Data-driven uncertainty quantification for systematic coarse-grained models

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ABSTRACT

In this work, we present methodologies for the quantification of confidence in bottom-up coarse-grained models for molecular and macromolecular systems. Coarse-graining methods have been extensively used in the past decades in order to extend the length and time scales accessible by simulation methodologies. The quantification, though, of induced errors due to the limited availability of fine-grained data is not yet established. Here, we employ rigorous statistical methods to deduce guarantees for the optimal coarse models obtained via approximations of the multi-body potential of mean force, with the relative entropy, the relative entropy rate minimization, and the force-matching methods. Specifically, we present and apply statistical approaches, such as bootstrap and jackknife, to infer confidence sets for a limited number of samples, i.e., molecular configurations. Moreover, we estimate asymptotic confidence intervals assuming adequate sampling of the phase space. We demonstrate the need for non-asymptotic methods and quantify confidence sets through two applications. The first is a two-scale fast/slow diffusion process projected on the slow process. With this benchmark example, we establish the methodology for both independent and time-series data. Second, we apply these uncertainty quantification approaches on a polymeric bulk system. We consider an atomistic polyethylene melt as the prototype system for developing coarse-graining tools for macromolecular systems. For this system, we estimate the coarse-grained force field and present confidence levels with respect to the number of available microscopic data.

Introduction

The research in systematic bottom-up coarse-graining methods for molecular systems has significantly advanced in the past decades. When adequate information is provided through the fine-grained data, the resulting coarse force fields are describing well structural properties. Moreover, there is active research and considerable progress on the dynamics of coarse models. However, there is a gap in the literature regarding the quantification of the induced errors due to the limited availability of fine-grained data. In the current work, we aim to incorporate rigorous statistical methods with coarse-graining methods to provide data-driven confidence sets.

Coarse-graining (CG) is a model reduction methodology that is used in order to extend the spatio-temporal scales accessible by microscopic (atomistic) simulations and to study molecular systems properties at mesoscale regimes. Systematic (chemistry specific) CG models are obtained by lumping groups of chemically connected atoms into CG particles (or CG beads) and deriving the effective coarse-grained interaction potentials from the microscopic details of the atomistic models. Such models are capable of predicting the properties of specific systems quantitatively and have been applied with great success to a vast range of molecular systems. To build CG models, one needs to derive (a) CG interaction potentials to describe equilibrium properties and (b) dynamical models to describe kinetic properties, directly from more detailed (microscopic) simulations. The effective CG potentials approximate the many-body potential, describing the equilibrium distribution of CG particles. These CG potentials can be developed through different numerical parameterizing methods at equilibrium, such as the iterative Boltzmann inversion (IBI), the inverse Newton (or inverse Monte Carlo), the force matching (FM), or Multiscale Coarse-Graining (MSCG) the Relative Entropy (RE) methods, and the cluster expansion methods. Also, during the last decade, bottom-up CG methods for treating molecular systems under non...
equilibrium conditions have been developed. Such are, the recently introduced, path-space relative entropy (PSRE), relative entropy rate (RER), and path-space force matching (PSFM) methods for providing effective CG models at equilibrium, non-equilibrium, transient, or stationary time regimes.\(^{[7,19]}\) The path-space methods have been further applied successfully to the dimensionality reduction of stochastic reaction networks,\(^{[20]}\) and the sensitivity analysis of molecular models.\(^{[21]}\) All these methods fall under the umbrella of statistical inference methods. Statistical inference is our point of view in the current study from which we draw the rigorous mathematical and statistical tools.\(^{[22-24]}\)

Quantifying parametric uncertainties accounts for assessing the model accuracy, variability, and sensitivity. Thus, naturally, a primary challenge in all above CG approaches is to quantify uncertainties in the effective CG model due to the involved approximations. We are considering the (limited) size of the available microscopic data, and the numerical/algorithmic errors. Two general ‘philosophies’ in inferential statistics are the frequentist inference and the Bayesian inference. The Bayesian approach has been studied recently for the coarse-graining of molecular systems. For example, Voth and coworkers\(^{[25]}\) have applied the empirical Bayes technique to estimate the force field parameters for the FM method. Authors in,\(^{[26,27]}\) in addition to parameter estimation, propose a methodology for model selection based on the Bayesian approach. Furthermore, in refs.\(^{[28,29]}\) authors focus on the derivation of credible intervals for CG models of water. Bayesian uncertainty estimation has also been applied to parametrize atomistic molecular models in refs.\(^{[30-33]}\)

The Bayesian perspective can provide a range of probabilistic properties, but it relies on prior knowledge, which is often not available. Thus, any credible interval estimation relies on uninformative priors. In contrast, estimating frequentist parametric and non-parametric confidence intervals requires no prior information.\(^{[22]}\)

Estimates of confidence intervals are given by asymptotic and non-asymptotic methods, chosen based on the available data. The asymptotic approach relies on the central limit theorem and the asymptotic Gaussian convergence theory. Additionally, concentration inequalities can provide reliable bound estimates for quantities of interest.\(^{[34]}\) The non-asymptotic methods concern estimating parameter statistics for finite data; typical examples are the jackknife and the bootstrap methods.\(^{[35,36]}\) Such methods have been employed to obtain estimates of the parameters in classical force fields. For example, Reiher and collaborators,\(^{[37,38]}\) employed frequentist statistical tools. Specifically, they utilize non-parametric bootstrapping to obtain reliable estimates of the fit parameters present in semi-classical dispersion interactions based on the Density Functional Theory (DFT). Recently, authors in ref.\(^{[39]}\) introduce a probabilistic potential ensemble method to estimate uncertainties in classical potential fitting based on DFT calculations. In addition, uncertainty quantification studies for the parameters of molecular models appear in\(^{[21]}\) using information theory tools, and in\(^{[40]}\) via a polynomial chaos approach.

Despite the above studies, according to our knowledge, asymptotic and non-asymptotic methods have not yet been explored in the context of CG modeling of high-dimensional systems, and in particular for macromolecular systems. Here we address the accuracy of CG models for molecular systems by employing frequentist statistical data analysis. Our goal is to present and apply rigorous statistical approaches, i.e., bootstrap and jackknife, to infer confidence sets for a limited number of samples.

We apply these methodologies to: (a) a relatively simple benchmarking problem of a two-scale fast/slow diffusion process and (b) a realistic bulk polymer model as a prototype example of a high-dimensional macromolecular system. The latter is essential if we consider that independent data are required to deduce the confidence sets with the non-asymptotic methods, though obtaining sufficiently uncorrelated data of high molecular weight model polymers is challenging.\(^{[5,41]}\)

The structure of this work is as follows. Firstly, we present a short review of the bottom-up coarse-graining methodologies of molecular systems from the perspective of statistical inference. Next, we construct the asymptotic and non-asymptotic confidence intervals for the RE, RER, and FM methods. We benchmark the methodology with a multi-scale confidence system with known corresponding stochastic averaging limits. We derive the bootstrap and jackknife estimates for the fitted interaction potential for a high-dimensional polyethylene melt, based on data derived from detailed atomistic simulations. Finally, we conclude and discuss our findings.

### Physics-based Data-driven Coarse-graining

Assume a prototypical problem of \(n\) particles (atoms or molecules) in a box of volume \(V\) at temperature \(T\). Let \(q = (q_1, \ldots, q_n) \in \mathbb{R}^{3n}\) describe the position of the particles in the atomistic (microscopic) description with potential energy \(U(q)\). The probability of a state \(q\) at the temperature \(T\) is given by the Gibbs canonical probability density...
\[ \mu(q) = Z^{-1} \exp \{-\beta U(q)\}, \]
\[ \text{where } Z = \int_{\mathbb{R}^m} e^{-\beta U(q)} dq \text{ is the configurational partition function, } \beta = \frac{1}{k_B T}, \text{ and } k_B \text{ is the Boltzmann constant. We should note that the studies presented in this work are performed on the configuration space. Moreover, we assume that the configurational time evolution of the particles is described by a continuous-time process } \{X_t\}_{t \geq 0} = \{q_t\}_{t \geq 0} \text{ in } \mathbb{R}^m, \text{ with path space distribution } P_{[0,t]} \text{, and invariant Gibbs probability density (1). If we assume Markovianity, then a temporal discretization of the process leads to a Markov chain with the transition probability kernel } p(x, x'). \text{ Thus, the path space probability density of } \{X_1, \ldots, X_N\}, \text{ observed at } t_1, \ldots, t_n, \text{ respectively, is}
\]
\[ P(X_1, \ldots, X_N) = v(X_1) \prod_{i=1}^{N-1} p(X_i, X_{i+1}), \]
\[ \text{where } v \text{ is the initial state probability density. We define coarse-graining through the configurational CG mapping } \Pi : \mathbb{R}^3 \rightarrow \mathbb{R}^m, \text{ determining the } m(<n) \text{ CG particles as a function of the microscopic configuration } q \text{. The mappings most commonly considered in coarse-graining of molecular systems are linear, represented by a set of non-negative real constants } \{\zeta_{ij}, i = 1, \ldots, m, j = 1, \ldots, n\}, \text{ for which } q_i := \Pi_i(q) = \sum_j \zeta_{ij} q_j \in \mathbb{R}^3, \text{ } i = 1, \ldots, m. \text{ The probability that the CG system has configuration } q = (\tilde{q}_1, \ldots, \tilde{q}_m) \in \mathbb{R}^m \text{ is } \bar{\mu}(q) = \int_{\Omega(q)} \mu(q) dq. \Omega(q) = \{q \in \mathbb{R}^m : \Pi(q) = q\}. \text{ The corresponding free energy at the CG level, described by the } m \text{ body potential of the mean force (PMF), is }
\]
\[ U^{\text{pmf}}(q) = -\frac{1}{\beta} \log \int_{\Omega(q)} e^{-\beta U(q)} dq. \]

