

Optimization of metastable timescales for accelerated sampling of trajectories

SMAI 2025

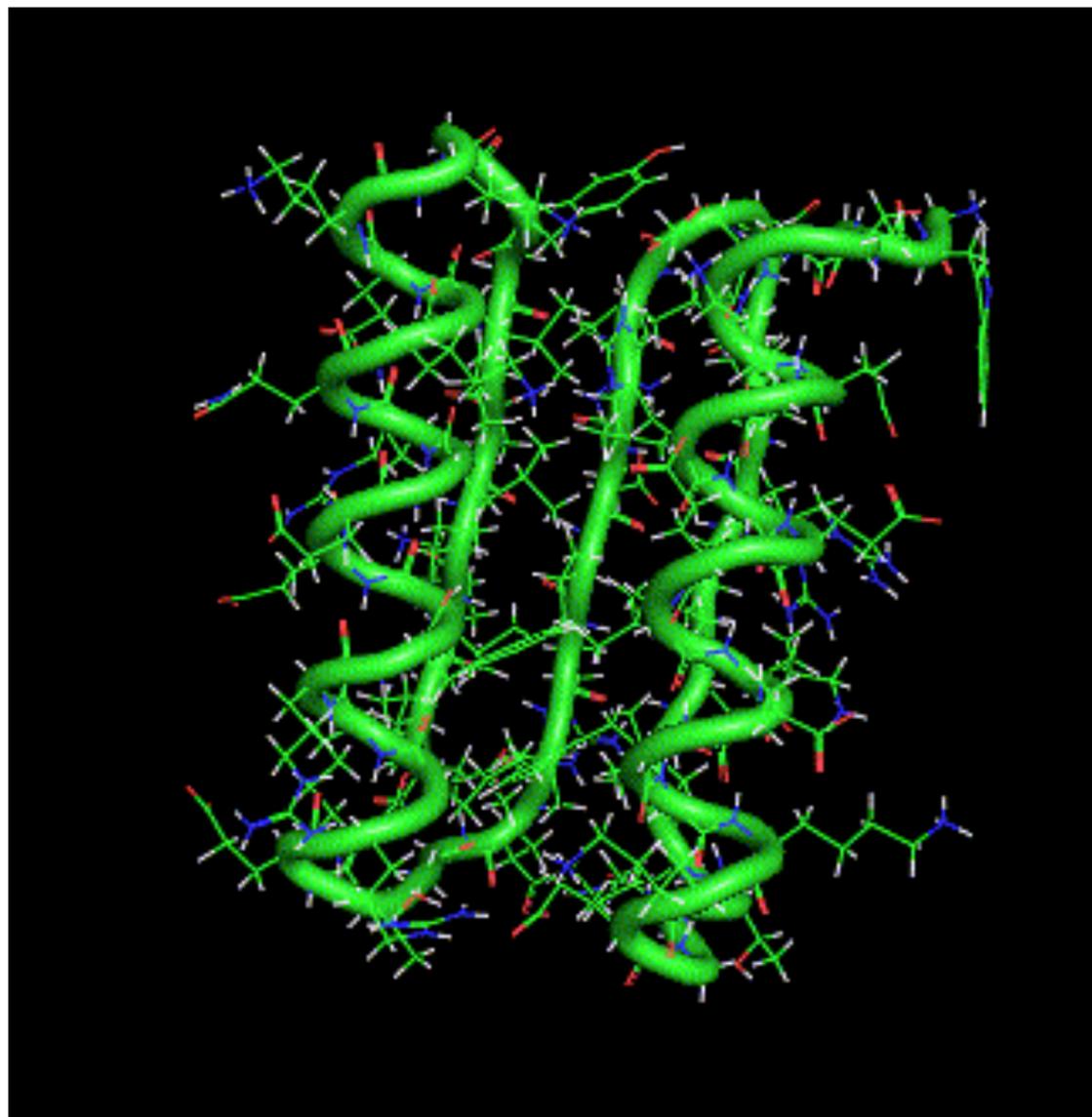
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Molecular dynamics

Molecular dynamics (MD) probes the behavior of atomistic system at the level of **classical motion** of nuclei.



5 picoseconds of the protein Foldit1 (PDB ID 6MRR) simulated using [Molly.jl](#), (courtesy of Joe Greener).

Aims to replace physical experiments in extreme or expensive conditions with numerical experiments.

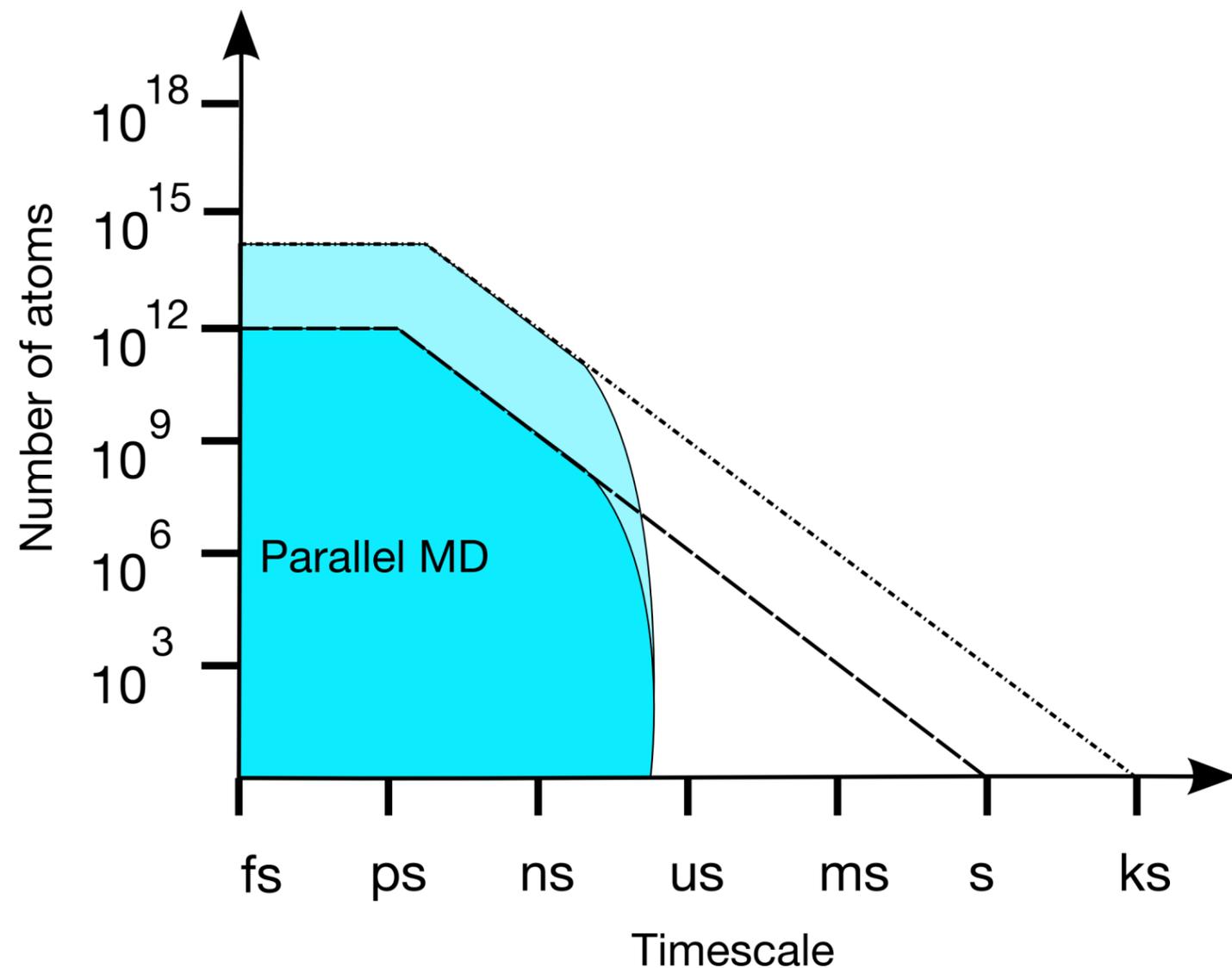
Long trajectories are necessary to access dynamical properties, and parametrize models on larger scales.

Many **algorithmic tricks** are needed to simulate **long trajectories reliably and efficiently**, and **sample the whole configuration space**.

Length of sampled trajectories is hindered by **metastability/stiffness/separation of timescales**, the manifestation of **free-energetic barriers** larger than typical thermal fluctuations.

Configurational ensemble has many modes, corresponding to **metastable states**.

The timescale problem in MD



Scaling in simulations: from petascale to exascale. Courtesy of Danny Perez (LANL)

Parallelization in space is “easy”, **parallelization in time** is much harder.

Accelerated dynamics methods: (Hyperdynamics (Voter 1997), Temperature Accelerated Dynamics (Sørensen and Voter 2000), Parallel Replica (Voter 1998)) can help.

Metastable dynamics jump **rarely and suddenly** between metastable states.

Accelerated MD aims at predicting the **sequence of states** and **transition times** correctly by **sacrificing resolution** of the dynamics inside each state.

Spatial coarse-graining strategy.

Key idea: the system will typically converge in a statistical sense to a **local equilibrium** within a metastable state Ω and remain there for a long time before exiting.

For this idea to be valid, and for **efficient algorithms**, we require:

$$\frac{\text{Typical time to converge to local equilibrium in } \Omega}{\text{Typical time to exit from } \Omega} \ll 1.$$

Dynamical setting

Molecular trajectories are solutions to a stochastic differential equation:

$$dX_t = -a(X_t)\nabla V(X_t) dt + \frac{1}{\beta} \operatorname{div} a(X_t) dt + \sqrt{\frac{2}{\beta}} a(X_t)^{1/2} dW_t,$$

$V : \mathbb{R}^d \rightarrow \mathbb{R}$ potential energy function, $a : \mathbb{R}^{d \times d}$ s.p.d. diffusion coefficient, W standard Brownian motion in \mathbb{R}^d .

Ergodic and **reversible** with respect to the standard Gibbs measure at temperature $(k\beta)^{-1}$

$$\pi(dx) = e^{-\beta V(x)} dx / Z_\beta.$$

Continuous-time **preconditioned Langevin Monte-Carlo** / diffusion on the **Riemannian manifold** $\mathcal{M} = (\mathbb{R}^d, a^{-1})$

Evolution semigroup generator is symmetric on $L^2(\mathbb{R}^d, \pi)$:

$$\mathcal{L}_\beta \varphi = \frac{1}{\beta} e^{\beta V} \operatorname{div} (e^{-\beta V} a \nabla \varphi).$$

We assume everywhere that $V, a \in \mathcal{W}_{\text{loc}}^{2,\infty}$, and a is locally elliptic: $a^{-1} \in L_{\text{loc}}^\infty$.

Local approach to metastability

For $\Omega \subset \mathbb{R}^d$, local equilibrium is given by a **quasi-stationary distribution** (QSD) in Ω i.e. a probability $\nu_\Omega \in \mathcal{M}_1(\Omega)$ for which

$$\forall A \subset \Omega, \quad \mathbb{P}_{\nu_\Omega} (X_t \in A \mid t < T_{\text{exit}}(\Omega)) = \nu_\Omega(A).$$

Since V, Ω are bounded and a is uniformly elliptic on Ω , the QSD is unique, and related to the **principal Dirichlet eigenvector**:

$$\nu_\Omega(dx) = \frac{u_{1,\Omega}(x)e^{-\beta V(x)} dx}{\int_\Omega u_{1,\Omega} e^{-\beta V}}, \quad -\mathcal{L}_\beta u_{1,\Omega}(x) = \lambda_{1,\Omega} u_{1,\Omega}(x),$$

Here, we consider the generator \mathcal{L}_β with **absorbing Dirichlet boundary conditions** on $\partial\Omega$:

$$\mathcal{D}(\mathcal{L}_\beta) = H_0^1(\Omega) \cap \{u \in L^2(\Omega) : \mathcal{L}_\beta u \in L^2(\Omega) \subset \mathcal{D}'(\mathbb{R}^d)\}.$$

It is self-adjoint with **compact resolvent** on $L_\beta^2(\Omega) := L^2(\Omega, e^{-\beta V(x)} dx)$ for bounded Ω .

