How to define good metastable states?

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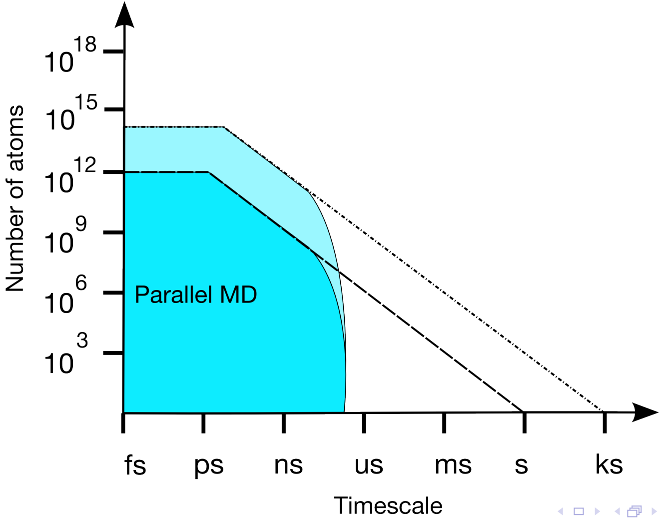
The timescale problem in MD

Increase in computational power $\Delta P \propto \Delta N_{\text{atoms}}$ for a given simulation time T_{sim}. But $\Delta P \not\propto \Delta T_{\text{sim}}$ for a given N_{atoms}!



Accelerated dynamics (Voter, A.F.)[18]

Exploiting metastability to speed up transitions. Metastability: the dynamics is "stuck" in a local equilibrium state Ω.

- Temperature Accelerated Dynamics: heat up the system and filter out "unrealistic" transitions in a post-processing step. (assumes Eyring–Kramers laws hold)
- Hyperdynamics: add a biasing potential to reduce energetic barriers surrounding Ω. (assumes Gibbs invariant measure)
- Parallel Replica: speed up transitions by following the first of many independent replicas to escape Ω (works for any Markov process if local equilibrium in Ω exists.)

Formulation using the QSD

Dynamics $X_t \in \mathbb{R}^d$.

Definition

A quasi-stationnary distribution (QSD) in $\Omega \subset \mathbb{R}^d$ is a probability distribution ν such that:

$$\mathbb{P}^\nu \left(X_t \in A \,|\, X_s \in \Omega,\, 0 \leq s \leq t \right) = \nu(A).$$

$$\text{Generally, } \nu = \lim_{t \to \infty} \mathrm{Law} \left(X_t \,|\, X_s \in \Omega,\, 0 \leq s \leq t \right).$$

Let $\tau =$ exit time from Ω.
Key property (four-line proof):

$$\exists \lambda > 0 \,\text{s.t.}\ \ \tau \sim \mathcal{E}(\lambda), \quad X_\tau \text{ independent of } \tau.$$

Metastable exit from Ω: sample independent replicas $X_0^{(1)}, \ldots, X_0^{(N)} \sim \nu$, $i =$ index of first replica to escape.
Using the key property:

$$(N\tau_i, X_{\tau_i}^{(i)}) \sim (\tau, X_\tau).$$

The ParRep algorithm

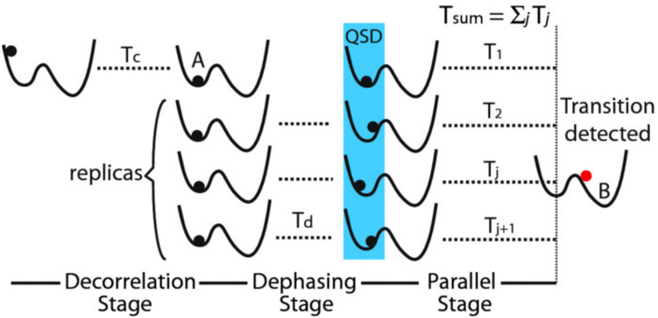


Figure: Taken from [16]

Gain: parallel sampling of metastable exit event.
Overhead: preparation of independent replicas $\sim \nu$.
Efficient if $T_{\mathrm{decorr+dephase}} \ll T_{\mathrm{exit}}$.

