Theory and Modeling of Reactive Events

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The evolution of many dynamical system can be viewed as a *navigation on an energy or free energy landscape.*

The system tends to spend long period of time in the regions of low energy, and it only rarely makes transition from one such region to another (*metastability*).

These transitions often are the most interesting part of the dynamics:

- kinetic phase transitions;

- conformation changes in macro-molecules;

- chemical reactions;

- regime changes in climate;

- etc.

Understanding the long time dynamics of these systems is a challenge, both from theoretical and computational viewpoints.

Simplest example of system displaying metastability:
Motion in a double-well potential, with two minima separated by a saddle point.

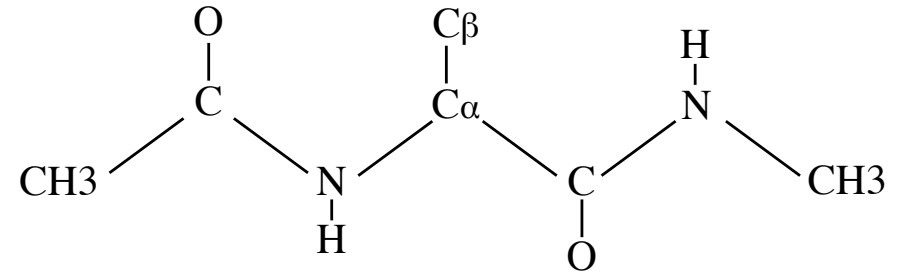$$\dot{x}(t) = -\nabla V(x(t)) + \sqrt{2\beta^{-1}}\eta(t)$$
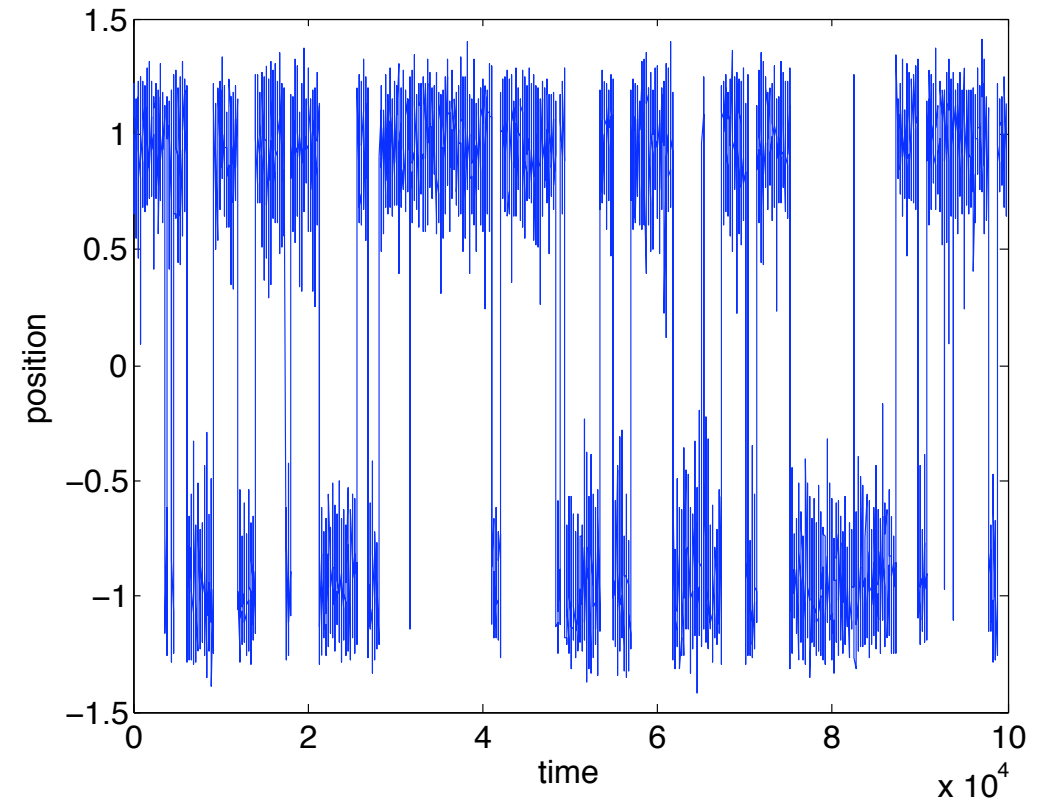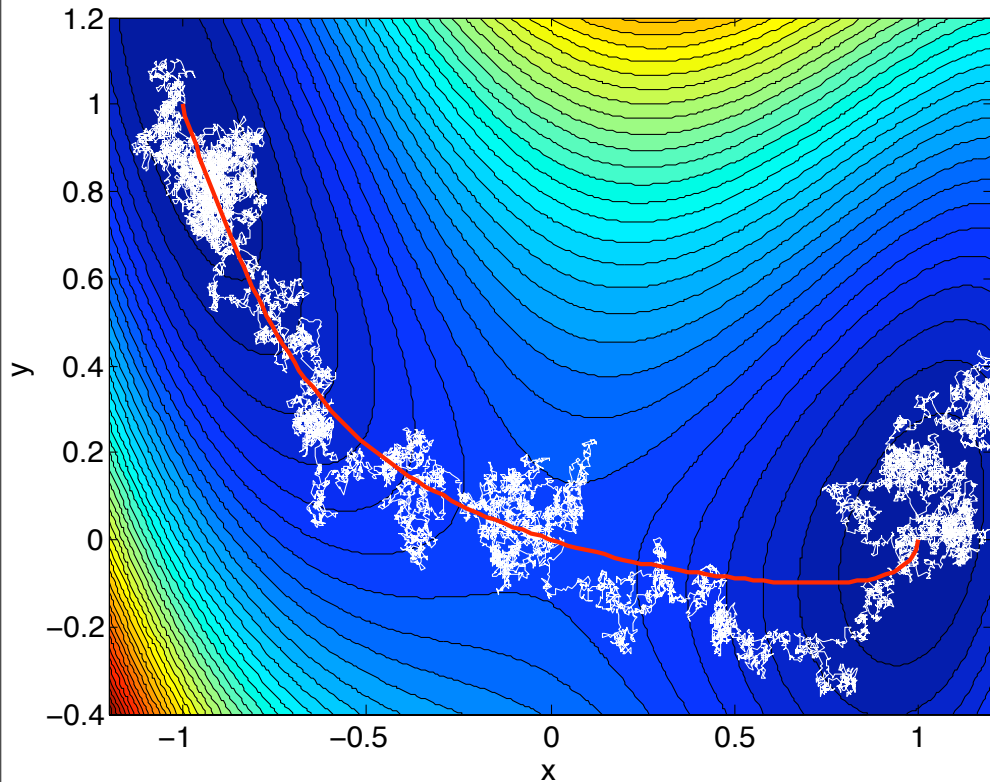
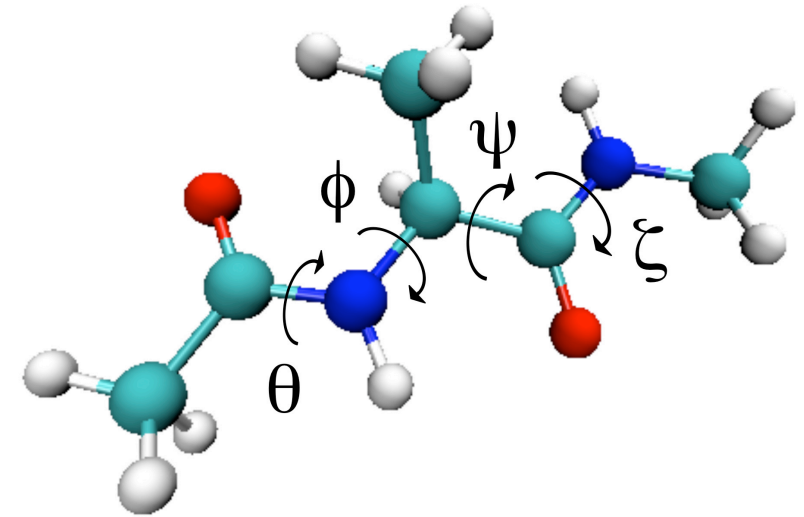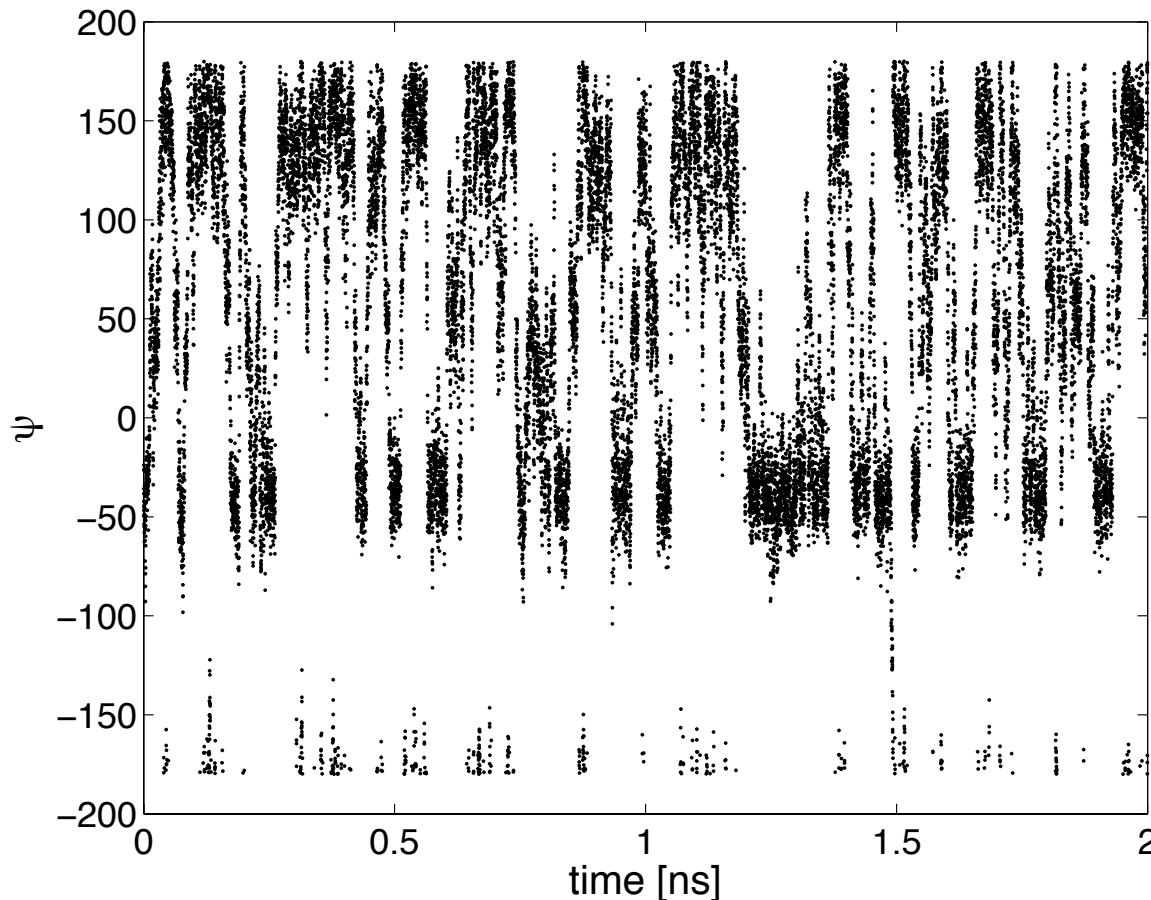*Examples of this type are easy to treat.*

