

Sampling the canonical distribution and the transition paths

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- 1 Comparing the efficiency of stochastic thermostats in molecular dynamics
- 2 Transition path theory:
 - Finding the most probable paths of transition (understanding the mechanism of the transition, what is the preferred paths for transition. For example how a polymer changes from one configuration to another.)
 - Reaction Rate (what is the mean frequency of transitions from A to B ?)

The average of an observable $O(q, p)$ defined on phase space $q, p \in \mathbb{R}^n$ is computable by

$$\langle O \rangle = \int_{\mathbb{R}^{2n}} O(q, p) d\rho_{\beta}(q, p),$$

where $\rho_{\beta} = \frac{1}{Z} \exp(-\beta H(q, p))$ is the density of the Gibbs measure and β is the inverse temperature.

Our aim is to find a process $\Phi(t; q, p)$ such that

$$\langle O \rangle = \lim_{\tau \rightarrow \infty} \frac{1}{\tau} \int_0^{\tau} O(\Phi(t; q, p)) dt.$$

IMPORTANT PROPERTIES

- 1 **Ergodicity:** $\rho_\beta(\{q, p : \langle O \rangle_\Gamma = \langle O \rangle\}) = 1$ (i.e., for almost all initial conditions the phase space averages are equal to long time averages)
- 2 **How fast it converges to equilibrium.**
- 3 **Can we obtain a correct qualitative dynamical information:** accurate calculation of correlation functions:

$$\int_{\mathbb{R}^{2n}} O \cdot O(s; q, p) d\rho_\beta(q, p) = \lim_{\tau \rightarrow \infty} \frac{1}{\tau} \int_0^\tau O(\Phi(t; q, p)) O(\Phi(t + s; q, p)) dt.$$

Two type of thermostats

- 1 Deterministic thermostat such as Nosé-Hoover
 - Better calculation of correlation functions.
- 2 Stochastic thermostats such as Langevin dynamics
 - Better convergence rate and proof of ergodicity.

Can we combine the two methods to achieve ergodicity while retaining the advantages of Nosé-Hoover?

Langevin

$$dq = M^{-1}p dt,$$

$$dp = -\nabla_q V(q) dt - \gamma p dt + \sigma dW.$$

- $\gamma : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ and $\sigma : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ are positive definite.
- $W = (W_1, \dots, W_n)^T$ is a family of n standard Brownian motion.
- For $\sigma \sigma^T = \frac{2}{\beta} \gamma M$ (fluctuation-dissipation) the density $f(q, p) = \frac{1}{Z} e^{-\beta H}$ is the invariant solution of the Fokker-Planck equation:

$$L^* f = -\nabla_q \cdot (M^{-1} p f) + \nabla_p \cdot (\nabla_q V(q) f) + \nabla_p \cdot \left(\frac{1}{2} \sigma \sigma^T \nabla_p f + \gamma p f \right) = 0.$$

Nose-Hoover

$$\begin{aligned}\frac{dq}{dt} &= M^{-1}p, \\ \frac{dp}{dt} &= -\nabla_q V(q) - \xi p, \\ \frac{d\xi}{dt} &= \frac{1}{\mu} \left(p^T M^{-1} p - \frac{n}{\beta} \right).\end{aligned}$$

- μ is a coupling parameter to an artificial heat bath.
- The augmented density $f_\beta^\xi(q, p, \xi) = \frac{1}{Z} e^{-\beta + \frac{\mu}{2}\xi^2}$ is the solution of the Liouville equation

$$\begin{aligned}L f_\beta^\xi &= \nabla_q \cdot (M^{-1} f_\beta^\xi) - \nabla_p \cdot (\nabla_q V(q) f_\beta^\xi) - \nabla_p \cdot (\xi p f_\beta^\xi) \\ &+ \frac{\partial}{\partial \xi} \left[\frac{1}{\mu} \left(p^T M^{-1} p - \frac{n}{\beta} \right) f_\beta^\xi \right] = 0.\end{aligned}$$

Nosé-Hoover-Langevin

$$\frac{dq}{dt} = M^{-1}p,$$

$$\frac{dp}{dt} = -\nabla_q V(q) - \xi p,$$

$$d\xi = \frac{1}{\mu} \left(p^T M^{-1} p - \frac{n}{\beta} \right) dt - \gamma' \xi dt + \sigma dW.$$

