

Transition pathways in complex systems: Reaction coordinates, isocommittor surfaces, and transition tubes

Weinan E^a, Weiqing Ren^a, Eric Vanden-Eijnden^{b,*}

^a Department of Mathematics and PACM, Princeton University, Princeton, NJ 08544, United States

^b Courant Institute of Mathematical Sciences, New York University, 251 Mercer Street, New York, NY 10012, United States

Received 6 May 2005; in final form 20 July 2005

Available online 18 August 2005

Abstract

The mechanism of transition (reaction coordinate) during an activated process is best described in terms of the isocommittor surfaces. These surfaces can be used to identify effective transition tubes inside which the reactive trajectories involved in the activated process stay confined. It is shown that the isocommittor surfaces can be identified directly, i.e., without ever sampling actual reactive trajectories, and some procedures to turn this observation into practical algorithms such as the finite temperature string method are discussed.

© 2005 Elsevier B.V. All rights reserved.

1. Introduction

Activated processes such as nucleation events during phase transition, conformational changes of macromolecules, or chemical reactions are rare events relative to the time scale of the atomic vibrations. The reason is that these events require the system to find its way through dynamical bottlenecks such as energetic or entropic barriers which separate metastable sets in configuration space. The wide separation of time-scales makes conventional molecular dynamics simulations ineffective for these rare events and there is a crucial need for alternative techniques that are capable of determining the transition pathways of activated processes arising in complex systems.

In this Letter, we argue that the best reaction coordinate to describe the activated process, in fact *the* reaction coordinate, consists of the isocommittor surfaces, defined in such a way that a trajectory launched any-

where on one of these surfaces has the same probability to reach first one of the metastable sets rather than the other. The idea of using the isocommittor surfaces as reaction coordinates is not new (see, e.g. [2,3,5,6]), and yet more can be said about these surfaces.

First, we show that the isocommittor surfaces are the only surfaces such that the distribution of where the reactive trajectories hit these surfaces is the same as the distribution of where all trajectories hit. Therefore, this distribution is given by the equilibrium distribution restricted to the isocommittor surfaces – on any other set of surfaces, there is a biasing factor to add to the equilibrium distribution to describe the distribution of hits by reactive trajectories. This property can be used to define tubes in configuration space inside which the reactive trajectories stay confined with high probability. This is done by weighting the isocommittor surfaces by the equilibrium probability distribution and identifying regions of large probability within these surfaces. The transition tubes generalize the notion of minimum energy path to situations where the energy landscape is rough and/or entropic effects dominate.

Second, we discuss how to identify the isocommittor surfaces directly, that is without ever having to

* Corresponding author. Fax: +1 212 995 4121.

E-mail addresses: weinan@princeton.edu (W. E), weiqing@math.princeton.edu (W. Ren), eve2@cims.nyu.edu (E. Vanden-Eijnden).

sample actual reactive trajectories. The direct identification is based on the observation that the isocommittor surfaces are the level sets (isosurfaces) of the solution of the backward Kolmogorov equation, a well known equation in stochastic process theory. The backward Kolmogorov equation admits a variational formulation (least square principle), which serves as a starting point to use appropriate test functions to identify the best approximation to the isocommittor surfaces within a certain class (like, e.g., hyperplanes). This way, practical algorithms can be designed. We shall discuss in particular the finite temperature string method (FTS), which can be thought of as an adaptive version of the blue moon sampling technique where one samples the equilibrium distribution within a family of hyperplanes, and updates these planes according to some criterion until they converge towards the isocommittor surfaces.

Identifying the isocommittor surfaces directly is quite different from what is usually done to determine transition pathways. Indeed, the idea behind most of the current techniques is to introduce some bias on the dynamics to enhance the probability to observe reactive trajectories. Following Pratt's original suggestion [1], this can be done by using Monte Carlo sampling in trajectory space, with the constraint that the end points of the trajectories belong to different metastable sets. Examples of techniques which sample reactive trajectories directly include transition path sampling (TPS) [2,3], or the action based methods introduced by Elber and collaborators [4].

