Published in final edited form as:

Comput Phys Commun. 2013 October ; 184(10): 2310–2315. doi:10.1016/j.cpc.2013.05.017.

Transition-Path Theory Calculations on Non-Uniform Meshes in Two and Three Dimensions using Finite Elements

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Abstract

Rare events between states in complex systems are fundamental in many scientific fields and can be studied by building reaction pathways. A theoretical framework to analyze reaction pathways is provided by transition-path theory (TPT). The central object in TPT is the committor function, which is found by solution of the backward-Kolmogorov equation on a given potential. Once determined, the committor can be used to calculate reactive fluxes and rates, among other important quantities. We demonstrate here that the committor can be calculated using the method of finite elements on non-uniform meshes. We show that this approach makes it feasible to perform TPT calculations on 3D potentials because it requires many fewer degrees of freedom than a regular-mesh finite-difference approach. In various illustrative 2D and 3D problems, we calculate the committor function and reaction rates at different temperatures, and we discuss effects of temperatures and simple entropic barriers on the structure of the committor and the reaction rate constants.

Keywords

committor function; rare events; reaction kinetics

1. Introduction

Rare transition events between different stable states characterize many problems in physics, chemistry, and biology. Historically, the main framework to study rare events and compute transition reaction rates are transition state theory [1–7], transition path sampling [8, 9] and action method [10, 11]. Recently, a novel theoretical framework, transition-path theory (TPT), was developed to describe the statistical properties of reactive trajectories [12, 13]. TPT provides statistical properties of the reaction from a reactant state A to a product state B, which arise from averages over reactive dynamical trajectories through the space in which A and B are defined.

Rather than spending a lot of computational effort to generate samples of the reactive trajectory ensemble, in TPT one calculates the committor function $q(z)$, which measures the probability that a trajectory launched from point z will arrive at B before arriving at A. From

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q , one can compute the probability density function of reactive trajectories, its flux, and the reaction rate. Systems with a rugged free energy landscape that lacks clear transition states can be analyzed using TPT. Previously, a collection of simple examples was used to illustrate how TPT calculations can be performed in two dimensions [14]. Here, q was found using a finite-difference method on a regularly-discretized domain. In practice, the discretization must be very fine to faithfully represent arbitrarily shaped boundaries of the regions of A and B, making such a regular-mesh approach impractical for three- (and higher-) dimensional calculations.

The purpose of this paper is to demonstrate how one can use the more sophisticated finite-element method (FEM) on non-uniform meshes to perform TPT calculations in both two and three dimensions. 2D examples are used to test our FEM approach, and they reproduce previous results by Metzner et al. [14] using a factor of approx. 30 fewer degrees of freedom. We further show how FEM can be applied to TPT calculations in three dimensions on both simple and fairly complicated geometries. We believe this clearly shows that the FEM approach is viable for extending TPT calculations into higher-dimensional spaces, which might include, for example, computing rates of diffusion of small molecules in proteins.

2. Methods

2.1. Transition-Path Theory

In this section, we provide a short and simple description of TPT; we refer the reader to the original references for details [12–16]. TPT is a framework to study the reaction from state A (reactant) to state B (product). It provides statistical properties of the ensemble of reactive trajectories. That is, if one imagines an infinitely long trajectory $\{z(t) : -\infty < t < \infty\}$ in the space $\Omega \subset \mathbb{R}^n$, (that is, z is an n -dimensional vector) and A and B are separately defined regions in that space, $z(t)$ can be divided into segments which remain in A, remain in B, leave A and return to A, leave B and return to B, or transit from A to B. This last category constitutes the ensemble of $A \rightarrow B$ reactive trajectories.

The central object in TPT is the committor function, $q(z)$, which is the probability that a trajectory launched from z will reach the product B before reaching the reactant A. The committor function monitors the progress of the reaction, and it represents the “true” reaction coordinate. In case of overdamped dynamics at temperature T for a trajectory $z(t)$ on a potential energy $V(z)$, the committor function $q(z)$ satisfies the backward Kolmogorov (bK) equation [17]:

$$\nabla V \cdot \nabla q - k_B T \nabla^2 q = 0 \quad (1)$$

where k_B is Boltzmann’s constant. (If z is a collective variable, then $V(z)$ is a free energy.) The backward Kolmogorov equation is closely related to the well-known Fokker-Planck equation. The committor is found by solving Eq. 1 with boundary conditions $q(z) = 0$ in A and $q(z) = 1$ in B.

