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Estimating exit rate for rare event dynamical systems by extrapolation -revised version-

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1 Abstract

In this article we present an idea to speed up the sampling exit rates of metastable molecular conformations. The idea is based on flattening the energy landscape by a global transformation which decreases the depth of the minima. In this matter we create different energy surfaces in which we sample the exit rate and use them to extrapolate the exit rate for the original potential. Because of the decreased depth of the minima the sampling is computationally cheaper and also the variance of the estimators for the exit rate in the transformed energy landscape are smaller.

2 Introduction

The problem we are interested in is motivated by molecular dynamics. The question we try to answer is how long stays a molecule in a specific conformation. Since one can connect the internal energy of a molecule and its conformation we know that metastable conformations have a low internal energy. We are interested in the time

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how long a molecule stays in a certain energetic minimum. In physical terms a change of conformation is related to a big change of the internal energy of the system. We say that these conformations are metastable because the molecule will stay in the basin around this energy for a very long time until it rapidly changes into another conformation or metastable state. Since these changes do not occur very often they are very hard to observe during a simulation. They can be seen as rare events. In order to build good estimators for these rare events one has to observe them more often. This can be done by decreasing the energetic barrier which the molecule has to cross, such that one can recover the original quantities of interest.

In this article we consider an atomistic model for the molecule given by a stochastic differential equation (SDE) We will go into detail of this model later. The first observation is that this equation consists of two parts one deterministic and one stochastic. It is obvious that the metastability is mainly caused by the deterministic part of this SDE if the stochastic part is rather small. So to speed up the sampling one has to change the deterministic part in a clever way so that the metastability is not so metastable any more. But in general it is very hard to find these minima which cause the metastability because of the high dimensionality of the problem. This problem is called the sampling problem.

In order to decrease the metastability we transform the energy landscape of the original system such that all main characteristic are approximately preserved but the metastability is weaker than before. As a global transformation we will use a convolution with a Gaussian kernel. The idea to use the convolution approach to find the global minimum of a energy landscape was introduced by [Piela et al., 1989] and further investigated by [Kostrowicki and Piela, 1991] and [Weber, 1999]. In this article we connect the convolution approach with a direct sampling of the exit rate. So we speed up the sampling of the underlying dynamics by lowering the depth of the minima without a priori knowledge of the location of metastable regions. The intuition of this method is that the convolution first smooths out the small minima in which a trajectory or simulation can get stuck in and second decreases the depth of the minima such that the metastability is decreased and thus the sampling gets be easier.

Because of the linearity of the convolution our approach is also applicable for many particle systems with distance dependent energy landscape. It is not quite

clear how the convolution will have an impact on the metastability. But if there is an impact on the metastable region and this is what our first experiments show one could use this strategy to build a multilevel Monte Carlo method for molecular dynamics.

Furthermore our approach does not rely on a specific simulation algorithm and is extendable to all existing simulation algorithms which are used in practice. We will show in detail of how to apply the convolution for a many particle system later in a theoretical setting and give a short impression how the metastability is influenced. In our examples we will also consider different algorithms for simulating the dynamical system. One big advantage of our approach is that it is applicable even if there are entropic barriers since the convolution is working directly on the energy landscape.

Of course there many algorithms in the literature that try to do speed up the sampling in a similar manner for example metadynamics [Laio and Parrinello, 2002], flat histogram approach [Wang and Landau, 2001] or adaptive biasing force [Darve and Pohorille, 2001]. The main idea of this ideas is the bias the sampling adaptively which is different to our approach. Other ideas to overcome this sampling problems are for example high temperature sampling or parallel tempering [Hansmann, 1997]. One could see our approach in a quite similar way because the smoothing can be seen as a solution of the heat equation. But we do not have a time evolution in mind by using the smoothing. We will go into detail of this discussion later. Another very interesting algorithm to speed up the sampling are splitting techniques like adaptive multilevel splitting [Cerou and Guyader, 2006] or [Elber and West, 2010]. Here one introduces intermediate sampling goals which are easier to reach. The sampling between these intermediate steps can be parallelized and so the overall sampling become a lot faster. A very nice overview with a lot of mathematical analysis of all these different methods can be found in [Lelièvre et al., 2010]. More mathematical tools to describe metastability can be found in [Lelièvre, 2011] and a mathematical analysis of simulation tools can be found here [Lelièvre, 2015].

