OPTIMAL ESTIMATION OF FREE ENERGIES AND STATIONARY
DENSITIES FROM MULTIPLE BIASED SIMULATIONS

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Abstract. When studying high-dimensional dynamical systems such as macromolecules, quantum systems and polymers, a prime concern is the identification of the most probable states and their stationary probabilities or free energies. Often, these systems have metastable regions or phases, prohibiting to estimate the stationary probabilities by direct simulation. Efficient sampling methods such as umbrella sampling, metadynamics and conformational flooding have developed that perform a number of simulations where the system’s potential is biased such as to accelerate the rare barrier crossing events. A joint free energy profile or stationary density can then be obtained from these biased simulations with weighted histogram analysis method (WHAM). This approach (a) requires a few essential order parameters to be defined in which the histogram is set up, and (b) assumes that each simulation is in global equilibrium. Both assumptions make the investigation of high-dimensional systems with previously unknown energy landscape difficult. Here, we introduce the transition matrix unweighting (TMU) method, a simple and efficient estimation method which dismisses both assumptions. The configuration space is discretized into sets, but these sets are not only restricted to the selected slow coordinate but can be clusters that form a partition of high-dimensional state space. The assumption of global equilibrium is replaced by requiring only local equilibrium within the discrete sets, and the stationary density or free energy is extracted from the transitions between clusters. We prove the asymptotic convergence and normality of TMU, give an efficient approximate version of it and demonstrate its usefulness on numerical examples.

Key words. Markov chain, maximum likelihood estimation, error analysis, free energy, stationary density, simulation

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1. Introduction. Stochastic simulations of chemical, physical or biological processes often involve rare events that render the exploration of relevant states, or the calculation of expectation values by direct numerical simulation difficult or impossible. Examples include phase transitions in spin systems [22, 23], transitions between different chemical states in quantum dynamics simulations [13] or conformational transitions in biomolecules [6]. For this reason, many enhanced sampling techniques have been developed to modify the dynamics of the original simulation system such that the relevant rare events become more frequent and can be accessed by direct numerical simulation of the modified simulation system. Such an approach is of course only reasonable if there exists a way to reliably compute at least some quantities of interest of the original simulation system from the realizations of the modified simulation system.

In this paper we focus on processes that are asymptotically stationary and ergodic, and on enhanced sampling approaches that use bias potentials (or equivalently conservative bias force fields) that attempt to modify the original system’s dynamics so as to avoid rare events. Well-known examples of such approaches are Umbrella Sampling [20], conformational flooding [8], Metadynamics and variants [12, 14]. These approaches assume that the modeler has some knowledge of coordinates or order parameters that are “slow”, i.e. that the rare event dynamics of the system is resolved by state transitions in these selected coordinates.

Umbrella sampling defines a series of $K$ biased simulations, each of which uses the forces from the original dynamics plus the forces due to one of $K$ harmonic poten-
tials. These potentials restrain the biased simulations to stay close to positions $x_k$ in the selected coordinates which are the centers of the umbrella potentials. The force constant(s) of these potentials must be chosen such that the corresponding biased stationary densities overlap significantly and the unification of all biased stationary densities covers the part of state space in which the original stationary density is significantly greater than zero. In this case, the $K$ biased simulations, together with the knowledge of the umbrella potentials can be used in order to estimate the original stationary density in the selected coordinates (or the corresponding free energy landscape).

Metadynamics is based on an opposite philosophy. Rather than by constraining the simulation to a set of points, it adds bias potentials to drive the simulation away from regions it has sampled sufficiently well. In practice this is often done by adding Gaussian hat functions to the bias potential every $n$ simulation steps, centered at the current simulation state. We consider that this happens a number $K$ times, leading to $K$ simulation snippets, each with a different biasing potential. Due to limitations of filling high-dimensional space volumes, these bias potentials live usually also in a few pre-defined coordinates. Since the sequence of added bias potentials depends on the simulation history, metadynamics is usually used to first “fill up” the free energy wells until the states that cause the rare event waiting times have been destabilized and the corresponding free energy landscape is approximately “flat”. It can be shown that at this point continuing the metadynamics simulation will sample bias potentials that are the negative free energy landscapes of the original system, up to an arbitrary additive constant. Since metadynamics does not require the modeler to know the relevant states along the slow coordinates, it is not only an approach to quantify the stationary distribution / free energy landscape of the original system but has been very successful in terms of exploring the state space in complex systems [16]. Unfortunately, this approach of using metadynamics also appears to suggest that all simulation effort that has been spent until the free energy surface is approximately flat cannot be used for quantitative estimations.

Here we concentrate on the step of unbiased the modified dynamics so as to obtain the stationary distribution of the original dynamical system. For both, umbrella sampling and metadynamics, the step of “unbiasing” is usually done with the weighted histogram method (WHAM) [5]. WHAM uses a discretization of the selected coordinates in which the biased simulation was done, collects a set of $K$ histograms, one for each of the biased simulations. These biased histograms are then combined to a single unbiased histogram by solving the self-consistent set of equations:

$$\pi_i = \left(\sum_{k=1}^{K} n_i^k\right) / \left(\sum_{k=1}^{K} M_k c_i^k / z^k\right)$$ and $$z^k = \sum_j c_j^k \pi_j,$$ where $n_i^k$ is the number of counts in histogram bin $i$ for simulation $k$, $M_k$ is the total number of samples generated by the $k$-th simulation, $z^k$ is a normalization constant, $c_i^k$ is the unbiasing factor of state $i$ at simulation $k$, and $\pi_i$ is the unbiased probability of state $i$ at simulation condition $k$.

The assumption used by WHAM is that each of the $K$ simulations done at different conditions is sufficiently long such that they generate unbiased samples of the corresponding biased stationary density $\pi_k$. In order words, each sub-simulation is assumed to be in global equilibrium at its conditions. We will see that restricting to this assumption is unnecessary, and a method that does not rely on this assumption can provide estimates that are substantially more precise (or, equivalently, require substantially less simulation effort for a given level of precision), even in trivial double-well examples.
This paper develops the transition-matrix based unbiasing method (TMU) which replaces the assumption that the $K$ biased simulations are in global equilibria by the much weaker assumption that each simulation is only in local equilibrium in the discrete states on which the stationary distribution is estimated. TMU has been motivated by the recent progresses in Markov modeling [25, 4, 15, 18], and constructs the joint unbiased stationary distribution from a series of $K$ transition count matrices estimated from the $K$ biased simulations. However, it is important to note that TMU does not need the discrete dynamics to be Markovian.

Subsequently, we describe the basic mathematical assumptions underlying our method, then describe TMU in its most general form and show that the method has always a solution that is asymptotically normal and convergent. We then provide an approximate TMU that is efficient for very large state spaces and a large number of sub-simulations. The method is demonstrated in conjunction with umbrella sampling and metadynamics on double-well potentials and its performance is compared with that of the standard WHAM method and a recently introduced method MMMM that had a similar motivation [21].

2. Background. In this section, we briefly review the mathematical background of biased simulation techniques. Let us consider a reference system in which the configuration space can be decomposed into a discrete state set $S$ with free energy $V = [V_i]$ by using some sort of discretization (where $V_i$ is the energy of the $i$-th state in $S$). If we denote the system state at time $t$ by $x_t$, the state sequence $\{x_t\}$ is then a stochastic process. In this paper, we focus on processes $\{x_t\}$ with the following properties, which are relevant for many physical simulation processes:

Asymptotic stationarity. It means that the sequence $\{x_t|t \geq \tau\}$ is approximately stationary if $\tau$ is large enough. More formally, $\{x_t\}$ is said to be asymptotically stationary if there exists a family of distribution functions $F_n: S^n \rightarrow \mathbb{R}$ such that $\lim_{\tau \to \infty} \Pr(I_S(x_{\tau+1}) = s_1, \ldots, x_{\tau+n} = s_n) = F_n(s_1, \ldots, s_n)$ for all $n \geq 1$ and $s_1, \ldots, s_n \in S$. Specifically, $\lim_{\tau \to \infty} \Pr(I_S(x_\tau) = i) = \pi_i$ with

$$\pi_i = \frac{\exp(-\beta V_i)}{\sum_j \exp(-\beta V_j)}$$

where $\pi = [\pi_i]$ denotes the system stationary distribution and $\beta$ is a constant and generally proportional to the inverse temperature in physical systems, and we denote the limit $\lim_{\tau \to \infty} \Pr(I_S(x_{\tau+1}) = j|I_S(x_\tau) = i)$ by $T_{ij}$.

Wide-sense ergodicity. That is,

$$\lim_{t \to \infty} \frac{1}{t+1} \sum_{\tau=0}^{t} 1_{I_S(x_\tau) = i} = \pi_i$$

and

$$\lim_{t \to \infty} \frac{1}{t} \sum_{\tau=0}^{t-1} 1_{I_S(x_\tau) = i} \cdot 1_{I_S(x_{\tau+1}) = j} = \pi_i T_{ij}$$

Detailed balance. The detailed balance condition can be written as

$$\lim_{t \to \infty} \Pr(I_S(x_t) = i, I_S(x_{t+1}) = j) = \lim_{t \to \infty} \Pr(I_S(x_t) = j, I_S(x_{t+1}) = i)$$
or equivalently $\pi_i T_{ij} = \pi_j T_{ji}$, for all $i, j$, which implies that each state transition has the same probability as its reverse. Note that this property clearly holds for systems that are time-reversible at equilibrium.

**Remark 2.1.** For convenience, we measure energies $V_i$ in units of thermal energy $k_B T_{\text{thermal}}$ with $k_B$ the Boltzmann constant and $T_{\text{thermal}}$ the thermodynamic temperature, yielding $\beta = 1$ in (2.1). Furthermore, we assume without losing generality that all involved free energies in this paper are zero-mean. Then (2.1) has a unique solution

$$V_j = -\log \pi_j + \frac{1}{|S|} \sum_i \log \pi_i$$

for a given stationary distribution.

Based on the asymptotic stationarity, we can define a matrix $T = [T_{ij}] \in \mathbb{R}^{|S| \times |S|}$ to represent the stationary state transition probabilities. It is easy to see that $T$ satisfies the condition that each row sums to 1, so here we call $T$ the transition matrix of $\{x_t\}$ for simplicity even if $\{x_t\}$ is not a Markov chain.

For now, our goal is to estimate $V$, or equivalently $\pi$, from simulations in the case that it is unknown. Due to the ergodicity (2.2), when sufficient simulation data can be generated, we can simply carry out one or multiple simulations of the reference system and get the estimate of $V$ through computing the histogram of simulation data. This approach, however, is very inefficient when the reference system has multiple metastable states, because the simulation process is very likely to get stuck in some local minima of the energy landscape for a long time. To this end, biased simulation techniques, such as umbrella sampling [23] and metadynamics [12], were developed to solve this problem, which perform simulations with a set of biased potentials so that the energy landscape can be explored more efficiently.

Although many practical algorithms use a different approach, we can roughly summarize the estimation of stationary distributions through biased simulations in terms of the following pseudocode:

**Step 1** Design a set of biasing potentials $\{U^k|k = 1, \ldots, K\}$ where $U^k = \left[U^k_i\right] \in \mathbb{R}^{|S_k| \times 1}$.

**Step 2** Repeat Steps 2.1 and 2.2 for $k = 1, \ldots, K$:

**Step 2.1** Reduce the state set to $S_k \subseteq S$ and change the system potential as

$$V^k = V_{\text{ID}^k(i)} + U^k_{\text{ID}^k(i)} - \frac{1}{|S_k|} \sum_{j \in J^k} (V_j + U^k_j)$$

where $V^k = \left[V^k_i\right] \in \mathbb{R}^{|S^k| \times 1}$ is called the biased potential, $\text{ID}^k(i) = I_S$ (i-th element of $S^k$), $J^k = \{I_S(s) | s \in S^k\}$, and the last term is used to shift the mean of $V^k$ to zero.

**Step 2.2** Perform a biased simulation using the same simulation model as the reference system except that the state set and potential energy are changed from $S, V$ to $S^k, V^k$, and record the simulation trajectory $x^k_{0:M_k}$.

**Step 3** Estimate the reference (unbiased) free energy $V$ from $\{x^k_{0:M_k}|k = 1, \ldots, K\}$. In this paper, we will focus on the estimation problem in Step 3. We start with the assumption that each simulation $x^k_{0:M_k}$ is a Markov chain, and the developed estimation method will then be proved to be applicable to more general simulation models.

