



THE UNIVERSITY *of* TEXAS

HEALTH SCIENCE CENTER AT HOUSTON

SCHOOL *of* HEALTH INFORMATION SCIENCES

Thermodynamics, Ergodicity and Monte Carlo

For students of HI 6327 “Biomolecular Modeling”

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<http://biomachina.org/courses/modeling/08.html>

Review of Thermodynamics

Free Energy. When one is concerned with changes in the state of a system, a full description requires knowledge of what is known as the free energy, including the Helmholtz free energy and the Gibbs free energy.

Helmholtz free energy (F): a function of the internal energy E_{int} , the absolute temperature T , and the entropy S .

$$F = E_{\text{int}} - TS$$

Gibbs free energy (G) : Helmholtz free energy plus an additional term that depends on pressure and volume

$$G = F + PV = E_{\text{int}} - TS + PV$$

Equilibrium Conditions

The general rule is that a system can spontaneously alter its status if the change results in a lowering of the free energy. Therefore the equilibrium condition is that the free energy of the system is minimized.

For a mechanically isolated system at constant temperature (no work)

$$\Delta F \leq 0 \quad (= \text{holds at equilibrium})$$

For a system kept at constant temperature and pressure

$$\Delta G \leq 0 \quad (= \text{holds at equilibrium})$$

Thermodynamic Potentials

Internal En. (E_{int}), Enthalpy (H), Helmholtz Free En. (F), Gibbs Free En. (G)

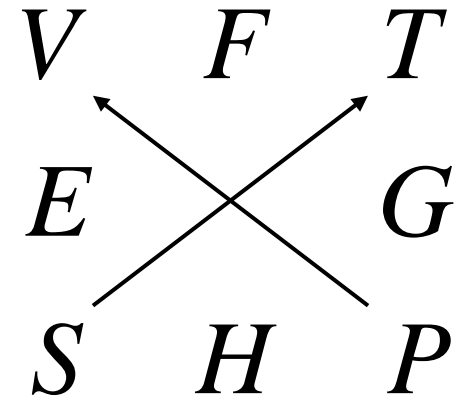
$$H = E_{\text{int}} + PV, \quad F = E_{\text{int}} - TS, \quad G = E_{\text{int}} - TS + PV$$

$$dE(S, V) = TdS - PdV = \left(\frac{\partial E}{\partial S} \right)_V dS + \left(\frac{\partial E}{\partial V} \right)_S dV,$$

$$dH(S, P) = TdS + VdP = \left(\frac{\partial H}{\partial S} \right)_P dS + \left(\frac{\partial H}{\partial P} \right)_S dP,$$

$$dF(T, V) = -SdT - PdV = \left(\frac{\partial F}{\partial T} \right)_V dT + \left(\frac{\partial F}{\partial V} \right)_T dV,$$

$$dG(S, V) = -SdT + VdP = \left(\frac{\partial G}{\partial T} \right)_P dT + \left(\frac{\partial G}{\partial P} \right)_T dP,$$



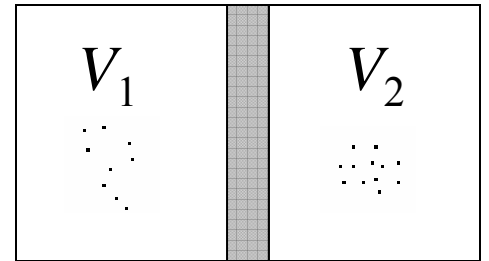
Maxwell Relations:

$$\left(\frac{\partial E}{\partial S} \right)_V = T \quad \left(\frac{\partial E}{\partial V} \right)_S = -P; \quad \left(\frac{\partial H}{\partial S} \right)_P = T \quad \left(\frac{\partial H}{\partial P} \right)_S = V$$

$$\left(\frac{\partial F}{\partial T} \right)_V = -S \quad \left(\frac{\partial F}{\partial V} \right)_T = -P; \quad \left(\frac{\partial G}{\partial T} \right)_P = -S \quad \left(\frac{\partial G}{\partial P} \right)_T = V$$

Principle of Minimizing Free Energy

Consider an isolated ideal gas system consisting of two compartments of volume V_1 and V_2 , respectively. The boundary between these two compartments is free to move. Find the equilibrium condition.



