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Conformational analysis Using Monte-Carlo methods :-

A Monte-Carlo method is ~~also~~ a completely different path for searching conformational space using random search. Random search are of statistical nature. At each stage of a Monte-Carlo search the actual conformation is modified randomly in order to obtain a new one. Essentially it can be thought as a game of chance, but with some theoretical and ~~practical~~ practical rules from probability theory, statistical physics. Statistical physics, includes Markov chain, Brownian motion

A random search starts with an optimized structure. At each iteration in the procedure, new torsional angles or new cartesian coordinates are assigned randomly. The resulting conformation is minimized using molecular mechanics and the randomization process is repeated. The minimized conformation is then compared with the previously generated structures and is stored only if it is unique. The random methods are designed mathematically or statistically in such a way that, it potentially covers all regions of conformational space. However, this happens only if the process is allowed

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The energy of an atom is given by the Hamiltonian expression

$$\hat{H} = K.E + P.E$$

K.E takes momentum consideration

P.E takes the position consideration


So;

$$\hat{H}(p^N, r^N) = \sum_{i=1}^N \frac{p_i^2}{2m} + V(r^N) \quad \text{--- (1)}$$

When we talk about a biomolecule, we consider the a portion of the molecule as an ensemble.

The Energy of an ensemble, also called partition function (Q) in the Subject of Statistical Mechanics

$$E(Q)_{NVT} = \frac{1}{N!} \frac{1}{h^{3N}} \iiint e^{-\hat{H}/k_B T} dp^N dr^N$$



 $\equiv \text{Natures} \quad (2)$

Since from ①, \hat{H} could be substituted in eqn ②

$$E = \frac{1}{N!} \frac{1}{h^{3N}} \iint e^{\left[-\frac{p^2}{2m k_B T} - \frac{V(r^N)}{k_B T} \right]} \cdot dp^N \cdot dr^N \quad \text{--- (3)}$$

Equation ③ could be split into two integrals

$$E = \frac{1}{N!} \frac{1}{h^{3N}} \int e^{\left[-\frac{p^2}{2m k_B T} \right]} \cdot dp^N \int e^{\frac{-V(r^N)}{k_B T}} \cdot dr^N \quad \text{--- (4)}$$

The first term (Integral) is the kinetic energy contribution and the second integral term is the potential energy contribution. In MC, the kinetic energy contribution is ~~not~~ neglected and only the potential energy contribution is evaluated. Or in other words, many configurations

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are generated by random methods
and the \hat{PE} is calculated for
each position or configuration
and then the total average PE
is estimated. How is this done?

~~The average PE is determined by
evaluating the integral~~

$$\bar{V}(r^N) = \int V(r^N) \cdot P(r^N) \cdot dr^N \quad (5)$$

~~Before this could be done, a small
further process of eq (4) has to be
done.~~

The potential energy or the contribution because of position in eq (4) is

$$Z = \int e^{\left[\frac{-V(r^N)}{k_B T} \right]} \cdot dr^N \quad (5)$$

is called the configurational integral and is denoted by Z .

Now the average potential of the ~~integral~~^{is} evaluated by the integral

$$\langle V(r^N) \rangle = \int V(r^N) \cdot P(r^N) \cdot dr^N \quad (6)$$

$P(r^N)$: is the probability of ^{obtaining} ~~the~~ the configuration at position r of N^{th} atom.

$V(r^N)$: is the potential energy at that position for N^{th} atom.

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$P(r^N)$ is given by equation

$$P(r^N) = \frac{\exp\left[-\frac{V(r^N)}{k_B T}\right]}{Z} \quad \text{--- (7)}$$

\therefore Equation (6) could be written as;

$$\langle V(r^N) \rangle = \frac{\int \pm V(r^N) \cdot \exp\left[-\frac{V(r^N)}{k_B T}\right] \cdot dv_n}{\int \exp\left[-\frac{V(r^N)}{k_B T}\right] \cdot dv_n} \quad \text{--- (8)}$$

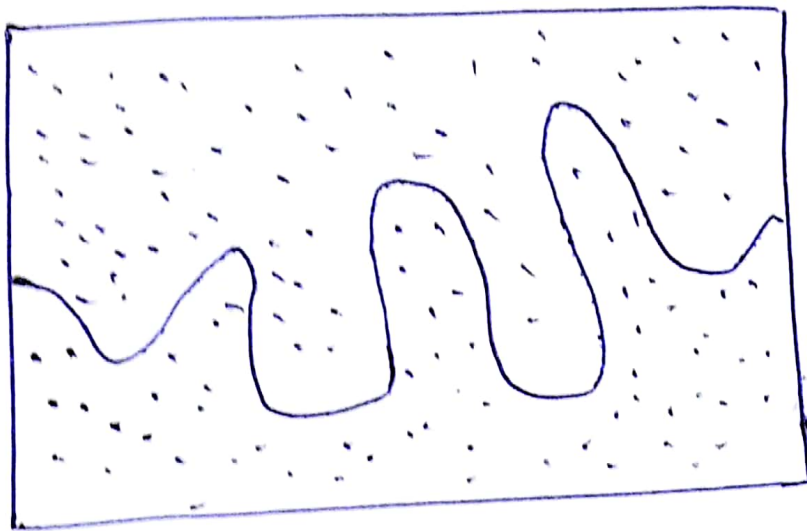
Now the problem is the evaluation of this integral (8).

This is done by Random Sampling method also called MC Method.

This is estimated as follows:

1. Obtain a configuration of the system by randomly generating $3N$ Cartesian coordinates which are assigned to particles.

Schematic representation is:



There are some atoms inside the curve and some outside it, which is the a pre-defined bound area.

2. To calculate the potential energy of this configuration $V(r^N)$ or at this position (fixed all atoms)

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This is nothing but to determine the area under the curve.

$$\text{The area under the curve} = A \times \frac{\text{NO of atoms in the shaded area (Curve)}}{\text{Total no of atoms or points generated}}$$

$$\text{Total area under the curve} = A \times \frac{\text{NO of points inside the curve}}{\text{Total no of atoms in the whole bounded area}}$$

This is ^{approximated} the potential energy.

3. From this the Boltzmann factor $e^{-v(r^N)/k_B T}$ is calculated

4. ~~These Boltzmann~~ Again return to step 1, ^{obtain} ~~generate~~ another configuration by randomly generating another $3N$ Cartesian coordinates.

5. Calculate PE and Boltzmann factor. Go on adding the P.E and the Boltzmann factor to previously calculated both the values.

6. After a ~~no~~ pre-determined, number of total N_{total} iterations, the mean value is calculated

$$\langle V(r^N) \rangle = \frac{\sum_{i=1}^{N_{\text{total}}} V_i(r^N) \exp \left[-V_i(r^N) / k_B T \right]}{\sum_{i=1}^{N_{\text{total}}} \exp \left[-V_i(r^N) / k_B T \right]}$$