Spectral characterization

Proposition (Le Bris, Lelièvre, Luskin, Perez 2012[11])

Assume $X_t = -\nabla V(X_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t$ (overdamped Langevin). The QSD in Ω is given by:

$$\nu(A) = \frac{\int_A u_1 \mathrm{e}^{-\beta V}}{\int_\Omega u_1 \mathrm{e}^{-\beta V}}, \mathbb{E}^\nu[\tau] = 1/\lambda_1,$$

where (λ_1, u_1) satisfying

$$\begin{cases} -\mathcal{L}_\beta u_1 := \nabla V \cdot \nabla u_1 - \beta^{-1}\Delta u_1 = \lambda_1 u_1, & \text{in } \Omega, \\ u_1 = 0, & \text{on } \partial\Omega, \end{cases}$$

is the smallest eigenpair of the generator $\mathcal{L}_\beta$ with absorbing conditions on $\partial\Omega$.

The QSD is computed with the solution to a Dirichlet eigenvalue problem in a weighted space

$$L^2_\mu(\Omega) = \{f : \int_\Omega f^2 \mathrm{e}^{-\beta V} < +\infty\},$$

and the **exit rate** from the QSD is the eigenvalue $\lambda_1 = T_{\mathrm{exit}}^{-1}$.

Speed of convergence to the QSD

Theorem (Le Bris, Lelièvre, Luskin, Perez 2012[11])

The law of the exit event (τ, X_τ) starting from $\mu_t := \mathrm{Law}(X_t | \tau > t)$ converges to the law of (τ, X_τ) under the QSD exponentially fast:

$$\sup_{\|f\|_\infty \leq 1} \left| \mathbb{E}^{\mu_t}\left[f(X_\tau, \tau)\right] - \mathbb{E}^{\nu}\left[f(X_\tau, \tau)\right] \right| \leq C \mathrm{e}^{-(\lambda_2 - \lambda_1)t}.$$

The **equilibration rate** to the QSD is given by the spectral gap $\lambda_2 - \lambda_1$ of the generator $\mathcal{L}_\beta$ killed at the boundary $\partial\Omega$.

How to choose Ω ?

- Maximize $J(\Omega) = \frac{\lambda_2(\Omega) - \lambda_1(\Omega)}{\lambda_1(\Omega)}$.
- Make the exit time as large as possible compared to the decorrelation time.
- Loosely: maximize the **separation of timescales** (make the domain as metastable as possible).
- Default choice: Ω is a bassin of attraction for steepest descent. Suboptimal because of recrossings around the saddle.

Direct approach: shape optimization of eigenvalues

Isolated Dirichlet eigenvalues of $\mathcal{L}_\beta$ are **shape-differentiable**:

Proposition (B., Lelièvre, Stoltz, 2024 (in preparation))

The map

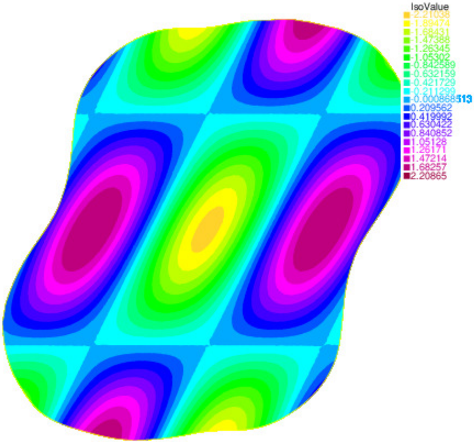
$$\begin{cases} \mathcal{W}^{1,\infty}(\mathbb{R}^d;\mathbb{R}^d) \to \mathbb{R} \\ \theta \mapsto \lambda_k((\theta+\mathrm{Id})\Omega) \end{cases}$$

is continuously Fréchet-differentiable at 0*, with:*

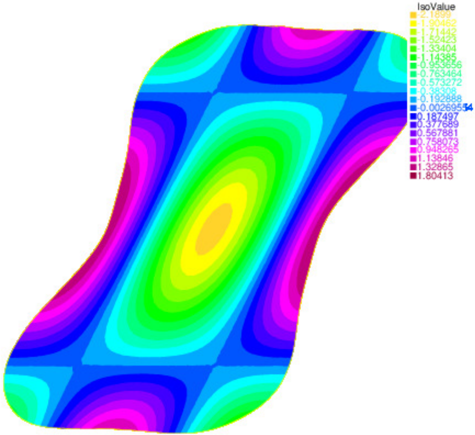
$$\mathrm{d}\lambda_k(\Omega_0)\xi = -\frac{1}{\beta}\int_{\partial\Omega_0}\left(\frac{\partial u_k(\Omega_0)}{\partial \mathrm{n}}\right)^2 (\xi\cdot\mathrm{n})\,\mathrm{e}^{-\beta V}\,\mathrm{d}\sigma, \quad \forall\,\xi\in\mathcal{W}^{1,\infty}(\mathbb{R}^d;\mathbb{R}^d),$$

where σ *denotes the surface measure on* $\partial\Omega_0$*, and* n *the outward surface normal to* Ω_0*.*