So: For an isolated system, the equilibrium condition is

$$\Delta F = 0 \quad \text{i.e.,} \quad \Delta F = \left(\frac{\partial F}{\partial V_1} \right) \Delta V_1 + \left(\frac{\partial F}{\partial V_2} \right) \Delta V_2 = 0$$

$$\Delta V_1 = -\Delta V_2$$

$$\left(\frac{\partial F}{\partial V_1} \right) = \left(\frac{\Delta F}{\Delta V_2} \right)$$

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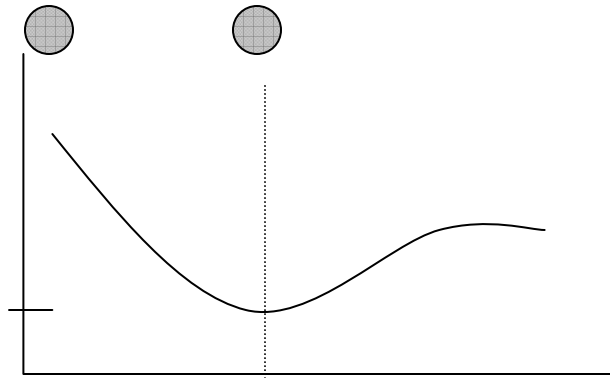
$$-P_1$$

$$-P_2$$

Equilibrium condition : $P_1 = P_2$

Internal Energy: $E_{\text{int}} = E_{\text{kin}} + E_{\text{pot}}$

Consider two atoms in equilibrium

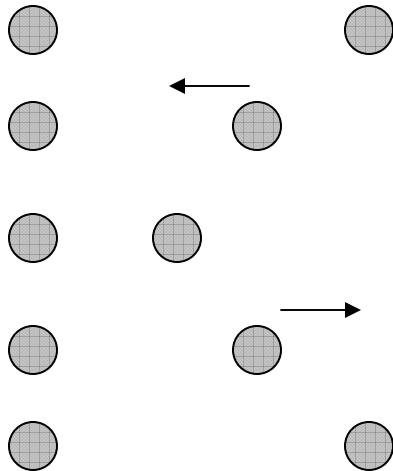


$$E_{\text{kin}} = 0$$

$$E_{\text{pot}} = 0$$

Small perturbation

$t = 0$



$$E_{\text{kin}} = 0 \quad E_{\text{pot}} > 0$$

$$E_{\text{kin}} > 0 \quad E_{\text{pot}} = 0$$

$$E_{\text{kin}} = 0 \quad E_{\text{pot}} > 0$$

$$E_{\text{kin}} > 0 \quad E_{\text{pot}} = 0$$

$$E_{\text{kin}} = 0 \quad E_{\text{pot}} > 0$$

Equipartition

For a system of N particles at temperature T

$$E_{kin} = \sum_{i=1}^N \frac{1}{2} m v_i^2$$

equipartition theorem

$$E_{pot} = \sum_{ij} v_{ij} (r_{ij}) \longrightarrow E_{kin} = \frac{3}{2} N k_B T$$

$k_B = 1.38 \times 10^{-23} \text{JK}^{-1}$: Boltzmann constant

$3N$ degrees of freedom

Each degree of freedom: $\frac{1}{2} k_B T$

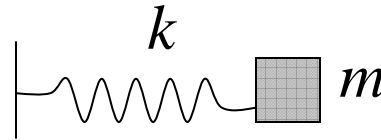
Entropy

$$S = k_B \ln \Omega \quad \Omega : \text{number of available states}$$

a state involves both the positions and the velocities of all the atoms in the system.