However they are very simplistic ...

... actual energy landscape of many systems of interest is enormously complicated!
     (and makes LD theory inapplicable directly).

Example: solvated alanine dipetide:

12 point particles (= atoms) + 252 water molecules (i.e. a dynamical system with about 1e3 degrees of freedom).


time series (in ns) of dihedral angle psi

Calculations by Luca Maragliano.

Energy landscape is typically <u>rugged</u>, i.e.

There are many features of the potential on small scales (e.g. many critical points) which are mostly irrelevant for the rare events. What matters are large scale features (& LD theory does not apply directly).

Example: Rugged Mueller potential

$$dx(t) = -\nabla V(x(t), \epsilon)dt + \sqrt{2\beta^{-1}}\, dW(t) \qquad V(x, \epsilon) = V_0(x) + \epsilon V_1(x/\epsilon)$$
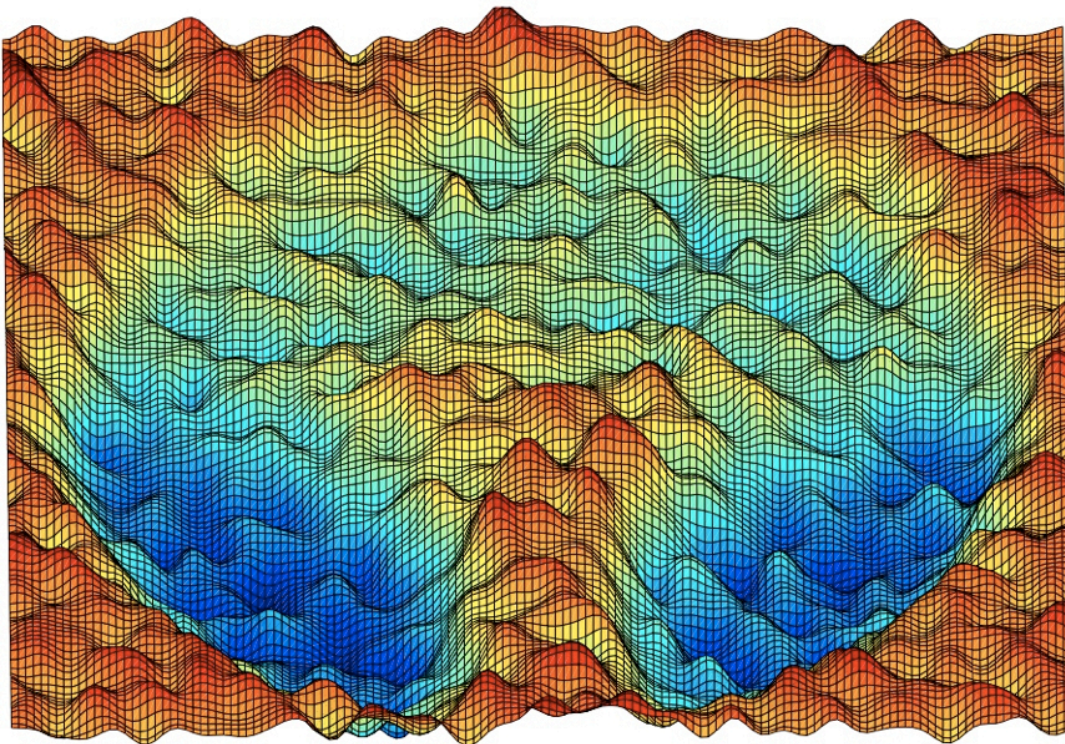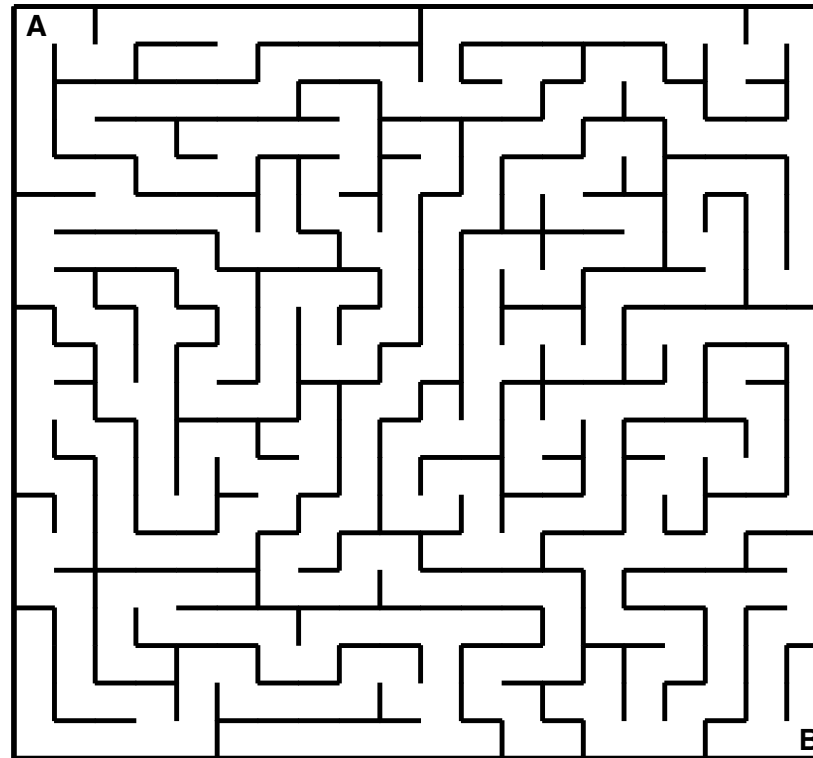

More difficult if $\varepsilon \approx \beta^{-1}$ small but finite.

and ...

Entropic (i.e. volume) effects matter, presence of dead-ends, dynamical traps, etc

Example: a maze

$$dx(t) = -\nabla V(x(t))dt + \sqrt{2\beta^{-1}}\, dW(t)$$

Assume that *V(x)* is a Morse function with growth condition at infinity.

Then dynamics is ergodic w.r.t. the invariant measure

$$d\mu(x) = C^{-1}\exp(-\beta V(x))dx$$

When $\beta \to \infty$ this measure becomes atomic on the minima of *V(x)*

Dynamics can be reduced to a continuous-time Markov chain (random walk on a network) by mapping the trajectory *x* onto the index of the last local minimum it visited

- elementary transitions are related to energy barriers and exponentially small in β;
- pathways of elementary transitions are predictable and follow minimum energy paths solution of $0 = [\nabla V(\gamma)]^{\perp}$

Full theory can be obtained by analyzing the Witten complex associated with the generator of the diffusion (Helffer, Kurchan, ...)

Complicated in practice (analysis must be done globally).

Transition Path Theory

Key concept: <u>reactive trajectories</u>, i.e. those trajectories by which the reaction occurs.

