Path-space variational inference for non-equilibrium coarse-grained systems

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Abstract

In this paper we discuss information-theoretic tools for obtaining optimized coarse-grained molecular models for both equilibrium and non-equilibrium molecular simulations. The latter are ubiquitous in physicochemical and biological applications, where they are typically associated with coupling mechanisms, multi-physics and/or boundary conditions. In general the non-equilibrium steady states are not known explicitly as they do not necessarily have a Gibbs structure.

The presented approach can compare microscopic behavior of molecular systems to parametric and non-parametric coarse-grained models using the relative entropy between distributions on the path space and setting up a corresponding path-space variational inference problem. The methods can become entirely data-driven when the microscopic dynamics are replaced with corresponding correlated data in the form of time series. Furthermore, we present connections and generalizations of force matching methods in coarse-graining with path-space information methods. We demonstrate the enhanced transferability of information-based parameterizations to **different observables, at a specific thermodynamic point**, due to information inequalities.

We discuss methodological connections between information-based coarse-graining of molecular systems and variational inference methods primarily developed in the machine learning community. However, we note that the work presented here addresses variational inference for correlated time series due to the focus on dynamics. The applicability of the proposed methods is demonstrated on high-dimensional stochastic processes given by overdamped and driven Langevin dynamics of interacting particles.

Keywords: coarse graining, non-equilibrium, information metrics, machine learning, variational inference, stochastic optimization, time series, Langevin dynamics

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1. Introduction

Molecular dynamics simulations at microscopic (e.g. atomistic) level have capability of providing quantitative information about rheological, mechanical, chemical and electrical properties of molecular systems, [48, 21]. However, the enormous range of length and time scales involved in such complex materials presents a challenging computational task, in particular, due to a wide disparity of relaxation times.

A standard methodology in order to overcome problems of long relaxation times of complex systems is to abandon the chemical detail and describe the molecular system by fewer (the most relevant) degrees of freedom. The choice of the latter depends entirely on the physical problem under question. Such particle-based, systematic *coarse-grained* (CG) models of molecular systems are developed by averaging out the details at the molecular level, and by representing groups of atoms by a single CG particle. Then the effective coarse-grained interaction potentials (more precisely free energies) are derived from the microscopic details of the atomistic model. The coarse-grained potentials and force fields can be derived through different methods, such as the inverse Boltzmann method, force matching and relative entropy, [53, 52, 70, 27, 33, 34, 69, 12]. Applying these methods in the context of best-fit procedures in parametrized families of CG models the structural properties of systems at *equilibrium* can be described with accuracy which is related to a metric used for the parameter fitting procedure. However, the above mentioned coarse-graining parametrization techniques do not address dynamical properties of the model and are restricted to systems already at a (equilibrium) Gibbs state.

Furthermore, there are several important issues related to systematic CG models using microscopic information for molecular systems under non-equilibrium conditions: (a) the whole approach is based on the fact that there is a direct connection between structural properties (like pair distribution functions) and CG interaction potentials; i.e., the renormalization group map or Boltzmann relation, see for instance [53, 72, 27]. This is certainly true at equilibrium and near to equilibrium but may not be the case for systems far from equilibrium; (b) since the CG interaction potential intrinsically involves entropy, it is not clear what is the dependence of the effective CG force field with respect to the external forces (if they are present); (c) predicting the dynamics (or incorporating the proper friction in the equations of motion) in the CG non-equilibrium model is not clear, [25, 3]. All these aspects are, in principle, relevant in any application of a systematic CG model for a molecular system under non-equilibrium conditions.

Recently, several methods for coarse-graining of stochastic models based on information theory have appeared in the literature, [14, 5, 6]. These methods employ entropy-based techniques that estimate discrepancy between (probability) measures. Using entropy-based analytical tools has proved essential for deriving rigorous results for passage from interacting particle models to mean-field description, e.g., [47]. Applications of these methods to the error analysis of coarse-graining of stochastic particle systems have been introduced in [46, 39, 44, 45, 40, 41]. Independently of such rigorous mathematical work, the engineering community developed entropy-based computational techniques that are used for constructing approximations of coarse-grained potentials for models of large biomolecules and polymeric

systems (fluids, melts), where the optimal parametrization of effective potentials is based on minimizing the relative entropy between *equilibrium* Gibbs states, e.g., [14, 10, 13, 5, 6]. Note, that other works in the literature are primarily based on observable-matching using either structural distribution functions, such as the inverse Boltzmann method, inverse Monte Carlo methods, [70, 53, 52], or averaged forces on CG particles [34, 33]. These methods were used with a great success in coarse-graining of macromolecules, see, e.g., [72, 58, 27, 28, 29, 25, 3]. Recent review articles [25, 67, 68] give a detailed overview of coarse-graining techniques applied to systems at equilibrium. Finally, effective coarse equilibrium dynamics for systems with temporal scale separation modeled by overdamped Langevin dynamics were studied in [49].

Evolution of coarse-grained variables corresponding to Hamiltonian microscopic dynamics can be described exactly with the Mori-Zwanzing formalism leading to a stochastic integro-differential system with strong memory terms, known as the generalized Langevin equation (GLE) [75, 57], that is in principle computationally intractable. Therefore either a scaling of CG dynamics or approximations of the GLE are used [62, 29, 30, 25, 63, 15, 31, 54, 18, 51].

Approximate dynamical models in a parametrized formulation have also been considered in recent studies, most of them based on the well established equilibrium parametrization methods described above. For example, authors in [35, 19] propose optimal CG parametrized Langevin dynamics based on the force matching method.

In order to extend the information-theoretic approach developed in [69] for coarse-graining of Gibbs states to dynamics, a parameter fitting procedure for dynamic coarse-grained models was developed in [23]. The method proposed there is based on minimization of the relative entropy between discrete two-time transition probabilities associated with the diffusion process, in this case Langevin dynamics. Moreover, authors demonstrate that the relative entropy minimization can be interpreted as a force-matching problem. The use of the two-time step probability limits the applicability of the approach to short time dynamics while the discretization time step appears explicitly in the minimization problem leading to time step depended optimal parameters. In a recent article, [20], authors attempt to overcome the short time limit using Bayesian inference to identify most probable parameters for a given time series of microscopic states, i.e. in a path space perspective. The authors provide also the connection with force-matching where though again the optimal parameter set depends on the time step of the numerical discretization scheme. The *relative entropy rate* (RER) functional for Markov Chains proposed in [64] and [42] is similar to the functional that defines the best-fit optimization in [23], being the relative entropy per unit time for stationary processes. The formulation of path-space relative entropy for continuous time process in the present work illustrates that both path-space relative entropy and RER are independent of the time step for any numerical discretization scheme. This fact is further demonstrated in Appendix B where we study the RER minimization for numerical schemes for the Langevin and the overdamped Langevin dynamics.

In fact, in the present article, as well as earlier in [42], we show that path-space information metrics such as RER provide a general framework in several additional directions: (a) they are applicable to discrete-time or discretized (as in [23]) dynamics and also to

broad classes of continuous time stochastic dynamics such as Kinetic Monte Carlo algorithms (e.g., reaction-diffusion mechanisms on lattices), biochemical reaction networks and semi-Markov processes, [64], [42], [65], (b) apply to non-equilibrium problems without analytically known Gibbs states and a detail balanced condition (irreversible processes), including driven Langevin models, Kinetic Monte Carlo algorithms and reaction networks, and most importantly, (c) our RER perspective shows that the corresponding optimization methods are extendable to both finite and infinite times, guaranteeing quantified predictive capability even at long time regimes, [22]. In order to demonstrate the abstract principles of the information-theoretic framework on the *path space* we present coarse-graining of dynamics described as solutions to Ito’s stochastic differential equations. The presented information-theoretic methodology allows us to build optimal coarse-grained dynamics as systematic approximations of microscopic stochastic dynamics in the same general class of Markovian dynamics, e.g., of stochastic differential equations. The path-space information approach compares microscopic and coarse-grained dynamics using the relative entropy between distributions on the path space (see Theorem 5.1) and sets up the corresponding path-space variational inference (parameter optimization) problems.

One of the mathematical and computational novelties of the presented approach lies in the derivation of *path space force-matching* conditions which are applicable to both equilibrium and non-equilibrium systems. This path-space information theory formulation provides a natural generalization to non-equilibrium systems of the force matching methods developed earlier for systems at equilibrium, [33, 37]. Moreover, we demonstrate here the equivalence of the relative entropy rate (RER) and force-matching type optimization methods, in analogy to the equilibrium case, studied in [60, 67, 37]. Furthermore, due to information inequalities such as (5) and (7), we have that path information-based coarse-graining implies transferability of the parameterization to all reasonable observables by only training a single observable, **at the specific thermodynamic point**, namely the relative entropy. We explore a different but asymptotically equivalent (in the number of data) perspective, which is data-driven in the sense that it treats the microscopic simulator only as means of producing statistical data in the form of time series.

We also stress in this work connections between information-based work for coarse-graining and the variational inference methods primarily developed in the machine learning community.

In Section 2 we give a short overview of variational inference and coarse-graining as well as connections to machine learning methods and computational approaches. Next in Section 3 we describe the **microscopic** and coarse-grained models and the corresponding dynamics. Section 4 describes the path space relative entropy and relative entropy rate minimization problems and sets up the theoretical tools for comparing the microscopic and coarse dynamics at finite and long-time, stationary regimes. In Section 5 we prove that the minimization of the path-space relative entropy is a path space force matching problem providing a generalization of the known equilibrium force matching method to non-equilibrium systems. Applications of our results are presented in Section 6 for the Langevin dynamics demonstrating applicability of the proposed method to molecular systems while presenting specific examples of coarse

graining transformations. Moreover, a direct study of the relative entropy rate minimization for the discretized Langevin and overdamped Langevin dynamics is discussed, verifying the validity of the continuous time optimal coarse-grained model for the corresponding time discretized schemes. In Section 7 we present the use of the relative entropy minimization as a means of optimizing the information content in a coarse model with respect to available time series data coming from a fine-scale simulation. Finally in the last section we summarize the contributions of the present work.

2. Variational inference methods and coarse-graining of molecular systems.

Here we give a short overview of information-based coarse-graining of molecular systems and highlight connections with variational inference methods primarily developed in the machine learning literature and discuss computational approaches.

2.1. Information-theoretic methods for coarse-graining molecular systems.

Computational methods developed for parameterizing coarse-grained models at equilibrium, such as inverse Monte Carlo, [53, 52], inverse Boltzmann, [72, 70, 52], force matching, [33, 34], and relative entropy, [69, 12], provide a development of the CG interaction potential by considering a pre-selected set of observables ϕ_i , $i = 1, \dots, \ell$ and then minimizing a fitting functional over the parameter space $\Theta \subseteq \mathbb{R}^k$. Typical choices of observables ϕ_i are radial distribution functions, [72, 58], and forces between CG particles, [34, 33, 68]. A family of parametrization methods is described by

$$\min_{\theta \in \Theta} \sum_{i=1}^{\ell} |\mathbb{E}_{\mu}[\phi_i] - \mathbb{E}_{\bar{\mu}^{\theta}}[\phi_i]|^2, \quad (1)$$

where μ denotes the fine-scale Gibbs equilibrium distribution and $\bar{\mu}^{\theta}$ the parametrized coarse-grained Gibbs distribution. Such methods are referred to as the iterative inverse Boltzmann method and the inverse Monte Carlo methods, [53, 52, 72, 70]. Clearly any parametrization based on a minimization principle such as (1) depends on the specific choice of observables, while the accurate simulation of other observables, which are not part of the parameterization (1) is not necessarily guaranteed.

Before we continue further we introduce mathematical concepts involved in coarse graining. In abstract terms we consider the original (microscopic) model defined on a measurable space $(\Omega, \mathcal{B})$, where Ω represents the state (configuration) space and $\mathcal{B}$ denotes the σ -algebra on Ω , and the coarse-grained model on $(\bar{\Omega}, \bar{\mathcal{B}})$ with the coarse-graining map

$$\Pi : \Omega \rightarrow \bar{\Omega}. \quad (2)$$

The elements of the coarse state space $\bar{\Omega}$ (the coarse degrees of freedom) are thus $\bar{\omega} = \Pi\omega$. We use the bar “ $\bar{\cdot}$ ” notation for objects related to the coarse-grained model. The (probability) measures on the microscopic space $(\Omega, \mathcal{B})$ are mapped (pushed-forward) by the map Π_* , $\bar{P} = \Pi_* P$,

$$\mathbb{E}_{\bar{P}}[\bar{\phi}] \equiv \int_{\bar{\Omega}} \bar{\phi} d(\Pi_* P) = \int_{\Omega} \bar{\phi} \circ \Pi dP, \quad (3)$$

where $\bar{\phi} : \bar{\Omega} \rightarrow \mathbb{R}$, or equivalently $(\Pi_* P)(\bar{B}) = P(\Pi^{-1}(\bar{B}))$ where $\bar{B} \in \bar{\mathcal{B}}$.

The relative entropy (Kullback-Leibler divergence), [17], of two probability measures $P(d\omega)$ and $Q(d\omega)$ on a common measurable space $(\Omega, \mathcal{B})$ is given by

$$\mathcal{R}(P|Q) = \int_{\Omega} \log \frac{dP(\omega)}{dQ(\omega)} P(d\omega), \quad (4)$$

provided $P \ll Q$, i.e., P is absolutely continuous with respect to Q , and $\mathcal{R}(P|Q) = +\infty$ otherwise. The functional $\mathcal{R}(P|Q)$ defines a pseudo-distance between two measures as $\mathcal{R}(P|Q) \geq 0$ and $\mathcal{R}(P|Q) = 0$ if and only if $P = Q$, P -a.s. In the case these probability measures have corresponding probability densities $p(\omega)$ and $q(\omega)$ relation (4) becomes $\mathcal{R}(P|Q) = \int_{\Omega} \log \frac{p(\omega)}{q(\omega)} p(\omega) d\omega$.

In contrast to the observable-centered perspective of (1), we turn our attention to information inequalities and their implications for coarse-graining. For instance, the Csiszár-Kullback-Pinsker (CKP) inequality, [17], when applied to an observable ϕ and the fine-scale and coarse-grained equilibrium distributions considered in (1) readily gives rise to an error bound

$$|\mathbb{E}_{\mu}[\phi] - \mathbb{E}_{\bar{\mu}^{\theta}}[\phi]| \leq \|\phi\|_{\infty} \sqrt{2\mathcal{R}(\Pi_* \mu | \bar{\mu}^{\theta})}, \quad (5)$$

where Π is the coarse-graining map, $\Pi_* \mu$ denotes the push-forward of the microscopic measure μ defined above, and $\|\phi\|_{\infty} = \sup\{|\phi(x)| : x \in \Omega\}$ is the uniform norm of ϕ .

Since the microscopic and coarse-grained problems are formulated on different measure spaces it is necessary to clarify how the relative entropy is defined in (5). Note that from the computational point of view $\mathcal{R}(\Pi_* \mu | \bar{\mu}^{\theta})$ is still computed on the microscopic space Ω using the formula (3) for the push-forward. We also refer to Section 7 for precise formulas and related estimators. Another option for comparing the two models in the terms of relative entropy is by mapping the coarse model on the microscopic space, i.e., defining a (microscopic) reconstruction map. The reconstruction map can be viewed as a generalized inverse $\Pi^{\dagger} : \bar{\Omega} \rightarrow \Omega$, and as such is not necessarily unique. Associated with the reconstruction map is the pull-back map $\Pi_*^{\dagger} \bar{P}$ that defines a measure on the microscopic space Ω . In that way we can also compare the models by considering $\mathcal{R}(P | \Pi_*^{\dagger} \bar{Q}^{\theta})$, a strategy we apply in Section 5.

Returning to (5), as was pointed out in [46] in the context of coarse-graining of stochastic lattice systems and Kinetic Monte Carlo algorithms, the CKP inequality provides a strong indication that the relative entropy can control all observables ϕ . In our context, the CKP inequality (5) demonstrates that minimizing the *single observable* given by the relative entropy $\mathcal{R}(\Pi_* \mu | \bar{\mu}^{\theta})$, as proposed in [14, 10, 6, 67], i.e., training the parametric coarse-grained model based on

$$\min_{\theta \in \Theta} \mathcal{R}(\Pi_* \mu | \bar{\mu}^{\theta}), \quad (6)$$

instead of (1), will provide reliable coarse-graining parameterizations, applicable to *various observables*. Hence, due to (5), information-theoretic methods give rise to enhanced *transferability* properties of the resulting coarse-grained model with respect to other observables ϕ , *at a specific thermodynamic point*.