Example: Consider a harmonic oscillator; Its Hamiltonian is

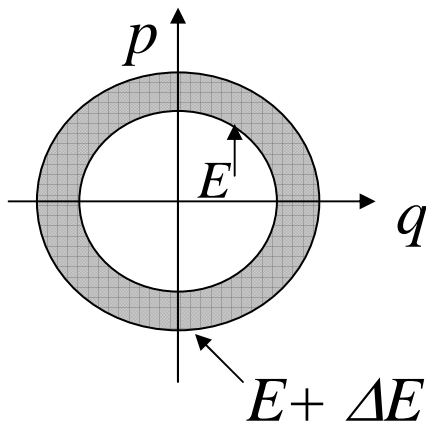
$$H(q, p) = \frac{p^2}{2m} + \frac{1}{2}kq^2 = E$$



$p = \text{momentum}$ $q = \text{position}$

phase space

Total available area in phase space = ΔW



Unit area in p - q phase space due to uncertainty principle is h

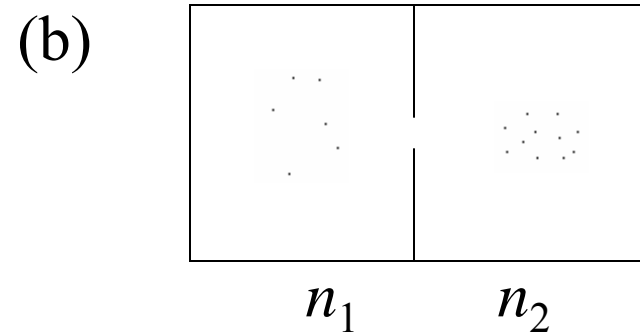
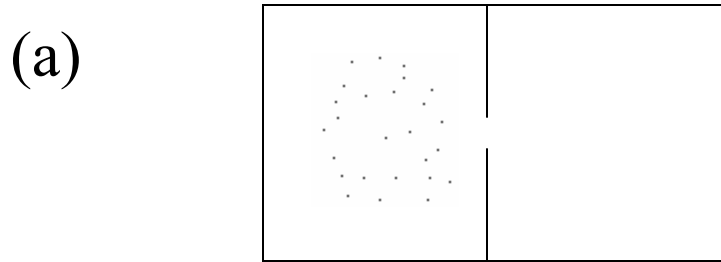
Number of states: $\Omega = \Delta W h$

For a system of N particles in 3-D space

$$\Omega(E, V, N) = \Delta W(E) h^{3N}$$

Example

A container is divided into two parts by a barrier that has a small hole in it. The gas molecules are indistinguishable.



$$\Omega = \frac{N!}{n_1!n_2!} \quad N = n_1 + n_2$$

$$\ln \Omega = \ln N! - \ln n_1! - \ln n_2!$$

$$= N \ln N - N - n_1 \ln n_1 + n_1 - n_2 \ln n_2 + n_2$$

$$= N \ln N - n_1 \ln n_1 - n_2 \ln n_2$$

$$\text{maximal entropy: } \frac{\partial (\ln \Omega)}{\partial n_1} = -\ln n_1 - 1 + \ln(N - n_1) + 1 = 0$$

$$n_1 = N - n_1 = \frac{N}{2} = n_2$$

Boltzmann Distribution

Consider a system that is described by a set of states 1, 2, 3, ..., i , ... with corresponding energies $\varepsilon_1, \varepsilon_2, \varepsilon_3, \dots, \varepsilon_i, \dots$. Let the number of particles in state 1 be n_1 , in state 2 be n_2 , ... and so on.