Conceptually, these reactive trajectories can be obtained by pruning a long ergodic trajectory which oscillates between A and B.
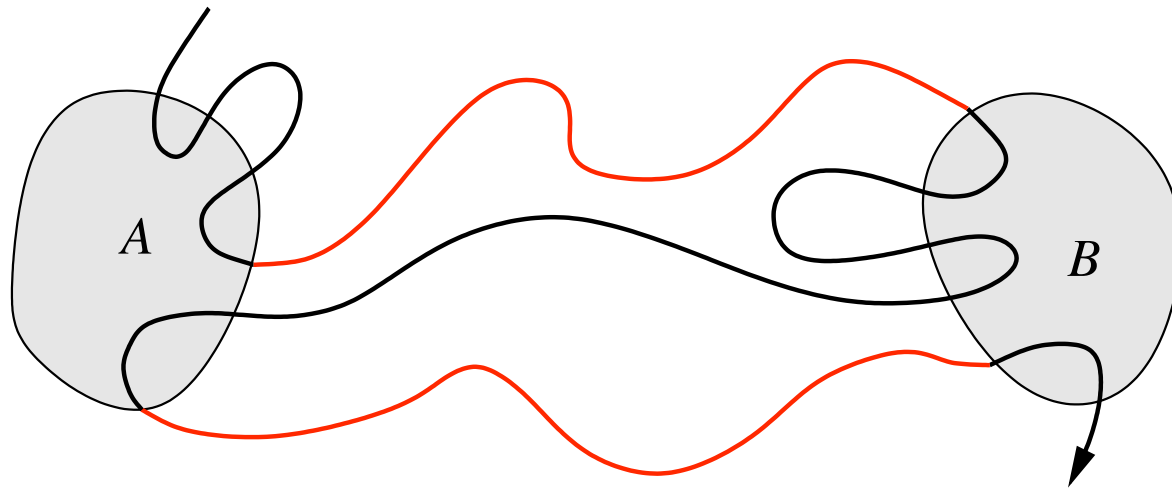
Trajectory $X(t)$ is reactive if $t \in R =$ all times when the trajectory is red in the figure.
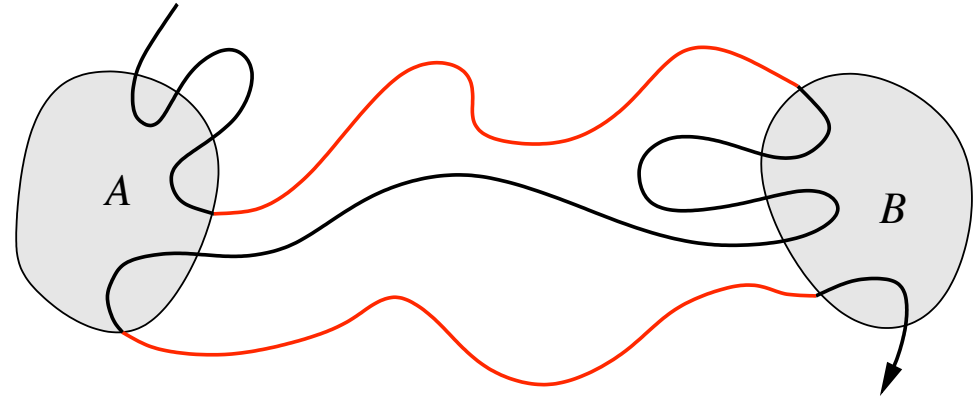
More precisely: $R = \bigcup_{j \in \mathbb{Z}} (t_j^-, t_j^+)$ where $\{t_j^-, t_j^+\}_{j \in \mathbb{Z}}$ such that

$$X(t_j^-) \in \partial A, \quad X(t_j^+) \in \partial B, \quad \text{and } X(t) \notin \overline{A \cup B} \quad \text{if } t \in R := \bigcup_{j \in \mathbb{Z}} (t_j^-, t_j^+)$$

<u>*Understanding the mechanism of the reaction*</u>
= characterizing the <u>statistical mechanics properties of the reactive trajectories</u>

Given a trajectory $x(t)$, let R be the set of times during which it is reactive (i.e. red in the figure).

Two key objects:

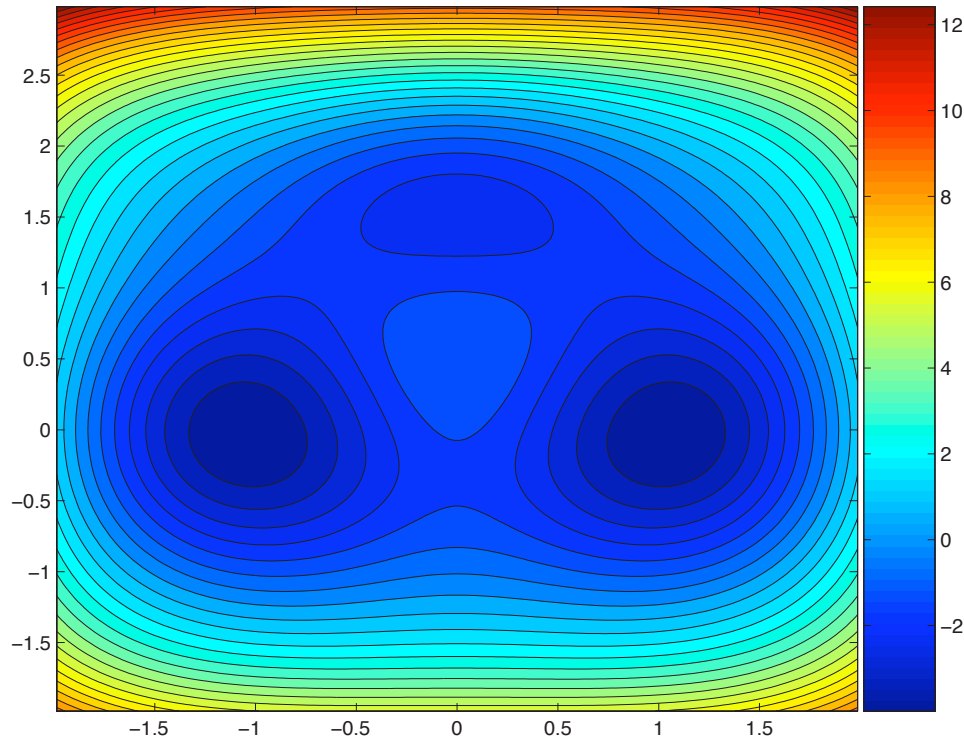*Probability density of reactive trajectories defined as:*

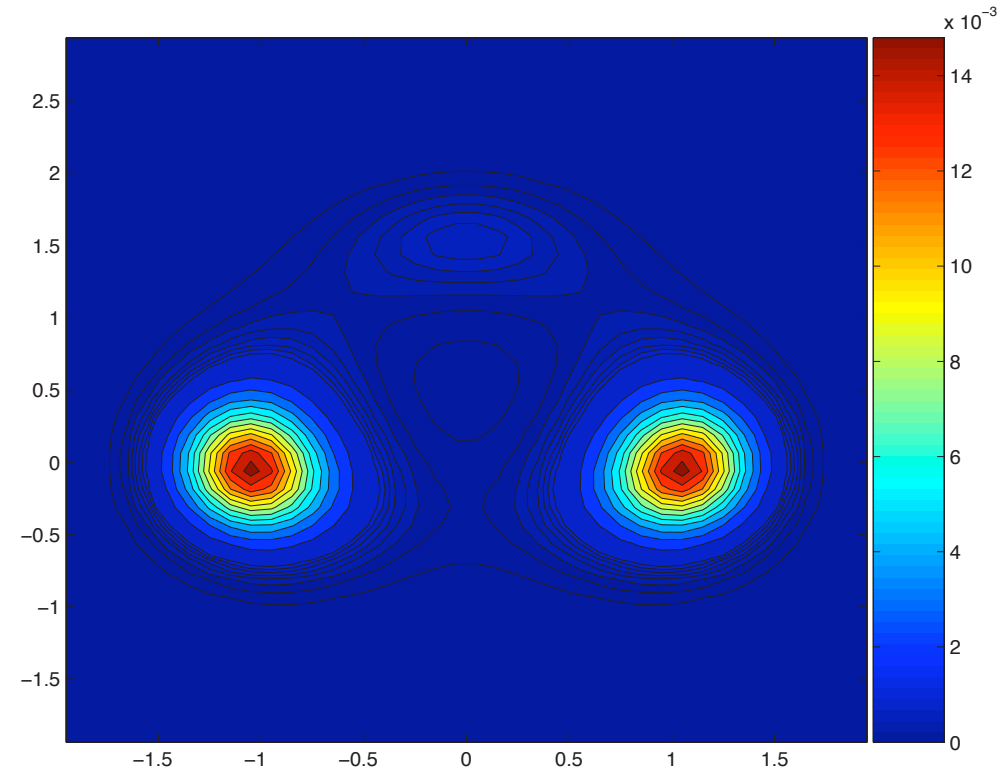$$\rho_R(x) = \lim_{T \to \infty} \frac{1}{T} \int_0^T \delta(x - x(t)) \mathbf{1}_R(t) dt$$

Probability current of reactive trajectories defined as:

$$J_R(x) = \lim_{T \to \infty} \frac{1}{T} \int_0^T \dot{x}(t) \delta(x - x(t)) \mathbf{1}_R(t) dt$$
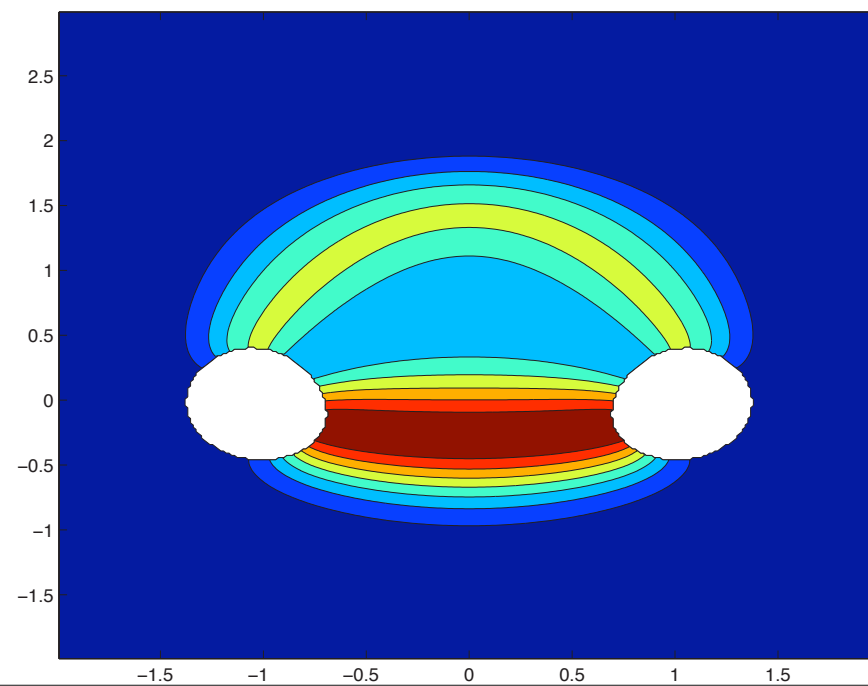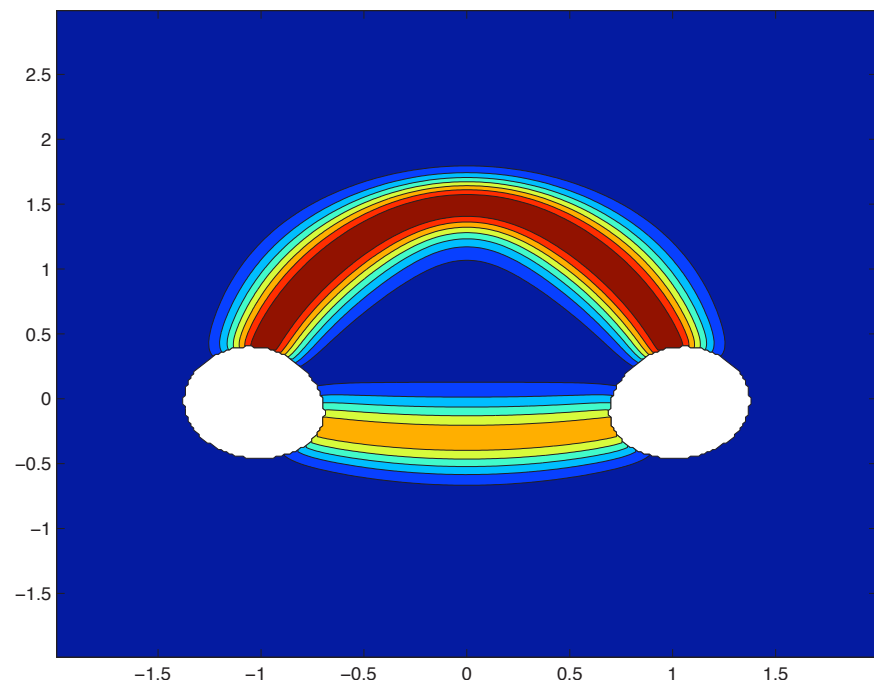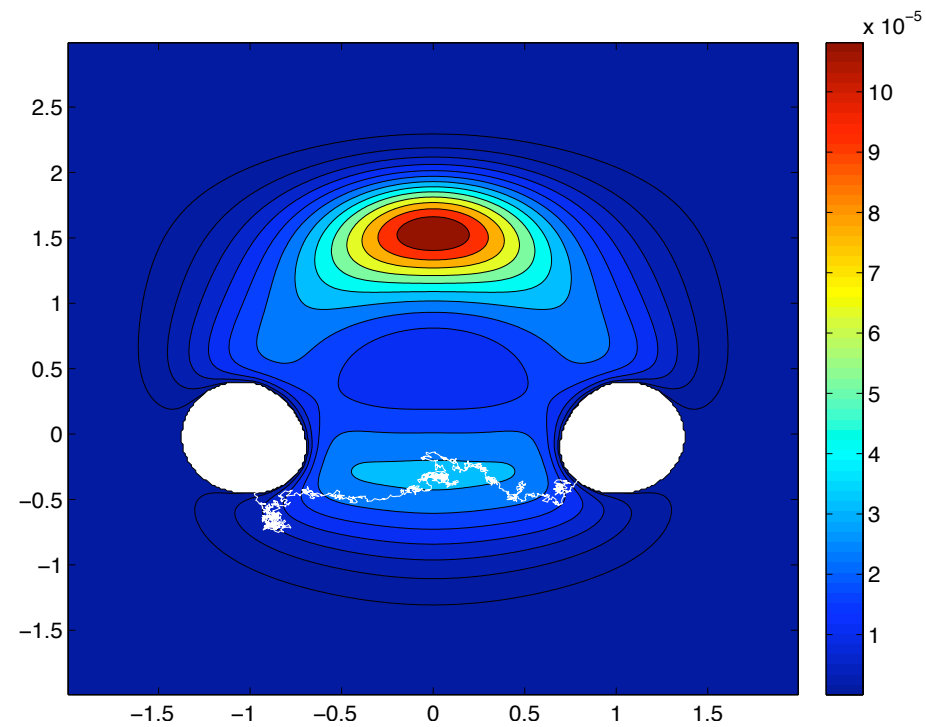
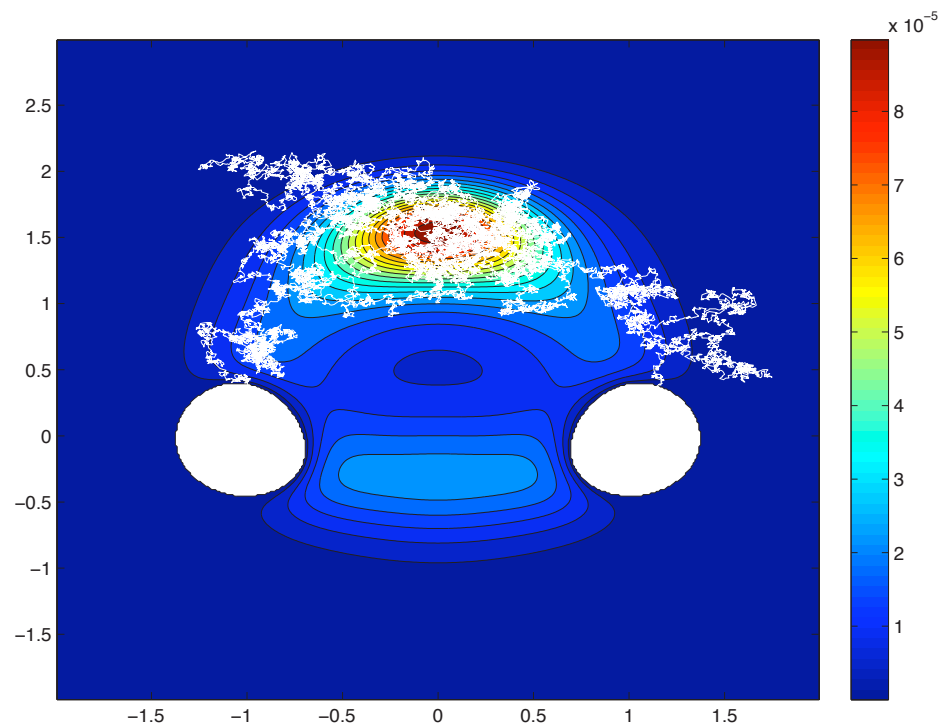*A simple illustrative example in 2d:*
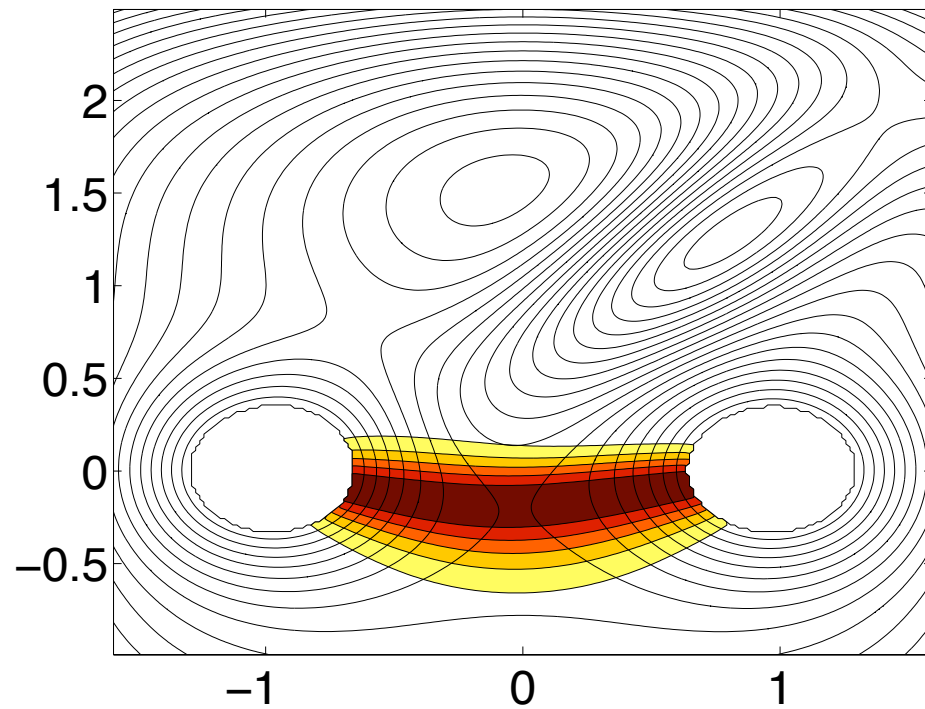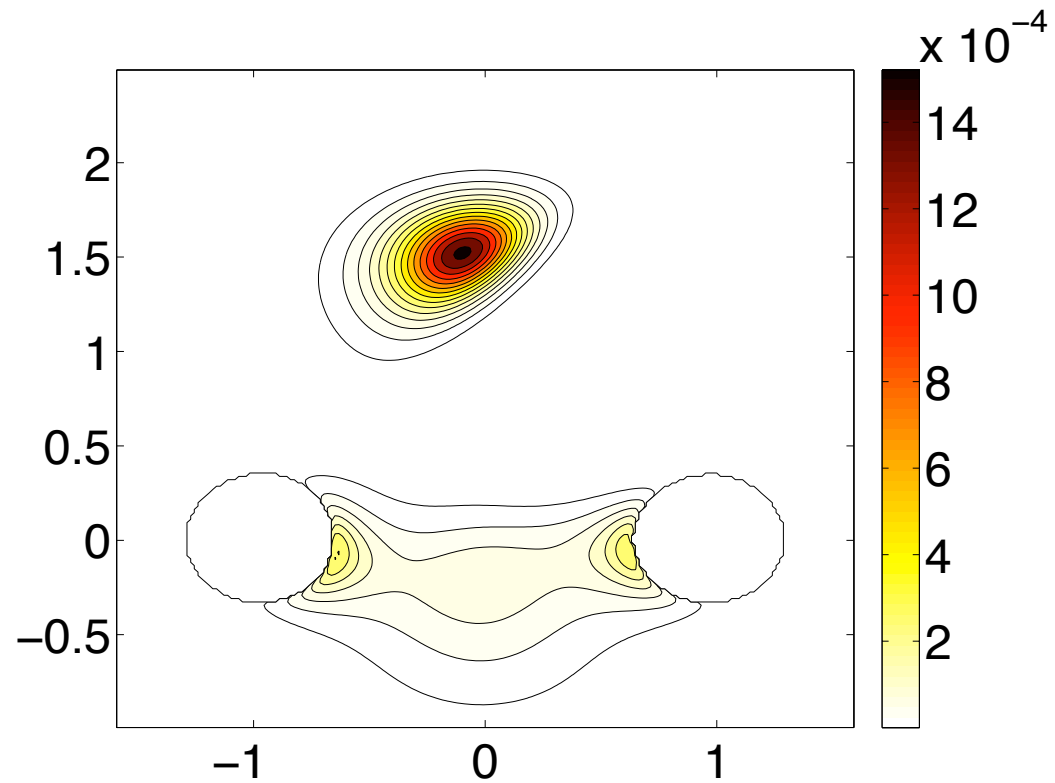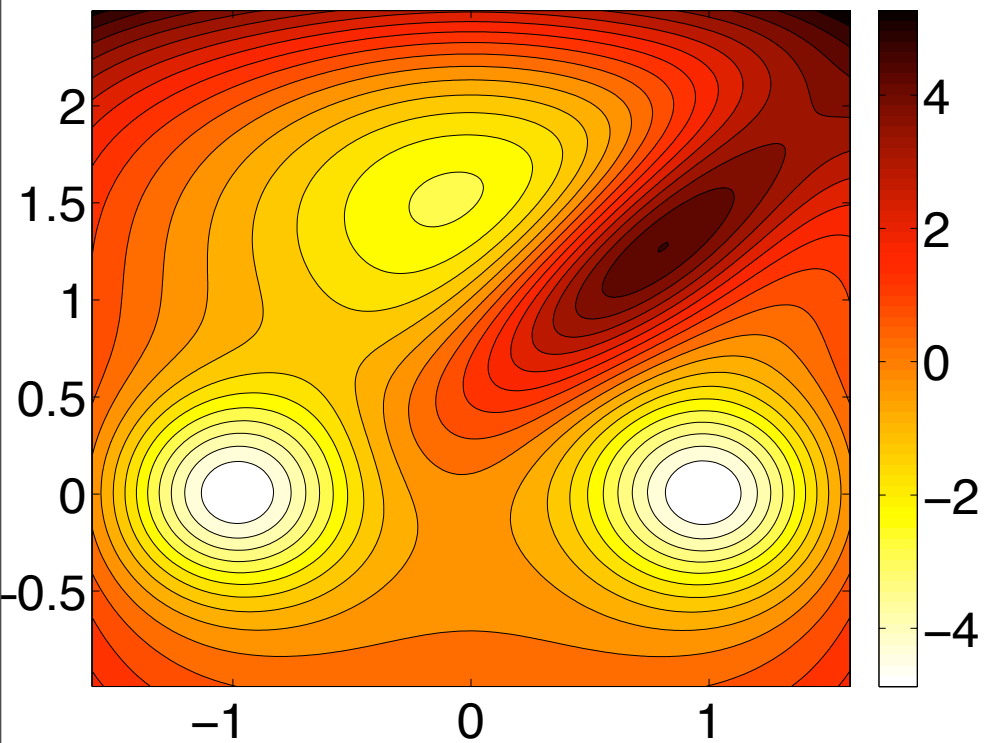

