Maximum Flux Transition Paths of Conformational Change

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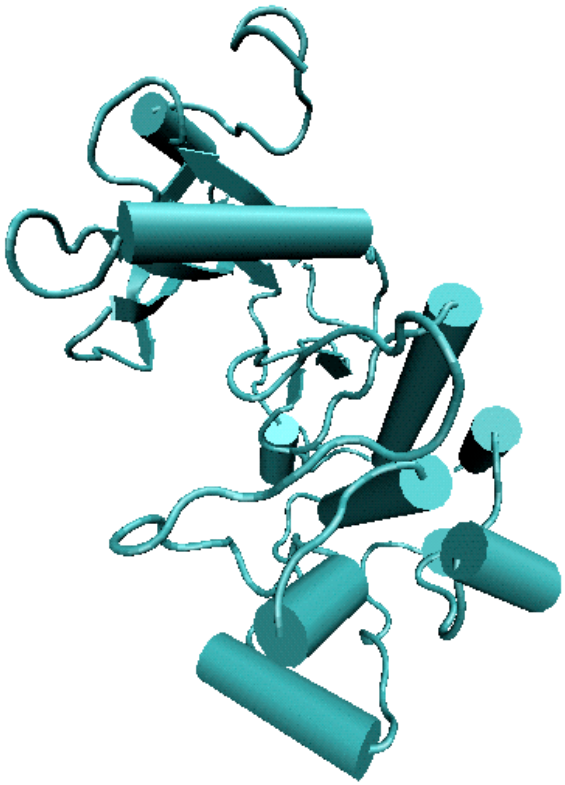
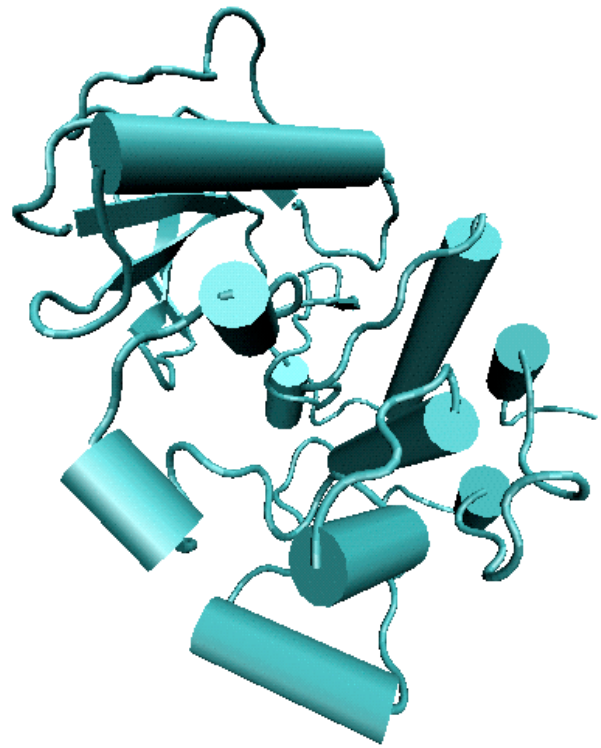
Voichita Dadarlat

Src tyrosine kinase

active catalytic domain



inactive catalytic domain



Message

We can do better than compute a minimum free energy path:
find a path which intersects each isocommittor
at that point through which there is
the highest number of crossings of distinct reactive trajectories.

Outline

I. What is the problem?
II. Three uncontrolled approximations
III. An algorithm
IV. Comparison

What to compute

Given two metastable states A and B in configuration space, the problem is to find one or several "representative" reaction paths connecting them.

Motivation:
calculating free energy differences,
finding intermediate meta-stable states
(targets for inhibitors of enhanced specificity)

Problems vs. Algorithms

Two steps:

1. define the problem,

---

2. construct an algorithm.

We follow the approach of Vanden-Eijnden, E, Ren, Ciccotti, ...

