Efficient Calculation of Maximum Flux Transition Paths

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Calculation involves

1. calculation of potentials of mean force (free energy functions)
2. discretization of the path and the flux resistance
3. minimization of the flux resistance

Talk focuses on 2. and 3.

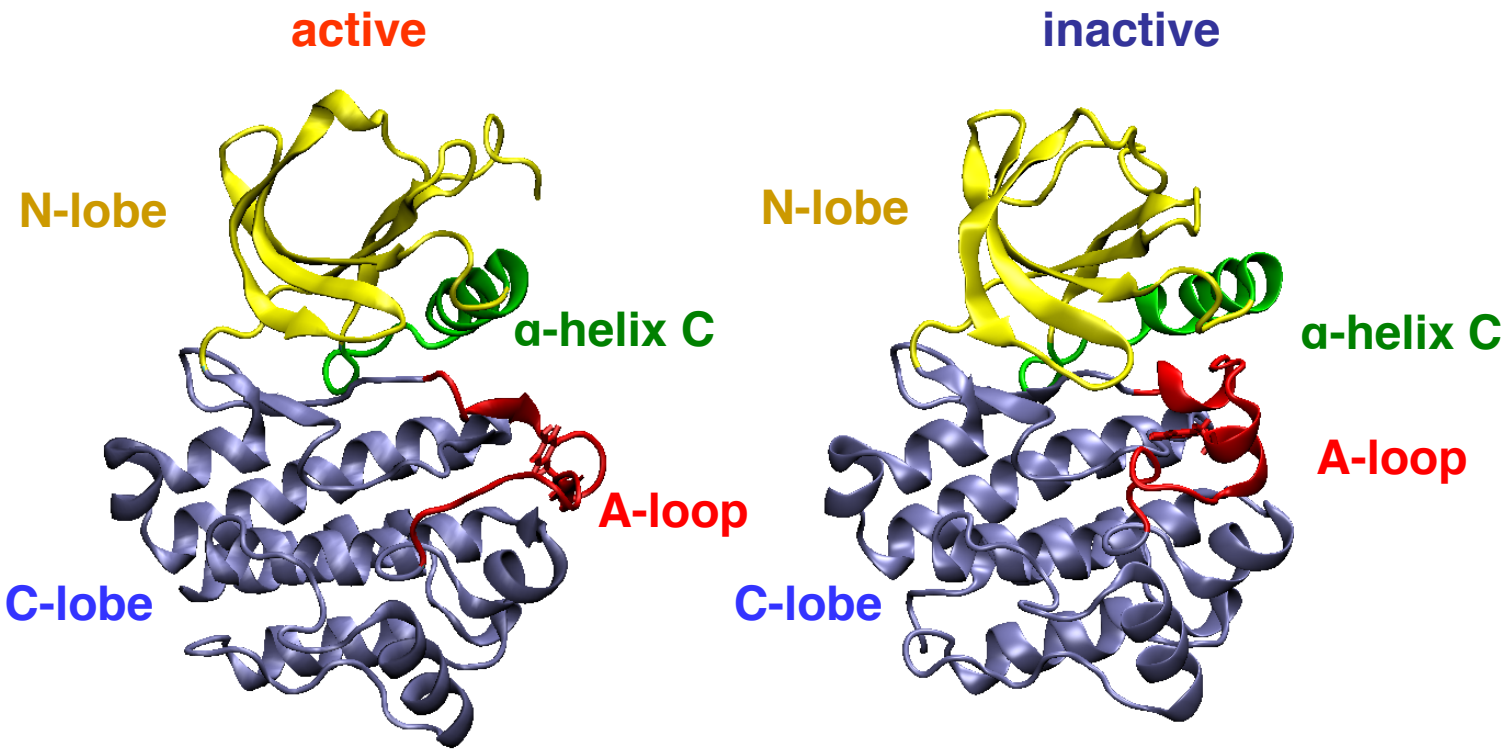
Improvements in any category have a *multiplicative* effect.

Summary

It is not easy to improve on the string method.

Outline

Motivation



Catalytic domain of Src tyrosine kinase
collaboration with Carol Post group

Biological questions

- What is the rate-limiting step in the transition from one conformation to another?
- What are possible intermediate states involved in the transition that can be used as targets for inhibitors of enhanced specificity?
- What is the free energy difference between the two conformational states?

Informal problem statement

Compute for minimal cost best possible representative paths of conformational change from conformation A to conformation B.

representative path: center of an isolated cluster of trajectories.

Collective variables

Transition paths might not cluster adequately
—in full configuration space.
Assume, however, there is a smaller set of *collective variables*,
functions of the configuration x,

$$\zeta_1 = \xi_1(x), \zeta_2 = \xi_2(x), \ldots, \zeta_\nu = \xi_\nu(x), \quad \text{abbreviated as } \zeta = \xi(x),$$

such that in colvar space,
paths cluster into one or several distinct isolated bundles.

e.g., torsion angles ϕ and ψ.

Best possible: tube in colvar space of specified cross-section area for which the flow rate of distinct reactive trajectories is maximum

—Best local maxima wanted.

Minimal cost: make simplifications to limit sampling to paths in colvar space. (Also, minimize programming effort by using existing features of simulators.)

Simplification: a *narrow* tube.

