Conditional Averaging for Diffusive Fast-Slow Systems: A Sketch for Derivation

Jessika Walter[1] and Christof Schütte[2]

[1] Department of Mathematics, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland. jessika.walter@epfl.ch
[2] Department of Mathematics and Computer Science, Free University Berlin. schuette@math.fu-berlin.de

Summary. This article is concerned with stochastic differential equations with disparate temporal scales. We consider cases where the fast mode of the system rarely switches from one almost invariant set in its state space to another one such that the time scale of the switching is as slow as the slow modes of the system. In such cases descriptions for the effective dynamics cannot be derived by means of standard averaging schemes. Instead a generalization of averaging, called conditional averaging, allows to describe the effective dynamics appropriately. The basic idea of conditional averaging is that the fast process can be decomposed into several 'almost irreducible' sub-processes, each of which can be treated by standard averaging and corresponds to one metastable or almost invariant state. Rare transitions between these states are taken into account by means of an appropriate Markov jump process that describes the transitions between the states. The article gives a derivation of conditional averaging for a class of systems where the fast process is a diffusion in a double well potential.

1 Introduction

In complex system modeling, one often finds mathematical models that consist of differential equations with different temporal and spatial scales. As a consequence, mathematical techniques for the elimination of some of the smallest scales have achieved considerable attention in the last years; the derivation of reduced models by means of averaging techniques [FW84, AKN93, SV85, Kif02, Fre78, Kif01, Kif92, BLP78], homogenization techniques [BS97, Bor98, BS99], or stochastic modelling [MTV01, Mor65, Zwa73, MTV02] may serve as typical links to this discussion.

This article is concerned with stochastic differential equations where the fast mode of the system rarely switches from one almost invariant set in its state space to another one such that the time scale of the switching is as slow as the slow modes of the system. The basic idea is that the fast process then can be decomposed into several 'almost irreducible' subprocesses, each

of which corresponds to one metastable or almost invariant state. To quantify this principle, the rare transitions between these states are described by means of the expected exit times that can be used to parametrize a Markov chain model mimicking the transitions between the states.

The Averaging Principle

Let $V : \mathbf{R}^m \times \mathbf{R}^n \to \mathbf{R}$ and consider the SDE

$$\dot{x}^\epsilon = -D_x V(x^\epsilon, y^\epsilon) + \sigma \dot{W}_1 \tag{1.1}$$

$$\dot{y}^\epsilon = -\frac{1}{\epsilon} D_y V(x^\epsilon, y^\epsilon) + \frac{\varsigma}{\sqrt{\epsilon}} \dot{W}_2, \tag{1.2}$$

with $\epsilon > 0$ and $W_j \, (j = 1, 2)$ standard Brownian motions. If we assume $\sigma = \varsigma$, the above SDE is well-known as the Smoluchowski equation. For $\epsilon \ll 1$, this system consists of a fast variable, y, and a slow one, x. Under suitable conditions on V (cf. [FW84]), averaging completely characterizes the limit x^0 of the slow dynamics x^ϵ for $\epsilon \to 0$ by an averaged SDE

$$\dot{x}^0 = -\int_{\mathbf{R}^n} D_x V(x^0, y) \, \mu_{x^0}(y) \mathrm{d}y + \sigma \dot{W}_1, \tag{1.3}$$

where μ_x denotes the invariant density of the fast dynamics for fixed x:

$$\mu_x(y) = \frac{1}{Z_x} \exp(-\frac{2}{\varsigma^2} V(x, y)), \quad Z_x = \int_{\mathbf{R}^n} \exp(-\frac{2}{\varsigma^2} V(x, y)) \, \mathrm{d}y, \tag{1.4}$$

which is assumed for each x to be the unique invariant density.

Metastable Fast Dynamics & Exit Times

Let us now assume that the fast dynamics exhibit *metastable states* , i.e., that the effective dynamics in the fast degrees of freedom (DOF) can be described by (rare) jumps between these sets, while in between the jumps the dynamics remains within one of these metastable subsets. Under this condition averaging may fail to reproduce the effective dynamics of the original system, mainly for the following reason: The averaging principle is based on the fact that the fast DOF completely explore the accessible state space before any change in the slow DOF happen; this can fail to hold if metastability is observed in the fast dynamics; in particular there is some subset of the accessible state space from which the fast motion will most probably exit only on some scale of order ord(1) or even larger. Let us make this rigorous by introducing the *mean exit time* for the process y_x^ϵ from one of the metastable subsets, where y_x^ϵ is governed by the SDE (1.2) for fixed x. If we assume the existence of two metastable sets $\mathbf{R}^n = B_x \cup B_x^c$ with $B_x \cap B_x^c = \emptyset$, the mean exit time $\bar{\tau}_x^\epsilon(y)$ from B_x is the expected value of the first exit time $\tau_x^\epsilon(y)$ of the process y_x^ϵ from B_x started at $y_x^\epsilon(t = 0) = y$, which is defined by

$$\tau_D^\epsilon(y) = \inf\left\{t \in \mathbf{R}^+ : \int_0^t \mathbf{1}_{D^c}(y_x^\epsilon(s))\,\mathrm{d}s > 0,\, y_x^\epsilon(0) = y\right\} \qquad (1.5)$$
$$\tau_x^\epsilon(y) = \tau_{B_x}^\epsilon(y)$$

where D^c denotes the complement of the set D.

Although we would expect that exit times depend on the starting point, i.e., $y_x^\epsilon(0) = y$, it can be shown that there do exist subsets D, for which the exit time is basically independent for all states $y \in D$. Especially for a metastable collection of sets D_i of the Smoluchowski dynamics, in the limit of vanishing noise intensity we are able to assign a first exit time $\bar{\tau}^\epsilon$ to an entire subset D_i rather than to single points $y \in D_i$, see [HMS02, SH02, SH00]. The question of the asymptotic behaviour of the mean exit time for vanishing noise term ς has been discussed in detail by, for example, Freidlin and Wentzell in [FW84], from which the following result is taken (up to some slight modifications tailored to (1.1)&(1.2)) :

Theorem 1.1 ([FW84, Thm. 4.1 of Chap. 4], [SH00]). *Let the potential $V(x,\cdot)$ be twice continuously differentiable, let $y_{\min}$ be one of its local minima, and B_x a metastable subset with sufficiently smooth boundary ∂B_x containing $y_{\min}$ in its interior, but containing no other local minimum of $V(x,\cdot)$ within its interior. Without loss of generality we may assume that $V(x, y_{\min}) = 0$. Suppose that y_0 is the unique point on the boundary ∂B_x with*

$$V_{\mathrm{bar}}^x \;=\; V(x,y_0) \;=\; \min\{V(x,y) : y \in \partial B_x\}.$$

The mean exit time $\bar{\tau}_x^\epsilon$ for the process y_x^ϵ with $y_x^\epsilon(0) \in B_x$ then satisfies

$$\lim_{\varsigma\to 0} \varsigma^2 \ln \frac{\bar{\tau}_x^\epsilon}{\epsilon} \;=\; 2\,V_{\mathrm{bar}}^x.$$

As we are interested in the case where the averaging principle fails, let us have a closer look on the relation between the time scale of the fast motion and the exit times from metastable subsets in the fast DOF. The result of the above theorem tells us two things: First, rapid mixing of the fast DOF ($\bar{\tau}_x^\epsilon \ll 1$) can be realized by fixing ς and the potential energy function; then we are always able to find an ϵ small enough such that averaging yields a good approximation of the effective dynamcis. Second, if we decrease ς or increase the potential energy barrier, the smallness parameter ϵ has to be chosen exponentially small such that the averaged system still is a satisfactory approximation. If we want to study the effect of metastabilities in the fast motion, it is natural to relate $V_{\mathrm{bar}}^x/\varsigma^2$ to ϵ so that the exit times from metastable sets vary on a timescale of order ord(1), that is, so that

$$\bar{\tau}_x^\epsilon \;\simeq\; C(x)\,\epsilon\,\exp(\frac{2}{\varsigma^2}V_{\mathrm{bar}}^x) \;=\; \mathrm{ord}(1), \qquad (1.6)$$

where $C(x)$ denotes the subexponential pre-factor that necessarily depends on x. Subsequently, the relation symbol $\simeq$ denotes asymptotic equality and ord is used to indicate comparison to the same order.

Conditional Averaging

The scaling assumption (1.6) on ς represents a modeling step which will lead towards the derivation of the *principle of conditional averaging* that may yield an appropriate reduced model in cases where the ordinary averaging scheme fails: Since we observe rapid sampling of the invariant density μ_x in each of the metastable subsets, we propose to average over each of these sets alone and to couple the resulting systems by a Markovian switching process which describes the flipping behaviour between the metastable sets. Then, in the case of (at most) two metastable subsets $B_x^{(1)}$ and $B_x^{(2)}$ for fixed x, the conditionally averaged limit dynamics has the form

$$\dot{x}^0 = -\int D_x V(x^0, y)\, \mu_{x^0}^{(\tilde{I}(t,x^0))}(y)\, \mathrm{d}y \; + \; \sigma \dot{W}_1, \tag{1.7}$$

$$\mu_x^{(1)}(y) = \frac{1}{\mu_x(B_x^{(1)})} \mu_x(y) \mathbf{1}_{B_x^{(1)}}(y), \quad \mu_x^{(2)}(y) \; = \; \frac{1}{\mu_x(B_x^{(2)})} \mu_x(y) \mathbf{1}_{B_x^{(2)}}(y), \tag{1.8}$$

with $\tilde{I}(t,x)$ denoting the Markov chain model with state space $\mathbf{S} = \{1,2\}$, where the rates of the jumps reproduce the transition rates of the original system. In [SW*03] explicit values for the generating rate matrix are obtained by using the most dominant eigenvalue $\lambda_1^\epsilon(x) < 0$ of the generator of the fast dynamics (1.2) together with the weights $\mu_x(B_x^{(i)})$ of the metastable states on the fiber of the fast state space.

Approach

The authors of [SW*03] derived the limit dynamics (1.7) in terms of multiscale analysis of the Fokker-Planck equation, but there is no rigorous proof. The goal of this paper is to obtain a deeper insight into the nature of the conditionally averaged system.

Subsequently we consider the SDE

$$\dot{x}^\epsilon = -D_x V(x^\epsilon, y^\epsilon) \; + \; \sigma \dot{W}_1 \tag{1.9}$$

$$\dot{y}^\epsilon = -\frac{1}{\epsilon} D_y V(x^\epsilon, y^\epsilon) \; + \; \frac{\varsigma}{\sqrt{\epsilon}}\, \dot{W}_2, \tag{1.10}$$

with $\epsilon > 0$ and W_j $(j = 1, 2)$ standard Brownian motions. We assume the fast dynamics (1.10) to exhibit metastable states $B_x^{(1)}$ and $B_x^{(2)}$ so that the exit times from the metastable subsets happen on a time scale of order ord(1) or even larger.

Under these assumptions, we may take advantage of the methodology employed to extract the effective dynamics (1.7). This result (each metastable subset of the fast dynamics is connected to one averaged equation) motivates the idea to construct a system of fast-slow equations which allows for the incorporation of temporal fast scale effects in a natural way: the fast motion

within one metastable subset is approximated by an irreducible subprocess that corresponds to a stochastic differential equation. The result is quantified by the parametrization of a Markov chain model $I(t,x)$ that controls the switches from one (sub)process to the other according to the transition rates between the metastable subsets of the original dynamics. We thus obtain a stochastic process where the slow variable at each instance is coupled to one of two fast variables but where a stochastic switching process controls the switches from one fast variable to the other. Then, under appropriate assumptions on the potential V and for ς small, a good approximation of the original dynamics (1.9)&(1.10) may be given by

$$\dot{x}^\epsilon = -D_x V(x^\epsilon, y^\epsilon) \,+\, \sigma \dot{W}_1 \tag{1.11}$$

$$\dot{y}^\epsilon = -\frac{1}{\epsilon}\,\omega^{(I(t,x^\epsilon))}(x^\epsilon)\big(y^\epsilon - m^{(I(t,x^\epsilon))}(x^\epsilon)\big) \,+\, \frac{\varsigma}{\sqrt{\epsilon}}\dot{W}_2, \tag{1.12}$$

where $\omega^{(i)}(x)$ denotes curvature of $V(x,\cdot)$ in the potential minima of the metastable subsets $B_x^{(i)}$ for $i = 1, 2$, and $m^{(i)}(x)$ the respective minima.

A reduced system in the slow variable solely is then obtained by applying the well-known averaging results from [Pap76, Kur73, FW84] to each of these stochastic differential equations. Denoting $\mu_x^{\mathrm{OU}(i)}$ the (unique) invariant density of the process defined by (1.12) for fixed x and $I(t,x) = i$, the averaged system then has the form

$$\dot{x}^0 = -\int D_x V(x^0, y)\, \mu_{x^0}^{\mathrm{OU}(I(t,x^0))}(y)\,\mathrm{d}y \,+\, \sigma\, \dot{W}_1, \tag{1.13}$$

where the $\mu_x^{\mathrm{OU}(i)}$ denote the invariant densities of the Ornstein-Uhlenbeck (OU) processes (1.12) (for these we have explicit expressions).

That is, we derive a description of the effective dynamics in two steps. In a first step we replace the fast dynamics in each of the metastable subsets by appropriate OU processes which are coupled to each other by a Markovian switching process that reproduces the transition times between $B_x^{(1)}$ and $B_x^{(2)}$ of the original process. In a second step we simply use the invariant density of the OU processes in order to obtain the reduced system (1.13) by means of standard averaging. Recalling the conditionally averaged system

$$\dot{x}^0 = -\int D_x V(x^0, y)\, \mu_{x^0}^{(\tilde{I}(t,x^0))}(y)\,\mathrm{d}y \,+\, \sigma \dot{W}_1, \tag{1.14}$$

with $\mu_x^{(i)}$, $i = 1, 2$ defined by (1.8), it is of considerable interest to compare the effective dynamics obtained by the two different approaches, namely (1.13) on the one hand and (1.14) on the other. Note that the jump processes I that corresponds to (1.13) will be derived in a different way than the jump process $\tilde{I}$ of (1.14). However, we will see that I and $\tilde{I}$ are comparable in a certain way.