Left: triple-well potential;

Right: Boltzmann equilibrium PDF.
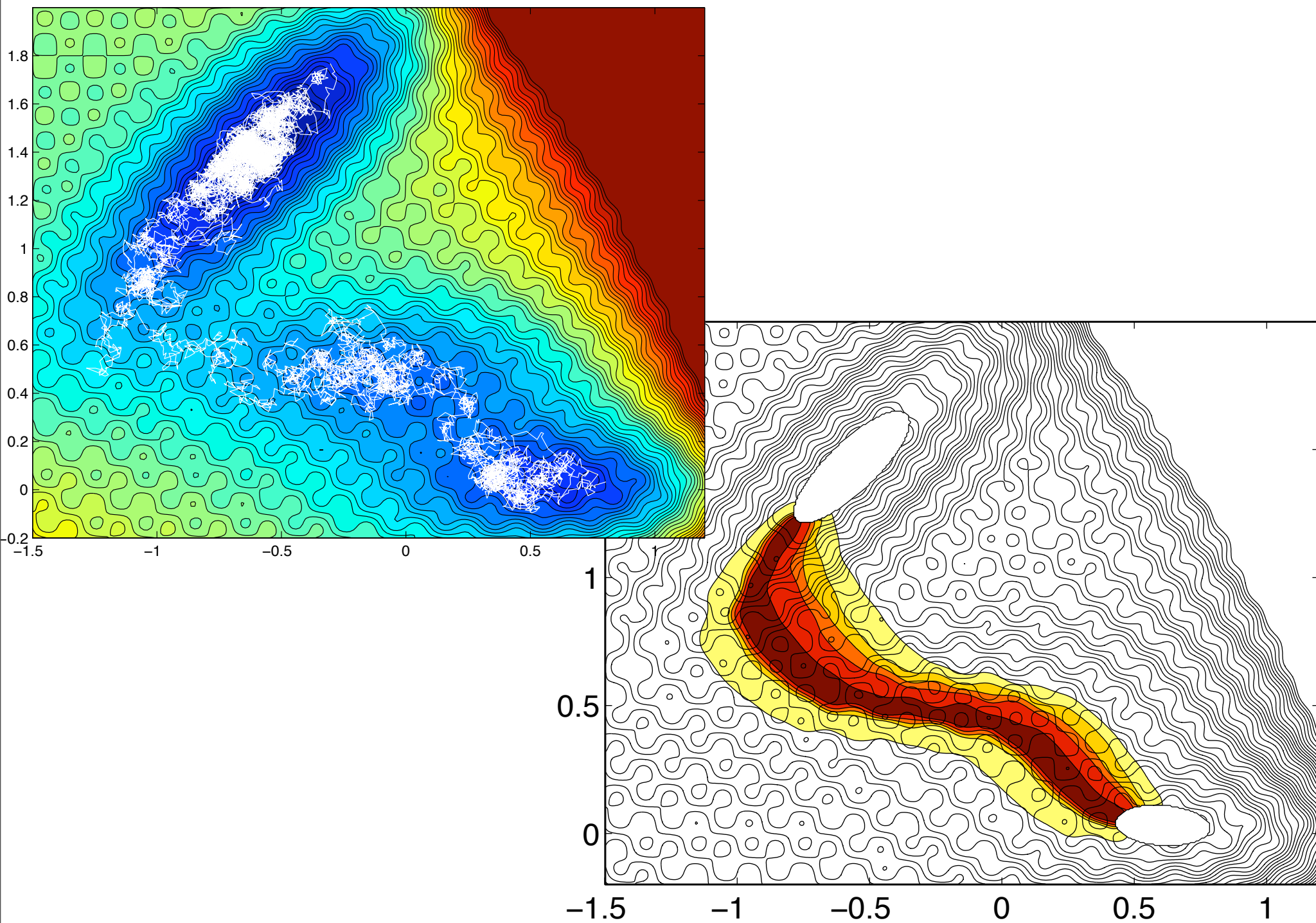
Calculations by Philipp Metzner.

PDF of reactive trajectories, probability current and flux

Another example:

Probability current and flux in rugged Mueller potential

The key object to quantify the statistical properties of the reactive trajectories is (beside the equilibrium PDF) the <u>committor function</u> q(x) (aka capacitor, p-fold, ...) whose value at point x is the probability to reach B first rather A starting from x:

$$q(x) = \mathbb{P}^x(\tau_B < \tau_A)$$

$$\tau_A = \inf\{t : x(t) \in A\},$$
$$\tau_B = \inf\{t : x(t) \in B\}$$

Thm (E, V.-E.): *a.s. as T→∞:*

$$\frac{1}{T}\int_0^T \delta(x - x(t))\mathbf{1}_R(t)dt \to Z^{-1}e^{-\beta V(x)}q(x)(1 - q(x))$$