In general it is very hard to determine in a system with a many interacting particles what is the reason of the metastability. This is why many methods only work on a low dimensional projection of the high dimensional system namely the

effective coordinates. How one can find those reactive coordinates is a very active field of research e.g. [Zhang et al., 2016]. The idea presented in this paper can be applied in either the case that the effective coordinates are known or in the high dimensional system with distance dependent force field. We focus on the low dimensional case here and only comment on the high dimensional setting since this is ongoing research.

The paper is organised as follows. First we describe the considered model in more detail. Then we introduce the convolution for the specific energy landscape we are looking at. In the third part we derive a formula for the extrapolation. The extrapolation is done with an exponential regression which is based on the Kramers' law. After introducing all necessary theory we give two examples in different dimensions. The last part is giving a partial differential equation point of view into the stated problem.

3 Modelling of metastable molecules

We will model the position of the atoms in the molecule with a stochastic process. The model is an overdamped Langevin equation and satisfies

$$dX_t = -\nabla V(X_t)dt + \sqrt{2\beta^{-1}}dB_t \quad X_0 = x. \quad (1)$$

Here $X \in \mathbb{R}^{3n}$ are the positions of the atoms, n is the number of atoms in the molecule, $V : \mathbb{R}^{3n} \rightarrow \mathbb{R}$ is the potential energy, B_t is a standard Brownian motion, β is $1/k_B T$ with k_B being the Boltzmann constant and T being the temperature and t is the time. With X^x we denote the process which started in x . This kind of model will stay a very long time in a minimum since it has a negative gradient form only perturbed by a Brownian motion. Since the equation (1) has not closed form solution we have to solve this equation numerically. For this we use a Euler Maruyama discretization with a small time step c.f. [Higham, 2001]. In general this model allows us to sample area around the minimum very well while the transition into another minimum will happen very rarely at least we have to simulate the SDE for quite some time to see this transition.

Let the metastable region S be a bounded domain in \mathbb{R}^n with smooth boundary.

We denote the exit time to leave the domain S of a stochastic process which started in x by

$$\tau_S^x = \inf\{t > 0, X_t^x \notin S\}. \quad (2)$$

The quantity of interest is the mean first exit time of the metastable set mathematically speaking $\mathbb{E}[\tau_S^x]$. Furthermore we know that this problem can be expressed as the following PDE problem c.f. [Øksendal, 2003]

$$-\nabla V(x)\nabla f(x) + \beta^{-2}\nabla^2 f(x) = -1 \quad x \in S \quad (3)$$

$$f(x) = 0 \quad x \in \delta S \quad (4)$$

with $f(x) = \mathbb{E}[\tau_S^x | X_0 = x]$, ∇ is the gradient and ∇^2 is the Laplacian. The solution of the PDE can be expressed with a Feynman Kac formula e.g. [Øksendal, 2003] and that sampling the exit time of the SDE is solving the PDE for one point $X_0 = x$. To solve the PDE we can sample the exit time of the above SDE due to this connection. So investigating the stability of our molecules corresponds to solving a PDE in the dimension of the molecule or sampling the SDE. Since the solution of the PDE is not available for high dimensional problems we have to use the sampling of the SDE. Sampling the solution of this PDE by the Feynman Kac formula is also quite expensive because of the metastability of the underlying stochastic process. The metastability will also cause a high variance for the estimator for the stopping time.