Remark 2.1. Very recently a sharper version of the CKP inequality has been established in [16]. Furthermore, in [22], it is shown that such information inequalities can be extended to path-space observables, e.g., ergodic averages, correlations, etc. The error between averaging an observable under the probabilistic model described by P as compared to the model given by Q can be then bounded

$$\Phi_{-}(P, Q; \phi) \leq \mathbb{E}_P[\phi] - \mathbb{E}_Q[\phi] \leq \Phi_{+}(P, Q; \phi). \quad (7)$$

In [22] the authors refer to $\Phi_{\pm}(P, Q; \phi)$ as “goal-oriented divergence” because it has the properties of a divergence both in the sense of probabilities P and Q and observables ϕ : $\Phi_{+}(P, Q; \phi) \geq 0$, (resp. $\Phi_{-}(P, Q; \phi) \leq 0$) and $\Phi_{\pm}(P, Q; \phi) = 0$ if and only if $P = Q$ a.s. or ϕ is constant P -a.s. Furthermore, $\Phi_{\pm}(P, Q; \phi)$ admits an expansion in the (small) relative entropy, [22]:

$$\Phi_{\pm}(P, Q; \phi) = \pm \sqrt{\text{Var}_P[\phi]} \sqrt{2\mathcal{R}(P|Q)} + \mathcal{O}(\mathcal{R}(P|Q)),$$

that captures the key properties of this new divergence. Similar relations hold for path-space observables, with the role of relative entropy played by the *relative entropy rate* (RER), [22], defined below in this section.

2.2. Variational inference and machine learning.

At this point we digress and point out connections between this and earlier information-based works for coarse-graining and variational inference methods. In the context of statistical variational inference (see for instance, [74, 55, 59]) one defines a flexible and rich enough parametrized family of distributions, and one finds the member of the family which is closest to the posterior distribution in a suitable metric. Subsequently one samples from that approximating distribution instead of the posterior itself. In this sense the inference problem is tackled using an optimization principle, hence the term “variational inference”.

More precisely, if we denote the posterior by P and the parametrized family by Q^{θ} over the parameter space $\theta \in \Theta \subseteq \mathbb{R}^k$ we typically consider in variational inference their “distance” as the minimization over all corresponding relative entropies

$$\min_{\theta \in \Theta} \mathcal{R}(P|Q^{\theta}). \quad (8)$$

Reversing the order to $\mathcal{R}(Q^{\theta}|P)$ can also be considered (as we also do in this paper), capturing different aspects of the posterior P due to the non-symmetry of the relative entropy, [59, 55]. In addition to the single parameter vector optimization in (8), we can also consider approximating Bayesian inference. This latter perspective gives rise to variational Bayesian inference, also known as ensemble learning, [55].

In many important cases, e.g., when Q^{θ} is a class of mean field models, that is a parametrized family of product distributions over the state space, the optimization problem (8) can be solved analytically, [74, 55, 59]. For instance, the mean field theory for the ferromagnetic Ising model can be also derived as the solution of (8), when Q^{θ} is a family of product distributions, [55]. Furthermore, more complex parametric families Q^{θ} than mean-field have been also considered in the literature, see for instance [74].

On the other hand, turning our attention towards the posterior P , an important class of models is exponential families, and in particular Gibbs distributions such as (12), also referred in the machine learning literature as Boltzmann machines, [59, 55]. For such posteriors, the minimization in (8) yields an equivalent variational free energy, [55]. Indeed this observation was also made in the coarse-graining literature and was the starting point of coarse-grained parameterizations based on a similar principle to the variational inference in (8), [69, 13, 6, 67], and [42]. However, an additional complexity to (8) arises in the coarse-graining case, where the coarse-graining map Π in (2) enters in the optimization problem (6),

$$\min_{\theta \in \Theta} \mathcal{R}(\Pi_* P | \bar{Q}^\theta) , \quad (9)$$

where $\bar{Q}^\theta$ is the parametrized coarse-grained model and P the microscopic Gibbs distribution. In addition to the variational inference point of view that allows for optimal parameterization of a coarse-grained model we can also use (9) as means to compare different coarse-graining maps $\Pi^{(i)}$. That is we can deploy (9) as an *Information Criterion* to assess and order their relative effectiveness, i.e., $\Pi^{(1)}$ is a superior coarse-graining map to $\Pi^{(2)}$, if and only if,

$$\min_{\theta \in \Theta} \mathcal{R}(\Pi_*^{(1)} P | \bar{Q}^\theta) < \min_{\theta \in \Theta} \mathcal{R}(\Pi_*^{(2)} P | \bar{Q}^\theta) . \quad (10)$$

The heuristic interpretation of (10) is that $\Pi^{(1)}$ provides better information compression than $\Pi^{(2)}$. **Authors in [24] compare different coarse-graining maps (resolutions) based on the entropic component of the many body potential of mean force.**

2.3. Computational variational inference methods in coarse-graining.

In equilibrium systems where the coarse-graining of Gibbs distributions P is considered, the coarse-grained family Q^θ in (9) is not necessarily mean field so there is no available analytic solution such as the ones discussed in [55]. In this case the minimization (9) is carried out using numerical optimization methods, [14, 6]. Although one can consider steepest descent and Newton-Raphson type methods for this optimization problem, the most efficient methods are stochastic optimization methods in the spirit of the Robbins-Monro algorithm, for the latter see [7] and references therein. In particular, in [6] the authors propose an algorithm that is essentially a stochastic optimization version of the Newton-Raphson algorithm. This method improves the Robbins-Monro algorithm by employing a *natural gradient* time-stepping, [2]. The natural gradient time-stepping arises as part of the Newton-Raphson scheme for (9), since the Hessian of the relative entropy is exactly the Fisher Information Matrix. A similar algorithm was also proposed in machine learning for stochastic variational inference, [32]. Finally, a Newton-Raphson method was introduced in [42] for the minimization of path-space relative entropy for dynamics and non-equilibrium systems discussed in Section 4. There the role of the natural gradient is played by the *path-space Fisher Information Matrix*, which is a type of Fisher Information for dynamics introduced first in the context of sensitivity analysis in [64].

3. Microscopic, coarse-grained and reconstructed processes for molecular systems

In this section we describe a prototypical molecular system at the microscopic scale and introduce its coarse graining as a configuration transformation that lumps together degrees of freedom. We define the underlying microscopic evolution in terms of a general stochastic differential equation and propose parametrized stochastic dynamics as a Markovian approximation of the coarse-grained process. We introduce a reconstruction of the coarse process defining a process that reintroduces the lost degrees of freedom and is approximating the microscopic evolution. The reconstructed process serves as an auxiliary process that connects the coarse-grained approximating dynamics with the microscopic dynamics on the same space.

3.1. Microscopic dynamics

We assume a prototypical system of N (classical) molecules in a box of the fixed volume V at the temperature T . Let $q = (q_1, \dots, q_N) \in \mathbb{R}^{3N}$ describe the position vectors of the N particles in the microscopic description and $p = (p_1, \dots, p_N) \in \mathbb{R}^{3N}$ the momentum vectors. We denote by $x = (q, p) \in \mathbb{R}^{6N}$ the joint vector of position and momentum. We consider the evolution of the N particles described by a diffusion process $\{X_t\}_{t \geq 0}$, a continuous time Markov process satisfying the stochastic differential equation (SDE)

$$\begin{cases} dX_t = b(X_t)dt + \sigma(X_t)dB_t, & t \geq 0, \\ X_0 \sim \mu_0, \end{cases} \quad (11)$$

where $b(x) \in \mathbb{R}^{6N}$ and $\sigma(x) \in \mathbb{R}^{6N \times k}$, $k \leq 6N$ are the drift and diffusion coefficients and B_t denotes the standard k -dimensional Brownian motion. The notation $X_0 \sim \mu_0$ means that the random variable X_0 is distributed according to the probability μ_0 . Throughout this paper we assume that the vector field $b(x)$ and the diffusion coefficient field $\sigma(x)$ are such that the system (11) has a unique solution for all $t \geq 0$, [61]. The general form (11) also accommodates the case of Hamiltonian equations of motions with the Langevin thermostat used for describing molecular systems at equilibrium in a thermal bath.

In general a Langevin process does not necessarily possess a stationary distribution, or such distribution may not be explicitly known. This can be the case when non-conservative external forces appear or when the detailed balance condition fails. Note that for stationary dynamics the detailed balance condition and time-reversibility are equivalent. If the force $F(q)$ is conservative and the fluctuation dissipation relation is satisfied, the Langevin dynamics are time irreversible up to momentum reversal, [50], which guarantees that the Gibbs canonical measure is a stationary distribution

$$\mu(dq) = Z^{-1} \exp\{-\beta U(q)\} dq, \quad (12)$$

where $U(q)$ is the potential energy such that $F(q) = -\nabla U(q)$, $Z = \int_{\mathbb{R}^{3N}} e^{-\beta U(q)} dq$ is the partition function and $\beta = \frac{1}{k_B T}$, k_B the Boltzmann constant. On the other hand for open systems, where the force $F(q)$ has a non conservative part, [26], i.e.

$$F(q) \neq -\nabla U(q).$$

a *non equilibrium steady state* (NESS) exists for which the condition of detailed balance fails.

We note here that in machine learning and neural networks distributions such as (12) are called Boltzmann machines and related reversible dynamics are considered for instance in stochastic Hopfield Models, [55].

3.2. Coarse-grained and reconstructed dynamics

Coarse-graining is considered as the application of a *linear* mapping (CG mapping) (see also (2) for a more general definition)

$$\mathbf{\Pi} : \mathbb{R}^n \rightarrow \mathbb{R}^m, \quad x \mapsto \mathbf{\Pi}x \in \mathbb{R}^m$$

on the microscopic state space. For notational simplicity we set $n = 6N$ and $m = 6M$. The mapping determines the $M(< N)$ CG particles with the state $\bar{x} = \mathbf{\Pi}x$ as a function of the microscopic state x . Examples of CG maps commonly used for molecular systems include the mapping to the centers of mass of groups of atoms, the end-to-end vector of molecular chains, projections to a collection of atoms, see also Section 6.2. We call ‘particles’ and ‘CG particles’ the elements of the microscopic and coarse configuration space respectively.

The *proposed coarse space dynamics* are described by a Markov process $\{\bar{X}_t\}_{t \geq 0}$ in $\mathbb{R}^m$ approximating the process $\{\mathbf{\Pi}X_t\}_{t \geq 0}$ which is, in principle, non-Markovian. The Markov process $\{\bar{X}_t\}_{t \geq 0}$ is given as the solution of the *parametrized* stochastic differential equations

$$\begin{cases} d\bar{X}_t = \bar{b}(\bar{X}_t; \theta)dt + \bar{\sigma}(\bar{X}_t; \theta)d\bar{B}_t, & t > 0, \\ \bar{X}_0 \sim \bar{\mu}_0, \end{cases} \quad (13)$$

where the drift $\bar{b}(x; \theta) \in \mathbb{R}^m$ and diffusion $\bar{\sigma}(x; \theta) \in \mathbb{R}^{m \times l}$, $l \leq m$, coefficients are parametrized with $\theta \in \Theta$. $\bar{B}_t$ is an l -dimensional standard Brownian motion. As we have already indicated the goal of our study is to find the most effective among the proposed CG models such that $\{\bar{X}_t\}_{t \geq 0}$ “best approximates” the process $\{\mathbf{\Pi}X_t\}_{t \geq 0}$, that is to find optimal $\bar{b}(x; \theta)$ and $\bar{\sigma}(x; \theta)$ in a parametric or non-parametric form, which is the subject of Section 5.

We define a *reconstructed* process of a coarse process $\{\bar{X}_t\}_{t \geq 0}$ in $\mathbb{R}^m$ onto the microscopic space $\mathbb{R}^n$ to be any stochastic process $\{\tilde{X}_t\}_{t \geq 0}$ which satisfies

$$\mathbf{\Pi}\tilde{X}_t = \bar{X}_t, \quad t \geq 0 \text{ in distribution.} \quad (14)$$

A reconstructed process $\{\tilde{X}_t\}_{t \geq 0}$ is obviously not unique, a trivial example is when $\mathbf{\Pi}$ is not a one-to-one transformation though the non-uniqueness is not of a concern for our methodology. The path-space measures in $[0, T]$ of the process we consider are denoted by

$$\begin{aligned} P_{[0, T]} & \text{ for the microscopic process } \{X_t\}_{t \geq 0}, \\ \bar{Q}_{[0, T]}^\theta & \text{ for the coarse process } \{\bar{X}_t\}_{t \geq 0} \text{ and} \\ Q_{[0, T]}^\theta & = \mathbf{\Pi}_*^\dagger \bar{Q}^\theta \text{ for the reconstructed process } \{\tilde{X}_t\}_{t \geq 0}, \end{aligned} \quad (15)$$

where the notation $\Pi_*^\dagger \bar{Q}^\theta$ is described in Section 2 as the reconstruction of the coarse path space measure $\bar{Q}_{[0,T]}^\theta$ onto the microscopic space. For the purpose of the present work we assume that the reconstructed process is the solution of the system

$$\begin{cases} d\tilde{X}_t = \tilde{b}(\tilde{X}_t; \theta)dt + \tilde{\sigma}(\tilde{X}_t; \theta)dB_t, & t \geq 0, \\ \tilde{X}_0 \sim \nu_0. \end{cases} \quad (16)$$

The coefficients $\tilde{b}(x; \theta)$ and $\tilde{\sigma}(x; \theta)$ must be such that the relation (14) is satisfied. Note that from the definition of the reconstructed process we have that for every observable of the form

$$f(x) = g(\Pi x),$$

i.e., a coarse observable, the expectations with respect to the probability of the reconstructed and the coarse process are identical

$$\mathbb{E}^x[f(\tilde{X}_\tau)] = \mathbb{E}^{\Pi x}[g(\bar{X}_\tau)], \quad (17)$$

when $\tilde{X}_0 = x$ and $\bar{X}_0 = \Pi x$ and for any stopping time $\tau > 0$. We denote $\mathbb{E}^x$ the expectation with respect to the probability of $\{\tilde{X}_t\}_{t \geq 0}$, $R(\tilde{X}_{t_1} \in F_1 \dots, \tilde{X}_{t_k} \in F_k) = P(\tilde{X}_{t_1}^x \in F_1 \dots, \tilde{X}_{t_k}^x \in F_k)$, for any $F_i, i = 1, \dots, k$ subsets of $\mathbb{R}^n$, where $\tilde{X}_t^x$ denotes that $\tilde{X}_t$ starts at $X_0 = x$. $\mathbb{E}^{\Pi x}$ denotes the expectation with respect to the probability of $\{\bar{X}_t\}_{t \geq 0}$ starting at $\bar{X}_0 = \Pi x$.

With the following theorem we give sufficient conditions that the $\tilde{b}(x; \theta)$ and $\tilde{\sigma}(x; \theta)$ must satisfy in order the relation (14) to hold. A detailed study of reconstructed processes is presented in the work [43], where explicit examples for stochastic lattice systems are presented. The proof of the theorem is given in Appendix A, and follows from the martingale uniqueness theorem, [38, 61].

Theorem 3.1. (Reconstruction)

Let the processes $\{\bar{X}_t\}_{t \geq 0}$ in $\mathbb{R}^m$ and $\{\tilde{X}_t\}_{t \geq 0}$ in $\mathbb{R}^n$ be solutions of (13) and (16) respectively, and $\Pi : \mathbb{R}^n \rightarrow \mathbb{R}^m$ a linear mapping. Assume that $\tilde{b}(x; \theta)$ and $\tilde{\sigma}(x; \theta)$ are such that the existence and uniqueness of solutions to (16) is guaranteed. If

$$\Pi \tilde{b}(x; \theta) = \bar{b}(\Pi x; \theta), \quad (18)$$

$$\Pi \tilde{\Sigma}(x; \theta) \Pi^{tr} = \bar{\Sigma}(\Pi x; \theta) \text{ for all } x \in \mathbb{R}^n, \quad (19)$$

where $\tilde{\Sigma}(x; \theta) = \tilde{\sigma}(x; \theta) \tilde{\sigma}^{tr}(x; \theta)$ and $\bar{\Sigma}(\bar{x}; \theta) = \bar{\sigma}(\bar{x}; \theta) \bar{\sigma}^{tr}(\bar{x}; \theta)$ and $\cdot^{tr}$ denotes matrix transpose, then

$$\Pi \tilde{X}_t = \bar{X}_t, \quad t \geq 0 \text{ in distribution.}$$

In particular, the relation (17) holds for all coarse observables $f(x) = g(\Pi x)$.

Remark 3.1. (a) For a non-linear CG mapping Π , such as transformations to reaction coordinates [37, 49], relations (18) and (19) do not hold. The proof of Theorem 3.1 demonstrates the direction how these relations can be generalized to non-linear mappings.

(b) In the rest of our work we assume that the diffusion term $\bar{\sigma}(\bar{x}; \theta)$ is not parametrized i.e., $\bar{\sigma}(\bar{x}; \theta) = \bar{\sigma}(\bar{x})$ and is such that

$$\bar{\Sigma}(\Pi x) = \Pi \Sigma(x) \Pi^{tr} ,$$

where $\Sigma(x) = \sigma(x) \sigma^{tr}(x)$ and $\bar{\Sigma}(\bar{x}; \theta) = \bar{\sigma}(\bar{x}) \bar{\sigma}^{tr}(\bar{x})$. This requirement ensures that the diffusion coefficient of the reconstructed process $\{\tilde{X}_t\}_{t \geq 0}$, coincides with the one of the microscopic process $\{X_t\}_{t \geq 0}$,

$$\tilde{\sigma}(x; \theta) = \sigma(x) , \quad (20)$$

a condition that we need for the development of the theoretical tools in Section 4.1. We point out that the assumption (20) is not necessary in the development of the variational inference problem for data driven systems; this will be further discussed in Section 7.