Bottom-up structural-based CG methods look for approximations of the m-body PMF \( U^{\text{pmf}}(q) \)
\[ \tilde{U}(q; \theta), \quad \theta \in \Theta \subseteq \mathbb{R}^K, \]
\[ \text{which define the corresponding approximating probability density}
\]
\[ \tilde{\mu}(q) = (Z^\theta)^{-1} \exp \{-\beta \tilde{U}(q; \theta)\}, \quad \theta \in \Theta \subseteq \mathbb{R}^K, \]
\[ \text{where } Z^\theta = \int_{\mathbb{R}^m} \exp \{-\beta \tilde{U}(q; \theta)\} dq \text{ is the normalization constant.}
\]

We introduce a Markov process \( \{\tilde{X}_t\}_{t \geq 0} \) in \( \mathbb{R}^3m \) to approximate the time evolution of the coarse variables \( \{\Pi X_t\}_{t \geq 0} \). The CG process \( \{\tilde{X}_t\}_{t \geq 0} \) is defined through its parametric path space distribution
\[ Q_{[0,t]}^\theta, \quad \theta \in \Theta \subseteq \mathbb{R}^K. \]

The goal is to find the most effective CG model given a set of either independent and identically distributed (i.i.d.) or time-series data. In this work, we elaborate with the relative entropy minimization, relative entropy rate minimization, and force-matching methods to find the effective CG model.

### I. Independent, Identically Distributed Data

Given \( N \) i.i.d. configurational observations from the microscopic Gibbs density (1),
\[ D_N^{\text{iid}} = \{X_1, \ldots, X_N\}, \]
we aim to infer the CG probability density (4).

The Force-Matching method determines a CG approximating force \( F(q; \theta) = -\nabla U(q; \theta) \), and thus an effective potential from atomistic force information, as the solution of the mean least-square minimization problem
\[ \min_{\theta \in \Theta} \mathbb{E}_\mu[|| F(q) - F(\Pi(q); \theta) ||^2], \]
\[ \text{where } \mathbb{E}_\mu[\cdot] \text{ denotes the average with respect to the probability density } \mu(q), \text{ and } || \cdot || \text{ the Euclidean norm in } \mathbb{R}^m. \text{ The reference field } F(q) \in \mathbb{R}^m \text{ is the local mean force whose component } F_I(q), I = 1, \ldots, m \text{ is the force exerted at the } I\text{-th CG particle and is a function of the microscopic forces. For example, if the CG particle corresponds to the center of mass of a group of atoms then } F_I(q) = \sum_{j \in [\text{group } I]} f_j(q), \quad I = 1, \ldots, m, \text{ where } f_j(q) \text{ is the force exerted at the } j\text{-th microscopic particle. Thus, given the set of i.i.d. data } D_N^{\text{iid}} \text{ described in (6), the discrete optimization problem corresponding to (7) is}
\]
\[ \tilde{Q}_N^{\text{iid}, f, \text{m}}(X_1, \ldots, X_N) = \arg \min_{\theta \in \Theta} \frac{1}{N} \sum_{i=1}^N \left| \sum_{j \in [\text{group } I]} f_j(q) \right|^2. \]

The Relative Entropy minimization method determines a CG effective potential \( \tilde{U}(q; \theta) \) by minimizing the relative entropy \( R(\mu || \tilde{\mu}) \) between the microscopic Gibbs measure \( \mu(q) \) and a back-mapping \( \mu^\theta(q) = \tilde{\mu}^\theta(q)v(q|q) \) of the approximate CG measure \( \bar{\mu}(q) \). That is
\[ \min_{\theta \in \Theta} R(\mu || \mu^\theta), \]
\[ \text{where}
\]
\[ \mathcal{R}(\mu \parallel \mu^\theta) = \mathbb{E}_\mu \left[ \log \frac{\mu(\mathbf{q})}{\mu^\theta(\mathbf{q})} \right]. \]

Thus, the RE estimator for the CG model is
\[ \hat{\theta}_N^{\text{RE}}(X_1, \ldots, X_N) = \arg \min_{\theta \in \Theta} \frac{1}{N} \sum_{i=1}^N \log \frac{\mu(X_i)}{\mu^\theta(\Pi X_i^t)}, \tag{10} \]
assuming that the back-mapping distribution does not depend on \( \theta \).

\section*{II. Time-series Data}

In path space we estimate the probability density \((5)\) at dynamical regimes, given \( N_p \) i.i.d. path observations
\[ \mathcal{D}^{\text{ts}}_{N_p, N_i} = \{ \mathbf{X}_i^1, \ldots, \mathbf{X}_i^{N_p} \}_{i=1}^{N_i}, \tag{11} \]
from the microscopic path space probability density \((2)\). Each path (or trajectory) observation consists of \( N_i \) discrete time observations, which, for simplicity, we consider of uniform time step. Also, each path observation can have different size \( N_k, k = 1, \ldots, N_p \).

The best approximation is given by entropy-based criteria to find the best Markovian approximation of the coarse-grained process. The optimization principle is defined in terms of the path-space relative entropy,
\[ \min_{\theta \in \Theta} \mathcal{R}\left( P_{[0,t]} \parallel Q_{[0,t]}^\theta \right), \tag{12} \]
where \( Q_{[0,t]}^\theta := \prod_{i=0}^t q^\theta(X_i) \) is the back-mapping to the microscopic space of the parameterized path-space coarse-grained distribution. The RER is defined by
\[ \mathcal{H}(P|Q^\theta) := \lim_{t \to \infty} \frac{1}{t} \mathcal{R}\left( P_{[0,t]} \parallel Q_{[0,t]}^\theta \right). \]

Therefore, the minimization of the RER
\[ \min_{\theta \in \Theta} \mathcal{H}(P|Q^\theta), \]
is the appropriate optimization problem for \( t \to \infty \), and for stationary Markov processes.\(^{[19]}\) In work,\(^{[7]}\) we prove that the path-space variational inference problem \((12)\) in continuous time reduces to a path-space force-matching optimization, for a class of CG mappings. In addition, the RER reduces to the FM for stationary processes with invariant probability density \( \mu(\mathbf{q}) \) defined in \((1)\).