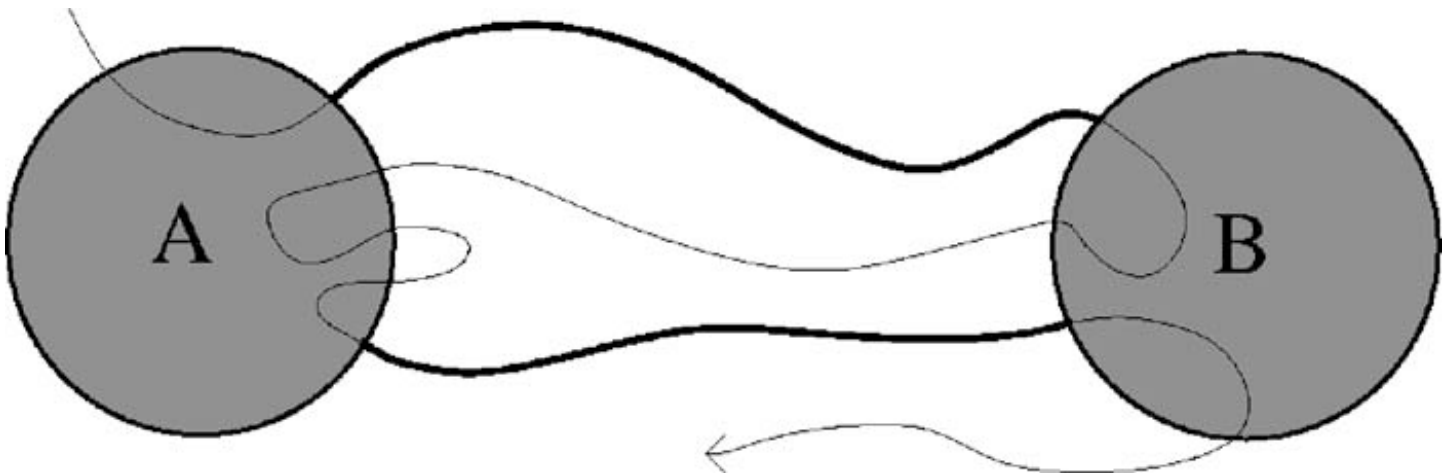
Dynamical equations

Consider a molecular system with potential energy function $U(x)$
Assume Newtonian dynamics with mass matrix M and
initial values from a Boltzmann-Gibbs distribution:
initial x from probability density $\rho(x) = \mathrm{const}\, \mathrm{e}^{-\beta U(x)}$
and $(\mathrm{d}/\mathrm{d}t)x$ from a Maxwell distribution.

An ensemble of paths

How to define an ensemble of transition paths from A to B:

Imagine an extremely long trajectory.
The trajectory enters and leaves A and B many times
yielding a huge set of reactive paths from A to B,
shown in dark in the figure below:



from Metzner, Schütte, and Vanden-Eijnden (2006)

Defining a path

Rather than generate an ensemble of transition paths,
which would have to be clustered anywhere,
one might directly determine a concise description of the paths.

Specifically, if the paths cluster into one or several distinct isolated channels, one might compute the "center" of each cluster.

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,

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

such that in ζ-space,
paths cluster into one or several distinct isolated channels.

Else, there is little of interest to compute.
Our alanine dipeptide tests use phi and psi angles.

Choice of collective variables

We want a minimal set of collective variables subject to two conditions:

- Coordinates ζ must suffice to describe states A_ζ, B_ζ in ζ-space corresponding to A, B.
- Coordinates ζ must also be rich enough to "express the mechanism of conformational change" along the transition path.

To make the second condition more precise, introduce . . .