**Remark 2.2.** (2.6) can be written in a more compact form by defining a potential
transformation matrix \( A^k = [A^k_{ij}] \in \mathbb{R}^{|S^k| \times |S|} \) with \( A^k_{ij} = 1_{j \in S^k \cdot (1_{1D^k(i) = j} - 1/|S^k|)} \) such that \( V^k = A^k (V + U^k) \).

3. Maximum likelihood estimation from multiple simulations.

3.1. Maximum likelihood estimation. In this section, we investigate a maximum likelihood approach to the estimation problem described in Section 2. Suppose that each simulation \( x^k_{0:M_k} \) is a time-homogeneous Markov chain. According to the third simulation property stated in Section 2, it is easy to see that \( x^k_{0:M_k} \) is a reversible Markov chain. (It can further be proved that \( x^k_{0:M_k} \) is irreducible and positive recurrent under the condition of finite \( V^k \) by using the first and second properties.) The maximum likelihood estimation (MLE) of the unbiased stationary distribution \( \pi \) can then be obtained by solving the following optimization problem:

\[
\max_{\pi, T^k} L = \sum_k \log \Pr (x^k_{1:M_k} | x^k_0, T^k) = \sum_{i,j,k} C^k_{ij} \log T^k_{ij}
\]

s.t. \( \pi \) is a probability vector

\( T^k \) is a transition matrix

\( \text{diag} (\pi^k) T^k = T^k \text{diag} (\pi^k) \), \hspace{1cm} k = 1, \ldots, K

where \( T^k = [T^k_{ij}] \) and \( \pi^k = [\pi^k_i] \) denote the transition matrix and stationary distribution of the \( k \)-th simulation, \( C^k = [C^k_{ij}] = \sum_{i=1}^{M_k} \Delta C^k_{i,j} \) is the count matrix of the \( k \)-th simulation and \( \Delta C^k_{i,j} = [\Delta C^k_{i,j}] = [I_{l_{2k}(x^k_{t}, j)} = (i,j)] \). (Here we set \( 0 \log 0 = 0 \) and \( a \log 0 = -\infty \) if \( a > 0 \).) The last constraint is obviously the detailed balance constraint for the biased simulations, and can be equivalently written as \( \text{diag} (\Lambda^k \pi) T^k = T^k \text{diag} (\Lambda^k \pi) \) with \( \Lambda^k = [\Lambda^k_{ij}] = [1_{1D^k(i) = j} \cdot \exp (-U^k)] \in \mathbb{R}^{|S^k| \times |S|} \). After performing the MLE of \( \pi \), the optimal estimate of \( V \) can also be obtained by using (2.5).

**Theorem 3.1.** The optimization problem (3.1) has at least one optimal solution satisfying

1. \( T^k_{ij} = 0 \) for \( (i,j,k) \in \{(i,j,k) | C^k_{ij} + C^k_{ji} = 0 \ and \ i \neq j \} \).
2. \( 1_{T^k_{ij} > 0} = 1_{C^k_{ij} > 0} \), if \( C^k_{ij} > 0 \) and \( 1_{C^k_{ij} > 0} = 1_{C^k_{ji} > 0} \) for all \( i, j, k \).

**Proof.** See Appendix A.

According to Theorem 3.1, we can reduce the dimension of the optimization variable of (3.1), and the reduced problem can be written as

\[
\max_{\pi, T^k_{ij} \mid C^k_{ij} + C^k_{ji} > 0 \ or \ i=j} L = \sum_{i,j,k} C^k_{ij} \log T^k_{ij}
\]

s.t.

\( \pi \) is a probability vector

\( T^k \) is a transition matrix

\( \text{diag} (\Lambda^k \pi) T^k = T^k \text{diag} (\Lambda^k \pi) \), \hspace{1cm} k = 1, \ldots, K

with \( T^k_{ij} = 0 \) for \( (i,j,k) \in \{(i,j,k) | C^k_{ij} + C^k_{ji} = 0 , i \neq j \} \). It is clear that the problem size of (3.2) is much smaller than that of (3.1), especially when count matrices are sparse. However, even if each \( C^k \) is sparse with \( O(|S|) \) nonzero elements, the reduced problem (3.2) involves \( O(K |S|) \) decision variables and nonlinear equality constraints. (Note that \( \pi \) and \( T^k \) are both unknown in the last constraint.) It is still inefficient to search the optimal solution of (3.2) by direct methods. In Section 4, we will adopt an approximate MLE method to improve the efficiency based on the decomposition strategy.
3.2. Convergence analysis. The MLE method of stationary distribution in Section 3.1 is motivated by the assumption that \( x_k^M, \) \( k \) is a Markov chain. Interestingly, it turns out that the Markov property is not necessary for the convergence of MLE. In this section we will prove the convergence of MLE under more general conditions.

First of all, we provide an intuitive explanation for why the MLE can work for non-Markovian stochastic processes. Generally speaking, if there is no other knowledge available, \( \hat{T}_k^i \) can be estimated as
\[
\hat{T}_k^i = \frac{C_{ij}^k}{\sum_l C_{il}^k}
\]
But the transition matrix estimates obtained from (3.3) generally do not satisfy the detailed balance condition and do not share the same unbiased stationary distribution for finite-time simulations. Therefore we search for the feasible transition matrices which are close to \( \hat{T}_1^i, \ldots, \hat{T}_K^i \):

\[
\min_{\pi, T^1, \ldots, T^K} \sum_{i,k} \hat{w}_k \hat{\pi}_i^k \text{KL} \left( \hat{T}_k^i || T_i^k \right)
\]

\[\text{s.t.} \quad \pi \text{ is a probability vector} \]
\[T^k \text{ is a transition matrix} \]
\[\text{diag} \left( \Lambda^k \pi \right) T^k = T^{kT} \text{diag} \left( \Lambda^k \pi \right), \quad k = 1, \ldots K\]

where \( \hat{w}_k = M_k / M \) is the weight of the simulation \( k \), \( M = \sum_k M_k \) denotes the total length of performed simulations, \( \hat{\pi}_i^k \propto \sum_j C_{ij}^k \) is an estimate of \( \pi_i^k \), and KL \( \left( \hat{T}_k^i || T_i^k \right) = \sum_j \hat{T}_k^{ij} \log \left( \hat{T}_k^{ij} / T_i^{ij} \right) \) denotes the KL divergence between the \( i \)-th rows of \( \hat{T}_k^i \) and \( T_i^k \). \( \hat{w}_k \hat{\pi}_i^k \) gives the fraction of occurrence of state \( i \) in simulation \( k \). Note that
\[
\sum_{i,k} \hat{w}_k \hat{\pi}_i^k \text{KL} \left( \hat{T}_k^i || T_i^k \right) = \sum_{i,j,k} \hat{w}_k \hat{\pi}_i^k \hat{T}_k^{ij} \left( \log \hat{T}_k^{ij} - \log T_i^{ij} \right)
\]

\[= \frac{1}{M} \left( \sum_{i,j,k} C_{ij}^k \left( \log \hat{T}_k^{ij} \right) - \sum_{i,j,k} C_{ij}^k \left( \log T_i^{ij} \right) \right) \]

and thus (3.4) is equivalent to (3.1). Therefore the MLE can be considered to be a projector which projects the counting estimates (3.3) onto the feasible space. Fig. 3.1 shows the relationship between different estimates and the true values of \( (T_1^i, \ldots, T^K_i) \), where the estimates obtained by counting converge to their true values due to the wide-sense ergodicity of simulations.

Remark 3.2. In [19], a KL divergence rate was derived to measure the distance between Markov chains. Suppose \( \{x'_t\} \) and \( \{x''_t\} \) are two Markov chains on the same state set with stationary distributions \( \pi', \pi'' \) and transition matrices \( T', T'' \), then the KL divergence rate between them can be defined as
\[
\text{KLR} (\pi', T' || \pi'', T'') \triangleq \frac{1}{t+1} \lim_{t \to \infty} \text{KL} (x'_0 || x''_0)
\]

\[= \sum_i \pi'_i \text{KL} (T'_i || T''_i) \]
where $\pi'_i$ denotes the $i$-th element of $\pi'$ and $T'_i, T''_i$ denote the $i$-th rows of $T', T''$. It is easy to see that the objective function of (3.4) is equivalent to the weighted sum of \( \text{KLR} \left( \hat{\pi}^k, \hat{T}^k || \pi^k, T^k \right) \) with weight $\hat{w}_k$.

The equivalence of (3.1) and (3.4) implies that the consistency of the MLE can hold without assuming the Markov property if it can be shown that the error of the MLE converges to zero when $\hat{T}^1, \ldots, \hat{T}^K$ converge to their true values. Before proving the main theorems, we make some assumptions and introduce some notation.

Unless stated otherwise, all convergence statements are made with respect to $M \to \infty$ in this paper.

**Assumption 3.3.** $U^1, \ldots, U^K$ and $\hat{V}$ are finite.

**Assumption 3.4.** The limit $\bar{w} \xrightarrow{p} \hat{w}$ exists and $\hat{w} > 0$, where $\hat{w} = [\hat{w}_i]$ and $\bar{w} = [\bar{w}_i]$.

**Assumption 3.5.** $x_{iM_k}^1, \ldots, x_{iM_k}^K$ are all asymptotically stationary and wide-sense ergodic processes with detailed balance.

**Assumption 3.6.** For any $i, j, k$, if there exists some $t$ such that $\Pr(I_{S_k}(x_i^t) = i, I_{S_k}(x_i^{t+1}) = j) > 0$, then $\lim_{t \to \infty} \Pr(I_{S_k}(x_i^t) = i, I_{S_k}(x_i^{t+1}) = j) > 0$.

**Assumption 3.7.** $\pi = \bar{\pi}$ is the unique solution of the following set of equations and inequalities:

$$
\begin{align*}
\text{diag} \left( \Lambda^k \pi \right) \bar{T}^k &= \bar{T}^k \text{diag} \left( \Lambda^k \pi \right), \quad \text{for } k = 1, \ldots, K \\
\sum_i \pi_i &= 1 \text{ and } \pi \succeq 0
\end{align*}
$$

The above assumption means the unbiased stationary distribution can be uniquely determined if all the transition matrices are given.

Furthermore, here we let $\theta$ be the vector consisting of elements of the unbiased stationary distribution $\pi$ and transition matrices $T^1, \ldots, T^K$, $X^k = [X_{ij}^k] = [\pi_i^k T_{ij}^k]$ with $\bar{X}^k = [\bar{X}_{ij}^k] = [\bar{\pi}^k \bar{T}_{ij}^k]$ and $\hat{X}^k = [\hat{X}_{ij}^k] = [\hat{\pi}^k \hat{T}_{ij}^k]$, $\Theta$ be the feasible set defined by constraints in (3.1), $V_{X_w} = \left( w_1 V(1)^T, \ldots, w_K V(K)^T \right)^T$ and

$$
\hat{Q}(\theta) = \sum_{i,j,k} \hat{w}_k \hat{X}_{ij}^k \log T_{ij}^k, \quad \bar{Q}(\theta) = \sum_{i,j,k} \bar{w}_k \bar{X}_{ij}^k \log T_{ij}^k
$$

Notice that functions $\hat{Q}(\theta)$ and $\bar{Q}(\theta)$ is linear in parameters $\hat{V}_{X_w}$ and $\bar{V}_{X_w}$, then we can construct a function $\Phi(\theta)$ such that

$$
\hat{Q}(\theta) = \hat{V}_{X_w}^T \Phi(\theta), \quad \bar{Q}(\theta) = \bar{V}_{X_w}^T \Phi(\theta)
$$
Based on the above assumptions and notations, the maximum likelihood estimate can be expressed as \( \hat{\theta} = \arg \max_{\theta \in \Theta} \hat{Q}(\theta) \), and we have the following theorems on the convergence of \( \hat{\theta} \).

**Theorem 3.8.** If Assumptions 3.3-3.7 hold, then \( \hat{\theta} \overset{p}{\to} \theta \).

**Proof.** See Appendix B

**Theorem 3.9.** If Assumptions 3.3-3.7 hold and the following conditions are satisfied:

1. For each \( k \), there exists a \( \Sigma_X \) such that
   \[
   (3.10) \quad \sqrt{M} \left( \nabla \left( \hat{X}^k \right) - \nabla \left( \hat{X}^k \right) \right) \overset{d}{\to} N \left( 0, \Sigma_X \right)
   \]
2. \( \hat{\theta} \) is obtained with variable reduction as in (3.2).
3. Diagonal elements of \( X^1, \ldots, X^K \) are positive.
4. All \( K \) simulations are statistically independent.
5. \( \sqrt{M} \left( \hat{w} - \bar{w} \right) \overset{p}{\to} 0 \).
6. \( H = \nabla \theta, \Phi (\hat{\theta}) \) is nonsingular with \( \theta \), the vector consisting of \( \{ T_{ij}^k | \hat{X}_{ij}^k > 0, i < j \} \) and \( \{ \pi_1, \ldots, \pi_{|S|-1} \} \),

then
\[
(3.11) \quad \sqrt{M} \left( \hat{\theta} - \theta \right) \overset{d}{\to} N \left( 0, H^{-1}\Sigma H^{-1} \right)
\]

where \( \Sigma = \left( \nabla \theta, \Phi (\hat{\theta}) \right)^T \Sigma_{Xw} \nabla \theta, \Phi (\hat{\theta}) \) and \( \Sigma_{Xw} = \text{diag} \left( \bar{w}_1 \Sigma_X^1, \ldots, \bar{w}_K \Sigma_X^K \right) \).