- W is only one standard Brownian motion, $\mu > 0$ and $\sigma^2 = \frac{2\gamma'}{\beta\mu}$.
- f_β^ξ satisfies the Fokker-Planck equation:

$$\begin{aligned} L^* f_\beta^\xi &= -\nabla_q \cdot (M^{-1} p f_\beta^\xi) + \nabla_p \cdot (\nabla_q V f_\beta^\xi) + \nabla_p \cdot (\xi p f_\beta^\xi) \\ &\quad - \frac{\partial}{\partial \xi} \left[\left(p^T M^{-1} p - \frac{n}{\beta} \right) f_\beta^\xi \right] + \frac{\partial}{\partial \xi} (\gamma \xi f_\beta^\xi) = \frac{1}{2} \sigma^2 \frac{\partial^2 f_\beta^\xi}{\partial \xi^2} = 0. \end{aligned}$$

Stochastic Velocity Rescaling Thermostat

$$\begin{aligned}dq_i &= \frac{\partial H}{\partial p_i} dt \\dp_i &= -\frac{\partial H}{\partial q_i} dt - \Psi(K)p_i dt + \sqrt{2kT\Phi(K)}p_i dW(t),\end{aligned}$$

where $W(t)$ is a single Wiener process, $\Phi(K)$ is an arbitrary positive-valued function of the kinetic energy $K = \sum_{i=1}^n \frac{p_i^2}{2m_i}$ and $\Psi(K)$ is defined by

$$\Psi(K) := (2K - (1+n)kT)\Phi(K) - 2kTK \frac{d\Phi}{dK}.$$

We use $\Phi(K) = \gamma/2K$ in our simulation here.

Hypoellipticity (A notion for regularity)

Let L be a linear differential operator, we say that L is hypoelliptic if, whenever $Lf = g$ and $g \in C^\infty$, then f is in C^∞ .

EXAMPLES

- 1 $L_1 f(x, y) = \frac{\partial^2 f(x, y)}{\partial x^2}$,
- 2 $L_2 f(x, y) = \frac{\partial f(x, y)}{\partial y} + \frac{\partial^2 f(x, y)}{\partial x^2}$.

Both examples have second order derivative only in one of the two spatial directions. The first example is not hypoelliptic whereas the second example is hypoelliptic.

Theorem

Let $U \subset \mathbb{R}^N$ be open, connected and invariant under the flow. If all solutions ρ of $L^ \rho = 0$ are continuous on U , then f_β is the unique invariant measure on U .*

- The theorem relates ergodicity to the regularity of the solutions for the operator L^* .

Theorem (2)

All distributional solutions of the operator L^* which is defined by

$$L^* \rho(z) := - \sum_{i=1}^N \frac{\partial}{\partial z_i} (\rho(z) X_{0,i}(z)) + \frac{1}{2} \sum_k \sum_{i,j=1}^N \frac{\partial^2}{\partial z_i \partial z_j} (\rho(z) X_{k,i}(z) X_{k,j}(z)),$$

are C^∞ , if for each $z \in U$ the vector space generated by $X_0(z), X_k(z)$ together with their Lie brackets, i.e.,

$$\text{Span}\{X_0(z), X_1(z), [X_0, X_1](z), [X_0, [X_0, X_1]](z) \dots\}$$

is \mathbb{R}^N .

$$H(q, p) = \frac{1}{2}p^T M^{-1}p + \frac{1}{2}q^T Bq.$$

Theorem

Let $M, B \in \mathbb{R}^{n \times n}$ be two symmetric and positive definite matrices such that

$$\omega_k \neq \omega_l \text{ for all } k \neq l, \quad (1)$$

where $\omega_k = \varphi_k^T M^{-1} B \varphi_k$ are the eigenvalues and $\varphi_1, \dots, \varphi_n \in \mathbb{R}^n$ are the normalized eigenvectors of $M^{-1}B$. If $H(q, p) = \frac{1}{2}p^T M^{-1}p + \frac{1}{2}q^T Bq$ and

$$U = \left\{ (q, p) \mid \prod_{k=1}^n ((q \cdot \varphi_k)^2 + (p \cdot \varphi_k)^2) \neq 0 \right\} \times \mathbb{R}, \quad (2)$$

then the process generated by new method is ergodic on U .