4. Variational inference for coarse-grained dynamics.

In analogy to the previous discussion in Section 2 for the coarse-graining of Gibbs distributions, our approach to coarse-graining of dynamics can also be viewed as a variational inference method, however, this time set in the path space. We present an extension of the information-theoretic approach to systems with *non-equilibrium steady states* as well as dynamics in *finite times*. The presented method also allows for approximation of *dynamical* observables, i.e., quantities that are averaged over the path distribution instead of over a distribution at a terminal time.

The relative entropy between two path measures $P_{[0,T]}$ and $Q_{[0,T]}$ (see [42] for a specific examples) for the processes on the interval $[0, T]$ is

$$\mathcal{R}(P_{[0,T]} | Q_{[0,T]}) = \int \log \frac{dP_{[0,T]}}{dQ_{[0,T]}} dP_{[0,T]} \equiv \mathbb{E}_{P_{[0,T]}} \left[\log \frac{dP_{[0,T]}}{dQ_{[0,T]}} \right] , \quad (21)$$

where $\frac{dP_{[0,T]}}{dQ_{[0,T]}}$ is the likelihood ratio (or the Radon-Nikodým derivative) of $P_{[0,T]}$ with respect to $Q_{[0,T]}$ and $\mathbb{E}_{P_{[0,T]}}[f]$ denotes averaging over the probability of paths $X_t(\omega)$, $t \in [0, T]$, $P_{[0,T]}$. Naturally, we have to assume that the measures $P_{[0,T]}$, $Q_{[0,T]}$ are absolutely continuous, that is if for an event A holds $Q_{[0,T]}(A) = 0$ then $P_{[0,T]}(A) = 0$, and $\log \frac{dP_{[0,T]}}{dQ_{[0,T]}}$ is $P_{[0,T]}$ -integrable.

In the setting of coarse-graining or model-reduction the measure $P_{[0,T]}$ is associated with the exact process (mapped to the coarse space) and $Q_{[0,T]}$ is associated with the approximating coarse-grained process. In general the relative entropy (21) in this dynamic setting is not a suitable object for analyzing steady states or long-time behavior, however, in practically relevant cases of *stationary* Markov processes we can work with the *relative entropy rate* (RER)

$$\mathcal{H}(P | Q) = \lim_{T \rightarrow \infty} \frac{1}{T} \mathcal{R}(P_{[0,T]} | Q_{[0,T]}) , \quad (22)$$

where P and Q denote the corresponding stationary processes. The definitions of (21) and (22) do not depend on knowing the distributions or an underlying Gibbs distribution

making them *suitable for non-equilibrium problems* where even the steady states are not known analytically. We also refer to [64, 73, 22] where this feature is employed to develop sensitivity analysis methods for non-equilibrium systems.

In order to select the best approximation of the coarse-grained model, i.e., of the exact coarse-grained measure $Q_{[0,T]}$, we define a parametrized family of measures $Q_{[0,T]}^\theta$ depending on parameters $\theta \in \Theta$. The best approximation is fitted using entropy based criteria in order to find the best Markovian approximation of the coarse-grained process. We consider the optimization principle

$$\min_{\theta \in \Theta} \mathcal{R}(P_{[0,T]} | \Pi_*^\dagger \bar{Q}_{[0,T]}^\theta), \quad (23)$$

where $P_{[0,T]}$ is the path distribution of the original microscopic process and $\Pi_*^\dagger \bar{Q}_{[0,T]}^\theta$ is the parametrized path-space coarse-grained distribution back-mapped to the microscopic space. Furthermore, for coarse-graining of stationary dynamics we consider the variational inference optimization problem based on the relative entropy rate (RER) instead of the full relative entropy

$$\min_{\theta \in \Theta} \mathcal{H}(P | \Pi_*^\dagger \bar{Q}^\theta). \quad (24)$$

We note that for dynamics we have essentially another Gibbs structure such as (12), however, this time in the space-time. Precisely this structure is used to obtain the relative entropy rate calculations in Theorem 4.1.

4.1. Path-space information methods for diffusion processes

The purpose of this section is to compare continuous time Markov processes at the same state space given as solutions of stochastic differential equations. We provide explicit representations of the relative entropy (RE) and relative entropy rate (RER) for the path-space measures of the processes $\{X_t\}_{t \geq 0}$ and $\{\tilde{X}_t\}_{t \geq 0}$ in $\mathbb{R}^n$, solutions of the SDEs (11) and (16) respectively, in terms of their drift and diffusion coefficients, for (a) the finite time and (b) the stationary (steady-state) regime for molecular systems under non-equilibrium conditions.

The key mathematical tool that allows us to express the RE $\mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta)$, and the RER $\mathcal{H}(P | Q^\theta)$, defined in (21) and (22) respectively, in terms of the drift and diffusion coefficients appearing in (11) and (16), is the Girsanov theorem, see Appendix A.2, [61, 38]. Suppose that there exists a process $\{u(X_s; \theta)\}_{s \geq 0}$ in $\mathbb{R}^k$ such that

$$\sigma(X_s)u(X_s; \theta) = b(X_s) - \tilde{b}(X_s; \theta), \text{ and } \mathbb{E} \left[e^{\frac{1}{2} \int_0^T |u(X_s; \theta)|^2 ds} \right] < \infty, \quad (25)$$

where $|u(x; \theta)|^2 = \sum_{i=1}^k u_i^2(x; \theta)$. Recall that a process $\{X_t\}_{t \geq 0}$ is stationary when its joint distribution does not change with time.

Theorem 4.1. *Let $\{X_t\}_{t \geq 0}$, $\{\tilde{X}_t\}_{t \geq 0}$ be Markov processes, solutions of (11) and (16) with path space distributions $P_{[0,T]}$, $Q_{[0,T]}^\theta$, respectively, and $X_0 \sim \mu_0$, $\tilde{X}_0 \sim \nu_0$ for which (20) holds. Suppose that there exists a process $\{u(X_t; \theta)\}_{t \geq 0}$, as defined in (25). Then*

426 a) the relative entropy between $P_{[0,T]}$ and $Q_{[0,T]}^\theta$, for any $[0, T]$, is

$$\mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) = \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) + \mathcal{R}(\mu_0 | \nu_0) , \quad (26)$$

427 where

$$\mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) = \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T |u(X_s; \theta)|^2 ds \right] . \quad (27)$$

428 b) If furthermore $\{X_t\}_{t \geq 0}$ and $\{\tilde{X}_t\}_{t \geq 0}$ are stationary Markov processes, with $\mu(dx)$ the in-
429 variant measure for $\{X_t\}_{t \geq 0}$ then

$$\mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) = T\mathcal{H}(P | Q^\theta) + \mathcal{R}(\mu | \nu_0) , \quad (28)$$

430 where $\mathcal{H}(P | Q^\theta)$ is the the relative entropy rate which is given by

$$\mathcal{H}(P | Q^\theta) = \mathbb{E}_\mu \left[\frac{1}{2} |u(X; \theta)|^2 \right] . \quad (29)$$

431 The proof of the theorem is given in Appendix A.3. Theorem 4.1 a) gives a form of
432 the relative entropy for any finite time interval $[0, T]$ while Theorem 4.1 b) addresses the
433 long time regimes providing a reduced form of (26). Note that the relation (26) holds for
434 any process $\{X_t\}_{t \geq 0}$, not necessarily stationary. Another important result that Theorem 4.1
435 states is that relation (29) holds for any initial condition $\tilde{X}_0 \sim \nu_0$, where ν_0 is not necessarily
436 an invariant measure. **The two properties that ensure the linear in time increase of the RE
437 and the existence of the RER are (a) the Markov property and (b) the stationarity. Thus
438 the ratio of the path probability densities on $[0, T]$ will be constant independent of the time
439 interval length T . Markovianity though is not the most general condition, for example the
440 semi-Markov property is also sufficient, [64].**

441 As we see from relation (26) the relative entropy $\mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta)$ is a quantity that
442 increases in time, thus calculation of the RE over long time intervals may become unfeasible.
443 Though for finite time intervals calculations may be tractable. This fact is depicted in the
444 following corollary where we provide an explicit formula of the finite time component (27)
445 along with one of RER (29) in terms of the drift and diffusion coefficients.

446 **Corollary 4.1. (a) (RER representation for stationary processes)**

447 Let $\sigma(x) \in \mathbb{R}^{n \times k}$, $x \in \mathbb{R}^n$ appearing in (11) with $\text{rank}(\sigma(x)) = r = k \leq n$. Suppose that
448 there exists $u(x; \theta) \in \mathbb{R}^k$ satisfying (25). Then

$$\mathcal{H}(P | Q^\theta) = \mathbb{E}_\mu \left[\frac{1}{2} \|b(X) - \tilde{b}(X; \theta)\|_\Xi^2 \right] , \quad (30)$$

449 where $\Xi(x) = [\sigma^{tr}(x)\sigma(x)]^{-1} \sigma^{tr}(x)$ and $\|\cdot\|_\Xi$ denotes the norm

$$\|z\|_\Xi = z^{tr} \Xi^{tr} \Xi z , \quad z \in \mathbb{R}^n . \quad (31)$$

(b) (RE representation for finite time)

$$\mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) = \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) + \mathcal{R}(\mu_0 | \nu_0) ,$$

where

$$\mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) = \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|b(X_s) - \tilde{b}(X_s; \theta)\|_\Xi^2 ds \right] . \quad (32)$$

The result of Corollary 4.1 can be generalized to any $\sigma(x)$ with $\text{rank}(\sigma(x)) = r < k \leq n$ if we use in place of $\Xi(x)$ a (Moore-Penrose) generalized inverse of $\sigma(x)$, [66, 4]. For completeness we provide the proof of Corollary 4.1(a) in Appendix A.4 and note that the proof of (b) is similar.

Remark 4.1. Note that the representations (30) and (32) are valid when $\{X_t\}_{t \geq 0}$ or $\{\tilde{X}_t\}_{t \geq 0}$ are Ito processes. The first time we need that $\{X_t\}_{t \geq 0}$ and $\{\tilde{X}_t\}_{t \geq 0}$ are both (Ito) diffusions is when we want to use the stationarity of the processes to simplify the RE to RER such that we have $u(x; \theta)$ independent of time t . If $b(x)$ is substituted by $b(x, t)$ (in which case the microscopic process is non-Markovian), [61], then we would have

$$\mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) = \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|b(X_s, s) - \tilde{b}(X_s; \theta)\|_\Xi^2 ds \right] .$$

Even if $\{X_t\}_{t \geq 0}$ is stationary it is not obvious that $b(X_s, s) - \tilde{b}(X_s; \theta)$ is stationary, and the reduction to the RER needs to be checked casewise.

5. Variational inference in coarse graining and path-space force matching

The goal of this section is to obtain optimal parameters θ^* of a coarse-grained dynamics model $\{\bar{X}_t\}_{t \geq 0}$, eq. (13), approximating the microscopic dynamics $\{X_t\}_{t \geq 0}$, eq. (11), based on the path-space variational inference described by (23) and (24). We prove that minimization of the RE reduces to time dependent weighted least squares type problems with weights that depend on the CG mapping and the diffusion coefficient. For stationary regimes the time dependence is altered with the minimization of the RER. The weighted least squares formulation provides a natural generalization of the force matching methods developed for systems at equilibrium, [33], to non-equilibrium systems. Moreover, the relation of RE and force matching type optimization methods is revealed, in analogy to the equilibrium case, studied in [60, 67, 37].

5.1. Properties of the CG mapping and the reconstructed process

We recall that the coarse-graining map $\mathbf{\Pi} : \mathbb{R}^n \rightarrow \mathbb{R}^m$ defined in Section 3 is a *linear transformation*. We denote with the same letter $\mathbf{\Pi} \in \mathbb{R}^{m \times n}$ the matrix representation of the linear map $\mathbf{\Pi}$. Furthermore, we assume that the CG map has full rank,

$$\text{rank}(\mathbf{\Pi}) = m .$$

We consider the reconstructed process $\{\tilde{X}_t\}_{t \geq 0}$ as defined in Section 3.2, Theorem 3.1, and Remark 3.1, i.e., such that

$$\mathbf{\Pi} \tilde{b}(x; \theta) = \bar{b}(\mathbf{\Pi} x; \theta), \text{ and } \bar{\sigma}(x; \theta) = \sigma(x) \text{ for all } x \in \mathbb{R}^n.$$

Thus the coarse diffusion coefficient $\bar{\sigma}(\bar{x})$ is independent of the parameters θ , and

$$\bar{\Sigma}(\mathbf{\Pi} x) = \mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr} \text{ for all } x \in \mathbb{R}^n. \quad (33)$$

The reconstructed drift term $\tilde{b}(x; \theta)$ is a vector field in $\mathbb{R}^n$ that can be written as

$$\tilde{b}(x; \theta) = \mathbf{\Pi}^\# \bar{b}(\mathbf{\Pi} x; \theta) + (I_n - \mathbf{\Pi}^\# \mathbf{\Pi}) y^\perp(x), \text{ for all } x \in \mathbb{R}^n, \quad (34)$$

where I_n denotes the identity matrix in $\mathbb{R}^n$, $\mathbf{\Pi}^\#$ is a right inverse of $\mathbf{\Pi}$, an $n \times m$ matrix such that

$$\mathbf{\Pi} \mathbf{\Pi}^\# = I_m, \quad (35)$$

and $y^\perp(x)$ is any arbitrary vector in $\mathbb{R}^n$ satisfying $\mathbf{\Pi} (I_n - \mathbf{\Pi}^\# \mathbf{\Pi}) y^\perp = 0_m$. In principle, $\mathbf{\Pi}^\#$ is not unique, though for any such $\mathbf{\Pi}^\#$ it holds $\bar{b} = \mathbf{\Pi} \tilde{b}$ which is the main property that we need. We choose $\mathbf{\Pi}$ to have the full rank so we have an explicit form $\mathbf{\Pi}^\#$, that is

$$\mathbf{\Pi}^\# = \mathbf{\Pi}^{tr} (\mathbf{\Pi} \mathbf{\Pi}^{tr})^{-1}.$$

Most of the CG maps related to specific applications we consider are of a full rank, e.g., mapping to the centers of mass of groups of atoms, or projecting to fewer state space coordinates, see Section 6.2. As already mentioned, and relation (34) verifies, the reconstructed process is not unique. Therefore one can always choose the term of the reconstructed drift $(I_n - \mathbf{\Pi}^\# \mathbf{\Pi}) y^\perp(x)$ in (34) independent of the parameter θ . In the rest of this work we assume that $(I_n - \mathbf{\Pi}^\# \mathbf{\Pi}) y^\perp(x)$ is independent of the parameter θ .

5.2. Optimal coarse-grained dynamics

Having set up the optimization problems (23) and (24), in this section we look for optimal solutions $\theta^*(T)$ and θ^* respectively, based on the first order optimality condition. That is if θ^* is a solution of (24) then

$$\nabla_\theta \mathcal{H}(P | Q^{\theta^*}) = 0. \quad (36)$$

Thus solutions of (36) reveal the local optima of the RER. Note that if the RER is a strictly convex function of θ then there is a unique (global minimum) θ^* . This property clearly depends on the choice of the parametrized model, i.e., through the definition of the parametrized drift $\bar{b}(\bar{x}; \theta)$, see for an example Remark 5.1.

Theorem 5.1. *Let $\mathbf{\Pi} : \mathbb{R}^n \rightarrow \mathbb{R}^m$ be a linear mapping with $\text{rank}(\mathbf{\Pi}) = m$. Consider the microscopic process $\{X_t\}_{t \geq 0}$ and the coarse process $\{\bar{X}_t\}_{t \geq 0}$ satisfying (11) and (13) respectively, with the drift $b(x)$, $\bar{b}(\bar{x}; \theta)$ and the diffusion terms $\sigma(x)$, $\bar{\sigma}(\bar{x})$, such that (33) holds, $\text{rank}(\sigma) = k$ and $X_0 \sim \mu_0$, $\bar{X}_0 \sim \bar{\mu}_0$. Let $\{\tilde{X}_t\}_{t \geq 0}$ be a reconstructed process of $\{\bar{X}_t\}_{t \geq 0}$ with the drift $\tilde{b}(x; \theta)$ defined in (34) and the diffusion coefficient $\sigma(x)$. Then, for any $\mathbf{\Pi}^\#$ satisfying (35),*

a)

$$\operatorname{argmin}_{\theta \in \Theta} \mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) = \operatorname{argmin}_{\theta \in \Theta} \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\Pi b(X_s) - \bar{b}(\Pi X_s; \theta)\|_{\Pi^\# \Xi}^2 ds \right].$$

where

$$\|z\|_{\Pi^\# \Xi}^2 = z^{tr} \Pi^\# \Xi^{tr} \Xi \Pi^\# z, \quad z \in \mathbb{R}^m \quad \text{and} \quad \Xi = [\sigma^{tr}(x) \sigma(x)]^{-1} \sigma^{tr}(x).$$

b) If moreover $\{X_t\}_{t \geq 0}$ is stationary with the invariant measure μ , then

$$\operatorname{argmin}_{\theta \in \Theta} \mathcal{H}(P | Q^\theta) = \operatorname{argmin}_{\theta \in \Theta} \mathbb{E}_\mu \left[\frac{1}{2} \|\Pi b(X) - \bar{b}(\Pi X; \theta)\|_{\Pi^\# \Xi}^2 \right],$$

We present the proof in Appendix A.5.

