# Estimation and uncertainty of reversible Markov models

Benjamin Trendelkamp-Schroer,[1] Fabian Paul,[1] Hao Wu,[1] and Frank Noé[1, a)]
*Institut für Mathematik und Informatik, FU Berlin, Arnimallee 6, 14195 Berlin*

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## I. INTRODUCTION

Reducing the large complexity of biomolecular dynamics to simple kinetic models which are yet representative of the underlying transitions between functionally distinct conformations can be achieved using Markov state models (MSM)[1–7]. MSMs allow to integrate multiple simulation trajectories into a single informative model of the relevant dynamics so that the benefits of a distributed computation infrastructure can be used to tackle demanding problems[8].

A variety of complex molecular processes have been successfully described using MSMs. Examples include the folding of unfolded proteins into their native folded structure[9–11], the dynamics of natively unstructured proteins[12], and the binding of a ligand to a target protein[13–16].

There are two key steps in the construction of a MSM. At first a suitable discretization of the continuous conformation space has to be obtained. It is sometimes possible to identify the relevant conformations beforhenad. In most cases however one has to identify them on the basis of the generated trajectories. In the second step one estimates the probabilities for transitions from observed counts between pairs of subsets specified by the discretization. In doing so the jump-process resulting from the projection of the observed dynamics onto these sets is approximated by a Markov process, hence the name Markov state model. The appropriate choice of discretization is a topic of ongoing research[12,17,18]. The error incurred by the discretization and by the subsequent approximation of the jump-process as a Markov process can be controlled[19].

The estimation of transition probabilites from observed counts can be either conducted via likelihood optimization or using the posterior ensemble. In the former setting one is only interested in finding the set of probabilities that maximizes the likelihood function for the given observation. Inference via the posterior considers the fact that a finite observation necessarily leads to uncertainties. There is an ensemble of models compatible with the given observation so that only expectation values with respect to the posterior can yield meaningful information about the desired probabilities. For a large amount of observation the posterior distribution will become sharply peaked about the maximum likelihood point so that expectation values with respect to the posterior can be safely replaced by quantities computed from the maximum likelihood estimate.

The estimation procedure offers some freedom in imposing constraints representing additional information about the underlying process. Many simulation procedures ensure microscopic reversibility of the generated trajectories[20,21]. This property is carried over to the discretized situation so that detailed balance is a desirable property for all estimates. Furthermore imposing detailed balance with respect to a given stationary vector can be used to aid the efficient estimation of rare-event processes from MSMs[22].

Algorithms imposing detailed balance during likelihood optimization have been discussed in[7,23]. A method for the sampling of reversible transition matrices using a Metropolis chain was given in[24]. A method working with natural priors for reversible chains was given in[25]. The sampling of transition matrices reversible with respect to a fixed stationary distribution was also presented in[24], an improved Gibbs sampling algorithm has been developed to speed up convergence[26].

We present a new method for the maximum likelihood estimation of transition matrices reversible with respect to a given stationary distribution and show how to compute statistical errors from linear perturbation theory in this setting. We also present an improved variant of the sampling algorithm for reversible transition matrices in[24] combining the Gibbs sampling approach in[26] with a new proposal step.

## II. MAXIMUM LIKELIHOOD PROBABILITY ESTIMATION

For a matrix of transition probabilities $P = (p_{ij})$ the likelihood of observing transition counts $C = (c_{ij})$ is

[a)] Electronic mail: frank.noe@fu-berlin.de

given by

$$\mathbb{P}(C|P) \propto \prod_i \left( \prod_j p_{ij}^{c_{ij}} \right) \tag{1}$$

For given counts $C$ the maximum likelihood estimate (MLE) maximizes (1) over the set of transition matrices.

### A. Non-reversible estimation

The non-reversible MLE for the transition probability from state $i$ to state $j$ is simply given by the ratio of observed counts from $i$ to $j$ divided by the total number of outgoing transitions from state $i$,

$$p_{ij} = \frac{c_{ij}}{\sum_k c_{ik}}. \tag{2}$$

### B. Reversible estimation

Imposing detailed balance with respect to an unknown stationary vector $(\pi_i)$,

$$\pi_i p_{ij} = \pi_j p_{ji} \tag{3}$$

and using the logarithm of the likelihood function as objective leads to the following constraint optimization problem,

$$\begin{aligned} \underset{\pi, P}{\text{maximize}} \quad & \sum_{i,j} c_{ij} \log p_{ij} \\ \text{subject to} \quad & \sum_j p_{ij} = 1 \\ & p_{ij} \geq 0 \\ & \pi_i p_{ij} = \pi_j p_{ji} \\ & \sum_i \pi_i = 1 \\ & \pi_i > 0. \end{aligned} \tag{4}$$

There is no closed form solution when including the detailed balance constraint so that (4) has to be solved numerically. An algorithm for the numerical solution of (4) has been developed in[23]. We include it into our discussion for completeness.

Since $P$ fulfills detailed balance with respect to $\pi$ there exists a symmetric count-matrx $X = (x_{ij})$ such that the estimate (2), $p_{ij} = x_{ij} / \sum_k x_{ik}$ solves (4). This leads to the following optimization problem

$$\begin{aligned} \underset{X}{\text{maximize}} \quad & \sum_{i,j} c_{ij} \log \frac{x_{ij}}{\sum_k x_{ik}} \\ \text{subject to} \quad & X_{ij} = X_{ji} \\ & \sum_k X_{ik} > 0 \\ & X_{ij} \geq 0 \end{aligned} \tag{5}$$

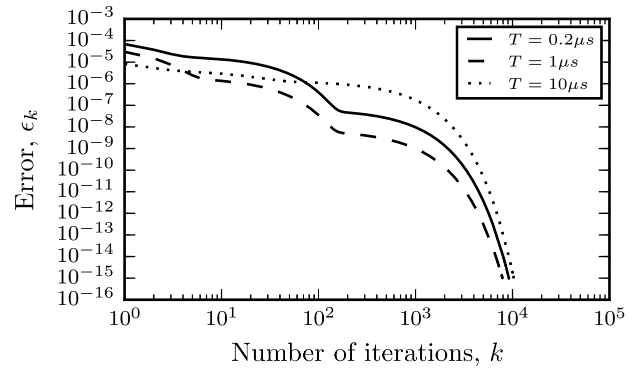


Figure 1. Reversible maximum likelihood estimation. The reversible transition matrix is estimated from a count-matrix with $n = 228$ states. The count-matrix was generated from alanine-dipeptide simulation data for different total sampling amount $T$.

Ignoring the inequality constraints the optimality conditions are

$$\frac{c_{ij} + c_{ji}}{x_{ij}} - \frac{c_i}{x_i} - \frac{c_j}{x_j} = 0 \tag{6}$$

with $c_i = \sum_j c_{ij}$ and $x_i = \sum_j x_{ij}$. This leads to the following iterative update procedure

$$x_{ij}^{(k+1)} = \frac{c_{ij} + c_{ji}}{\frac{c_i}{x_i^{(k)}} + \frac{c_j}{x_j^{(k)}}} \tag{7}$$

For a starting iterate $x_{ij}^{(0)}$ fulfilling the constraints, $x_{ij}^{(0)} \geq 0$, $\sum_k x_{ik}^{(0)} > 0$ the iterates will be symmetric and fulfill the inequality constraints for all $k > 0$. The iteration can for example be initialized with the matrix of observed counts $x_{ij}^{(0)} = c_{ij}$. The iteration is terminated when $||x^{(k+1)} - x^{(k)}|| < \epsilon$ with $x = (x_1, x_2, \dots)$. Progress of the self-consistent iteration is shown in Figure 1.