For discrete-time observations the CG path-space distribution \((5)\), assuming Markovianity for the CG model, is
\[ Q^\theta(X_1, \ldots, X_N) = \tilde{v}(X_1) \prod_{i=1}^{N-1} q^\theta(X_i, X_{i+1}), \]
where \( q^\theta(x, x') \) is the transition probability kernel of the proposed approximate CG process, and \( \tilde{v}(x) \) denotes the initial distribution. Introducing an unbiased estimator for the relative entropy, the optimal parameter estimate for \( \mathcal{D}_{N_p, N_i}^{\text{ts}} \) is given by
\[ \hat{\theta}_N^{\text{RE}}(X_1, \ldots, X_{N_i}) = \arg \min_{\theta \in \Theta} \frac{1}{N_p} \sum_{k=1}^{N_p} \log \frac{P(X_k^1, X_k^2 \ldots X_k^{N_i})}{Q^\theta(\Pi X_k^1, \Pi X_k^2 \ldots \Pi X_k^{N_i})}, \tag{13} \]
where we assume that the \( Q_{[0,t]}^\theta \) in relation \((12)\) is given as the product of \( Q^\theta \) and a back-mapping probability independent of \( \theta \), which for notation simplicity we do not present here. In terms of the transition probability kernels, the parameter estimator is
\[ \hat{\theta}_N^{\text{RE}}(X_1, \ldots, X_{N_i}) \]
\[ = \arg \min_{\theta \in \Theta} \frac{1}{N_i} \sum_{k=1}^{N_i} 1 - \sum_{i=1}^{N_i-1} \log \frac{p(X_k^i, X_k^{i+1})}{q^\theta(\Pi X_k^i, \Pi X_k^{i+1})}. \tag{14} \]

Note that when the time series are stationary, then they are statistically indistinguishable and the path-space optimization problem \((14)\) reduces to the RER optimization.\(^{[7]}\) That is, for observations \( \mathcal{D}_{N_i} = \{ X_1, \ldots, X_{N_i} \} \) the optimal parameter set is given by
\[ \hat{\theta}_N^{\text{RE}}(X_1, \ldots, X_{N_i}) \]
\[ = \arg \min_{\theta \in \Theta} \frac{1}{N_i} \sum_{i=1}^{N_i-1} \log \frac{p(X_i, X_{i+1})}{q^\theta(\Pi X_i, \Pi X_{i+1})}. \tag{15} \]

The RER estimator becomes the RE estimator when the samples are replaced by i.i.d. samples generated from the stationary probability distribution \( \mu(\mathbf{q}) \) and \( q^\theta(\Pi X_i, \Pi X_{i+1}) = \mu(\Pi X_{i+1}; \theta) \).

Note that the major difference between the RE minimization and the RER minimization is that in the first we need i.i.d. data from \( \mu(\mathbf{q}) \) while in later we need time series data from \( P_{[0,t]} \). This is an advantage of the path-space methods since there is no computational effort to generate the i.i.d. data. On the other hand, due to the ergodic theory, when the time-series data are long enough we can substitute the configuration space average with the time space average where correlated data are admissible. Thus, the effort to generate i.i.d. data is transferred to the effort to generate long time correlated data.

\section*{Confidence Intervals for Coarse-grained Methods}

In this section, we assess the uncertainty of the estimated parameters \( \theta \), as well as quantities of interest given as functions of the parameters. Specifically, we construct confidence intervals (CIs) of the CG model parameters.
for a given set of data for both equilibrium and pathspace models. We demonstrate the methodology of constructing non-asymptotic and asymptotic confidence intervals in detail for the relative entropy estimation \( \hat{\theta}^{\text{id,re}}_N \). The methodology is also valid for the force-matching estimation \( \hat{\theta}^{\text{id,fm}}_N \), if we consider it as a regression problem with the corresponding likelihood which is proportional to \( \exp\{- \| F(q) - \tilde{F}(q; \theta) \|^2 \} \). Similarly, we present confidence sets for the path-space estimators.

### Statistical Estimation and Path-space Relative Entropy Optimization

As described in the previous section, we consider two types of data; i.e., sets of configurations derived from the more detailed microscopic simulations in the form of: (a) independent and identically distributed data, \( D^{\text{id}}_N \), generated from the invariant distribution \( \mu \), and (b) discrete time-series data \( D^{\text{ts}}_N, X_i \), eq. (11), generated from the path distribution of the original microscopic process \( P_{[0,1]} \). Note that eq. (10) simplifies further since the invariant measure \( \mu \) is independent of \( \theta \),

\[
\hat{\theta}^{\text{id,re}}_N (X_1, \ldots, X_N) = \arg\max_{\theta \in \Theta} \frac{1}{N} \sum_{i=1}^{N} \log \mu^\theta (I X_i). \tag{16}
\]

For the time-series data, the optimization problem (14) is equivalent to

\[
\hat{\theta}^{\text{gs}}_{N_p, N_t} (X_1^1, \ldots, X_{N_t}^{N_p}) = \arg\max_{\theta \in \Theta} \frac{1}{N_p} \sum_{k=1}^{N_p} \frac{1}{N_t - 1} \sum_{i=1}^{N_t - 1} \log \mu^\theta (I X_i^k, I X_{i+1}^k). \tag{17}
\]

Thus, to derive the optimal CG model parameter, in both cases, we need (a) the data from the microscopic process, (b) the pre-defined CG mapping \( \Pi \), and (c) the parametrized coarse-grained model. These characterize the data and physics-driven nature of the coarse-graining approach, which relates the true CG model to its digital-twin, the approximate CG model.\(^{[42]}\)

However, in many situations, only a small number \( N \) of data are available due to the extreme cost to generate them, either experimentally or numerically. This is precisely the case in the coarse-graining of macromolecular (polymeric) systems, where the cost to generate i.i.d. samples increases strongly with the molecular length. For example, for polymer melts, the maximum relaxation time of entangled linear chains scales with the cubic power of their length; for other architectures, the dependence is even stronger, e.g., for star polymers becomes exponential.\(^{[43]}\) This is evident later, where we derive the optimal CG force field for a polyethylene melt and the corresponding confidence intervals.

### Non-asymptotic Confidence Intervals

There is a vast need for statistical information about parameters in CG models, especially when the size of data is limited. Such information would provide estimates of whether those parameters are in a reasonable region, and whether they are sensitive to the data. Here we present two statistically rigorous non-asymptotic methods to compute standard errors and construct confidence intervals, namely the jackknife and the bootstrap.\(^{[22,23]}\) These techniques are valid for the i.i.d. case \( D^{\text{id}}_N \), as well as for multiple i.i.d. time-series \( D^{\text{ts}}_{N,N_t} \), but not for the correlated data of a single time-series. We will apply the jackknife and bootstrap methods to construct confidence bounds for the CG parameters.

#### The Jackknife

Let us denote \( \hat{\theta}_N = \hat{\theta}^{\text{id}}_N \) and \( \hat{\theta}_{(i)} \) the estimators of the CG parameters from \( D_N = \{X_1, \ldots, X_N\} \) and with the \( i \)-th observation \( X_i \) removed, respectively, i.e.,

\[
\hat{\theta}_{(i)} = \hat{\theta}_{N-1} (X_1, \ldots, X_{i-1}, X_{i+1}, \ldots, X_N). \quad \text{Let also} \quad \tilde{T}_i = \text{the pseudo-values} \quad \tilde{T}_i = N\hat{\theta}_N - (N - 1)\hat{\theta}_{(i)}. \quad \text{Then, the jackknife variance estimation is}
\]

\[
V_{\text{jack}} = \frac{1}{N(N-1)} \sum_{i=1}^{N} \left( \tilde{T}_i - \frac{1}{N} \sum_{i=1}^{N} \tilde{T}_i \right)^2 = \frac{N - 1}{N} \sum_{i=1}^{N} \left( \hat{\theta}_{(i)} - \frac{1}{N} \sum_{i=1}^{N} \hat{\theta}_{(i)} \right)^2,
\]

and the corresponding a standard confidence interval is

\[
CI_{\text{jack}} = \left[ \hat{\theta}_N - z_{\alpha/2} \sqrt{V_{\text{jack}}}, \hat{\theta}_N + z_{\alpha/2} \sqrt{V_{\text{jack}}} \right]. \tag{18}
\]

The jackknife method consistently estimates the variance of \( \hat{\theta}_N \), though it cannot produce consistent estimates of the standard error of sample quantiles. The bootstrap method, on the other hand, is able to produce not only variance estimation but also quantile estimates and thus non-symmetric confidence intervals, as discussed below.

#### The Bootstrap

To construct bootstrap confidence intervals, firstly we assume that the empirical distribution of the data \( D_N \) is
\( \hat{F}_N \) mimicking the true distribution. Then, \( B \) bootstrap samples are generated, i.e., \( B \) sets of samples \( X_1^*, \ldots, X_N^* \) are drawn from \( \hat{F}_N \). The procedure is described by the following steps:

1. Draw \( N \) new samples \( X_1^*, \ldots, X_N^* \sim \hat{F}_N \), i.e., draw \( X_i^* \) randomly from \( D_N = \{X_1, \ldots, X_N\} \) with equal probability and with replacement.