For simplicity assume that $M = \text{Id}$, all parameters are 1, then we have:

$$X_0 = (p, -Bq - \xi p, p^2 - n - \frac{1}{2}\xi), \quad X_1 = (0, 0, 1).$$

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Next, we define recursively

$$Z_k = \frac{1}{2}[Y_k, X_3], \quad Y_{k+1} = -\frac{1}{2}[Z_k, X_3],$$

where

$$\begin{aligned} X_2 &= [X_1, (p^2 - n - \frac{1}{2}\xi)X_1 - X_0] = (0, p, 0), \\ X_3 &= X_0 - (p^2 - n - \frac{1}{2}\xi)X_1 + \xi X_2 = (p, -Bq, 0), \\ Y_1 &= [X_2, X_3] = (p, Bq, 0). \end{aligned}$$

Induction yields that

$$Y_k = (B^{k-1}p, B^kq, 0), \quad Z_k = (B^kq, -B^kp, 0), \quad k = 1, 2, \dots$$

Since B is diagonal and positive definite, using condition (2) implies that the vectors:

$$Y_1, Z_1, \dots, Y_{n-1}, Z_{n-1}, Y_n, Z_n,$$

span \mathbb{R}^{2n} .

The question considered here is how best to use molecular dynamics to compute time-dependent properties (such as autocorrelation functions) when we use stochastic dynamics to sample Gibbs distribution.

We answer this by defining a term efficiently as the reciprocal of the amount of error that accumulates during the time that was needed to bring the system to equilibrium the prescribed temperature.

Assumption 1

There is a time-dependent 'empirical temperature' $\theta(t)$ such that, for all phase-space functions f that are even in the momenta,

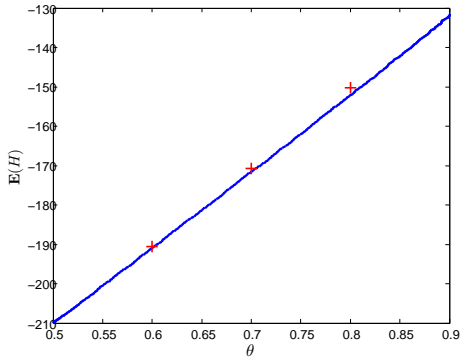
$$\mathbf{E}^t \{f(p_1, \dots, q_n)\} \approx \frac{1}{Z(\theta)} \int_{\Gamma} d^{2n}x f(x) e^{-H(x)/k\theta}, \quad (3)$$

where,

$$Z(\theta) := \int_{\Gamma} d^{2n}x e^{-H(x)/k\theta}.$$

In Particular, taking f to be kinetic energy, we have

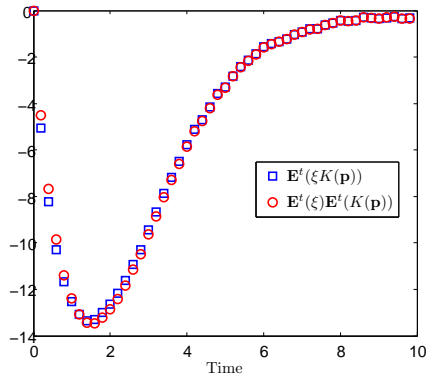
$$\mathbf{E}^t \{K\} = \frac{1}{2}nk\theta.$$



Assumption 2

The random variables $\xi(t)$ and $K(t)$, which are uncorrelated when $t = 0$, remain uncorrelated for all $t > 0$:

$$\mathbf{E}^t\{\xi K\} \approx \mathbf{E}^t\{\xi\}\mathbf{E}^t\{K\}.$$



As a simple criterion for convergence to equilibrium with the thermostat we consider the time evolution of the expectation of the energy. For simplicity we use same mass $m_i = m$.

