Energy Landscapes and Rare Events

Weinan E*  Weiqing Ren†  Eric Vanden-Eijnden‡

Abstract

Many problems in physics, material sciences, chemistry and biology can be abstractly formulated as a system that navigates over a complex energy landscape of high or infinite dimensions. Well-known examples include phase transitions of condensed matter, conformational changes of biopolymers, and chemical reactions. The energy landscape typically exhibits multiscale features, giving rise to the multiscale nature of the dynamics. This is one of the main challenges that we face in computational science. In this report, we will review the recent work done by scientists from several disciplines on probing such energy landscapes. Of particular interest is the analysis and computation of transition pathways and transition rates between metastable states. We will then present the string method that has proven to be very effective for some truly complex systems in material science and chemistry.

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1. Introduction

Many problems in biology, chemistry and material science can be formulated as the study of the energy or free energy landscape of the underlying system. Well-known examples of such problems include the conformational changes of macromolecules, chemical reactions and nucleation in condensed systems. Very often the dimension of the state space is very large, and the energy landscape exhibits a hierarchy of structures and scales. These problems are becoming a major challenge in their respective scientific disciplines and are beginning to receive attention from

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*Department of Mathematics and PACM, Princeton University, Fine Hall, Princeton, NJ 08544, USA and School of Mathematics, Peking University, Beijing, 100871, China. E-mail: weinan@math.princeton.edu
†Courant Institute of Mathematical Sciences, New York University, New York 10012, USA. Email: weiqing@cims.nyu.edu
‡Courant Institute of Mathematical Sciences, New York University, New York 10012, USA. Email: eve2@cims.nyu.edu
the mathematics community. In this article, we report recent work in this direction. For a detailed account, we refer to [4, 5, 6, 7, 12].

We begin with a simple example. Plotted in Figure 1 is the solution of the stochastic differential equation

\[ dx(t) = -\nabla_x V(x(t))dt + \sqrt{\epsilon}dW(t) \] (1.1)

where the potential

\[ V(x) = \frac{1}{4}(1-x^2)^2 \] (1.2)

and \( dW(t) \) is Gaussian white noise, \( \epsilon = 0.06, x(0) = -1 \). Without the random perturbation, the solution would be \( x(t) \equiv x(0) = -1 \). Indeed the deterministic part of dynamics in (1.1) does nothing but taking the system to local equilibrium states. With the random perturbation, the solution, over long time, exhibits completely different behavior. It fluctuates around the two local minima of \( V, x = -1 \) and 1, with sudden transitions between these two states. The time scale of the transition, \( t_M \) is much larger than the time scale of the fluctuation around the local minima, \( t_R \). For this reason, we refer to \( x = -1 \) and 1 as the metastable states.

![Figure 1. Time series of the solution to the stochastic differential equation (1.1), with \( \epsilon = 0.06 \).](image)

Obviously the transition between the metastable states is of more interest than the local fluctuation around them. The transition time is much larger since it requires the system to overcome the energy barrier between the two states. This is only possible because of the noise. When \( \epsilon \) is small, a huge noise term is required
to accomplish this. For this reason, such events are very rare, and this is the origin of the disparity between the time scales $t_M$ and $t_R$.

This simple example illustrates one of the major difficulties in modeling such systems, namely the disparity of the time scales. It does not, however, illustrate the other major difficulty, namely, the large dimension of the state space and the complexity of the energy landscapes. Indeed for typical systems of interests the energy landscape can be very complex. There can be a huge number of local minima in the state space. The usual concept of hopping over barriers via saddle points may not apply (see [3]).

In applications, the noise comes typically from thermal noise. In this case, we should note that even though the potential energy landscapes might be rough and contain small scale features, the system itself experiences a much smoother landscape, the free energy landscape, since some of the small scale features on the potential energy landscape are smoothed out by the thermal noise.