—a maximum flux transition path (MFTP)

An alternative to maximum flux: maximum probability

- minimizing Onsager-Machlup action, Olender & Elber (1996)
- minimizing free energy, Maragliano, Fischer, Vanden-Eijnden & Ciccotti (2006)

Outline

Free energy function

Assume Newtonian dynamics with initial positions x and velocities drawn from the canonical ensemble with inverse temperature β.
Let $\rho_\xi(\zeta)$ be the probability density of $\zeta = \xi(x)$.
An "effective energy" function $F(\zeta)$ is obtained via

$$\mathrm{e}^{-\beta F(\zeta)} \stackrel{\mathrm{def}}{=} \rho_\xi(\zeta) = \langle \delta(\xi(x) - \zeta) \rangle,$$

sometimes called a *free energy function*.

Metric tensor

The appropriate metric to measure distance from ζ to $\zeta + \mathrm{d}\zeta$ is

$$|\mathrm{d}\zeta|_\zeta = (\mathrm{d}\zeta^\mathsf{T} M(\zeta)\mathrm{d}\zeta)^{1/2}$$

with metric tensor

$$M(\zeta)^{-1} \stackrel{\mathrm{def}}{=} m_{\mathrm{tot}} \left\langle \xi_x(x) M_0^{-1} \xi_x(x)^\mathsf{T} \right\rangle_{\xi(x)=\zeta}$$

where M_0 is a diagonal matrix of masses.

The distance $|\mathrm{d}\zeta|_\zeta$ is cartesian RMSD!

The formula

The maximum flux transition path (MFTP)

$$\zeta = Z(s), \quad 0 \le s \le 1,$$

minimizes

$$\int_0^1 \mathrm{e}^{\beta F(Z)} (\det M(Z))^{-1/2} \underbrace{|Z_s|_Z \mathrm{d}s}_{\text{arc length}}$$

where $Z = Z(s)$, $Z_s = (\mathrm{d}/\mathrm{d}s)Z(s)$,

Zhao, Shen, and Skeel, *J. Chem. Theory Comput.*, 2010,

building on work by E. Vanden-Eijnden et al.

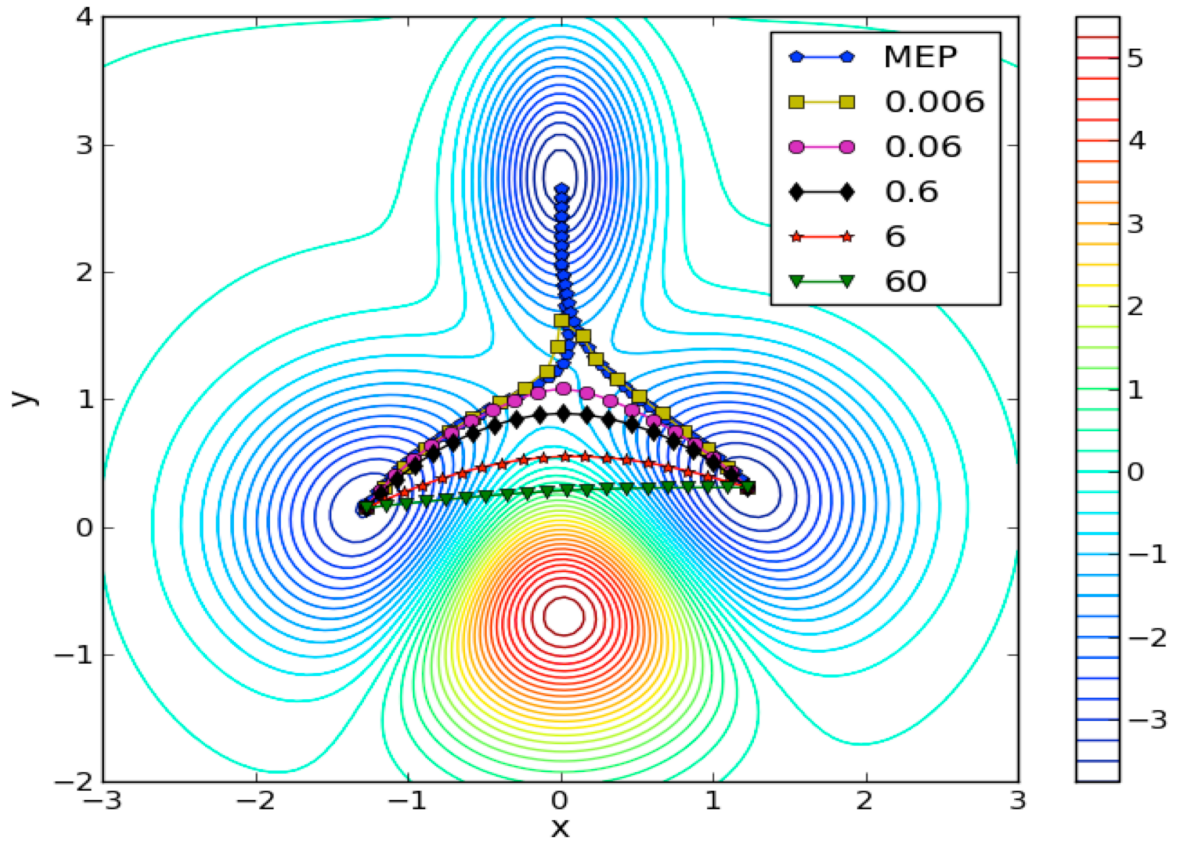
Claim: An MFTP is the best representation of trajectories obtainable at minimal computing cost.