The committor

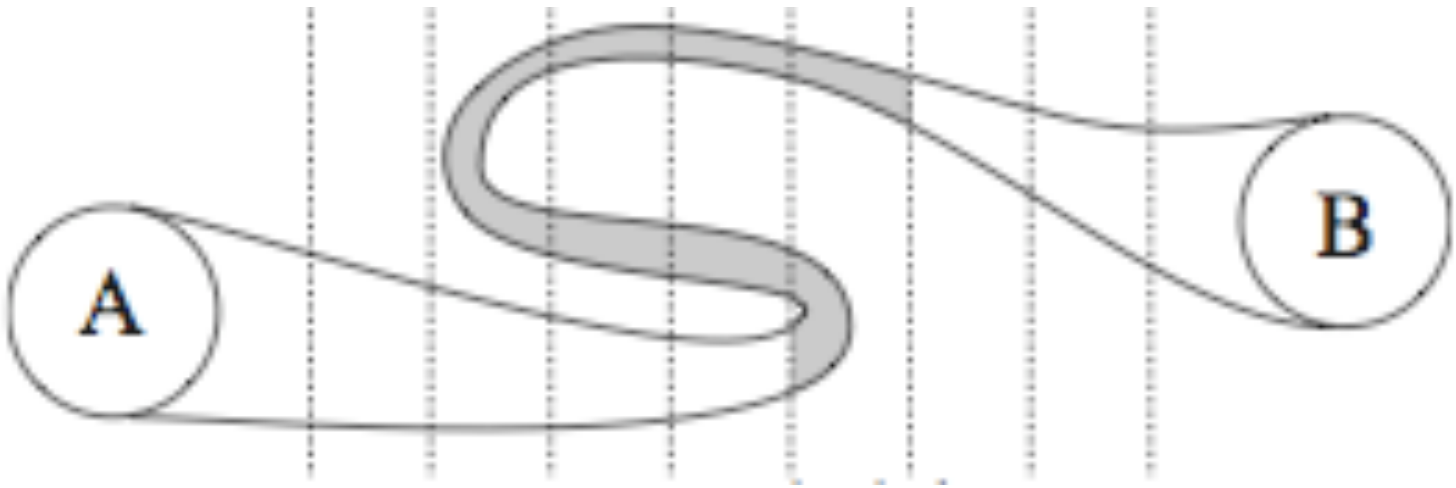
To measure the progress of a transition, there is a natural reaction coordinate, known as the *committor*:
For each point ζ, consider a trajectory starting with random initial values conditioned on $\xi(x) = \zeta$ and define the committor $q(\zeta)$ to be the probability of reaching B_ζ before A_ζ:

$$q(\zeta) = \Pr(X(t) \text{ reaches } B_\zeta \text{ before } A_\zeta \mid \xi(X(0)) = \zeta).$$

Expressing mechanism of change

The variables $\zeta = \xi(x)$ are rich enough to express the mechanism of conformational change if the committor $q(\zeta)$ has no local minima or maxima.

Else, there is some unexpressed DOF important to the transition.



from Dickson, Warmflash, and Dinner (2009)

Defining a path

How to define the "center" of a cluster of paths in ζ-space:

most probable path
    swarm-of-trajectories string method
maximum flux path
    our choice
center of flux path
    finite temperature string method

Maximum flux path

A hypersurface $\{\zeta \mid q(\zeta) = p\}$ of equal probability p is called an isocommittor. On each isocommittor consider the distribution $j(\zeta)$ of crossing points for distinct reactive trajectories (last hitting points).

Seek the path $\zeta = Z(s)$, $0 \leq s \leq 1$, which (locally) maximizes $j(\zeta)$ on each isocommittor through which it passes.

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Short Anecdote

. . .

Is it offensive
to suggest that computational scientists are not in control
of the errors that they are introducing?

Intractible.

Uncontrolled approximation #1:

separation of time scales. Suppose there is some time interval $\tau_{\rm rlx}$
(i) over which the collective variables change only a little, but
(ii) during which all other degrees of freedom almost fully relax.

Hence, evolve the dynamics of $\zeta(t) \stackrel{\rm def}{=} \xi(x(t))$ as follows:
Choose $x(t)$ at random from $\rho(x)$ conditioned on $\xi(x(t)) = \zeta(t)$.
Choose $({\rm d}/{\rm d}t)x(t)$ at random from a Maxwell distribution.
Determine $x(t + \tau_{\rm rlx})$, from Newtonian dynamics.
Set $\zeta(t + \tau_{\rm rlx}) = \xi(x(t + \tau_{\rm rlx}))$.