2 System under Consideration

Subsequently we study the SDE (1.1)&(1.2), where the following basic assumptions about the potential $V = V(x, y)$ are made:

Assumption 2.1 (i) $V \in \mathcal{C}^\infty(\mathbf{R}^{m+1})$;
(ii) $V(x, \cdot)$ *is a double-well potential for all* $x \in \mathbf{R}^m$ *with two local minima at* $y = m^{(1)}, m^{(2)}$ *and one local maximum at* $y = y_0$ *with* $m^{(1)} < y_0 < m^{(2)}$; *to point out the dependence on* x *we will also write* $m^{(i)}(x)$, $i = 1, 2$.
(iii) *the position of the saddle point does not depend on* x, *without loss of generality we may assume* $y_0(x) = 0$ *for every* x;
(iv) *the extrema are non-degenerate uniformly in* x, *i.e., for* $i = 1, 2$

$$D_{yy}V(x, m^{(i)}) = \omega^{(i)}(x) \geq \tilde{\omega}^{(i)} > 0, \; D_{yy}V(x, y_0) = -\omega_0(x) \leq -\tilde{\omega}_0 < 0.$$

Therefore, for fixed x, the particle spends a 'long time' in one basin (=potential well), then quickly undergoes a transition into the other basin, in which it spends another 'long time', and so on. The condition $y_0(x) = 0$ implies that for every $x \in \mathbf{R}^m$ the locations of the two basins do not depend on x such that the natural decomposition of the entire state space into metastable subsets is simply given by $B^{(1)} \cup B^{(2)}$, where[3]

$$B^{(1)} = \{(x, y) \in \mathbf{R}^{m+1} \mid y < 0\}, \quad B^{(2)} = \{(x, y) \in \mathbf{R}^{m+1} \mid y > 0\}. \tag{2.1}$$

The double-well potentials may serve as toy models mimicking a larger system whose potential energy surface presents several basins corresponding to metastable states.

As outlined in the introduction, we proceed in two steps to derive a reduced model for the effective slow variable dynamics. The key point for the first step is rooted in the design of $V(x, \cdot)$ which already suggests that an averaging procedure should incorporate metastabilities in the fast dynamics that are induced by the double-well structure: If the noise level in the fast equation is small, the diffusion sample paths of the fast process are located near the local minima of the potential wells, and transitions between the two potential wells can be considered as rare events. Then, the diffusion can be decomposed into two sub-processes

$$(x^\epsilon(t), y^\epsilon_{(i)}(t)) = (x^\epsilon(t), y^\epsilon(t))\, \mathbf{1}_{B^{(i)}}(x^\epsilon(t), y^\epsilon(t)), \qquad i = 1, 2,$$

and a two-state Markov chain $I(t, x)$ mimicking the transitions between $B^{(1)}$ and $B^{(2)}$ which happen along the y dynamics and thus depend on the position of the slow one. Our approach is based on a quantification of the rates at

[3] In [SW*03], the metastable decomposition for fixed x is defined by the zero z of the second eigenfunction $u_1(x, \cdot)$ of the fast dynamics generator. It is shown in [Wal05] that the zero z of $u_1(x, \cdot)$ actually is approximated by the saddle point of the potential $V(x, \cdot)$.

which the fast process moves between the two subsets on the one hand and, on the other, on an appropriate replacement of the almost irreducible fast (sub)processes by appropriately chosen OU-processes evolving independently of each other. Thus, the most basic questions we have to address concern the fast process (1.2) for fixed slow variable x, which is done in Sect. 3. In so doing, we basically have to decompose the fast process into the *intra-well* small fluctuations of the diffusion around the potential minima and the *inter-well* dynamics of the diffusion. For both parts we then obtain by means of small noise asymptotics basic results that are then picked up in order to assemble in Sect. 4 the full dynamics approximation (1.11)&(1.12) including the slow variables motion.

The second step of the approach relies on the small noise approximation and is based upon averaging results that can be found in a vast number of articles. A simple application of a theorem in [FW84] then provides us in Theorem 4.1 with the reduced dynamics (1.13). In the Appendix we show how the averaged dynamics can be derived by using multiscale asymptotics of the Fokker-Planck equation corresponding to the small noise approximation (1.11)&(1.12). In Sect. 5 we compare the averaged dynamics (1.13) to the conditionally averaged system (1.7).

Another important concern of the approach is the relationship between the noise level ς in the fast diffusion and the smallness parameter ϵ: The fast diffusions inter-well and intra-well approximations are justified for vanishing noise ς, so that we suggest $\varsigma \to 0$ to zero as $\epsilon \to 0$. Our considerations will result in a coupling rule for ς and ϵ that incorporates the asymmetry of the double-well potential. In Lemma 3.5 the choice of the noise level ς is coupled to ϵ as well as the slow variable x so that the exit times from the metastable subsets of the fast dynamics vary on a time scale of ord(1) or larger resulting in (1.6).

Biomolecules operate at ambient temperature and solvent condition, and most biomolecular processes can only be understood in a thermodynamical context. Therefore, most experiments on biomolecular systems are performed under the equilibrium conditions of constant temperature T, particle number, and volume. Statistical mechanics tells us that statistical ensembles of molecular systems with internal energy V under these circumstances should be modelled by the equilibrium density $\exp(-\beta V)$. For the Smoluchowski system (1.1)&(1.2) this means to enforce $\sigma = \varsigma$ (for fixed ϵ), such that experiments can be arranged with inverse temperature $\beta = -2/\varsigma^2$. However, if the noise intensity ς depends on the slow variable x, it is hardly possible to interpret the model system in the context of equilibrium ensembles. Therefore our later Lemma 3.5 is not satisfactory as its application removes the system under consideration far away from the mathematical modeling of biological processes. Thus, the investigations have to be extended to situations where ς depends on ϵ solely. This will be done in Appendix B.

3 Basic Results on Fast Process

Let Assumption 2.1 be valid in all of the following. For small noise intensity ς, the process y^ϵ corresponding to the Smoluchowski equation (1.2) for fixed x is almost decomposable into two subprocesses $y^\epsilon_{(1)}$, $y^\epsilon_{(2)}$, each attracted to a minimum $m^{(i)}(x)$, $i = 1, 2$ of the function $V(x, \cdot)$.

Thus, we consider the fast motion $y^\epsilon_x(t)$ for fixed slow variables $x \in \mathbf{R}^m$:

$$\dot{y}^\epsilon_x \;=\; -\frac{1}{\epsilon} D_y V(x, y^\epsilon_x) \;+\; \frac{\varsigma}{\sqrt{\epsilon}}\, \dot{W}_2, \tag{3.1}$$

and distinguish between the two different regions of attraction $O^{(1)}_x$ and $O^{(2)}_x$ where $O^{(i)}_x$ is an open subset of $B^{(i)}_x$ with $m^{(i)}(x)$ in its interior. The subsets $B^{(1)}_x$ and $B^{(2)}_x$ are defined by the potential energy barrier:

$$B^{(1)}_x \;=\; \{y \in \mathbf{R} : \, y \,<\, y_0(x)\}, \quad \text{and} \quad B^{(2)}_x \;=\; \{y : \, y \,>\, y_0(x)\}, \tag{3.2}$$

with $y_0(x) = 0$ denoting the saddle point of the potential $V(x, \cdot)$.

In the limit of small noise level ς, Theorem 3.1 below will provide us for small ς with an approximation of the fast dynamics (3.1) restricted to a single metastable set by a simple Ornstein-Uhlenbeck (OU) process mimicking the rapid mixing in each of these subsets prior to exiting. There is no information in these stationary limits about the possible jumps from the branch $y = m^{(1)}(x)$ to the branch $y = m^{(2)}(x)$, or conversely. To address the question of the overall behaviour of the stationary state, we will consider in Theorem 3.3 and Corollary 3.4 below the new discrete-space process on $\{m^{(1)}(x), m^{(2)}(x)\}$ assigning information about the inter-well dynamics.

3.1 Approximation of Intra-well Dynamics

For vanishing noise intensity ς, in each of the subsets $O^{(i)}_x$ the fast diffusion will consist of small fluctuations around the potential minima $m^{(1)}(x)$ and $m^{(2)}(x)$, respectively. The drift term in (1.2) can now be expanded in a Taylor series with respect to y. Taylor-expansion of $D_y V(x, \cdot)$ around $m^{(i)}(x)$, $i = 1, 2$ gives

$$D_y V(x, y) = D_{yy} V(x, m^{(i)}(x))\, (y - m^{(i)}(x)) + \mathcal{O}(|y - m^{(i)}(x)|^2), \tag{3.3}$$

where we have used $D_y V(x, m^{(i)}(x)) = 0$. For y sufficiently close to $m^{(i)}(x)$, this provides us with an approximation of the SDE (3.1):

$$\dot{y}^\epsilon_{\mathrm{OU}(i)} \;=\; -\frac{1}{\epsilon} \omega^{(i)}(x)\, (y^\epsilon_{\mathrm{OU}(i)} - m^{(i)}(x)) \;+\; \frac{\varsigma}{\sqrt{\epsilon}}\, \dot{W}_2, \tag{3.4}$$

with $\omega^{(i)}(x)$, $i = 1, 2$ denoting the curvature of $V(x, \cdot)$ in $m^{(i)}(x)$, see Assumption 2.1. The solution of the stochastic differential equation (3.4) is known as a process of Ornstein-Uhlenbeck type, or OU process for short. To distinguish

it from the 'decoupled' processes $y^\epsilon_{(i)} \in O^{(i)}_x$, $i = 1, 2$ that originate from (3.1) we denote it $y^\epsilon_{\mathrm{OU}(i)}$ for $i = 1, 2$. We omit the index for the fixed variable x.

The quality of the approximation will depend on how close the original motion stays in the vicinity of the minima $m^{(i)}(x)$, $i = 1, 2$. This can be made more precise by applying the small noise expansion method for stochastic differential equations. The basic assumption of asymptotically expanding the solution process $y^\epsilon_{(i)}$ for $i = 1, 2$ into powers of the noise intensity ς leads to a reduction of the equation (3.1) into a sequence of time-dependent OU processes. Mostly the first order is quite adequate and amounts to a linearisation of the original equation about the deterministic solution. The reader may refer to [Gar85], where it is shown that the procedure yields a convergent power series of ς. Tailored to the approach (3.4), the procedure yields a power series

$$y^\epsilon_x \;=\; y^\epsilon_{\mathrm{OU}(i)} \;+\; \varsigma^2\, R(\varsigma),$$

where the remainder $R(\varsigma, t)$ is the solution of an SDE and stochastically converges to $r(0, t)$. That is, it exists a limiting SDE with solution $R(0, t)$ such that for all $T \in \mathbf{R}^+$

$$\text{st-}\lim_{\varsigma\to 0}\Big\{\sup_{t\in[0,T]} |R(\varsigma, t) - R(0, t)|\Big\} \;=\; 0,$$

where st-$\lim_{n\to\infty} \xi_n = \xi$ denotes $\lim_{n\to\infty} \mathbf{P}\{|\xi_n - \xi| \geq \delta\} = 0$ for every $\delta > 0$ and a sequence $\{\xi_n\}$ of random variables.

Theorem 3.1 ([Gar85, Chapters 6.2, 4.3.7]). *Let y^ϵ_x be given by the SDE (3.1) where ϵ and x are chosen arbitrary but fixed. Suppose that the process starts for some $i = 1, 2$ in an open subset $O^{(i)}_x$ of $B^{(i)}_x$ containing $m^{(i)}(x)$ in its interior, and let $y^\epsilon_{\mathrm{OU}(i)}$ be the solution of (3.4). Then we have for all $T \in \mathbf{R}^+$*

$$|y^\epsilon_x(t) \;-\; y^\epsilon_{\mathrm{OU}(i)}(t)| \;=\; \mathcal{O}(\varsigma^2),$$

where $\mathcal{O}$ is understood as being satisfied with respect to stochastic convergence uniformly in $t \in [0, T]$ (as $\varsigma \to 0$).

Remark 3.2. As the OU process (3.4) is ergodic, the stationary density $\mu^{\mathrm{OU}(i)}_x$ is simply given by the Gaussian with mean $m^{(i)}(x)$ and variance $\varsigma^2/(2\omega^{(i)}(x))$. Aiming at a comparison of $\mu^{\mathrm{OU}(i)}_x$ and $\mu^{(i)}_x$, as defined by (1.8) and (1.4), it is shown in [Wal05] that

$$\lim_{\varsigma\to 0}(\mu^{\mathrm{OU}(i)}_x - \mu^{(i)}_x) = 0 \qquad \text{in } L^1(\mathbf{R}).$$

Note that we do not get convergence in L^∞.

3.2 Asymptotics of Inter-well Dynamics

To give a picture of the essential dynamics in the fast state space, we consider the statistics of the exit times from the metastable sets and approximate the transition events of the diffusion by jump times of an associated continuous-time, finite state-space Markov chain (the double-well potential implies a two-state Markov chain). In principle, one can compute the exit times via direct numerical simulation. The approximated exit times can then be used to construct a transition rate matrix $\mathcal{Q}$ that generates stochastic matrices $\exp(t\mathcal{Q})$ for all times $t > 0$. However, the computational effort of estimating the expected exit times can be avoided by resorting to the rich literature on the derivation of asymptotic formula for the jump times that are strongly connected to the dominant spectrum of the corresponding generator, see e.g. [Pav02, BGK02, BE*02, HKN04]. Whereas the first papers only gave the asymptotic behaviour of the logarithm of expected exit times (cf. Theorem 1.1), in [Pav02, BGK02, BE*02] one also finds estimates for the prefactor.

For small noise intensity ς, transitions between the potential wells occur at Kramers' time that is given up to exponential order by $\exp((2/\varsigma^2)\Delta V)$, where ΔV is the potential barrier that the process must cross to reach the other potential well. The first exit time of the Markov process $y_x^\epsilon(t)$ from D started at $y_x^\epsilon(0) = y$ as defined in (1.5) measures only exits that happen for some non-null time interval and depends on the realization of the Markov process.

We are interested in the transition times between the metastable subsets $B_x^{(1)}$ and $B_x^{(2)}$. If the noise intensity does not vanish, they are not identical to the exit times $\tau^\epsilon_{B_x^{(i)}}$, $i = 1, 2$. Instead we have to modify the metastable subsets slightly such that a (small) neighbourhood around the saddle point is included, i.e., we consider $B_x^{(1)} + \delta = (-\infty, \delta)$ and $B_x^{(2)} - \delta = (-\delta, \infty)$ instead with $\delta > 0$ being a small parameter. Recall that $O_x^{(i)} \subset B_x^{(i)}$, $i = 1, 2$ are some regions of attraction (excluding a neighbourhood around the saddle point and including the potential minima, that is, $m^{(i)}(x) \in O_x^{(i)}$ for $i = 1, 2$). Then, the first exit times from $B_x^{(1)} + \delta$ and $B_x^{(2)} - \delta$ are basically independent for all starting points $y \in O_x^{(1)}$ and $y \in O_x^{(2)}$, respectively. This enables us to assign the expected exit times from $B_x^{(1)} + \delta$ and $B_x^{(2)} - \delta$ to the entire subsets $O_x^{(1)}$ and $O_x^{(2)}$ rather than to single points.

In the next theorem, we denote the expected transition times from $B_x^{(i)}$ to $B_x^{(j)}$ with $i \neq j$ by $\mathcal{T}^\epsilon_{i\to j}(x)$, $i = 1, 2$.