Spectral characterization of timescales

Denote $\mu_t = \text{Law}(X_t | t < T_{\text{exit}}(\Omega))$ the law of the process conditioned on remaining trapped.

Theorem (Le Bris et al. (2012))

$$\mu_0 = \nu_\Omega \implies T_{\text{exit}}(\Omega) \sim \mathcal{E}(\lambda_{1,\Omega}), \quad T_{\text{exit}}(\Omega) \perp\!\!\!\perp X_{T_{\text{exit}}(\Omega)}.$$

This result justifies the use of the Parallel Replica algorithm.

The **exit rate** is given by the principal Dirichlet eigenvalue $\lambda_{1,\Omega} = 1/\mathbb{E}_{\nu_\Omega}[T_{\text{exit}}(\Omega)]$.

Theorem (Le Bris et al. (2012))

Convergence to the QSD and bias on the exit event are **exponentially decaying**. There exist $C_1, C_2 > 0$ depending on μ_0 such that

$$\begin{aligned} \|\mu_t - \nu_\Omega\|_{\text{TV}} &\leq C_1 e^{-(\lambda_{2,\Omega} - \lambda_{1,\Omega})t}, \\ \|\text{Law}_{\mu_t}(T_{\text{exit}}(\Omega) - t, X_{T_{\text{exit}}(\Omega)}) - \text{Law}_{\nu_\Omega}(T_{\text{exit}}(\Omega), X_{T_{\text{exit}}(\Omega)})\|_{\text{TV}} &\leq C_2 e^{-(\lambda_{2,\Omega} - \lambda_{1,\Omega})t}. \end{aligned}$$

The **decorrelation rate** is given by the spectral gap of the Dirichlet generator $\lambda_{2,\Omega} - \lambda_{1,\Omega}$.

Set $T_{\text{corr}}(\Omega) = -\log \varepsilon_{\text{corr}} / (\lambda_{2,\Omega} - \lambda_{1,\Omega})$ in ParRep, for some fixed tolerance parameter $0 < \varepsilon_{\text{corr}} < 1$.

In practice, raises the need for **quantitative or statistical estimates** of $\lambda_{2,\Omega} - \lambda_{1,\Omega}$ (and also C_1, C_2).

A spectral shape optimization problem

The goal becomes to maximize the efficiency of ParRep by maximizing the separation of timescales:

$$\max_{\Omega \subset \mathbb{R}^d \text{ open, bounded, connected}} (\lambda_{2,\Omega} - \lambda_{1,\Omega}) / \lambda_{1,\Omega}.$$

Make the **exit rate** as small as possible compared to the **decorrelation rate**. Quantitative measure of **local metastability / timescale separation** inside Ω .

Standard choice takes $\Omega = \mathcal{A}(z_0)$, the basin of attraction of some local minimum z_0 for V under the steepest-descent dynamics $\dot{X}(t) = -a(X(t))\nabla V(X(t))$.

The case of the Dirichlet Laplacian $a = \text{Id}$, $V = 0$ is a famous question in spectral geometry (Payne-Polya-Weinberger conjecture).

Question has been identified by MD practitioners, e.g. in Perez, Uberuaga, and Voter (2015), but not studied in depth.

Problem is **ill-posed** as a global optimization problem, e.g., for $V(x) = |x|^2/2 + \delta V(x)$, $\delta V \in C_c^\infty(\mathbb{R}^d)$:

$$\lambda_{2,B(0,R)} / \lambda_{1,B(0,R)} \xrightarrow{R \rightarrow +\infty} +\infty.$$

Typical situation in spectral optimization: introduce constraints, or focus on **local optimization**.

Local optimization with steepest ascent method

Expressions for **shape-perturbations** of the Dirichlet eigenvalues, using Hadamard calculus.

Given a space of perturbations: $\theta \in \mathcal{W}^{1,\infty}(\mathbb{R}^d, \mathbb{R}^d)$, consider the transported domain

$$\Omega_\theta = \{x + \theta(x), x \in \Omega\}.$$

Study properties of the **eigenvalue perturbation maps**

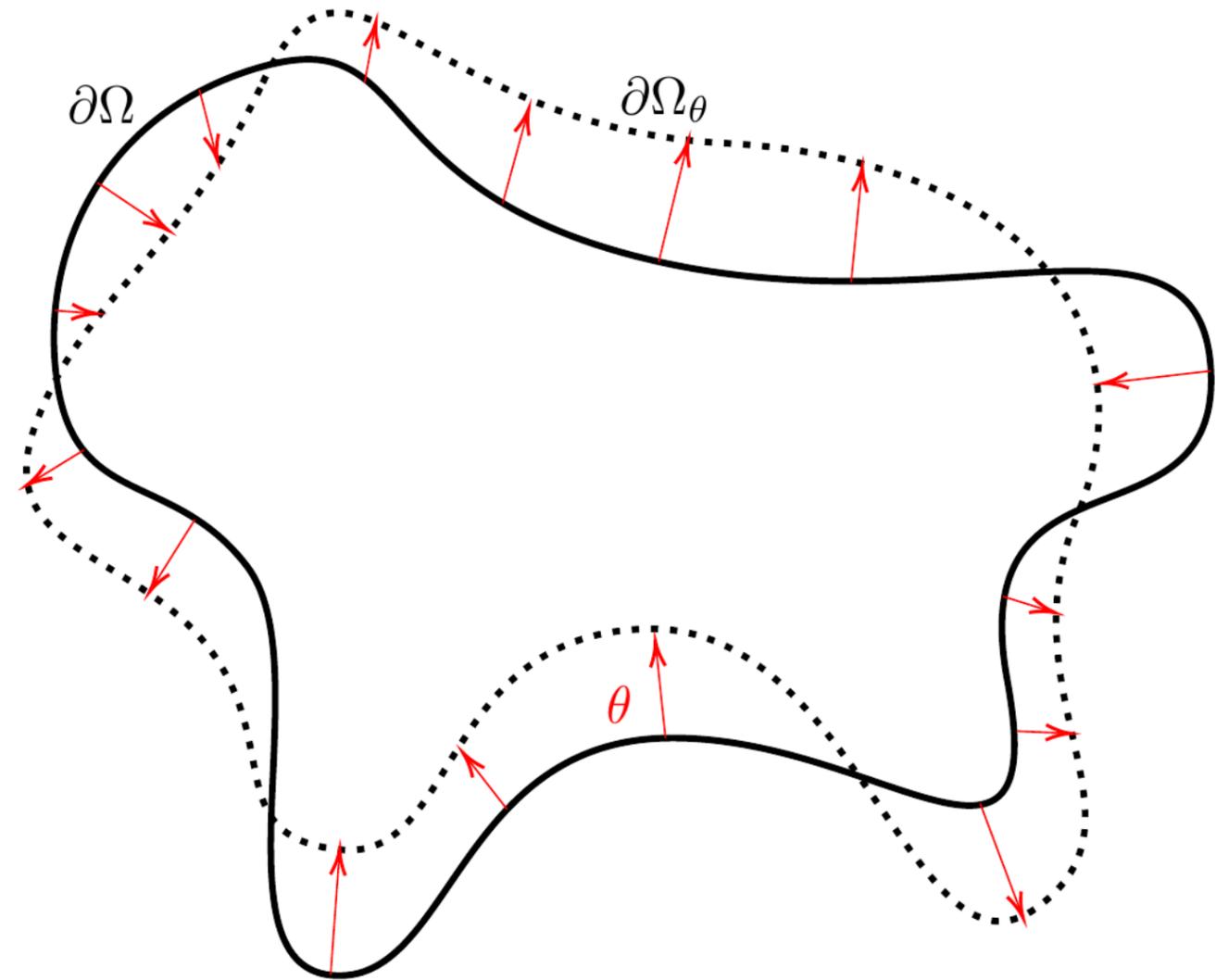
$$\lambda_k : \theta \mapsto \lambda_{k,\Omega_\theta}.$$

The spectrum (of $-\mathcal{L}_\beta$ with Dirichlet b.c. on Ω) is enumerated with multiplicity in order of increasing magnitude

$$0 < \lambda_{1,\Omega} < \lambda_{2,\Omega} \leq \lambda_{3,\Omega} \leq \dots$$

with an associated basis of eigenvectors

$$\int_{\Omega} u_{i,\Omega} u_{j,\Omega} e^{-\beta V} = \delta_{ij}, \quad \forall i, j \geq 1.$$



A domain Ω and its perturbation Ω_θ .

Explicit formulas for shape perturbations

Assume $\Omega \subset \mathbb{R}^d$ is a bounded $C^{1,1}$ (or convex Lipschitz) domain and $\lambda_{k,\Omega}$ has multiplicity $m_k \geq 1$:

$$\lambda_{k-1,\Omega} < \lambda_{k,\Omega} = \dots = \lambda_{k+m_k-1,\Omega} < \lambda_{k+m_k,\Omega}.$$

Theorem (Bassel, Lelièvre, and Stoltz (2025b), in preparation)

The map $\theta \mapsto (\lambda_{k+\ell,\Omega_\theta})_{0 \leq \ell < m_k}$ is locally Lipschitz in a $\mathcal{W}^{1,\infty}(\mathbb{R}^d; \mathbb{R}^d)$ -neighborhood of $\theta = 0$.

If $m_k = 1$, λ_k is C^1 in a $\mathcal{W}^{1,\infty}(\mathbb{R}^d; \mathbb{R}^d)$ -neighborhood of $\theta = 0$, with Fréchet derivative

$$D\lambda_k\theta = -\frac{1}{\beta} \int_{\partial\Omega} \left(\frac{\partial u_{k,\Omega}}{\partial n} \right)^2 n^\top a n \theta^\top n e^{-\beta V},$$

the **shape derivative** of λ_k .