**Proof.** See Appendix D

**Remark 3.10.** Since \( X^k = C^k / M^k \), Condition 1 stated in Theorem 3.9 means that the central limit theorem holds for \( \{ V \left( \Delta C_{ij}^k \right) \} \), and can be justified by using Markov chain central limit theorems [10] in many practical situations. For example, one sufficient condition for this is that for each simulation \( k \), \( \{ x^k \} \) is obtained by coarse-graining a geometrically ergodic Markov chain \( \{ y^k \} \) with \( x^k = f^k (y^k) \), which implies that \( S^k \) defines a partition of the state space of \( \{ y^k \} \) and each \( s \in S^k \) is associated with a cluster \( \{ r | f^k (r) = s \} \) in the state space. (See Appendix D for details.)

**Remark 3.11.** In this section we only characterize the convergence of \( \hat{\pi} \). For the MLE of free energy \( V \), the consistency and asymptotic normality are immediate consequences of Theorems 3.8 and 3.9 by considering that \( V \) is a smooth function of \( \pi \). Here we omit the detailed description and proof as they are trivial.

**4. Approximate maximum likelihood estimation.** In this section, we develop an approximate MLE method based on a decomposition strategy in order to improve the efficiency of MLE, and the convergence of the method is shown.

For convenience of analysis and computation, here we introduce two new variables, \( C^k \) and \( Z^k \). \( C^k = \left[ C^k_{ij} \right] \) is a modified count matrix used to replace \( C^k \) in the approximate MLE, and is assumed to satisfy the following assumption:

**Assumption 4.1.** \( C^1, \ldots, C^K \) are irreducible matrices with positive diagonal elements, and satisfy that \( 1_{C_{ij}^k > 0} = 1_{C_{ij}^k > 0} \text{ and } 1_{C_{ij}^k = 0} \overset{p}{\to} 1 \) for all \( i, j, k \).

One way to perform the count matrix modification is as follows:

\[
(4.1) \quad C^k_{ij} = \begin{cases} \max \left\{ C^k_{ij}, \delta \right\}, & C^k_{ij} > 0 \text{ or } i = j \\ C^k_{ij}, & \text{otherwise} \end{cases}
\]
Thus, model under the condition that lowing equivalent formulation:

\[ \sum_{i=0}^{\infty} 1_{I_S(x_t^k) = i} > 0 \text{ for all } i, k, \]

satisfy Assumption \[4.1\].

Proof. See Appendix \[3\].

The variable \( Z^k = [Z^k_{ij}] \) is defined by

\[ \exp (-Z^k_{ij}) \propto X^k_{ij} \]

which can be interpreted as the “free energy matrix” of state transitions in the \( k \)-th simulation because \( \lim_{t \to \infty} \Pr \{ I_S(x_t^k) = i, I_S(x_{t+1}^k) = j \} \). Like the free energies of states, we also assume that \( \sum_{(i,j) \in \{(i,j) | X^k_{ij} > 0\}} Z^k_{ij} = 0 \) such that \( \text{(4.2)} \) has a unique solution with given \( X^k \).

### 4.1. Decomposition and approximation of MLE problem.
Under the above assumption and variable definitions and replacing \( C^k \) by \( C^k \), \( (3.2) \) can be decomposed into \( K + 1 \) subproblems as follows:

**Local subproblems** \((k = 1 \ldots, K)\).

\[
L^k (V^k) = \max_{\{Z^k_{ij} | C^k_{ij} > 0\}} \quad - \sum_{i,j} C^k_{ij} Z^k_{ij} + \sum_i C^k_i Z^k_i \\
\text{s.t.} \\
Z^k = Z^k_T \\
\sum_{(i,j) \in \{(i,j) | X^k_{ij} > 0\}} Z^k_{ij} = 0 \\
V^k_Z = V^k
\]

where \( Z^k_{ij} = \infty \) if \( C^k_{ij} = 0 \), \( 0 \cdot \infty \) is set to be \( 0 \), \( Z^k_i = -\log \sum_j \exp (-Z^k_{ij}) \), \( C^k_i = \sum_j C^k_{ij} \) and \( V^k_Z = V^k \) are zero-mean vectors, so this constraint can be equivalently written as \( [I \quad 0] V^k_Z = [I \quad 0] V^k \). Thus, \( L^k (V^k) \) is equal to the maximum log-likelihood of a reversible Markov chain model under the condition that \( V^k \) is known, and the local subproblem has the following equivalent formulation:

\[
L^k (V^k) = \max_{\rho^k} \quad - \sum_{i,j} C^k_{ij} \rho^k_{ij} + \sum_i C^k_i \rho^k_i \\
\text{s.t.} \\
[I \quad 0] V^k_Z = [I \quad 0] V^k
\]
where $Z^k$ and $V^k_z$ are both viewed as functions of $\rho^k$. In comparison with (3.2), each local subproblem with a given $V^k$ only depends on one simulation and independent of the others.

**Global subproblem.**

\[
\max_{V^k} \sum_{k=1}^K L^k \left( A^k \left( V + U^k \right) \right)
\text{ s.t. } \mathbf{1}^T V = 0
\]  
\[(4.6)\]

The objective of this subproblem is to maximize the sum of maximum log-likelihoods for $K$ biased simulations by selecting the best unbiased free energy.

Obviously, if local subproblems can be efficiently and exactly calculated, the MLE of unbiased free energy $V$ can be easily obtained from (4.6) because only $|S|$ variables and one linear equality constraint are involved in the global subproblem. However, local subproblems are nonlinear optimization problems with nonlinear equality constraints, of which solutions are generally computationally expensive and time-consuming. It is therefore necessary to find tractable approximate solutions of local subproblems. In the following, we address the approximations and solutions of the subproblems in detail.

4.1.1. **Local subproblems.** Inspired by the fact that equality constrained quadratic programming problems can be solved analytically, here we present a tractable approximate solution of (4.6) based on Taylor expansions of the objective function and the constraint equation. The approximate solution method consists of the following three steps.

**Search for the optimal solution of (4.5) without the constraint on the free energy.** Omitting the constraint on the free energy, (4.5) can be written as

\[
\max_{\rho^k} L^k = - \sum_{i,j} C^k_{ij} Z^k_{ij} + \sum_i C^k_i Z^k_i
\]  
\[(4.7)\]

and the gradient and Hessian matrix of the objective function used in optimization can be simply obtained by the following equations:

\[
\frac{\partial Z^k_i}{\partial Z^k_{lj}} = 1 \quad \text{if } l = i \\
\frac{\partial^2 Z^k_i}{\partial Z^k_{jm} \partial Z^k_{ln}} = 1 \quad \text{if } j = l = i \quad \text{and } m = n = T^k_{jm} - 1
\]  
\[(4.8) \quad (4.9)\]

Furthermore, we can verify that the Hessian matrix $H^k_\rho \left( C^k, \rho^k \right) = \sum_i C^k_i \nabla_{\rho^k} Z^k_i$ is negative-definite under Assumption 4.1 (see Appendix F), which means (4.5) is a convex optimization problem with a single global optimum that can be solved efficiently using any local optimization algorithm. Here we denote the solution of (4.7) by $\hat{\rho}^k$, and we will employ a conjugate gradient algorithm [27] to find $\hat{\rho}^k$ in our numerical experiments.

**Construct a quadratic programming approximation of (4.5) by Taylor expansions.** Replacing the objective function and the nonlinear constraint of (4.5) by their second-order and first-order Taylor expansions around $\hat{\rho}^k$, we can get the following approximate local subproblem:

\[
L^k_\rho (V^k) = \max_{\rho^k} \bar{L}^k + \frac{1}{2} (\rho^k - \hat{\rho}^k)^T H^k_\rho \left( C^k, \hat{\rho}^k \right) (\rho^k - \hat{\rho}^k)
\text{ s.t. } \left[ \begin{array}{c} \mathbf{1} \ \mathbf{0} \end{array} \right] \nabla_{\rho^k} V^k \left( \hat{\rho}^k \right) (\rho^k - \hat{\rho}^k) = \left[ \begin{array}{c} \mathbf{1} \ \mathbf{0} \end{array} \right] (V^k - \hat{V}^k)
\]  
\[(4.10)\]
where \( \hat{V}^k = V^k \hat{\rho}^k \) and \( L^k = L^k(\hat{V}^k) \).

**Calculate \( L^k_q(V^k) \) from (4.10).** It is easy to verify that \([ I \ 0 ] \nabla_{\rho^k} V^k \hat{\rho}^k \) is full row rank. Then using the Lagrange multiplier method, we get

\[
L^k_q(V^k) = \frac{1}{2} (V^k - \hat{V}^k)^T \Xi^k \left( C^k, \hat{\rho}^k \right) (V^k - \hat{V}^k) + \hat{L}^k
\]

where

\[
\Xi^k \left( C^k, \hat{\rho}^k \right) = \begin{bmatrix} I & 0^T \end{bmatrix} \left( \begin{bmatrix} I & 0 \end{bmatrix} \nabla_{\rho^k} V^k \hat{\rho}^k \left( H^k \left( C^k, \hat{\rho}^k \right) \right)^{-1} \right) \cdot \left( \begin{bmatrix} I & 0 \end{bmatrix} \nabla_{\rho^k} V^k \hat{\rho}^k \right)^T \begin{bmatrix} I & 0 \end{bmatrix}
\]

is negative-semidefinite and satisfies \([ I \ 0 ] \Xi^k \left( C^k, \hat{\rho}^k \right) [ I \ 0 ]^T < 0 \).

**4.1.2. Global subproblem.** Substituting (4.11) into (4.6) leads to the approximate global subproblem:

\[
\max_V \sum_{k=1}^K \frac{1}{2} \left( A^k (V + U^k) - \hat{V}^k \right)^T \Xi^k \left( C^k, \hat{\rho}^k \right)
\]

\[\text{s.t.} \quad (A^k (V + U^k) - \hat{V}^k) + \hat{L}^k = 0 \quad 1^T V = 0\]

By applying the KKT conditions, it is easy to verify that the solution of (4.13) is

\[
\hat{V} = \left( \sum_{k=1}^K A^k T \Xi^k \left( C^k, \hat{\rho}^k \right) A^k \right)^+ \left( \sum_{k=1}^K A^k T \Xi^k \left( C^k, \hat{\rho}^k \right) (\hat{V}^k - A^k U^k) \right)
\]

**Remark 4.3.** We can now explain why variables \( Z^k, V^k \) are used instead of \( T^k, \pi^k \) in the problem decomposition and approximation. First, the approximate local subproblem based on Taylor expansions w.r.t. \( T^k, \pi^k \) involves inequality constraints and therefore has no analytic solution. Secondly, even if we can get a quadratic polynomial approximation to the function \( L^k(V^k(\pi^k)) \) by some method (e.g., omitting the inequality constraints in approximate local subproblems as in [24]), the resulting approximate global problem cannot be solved as easily as (4.13) because both \( V \) and \( \pi \) are nonlinear functions of \( \pi^k \).

**4.2. Approximate MLE algorithm.** Summarizing the above discussions, the approximate MLE algorithm of the unbiased free energy is described as follows:

**Step 1.** For \( k = 1, \ldots, K \), calculate the modified count matrix \( C^k \) by (4.1).

**Step 2.** For \( k = 1, \ldots, K \), search for the optimal point \( \hat{\rho}^k \) of the programming problem (4.7).