Theorem 3.3 ([Pav02, BGK02]). *The metastable inter-well transitions of the dynamics (3.1) are given by the following precise asymptotic estimates*[4] *as* $\varsigma \to 0$*:*

[4] We emphasize again that in the following we will speak of (metastable) transition times between $B_x^{(1)}$ and $B_x^{(2)}$ or *metastable* exit times instead of exit times from

$$\mathcal{T}^{\epsilon}_{1\to 2}(x) \;=\; \mathbf{E}_{y\in O_x^{(1)}}[\tau^{\epsilon}_{B_x^{(1)}+\delta}] \simeq \epsilon\,\frac{2\pi}{\sqrt{\omega^{(1)}(x)\,\omega_0(x)}}\,\exp\big(\frac{2}{\varsigma^2}V^{(1)}_{\rm bar}(x)\big), \quad (3.5)$$

$$\mathcal{T}^{\epsilon}_{2\to 1}(x) \;=\; \mathbf{E}_{y\in O_x^{(2)}}[\tau^{\epsilon}_{B_x^{(2)}-\delta}] \simeq \epsilon\,\frac{2\pi}{\sqrt{\omega^{(2)}(x)\,\omega_0(x)}}\,\exp\big(\frac{2}{\varsigma^2}V^{(2)}_{\rm bar}(x)\big), \quad (3.6)$$

where $V^{(1)}_{\rm bar}(x) = V(x,y_0) - V(x,m^{(1)}(x))$ *and* $V^{(2)}_{\rm bar}(x) = V(x,y_0) - V(x,m^{(2)}(x))$ *denote the left and right potential barriers.*

In [Pav02] the result is obtained in terms of the largest eigenvalue $\neq 0$ of the associated infinitesimal generator, which corresponds (apart from suitable weights) to the inverse of the expected diffusion exit times. The connection will be discussed in the next corollary.

Our goal is to build a two-state Markov chain and view inter-well transitions of the diffusion as simple jumps of this chain. Correspondence between the diffusion and the chain will be established by exploiting that exit times are asymptotically almost exponential random variables which is shown in [SH02, HMS02]. Relying on this fact, we define the jump rates for the reducing Markov-chain as the reciprocal of the expected exit times $\mathcal{T}^{\epsilon}_{i\to j}(x)$, $i \neq j$, which provides us with the rate matrix $\mathcal{Q}^{\epsilon}_x$ being defined by

$$\mathcal{Q}^{\epsilon}_x := \begin{pmatrix} -1/\mathcal{T}^{\epsilon}_{1\to 2}(x) & 1/\mathcal{T}^{\epsilon}_{1\to 2}(x) \\ 1/\mathcal{T}^{\epsilon}_{2\to 1}(x) & -1/\mathcal{T}^{\epsilon}_{2\to 1}(x) \end{pmatrix}, \qquad \mathcal{Q}^{\epsilon}_x \begin{pmatrix} 1 \\ 1 \end{pmatrix} = 0. \quad (3.7)$$

The following corollary shows that the invariant density of the reducing Markov chain is asymptotically given by the weights over the potential wells.

Corollary 3.4. *Let us denote the (assumed positive and unique) invariant density of* $\mathcal{Q}^{\epsilon}_x$ *by* $\psi(x) = (\psi_1(x), \psi_2(x))$*, that is,*

$$\psi(x)\,\mathcal{Q}^{\epsilon}_x = 0 \qquad \textit{with} \quad \psi_1(x) + \psi_2(x) \;=\; 1.$$

Then we find that $\psi(x)$ *is given asymptotically as* $\varsigma \to 0$ *by* $(\mu_x(B_x^{(1)}), \mu_x(B_x^{(2)}))$*, explicitly,*

$$\psi_i(x) \simeq \mu_x(B_x^{(i)}), \qquad i = 1,2. \quad (3.8)$$

The rate matrix $\mathcal{Q}^{\epsilon}_x$ *can be expressed in terms of the invariant density by introducing the second eigenvalue* $\lambda^{\epsilon}_1(x)$ *of the infinitesimal generator that corresponds to the diffusion (3.1). In so doing, we asymptotically obtain*

$$\mathcal{T}^{\epsilon}_{1\to 2}(x) \;\simeq\; \frac{1}{|\lambda^{\epsilon}_1(x)|\mu_x(B_x^{(2)})} \quad \textit{and} \quad \mathcal{T}^{\epsilon}_{2\to 1}(x) \;\simeq\; \frac{1}{|\lambda^{\epsilon}_1(x)|\mu_x(B_x^{(1)})},$$

and, conclusively,

$B_x^{(i)}$, $i = 1,2$, for the asymptotic estimates are given for the mean values of the first exit times from $B_x^{(1)} + \delta$ and $B_x^{(2)} - \delta$ with $\delta > 0$, where the precise choice of the parameter δ is not important.

$$\mathcal{Q}_x^\epsilon \simeq |\lambda^\epsilon(x)| \begin{pmatrix} -\mu_x(B_x^{(2)}) & \mu_x(B_x^{(2)}) \\ \mu_x(B_x^{(1)}) & -\mu_x(B_x^{(1)}) \end{pmatrix}. \tag{3.9}$$

Proof. To establish (3.8), we simply have to verify

$$\frac{\mu_x(B_x^{(1)})}{\mu_x(B_x^{(2)})} \simeq \frac{\mathcal{T}_{1\to 2}^\epsilon(x)}{\mathcal{T}_{2\to 1}^\epsilon(x)}. \tag{3.10}$$

To this end, we may apply Laplace's method of asymptotic evaluation of integrals depending on the parameter ς. According to Laplace , we easily get the asymptotic estimates in the small noise limit

$$\frac{\mu_x(B_x^{(1)})}{\mu_x(B_x^{(2)})} = \tag{3.11}$$
$$\sqrt{\frac{\omega^{(2)}(x)}{\omega^{(1)}(x)}}\, \exp\Big(-\frac{2}{\varsigma^2}\big(V(x,m^{(1)}(x)) - V(x,m^{(2)}(x))\big)\Big)\,\big(1+\mathcal{O}(\varsigma)\big),$$

and, by using $V(x,m^{(1)}(x)) - V(x,m^{(2)}(x)) = -(V_{\rm bar}^{(1)}(x) - V_{\rm bar}^{(2)}(x))$ together with (3.5)&(3.6), we end up with (3.10). The informations about the behaviour of $\lambda_1^\epsilon(x)$ are again based on the results of Pavlyukevich in [Pav02] who derived the asymptotic formula of $\lambda_1^\epsilon(x)$ in the small noise limit by expanding λ_1^ϵ into a power series. For *asymmetric* double-well potential this gives the accurate asymptotics for $\lambda_1^\epsilon(x)$ in terms of quantities concerning the *shallow* well of the potential:

$$|\lambda_1^\epsilon(x)| = \frac{1}{\epsilon}\frac{\sqrt{\omega^{(1)}(x)\omega_0(x)}}{2\pi}\, \exp\big(-\frac{2}{\varsigma^2}V_{\rm bar}^{(1)}(x)\big)\,\big(1+\mathcal{O}(\varsigma)\big),$$

where we assume without loss of generality

$$V_{\rm bar}^{(1)}(x) = \min\{V_{\rm bar}^{(1)}(x), V_{\rm bar}^{(2)}(x)\}.$$

This result has been derived for asymmetric double-well potentials, such that the weight on the deep well is approximately 1, that is, $\mu_x(B_x^{(2)}) \approx 1$. This obviously is fulfilled for small values of ς due to $\mu_x(B_x^{(2)}) \to 1$ as $\varsigma \to 0$. However, to include the case of symmetric double-well potentials (then we have $\mu_x(B_x^{(2)}) = \mu_x(B_x^{(1)}) = 0.5$) we prefer to rewrite the asymptotics of λ_1^ϵ according to

$$|\lambda_1^\epsilon(x)|\,\mu_x(B_x^{(2)}) = \frac{1}{\epsilon}\frac{\sqrt{\omega^{(1)}(x)\omega_0(x)}}{2\pi}\, \exp\big(-\frac{2}{\varsigma^2}V_{\rm bar}^{(1)}(x)\big)\,\big(1+\mathcal{O}(\varsigma)\big) \tag{3.12}$$

which allows us due to (3.5) to express the transition rate $1 \to 2$ asymptotically by $|\lambda_1^\epsilon|\mu_x(B_x^{(2)})$. Using the asymptotic estimates (3.11) and (3.12)

provides us with an alternative formulation for the asymptotics of $\lambda_1^\epsilon(x)$ by using the curvature in the deep well (and the weight over the shallow well):

$$|\lambda_1^\epsilon(x)|\,\mu_x(B_x^{(1)}) = \frac{1}{\epsilon}\frac{\sqrt{\omega^{(2)}(x)\omega_0(x)}}{2\pi}\,\exp\big(-\frac{2}{\varsigma^2}V_{\mathrm{bar}}^{(2)}(x)\big)\,\big(1+\mathcal{O}(\varsigma)\big).$$

3.3 Freezing Metastable Transitions

We complete the analysis of the fast process (3.1) with establishing a relationship between the smallness parameter ϵ and the noise level ς such that the scaling assumption (1.6) is fulfilled. According to Theorem 3.3 this can explicitly be realized only if $\exp(-(2/\varsigma^2)\Delta V)$ scales like ϵ. Here, ΔV denotes the barrier that has to be crossed, that is, $\Delta V = V_{\mathrm{bar}}^{(1)}(x)$ or $\Delta V = V_{\mathrm{bar}}^{(2)}(x)$. A natural way of realizing (1.6) was to rescale the potential energy barrier in an appropriate manner (see [Wal05]).

However, due to the asymptotic investigations in Theorem 3.3 we leave the potential untouched and rescale the diffusion ς instead. An easy calculation leads to the following lemma.

Lemma 3.5. *To freeze the metastable transition times on a time scale* $t \geq \mathrm{ord}(1)$ *for every* x *as* $\epsilon \to 0$ *it is convenient to set*

$$\varsigma = \varsigma(\epsilon, x) = \left(\frac{2\min\{V_{\mathrm{bar}}^{(i)}(x)\mid i=1,2\}}{\ln(K/\epsilon)}\right)^{1/2}, \qquad K > 0. \tag{3.13}$$

Remark 3.6. In Lemma 3.5 we actually have to use the minimum of the two barriers $V_{\mathrm{bar}}^{(1)}$, $V_{\mathrm{bar}}^{(2)}$: Replacing $\min\{V_{\mathrm{bar}}^{(i)}(x)\}$ by $V_{\mathrm{bar}}^{(2)} = (1+\delta)V_{\mathrm{bar}}^{(1)}$ for $\delta > 0$ would lead to $\mathcal{T}_{1\to 2}^\epsilon = \mathrm{ord}(\epsilon^\delta)$. According to Corollary 3.4, the need for using the minimal barrier is equally expressed by demanding that the second eigenvalue $\lambda_1^\epsilon(x)$ asymptotically is part of the dominant spectrum.

As outlined in Sect. 2, it is of considerable interest to study how to avoid coupling of the diffusion ς to x and still obtain large time conformational changes in the asymptotic limit $\epsilon \to 0$. Based upon Lemma 3.5, the following considerations will lead to meaningful conclusions (a short description is given in Appendix B) that are strongly connected to results obtained by the approach via multiscale asymptotics with disparate transition scales (see [Wal05, Chapter 3]): Depending on the noise intensity σ in the slow variable dynamics (1.1), the x trajectory will stay with overwhelming probability in a bounded domain $D(\sigma)$ of its state space[5]; if we choose $V_{\mathrm{bar}}^{\mathrm{small}}$ according to the rule

[5] Note that σ is not related to ς, and we do not demand for small values of σ. However, it should be clear that a choice of $V_{\mathrm{bar}}^{\mathrm{small}}$ could depend on the actual size of σ. This becomes more clear by considering Figures 6.5 and B.1. Therefore, we write $D = D(\sigma)$ for the bounded region.

$$V_{\text{bar}}^{\text{small}} = \min\{V_{\text{bar}}^{(i)}(x) \mid x \in D(\sigma),\ i = 1, 2\},$$

and set

$$\varsigma(\epsilon) = \left(\frac{2V_{\text{bar}}^{\text{small}}}{\ln(K/\epsilon)}\right)^{1/2}, \qquad K > 0, \tag{3.14}$$

we expect the metastable transitions to happen on a time scale $t \geq \text{ord}(1)$. If the potential energy barriers outside the domain $D(\sigma)$ are smaller than $V_{\text{bar}}^{\text{small}}$, the particle will for very small ϵ instantly jump over the barrier once it has reached the complement of $D(\sigma)$. Then, the time of the metastable transitions will be somehow connected to the expected exit time of the x dynamics from $D(\sigma)$. The above idea is justified by rigorously examining the asymptotics of the metastable transition times considered in the entire state space. Tailored to exemplary situations we outline the procedure in Appendix B.

4 Derivation of Reduced Dynamics

We return to the dynamics (1.1)&(1.2) and use the results of the preceding section for the design of a small noise approximation of the original process. The approximated system is then used in Theorem 4.1 as the basic system for the application of standard averaging theorems resulting in the reduced slow variable dynamics.

Small Noise Approximation

In all of the following let (x^ϵ, y^ϵ) be the solution of the SDE (1.1)&(1.2).

Exact jump process.

As a first step let us introduce the process $\hat{I}$ that describes the jumps between the metastable sets in y-direction as given by the original dynamics:

$$\hat{I}(t) = 1 + \mathbf{1}_{B^{(2)}_{x^\epsilon(t)}}(y^\epsilon(t)). \tag{4.1}$$

With this defined, let us denote by $(\hat{x}^\epsilon_{\text{OU}}, \hat{y}^\epsilon_{\text{OU}})$ the random process determined by

$$\dot{x} = -D_x V(x, y) + \sigma \dot{W}_1 \tag{4.2}$$

$$\dot{y} = -\frac{1}{\epsilon}\,\omega^{(\hat{I}(t))}(x)\big(y - m^{(\hat{I}(t))}(x)\big) + \frac{\varsigma}{\sqrt{\epsilon}}\dot{W}_2, \tag{4.3}$$

Now, suppose that the initial points are chosen such that $(x^\epsilon(0), y^\epsilon(0)) = (\hat{x}^\epsilon_{\text{OU}}(0), \hat{y}^\epsilon_{\text{OU}}(0)) = (x, y)$.

According to Theorem 3.1 we obtain for any $x, y, T > 0$ and $\epsilon > 0$ that the process $(x^\epsilon(t), y^\epsilon(t))$, $t \in [0, T]$ of the original dynamics and the random process $(\hat{x}^\epsilon_{\mathrm{OU}}(t), \hat{y}^\epsilon_{\mathrm{OU}}(t))$ get arbitrarily close to each other for $\varsigma \to 0$.

However, we will not concentrate on the rigorous mathematical justification of this result, mainly for reasons given in the next paragraph.

Approximate jump process.