Discussion deferred.

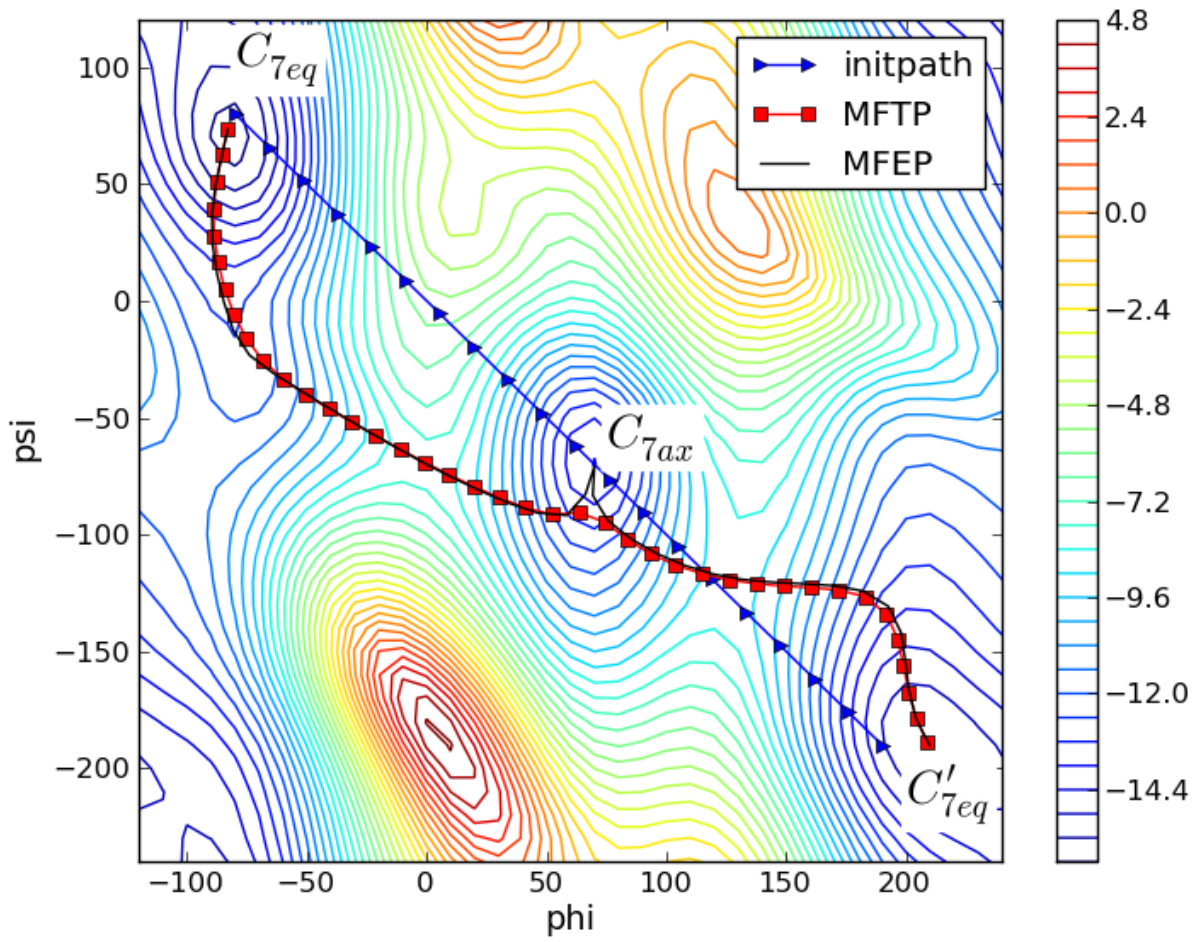
Objective: a more efficient algorithm for calculating an MFTP.

Examples of MFTPs follow:

Three-hole potential



The MFTP at different temperatures
and the minimum energy path



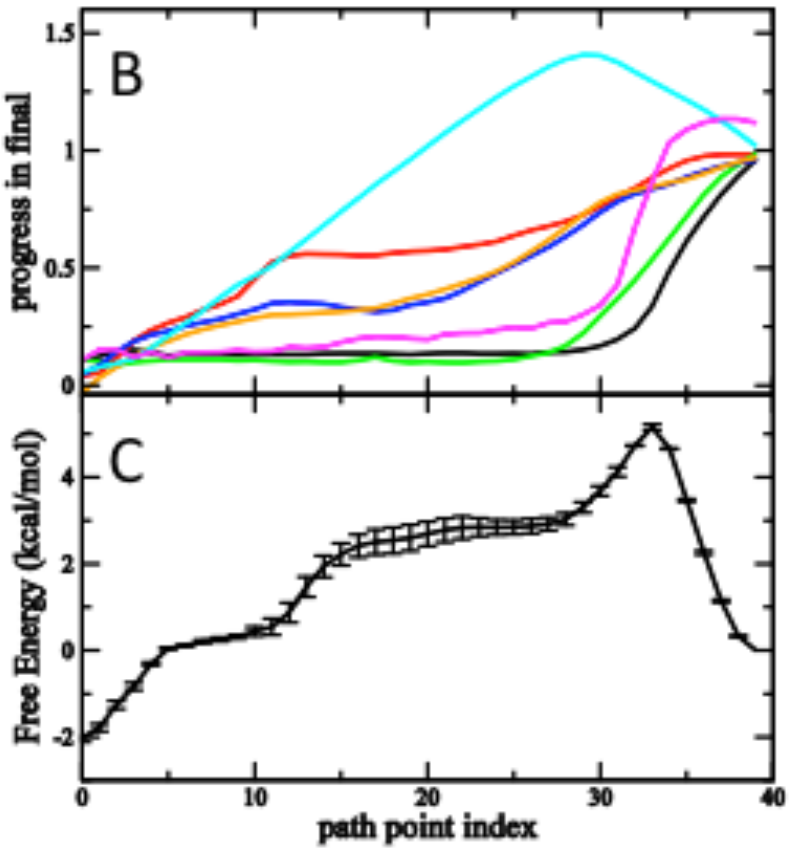
MFEP vs. MFTP for alanine dipeptide in vacuo at $T = 300\,\mathrm{K}$. Contours of (zero-temperature) free energy in increments of 0.6 kcal/mol in φ and ψ torsion angles, red squares are MFTP, and black line is MFEP.

Double basin Gō model of CDK2 kinase

813 DOFs, 7 colvars $\zeta = Z(s)$

Same final results
for 3 different initial paths.
Reorientation of α-helix C
is rate-limiting step.

free energy $F(Z(s))$
Huang, Zhao, Dickson, Skeel & Post (2012)



Outline

$F(\zeta)$ and its Hessian

- Free energy differences can be constructed from free energy derivatives using piecewise quadratic interpolation.
- Calculating an approximate Hessian seems infeasible.

To simplify discussion

consider case of Cartesian coordinates scaled so that masses are 1:
Find $\zeta = Z(s)$, $0 \leq s \leq 1$, that minimizes

$$\int_0^1 \mathrm{e}^{\beta F(Z)} |Z_s| \mathrm{d}s$$

given $Z(0)$ and $Z(1)$.

(Difficulties due to colvars are technical only.)

many minima

We consider the computation of local minima (in path space).

Start from an initial guess,
which could be a straight line for a simple problem.

Fluxes of different minima can be compared.

Minimize a discrete integral?

Generally, the most effective approach would be to discretize the integral

$$\int_0^1 \mathrm{e}^{\beta F(Z)} |Z_s| \mathrm{d}s$$

and minimize the resulting sum.

However, accelerated minimization methods
assume a local quadratic model,
and this is not appropriate.

Conclusion: use a dynamical embedding for minimization.

Embedding minimization in dynamics

Let the path evolve in time

$$\zeta = Z(s,t), \quad t \geq 0.$$

The goal is to

$$\text{define} \quad \frac{\partial}{\partial t} Z = \cdots \quad \text{so that} \quad \frac{\mathrm{d}}{\mathrm{d}t} \int_0^1 \mathrm{e}^{\beta F(Z)} |Z_s| \mathrm{d}s < 0$$

and integrate until path becomes stationary.

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_0^1 \mathrm{e}^{\beta F(Z)}|Z_s|\mathrm{d}s =$$

$$\int_0^1 \left(\frac{\partial}{\partial t}Z\right)^{\mathsf{T}} \mathrm{e}^{\beta F(Z)}|Z_s|\left(I - \frac{Z_s Z_s^{\mathsf{T}}}{|Z_s|^2}\right)\left(\beta\nabla F(Z) - \frac{1}{|Z_s|^2}Z_{ss}\right)\mathrm{d}s$$

To make this negative, define

$$\frac{\partial}{\partial t}Z = \alpha\left(-\beta\nabla F(Z) + \frac{1}{|Z_s|^2}Z_{ss}\right) + \lambda Z_s$$

where $\alpha > 0$ and λ is arbitrary. Choose $\alpha = 1$.

Parameterizing the path

arbitrariness in parameterization $\zeta = Z(s)$,
manifested in the underdetermined Euler-Lagrange equations

$$\left(I - \frac{Z_s Z_s^{\mathsf{T}}}{|Z_s|^2} \right) \left(-\frac{1}{|Z_s|^2} Z_{ss} + \beta \nabla F(Z) \right) = 0.$$

Possible normalization: $s =$ relative arclength

$$|Z_s| = \text{ constant }, \text{ i.e., } Z_s^{\mathsf{T}} Z_{ss} = 0.$$

determines λ.
Let $L = |Z_s|$.

Spatial discretization

Let $z = \left[\; z_1, z_2, \ldots, z_{K-1} \; \right]^{\mathsf{T}}$ be the replica colvars defining a piecewise linear path.
For the dynamics use

$$\frac{\mathrm{d}}{\mathrm{d}t} z_k = f_k(z) + \lambda_k \tau_k(z)$$

where

$$f_k = -\beta \nabla F(z_k) + \frac{z_{k+1} - 2z_k + z_{k-1}}{L^2 \Delta s^2}$$

and $\tau_k(z)$ is a tangent vector—given by upwinded differencing:

if $f_k^{\mathsf{T}}(z_{k+1} - z_{k-1}) > 0$, use $z_k - z_{k-1}$; else, ...