Before describing our numerical approach to solving Eq. 1, we point out a few other statistical properties important to describe transition pathways. The probability density $\rho_{AB}(z)$ to observe a reactive trajectory at point $z \notin A \cup B$ at time t is

$$\rho_{AB}(z) = Z_{AB}^{-1} Z^{-1} e^{-\beta V(z)} q(z) (1 - q(z)) \quad (2)$$

where Z_{AB}^{-1} is the probability to observe a reactive trajectory in the subdomain $\Omega_{AB} = \mathbb{R}^n \setminus (A \cup B)$ at time t , and $Z^{-1} e^{-\beta V(z)}$ the probability of observing the trajectory at z at time t [14, 18, 19]. The reactive flux along direction i $J_{AB,i}$ can be defined as:

$$J_{AB,i}(z) = Z^{-1} e^{-\beta V(z)} k_B T \gamma_i^{-1} \frac{\delta q(z)}{\delta z_i} \quad (3)$$

The rate constant for the $A \rightarrow B$ reaction is defined as

$$k_{AB} = \int_S n_{\bar{S}}(z) J_{AB}(z) d\sigma_S(z) \quad (4)$$

where S is surface that divides the phase space between A and B, $n_{\bar{S}}(z)$ is the unit normal on S pointing toward B, and $d\sigma_S(z)$ is the surface element on S .

2.2. Finite-Element Method

The FEM is an attractive approach to solve Eq. 1 for the committor primarily because of the ease of handling arbitrarily-shaped reactant and product regions using non-uniform meshes, rather than having to use very finely resolved regular meshes. Consider that the value of q inside A and B is irrelevant; we must only specify the values of q on the bounding surfaces of A and B, S_A and S_B , respectively. So we treat S_A and S_B as boundaries on the solution domain of q , $\Omega_{AB} = \Omega(A \cup B)$. The total domain of q includes the interiors of A and B, but the value of q is constant in these regions and need not be treated in the solving the bK equation. This has the benefit that the boundaries can be optimally discretized with non-uniform meshes using nodes that are snapped precisely to the desired boundary surfaces.

For the 2D examples, we used a rectangular domain $\Omega \subset \mathbb{R}^2$ with a non-uniform triangular mesh snapped around the boundaries of the A and B regions. For the 3D examples, we used a cubical domain $\Omega \subset \mathbb{R}^3$ with a non-uniform tetrahedral mesh snapped onto the boundaries of A and B. We used the FEniCS package to set up our meshes, and boundaries are regions A and B are defined as surfaces of constant energy above their respective local minima (details for each case appear below). We use the finite element method implemented in the DOLFIN library v.1.0.0 [20] to solve the “weak form” of the bK equation:

$$\int_{\Omega} (v \nabla V + \nabla v) \cdot \nabla q dz = 0 \quad (5)$$

where $v(z)$ are the linear trial functions in each element. This weak form enforces Neumann (zero-flux) conditions on the global system boundaries. Finally, it bears mentioning that execution times for our most demanding 3D examples were uniformly about 14 minutes on an Intel Core i7-2670QM CPU 2.20 GHz with 8GB RAM.

3. Results

3.1. Two-dimensional examples

Here we work in two dimensions, $z \equiv (x, y)$. Following Metzner et al. [14], we first consider the two-well potential

$$V(x, y) = \frac{5}{2} (x^2 - 1) + 5y^2 \quad (6)$$

This potential has local minima at $(-1, 0)$ and $(0, 1)$ and a saddle point at $(0, 0)$. The reactant state A is defined as the union of all points in the vicinity of $(-1, 0)$ for which $V(x, y) < 0.4$.

and region B is similarly defined in the vicinity of (1,0). The domain was set to $\Omega = [-1.5, 1.5] \times [-1, 1]$. We set up an initial mesh of 64×64 nodes, removed nodes within regions A and B, and then snapped nodes closest to the boundary curves of A and B onto those curves. Our discretization had 7,786 degrees of freedom, a factor of approximately 30 lower than the finite-difference approach of Metzner et al. for the same potential [14].