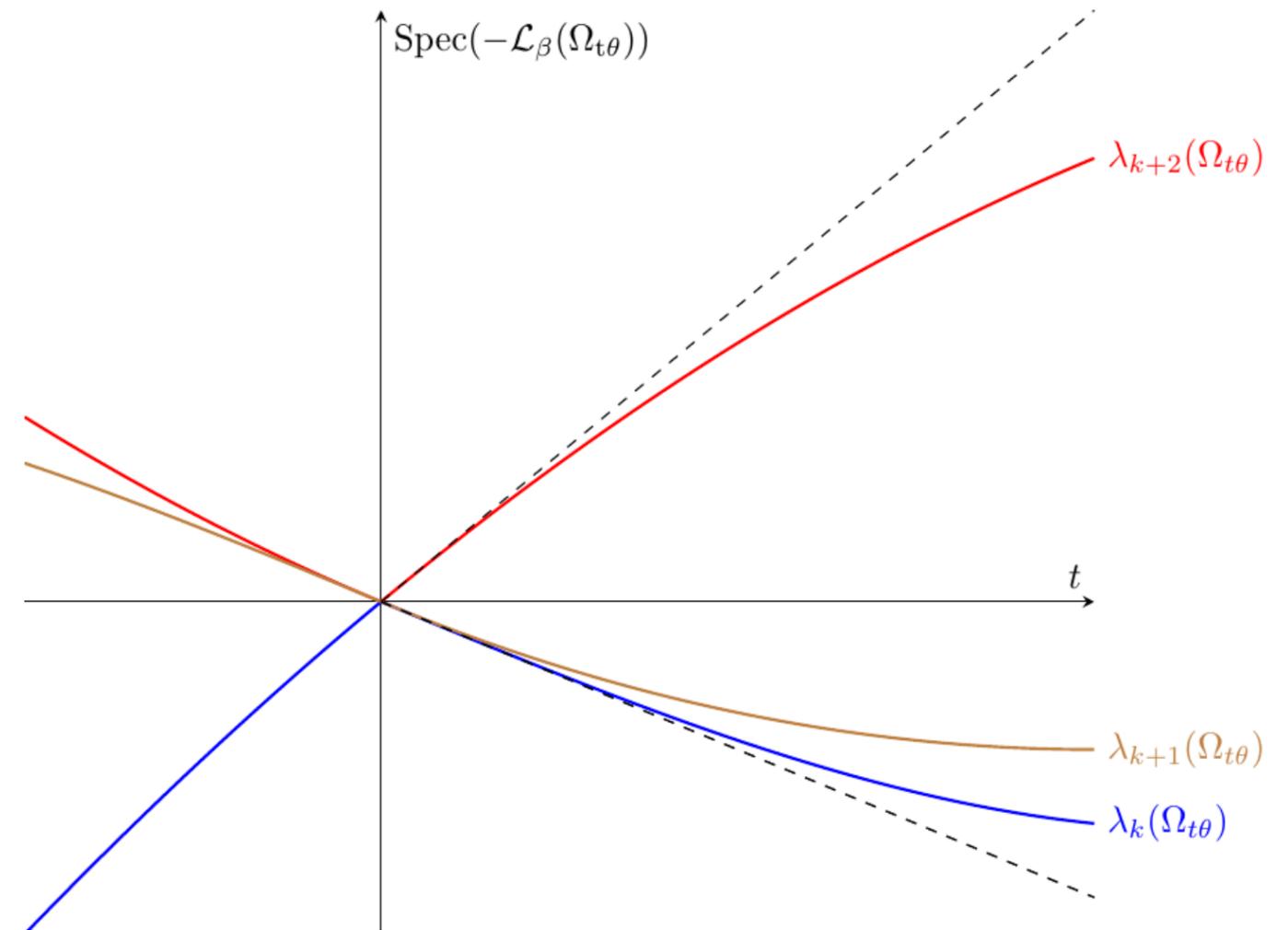
If $m_k > 1$, λ_k is only Gateaux semi-differentiable: $t \mapsto \lambda_{k,\Omega_{t\theta}}$ is right-differentiable at $t = 0$. Its derivative is the bottom eigenvalue of the matrix

$$M_{ij}^{\Omega,k}(\theta) = -\frac{1}{\beta} \int_{\partial\Omega} \frac{\partial u_{k+i-1,\Omega}}{\partial n} \frac{\partial u_{k+j-1,\Omega}}{\partial n} n^\top a n \theta^\top n e^{-\beta V}, \quad \forall 1 \leq i, j \leq m_k.$$

Idea of proof

Transport variational formulation of eigenvalue PDE on $\Omega_\theta = \Phi_\theta\Omega$ back to Ω , transforming it into a θ -dependent PDE on a fixed domain.

Regularity results follow from perturbation theory (Kato (2013)), using an approach inspired by Haug and Rousselet (1980), Rousselet (1983) (for problems in structural mechanics).



Perturbation of the eigenvalue $\lambda_{k,\Omega}$ in the direction θ (here $m_k = 3$)

Slopes of the right-tangents are the eigenvalues of $M^{\Omega,k}(\theta)$ (with multiplicity).

Efficient numerical optimization requires taking eigenvalue degeneracies into account, and regularization of the ascent direction.

Galerkin objective for high-dimensional systems

For systems of interest, $d \gg 1$. In MD, common to use a **collective variable (CV)** $\xi : \mathbb{R}^d \rightarrow \mathbb{R}^m$ with $m \ll d$ for **interpretation** and **biasing**. Consider states defined in CV space: $\Omega = \xi^{-1}(\Omega^\xi)$ for some $\Omega^\xi \subset \mathbb{R}^m$

Coarse-grained spectrum

Consider the test space

$$\mathcal{V}_\xi(\Omega^\xi) = \{\varphi \circ \xi, \varphi \in H_0^1(\Omega_\xi)\} \subset H_0^1(\xi^{-1}(\Omega_\xi)),$$

introduce the Rayleigh-Ritz (or “**coarse-grained**”) eigenpairs:

$$Q_\xi(\varphi, \psi; \Omega_\xi) = Q(\varphi \circ \xi, \psi \circ \xi; \xi^{-1}(\Omega_\xi)), \quad Q_\xi(u_{k, \Omega_\xi}^\xi, u_{\ell, \Omega_\xi}^\xi) = \lambda_{k, \Omega_\xi}^\xi \delta_{k\ell},$$

where Q is the Rayleigh quotient for $-\mathcal{L}_\beta$

$$Q(u, v; \Omega) = \frac{1}{\beta} \frac{\int_\Omega \nabla u^\top a \nabla v e^{-\beta V}}{\int_\Omega u v e^{-\beta V}}.$$

Co-area formula gives (Blassel, Lelièvre, and Stoltz (2025b))

$$\forall \varphi, \psi \in \mathcal{V}_\xi(\Omega^\xi), \quad Q_\xi(\varphi, \psi; \Omega_\xi) = \frac{1}{\beta} \frac{\int_{\Omega_\xi} \nabla \varphi^\top a_\xi \nabla \psi e^{-\beta F_\xi}}{\int_{\Omega_\xi} \varphi \psi e^{-\beta F_\xi}},$$

where F_ξ, a_ξ are the **free-energy** and **effective diffusion** through ξ :

$$F_\xi(z) = -\frac{1}{\beta} \log \int_{\xi^{-1}(z)} e^{-\beta V} (\det[\nabla \xi^\top \nabla \xi])^{-1/2} d\sigma, \quad a_\xi(z) = \int_{\xi^{-1}(z)} \nabla \xi^\top a \nabla \xi d\mu_z,$$

where μ_z is a conditional distribution $\mu|_{\xi^{-1}(z)}$ on the level-set of the CV.

Error estimate for all $k \geq 1$:

$$0 \leq \lambda_k^\xi - \lambda_k \leq \frac{1}{\beta} \int_{\xi^{-1}(\Omega_\xi)} \nabla [u_j - u_j^\xi \circ \xi]^\top a \nabla [u_j - u_j^\xi \circ \xi] e^{-\beta V}.$$

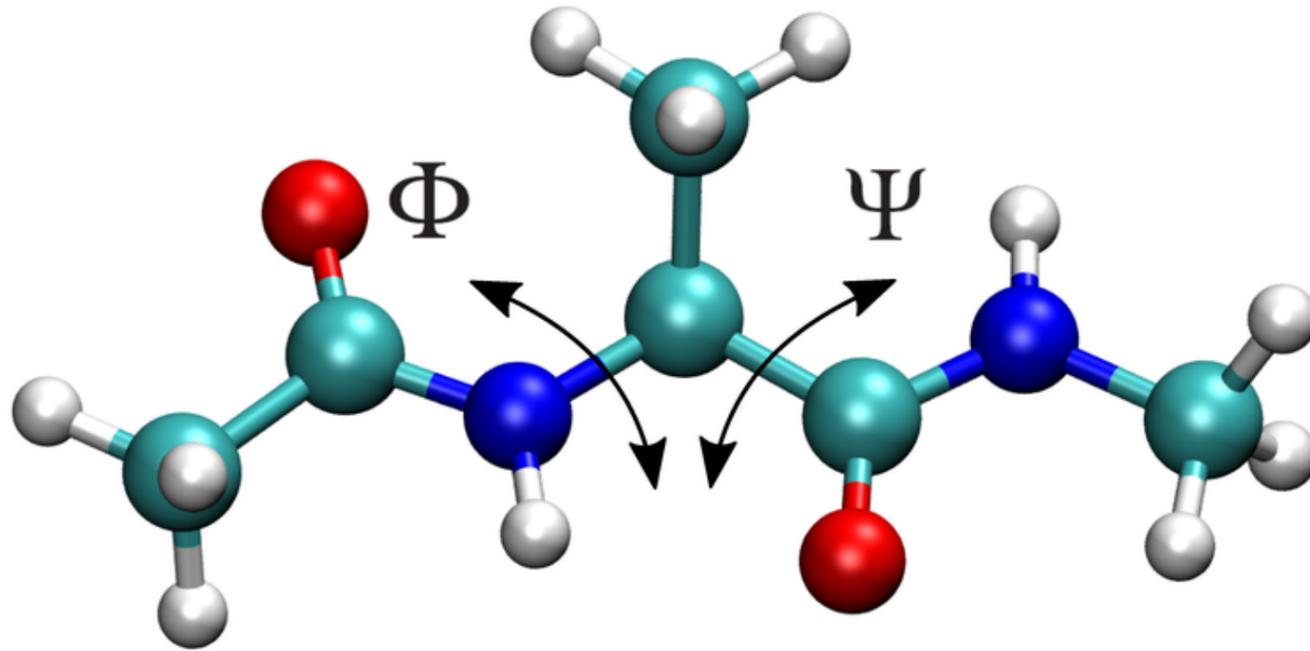
Dynamical interpretation

Rates $\lambda_{k, \Omega_\xi}^\xi$ correspond to rates for an **effective dynamics** in \mathbb{R}^m . Shape perturbation results apply verbatim if $\xi \in \mathcal{W}^{3, \infty}(\mathbb{R}^d, \mathbb{R}^m)$ and $\text{rank } \nabla \xi \equiv m$.

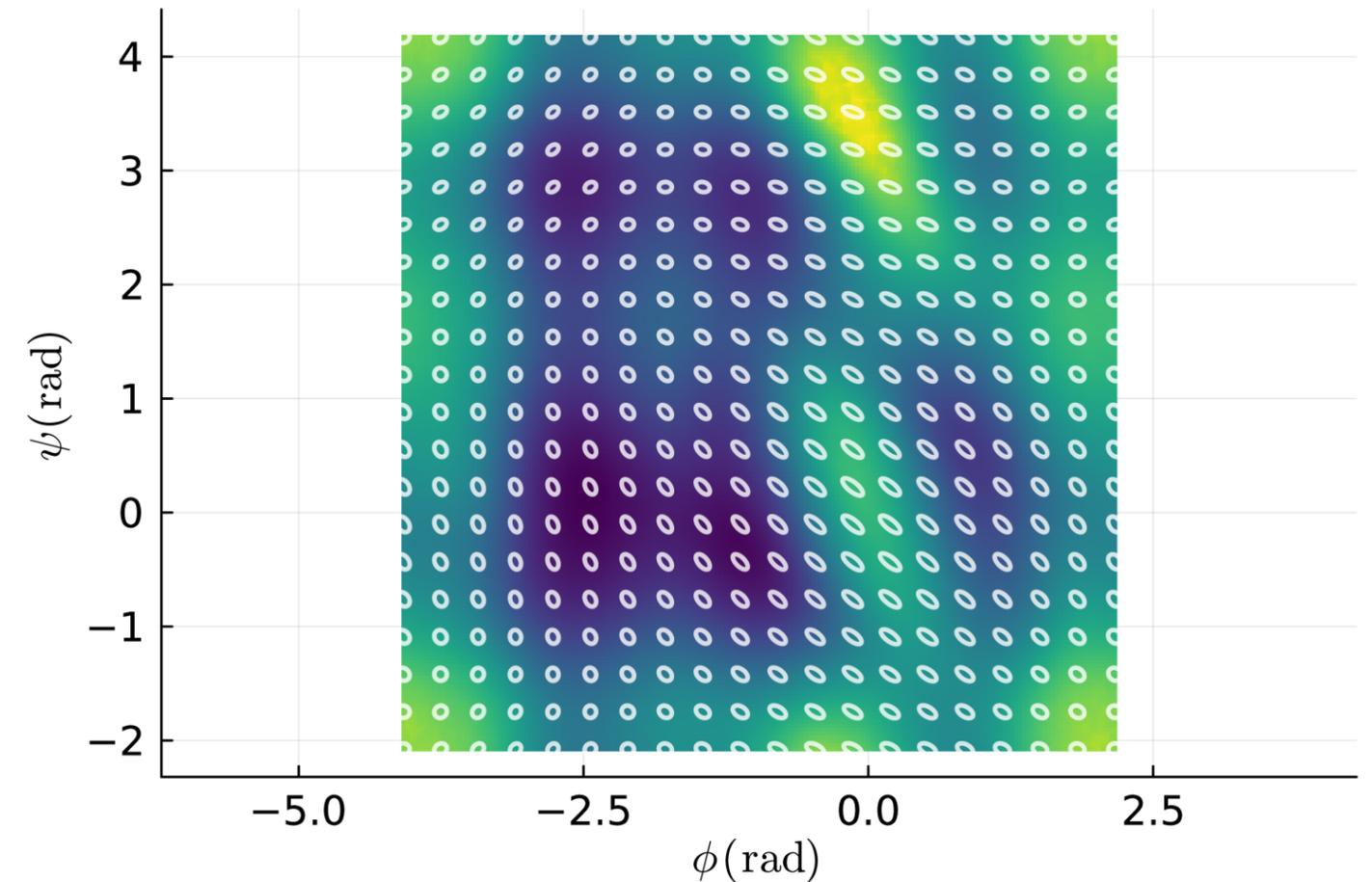
$$dZ_t^\xi = \left(-a_\xi \nabla F_\xi + \frac{1}{\beta} \text{div } a_\xi \right) (Z_t^\xi) dt + \sqrt{\frac{2}{\beta}} a_\xi(Z_t^\xi)^{1/2} dB_t.$$