Total number of particles:
$$N = \sum_i n_i$$

Total energy:
$$E_{tot} = \sum_i n_i \varepsilon_i$$

Number of different ways:
$$\Omega = \frac{N!}{n_1! \times n_2! \times \dots \times n_i! \times \dots}$$

Maximizing entropy with the constraints of fixed particle number and total energy, we get

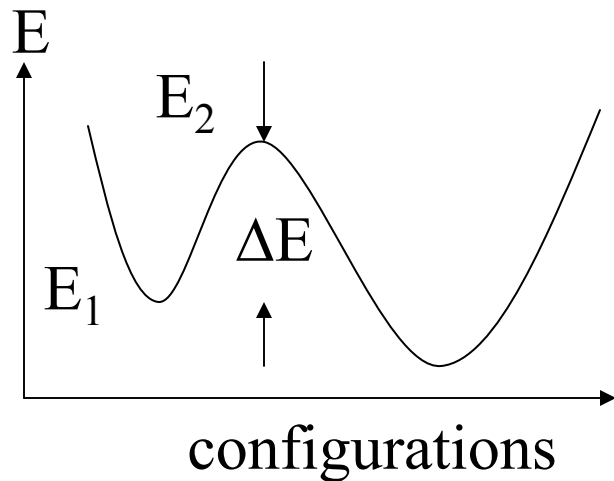
$$n_i = N \frac{\exp\left(-\varepsilon_i / k_B T\right)}{\sum_i \exp\left(-\varepsilon_i / k_B T\right)}$$

Partition Function

$$Q = \sum_i \exp\left(-\varepsilon_i / k_B T\right)$$

At equilibrium, the probability to jump from state i to state j is

$$P(n_i \rightarrow n_j) = \frac{n_j}{n_i} = \exp\left[-\left(\varepsilon_j - \varepsilon_i\right) / k_B T\right] \quad (\text{detailed balance})$$



$$f(E)dE = \frac{\exp\left(-E/k_B T\right)dE}{\int_0^\infty \exp\left(-E/k_B T\right)dE}$$

$$f(E > E_1) = \frac{\int_{E_1}^\infty \exp\left(-E/k_B T\right)dE}{\int_0^\infty \exp\left(-E/k_B T\right)dE}$$

$$= \exp\left(-E_1/k_B T\right)$$

$$f(E > E_2) = \exp\left(-E_2/k_B T\right)$$

$$\text{fraction} \equiv \frac{f(E > E_2)}{f(E > E_1)} = \exp\left(-\Delta E/k_B T\right)$$

Free Energy and Partition Function

Define $F = -Nk_B T \ln Q$ what is F ?

$$Q = e^{-\beta F/N} = \sum_i e^{-\beta \varepsilon_i}, \quad \beta \equiv \frac{1}{k_B T}$$

$$\sum_i e^{-\beta \varepsilon_i} / e^{-\beta F/N} = \sum_i e^{-\beta (\varepsilon_i - F/N)} = 1$$

$$\frac{\partial}{\partial \beta} \left(\sum_i e^{-\beta (\varepsilon_i - F/N)} \right) = \frac{\partial}{\partial \beta} (1) = 0$$

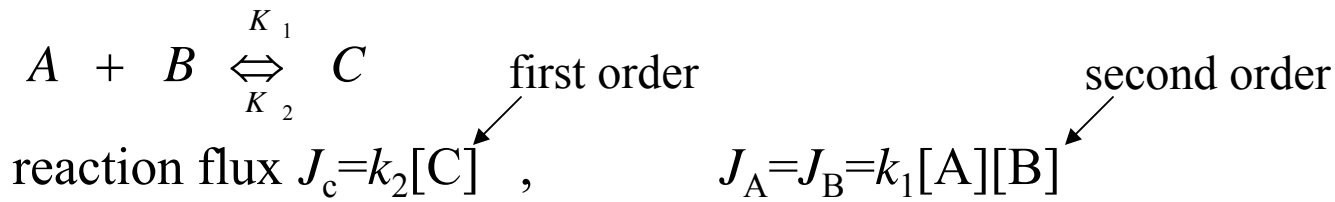
$$\sum_i \left[\left(\frac{F}{N} - \varepsilon_i \right) e^{-\beta (\varepsilon_i - F/N)} + \frac{\beta}{N} \cdot \frac{\partial F}{\partial \beta} e^{-\beta (\varepsilon_i - F/N)} \right] = 0$$

$$F - N \sum_i \varepsilon_i \cdot e^{-\beta \varepsilon_i} / Q + \beta \cdot \frac{\partial F}{\partial \beta} = 0$$

$$F = E_{tot} + T \cdot \frac{\partial F}{\partial T} = E_{tot} - T S$$

F is the Helmholtz free energy!