It should be noted, however, that the reactive trajectories can be very complicated, and the information these trajectories provide on the mechanism of the transition is very indirect. In particular, the isocommittor surfaces cannot be identified directly from the ensemble of reactive trajectories since, by definition, these trajectories always connect one metastable set to the other and therefore any point along these trajectories seems to have committor value either one or zero. Another way to see the problem is to realize that the reactive trajectories are parametrized by time, and time is not a good indicator of the advancement of the reaction. In general, two trajectories leaving a set at the same time will hit an isocommittor surface at different times. Even worse, a single reactive trajectory may hit an isocommittor surface many times during a transition. This makes the reconstruction of the isocommittor surfaces from the reactive trajectories a very challenging numerical task [6]. By identifying the isocommittor surfaces directly we avoid these difficulties altogether.

A few words about the organization of the Letter. We are primarily interested in systems governed by the Langevin equation

$$\begin{cases} \dot{x} = v(t), \\ \dot{v}(t) = -\nabla V(x(t)) - \gamma M^{-1}v(t) + \sqrt{2\gamma\beta^{-1}}M^{-1/2}\eta(t), \end{cases} \quad (1)$$

where $(x(t), v(t)) \in \mathbb{R}^n \times \mathbb{R}^n$ (n degrees of freedom with n large in general), $V(x)$ is the potential, $\beta = 1/k_B T$, the inverse temperature, γ , the friction coefficient, M , the diagonal mass matrix, and $\eta(t)$, a white-noise satisfying $\langle \eta_i(t)\eta_j(t') \rangle = \delta_{ij}\delta(t-t')$. Most of our results formally apply in the limit of zero friction, $\gamma \rightarrow 0$, when (1) reduces to Hamilton's equation of motion, but it should be stressed that the results below are rigorous only when the friction coefficient is positive. For simplicity of presentation, we will consider first in Sections 2 and 3 the high friction situation when $\gamma \gg 1$ which is technically simpler. Then, in Section 4 we will show that the conclusions we draw from the high friction dynamics in terms of mechanism of transition also apply to (1), provided that the mechanism of transition can be described accurately in configuration space alone. Finally, in Section 5 we discuss algorithms like the finite temperature string method (FTS) which allow to identify the isocommittor surfaces.

2. Isocommittor surfaces and backward Kolmogorov equation

Consider a system governed by

$$\gamma\dot{x}(t) = -\nabla V(x(t)) + \sqrt{2\gamma\beta^{-1}}\eta(t). \quad (2)$$

This equation arises from (1) in the high friction limit, $\gamma \gg 1$, and we will return to (1) in Section 4.

The dynamics in (2) is ergodic with respect to the Boltzmann–Gibbs probability density function (NVT ensemble)

$$Z^{-1}e^{-\beta V(x)}, \quad \text{where } Z = \int_{\mathbb{R}^n} e^{-\beta V(x)} dx. \quad (3)$$

We will assume that it has been established that (1) is metastable over the two sets $A \subset \mathbb{R}^n$ and $B \subset \mathbb{R}^n$ in configuration space. By this we mean that the volume of these sets may be relatively small, and yet the probability to find the system inside one of these sets is close to one:

$$1 \approx Z^{-1} \int_{A \cup B} e^{-\beta V(x)} dx. \quad (4)$$

By ergodicity, transitions between these sets must occur, and our main purpose is to understand how they occur. How to systematically identify A and B may for instance be done by analyzing the spectrum of the infinitesimal generator associated with (1) – metastability is related to the existence of a spectral gap, and the metastable sets can be identified from the eigenfunctions associated with

the smallest eigenvalues (see, e.g., Ref. [16]) – but we will not dwell on this issue here. Also, we note that the situation with more than two metastable sets, say, $\{A_j\}_{j=1,\dots,n}$ can be considered as well by iterating the arguments below on $A_1, \cup_{j \neq 1} A_j$, then $A_2, \cup_{j \neq 2} A_j$, etc.

As mentioned in Section 1, the reaction coordinate for describing the mechanism of transition between A and B consists of the isocommittor surfaces. We explain why this is the case Section 3, but before doing so we note that, in principle at least, there is a systematic way to identify these isocommittor surfaces without running any dynamical trajectories. Indeed, let $q(x)$ be the solution of

$$0 = Lq \equiv -\nabla V \cdot \nabla q + \beta^{-1} \Delta q, \quad q|_{x \in A} = 0, \quad q|_{x \in B} = 1, \quad (5)$$

The operator L is infinitesimal generator of the Markov process defined by (2), and (5) is the backward Kolmogorov equation associated with (2). Then $q(x)$ has the following probabilistic interpretation:

$q(x)$ is the probability that a trajectory initiated at x reaches the set B before reaching the set A .