Theorem 5.1 proves that the variational inference problems (23) and (24) are force matching type problem with the norm $\|z\|_{\Pi^\# \Xi}$ instead of the usual Euclidean norm. Moreover, Theorem 5.1 a) is a time dependent force matching, i.e., force matching over paths, thus we may call the optimization problem the *path-space force matching*. Note that the calculations involved in the proof of Theorem 5.1 are independent of the fluctuation-dissipation and detailed balance, thus they apply to non-equilibrium systems directly. Theorem 5.1 b) shows that relative entropy rate (RER) minimization and FM are essentially identical. In particular formula (28) reveals what each method is doing: the one minimizes $\mathcal{R}(\mu | \mu^\theta)$ and the other the relative entropy rate $H(P | Q^\theta)$.

Remark 5.1. The existence of the *unique global minimum* is guaranteed if, for example, the force field $\bar{b}(\bar{x}; \theta)$ depends linearly on θ . Let $\{\phi_k(\bar{x})\}_{k=1}^K$ be a set of m -valued polynomials on $\mathbb{R}^m$ and approximate the force field $\bar{b}(\bar{x}; \theta)$ by

$$\bar{b}(\bar{x}; \theta) = \sum_k^K \theta_k \phi_k(\bar{x}).$$

In this case the minimization of RER is the least squares fit with respect to the stationary measure $\mu(dx)$. Due to the linear dependence on θ the minimization problem has a unique solution due to strict convexity of RER. Note that RE is also convex in this case and uniqueness of the corresponding optimization problem is guaranteed. The optimization problem reduces to solution of the linear system

$$\Phi \theta = \mathbf{a}, \quad \text{where} \quad \Phi_{ij} = \mathbb{E}_\mu[\langle \phi_i, \phi_j \rangle_{\Pi^\# \Xi}], \quad \mathbf{a}_i = \mathbb{E}_\mu[\langle \phi_i, b \rangle_{\Pi^\# \Xi}], \quad i, j = 1, \dots, K.$$

Moreover, this set-up is also used in estimation of non-parametric models, for example by specifying the basis set $\{\phi_i\}$ to be splines, or wavelets, [56].

6. Effective Langevin dynamics and path-space force matching.

We present the application of the path-space force matching described in the previous section to the stochastic Langevin dynamics for molecular systems. We propose Langevin-type coarse dynamics with a parametrized force (and friction) and derive the optimal parameter set for which the path space relative entropy is minimized, both for finite time and stationary dynamics. Furthermore, we present two specific coarse graining maps: (a) The transformation to the centers of mass of groups of atoms, and (b) the projection to a selected subset of atoms.

The Langevin dynamics are described by the process $\{(q_t, p_t)\}_{t \geq 0}$, for an N -particle molecular system with positions $q = (q_1, \dots, q_N) \in \mathbb{R}^{3N}$ and momenta $p = (p_1, \dots, p_N) \in \mathbb{R}^{3N}$ which satisfies

$$\begin{cases} dq_t = \mathbb{M}^{-1} p_t dt, \\ dp_t = F(q_t) dt - \gamma \mathbb{M}^{-1} p_t dt + \sigma dB_t, \end{cases} \quad (37)$$

a Hamiltonian system coupled with a thermostat, where $F(q)$ is the force field that is not necessarily a gradient, see also discussion in Section 3.1. $\mathbb{M} = \text{diag}(m_1 I_3, \dots, m_N I_3) \in \mathbb{R}^{3N \times 3N}$ is the mass matrix, $\gamma \in \mathbb{R}^{3N \times 3N}$ is the friction and $\sigma \in \mathbb{R}^{3N \times 3N}$ the diffusion coefficients respectively, and B_t is the $3N$ -dimensional Brownian motion. The diffusion and friction coefficients satisfy the fluctuation-dissipation relation $\sigma \sigma^{tr} = 2\beta^{-1} \gamma$.

Note that we have assumed that friction and diffusion coefficients are independent of the process, though our methodology is also applicable for $\gamma = \gamma(q)$ and $\sigma = \sigma(q)$, see Remark 6.5. The latter can be crucial if the microscopic and the CG molecular systems are not diffusive or when one wants to restrict the thermostat at the boundaries.

Let $M(< N)$ be the degrees of freedom of the coarse space, i.e., the number of CG particles, and define the linear coarse-graining map $\Pi_q : \mathbb{R}^{3N} \rightarrow \mathbb{R}^{3M}$ by

$$\Pi_q q_j = \sum_{i=1}^N \zeta_{ji} q_i, \quad j = 1, \dots, M, \text{ for any } q \in \mathbb{R}^{3N}, \quad (38)$$

for any set $\zeta_{ji} \in \mathbb{R}$, $j = 1, \dots, M, i = 1, \dots, N$, such that $\text{rank}(\Pi_q) = 3M$, Π_q denotes the matrix representing the transformation (38)

$$\Pi_q = [\zeta_{ji} I_3],$$

where I_3 is the 3-dimensional identity matrix. Furthermore, we denote

$$\Pi : \mathbb{R}^{6N} \rightarrow \mathbb{R}^{6M}, \quad \Pi x = (\Pi_q q, \Pi_p p), \quad x = (q, p),$$

where $\Pi_p : \mathbb{R}^{3N} \rightarrow \mathbb{R}^{3M}$ denotes the momentum transformation. Let the CG particles have mass matrix

$$\bar{\mathbb{M}} = \text{diag}(\bar{m}_1 I_3, \dots, \bar{m}_M I_3) \in \mathbb{R}^{3M \times 3M}.$$

The momentum mapping Π_p is given by

$$\Pi_p = \bar{\mathbb{M}} \Pi_q \mathbb{M}^{-1}, \quad (39)$$

such that $\mathbf{\Pi}_q dq_t = \mathbf{\Pi}_q \mathbb{M}^{-1} p_t dt = \overline{\mathbb{M}}^{-1} \mathbf{\Pi}_p p_t dt$. In the work [60] the mass matrix $\overline{\mathbb{M}}$ is defined such that a consistency condition in the momentum space is satisfied which, with (39), defines the mass of the CG particles $\bar{m}_j, j = 1, \dots, M$. The consistency condition states that the momentum probability distribution of the coarse variables is the same on the coarse space and the microscopic space, that is $e^{-\beta \bar{p}^{tr} \overline{\mathbb{M}}^{-1} \bar{p}} \propto \int e^{-\beta p^{tr} \mathbb{M}^{-1} p} \delta(\mathbf{\Pi}_p p - \bar{p}) dp$.

The proposed dynamics for the coarse variables $\bar{x} = (\bar{q}, \bar{p}) \in \mathbb{R}^{6M}$ are given by the Langevin system

$$\begin{cases} d\bar{q}_t = \overline{\mathbb{M}}^{-1} \bar{p}_t dt, \\ d\bar{p}_t = \bar{F}(\bar{q}_t; \theta) dt - \bar{\gamma} \overline{\mathbb{M}}^{-1} \bar{p}_t dt + \bar{\sigma} d\bar{B}_t, \end{cases} \quad (40)$$

where $\bar{B}_t$ is a $3M$ -dimensional Brownian motion. The diffusion coefficient $\bar{\sigma}$ is defined, according to relation (33), such that

$$\bar{\sigma} \bar{\sigma}^{tr} = \mathbf{\Pi}_p \sigma \sigma^{tr} \mathbf{\Pi}_p^{tr}.$$

We examine two cases for the friction coefficient:

(a) It matches the coarse graining transformation of the microscopic friction forces

$$\bar{\gamma} \mathbf{\Pi}_q = \mathbf{\Pi}_p \gamma. \quad (41)$$

(b) The fluctuation-dissipation relation is satisfied for the coarse space dynamics. Since the fluctuation dissipation relation is satisfied for the microscopic dynamics the friction coefficient in CG dynamics must be

$$\bar{\gamma} = \frac{1}{2} \beta \bar{\sigma} \bar{\sigma}^{tr} = \mathbf{\Pi}_p \gamma \mathbf{\Pi}_p^{tr}. \quad (42)$$

Hence, the parametrization of the coarse dynamics is described here only through the force

$$\bar{F}(\bar{q}; \theta), \quad \theta \in \Theta,$$

where Θ is the parameter space. The Langevin system (37) is written in the form of the SDE (11) if we set $n = 6N$, $x = (q, p)$,

$$b(x) = (\mathbb{M}^{-1} p, F(q) - \gamma \mathbb{M}^{-1} p)^{tr},$$

and

$$\sigma(x) = \sigma_0 = (0_{3N}, \sigma)^{tr} \in \mathbb{R}^{6N \times 3N}.$$

We also associate the coarse-grained dynamics with the SDE (13) where $m = 6M$, $\bar{x} = (\bar{q}, \bar{p})$ and

$$\bar{b}(\bar{x}; \theta) = (\overline{\mathbb{M}}^{-1} \bar{p}, \bar{F}(\bar{q}; \theta) - \bar{\gamma} \overline{\mathbb{M}}^{-1} \bar{p})^{tr}.$$

Note that $\text{rank}(\sigma_0) = 3N$ and $\text{rank}(\mathbf{\Pi}) = 6M$ since $\text{rank}(\mathbf{\Pi}_q) = 3M$. **Moreover, we assume that given the CG map we can find a reconstructed process as described in Section 3.2.**

547 Applying the results of Sections 4.1 and 5 we provide the optimal parameter set θ^* for
 548 which the CG Langevin process $(\bar{q}_t, \bar{p}_t)_{t \geq 0}$ best approximates $\mathbf{\Pi}(q_t, p_t)_{t \geq 0} = (\mathbf{\Pi}_q q_t, \mathbf{\Pi}_p p_t)_{t \geq 0}$,
 549 in the sense that the path space RE (or RER) is minimized, see Theorem 5.1. We state the
 550 result for the stationary regime and for the finite-time evolution.

Stationary regime. Considering the description of the CG dynamics and assumptions on $\bar{\gamma}$, $\bar{\sigma}$ and $\mathbf{\Pi}$ mentioned above, conditions of Theorem 5.1 b) are satisfied thus we have that, for stationary microscopic Langevin dynamics

$$\theta^* = \operatorname{argmin}_{\theta} \mathbb{E}_{\mu} \left[\frac{1}{2} \|\mathbf{\Pi} b(X) - \bar{b}(\mathbf{\Pi} X; \theta)\|_{2, \mathbf{\Pi}^{\#} \Xi}^2 \right]$$

where $\mu(dq, dp)$ is the stationary distribution for $\{(q_t, p_t)\}_{t \geq 0}$ and

$$\|z\|_{2, \mathbf{\Pi}^{\#} \Xi}^2 = z^{tr} \mathbf{\Pi}^{\#} \Xi^{(2), tr} \Xi^{(2)} \mathbf{\Pi}^{\#} z, \quad z \in \mathbb{R}^{6M},$$

with

$$\Xi^{(2)} = [\sigma^{tr} \sigma]^{-1} \sigma_0^{tr},$$

551 and $\mathbf{\Pi}^{\#} \in \mathbb{R}^{6N \times 6M}$ is a right inverse of $\mathbf{\Pi}$, that has the form $\mathbf{\Pi}^{\#} = \begin{bmatrix} \mathbf{\Pi}_q^{\#} & 0 \\ 0 & \mathbf{\Pi}_p^{\#} \end{bmatrix}$ for any

552 $\mathbf{\Pi}_q^{\#} \in \mathbb{R}^{3N \times 3M}$ such that $\mathbf{\Pi}_q \mathbf{\Pi}_q^{\#} = I_{3M}$ and $\mathbf{\Pi}_p^{\#} = \mathbb{M} \mathbf{\Pi}_q^{\#} \bar{\mathbb{M}}^{-1}$.

Therefore,

$$\|\mathbf{\Pi} b(x) - \bar{b}(\mathbf{\Pi} x; \theta)\|_{2, \mathbf{\Pi}^{\#} \Xi}^2 = \|\mathbf{\Pi}_p F(q) - \bar{F}(\mathbf{\Pi}_q q; \theta) - (\mathbf{\Pi}_p \gamma \mathbb{M}^{-1} p - \bar{\gamma} \bar{\mathbb{M}}^{-1} \mathbf{\Pi}_p p)\|_{\mathbf{\Pi}_p^{\#} \Xi}^2,$$

where

$$\|u\|_{\mathbf{\Pi}_p^{\#} \Xi}^2 = u^{tr} \mathbf{\Pi}_p^{\#} \Xi^{tr} \Xi \mathbf{\Pi}_p^{\#} u, \quad u \in \mathbb{R}^{3M}$$

and

$$\Xi = [\sigma^{tr} \sigma]^{-1} \sigma^{tr}.$$

553 If the friction coefficient is given as in the case (a), eq. (41), the optimal parameter set is

$$\theta^* = \operatorname{argmin}_{\theta} \mathbb{E}_{\mu_p} \left[\frac{1}{2} \|\mathbf{\Pi}_p F(q) - \bar{F}(\mathbf{\Pi}_q q; \theta)\|_{\mathbf{\Pi}_p^{\#} \Xi}^2 \right]. \quad (43)$$

554 This is exactly the force matching problem related to the Hamiltonian dynamics. On the
 555 other hand, if the friction coefficient is given by (b), eq. (42),

$$\theta^* = \operatorname{argmin}_{\theta} \mathbb{E}_{\mu_p} \left[\frac{1}{2} \|\mathbf{\Pi}_p F(q) - \bar{F}(\mathbf{\Pi}_q q; \theta) - (\mathbf{\Pi}_p \gamma - \mathbf{\Pi}_p \gamma \mathbf{\Pi}_p^{tr} \mathbf{\Pi}_q) \mathbb{M}^{-1} p\|_{\mathbf{\Pi}_p^{\#} \Xi}^2 \right]. \quad (44)$$

556 **Remark 6.1.** The appearance of the term $(\mathbf{\Pi}_p \gamma - \mathbf{\Pi}_p \gamma \mathbf{\Pi}_p^{tr} \mathbf{\Pi}_q) \mathbb{M}^{-1} p$ in the optimization is
 557 the result of the difference of the friction forces that contribute to the CG particle, since
 558 we consider a fixed diffusion term $\bar{\sigma}$, which is related to the chosen stochastic CG dynamics
 559 (40).

Remark 6.2. Note that if $F(q) = -\nabla U(q)$, then

$$\mu_p(dq, dp) = Z^{-1} \exp\{-\beta H(q, p)\},$$

is the Gibbs distribution, where $H(q, p) = \frac{1}{2}p^{tr}\mathbb{M}^{-1}p + U(q)$. If $F(q) \neq -\nabla U(q)$, i.e., driven Langevin dynamics, the form of $\mu_p(dq, dp)$ is not analytically known, though in numerical implementations it is not needed as sets of samples $(q^{(i)}, p^{(i)})$ used to estimate the average are found as solutions of the Langevin system at the stationary regime.

Finite time regime. For parametrization on a finite time interval $[0, T]$, where the system has not reached stationarity the approach to find (time dependent) optimal parameters $\theta(T)$ is given by application of Theorem 5.1(a). Using the same steps as for the stationary case, we have that the optimal parameter set for which the process $\{(\bar{q}_t, \bar{p}_t)\}_{t \geq 0}$ best approximates $\{(q_t, p_t)\}_{t \geq 0}$ at the time interval $[0, T]$ is given by, if $\bar{\gamma}\mathbf{\Pi}_q = \mathbf{\Pi}_p\gamma$,

$$\theta^*(T) = \operatorname{argmin}_{\theta} \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\mathbf{\Pi}_p F(q_s) - \bar{F}(\mathbf{\Pi}_q q_s; \theta)\|_{\mathbf{\Pi}_p^{\sharp} \Xi}^2 ds \right], \quad (45)$$

and if $\bar{\gamma} = \frac{1}{2}\beta\bar{\sigma}\bar{\sigma}^{tr}$

$$\theta^*(T) = \operatorname{argmin}_{\theta} \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\mathbf{\Pi}_p F(q) - \bar{F}(\mathbf{\Pi}_q q_s; \theta) - (\mathbf{\Pi}_p \gamma - \mathbf{\Pi}_p \gamma \mathbf{\Pi}_p^{tr} \mathbf{\Pi}_q) \mathbb{M}^{-1} p_s\|_{\mathbf{\Pi}_p^{\sharp} \Xi}^2 ds \right]. \quad (46)$$

Remark 6.3. (Connection to equilibrium force matching) When the system is at equilibrium the optimization problem is defined by (43) and (44), where the expectation is taken with respect to the Gibbs measure $\mu_p(dq, dp)$. As the averaged quantity in (43) does not depend on p the $\mu_p(dq, dp)$ expectation is equal to the expectation with respect to $\mu(dq) = Z^{-1} \exp\{-\beta U(q)\}$. Therefore the optimization problem is

$$\theta^* = \operatorname{argmin}_{\theta} \mathbb{E}_{\mu} \left[\frac{1}{2} \|\mathbf{\Pi}_p F(q) - \bar{F}(\mathbf{\Pi}_q q; \theta)\|_{\mathbf{\Pi}_p^{\sharp} \Xi}^2 \right],$$

where $\mathbf{\Pi}_p = \bar{\mathbb{M}}\mathbf{\Pi}\mathbb{M}^{-1}$ and $\|u\|^2 = u^{tr}\mathbf{\Pi}_p^{\sharp, tr}\Sigma^{-1}\mathbf{\Pi}_p^{\sharp}u$, with $\Sigma = \sigma\sigma^{tr}$ the covariance matrix. Moreover, if the diffusion coefficient σ is constant, identical for all particles, then $\Sigma^{-1} = \sigma^{-2}I_{3N}$ and if $\mathbf{\Pi}_p^{\sharp, tr}\mathbf{\Pi}_p^{\sharp} = I_{3M}$, then

$$\theta^* = \operatorname{argmin}_{\theta} \mathbb{E}_{\mu} \left[\frac{1}{2\sigma^2} \|\mathbf{\Pi}_p F(q) - \bar{F}(\mathbf{\Pi}_q q; \theta)\|^2 \right],$$

where $\|\cdot\|$ denotes the Euclidean norm in $\mathbb{R}^{3M}$. Therefore the path-space force matching is equivalent to the force matching for systems at equilibrium. Note that $\mathbf{\Pi}_q^{\sharp, tr}\mathbf{\Pi}_q^{\sharp} = I_{3M}$ holds, for example, if $\mathbf{\Pi}_q$ is the mapping to the group's center of mass or an orthogonal map, see the examples in Section 6.2.