In Fig. 1, we show selected isocommittor curves computed by solving Eq. 1 with $\beta = 1/k_B T = 1$; as expected, the isocommittor curve for $q = 0.5$ (denoted “ $S_{1/2}$ ”) is coincident with the y axis. In Fig. 2, we show the reactive flux J_{AB} along the isocommittor surface $S_{1/2}$, which again shows the expected behavior of a peak along $y = 0$. These results are identical to those obtained by Metzner et al.

In the second example, we again follow Metzner et al. and use a three-well potential:

$$V(x, y) = 3e^{-x^2 - (y - \frac{1}{3})^2} - 3e^{-x^2 - (y - \frac{5}{3})^2} - 5e^{-(x-1)^2 - y^2} - 5e^{-(x+1)^2 - y^2} + 0.2x^4 + 0.2\left(y - \frac{1}{3}\right)^4 \quad (7)$$

As shown in Fig. 3, the $V(x, y)$ of Eq. 7 has two deep minima at (1,0) and (-1,0), another minimum is at (0,1.5), and three saddle points at $(\pm 0.6, 1.0)$, and (0,-0.4). A maximum is present at (0,0.5). Therefore, two channels connect the deep minima, and the upper channel contains the additional shallow minimum. We carry out two different calculations with this potential. The first calculation is performed using $\beta = 6.67$ which corresponds to low temperature, and a second at $\beta = 1.67$, which corresponds to high temperature. As in the previous example, we define the region A as the union of all points in the vicinity of the left-hand deep minimum (-1,0) such that $V(x, y) < 0.4$, and likewise for region B in the vicinity of the right-hand minimum (1,0). For both calculations we again start with a 64×64 regular mesh with points in A and B deleted and points just outside snapped to the boundaries of A and B.

We show in Fig. 4 representative isocommittor curves for the three-well potential calculated at $\beta = 1.67$. Here we see the effect of the shallow third minima in broadening the transition region where $q \approx 0.5$ as one would expect. In Fig. 5 we show the probability densities of reactive trajectories for the three-well potential for both $\beta = 1.67$ and 6.67. The major effect demonstrated here is that higher temperatures increase the density of reactive trajectories that take the lower channel; i.e., these do not need to pass through the intermediate shallow well. These results again perfectly match those reported by Metzner et al. [14]

Rate constants for both temperatures on the three-well potential are reported in Table 1, where we also report the rate constants of Metzner et al. for comparison. We observe exact agreement at high temperature, and a slight discrepancy (about 2%) at the lower temperature. Given that our approach uses many fewer degrees of freedom in solving for the committor, and that the irregular mesh we used provides a more faithful representation of the shapes of the boundaries of the A and B regions, we do not believe this slight discrepancy to be an indication that our approach is any less accurate than that of Metzner et al.

3.2. Three-dimensional examples

Satisfied that our finite-element approach is accurate in comparison to the finite-difference approach of Metzner et al. in two dimensions, we now turn to examples in three dimensions, $z \equiv (x, y, z)$, that would be impractical to attack using a regular-mesh finite-difference approach. We will illustrate several example committor and rate calculations based on a simple two-well potential:

$$V_0(x, y, z) = -3e^{-(x-3.5)^2-(y-3.5)^2-(z-3.5)^2} - 3e^{-(x+3.5)^2-(y+3.5)^2-(z+3.5)^2} \quad (8)$$

V_0 has a minimum at $(-3.5, -3.5, -3.5)$ and another at $(3.5, 3.5, 3.5)$. We consider a domain $\Omega = [-5.5, 5.5] \times [-5.5, 5.5] \times [-5.5, 5.5]$. Within this domain, we used a baseline $32 \times 32 \times 32$ cubical mesh that defines tetrahedral elements. Region A is defined as the union of all points in the vicinity of the minimum at $(-3.5, -3.5, -3.5)$ such that $V_0(x, y, z) < -2.0$, and similarly for region B in the vicinity of the minimum at $(3.5, 3.5, 3.5)$. The mesh nodes within the two regions are deleted and those just on the outside are snapped to their respective surfaces, creating the irregular mesh. We show this mesh in Fig. 6. Our mesh had 196,535 degrees of freedom, which is comparable to the number of degrees of freedom Metzner et al. used for their *two*-dimensional calculations [14], and a factor of about 600 times smaller than would be required for finite-differences on uniform mesh at the same resolution used by the previous work. (We use the same mesh and definitions of A and B in the other examples.)

