$$x = x_{min} + \sum_l u_l \exp(i\omega_l t) \tag{2.301}$$

Here ω_l are the frequencies and u_l are the normal modes.

Monte Carlo Method

Let us assume that we want to generate states that are distributed with a distribution π. The dynamical Monte-Carlo-Method, to generate a sample from an ensemble can be specified as follows:

- Determine the matrix of transition probabilities from state to the other

$$\mathbf{P} = \{p_{xy}\} = \{p(x \rightarrow y)\}, \tag{2.302}$$

that satisfies the following transition probabilities

(i) $\forall x, y \in S \quad \exists \quad n \geq 0 : p_{xy}^{(0)} > 0$

(ii) $\forall y \in S : \sum_x \pi_x p_{xy} = \pi_y$.

A sufficient, but by no means necessary condition to satisfy (ii) is the condition of *detailed balance* for die for the distribution π,

(ii') $\forall x, y \in S : \pi_x p_{xy} = \pi_y p_{yx}$.

We will now construct an algorithm for constant temperature. The condition of detailed balance is

$$\pi_x p_{xy} = \pi_y p_{yx} \qquad \forall x, y \in S .$$

Let $\mathbf{P}^0 = \{p_{xy}^{(0)}\}$ be a irreducible transition matrix. We will use $\mathbf{P}^0$ to propose transitions from x to y. These transitions will then either be accepted with a probability a_{xy} and rejected $1 - a_{xy}$. The complete transition matrix $\mathbf{P}$ is then constructed as:

$$\begin{aligned} p_{xy} &:= p_{xy}^{(0)} a_{xy} \quad \text{if } x \neq y\,, \\ p_{xx} &:= p_{xx}^{(0)} + \sum_{x \neq y} p_{xy}^{(0)}(1 - a_{xy}) \quad [\text{zero transition}]\,, \\ \text{where} \quad &\forall\ x\,y \in S : 0 \leq a_{xy} \leq 1\,. \end{aligned}$$

With this we have

$$\frac{a_{xy}}{a_{yx}} = \frac{\pi_y p_{yx}^{(0)}}{\pi_x p_{xy}^{(0)}} \quad \forall x, y \in S : x \neq y \,.$$

If we use

$$a_{xy} := F\left(\frac{\pi_y \rho_{yx}^{(0)}}{\pi_x \rho_{xy}^{(0)}}\right) \forall x, y \in \mathcal{S} : x \neq y \tag{2.303}$$

then

$$\frac{a_{xy}}{a_{yx}} = \frac{F\left(\frac{\pi_y p_{yx}^{(0)}}{\pi_x p_{xy}^{(0)}}\right)}{F\left(\frac{\pi_x p_{xy}^{(0)}}{\pi_y p_{yx}^{(0)}}\right)} = \frac{F(z)}{F(1/z)} \stackrel{!}{=} z \tag{2.304}$$

with

$$z := \frac{\pi_x p_{xy}^{(0)}}{\pi_y p_{yx}^{(0)}} \quad . \tag{2.305}$$

The condition of detailed balance is satisfied if

$$\text{for} \quad \text{all} z : \frac{F(z)}{F(1/z)} \stackrel{!}{=} z \quad . \tag{2.306}$$

Often used choices are

$$F(z) = \min(z, 1) \tag{2.307}$$

and

$$F(z) = \frac{z}{1+z} \quad . \tag{2.308}$$

Note that the proposals of states need not to be symmetric.

Further Reading 2.6.1 (Hybrid Monte-Carlo)

In the above outlined Monte-Carlo (MC) calculations only local moves (displacement of a single particle) are made [73, 74, 78]. Updating more than one particle typically results in a prohibitively low average acceptance probability $\langle P_A \rangle$. This implies large relaxation times and high autocorrelations especially for macromolecular systems. In a Molecular Dynamics (MD) simulation, with $H = T + U$,

---

Algorithm 1 Metropolis Monte Carlo

1: **for** i=0; i $<$ mcsmax **do**
2:     sample a new state x_p;
3:     sample a uniform random number r from (0,1);
4:     if $r \leq \min\{f(x_p)/f(x_i), 1\}$ then $x_{i+1} = x_p$;
5:     else $x_{i+1} = x_i$;
6: **end for**

---

on the other hand, global moves are made. The MD scheme, however, is prone to errors and instabilities due to the finite step size in time. In order to introduce temperature in the microcanonical context, isokinetic MD schemes are often used [78]. However, they do not yield directly the canonical probability distribution, unlike Monte-Carlo calculations.