Remark 6.4. We should also state here that in all above applications a typical diffusive process is assumed for the dynamics of the molecular systems. However, for realistic molecular systems this might not be a good approximation due to sub-diffusive behavior and the importance of long-time dynamical behavior or memory in a generalized Langevin equation (GLE) framework. In such a case, either a scaling of the CG dynamics in a post-processing stage, or an approximation of the memory terms appeared in GLE through a parameterization of the diffusion term in the Langevin equation are required [62, 29, 30, 25, 31, 54, 8]. This is the topic of a future work.

Remark 6.5. (Parametrized friction) Note that if we consider that $\bar{\gamma} = \bar{\gamma}(q; \vartheta)$ then the same methodology can be applied with $\bar{b}(\bar{x}; \theta, \vartheta) = (\bar{\mathbb{M}}^{-1} \bar{p}, \bar{F}(\bar{q}; \theta) - \bar{\gamma}(q; \vartheta) \bar{\mathbb{M}}^{-1} \bar{p})^{tr}$. For this generalization one should be careful to ensure the existence of CG processes with such friction and of its stationary measure. For example, consider whether fluctuation-dissipation condition holds. We also refer to related works [63, 35, 31, 51].

6.1. Numerical implementation and optimal parameters

In Appendix B we study the RER minimization problem induced by discrete time numerical schemes of the Langevin dynamics and overdamped Langevin dynamics. We consider the Langevin (37) and the coarse space Langevin (40) dynamics, apply the Brooks-Brunger-Karplus (BBK), [9], discretization scheme in both systems and study the RER defined for the discrete Markov chains, see (57).

We also study the discrete time RER minimization problem for the overdamped Langevin dynamics $\{X_t\}_{t \geq 0}$ in $\mathbb{R}^n$,

$$dX_t = -\frac{1}{2}\Sigma(X_t)\nabla U(X_t)dt + \frac{1}{2}\nabla\Sigma(X_t)dt + \sigma(X_t)dB_t, \quad (47)$$

with a θ -parametrized coarse-grained approximation considered in the spirit of Section 3.2, presented in detail in Appendix B, using the Euler-Maruyama scheme. Here $\sigma(x) \in \mathbb{R}^{n \times k}$, $k \leq n$ and $\Sigma(x) = \sigma(x)\sigma^{tr}(x)$ is non-singular and positive definite. Note also that the invariant measure is $\mu(dx) = Z^{-1} \exp\{-U(x)\}dx$, where Z is the normalizing constant. This example demonstrates the applicability of our approach for stochastic dynamics with multiplicative noise. Moreover, it proves once more that the optimal parameter set θ_h^* derived from the discrete time analogue of (47) does not depend on the discretization time step h as $h \rightarrow 0$.

The reason for studying the optimization through the discrete schemes is (i) the numerical parametrization and minimization are done always in a context of discretized dynamics, (ii) it demonstrates clearly the passage from Markov chain approximation to continuous time process in the variational problem that defines the best-fit procedure. Indeed, as proved in Theorem 2, Appendix B, when the discretization time step of the numerical scheme tends to zero the local minima of RER agree with the results for the continuous time case, Theorem 5.1 b).

610 *6.2. Examples of coarse graining maps*

Center of mass. We consider the linear transformation $\mathbf{\Pi}_q$, eq. (38), with

$$\zeta_{ji} = \bar{m}_j^{-1} m_i \chi_{C_j}(i) \quad j = 1, \dots, M, \quad i = 1, \dots, N,$$

that maps N/M microscopic particles to its center of mass (the CG particle), where m_i is the mass of the i -th particle, $\bar{m}_j = \sum_{i \in C_j} m_i$ and χ_{C_j} is the indicator function of the set $C_j = \{i : \text{particle } i \text{ contributes to CG particle } j\}$. In order to simplify the demonstration we consider the special case where $M = 2$ and N is even and

$$\mathbf{\Pi}_q = \begin{bmatrix} \bar{m}_1^{-1} m_1 I_3 & \dots & \bar{m}_1^{-1} m_{N/2} I_3 & 0 & \dots & 0 \\ 0 & \dots & 0 & \bar{m}_2^{-1} m_{(N/2)+1} I_3 & \dots & \bar{m}_2^{-1} m_N I_3 \end{bmatrix}$$

where $\bar{m}_1 = \sum_{i=1}^{N/2} m_i$, $\bar{m}_2 = \sum_{i=(N/2)+1}^N m_i$, and note that $\text{rank}(\mathbf{\Pi}_q) = 6 = 3M$, and

$$\mathbf{\Pi}_p = \bar{\mathbf{M}} \mathbf{\Pi}_q \mathbf{M}^{-1} = \begin{bmatrix} I_3 & \dots & I_3 & 0 & \dots & 0 \\ 0 & \dots & 0 & I_3 & \dots & I_3 \end{bmatrix},$$

with $\mathbf{\Pi}_p^\# = \mathbf{M} \mathbf{\Pi}_q^\# \bar{\mathbf{M}}^{-1} = \mathbf{\Pi}_p^{tr}$. Thus the weighted norm $\|\cdot\|_{\mathbf{\Pi}_p^\# \Xi}$ appearing in the optimization problems (43)-(46), for the case of identical and constant covariance coefficients σ for which $\Xi = \sigma^{-1} I_{3N}$, is

$$\|u\|_{\mathbf{\Pi}_p^\# \Xi}^2 = \sigma^{-2} u^{tr} (\mathbf{\Pi}_p^\#)^{tr} \mathbf{\Pi}_p^\# u = \frac{N}{2\sigma^2} u^{tr} u, \quad u = (u_1, u_2)^{tr} \in \mathbb{R}^6,$$

as $\mathbf{\Pi}_p^\# u = (u_1, \dots, u_1, u_2, \dots, u_2)^{tr}$. The minimization problem (43) becomes

$$\theta^* = \underset{\theta}{\operatorname{argmin}} \mathbb{E}_\mu \left[\frac{N}{4\sigma^2} \sum_{j=1}^2 \left\| \sum_{i \in C_j} F_i(q) - \bar{F}_j(\mathbf{\Pi}_q q; \theta) \right\|^2 \right],$$

611 for $\bar{F}(\bar{q}; \theta) = (\bar{F}_1(\bar{q}; \theta), \bar{F}_2(\bar{q}; \theta))^{tr} \in \mathbb{R}^6$, where $\|\cdot\|$ denotes the Euclidean norm in $\mathbb{R}^3$.

An orthogonal projection. A simple example of an orthogonal mapping is the projection on the first M coordinates, i.e., for $q = (q_1, \dots, q_N)^{tr}$, $\mathbf{\Pi}_q q = (q_1, \dots, q_M)^{tr}$, represented by the $3M \times 3N$ matrix

$$\mathbf{\Pi}_q = \begin{bmatrix} I_{3M} & 0_{3M \times (3N-3M)} \end{bmatrix},$$

and

$$\mathbf{\Pi}_p = \bar{\mathbf{M}} \mathbf{\Pi}_q \mathbf{M}^{-1} = \begin{bmatrix} I_{3M} & 0_{3M \times (3N-3M)} \end{bmatrix} = \mathbf{\Pi}_q,$$

with $\bar{\mathbf{M}} = \text{diag}(m_1 I_3, \dots, m_M I_3)$, for which holds $\mathbf{\Pi}_p^\# = \mathbf{\Pi}_p^{tr}$. When the diffusion coefficient σ is a constant same for all particles the weighted norm appearing in the optimization problems (43)-(44) is

$$\|u\|_{\mathbf{\Pi}_p^\# \Xi}^2 = \frac{1}{\sigma^2} u^{tr} u, \quad \text{for any } u \in \mathbb{R}^{3M},$$

and the minimization problem

$$\theta^* = \underset{\theta}{\operatorname{argmin}} \mathbb{E}_\mu \left[\frac{1}{2\sigma^2} \sum_{i=1}^M \|F_i(q) - \bar{F}_i(\mathbf{\Pi}_q q; \theta)\|^2 \right].$$

7. Data driven coarse-graining and path-space variational inference

In the previous sections we built optimal coarse-grained dynamics such as (40) as approximations of microscopic stochastic dynamics in the same general class of stochastic differential equations, e.g., the microscopic Langevin dynamics (37). The path-space information approach proposed there, allowed us to systematically compare microscopic and coarse-grained dynamics using the path-space relative entropy approach in Theorem 5.1 and set up the corresponding parameter path-space variational inference problems.

In this section we explore a different but asymptotically equivalent (in the number of data) perspective, which is *data-driven* in the sense that it treats any available microscopic simulator purely as a means of producing statistical data in the form of time series.

The primary new elements of this coarse-graining approach are: (a) We derive the parametrization of the coarse-grained models $\bar{Q}_{[0,T]}^\theta$ by optimizing their information content (in the path space) with respect to available time series data $\mathcal{D}$ coming from a fine-scale simulation. We use computable formulas similar to those for the relative entropy rate (RER) discussed earlier; (b) In (a) we do not need that the microscopic scale time series data $\mathcal{D}$ are obtained from a model $P_{[0,T]}$ in the same mathematical class as the coarse-grained models or that it is even Markovian. Thus we do not require a microscopic Langevin model $P_{[0,T]}$ as was done in Section 5 and Section 6 or any other explicitly known molecular dynamics, at least provided sufficient data is available; (c) Due to information inequalities such as (5) and (7), the present data-driven, path information-based coarse-graining methodology implies transferability of the parameterization to **different observables, at a specific thermodynamic point, by only training a single observable, namely the relative entropy. Numerical tests for the verification of this observation is the subject of ongoing work. We also refer to some recent prior work that relates observables and relative entropy, [22, 73].** (d) The relative entropy rate (RER) approach in (24) which is also reflected in our data-driven approach, see for instance eq. (56) below, allows us to train models to be predictive at long-time regimes, and not just for any fixed finite time window $[0, T]$.

One of the key points in this method is taking advantage of the ordering of the distributions in relative entropy, that allows us to write the path-space variational inference problem as an average of the available fine-scale time series data. In this sense the method relies specifically on the availability of “big data” from the microscopic solver. Furthermore, it provides a systematic approach to compress them in the form of the coarse-grained model $\bar{Q}_{[0,T]}^\theta$ with controlled loss of information measured by RER, in analogy to information criteria, [1], [71], see formula (10).

For simplicity in the presentation, we focus on discrete in time parametrized coarse dynamics, for instance numerical schemes for Langevin equations, such as the ones considered in Appendix B. In analogy to the parametrized dynamics (40), we consider the parametrized coarse-grained transition probabilities $\bar{p}^\theta(\mathbf{I}X, \mathbf{I}X')$, i.e., the probability for the CG state $\mathbf{I}X$ given that the system is at $\mathbf{I}X$, that correspond to a discretization scheme for (40), see also Appendix B. Then the corresponding coarse-grained path-distribution is, assuming Markovianity,

$$\bar{Q}_{[0,T]}^\theta = \bar{Q}^\theta(\mathbf{I}X_0, \dots, \mathbf{I}X_T) = \mu(\mathbf{I}X_0) \bar{p}^\theta(\mathbf{I}X_0, \mathbf{I}X_1) \dots \bar{p}^\theta(\mathbf{I}X_{T-1}, \mathbf{I}X_T), \quad (48)$$

where μ denotes the initial distribution of the process and $\bar{\mathcal{D}} = \{\Pi X_1, \Pi X_2, \dots, \Pi X_T\}$ is a typical coarse-grained time series corresponding to the microscopic time series $\mathcal{D} = \{X_1, X_2, \dots, X_T\}$.

Finite-time regime: We first consider an ensemble of fine-scale data given in the form of M time series $\mathcal{D}^k = \{X_1^k, X_2^k, \dots, X_T^k\}$, $k = 1, \dots, M$, obtained from a fine-scale molecular simulation algorithm, up to a prescribed time horizon T . The corresponding coarse space time series is $\bar{\mathcal{D}}^k = \{\Pi X_1^k, \Pi X_2^k, \dots, \Pi X_T^k\}$, $k = 1, \dots, M$. We note here that in this case we do not necessarily need that this data set is obtained from a Langevin or any other Markovian algorithm. Then the *typically unknown* path-space distribution of this coarse-space time series is denoted by

$$\bar{P} = \bar{P}(\Pi X_0, \dots, \Pi X_T).$$

Note that $\bar{P}$ is the push forward of the microscopic measure P , see relation (3) Section 2.1. Furthermore $\bar{P}$ is computationally accessible from the microscopic simulation which samples P and projects the X_i 's onto ΠX_i 's.

On the other hand we also consider the parametrized coarse-grained family, defined in (48), $\bar{Q}^\theta = \bar{Q}^\theta(\Pi X_0, \dots, \Pi X_T)$. In order to obtain the optimal parametrized coarse-grained transition probabilities $\bar{p}^{\theta*}(\Pi X, \Pi X')$, for a parameter vector $\theta = \theta^*$, we need to minimize the path-space relative entropy, i.e., consider the minimization problem

$$\theta_T^* = \arg \min_{\theta} \mathcal{R}(\bar{P} | \bar{Q}^\theta). \quad (49)$$

Furthermore, for the path-space relative entropy we have by the law of large numbers that

$$\mathcal{R}(\bar{P} | \bar{Q}^\theta) = \lim_{M \rightarrow \infty} \hat{\mathcal{R}}_M(\bar{P} | \bar{Q}^\theta)$$

where we define the unbiased estimator for the relative entropy

$$\hat{\mathcal{R}}_M(\bar{P} | \bar{Q}^\theta) := \frac{1}{M} \sum_{k=1}^M \log \frac{\bar{P}(\Pi X_1^k, \Pi X_2^k, \dots, \Pi X_T^k)}{\bar{Q}^\theta(\Pi X_1^k, \Pi X_2^k, \dots, \Pi X_T^k)}. \quad (50)$$

Therefore, the minimization principle (49) becomes

$$\begin{aligned} \arg \min_{\theta} \hat{\mathcal{R}}_M(\bar{P} | \bar{Q}^\theta) &= \arg \max_{\theta} \frac{1}{M} \sum_{k=1}^M \log \bar{Q}^\theta(\Pi X_1^k, \Pi X_2^k, \dots, \Pi X_T^k) \\ &\quad - \frac{1}{M} \sum_{k=1}^M \log \bar{P}(\Pi X_1^k, \Pi X_2^k, \dots, \Pi X_T^k), \end{aligned} \quad (51)$$

which does not require a priori the knowledge of the microscopic probability distribution or its push-forward $\bar{P}(\Pi X_1^k, \Pi X_2^k, \dots, \Pi X_T^k)$. Therefore, we obtain from (51) and (48) the following maximization principle

$$\theta_T^* \approx \arg \max_{\theta} \sum_{i=1}^T \sum_{k=1}^M \log \bar{p}^\theta(\Pi X_i^k, \Pi X_{i+1}^k) + \sum_{k=1}^M \log \mu(\Pi X_0^k). \quad (52)$$

For a time window $T \gg 1$ the last term in (52) that involves the initial data becomes negligible, therefore we obtain a coarse-grained path-space likelihood maximization principle and the corresponding estimator $\hat{\theta}(M, T)$ of θ^* :

$$\hat{\theta}(M, T) = \arg \max_{\theta} L(\theta; \{\mathbf{P}X_i^k\}_{i=1, k=1}^{T, M}), \quad (53)$$

where

$$L(\theta; \{\mathbf{P}X_i^k\}_{i=1, k=1}^{T, M}) = \sum_{i=1}^T \sum_{k=1}^M \log \bar{p}^{\theta}(\mathbf{P}X_i^k, \mathbf{P}X_{i+1}^k). \quad (54)$$

Note that if the transition probabilities in (54) are replaced with a stationary measure and T corresponding to independent samples $\mathcal{D} = \{X_1, X_2, \dots, X_T\}$, then (53) becomes the classical Maximum Likelihood Principle (MLE), [11]. In this sense (52) is a maximum likelihood for the coarse-grained time series, $\bar{\mathcal{D}} = \{\mathbf{P}X_1, \mathbf{P}X_2, \dots, \mathbf{P}X_N\}$ of the fine-scale process, and thus includes dynamics information and temporal correlations.