Because of the symmetry of the system, we expect the $q=0.5$ isocommittor to bisect the cubic domain along the global diagonal. We show isocommittor surfaces of the potential in Eq. 8 computed at $\beta = 6.67$ in Fig. 7. Indeed, the isocommittor with $q(z) = 0.5$ is located in the middle of the cube at equal distance from the two minima. After we change from $\beta = 6.67$ to $\beta = 1.67$ we do not see any change in the behavior of the isocommittors. This reflects the fact that the reactive flux is centered on the diagonal of the cube. However, the rate constant of the $A \rightarrow B$ reaction on V_0 is of course very sensitive to temperature, as shown in Table 2.

The second example, we modify V_0 to steer reactive flux away from the diagonal, using a weak 1-D harmonic well at $y=0$:

$$\begin{aligned} V_1(x, y, z) &= -3e^{-(x-3.5)^2-(y-3.5)^2-(z-3.5)^2} - 3e^{-(x+3.5)^2-(y+3.5)^2-(z+3.5)^2} + 0.2y^2 \\ &= V_0(x, y, z) + 0.2y^2 \end{aligned} \quad (9)$$

Fig. 8, we show isocommittors for the potential in Eq. 9 calculated at $\beta = 6.67$ and 1.67. For the lower temperature ($\beta = 6.67$) we see that the isocommittor at $q = 0.5$ aligns along y . This happens because the weak attraction to $y=0$ channels reactive trajectories, resulting in isocommittors near $q = 0.5$ parallel to the y axis as trajectories must settle for moving along x and z equivalently to make reactive progress. This diffusive motion along x and z near the middle of the domain also results in a relatively slowly changing committor, and hence isocommittors at regular intervals appear more sparse in this region and more dense nearer to the reactant and product states. In the case of the higher temperature, this channeling is weaker, and the isocommittors appear more like those from the original potential without the weak well at $y = 0$. The rate constant for the $A \rightarrow B$ reaction on V_1 at high temperature is only slightly lower than that on V_0 (Table 2). Surprisingly, however, at the lower temperature, the rate on V_1 is much larger than on V_0 . This may reflect the fact that the weak harmonic well at $y = 0$ effectively reduces the dimensionality of the space in which trajectories must diffuse in order to make reactive progress, relative to the case with V_0 .

The third example illustrates how additional local minima between the reactant and product states alter the isocommittors and reaction rates. Here, we consider the potential:

$$\begin{aligned} V_2(x, y, z) &= -3e^{-(x-3.5)^2-(y-3.5)^2-(z-3.5)^2} - 3e^{-(x+3.5)^2-(y+3.5)^2-(z+3.5)^2} \\ &\quad - 3e^{-(x-1)^2-(y-1)^2-(z-1)^2} - 3e^{-(x+1)^2-(y+1)^2-(z+1)^2} \\ &= V_0(x, y, z) - 3e^{-(x-1)^2-(y-1)^2-(z-1)^2} - 3e^{-(x+1)^2-(y+1)^2-(z+1)^2} \end{aligned} \quad (10)$$

This includes two additional minima at $(-1.0, -1.0, -1.0)$ and $(1.0, 1.0, 1.0)$ of equal depth as the minima of the reactant and product states. Isocommittors computed for V_2 at $\beta = 6.67$ appear in the upper panel of Fig. 9. We see that the effect of the additional minima is to pull the isocommittors locally toward the two states and away from the middle of the domain. The rate constants for $A \rightarrow B$ on V_2 (Table 2), as on V_1 , show a significant enhancement at low temperature compared to V_0 . Here, this may also reflect the fact that the two additional minima help to define a reactive channel that pulls trajectories toward the diagonal.

As a final example, we reconsider the two-well potential V_0 by introducing a spherical obstacle of radius 3 at the center of the box. Isocommittors in this case at $\beta = 6.67$ are shown in the lower panel of Fig. 9. The obstacle represents an entropic barrier that completely blocks the reactive channel through the diagonal. The isocommittors' become more conical around the diagonal and encroach further toward the center, reflecting the fact that trajectories already on the diagonal must cover a longer distance to make reactive progress. The rate constants for $A \rightarrow B$ on this potential (Table 2) are not significantly different from the case with no obstacle.