2. Compute \( \hat{\theta}^* \) according to the chosen estimator, e.g., (16) for i.i.d. data.

3. Repeat steps 1 and 2, \( B \) times to get \( \hat{\theta}_1^*, \ldots, \hat{\theta}_B^* \).

With this procedure, we construct an approximate distribution of the statistical estimator \( \hat{\theta}_N \). There are several approaches to construct bootstrap confidence intervals, such as the standard, the pivotal, the percentile, and the bootstrap-t intervals.\(^{22,23}\) In the current work, we estimate the standard and percentile confidence intervals which we present next. The bootstrap variance estimation is

\[
V_{\text{boot}} = \frac{1}{B} \sum_{i=1}^{B} \left( \hat{\theta}_i^* - \frac{1}{B} \sum_{i=1}^{B} \hat{\theta}_i^* \right)^2 ,
\]

(19)

and the bootstrap a standard confidence interval is

\[
\text{CI}_{s,\text{boot}} = \left[ \hat{\theta}_N - z_{\alpha/2} \sqrt{V_{\text{boot}}} , \; \hat{\theta}_N + z_{\alpha/2} \sqrt{V_{\text{boot}}} \right].
\]

(20)

The bootstrap percentile confidence interval is given directly from the bootstrap distribution of the statistical estimator \( \hat{\theta} \), and is

\[
\text{CI}_{p,\text{boot}} = \left[ \hat{\theta}_{\alpha/2}^* , \; \hat{\theta}_{1-\alpha/2}^* \right],
\]

(21)

where \( \hat{\theta}_{\alpha/2}^* \) is the \( \alpha/2 \) percentile of \( \hat{\theta}_1^*, \ldots, \hat{\theta}_B^* \).

The percentile bootstrap intervals are not accurate, though, if bootstrap estimates are highly biased and skewed. Highly biased bootstrap estimates can not represent the true distribution, and highly skewed bootstrap estimates concentrate more on one side of the distribution and thus has a long tail on the other side. There are improved intervals but more complicated, such as the bias-corrected and accelerated bootstrap (BCa). BCa corrects for bias and skewness in the distribution of bootstrap estimates and improves the coverage accuracy of standard intervals from first order to second order, thus provides reasonably narrow intervals but is complicated to implement.\(^{44}\) Both techniques, the jackknife and bootstrap, use part of the data to get several estimators for the parameters and then use those estimators to construct confidence intervals. Bootstrap can have higher computational cost if the number of bootstrap samples (\( B \)) is larger than the number of data (\( N \)), which is often the case. Thus, the jackknife method is less computationally expensive but is less general. As reported in literature,\(^{22}\) empirical evidence suggests that \( B = 200 \) is usually sufficient for evaluating the bootstrap estimate of the standard error, but larger values should be considered for the bootstrap confidence intervals.

### Asymptotic Confidence Intervals

#### I. Independent, Identically Distributed Data

Recall that for i.i.d. data, the RE optimal parameter is

\[
\hat{\theta}_N^{\text{RE}} = \arg\max_{\theta \in \Theta} \frac{1}{N} \sum_{i=1}^{N} \log \mu^\theta (\text{II}X_i) .
\]

Note that \( \hat{\theta}_N^{\text{RE}} \) is similar to the maximum likelihood estimator.\(^{22}\) The difference is that the maximum likelihood estimator assumes that \( \text{II}X_i \) has a measure \( \mu^\theta \), while this assumption is not true here. Thus, a confidence interval directly obtained from maximum likelihood estimator is inaccurate. We resolve this issue by constructing a slightly different confidence interval along with two versions of the Fisher information:

\[
\hat{\mathcal{F}}_1 = -\frac{1}{N} \sum_{i=1}^{N} \nabla^2 \log \mu^\theta (\text{II}X_i) |_{\theta = \hat{\theta}_N^{\text{RE}}} ,
\]

\[
\hat{\mathcal{F}}_2 = \frac{1}{N} \sum_{i=1}^{N} \nabla \nabla^T \log \mu^\theta (\text{II}X_i) |_{\theta = \hat{\theta}_N^{\text{RE}}} .
\]

... These two Fisher information matrices are close if \( \text{II}X_i \) has distribution \( \mu^\theta \) and under the assumption that \( N \) is large enough (see Corollary 1.1.3 in supplementary information). Whether \( \hat{\mathcal{F}}_1 \) is close to \( \hat{\mathcal{F}}_2 \) could be an indirect indicator of whether the parameterized CG distribution \( \mu^\theta \) can mimic the distribution of \( \text{II}X_i \). That is, \( \hat{\mathcal{F}}_1 \) is close to \( \hat{\mathcal{F}}_2 \) indicates that \( \text{II}X_i \) has a measure close to \( \mu_N^{\text{RE}} \), which means that the parameterized family of \( \mu^\theta \) can reconstruct the distribution of \( \text{II}X_i \). But the inverse might not be true in general. The asymptotic theory provides the \( 1 - \alpha \) confidence interval for \( \theta \) in the equilibrium model (see Theorem 1.1.1 in supplementary information), which is

\[
\text{CI}_{\text{IID}} = \left[ \frac{\hat{\theta}_N^{\text{RE}} + z_{\alpha/2} \sqrt{\hat{\mathcal{F}}_1^{-1} \hat{\mathcal{F}}_2^{-1}}}{\sqrt{\frac{\hat{\mathcal{F}}_2^{-1} \hat{\mathcal{F}}_1^{-1}}{2}}} , \frac{\hat{\theta}_N^{\text{RE}} - z_{\alpha/2} \sqrt{\hat{\mathcal{F}}_1^{-1} \hat{\mathcal{F}}_2^{-1}}}{\sqrt{\frac{\hat{\mathcal{F}}_2^{-1} \hat{\mathcal{F}}_1^{-1}}{2}}} \right].
\]

(22)

#### II. Time-series Data

In the path-space models, the result is similar to the one in the equilibrium models where \( \mu^\theta \) is replaced by
transition probability density \( \bar{q}^\theta \) and a more complicated Fisher information. Recall that

\[
\hat{\theta}_N^* = \operatorname{argmax}_{\theta \in \Theta} \frac{1}{N-1} \sum_{i=1}^{N-1} \log \bar{q}^\theta (\Pi X_i, \Pi X_{i+1}).
\]

The first Fisher information matrix is

\[
\hat{I}_1 = -\frac{1}{N-1} \sum_{i=1}^{N-1} \nabla \theta \log \bar{q}^\theta (\Pi X_i, \Pi X_{i+1}) |_{\theta = \hat{\theta}_N^*},
\]

while the second Fisher information matrix is given by the central limit theorem for Markov chains and is estimated by a batch means estimator,

\[
\hat{I}_{2, BM} = \frac{b}{a-1} \sum_{j=1}^a (\tilde{Y}_j - \tilde{Y})^2,
\]

where \( \tilde{Y}_j = \frac{1}{b} \sum_{i=(j-1)b+1}^{jb} \log \bar{q}^\theta (\Pi X_i, \Pi X_{i+1}), \)

\[
\tilde{Y} = \frac{1}{N-1} \sum_{i=1}^{N-1} \log \bar{q}^\theta (\Pi X_i, \Pi X_{i+1})
\]

and \( N = ab \). Thus, the 1 - \( \alpha \) confidence interval for \( \theta \) in the path-space models is

\[
\operatorname{CI}_{1\beta} = \left[ \hat{\theta}_N^* - \frac{z_{1-\frac{\alpha}{2}}}{\sqrt{N-1}} \sqrt{\hat{I}_{1, tr}^{-1} \hat{I}_{2, BM} \hat{I}_{1, tr}^{-1}}, \ \hat{\theta}_N^* + \frac{z_{1-\frac{\alpha}{2}}}{\sqrt{N-1}} \sqrt{\hat{I}_{1, tr}^{-1} \hat{I}_{2, BM} \hat{I}_{1, tr}^{-1}} \right],
\]

(23)

In the supplementary information accompanying this work, we present the mathematical justification for the confidence intervals provided here.

**Estimating Quantities of Interest**

Thus far, we have estimated the coarse model parameters and assessed their accuracy. Now, our interest is in finding estimators and their uncertainty for quantities of interest (QoI),

\[
\tau = g(\theta),
\]

(24)

which are functions of \( \theta \). Given a data set \( D_N^{\text{in}} \), the invariance principle ensures that the estimator of the QoI \( \tau \), is

\[
\hat{\tau} = \hat{\tau}(X_1, \ldots, X_N) = g \left( \hat{\theta}_N(X_1, \ldots, X_N) \right),
\]

(25)

where \( \hat{\theta}_N \) is the set of estimated model parameters. The delta method provides asymptotic standard errors

\[
\hat{\sigma}(\hat{\tau}) = \sqrt{\left( \hat{\nabla} g \right)^T \hat{J}_N \hat{\nabla} g},
\]

where \( \hat{J}_N = \hat{J}^{-1} \), and \( \hat{\nabla} g \) is \( \nabla g = \left( \frac{\partial g}{\partial \theta_1}, \ldots, \frac{\partial g}{\partial \theta_k} \right)^{tr} \) evaluated at \( \theta = \hat{\theta}_N \).