Since we are interested in the exit time of the stochastic process we consider this situation as a double well situation. We have one well in which the process starts and everything which is outside of this metastable region will be seen as one well. We assume that there is one minimal point which will be passed by the trajectory the significant saddle point z . We will call the minimum x . So the height of the barrier is defined by

$$\Delta E = V(z) - V(x). \quad (5)$$

We will further assume that there is only a weak thermal fluctuation namely

$$\frac{k_B T}{\Delta E} \ll 1. \quad (6)$$

The relevant time scale of the exit event to happen scales exponentially in $\frac{1}{k_B T}$

$$\tau_S^x = \nu^{-1} \exp\left(\frac{\Delta E}{k_B T}\right). \quad (7)$$

In the literature it is common to define now the reaction rate $\kappa = \tau^{-1}$ which is the rate with which the molecules leave the well. The reaction rate is given by

$$\kappa = \nu \exp\left(-\frac{\Delta E}{k_B T}\right). \quad (8)$$

The difficulties to sample this rate arise by the dependence on the barrier heights. In general a lower barrier leads to a smaller exit time and thus it is easier to sample. Thus the convolution causes the event to occur more frequently. In general it is necessary to have the global information where the minimum which causes the metastability is located. But due to the high dimensionality only local information by sampling are accessible. So it is very hard to decrease the metastability a priori. If the minima is known there are methods to speed up the sampling for example [Hartmann and Schütte, 2012].

4 Decreasing the Metastability by Convolution

The main idea to level the depth of the minima is to smooth the energy landscape. So we can solve the problem by solving some easier related problems and extrapolate to solve the real problem.

This approach is motivated by [Piela et al., 1989]. In this article a transformation is proposed to destabilize any potential well. We assume that $V : \mathbb{R}^n \rightarrow \mathbb{R}$ be a function in \mathcal{C}^2 . Then they use as a transformation

$$V^{[1]} = V(x) + \xi V''(x) \quad \text{for } \xi > 0. \quad (9)$$

Under this transformation the inflection point does not under go any change since $V'' = 0$ for this point but the convex part of the function goes up and the concave part goes down. So the existing extrema are destabilized. A repetition of this transformation leads to a connection to the heat equation see [Piela et al., 1989] or

[Kostrowicki and Piela, 1991] for details. This is why we use the general solution of the heat equation as the global transformation. It is given by

$$V(x, \lambda) = \int_{\mathbb{R}^n} V(y) \exp\left(-\frac{(x-y)^2}{2\lambda^2}\right) dy. \quad (10)$$

From now on we will use $V(x, \lambda)$ to denote the convolution of the function V . We smooth the energy landscape for a fixed parameter λ and use the result as a new energy landscape. We then sample the exit rate in this smoothed energy landscape. We repeat this procedure a couple of time for a decreasing sequence of λ . In this way we can get information about the underlying system in a cheaper way because the metastability is not that strong but it is not completely vanished. We use this information to extrapolate the real exit time or rate.

In the literature one finds that this is the solution of the heat equation $\nabla^2 V(x, \lambda) = \frac{\partial}{\partial \lambda} V(x, \lambda)$ where ∇^2 is the Laplacian and λ is the 'time' [Evans, 2010]. But as we explained above we are not interested in a λ evolution of the underlying energy landscape. We will only solve this equation for fixed parameter λ and sample the exit time in the resulting energy landscape. This is why we call λ the smoothing parameter.

Remark: Since λ is converging to 0 and not to ∞ one could get the impression the we are interested in solving the heat equation backwards in 'time'. This is not the case. We solve the heat equation for a sequence of fixed λ which converge to 0. But we use the original potential as the boundary condition. We set $V(x, 0) = V(x)$. Solving the heat equation backwards in time is actually a hard inverse problem c.f [Evans, 2010].