Convergence rate for Langevin

$$\begin{aligned}\frac{d}{dt}\mathbf{E}^t\{H\} &= \mathbf{E}^t\{LH(q,p)\} \\ &= \mathbf{E}^t\left\{\sum_i^n \left(p_i \frac{\partial H}{\partial q_i} - \frac{\partial H}{\partial q_i} p_i - \gamma p_i^2 + \gamma m_i kT\right)\right\} \\ &= \gamma(nkT - \mathbf{E}^t\{2K\}).\end{aligned}$$

Now to relate $\mathbf{E}^t\{H\}$ to $\mathbf{E}^t\{2K\}$, we use the Assumption 1.

Define $\mathbf{E}^t\{H\} \approx U(\theta) := \frac{1}{Z(\theta)} \int_{\Gamma} d^{2n}H(x)e^{-H(x)/k\theta}$. Then using the Assumption 1, we have

$$C(\theta) \frac{d\theta}{dt} = nk\gamma(T - \theta),$$

where, $C(\theta) := \frac{dU(\theta)}{d\theta}$ is the heat capacity at temperature θ . The general solution of the above is $\theta = T - \text{const} \times e^{-nk\gamma t/C(T)}$, which estimates the rate of convergence to the thermostat temperature at $nk\gamma/C(T)$.

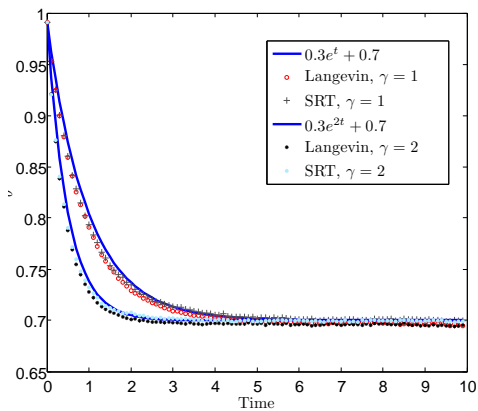
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Convergence rate for Velocity Rescaling

Following similar analysis as in the case of Langevin we estimate the rate of convergence to thermostat temperature as $4\mathbf{E}_{eq}\{K^2\Phi(K)\}/TC(T)$. For the choice $\Phi(K) = \gamma/2K$ which we use in our numerical simulation, the rate of convergence becomes $\gamma nk/C(T) \approx \gamma$.



Convergence rate for the NHL Thermostat

Using assumption 1 and 2 we see that the convergence to thermostat temperature is governed by nonlinear system:

$$C(\theta) \frac{d\theta}{dt} \approx -nk \mathbf{E}^t \{\xi\},$$
$$\frac{d}{dt} \mathbf{E}^t \{\xi\} = \frac{nk}{\mu} (\theta - T) - \gamma' \mathbf{E}^t \{\xi\}.$$

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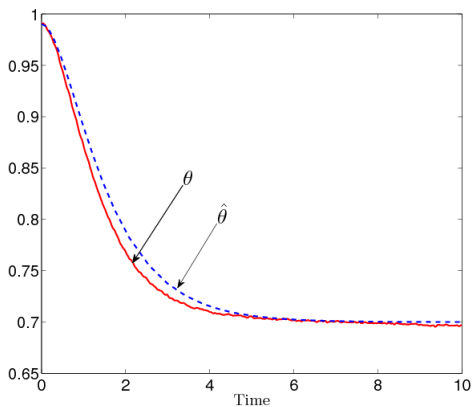
$$C(\theta) \frac{d\theta}{dt} \approx -nk \mathbf{E}^t \{\xi\},$$
$$\frac{d}{dt} \mathbf{E}^t \{\xi\} = \frac{nk}{\mu} (\theta - T) - \gamma' \mathbf{E}^t \{\xi\}.$$

An estimate of the rate of approach can be obtained by considering the linearized system, which (after eliminating $\mathbf{E}^t \{\xi\}$) can be written

$$\frac{d^2\theta(t)}{dt^2} + \gamma' \frac{d\theta(t)}{dt} + \frac{n^2 k^2 T}{\mu C(T)} (\theta(t) - T) = 0.$$

This is the equation of a damped harmonic oscillator. The optimal decay rate is the critical damping value

$$\gamma'_{\text{crit}} := 2 \sqrt{\frac{n^2 k^2 T}{\mu C(T)}}.$$



Comparison of the relaxation of θ , obtained as the mean of $2K/nk$ over a sample of 10,000 NHL trajectories, with $\hat{\theta}$, the numerical solution of the above nonlinear system.