Before stating the result

Define

$$\exp(-\beta F(\zeta)) = \mathrm{const}\langle\delta(\xi(x)-\zeta)\rangle,$$

$$\langle O(x)\rangle_{\xi(x)=\zeta} = \frac{\langle\delta(\xi(x)-\zeta)O(x)\rangle}{\langle\delta(\xi(x)-\zeta)\rangle},$$

$$D(\zeta) = \frac{\tau_{\mathrm{rlx}}}{2\beta}\langle\xi_x(x)M^{-1}\xi_x(x)^{\mathsf{T}}\rangle_{\xi(x)=\zeta},$$

and $D_{1/2}D_{1/2}^{\mathsf{T}} = D$.

Assumptions (i) and (ii) imply that approximately

$$\begin{aligned}\zeta(t+\tau_{\mathrm{rlx}}) &= \zeta + \sqrt{2\tau_{\mathrm{rlx}}} D_{1/2}(\zeta)\mathrm{N}(0,1)^k \\ &\quad + \tau_{\mathrm{rlx}}(-\beta D(\zeta)\nabla F(\zeta) + (\nabla \cdot D(\zeta))^{\mathsf{T}}) + \mathcal{O}(\tau_{\mathrm{rlx}}^{3/2})\end{aligned}$$

where $\zeta = \zeta(t)$. This is the Euler-Maruyama discretization for stochastic dynamics and assumption (i) implies that $\zeta(t)$ approximately satisfies Brownian dynamics (BD) equations

$$\frac{\mathrm{d}}{\mathrm{d}t}\zeta = -\beta D(\zeta)\nabla F(\zeta) + (\nabla \cdot D(\zeta))^{\mathsf{T}} + \sqrt{2} D_{1/2}(\zeta)\frac{\mathrm{d}}{\mathrm{d}t}W(t).$$

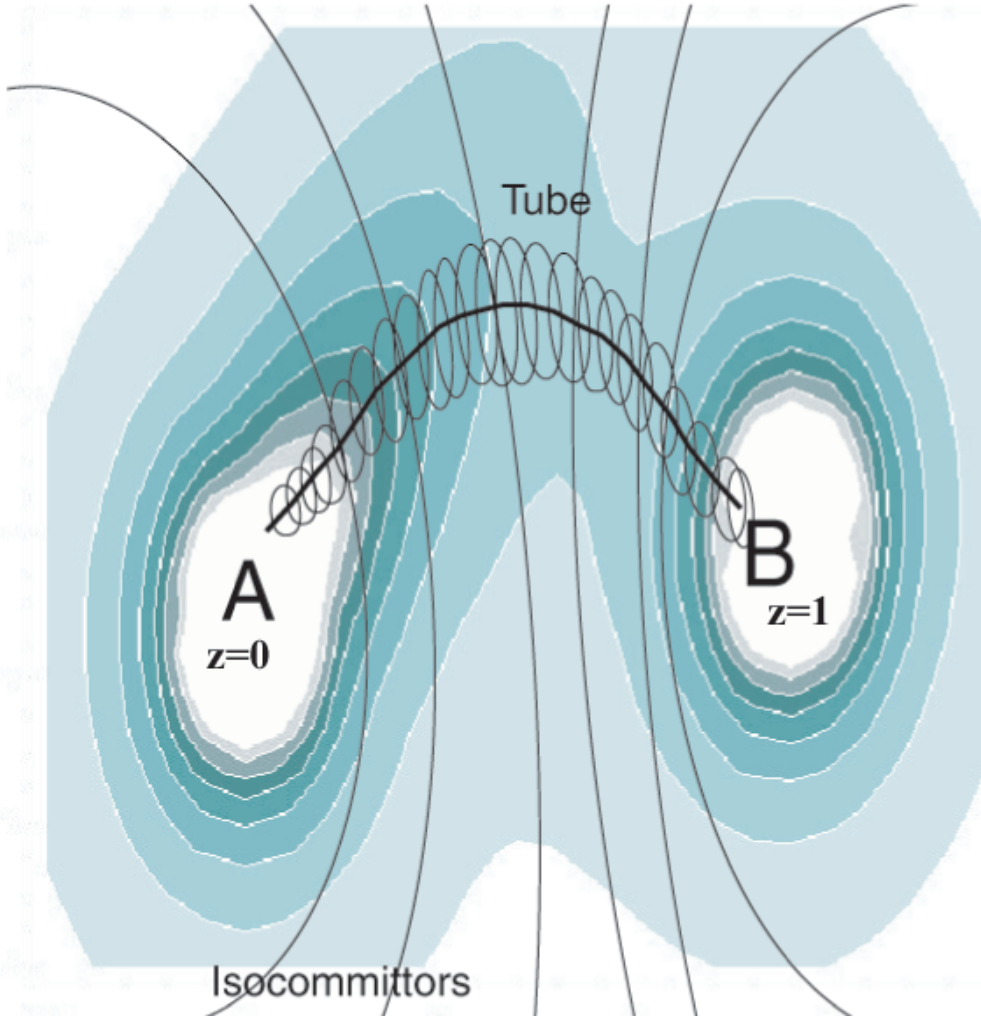
Validity of the assumptions might be checked a posteriori by comparing committor values of the Brownian dynamics to those of actual dynamics.