Temporal discretization

As a single system, the equations have the form

$$\frac{\mathrm{d}}{\mathrm{d}t}z = f(z) + \tau(z)\Lambda$$

where $\Lambda = \mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_{K-1})$.
Only rough accuracy needed; stability is the main aim.
A semi-implicit scheme:

$$\frac{1}{\Delta t}(z' - z) = f(z) + (z' - z)\,T_2(z) + \big(\tau(z) + (z' - z)\,T_1(z)\big)\,\Lambda$$

where T_1, T_2 are tridiagonal.
Also, Vanden-Eijnden and Heymann. *J. Chem. Phys.*, 2008.
For purpose of discussion, neglect implicit terms.

The simplified string method

E, Ren, and Vanden-Eijnden, *J. Chem. Phys.*, 2007.
dispenses with Λ and imposes parameter normalization by a 2-stage process:

$$\bar{z} = z + \Delta t f(z)$$

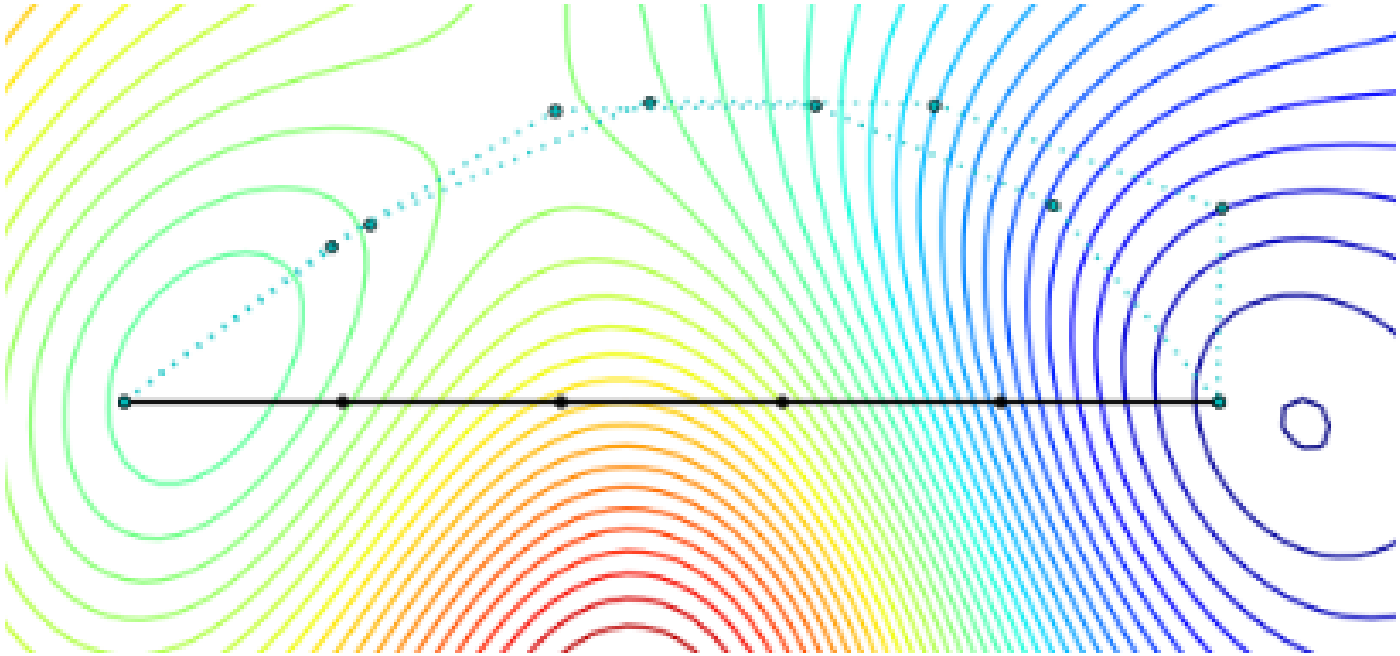
$$z' = \mathrm{eqlz}(\bar{z})$$

where eqlz
redistributes the replicas along the path defined by $\bar{z}$.
When the solution becomes stationary, we have only that

$$\mathrm{eqlz}(\Delta t f(z^*) + z^*) - z^* = 0,$$

not $f(z^*) = 0$.

Also, z^* depends on Δt.



A good fix

is to retain Λ.

E, Ren, and Vanden-Eijnden, *Phys. Rev. B*, 2002.

