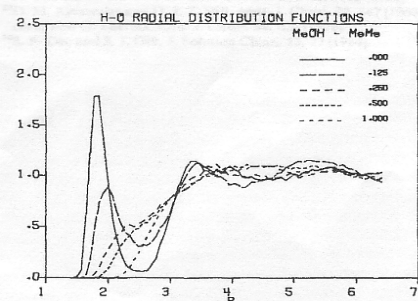


FIG. 5. Computed radial distribution functions between oxygens of water and the atom that is the hydroxyl hydrogen in methanol.

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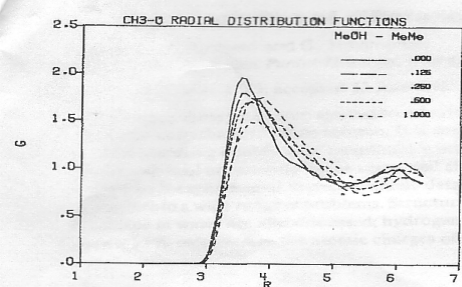


FIG. 6. Computed radial distribution functions between oxygens of water and the atom that is transformed from the carbon of methanol to a carbon in ethane.

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## Summary

- Perturbation theory is investigated for interconversion of methanol and ethane in water. Results are encouraging for further chemical and biochemical applications.
- The results are in good accord with experimental differences in free energies of hydration for methanol and ethane.
- Double wide sampling along with 2 or 3 Monte Carlo simulations give good estimation of free energy change with good precision.
- Dominant changes occur for small perturbation near the solute with largest dipole moment.

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## Acknowledgments

- Dr. Robert Rizzo

Thank you

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