Example: solvated Alanine dipeptide

Consider alanine-dipeptide in solution ($d = 1857$).



We use standard dihedral angles $\xi = (\phi, \psi)$ as a CV.

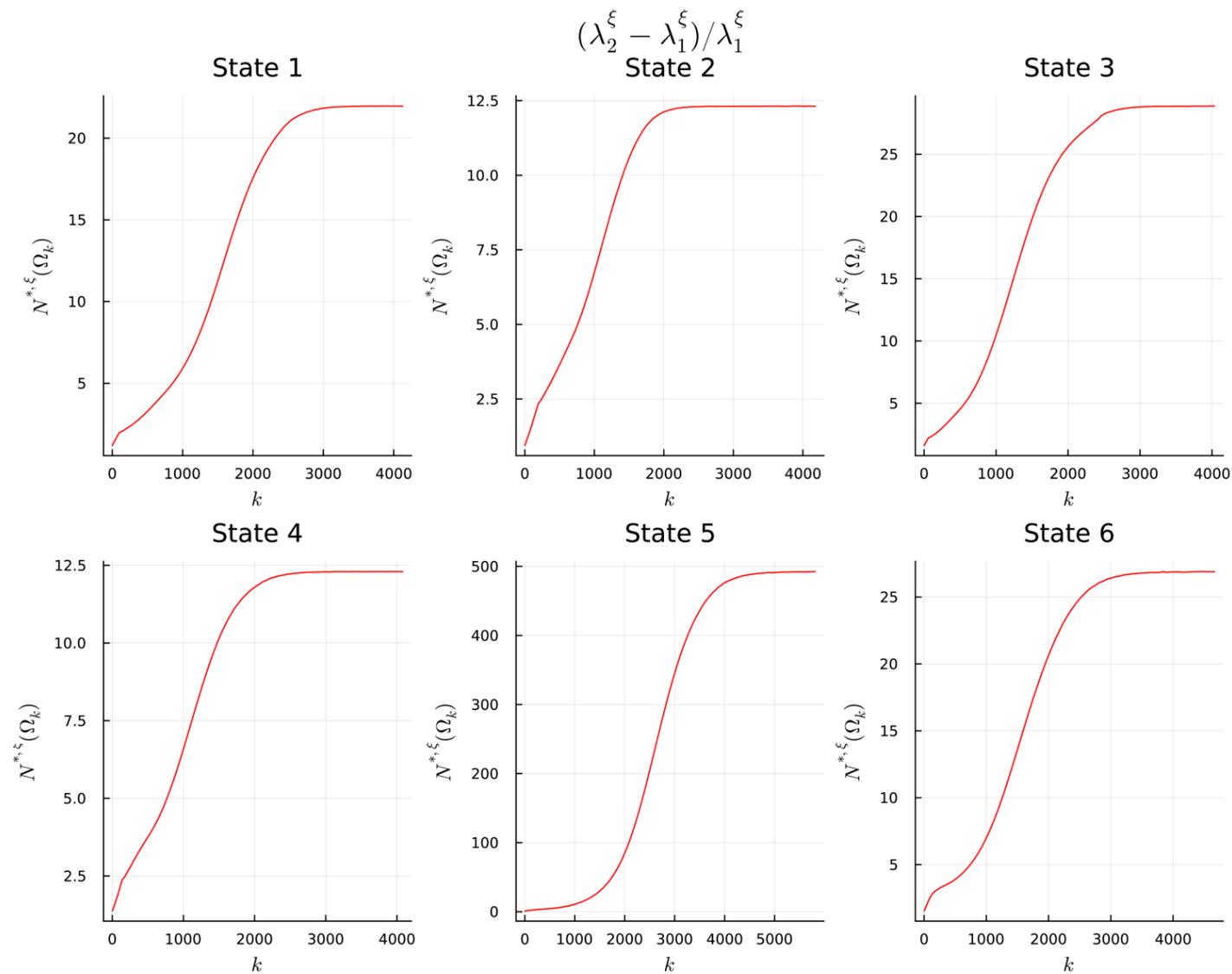


Computed effective diffusion tensor (a_ξ).

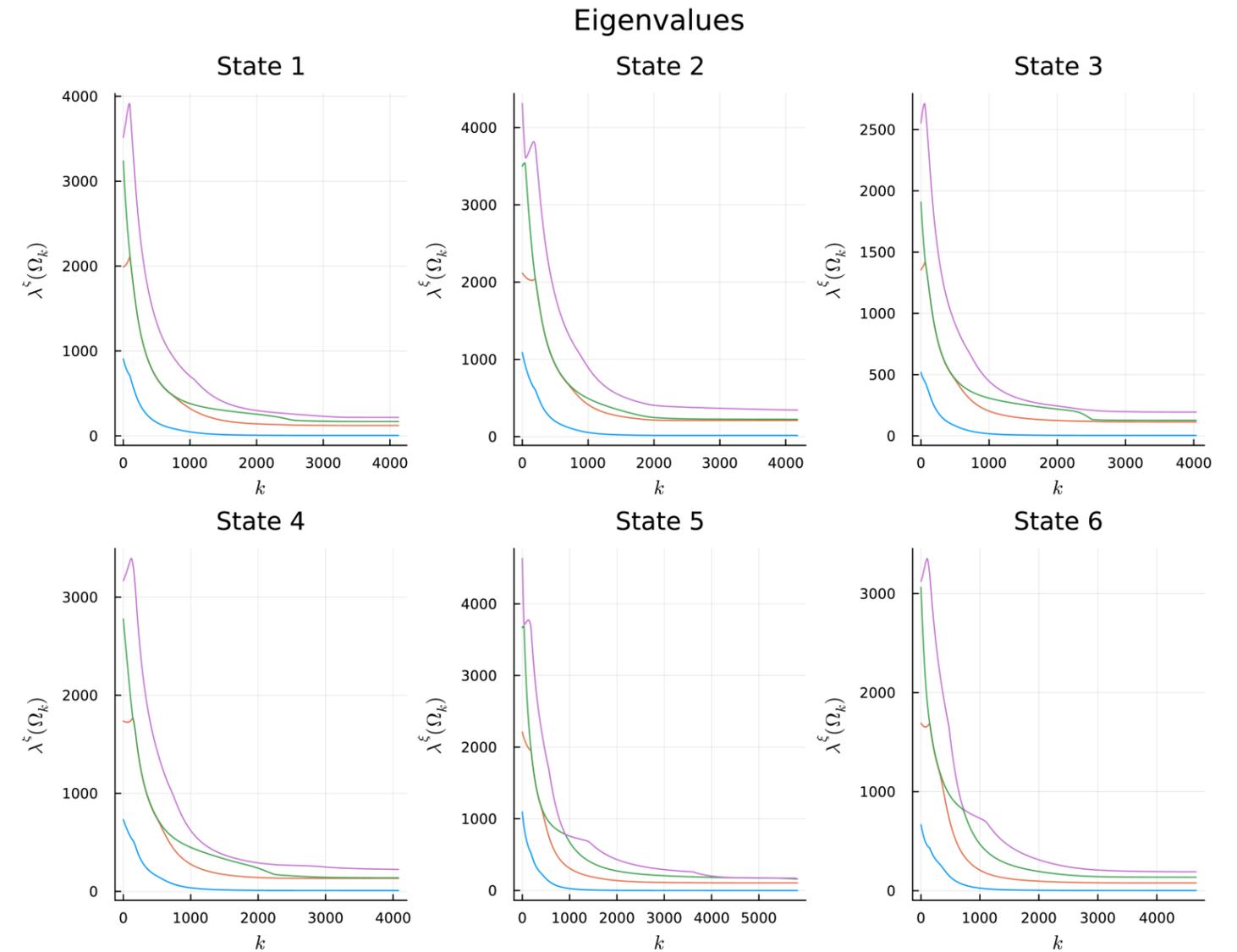
As F_ξ , a_ξ are **thermodynamic quantities**, can be computed efficiently with enhanced sampling methods. Here, umbrella sampling using Tinker-HP and Colvars.

Shape-optimization results

Shape-gradient ascent, implemented with FreeFem++.