Stationary regime: If the time series associated with the data set $\mathcal{D}^k = \{X_1^k, X_2^k, \dots, X_T^k\}$, $k = 1, \dots, M$ are stationary, then they are statistically indistinguishable and we will eventually drop the index k , referring to the data set as $\mathcal{D} = \{X_1, X_2, \dots, X_T\}$. In this case the estimator in (54) simplifies significantly. Indeed, for $M \gg 1$, we have that

$$L(\theta; \{\mathbf{P}X_i^k\}_{i=1, k=1}^{T, M}) = \sum_{i=1}^T \sum_{k=1}^M \log \bar{p}^{\theta}(\mathbf{P}X_i^k, \mathbf{P}X_{i+1}^k) \approx M \sum_{i=1}^T \mathbb{E}_{\bar{P}}[\bar{p}^{\theta}(\mathbf{P}X_i, \mathbf{P}X_{i+1})], \quad (55)$$

$\mathbb{E}_{\bar{P}}$ denotes the expectation with respect to the path distribution $\bar{P}(\mathbf{P}X_1, \mathbf{P}X_2, \dots, \mathbf{P}X_T)$. Using the stationarity of the time series in (55) we have that

$$\sum_{i=1}^T \mathbb{E}_{\bar{P}}[\bar{p}^{\theta}(\mathbf{P}X_i, \mathbf{P}X_{i+1})] = T \mathbb{E}_{\bar{P}}[\bar{p}^{\theta}(\mathbf{P}X_1, \mathbf{P}X_2)].$$

However, due to stationarity we have the unbiased estimator for $\mathbb{E}_{\bar{P}}[\bar{p}^{\theta}(\mathbf{P}X_1, \mathbf{P}X_2)]$, [42], [64], using a single time series $\mathcal{D} = \{X_1, X_2, \dots, X_T\}$:

$$\mathbb{E}_{\bar{P}}[\bar{p}^{\theta}(\mathbf{P}X_1, \mathbf{P}X_2)] \approx \frac{1}{T} \sum_{i=1}^T \bar{p}^{\theta}(\mathbf{P}X_i, \mathbf{P}X_{i+1}).$$

Therefore the stationary analogue of (53) is

$$\theta^* \approx \hat{\theta}_s(T) = \arg \max_{\theta} L_s(\theta; \{\mathbf{P}X_i\}_{i=1}^T), \quad (56)$$

where for the stationary time series $\mathcal{D} = \{X_1, X_2, \dots, X_T\}$ we define

$$L_s(\theta; \{\mathbf{P}X_i\}_{i=1}^T) = \sum_{i=1}^T \log \bar{p}^{\theta}(\mathbf{P}X_i, \mathbf{P}X_{i+1}). \quad (57)$$

Time dependent regime: The optimization principle in (53) can be also easily extended so that we can obtain a further improved but computationally more costly time-dependent optimal parametrization for (49) where now we seek

$$\theta^* = \theta^*(i), \quad \text{where } 0 \leq i \leq T,$$

solving the approximate optimization problem for $\theta = \theta(i)$, $i = 0, \dots, T$:

$$\arg \min_{\theta} \sum_{i=0}^{T-1} \sum_{k=1}^M \log \bar{p}^{\theta(i)}(\Pi X_i^k, \Pi X_{i+1}^k).$$

In [36] the authors also obtained data-driven parametrization of multi-scale diffusions on a finite time window $[0, T]$ based on minimizing (1) for particular observables ϕ_i . On the other hand, in [42] a similar problem was considered for multi-scale diffusions, where coarse-grained parametrization was based on minimizing instead information metrics, e.g., (24).

Remark 7.1. Confidence intervals for the estimator $\hat{\theta}_s(T)$ in (57) can be provided in terms of the asymptotic normality (in $T \gg 1$) of the estimator. The corresponding (Gaussian) asymptotic variance is given in terms of the inverse of the path-space Fisher information matrix (FIM). We refer to [42, 65, 73] for a discussion of such results, as well as the definition of the path FIM and its use for sensitivity analysis of stochastic dynamics that include Langevin dynamics and kinetic Monte Carlo algorithms.

8. Conclusions

In this work we presented a thorough examination of coarse-graining of *non-equilibrium* molecular systems using *path-wise information metrics*. We have introduced the minimization problem for optimizing coarse models based on relative entropy for comparing continuous time diffusion processes. The derived scheme is similar to the widely applied force-matching method used in computational coarse-graining which, however, is restricted to equilibrium processes.

The main novelties of the proposed approach are summarized in the following points: (a) It is applicable to transient regimes of non-equilibrium processes, since it directly involves information along the whole path-space; (b) It connects the path-space relative entropy minimization with an (extended) force matching problem for continuous time dynamics. (c) It becomes entirely data-driven when the microscopic dynamics are replaced with corresponding correlated data in the form of time series. From a more general perspective the proposed scheme is directly related to dynamical data fitting as well as to machine learning algorithms. Indeed, the path-space information approach allowed us to relate the RER minimization problem to corresponding parameter optimization problems, obtained from data-driven methodologies, in the sense that it treats the microscopic simulator as means of producing statistical data in the form of time-series; (d) The interpretation of the dynamics with continuous time process demonstrates that the RER for stationary dynamics is independent of the time step for any numerical discretization scheme. Most importantly the

RER perspective shows that the corresponding optimization method is extendable to infinite times and non-reversible systems as is demonstrated in the current study for continuous time diffusion processes and in [42] for Markov chains; (e) The approach is generally applicable to stochastic dynamics such as Kinetic Monte Carlo algorithms and reaction networks.

Current work concerns the numerical application of the proposed RER minimization methodology to coarse-graining of molecular systems under equilibrium and non-equilibrium conditions.

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Appendix A. Proofs

Appendix A.1. Proof of Theorem 3.1

We consider a coarse observable function $f(x) = g(\mathbf{\Pi}x)$, where $f \in C^2(\mathbb{R}^n; \mathbb{R})$ and $g \in C^2(\mathbb{R}^m; \mathbb{R})$, and such that the conditions of Theorem 3.1 are guaranteed. $C^2(\mathbb{R}^n; \mathbb{R})$ denotes the space of twice differentiable functions $f : \mathbb{R}^n \rightarrow \mathbb{R}$.

From the martingale problem, [61, Section 8.3], [38], given $\tilde{b}, \tilde{\Sigma}$, defined in relations (18) and (19), there exists unique process $\{\tilde{X}_t\}_{t>0}$ which is the solution of (16) such that

$$\bar{X}_t = \mathbf{\Pi}\tilde{X}_t, \quad \text{in distribution.}$$

Denote

$$\mathcal{L}f(x) = \sum_{i=1}^n \tilde{b}_i(x) \frac{\partial f}{\partial x_i}(x) + \frac{1}{2} \sum_{i,j} \tilde{\Sigma}_{ij}(x; \theta) \frac{\partial^2 f}{\partial x_i \partial x_j}(x)$$

with generator of X_t . For $f(x) = g(\mathbf{\Pi}x)$, using relations (18) and (19), see also [61, Lemma 7.3.2], we can write

$$\mathcal{L}f(x) = \sum_{I=1}^m (\bar{b}(\mathbf{\Pi}x))_I \frac{\partial g}{\partial \bar{x}_I}(\mathbf{\Pi}x) + \frac{1}{2} \sum_{I,J=1}^m \bar{\Sigma}_{IJ}(\mathbf{\Pi}x; \theta) \frac{\partial^2 g}{\partial \bar{x}_I \partial \bar{x}_J}(\mathbf{\Pi}x) ds$$

Let $\tau > 0$ be a stopping time, from Ito's formula

$$f(\tilde{X}_t) = f(x) + \int_0^t \mathcal{L}f(\tilde{X}_s) ds + \int_0^t \nabla f(\tilde{X}_s)^{tr} \tilde{\sigma} dB_s$$

735 where $X_0 = x$, by applying expectation on both sides,

$$\begin{aligned}\mathbb{E}^x[f(\tilde{X}_\tau)] &= f(x) + \mathbb{E}^x \left[\int_0^t \mathcal{L}f(\tilde{X}_s) ds + \int_0^t \nabla f(\tilde{X}_s)^{tr} \tilde{\sigma} dB_s \right] \\ &= g(\Pi x) + \mathbb{E}^{\Pi x} \left[\int_0^\tau \sum_{I=1}^m (\bar{b}(\bar{X}_s))_I \frac{\partial g}{\partial \bar{x}_I}(\bar{X}_s) \right. \\ &\quad \left. + \frac{1}{2} \sum_{I,J=1}^m \bar{\Sigma}_{IJ}(\bar{X}_s; \theta) \frac{\partial^2 g}{\partial \bar{x}_I \partial \bar{x}_J}(\bar{X}_s) ds \right]\end{aligned}$$

Thus

$$\mathbb{E}^x[f(\tilde{X}_\tau)] = \mathbb{E}^{\Pi x}[g(\bar{X}_\tau)],$$

736 for any coarse observable $f(x)$. □

737 *Appendix A.2. Girsanov Theorem*

The Girsanov theorem states the conditions under which the path space measures $P_{[0,T]}$ and $Q_{[0,T]}^\theta$ are absolutely continuous and provides a closed form of the Radon-Nikodym density $\frac{dP_{[0,T]}}{dQ_{[0,T]}^\theta}(X_t, t)$. Suppose that there exists a process $\{u(X_s; \theta)\}_{s \geq 0}$ in $\mathbb{R}^k$ such that

$$\sigma(X_s)u(X_s; \theta) = b(X_s) - \tilde{b}(X_s; \theta),$$

738 and satisfies Novikov's condition $\mathbb{E} \left[e^{\frac{1}{2} \int_0^T |u(X_s; \theta)|^2 ds} \right] < \infty$, [61]. We define

$$M_t := \frac{d\mu_0}{d\nu_0}(X_0) \exp \left\{ - \int_0^t \langle u(X_s; \theta), dB_s \rangle - \frac{1}{2} \int_0^t |u(X_s; \theta)|^2 ds \right\},$$

739 where $\langle u(X_s; \theta), dB_s \rangle = \sum_{i=1}^k u_i(X_s; \theta) dB_s^i$ and $|u(X_s; \theta)|^2 = \sum_{i=1}^k u_i^2(X_s; \theta)$. Then the Gir-
740 sanov theorem yields that $Q_{[0,T]}^\theta$ is absolutely continuous with respect to $P_{[0,T]}$, $Q_{[0,T]}^\theta \ll P_{[0,T]}$,
741 and

$$\frac{dP_{[0,T]}}{dQ_{[0,T]}^\theta}(X_t, t) = M_t. \tag{A.1}$$

742 Furthermore, the process $\hat{B}_t := \int_0^t u(X_s; \theta) ds + B_t$ is a k -dimensional Brownian motion with
743 respect to $P_{[0,T]}$.

744 *Appendix A.3. Proof of Theorem 4.1*

a) The Novikov condition

$$\mathbb{E} \left[e^{\frac{1}{2} \int_0^T |u(X_s; \theta)|^2 ds} \right] < \infty$$

745 ensures that $\mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) < \infty$. Thus

$$\begin{aligned}
& \mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) - \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) - \mathcal{R}(\mu_0 | \nu_0) = \\
& = \mathbb{E}_{P_{[0,T]}} \left[\log \frac{dP_{[0,T]}}{dQ_{[0,T]}^\theta} \right] - \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T |u(X_s; \theta)|^2 ds \right] - \mathcal{R}(\mu_0 | \nu_0) \\
& = \mathbb{E}_{P_{[0,T]}} \left[- \int_0^T \langle u(X_s; \theta), dB_s \rangle - \int_0^T |u(X_s; \theta)|^2 ds \right] \\
& = \mathbb{E}_{P_{[0,T]}} \left[- \int_0^T \langle u(X_s; \theta), dB_s + u(X_s; \theta) ds \rangle \right] = \mathbb{E}_{P_{[0,T]}} \left[- \int_0^T \langle u(X_s; \theta), d\hat{B}_s \rangle \right] = 0,
\end{aligned}$$

746 the last term is zero since $d\hat{B}_s$ is a Brownian motion with respect to $P_{[0,T]}$.

b) Since $\{X_t\}_{t \geq 0}$ is stationary

$$\mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) = T \mathbb{E}_\mu \left[\frac{1}{2} |u(X; \theta)|^2 \right],$$

747 thus, based on the representation (26) of the relative entropy,

$$\begin{aligned}
\lim_{T \rightarrow \infty} \frac{1}{T} \mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) &= \lim_{T \rightarrow \infty} \left[\frac{1}{T} \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) + \mathcal{R}(\mu | \nu) \right] \\
&= \mathbb{E}_\mu \left[\frac{1}{2} |u(X; \theta)|^2 \right].
\end{aligned}$$

Recalling the definition of the RER,

$$\mathcal{H}(P | Q^\theta) = \lim_{T \rightarrow \infty} \frac{1}{T} \mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta),$$

748 we conclude that $\mathcal{H}(P | Q^\theta) = \mathbb{E}_\mu \left[\frac{1}{2} |u(X; \theta)|^2 \right]$.

749 *Appendix A.4. Proof of Corollary 4.1*

750 By assumption there exists $u(x; \theta)$ such that

$$\sigma(x)u(x; \theta) = b(x) - \tilde{b}(x; \theta), \text{ for all } x \in \mathbb{R}^n.$$

751 Since $\text{rank}(\sigma(x)) = r = k$, i.e., $\sigma(x)$ has full rank, then $\sigma^{tr}(x)\sigma(x) \in \mathbb{R}^{k \times k}$ is invertible, thus
752 a solution $u(x; \theta) \in \mathbb{R}^k$ is given by

$$u(x; \theta) = [\sigma^{tr}(x)\sigma(x)]^{-1} \sigma^{tr}(x) (b(x) - \tilde{b}(x; \theta)) = \Xi(x) (b(x) - \tilde{b}(x; \theta)),$$

753 where $\Xi(x) = [\sigma^{tr}(x)\sigma(x)]^{-1} \sigma^{tr}(x)$ and

$$\begin{aligned}
|u(x; \theta)|^2 &= u^{tr}(x; \theta)u(x; \theta) \\
&= (b(x) - \tilde{b}(x; \theta))^{tr} \Xi^{tr}(x)\Xi(x) (b(x) - \tilde{b}(x; \theta)) = \|b(x) - \tilde{b}(x; \theta)\|_\Xi^2,
\end{aligned}$$

From Theorem 4.1 b) the RER is

$$\mathcal{H}(P | Q^\theta) = \mathbb{E}_\mu \left[\frac{1}{2} |u(X; \theta)|^2 \right],$$

thus substituting of the previously derived form of $u(x; \theta)$ we prove (30),

$$\mathcal{H}(P | Q^\theta) = \mathbb{E}_\mu \left[\frac{1}{2} \|b(x) - \tilde{b}(x; \theta)\|_\Xi^2 \right],$$

754 where the norm $\|\cdot\|_\Xi$ is defined in (31).