4. Conclusions

We have shown here demonstrations of transition-path theory calculations in both two and three dimensions using the method of finite elements. Compared to previous demonstrations of TPT calculations in 2D using finite differences [14], we show the same accuracy with approximately a factor of 30 fewer degrees of freedom, which we attribute to the ability to better conform to the (arbitrary) boundaries of the reactant and product regions with a non-uniform mesh. We show the first TPT calculations in three dimensions, and demonstrate the effects of systematic complications in the 3D potential on the isocommittor foliation and $A \rightarrow B$ rate constants. We show that rates can be surprisingly sensitive to seemingly small changes in the potential that act to reduce the effective dimensionality of the space through which trajectories must diffuse in order to make reactive progress. The solution of 3D example problems supports the idea that TPT can be used in more complex systems in biology and chemistry. One example which we are currently pursuing is the case of diffusion of penetrant molecules in proteins, where the potential is defined as a free energy associated with molecule position within the protein [21], and we are interested in reaction rates between free energy minima. Finite-element-enabled TPT calculations in three (and perhaps higher) dimensions can shed light on kinetic process allowing not only calculation of rates, but also determination of statistical properties of reactive mechanisms in many diffusion-dominated problems.

Acknowledgments

Research reported in this publication was supported by the National Institutes of Health under Award Number 1R01GM100472 (CFA). We would like to thank Eric Vanden-Eijnden for useful suggestions.

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Figure 1. Isocommittor contours for the potential $V(x, y)$ of Eq. 6 with $\beta = 1$. The white region on the left is A, and on the right is B.

Figure 2.
Flux of reactive trajectories J_{AB} along the $S_{1/2}$ isocommittor for the potential $V(x, y)$ of Eq. 6 with $\beta = 1$.

Figure 3.
Contour plot of the three-well potential $V(x, y)$ defined by Eq. 7.

Figure 4. Isocommittors on the potential defined by Eq. 7 calculated at $\beta = 1.67$.

Figure 5. Contour plots of the reactive trajectory density $\rho_{AB}(z)$ with $\beta = 1.67$ (top) and $\beta = 6.67$ (bottom) on the three-well potential $V(x, y)$ defined by Eq. 7.

Figure 6.

3D finite-element mesh for the 3D potential of Eq. 8, with $32 \times 32 \times 32$ nodes except for those inside region A (sphere on lower left) and region B (sphere on upper right). Nodes just outside the two regions are snapped to the region boundaries.

Figure 7. Isocommittor surfaces of the 3D potential V_0 (Eq. 8) calculated at $\beta = 6.67$.

Figure 8. Isocommittor surfaces of the potential V_1 (Eq. 9) calculated at $\beta = 6.67$ (top) and 1.67 (bottom).

Figure 9.

Upper panel: Isocommittors at $\beta = 6.67$ for the potential V_2 (Eq. 10). Lower panel: Isocommittors at $\beta = 6.67$ for V_0 (Eq. 8) in a domain with a spherical obstacle of radius 3 at the center.

Table 1

Rate constants for the 2D potential $V(x, y)$ defined in Eq. 7 at two temperatures compared to those computed based on a finite-difference solution to the bK equation of Ref. [14].

β	k_{AB} (this work)	k_{AB} (Metzner [14])
1.67	1.91×10^{-2}	1.91×10^{-2}
6.67	9.32×10^{-8}	9.47×10^{-8}

Table 2

Rate constants for the 3D potentials $V_0(x, y, z)$ (Eq. 8), $V_1(x, y, z)$ (Eq. 9), and $V_2(x, y, z)$ (Eq. 10), and for V_0 with a spherical obstacle, at two temperatures.

β	V_0	V_1	V_2	$V_0+\text{obst.}$
1.67	1.73×10^{-3}	8.88×10^{-4}	1.60×10^{-3}	1.56×10^{-3}
6.67	1.83×10^{-8}	3.36×10^{-5}	1.23×10^{-6}	2.22×10^{-8}