In general solving the heat equation in a high dimension is also very challenging. This is why we restrict ourself to a distance dependent energy landscape. In this situation we can use the linearity of the convolution to calculate the convolution and thus the solution of the heat equation in high dimensions. Because of this our approach can be applied in a many particle system with distance dependent energy landscape. The idea of smoothing function for global optimization is not new and was developed by [Kostrowicki and Piela, 1991, Moré and Wu, 1995]. Because of the intense research in this field there are different special cases in which the convolution can be expressed in a much simpler way as (10). One case is if V is

a polynomial then the convolution can be expressed as a finite sum of polynomials. This makes the convolution extremely efficient and also numerical applicable in many particle systems with a distance dependent interaction potential. We give here a short summary of the theory of global optimization for polynomials first following [Kostrowicki and Piela, 1991] for deriving the method and then following [Moré and Wu, 1995] for the numerical treatment.

We assume first that the energy is the sum of the different atom-atom-interactions. Further we assume that these interactions are distance dependent and can be expressed in a polynomial way. For this kind of energy landscapes we can now use the linearity of the convolution. Thus we can calculate the convolution of every atom-atom-interaction itself in order to calculate the convolution of the energy landscape. The assumption that every atom-atom-interaction is distance dependent reduces the dimension of the energy landscape. Each atom-atom-interaction is now only a function from \mathbb{R} to \mathbb{R} .

We assume that the underlying distance dependent interactions for atoms i and j $V_{ij} : \mathbb{R} \rightarrow \mathbb{R}$ has following structure

$$V_{ij}(x) = \sum_{i=0}^d a_i x^i. \quad (11)$$

Since we know that the convolution is the fundamental solution of the diffusion equation and the atom-atom-interactions are polynomials of order d we can write

$$\begin{aligned} V_{ij}(x, \lambda) &= \exp(\lambda \nabla^2) V_{ij}(x) = \prod_{j=1}^d \exp(\lambda (\partial / \partial x_j^2)) V_{ij}(x) \\ &= \sum_i a_i \prod_{j=1}^d \exp(\lambda (\partial / \partial x_j^2)) x^i \\ &= \sum_i a_i \sum_{k=0}^{\lfloor n/2 \rfloor} \frac{n!}{k!(n-2k)!} \left(\frac{\lambda}{2}\right)^k k x^{n-2k}. \end{aligned}$$

Using the linearity of the convolution we can express the energy landscape as

$$V(x) = \sum_{i>j}^n V_{ij}(x) = \sum_{i>j}^n H_{ij}(r_{ij}(x)) \quad (12)$$

with $H_{ij} : \mathbb{R}^3 \rightarrow \mathbb{R}$ being the potential function for a certain distance and $r_{ij}(x) : \mathbb{R}^3 \times \mathbb{R}^3 \rightarrow \mathbb{R}$ the distance between two points in \mathbb{R}^3 defined by $r_{ij}(x) = \|x_i - x_j\|_2$.

Due to this structure the can express the convolution as

$$V(x, \lambda) = \sum_{i>j}^n H_{ij}(r_{ij}(x), \lambda)$$

where $H_{ij}(r_{ij}(x), \lambda)$ denotes the convolution of the atom-atom interaction.

5 Extrapolation

Since we are interested in simulating the mean first exit time of a stochastic process from a certain region we can assume Kramers' law to be true. The situation we are interested is that the molecule is in a minimum and will leave this at one point. This is why we consider this as a double well situation. In order to leave the basin around the minimum the stochastic process will have to cross the minimum on the boundary. From this we can then define a rate.