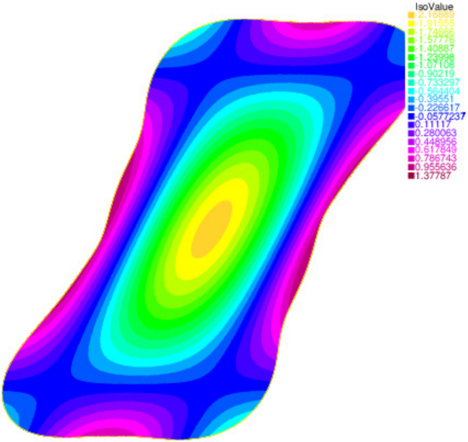
Shape gradient descent: $\beta = 3$



Shape gradient descent: $\beta = 6$



Shape gradient descent: $\beta = 9$



The computed domains seem to close in on the energetic well at low temperatures, and "spill out" past the saddle point to a certain energy level.

Indirect approach: optimization of the low-temperature asymptotics

For real systems, solving $-\mathcal{L}_\beta u = \lambda u$ is impossible.

- **Idea**: parametrize a family of domains $(\Omega_{\beta,\alpha})_{\beta>0}$ with $\alpha \in \mathbb{R}^p$, $p \ll d$. Find **asymptotically optimal** $\Omega_{\beta,\alpha}$ as $\beta \to \infty$.
- **Goal**: find asymptotics of $\lambda_1(\Omega_{\beta,\alpha}), \lambda_2(\Omega_{\beta,\alpha})$ in the limit $\beta \to 0$.
- **Allows**: optimization of asymptotics for $\lambda_2(\Omega_{\beta,\alpha})/\lambda_1(\Omega_{\beta,\alpha})$ w.r.t. α.
- **Mathematically**: a question in spectral asymptotics with moving boundary.

Mathematical approaches to metastability

- **Large deviations:** (Friedlin & Wentzell): first mathematical proof of Ahrennius' law [19]
- **Potential theory for Markov processes:** approaches (Bovier, Eckhoff & al.) first sharp estimates of low-lying eigenvalues [2, 3]
- **Semiclassical analysis, Witten Laplacians:** (Hellfer, Sjöstrand, Nier & al.): alternative point of view [17, 7, 8, 6]
- **Numerical analysis for accelerated dynamics:** (Nier, Lelièvre & al.) Hyperdynamics [14], TAD/KMC [4, 13], rigorous Eyring–Kramers transition rates.
- **Recent developments:** non-reversible diffusions [1, 10, 12], entropic barriers [15, 5], resolvent formulation [9].

And many more... Active field with many open questions.

Assumption/choice: local geometry of the boundary

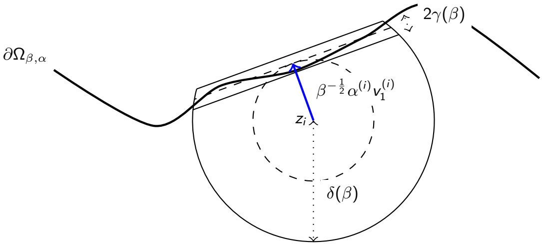


Figure: Local geometry of $\partial\Omega_{\beta,\alpha}$ around a saddle point z_i. Length scales: $\gamma(\beta) \ll \beta^{-\frac{1}{2}} \ll \delta(\beta)$. Direction $v_1^{(i)}$ is unstable eigenvector of $\nabla^2 V(z_i)$.

- $\alpha = (\alpha^{(i)})_{i=1,\dots,m}$ signed distances of the boundary to the saddle points on the scale $\beta^{-\frac{1}{2}}$. $\alpha^{(i)} = \lim_{\beta\to\infty} \sqrt{\beta}\sigma(\partial\Omega_{\beta,\alpha}, z_i)$. where $(z_i)_{i=1,\dots,m}$ are the saddle points.
- Domains whose boundaries are roughly **perpendicular to minimum energy paths**.