The rate of accumulation of the thermostat perturbation

we estimate the rate at which the resulting perturbation of the motion (due to the stochastic term) builds up over time. As a concrete example, we consider the effect of the perturbation on the calculation of the velocity autocorrelation function (VAF). Assuming all the particles have same mass m , the VAF can be defined as

$$F(t) := \frac{1}{nmkT} \sum_{i=1}^n \mathbf{E}^t \{p_i(0)p_i(t)\}.$$

In this formula, the evolution $p(t)$ is Hamiltonian.

We estimate $F(t)$ for small time using Taylor's expansion, under the assumption that one of stochastic dynamics has been used instead of Hamiltonian dynamics. For this, it will be necessary to calculate the first derivative dF/dt at $t = 0$ and, in the case of the NHL thermostat, the second derivative as well.

Langevin

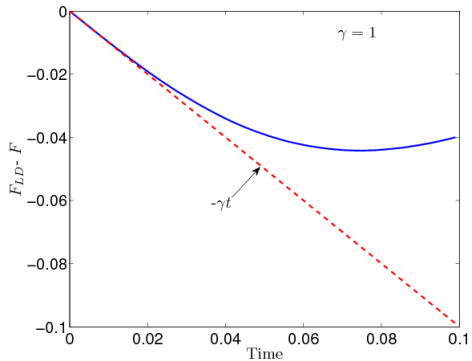
$$\Delta_{LD}F(t) := F(t) - F_{LD}(t) = -\gamma t + \mathcal{O}(t^2),$$

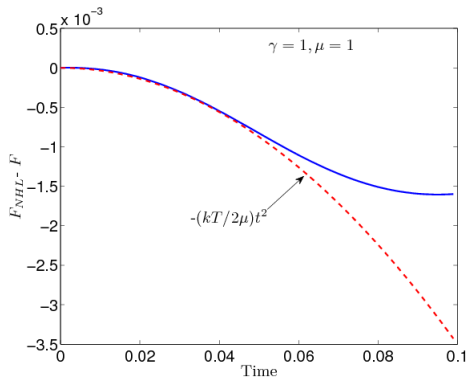
velocity rescaling

$$\Delta_{VR}F(t) := F(t) - F_{VR}(t) = -\frac{2}{n} \mathbf{E}\{K\Phi(K)\}t + \mathcal{O}(t^2),$$

NHL

$$\Delta_{NHL}F(t) := F(t) - F_{NHL}(t) = -\frac{kT}{\mu} \frac{t^2}{2} + \mathcal{O}(t^3).$$





Estimated convergence rates, error-accumulation rates and efficiencies for various thermostats.

Method	Convergence rate	Error rate	Efficiency
Langevin	$\frac{nk\gamma}{C(T)}$	γt	$\frac{nk}{C(T)} \approx 1$
Velocity rescaling	$4 \frac{\mathbf{E}_{eq}\{K^2\Phi(K)\}}{TC(T)}$	$\frac{2}{n} \mathbf{E}_{eq}\{K\Phi(K)\} t$	$\mathcal{O}(n)$
VR with $\Phi(K) = \frac{\gamma}{2K}$	$\frac{nk\gamma}{C(T)}$	$\frac{\gamma}{n} t$	$\frac{n^2k}{C(T)} \approx n$
NHL	$\gamma'_{\text{crit}}/2 = \sqrt{\frac{n^2k^2T}{\mu C(T)}}$	$\frac{kT}{2\mu} t$	$\frac{2n^2k}{C(T)} \approx 2n$

Transition paths theory

Ref: Weinan E and E. Vanden-Eijnden: *Towards a theory of transition paths* *Journal of Statistical Physics* 123, 3, 503-523. (2006)