A different method of iterative solution presented in[7] proceeds using the exact solution to the quadratic problem arising from (6) if all variables but the $x_{ij}$ are held fixed during the $k$-th iteration.

### C. Reversible estimation for given stationary vector

Enforcing reversibility with respect to a given stationary vector results in the following constrained optimization problem

$$\underset{P}{\text{maximize}} \quad \sum_{i,j} c_{ij} \log p_{ij} \tag{8a}$$

$$\text{subject to} \quad \sum_j p_{ij} = 1 \tag{8b}$$

$$p_{ij} \geq 0 \tag{8c}$$

$$\pi_i p_{ij} = \pi_j p_{ji}. \tag{8d}$$

To solve the maximization problem, we ignore the inequality constraint (8c) at first. The detailled balance constraint (8d) is included into the likelihood explicitly by the change of variables

$$p_{ij} = \begin{cases} p'_{ij} & \text{if } i \leq j \\ \frac{\pi_j}{\pi_i} p'_{ji} & \text{else} \end{cases}$$

The row-stochasticity constraint (8b) is enforced by introducing Lagrange multipliers $\lambda_i$ and adding penalty terms to the objective function

$$F \equiv \log \mathbb{P}(C|P) - \sum_i \lambda_i \left( \sum_j p_{ij} - 1 \right) + const$$

Carrying out all substitutions in $F$ yields

$$\begin{aligned} F = \sum_i c_{ii} \log p'_{ii} + \sum_{i<j} (c_{ij} + c_{ji}) \log p'_{ij} \\ - \sum_{i<j} p'_{ij} \left( \lambda_i + \lambda_j \frac{\pi_i}{\pi_j} \right) - \sum_i \lambda_i p'_{ii} + \sum_i \lambda_i + const \end{aligned} \tag{9}$$

By setting the gradient of $F$ with respect to all $p'_{ij}$ to zero and subsequently reversing the change of variables, we find the following expression for the maximum likelihood estimate

$$\hat{p}_{ij} = \frac{(c_{ij} + c_{ji}) \pi_j}{\lambda_i \pi_j + \lambda_j \pi_i} \tag{10}$$

The values of the Lagrange multipliers can be found from the constraint (8b):

$$\sum_j \frac{(c_{ij} + c_{ji}) \pi_j}{\lambda_i \pi_j + \lambda_j \pi_i} = 1$$

This doesn't give a closed-form expression for $\lambda_i$. However, based on this equation, we propose the following fixed-point iteration for the Lagrange multipliers

$$\lambda_i^{(n+1)} = \sum_j \frac{c_{ij} + c_{ji}}{\frac{\lambda_j^{(n)} \pi_i}{\lambda_i^{(n)} \pi_j} + 1} \tag{11}$$

starting from

$$\lambda_i^{(0)} = \frac{1}{2} \sum_j (c_{ij} + c_{ji}) \tag{12}$$

After iterating the Lagrange mutipliers with (11), (12) till convergence, $\hat{p}_{ij}$ can be found from (10).

For this algorithm the inequality constraints (8c) are automatically fulfilled when $c_{ij} \geq 0$ for all $i, j$.

Care must be taken when some diagonal element $c_{ii}$ is zero. Depending on the values of $\pi$, the solution $\lambda_i$ may take the value of zero such that equation (10) for $i = j$ becomes

$$\hat{p}_{ii} = \frac{c_{ii}}{\lambda_i} = \frac{0}{0}$$

which is meaningless and is not the correct limit of $p_{ii}$ as $c_{ii}$ goes to zero. However this can be fixed easily by using

$$\hat{p}_{ii} = 1 - \sum_{\substack{j \\ j \neq i}} \hat{p}_{ij}$$

in place of (10) for the diagonal elements of $P$ and by dropping all terms where $c_{ij} + c_{ji} = 0$ in equation (10) for the computation of $P$. For the computation of the Lagrange multipliers, terms with $c_{ij} + c_{ji} = 0$ (and $c_{ii} = 0$) should be skipped in equation (11).

$\pi$ can only be the stationary distribution of $P$ if $P$ is irreducible. To ensure irreducibility, we restrict the state space to the largest (weakly) connected set of the undirected graph that is defined by the adjacency matrix $C + C^T$.

## III. THE POSTERIOR ENSEMBLE

Bayes' formula relates the likelihood of an observation $C$ given a probability model $P$ to the posterior probability of the model given the observation,

$$\underbrace{\mathbb{P}(P|C)}_{posterior} \propto \underbrace{\mathbb{P}(P)}_{prior} \underbrace{\mathbb{P}(C|P)}_{likelihood} . \tag{13}$$

The posterior accounts for the uncertainty coming from a finite observation. It incorporates a-priori knowledge about the quantity of interest using the prior probability $\mathbb{P}(P)$.

In general we would like to compute posterior expectation values for various observables, i.e. suitable functions $f$ on the set of transition matrices. Obtaining the expectation value amounts to computing an extremely high dimensional integral over a complicated domain so that grid-based approaches to the numerical solution are prohibitevly inefficient and we need to use Monte Carlo strategies to tackle the problem.

In Monte Carlo we generate a sample of transition matrices $\{P^{(k)}\}_{k=1}^N$ distributed according to the posterior and evaluate $f$ at each element $P^{(k)}$ in the ensemble. We then approximate the posterior expectation value $\mathbb{E}[f(P)]$ as

$$\mu_N = \frac{1}{N} \sum_{k=1}^N f(P^{(k)}). \tag{14}$$

A central limit theorem shows that asymptotically the estimated value follows a normal distribution around the true expectation value. The asymtotic variance is given by

$$\mathbb{E}[(\mu_N - \mathbb{E}[f(P)])^2] = \frac{\sigma^2}{N} \tag{15}$$

with $\sigma$ depending on the specific observable $f$ and the auto-correlation time of the sequence $\{f(P^{(k)})\}_{k=1}^{N}$. A more thorough discussion of these points can be found in[27].

For a non-reversible transition matrix there are $n^2$ matrix elements and $n$ linear equality constraints ensuring unit normalization for each row, so that in total a non-reversible transition matrix has $n(n-1)$ degrees of freedom.

Detailed balance with respect to a given stationary vector introduces another $n(n-1)/2$ linear constraints so that a transition matrix reversible with respect to a fixed stationary vector has $n(n-1)/2$ degrees of freedom.

For a general reversible transition matrix the stationary vector is unknown. The unknown stationary vector adds $n-1$ degrees of freedom so that in total a reversible transition matrix has $n(n-1)/2 + (n-1)$ degrees of freedom.