$$\frac{1}{T}\int_0^T \delta(x - x(t))\mathbf{1}_R(t)\circ dx(t) \to Z^{-1}e^{-\beta V(x)}\nabla q(x)$$
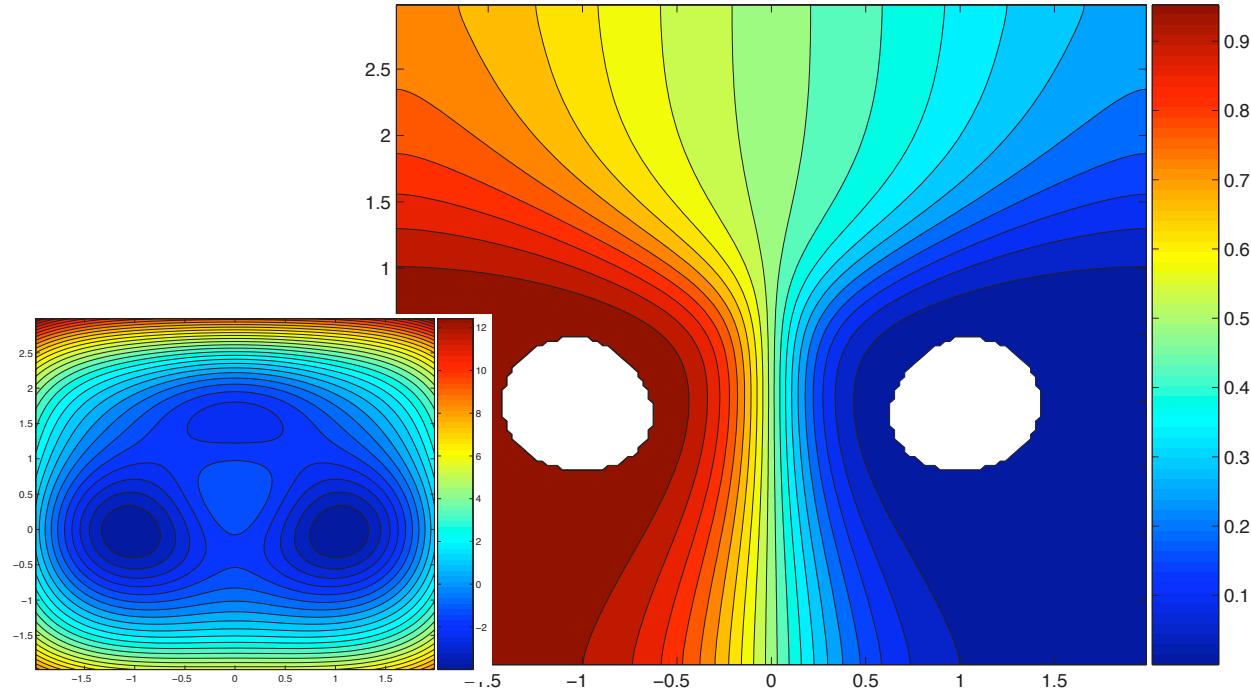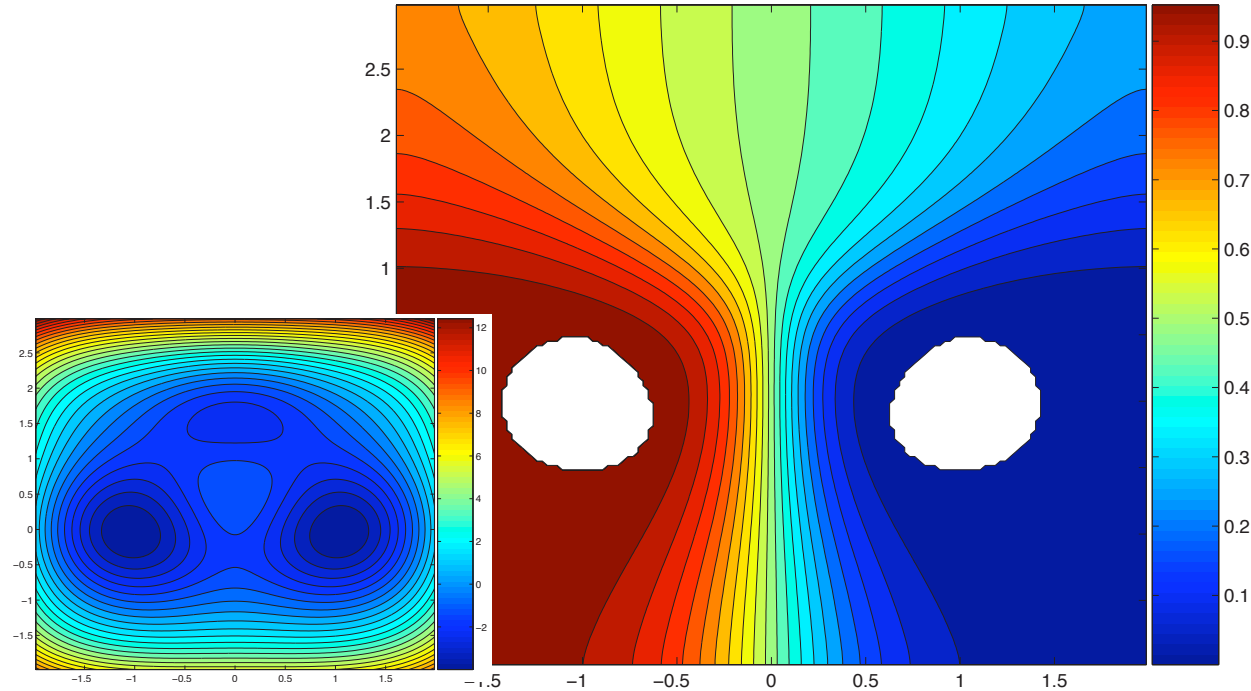
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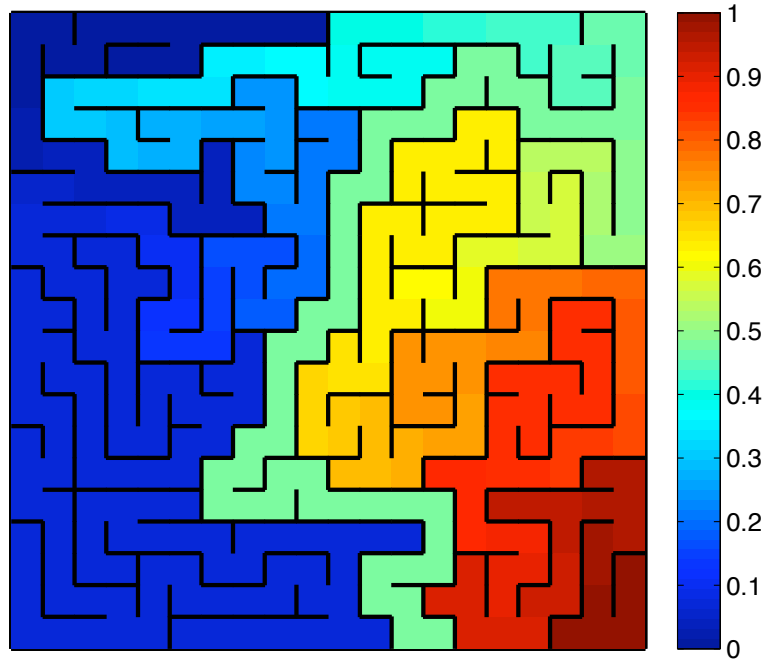$$\tau_B = \inf\{t : x(t) \in B\}$$

$q(x)$ is THE reaction coordinate!

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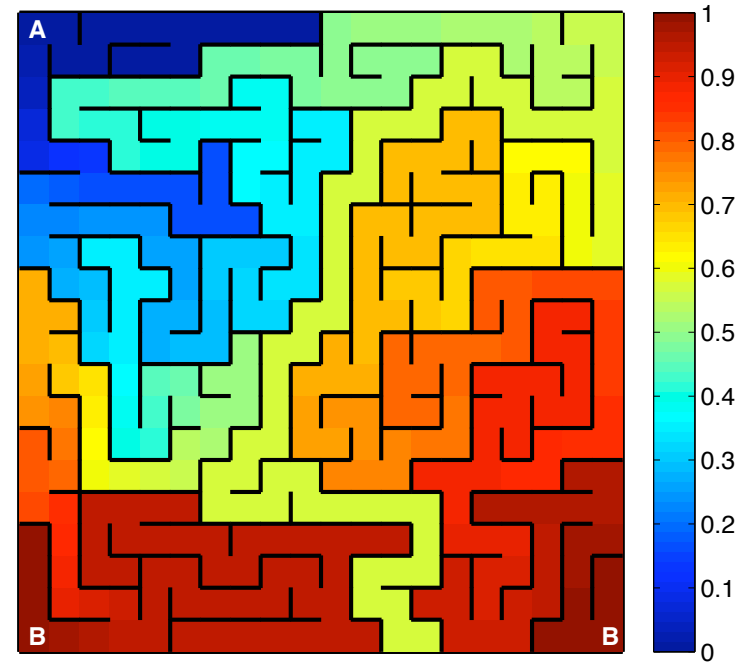$$\frac{1}{T}\int_0^T \delta(x - x(t))\mathbf{1}_R(t)dt \rightarrow Z^{-1}e^{-\beta V(x)}q(x)(1 - q(x))$$

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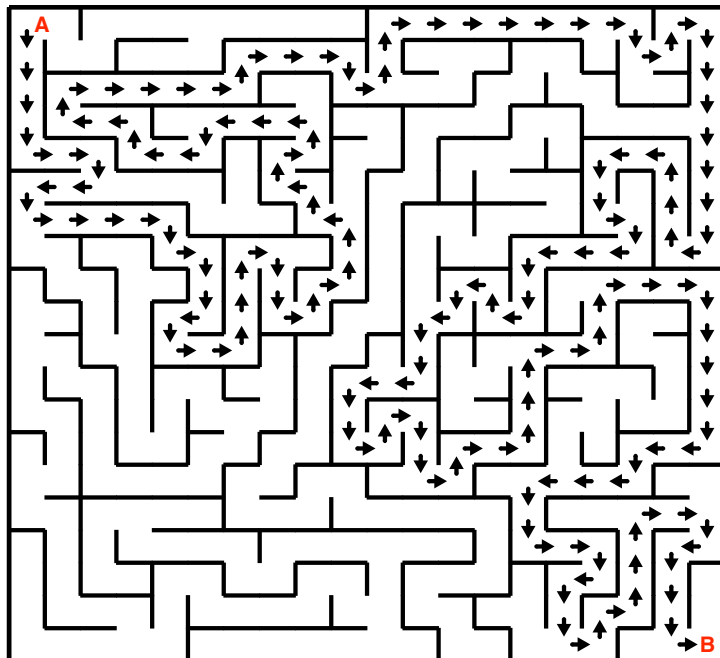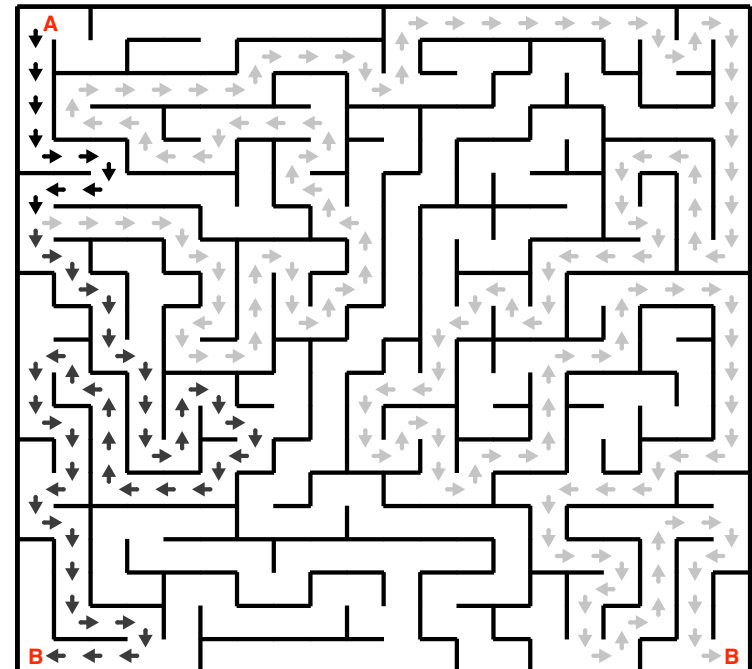
The maze example:

Committor

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Effective current

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Or, it can be done by direct manipulations on the equation for $q(x)$ under specific assumption (e.g. small temperature, localized tubes concentrating the flux of reactive trajectories, etc.)