This result may be very nice. However, it has the crucial disadvantage that we will never have the process $\hat{I}$ without knowing the actual solution of the original process. Therefore, we replace the jump process $\hat{I}$ by its approximate version I as constructed above. Obviously, this will prevent us from being able to construct any kind of *pathwise* convergence. However, it will finally allow to construct an approximate dynamics that is explicit in the sense that it does not depend on any knowledge about the original process. To this end, we denote by $(x^\epsilon_{\mathrm{OU}}, y^\epsilon_{\mathrm{OU}})$ the random process determined by

$$\dot{x} = -D_x V(x, y) \, + \, \sigma \dot{W}_1 \tag{4.4}$$

$$\dot{y} = -\frac{1}{\epsilon}\, \omega^{(I(t,x))}(x)\big(y - m^{(I(t,x))}(x)\big) \, + \, \frac{\varsigma}{\sqrt{\epsilon}} \dot{W}_2, \tag{4.5}$$

with $I(t, x) \in \mathbf{S} = \{1, 2\}$ denoting the x-dependent Markov chain model whose transition rate matrix $\mathcal{Q}^\epsilon_x = (q_{ij})_{i,j}$ is given by its entries

$$\begin{aligned} q_{11}(x) &= -q_{12}(x), \qquad\qquad q_{22}(x) \, = \, -q_{21}(x), \\ q_{12}(x) &= \frac{1}{\epsilon} \frac{\sqrt{\omega^{(1)}(x)\omega_0(x)}}{2\pi} \exp(-\frac{2}{\varsigma^2} V^{(1)}_{\mathrm{bar}}(x)), \\ q_{21}(x) &= \frac{1}{\epsilon} \frac{\sqrt{\omega^{(2)}(x)\omega_0(x)}}{2\pi} \exp(-\frac{2}{\varsigma^2} V^{(2)}_{\mathrm{bar}}(x)). \end{aligned} \tag{4.6}$$

Again, suppose that the initial points are chosen such that $(x^\epsilon(0), y^\epsilon(0)) = (x^\epsilon_{\mathrm{OU}}(0), y^\epsilon_{\mathrm{OU}}(0)) = (x, y)$ and $I(t = 0, x) = i$ for $(x, y) \in B^{(i)}$.

According to Theorems 3.1 and 3.3 and Corollary 3.4 we can expect for any $x, y, T > 0$ and $\epsilon > 0$ to obtain a good approximation of $(x^\epsilon(t), y^\epsilon(t))$, $t \in [0, T]$ by the random process $(x^\epsilon_{\mathrm{OU}}(t), y^\epsilon_{\mathrm{OU}}(t))$ whenever the noise level ς in the fast equation is small enough.
We will call the dynamics (4.4)&(4.5) in the following *small noise approximation* or *OU approximated dynamics*.

Averaging

In Theorem 4.1 we finally arrive at the reduced slow variable system by applying standard averaging theorems to the small noise approximation (4.4)&(4.5) where the transition rates of the jump process $I(t, x)$ are given by (4.6).

Theorem 4.1 ([FW84, Chapter 7]). *Let $(x^\epsilon_{\mathrm{OU}}, y^\epsilon_{\mathrm{OU}})$ be given by (4.4)&(4.5) and denote by $x^0(t)$ the solution of the differential equation*

$$\dot{x} = -\int D_x V(x,y)\, \mu_x^{\mathrm{OU}(I(t,x))}(y)\, \mathrm{d}y \;+\; \sigma\, \dot{W}_1, \tag{4.7}$$

where $\mu_x^{\mathrm{OU}(i)}$ is the (unique) invariant density of the process defined by (3.4) for fixed x. Then for any $T > 0$ and $\varsigma > 0$ we have

$$\text{st-}\lim_{\epsilon \to 0} \{ \sup_{t \in [0,T]} |x^\epsilon_{\mathrm{OU}}(t) - x^0(t)| \} \;=\; 0.$$

Subsequently, we refer to the slow variable dynamics (4.7) as the *OU averaged dynamics*. In Appendix A we use multiscale asymptotics of the corresponding Fokker-Planck equation to derive the OU averaged dynamics from the small noise approximation.

5 Comparison to Conditional Averaging

To complete the discussion and re-establish reference to the conditionally averaged system (1.7) we finally examine its closeness to the OU averaged dynamics (4.7). In so doing, we basically compare the behaviour in the asymptotic limit $\varsigma \to 0$ of

1. the drift term in (4.7) and (1.7) for fixed $\tilde{I}(t,x) = I(t,x) = i$;
2. the corresponding transition chains $\tilde{I}$ and I that control the switches between $i = 1$ and $i = 2$.

First, let us consider the transition chain $\tilde{I}(t,x)$ of the conditionally averaged system (1.7) as given in [SW*03]. There, the transition rates of the jump process $\tilde{I}$ are defined by the rate matrix

$$\tilde{\mathcal{Q}}_x = |\lambda_1^\epsilon(x)| \begin{pmatrix} -\mu_x(B_x^{(2)}) & \mu_x(B_x^{(2)}) \\ \mu_x(B_x^{(1)}) & -\mu_x(B_x^{(1)}) \end{pmatrix}, \tag{5.1}$$

where $\lambda_1^\epsilon(x)$ is the second eigenvalue of the infinitesimal generator of the diffusion (1.2) that is assumed to be of order ord(1). We compare the entries in (5.1) to the transition rates q_{ij} of the jump process $I(t,x)$ corresponding to the OU averaged dynamics that are defined in (4.6). Exploiting the asymptotic results of Corollary 3.4 and under a certain additional assumption, the transitions rates q_{ij} are asymptotically equal to the rates of $\tilde{Q}_x$. The additional assumption that has to be fulfilled concerns the metastable decomposition as derived by applying conditional averaging: In [SW*03], the limit dynamics are derived by *projecting the ensemble dynamics of the original system onto the subspace spanned by the dominant spectrum* of the infinitesimal generator $\mathcal{L}_x$ of (1.2). Then, the metastable decomposition $B_x^{(1)}$ and $B_x^{(2)}$ will be defined in

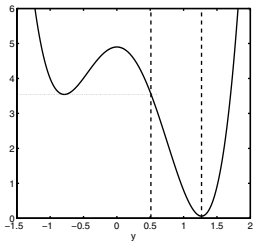

Fig. 5.1. Asymmetric double-well potential. Any decomposition defined by a point z_* that is situated between the dashed lines leads to asymptotically wrong results if the decomposition is used for the conditionally averaged dynamics.

terms of the second eigenfunction $u_1(x,\cdot)$ of $\mathcal{L}_x$ and not by the saddle point of the potential $V(x,\cdot)$ as is done in (3.2). Thus, for the definition of $\tilde{Q}$ we have to use

$$B_x^{(1)} = \{y : u_1(x,y) < 0\} \quad \text{and} \quad B_x^{(2)} = \{y : u_1(x,y) > 0\},$$

where we can assume that $B_x^{(1)}$ is the left subset. It should be clear that the zero z of $u_1(x,\cdot)$ must be somewhere between the two potential minima $m^{(1)}$ and $m^{(2)}$, and in fact, it is only a small step from using results in [Pav02] to show that z asymptotically (as $\varsigma \to 0$) approaches the saddle point $y_0(x)$, cf. [Wal05]. The attentive reader may convince himself that it the result is of crucial importance, as other choices of the zero z between the potential minima may lead to fatal approximation errors (not only for the transition rates but also for the drift term), compare illustration in Fig. 5.1.

Having obtained the asymptotic equality as $\varsigma \to 0$ of the jump rates of $\tilde{I}$ and I, we still have to compare the drift terms in (4.7) and (1.7) for fixed $\tilde{I}(t,x) = I(t,x) = i$. The terms vary for fixed x in the probability density that is used to obtain the averaged force on the slow variable x. We apply standard Laplacian asymptotics in the limit of vanishing noise $\varsigma \to 0$, which provides us for $i = 1, 2$ with the precise estimates

$$\begin{aligned} \int D_x V(x,y)\, \mu_x^{\mathrm{OU}(i)}(y)\, \mathrm{d}y &= D_x V(x, m^{(i)}(x)) \big(1 + \mathcal{O}(\varsigma)\big), \\ \int D_x V(x,y)\, \mu_x^{(i)}(y)\, \mathrm{d}y &= D_x V(x, m^{(i)}(x)) \big(1 + \mathcal{O}(\varsigma)\big), \end{aligned} \tag{5.2}$$

where the derivative $D_x V(x, m^{(i)}(x))$ is taken wrt. the first component solely.

Conclusively, let us suppose that $\varsigma = \varsigma(\epsilon)$ is coupled to ϵ by using (3.14). Replacing ς by $\varsigma(\epsilon)$ in the fast equation (1.2) of the original process will lead to a time scale separation of the fast dynamics in y and the metastable transitions between the potential wells. Then, application of the ordinary averaging procedure will destroy the information about slow mixing between the two

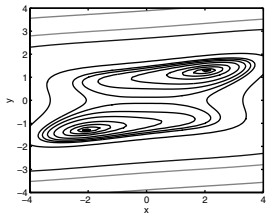

Fig. 6.1. Full potential V.

branches and the result becomes inappropriate to render the effective dynamics. By contrast, application of Theorem 4.1 does not require to fix ς: Even if $\varsigma = \varsigma(\epsilon)$ due to (3.14), the reduced model (4.7) will represent the effective dynamics of (4.4)&(4.5). We get this result because the averaging procedure does not affect the Markov chain $I(t, x)$ that stores the distributional information of the metastable transitions. Therefore, by examining the averaged system (4.7) as $\varsigma \to 0$, we will obtain the differential equation

$$\dot{x} = D_x V(x, m^{(I(t,x))}(x)) \, + \, \sigma \, \dot{W},$$

that is considered as the final limit SDE of the original process (1.1)&(1.2) with $\varsigma = \varsigma(\epsilon)$ given by (3.14) as $\epsilon \to 0$.

6 Numerical Experiments

In this section we illustrate the results from the preceding section by numerical experiments with an appropriate test example.

We consider the Smoluchowski equation (1.1)&(1.2) where the potential for the numerical analysis is given by:

$$V(x, y) = 2.5\,(y^2 - 1)^2 \, - \, 0.8\,x\,y^3 \, + \, 0.005\,x^4 \, + \, 1.6, \tag{6.1}$$

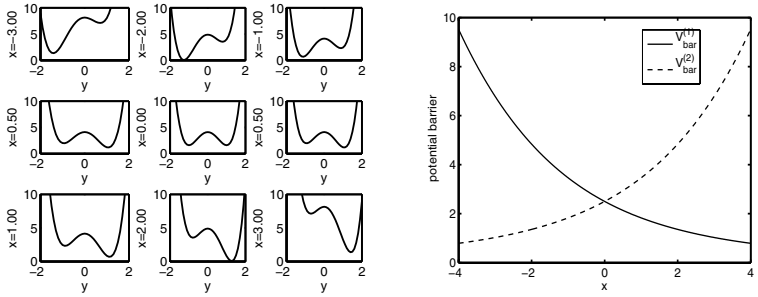

Fig. 6.2. Left: Potentials $V(x, \cdot)$ in y for different values of x. Right: potential barriers $V_{\mathrm{bar}}^{(1)}(x)$ (full line) and $V_{\mathrm{bar}}^{(2)}(x)$ (dashed line).

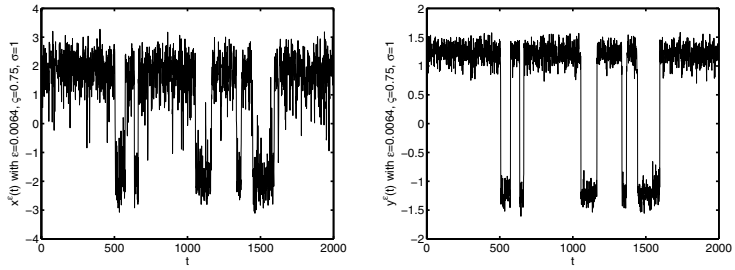

Fig. 6.3. Typical realization of the original dynamics for $\sigma = 1.0$, $\varsigma = 0.75$ and $\epsilon = 0.0064$. Left: trajectories x coordinate; right: trajectories y coordinate.

which clearly satisfies Assumption 2.1. The potential energy surface is shown in Fig. 6.1. At the left hand side of Fig. 6.2 we illustrate the double-well potentials $V(x, \cdot)$ for different values of x. The saddle point always is $y_0(x) = 0$ and takes the value $V(x, 0) = 4.1 + 0.005\, x^4$, the potential minima are

$$m^{(i)}(x) \;=\; 0.12\, x \;+\; (-1)^i \sqrt{0.0576\, x^2 + 4}, \qquad i = 1, 2.$$

The right side of Fig. 6.2 shows the potential barriers $V^{(1)}_{\rm bar}(x)$ (the left barrier) and $V^{(2)}_{\rm bar}(x)$ (the right barrier) as functions of x.

In Fig. 6.3 we show a typical realization of the dynamics (1.1)&(1.2) with $\sigma = 1.0$, $\varsigma = 0.75$ and $\epsilon = 0.0064$. For the generation of the trajectories we use the Euler-Maryuana scheme with internal time step $\mathrm{d}t = \epsilon/100$. We clearly observe that jumps between the metastable decomposition $B^{(1)} = \{(x, y) \,|\, y < 0\}$ and $B^{(2)} = \{(x, y) \,|\, y > 0\}$ induce metastable transitions in the x dynamics between $x < 0$ and $x > 0$. Comparison with the averaged trajectory in Fig. 6.4 reveals inappropriateness of the standard averaging procedure (1.3). In Fig. 6.4 right we illustrate the averaged potential $\overline{V}$ (known as Fixman potential or conformational free energy landscape)that is associated with the realization at the left:

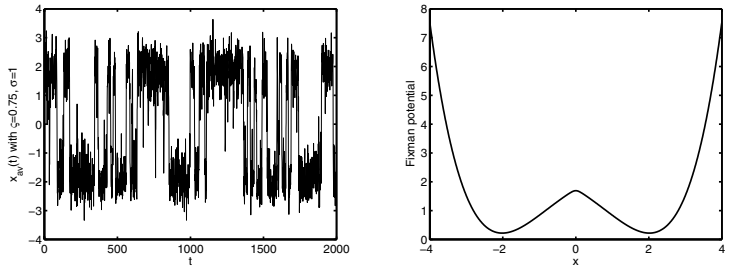

Fig. 6.4. Left: Typical realization of the simply averaged dynamics (1.3) for $\sigma = 1.0$, $\varsigma = 0.75$. Right: Fixman potential that corresponds to the trajectory at the left.

$$\overline{V}(\varsigma, x) \;=\; -\frac{\varsigma^2}{2} \ln \int \exp\big(-\frac{2}{\varsigma^2} V(x,y)\big)\, \mathrm{d}y.$$

Using standard Laplace asymptotics provides us with the potential in the limit $\varsigma \to 0$ of vanishing fast diffusion

$$\overline{V}(x) \;=\; \min\big\{V\big(x, m^{(1)}(x)\big), V\big(x, m^{(1)}(x)\big)\big\}.$$

In Fig. 6.4 we additionally plotted $\overline{V}(x)$, which graphically is completely identical to $\overline{V}(\varsigma = 0.75, x)$.