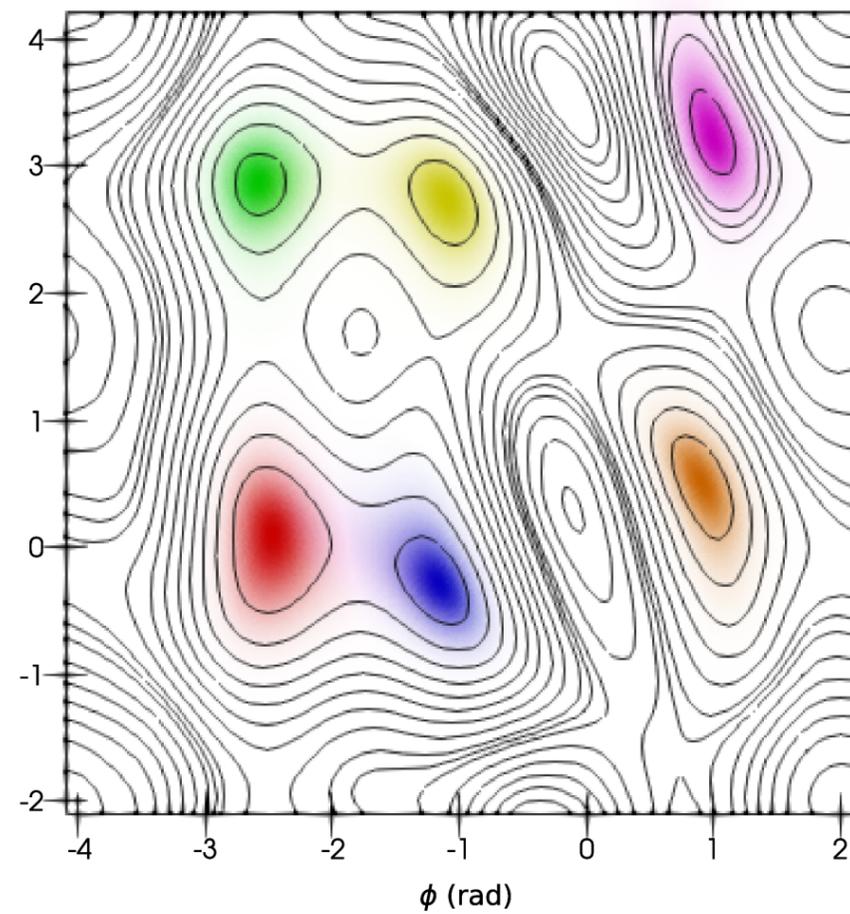
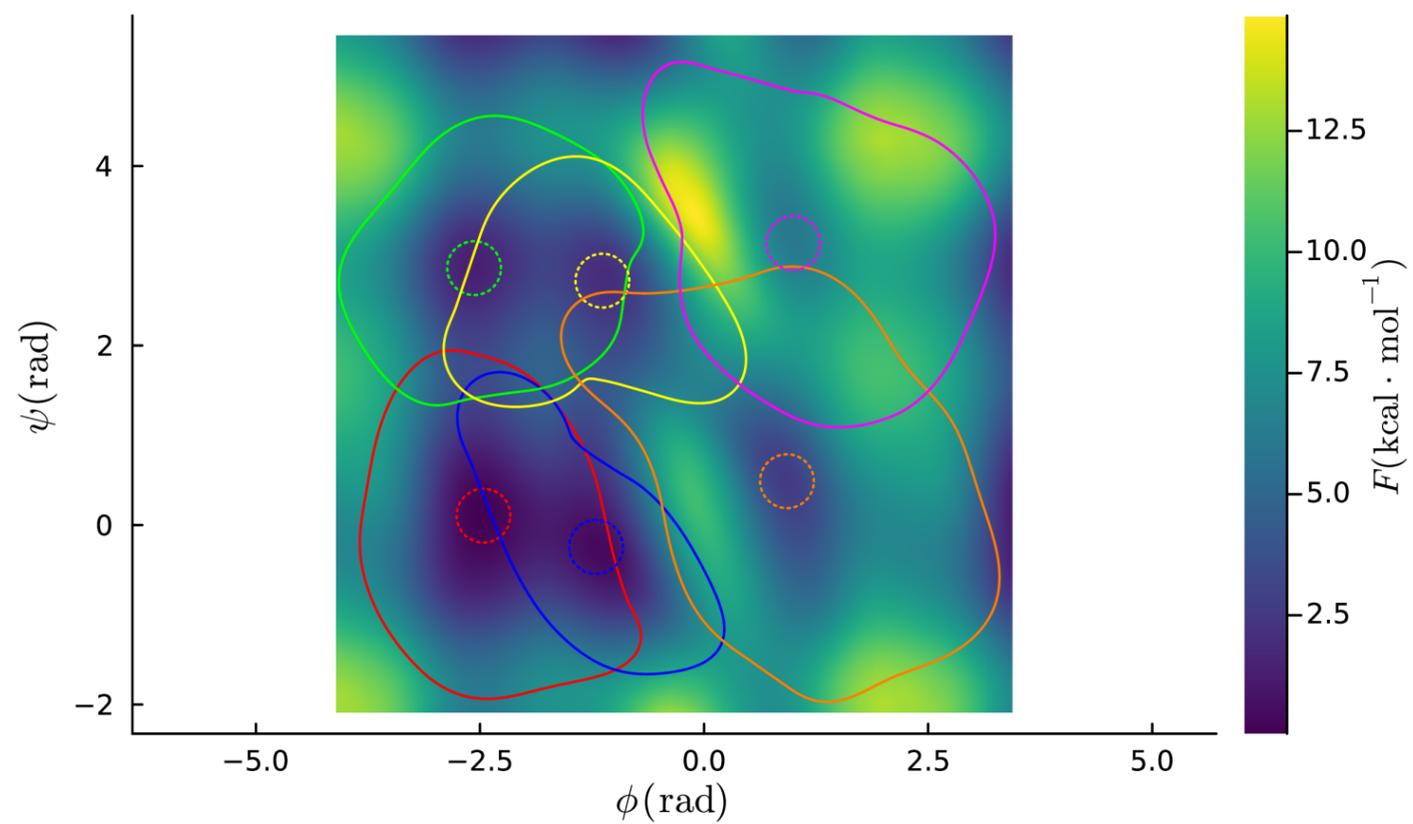
Convergence of the Galerkin objective.



Behavior of eigenvalues throughout the ascent iterations.

Shape-optimization results

Degeneracy-aware steepest ascent method implemented in FreeFem++.

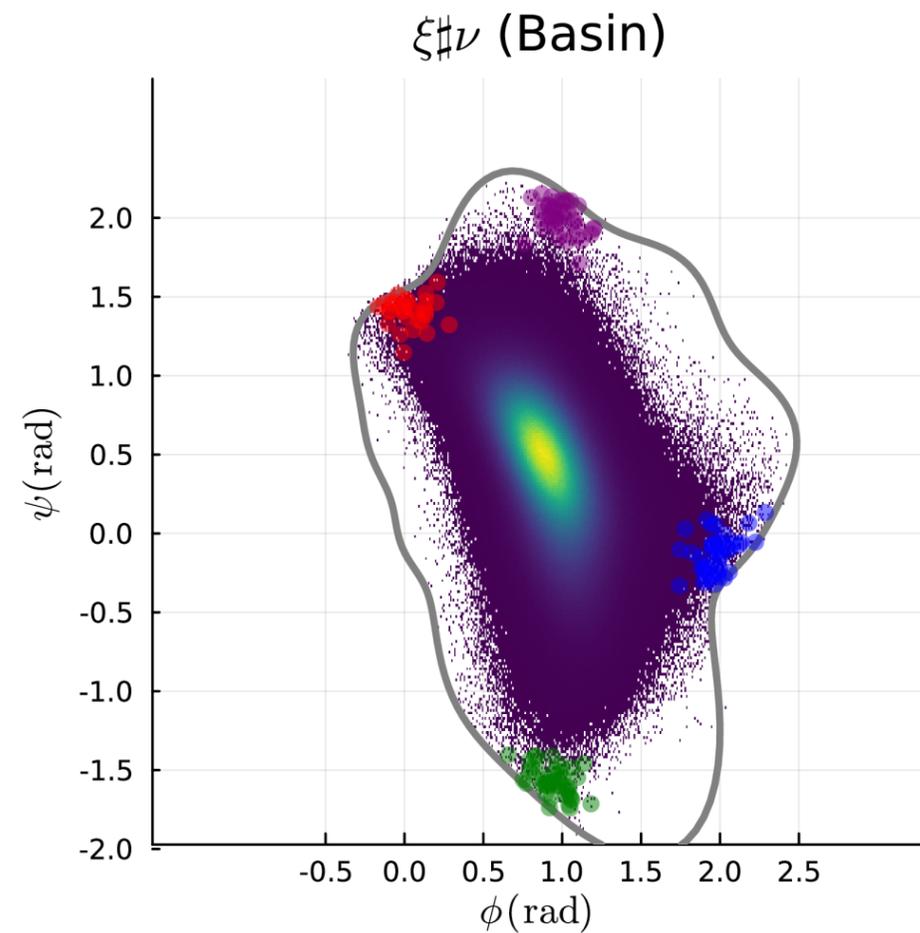


Initial and optimized domains, associated effective QSDs.

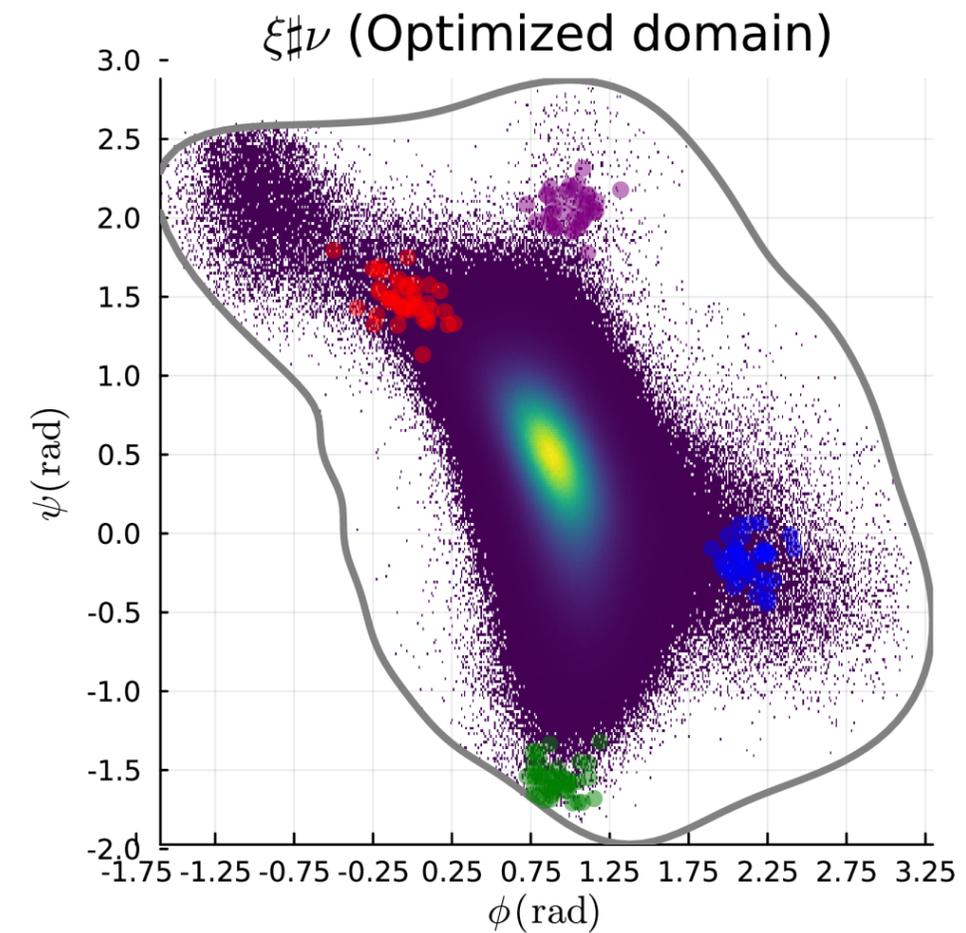
Quantifying gains in the original objective

Measure gain in timescale separation with respect to reference state definition, in a **practical dynamical setting** (underdamped Langevin dynamics).

Simulate Fleming-Viot process (in a modded Tinker-HP with 50 replicas), sampling initial configurations in transition regions.