### A. Non reversible sampling

A possible choice for the prior is the Dirichlet prior

$$\mathbb{P}(P) \propto \prod_i \prod_j p_{ij}^{b_{ij}} \tag{16}$$

where $B = (b_{ij})$ is a matrix of prior-counts. For this choice of prior the posterior is given by

$$\mathbb{P}(P|C) \propto \prod_i \left( \prod_j p_{ij}^{z_{ij}} \right). \tag{17}$$

$z_{ij} = c_{ij} + b_{ij}$ is the matrix of posterior pseudo-counts.

In the non-reversible case we can generate independent samples from (17) by drawing rows of $P^{(k)}$ independently from Dirichlet distributions with parameters specified by the posterior pseudo-counts.

Using the prior (16) the mean of the posterior (17) for individual transition matrix elements is given by

$$\mathbb{E}(p_{ij}) = \frac{z_{ij} + 1}{\sum_k (z_{ik} + 1)}. \tag{18}$$

The simplest choice encoding no prior information about $P$ is the uniform prior, $b_{ij} = 0$. For this prior the expected value (18) and the maximum likelihood estimator (2) do *not* coincide. Only in the large sampling limit $c_{ij} \gg 1$ for all $p_{ij} > 0$ will they match.

This can lead to serious problems when estimating quantities for meta-stable systems. Consider for example the following transition matrix for a birth-death chain consisting of two meta-stable sets $A = \{1, \dots, m\}$, $B = \{m+2, \dots, n\}$, seperated by a kinetic bottleneck in form of a single transition state,

$$P = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & 0 & & & & & & \\ \frac{1}{2} & 0 & \frac{1}{2} & & & & & & \\ & \ddots & \ddots & \ddots & & & & & \\ & & 1-10^{-b} & 0 & 10^{-b} & & & & \\ & & & \frac{1}{2} & 0 & \frac{1}{2} & & & \\ & & & & 10^{-b} & 0 & 1-10^{-b} & & \\ & & & & & \ddots & \ddots & \ddots & \\ & & & & & & \frac{1}{2} & 0 & \frac{1}{2} \\ & & & & & & & \frac{1}{2} & \frac{1}{2} \end{pmatrix}. \tag{19}$$

For barrier parameter $b = 3$ and sets with $m = 5$ and $n = 11$ the expected time for hitting $B$ from a state $x \in A$ is

$$\mathbb{E}_x(T_B) = 1.8 \cdot 10^4. \tag{20}$$

The expected hitting time does vary only slightly with the given starting state $x \in A$.

The expected hitting time $\tau_{x,B}$ computed from the non-reversible MLE estimator (2) for a chain of length $L = 10^6$ starting in $A$ typically lies within the following interval around the true value,

$$\tau_{x,B} \in [1.5, 2.3] \cdot 10^4. \tag{21}$$

Given values are the 10th and 90th percentile for a sample computed from $N = 10^3$ independent chains.

For a choice of uniform prior, $b_{ij} = 0$, the estimator (18) will result in non-zero transition probabilities for elements $p_{ij}$ which are zero in the true transition matrix. As a result artifical kinetic pathways circumventing the bottleneck are appearing in the posterior ensemble. This can have dramatic effects on computed estimates as we show below.

The expected hitting times $t_{x,B}$ computed from the non-reversible posterior ensemble with $b_{ij} = 0$ and transition counts given by the expected count-matrix for a chain of length $L = 10^6$ starting in $A$ has typical values

$$t_{x,B} \in [0.8, 1.1] \cdot 10^4 \tag{22}$$

Given values are the 10th and 90th percentile computed from $N = 10^3$ posterior draws. In comparison to the values estimated from the MLE, posterior sampling severly underestimates the correct value for the expected hitting time for the same observation length.

Using $b_{ij} = -1$ instead leads to expected hitting times $t'_{x,B}$ distributed around the correct value,

$$t'_{x,B} \in [1.5, 2.3] \cdot 10^4. \tag{23}$$

Given values are again the 10th and 90th percentile of the sample. This choice of prior apparently leads to 'good' estimates of the expected hitting times from the posterior. Enforcing zero probabilites for all transitions with zero observed counts apparently lead to correct estimates.

We would like to emphasize that in the MLE approach we needed $N = 10^3$ different count-matrices to estimate the interval given in (21) while for posterior sampling values in (22), (23) were estimated for a single count-matrix. In interesting applications we will often only have sufficient data to form a single count-matrix so that in order to estimate errors or confidence intervals we can only use the posterior approach or resort to bootstrap methods.

### B. Reversible sampling

We are now going to present a new method for the sampling of reversible transition matrices as well as a new method for the sampling of transition matrices reversible with respect to a fixed stationary vector. In our new approach we replace the Dirichlet prior (16) by a new type of priors for reversible sampling.

There is no known method to generate independent samples from the posterior under the reversibility requirement. Instead we will use a a Markov chain Monte Carlo (MCMC) method to generate samples from the posterior ensuring that each sampled transition matrix fulfills the detailed balance condition (3). The Markov chain will generate the sample $\{P^{(k)}\}_{k=1}^{N}$ via a set of updates advancing the chain from $P^{(k)} \rightarrow P^{(k+1)}$ starting from a valid initial state $P^{(0)}$. Expectation values will again be estimated using (14).

Before we are introducing the new prior for reversible sampling we need a new set of coordinates parametrizing the set of reversible transition matrices. Similar to the approach in reversible maximum likelihood estimation we will use

$$x_{ij} \propto \pi_i p_{ij} \tag{24}$$

and represent reversible transition matrices by symmetric matrices $X = (x_{ij})$ with non-negative entries and the normalization condition

$$\sum_{i \geq j} x_{ij} = 1. \tag{25}$$

As in the case of reversible transition matrices there are $n(n-1)/2 + (n-1)$ degrees of freedom for $X$. The mapping from $X$ back to $P$ is given by

$$p_{ij} = \frac{x_{ij}}{\sum_k x_{ik}}. \tag{26}$$

Our new prior for reversible sampling is specified on the set of $X$ matrices instead of on the set of transition matrices,

$$\mathbb{P}(X) \propto \prod_{i \geq j} x_{ij}^{b_{ij}-1}. \tag{27}$$

The posterior for reversible sampling is then given as

$$\mathbb{P}(X|C) \propto \prod_{i \geq j} x_{ij}^{b_{ij}-1} \prod_{i,j} p_{ij}(X)^{c_{ij}} \tag{28}$$

with $p_{ij}(X)$ given by (26).

We propose the following set of updates for sampling from the posterior (28). For given $X$ we fix $k$, $l$ with $k \geq l$ and generate a random sample $y$ from the one-dimensional conditional distribution of elements at position $(k,l)$ for given elements at all other positions,

$$y \sim \mathbb{P}(x_{kl} | \{x_{ij}\}_{i \geq j} \backslash \{x_{kl}\}, C). \tag{29}$$

Scale all other elements so that the new sample $X'$ fulfills the normalization condition (25). The new entries $x'_{ij}$ with $i \geq j$ are then given by

$$x'_{ij} = \begin{cases} y & (i,j) = (k,l) \\ \frac{1-y}{1-x_{kl}} x_{ij} & \text{else} \end{cases} \tag{30}$$

and the upper triagular part is filled so that symmetry is restored.