**Step 3.** For \( k = 1, \ldots, K \), calculate \( \Xi^k \left( C^k, \hat{\rho}^k \right) \) by (4.12).

**Step 4.** Calculate the approximate maximum likelihood estimate of \( V \) by (4.14).

**4.3. Convergence analysis.** In this section, we will analyze consistency and asymptotic normality of the approximate MLE as the exact MLE under the assumptions stated in Section 3.2 and Assumption 4.1. Before introducing the main theorem, some definitions and a lemma are needed. Let \( \rho^k \) and \( \hat{\rho}^k \) be vectors consisting of \( \{Z^k_{ij}, A^k_{ij} > 0, i \leq j, (i, j) \neq (|S^k|, |S^k|)\} \) and \( \{\bar{Z}^k_{ij}, \bar{A}^k_{ij} > 0, i \leq j, (i, j) \neq (|S^k|, |S^k|)\} \),

\[
\hat{Q}^k (\hat{\rho}^k) = -\sum_{i,j} \hat{\omega}_{ij} \bar{A}^k_{ij} Z^k_{ij} (\hat{\rho}^k) + \sum_{i,j} \hat{\omega}_{ij} \bar{A}^k_{ij} Z^k_{ij} (\rho^k)
\]
and \( \hat{X}^k = [\hat{X}^k_{ij}] = C^k/M^k \). Like \( \hat{Q}(\theta) \) and \( \hat{Q}(\theta) \) in Section 3.2, \( \hat{Q}(\hat{\rho}^k) \) and \( \hat{Q}(\hat{\rho}^k) \) can also be written as

\[
\hat{Q}^k(\hat{\rho}^k) = -\sum_{i,j} \bar{w}_k \hat{X}^k_{ij} Z^k_{ij}(\hat{\rho}^k) + \sum_{i,j} \bar{w}_k \hat{X}^k_{ij} Z^k_{ij}(\hat{\rho}^k)
\]

and \( \hat{X}^k = [\hat{X}^k_{ij}] = C^k/M^k \). Like \( \hat{Q}(\theta) \) and \( \hat{Q}(\theta) \) in Section 3.2, \( \hat{Q}^k(\hat{\rho}^k) \) and \( \hat{Q}(\hat{\rho}^k) \) can also be written as

\[
\hat{Q}^k(\hat{\rho}^k) = \hat{w}_k \nu (\hat{X})^T \Phi^k(\hat{\rho}^k), \quad \hat{Q}^k(\hat{\rho}^k) = \hat{w}_k \nu (\hat{X})^T \Phi^k(\hat{\rho}^k)
\]

and \( \hat{\rho}^k = \arg \max_{\rho^k} \hat{Q}(\rho^k) \) if \( \dim (\hat{\rho}^k) = \dim (\hat{\rho}^k) \).

**Lemma 4.4.** Provided that Assumptions 3.3-3.7 and 4.1 hold.
1. \( \hat{\rho}^k \xrightarrow{p} \hat{\rho}^k \) and \( \hat{V}^k \xrightarrow{p} \hat{V}^k \).
2. \( \sqrt{M_k} (\hat{V}^k - \bar{V}^k) \xrightarrow{d} \mathcal{N}(0, \Sigma^k_Y) \) if (4.10) is satisfied, where

\[
(4.18) \quad \Sigma^k_Y = \nabla_{\rho^k} V^k_{ij} (\hat{\rho}^k) \Sigma^k_{\nu} \left( \nabla_{\rho^k} V^k_{ij} (\hat{\rho}^k) \right)^T
\]

\[
(4.19) \quad \Sigma^k_{\nu} = \bar{w}_k^2 (H^k_{\rho} (\bar{w}_k \hat{X}^k, \hat{\rho}^k))^{-1} \left( \nabla_{\rho^k} \Phi^k (\hat{\rho}^k) \right)^T \Sigma^k_X
\]

**Proof.** See Appendix G.

**Theorem 4.5.** Provided that Assumptions 3.3-3.7 and 4.1 hold.
1. \( \hat{V}^k \xrightarrow{p} \hat{V}^k \).
2. \( \sqrt{M} (\hat{V} - \bar{V}) \xrightarrow{d} \mathcal{N}(0, \Sigma_Y) \) if (4.10) is satisfied for all \( k \) and \( K \) simulations are statistically independent, where

\[
(4.20) \quad \Sigma^k_Y = \left( \sum_{k=1}^{K} A^{kT} \Sigma^k (\bar{w}_k \hat{X}^k, \hat{\rho}^k) A^k \right)^+
\]

and \( \Sigma^k_Y \) has the same definition as in Lemma 4.4.

**Proof.** See Appendix H.

**4.4. Error analysis.** According to Theorem 4.5, the estimation error of \( \hat{V} \) follows approximately a multivariate normal distribution \( \mathcal{N}(0, \Sigma_Y/M) \) when \( M \) is large enough, and \( \Sigma_Y \) can be estimated by (4.18), (4.19) and (4.20) with replacing \( \bar{w}_k, \hat{X}^k, \hat{\rho}^k \) with \( \bar{w}_k, \hat{X}^k, \hat{\rho}^k \) if \( \Sigma_X \) is given. Therefore, the remaining key problem is how to estimate \( \Sigma_X \). In this section we present an algorithm for estimating \( \Sigma_X \) based on the following assumption, which is similar to the assumption proposed in Remark 3.10 and implies that each simulation is driven by a stationary, irreducible and reversible Markov model.

**Assumption 4.6.** For each simulation \( k \), \( x^k_t \) can be expressed as a function of a latent variable \( y^k_t \) with \( x^k_t = f^k(y^k_t) \) and \( \{y^k_t\} \) is a stationary, irreducible and reversible Markov chain.
Under Assumption 4.6, it can be seen that \( \{V(\Delta C^k_t)\} \) is also a stationary process. To describe the estimation algorithm, we also need some new notation. We denote by

\[
(4.21) \quad k^k(h) = \text{Cov} \left( V(\Delta C^k_t), V(\Delta C^k_{t+h}) \right)
\]

the autocovariance of \( \{V(\Delta C^k_t)\} \) with lag \( h \). It is clear that the \((i-1) S^k + j, (m-1) S^k + n\)-th element of \( k^k(h) \) is equal to the covariance between \( 1_{(x^k_t, x^k_{t+h}) = (i,j)} \) and \( 1_{(x^k_t, x^k_{t+h}) = (m,n)} \). Furthermore, let \( \Gamma^k(l) = k^k(2l+1) + k^k(2l+2) \), and \( \eta^k(l) \) be a sum of some elements of \( \Gamma^k(l) \), which can be represented as

\[
\eta^k(l) = \sum_{i,j} \text{Cov} \left( 1_{(x^k_{t-1}, x^k_t) = (i,j)}, 1_{(x^k_{t+2l}, x^k_{t+2l+1}) = (i,j)} \right) + \text{Cov} \left( 1_{(x^k_{t-2}, x^k_t) = (i,j)}, 1_{(x^k_{t+2l+1}, x^k_{t+2l+2}) = (i,j)} \right)
\]

(4.22)  

**Theorem 4.7.** If Assumption 4.6 and (3.10) holds, and the series \( \sum_{h=0}^{\infty} k^k(h) \) is convergent, then

1. \( \Sigma_{X}^k = k^k(0) + \sum_{i=0}^{\infty} \left( \Gamma^k(l) + \Gamma^k(l)^T \right) \).
2. \( \eta^k(l) \geq \| \Gamma^k(l) \|_{\text{max}} \) and \( \eta^k(l) \leq \eta^k(l+1) \) for \( l \geq 0 \).

**Proof.** See Appendix 1. 

The above theorem provides an intuitive way to estimate \( \Sigma_{X}^k \):

\[
(4.23) \quad \hat{\Sigma}_{X}^k = \hat{k}^k(0) + \sum_{i=0}^{\left[ \frac{M_k-1}{2} \right]} \left( \hat{\Gamma}^k(l) + \hat{\Gamma}^k(l)^T \right)
\]

where \( \hat{k}^k(0) \) and \( \hat{\Gamma}^k(l) \) denote the estimates of \( k^k(0) \) and \( \Gamma^k(l) \). We now investigate the calculation of \( \hat{k}^k(0) \) and \( \hat{\Gamma}^k(l) \).

**Estimation of \( k^k(0) \).** It is easy to verify that the \((i-1) S^k + j, (m-1) S^k + n\)-th element of \( k^k(0) \) equals \( 1_{(i,j)=(m,n)} \hat{X}_{ij}^k - \hat{X}_{ij}^k \), therefore we can calculate the \( \hat{X}_{ij}^k \) in the same position in \( \hat{k}^k(0) \) by \( 1_{(i,j)=(m,n)} X_{ij}^k - \hat{X}_{ij}^k \), with \( \hat{X}_{ij}^k = X_{ij}^k \).

**Estimation of \( \Gamma^k(l) \).** For \( h > 0 \), \( k^k(h) \) can be estimated by the empirical autocovariance:

\[
(4.24) \quad \hat{k}^k(h) = \frac{1}{M_k} \sum_{t=1}^{M_k-h} \left( V(\Delta C^k_t) - V(\hat{X}^k) \right) \left( V(\Delta C^k_{t+h}) - V(\hat{X}^k) \right)^T
\]

where \( \hat{X}^k \) is an estimate of \( \mathbb{E}[\Delta C^k] = \bar{X}^k \). Then the \( \Gamma^k(l) \) can be estimated as

\[
(4.25) \quad \hat{\Gamma}^{\tau k}(l) = \hat{k}^k(2l+1) + \hat{k}^k(2l+2)
\]

However, the estimation error (4.25) will increase substantially as \( l \) approaches to \( [(M_k-3)/2] \). So here we modify the \( \hat{\Gamma}^{\tau k}(l) \) by correcting the corresponding estimated value of \( \eta^k(l) \):

\[
(4.26) \quad \hat{\Gamma}^{k}(l) = \begin{cases} 
\hat{\Gamma}^{\tau k}(l), & l = 0 \\
\min \left\{ \eta^k(l-1), \hat{\Gamma}^{\tau k}(l) \right\}, & l > 1 \text{ and } \eta^k(l) > 0 \\
0, & l > 1 \text{ and } \eta^k(l) \leq 0
\end{cases}
\]
where \( \tilde{\eta}^k (l) \) and \( \tilde{\eta}^k (l) \) denote the values of \( \eta^k (l) \) obtained from \( \hat{\Gamma}^k (l) \) and \( \hat{\Gamma}^k (l) \). It can be seen that \( \tilde{\eta}^k (l) \) is non-negative and decreasing with \( l \), which is consistent with the conclusion of Theorem 4.7. Besides, we can show that \( \hat{\Gamma}^k (l) \equiv 0 \) for \( l \geq l_n \) if there exists an \( l_n \) such that \( \tilde{\eta}^k (l_n) \leq 0 \). Thus the estimator of \( \Sigma_X^k \) in this section is in fact a time window estimator [2] where the large-lag terms outside the window are set to be zero, and the window size \( l_w = \min \{ l | \tilde{\eta}^k (l) \leq 0 \} \) implies that the curve of \( \| \Gamma^k (l) \|_{\text{max}} \) goes below the noise level at \( l = l_w \).

Remark 4.8. From the definition of \( \Sigma_X^k \) we can deduce that \( \Sigma_X^k \geq 0 \) and \( \Sigma_X^k \) obtained by (4.23) may not satisfy the constraints. For this problem, we can correct the value of \( \Sigma_X^k \) as \( \hat{\Sigma}_X^k := \mathcal{M}_1 \left( \mathcal{M}_P \left( \hat{\Sigma}_X^k \right) \right) \), where \( \mathcal{M}_P (G) = G - \min \{ \lambda_{\min} (G), 0 \} I \) can map a symmetric matrix to a positive-semidefinite matrix with \( \lambda_{\min} (G) \) denoting the smallest eigenvalue of \( G \), and \( \mathcal{M}_1 (G) = (I - \frac{1}{n} \mathbf{1} \mathbf{1}^T) \cdot G \cdot (I - \frac{1}{n} \mathbf{1} \mathbf{1}^T) \) for \( G \in \mathbb{R}^{n \times n} \) is a mapping from the positive-semidefinite matrix set to the set \( \{ \Sigma | \Sigma \geq 0, \mathbf{1}^T \Sigma \mathbf{1} = 0 \} \).

5. Numerical experiments. In this section, the approximate MLE proposed in this paper will be applied to some numerical examples of multiple biased simulations, and the performance will be compared to that of WHAM and MMMM. For convenience, here we denote a set of multiple biased simulations described in Section 2 by MBS \((K, M_0)\) if there are \( K \) biased simulations and each simulation has the same length with \( M_k \equiv M_0 \).

5.1. Umbrella sampling with Markovian simulations. Umbrella sampling is a commonly used biased simulation technique, where each biasing potential (also called “umbrella potential”) is designed to confine the system around some region of state space and achieve a more efficient sampling especially at transition states which the unbiased simulation would visit only rarely. In this example, the umbrella sampling simulations are employed on a reference system with state set \( S = \{ s_i = -5 + 10 (i - 1) / 99 \mid i = 1, \ldots, 100 \} \) and free energy \( V = [V_i] = [0.25 s_i^4 - 5 s_i^2 - 9.9874] \). As shown in Fig. 3.1, the reference system has two metastable states centered at \( A \) and \( B \), and the switching between metastable states is blocked by an energy barrier with peak position \( O \).