Fig. 6.3&6.4 explicitly visualize the simply averaged dynamics to be inappropriate to render the effective dynamical behaviour of $x^\epsilon(t)$ as $\epsilon \to 0$. For small ϵ diffusion in y is very fast compared to diffusion in x. However, the important (and only) barriers of the potential are barriers in y direction. Thus, for fixed ϵ, decreasing the noise intensity ς in the fast equation increases the metastability in y. Consequently, by choosing different ς one can analyze the effect of increasing metastability on averaging. To this end, it is convenient to use the x averaged values of the expected transition rates $1/\mathcal{T}^\epsilon_{i\to j}(x)$. As detailed in Appendix B this provides us in the asymptotic limit $\varsigma \to 0$ with the expected transition times $\overline{\mathcal{T}}^\epsilon_{1\to 2}$ between the metastable decomposition $B^{(1)} \cup B^{(2)}$ in the (x, y) state space.

We generated $N = 2000$ realizations of the original dynamics for $\epsilon = 0.0064$, $\sigma = 1.0$ and $\varsigma = 0.75, 0.7, 0.65, 0.60$, and waited for the first exit times from $B^{(1)}$. The top row in Fig. 6.5 illustrates the location of the trajectories x-coordinate right before the transitions occured; the pictures at the bottom display the function under the integral in (B.4) (normalized to 1) and nicely illustrate that the major contribution to the integral in (B.4) will move rightwards as $\varsigma \to 0$, for $V^{(1)}_{\mathrm{bar}}(x) \to 0$ as $x \to \infty$. Comparison of the upper and

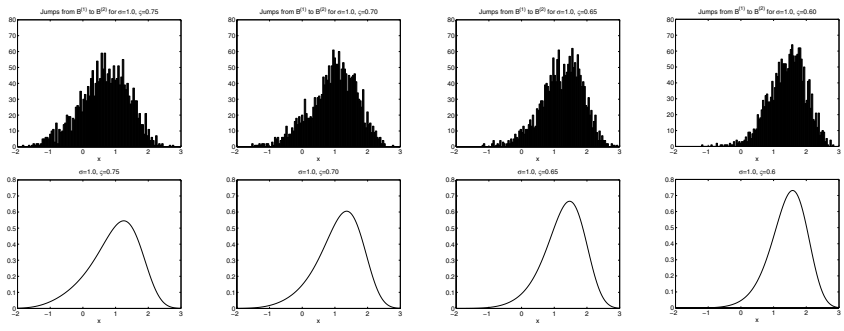

Fig. 6.5. Top: Transition location (from $B^{(1)}$ to $B^{(2)}$) of the trajectories x-coordinate computed by means of $N = 2000$ realizations of the conditionally averaged dynamics for $\sigma = 1.0$, $\epsilon = 0.0064$ fixed and $\varsigma = 0.75, 0.7, 0.65, 0.6$. Bottom: Function under the integral in (B.4) normalized to 1 by using the same parameters as above.

Table 6.1. Expectation values of transition times from $B^{(1)}$ to $B^{(2)}$ corresponding to Fig. 6.5. The values for $\overline{\mathcal{T}}^{\epsilon}_{1\to 2}$ are obtained by using (B.2) or (B.4).

Mean transition times	$\varsigma = 0.75$	$\varsigma = 0.7$	$\varsigma = 0.65$	$\varsigma = 0.60$
mean value from 2000 real.	213	462	1240	4285
averaged value $\overline{\mathcal{T}}^{\epsilon}_{1\to 2}$	119	323	1037	4157

the lower pictures reveals almost coincidence between the contribution to the integral in (B.4) and the actual location in the x space of the jumps from $B^{(1)}$ to $B^{(2)}$. Finally, we compare in Table 6.1 the averaged values of the transition times to the numerically obtained values by means of the $N = 2000$ realizations. We observe that ς has to be chosen small to get closeness.

Discretization

The pathwise simulation of the dynamics consisting of the two state Markov jump process $I(t, x)$ is developed by using a specific stochastic particle method ([HSS01]). To this end, recall the infinitesimal generator $\mathcal{Q}^{\epsilon}_x = (q^{\epsilon}_{ij}(x))_{i,j}$ that allows to calculate the hopping probabilities between the states $\mathbf{S} = \{1, 2\}$. The transition matrix $P^{\epsilon}_{\tau}(x) = (p^{\epsilon}_{ij}(\tau, x))$ at time τ is then obtained by

$$P^{\epsilon}_{\tau}(x) \,=\, \exp(\tau \mathcal{Q}^{\epsilon}_x).$$

A straightforward calculation reveals

$$p^{\epsilon}_{12}(\tau, x) = \frac{q^{\epsilon}_{12}(x)}{q^{\epsilon}_{12}(x) + q^{\epsilon}_{21}(x)} \, (1 - e^{-\tau(q^{\epsilon}_{12}(x)+q^{\epsilon}_{21}(x))}), \tag{6.2}$$

$$p^{\epsilon}_{21}(\tau, x) = \frac{q^{\epsilon}_{21}(x)}{q^{\epsilon}_{12}(x) + q^{\epsilon}_{21}(x)} \, (1 - e^{-\tau(q^{\epsilon}_{12}(x)+q^{\epsilon}_{21}(x))}). \tag{6.3}$$

The entries of $\mathcal{Q}^{\epsilon}_x$ are given in (4.6) by the inverse of the precise estimates of the expected transition times over the potential energy barrier in y direction.

The stochastic particle method requires two steps. We shortly demonstrate it for the OU averaged dynamics (4.7).

Step 1: Transport. The first step consists of determining an updated position $x(t + \mathrm{d}t)$ by solving

$$\dot{x} = -\int D_x V(x, y) \, \mu^{\mathrm{OU}(i)}_x(y) \, \mathrm{d}y \,+\, \sigma \dot{W}_1,$$

over $[0, \mathrm{d}t]$ with initial point $x(t)$.

Step 2: Exchange. The second step models the exchange between the states $I(t, x) = 1$ and $I(t, x) = 2$. Thus, if $i = 1$, we set $i = 2$ with hopping probability $p_{1\to 2} = p^{\epsilon}_{12}(\mathrm{d}t, x(t + \mathrm{d}t))$ and remain at $i = 1$ with probability $1 - p_{1\to 2}$. Vice versa, if $i = 2$, we set $i = 1$ with hopping probability $p_{2\to 1} = p^{\epsilon}_{21}(\mathrm{d}t, x(t + \mathrm{d}t))$ and remain at $i = 2$ with probability $1 - p_{2\to 1}$. Return to step 1 by setting $x(t) = x(t + \mathrm{d}t)$.

Parameter Choice

Subsequently, we choose the noise intensity in the slow equation $\sigma = 1$ and the smallness parameter is $\epsilon = 0.0064$. Trajectories are illustrated with $\varsigma = 0.75$, whereas for comparison of exit times we use different values of ς.

Recalling coupling ς to ϵ according to (3.14), some words seem to be necessary concerning the comparison of the full dynamics to the OU approximated ones: Without loss of generality we can choose ς arbitrary without considering the coupling, for the experiments are performed for a fixed value of ϵ. Therefore, for fixed $\epsilon = \epsilon^*$ and fixed $\varsigma = \varsigma^*$ we can always find a constant $K = K^*$ (or a barrier $V_{\text{bar}}^{\text{small}} = V_{\text{bar}}^{\text{small}*}$) such that $\varsigma(\epsilon^*) = \varsigma^*$ under (3.14). Even if we take (3.13) as the basis of our computation, we can desist from the coupling rule, for the constant K then can be chosen dependent of x, such that we still arrive at $\varsigma(\epsilon^*, x) = \varsigma^*$. Actually, the postulation of relating ς to ϵ only serves as a formal justification of the OU approximation. For the numerical implementation only the size of ς by its own is of importance, not its relation to ϵ.

The motivation to choose $\sigma = 1.0$ and not $\sigma = \varsigma$ can be infered from Fig. 6.5. In case of smaller values of σ, say $\sigma = 0.75$, the x-coordinate of the trajectory will hardly reach the region where the jumps mostly happen. Then we had to choose ς larger, which on its part would result in a worse approximation of the intra-well fast dynamics. We will come back to this problem below.

6.1 Comparison Between Original Dynamics and Small Noise Approximation

Here, we carry out numerical studies in order to compare the Smoluchowski dynamics (1.1)&(1.2) with those governed by system (4.4)&(4.5) with fast OU processes and transition chain $I(t, x)$ that controls the switches between the two OU processes.

Typical realizations of both the original dynamics and the OU approximated ones are shown in Fig. 6.6. The trajectories have been generated using the Euler-Maruyama scheme with time step $\mathrm{d}t = \epsilon/100$ for both systems. Apparently, the transition rates between $B^{(1)}$ and $B^{(2)}$ coincide to some extend and the oscillating motion (around the potential minima in y) inbetween the transitions seems to be well approximated by using OU processes in the fast equation. We clearly observe that jumps induce metastable transitions in the x dynamics between $x < 0$ and $x > 0$. However, for the trajectories being in $B^{(1)}$ we observe that the x-coordinate of the original dynamics spreads considerably further rightwards than the x trajectory of the OU approximated system (and for the trajectories in $B^{(2)}$ the original dynamics x-coordinate spreads further leftwards).

The above observation suggests that the original dynamics have noticeable smaller transition times between $B^{(1)}$ and $B^{(2)}$, as the original dynamics more

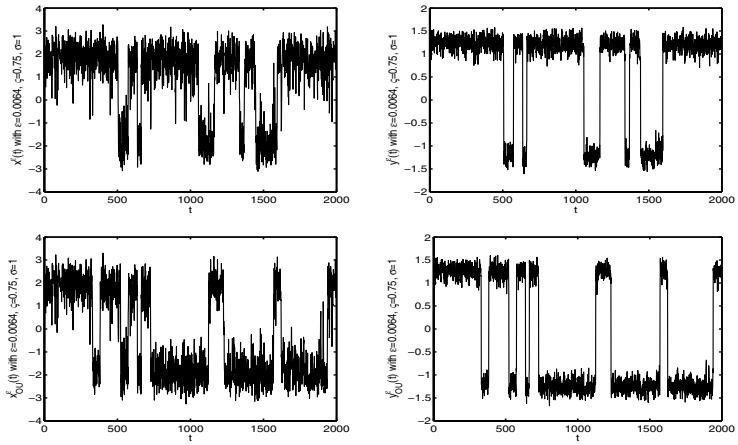

Fig. 6.6. Typical realization of the original dynamics (top) and the approximated dynamics with fast OU processes (bottom). At the left we see the x, at the right the y coordinate. The realizations have been computed for the same realization of the white noise (in the slow and in the fast equation).

often reaches a domain where the potential barriers (in y direction) are small. This is confirmed by Table 6.2, where we computed the expected transition times from $B^{(1)}$ to $B^{(2)}$ by means of $N = 2000$ realizations for two different values of ς and $\sigma = 1.0$, $\epsilon = 0.0064$ fixed. We come back to this problem in the next section where we include the averaged dynamics into the numerical examinations. Actually, it will turn out that ς has to be chosen very small to get perfect coincidence of both the original and the OU approximated system.

6.2 Results Including Averaged Dynamics

We now demonstrate pre-eminence of the OU averaged dynamics (4.7). To complete the representation we include the conditionally averaged dynamics (1.7).

In Fig. 6.7 we compare realizations of the averaged to the full dynamics' x-coordinate. Every trajectory has been computed with the same realization of white noise $\dot{W}_1, \dot{W}_2$, such that the internal time step has been set to $\mathrm{d}t = \epsilon/100$

Table 6.2. Exit times from the set $B^{(1)}$ for the original dynamics and the OU approximated system.

dynamical model	$\varsigma = 0.8$	$\varsigma = 0.75$
original dynamics	113	210
OU approximated dynamics	136	265

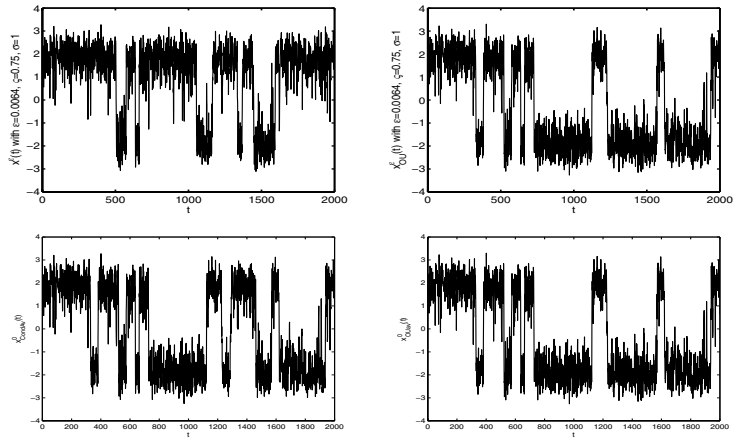

Fig. 6.7. Realizations of the original dynamics x coordinate (top, left), the x coordinate of the (full) OU approximated dynamics (top, right), the OU averaged dynamics (bottom, right), and the conditionally averaged system (bottom, left).

even for the averaged dynamics. The Markov jump process $I(t, x)$ is realized by using the same realization of random numbers for every concerned system. Concerning the systems with OU processes (full and OU averaged), we observe pathwise convergence of the x trajectories, whereas comparison of the original dynamics with the conditionally averaged system reveals distributional coincidence.

In order to present numbers instead of pictures we want to compute the expectation values of the metastable transition times from $x < 0$ to $x > 0$ for different values of ς. It is natural to expect that this is realized by computing the first exit times from the set $S + \delta$ with $S = \{x \in \mathbf{R} \mid x < 0\}$, where $\delta > 0$ has to be large enough to guarantee that the process effectively reaches some (small) region of attraction in the complement of S. But Fig. 6.5 nicely shows that the x-coordinate can spread far into the positive region even when it is restricted to the metastable set S. Thus, we suggest to define the stopping time as the first exit from $B^{(1)}$ instead, respectively the first jump from $I(t, x) = 1$ to $I(t, x) = 2$. At least for $\varsigma \leq 7.5$ (compare Fig. 6.6) this is equivalent to the metastable transitions from $x < 0$ to $x > 0$. From $N = 2000$ realizations for $\epsilon = 0.0064$ and $\sigma = 1.0$ we get a very good agreement between the OU approximated dynamics and the OU averaged dynamics, and a good agreement between the original and the conditionally averaged dynamics.