Another set of coordinates valid for any fixed $(k,l)$ is given by the transformation $\Phi$,

$$v_{ij} = \frac{x_{ij}}{1 - x_{kl}}. \tag{31}$$

For fixed $(k,l)$ and given matrix $V = (v_{ij})$ with $v_{ij} \geq 0$, $v_{ij} = v_{ji}$, and

$$\sum_{i \geq j} v_{ij} = 1 + v_{kl} \tag{32}$$

the matrix $X$ can be recovered using the inverse transformation $\Phi^{-1}$,

$$x_{ij} = \frac{v_{ij}}{1 + v_{kl}}. \tag{33}$$

From (26) and (33) it can be immediately seen that the elements of $P$ can be directly expressed in terms of the elements of $V$,

$$p_{ij} = \frac{v_{ij}}{\sum_k v_{ik}} \tag{34}$$

The determinant of the Jacobian $D\Phi^{-1}$ is

$$|D\Phi^{-1}| = (1 + v_{kl})^{-n(n+1)/2} \tag{35}$$

so that the prior (27) becomes

$$\mathbb{P}(V) \propto (1 + v_{kl})^{-n(n+1)/2} \prod_{i \geq j} \left( \frac{v_{ij}}{1 + v_{kl}} \right)^{b_{ij}-1}. \tag{36}$$

The posterior of $V$ is then given by

$$\mathbb{P}(V|C) \propto (1 + v_{kl})^{-b_0} \prod_{i \geq j} v_{ij}^{b_{ij}-1} \prod_{i,j} \left( \frac{v_{ij}}{v_i} \right)^{c_{ij}}, \tag{37}$$

with $v_i = \sum_k v_{ik}$ and $b_0 = \sum_{i \geq j} b_{ij}$. The conditional distribution for the diagonal element $v_{kk}$ can now be indentified as

$$\begin{aligned} \mathbb{P}(v_{kk} | \{v_{ij}\}_{i \geq j} \backslash \{v_{kk}\}, C) &\propto (1 + v_{kk})^{-b_0} \\ &\quad v_{kk}^{c_{kk}+b_{kk}-1} (v_{k,-k} + v_{kk})^{-c_k} \end{aligned} \tag{38}$$

while the conditional distribution for the stricly lower triangular elements $v_{kl}$ is given by

$$\begin{aligned}\mathbb{P}(v_{kl}|\{v_{ij}\}_{i\geq j}\backslash\{v_{kl}\},C) \propto (1+v_{kl})^{-b_0} \\ v_{kl}^{c_{kl}+c_{lk}+b_{kl}-1}(v_{k,-l}+v_{kl})^{-c_k} \\ (v_{l,-k}+v_{kl})^{-c_l},\end{aligned} \tag{39}$$

with $v_{i,-j}=\sum_{k\neq j} v_{ik}$.

For $c_{kk}+b_{kk}=0$ the conditional (38) degenerates to a point probability at zero. The same is true for (39) for $c_{kl}+c_{lk}+b_{kl}=0$. Setting $b_{ij}=0$ thus encodes the a-priori belief that any transition for which neither the forward direction nor the backward direction has ever been observed in the data has zero probability in the posterior ensemble. The reversible MLE exhibits the same property as can be seen from the update rule (7).

In the non-reversible case prior parameters $b_{ij}=-1$ were required to achieve a similar effect. As we have shown above this choice led to satisfactory results for posterior sampling in the non-reversible case. Below we will show that an efficient sampling algorithm can be constructred choosing $b_{ij}=0$ in (27) and that similar to the non-reversible case it is able to produce 'good' estimates for this choice of prior parameters.

It is clear that a global scaling of $V$ leaves (34) invariant. In the case $b_{ij}=0$ the conditional probability (38), (39) is, up to constant factor, also invariant under an arbitrary global scaling of $V$ so that in this case the normalization condition (32) can be dropped alltogether.We will now outline an efficient method to generate samples from the conditional.

For (38) we can transform $v_{kk}$ back to $p_{kk}$ via (34) and obtain the conditional

$$\mathbb{P}(p_{kk}|\{v_{ij}\}_{i\geq j}\backslash\{v_{kk}\},C) \propto p_{kk}^{c_{kk}-1}(1-p_{kk})^{c_k-c_{kk}-1}. \tag{40}$$

(40) is just a Beta-distribution with parameters $\alpha=c_{kk}$ and $\beta=c_k-c_{kk}$ and can be efficiently sampled as discussed in[28]. The new element $v'_{kk}$ can be obtained from the sampled $p'_{kk}$ via

$$v'_{kk}=\frac{p'_{kk}}{1-p'_{kk}}v_{k,-k}. \tag{41}$$

For (39) we use the following representation

$$v_{kl}^{c_{kl}+c_{lk}-1}(v_{k,-l}+v_{kl})^{-c_k}(v_{l,-k}+v_{kl})^{-c_l}=v_{kl}^{-1}\exp f(v_{kl}). \tag{42}$$

The function $f(v_{kl})$ is then given by

$$\begin{aligned}f(v_{kl})=(c_{kl}+c_{lk})\log v_{kl}-c_k\log(v_{k,-l}+v_{kl}) \\ -c_l\log(v_{l,-k}+v_{kl}).\end{aligned} \tag{43}$$

We approximate $f$ using a three parameter family of functions

$$\hat{f}(v|\alpha,\beta,f_0)=\alpha\log v-\beta v+f_0 \tag{44}$$

so that the corresponding approximate conditional is

$$q(v_{kl}|\alpha,\beta,f_0)=v_{kl}^{-1}\exp\hat{f}(v_{kl}|\alpha,\beta,f_0). \tag{45}$$

(45) is, up to a constant factor, a Gamma distribution with parameters $\alpha$, $\beta$ which can be efficiently sampled[28].

The three parameters $\alpha$, $\beta$, $f_0$ are obtained matching $f$ and $\hat{f}$ up to second derivatives at the maximum point

$$\bar{v}_{kl}=\arg\max f(v_{kl}). \tag{46}$$

This leads to the following linear system

$$\log\bar{v}_{kl}\,\alpha+\bar{v}_{kl}\beta+f_0=f(\bar{v}_{kl}) \tag{47a}$$
$$\frac{\alpha}{\bar{v}_{kl}}-\beta=f'(\bar{v}_{kl})=0 \tag{47b}$$
$$-\frac{\alpha}{\bar{v}_{kl}^2}=f''(\bar{v}_{kl}) \tag{47c}$$

with solution

$$\alpha=-f''(\bar{v}_{kl})\bar{v}_{kl}^2 \tag{48a}$$
$$\beta=-f''(\bar{v}_{kl})\bar{v}_{kl} \tag{48b}$$
$$f_0=f(\bar{v}_{kl})+f''(\bar{v}_{kl})\bar{v}_{kl}^2(\log\bar{v}_{kl}-1) \tag{48c}$$

The maximum point can be computed as the root of a quadratic equation in the usual way,

$$\bar{v}_{kl}=\frac{-b+\sqrt{b^2-4ac}}{2a} \tag{49}$$

with parameters $a$, $b$, $c$ given by

$$a=c_k+c_l-c_{kl}-c_{lk} \tag{50a}$$
$$b=c_kv_{l,-k}+c_lv_{k,-l}-(c_{kl}+c_{lk})(v_{k,-l}+v_{l,-k}) \tag{50b}$$
$$c=-(c_{kl}+c_{lk})v_{k,-l}v_{l,-k} \tag{50c}$$

The second solution corresponding to (49) with negative sign in front of the square root can be safely excluded since $\bar{v}_{kl}$ is required to be nonnegative.