The Hybrid Monte-Carlo (HMC) method [63, 64] combines the advantages of Molecular Dynamics and Monte-Carlo methods: it allows for global moves (which essentially consist in integrating the system through phase space); HMC is an exact method, i.e., the ensemble averages do not depend on the step size chosen; algorithms derived from the method do not suffer from numerical instabilities due to finite step size as MD algorithms do; and temperature is incorporated in the correct statistical mechanical sense.

The application of the Hybrid Monte-Carlo method has been proposed [64] for condensed-matter systems and investigated for atomic fluids. In the HMC scheme global moves can be made while keeping the average acceptance probability $\langle P_A \rangle$ high. One global move in configuration space consists in integrating the system through phase space for a fixed time t using some discretization scheme (Δ denotes the step size)

$$
\begin{aligned}
\Psi^\Delta : \quad & \mathbb{R}^{6N} \longrightarrow \mathbb{R}^{6N} \\
& (x, p) \longrightarrow \Psi^\Delta(x, p) =: (x', p')
\end{aligned}
\tag{2.309}
$$

of Hamilton's equations

$$\frac{dx}{dt} = \frac{\partial H}{\partial p} \tag{2.310}$$

$$\frac{dp}{dt} = -\frac{\partial H}{\partial x}. \tag{2.311}$$

Since the system is moved deterministically through phase space, the conditional probability of suggesting configuration x' starting at x is given by

$$p_C(x \rightarrow x')dx' = p_C(p)dp. \tag{2.312}$$

The initial momenta are drawn from a Gaussian distribution at inverse temperature β:

$$p_C(p) \propto e^{-\beta \sum_{j=1}^{N} \frac{p_j^2}{2m}}. \tag{2.313}$$

One has thus from (2.312) and (2.313)

$$P_A((x,p) \rightarrow \Psi^{\Delta}(x,p)) = \min\{1, e^{-\beta \delta H}\}, \tag{2.314}$$

where

$$\delta H = H(\Psi^{\Delta}(x,p)) - H(x,p)$$

is the discretization error associated with Ψ^{Δ}. Using the algebraic identity

$$e^{-H(x,p)} \min\{1, e^{-\delta H}\} = e^{-H(\Psi^{\Delta}(x,p))} \min\{e^{\delta H}, 1\} \tag{2.315}$$

it can be shown that for a discretization scheme which is *time-reversible*

$$\Psi^{-\Delta} \circ \Psi^{\Delta} = id \tag{2.316}$$

and *area-preserving*

$$\det \frac{\partial \Psi^{\Delta}(x,p)}{\partial(x,p)} = 1, \tag{2.317}$$

detailed balance is satisfied:

$$
\begin{aligned}
p(x)p_M(x \to x')dxdp &= p(x)p_C(p)P_A((x,p) \to g^{\delta t}(x,p))dxdp \\
&= p(x')p_C(p')P_A(\Psi^\Delta(x,p) \to (x,p))dxdp \\
&= p(x')p_C(p')P_A((x',p') \to \Psi^{-\Delta}(x',p'))dxdp \\
&= p(x')p_C(p')P_A((x',p') \to \Psi^{-\Delta}(x',p'))dx'dp' \\
&= p(x')p_M(x' \to x)dx'dp'.
\end{aligned}
$$

Thus, provided the discretization scheme used is time-reversible and area-preserving, the HMC algorithm generates a Markov chain with the stationary probability distribution $p(x)$. The probability distribution is entirely determined by the detailed balance condition. Therefore neither $p(x)$ nor any ensemble averages depend on the step size Δ chosen.

However, the average acceptance probability $\langle P_A \rangle$, because of (2.314), depends on the average discretization error $\langle \delta H \rangle$ and hence does depend on δt.

Lattice models

If we are to us a lattice to hold a protein chain, then monomers are represented using uniform size and the bond length is considered uniform. Consider a N-amino acid polypeptide which is described by polymer on a lattice in dimension D with a prescribed symmetry. We shall for the moment use any general lattice λ generated by the symmetry group G that consists only of translations. Each amino acid occupies one site on the lattice, and each peptide bond sits on a bond of the lattice. The folding of lattice proteins amounts to exploration of the ensemble of self-avoiding walk (SAW) configurations. What we are interested in is to count conformational states: How many conformational states are there for the N-monomer polymer that have a low energy (we will be more precise later).

If we are to enummerate the number of possible conformation one strategy is to use a Monte Carlo method to generate a Markov chain that will give the appropriate distribution at temperatures $T < \infty$. Starting with a given chain on our lattice we can change the conformation of the chain using three basic moves as depicted in figure 2.34. The repeated application of the move set containing end bends, kink and crankshaft moves respects linear connectivity and is applied such