755 *Appendix A.5. Proof of Theorem 5.1*

a) From Corollary 4.1(b), we have that

$$\mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) = \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) + \mathcal{R}(\mu_0 | \nu_0),$$

where

$$\mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) = \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|b(X_s) - \tilde{b}(X_s; \theta)\|_\Xi^2 ds \right].$$

As μ_0, ν_0 , are independent of θ , we only need to prove that

$$\nabla_\theta \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|b(X_s) - \tilde{b}(X_s; \theta)\|_\Xi^2 ds \right] = \nabla_\theta \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\Pi b(X_s) - \bar{b}(\Pi X_s; \theta)\|_{\Pi^\# \Xi}^2 ds \right].$$

Recall the representation (34)

$$\tilde{b}(x; \theta) = \Pi^\# \bar{b}(\Pi x; \theta) + (I - \Pi^\# \Pi) y^\perp(x), \quad \text{and} \quad \Pi(I - \Pi^\# \Pi) y^\perp(x) = 0,$$

756 for all $x \in \mathbb{R}^n$. We also write $b(x) = \Pi^\# \Pi b(x) + (I - \Pi^\# \Pi) b(x)$ and have

$$\begin{aligned} \|b(x) - \tilde{b}(x; \theta)\|_\Xi^2 &= \|\Pi^\# \Pi (b(x) - \tilde{b}(x; \theta))\|_\Xi^2 + \|(I - \Pi^\# \Pi) (b(x) - \tilde{b}(x; \theta))\|_\Xi^2 \\ &= \|\Pi (b(x) - \tilde{b}(x; \theta))\|_{\Pi^\# \Xi}^2 + \|(I - \Pi^\# \Pi) (b(x) - \tilde{b}(x; \theta))\|_\Xi^2, \end{aligned}$$

757 for all $x \in \mathbb{R}^n$, where the cross terms are zero as $\Pi(I - \Pi^\# \Pi) y^\perp(x) = 0$. Thus from the
758 assumption that $y^\perp(x)$ is independent of θ we have

$$\begin{aligned} \nabla_\theta \mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) &= \nabla_\theta \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) \\ &= \nabla_\theta \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\Pi b(X_s) - \bar{b}(\Pi X_s; \theta)\|_{\Pi^\# \Xi}^2 ds \right], \end{aligned}$$

and

$$\operatorname{argmin}_{\theta \in \Theta} \mathcal{R}(P_{[0,T]} | Q_{[0,T]}^\theta) = \operatorname{argmin}_{\theta \in \Theta} \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\Pi b(X_s) - \bar{b}(\Pi X_s; \theta)\|_{\Pi^\# \Xi}^2 ds \right].$$

b) We recall that for stationary process $\{X_t\}_{t \geq 0}$, see Corollary 4.1

$$\mathcal{H}(P | Q^\theta) = \frac{1}{T} \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta),$$

and from a) we have

$$\nabla_\theta \mathcal{H}^T(P_{[0,T]} | Q_{[0,T]}^\theta) = \nabla_\theta \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\Pi b(X_s) - \bar{b}(\Pi X_s; \theta)\|_{\Pi^\# \Xi}^2 ds \right],$$

thus

$$\begin{aligned} \nabla_\theta \mathcal{H}(P | Q^\theta) &= \frac{1}{T} \nabla_\theta \mathbb{E}_{P_{[0,T]}} \left[\frac{1}{2} \int_0^T \|\Pi b(X_s) - \bar{b}(\Pi X_s; \theta)\|_{\Pi^\# \Xi}^2 ds \right] \\ &= \frac{1}{T} T \nabla_\theta \mathbb{E}_\mu \left[\frac{1}{2} \|\Pi b(X) - \bar{b}(\Pi X; \theta)\|_{\Pi^\# \Xi}^2 \right] \\ &= \nabla_\theta \mathbb{E}_\mu \left[\frac{1}{2} \|\Pi b(X) - \bar{b}(\Pi X; \theta)\|_{\Pi^\# \Xi}^2 \right], \end{aligned}$$

where we used that $\{X_t\}_{t \geq 0}$ is stationary with the invariant measure $\mu(dx)$. Thus

$$\operatorname{argmin}_{\theta \in \Theta} \mathcal{H}(P | Q^\theta) = \operatorname{argmin}_{\theta \in \Theta} \mathbb{E}_\mu \left[\frac{1}{2} \|\Pi b(X) - \bar{b}(\Pi X; \theta)\|_{\Pi^\# \Xi}^2 \right]. \quad \square$$

Appendix B. Relative entropy rate minimization for numerical schemes

The relative entropy rate $\mathcal{H}(P | Q^\theta)$, for discrete time Markov chains $\{x_i\}_i, \{\tilde{x}_i\}_i$ with transition probabilities $p^h(x, x')$ and $q_\theta^h(x, x')$ respectively is, [42],

$$\mathcal{H}(P | Q^\theta) = \frac{1}{h} \int \int \mu(x) p^h(x, x') \log \frac{p^h(x, x')}{q_\theta^h(x, x')} dx' dx. \quad (\text{B.1})$$

The RER is described here for the specific (stationary) Markov chains generated by the numerical schemes for the Langevin (37) and the overdamped Langevin (47) thus formula (B.1) is a statistical estimator of the RER, see [42].

In terms of the description in Section 7, where the discrete time version of the RE is introduced on the coarse space for $\bar{Q}^\theta$, eq. (50), here we use the same description though on the microscopic space where Q^θ is a reconstruction of $\bar{Q}^\theta$.

Appendix B.1. Euler discretization for over-damped Langevin

The Euler discretization scheme for (47) with time step h defines the discrete stochastic system

$$x_{i+1} = x_i - \frac{1}{2} \Sigma(x_i) \nabla U(x_i) h + \frac{1}{2} \nabla \Sigma(x_i) h + \sigma(x_i) \Delta W_i,$$

with the solution given by the Markov chain $\{x_i\}_{i \geq 0}$ on the state space $\mathbb{R}^n$, $\Delta W_i \sim N(0, hI_n)$ are normally distributed increments. The transition probability density for the chain $\{x_i\}_i$ is

$$p^h(x, x') = \frac{1}{Z^h(x)} \exp \left\{ -\frac{1}{2h} (x' - \Delta x)^{tr} \Sigma^{-1}(x) (x' - \Delta x) \right\},$$

where we denote

$$\Delta x = x - \frac{1}{2} \Sigma(x) \nabla U(x) h + \frac{1}{2} \nabla \Sigma(x) h,$$

772 and $Z^h(x) = (2\pi h)^{n/2} |\Sigma(x)|^{1/2}$, with the notation $|A|$ for the determinant of the matrix A .

773 Consider the linear CG map $\mathbf{\Pi} : \mathbb{R}^n \rightarrow \mathbb{R}^m$, which for simplicity we assume it is an
774 orthogonal projection from the state space $\mathbb{R}^n$ onto $\mathbb{R}^m$ such that

$$x = \mathbf{\Pi}x + (I - \mathbf{\Pi})x = \bar{x} + \hat{x}. \quad (\text{B.2})$$

775 Note that we use the same letter $\mathbf{\Pi}x \in \mathbb{R}^m$ for denoting the representation of $\mathbf{\Pi}$ in $\mathbb{R}^n$.

776 The reduced model based on the CG mapping $\mathbf{\Pi}$ is given by $\{\bar{x}_i\}$, approximating the
777 projected Markov chain $\{\mathbf{\Pi}x_i\}$, satisfying

$$\bar{x}_{i+1} = \bar{x}_i - \frac{1}{2} \bar{\Sigma}(\bar{x}_i; \theta) \nabla \bar{U}(\bar{x}_i; \theta) h + \frac{1}{2} \nabla \bar{\Sigma}(\bar{x}_i; \theta) h + \Delta \bar{W}_i,$$

where $\Delta \bar{W}_i \sim N(0, h \bar{\Sigma}(\bar{x}_i; \theta))$. Hence the transition probability density for the CG chain $\{\bar{x}_i\}_i$ is

$$p_\theta^h(\bar{x}, \bar{x}') = \frac{1}{\bar{Z}^h(\bar{x}; \theta)} \exp \left\{ -\frac{1}{2h} (\bar{x}' - \Delta_\theta \bar{x})^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\bar{x}' - \Delta_\theta \bar{x}) \right\},$$

where

$$\Delta_\theta \bar{x} = \bar{x}_i - \frac{1}{2} \bar{\Sigma}(\bar{x}_i; \theta) \nabla \bar{U}(\bar{x}_i; \theta) h + \frac{1}{2} \nabla \bar{\Sigma}(\bar{x}_i; \theta) h,$$

and $\bar{Z}^h(\bar{x}; \theta) = (2\pi h)^{m/2} |\bar{\Sigma}(\bar{x}; \theta)|^{1/2}$. We consider the reconstructed chain $\{\tilde{x}_i\}_{i \geq 0}$ of $\{\bar{x}_i\}_{i \geq 0}$ that has the transition probability density

$$q_\theta^h(x, x') = \nu(x' | \bar{x}') p_\theta(\bar{x}, \bar{x}'),$$

where ν is a probability measure associated with the reconstruction, that we assume independent of the parameter θ . Note that we can write the covariance matrix $\Sigma(x)$ as

$$\Sigma(x) = \begin{bmatrix} \Sigma_{11}(x) & \Sigma_{12}(x) \\ \Sigma_{21}(x) & \Sigma_{22}(x) \end{bmatrix}$$

778 with $\Sigma_{11}(x) = \mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr} \in \mathbb{R}^{m \times m}$, $\Sigma_{22}(x) = \mathbf{\Pi}^\perp \Sigma(x) \mathbf{\Pi}^{\perp, tr} \in \mathbb{R}^{(n-m) \times (n-m)}$, $\mathbf{\Pi}^\perp = (I - \mathbf{\Pi})$

779 and $\Sigma_{21}^{tr}(x) = \Sigma_{12}(x)$. Then we can rewrite $p^h(x, x')$ as

$$p^h(x, x') = p_1(x, \bar{x}') p_2(x, \hat{x}' | \bar{x}'), \quad (\text{B.3})$$

780 where

$$p_1(x, \bar{x}') = \frac{1}{Z_1^h(x)} \exp \left\{ -\frac{1}{2h} (\bar{x}' - \mathbf{\Pi} \Delta x)^{tr} \Sigma_{11}^{-1}(x) (\bar{x}' - \mathbf{\Pi} \Delta x) \right\},$$

781 $Z_1^h(x) = (2\pi h)^{m/2} |\Sigma_{11}(x)|^{1/2}$ and

$$p_2(x, \hat{x}' | \bar{x}') = \frac{1}{Z_2^h(x)} \exp \left\{ -\frac{1}{2h} (\hat{x}' - g(x, \bar{x}'))^{tr} \Xi^{-1}(x) (\hat{x}' - g(x, \bar{x}')) \right\},$$

782 where

$$\begin{aligned} \Xi(x) &= \Sigma_{22}(x) - \Sigma_{12}^{tr}(x) \Sigma_{11}^{-1}(x) \Sigma_{12}(x) \in \mathbb{R}^{(n-m) \times (n-m)}, \\ g(x, \bar{x}') &= \mathbf{\Pi}^\perp \Delta x + \Sigma_{12}^{tr}(x) \Sigma_{11}^{-1}(x) (\bar{x}' - \mathbf{\Pi} \Delta x), \end{aligned}$$

783 $\Sigma_{22}(x) = \mathbf{\Pi}^\perp \Sigma(x) \mathbf{\Pi}^{\perp, tr} \in \mathbb{R}^{(n-m) \times (n-m)}$, $\Sigma_{21}^{tr}(x) = \Sigma_{12}(x)$ and $Z_2^h(x) = (2\pi h)^{(n-m)/2} |\Xi(x)|^{1/2}$.

784 The variational problem for the best-fit of parameters in terms of the relative entropy
785 rate between the Markov chains $\{x_i\}_{i \geq 0}$ and $\{\tilde{x}_i\}_{i \geq 0}$ is demonstrated by the following theorem
786 revealing its relation to a weighted force-matching optimization.

787 **Theorem 1.** Given $h > 0$

788 a) $\operatorname{argmin}_{\theta \in \Theta} \mathcal{H}(P|Q^\theta) = \operatorname{argmin}_{\theta \in \Theta} \left[\frac{1}{h} A(\theta) + B(\theta) \right],$

789 where

$$\begin{aligned} A(\theta) &= \frac{1}{2} \int \left[-\log |\mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta)| + \operatorname{Tr} (\mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta)) \right] \mu(x) dx \\ B(\theta) &= \frac{1}{2} \int \left[(\mathbf{\Pi} b(x) - \bar{b}(\bar{x}; \theta))^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\mathbf{\Pi} b(x) - \bar{b}(\bar{x}; \theta)) \right] \mu(x) dx \end{aligned}$$

790 with

$$\begin{aligned} b(x) &= -\frac{1}{2} \Sigma(x) \nabla U(x) + \frac{1}{2} \nabla \Sigma(x), \\ \bar{b}(\bar{x}; \theta) &= -\frac{1}{2} \bar{\Sigma}(\bar{x}; \theta) \nabla \bar{U}(\bar{x}; \theta) + \frac{1}{2} \nabla \bar{\Sigma}(\bar{x}; \theta). \end{aligned}$$

791 b) In the limit $h \rightarrow 0$ we have

$$\lim_{h \rightarrow 0} \min_{\theta \in \Theta} \left[\frac{1}{h} A(\theta) + B(\theta) \right] = \min_{\theta \in \Theta} [E(\theta) + m/2] \quad (\text{B.4})$$

792 where $E(\theta) = B(\theta)|_{\bar{\Sigma} = \mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr}}$, that is

$$E(\theta) = \frac{1}{2} \int \mu(x) (\mathbf{\Pi} b(x) - \bar{b}(\bar{x}; \theta))^{tr} (\mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr})^{-1} (\mathbf{\Pi} b(x) - \bar{b}(\bar{x}; \theta)) dx$$

793 where

$$\bar{b}(\bar{x}; \theta) = -\frac{1}{2} \mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr} \nabla \bar{U}(\bar{x}; \theta) + \frac{1}{2} \nabla \mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr}.$$

Proof. a) Recall the definition of the relative entropy rate $\mathcal{H}(P|Q^\theta)$, [42],

$$\mathcal{H}(P|Q^\theta) = \frac{1}{h} \int \int \mu(x) p^h(x, x') \log \frac{p^h(x, x')}{q_\theta^h(x, x')} dx' dx .$$

794 From the definition of p^h, q_θ^h and the factorization of p^h given in (B.3), we get that

$$\begin{aligned} \log \frac{p^h(x, x')}{q_\theta^h(x, x')} &= \log \frac{p_1(x, \bar{x}') p_2(x, \hat{x}' | \bar{x}')}{p_\theta(\bar{x}, \bar{x}') \nu(x' | \bar{x}')} = \\ &= \log \frac{p_2(x, \hat{x}' | \bar{x}')}{\nu(x' | \bar{x}')} - \frac{1}{2h} [(\bar{x}' - \mathbf{\Pi} \Delta x)^{tr} \Sigma_{11}^{-1}(x) (\bar{x}' - \mathbf{\Pi} \Delta x)] \\ &\quad + \log \frac{\bar{Z}^h(\bar{x}; \theta)}{Z_1^h(x)} + \frac{1}{2h} [(\bar{x}' - \Delta_\theta \bar{x})^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\bar{x}' - \Delta_\theta \bar{x})] . \end{aligned}$$

795 Note that the first two terms are θ independent, therefore they will not contribute to the
796 minimization problem $\nabla_\theta \mathcal{H}(P|P^\theta) = 0$. Thus

$$\begin{aligned} h \nabla_\theta \mathcal{H}(P|Q^\theta) &= \nabla_\theta \left[\int \int \int \mu(x) p_1(x, \bar{x}') p_2(x, \hat{x}' | \bar{x}') \times \right. \\ &\quad \times \left(\log \frac{\bar{Z}^h(\bar{x}; \theta)}{Z_1^h(x)} + \frac{1}{2h} [(\bar{x}' - \Delta_\theta \bar{x})^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\bar{x}' - \Delta_\theta \bar{x})] \right) d\hat{x}' d\bar{x}' dx \Big] \\ &= \nabla_\theta \text{I} + \nabla_\theta \text{II} . \end{aligned}$$

797

$$\text{I} = \int \int \mu(x) p_1(x, \bar{x}') \log \frac{\bar{Z}^h(\bar{x}; \theta)}{Z_1^h(x)} d\bar{x}' dx = \frac{1}{2} \int \mu(x) \log |\bar{\Sigma}(\bar{x}; \theta) (\mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr})^{-1}| dx .$$

$$\begin{aligned} \text{II} &= \frac{1}{2h} \int \int \mu(x) p_1(x, \bar{x}') [(\bar{x}' - \Delta_\theta \bar{x})^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\bar{x}' - \Delta_\theta \bar{x})] d\bar{x}' dx \\ &= \frac{1}{2h} \int \mu(x) [(\mathbf{\Pi} \Delta x - \Delta_\theta \bar{x})^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\mathbf{\Pi} \Delta x - \Delta_\theta \bar{x})] dx + \text{III} \end{aligned}$$

798 where the first term on the right hand side in the previous equality is zero and

$$\begin{aligned} \text{III} &= \frac{1}{2h} \int \int \mu(x) \frac{1}{Z_1^h(x)} e^{-\frac{1}{2h} (\bar{x}' - \mathbf{\Pi} \Delta x)^{tr} \Sigma_{11}^{-1}(x) (\bar{x}' - \mathbf{\Pi} \Delta x)} \\ &\quad \times [(\bar{x}' - \mathbf{\Pi} \Delta x)^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\bar{x}' - \mathbf{\Pi} \Delta x)] d\bar{x}' dx . \end{aligned}$$

799 Since $\bar{\Sigma}$ is positive definite and symmetric we can write $\bar{\Sigma}^{-1}(\bar{x}; \theta) = D^{tr}(\bar{x}; \theta) D(\bar{x}; \theta)$, and
800 perform the change of variables $s = D(\bar{x}' - \mathbf{\Pi} \Delta x)$ in the integral appearing in *III*. Then

$$\begin{aligned} \text{III} &= \frac{1}{2h} \int \int \mu(x) \frac{1}{Z_1^h(x) |D(\bar{x}; \theta)|} e^{-\frac{1}{2h} s^{tr} D^{-tr}(\bar{x}; \theta) \Sigma_{11}^{-1}(x) D^{-1}(\bar{x}; \theta) s} s^{tr} s ds dx \\ &= \frac{1}{2} \int \mu(x) \text{Tr} (\bar{\Sigma}^{-1}(\bar{x}; \theta) \mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr}) dx . \end{aligned}$$