However, there still remains the problem of difference between the OU averaged and the conditionally averaged dynamics. To overcome the problem, we illustrate in Fig. 6.8 the potentials that correspond to the respective trajectories for $\varsigma = 0.75, 0.60, 0.3$. For $I(t, x) = i \in \{1, 2\}$ and ς fixed, the conditionally averaged potential $\overline{V}^{(i)}(\varsigma, x)$ and the OU averaged potential $\overline{V}^{\mathrm{OU}(i)}(\varsigma, x)$ are

Table 6.3. Comparison of exit times from the metastable set $S = \{x \in \mathbf{R} \mid x < 0\}$. For $\varsigma = 0.65$, it was not possible to compute the exit times of the full dynamics' motion within a reasonable period of time.

dynamical model	$\varsigma = 0.8$	$\varsigma = 0.75$	$\varsigma = 0.65$
original dynamics	113	210	$--$
conditinally averaged dynamics	105	213	1240
OU approximated dynamics	136	265	$--$
OU averaged dynamics	135	265	1537

defined implicitly by

$$D_x \overline{V}^{\mathrm{OU}(i)}(\varsigma, x) = \int D_x V(x,y)\, \mu_x^{\mathrm{OU}(i)}(y)\, \mathrm{d}y,$$
$$D_x \overline{V}^{(i)}(\varsigma, x) = \int D_x V(x,y)\, \mu_x^{(i)}(y)\, \mathrm{d}y,$$

and we easily show that

$$\overline{V}^{(i)}(\varsigma, x) \;=\; -\frac{\varsigma^2}{2} \ln \int_{B_x^{(i)}} \exp\big(-\frac{2}{\varsigma^2} V(x,y)\big)\, \mathrm{d}y.$$

Exploiting the estimation method of Laplace we obtain asymptotical identity of both potentials:

$$\lim_{\varsigma \to 0} \overline{V}^{(i)}(\varsigma, x) \;=\; \lim_{\varsigma \to 0} \overline{V}^{\mathrm{OU}(i)}(\varsigma, x) \;=\; V(x, m^{(i)}(x)).$$

Fig. 6.8 reveals $V^{(i)}(\varsigma, x) \approx \overline{V}^{\mathrm{OU}(i)}(\varsigma, x)$ for $\varsigma \leq 0.3$, whereas they differ visibly for $\varsigma \geq 0.60$ mainly in that region where the jumps from $i = 1$ to $i = 2$ mostly happen. This perfectly explains the significant difference concerning the transition times in Tables 6.2&6.3.

A Derivation of Reduced System by Multiscale Analysis

Here, we show how the averaged system (4.7) can be derived from the system (4.4)&(4.5) with fast OU processes by using multiscale asymptotics wrt.

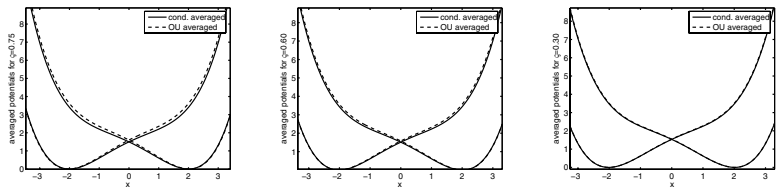

Fig. 6.8. Comparison of conditinally averaged (full line) to OU averaged potentials (dashed line). From left to right: $\varsigma = 0.75, 0.60, 0.3$.

the smallness parameter ϵ. As the method is applied to ensemble instead of single dynamics we have to set up before the necessary requirements concerning the evolution of probability densities.

Let us extend the fast-slow system with two OU processes to a finite number of OU processes. Thus, we consider the process $(x^\epsilon_{\mathrm{OU}}, y^\epsilon_{\mathrm{OU}}) \in \mathbf{R}^m \times \mathbf{R}$ that is determined by the following SDE:

$$\dot{x}(t) = -D_x V(x,y) \,+\, \sigma \dot{W}_1, \tag{A.1}$$

$$\dot{y}(t) = -\frac{1}{\epsilon}\,\omega^{(I(t,x))}(x)\,\big(y - m^{(I(t,x))}(x)\big) \,+\, \frac{\varsigma(x)}{\sqrt{\epsilon}}\dot{W}_2, \tag{A.2}$$

where $I(t,x)$ is a right-continuous Markov chain on a probability space taking values in a finite state space $\mathbf{S} = \{1,2,...,N\}$ and $\omega^{(i)}(x)$ takes values in $\mathbf{R}^+$ for all $i \in \mathbf{S}$. The noise intensity of the fast diffusion may depend on x, but is assumed to be strictly positive, that is $\varsigma(x) \geq c > 0$. To simplify notation we perform the asymptotic procedure without a possible dependence of ς on the Markov chain $I(t,x)$; a generalization in this direction had no effect on the computation. The generator $\mathcal{Q}_x = (q_{ij}(x))_{N\times N}$ of the switching chain $I(t,x)$ depends on the slow variable x and contains the transition rates $q_{ij} = q_{ij}(x) > 0$ from i to j if $i \neq j$ while

$$q_{ii}(x) \,=\, -\sum_{i\neq j} q_{ij}(x). \tag{A.3}$$

For fixed $x \in \mathbf{R}^m$ and $i \in \mathbf{S}$ the diffusion dynamics (A.2) is known as OU process and consequently ergodic. The (unique) stationary density $\mu_x^{\mathrm{OU}(i)}$ is given by

$$\mu_x^{\mathrm{OU}(i)}(y) \,=\, \frac{1}{\varsigma(x)}\sqrt{\frac{\omega^{(i)}(x)}{\pi}}\exp\Big(-\omega^{(i)}(x)\frac{\big(y-m^{(i)}(x)\big)^2}{\varsigma(x)^2}\Big), \tag{A.4}$$

which is a Gaussian with mean $m^{(i)}(x)$ and variance $\varsigma(x)^2/(2\omega^{(i)}(x))$, and thus independent of ϵ.

The evolution of probability densities $p^\epsilon \in L^1(\mathbf{R}^{m+1}\times\mathbf{S})$ under the dynamics given by (A.1)&(A.2) is described by the forward *Fokker-Planck equation*. Here, we are working in unweighted function spaces, that is, the density p^ϵ gives the physical probability to find the system in state (x,y) at time t. For later use it may be helpful to slightly change notation for the densities p^ϵ: The agreement $p^\epsilon_{(i)}(t,x,y) := p^\epsilon(t,x,y,i)$ enables us to represent p^ϵ as an N-dimensional vector according to $p^\epsilon = (p^\epsilon_{(1)},...,p^\epsilon_{(N)})$ with $p^\epsilon_{(i)} \in L^1(\mathbf{R}^{m+1})$. Now, the Fokker-Planck equation is regarded on some suitable subspace of $L^1(\mathbf{R}^{m+1}\times\mathbf{S})$, and reads

$$\partial_t p^\epsilon = \mathcal{A}^\epsilon p^\epsilon, \qquad \mathcal{A}^\epsilon \,=\, \frac{1}{\epsilon}\mathcal{A}_x \,+\, \mathcal{A}_y \,+\, \mathcal{Q}^T, \tag{A.5}$$

$$\mathcal{A}_x \;=\; \begin{pmatrix} \mathcal{A}_x^{(1)} & 0 & 0 & 0 \\ 0 & \mathcal{A}_x^{(2)} & 0 & 0 \\ 0 & 0 & \ddots & 0 \\ 0 & 0 & 0 & \mathcal{A}_x^{(N)} \end{pmatrix}, \mathcal{A}_y \;=\; \begin{pmatrix} \mathcal{A}_y^{(1)} & 0 & 0 & 0 \\ 0 & \mathcal{A}_y^{(2)} & 0 & 0 \\ 0 & 0 & \ddots & 0 \\ 0 & 0 & 0 & \mathcal{A}_y^{(N)} \end{pmatrix}$$

where $\mathcal{A}_x^{(i)}$ and $\mathcal{A}_y^{(i)}$ are given for $f \in L^1(\mathbf{R}^{m+1})$ by

$$\mathcal{A}_x^{(i)} f(x,y) = \frac{\varsigma(x)^2}{2} \Delta_y f(x,y) \;+\; D_y\Big(\omega^{(i)}(x)\big(y - m^{(i)}(x)\big)\, f(x,y)\Big)$$
$$\mathcal{A}_y^{(i)} f(x,y) = \frac{\sigma^2}{2} \Delta_x f \;+\; D_x\big(D_x V(x,y)\, f(x,y)\big).$$

Note that we actually have to use $\mathcal{Q}^T$ in (A.5), for the rate matrix $\mathcal{Q}$ is basically considered to be part of the backward Chapman-Kolmogorov equation, that is, it describes the evolution of the expectations of functions of the state of the system. Consequently, the probability to be in state (x, y) is given by

$$\langle p^\epsilon(t,x,y), \mathbf{1}\rangle_{\mathbf{S}} \;=\; \sum_{i \in \mathbf{S}} p^\epsilon_{(i)}(t,x,y),$$

$\langle \cdot, \cdot \rangle_{\mathbf{S}}$ denoting the Euclidean inner product in $\mathbf{R}^N$.

Our aim is to average with respect to the fast variable y and obtain an averaged equation for the slow variable x alone. To this end, we will use multiscale analysis.

Projection Operator

We would like to derive an equation for the distribution function in x:

$$\int \langle p^\epsilon(t,x,y), \mathbf{1}\rangle_{\mathbf{S}}\, \mathrm{d}y \;=\; \sum_{i \in \mathbf{S}} \int p^\epsilon_{(i)}(t,x,y)\, \mathrm{d}y,$$

which would be valid in the limit where ϵ becomes very small. To this end, we introduce the vector $\overline{p}^\epsilon(t,x) = (\overline{p}^\epsilon_{(1)}, ..., \overline{p}^\epsilon_{(N)})^T$ with densities $\overline{p}^\epsilon_{(i)} \in L^1(\mathbf{R}^m)$ defined by

$$\overline{p}^\epsilon_{(i)}(t,x) \;=\; \int p^\epsilon_{(i)}(t,x,y)\, \mathrm{d}y.$$

It is expected that an approximate solution of the full dynamics would be obtained by multiplying each $\overline{p}^\epsilon_{(i)}(t,x)$ by the stationary distribution $\mu_x^{\mathrm{OU}(i)}$ of the SDE (A.2) for fixed $I(t,x) = i$. We formalize this by defining a *projection operator* $\mathit{\Pi} = \mathrm{diag}(\mathit{\Pi}^{(1)}, ..., \mathit{\Pi}^{(N)})$ acting on functions $f = (f_1, ..., f_N)^T \in L^1(\mathbf{R}^{m+1} \times \mathbf{S})$ by

$$(\mathit{\Pi} f)(x,y) \;=\; \mathrm{diag}(\mu_x^{\mathrm{OU}(1)}, ..., \mu_x^{\mathrm{OU}(N)}) \int f(x,y)\, \mathrm{d}y.$$

It is obvious that Π projects any function into the subspace of all functions which can be written in the form

$$f \;=\; (f_1, ..., f_N)^T, \quad f_i(x,y) = \overline{f}_i(x)\, \mu_x^{\mathrm{OU}(i)}(y), \tag{A.6}$$

where $\overline{f}_i$ is an arbitrary function of $L^1(\mathbf{R}^m)$, thus $\overline{f} \;=\; (\overline{f}_1, ..., \overline{f}_N)^T \;\in\; L^1(\mathbf{R}^m \times \mathbf{S})$. In the following we study the case where the initial condition $p^\epsilon(t=0,x,y)$ can be expressed by

$$p^\epsilon(t=0,x,y) \;=\; (\Pi p^\epsilon(t=0))(x,y).$$

However, functions f of the form (A.6) are all solutions of

$$\mathcal{A}_x f \;=\; 0,$$

that is, the space into which Π projects is the kernel or nullspace of $\mathcal{A}_x$ expressed by $\mathcal{A}_x \Pi = 0$. Due to the properties of $\mathcal{A}_x^{(i)}$ considered as an operator acting on functions g in y, that is $g = g(y) \in L^1(\mathbf{R})$, we furthermore have:

$$\Pi \mathcal{A}_x \;=\; 0 \;=\; \mathcal{A}_x \Pi. \tag{A.7}$$

This is easily seen by introducing the formal adjoint $\mathcal{T}_x^{(i)}$ of $\mathcal{A}_x^{(i)}$, i.e., a differential operator such that for all $u \in L^1(\mathbf{R})$, $v \in L^\infty$ (or $u, v \in L^2(\mathbf{R})$) we have

$$\langle \mathcal{A}_x^{(i)} u, v \rangle_{L^2} \;=\; \langle u, \mathcal{T}_x^{(i)} v \rangle_{L^2}, \qquad \langle u, v \rangle_{L^2} := \int u(y)\, \overline{v(y)}\, \mathrm{d}y.$$

If we consider $\Pi^{(i)}$ – for fixed x – as an operator acting on functions in y, we can rewrite it by

$$\Pi^{(i)} u \;=\; \langle u, \mathbf{1} \rangle_{L^2}\, \mu_x^{\mathrm{OU}(i)}.$$

Together with the well-known fact that $\mathcal{T}_x^{(i)} \mathbf{1} = 0$ (see, e.g., [SHD01, Hui01]) we finally get the desired result (A.7).

Multiscale Analysis

We now make the following ansatz for the solution of the Fokker-Planck equation with the initial conditions described above:

$$p^\epsilon \;=\; p^0 \;+\; \epsilon\, p^1 \;+\; \epsilon^2\, p^2 \;+ ...$$

This ansatz is inserted into the Fokker-Planck equation (A.5) and then, by comparison of coefficients of different powers of ϵ we get:

$$\epsilon^{-1}: \quad \mathcal{A}_x\, p^0 \;=\; 0 \tag{A.8}$$

$$\epsilon^{0}: \quad \mathcal{A}_x\, p^1 \;+\; (\mathcal{A}_y + \mathcal{Q}^T)\, p^0 \;=\; \partial_t p^0 \tag{A.9}$$

$$\epsilon^{1}: \quad \mathcal{A}_x\, p^2 \;+\; (\mathcal{A}_y + \mathcal{Q}^T)\, p^1 \;=\; \partial_t p^1 \tag{A.10}$$

Step 1: (A.8) immediately yields that $p^0 \in \mathcal{N}(\mathcal{A}_x)$, i.e.,

$$\begin{aligned} \Pi p^0 = p^0, \quad \text{equivalently} \\ p^0(t,x,y) = \operatorname{diag}(\mu_x^{\mathrm{OU}(1)}, ..., \mu_x^{\mathrm{OU}(N)})\, \overline{p}^0(t,x), \end{aligned} \tag{A.11}$$

for a function $\overline{p}^0 \in L^1(\mathbf{R}^m \times \mathbf{S})$ depending only on x.