Our objective in modeling such systems are the following:

1. Find the transition mechanism between the metastable states.
2. Find the transition rates.
3. Reduce the original dynamics to the dynamics of a Markov chain on the metastable states.

Our discussion will be centered around the following model problems:

\[
\gamma \dot{x}(t) = -\nabla V(x(t)) + \sqrt{\varepsilon} \dot{W}(t)
\]  

or

\[
m \ddot{x}(t) + \gamma \dot{x}(t) = -\nabla V(x(t)) + \sqrt{m \varepsilon} \dot{W}(t)
\]

$\varepsilon$ is related to the temperature of the system by $\varepsilon = 2\gamma k_B T$ where $k_B$ is the Boltzmann constant. We refer to (1.3) as type-I gradient flow and (1.4) as type-II gradient flow.

Before proceeding further, let us remark that there is a very well-developed theory, the large-deviation theory, or the Wentzell-Freidlin theory [8], that deals precisely with questions of the type that we discussed above. However as was explained in [7, 12], this theory is not best suited for numerical purpose. Therefore we will seek an alternative theoretical framework that is more useful for numerical computations.

2. Transition state theory

Transition state theory (TST) [9] has been the classical framework for addressing the questions we are interested in. It assumes the existence and explicit knowledge of a reaction coordinate, denoted by $q$, that connects the two metastable states. In addition it assumes that along the reaction coordinate there exists a well-defined transition state, which is typically the saddle point configuration, say at $q = 0$, and the two regions $\{q < 0\}$ and $\{q > 0\}$ defines the two metastable regions $A$ and $B$. For these reasons, transition state theory is restricted to cases when the
system is simple and the energy landscape is smooth, i.e. the energy barriers are larger than the thermal energy $k_B T$.

Knowing the transition state, TST calculates the transition rates by placing particles at the transition state, and measuring the flux that goes into the two regions. For example, the transition rate from $A$ to $B$ is given approximately by

$$k_{A \rightarrow B} = \frac{1}{Z_0} \int \dot{q}(t) \delta T(q(t)) \theta(q(t)) d\mu_A(q(0))$$  \hspace{1cm} (2.1)

where

$$Z_0 = \int d\mu_A(q(0))$$  \hspace{1cm} (2.2)

Here $\delta T$ is the surface delta function at $q = 0$, $\theta$ is the Heaviside function, $\mu_A$ is the Lebesgue measure restricted to $A$. For a system with a single particle of mass $m$ and potential $V$, this gives [9]

$$k_{A \rightarrow B} = \frac{\omega_0}{2\pi} e^{-\frac{\delta E}{k_B T}}$$  \hspace{1cm} (2.3)

where $\delta E$ is the energy barrier at the transition state, $\omega_0 = \left(\frac{V''(x_A)}{m}\right)^{\frac{1}{2}}$, $x_A$ denotes the location of the local minimum inside $A$. Formulas such as (2.3) are the origin of the Arrhenius law for chemical reaction rates and Boltzmann factor for hopping rates in kinetic Monte Carlo models.

### 3. Reduction to Markov chains on graphs

For simplicity, we will discuss mainly type-I gradient flows (1.3). The Fokker-Planck equation can be expressed as

$$\frac{\partial p}{\partial t}(x,t) = \nabla \cdot \left(p_s(x) \nabla \left(\frac{p(x,t)}{p_s(x)}\right)\right)$$  \hspace{1cm} (3.1)

where $p_s$ is the equilibrium distribution

$$p_s(x) = \frac{1}{Z} e^{-\frac{V(x)}{k_B T}}$$

$Z$ is the normalization constant $Z = \int_{\mathbb{R}^n} e^{-\frac{V(x)}{k_B T}} dx$. The states of the Markov chain consist of the sets $\{B_j\}_{j=1}^J$, where $\{B_j\}_{j=1}^J$ satisfies