Limit behavior of the low-lying of the spectrum

Convergence of any finite number of eigenvalues.

Theorem (B., Lelièvre, Stoltz 2024 (in preparation))

Let $k \in \mathbb{N}$. Then:

$$\lim_{\beta \to \infty} \lambda_k(\Omega_{\beta,\alpha}) = \lambda^{\mathrm{H}}_{k,\alpha},$$

where $\lambda^{\mathrm{H}}_{k,\alpha}$ is the k-th eigenvalue of a certain operator $-\mathcal{L}^{\mathrm{H}}_{\beta,\alpha}$.

The operator $\mathcal{L}^{\mathrm{H}}_{\beta,\alpha}$ is the **harmonic approximation**, with tractable spectrum. Assume single minimum z_0, only order-one saddle points $z_1, \dots, z_m$.

$$\lambda_1(\Omega_{\beta,\alpha}) \xrightarrow{\beta\to\infty} 0, \quad \lambda_2(\Omega_{\beta,\alpha}) \xrightarrow{\beta\to\infty} \min\left[\nu_1^{(0)}, \min_{i=1,\dots,m} |\nu_1^{(i)}| \left(\mu_{0,\alpha^{(i)}\sqrt{|\nu_1^{(i)}|/2}} + \frac{1}{2}\right)\right],$$

- $\nu_1^{(i)}$ = bottom eigenvalue of $\nabla V^2(z_i)$,
- $\mu_{0,\theta}$ = ground-state energy for $\frac{1}{2}(x^2 - \partial_x^2)$ with infinite potential on $x > \theta$.

Sharp asymptotics for $\lambda_1(\Omega_{\beta,\alpha})$

Extension of the Eyring–Kramers formula to moving boundaries.

Theorem (B., Lelièvre, Stoltz 2024 (in preparation))

$$\lambda_1(\Omega_{\beta,\alpha}) = \mathrm{e}^{-\beta(V^*-V(z_0))}\left[\sum_{i\in I_{\min}} \frac{|\nu_1^{(i)}|}{2\pi\Phi\left(|\nu_1^{(i)}|^{\frac{1}{2}}\alpha^{(i)}\right)}\sqrt{\frac{\det \nabla^2 V(z_0)}{|\det \nabla^2 V(z_i)|}}\right](1+r(\beta)).$$

$$\Phi(x) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{x} \mathrm{e}^{-\frac{t^2}{2}}\,\mathrm{d}t$$

$$I_{\min} = \operatorname*{Argmin}_{i=1,\dots,m} V(z_i), \quad V^* = \min_{i=1,\dots,m} V(z_i)$$

$$r(\beta) \xrightarrow{\beta\to\infty} 0$$

Main technical tool: an extension of Laplace's method for moving domains of integration.

Application: asymptotic optimization in the one-saddle case

Theorems 1 and 2 give sharp asymptotics for $[(\lambda_2-\lambda_1)/\lambda_1](\Omega_{\beta,\alpha})$. We can optimize!

Instructive: the case of a single saddle point z_1 ($\alpha\in\mathbb{R}$).

$$\frac{\lambda_2(\Omega_{\beta,\alpha})-\lambda_1(\Omega_{\beta,\alpha})}{\lambda_1(\Omega_{\beta,\alpha})} \overset{\beta\to\infty}{\sim} C\mathrm{e}^{-\beta(V(z_1)-V(z_0))}\lambda^{\mathrm{H}}_{2,\alpha}\Phi\left(|\nu_1^{(i)}|^{\frac12}\alpha^{(i)}\right).$$

The prefactor depends on α:

$$\lambda^{\mathrm{H}}_{2,\alpha}\Phi\left(|\nu_1^{(i)}|^{\frac12}\alpha^{(i)}\right)=|\nu_1^{(1)}|^{\frac12}\left(\kappa\wedge\left[\mu_{0,\theta/\sqrt2}+\frac12\right]\right)\Phi(\theta),$$

$\kappa=\nu_1^{(0)}/|\nu_1^{(1)}|$ is a curvature ratio, and $\theta=|\nu_1^{(1)}|^{\frac12}\alpha$ is a reduced distance to the boundary.