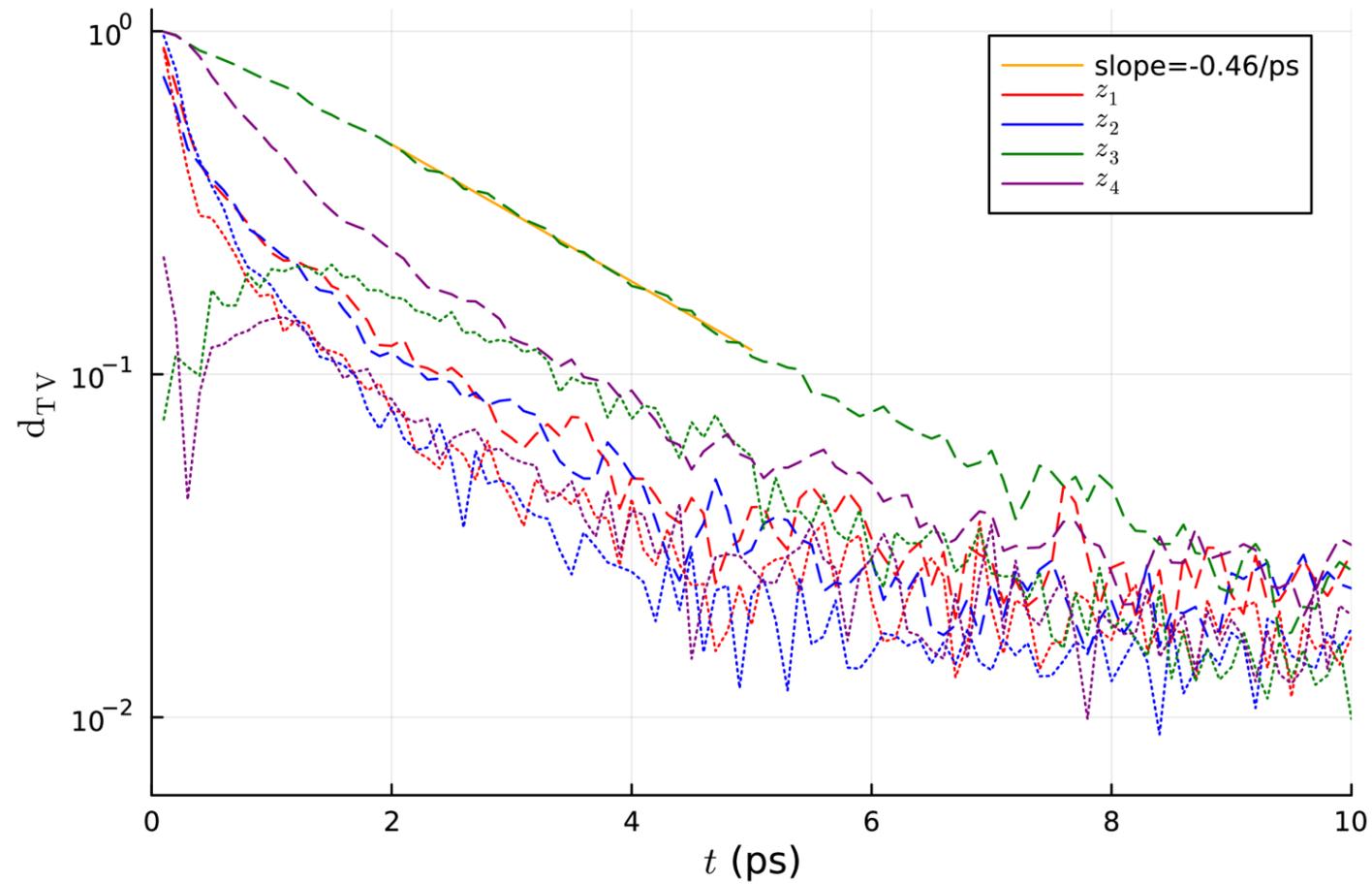
ξ -marginal of the QSD for $\mathcal{A}(z_5)$.



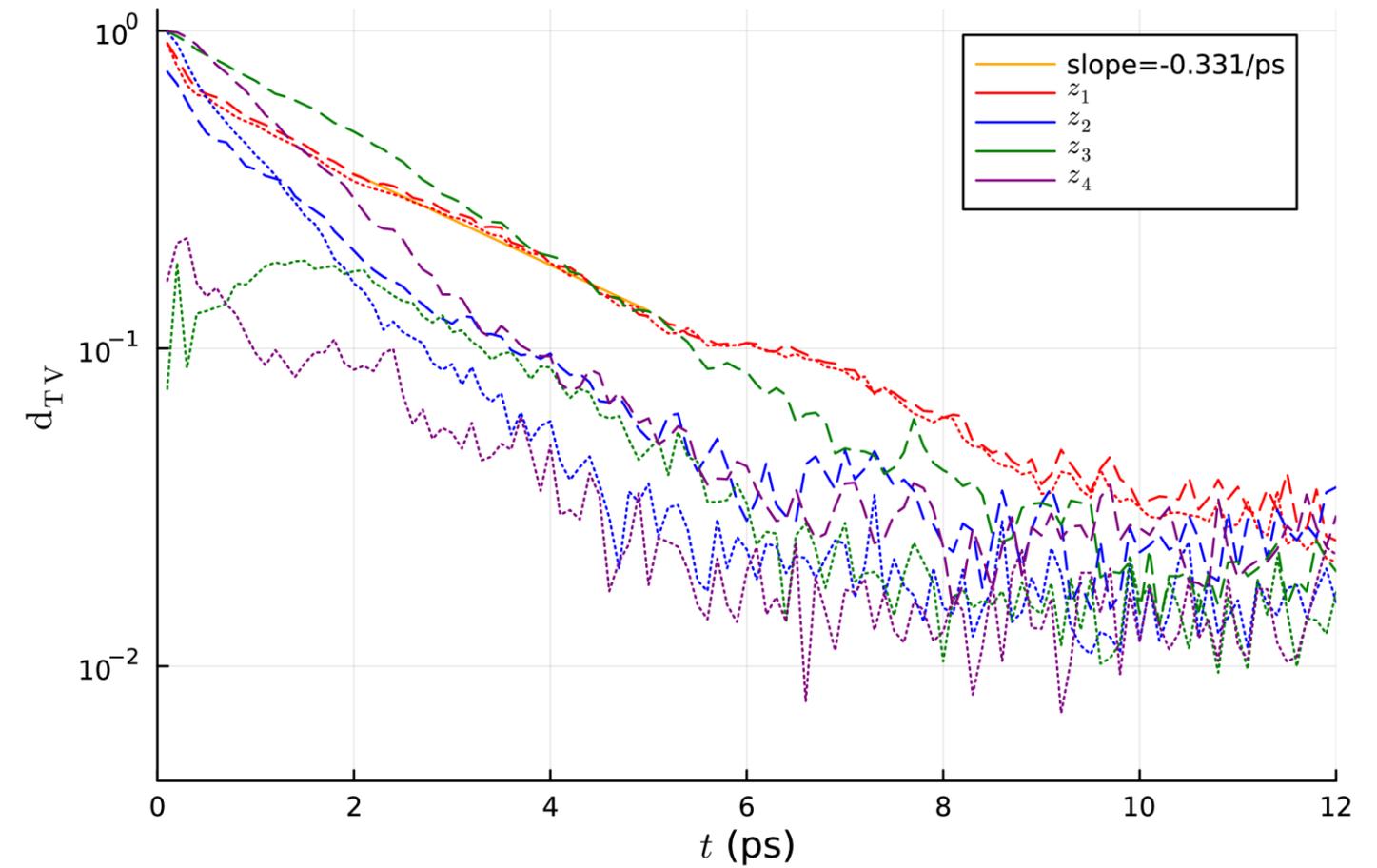
ξ -marginal for Ω_ξ^* around z_5 .

Inference of decorrelation timescale

For the various ensembles of initial conditions, infer decorrelation rate at the level of histogram convergence.



Free-energy basin ($\gamma = 2 \text{ ps}^{-1}$).



Optimized state ($\gamma = 2 \text{ ps}^{-1}$).

Comparison of free-energy basin and optimized state

State	Exit rate $\pm 1.96\sigma$ (ps^{-1})	Decorrelation rate (ps^{-1})	Ratio $\pm 1.96\sigma$	Mixing time (ps, tol = 0.05)
$\mathcal{A}(z_5)$ ($\gamma = 1 \text{ ps}^{-1}$)	$5.6 \times 10^{-3} \pm 1.6 \times 10^{-4}$	0.49	88.1 ± 2.5	5.8
Ω_{ξ}^* ($\gamma = 1 \text{ ps}^{-1}$)	$1.8 \times 10^{-3} \pm 8 \times 10^{-5}$	0.33	177.5 ± 7.7	7.8
$\mathcal{A}(z_5)$ ($\gamma = 2 \text{ ps}^{-1}$)	$5.4 \times 10^{-3} \pm 1.4 \times 10^{-4}$	0.46	85.3 ± 2.3	7.1
Ω_{ξ}^* ($\gamma = 2 \text{ ps}^{-1}$)	$1.8 \times 10^{-3} \pm 8.5 \times 10^{-5}$	0.33	187.0 ± 9.0	8.4
$\mathcal{A}(z_5)$ ($\gamma = 5 \text{ ps}^{-1}$)	$5.1 \times 10^{-3} \pm 1.4 \times 10^{-4}$	0.39	76.9 ± 2.2	9.0
Ω_{ξ}^* ($\gamma = 5 \text{ ps}^{-1}$)	$1.5 \times 10^{-3} \pm 8 \times 10^{-5}$	0.34	233.0 ± 13.0	10.8
$\mathcal{A}(z_5)$ ($\gamma = 10 \text{ ps}^{-1}$)	$4.2 \times 10^{-3} \pm 1.4 \times 10^{-4}$	0.3	70.4 ± 2.3	11.1
Ω_{ξ}^* ($\gamma = 10 \text{ ps}^{-1}$)	$1.2 \times 10^{-3} \pm 7.8 \times 10^{-5}$	0.27	230.0 ± 15.0	12.1
$\mathcal{A}(z_5)$ ($\gamma = 50 \text{ ps}^{-1}$)	$2.0 \times 10^{-3} \pm 1.2 \times 10^{-4}$	0.088	44.0 ± 2.6	41.2
Ω_{ξ}^* ($\gamma = 50 \text{ ps}^{-1}$)	$3.3 \times 10^{-4} \pm 4.7 \times 10^{-5}$	0.077	233.0 ± 33.0	55.0

Throughout range of conditions, optimized state definition leads to $\approx 2 - 5\times$ increase in timescale separation with respect to reference state.

Asymptotic optimization methodology in the low-temperature limit

Introduce a parametric family of domains $(\Omega_{\beta,\alpha})_{\alpha \in \mathcal{X}, \beta > 0}$, jointly parametrized by the asymptotic parameter β and the shape parameter α .

Compute quantitative asymptotics of the objective:

$$\frac{\lambda_2(\Omega_{\beta,\alpha})}{\lambda_1(\Omega_{\beta,\alpha})} = \mathcal{F}(\beta, \alpha)(1 + o(1))$$

for some explicit \mathcal{F} in the limit $\beta \rightarrow +\infty$.

Optimize \mathcal{F} with respect to α (the optimal parameter may itself depend on β).

Main difficulty is to compute **spectral asymptotics** for domains which change with the temperature.

Equivalent to the semiclassical analysis of the Witten Laplacian

$$-e^{-\beta V/2} \mathcal{L}_\beta e^{\beta V/2} = -\frac{1}{\beta} \Delta + \frac{\beta}{4} |\nabla V|^2 - \frac{1}{2} \Delta V$$

with $\hbar := 1/\beta$ -dependent Dirichlet boundary conditions.

Main geometric assumption

We restrict to $a = \text{Id}$, assume V is a smooth Morse function (non-degenerate Hessians at critical points), and $\Omega_\beta \subset \mathcal{K}$ with $\text{Crit}V|_{\mathcal{K}} = \{z_0, \dots, z_{N-1}\}$.