The non-parametric resampling methods, jackknife and bootstrap, apply straightforwardly on \( \hat{\tau}(X_1, \ldots, X_N) \) through \( \hat{\theta}_N \), and the use of the invariance property. Indeed, the percentile bootstrap CI is

\[
\operatorname{CI}_{p, \text{boot}}^{\text{p}} = \left[ \tau_{a/2}, \tau_{1-a/2} \right],
\]

(26)

where \( \tau_{a/2} \) is the \( a/2 \) percentile of \( \tau_1, \ldots, \tau_N \), and \( \tau^* = (\tau_1, \ldots, \tau_N) \), for a bootstrap sample \( (X_1^*, \ldots, X_N^*) \).

**Remark**

Bayesian analysis can provide a range of information about the model through the posterior probability distribution of the model parameters. Credible intervals are thus obtained from the posterior. However, the need for prior information for the parameters is a drawback, since it is often not available. Of course, there exist techniques to overcome this, such as uninformative priors and hyper-parameters, but still some prior knowledge is necessary. In contrast, frequentist parametric and non-parametric confidence intervals require no prior information. Also, a non-parametric, uninformative posterior distribution can be approximately represented by a bootstrap distribution which may be much easier to obtain.

**Test-bed 1: Two-scale Diffusion Processes**

In this section, we benchmark our methodology by considering a two-dimensional, two-scale diffusion process. This diffusion process is a good, relatively simple, example that allows us to: (a) test and compare the accuracy of the estimated parameters by the different optimization methods, (b) provide the corresponding confidence intervals, and (c) validate the results since we know the effective dynamics analytically.

The two-scale diffusion process consists of a slow variable \( X_t^s \in \mathbb{R} \) and a fast variable \( Y_t^f \in \mathbb{R} \) for \( t \geq 0 \), which satisfy the system of stochastic differential equations,

\[
dX_t^s = -Y_t^f dt + dW_t^1,
\]

\[
dY_t^f = -e^{-1}(Y_t^f - X_t^s)dt + e^{-0.5}dW_t^2,
\]

for \( \epsilon > 0 \), where \( dW_t^1 \) and \( dW_t^2 \) are independent standard Wiener processes. As \( \epsilon \to 0 \), \( X_t^s \) follows the effective process \( \hat{X}_t \), which is proved to satisfy, by the averaging principle,

\[
d\hat{X}_t = -\hat{X}_t dt + d\hat{W}_t.
\]

(28)

Note that the effective potential driving the process \( \hat{X}_t \) is the harmonic potential \( U(x) = \frac{1}{2}x^2 \), depicted in Figure 1.

We are interested in constructing a coarse-grained model for the slow variable \( X_t^s \) and for a finite value of
$\epsilon > 0$. Thus, the CG map is $\Pi : (X_t^i, Y_t^i) \rightarrow X_t^i$. The CG process $X_t^{CG}$, approximating $\Pi(X_t^i, Y_t^i)$, is assumed to satisfy

$$dX_t^{CG} = a(X_t^i; \theta) dt + dW_t,$$

where $W_t$ is a standard Wiener process. To approximate the coarse-grained dynamics, we propose an effective drift

$$a(x; \theta) = \sum_{k=1}^{K} \theta_k x^{k-1},$$

which is an approximation over the set of polynomials \{1, x, \ldots, x^{K-1}\}. In our presented example, we choose $K = 5$. Note that in this example, we expect that the estimated parameters of the coarse-grained model are close to $\theta^* = [0, -1, 0, 0, 0]$, due to the known analytical form of the effective dynamics for the process, (28). We present next a comparison between (28) and (29) by investigating the uncertainty of parameters through confidence intervals.

I. Independent, Identically Distributed Data

Firstly, we investigate the results with i.i.d. data $D_{N_0 N_1}$, corresponding to the invariant density of (27). We omit the notation of $\epsilon$-dependence for notation simplicity. We minimize the RE, based on the invariant densities of $X_t^i$ and of $X_t^{CG}$. The invariant density of $X_t^{CG}$ is

$$\pi^{\theta}(x) = \frac{1}{Z^\theta} e^{-\mathcal{U}(x; \theta)},$$

where $\mathcal{U}(x; \theta)$ is defined by $a(x; \theta) = -\frac{\partial}{\partial x} \mathcal{U}(x; \theta)$ and $Z^\theta = \int e^{-\mathcal{U}(x; \theta)} dx$. The optimal parameter is given by

$$\hat{\theta}^{iid}_{N} = \arg\max_{\theta \in \Theta} E_{\pi}[\log \hat{\mu}^\theta]$$

$$= \arg\max_{\theta \in \Theta} \left\{ -2E_{\pi}[\mathcal{U}(\cdot; \theta)] - \log Z^\theta \right\}. \quad (31)$$

The RE estimator is described in section 2.3 of the supplementary information. We also apply the FM method for which the optimal parameters estimator is

$$\hat{\theta}^{id, fm}_{N} = \arg\min_{\theta \in \Theta} \frac{1}{N} \sum_{i=1}^{N} |Y_i + a(X_i; \theta)|^2. \quad (32)$$

II. Time-series Data

Secondly, we estimate the parameters for time-series data $D_{N_0 N_1}$. The approximate transition probability density of (29) is

$$q^\theta_t(X_t, X_{t+1}) = \frac{1}{z} e^{-\frac{1}{2h} ||X_{t+1} - X_t - a(X_t; \theta)h||^2}, \quad (33)$$

where $z$ is a normalizing factor independent of $\theta$, $h$ is the discretization time step for the Euler-Maruyama approximation of $X_t^{CG}$ with corresponding transition density $q^\theta_t(x, x')$. For multiple time-series data $D_{N_0 N_1}$, the appropriate estimator is the path-space RE (PSRE). The optimal estimate given by the minimization problem (17) is

$$\hat{\theta}^{psre}_{N} = \arg\min_{\theta \in \Theta} \frac{1}{N_p} \frac{1}{N_t - 1} \sum_{i=1}^{N_t-1} \frac{1}{N_t} \sum_{k=1}^{N_t} |X_{i+k}^t - X_i^t - a(X_i; \theta)h|^2. \quad (34)$$

The corresponding RER estimator, valid for a long, stationary time series, is

Figure 1. The effective potential for the coarse process $\hat{X}_t$ is the harmonic interaction potential.
\[
\hat{\theta}_{N}^{rer} = \arg\min_{\theta \in \Theta} \frac{1}{N_t - 1} \sum_{i=1}^{N_t-1} |X_{i+1} - X_i - a(X_i; \theta)|^2.
\] (35)

Moreover, in the equilibrium region, the RER minimization is equivalent to the FM minimization. We describe the proof in section 2.2 of the supplementary information.

### III. Asymptotic Results

We begin with reporting the results for a ‘large’ sample size and the corresponding asymptotic confidence intervals. In all the numerical tests we fix \( \epsilon = 0.005 \) and \( h=0.01 \). For the RE estimation, (31), we applied the Newton-Raphson (NR) algorithm. To estimate the normalization parameter \( Z^\theta \) which changes at each NR iteration, we generated 5,000 CG i.i.d. samples from \( \mu^\theta(x) \) with a Hamiltonian Monte Carlo sampler. The NR algorithm converged after 20 iterations, with the initial value of \( \theta \) near \( \theta^\ast \). The details of the method are described in the supplementary information. For the FM and RER estimation, we solve the corresponding least-squares problems described in (32) and (35).

Firstly, we generate two sets of samples: (a) \( D_N \), i.i.d. samples from the invariant distribution of the exact process with \( N = 500 \), and (b) \( D_N \), one time-series samples with \( N_t = 50,000 \). Note that we have experimented with various values of \( N \) and \( N_t \). We chose to report the \( N = 500 \) and \( N_t = 50,000 \) so that the optimization methods show variance estimates of the same order.

Figures 2 and 3 show the results for the FM and the relative entropy minimization with \( N = 500 \) i.i.d. data, respectively. In both figures, the right-hand side depicts the invariant probability density function of the estimated coarse process \( X_N \) and of the exact process \( X \).

The left-hand side figure presents the estimated parameters and the corresponding 95% asymptotic standard confidence interval, defined in (22). Similarly, figure 4 depicts the parameter estimates with the asymptotic CI and the invariant probability density functions of the estimated and the exact process with one correlated time-series with time step \( h = 0.01 \) and size \( N_t = 50,000 \). Also, in table 1 we present the point parameter estimates, the asymptotic variance, and the computational cost for the RE, the FM, and the RER optimization methods.