It follows that the level set (or isosurface) $q(x) = z \in [0, 1]$ is the set of points which have a uniform probability z to reach B before A , i.e., it is the isocommittor surface with committor value z . These statements are classical results of stochastic process theory and are reviewed, e.g., in Chapter 5 of [10] or Chapter 4 in [11].

3. Reaction coordinate and transition tubes

The main purpose of this section is to show that by weighting the isocommittor surfaces $q(x) = z$ by the equilibrium probability density (3) restricted to these surfaces, we can define regions on the isocommittor surface through which reactive trajectories pass with high probability. (Recall that by reactive trajectories we mean the portions of a trajectory when, after leaving the metastable set A , it enters first B before returning to A , or the other way around.)

Consider an arbitrary surface S (i.e., not necessarily an isocommittor surface) in the configuration space and an arbitrary point x on S . Then the probability density that a reactive trajectory hits S at x is

$$\rho_S(x) = Z_S^{-1} q(x)(1 - q(x))e^{-\beta V(x)}, \quad (6)$$

where $Z_S = \int_S q(x)(1 - q(x))e^{-\beta V(x)} d\sigma(x)$ and $d\sigma(x)$ is the surface element on S . To understand (6), note that $\rho_S(x)$ is equal to the probability density that a trajectory (whether reactive or not) hits S at x , times the probability that the trajectory came from A in the past and that it reaches B before reaching A in the future. Using the strong Markov property and the statistical time revers-

ibility of the dynamics in (2) (i.e., the time series $x(-t)$ is statistically equivalent to $x(t)$), this probability is given by $q(x)(1 - q(x))$, and this gives (6).

On an isocommittor surface, $q(x) = cst$ by definition, and therefore (6) simply reduces to the equilibrium probability density on this surface

$$\rho_S(x) = \bar{Z}_S^{-1} e^{-\beta V(x)}, \quad (S = \text{isocommittor surface}), \quad (7)$$

where $\bar{Z}_S = \int_S e^{-\beta V(x)} d\sigma(x)$. In other words,

The isocommittor surfaces have no bias, in the sense that the distribution of where the reactive trajectories hit these surfaces is the same as the distribution of where all the trajectories hit.

Note that the isocommittor surfaces are the only surface where the factor $q(x)(1 - q(x))$ in (6) is constant, i.e., they are the only surfaces that can be weighted by the equilibrium density and yet provide some dynamical information about the reactive trajectories.

These special properties of the isocommittor surfaces can be used to define the transition tubes. Let $C(z) \subset \{q(x) = z\}$ be the region with the smallest volume in the isocommittor surface such that

$$\int_{C(z)} e^{-\beta V(x)} d\sigma(x) = p \int_{q(x)=z} e^{-\beta V(x)} d\sigma(x), \quad (8)$$

where $p \in (0, 1)$ is a parameter. Then we have:

The family $\{C(z): z \in [0, 1]\}$ defines one or more tubes connecting a and b which are such that the reactive trajectories stay inside this tube with probability p .

Each such tube is naturally referred to as an *effective transition tube* (or a p -transition tube to be more precise). If p is taken to be close to 1 in (8), then the regions within the tubes where $q(x)$ is close to 1/2 define the transition regions: these regions have a significant probability to be visited by the reactive trajectories and from these regions, the probability of subsequently committing to either A or B is close to 1/2. Notice that both the tubes and the transition regions can be quite wide.

Because the probability weight on the isocommittor surface is simply the equilibrium probability density, it is quite straightforward to sample these surfaces using, e.g., the blue moon sampling method [12,13]. The difficult part is of course to identify the isocommittor surfaces using (5). We will consider this question in Section 5.