The approximate conditional $q$ in (45) is not necessarily a bounding envelope for the true conditional (39) so that instead of rejection sampling we use the approximation $q$ as a proposal density in a Metropolis sampling step. The acceptance probability for the step is then given as $\min\{1,p_{acc}\}$ with

$$p_{acc}=\frac{q(v_{kl})(v'_{kl})^{-1}\exp f(v'_{vkl})}{q(v'_{kl})v_{kl}^{-1}\exp f(v_{vkl})}. \tag{51}$$

In summary the proposed algorithm 1 is a Metropolis within Gibbs MCMC algorithm with adapted proposal probabilites for each Gibbs sampling step.

### C. Reversible sampling with fixed stationary vector

As in the reversible case we will be working with new variables $x_{ij}$ related to transition matrix entries $p_{ij}$ via (24). The single normalization condition (25) needs to be replaced by a condition valid for each row,

$$\sum_j x_{ij}=\pi_i, \tag{52}$$

**Algorithm 1:** Reversible sampling algorithm

```
Input: C, V^(j)
Output: V^(j+1)
for k = 1,...,n do
    for l = 1,...,k do
        if c_kl + c_lk > 0 then
            if k = l then
                Sample v_kk^(j+1) according to (40), (41)
            else
                Obtain parameters a, b, c from (50a),
                (50b), (50c)
                Compute v̄_kl according to (49)
                Compute parameters α, β, f_0 using (48a),
                (48b),(48c)
                Sample v'_kl according to (45)
                Compute p_acc from (51)
                U from [0,1] uniformly distributed
                if U < min{1, p_acc} then
                    v_kl^(j+1) = v'_kl
                else
                    v_kl^(j+1) = v_kl^(j)
                end
                v_lk^(j+1) = v_kl^(j+1)
            end
        end
    end
end
```

in order to ensure reversibility with respect to a given stationary vector $\pi$.

We will again use the prior (27) defined on the set of $X$ matrices.

We will view all $x_{kl}$ with $k > l$ as independent variables. An update of a valid $X$ matrix respecting the constraints is given by

$$x_{kl} \rightarrow x'_{kl} \tag{53a}$$
$$x_{kk} \rightarrow x_{kk} + (x'_{kl} - x_{kl}) \tag{53b}$$
$$x_{lk} \rightarrow x'_{kl} \tag{53c}$$
$$x_{ll} \rightarrow x_{ll} + (x'_{lk} - x_{lk}). \tag{53d}$$

(53b) and (53d) ensure that the normalization condition (52) holds for the new sample, while (53c) restores the symmetry.

As before we will sample $x'_{kl}$ from the conditional distribution,

$$\mathbb{P}(x_{kl}|\{x_{ij}\}_{i>j}\backslash\{x_{kl}\}, \pi, C) \propto x_{kl}^{c_{kl}+c_{lk}+b_{kl}-1} (\Delta_{kl} - x_{kl})^{c_{kk}+b_{kk}-1} (\Delta_{lk} - x_{kl})^{c_{ll}+b_{ll}-1}, \tag{54}$$

with residual

$$\Delta_{kl} = \pi_k - \sum_{j\neq k,l} x_{kj}. \tag{55}$$

We have seen that a correct choice of prior parameters was essential in order to successfully apply the posterior sampling for meta-stable systems. As in the reversible case we will use $b_{kl} = 0$ for $k > l$ to enforce $x_{kl} = 0$ whenever $c_{kl} + c_{lk} = 0$.

The choice of good prior parameters for the diagonal elements $b_{kk}$ requires further analysis. For the non-reversible case a good choice of prior ensured equality between the MLE (2) and the posterior expectation (18).

For rows $k$ with $c_{kk} > 0$ we choose $b_{kk} = 0$ as in the reversible case. In the case $c_{kk} = 0$ we can not choose $b_{kk} = 0$ since the conditional (54) would then degenerate so that $x_{kl} = \Gamma_{kl}$ and $x_{kk} = 0$ with probability one. In that case we need to regularize the problem by setting $b_{kk} = \epsilon$ for some small number $\epsilon$, so that (54) does not degenerate.

In the case that the MLE (10) leads to $\hat{p}_{kk} > 0$ for $c_{kk} = 0$ the choice $b_{kk} = \epsilon$ will result in samples with $x_{kk} \approx 0$. In that case we choose $b_{kk} = 1$ so that the conditional expectation of (54),

$$\mathbb{E}(x_{kl}|\{x_{ij}\}_{i>j}\backslash\{x_{kl}\}, C) = \frac{c_{kl} + c_{lk}}{c_{kl} + c_{lk} + c_{ll}} \Delta_{lk} \tag{56}$$

matches the MLE of the one-dimensional likelihood function for $x_{kl}$ given all other variables $\{x_{ij}\}_{i>j}\backslash\{x_{kl}\}$.

We will now investigate how to efficiently sample from the posterior. The conditional (54) is of the form,

$$p(x) \propto x^{a_1}(s_2 - x)^{a2}(s_3 - x)^{a_3} \tag{57}$$

with $s_2 < s_3$ and $a_1, a_2, a_3 > -1$.

We will transform $x \in (0, s_2)$ into a new variable $v \in (0, +\infty)$ via

$$v = \frac{x}{s_2 - x}. \tag{58}$$

The inverse transformation from $v$ back to $x$ is given by

$$\frac{s_2 v}{1 + v}. \tag{59}$$

The conditional (57) changes to

$$p(v) \propto v^{a_1} \left(\frac{s}{s-1} + v\right)^{a_3} \left(1 + v\right)^{-(a_1+a_2+a_3+2)}. \tag{60}$$

with $s = s_3/s_2 > 1$.

As in the reversible case we will use the representation

$$p(v) = v^{-1} \exp f(v) \tag{61}$$

and approximate $f(v)$ using the three parameter familiy, $\hat{f}(v|\alpha, \beta, f_0)$, given in (44). The resulting approximate conditional, $q(v|\alpha, \beta, f_0)$, has the same nice properties as the one from (45).

Parameters $\alpha$ $\beta$ and $f_0$ are given by (48a), (48b) and (48c). The maximum point $\hat{v}$ is given by (49). The parameters $a$, $b$, $c$ are,

$$a = a_2 + 1 \tag{62a}$$
$$b = a_2 - a_1 + \frac{a_2 + a_3 + 1}{s - 1} \tag{62b}$$
$$c = \frac{s(a_1 + 1)}{1 - s} \tag{62c}$$

with $a_1 = c_{kl} + c_{lk} + b_{kl} - 1$, and $a_2 = c_{kk} + b_{kk} - 1$, $a_3 = c_{ll} + b_{ll} - 1$, and $s_2 = \Delta_{kl}$ $s_3 = \Delta_{lk}$ if $\Delta_{kl} \leq \Delta_{kl}$. In the case $\Delta_{kl} > \Delta_{lk}$ the definitions of $a_2$ and $a_3$ as well as the definitions of $s_2$ and $s_3$ are interchanged.