We use the definition from above

$$\mathbb{E}[\tau_S^x] \approx \nu e^{\left(-\frac{\Delta E}{k_B T}\right)}. \quad (13)$$

It is known from literature e.g. [Berglund, 2013] that in the double well potential situation it is possible to prove

$$\lim_{\beta \rightarrow 0} \beta \log \mathbb{E}[\tau_S^x] = V(z) - V(x). \quad (14)$$

We note that the convolution of a polynomial is again a polynomial with the same degree as before c.f [Piela et al., 1989]. The above formula show that the convoluted polynomial is also a polynomial new variable. So we assume that we can

approximate the difference of the saddle point and the minimum with a polynomial. So we approximate

$$\begin{aligned}
\log(\mathbb{E}^x[\tau_S^x(\lambda)]) &\approx V(z, \lambda) - V(x, \lambda) \\
&= \sum_{k=0}^{\lfloor n/2 \rfloor} \frac{n!}{k!(n-2k)!} t^k z^{n-2k} - \sum_{k=0}^{\lfloor n/2 \rfloor} \frac{n!}{k!(n-2k)!} t^k x^{n-2k} \\
&= \sum_{k=0}^{\lfloor n/2 \rfloor} \frac{n!}{k!(n-2k)!} (z-x)^{n-2k} t^k
\end{aligned} \tag{15}$$

and see that the exit time of the transformed dynamics is changing in a polynomial fashion in t . We will use this in order to extrapolate the exit time for the unperturbed potential. For this we sample the exit rate for different fixed values of t . From (15) we know that the log exit time depends polynomial on λ . To determine the coefficients in front of λ we use the calculated data and solve a least square problem. To find the reaction rate we use the definition by bringing the logarithm on the other side and inverting it. This kind of regression is known in literature as logarithmic regression c.f. [Guest, 2012].

So the idea of the method is to create less metastable energy landscape in which we can sample the exit time easier. This information is then used to extrapolate the exit time in the original energy landscape. In order to extrapolate we use a logarithmic regression based on Kramers' law. We will give an example in the next section.

6 Example 1D

In order to show how our method works we will give a 1D example of a particle moving in a energy landscape over time. We are interested in the mean first exit time of the particle leaving a basin around the minimum.

The position of the particle $X_t \in \mathbb{R}$ at time t is given by (1). For our toy example the potential V is

$$V(x) = 8x^4 - 44/3x^3 + 2x^2 + 11/3x + 1. \tag{16}$$

The plain Monte Carlo sampling gives an estimator of the exit time which has a very high variance and needs a long time to compute. The Monte Carlo sampling gives $\mathbb{E}[\tau_S^x] \approx 1.6958E + 03$ with variance $Var[\tau_S^x] = 2.9471E + 06$. We have calculated 100 trajectories and set the parameter $\sqrt{2\beta^{-1}} = 0.6$. This computation took 227.260852 seconds. The estimator for the stopping time has a confidence interval $[1.4238e+03, 2.1019e+03]$.

According to the above formula the convolution of this polynomial is given by

$$V(x, \lambda) = V(x) + 48\lambda^4 + (2 - 44x + 48x^2)\lambda^2. \quad (17)$$

We now perturb the dynamics with three different λ s and sample the expected exit time in these perturbed landscapes. We then use this sampled exit times to approximate the different rates for the different perturbed energy landscapes. We use these different rates as input data for our logarithmic regression.

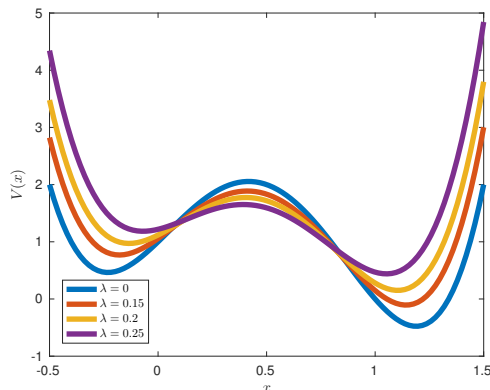


Figure 1: The landscapes for the different perturbation parameters.