4. Generalization to the finite friction case: least square principle, etc.

Let us now go back to the Langevin equation in (1). This dynamics is also ergodic with respect to the Boltzmann–Gibbs density in (3), and if A and B are metasta-

ble sets for (2) in the sense that they satisfy (4), these sets are also metastable sets for (1). Since (1) defines a Markov process as well, one can understand the mechanism of transition between the sets A and B using as reaction coordinate the solution of the equation similar to (5) associated with (1):

$$\begin{cases} 0 = \tilde{L}\tilde{q} \equiv v \cdot \nabla \tilde{q} - \nabla V \cdot \partial \tilde{q} - \gamma M^{-1} v \cdot \partial \tilde{q} + \gamma \beta^{-1} M^{-1} : \partial \partial \tilde{q}, \\ \tilde{q}|_{x \in A} = 0, \quad \tilde{q}|_{x \in B} = 1, \end{cases} \quad (9)$$

where ∇ denotes the gradient with respect to x , and ∂ the gradient with respect to v . The operator \tilde{L} is infinitesimal generator of the Markov process defined by (1) and (9) is the backward Kolmogorov equation associated with (1). The main difference with (5) is that the solution of (9) is defined on phase-space, $\tilde{q} \equiv \tilde{q}(x, v)$, but it has the same probabilistic interpretation as $q(x)$: $\tilde{q}(x, v)$ is the probability that a trajectory initiated at (x, v) reaches set B before set A . In other words the level set $\tilde{q}(x, v) = z \in [0, 1]$ is the location of the points (in phase-space) which have a uniform probability z to reach B before A .

Eq. (9) seems even more complicated than (5). However, we claim that:

If the mechanism of transition between A and B can be accurately described in configuration space alone, then $\tilde{q}(x, v) \approx q(x)$, where $q(x)$ is the solution of (5).

To see this, let us associate with (9) a least square variational principle. Specifically, consider

$$I = \int_{\mathbb{R}^n \times \mathbb{R}^n} e^{-\beta H(x, v)} |\tilde{L}\tilde{q}(x, v)|^2 dx dv, \quad (10)$$

where $H(x, v) = \frac{1}{2}|v|^2 + V(x)$ is the Hamiltonian. The solution of (9) minimizes I over all test functions \tilde{q} satisfying $\tilde{q}(x, v)|_{x \in A} = 0$, $\tilde{q}(x, v)|_{x \in B} = 1$, and we have not made any approximation yet. Let us now assume that \tilde{q} depends on x only, i.e., $\tilde{q}(x, v) \equiv \tilde{q}(x)$. This amounts to making the assumption that the mechanism of transition can be described accurately in configuration space alone. In this case, $\tilde{L}\tilde{q} = v \cdot \nabla \tilde{q}$, and the integration over v in (10) can be done explicitly. Up to an irrelevant constant, the result is

$$I = \int_{\mathbb{R}^n} e^{-\beta V(x)} |\nabla \tilde{q}(x)|^2 dx. \quad (11)$$

The Euler–Lagrange equation associated with minimizing this object function subject to $\tilde{q}(x)|_{x \in A} = 0$, $\tilde{q}(x)|_{x \in B} = 1$ precisely is (5). It means that, in the range of value of γ such that to a good approximation, $\tilde{q}(x, v)$ depends only on x , the mechanism of transition is insensitive to γ and $\tilde{q}(x, v) = q(x)$ as claimed. In the sequel, we will work within this approximation but we note that, should it fail in a given situation, one can in

principle refine upon it by going back to (10) and choosing test functions that are more appropriate than $\tilde{q}(x, v) = \tilde{q}(x)$.

5. Practical implementation: string method, etc.

The variational principle associated with (11) (or (10) if necessary) offers ways to systematically develop practical procedure to identify $q(x)$ and the isocommittor surfaces. The idea is to use appropriate test functions to approximate $q(x)$. For instance, we could assume that $q(x) = f(\eta_1(x), \dots, \eta_N(x))$, where $\{\eta_1(x), \dots, \eta_N(x)\}$ are given coarse variables in terms of which the transition can be described accurately. Minimizing (11) over such test functions can be done, and it leads to a description of the transition pathways in terms of the minimum free energy paths defined on the free energy associated with the variables $\{\eta_1(x), \dots, \eta_N(x)\}$. These results will be presented elsewhere. Here, we focus on the main ideas behind the finite temperature string method (FTS) [7–9] which makes only minimum a priori assumptions about the mechanism of transition. We refer the reader to [9] for more details about the implementation of the method and its application for the study of the isomerization of alanine dipeptide.