As in the reversible case we need to perform a Metropolis sampling step using the acceptance ratio from (51).

The proposed algorithm 2 for sampling of reversible transition matrices with fixed stationary vector can again be characterized as a Metropolis within Gibbs MCMC algorithm with adapted proposal probabilities.

**Algorithm 2:** Reversible sampling algorithm with fixed stationary vector

```
Input: C, X^(j)
Output: X^(j+1)
for k = 2, ..., n do
    for l = 1, ..., k-1 do
        if c_kl + c_lk > 0 then
            Cmpute v = x_kl (s_2 - x_kl)^{-1}
            Obtain parameters a, b, c from (62a), (62b), (62c)
            Compute v̄ according to (49); Compute parameters α, β, f_0 using (48a), (48b),(48c)
            Sample v' according to (45)
            Compute p_acc from (51)
            U from [0,1] uniformly distributed
            if U < min{1, p_acc} then
                x_kl^(j+1) = s_2 v' (1 + v')^{-1}
            else
                x_kl^(j+1) = x_kl^(j)
            end
            x_lk^(j+1) = x_kl^(j+1)
        end
    end
end
```

## IV. RESULTS

To demonstrate the success of the proposed algorithms we apply them to simulation data for the alanine-dipeptide molecule. The system was simulated on GPU-hardware using the OpenMM simulation package[29] using the *amber99sb-ildn* forcefield[30] and the *tip3p* water model[31]. The cubic box of length $2.7nm$ contained a total of 652 solvent molecules. We used Langevin equations at $T = 300K$ with a time-step of $2fs$. A total of $1\mu s$ of simulation data was generated.

The $\phi$ and $\psi$ dihedral angles were discretized using a $20\times 20$ regular grid to obtain a matrix of transition counts $C = (c_{ij})$. The stationary distribution, $\pi_i$ was, for sake of simplicity, computed using the relative frequencies of state occurences,

$$\pi_i = \frac{\sum_k c_{ik}}{\sum_{j,k} c_{jk}}. \tag{63}$$

It should be noted that in general the stationary vector will be obtained from a set of enhanced sampling simulations targeted at rapidly generating a good estimate for $\pi$ alone. Further discussion of this point can be found in[22].

Below we will show histograms for two important observables, *largest implied time-scales* $t_i$ and *expected hitting times*, $\tau(A \to B)$, for pairs $A$, $B$ of meta-stable sets. We compute the posterior sample-mean and the corresponding MLE value and show that they are in good agreement supporting the proposed prior as a 'good' choice for reversible sampling in meta-stable systems.

To assess the efficiency of the MCMC algorithm we show the autocorrelation functions for the above observables and compute autocorrelation times.

### A. Reversible sampling

In Figure 2 we show histograms of implied time-scales computed from the posterior sample. Figure 3 shows expected hitting times for the three transitions $C_5 \to C_7^{ax}$, $C_5 \to \alpha_L$ and $C_5 \to \alpha_R$ between meta-stable sets in the $\phi$ and $\psi$ dihedral angle plane. Figure 4 shows autocorrelation functions for all sampled observables.

### B. Reversible sampling with fixed stationary vector

In Figure 5 we show histograms of implied time-scales computed from the posterior sample. Figure 6 shows expected hitting times for the three transitions $C_5 \to C_7^{ax}$, $C_5 \to \alpha_L$ and $C_5 \to \alpha_R$ between meta-stable sets in the $\phi$ and $\psi$ dihedral angle plane. Figure 7 shows autocorrelation functions for all sampled observables.

## V. CONCLUSION

## ACKNOWLEDGMENTS

We thank various people here.

### Appendix A: Some calculation

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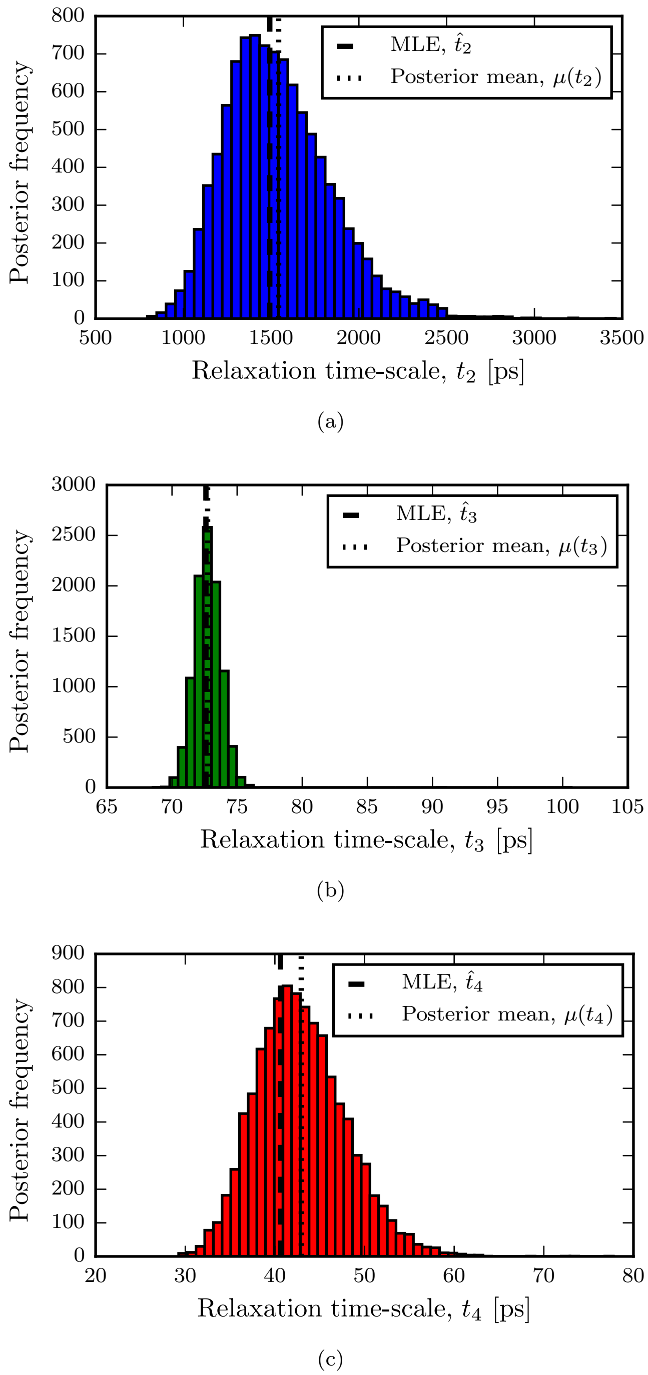


Figure 2. Implied time-scales, $t_i$. Histograms obtained from reversible posterior sampling. Dashed lines indicate the maximum likelihood (MLE) estimates, $\hat{t}_i$, dotted lines indicate the posterior sample mean, $\mu(t_i)$. MLE and posterior mean are in very good agreement for the proposed choice of prior.