Now we repeat this calculation for the perturbed dynamics and extrapolate. For sampling 3 times 100 trajectories with $\lambda = 0.15, 0.2, 0.25$ in the perturbed dynamics we needed 177.579312 seconds. The estimators are $\mathbb{E}[\tau_S^x(0.15)] \approx 528.6703$ with variance $Var[\tau_S^x(0.15)] = 3.2286E + 05$, $\mathbb{E}[\tau_S^x(0.2)] \approx 158.7054$ with variance $Var[\tau_S^x(0.2)] = 0.2507E+05$ and $\mathbb{E}[\tau_S^x(0.25)] \approx 31.3443$ with variance $Var[\tau(0.25)] = 0.0081E + 05$. These estimators have a smaller variance compared to the MC estimator in the original dynamics.

We want to use this data to extrapolate the rate for the unperturbed dynamics.

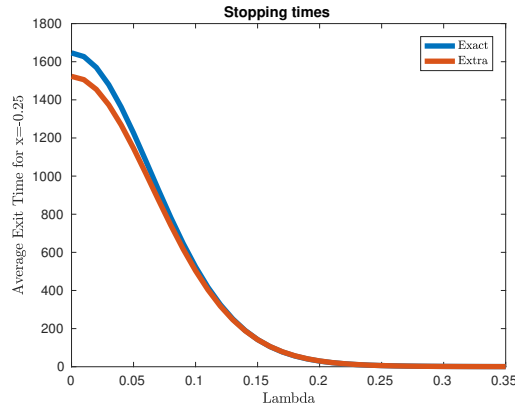


Figure 2: PDE solution for different parameters λ in $[0,0.35]$ at $x=-0.25$ and the extrapolation which is calculated of the sampled data from the smoothed dynamics.

For this we have to know approximately the dependency of the parameter λ on the mean first exit time. In order to show that the method is working quite well we calculate the corresponding PDE problems (4) for $\lambda \in [0, 0.25]$. We then compare the PDE solution with our sampled solution. Because of the assumption that the dependency of the exit time on the parameter λ we use exponential regression to approximate the real solution for $\lambda = 0$.

We clearly see that the extrapolation is very bad for high values of λ but since we are interested in the value at $\lambda = 0$ this is not of our bigger concern.

Here we see that the extrapolated solution and the real PDE solution fit quite well in the extrapolation region. We also see that the exponential dependency on λ based on Kramer's law is quite reasonable. Since we are extrapolating the exit time we have an error. The error for this extrapolation is compare to the PDE solution is $|\mathbb{E}[\tau_S^x(0)]_{PDE} - \mathbb{E}[\tau_S^x(0)]_{sampling}| = 123.1427$. So one can clearly see that our estimator is in the confidence interval of the MC estimator.

Here in this example we can calculate the approximation error which is $err = |\kappa_{PDE} - \kappa_{sampling}| = 4.9108e - 05$. All together we have a very good approximation of the exit rate with less computational cost.

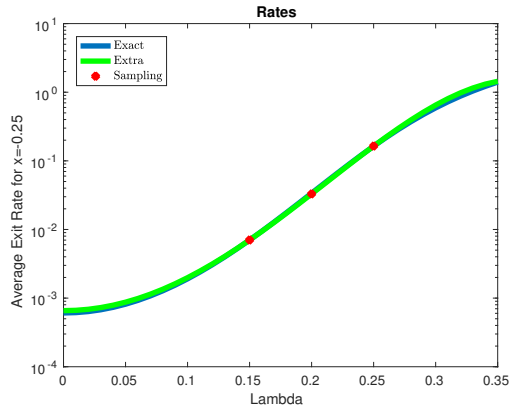


Figure 3: Semilog plot of PDE solution for different parameters λ in $[0,0.35]$ (blue) and extrapolated solution (green) with the two calculated data points for $\lambda = 0.15$, $\lambda = 0.2$ and $\lambda = 0.25$ (red) for $x = -0.25$.