The stationary solution then satisfies both

$$f(z^*) + \tau(z^*)\Lambda^* = 0$$

and the constraint

$$z^* = \mathrm{eqlz}(z^*).$$

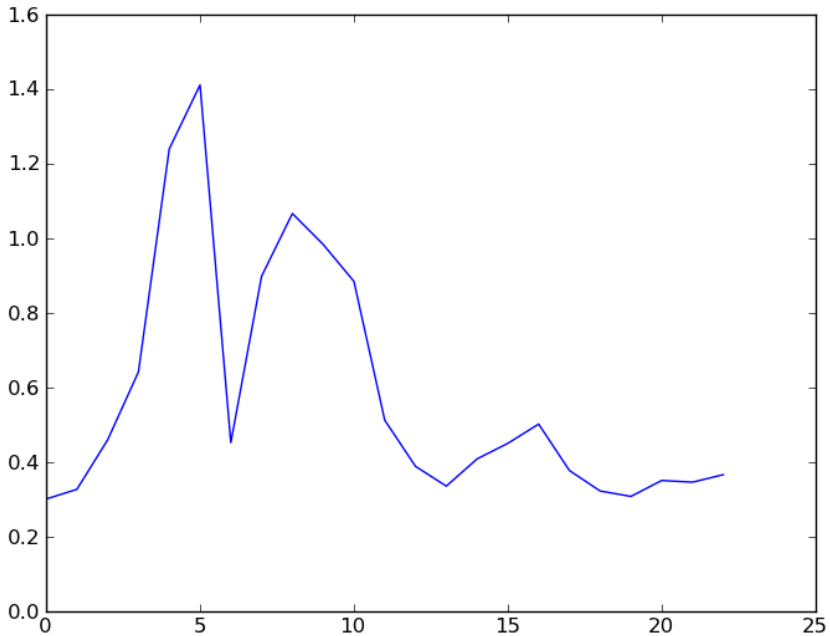
Also slightly enhancing stability:

Convergence test

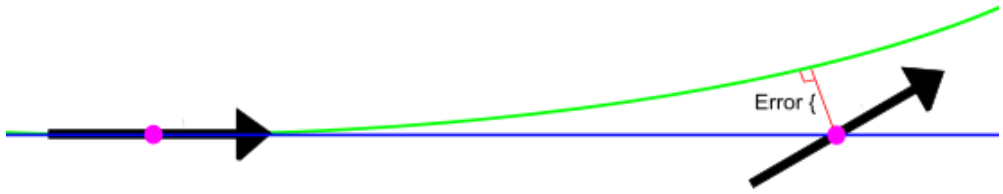
$$\|\|z' - z^*\| \approx \frac{\|z' - z\|}{\|f(z') - f(z)\|}\|f(z')\|$$

where $f(x^*) = 0$.

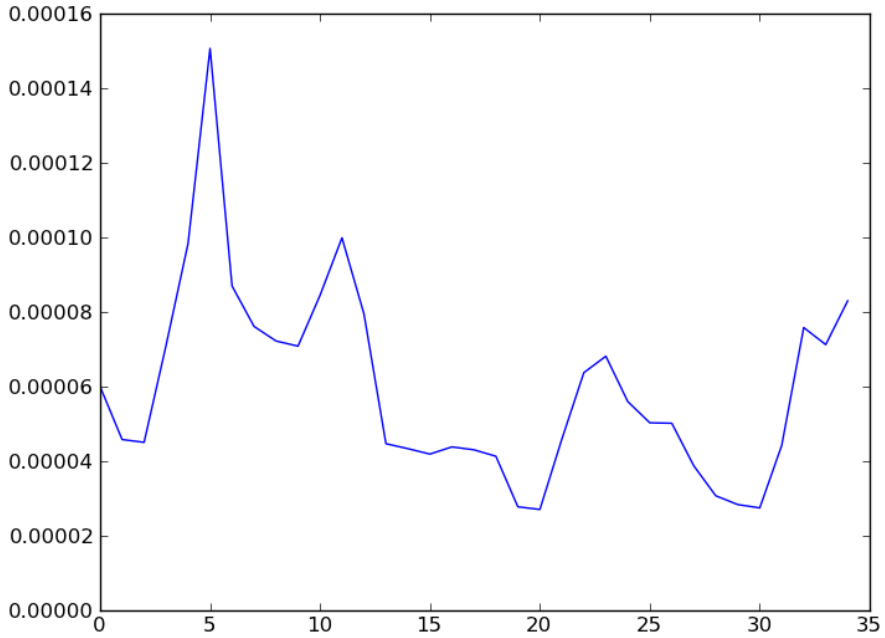
Ratio of error estimate to actual error for Mueller potential:

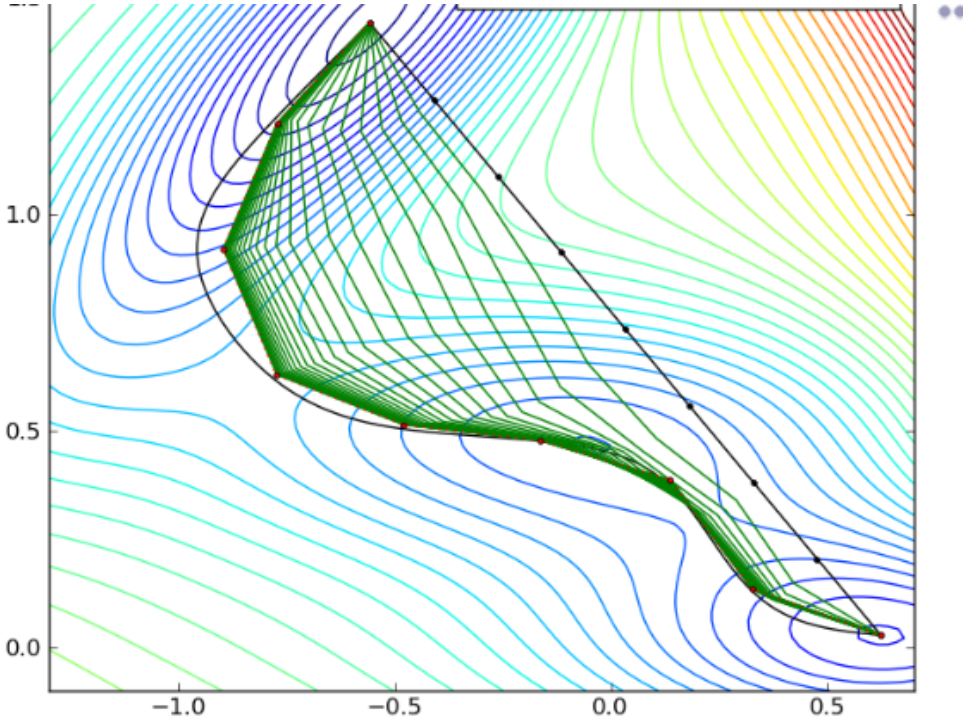


Step size control



Step sizes for the Mueller potential:




1.0
0.5
0.0
−1.0
−0.5
0.0
0.5

Because most of the time is spent calculating $\nabla F(\zeta)$ at replicas along the path,
the computation is highly parallelizable:

MPI for Python: `mpi4py`
Lisandro Dalcín, CONICET, Santa Fé, Argentina

Challenges

- noisy gradient: step size selection and convergence test must tolerate noise
- cost of gradient evaluation increases with size of minimization step.

Outline

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Objective

Discretization and Minimization

Calculation of Free Energy and Metric Tensor

Weaknesses and Strengths of an MFTP

Footnotes and Closing Remarks

The Dirac delta function

Convenient to work with a blurred delta function:

$$\delta_\varepsilon(s) = (2\pi\varepsilon^2)^{-1/2} \exp(-s^2/(2\varepsilon^2))$$

e.g., $\varepsilon = 1$ degree

effectively stiff restraints

Energy function and metric tensor

Calculation of the free energy

$$F(\zeta) = -\frac{1}{\beta} \log \langle \delta(\xi(x) - \zeta) \rangle$$

requires extensive sampling.
However, the gradient can be expressed as an average conditioned on $\xi(x) = \zeta$:

$$\nabla F(\zeta) = -\frac{1}{\beta} \langle \nabla_\zeta \log \delta(\xi(x) - \zeta) \rangle_{\xi(x)=\zeta}.$$

Additionally, recall that

$$M(\zeta)^{-1} = m_{\text{tot}} \left\langle \xi_x(x) M_0^{-1} \xi_x(x)^{\mathsf{T}} \right\rangle_{\xi(x)=\zeta}.$$

Averaging

It is practical to compute $M(\zeta)$, $\nabla_\zeta F(\zeta)$, and 1st derivative of $M(\zeta)$ w.r.t. ζ

as averages from a single (yet very long) simulation

at a point ζ for which *we have a value* x *such that* $\xi(x) \approx \zeta$
(to initiate the Markov chain).

an equilibration (burn-in) phase is followed by a production phase:

sampling for alanine dipeptide uses 50+500 ps of Langevin or Nosé-Hoover dynamics per gradient evaluation.

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Underlying assumption #1

Assume trajectories are *confined* to the tube from A_ξ to B_ξ.

This transforms a PDE in high dimension
to one that is essentially one dimensional.

Underlying assumption #2

Assume that paths $\zeta = Z(s)$,
but not trajectories $\zeta = \xi(X(t))$,
are well approximated by
those of the Brownian dynamics.

The geometric property

Use of metric $|\mathrm{d}\zeta|_\zeta$ to measure arc length and cross-section area.
ensures that the minimizing path is invariant
under a change of coordinates:

e.g., it matters not whether you use distances or their squares
—the paths are equivalent.

For comparison

Minimum resistance path (MRP) minimizes

$$\int_0^1 \exp(\beta F(Z))|Z_s|^{-1}|Z_s|_Z^2 \, \mathrm{d}s.$$

Path depends on how colvar space is parameterized

Berkowitz, Morgan, McCammon, and Northrup,
J. Chem. Phys., 1983.

Huo and Straub, "MaxFlux . . . ," *J. Chem. Phys.*, 1997.