The main assumption behind FTS is that the family of level sets $q(x) = z$, $z \in [0, 1]$, can be approximated by a family of planes, at least locally around each transition tube specified by (8) for p close to one. This family of planes can be represented by a parameterized curve in configuration space (*a string*) $\varphi(\alpha)$, with $\alpha \in [0, 1]$, such that: (i) the plane labeled by α , which we will denote by $P(\alpha)$ contains the point $x = \varphi(\alpha)$; (ii) the unit normal of $P(\alpha)$ is $\hat{n}(\alpha)$; (iii) the point $\varphi(\alpha)$ is the mean position in the plane with respect to the equilibrium density (3) now restricted to $S = P(\alpha)$, i.e.

$$\varphi(\alpha) = \langle x \rangle_{P(\alpha)} \equiv \frac{\int_{P(\alpha)} x e^{-\beta V(x)} d\sigma(x)}{\int_{P(\alpha)} e^{-\beta V(x)} d\sigma(x)}. \quad (12)$$

Note that the parametrization by α may be different from the one by z . Using the identity

$$\begin{aligned} I &= \int_{\mathbb{R}^n} |\nabla q(x)|^2 e^{-\beta V(x)} dx \\ &= \int_0^1 \left(\int_{\mathbb{R}^n} |\nabla q(x)|^2 e^{-\beta V(x)} \delta(q(x) - z) dx \right) dz, \end{aligned} \quad (13)$$

it was shown in [7] (see also the remark at the end of this section) that, under the planar approximation, this objective function reduces to

$$I = \int_0^1 (f'(\alpha))^2 e^{-\beta F(\alpha)} |\hat{n}(\alpha) \cdot \varphi'(\alpha)|^{-1} d\alpha, \quad (14)$$

where $f(\alpha) = q(\varphi(\alpha))$, the prime denotes derivative with respect to α , and we defined the free energy

$$F(\alpha) = -\beta^{-1} \ln \int_{\mathbb{R}^n} e^{-\beta V(x)} \delta(\hat{n}(\alpha) \cdot (x - \varphi(\alpha))) dx. \quad (15)$$

The derivation of (14) uses $f'(\alpha) = dq(\varphi)/d\alpha = |\hat{n} \cdot \varphi'| |\nabla q(\varphi)|$ and requires localization in the sense that

$$(\hat{n}(\alpha) \cdot \varphi'(\alpha))^2 \gg \langle (\hat{n}(\alpha) \cdot (x - \varphi(\alpha)))^2 \rangle_{P(\alpha)}, \quad (16)$$

which relates the width of the transition tube to the local curvature of the string. (16) is required since otherwise the regions of high probability on the planes would include regions where these planes intersect, thereby invalidating the local planar assumption for the level sets of $q(x)$.

Eq. (14) must be minimized over φ, \hat{n} and f , subject to (12) and the conditions that $f(0) = 0, f(1) = 1$, and that the end points of φ belong to the metastable sets A and B . This calculation was performed in [7], and it was shown that the minimum is achieved when:

$$\hat{n}(\alpha) \parallel \varphi'(\alpha) \quad (17)$$

and

$$f(\alpha) = \frac{\int_0^\alpha e^{\beta F(\alpha')} d\alpha'}{\int_0^1 e^{\beta F(\alpha')} d\alpha'}. \quad (18)$$

The region such that $f(\alpha_\star) \approx \frac{1}{2}$ is the transition state region. Notice that this region is also the one where the free energy is maximum.

Eqs. (17) and (18) can be justified heuristically as follows. The minimum of the factor $|\hat{n} \cdot \varphi'|^{-1}$ in (14) is achieved under the condition (17) (without loosing in generality, we assume the length of $\varphi'(\alpha)$ is a constant). When (17) holds, (14) reduces to

$$I = \int_0^1 (f'(\alpha))^2 e^{-\beta F(\alpha)} d\alpha, \quad (19)$$

up to a constant. The minimizer of (19) is given by (18), which is also the solution to the one-dimensional version of the backward Kolmogorov equation:

$$-F'(\alpha)f'(\alpha) + \beta^{-1}f''(\alpha) = 0 \quad (20)$$

with boundary conditions $f(0) = 0$ and $f(1) = 1$. In particular, notice that (18) simply is the equivalent of the function $q(x)$ for a one-dimensional particle moving by high friction dynamics in the free energy potential.

Eqs. (12) and (17) indicate that the family of planes $P(\alpha)$ is such that the mean position within these planes form a curve φ which must be everywhere perpendicular to the planes. In fact, (12) and (17) are a natural finite temperature generalization of the concept of minimum energy path (recall that if φ were a minimum energy path, then $0 = \nabla V(\varphi)^\perp$ along it, see, e.g. [7]). As a result FTS is a natural generalization of the zero temperature string method developed in [14,15], and it can be implemented numerically in a similar way by moving curves in configuration space.