7 Mean first exit time and λ dependency

The smoothing of the potential influences the mean first exit time of the stochastic process. To extrapolate the real exit time we used Kramers' law and used the explicit formula for the convolution of polynomials. This is only an approximation. To express the dependency of the smoothing parameter we can use the PDE stated above. This could be used to find a better extrapolation technique which would give rise build a better estimator. But as we will see the underlying equation is even harder to solve than the original problem. For this we express the exit time in terms of a PDE Feynman Kac formula and the infinitesimal generator. Thus we would have to solve the following boundary value problem on some domain $\Omega \in \mathbb{R}^d$ with a smooth boundary

$$\begin{aligned} \mathcal{L}(x, \lambda)f(x, \lambda) &= -1 & x \in \Omega \\ f(x; \lambda) &= 0 & x \in \delta\Omega \end{aligned}$$

where the generator of the convoluted potential is depending on λ and can be written as

$$\mathcal{L}(x, \lambda)f(x, \lambda) = -\nabla V(x; \lambda)\nabla f(x, \lambda) + \frac{1}{2}\Delta f(x, \lambda). \quad (19)$$

This equation is a second order linear elliptic PDE.

In order to find the λ dependency of the solution we could just calculate the derivative of the boundary value problem.

$$\begin{aligned}
& \frac{\partial}{\partial \lambda} \mathcal{L}(x, \lambda) f(x, \lambda) = -1 \\
& \Leftrightarrow -\frac{\partial}{\partial \lambda} \nabla_x V(x, \lambda) \nabla_x f(x, \lambda) + \frac{\partial}{\partial \lambda} \frac{1}{2} \Delta_x f(x, \lambda) = 0 \\
& \Leftrightarrow -\nabla_x \frac{\partial}{\partial \lambda} V(x, \lambda) \nabla_x f(x, \lambda) - \nabla_x V(x, \lambda) \frac{\partial}{\partial \lambda} \nabla_x f(x, \lambda) + \frac{1}{2} \Delta_x \frac{\partial}{\partial \lambda} f(x, \lambda) = 0 \\
& \Leftrightarrow \mathcal{L}(x, \lambda) \frac{\partial}{\partial \lambda} f(x, \lambda) = \nabla_x \frac{\partial}{\partial \lambda} V(x, \lambda) \nabla_x f(x, \lambda) \\
& \Leftrightarrow \mathcal{L}(x, \lambda) \frac{\partial}{\partial \lambda} f(x, \lambda) = \nabla_x \Delta_x V(x, \lambda) \nabla_x f(x, \lambda)
\end{aligned}$$

This result shows that the mean first exit time in case of smoothing the potential is changing the most in the direction of the curvature. Thus it fits the observation from Kramer's law that a smaller curvature in the stable direction decreases the mean first exit time c.f. [Berglund, 2013]. Since we are interested in the exit rate we leave the investigation in the solution of this PDE for future work.

8 Discussion and Conclusion

In this article we have shown a method of how to decrease a metastability in a structural way without a priori knowledge where the metastability is located. We have used a convolution as a global transformation for the energy landscape of the dynamics. We used the results coming from the convoluted potential to extrapolate the quantity of interest in the unperturbed dynamics by a logarithmic regression based in Kramer's law. We compared our 1D result to the real PDE solution for the exit rate of a metastable domain. The results show that the method is working quite reasonable in comparison of a Monte Carlo estimator. We could decrease the computational cost and also get results which are not too far from the truth. But since we use an extrapolation technique the result is highly susceptible to sampling errors.

The extrapolation is based on Kramer's law which is totally valid in the con-

sidered situation. But there is a way to generalize the extrapolation by the PDE formulation of the problem. Our approaches to solve the PDE problem failed so far. It would be very interesting to investigate further in this direction since the solution of this PDE problem would give rise to a better extrapolation technique. But since the original problem is quite hard to solve our expectations are not pitched very high. A perturbation analysis in λ does not give the desired result. Even the analysis for the 1D ODE problem turns out to be quite hard.

We only commented on the possibility to extend our approach to a high dimensional system. Our first results look very promising but experiments have to be done in order to give a reliable answer to all the open questions.

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