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The second approach is the one taken in the string method (E, Ren, V.-E.) based on:

Variational formulation: The committor function is the minimizer of:

$$\int_{\Omega} e^{-\beta V(x)} |\nabla q(x)|^2 dx,$$

among all $q(x)$ such that $q(x) = 0$ in A and $q(x) = 1$ in B.

Lower bound argument to find the flowline of max-flux:

Given a curve γ connecting A and B, let $B_\delta = \{x : d(x, \gamma) \leq \delta\}$.

$$\int_\Omega e^{-\beta V(x)} |\nabla q(x)|^2 dx \geq \int_{B_\delta} e^{-\beta V(x)} |\nabla q(x)|^2 dx$$

$$\geq \int_{B_\delta} e^{-\beta V(x)} |\gamma' \cdot \nabla q(x)|^2 dx$$

Optimizing the bound:

$$\inf_q \int_\Omega e^{-\beta V(x)} |\nabla q(x)|^2 dx \geq \sup_\gamma \inf_q \int_{B_\delta} e^{-\beta V(x)} |\gamma' \cdot \nabla q(x)|^2 dx$$

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(NB: line of max-flux is the MEP from LD theory in small noise limit)

String method in a nutshell:

Parametrize the curve e.g. by normalized arc-length;

Evolve it using a time-splitting method:

- one step of steepest descent along gradient of objective function (or CG, BFGS, etc.);

*- one step of interpolation-reparametrization to control the parametrization of the curve*

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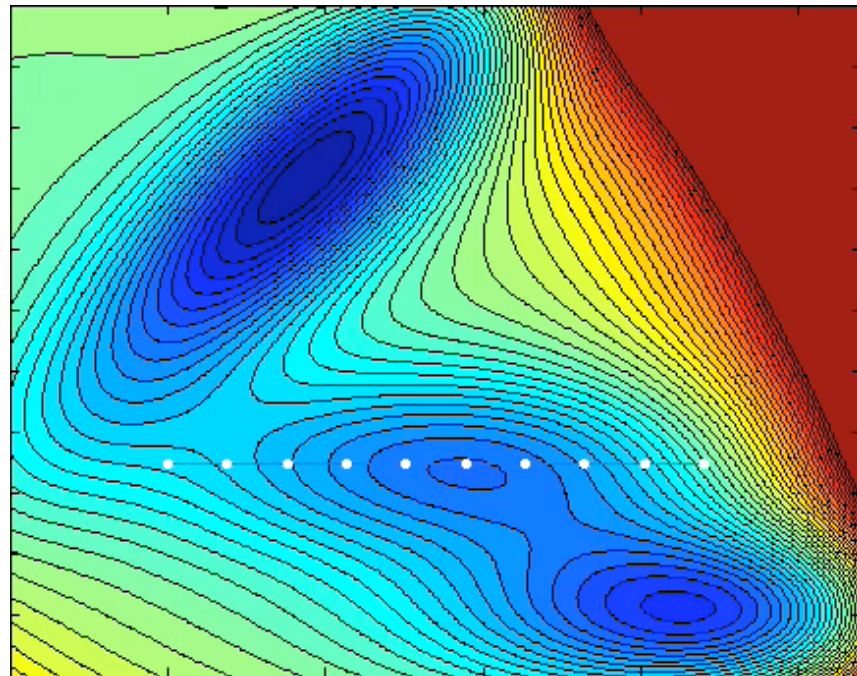
Application: hydrophobic collapse of a polymeric chain

in collaboration with Tommy Miller (Caltech) and David Chandler (UC Berkekeley)
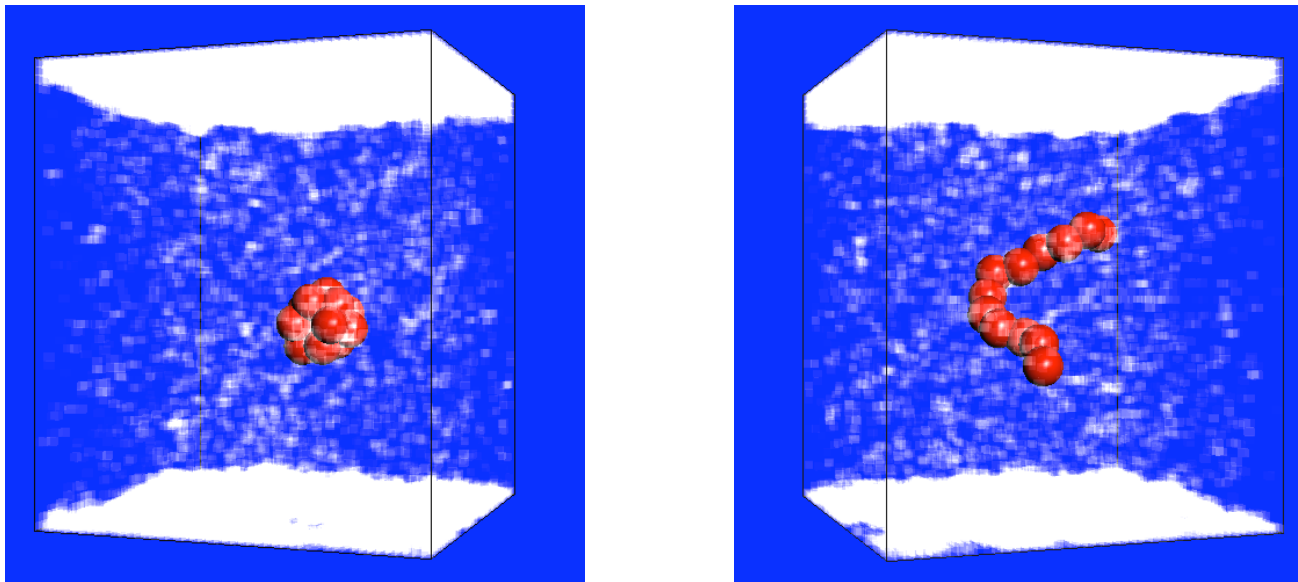
Chain made of 12 monomers of size 7.2 A solvated in a periodic box of size 99.5 A x 99.5 A x 116.1 A containing 34,000 rigid water molecules modeled by SPC/E.