Reaction Kinetics



chemical potential of a given component

$$\mu_i = \mu_i^0 + RT \ln a_i \quad \text{chemical activity} \quad a_i = \gamma_i [i]$$



the change in the Gibbs free energy

$$\begin{aligned} \Delta G &= \nu_C \mu_C + \nu_D \mu_D - \nu_A \mu_A - \nu_B \mu_B \\ &= \Delta G^0 + RT (\nu_C \ln a_C + \nu_D \ln a_D - \nu_A \ln a_A - \nu_B \ln a_B) \\ &= \Delta G^0 + RT \ln \left(\frac{a_C^{\nu_C} a_D^{\nu_D}}{a_A^{\nu_A} a_B^{\nu_B}} \right) \end{aligned}$$

$$\Delta G^0 = \nu_C \mu_C^0 + \nu_D \mu_D^0 - \nu_A \mu_A^0 - \nu_B \mu_B^0$$

At equilibrium $\Delta G = 0$

$$K_{eq} = \frac{[C]_{eq}^{\nu_C} [D]_{eq}^{\nu_D}}{[A]_{eq}^{\nu_A} [B]_{eq}^{\nu_B}} = e^{\frac{\Delta G^0}{RT}} = A e^{\frac{\Delta E_{int}^0}{RT}}$$

activation energy

Statistical Ensembles

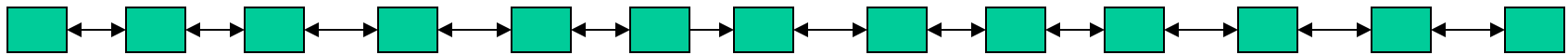
- Classical phase space has $6N$ variables ($\mathbf{p}_i, \mathbf{q}_i$) and a Hamiltonian function $H(\mathbf{q}, \mathbf{p}, t)$.
- We may know a few constants of motion such as energy, number of particles, volume...
- Ergodic hypothesis: each state consistent with our knowledge is equally “likely”; the *microcanonical* ensemble.
- Implies the average value does not depend on initial conditions.
- A system in contact with a heat bath at temperature T will be distributed according to the canonical ensemble:

$$\exp(-H(\mathbf{q}, \mathbf{p})/k_B T) / Q$$

- The momentum integrals can be performed.
- Are systems in nature really ergodic? Not always!

Ergodicity

- Fermi- Pasta- Ulam computer experiment (1954)
- 1-D anharmonic chain: $V = \sum [(q_{i+1} - q_i)^2 + \alpha (q_{i+1} - q_i)^3]$



- The system was started out with energy with the lowest energy mode. Equipartition would imply that the energy would flow into the other modes.
- Systems at low temperatures **never come into equilibrium**. The energy sloshes back and forth between various modes forever.
- At higher temperature many-dimensional systems become ergodic.
- Field of non-linear dynamics devoted to these questions.

Ergodicity

Let us say here that the results of our computations were, from the beginning, surprising us. Instead of a continuous flow of energy from the first mode to the higher modes, all of the problems show an entirely different behavior. ... Instead of a gradual increase of all the higher modes, the energy is exchanged, essentially, among only a certain few. It is, therefore, very hard to observe the rate of “thermalization” or mixing in our problem, and this was the initial purpose of the calculation.

Fermi, Pasta, Ulam (1954)

Ergodicity

- Equivalent to exponential divergence of trajectories, or sensitivity to initial conditions. (This is a blessing for numerical work. Why?)
- What we mean by ergodic is that after some interval of time the system is any state of the system is possible.
- Time average = ensemble average.
- Example: shuffle a card deck 10 times. Any of the $52!$ arrangements could occur with equal frequency.
- Aside from these mathematical questions, there is always a practical question of convergence. How do you judge if your results converged? There is no sure way. Why? Only “experimental” tests.
 - Occasionally do very long runs.
 - Use different starting conditions.
 - Shake up the system.
 - Compare to experiment.