801 We use $\text{Tr}(\cdot)$ to denote the trace of a matrix. Concluding, a local minimizer θ^* of $\mathcal{H}(P|P^\theta)$
 802 is given as the solution of $\nabla_\theta \mathcal{H}(P|Q^\theta) = 0$ where

$$\begin{aligned} h\nabla_\theta \mathcal{H}(P|Q^\theta) &= \nabla_\theta \left[\frac{1}{2} \int \mu(x) \log |\bar{\Sigma}(\bar{x}; \theta) (\mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr})^{-1}| dx + \right. \\ &\quad + \frac{1}{2} \int \mu(x) \text{Tr} (\mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta)) dx + \\ &\quad \left. + \frac{1}{2h} \int \mu(x) (\mathbf{\Pi} \Delta x - \Delta_\theta \bar{x})^{tr} \bar{\Sigma}^{-1}(\bar{x}; \theta) (\mathbf{\Pi} \Delta x - \Delta_\theta \bar{x}) dx \right] \\ &= \nabla_\theta \left[\frac{1}{h} A(\theta) + B(\theta) \right] \end{aligned}$$

b) We have that $\lim_{h \rightarrow 0} \min_{\theta \in \Theta} \left[\frac{1}{h} A(\theta) + B(\theta) \right] = \min_{\{\theta \in \Theta: A(\theta) = \frac{m}{2}\}} [B(\theta)]$ where $\frac{m}{2} = \min_\theta A(\theta)$.
 This relation can be easily proved using optimality arguments as $h \rightarrow 0$. Note that $A(\theta) = \frac{m}{2}$
 when

$$\bar{\Sigma}(\bar{x}; \theta) = \mathbf{\Pi} \Sigma(x) \mathbf{\Pi}^{tr}.$$

803 The proof is thus completed if we substitute the above relation in the form of $B(\theta)$. $\square$

804 *Appendix B.2. The BBK scheme for Langevin dynamics*

The explicit Euler-Maruyama-Verlet followed by implicit Euler-Maruyama scheme, also
 known as BBK scheme, is applied for the discretization of the Langevin dynamics (37)

$$\begin{cases} p_{i+1/2} = p_i - F(q_i) \frac{h}{2} - \gamma \mathbb{M}^{-1} p_i \frac{h}{2} + \sigma \Delta W_i, \\ q_{i+1} = q_i + \mathbb{M}^{-1} p_{i+1/2} h, \\ p_{i+1} = p_{i+1/2} - F(q_{i+1}) \frac{h}{2} - \gamma \mathbb{M}^{-1} p_{i+1} \frac{h}{2} + \sigma \Delta W_{i+1/2} \end{cases}$$

805 with $\Delta W_i, \Delta W_{i+1/2}$ a sequence of i.i.d. Gaussian random vectors with mean zero and
 806 covariance $\frac{h}{2} I_n$, where for notation simplicity we set $n = 3N$. For simplicity we set $\gamma = \gamma I_n$
 807 be constant and similarly for $\sigma = \sigma I_n$. Also we set the same mass $M = 1$ for all particles.
 808 The discretized Langevin process (q_i, p_i) is a Markov chain, with transition probability from
 809 the state (q, p) to (q', p') given by

$$P^h(q, p, q', p') = P^h(q' | q, p) P^h(p' | q', q, p),$$

810 where

$$\begin{aligned} P^h(q' | q, p) &= \frac{1}{Z_0^h} \exp \left\{ -\frac{1}{\sigma^2 h^3} |q' - \Delta_0^h(q, p)|^2 \right\} \quad \text{and} \\ P^h(p' | q', q, p) &= \frac{1}{Z_1^h} \exp \left\{ -\frac{1}{\sigma^2 h} |p'(1 + \frac{\gamma h}{2}) - \Delta_1^h(q, q')|^2 \right\}, \end{aligned}$$

811 where we introduce the notation

$$\Delta_0^h(q, p) = q - h \left[p - F(q) \frac{h}{2} + p \frac{h\gamma}{2} \right], \quad \Delta_1^h(q, q') = \frac{1}{h} (q' - q) - \frac{h}{2} F(q'),$$

and the normalizing constants $Z_0^h = (\pi h^3 \sigma^2)^{n/2}$ and $Z_1^h = \left(\frac{\pi h \sigma^2}{(1+\gamma h/2)^2} \right)^{n/2}$. The reduced discrete model based on the CG mapping $\mathbf{\Pi}$ given by the projected process $(\mathbf{\Pi}q_i, \mathbf{\Pi}p_i) \in \mathbb{R}^n \times \mathbb{R}^n$ is approximated by the Markov chain $(\bar{q}_i, \bar{p}_i) \in \mathbb{R}^m \times \mathbb{R}^m$ satisfying

$$\begin{cases} \bar{p}_{i+1/2} = \bar{p}_i - \bar{F}(\bar{q}_i; \theta) \frac{h}{2} - \gamma \bar{p}_i \frac{h}{2} + \sigma \Delta \bar{W}_i, \\ \bar{q}_{i+1} = \bar{q}_i + \bar{p}_{i+1/2} h, \\ \bar{p}_{i+1} = \bar{p}_{i+1/2} - \bar{F}(\bar{q}_{i+1}; \theta) \frac{h}{2} - \gamma \bar{p}_{i+1} \frac{h}{2} + \sigma \Delta \bar{W}_{i+1/2} \end{cases}$$

where $\Delta \bar{W}_i, \Delta \bar{W}_{i+1/2} \sim \mathcal{N}(0, \frac{h}{2} I_m)$. The Markov chain $(\bar{q}_i, \bar{p}_i)$ has transition probabilities

$$\bar{P}_\theta^h(\bar{q}, \bar{p}, \bar{q}', \bar{p}') = \bar{P}_\theta^h(\bar{q}' | \bar{q}, \bar{p}) \bar{P}_\theta^h(\bar{p}' | \bar{q}', \bar{q}, \bar{p}),$$

812 where

$$\begin{aligned} \bar{P}_\theta^h(\bar{q}' | \bar{q}, \bar{p}) &= \frac{1}{\bar{Z}_0^h} \exp \left\{ -\frac{1}{\sigma^2 h^3} |\bar{q}' - \bar{\Delta}_0^h(\bar{q}, \bar{p})|^2 \right\} \quad \text{and} \\ \bar{P}_\theta^h(\bar{p}' | \bar{q}', \bar{q}, \bar{p}) &= \frac{1}{\bar{Z}_1^h} \exp \left\{ -\frac{1}{\sigma^2 h} |\bar{p}'(1 + \frac{\gamma h}{2}) - \bar{\Delta}_1^h(\bar{q}, \bar{q}')|^2 \right\}, \end{aligned}$$

with $\bar{\Delta}_0^h(\bar{q}, \bar{p}) = \bar{q} - h [\bar{p} - \bar{F}(\bar{q}; \theta) \frac{h}{2} + \bar{p} \frac{h\gamma}{2}]$ and $\bar{\Delta}_1^h(\bar{q}, \bar{q}') = \frac{1}{h}(\bar{q}' - \bar{q}) - \frac{h}{2} \bar{F}(\bar{q}'; \theta)$, and normalizing constants $\bar{Z}_0^h = (\pi h^3 \sigma^2)^{m/2}$, $\bar{Z}_1^h = \left(\frac{\pi h \sigma^2}{(1+\gamma h)^2} \right)^{m/2}$. We denote with $\nu(q', p' | \bar{q}', \bar{p}', q, p)$ a probability measure associated with the reconstruction map and assume that is independent of the parameters θ . Then the reconstructed chain (q_i, p_i) from $(\bar{q}_i, \bar{p}_i)$ has transition probability

$$Q_\theta^h(q, p, q', p') = \bar{P}_\theta^h(\bar{q}, \bar{p}, \bar{q}', \bar{p}') \nu(q', p' | \bar{q}', \bar{p}', q, p).$$

813 **Theorem 2.** Given $h > 0$ the variational problem for the best-fit of parameters is

$$\operatorname{argmin}_\theta \mathcal{H}(P^h | Q_\theta^h) = \operatorname{argmin}_\theta [C(\theta) + D_h(\theta)], \quad (\text{B.5})$$

814 where

$$\begin{aligned} C(\theta) &= \frac{1}{4} \mathbb{E}_\mu \left[|\sigma^{-1}(\mathbf{\Pi}F(q) - \bar{F}(\bar{q}; \theta))|^2 \right], \\ D_h(\theta) &= \mathbb{E}_\mu \left[\frac{1}{Z_0^h} \int e^{-\frac{1}{\sigma^2 h^3} |q' - \Delta_0^h(q, p)|^2} |\sigma^{-1}(\mathbf{\Pi}F(q') - \bar{F}(\bar{q}'; \theta))|^2 dq' \right]. \end{aligned}$$

815 Furthermore, as $h \rightarrow 0$ we have the optimality condition

$$\lim_{h \rightarrow 0} \nabla_\theta \mathcal{H}(P^h | Q_\theta^h) = \frac{5}{4} \nabla_\theta \mathbb{E}_\mu \left[|\sigma^{-1}(\mathbf{\Pi}F(q) - \bar{F}(\mathbf{\Pi}q; \theta))|^2 \right]. \quad (\text{B.6})$$

Proof. Based on the orthogonality of the coarse graining mapping $\mathbf{\Pi}$ we can factorize $P^h(q' | q, p)$ and $P^h(p' | q', q, p)$ as

$$P^h(q' | q, p) = \frac{1}{Z_0^h} e^{-\frac{1}{\sigma^2 h^3} |q' - \mathbf{\Pi} \Delta_0^h(q, p)|^2} e^{-\frac{1}{\sigma^2 h^3} |\bar{q}' - \mathbf{\Pi}^\perp \Delta_0^h(q, p)|^2}$$

816 and

$$P^h(p'|q', q, p) = \frac{1}{Z_1^h} e^{-\frac{1}{\sigma^2 h} |\bar{p}'(1 + \frac{\gamma h}{2}) - \mathbf{\Pi} \Delta_1^h(q, q')|^2} e^{-\frac{1}{\sigma^2 h} |\bar{p}'(1 + \frac{\gamma h}{2}) - \mathbf{\Pi}^\perp \Delta_1^h(q, q')|^2}$$

817 where $\hat{x}$ denotes $\mathbf{\Pi}^\perp x = (I - \mathbf{\Pi})x$, for $\mathbf{\Pi}$ a projection, $\mathbf{\Pi} \Delta_0^h(q, p) = \bar{q} - h [\bar{p} - \mathbf{\Pi} F(q) \frac{h}{2} + \bar{p} \frac{h\gamma}{2}]$
 818 and $\mathbf{\Pi} \Delta_1^h(q, q') = \frac{1}{h} (\bar{q}' - \bar{q}) - \frac{h}{2} \mathbf{\Pi} F(q')$, $\mathbf{\Pi}^\perp \Delta_0^h(q, p)$ and $\mathbf{\Pi}^\perp \Delta_1^h(q, q')$ are similarly defined.
 819 From the definition of the RER functional $\mathcal{H}(P^h|P_\theta^h)$ and the fact that $\nu(q', p'|\bar{q}', \bar{p}', q, p)$ is
 820 independent of the parameters θ , we have

$$\begin{aligned} h \nabla_\theta \mathcal{H}(P^h|Q_\theta^h) &= \nabla_\theta \left\{ \int \cdots \int P^h(q, p, q', p') \log \frac{P^h(q, p, q', p')}{P_\theta^h(q, p, q', p')} dq' dp' \mu(dq, dp) \right\} \\ &= \nabla_\theta \text{I} + \nabla_\theta \text{II} \end{aligned}$$

821 where

$$\begin{aligned} \text{I} &= \frac{1}{\sigma^2 h} \frac{\hat{Z}_1^h}{Z_1^h} \int \cdots \int e^{-\frac{1}{\sigma^2 h} |\bar{p}'(1 + \frac{\gamma h}{2}) - \mathbf{\Pi} \Delta_1^h(q, q')|^2} P^h(q'|q, p) \\ &\quad \times \left| \bar{p}'(1 + \gamma \frac{h}{2}) - \bar{\Delta}_1^h(\bar{q}, \bar{q}') \right|^2 d\bar{q}' d\bar{p}' d\bar{q}' \mu(dq, dp), \\ \text{II} &= \frac{1}{\sigma^2 h^3} \frac{\hat{Z}_1^h}{Z_1^h} \int \cdots \int e^{-\frac{1}{\sigma^2 h} |\bar{p}'(1 + \frac{\gamma h}{2}) - \mathbf{\Pi} \Delta_1^h(q, q')|^2} P^h(q'|q, p) \\ &\quad \times \left| \bar{q}' - \bar{\Delta}_0^h(\bar{q}, \bar{p}) \right|^2 d\bar{q}' d\bar{p}' d\bar{q}' \mu(dq, dp), \end{aligned}$$

and

$$\hat{Z}_1^h = \left(\frac{\pi h \sigma^2}{(1 + \gamma h/2)^2} \right)^{(n-m)/2}.$$

822 After integrating with respect to $d\bar{p}'$ and $d\bar{q}'$ we obtain

$$\begin{aligned} \text{II} &= \frac{1}{\sigma^2 h^3} \frac{1}{Z_0^h} \int \cdots \int e^{-\frac{1}{\sigma^2 h^3} |\bar{q}' - \mathbf{\Pi} \Delta_0^h(q, p)|^2} \left| \bar{q}' - \bar{\Delta}_0^h(\bar{q}, \bar{p}) \right|^2 d\bar{q}' \mu(dq, dp) \\ &= \frac{1}{\sigma^2 h^3} \frac{1}{Z_0^h} \int \cdots \int e^{-\frac{1}{\sigma^2 h^3} |\bar{q}' - \mathbf{\Pi} \Delta_0^h(q, p)|^2} \left| \mathbf{\Pi} \Delta_0^h(q, p) - \bar{\Delta}_0^h(\bar{q}, \bar{p}) \right|^2 d\bar{q}' \mu(dq, dp) \\ &\quad + \frac{2}{\sigma^2 h^3} \frac{1}{Z_0^h} \int \cdots \int e^{-\frac{1}{\sigma^2 h^3} |\bar{q}' - \mathbf{\Pi} \Delta_0^h(q, p)|^2} (\bar{q}' - \bar{\Delta}_0^h(\bar{q}, \bar{p})) (\mathbf{\Pi} \Delta_0^h(q, p) - \bar{\Delta}_0^h(\bar{q}, \bar{p})) d\bar{q}' \mu(dq, dp) \\ &\quad + \frac{1}{\sigma^2 h^3} \frac{1}{Z_0^h} \int \cdots \int e^{-\frac{1}{\sigma^2 h^3} |\bar{q}' - \mathbf{\Pi} \Delta_0^h(q, p)|^2} \left| \bar{q}' - \mathbf{\Pi} \Delta_0^h(q, p) \right|^2 d\bar{q}' \mu(dq, dp). \end{aligned}$$

823 Therefore

$$\begin{aligned} \nabla_\theta \text{II} &= \nabla_\theta \left\{ \frac{1}{\sigma^2 h^3} \frac{1}{Z_0^h} \int \cdots \int e^{-\frac{1}{\sigma^2 h^3} |\bar{q}' - \mathbf{\Pi} \Delta_0^h(q, p)|^2} \left| \mathbf{\Pi} \Delta_0^h(q, p) - \bar{\Delta}_0^h(\bar{q}, \bar{p}) \right|^2 d\bar{q}' \mu(dq, dp) \right\} \\ &= \nabla_\theta \left\{ \frac{1}{\sigma^2 h^3} \iint \left| \mathbf{\Pi} \Delta_0^h(q, p) - \bar{\Delta}_0^h(\bar{q}, \bar{p}) \right|^2 \mu(dq, dp) \right\} \\ &= \nabla_\theta \left\{ \frac{h}{4} \iint \left| \sigma^{-1} (\mathbf{\Pi} F(q) - \bar{F}(\bar{q}; \theta)) \right|^2 \mu(dq, dp) \right\}. \end{aligned}$$

824 Similarly,

$$\nabla_{\theta} \mathbf{I} = \nabla_{\theta} \left\{ h \frac{1}{Z_0^h} \iiint e^{-\frac{1}{\sigma^2 h^3} |q' - \Delta_0^h(q,p)|^2} |\sigma^{-1}(\mathbf{\Pi} F(q') - \bar{F}(\bar{q}'; \theta))|^2 dq' \mu(dq, dp) \right\}.$$

825 Summarizing all steps we get

$$\begin{aligned} \nabla_{\theta} \mathcal{H}(P^h | Q_{\theta}^h) &= \nabla_{\theta} \left\{ \frac{1}{Z_0^h} \mathbb{E}_{\mu} \left[\int e^{\frac{1}{\sigma^2 h^3} |q' - \Delta_0^h(q,p)|^2} |\sigma^{-1}(\mathbf{\Pi} F(q') - \bar{F}(\bar{q}'; \theta))|^2 dq' \right] \right\} \\ &\quad + \nabla_{\theta} \left\{ \frac{1}{4} \mathbb{E}_{\mu} \left[|\sigma^{-1}(\mathbf{\Pi} F(q) - \bar{F}(\bar{q}; \theta))|^2 \right] \right\}. \end{aligned}$$

826 Furthermore, as $h \rightarrow 0^+$ we have that $\frac{1}{Z_0^h} e^{-\frac{1}{\sigma^2 h^3} |\bar{q}' - \mathbf{\Pi} \Delta_0^h(q,p)|^2} \rightarrow \delta(q' - q)$ weakly, where δ
827 denotes the Dirac distribution. Thus

$$\begin{aligned} \lim_{h \rightarrow 0} \nabla_{\theta} \mathcal{H}(P^h | Q_{\theta}^h) &= \mathbb{E}_{\mu} \left[|\sigma^{-1}(\mathbf{\Pi} F(q) - \bar{F}(\bar{q}; \theta))|^2 \right] + \frac{1}{4} \mathbb{E}_{\mu} \left[|\sigma^{-1}(\mathbf{\Pi} F(q) - \bar{F}(\bar{q}; \theta))|^2 \right] \\ &= \frac{5}{4} \mathbb{E}_{\mu} \left[|\sigma^{-1}(\mathbf{\Pi} F(q) - \bar{F}(\mathbf{\Pi} q; \theta))|^2 \right], \end{aligned}$$

828 which concludes the proof. □

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