The path of most probable points

It can be shown that *on an isocommittor* the distribution of last hitting points of reactive trajectories, as well as the net normal reactive flux, is given by

$$j(\zeta) = \mathrm{const}\, \mathrm{e}^{-\beta F(\zeta)} \nabla q(\zeta) \cdot D(\zeta) \nabla q(\zeta) / |\nabla q(\zeta)|.$$

An illustration follows.


Tube
A
z=0
B
z=1
Isocommittors

The BD committor minimizes the functional

$$I(q) = \int \mathrm{e}^{-\beta F(\zeta)} \nabla q(\zeta) \cdot D(\zeta) \nabla q(\zeta) \mathrm{d}\zeta$$

subject to $q(\zeta) = 0$ on the boundary of A_ζ and $q(\zeta) = 1$ on the boundary of B_ζ.

Uncontrolled approximation #2:

localized tube assumption.

Assume that regions of low $F(\zeta)$ constitute a tube
and that isocommittors are nearly planar there
and that $D(\zeta)$ is nearly constant on each plane.

(Approximating the isocommittor)

Take for $q(\zeta)$ an approximation constructed
from $q(Z(s))$ and $\nabla q(Z(s))$, $0 \leq s \leq 1$,
by extrapolation.

Need solve only for $k + 1$ functions of s to get committor.

Uncontrolled approximation #3:

narrow tube assumption.

Assume that on each isocommittor

the probability is strongly peaked around path.

Then the probability flux of reactive trajectories is tangent to the path

$$const\, \mathrm{e}^{-\beta F(Z)} D(Z) \nabla q(Z) \parallel Z_s.$$

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

result is a

Maximum flux transition path

$$Z_s \parallel g, \quad g = -D(Z)\nabla F(Z) + \frac{1}{\beta}\frac{D(Z)(D(Z)^{-1}Z_s)_s}{Z_s^{\mathsf{T}} D(Z)^{-1} Z_s}.$$

Uncontrolled approximation #4:

zero temperature assumption.

Neglect the term $\frac{1}{\beta}\frac{D(Z)(D(Z)^{-1}Z_s)_s}{Z_s^{\mathsf{T}}D(Z)^{-1}Z_s}$.

result is a

Minimum free energy path

$$Z_s \parallel -D(Z)\nabla F(Z).$$

Free energy is minimized "orthogonal" to the path.

We can prove that the MFEP
has cusps at some intermediate local minima.
This undermines the localized tube assumption.

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Controlled approximations

- discretization of path
- solution of nonlinear discrete equations
- sampling

Discretization of path

Sequence of replicas for $\zeta = Z_j$, $j = 0, 1, \ldots, J$.
Upwinded differencing for $(Z_s)_j$
based on direction of modified mean force g_j

Normalization: $(|Z_s|)_s = 0$.

MFEP would have cusps at some intermediate local minima, which requires adaptive discretization methods.

Solution of nonlinear discrete equations

For large systems, targeted MD has been used to get initial path. Simplified string method is good for refining it:

1. $Z_j^* = Z_j + \tau g_j$
2. choose the Z_{j+1} to be equidistant along the resulting curve

$(\tau_{\mathrm{rlx}}\tau)^{1/2} = 48.89$ fs
Number of iterations $= 50$.