Statistical Ensembles

- (E, V, N) microcanonical, constant volume
- (T, V, N) canonical, constant volume
- (T, P, N) constant pressure
- (T, V, μ) grand canonical

- Which is best? It depends on:
 - the question you are asking
 - the simulation method: MC or MD (MC better for phase transitions)
 - your code.
- Lots of work in last 2 decades on various ensembles.

Another Definition of Simulation

- What is a simulation?
 - An internal state “S”
 - A rule for changing the state $S_{n+1} = T(S_n)$
 - We repeat the iteration many times.
- Typically systems are **ergodic**: there is a correlation time T . For times much longer than that, all non-conserved properties are close to their equilibrium value. Used for:
 - Warm up period.
 - To get independent samples for computing errors.

Monte Carlo Simulation

- Invented in Los Alamos in 1944 and named after the famous casino.
- A way of doing integrals by using random numbers:

$$I = \int dR f(R) = \int dR P(R) \frac{f(R)}{P(R)}$$

$$= \left\langle \frac{f(R)}{P(R)} \right\rangle = \lim_{N \rightarrow \infty} \frac{1}{N} \sum_i \frac{f(R_i)}{P(R_i)}$$

$P(R)$ =sampling function

Convergence guaranteed by the Central Limit Theorem

- If $P(R) \propto f(R)$ then variance $\rightarrow 0$
- faster way of doing integrals for dimensions > 4

Markov Processes

- Markov process is a random walk through phase space:

$$S_1 \Rightarrow S_2 \Rightarrow S_3 \Rightarrow S_4 \Rightarrow \dots$$

- If it is ergodic, then it will converge to a unique stationary distribution

- Detailed balance: $\Pi(s) P(s \Rightarrow s') = \Pi(s') P(s' \Rightarrow s)$.

Rate balance from s to s' .

- We achieve detailed balance by *rejecting* moves. Acceptance probability is:

$$\min \left[1, \frac{T(s' \rightarrow s) \Pi(s')}{T(s \rightarrow s') \Pi(s)} \right]$$

“Classic” Metropolis Method

Metropolis Rosenbluth Teller (1953) method:

- Move from s to s' with probability $T(s \rightarrow s') = \text{constant}$
- Accept with move with probability:

$$a(s \rightarrow s') = \min [1 , \exp (- (E(s') - E(s)) / k_B T)]$$

- Repeat many times

Given ergodicity, the distribution of s will be the canonical distribution:

$$\Pi(s) = \exp(-E(s)/k_B T) / Q$$

Optimizing the Moves

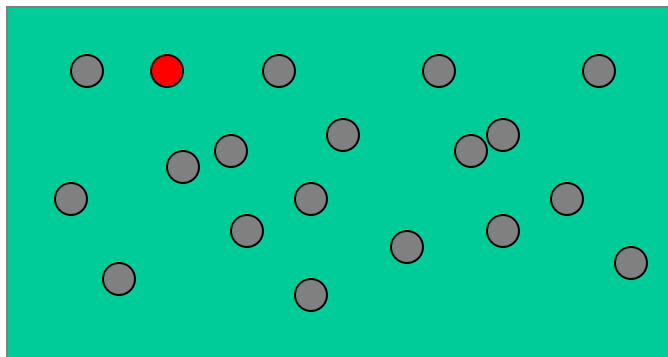
- Any transition rule is allowed as long as you can go anywhere in phase space with a finite number of them. (ergodic)
- Try to find a $T(s \Rightarrow s') \approx \Pi(s')$. If you can the acceptance ratio will be 1.
- We can use the forces to push the walk in the right direction. Taylor expand about the current point.