Minimum free energy path (MFEP) minimizes

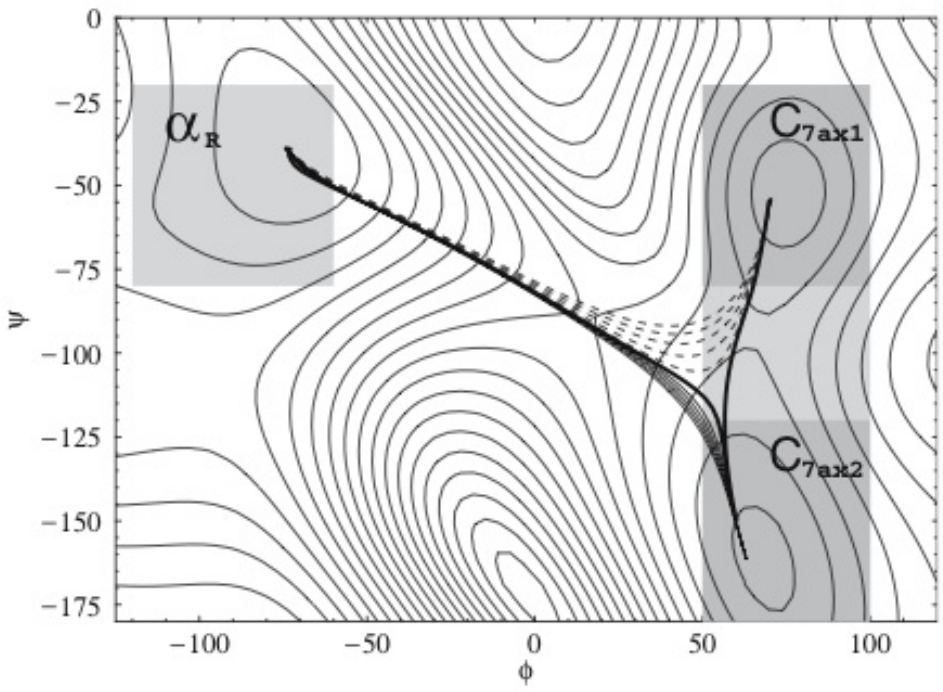
$$\int_0^1 |M(Z)^{-1}\nabla F(Z)|_Z |Z_s|_Z \, \mathrm{d}s.$$

It is the limiting case $\beta \to \infty$ of an MFTP
but with β held fixed in $F(\zeta;\beta)$ and $M(\zeta;\beta)$.

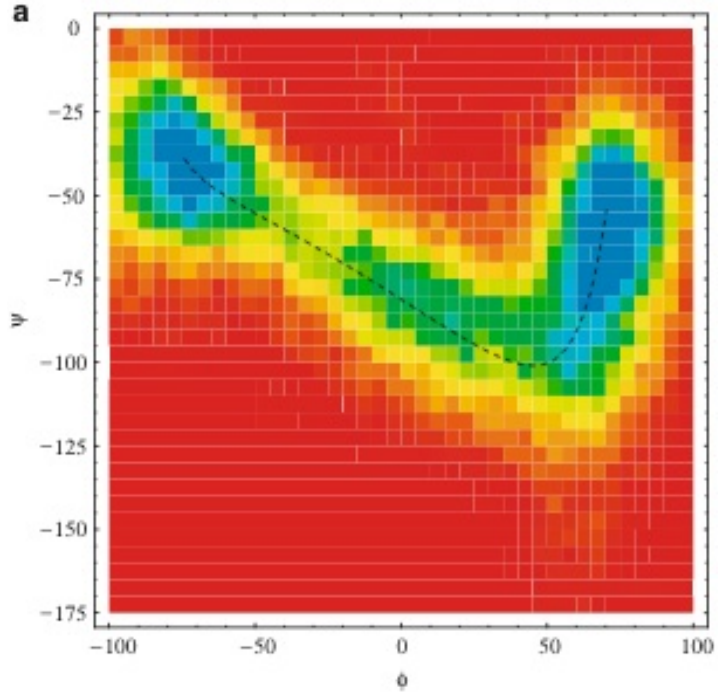
Maragliano, Fischer, Vanden-Eijnden, and Ciccotti,
J. Chem. Phys., 2006.

The MFEP neglects finite temperature effects
—in the explicit degrees of freedom.
alanine dipeptide (OPLS-AA with GBSA)

MFEP & MFTPs



density of dynamical trajectories



Jiménez and Crehuet, Theor. Chem. Account, 2007.

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Initiating the Markov chains

Evaluation of $\nabla F(Z_j)$ at time step $n+1$
requires x_j such that $\xi(x_j) \approx Z_j$.
One can use for x_j a value generated during the production phase of sampling for Z_j at time step n, e.g., the last value.
The number of equilibration steps depends on the change in Z_j.
Greater increments result in longer equilibration times.
Therefore, taking larger steps may or *may not be helpful*.

A reference path in Cartesian space

In addition to $\zeta = \xi(x)$, we should define a *reference path* $x = X(s)$ in Cartesian coordinates.

An attractive choice:
Ask that $X(s)$ be an MFTP in Cartesian configuration space subject to the constraint $\xi(X(s)) = Z(s)$.

Interpretation of $M(\zeta)$

The point ζ in colvar space
represents a manifold in Cartesian configuration space.

The distance

$$|\mathrm{d}\zeta|_\zeta = \left(\mathrm{d}\zeta^\mathsf{T} \left(\left\langle \xi_x(x) M_0^{-1} \xi_x(x)^\mathsf{T} \right\rangle_\zeta \right)^{-1} \mathrm{d}\zeta \right)^{1/2}$$

somehow corresponds to the RMSD between Cartesian space manifolds $\xi(x) = \zeta$ and $\xi(x) = \zeta + \mathrm{d}\zeta$

$$\left(\mathrm{d}\zeta^\mathsf{T} \left\langle \left(\xi_x(x) M_0^{-1} \xi_x(x)^\mathsf{T} \right)^{-1} \right\rangle_\zeta \mathrm{d}\zeta \right)^{1/2}.$$

Closing Remarks

- To minimize an integral of an exponential,
  embed the problem in dynamics, as in the string method.
- Yet improvements are desirable and almost certainly attainable.

Acknowledgments

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NIH

and . . .