For umbrella sampling simulations, we design the following 15 different biased potentials:

\[
U^k = \left[ U_i^k \right] = \left[ 4 \left( s_i + \frac{15}{14} k - \frac{60}{7} \right)^2 \right], \quad 1 \leq k \leq 15
\]

Note that these potentials will be repeatedly used if the simulation number is larger than 15, i.e., \( U^k = U^{(k - 1) \mod 15} + 1 \) if \( k > 15 \). The simulation trajectory \( x_{0, M_k} \) is generated by a Metropolis simulation model (see Appendix J for details), which is a reversible Markov chain with initial distribution

\[
\Pr \left( x_0^k = s_i \right) \propto \exp \left( -U_i^k \right)
\]

and stationary distribution

\[
\pi_i^k \propto \exp \left( -V_i - U_i^k \right)
\]

The comparisons between the estimation methods are based on the mean error of approximations of energy barrier heights:

\[
e_{\Delta V} = \frac{1}{2} \left( |\Delta V_{AB} - \Delta V_{AB}^{\text{approx}}| + |\Delta V_{BA} - \Delta V_{BA}^{\text{approx}}| \right)
\]
Figure 5.1: Free energy profile of the reference system, which has two potential wells with minima at $A$ and $B$ separated by an energy barrier. The highest energy position $O$ of the barrier represents the transition state, and the energy barrier heights for transitions $A \rightarrow B$ and $B \rightarrow A$ are defined as $\Delta V_{AB} = |V_O - V_A|$ and $\Delta V_{BA} = |V_O - V_B|$ with $V_A$, $V_B$ and $V_O$ the potentials of $A$, $B$ and $O$.

where the definitions of $\Delta V_{AB}$ and $\Delta V_{BA}$ are given in Fig. 3.1 and the superscript “approx” represents the approximate value obtained from the estimated $V$.

We first set $K = 15$ and $M_0 = 500, 910, 1657, 3017, 5493, 10000$, and perform 30 independent MBS $(K, M_0)$ for each value of $M_0$. Fig. 5.2a displays the average $e_{\Delta V}$ of the approximate MLE, MMMM and WHAM for different $M_0$, and Figs. 5.2c and 5.2d show the estimates of $V$ obtained from a run of MBS $(15, 500)$ and MBS $(15, 10000)$. It can be seen that the estimation errors of all the three methods decrease with increasing simulation length, and the proposed approximate MLE performs significantly better than the other two methods. Note that MMMM is also a Markov chain model based method, but its performance turns out to be worse than WHAM in this numerical experiment, especially for large simulation lengths $M_0$.

Next, we validate whether the estimation methods can reconstruct the free energy $V$ from very short simulations. Here we fix the total simulation time $M_0 K$, and set $M_0 = [22500/K]$ with $K = 45, 90, 135, 180, 225, 270$. The estimation results are summarized in Figs. 5.2e, 5.2f and 5.2g. (The 1σ confidence intervals in Fig. 5.2f are provided by using the sample standard deviation of $\hat{V}$ calculated from the 30 independent runs of MBS $(270, 83)$ because the simulation length is too short such that the error analysis approach in Section 4.4 is not applicable.) It should be noticed the equilibrium assumption used by WHAM does not hold if $M_0$ is too small, because the initial distributions of simulations differ from the biased stationary distributions (see Appendix G). Therefore the estimation accuracy of WHAM is reduced when the individual simulation lengths are shorter although the total data size stays almost the same. In contrast, the proposed approximate MLE and MMMM are less affected by the change in the length of individual simulations. This is because these methods rely on having local rather than global equilibrium assumptions. Furthermore, the proposed method outperforms both WHAM and MMMM in this numerical experiment.

5.2. Umbrella sampling with non-Markovian simulations. We now consider the estimation problem from an umbrella sampling simulation in the case that the Markov assumption does not hold, i.e., the bins used to estimate the free energy do not correspond to the Markov states of the underlying simulation. The simulation model and the other settings in this section is basically the same as in Section 5.1.
(a) Average $\epsilon_{\Delta V}$ calculated over 30 independent runs of MBS ($K, M_0$) for $K = 15$ and $M_0 = 500, 910, 1657, 3017, 5493, 10000$.

(b) Average $\epsilon_{\Delta V}$ calculated over 30 independent runs of MBS ($K, M_0$) for $K = 45, 90, 135, 180, 225, 270$ and $M_0 = [22500/K]$.

(c) Estimates of $V$ generated by the different estimators on a run of MBS (15, 500) where the $\epsilon_{\Delta V}$ of approximate MLE = 3.5015, $\epsilon_{\Delta V}$ of MMMM = 6.3153 and $\epsilon_{\Delta V}$ of WHAM = 6.3500.

(d) Estimates of $V$ generated by the different estimators on a run of MBS (15, 10000) where the $\epsilon_{\Delta V}$ of approximate MLE = 0.3060, $\epsilon_{\Delta V}$ of MMMM = 0.6002 and $\epsilon_{\Delta V}$ of WHAM = 0.3397.

(e) Estimates of $V$ generated by the different estimators on a run of MBS (45, 500) where the $\epsilon_{\Delta V}$ of approximate MLE = 1.4570, $\epsilon_{\Delta V}$ of MMMM = 1.5012 and $\epsilon_{\Delta V}$ of WHAM = 1.8948.

(f) Estimates of $V$ generated by the different estimators on a run of MBS (270, 83) where the $\epsilon_{\Delta V}$ of approximate MLE = 3.1939, $\epsilon_{\Delta V}$ of MMMM = 4.2559 and $\epsilon_{\Delta V}$ of WHAM = 7.2764.

Figure 5.2: Estimation results of umbrella sampling with Markovian simulations. The 1σ confidence intervals in (c), (d) and (e) are obtained by the approach described in Section 4.4 and those in (f) are obtained from the sample standard deviation of $V$ in the 30 independent runs.
except that the state set is defined as $S = \{\bar{s}_1, \ldots, \bar{s}_{10}\}$ with $\bar{s}_1 = \{s_1, \ldots, s_{10}\}$, $\bar{s}_2 = \{s_{11}, \ldots, s_{15}\}$, $\bar{s}_3 = \{s_{16}, \ldots, s_{20}\}$, $\ldots$, $\bar{s}_7 = \{s_{86}, \ldots, s_{90}\}$ and $\bar{s}_8 = \{s_{91}, \ldots, s_{100}\}$. It is clear that the observed state sequences in simulations do not satisfy the Markov property with this definition of states.

We utilize the three methods to approximate the free energy $V$ by using the non-Markovian simulation data, and the estimation results with different $(K, M_0)$ are shown in Fig. 5.3, where $e_\Delta V$ is defined in the same way as in Section 5.1 with $A, B$ and $O$ the local minimum and peak positions in $S$. As observed from the figures, the estimates obtained from the approximate MLE are more precise than those obtained from the other estimators for various values of $(K, M_0)$.

5.3. Metadynamics with Markovian simulations. Metadynamics is another biased simulation technique often employed in computational physics and chemistry, which is able to escape local free energy minima and improve the searching properties of simulations through iteratively modifying the biasing potential. Given $K, M_0$ and a reference system as in Section 5.1, a metadynamics procedure can also be expressed as a run of $MBS (K, M_0)$ with

\[
U^k_s = \begin{cases} 
0, & k = 1 \\
U^{k-1}_s + u_c(s_i|x_{M_0}^{k-1}), & k > 1
\end{cases}, \quad \text{for } k = 1, \ldots, K
\]  

(5.5)

where $u_c(s|x)$ denote a Gaussian function of $s$ centered at $x$. Thus, for each of the $K$ simulations in a MBS run, a Gaussian hat is added to the potential at the last point of the previous simulation. This effectively fills up the potential energy basins with increasing $k$. Ultimately the effective potential becomes approximately flat. Here we define $u_c(s|x) = 5 \exp\left( - (s - x)^2 \right)$, and the simulation data $x^{k}_{0:M_0}$ is also generated by the Metropolis sampling model with $x^{k}_{0} = x^{k-1}_{M_0}$.

The three estimation methods are applied to reconstruct the free energy of the reference system by data generated by metadynamics with different $(K, M_0)$, and the estimation results are shown in Fig. 5.4. The superior performance of the presented method is clearly evident from the figures.

5.4. Metadynamics with non-Markovian simulations. In this example, the free energy estimation problem of metadynamics with non-Markovian simulations is investigated. We generate the simulation data as in Section 5.3 and convert the state sequences to non-Markov processes as in Section 5.2. Then the three methods can be used to estimate the unbiased free energy of states $\bar{s}_1, \ldots, \bar{s}_{18}$.

All the estimation results are displayed in Fig. 5.5. It is obvious that the approximate MLE does a much better job in the free energy estimation than the other two methods.

6. Conclusions. We have presented a transition-matrix-based estimation method for stationary distributions or free energy profiles using data from biased simulations, such as umbrella sampling or metadynamics. In contrast to existing estimators such as the weighted histogram method (WHAM), the present estimators is not based on absolute counts in histogram bins, but rather based on the transition counts between an arbitrary state space discretization. This discretization may be in a single or a few order parameters, e.g. those order parameters in which the umbrella sampling or metadynamics simulations are driven, or they may come from the clustering of a higher-dimensional space, such as frequently used in Markov modeling. The only condition is that the energy bias used in the biased simulations can be associated
Figure 5.3: Estimation results of umbrella sampling with non-Markovian simulations.
The $1\sigma$ confidence intervals in (c), (d) and (e) are obtained by the approach described in Section 4.4, and those in (f) are obtained from the sample standard deviation of $\hat{V}$ in the 30 independent runs.
(a) Average $\epsilon_{\Delta V}$ calculated over 30 independent runs of MBS $(K, M_0)$ for $K = 15$ and $M_0 = 500, 910, 1657, 3017, 5493, 10000$.

(b) Average $\epsilon_{\Delta V}$ calculated over 30 independent runs of MBS $(K, M_0)$ for $K = 40, 80, 120, 160, 200$ and $M_0 = [2000/K]$.

(c) Estimates of $V$ generated by the different estimators on a run of MBS $(15, 500)$ where the $\epsilon_{\Delta V}$ of approximate MLE = 6.2858, $\epsilon_{\Delta V}$ of MMMM = 11.9022 and $\epsilon_{\Delta V}$ of WHAM = 12.4188.

(d) Estimates of $V$ generated by the different estimators on a run of MBS $(15, 10000)$ where the $\epsilon_{\Delta V}$ of approximate MLE = 0.8246, $\epsilon_{\Delta V}$ of MMMM = 3.1642 and $\epsilon_{\Delta V}$ of WHAM = 5.7601.

(e) Estimates of $V$ generated by the different estimators on a run of MBS $(40, 50)$ where the $\epsilon_{\Delta V}$ of approximate MLE = 1.6589, $\epsilon_{\Delta V}$ of MMMM = 3.6707 and $\epsilon_{\Delta V}$ of WHAM = 7.5342.

(f) Estimates of $V$ generated by the different estimators on a run of MBS $(200, 10)$ where the $\epsilon_{\Delta V}$ of approximate MLE = 2.8518, $\epsilon_{\Delta V}$ of MMMM = 6.5913 and $\epsilon_{\Delta V}$ of WHAM = 10.9540.

Figure 5.4: Estimation results of metadynamics with Markovian simulations. The 1σ confidence intervals in (c) and (d) are obtained by the approach described in Section 4.4, and those in (e) and (f) are obtained from the sample standard deviation of $\hat{V}$ in the 30 independent runs.
(a) Average $e_{\Delta V}$ calculated over 30 independent runs of MBS ($K, M_0$) for $K = 15$ and $M_0 = 500, 910, 1657, 3017, 5493, 10000$.

(b) Average $e_{\Delta V}$ calculated over 30 independent runs of MBS ($K, M_0$) for $K = 40, 80, 120, 160, 200$ and $M_0 = [2000/K]$.

(c) Estimates of $V$ generated by the different estimators on a run of MBS (15, 500) where the $e_{\Delta V}$ of approximate MLE = 2.6950, $e_{\Delta V}$ of MMMM = 8.2297 and $e_{\Delta V}$ of WHAM = 9.7315.