Step 2: Let Π act on (A.9) and use (A.7). This time we get:

$$\Pi(\mathcal{A}_y + \mathcal{Q}^T)\Pi p^0 = \partial_t \Pi p^0. \tag{A.12}$$

By using (A.11) simple calculations reveal for $\overline{p}^0 = (\overline{p}^0_{(1)}, ..., \overline{p}^0_{(N)})^T$:

$$\partial_t \overline{p}^0 = (\overline{\mathcal{A}} + \mathcal{Q}^T)\, \overline{p}^0, \tag{A.13}$$

with

$$\overline{\mathcal{A}} = \begin{pmatrix} \overline{\mathcal{A}}^{(1)} & 0 & 0 & 0 \\ 0 & \overline{\mathcal{A}}^{(2)} & 0 & 0 \\ 0 & 0 & \ddots & 0 \\ 0 & 0 & 0 & \overline{\mathcal{A}}^{(N)} \end{pmatrix},$$

$$\overline{\mathcal{A}}^{(i)} = \frac{\sigma^2}{2}\Delta_x + D_x\Big(\int D_x V(x,y)\, \mu_x^{\mathrm{OU}(i)}(y)\, \mathrm{d}y \cdot \Big),$$

$\overline{\mathcal{A}}$ acting on $L^1(\mathbf{R}^m \times \mathbf{S})$. Thus $\overline{p}^0$ is determined by a Fokker-Planck equation, and its solution gives us p^ϵ up to error $\mathcal{O}(\epsilon)$. The associated SDE is given by

$$\dot{x} = -\int D_x V(x,y)\, \mu_x^{\mathrm{OU}(I(t,x))}(y)\, \mathrm{d}y + \sigma \dot{W}_1, \tag{A.14}$$

with solution process $x^0(t)$ where $I(t,x) \in \mathbf{S}$ controls the switches between the different OU processes due to the rate matrix $\mathcal{Q} = \mathcal{Q}_x$. The SDE (A.14) describes the limit dynamics of (A.1)&(A.2) in the sense that its solution satisfies $x^\epsilon_{\mathrm{OU}} \to x^0$ as $\epsilon \to 0$ either pathwise [FW84], or in the distributional sense [Kur73, MTV99].

B Asymptotics of Transition Times

Here, we come back to the problem addressed in Sect. 3.3. In order to avoid coupling ς to the slow variable dynamics x we relax the postulation $\mathcal{T}^\epsilon_{i\to j}(x) \geq \mathrm{ord}(1)$, $i \neq j$ in Lemma 3.5 that is required for every x and $i = 1, 2$. Instead of considering the transition times on every fibre of the fast state space for fixed x, we introduce the expected transition times $\overline{\mathcal{T}}^\epsilon_{1\to 2}$ and $\overline{\mathcal{T}}^\epsilon_{2\to 1}$ between

the metastable decomposition $B^{(1)} \cup B^{(2)}$ in the entire (x, y) state space. This enables us to identify large time conformational changes with the stipulation

$$\overline{\mathcal{T}}^{\epsilon}_{1\to 2},\, \overline{\mathcal{T}}^{\epsilon}_{2\to 1} \geq \mathrm{ord}(1).$$

We obviously have

$$\mathcal{T}^{\epsilon}_{i\to j}(x) \,\geq\, \mathrm{ord}(1) \qquad \Longrightarrow \qquad \overline{\mathcal{T}}^{\epsilon}_{1\to 2},\, \overline{\mathcal{T}}^{\epsilon}_{2\to 1} \,\geq\, \mathrm{ord}(1),$$

whereas the other direction need not to be valid.

With these preparations we claim the following: If we define the relationship between ς and ϵ by

$$\varsigma(\epsilon) = \left(\frac{2V^{\mathrm{small}}_{\mathrm{bar}}}{\ln(K/\epsilon)}\right)^{1/2}, \tag{B.1}$$

$$V^{\mathrm{small}}_{\mathrm{bar}} = \min\{V^{(i)}_{\mathrm{bar}}(x) \;|x \in D(\sigma),\, i = 1, 2\},$$

where $D(\sigma)$ is some appropriately chosen bounded connected domain[6] of the slow variable state space, the metastable transitions $\overline{\mathcal{T}}^{\epsilon}_{1\to 2}$, $\overline{\mathcal{T}}^{\epsilon}_{2\to 1}$ are of order one or even larger.

In what follows we show how to compute $\overline{\mathcal{T}}^{\epsilon}_{i\to j}$ which is strongly connected to the asymptotic order of the transition times $\mathcal{T}^{\epsilon}_{i\to j}(x)$ on every fiber. We will consider two possible situations that are exemplary for the different approaches. We first examine the consequences of the asymptotic order of $\mathcal{T}^{\epsilon}_{i\to j}(x)$ in general, and afterwards relate the results to the functions $V^{(i)}_{\mathrm{bar}}(x)$ and a coupling $\varsigma = \varsigma(\epsilon)$ given by (B.1).

In Theorem B.1 below we assume the transition times $\mathcal{T}^{\epsilon}_{i\to j}(x)$ to asymptotically go to infinity, where we do not specify wherefrom the asymptotic investigations come from, that is, we leave open which parameter causes the asymptotic behaviour. Thus, possible (and reasonable) choices were $\varsigma \to 0$ and ϵ fixed, $\epsilon \to 0$ so that $\varsigma(\epsilon) \to 0$, or, not less supposable, we could assume a scaling of the potential barrier. The next result becomes apparent in [Wal05, Chapter 3], where the approach is justified by means of multiscale analysis for distinguished time scales. There the metastable transitions are assumed to happen on the longest time scale, which requires the averaging of the metastable transition rates (represented by the second eigenvalue of the corresponding generator) for fixed x wrt. the invariant density of the conditionally averaged potentials.

Theorem B.1 ([Wal05, Chapter 3.3.3]). *Suppose $\mathcal{T}^{\epsilon}_{i\to j}(x) \to \infty$ almost everywhere for $i, j = 1, 2$ and $i \neq j$. Then the metastable transition times $\overline{\mathcal{T}}^{\epsilon}_{i\to j}$ are basically independent of the starting point and are asymptotically derived by means of averaging the x-dependent transition rates[7] against the invariant*

[6] See explanation in Sect. 3.3.

[7] Note, that we actually have to average the transition rates and *not* the transition times.

probability distribution of the x dynamics conditioned upon remaining within the metastable set $B^{(i)}$ *and taking the inverse of the averaged transition rates, that is,*

$$\overline{\mathcal{T}}^{\epsilon}_{i\to j} \simeq \frac{1}{\mathbf{E}_{\bar\mu^{(i)}}[1/\mathcal{T}^{\epsilon}_{i\to j}(x)]},$$

where the quantity $\mathbf{E}_{\bar\mu^{(i)}}[1/\mathcal{T}^{\epsilon}_{i\to j}(x)]$ *is given by*

$$\mathbf{E}_{\bar\mu^{(i)}}[1/\mathcal{T}^{\epsilon}_{i\to j}(x)] = \int 1/\mathcal{T}^{\epsilon}_{i\to j}(x)\,\bar\mu^{(i)}(x)\,\mathrm{d}x, \tag{B.2}$$

$$\bar\mu^{(i)}(x) = \frac{1}{Z^{(i)}}\exp\Big(-\frac{2}{\sigma^2}\Big(-\frac{\varsigma^2}{2}\ln\int_{B^{(i)}_x}\exp\big(-\frac{2}{\varsigma^2}V(x,y)\big)\mathrm{d}y\Big)\Big). \tag{B.3}$$

Here, $Z^{(i)}$ denotes the normalization constant and depends on ς as well. Define the jump process $\overline{I}(t)$ by its transition rates $1/\overline{\mathcal{T}}^{\epsilon}_{i\to j}$. Then we find that the random process $(x^{\epsilon}_{\mathrm{OU}}, y^{\epsilon}_{\mathrm{OU}})$ determined by system (4.4)&(4.5) is asymptotically given by the SDE

$$\begin{aligned}\dot x &= -D_xV(x,y) + \sigma\dot W_1\\ \dot y &= -\frac{1}{\epsilon}\,\omega^{(\overline{I}(t))}(x)\big(y - m^{(\overline{I}(t))}(x)\big) + \frac{\varsigma}{\sqrt{\epsilon}}\dot W_2.\end{aligned}$$

In the limit of small noise ς the evaluation of the expression (B.2) asymptotically reduces to

$$\begin{aligned}&\mathbf{E}_{\bar\mu^{(i)}}[1/\mathcal{T}^{\epsilon}_{i\to j}(x)] \simeq \\ &\frac{1}{\epsilon}\,\frac{1}{Z^{(i)}}\int\frac{\sqrt{\omega^{(i)}(x)\omega_0(x)}}{2\,\pi}\exp(-\frac{2}{\varsigma^2}V^{(i)}_{\mathrm{bar}}(x))\exp(-\frac{2}{\sigma^2}V(x,m^{(i)}(x)))\,\mathrm{d}x.\end{aligned} \tag{B.4}$$

Proof. We only have to show (B.4). The rest is verified in [Wal05]. First, we consider the averaged density $\bar\mu^{(i)}(x)$: Using standard Laplacian asymptotics, we get for ς small

$$\int_{B^{(i)}_x}\exp\big(-\frac{2}{\varsigma^2}V(x,y)\big)\mathrm{d}y = \varsigma\sqrt{\frac{\pi}{\omega^{(i)}(x)}}\exp\big(-\frac{2}{\varsigma^2}V(x,m^{(i)}(x))\big)\big(1+\mathcal{O}(\varsigma)\big),$$

and, exploiting $(\varsigma^2/2)\ln(\varsigma\sqrt{\pi/\omega^{(i)}(x)}) \to 0$ as $\varsigma\to 0$, we end up with the asymptotic limit (from (B.3))

$$\bar\mu^{(i)}(x) \simeq \frac{1}{Z^{(i)}}\exp\big(-\frac{2}{\sigma^2}V(x,m^{(i)}(x))\big).$$

Together with Theorem 3.3 we immediately obtain (B.4).

Remark B.2. If we consider the asymptotics of the transition times for vanishing ς and ϵ fixed, it is easily seen that the assumptions of Theorem B.1 are fulfilled. However, if we consider the asymptotic limit for $\epsilon\to 0$ and $\varsigma = \varsigma(\epsilon)$ as given by (B.1), the behaviour of $\mathcal{T}^{\epsilon}_{i\to j}(x)$ will depend on the course of the functions $V^{(i)}_{\mathrm{bar}}(x)$, $i = 1, 2$.

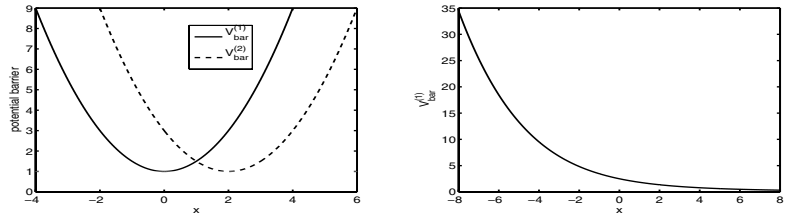

Fig. B.1. Exemplary possibilities for the functions $V_{\mathrm{bar}}^{(i)}(x)$, $i = 1, 2$. In the left picture we find that the left and right potential barriers are bounded away from zero by a positive constant. This is prevented in the picture at the right, for $V_{\mathrm{bar}}^{(1)}$ converges to zero.

In the situation illustrated in the left panel of Fig. B.1 we may apply the approach in Theorem for sure, if the relationship between ς and ϵ is defined in an appropriate way. This is formulated in the next corollary.

Corollary B.3. *Suppose that* $\inf\{V_{\mathrm{bar}}^{(i)}(x) \mid x \in \mathbf{R},\, i = 1, 2\} = V_{\mathrm{bar}}^{\mathrm{small}} > 0$ *and* $V_{\mathrm{bar}}^{(i)} > V_{\mathrm{bar}}^{\mathrm{small}}$ *almost everywhere. Let us define the small noise intensity* ς *by*

$$\varsigma(\epsilon) = \left(\frac{2V_{\mathrm{bar}}^{\mathrm{small}}}{\ln(K/\epsilon)}\right)^{1/2}, \qquad K > 0. \tag{B.5}$$

Then, we obtain in the asymptotic limit $\epsilon \to 0$

$$\overline{\mathcal{T}}_{i\to j}^{\epsilon} \simeq \left(\int 1/\mathcal{T}_{i\to j}^{\epsilon}(x)\, \bar{\mu}^{(i)}(x)\, \mathrm{d}x\right)^{-1}$$

Assume in addition that $V_{\mathrm{bar}}^{(1)}$ *attains its smallest value and let the minimum of* $V_{\mathrm{bar}}^{(1)}$ *occur at, say,* x_0*. Moreover, we assume* $V_{\mathrm{bar}}^{(1)} > V_{\mathrm{bar}}^{(1)}(x_0) \geq V_{\mathrm{bar}}^{\mathrm{small}}$ *for all* $x \neq x_0$ *and* $D_{xx}V_{\mathrm{bar}}^{(1)}(x_0) \neq 0$*. Then*

$$\mathbf{E}_{\bar{\mu}^{(1)}}[1/\mathcal{T}_{1\to 2}^{\epsilon}(x)] \simeq \tag{B.6}$$
$$\sqrt{\frac{\omega^{(1)}(x_0)\omega_0(x_0)}{4\,\pi\,\partial_x^2 V_{\mathrm{bar}}^{(1)}(x_0)}}\,\frac{1}{Z^{(1)}}\,\exp(-\frac{2}{\sigma^2}V(x_0, m^{(1)}(x_0)))\,\frac{\varsigma}{\epsilon}\,\exp(-\frac{2}{\varsigma^2}V_{\mathrm{bar}}^{(1)}(x_0)).$$

For $\delta \geq 0$ *so that* $V_{\mathrm{bar}}^{(1)}(x_0) = (1+\delta)V_{\mathrm{bar}}^{\mathrm{small}}$*, we finally obtain*

$$\overline{\mathcal{T}}_{1\to 2}^{\epsilon} = \mathrm{ord}(\epsilon^{-\delta}\sqrt{\ln(1/\epsilon)}). \tag{B.7}$$

Proof. The first part immediately follows from Theorem B.1, for we have almost everywhere

$$V_{\mathrm{bar}}^{(i)}(x) = (1+\delta_x^{(i)})V_{\mathrm{bar}}^{\mathrm{small}}, \quad \delta_x^{(i)} > 0 \quad \Longrightarrow \quad \mathcal{T}_{i\to j}^{\epsilon}(x) = \mathrm{ord}(\epsilon^{-\delta_x^{(i)}}).$$

(B.6) follows from (B.4) by using Laplace's method in the limit of vanishing noise ς. With the assumed coupling of ς according to (B.5), we then obtain from (B.6)

$$\mathbf{E}_{\bar{\mu}^{(1)}}[1/\mathcal{T}^{\epsilon}_{1\to 2}(x)] \;=\; \mathrm{ord}(\epsilon^{-\delta}\sqrt{\ln(1/\epsilon)}).$$

One could also contemplate a situation, such as that schematically indicated at the right-hand side of Fig. B.1. Here, $V^{(1)}_{\mathrm{bar}}(x) \to 0$ as $x \to \infty$, and there is no local minimum $V^{\mathrm{small}}_{\mathrm{bar}}$ such that $V^{\mathrm{small}}_{\mathrm{bar}} \leq V^{(1)}_{\mathrm{bar}}(x)$ for all x. Access to this problem is established in the next proposition where the argumentation has to be carried out rather intuitively. As outlined in Remark B.2, in Proposition B.4 it is coercive to consider the asymptotic behaviour as $\epsilon \to 0$ together with a reasonable coupling of $V^{(i)}_{\mathrm{bar}}(x)/\varsigma^2$ that is not yet specified.