All methods approximate well the expected \( \theta^\ast = [0, -1, 0, 0, 0] \), corresponding to the asymptotic model as \( \epsilon \to 0 \), as \( \theta^\ast \) falls into the confidence interval for all methods. The RE method presents a larger asymptotic variance compared to the FM. Moreover, the RE has higher computational cost than the FM. Its benefit though is the better estimation of the ‘true’ probability density, which in return will give better estimations of quantities of interest given as expected values. We can notice an excellent match of the CG invariant density with RE estimation to the exact one, while there is a small difference between the FM and RER estimation. We attribute this difference to the fact the RE matches directly the probability densities while the FM and RER match the drift terms (i.e. the force).

Next, we comment on the FM and the RER methods from the point of view of comparing an i.i.d. method and a path-space method. The results show that we can achieve estimates with the same order of magnitude with the FM with i.i.d. data and the RER with correlated data if we use about hundred times more data in the later. This naturally increases the computational cost of the RER optimization problem. However, there is a computational benefit on the generation of the samples, since for the path-space samples (time series) we do not need to reject any generated data. On the contrary, to generate the i.i.d. observations we have to reject a large number of simulated data. This is extremely insufficient in high-dimensional applications, as in long polymer chains discussed in the next section. Therefore, the path-space methods can be advantageous when we have to generate high-dimensional samples.

On the other hand, the ergodic theory ensures that we can apply the FM method for correlated time series data, as long as the time-series is long enough. Therefore, our next numerical study examines the validity of the FM for short and long correlated time-series. That is we use the FM estimator for correlated data, and thus introduce the estimator for time series data \( D_{N_t} \),

\[
\hat{\theta}_{N}^{rer} = \arg\min_{\theta \in \Theta} \frac{1}{N_t} \sum_{k=1}^{N_t} \frac{1}{N_t} \sum_{i=1}^{N_t} |Y^k_i - a(X^k_i; \theta)|^2.
\] (36)

Table 2 reports the point estimates for time-correlated samples, resulting from the FM estimator (36) and the PSRE (and RER) estimator (35). For better readability, we report results only for the parameter \( \theta_2 \). The table with the estimates for all parameters is provided in the supplementary information. We observe that the FM point estimates improve as the size of the time-series increases, as expected. Comparing the \( N_t = 50,000 \) for the FM and the \( N_t = 100, N_t = 500 \) cases for which the number of samples is the same, they both yield estimates close to the truth. We notice that the FM estimator gives slightly better estimates than the PSRE estimator for short time trajectories, e.g., \( N_t = 500, N_t = 5,000 \). We ascribe this difference to that the first uses all fine-scale observations \( (X_t, Y_t) \), while the latter only uses the partial observations \( (X_t) \). To have thus reliable PSRE
estimates, we need to guarantee that either the trajectory is long enough or the number of trajectories is large enough. Important to note is that for the RER we can estimate the asymptotic CIs while the FM CIs are no longer valid.

**IV. Non-asymptotic Results**

For a 'small' number of samples, we test the case (a) of i.i.d. samples with $N = 50, 100, 200$, and $500$ and (b) of multiple i.i.d. trajectories consisting of correlated time-series data, $N_p = 1, N_t = 50, 000$, and $N_p = 100, N_t = 500$. In all

---

**Figure 2.** The estimator and 95% confidence intervals for FM method is shown on the left. The expected values $[0, -1, 0, 0, 0]$ are located inside the intervals. A distribution of constructed CG variable by using $\hat{\theta}_N$ and a comparison with fine-scaled $X^\varepsilon$ is shown on the right.

**Figure 3.** The left plot shows the results for Relative Entropy minimization. The density of CG variable matches well the one of $X^\varepsilon$.

**Figure 4.** Path-space optimization with the RER method.
Table 1. Parameter and asymptotic variance estimates for ‘large sample’ sets for the two-scale diffusion benchmarking problem. The exact parameters for $\epsilon \to 0$ are $\theta^*$.  

| Method | $\hat{\theta}$ | $\hat{\sigma}^2$ | CI | Number of samples | CPU time (sec) |
|--------|----------------|----------------|----|------------------|---------------|
| FM     | $[0.0236]$    | $[0.0021]$    | $[-0.0663, 0.1135]$ | 500 | 0.02            |
|        | $[-1.0240]$   | $[0.0063]$    | $[-1.1790, -0.8689]$ |        |                |
|        | $[0.0039]$    | $[0.0138]$    | $[-0.2345, 0.2342]$ |        |                |
|        | $[-0.0012]$   | $[0.0023]$    | $[-0.0947, 0.0922]$ |        |                |
|        | $[-0.0338]$   | $[0.0019]$    | $[-0.1189, 0.0513]$ |        |                |
| RE     | $[0.0247]$    | $[0.0046]$    | $[-1.3909, 0.1151]$ | 500 | 5.32            |
|        | $[-0.9827]$   | $[0.0261]$    | $[-1.2287, -0.7505]$ |        |                |
|        | $[0.0260]$    | $[0.0439]$    | $[-0.3205, 0.3572]$ |        |                |
|        | $[-0.0640]$   | $[0.0145]$    | $[-0.1345, 0.1509]$ |        |                |
|        | $[0.0001]$    | $[0.0048]$    | $[-0.0913, 0.0572]$ |        |                |
| RER    | $[0.0746]$    | $[0.0040]$    | $[-0.0491, 0.1983]$ | 50,000 | 0.19        |
|        | $[-0.9805]$   | $[0.0112]$    | $[-1.1876, -0.7733]$ |        |                |
|        | $[0.0483]$    | $[0.0158]$    | $[-0.1979, 0.2944]$ |        |                |
|        | $[-0.0313]$   | $[0.0040]$    | $[-0.1559, 0.0925]$ |        |                |
|        | $[-0.0255]$   | $[0.0013]$    | $[-0.0965, 0.0455]$ |        |                |

Results: Presented next, the number of bootstrap samples is $B = 200$. We compare the RE and FM estimates and confidence intervals for the sets of $N = 50$, $N = 200$ and $N = 50,000$, see Table 3. For better readability, we report the parameter estimates obtained with the FM method for $N = 50$, 100, and 200.
Table 2. Point estimates for the $\hat{\theta}_2 = -1$, with correlated time-series data, and with the different estimators (36) and (34) for the FM and PSRE. Note that the point estimates by FM (36) has the same form with FM estimator.

| $N_p$ | $N_t$ | $\hat{\theta}_2$ | $\bar{C}^{\text{FM}}_{1-M}$ | $\bar{C}^{\text{RE}}_{1-M}$ |
|-------|-------|-------------------|-------------------------------|-------------------------------|
| 1     | 500   | $-0.4328$         | $-6.0944$                     |
| 1     | 5,000 | $-0.9485$         | $-1.1251$                     |
| 1     | 50,000| $-0.9734$         | $-0.9805$                     |
| 10    | 500   | $-0.8960$         | $1.3288$                      |
| 100   | 500   | $-0.9728$         | $0.7976$                      |
| 100   | 5,000 | $-0.9777$         | $0.9673$                      |

Table 3. Comparison of the FM and RE methods and the corresponding asymptotic, jackknife, and bootstrap 95% CIs, with i.i.d. samples.

| $N$ | Asymptotic with FM | Jackknife with FM | Bootstrap with FM | Asymptotic with RE | Jackknife with RE | Bootstrap with RE |
|-----|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| 50  | $\hat{\theta}_2$  | $-0.8575$         | $-0.8720$         | $-0.9759$         | $-0.9827$         |                   |
| CI  | $[-1.3589, -0.3562]$ | $[-1.4674, -0.2477]$ | $[-1.4717, -0.2433]$ | $[-1.1165, -0.6275]$ | $[-2.2984, 0.5543]$ | $[-1.0670, -0.6771]$ |
| 200 | $\hat{\theta}_2$  | $-0.9702$         |                   | $-0.9759$         |                   |                   |
| CI  | $[-1.2233, -0.7172]$ | $[-1.2476, -0.6929]$ | $[-1.2452, -0.6953]$ | $[-1.2574, -0.6945]$ | $[-2.9675, 1.0157]$ | $[-1.1523, -0.7996]$ |
| 500 | $\hat{\theta}_2$  | $1.0240$          |                   | $-0.9827$         |                   |                   |
| CI  | $[-1.1790, -0.8689]$ | $[-1.1900, -0.8579]$ | $[-1.1868, -0.8611]$ | $[-1.2287, -0.7505]$ | $[-4.2963, 2.3272]$ | $[-1.1491, -0.8200]$ |

the corresponding quantiles of the set $\Lambda\left(\{x_i, \hat{\theta}_i\}_{i=1}^{B}\right)$, following (26). We observe that for only $N = 50$ samples the bootstrap confidence interval captures the ‘large sample’ ($N = 500$ in FM and RE, $N = 50000$ in RER) parameter estimates for all values of $x$. Note though, that the CI is wider for larger absolute values of $x$ which depicts a wider uncertainty in the estimate.