Reduced objective:

$$J(\kappa,\theta)=\left(\kappa\wedge\left[\mu_{0,\theta/\sqrt2}+\frac12\right]\right)\Phi(\theta).$$

Optimization of $J(\kappa, \theta)$

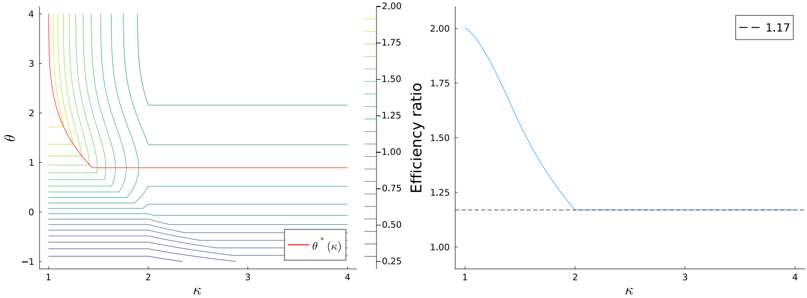
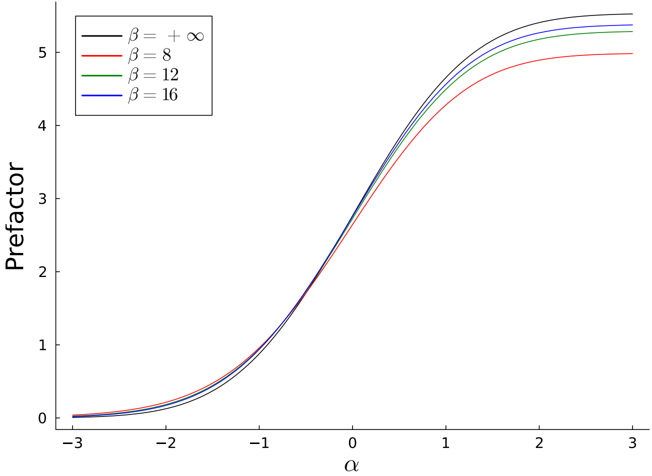


Figure: Left: objective landscape and optimal choice $\theta^*(\kappa)$. Right: $J(\kappa, \theta^*(\kappa))/J(\kappa, 0)$.

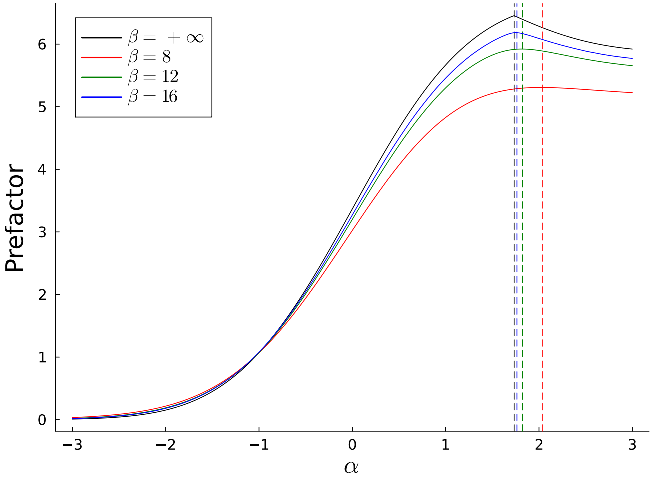
Case of a sharp saddle ($\kappa \leq 1$)

The benefits of spilling out outweighs the cost ($\alpha^* = +\infty$), but taper off quickly for $\theta \gtrapprox 1.96$.



Case of a soft saddle ($\kappa > 1$)

Non-trivial optimal α^*, but easy to find by precomputing $\kappa \mapsto \theta^*(\kappa)$.



Compute good domains on the fly

Practical algorithm:

- Run the dynamics until you detect a saddle point z_{ij}.
- Compute imaginary frequency $\omega_{ij} = |\nu_1^{(ij)}|^{\frac{1}{2}}$ at the saddle.
- Find minima m_i, m_j on both sides of the saddle. Compute corresponding bottom frequencies $\omega_i = |\nu_1^{(i)}|^{\frac{1}{2}}, \omega_j = |\nu_1^{(j)}|^{\frac{1}{2}}$.
- Parametrize the boundary around z_{ij} for the transition $i \to j$ with a hyperplane at a distance $\beta^{-\frac{1}{2}}\omega_{ij}^{-1}\theta^*(\kappa_{i\to j})$, where $\kappa_{i\to j} = \omega_i^2/\omega_{ij}^2$ in the unstable direction.
- Do the same for the reverse transition $j \to i$.
- Far from a saddle point, revert to the standard definition of the state.

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