(d) Estimates of $V$ generated by the different estimators on a run of MBS (15, 10000) where the $e_{\Delta V}$ of approximate MLE = 0.2325, $e_{\Delta V}$ of MMMM = 2.5563 and $e_{\Delta V}$ of WHAM = 3.7233.

(e) Estimates of $V$ generated by the different estimators on a run of MBS (40, 50) where the $e_{\Delta V}$ of approximate MLE = 2.4020, $e_{\Delta V}$ of MMMM = 4.0281 and $e_{\Delta V}$ of WHAM = 6.3157.

(f) Estimates of $V$ generated by the different estimators on a run of MBS (200, 10) where the $e_{\Delta V}$ of approximate MLE = 2.5255, $e_{\Delta V}$ of MMMM = 8.0536 and $e_{\Delta V}$ of WHAM = 8.6291.

Figure 5.5: Estimation results of metadynamics with Markovian simulations. The 1σ confidence intervals in (c) and (d) are obtained by the approach described in Section 4.4, and those in (c) and (f) are obtained from the sample standard deviation of $\hat{V}$ in the 30 independent runs.
to the discrete states, suggesting that at least the order parameters used to drive the umbrella sampling/metadynamics simulation should be discretized finely. The stationary probabilities or free energies are then reconstructed on the discrete states used. The estimator presented here has a number of advantages over existing methods such as WHAM. Most importantly, in all scenarios tested here, the estimation error of the transition-matrix-based estimator was significantly smaller than that of existing estimation methods. The reason for this is that the estimator does not rely the biased simulation to fully equilibrate within one simulation condition, but only asks for local equilibrium in the discrete states - which is a much weaker requirement. As a consequence, the present method can also be used to estimate free energy profiles and stationary distributions from metadynamics simulations using all simulation data. Previously, metadynamics simulations could only be analyzed using the fraction of the simulation generated after the free energy minima have been filled and the simulation samples from an approximately flat free energy landscape. These advantages may lead to very substantial savings of CPU time for a given system, and on the other hand, permit the simulation of systems that were otherwise out of reach.

Appendix A. Proof of Theorem 3.1

For convenience, here we define $\Theta$ to be the solution set defined by constraints in (3.1). $\Theta_1$ be the set of feasible solutions which satisfies $T_{ij}^k = 0$ for $(i, j, k) \in \{(i, j, k) | c_{ij}^k + c_{ji}^k = 0 \text{ and } i \neq j\}$, $\Theta_2$ be the set of feasible solutions which satisfies $1 T_{ij}^k > 0 = 1 c_{ij}^k > 0$ for all $i, j, k$, and the condition

$$\omega: \quad c_{ij}^k > 0 \text{ and } 1 c_{ij}^k > 0 = 1 c_{ij}^k > 0 \text{ for all } i, j, k$$

Part (1). In this part, we will prove the optimal solution existence of (3.1). Suppose that $\left(\pi', T^{1}, \ldots, T^{K}\right)$ is a feasible solution with objective value $L' \geq -\infty$. We can define a new objective function $L_+\left(\pi, T^{1}, \ldots, T^{K}\right) = \max\{L\left(\pi, T^{1}, \ldots, T^{K}\right), L' - a\}$ where $a > 0$ is a constant. It is easy to verify that $L_+$ is a continuous function on $\Theta$. Thus, the optimization problem $\max_{\pi, T^{1}, \ldots, T^{K}} \in \Theta L_+\left(\pi, T^{1}, \ldots, T^{K}\right)$ has a global optimal solution $\left(\pi'', T^{1'}, \ldots, T^{K'}\right)$ with $L_+\left(\pi'', T^{1'}, \ldots, T^{K'}\right) = L''$ for $\Theta$ is a closed set. Noting that $L'' \geq L' > L' - a$, we have $L\left(\pi'', T^{1'}, \ldots, T^{K'}\right) = L''$. Therefore, for any $\left(\pi, T^{1}, \ldots, T^{K}\right) \in \Theta$, $L\left(\pi, T^{1}, \ldots, T^{K}\right) \leq L_+\left(\pi, T^{1}, \ldots, T^{K}\right) = L\left(\pi'', T^{1'}, \ldots, T^{K'}\right)$.

Part (2). In this part, we will prove the first conclusion of the theorem. Suppose that $\left(\pi', T^{1}, \ldots, T^{K}\right)$ is an optimal solution. We can define a new solution $\left(\pi', T^{1'}, \ldots, T^{K'}\right)$ with

$$T^{1'}_{ij} = \begin{cases} 1 c_{ij}^k > 0 \cdot T^{1}_{ij}, & i \neq j \\ 1 - \sum_{j \neq i} T^{1}_{ij}, & i = j \end{cases}$$

Obviously, $\left(\pi', T^{1'}, \ldots, T^{K'}\right)$ is a feasible solution belonging to $\Theta_1$, and $T^{1'}_{ii} \geq T^{1}_{ii}$.

We have

$$L\left(\pi', T^{1'}, \ldots, T^{K'}\right) = L\left(\pi', T^{1}, \ldots, T^{K}\right) + \sum_{i,k} c_{ii}^k \left(\log T^{1'}_{ii} - \log T^{1}_{ii}\right) \geq L\left(\pi', T^{1}, \ldots, T^{K}\right)$$

(A.3)
Therefore, \( \left( \pi', T'^1, \ldots, T'^K \right) \) is also an optimal solution.

**Part (3).** We now prove the second conclusion. Suppose there is an optimal solution \( \left( \pi', T'^1, \ldots, T'^K \right) \) belonging to \( \Theta_1 \setminus \Theta_2 \). Then there exist \( i, j, k \) such that \( T^k_{ij} = 0 \) and \( C^k_{ij} > 0 \), and \( L \left( \pi', T'^1, \ldots, T'^K \right) = -\infty \). This leads to a contradiction with the optimality of \( \left( \pi', T'^1, \ldots, T'^K \right) \). Thus, the optimal solution belonging \( \Theta_1 \) must be an element of \( \Theta_2 \) if \( \omega \) holds.

**Appendix B. Proof of Theorem 3.8.**

From Assumption 3.6, we have \( X^k_{ij} = 0 \) if \( \bar{X}^k_{ij} = 0 \). Then \( \hat{Q} (\bar{\theta}), \bar{Q} (\bar{\theta}) > -\infty \) and we can define the following new functions, \( \bar{Q}_+ (\theta) = \max \{ \hat{Q} (\theta), \bar{Q} (\bar{\theta}) - a \} \) and \( \bar{Q}_+ (\theta) = \max \{ \hat{Q} (\theta), \bar{Q} (\bar{\theta}) - a \} \), where \( a > 0 \) is a constant.

**Part (1).** First of all, we will prove that \( \bar{\theta} \) is the unique solution of \( \max_{\theta \in \Theta} \bar{Q} (\theta) \).

Noting that \( \bar{Q} (\theta) = \max_{\theta \in \Theta} \bar{Q} (\theta) \), we have

\[
\bar{Q} (\theta) = \sum_k \bar{w}_k \sum_i \left( \sum_j \bar{X}^k_{ij} \right) \sum_j \bar{T}^k_{ij} \log \bar{T}^k_{ij}
\]

According to the property of the KL divergence, \( \bar{Q} (\theta) \) can achieve the maximal value if and only if \( \bar{T}^k_{ij} = \bar{T}^k_{ij} \) for all \( i, j, k \). Then we can conclude from Assumption 3.7 that \( \theta = \bar{\theta} \) is the unique solution of \( \max_{\theta \in \Theta} \bar{Q} (\theta) \).

**Part (2).** It is easy to verify that

\[
\bar{\theta} = \arg \max_{\theta \in \Theta} \hat{Q} (\theta) \iff \theta = \arg \max_{\theta \in \Theta} \bar{Q}_+ (\theta)
\]

and \( \bar{\theta} = \arg \max_{\theta \in \Theta} \bar{Q}_+ (\theta) \). The proof is omitted because it is trivial.

**Part (3).** In this part, we will prove that \( \sup_{\theta \in \Theta} \left| \bar{Q}_+ (\theta) - \bar{Q}_+ (\theta) \right| \rightarrow 0 \). Define event

\[
\omega : \quad \bar{w}_k \bar{X}^k_{ij} \geq \epsilon \quad \text{for all } (i, j, k) \in S_I \text{ and } \hat{Q} (\bar{\theta}) \geq \bar{Q} (\bar{\theta}) - \epsilon
\]

and event

\[
\Theta_1 = \left\{ \theta \mid \bar{T}^k_{ij} \geq \exp \left( \frac{\bar{Q} (\bar{\theta}) - \epsilon - a}{\epsilon} \right) \text{ for } (i, j, k) \in S_I \right\} \cap \Theta
\]

where \( S_I = \{(i, j, k) \mid \bar{X}^k_{ij} > 0\} \) and \( \epsilon \in (0, \min_{(i,j,k) \in S_I} \bar{w}_k \bar{X}^k_{ij}) \). We now analyze the value of \( \left| \bar{Q}_+ (\theta) - \bar{Q}_+ (\theta) \right| \) when \( \omega \) holds.

**Case (i) \( \theta \in \Theta \setminus \Theta_1 \).** There is a \((i, j, k)\) such that \((i, j, k) \in S_I\) and \( \bar{T}^k_{ij} \geq \exp \left( \frac{\bar{Q} (\bar{\theta}) - \epsilon - a}{\epsilon} \right) \).

We have

\[
\bar{Q} (\theta) \leq \bar{w}_k \bar{X}^k_{ij} \log \bar{T}^k_{ij} < \bar{Q} (\bar{\theta}) - \epsilon - a \leq \bar{Q} (\bar{\theta}) - a
\]

and

\[
\bar{Q} (\theta) \leq \bar{w}_k \bar{X}^k_{ij} \log \bar{T}^k_{ij} < \bar{Q} (\bar{\theta}) - \epsilon - a < \bar{Q} (\bar{\theta}) - a
\]
Then $\tilde{\theta} \in \Theta_1$ and
\[
\left| \hat{Q}_+ (\theta) - Q_+ (\theta) \right| \leq \sum_{(i,j,k) \in S_I} \left| \tilde{w}_k \hat{X}^k_{ij} - \tilde{w}_k \hat{X}^k_{ij} \right| \left| \log \hat{T}^k_{ij} \right|
\]
(B.7)
\[
\leq \frac{Q (\tilde{\theta}) - \epsilon - a}{\epsilon} \left| \sum_{(i,j,k) \in S_I} \tilde{w}_k \hat{X}^k_{ij} - \tilde{w}_k \hat{X}^k_{ij} \right|
\]

**Case (ii) $\theta \in \Theta_1$.** Investigating all possible orders among values of $\{Q (\theta), \hat{Q} (\tilde{\theta}) - a, Q (\tilde{\theta}) - \epsilon, \tilde{Q} (\tilde{\theta}) - a\}$ (i.e., $\hat{Q} (\theta) \leq \tilde{Q} (\tilde{\theta}) - a \leq \tilde{Q} (\tilde{\theta}) - a$ and so on), we have
\[
\left| \hat{Q}_+ (\theta) - Q_+ (\theta) \right| \leq \max \left\{ \left| \hat{Q} (\theta) - Q (\theta) \right|, \left| \tilde{Q} (\tilde{\theta}) - Q (\tilde{\theta}) \right| \right\}
\]
\[
\leq \sum_{(i,j,k) \in S_I} \left| \tilde{w}_k \hat{X}^k_{ij} - \tilde{w}_k \hat{X}^k_{ij} \right| \max \left\{ \left| \log T^k_{ij} \right|, \left| \log \hat{T}^k_{ij} \right| \right\}
\]
(B.8)
\[
\leq \frac{Q (\tilde{\theta}) - \epsilon - a}{\epsilon} \left| \sum_{(i,j,k) \in S_I} \tilde{w}_k \hat{X}^k_{ij} - \tilde{w}_k \hat{X}^k_{ij} \right|
\]

Combining the above results, we get
\[
(1_\omega \cdot \sup_{\theta \in \Theta} \hat{Q}_+ (\theta) - Q_+ (\theta) \right| \leq \frac{Q (\tilde{\theta}) - \epsilon - a}{\epsilon} \left| \sum_{(i,j,k) \in S_I} \tilde{w}_k \hat{X}^k_{ij} - \tilde{w}_k \hat{X}^k_{ij} \right|
\]
(B.9)

Moreover, considering that $\tilde{w}_k \overset{p}{\rightarrow} \bar{w}_k, \hat{X}^k_{ij} \overset{p}{\rightarrow} \hat{X}^k_{ij}$ and
\[
\left| \hat{Q} (\tilde{\theta}) - \bar{Q} (\tilde{\theta}) \right| \leq \frac{Q (\tilde{\theta}) - \epsilon - a}{\epsilon} \left| \sum_{(i,j,k) \in S_I} \tilde{w}_k \hat{X}^k_{ij} - \tilde{w}_k \hat{X}^k_{ij} \right|
\]
(B.10)

we have $1_\omega \overset{p}{\rightarrow} 1$. Therefore
\[
\sup_{\theta \in \Theta} \left| \hat{Q}_+ (\theta) - Q_+ (\theta) \right| \overset{p}{\rightarrow} 0
\]
(B.11)

According to the definitions of $\hat{Q}_+ (\theta)$ and $Q_+ (\theta)$ and conclusions of Parts (1)-(3), it can be easily verified that $\hat{Q}_+ (\theta)$ satisfies the following conditions: (i) $\hat{Q}_+ (\theta)$ is uniquely maximized at $\tilde{\theta}$, (ii) $\Theta$ is compact; (iii) $\hat{Q}_+ (\theta)$ is continuous; (iv) $\hat{Q}_+ (\theta)$ converges uniformly in probability to $Q_+ (\theta)$. Then we have $\tilde{\theta} \overset{p}{\rightarrow} \theta$ by using Theorem 2.1 in [14] and (B.2).