1. The $B_j$’s are mutually disjoint
2. $\int_B p_s(x) dx = 1 + o(k_B T)$  \hspace{1cm} (3.2)

where $B = \cup_{j=1}^J B_j$. An illustration of the collection the $\{B_j\}_{j=1}^J$ is given in Figure 2. $\{B_j\}$ depends on $T$. As $T$ decreases, the $B_j$’s exhibits a hierarchical structure.
Having defined the states of the Markov chain, we next compute the transition rates between neighboring states. Denote by $A$ and $B$ two such neighboring states. We would like to compute the transition rate from $A$ to $B$. Without loss of generality, we may assume $J = 2$. Let $B_1, B_2$ be the metastable region containing $A$ and $B$ respectively, and let $n_j(t) = \int_{B_j} p(x,t)dx$, $N_j = \int_{B_j} p_s(x)dx$, $j = 1, 2$. Applying Laplace’s method to (3.1) we get [7]

$$
\dot{n}_j(t) = \frac{\varepsilon}{\kappa} \left( \frac{n_2(t)}{N_2} - \frac{n_1(t)}{N_1} \right) + \text{higher order terms (3.3)}
$$

where

$$
\kappa = \int_0^1 d\alpha \left( \int_{S^0(\alpha)} p_s(x)dx \right)^{-1} |\varphi^0(\alpha)| \quad (3.4)
$$

$\{\varphi^0(\alpha), 0 \leq \alpha \leq 1\}$ is a so-called minimal energy path, to be defined below, $\{S^0(\alpha)\}$ is the family of hyperplanes normal to $\varphi^0$.

The minimal energy path (MEP) is defined as follows. If $V$ is smooth, then $\varphi^0$ is a MEP if

$$
(\nabla V)^\perp(\varphi^0(\alpha)) = 0 \quad (3.5)
$$

for all $\alpha \in [0,1]$, i.e. $\nabla V$ restricted to $\varphi^0$ is parallel to $\varphi^0$. In general there is not a unique $\varphi^0$ that is particularly significant, but rather a collection (a tube or several tubes) of paths contribute to the transition rates. However, one can define a MEP self-consistently via the equation

$$
\varphi^0(\alpha) = \frac{1}{Z(\alpha)} \int_{S^0(\alpha)} xe^{-\frac{V(x)}{k_B T}} dx \quad (3.6)
$$
where \( Z(\alpha) = \int_{S_{\alpha}} e^{-V(\alpha) / k_B T} dx \). In the case when \( V \) has two scales: \( V = \bar{V} + \delta V \), \( |\delta V| \leq O(k_B T) \), and \( \bar{V} \) is smooth, then \( \phi^0 \) can be defined as the MEP of \( \bar{V} \).

For type-I gradient systems, if the two metastable sets are separated by a single saddle point, then the MEP is the unstable manifold associated with the saddle point. MEP for type-II gradient systems is less trivial. In this case (3.3)-(3.6) have to be modified [7]. Consider the simple example

\[
\begin{align*}
\dot{q} &= p \\
\dot{p} &= -\frac{\partial V}{\partial q}(q) - p + \sqrt{\varepsilon} \dot{W}
\end{align*}
\]

where \( V(q) = \frac{1}{4}(1 - q^2)^2 \). It has two local equilibrium states \( A = (-1, 0) \) and \( B = (1, 0) \). The MEP that connects \( A \) and \( B \) is plotted in Figure 3. It is not a smooth curve. The velocity is reversed at the saddle point. To verify that the MEP does reflect the true behavior of the transition path, we also plot the transition path obtained from direct simulation of the stochastic differential equation.

**Figure 3.** MEP for type-II gradient systems. The red line is the MEP in phase space, the green line is the transition path computed from solving the stochastic differential equation.

MEP is a very important concept since it defines the “most probable” transition path from which transition rates can be computed via equation (3.3). However we should emphasize that from a numerical point of view our task is not that of a conventional optimization or control problem, since there is not an objective function that we can easily work with. Instead our aim is to perform importance sampling in path space to sample the paths that contribute significantly to the switching.
Finally, if there exists a MEP that connects two metastable sets without going through a third one, then we connect these two metastable sets by a link. In this way, we form a graph. The original dynamics is then reduced to a Markov chain on this graph.