$$V(\mathbf{r}) = V(\mathbf{r}_0) - \mathbf{F}(\mathbf{r}_0)(\mathbf{r} - \mathbf{r}_0)$$

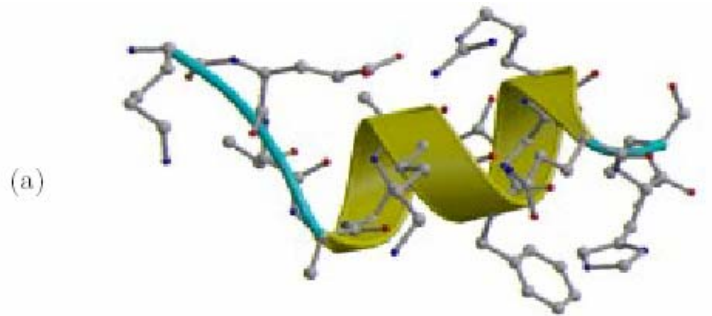
- Set $T(s \Rightarrow s') \approx \exp[-\beta(V(\mathbf{r}_0) - \mathbf{F}(\mathbf{r}_0)(\mathbf{r} - \mathbf{r}_0))]$
- Leads to Force-Bias Monte Carlo
- Related to Brownian motion (Smoluchowski Eq.)

Other Ensembles in MC

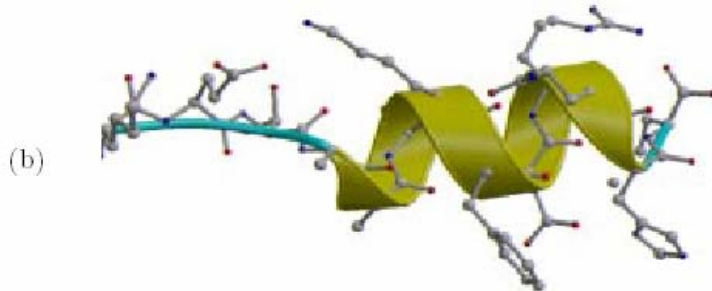
- Monte Carlo can handle discrete and continuous variables at the same time.
- This allows us to treat other ensembles. For example consider the (μ, V, T) ensemble. The number of particles is variable.
- We consider moves that change the number of particles by adding or subtracting 1 and accepting or rejecting the move.



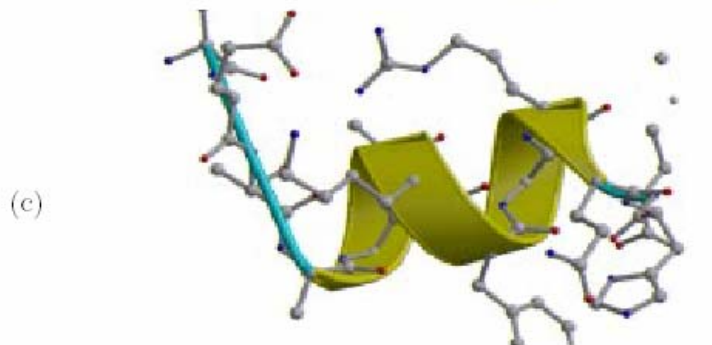
Monte Carlo Simulation of C-Peptide



(a) X-ray structure of C-peptide



(b) the lowest conformations of C-peptide obtained from a multicanonical Monte Carlo run of 1,000,000 MC sweeps in gas phase

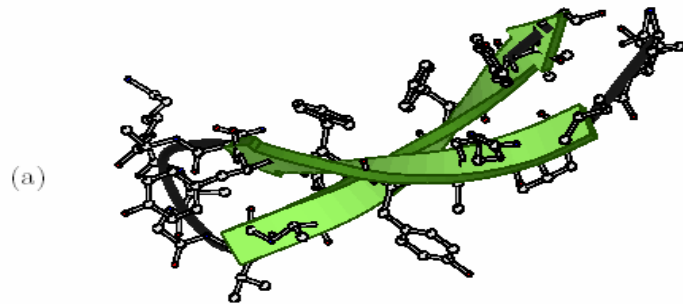


(c) and in aqueous solution represented by the distance-dependent dielectric function.