**Appendix C. Proof of Theorem 3.9**

For any $k$,
\[
\sqrt{M} \tilde{w}_k \hat{V}^k_X - \sqrt{M} \bar{w}_k \hat{V}^k_X = \sqrt{\tilde{w}_k} \sqrt{M} \left( \hat{V}^k_X - \bar{V}^k_X \right) + \sqrt{M} (\tilde{w}_k - \bar{w}_k) \hat{V}^k_X
\]
(C.1)
\[
\overset{d}{\rightarrow} \mathcal{N} (0, \Sigma \hat{V}^k_X)
\]

Then $\sqrt{M} \left( \hat{V}_X - \bar{V}_X \right) \overset{d}{\rightarrow} \mathcal{N} (0, \Sigma_{Xw})$. 

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Because (D.3) holds for any Cramer-Wold device \[20\], we can conclude that \(\mu\) is a function of \(\theta\), kernel and multi-step transition kernel of \((D.2)\) is a closed neighborhood of \((C.2)\), where \(\epsilon \in (0, \min \{\min_{(i,j,k) \in S_I} \bar{T}_{ij}, \min_{i} \bar{\pi}_i\}\} \} \cap \Theta_{\epsilon}, \) and \((C.3)\) is a closed neighborhood of \((C.2)\), where \(\epsilon \in (0, \min \{\min_{(i,j,k) \in S_I} \bar{T}_{ij}, \min_{i} \bar{\pi}_i\}\} \} \cap \Theta_{\epsilon}, \) is a closed neighborhood of \((C.2)\), where \(\epsilon \in (0, \min \{\min_{(i,j,k) \in S_I} \bar{T}_{ij}, \min_{i} \bar{\pi}_i\}\} \} \cap \Theta_{\epsilon}, \) is a closed neighborhood of \((C.2)\), where \(\epsilon \in (0, \min \{\min_{(i,j,k) \in S_I} \bar{T}_{ij}, \min_{i} \bar{\pi}_i\}\} \) and \(S_I\) has the same definition as in Appendix \[3\].

It is easy to verify that 
\[
\sqrt{M} \left( \nabla_{\theta, \bar{Q}} (\theta (\bar{\theta})) - \nabla_{\theta, \bar{Q}} (\theta (\bar{\theta})) \right)^T = \sqrt{M} \nabla_{\theta} \Phi (\theta (\bar{\theta}))^T \left( \bar{V}_{Xw} - \bar{V}_{Xw} \right)
\]
and \(\sup_{\theta, \epsilon \in \Theta_{\epsilon}} \left\| \nabla_{\theta, \bar{Q}} (\theta (\bar{\theta})) - \nabla_{\theta, \bar{Q}} (\theta (\bar{\theta})) \right\| \xrightarrow{p} 0\). Then by Theorem 3.1 in \[14\], 
\[
\sqrt{M} \left( \bar{\theta}_r - \bar{\theta}_r \right) \xrightarrow{d} \mathcal{N} (0, H^{-1} \Sigma H^{-1}).
\]

**Appendix D. Proof of Remark 3.10.**
In this appendix we will show that (3.10) holds if \(x^k_t = f^k(y^k_t)\) and \(\{y^k_t\}\) is a geometrically ergodic Markov chain.

Let \(\mathcal{R}\) and \(\mu (\cdot)\) denote the state space and stationary distribution of \(\{y^k_t\}\). Then for any \(y^k_0, y^k_1, t > 1\) and set \(A \subset \mathcal{R} \times \mathcal{R}\), we have 
\[
\Pr \left( (y^k_t, y^k_{t+1}) \in A | y^k_0, y^k_1 \right) - \int_{A_0} \mu (dy^k_0) \mathcal{K} (y^k_0, A_1 (y^k_0)) \right) 
\]
with 
\[
g (y^k_t) = \left\{ \begin{array}{ll} \mathcal{K} (y^k_0, A_1 (y^k_0)) , & y^k_t \in A_0 \\ 0 , & y^k_t \notin A_0 \end{array} \right. 
\]
where \(A_0 = \{ u | \text{there exists } v \text{ such that } (u, v) \in A \}, A_1 (u) = \{ v | (u, v) \in A \}, \mathcal{K} (u, B) = \Pr (y^k_{t+1} \in B | y^k_t = u) \text{ and } \mathcal{K}^n (u, B) = \Pr (y^k_{t+n} \in B | y^k_t = u)\) denote the transition kernel and multi-step transition kernel of \(\{y^k_t\}\). It is clear that \(g (y^k_t) \leq 1\) for any \(y^k_t\), Considering that \(\{y^k_t\}\) is geometrically ergodic, we can deduce that there exist a function \(a (\cdot)\) and a constant \(\eta \in (0, 1)\) such that 
\[
\Pr \left( (y^k_t, y^k_{t+1}) \in A | y^k_0, y^k_1 \right) - \int_{A_0} \mu (dy^k_0) \mathcal{K} (y^k_0, A_1 (y^k_0)) \right) 
\]
with 
\[
\Pr \left( (y^k_t, y^k_{t+1}) \in A | y^k_0, y^k_1 \right) - \int_{A_0} \mu (dy^k_0) \mathcal{K} (y^k_0, A_1 (y^k_0)) \right) 
\]
and 
\[
\Pr \left( (y^k_t, y^k_{t+1}) \in A | y^k_0, y^k_1 \right) - \int_{A_0} \mu (dy^k_0) \mathcal{K} (y^k_0, A_1 (y^k_0)) \right) 
\]
Because (D.3) holds for any \(A \subset \mathcal{R} \times \mathcal{R}\), the stochastic process \(\{y^k_t\}\) with \(y^k_t = (y^k_t, y^k_{t+1})\) is also a geometrically ergodic Markov chain with stationary distribution \(\mu^* (dy^k_t, dy^k_{t+1}) = \mu (dy^k_t) \mathcal{K} (y^k_t, y^k_{t+1})\). Hence, combining Theorem 1.2 in \[9\] and the Cramer-Wold device \[20\], we can conclude that \(\sqrt{M} \left( \nu (\hat{X}^k) - \nu (\hat{X}^k) \right) \text{ converges in distribution to a multivariate normal distribution with zero mean.} \)

**Appendix E. Proof of Theorem 4.2**
It is clear that according to Assumptions 3.5 and 3.6, we have the other hand, \( \bar{C} \) part. Assume without loss of generality that there exists \( n \in [1, |S^k|] \) such that

\[
(C^k)_{ij} = 0, \quad \text{for } i \leq n \text{ and } j > n
\]

Then \( C^k_{ij} = C^k_{ji} = 0 \) for \( i \leq n \) and \( j > n \), which implies the states \( s_1 \) and \( s_2 \) can not both appear in the \( k \)-th simulation if \( I_{S^k}(s_1) \leq n \) and \( I_{S^k}(s_2) > n \). This contradicts the condition that \( \sum_{i=0}^{M} I_{S^k}(x^k_i) = 0 \) for all \( i \). So \( C^k \) is irreducible.

Part (2). We now show that \( \bar{X}^k \) is irreducible in the same way as in the first part. Assume without loss of generality that there exists \( n \in [1, |S^k|] \) such that

\[
(X^k)_{ij} = 0, \quad \text{for } i \leq n \text{ and } j > n
\]

Then \( X^k_{ij} = \bar{X}^k_{ij} = 0 \) for \( i \leq n \) and \( j > n \) since \( X^k \) is symmetric. According to Assumption 3.6, for any \( s_1, s_2 \in S^k \) which satisfy \( I_{S^k}(s_1) \leq n \) and \( I_{S^k}(s_2) > n \), the probability of that \( s_1 \) and \( s_2 \) both appear in the \( k \)-th simulation is zero. This contradicts the ergodicity of the simulation. So \( \bar{X}^k \) is irreducible.

Part (3). In this part we will prove that \( 1_{\bar{C}^k = C^k} \overset{\mathbb{P}}{\rightarrow} 1 \). Define

\[
(C^k)_{ii} = 0 \quad \text{and } \quad 1_{C^k_{ij} > 0} = 1_{C^k_{ij} > 0}
\]

According to Assumptions 3.5 and 3.6, we have \( 1_{C^k_{ij} > 0} \overset{\mathbb{P}}{\rightarrow} 1_{\bar{C}^k_{ij} > 0} \). Therefore \( 1_{\omega} \overset{\mathbb{P}}{\rightarrow} 1 \) since \( \bar{X}^k \) is a symmetric and irreducible matrix with positive diagonal elements. On the other hand, \( C^k = C^k \) if \( \omega \) holds. Hence \( 1_{\bar{C}^k = C^k} \overset{\mathbb{P}}{\rightarrow} 1 \).

Appendix F. Proof of \( H^k_\rho < 0 \)

Define \( \rho^k_\alpha \) to be the vector consisting of \( \{ Z^k_{ij} | C^k_{ij} > 0 \} \) and \( H^k_\rho = \sum_i C^k_i \nabla_{\rho^k_\alpha} \rho^k_\alpha Z^k_i \).

It is clear that \( \rho^k_\alpha \) can be expressed as a linear function of \( \rho^k \) with \( \rho^k_\alpha = A^k_\alpha \rho^k \). Then \( H^k_\rho \) can be written as \( H^k_\rho = (A^k)^T H^k_\rho A^k_\alpha \).

According to (4.9), for any \( \rho^k_\alpha = \{ Z^k_{ij} | C^k_{ij} > 0 \} \),

\[
\left( \rho^k_\alpha \right)^T H^k_\rho \rho^k_\alpha = \sum_i C^k_i \sum_{m,n} \frac{\partial^2 Z^k_{im}}{\partial Z^k_{im} \partial Z^k_{in}} Z^k_{im} Z^k_{in}
\]

\[
= - \sum_i C^k_i \left( \sum_{j \in \{j | C^k_{ij} > 0\}} T^k_{ij} \left( Z^k_{ij} \right)^2 - \left( \sum_{j \in \{j | C^k_{ij} > 0\}} T^k_{ij} Z^k_{ij} \right)^2 \right)
\]

Noting that for any \( i \), the term

\[
\sum_{j \in \{j | C^k_{ij} > 0\}} T^k_{ij} \left( Z^k_{ij} \right)^2 - \left( \sum_{j \in \{j | C^k_{ij} > 0\}} T^k_{ij} Z^k_{ij} \right)^2
\]

is negative, we have

\[
\left( \rho^k_\alpha \right)^T H^k_\rho \rho^k_\alpha < 0
\]
is equal to the variance of a discrete random variable $a_i$ with distribution $\Pr \left( a_i = Z^k_{ij} \right) = T^k_{ij}$ and support $\left\{ Z^k_{ij} | C^k_{ij} > 0 \right\}$ $\left( T^k_{ij} = \exp \left( -Z^k_{ij} \right) / \sum_i \exp \left( -Z^k_{ih} \right) > 0 \text{ if } C^k_{ij} > 0 \right)$. We can conclude that $H^k_{\rho_a} \leq 0$, and $\left( \rho^k_a \right)^T H^k_{\rho_a} \rho^k_a = 0$ if and only if

$$Z^k_{im} = Z^k_{in} \text{ for any } m, n \in \left\{ j | C^k_{ij} > 0 \right\}, 1 \leq i \leq |\Sigma^k|$$

Further, if there exists a $\rho^k$ such that $\rho^k_a = A^k_a \rho^k$, $\rho^k_a$ should satisfy

$$Z^k_{ij} = Z^k_{ji} \text{ for any } i, j, \text{ and } \sum_{(i,j) \in \{ (i,j) | C^k_{ij} > 0 \}} Z^k_{ij} = 0$$

According to (F.2), (F.3) and Assumption 4.1, it is easy to see $\rho^{kT} A^{kT}_a H^k_\rho A^k_a \rho^k = 0$ if and only if $\rho^k = 0$, which implies $H^k_\rho = A^{kT}_a H^k_\rho A^k_a < 0$.