Sampling

Strong harmonic restraints are good for constrained sampling.

Our alanine dipeptide simulations use
force constant $K = 1000\,\mathrm{kcal/mol/rad^2}$,
Langevin dynamics with friction coefficient $10/\mathrm{ps}$ on all atoms,
timestep $= 1\,\mathrm{fs}$,
$10\,\mathrm{ps}$ equilibration, $100\,\mathrm{ps}$ production.

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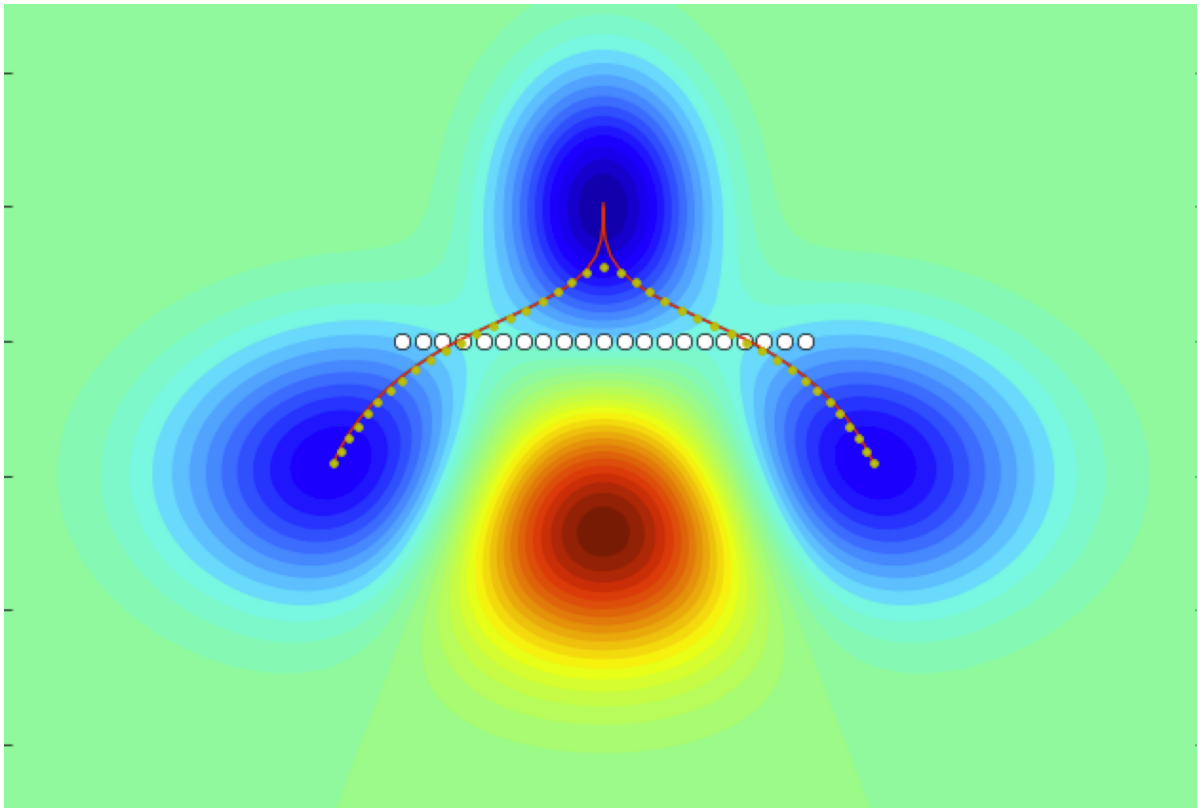
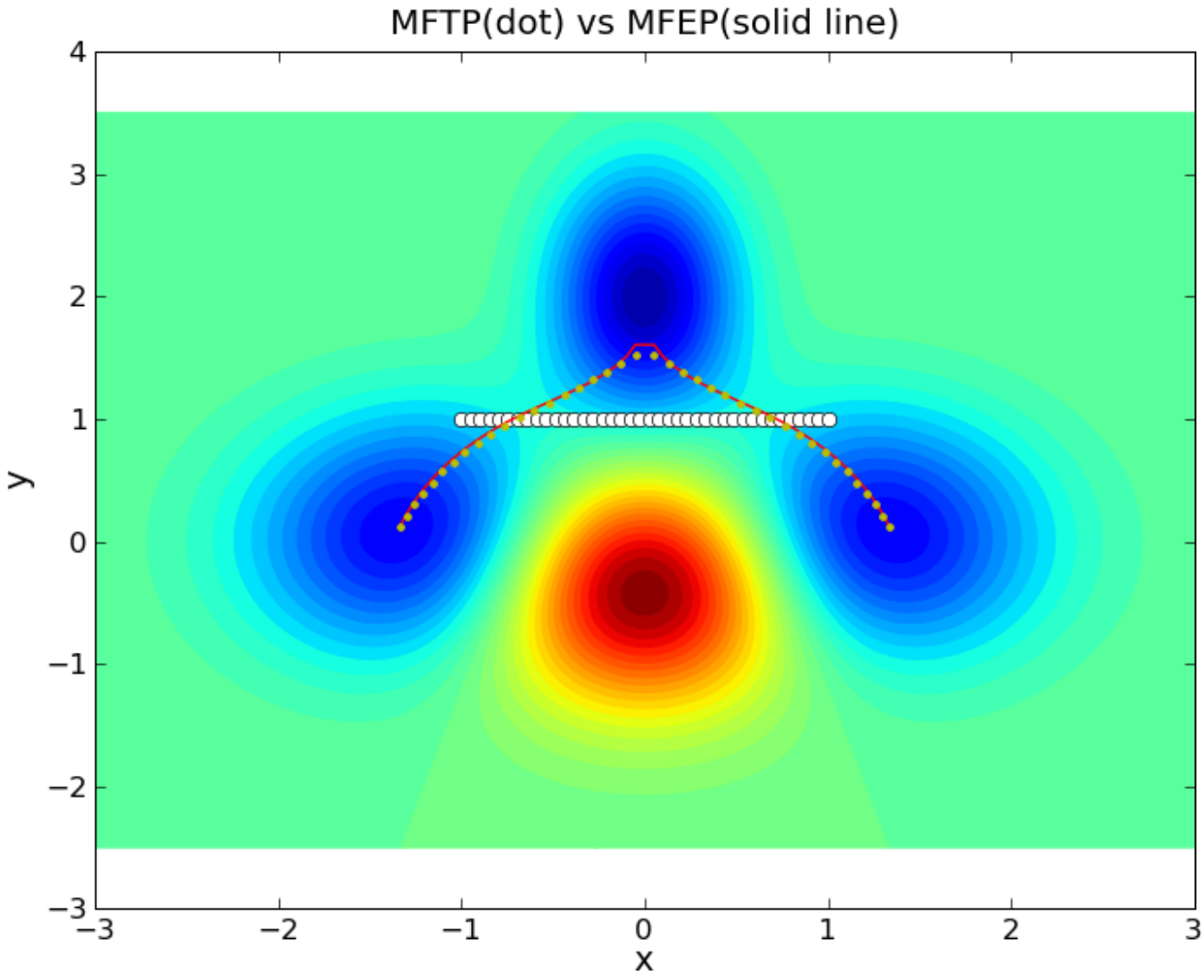
The following figure compares MEP (having a cusp) and MFTP for the potential energy function