Assume the following limit is well-defined in $(-\infty, +\infty]$ for each $0 \leq i < N$.

$$\alpha_i = \lim_{\beta \rightarrow \infty} \sqrt{\beta} \sigma_{\Omega_\beta}(z_i), \quad \sigma_{\Omega_\beta}(x) = \begin{cases} -d(x, \partial\Omega_\beta), & x \in \Omega_\beta, \\ d(x, \partial\Omega_\beta) & x \in \mathcal{X} \setminus \Omega_\beta \end{cases}.$$

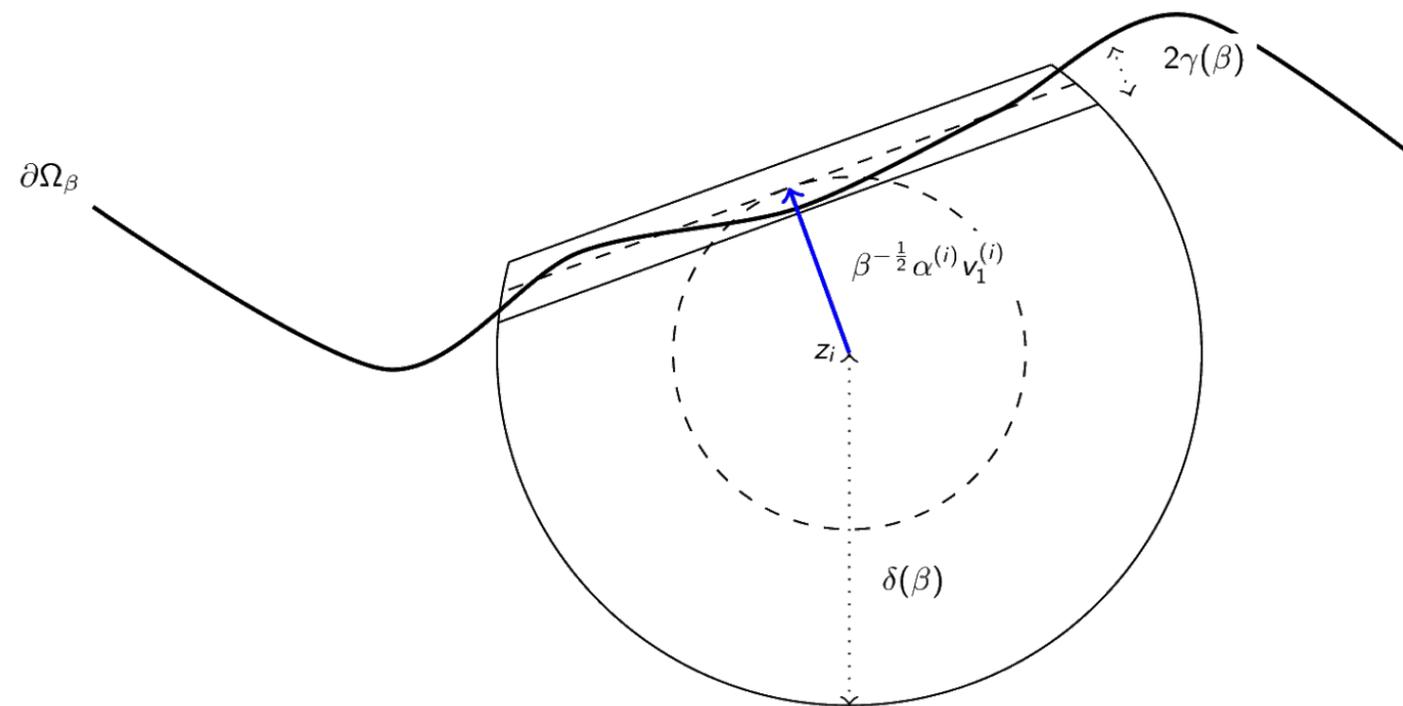
If $\alpha_i = +\infty$, z_i is far from the boundary, and if not, it is close.

Assume there exists a function $\delta : \mathbb{R}_+ \rightarrow (0, \varepsilon(V))$ such that

$$\delta(\beta) \gg 1/\sqrt{\beta}, \quad \mathcal{O}_i^-(\beta) \subseteq B(z_i, \delta(\beta)) \cap \Omega_\beta \subseteq \mathcal{O}_i^+(\beta),$$

where the sets \mathcal{O}_i^\pm constrain the geometry of the boundary near the z_i in a specific way.

Main geometric assumption



In the drawing, \mathcal{O}_i^\pm are the two capped balls, $\gamma(\beta) \ll 1/\sqrt{\beta}$, and $v_1^{(i)}$ is an eigenvector of $\nabla^2 V(z_i)$.

If z_i is an index 1 saddle points, we assume $v_1^{(i)}$ is the **unique eigenvector for the negative eigenvalue**.

Boundary near a saddle $z_i \approx$ level set of the position along the **minimum energy path** through the saddle.

Standard settings ($\Omega_\beta = \Omega$ satisfying a transversality condition) are included.

First-order behavior for the full spectrum

Theorem: Harmonic approximation (Blassel, Lelièvre, and Stoltz (2025a)):

For any k , it holds

$$\lim_{\beta \rightarrow \infty} \lambda_{k, \Omega_\beta} = \lambda_k^H,$$

where λ_k^H is the k -th (temperature independent) eigenvalue of a direct sum of **local harmonic models**

$$H_\beta^\alpha = \bigoplus_{i=0}^{N-1} H_\beta^{(i), \alpha_i}, \quad H_\beta^{(i), \alpha_i} = \beta(x - z_i)^\top \nabla V^2(z_i)(x - z_i)/4 - \Delta V(z_i)/2 - \frac{1}{\beta} \Delta,$$

acting on the half-space $\{(x - z_i)^\top \nu_1^{(i)} < \alpha^{(i)}/\beta\}$ with **Dirichlet boundary conditions**.

Example

Assume only one minimum z_0 and index 1 saddle points z_1, \dots, z_{N-1} .

$$\lambda_{1, \Omega_\beta} \xrightarrow{\beta \rightarrow \infty} 0, \quad \lambda_{2, \Omega_\beta} \xrightarrow{\beta \rightarrow \infty} \min \left[\nu_1^{(0)}, \min_{0 < i < N} |\nu_1^{(i)}| \left(\mu_{0, \alpha^{(i)}} \sqrt{|\nu_1^{(i)}|/2} + \frac{1}{2} \right) \right],$$

where $\mu_{0, \theta}$ = ground-state energy of $\frac{1}{2}(x^2 - \partial_x^2)$ acting on $(-\infty, \theta)$ with Dirichlet boundary conditions and $\nu_k^{(i)}$ = k -th eigenvalue of $\nabla^2 V(z_i)$.

In particular, **quantitative** asymptotics for the decorrelation rate $\lambda_{2, \Omega_\beta} - \lambda_{1, \Omega_\beta}$ whenever $\lambda_2^H > 0$.

Theorem says that $-\mathcal{L}_\beta$ is well-approximated by a **block-diagonal operator**, with each block corresponds to a **local harmonic model** of $-\mathcal{L}_\beta$ around a critical point of V .

Proof relies on the construction of approximate eigenvectors, **harmonic quasimodes**, constructed using Dirichlet quantum oscillators localized around each critical point.

Adaptation of a method of Simon (1983) from semiclassical analysis to the (new) setting of moving Dirichlet boundaries.

Dependence on shape parameter α : [eigenvalues of 1D Dirichlet harmonic oscillators](#).

Further geometric assumptions

We now restrict the setting to the case of **only one minimum far from the boundary** z_0 (plus arbitrary other critical points).

Harmonic approximation then implies $\lambda_{1,\Omega_\beta} \rightarrow 0$, $\lambda_{2,\Omega_\beta} \rightarrow \lambda_{2,\alpha}^H > 0$.

Define $V^* = \min \{ V(z), z \in \partial [\mathbb{R}^d \setminus \mathcal{A}(z_0)] \}$, where $\mathcal{A}(z_0) =$ basin of attraction of z_0 for $X'(t) = -\nabla V(X(t))$.

The minimizers are index one saddle points $\{z_i, i \in I_{\min}\}$.

Assume also the **energetic condition** $(\mathcal{A}(z_0) \cap \{V < V^* + c\delta(\beta)^2\} \setminus \cup_{i \in I_{\min}} B(z_i, \delta(\beta))) \subset \Omega_\beta$ for all β and some $c > 0$.

This condition avoids the presence of **generalized saddle points** with energy $\leq V^*$, ensuring that the likeliest exit pathway is intrinsic to V , and not an artefact of the domain geometry.

Modified Eyring-Kramers formula

Theorem (Blassel, Lelièvre, and Stoltz (2025a)):

In the limit $\beta \rightarrow \infty$, it holds

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

where

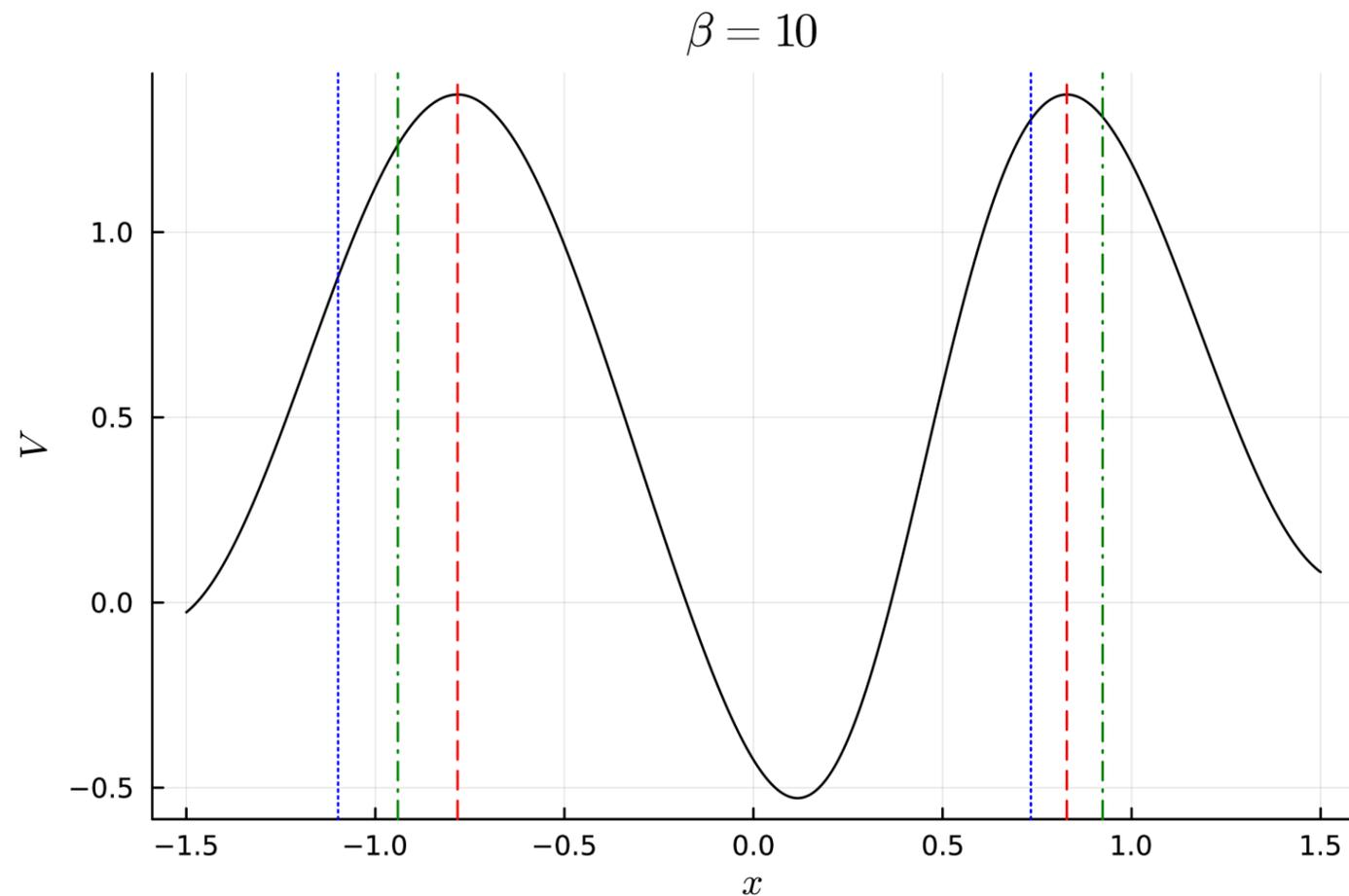
$$\Phi(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^x e^{-\frac{t^2}{2}} dt.$$

Result provides **sharp quantitative** estimate for the metastable exit rate λ_{1,Ω_β} . Dependence on α is only in the prefactor P .

Adds **geometric corrections** to standard Eyring-Kramers ($\alpha = +\infty, P = 1$) and ($\alpha = 0, P = 1/2$) formulas.

Proof relies on the construction of very precise approximations for u_{1,Ω_β} , inspired by works in potential theory (Bovier, Gayrard, and Klein (2005)) and semiclassical analysis of Witten Laplacians (Le Peutrec and Nectoux (2021)).