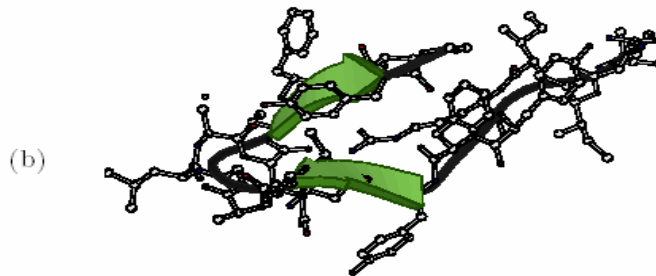
Monte Carlo Simulation of C-Peptide

- C-peptide, residues 1-13 of ribonuclease A
- structure of the enzyme exhibits a nearly 3-turn α -helix
- simulations predicted a similar α -helix in the lowest-energy conformation in aqueous solution
- conformation of the α -helix is reproduced in the simulations

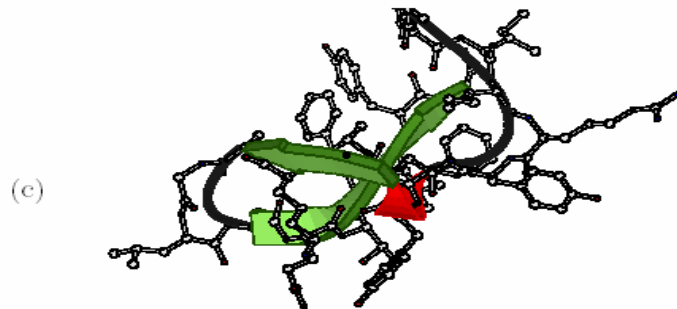
Monte Carlo Simulation of BPTI



(a) X-ray structure of BPTI(16-36)



(b) the lowest conformations of BPTI(16-36) obtained from a multicanonical Monte Carlo run of 1,000,000 MC sweeps in gas phase



(c) and in aqueous solution represented by a solvation term proportional to the solvent-accessible surface area.

Monte Carlo Simulation of BPTI

- α -helix and β -sheets from residues 16-36 of bovine pancreatic trypsin inhibitor (BPTI) studied
- simulated structures are rather different from x-ray structures of the entire BPTI
- but agreement between simulation and NMR experiment on fragment corresponding to residues 16-36

MC vs. MD

- MD can compute dynamics. MC has a kinetics under user control, but dynamics is not necessarily physical. MC dynamics is useful for studying long-term diffusive process.
- MC is simpler: no forces, no time step errors and a direct simulation of the canonical ensemble.
- In MD you can only work on how to make the CPUtime/physical time faster. In MC you can invent better transition rules and ergodicity is less of a problem. MD is sometimes very effective in highly constrained systems.
- MC is more general, it can handle discrete degrees of freedom (e. g. spin models, quantum systems), grand canonical ensemble...

“An intelligent being who, at a given moment, knows all the forces that cause nature to move and the positions of the objects that it is made from, if also it is powerful enough to analyze this data, would have described in the same formula the movements of the largest bodies of the universe and those of the lightest atoms. Although scientific research steadily approaches the abilities of this intelligent being, complete prediction will always remain infinitely far away.”

Laplace, 1820

Resources and Further Reading

Textbook:

Schlick Chapter 11

WWW Paper on Monte Carlo:

Yuko Okamoto, 'Ab Initio Predictions of Three-Dimensional Structures of Proteins by Monte Carlo Simulations:

<http://citeseer.ist.psu.edu/cache/papers/cs/12824/http:zSzzSzwww.scri.fsu.edu:zSzMCatSCRIZSzproceedingszSzOkamotozSzokamoto.pdf/okamoto99ab.pdf>

Textbook on Statistical Mechanics, Thermodynamics, Free Energy, etc:

McQuarrie, Statistical Mechanics, 1976

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