$$\begin{aligned} U(x,y) &= -4\exp(-4x^2-(y-2)^2) - 5\exp(-(x-1)^2-y^2) \\ &\quad - 5\exp(-(x+1)^2-y^2) + 8\exp(-x^2-(y+\frac{1}{4})^2). \end{aligned}$$



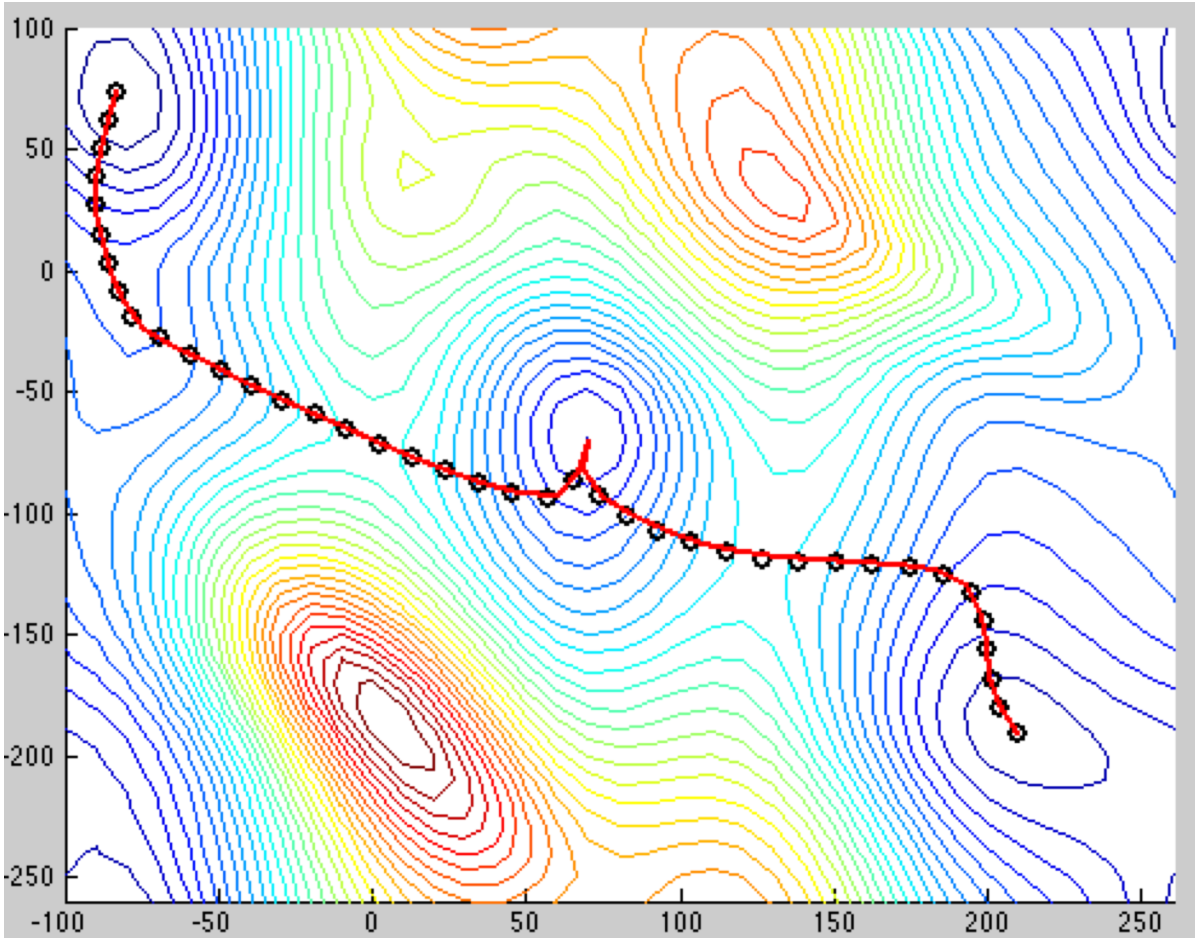
Contour plot of potential energy, white circles are initial string, yellow dots are MFTP, and red line is MEP.

The cusp of MEP/MFEP is hard to compute. For example, the cusp will be missed if there are 40 replicas along the string rather than 41 as shown below:


MFTP(dot) vs MFEP(solid line)
4
3
2
1
0
−1
−2
−3
y
−3
−2
−1
0
1
2
3
x

The next figure compares MFEP and MFTP for alanine dipeptide in vacuo at $T = 300$ using CHARMM22 force field.

MPI for Python + CHARMM
hours of CPU time on 8 cores



Contour plot of potential energy in φ and ψ torsion angles, black circles are MFTP, and red line is MFEP.

Conclusion

The maximum flux transition path (MFTP) involves one less approximation than the minimum free energy path (MFEP).

The MFEP has cusps, which makes it

- unsuitable for defining an isocommitor,
- unsuitable for defining a reaction coordinate, and
- harder to compute.