V. Validation of Confidence Intervals

In the previous sections, we estimated the asymptotic confidence intervals for i.i.d. data and time-series data. Table 5 shows the experiment results on validating those confidence intervals. For each method, sample size, and confidence level we calculate the corresponding confidence intervals for 500 independent sets of synthetic samples generated from (27). Then, we calculate the percentage of those confidence intervals containing the true value of the parameters. Those probabilities are close to the confidence levels, with RER’s probability being slightly smaller than the confidence level.

Test-bed 2: Effective Force-fields and Confidence in Coarse-graining of Linear Polymer Chains

In the present section, we apply the methodology on the CG approximation of a polyethylene bulk system. Specifically, we derive effective force fields with the FM method and the corresponding confidence intervals. Our focus is to understand the behavior of the output model when the available data is limited. Thus, we concentrate on the non-asymptotic methods.

To generate the simulated data sets $D_N$ of i.i.d. configurations, Molecular Dynamics (MD) simulations of a united-atom polyethylene (PE) system were performed using home made (parallel) MD code. A PE chain is represented

Table 4. Jackknife and bootstrap 95% CI by RER and PSRE on correlated data with multiple trajectories. NA means that the CI does not apply to that type of data.

| $N_p$ | $N_t$ | $\hat{\theta}$ | Asymptotic CI | Jackknife CI | Bootstrap CI |
|-------|-------|----------------|---------------|--------------|--------------|
| 1     | 50,000| $0.0746$       | $-0.0491, 0.1983$ | NA           | NA           |
|       |       | $-0.9805$      | $-1.1876, -0.7733$ |              |              |
|       |       | $0.0483$       | $-0.1979, 0.2944$ |              |              |
|       |       | $-0.0313$      | $-0.1550, 0.0925$ |              |              |
|       |       | $-0.0255$      | $-0.0965, 0.0455$ |              |              |
| 100   | 300   | $-0.0807$      | NA             | $-0.2546, 0.0932$ | $-0.2498, 0.0884$ |
|       |       | $-0.9358$      | $1.1718, -0.6997$ | $-1.1897, -0.6818$ |
|       |       | $0.0270$       | $-0.4219, 0.4759$ | $-0.3791, 0.4331$ |
|       |       | $-0.0546$      | $-0.1722, 0.0630$ | $-0.1928, 0.0836$ |
|       |       | $0.0169$       | $-0.1009, 0.1346$ | $-0.0939, 0.1276$ |

Table 5. Experiment results on validating the confidence intervals.
via a united-atom model in which each methylene CH₂ and methyl CH₃ group are considered as a single Van der Waals interacting site. Details of the model parameters are given in the supplementary information. The model system consists of 96 polyethylene chains of 99 monomer units (−CH₂−), i.e., the number of atomistic degrees of freedom is \( n = 9504 \). The simulations were performed under NVT conditions at temperature \( T = 450 \text{ K} \), and density \( \rho = 0.76868 \text{gr/cm}^3 \). The integration time step was 2fs. We record system configurations every 50 ps for about 500 ns = 500,000 ps. Thus, the size of the available data set is 10,000 (number of configurations). In the following, results are reported for a large (\( N = 2,000 \)) and smaller (\( N = 200, 100, 30 \)) data sets, to examine the dependence of the predictions on the size of the actual data set. Note that we choose \( N \) configurations from the 10,000 to be equidistant, e.g., the configurations for the set \( N = 2,000 \) have distance (10,000/2,000) = 50 ps = 250 ps, and for \( N = 200 \) the distance is 2,500 ps. We should also note that the maximum relaxation time of the polymer chains is around 1,700 ps, calculated by fitting the end-to-end vector autocorrelation function using a stretched exponential. This suggests that the large set \( (N = 2,000) \) is composed of correlated data while the smaller ones \( (N = 200, 100, 30) \) are uncorrelated.

For the coarse-grained representation of the PE, we consider a 3 : 1 mapping representation, i.e., three monomer units form one CG particle, see Figure 6. Thus, the total number of CG particles in the system is \( m = 33 \times 96 = 3168 \).

The CG PE model exhibits both bonded and non-bonded interactions. First, we estimate all the CG interactions with the Iterative Inverse Boltzmann (IBI)\(^3\) method. Both non-bonded and bonded interactions (bonds, angles, dihedrals) are presented in a tabulated form. We disregard the non-bonded estimates and keep only the bonded ones which are input for the FM method applied next. The resulting interaction potentials are reported in the supplementary information. Then, we estimate the non-bonded interactions with the FM method. We represent the non-bonded interactions with a two-body pair potential, which only depends on the distance between monomers. That is, the proposed CG potential described in eq. (3) is

\[
\mathcal{U}(\mathbf{q}; \theta) = \sum_{i=1}^{m} \sum_{j=1}^{m} u(r; \theta),
\]

where \( r = |\mathbf{q}_i - \mathbf{q}_j| \). The CG pair interaction potential \( u(r; \theta) \) is approximated via a functional basis of the form:

\[
\bar{u}(r; \theta) = \sum_{k=1}^{K} \theta_k \phi_k(r),
\]

using the linear or the cubic B-splines \( \{ \phi_k(r) \}_{k=1}^{K} \). The cutoff range for the non-bonded interactions is 1.4 nm. The size of the parameter set \( \theta \) is determined by the number of knots \( K \). We present results for a varying number of (a) parameters \( K \) and (b) all-atom configurations \( N \), given in Table 6.

The QoI is the pair potential \( u(r; \theta) \), \( r > 0 \), with estimator the random variable

\[
\hat{u}_N(r; \theta) = \sum_{k=1}^{K} \theta_{k,N} \phi_k(r),
\]

that is a linear combination of the parameter estimators \( \hat{\theta}_N \).

For each combination of parameters and data set size, we find the optimal force field with the FM method. For the small data sets, we also derive the bootstrap and jackknife statistics for the parameters. Next, we report the results for the cubic B-splines representation with \( K = 30 \) parameters. The results for the linear B-splines and comparisons between the different functional basis are reported in the supplementary information. In the results reported below, the number of bootstrap samples is \( B = 200 \). We consider the large data set \( (N = 2,000) \) estimation as a reliable approximation, and thus we use it as a reference result to compare to estimations with the small data sets.

Figure 8(a) depicts the parameters \( \hat{\theta}_N \) estimated with the large \( (N=2,000) \) and the small \( (N=200) \) data set, along with the 95% bootstrap percentile CI. In Figure 8(b) we report the relative standard deviation (RSTD) of each nonzero parameter, defined by \( \text{RSTD} = \hat{\sigma}_k / \hat{\theta}_k \), where \( \hat{\sigma}_k \) is the standard deviation estimated with the bootstrap method. The RSTD reveals the most uncertain parameters, e.g., the spline parameters with index 12, 20, 23, 26, 29. We compare the asymptotic and bootstrap standard deviation \( \hat{\sigma} \) in Figure 7 for the \( N = 30 \) and \( N = 200 \) configurations. It is evident that the asymptotic and bootstrap variance differ for the \( N = 30 \) but are very close when \( N = 200 \).

Table 5. The percentage of the estimated confidence intervals that include the true values of the parameters. The percentage presented is the average over the corresponding percentages of the parameters.

| Method | Sample size | FM 90% CI | 95% CI | 99% CI |
|--------|-------------|-----------|--------|--------|
| FM     | 50          | 89.40%    | 93.84% | 98.28% |
| FM     | 500         | 90.16%    | 95.68% | 98.89% |
| FM     | 5,000       | 87.56 %   | 92.96 %| 98.56% |
| RER    | 5,000       | 87.76 %   | 92.80% | 97.56% |
| RER    | 50,000      | 88.00%    | 93.84% | 98.76% |
percentile confidence intervals. We observe that the estimated potential captures the minimum value point of the reference, though there is an amplitude deviation. Most importantly, the reference potential falls inside the 95% and 99% bootstrap CI for the whole range of distances. This observation suggests that for \( N = 200 \), the bootstrap CI is capable of providing useful information for the range and minima of the potential.

In order to examine the dependence of the CG potential on the size of the data set, we present in figure 10 the resulting effective potential of CG PE beads, as well as its 95% CI, for an increasing number of atomistic configurations. We observe that the CI for \( N = 30 \) is practically uninformative, as its range is too wide.