More precisely, FTS method is an iterative method for solving

$$\varphi(\alpha) = \langle x \rangle_{P_\alpha}, \quad (21)$$

subject to

$$\hat{n}(\alpha) \parallel \varphi'(\alpha). \quad (22)$$

This is done sampling on hyperplanes satisfying (22), then updating the position of these hyperplanes until (21) is satisfied. For more details, see [8,9].

Remark. We derive the formula (14) from (13):

$$\begin{aligned} I &= \int_{\Omega'} |\nabla q(x)|^2 e^{-\beta V(x)} dx \\ &= \int_0^1 dz \int_{\Omega'} |\nabla q(x)|^2 e^{-\beta V(x)} \delta(q(x) - z) dx \\ &= \int_0^1 f'(\alpha) d\alpha \int_{\Omega'} |\nabla q(x)| e^{-\beta V(x)} \delta(\hat{n}(\alpha) \cdot (x - \varphi(\alpha))) dx \\ &= \int_0^1 f'(\alpha) |\nabla q(\varphi(\alpha))| d\alpha \int_{\Omega'} e^{-\beta V(x)} \\ &\quad \times \delta(\hat{n}(\alpha) \cdot (x - \varphi(\alpha))) dx \\ &= \int_0^1 f'(\alpha)^2 (\hat{n}(\alpha) \cdot \varphi'(\alpha))^{-1} e^{-\beta F(\alpha)} d\alpha. \end{aligned} \quad (23)$$

where $\Omega' = \mathbb{R}^n \setminus (A \cup B)$. To go from the third to the fourth line, we made the assumption that the isocommitator surface is locally planar with normal $\hat{n}(\alpha)$, and defined $f(\alpha) = q(\varphi(\alpha))$. To go from the fourth to the fifth line, we used (16). In the last step, we defined the free energy $F(\alpha)$ as in (15) and used $f'(\alpha) = \nabla q(\varphi) \cdot \varphi' = |\nabla q(\varphi)| (\hat{n} \cdot \varphi')$.

Acknowledgements

We thank David Chandler, Giovanni Ciccotti, and Paul Maragakis for their comments. This work was partially supported by NSF grants DMS01-01439, DMS02-09959 and DMS02-39625, and by ONR grants N00014-01-1-0674 and N00014-04-1-0565.

References

- [1] L.R. Pratt, J. Chem. Phys. 85 (1986) 5045.
- [2] P.G. Bolhuis, D. Chandler, C. Dellago, P.L. Geissler, Ann. Rev. Phys. Chem. 59 (2002) 291.
- [3] C. Dellago, P.G. Bolhuis, P.L. Geissler, Adv. Chem. Phys. 123 (2002).
- [4] R. Olender, R. Elber, J. Chem. Phys. 105 (1996) 9299.
- [5] G. Hummer, J. Chem. Phys. 120 (2004) 516.
- [6] A. Ma, A.R. Dinner, J. Phys. Chem. B (2005).
- [7] W.E, E. Vanden-Eijnden, in: S. Attinger, P. Koumoutsakos (Eds.), Multiscale Modelling and Simulation, LNCSE 39, Springer, 2004.
- [8] W. E, W. Ren, E. Vanden-Eijnden, J. Phys. Chem. B (2005).

- [9] W. Ren, E. Vanden-Eijnden, P. Maragakis, W. E, J. Chem Phys. (accepted).
- [10] C.W. Gardiner, *Handbook of Stochastic Methods*, Springer, Berlin, 1985.
- [11] R. Durrett, *Stochastic Calculus*, CRC Press, Washington, DC, 1996.
- [12] E.A. Carter, G. Ciccotti, J.T. Hynes, R. Kapral, Chem. Phys. Lett. 156 (1989) 472.
- [13] M. Sprik, G. Ciccotti, J. Chem. Phys. 109 (1998) 7737.
- [14] W.E.W. Ren, E. Vanden-Eijnden, Phys. Rev. B 66 (2002) 052301.
- [15] W.E.W. Ren, E. Vanden-Eijnden, J. App. Phys. 93 (2003) 2275.
- [16] W. Huisinga, S. Meyn, C.H. Schütte, Ann. Appl. Probab. 14 (2004) 419.