**Appendix G. Proof of Lemma 4.4**

Under Assumptions 3.3, 3.7 and 4.1, it is easy to see that $\bar{X}^k$ is irreducible and its diagonal elements are positive (see Appendix E), which implies that $\bar{T}^k$ is an ergodic transition matrix. Thus $\bar{V}^k = V^k_\rho \left( \rho^\kappa \right)$.

Define event

(G.1) \[ \omega^k : 1_{C^k_{ij} > 0} = 1_{\bar{X}^k_{ij} > 0} \text{ for all } i, j \]

and

(G.2) \[ \hat{\rho}^k = \begin{cases} \hat{\rho}^k, & \text{dim} \left( \hat{\rho}^k \right) = \text{dim} \left( \hat{\rho}^k \right) \\ 0, & \text{dim} \left( \hat{\rho}^k \right) \neq \text{dim} \left( \hat{\rho}^k \right) \end{cases} \]

It is clear that the functions $1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right)$ and $\bar{Q}^k \left( \rho^k \right)$ satisfy: (i) $\bar{Q}^k = \arg \max_{\rho^k} 1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right)$ and $\bar{Q}^k \left( \rho^k \right)$ is uniquely maximized at $\bar{\rho}^k$, (ii) $1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right)$ is concave for $\nabla_{\rho^k} \bar{Q}^k \left( \rho^k \right) = H^k_\rho \left( \hat{\rho}, \bar{X}^k, \rho^k \right) < 0$, (iii) $1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right) \bar{Q}^k \left( \rho^k \right)$ for any $\rho^k$ because $1_{\omega^k} \bar{Q}^k \left( \rho^k \right) \rightarrow 1$. Then we have $\bar{\rho}^k \bar{Q}^k \left( \rho^k \right)$, $\bar{Q}^k \left( \rho^k \right)$ is a continuous function of $\rho^k$.

We now show the second conclusion of the lemma. Because $\hat{\rho}^k = \arg \max_{\rho^k} \bar{Q}^k \left( \rho^k \right)$, $\nabla_{\rho^k} \bar{Q}^k \left( \rho^k \right) = 0^T$. Then we have

\[
\sqrt{M_k} \left( \nabla_{\rho^k} \left( 1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right) \right) \right)^T = 1_{\omega^k} \cdot \hat{w}_k \cdot \left( \nabla_{\rho^k} \Phi^k \left( \rho^k \right) \right)^T \cdot \left( \nu \left( \hat{X}^k \right) - \nu \left( \bar{X}^k \right) \right) \\
\overset{p}{\rightarrow} 1_{\omega^k} \cdot \hat{w}_k \cdot \left( \nabla_{\rho^k} \Phi^k \left( \rho^k \right) \right)^T \cdot \left( \nu \left( \hat{X}^k \right) - \nu \left( \bar{X}^k \right) \right) \\
\overset{d}{\rightarrow} \mathcal{N} \left( 0, \left( \nabla_{\rho^k} \Phi^k \left( \rho^k \right) \right)^T \Sigma^k_X \left( \nabla_{\rho^k} \Phi^k \left( \rho^k \right) \right) \right)
\]

Furthermore, the Hessian matrices of $1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right)$ and $\bar{Q}^k \left( \rho^k \right)$ satisfy $\nabla_{\rho^k} \bar{Q}^k \left( 1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right) \right) \overset{p}{\rightarrow} \nabla_{\rho^k} \bar{Q}^k \left( 1_{\omega^k} \cdot \bar{Q}^k \left( \rho^k \right) \right)$ for any $\rho^k$. Using the mean value theorem and Theorem 3.1 in [13], we can conclude that $\sqrt{M_k} \left( \rho^k - \hat{\rho}^k \right) \overset{d}{\rightarrow} \mathcal{N} \left( 0, \Sigma_{\rho^k} \right)$ and

\[
\sqrt{M_k} \left( \bar{V}^k - \bar{V}^k \right) \overset{p}{\rightarrow} \sqrt{M_k} \nabla_{\rho^k} V^k_\rho \left( a \hat{\rho}^k + \left( 1 - a \right) \rho^k \right) \left( \rho^k - \hat{\rho}^k \right)
\]

(G.4) \[ \overset{d}{\rightarrow} \mathcal{N} \left( 0, \Sigma_{V^k} \right) \]
where \( a \in [0, 1] \) is a function of \( \hat{\rho}^k \).

**Appendix H. Proof of Theorem 4.5**

Since the value of \( \hat{V} \) will not be affected if we replace \( C^k \) with \( \hat{\omega}^k \bar{X}^k = C^k / M \), \( \hat{V} \) can be expressed as

\[
\hat{V} = \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) \right) ^+ = \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) \right) \cdot \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) \right) ^+ \tag{H.1}
\]

and \( \hat{V} = \arg \max_{1 \leq V \leq 0} Q_q (V, \{ \hat{V}^k \}) \) with

\[
Q_q (V, \{ \hat{V}^k \}) = \sum_{k=1}^{K} \frac{1}{2} \left( A^k (V + U^k) - \hat{V}^k \right) + \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) \right) \cdot \left( A^k (V + U^k) - \hat{V}^k \right) \tag{H.2}
\]

**Part (1).** We first prove that \( \hat{V} \) is the unique maximum point of \( Q_q (V; \{ \hat{V}^k \}) \) under the constraint \( 1^T V = 0 \). It is clear that \( \hat{V} \) is a maximum point since \( Q_q (\vec{V}; \{ \hat{V}^k \}) = 0 \) and \( Q_q (V; \{ \hat{V}^k \}) \leq 0 \). We now show the uniqueness of \( \hat{V} \) by contradiction. Suppose that \( V' \) is another maximum point which satisfies \( Q_q (V'; \{ \hat{V}^k \}) = 0 \) and \( V' \neq \hat{V} \). Then \([1 \ 0] [A^k (V' + U^k) - \hat{V}^k] = 0 \) for any \( k \) because \([1 \ 0] [A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right)] \cdot [1 \ 0] > 0 \), which implies that the first \( |S^k| - 1 \) elements of \( A^k (V' + U^k) - \hat{V}^k \) are zero. Further, considering that \( 1^T A^k (V' + U^k) = 1^T \hat{V}^k = 0 \), we can conclude that \( A^k (V' + U^k) = \hat{V}^k \) for each \( k \). Therefore probability distribution \( \pi' = [\pi'_i] \) with \( \pi'_i \propto \exp (-V'_i) \) satisfies \( (B.5) \), which contradicts Assumption 3.7. Thus \( \hat{V} \) is the unique solution of \( \arg \max_{1 \leq V \leq 0} Q_q (V; \{ \hat{V}^k \}) \).

**Part (2).** In this part we will prove that null \( \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) A^k \right) = \text{span} (1) \) for any \( \hat{\omega}^k, \hat{X}^k, \hat{\rho}^k \). It is clear that span \( (1) \subseteq \text{null} \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) A^k \right) \) since \( A^k 1 = 0 \). Suppose that \( v \notin \text{span} (1) \) is another vector which belongs to \( 1^T v = 0 \), then \( V + v \neq \hat{V} \) is also a maximum point of \( \arg \max_{1 \leq V \leq 0} Q_q (V; \{ \hat{V}^k \}) \). This is a contradiction to the result of Part (1). Therefore null \( \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) A^k \right) = \text{span} (1) \).

**Part (3).** According to the result of Part (2) and Theorem 5.2 in [24], we have

\[
\left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) A^k \right) ^+ \overset{P}{\to} \left( \sum_{k=1}^{K} A^k \Xi^k \left( \hat{\omega}^k \hat{X}^k, \hat{\rho}^k \right) A^k \right) ^+ \tag{H.3}
\]

Substituting \( \text{(H.1)} \) and \( \text{(H.3)} \) into \( \hat{V} - \hat{\nu} \) and \( \sqrt{M} (\hat{V} - \hat{\nu}) \) leads to the conclusions of the theorem.

**Appendix I. Proof of Theorem 4.7**

Let \( G (\cdot) \) be a function of \( y^k_i \) with

\[
G (y^k_i) = [G_{ij} (y^k_i)] = \left[ I_{S^k} (\mu^k (y^k_i)) \right] \Pr (I_{S^k} (y^k_{i+1}) = j | y^k_i) \tag{I.1}
\]
and \( \kappa_{ij}^k(h) = \text{Cov}(\mathcal{V}(G(y_i^k)), \mathcal{V}(G(y_j^{k+h}))) \) be the \( h \)-lag autocovariance of \( \{\mathcal{V}(G(y_i^k))\} \).

It is easy to verify that \( \kappa_{ij}^k(h) \) and \( \kappa^k(h+1) \) composed of the same elements but in different arrangements for \( h \geq 0 \), and \( \eta^k(l) = \text{tr}(\kappa_{ij}^k(2l) + \kappa_{ij}^k(2l+1)) \).

From the above results, we can conclude that \( \eta^k(l) = \text{tr}(\kappa_{ij}^k(2l) + \kappa_{ij}^k(2l+1)) \) is a non-negative and decreasing function of \( l \) for \( l \geq 0 \), and \( \kappa_{ij}^k(2l) + \kappa_{ij}^k(2l+1) \geq 0 \) by using Theorem 3.1 in [7]. Therefore the second conclusion of the theorem can be proved since \( \text{tr}(\kappa_{ij}^k(2l) + \kappa_{ij}^k(2l+1)) \) is convergent.

We now show the first conclusion. According to Theorem 2.1 in [7] and considering that \( \sum_{h=0}^{\infty} \kappa_{ij}^k(h) \) is convergent, we have

\[
(1.2) \quad \lim_{N \to \infty} N\text{Var} \left( \frac{1}{N} \sum_{t=0}^{N-1} \mathcal{V}(G(y_i^k)) \right) = \kappa_{ij}^k(0) + 2 \sum_{h=1}^{\infty} \kappa_{ij}^k(h)
\]

On the other hand,

\[
(1.3) \quad N\text{Var} \left( \frac{1}{N} \sum_{t=0}^{N-1} \mathcal{V}(G(y_i^k)) \right) = \kappa_{ij}^k(0) + 2 \sum_{h=1}^{N-1} \frac{N-h}{N} \kappa_{ij}^k(h)
\]

Combining the above two equations leads to

\[
(1.4) \quad \lim_{N \to \infty} \sum_{h=1}^{N-1} \frac{h}{N} \kappa_{ij}^k(h) = \lim_{N \to \infty} \sum_{h=1}^{N-1} \frac{h-1}{N} \kappa_{ij}^k(h) = 0^T
\]

Therefore

\[
N\text{Var} \left( \frac{1}{N} \sum_{t=1}^{N} \mathcal{V}(\Delta C_i^k) \right) = \kappa^k(0) + \sum_{h=1}^{N-1} \frac{N-h}{N} \left( \kappa^k(h) + \kappa^k(h)^T \right)
\]

\[
(1.5) \quad \rightarrow \kappa^k(0) + \sum_{h=1}^{\infty} \left( \kappa^k(h) + \kappa^k(h)^T \right)
\]

as \( N \to \infty \), and \( \Sigma^k = \kappa^k(0) + \sum_{l=0}^{\infty} \left( \Gamma^k(l) + \Gamma^k(l)^T \right) \).

Appendix J. Metropolis simulation model.

The Metropolis simulation model generates the \( x_{0:M_k}^k \) by the following steps if the reference \( V \) and biasing potential \( U^k \) are given:

**Step 1.** Let \( t := 0 \) and sample \( x_0^k \sim \text{Pr} \left( x_0^k = s_i \right) \propto \exp(-U_i^k) \).

**Step 2.** Sample \( x' = s_j \) from the proposal distribution \( \Pr \left( x' = s_j | x_i^k = s_i \right) = q_{ij} \propto 1_{|i-j| \leq 2} \) and calculate the acceptance ratio \( a = \min \left\{ \exp(-V_j-U_j^k)q_{ij}, 1 \right\} \).

**Step 3.** Set \( x_{i+1}^k \) to be \( x' \) with probability \( a \) and \( x_i^k \) with probability \( 1 - a \).

**Step 4.** Terminate the simulation if \( t = M_k \). Otherwise, let \( t := t + 1 \) and go to Step 2.

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