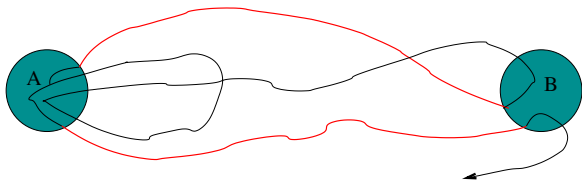
Consider a system whose state-space is $\Omega \subseteq \mathbb{R}^n$ and has two long-lived states $A \subset \Omega$ and $B \subset \Omega$. The state of the system at time t is given by

$$dx = -\nabla V(x(t))dt + \sqrt{2kT}dW, \quad x(0) = x,$$

where W is n -dimensional Wiener process. $V(x)$ is the potential of the system which governs interaction between atoms. The stationary probability density of x is the Boltzmann-Gibbs density

$$\rho(x) = \frac{1}{Z}e^{-\beta V(x)}, \quad Z = \int_{\Omega} e^{-\beta V(x)} dx,$$

where $\beta = \frac{1}{kT}$.



A piece of trajectory $x(t)$, $t \in [t_A, t_B]$ is considered reactive if $x(t) \notin A \cup B$ and such that it came from A last and will go to B next

What is the probability density of reactive trajectories?

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The committor Function $q(x)$

The probability that $x(t)$ reaches B first rather than A , given that $x(0) = x$. (By definition $q(x)$ is in fact the collective variable.)

What is the probability density of reactive trajectories?

The committor Function $q(x)$

The probability that $x(t)$ reaches B first rather than A , given that $x(0) = x$. (By definition $q(x)$ is in fact the collective variable.)

Because $x(t)$ is a reversible process, the probability that $x(t)$ left A rather than B is $(1 - q)$. Thus the probability that a trajectory is reactive is $q(x)(1 - q(x))$. Moreover the probability density of reactive trajectories is

$$\rho_{AB}(x) = Z_{AB}^{-1} q(x)(1 - q(x))\rho(x),$$

where

$$Z_{AB} = \int_{\Omega \setminus (A \cup B)} q(x)(1 - q(x))\rho(x)dx.$$

It can be shown that $q(x)$ satisfies a backward Kolmogorov equation with boundary conditions (that is, 0 on the boundary of A and is 1 on the boundary of B):

$$\begin{cases} 0 = -\sum_i^n \frac{\partial V(x)}{\partial x_i} \frac{\partial q(x)}{\partial x_i} + \sum_i^n kT \frac{\partial^2 q(x)}{\partial x_i^2}, \\ q(x)|_{x \in \partial A} = 0, \quad q(x)|_{x \in \partial B} = 1. \end{cases}$$

Once $q(x)$ is found we can answer other questions such as probability current of reactive trajectories J_{AB} , given by

$$J_{AB} = kT \rho(x) \nabla q(x),$$

and reaction rate k_{AB} , given by

$$k_{AB} = \frac{kT}{Z} \int_{\Omega \setminus (A \cup B)} \sum_{i=1}^n \left(\frac{\partial q(x)}{\partial x_i} \right)^2 e^{-\beta V(x)} d^n x$$

or by

$$k_{AB} = \int_S J_{AB}(x) n_S(x) d\sigma_S(x),$$

where S is any dividing surface in $\Omega \setminus (A \cup B)$, n_S is the unit normal to S pointing toward B and $d\sigma_S$ is the surface element.

How to solve for $q(x)$?

- The main problem is finding q which involves solving the backward Kolmogorov equation, which is not possible except for systems of low dimension up to 3.
- For any successful solution, we must exploit structure within the problem and reduce the dimension as much as possible.

Collective variables

In most physical phenomena the reaction or transition can be described by changes in a set of collective variables $\xi(x) = \{\xi_1(x), \dots, \xi_m(x)\} \in D \subset \Omega$, where $m \ll n$ and n is the dimension of the system. (For example the transition of alanine dipeptide can be described by changes in two dihedral angles.)