4. Previous numerical techniques

A variety of numerical techniques have been developed, most prominently in chemistry, but also in biology and material science, for computing MEPs and sometimes transition rates. Among the most well-known techniques in the chemistry literature are the nudged elastic band method and the transition path sampling technique. The nudged elastic band method (NEB) aims at computing the MEP defined by (3.5). It represents the MEP by a discrete chain of states. These states evolve according to the potential forces of the system. To prevent the states from all falling to the two local equilibrium states, a spring force is applied to neighboring states to penalize the non-uniformity in the distribution of the states along the chain. This by itself may cause convergence to a path which is not a MEP. Hence a nudging technique is used, namely only the normal component of the potential force and the tangential component of the spring force is applied. NEB is a very effective method for small systems with relatively smooth energy landscapes. It has two main drawbacks. One is that it is highly inefficient and may not even be applicable to systems with rough energy landscapes. The other is the choice of the elastic constant. A large elastic constant requires a small time step in the evolution of the states. A small elastic constant will not achieve the desired uniformity of the states and hence will not give the required accuracy for the energy barrier.

A second important technique is transition path sampling (TPS). This method aims at complex systems with rough energy landscapes by developing a Monte Carlo technique that samples the path space. Its efficiency hinges on the ability to produce new accepted paths from old ones.

Other techniques include the ridge method, smooth sampling, etc. Often these methods require knowing beforehand the reaction coordinate.

Elber et. al propose to minimize the Onsager-Machlup action as a way of finding the most probable path for macromolecular systems. The Onsager-Machlup action is the same as the Wentzell-Freidlin action. From a numerical point of view, there are certain difficulties associated with minimizing this action functional. These issues are discussed in 

5. The string method

The basic idea in the string method, developed in, is to represent transition paths by their intrinsic parameterization in order to efficiently evolve and sample paths in path space. It has two versions. The zero temperature version is designed for smooth energy landscapes. The finite temperature version is designed
for rough energy landscapes in which case thermal noise acts to smooth out the small scale features.

The simplest example of a zero-temperature string method is to evolve curves in path space by the gradient flow

$$\varphi_t(\alpha, t) = -(\nabla V)^\perp(\varphi(\alpha, t)) + r(\alpha, t)\hat{\tau}(\alpha, t)$$  \hspace{1cm} (5.1)

Here $\hat{\tau}$ is the tangent vector of the curve $\{\varphi(. , t)\}$, $(\nabla V)^\perp(\varphi)$ denotes the component of $\nabla V$ normal to $\hat{\tau}$, $r$ is the Lagrange multiplier that enforces certain specific parameterization of the curves. For example if we require equal arclength parameterization, then we need $\frac{d}{d\alpha}|\varphi_\alpha| = 0$, i.e.

$$r(\alpha, t) = \alpha \int_0^1 \nabla V(\varphi(\alpha', t)) \cdot \hat{\tau}(\alpha', t) d\alpha' - \int_0^\alpha \nabla V(\varphi(\alpha', t)) \cdot \hat{\tau}(\alpha', t) d\alpha'$$  \hspace{1cm} (5.2)

We call such curves with intrinsic parameterization strings.

In practice the strings are discretized into a collection of points. These points move according to the normal component of the potential force. A reparameterization step is applied once in a while to enforce the proper parameterization of the strings.