Proposition B.4. *Suppose that* $\min\{\mathcal{T}^{\epsilon}_{1\to 2}(x), \mathcal{T}^{\epsilon}_{2\to 1}(x)\} \to 0$ *asymptotically for* $x \in D$ *where* D *is some subset of positive Lebesgue measure. We define a decomposition of* $D = D_1 \cup D_2$ *by*

$$D_1 = \{x \in D \mid \min\{\mathcal{T}^{\epsilon}_{1\to 2}(x), \mathcal{T}^{\epsilon}_{2\to 1}(x)\} = \mathcal{T}^{\epsilon}_{1\to 2}(x)\},$$
$$D_2 = \{x \in D \mid \min\{\mathcal{T}^{\epsilon}_{1\to 2}(x), \mathcal{T}^{\epsilon}_{2\to 1}(x)\} = \mathcal{T}^{\epsilon}_{2\to 1}(x)\}.$$

To simplify argumentation, we assume that D_i, $i = 1, 2$ *are connected subsets of* D *and* $(D_1 \cap D_2)\backslash\partial(D_1 \cap D_2) = \emptyset$. *Moreover, we restrict to the case where for* $x \in D^c$ *with* D^c *denoting the complement of* D *we have* $\min\{\mathcal{T}^{\epsilon}_{1\to 2}(x), \mathcal{T}^{\epsilon}_{2\to 1}(x)\} \to \infty$. *Now, the following is satisfied: The metastable transition times* $\overline{\mathcal{T}}^{\epsilon}_{i\to j}$ *from* $B^{(i)}$ *to* $B^{(j)}$ *will depend on the starting point* $x_0 = x^{\epsilon}(0)$ *and we write* $\overline{\mathcal{T}}^{\epsilon}_{i\to j}[x_0]$. *For* $(x^{\epsilon}(0), y^{\epsilon}(0)) \in B^{(1)}$ *with* $x^{\epsilon}(0) = x_0$ *we asymptotically obtain*

$$\overline{\mathcal{T}}^{\epsilon}_{1\to 2}[x_0] \simeq \mathbf{E}_{x_0}[\tau_{D^c\cup D_2}(x^{\epsilon}(t))], \tag{B.8}$$

where $\tau_{D^c\cup D^2}(x^{\epsilon}(t))$ *denotes first exit time of the process* $x^{\epsilon}(t)$ *from the set* $D^c \cup D^2$. *Instead of considering the exit times of the process* $x^{\epsilon}(t)$, *we can equally well consider the exit times of the conditionally averaged dynamics (1.7) with* $I(t, x) = 1$ *fixed. In the limit of* $\varsigma \to 0$ *we will be allowed to replace* x^{ϵ} *in (B.8) by the small noise approximation or the OU averaged dynamics as defined in Sect. 4 and still obtain the correct asymptotics. And, conclusively, by using (5.2), we arrive for vanishing* ς *at*

$$\overline{\mathcal{T}}^{\epsilon}_{1\to 2}[x_0] \;\simeq\; \mathbf{E}_{x_0}[\tau_{D^c\cup D_2}(x^0(t))] \;=\; \mathrm{ord}(1)$$

where $x^0(t)$ *is determined by*

$$\dot{x} \;=\; -D_x V(x, m^{(1)}) \,+\, \sigma\dot{W}_1.$$

In exact the same way we obtain asymptotics for $\overline{\mathcal{T}}^{\epsilon}_{2\to 1}$.

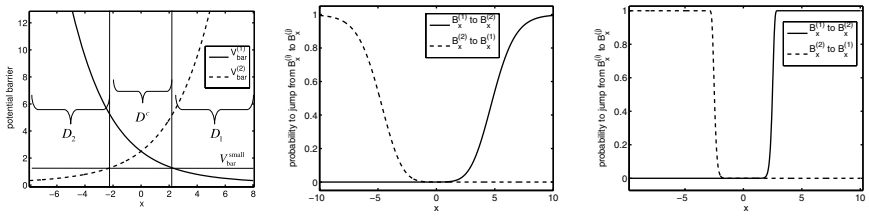

Fig. B.2. left: Illustration of $V_{\rm bar}^{(i)}$, $i = 1, 2$ and $V_{\rm bar}^{\rm small}$ and the resulting subsets D_1, D_2, D^c; middle: transition probabilities (time step $\mathrm{d}t = 0.01$) corresponding to (B.1) with $V_{\rm bar}^{\rm small} < V_{\rm bar}^{(1)}(m)$ and $\epsilon = 10^{-3}$; right: transition probabilities with $\epsilon = 10^{-12}$.

Proof. A careful inspection of the transition probabilities $p_{12}^{\epsilon}(t, x)$ as defined in (6.2) and (6.3) with $q_{ij}^{\epsilon}(x) = 1/\mathcal{T}_{i\to j}^{\epsilon}$ reveals for each time step $\mathrm{d}t$ pointwise convergence for almost every x

$$\lim_{\epsilon\to 0} p_{12}^{\epsilon}(\mathrm{d}t, x) = 0, \quad x \in D_2 \cup D^c, \qquad \lim_{\epsilon\to 0} p_{12}^{\epsilon}(\mathrm{d}t, x) = 1, \quad x \in D_1.$$

This shows that for ϵ small enough, the particle in $B^{(1)}$ will instantly jump over the barrier once it has reached D_1 and as long as it stays in $D_2 \cup D^c$ nothing will happen.

Example B.5. Let $V_{\rm bar}^{(i)}$ be given as illustrated in the left picture[8] of Fig. B.2, that is, $V_{\rm bar}^{(1)}$ is strictly monotonically decreasing with $V_{\rm bar}^{(1)}(x) \to 0$ as $x \to \infty$, and $V_{\rm bar}^{(2)}$ is strictly monotonically increasing with $V_{\rm bar}^{(2)}(x) \to 0$ as $x \to -\infty$. Then there exists an intersection point m such that $V_{\rm bar}^{(1)}(m) = V_{\rm bar}^{(2)}(m)$. Now, choose $V_{\rm bar}^{\rm small}$ such that $V_{\rm bar}^{\rm small} < V_{\rm bar}^{(i)}(m)$ and define the relation between ϵ and ς according to (B.1). The resulting subsets D_1, D_2 and $D^c = (D_1 \cup D_2)^c$ are shown in Fig. B.2. The picture in the middle shows the transition probabilities $p_{1\to 2} = p_{12}^{\epsilon}(\mathrm{d}t, x)$, $p_{2\to 1} = p_{21}^{\epsilon}(\mathrm{d}t, x)$ to jump over the barrier for moderately chosen $\epsilon = 10^{-3}$ and time step $\mathrm{d}t = 1/100$. At the right we illustrate the transition probabilities for very small $\epsilon = 10^{-12}$. We clearly observe that for vanishing ϵ the particle will jump over the barrier once it has reached D_1 and D_2, respectively.

Example B.6. Let the assumptions be given as in Example B.5, but this time we choose $V_{\rm bar}^{\rm small} > V_{\rm bar}^{(i)}(m)$. In this case, $D^c = \emptyset$ and the state space is decomposed into the sets D_1 and D_2 that are separated by the point m with $V_{\rm bar}^{(1)}(m) = V_{\rm bar}^{(2)}(m)$. An illustration is given in Fig. B.3. Again, the transition probabilities for $\epsilon = 10^{-12}$ at the right-hand side reveal

$$p_{1\to 2} = p_{12}^{\epsilon}(\mathrm{d}t, x) \approx 0 \ \text{ for } x \in D_2, \quad p_{2\to 1} = p_{12}^{\epsilon}(\mathrm{d}t, x) \approx 1 \ \text{ for } x \in D_1.$$

[8] We have chosen the potential from Sect. 6.

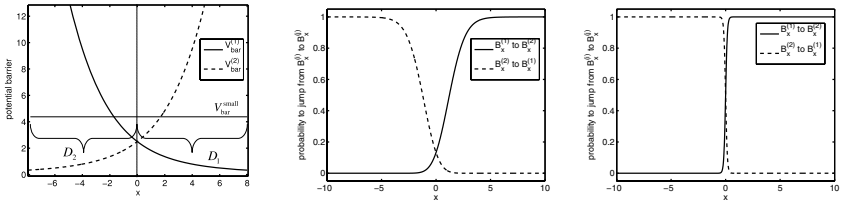

Fig. B.3. Same as Fig. B.2, but this time $V_{\rm bar}^{\rm small} > V_{\rm bar}^{(1)}(m)$.

References

[AKN93] V. I. Arnold, V. V. Kozlov, and A. I. Neishtadt. *Mathematical Aspects of Classical and Celestial Mechanics*. Springer, Berlin, 1993.

[BLP78] A. Bensoussan, J. L. Lions, G. Papanicolaou. *Asymptotic Analysis for Periodic Structures*. Elsevier Science & Technology Books, July 1978.

[Bor98] F. A. Bornemann. *Homogenization in Time of Singularly Perturbed Mechanical Systems*. Number 1687 in Lecture Notes in Mathematics. Springer-Verlag, 1998.

[BS97] F. A. Bornemann and C. Schütte. Homogenization of Hamiltonian systems with a strong constraining potential. *Physica D*, 102:57–77, 1997.

[BS99] F. A. Bornemann and C. Schütte. On the singular limit of the quantum-classical molecular dynamics model. *1999*, 59:1208–1224, SIAM J. Appl. Math.

[BE*02] A. Bovier, M. Eckhoff, V. Gayrard, and M. Klein. Metastability in reversible diffusion processes I: Sharp estimates for capacities and exit times. *J. Eur. Math. Soc.*, 6:399–424, 2004.

[BGK02] A. Bovier, V. Gayrard, and M. Klein. Metastability in reversible diffusion processes II: Precise estimates for small eigenvalues. *J. Eur. Math. Soc.*, 7:69–99, 2005.

[Fre78] M. Freidlin. The averaging principle and theorems on large deviations. *Russ. Math. Surv.*, 33(5):107–160, 1978.

[FW84] M. Freidlin and A. Wentzell. *Random Perturbations of Dynamical Systems*. Springer, New York, 1984. Series in Comprehensive Studies in Mathematics.

[Gar85] C. W. Gardiner. *Handbook of Stochastic Methods*. Springer, Berlin, 2nd enlarged edition edition, 1985.

[HKN04] B. Helffer, M. Klein, and F. Nier. Quantitative analysis of metastability in reversible diffusion processes via a witten complex approach. preprint, 2004.

[HSS01] I. Horenko, B. Schmidt, and C. Schütte. A theoretical model for molecules interacting with intense laser pulses: The Floquet–based quantum–classical Liouville equation. *J. Chem. Phys.*, 115(13):5733–5743, 2001.

[Hui01] W. Huisinga. *Metastability of Markovian systems: A transfer operator based approach in application to molecular dynamics*. PhD thesis, Free University Berlin, 2001.

[HMS02] W. Huisinga, S. Meyn, and C. Schütte. Phase transitions & metastability in Markovian and molecular systems. accepted in Ann. Appl. Probab., 2002.

[Kif92] Y. Kifer. Averaging in dynamical systems and large deviations. *Invent. Math.*, 110:337–370, 1992.

[Kif01] Y. Kifer. Stochastic versions of Anosov's and Neistadt's theorems on averaging. *SD*, 1:1–21, 2001.

[Kif02] Y. Kifer. L^2–diffusion approximation for slow motion in averaging. preprint, 2002.

[Kur73] T. G. Kurtz. A limit theorem for perturbed operator semigroups with applications to random evolutions. *J. Funct. Anal.*, 12:55–67, 1973.

[MTV01] A. J. Majda, I. Timofeyev, and E. Vanden–Eijnden. A mathematical framework for stochastic climate models. *Comm. Pure Applied Math.*, 54:891–974, 2001.

[MTV99] A. J. Majda, I. Timofeyev, and E. Vanden-Eijnden. Models for stochastic climate prediction. *Proc. Natl. Acad. Sci.*, 96(26):14687–14691, 1999.

[MTV02] A. J. Majda, I. Timofeyev, and E. Vanden-Eijnden. A priori tests of a stochastic mode reduction strategy. *Physica D*, 170:206–252, 2002.

[Mor65] H. Mori. Transport collective motion and Brownian motion. *Prog. Th. Phys. Supp.*, 33:423–455, 1965.

[Pap76] G. Papanicolaou. Some probabilistic problems and methods in singular perturbation. *Rocky Mountain Math. J.*, 6:653–674, 1976.

[Pav02] I. Pavlyukevich. *Stochastic Resonance*. Logos, Berlin, 2002.

[SV85] J. Sanders and F. Verhulst. *Averaging Methods in Nonlinear Dynamical Systems*. Springer, New York, 1985.

[SH00] C. Schütte and W. Huisinga. On conformational dynamics induced by Langevin processes. In B. Fiedler, K. Gröger, and J. Sprekels, editors, *EQUADIFF 99 - International Conference on Differential Equations*, volume 2, pages 1247–1262, Singapore, 2000. World Scientific.

[SH02] C. Schütte and W. Huisinga. Biomolecular conformations can be identified as metastable sets of molecular dynamics. In P. G. Ciaret and J.-L. Lions, editors, *Handbook of Numerical Analysis*, volume Computational Chemistry. North–Holland, 2002. in press.

[SHD01] C. Schütte, W. Huisinga, and P. Deuflhard. Transfer operator approach to conformational dynamics in biomolecular systems. In B. Fiedler, editor, *Ergodic Theory, Analysis, and Efficient Simulation of Dynamical Systems*, pages 191–223. Springer, 2001.

[SW*03] C. Schütte, J. Walter, C. Hartmann, and W. Huisinga. An averaging principle for fast degrees of freedom exhibiting long-term correlations. *SIAM Multiscale Modeling and Simulation*, submitted. Presently available via www.math.fu-berlin.de/∼biocomp, 2003.

[Wal05] J. Walter. *Averaging for Diffusive Fast-Slow Systems with Metastability in the Fast Variable*. PhD thesis, Free University Berlin, 2005.

[Zwa73] R. Zwanzig. Nonlinear generalized Langevin equations. *J. Stat. Phys.*, 9:215–220, 1973.