Illustration on a 1D energy well



Potential with several domains.

$\Omega_{\beta,\alpha} = (z_1 - \alpha_1/\sqrt{\beta}, z_2 + \alpha_2/\sqrt{\beta})$. Parameters
 $\alpha = (0.5, 0.3), (1.0, -0.3), (0.0, 0.0)$.

We aim to maximize

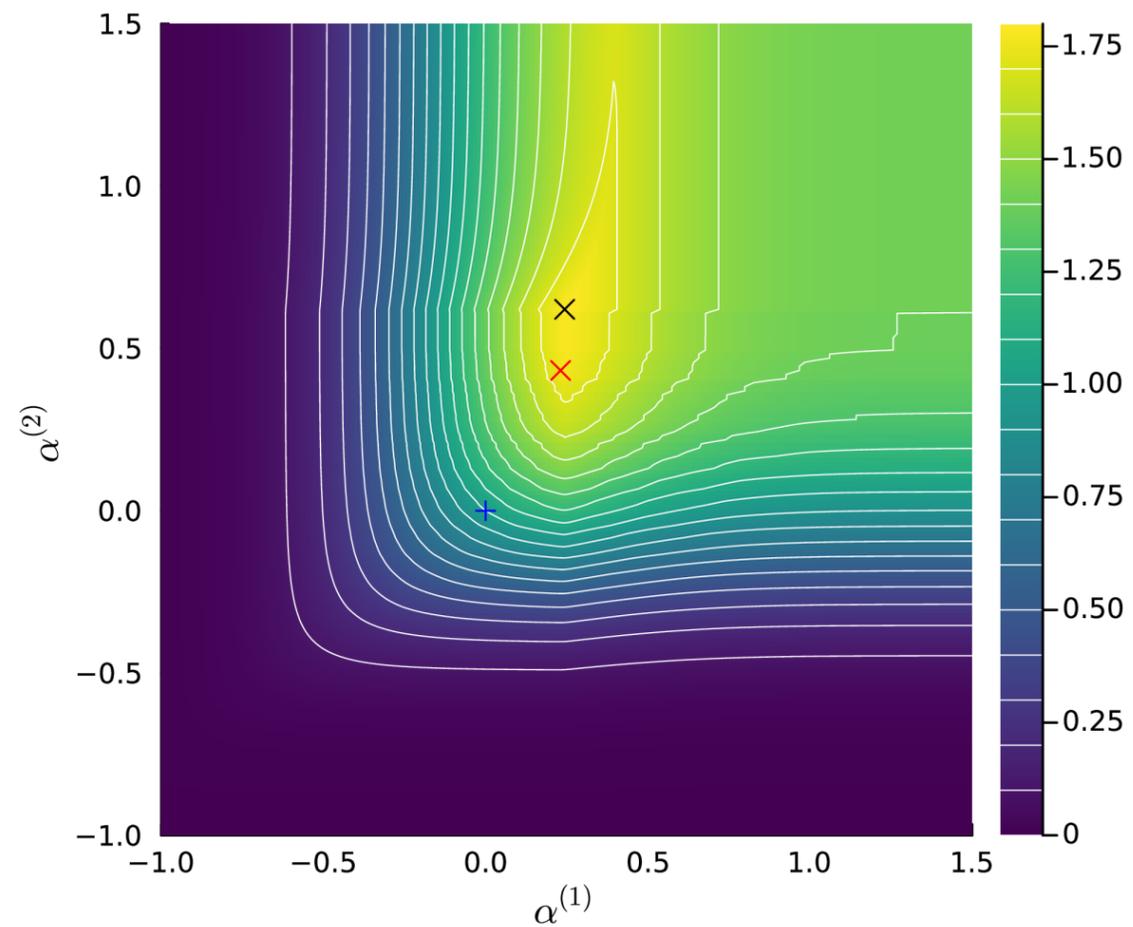
$$\frac{\lambda_{2,\beta}(\Omega_{\beta,\alpha}) - \lambda_{1,\beta}(\Omega_{\beta,\alpha})}{\lambda_{1,\beta}(\Omega_{\beta,\alpha})}$$

with respect to α . Equivalently, maximize

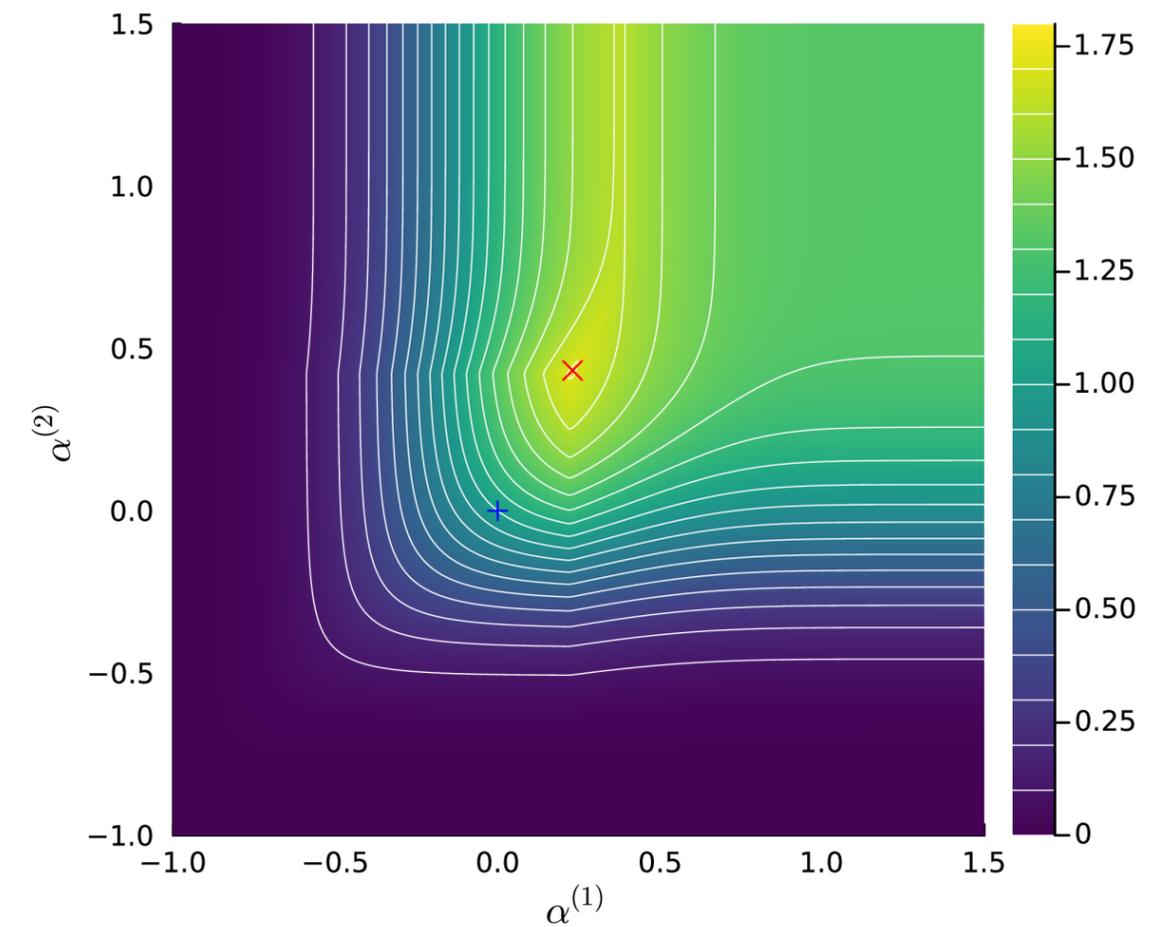
$$J_{\beta}(\alpha) = \frac{\lambda_{2,\beta}(\Omega_{\beta,\alpha})\lambda_{1,\beta}(\Omega_{\beta,0})}{\lambda_{1,\beta}(\Omega_{\beta,\alpha})\lambda_{2,\beta}(\Omega_{\beta,0})},$$

where $\Omega_{\beta,0}$ is the basin of attraction for the local minimum z_0 . According to the results of Blassel, Lelièvre, and Stoltz (2025a), $J_{\beta} \xrightarrow{\beta \rightarrow +\infty} J_{\infty}$ pointwise, where J_{∞} is a complicated but fully explicit function of α .

Semiclassical approximation of shape-optimization landscape



Shape-optimization landscape for $J_\beta(\alpha)$ for $\beta = 10$. Basin of attraction: +. Optimal domain: X.



Semiclassical approximation $J_\infty(\alpha)$. Semiclassical optimizer: X.

Thank you !



[Preprint](#) on shape-sensitive semiclassical asymptotics.
Numerical shape-optimization preprint available soon.
Some bibliography on the next slide.

Bibliography

- Aristoff, D., M. Johnson, and D. Perez. 2023. “Arbitrarily Accurate, Nonparametric Coarse Graining with Markov Renewal Processes and the Mori–Zwanzig Formulation.” *AIP Advances* 13 (9): 095131-1 - 11.
- Blassel, N., T. Lelièvre, and G. Stoltz. 2025a. “Quantitative Low-Temperature Spectral Asymptotics for Reversible Diffusions in Temperature-Dependent Domains.” *ArXiv Preprint: 2501.16082*.
- . 2025b. “Shape Optimization of Metastable States.”
- Bovier, A., V. Gaynard, and M. Klein. 2005. “Metastability in Reversible Diffusion Processes. II: Precise Asymptotics for Small Eigenvalues.” *Journal of the European Mathematical Society* 7 (1): 69–99.
- Cox, S. J. 1995. “The Generalized Gradient at a Multiple Eigenvalue.” *Journal of Functional Analysis* 133 (1): 30–40.
- Haug, E. J., and B. Rousselet. 1980. “Design Sensitivity Analysis in Structural Mechanics. II. Eigenvalue Variations.” *Journal of Structural Mechanics* 8 (2): 161–86.
- Kato, T. 2013. *Perturbation Theory for Linear Operators*. Vol. 132. Springer Science & Business Media.
- Kirsch, W., H. L. Cycon, R. G. Froese, and B. Simon. 1987. *Schrödinger Operators: With Applications to Quantum Mechanics and Global Geometry*. Springer, Berlin.
- Le Bris, C., T. Lelièvre, M. Luskin, and D. Perez. 2012. “A Mathematical Formalization of the Parallel Replica Dynamics.” *Monte–Carlo Methods and Applications* 18: 119–46.
- Le Peutrec, D., and B. Nectoux. 2021. “Small Eigenvalues of the Witten Laplacian with Dirichlet Boundary Conditions: The Case with Critical Points on the Boundary.” *Analysis & PDE* 14 (8): 2595–2651.
- Perez, D., B. P. Uberuaga, and A. F. Voter. 2015. “The Parallel Replica Dynamics Method – Coming of Age.” *Computational Materials Science*, Special Issue on Advanced Simulation Methods, 100: 90–103.
- Rousselet, B. 1983. “Shape Design Sensitivity of a Membrane.” *Journal of Optimization Theory and Applications* 40: 595–623.
- Simon, B. 1983. “Semiclassical Analysis of Low Lying Eigenvalues. I. Non-Degenerate Minima: Asymptotic Expansions.” *Annales de l’IHP: Physique Théorique* 38 (3): 295–308.
- Sørensen, M., and A. F. Voter. 2000. “Temperature-Accelerated Dynamics for Simulation of Infrequent Events.” *The Journal of Chemical*

Physics 112 (21): 9599–9606.

Voter, A. F. 1997. “Hyperdynamics: Accelerated Molecular Dynamics of Infrequent Events.” *Physical Review Letters* 78 (20): 3908–11.

———. 1998. “Parallel Replica Method for Dynamics of Infrequent Events.” *Physical Review B* 57 (22): 9599–9606.