Assumption

We assume that the transition can be described by a set of collective variables ξ with dimension $m \leq 3$ and there exists a quasi-committor function $\tilde{q}(\xi) \approx q(x)$, in the sense that:

$$\tilde{q}(z) = q(x), \text{ for all } x \in \xi^{-1}(z), \text{ where } \xi^{-1}(z) = \{x : \xi(x) = z\}.$$

Now q is the probability that $x(t)$ starting at x hits B first rather than A , and it can be written as an expectation of an indicator function

$$u_t(x) := \chi_B(x(t)) \prod_{s \leq t} \chi_{\Omega \setminus A}(x(s))$$

over all paths that start from x :

$$q(x) := \mathbf{E}[u_s(x)] = \int_{\Omega} u_s(x) \rho(x) dx.$$

Having defined q we next define

$$\tilde{q}(\xi) := \int_D \tilde{u}_s(\xi) f(\xi) d\xi,$$

where $f(\xi)$ is the probability density of ξ and \tilde{u}_s is an equivalent indicator function in ξ variable.

Now consider

$$d\xi = G(\xi)dt + \sqrt{2kT}dW, \quad (4)$$

where $G(q)$ is some approximation of $\nabla V(x)$, for a given ξ . Let $h(\xi, t)$ be the density for solution $\xi(t)$ of (4). The time evolution of h is governed by the following Fokker-Planck equation

$$\frac{\partial h}{\partial t} = \nabla_{\xi} \cdot (kT\nabla_{\xi}h - hG).$$

If $h(\xi, t) \rightarrow f(\xi)$ as $t \rightarrow \infty$, then we could use (4) to compute the average of a function of ξ .

We can show that, if $G(\xi) = \langle \nabla_{\xi} V - kT\nabla_{\xi} \log |J| | \xi(x) = \xi \rangle$ then h converges exponentially fast to f .

$G(\xi)$ is known as the potential of mean force. For the case $m \leq 3$ one can compute $G(\xi)$ using constrained dynamics, and this may be performed using parallel computer.

Once $G(\xi)$ is computed then $\tilde{q}(\xi)$ can be obtained by solving the following reduced backward Kolmogorov equation:

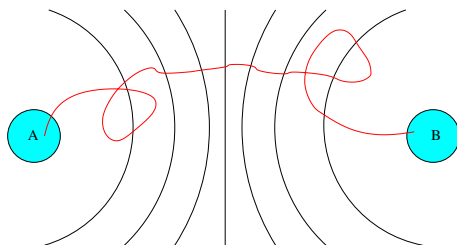
$$\begin{cases} 0 = \sum_i^m G(\xi) \frac{\partial \tilde{q}(\xi)}{\partial \xi_i} + \sum_i^m kT \frac{\partial^2 \tilde{q}(\xi)}{\partial \xi_i^2}, \\ \tilde{q}(\xi)|_{\xi \in \partial \tilde{A}} = 0, \quad \tilde{q}(\xi)|_{\xi \in \partial \tilde{B}} = 1. \end{cases} \quad (5)$$

The reduced equation (5), being of low dimension, may be solved by discretization methods such as the finite element method.

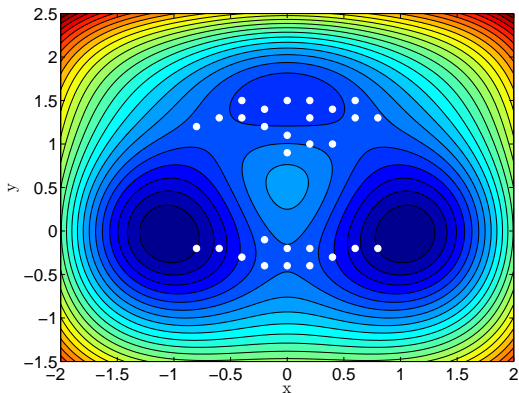
Assumption

- We are given two long-lived states A and B , and the transition can be described by set of collective variable ξ .
- The transition flux is clustered in one or few localized regions in $\Omega \setminus (A \cup B)$ (this is not to say that reactive trajectories are clustered as they are usually complex object and they are likely to visit many part of the $\Omega \setminus (A \cup B)$ before making the transition).

Sampling isocommittor surfaces



The transition is most likely to occur where the probability density is maximized on the isocommittor surface. Hence we search for points on isocommittor surfaces where the probability density is locally maximized.



We computed reaction rate, using interval $[-0.6, -0.1]$ and $[0.7, 1.8]$ on isocommittor $x = 0$. We obtained 1.104×10^{-7} which is close to the exact rate 0.947×10^{-7}

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