Next, we examine the bootstrap standard deviation (STD) of the CG pair potential values, as a function of the CG beads distance. Results for the bootstrap STD are shown in figure 11, evaluated for a varying number of configurations. Two useful observations can be made out of these data. First, it is interesting that the STD

![Figure 5](image_url) Drift function \( a(x; \hat{\theta}) \), with \( \hat{\theta} \) estimated by different methods and 95% bootstrap percentile confidence interval. The number of bootstrap samples is 200.

![Figure 6](image_url) Snapshot of model polyethylene bulk system, shown in atomistic and CG (3:1 mapping scheme) description: a) single PE chain, b) PE bulk system.

### Table 6. Available sample sets for the PE model.

| Number of parameters | Small data set size | Large data set size |
|----------------------|---------------------|---------------------|
| Linear               |                     |                     |
| 75                   | 30                  | 5000                |
| 30                   | 200                 | 2000                |
| Cubic                |                     |                     |
| 30                   | 30                  | 5000                |
|                     | 100                 | 2000                |
|                     | 200                 | 2000                |
decreases with increasing the potential interaction range, i.e., the distance between CG particles, for all cases. Indeed, the most uncertain values of the CG pair potential are for small distances. This is not surprising if we consider that at larger distances the configurations are more 'homogeneous' (pair distribution function approaches one), and thus the variance is expected to be smaller. Second, the STD decreases with increasing the number of configurations, and the deviation between them is lower as the data set increases. Thus, given a desired accuracy, the STD can serve as a criterion for choosing a sufficient number of configurations.

The 95% jackknife CI for the CG PE pair potential is presented in figure 12, for N = 200. It is clear that the jackknife CI can also capture the reference potential for this size of the data set.

Furthermore, to examine the CG interaction potential predictions at specific particle distances, the mean, the standard deviation, and the percentile CI values are shown in figure 13 and in tables 7, 8 and 9 for three distances r = 0.45, 0.65, 0.95. In more detail, figure 13 and table 7 depict the estimate and CI for the pair potential at distance r = 0.65 nm for various data sets. This distance corresponds to the reference potential minimum. We observe the improvement of the probability density, and the most probable CG potential value, with the increase of the data set size. Indeed, as the size of the available configurations change from 30 up to 200 a 'concentration of the density' is also observed. At the same time, the expected value approaches the one of the underlying reference system (N = 2,000), shown in table 7.

Qualitatively similar are the results for the other two distances r = 0.45 nm, which is in the repulsive part of the potential, and r = 0.95 nm in the attractive ‘tail,’ shown in tables 8 and 9 respectively. For both distances, the bootstrap predictions become more accurate (CIs are reduced) as the size of the data set increases. For N = 200 the bootstrap an jackknife predictions are very similar.
As a final check, and in order to understand the effect of the correlated data on the effective model we present in figure 14 the pair potential point estimates obtained by the FM method with (a) a set of 200 correlated configurations with distance $\tau = 50$ ps, (b) the reference large set of $N = 2,000$ configurations with distance $\tau = 250$ ps and (c) the set of $N = 200$ uncorrelated configurations with distance $\tau = 2,500$ ps. Recall, that the estimated relaxation time is $1,700$ ps.

### Guidelines and Discussion

To conclude, in this work, we presented an array of methodologies to generate confidence intervals for systematic bottom-up coarse-grained models, derived from both invariant density and path-space observations. The coarse-graining approach is physics and data-driven, relating the true CG model to its digital-twin, the approximate CG model.
We have employed rigorous statistics theory tools for constructing asymptotic and non-asymptotic CIs, and examined their applicability to coarse-graining strategies. We present a schematic guideline in Figure 15 for the methodology we propose. The main features of the methodology, as depicted in the schematic guideline and observed in the test-bed problems, are:

- Asymptotic vs. non-asymptotic: The asymptotic methods need a parametric form of the variance since we compute the expectation of the first and second derivatives of the log density or transition probability function. While the non-asymptotic methods do not need a parametric form of the variance they have an additional computation cost due to the repeated optimization to compute sample estimates. Therefore, if an analytic form of variance can be derived, asymptotic methods are more computationally efficient.
- Time-series data vs. independent data: Independent data can provide more information as their statistical analysis is well established, but obtaining independent data in real-world problems is often impractical. Correlated data, such as time-series data, are more commonly used. Our proposed confidence intervals for the RER minimization, provides a useful uncertainty quantification of the estimated parameters for time-series data, under the assumption of stationarity and ergodicity.
- Correlated data in multiple independent trajectories: We also demonstrated in Table 4 that by using the independence between trajectories a resampling

Figure 11. Bootstrap standard deviation of the CG PE pair effective potentials for the data sets of 200, 100, and 30 configurations.

Figure 12. The jackknife 95% CI for the estimated CG PE pair effective interaction potential \(u(r)\), for the \(N = 200\) configurations data set.
technique, jackknife and bootstrap, can also construct non-asymptotic confidence intervals for this type of data.

In short, we have demonstrated:

- the need for employing non-asymptotic methods in coarse-graining high-dimensional molecular systems, and
- the benefit of applying time series, path-space techniques.

As it is often extremely time-consuming to generate 'large' data sets of atomistic model configurations in molecular, and especially macromolecular systems, the asymptotic confidence intervals are often not valid. Therefore, we propose non-parametric, non-asymptotic methods, i.e., bootstrap and jackknife methods to provide

Figure 13. Probability density function of CG PE pair effective potential $u(r)$, at $r = 0.65\text{nm}$, derived from bootstrap, for three small data sets involving 200, 100, and 30 atomistic configurations. The corresponding reference value is $\hat{u} = -0.6289$.

Table 7. Mean, standard deviation, and percentile CI for $u(r)$, $r = 0.65$.

| Method        | $\hat{u}$ | $\sigma_u$  | CI                | Number of samples |
|---------------|-----------|-------------|-------------------|-------------------|
| Large data set| -0.6289   |             |                   | 200               |
| Bootstrap     | -0.5027   | 0.2259      | (-0.9343, -0.0145)| 30                |
|               | -0.4706   | 0.1079      | (-0.6847, -0.2796)| 100               |
|               | -0.6900   | 0.0770      | (-0.8504, -0.5417)| 200               |
| Jackknife     | -0.6900   | 0.0794      | (-0.8463, -0.5348)| 200               |

Table 8. Mean, standard deviation, and percentile CI for $u(r)$, $r = 0.45$.

| Method        | $\hat{u}$ | $\sigma_u$  | CI                | Number of samples |
|---------------|-----------|-------------|-------------------|-------------------|
| Large data set| 4.3263    |             |                   | 200               |
| Bootstrap     | 4.5663    | 0.2896      | (3.9611, 5.1605)  | 30                |
|               | 4.3743    | 0.1716      | (4.0619, 4.6749)  | 100               |
|               | 4.2631    | 0.1036      | (4.0542, 4.4686)  | 200               |
| Jackknife     | 4.2631    | 0.1078      | (4.0522, 4.4748)  | 200               |

Table 9. Mean, standard deviation, and percentile CI for $u(r)$, $r = 0.95$.

| Method        | $\hat{u}$ | $\sigma_u$  | CI                | Number of samples |
|---------------|-----------|-------------|-------------------|-------------------|
| Large data set| -0.1210   |             |                   | 200               |
| Bootstrap     | -0.1488   | 0.1571      | (-0.3974, 0.1313) | 30                |
|               | 0.0687    | 0.0799      | (-0.0583, 0.2453) | 100               |
|               | -0.2216   | 0.0582      | (-0.3312, -0.1156)| 200               |
| Jackknife     | -0.2138   | 0.0613      | (-0.3339, -0.0937)| 200               |
guarantees of the coarse-grained output model in terms of the size of the available data.

Moreover, we show with the benchmark example that the path-space method, i.e., the RER optimization, is best in terms of the cost of generating simulated data, for which we can also provide confidence intervals. Also, the FM estimator for correlated data gives reliable point estimates, though corresponding confidence sets cannot be obtained. Indeed, since the bottom-up CG methods are based on simulated data, often for high-dimensional systems, not discarding simulated data, to achieve independence, saves a large amount of computational time.

For the polymer melt, at realistic conditions, we have presented the bootstrap and jackknife confidence intervals for the FM estimated parameters and the pair potential. A detailed analysis of the CIs for the derived effective CG non-bonded potential suggests that the sufficiency of the data size can be estimated along with the estimated bootstrap variance.

We believe that our work could stimulate further studies on the development and application of rigorous statistical inference methods for coarse-grained models of soft-condensed matter, and in particular, of macromolecular systems. This is even more important for hybrid polymer-based complex materials, for which the relaxation times increase rapidly with the complexity of the underlying physico-chemical interactions, thus making the sampling of either a large number of atomistic i.i.d. or long time-correlated configurations infeasible.\(^{53,54}\)
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