Collective variables = monomer positions + local density field
            - in total over 129,000 collective variables
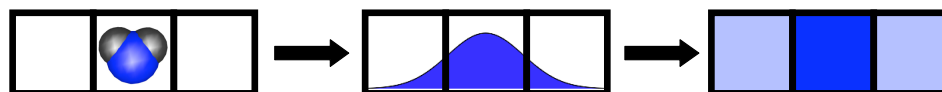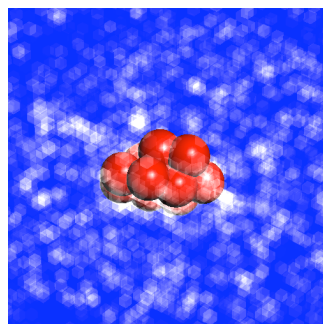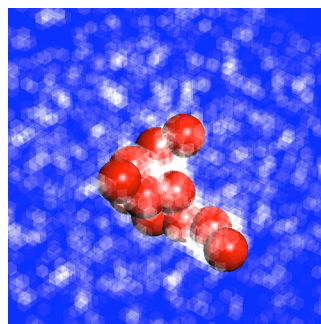
MFEP identified by the string method
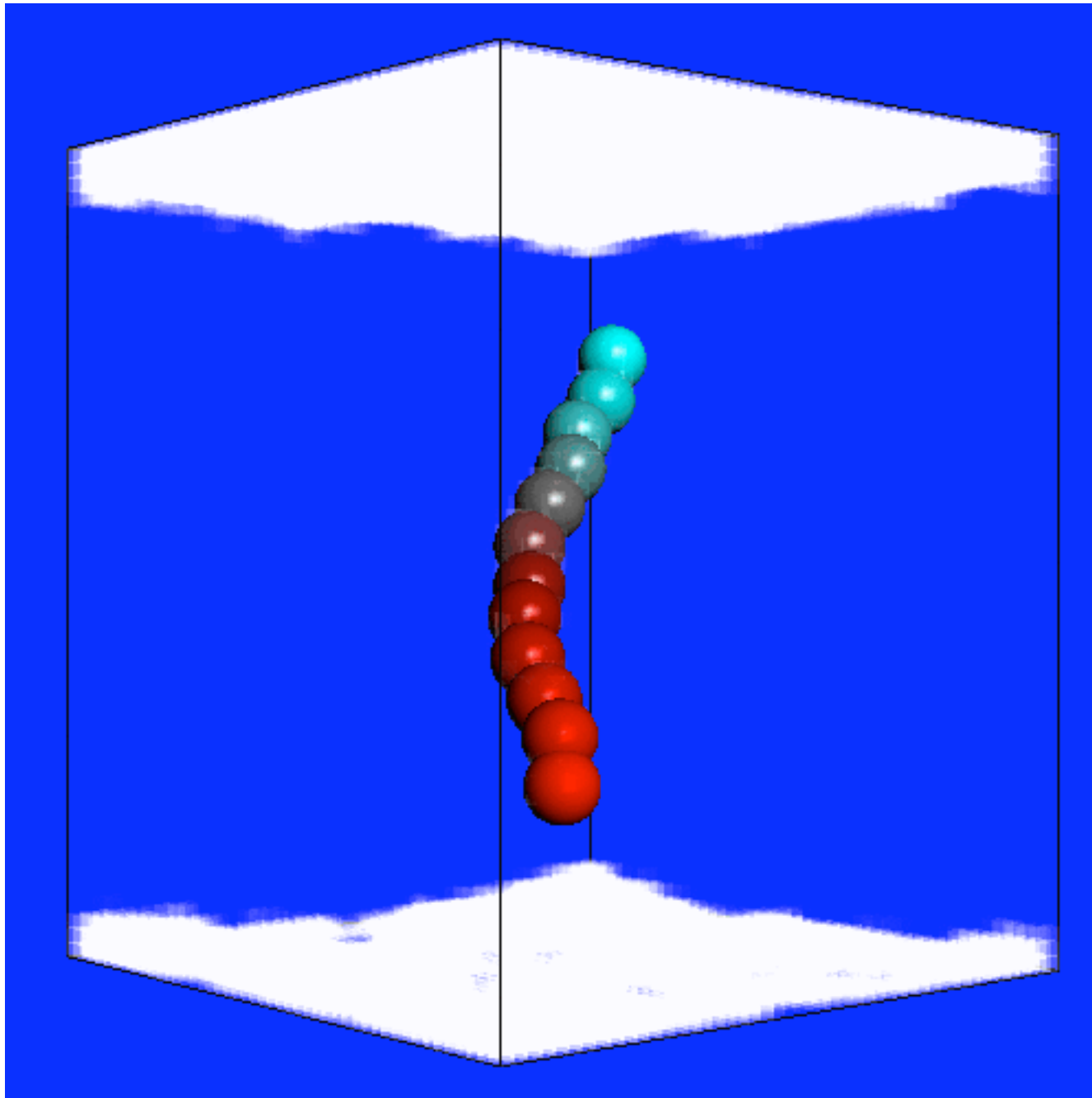
Free energy
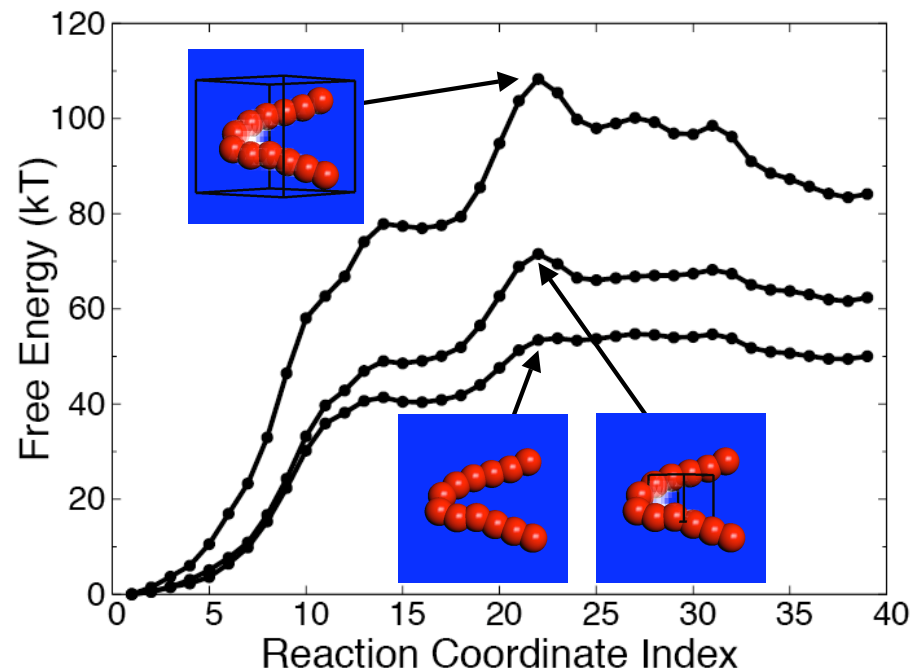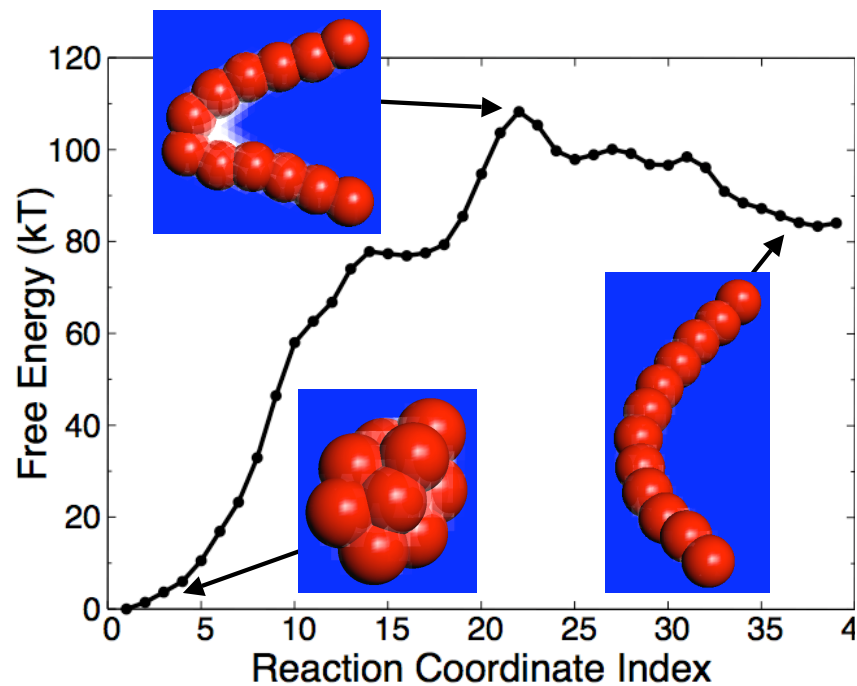
Dominated by work done by the solvent degrees of freedom.
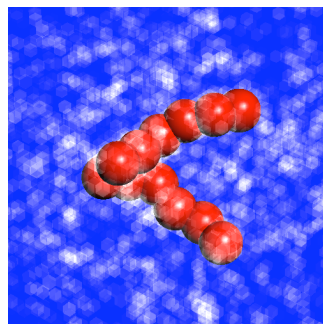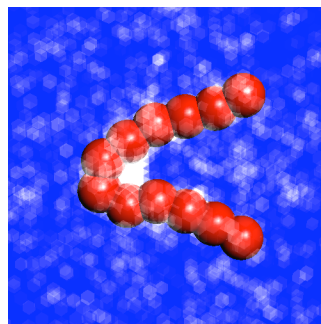
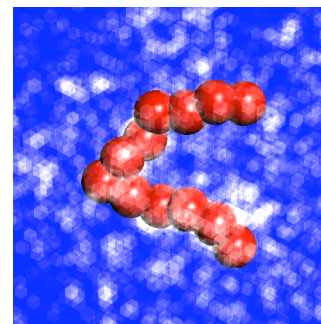Dynamical trajectories initiated from the transition state region
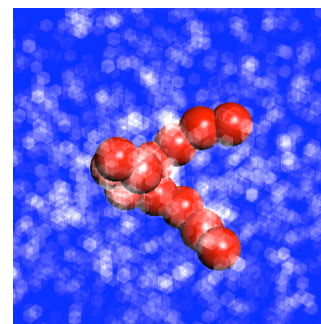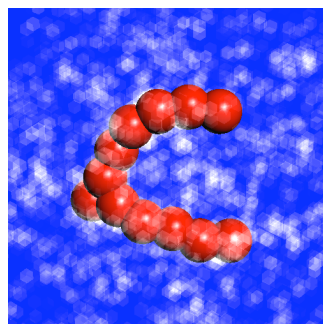

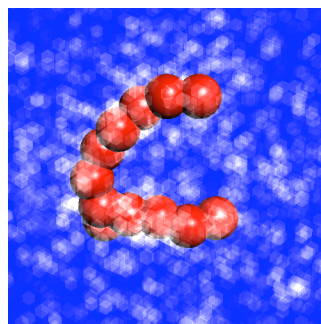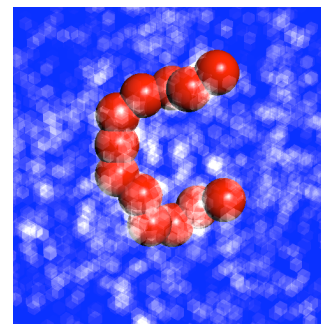-150 ps   -90 ps   -60 ps

-30 ps   0 ps   30 ps

60 ps   90 ps   150 ps

Summarizing:

Reactive events can be understood from a probabilistic (i.e. statistical mechanistic) viewpoint. In the context of reactive events, this means focusing on the <u>statistical mechanics description</u> of the reactive trajectories;

Concepts for probability theory permit to define <u>precisely</u> the concept of reaction coordinate to describe the transition from a reactant state A to a product state B in terms of the committor function;

Open the door to <u>accelerated computing strategies</u> (i.e. with biased/artificial dynamics) to analyze rare reactive events like e.g. the string method.