The finite temperature string method is designed for systems with rough energy landscapes, particularly the case when the potential can be expressed in the form

$$V(x) = \bar{V}(x) + \delta V(x)$$

where $\bar{V}$ is smooth and $|\delta V| \leq O(k_B T)$. In this case we would like to compute the MEP of $\bar{V}$ without first computing $\bar{V}$ explicitly. This is achieved by creating an ensemble of a special type. Our computational object will be a string connecting the two metastable sets, together with a family of probability measures on the hyperplanes normal to the string. Consider the stochastic equation

$$\varphi^\omega_t(\alpha, t) = -P^0_\alpha(\nabla V(\varphi^\omega(\alpha, t))) + r^0(\alpha, t)\hat{\tau}^0(\alpha, t) + P^0_\alpha \eta^\omega(\alpha, t)$$  \hspace{1cm} (5.3)

where $\eta^\omega$ is Gaussian noise with mean 0 and correlation

$$E\eta^\omega(\alpha, t)\eta^\omega(\alpha', \tau) = \begin{cases} 2k_B T \delta(t - \tau), & \text{if } \alpha = \alpha' \\ 0, & \text{if } \alpha \neq \alpha' \end{cases}$$

The projection operator $P^0_\alpha$ is defined by projecting to the hyperplane normal to the string $\{\varphi^0(\alpha, t), 0 \leq \alpha \leq 1\}$, where

$$\varphi^0(\alpha, t) = E\varphi^\omega(\alpha, t)$$

$\hat{\tau}^0(\alpha, t)$ is the tangent vector of $\varphi^0$ at $\alpha$, $r^0$ is the Lagrange multiplier that enforces proper parameterization of $\varphi^0$.

**Theorem 1.1.**

1. The statistical steady state of (5.3) satisfies:

$$\varphi^0(\alpha) = \frac{1}{Z(\alpha)} \int_{S^0(\alpha)} xe^{\frac{\bar{V}(x)}{k_B T}} dx$$  \hspace{1cm} (5.4)

where $S^0(\alpha)$ is the hyperplane normal to $\varphi^0$ at $\alpha$, $Z(\alpha) = \int_{S^0(\alpha)} e^{\frac{\bar{V}(x)}{k_B T}} dx$. 

2. The stationary distribution of (5.3) is given by the family of distributions

\[ \mu_\alpha(x) = \frac{1}{Z(\alpha)} e^{-\frac{V(x)}{k_B T}} \delta S^0(\alpha)(x) \]  

(5.5)

Knowing \{\phi^0\} and \{\mu_\alpha\}, the transition rates and free energy landscapes can be computed, see [7].

The finite temperature string method is applied to the perturbed Mueller potential

\[ V(x) = V_m(x) + \delta V(x) \]

where \( V_m(x) \) is the so-called Mueller potential (see [11]), \( \delta V \) is a random perturbation. The results of the (finite temperature) string method is shown in Figure 4. Also plotted is the MEP of \( V_m \) (since \( \bar{V} = V_m \) is explicitly known for this particular example) as well as the fluctuations around \( \phi^0 \).

![Figure 4](image)

**Figure 4.** Effective MEP and local fluctuations for the perturbed mueller potential. The red curve is the MEP for \( \bar{V} = V_m \). The black curve is the MEP computed from the finite temperature string method. The green curves show the size of the fluctuations.

6. Concluding remarks

There are several important topics that we did not cover in this brief report. These include the effect of dynamics, non-gradient systems, and acceleration techniques. These are discussed in [4, 5, 7, 12]. Also found in these references are applications of the ideas discussed here to thermal activated reversal of magnetic thin films, models of martensitic transformations, and the formation of \( C_{60} \) from 60 carbon atoms. The last example is a case when the barrier is entropic. Even though the potential energy is mainly going downhill, the free energy has barriers because of entropic effects. Such examples are found frequently in biopolymers.
From a numerical point of view, our main idea for overcoming the difficulty caused by the disparity of the times scales is to reformulate the problem as a boundary value problem instead of initial value problem, since we have some knowledge of the initial and final state of the system. Compared with other existing methods that assume explicit knowledge of a reaction coordinate, our method finds the reaction coordinate self-consistently during the computation.

The topic discussed here is relatively new in applied mathematics, but it is of paramount importance in science and particularly computational science. Progress in this area will likely have a fundamental impact in many areas of applications.

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