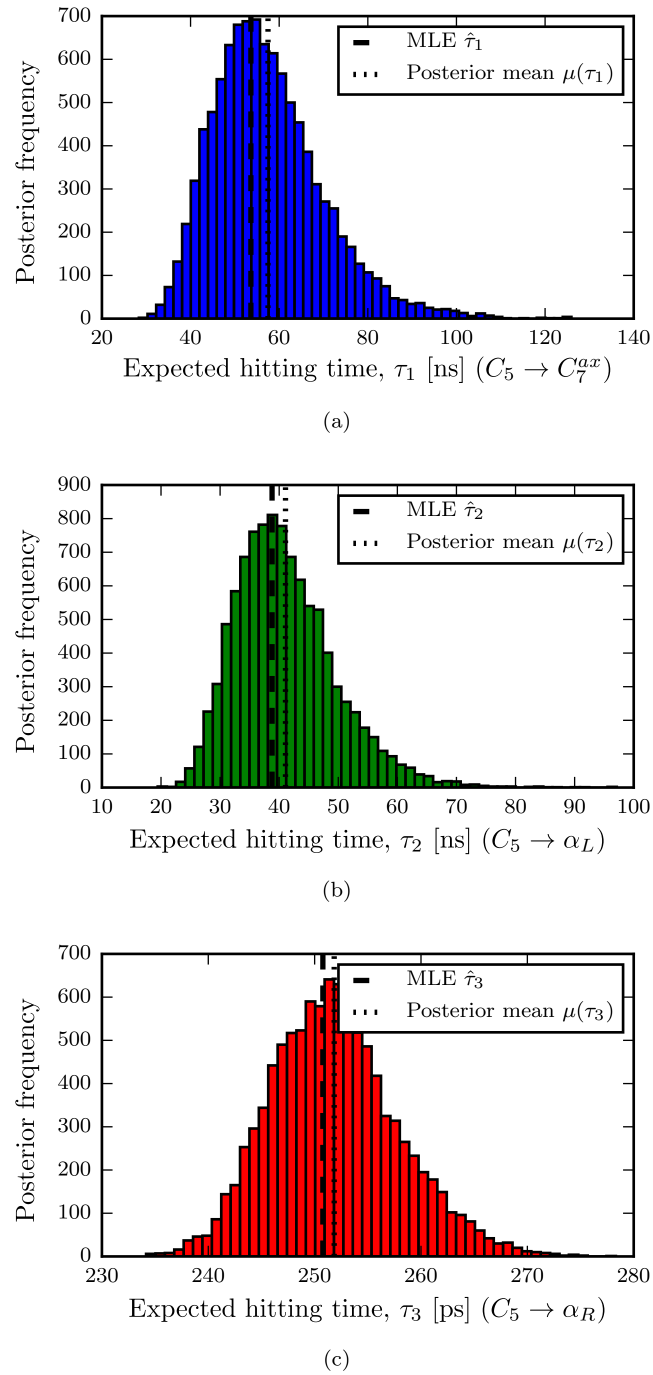


Figure 3. Expected hitting times $\tau$. Histograms obtained from reversible posterior sampling. Dashed lines indicate the maximum likelihood (MLE) estimates, $\hat{\tau}$, dotted lines indicate the posterior sample mean, $\mu(\tau)$. MLE and posterior mean are in very good agreement for the proposed choice of prior.


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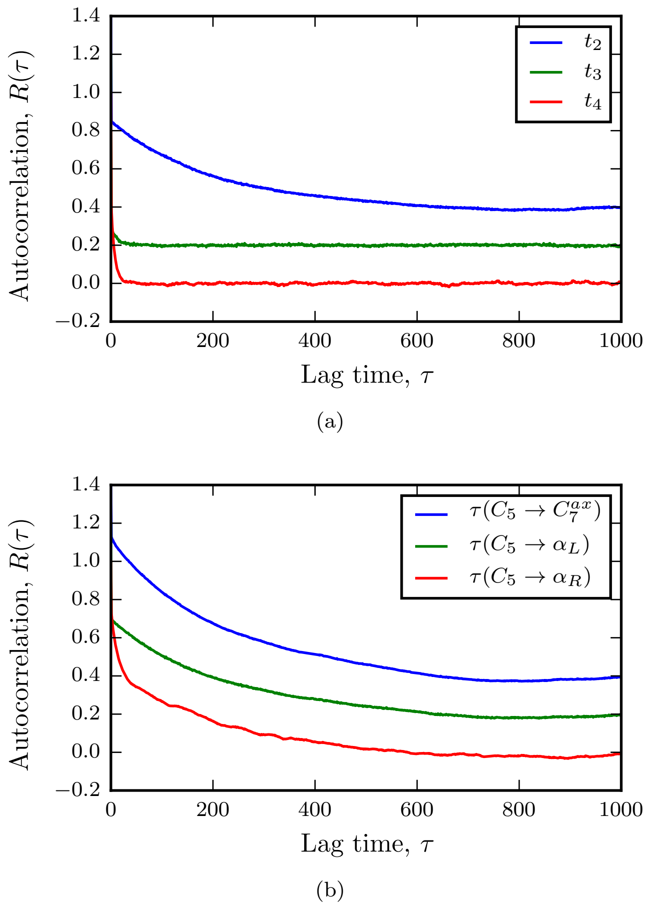
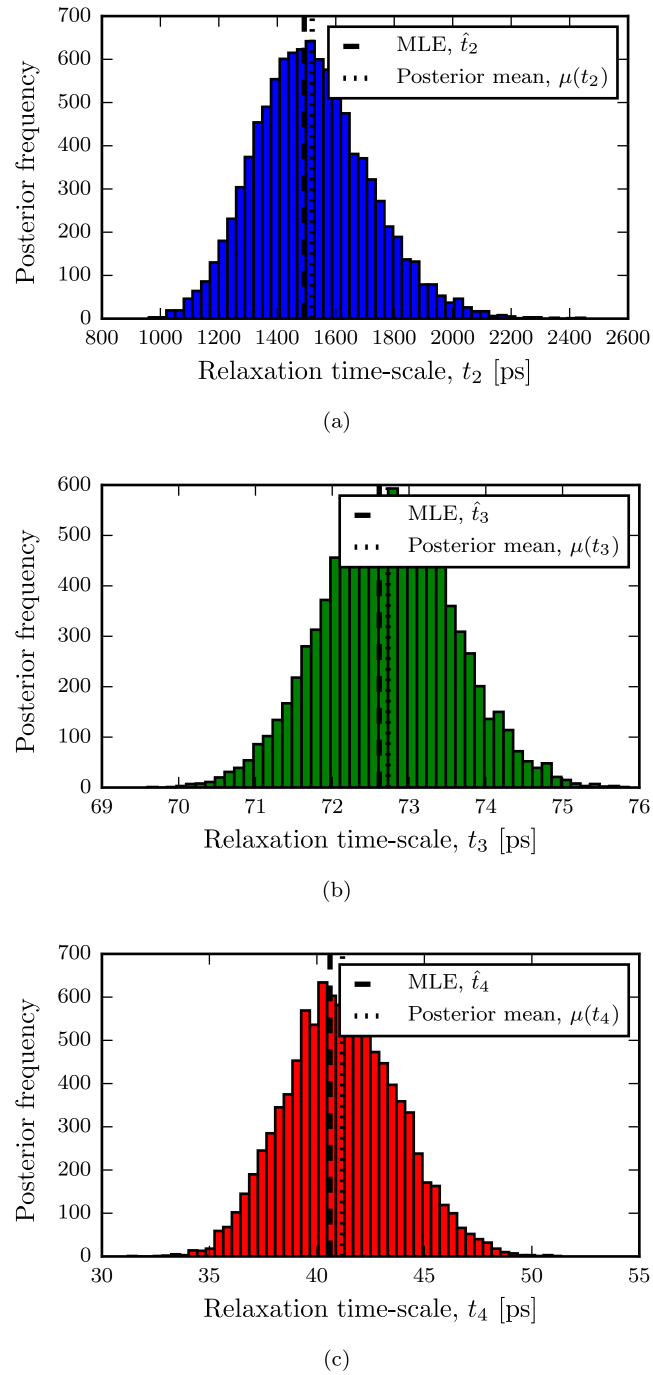



Figure 4. Autocorrelation functions for reversible sampler. The autocorrelation function for $t_3$ and $t_4$ show a rapid decay, while the autocorrelation of $t_2$ decays more slowly indicating the remaining dependence of successive MCMC samples. Autocorrelation functions of expected hitting-times show a similar decay as the one of $t_2$.

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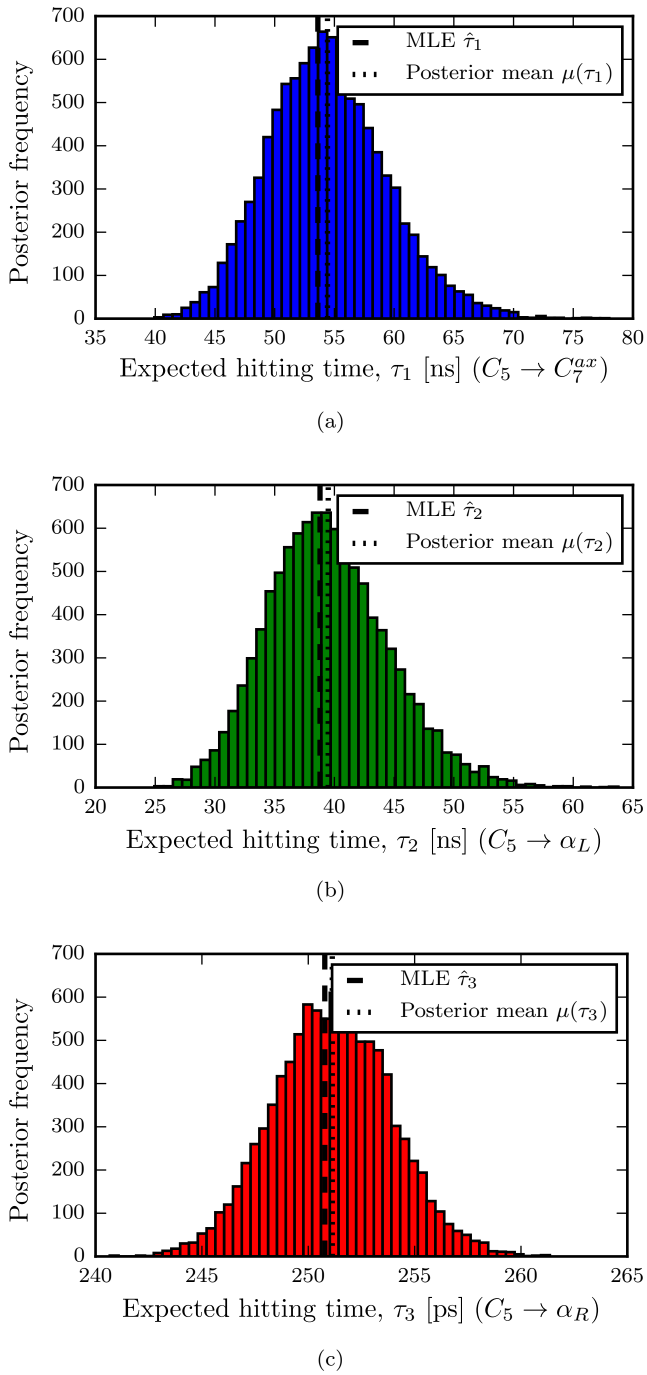


Figure 6. Expected hitting times $\tau$. Histograms obtained from reversible posterior sampling. Dashed lines indicate the maximum likelihood (MLE) estimates, $\hat{\tau}$, dotted lines indicate the posterior sample mean, $\mu(\tau)$. MLE and posterior mean are in very good agreement for the proposed choice of prior.

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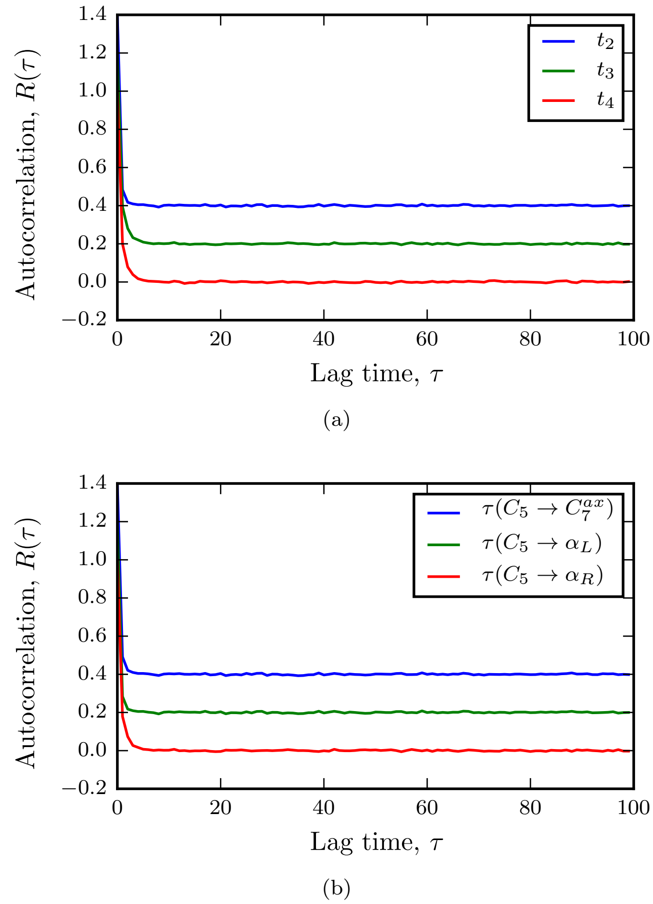


Figure 7. Autocorrelation functions for reversible sampler with fixed stationary distribution. The autocorrelation function for $t_3$ and $t_4$ show a rapid decay, while the autocorrelation of $t_2$ decays more slowly indicating the remaining dependence of successive MCMC samples. Autocorrelation functions of expected hitting-times show a similar decay as the one of $t_2$.

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