REVERSIBLE MARKOV CHAIN ESTIMATION USING CONVEX-CONCAVE PROGRAMMING

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Abstract. We present a convex-concave reformulation of the reversible Markov chain estimation problem and outline an efficient numerical scheme for the solution of the resulting problem based on a primal-dual interior point method for monotone variational inequalities. Extensions to situations in which information about the stationary vector is available can also be solved via the convex-concave reformulation. The method can be generalized and applied to the discrete transition matrix reweighting analysis method to perform inference from independent chains with specified couplings between the stationary probabilities. The proposed approach offers a significant speed-up compared to a fixed-point iteration for a number of relevant applications.

Key words. Markov chain estimation, Reversible Markov chain, Convex-concave program

AMS subject classifications. 62M05, 65K15, 62F30, 62P10

1. Introduction. The study of reversible Markov chains is a recurrent theme in probability theory with many important applications, [1, 13, 20]. Surprisingly, statistical inference for reversible Markov chains has been studied only recently. The reversible maximum likelihood estimation (MLE) problem was previously discussed in [3, 18, 22]. [2, 9, 14, 16, 22] study the the posterior ensemble of reversible stochastic matrices and discuss algorithms for Bayesian posterior inference. For a given stochastic matrix the best approximation which is reversible with respect to a given stationary vector was found in [15].

Maximum likelihood estimation and posterior inference of reversible stochastic matrices have important applications in the context of Markov state models [4]. Markov state models are simplified kinetic models for the complex dynamics of biomolecules. Transition probabilities between relevant molecular conformations are estimated from simulation data. The estimated transition matrix is then used to compute quantities of interest and to extract a simplified picture of the kinetic pathways present in the dynamics. In [21] it is shown that a significant speed-up in the estimation of rare events is possible if additional information about the stationary vector is incorporated via a detailed balance constraint.

The reversible MLE problem was previously solved using a self consistent iteration method which can require a large number of iterations to converge [3, 18, 22]. Here we outline an efficient numerical algorithm for solving the reversible MLE problem via a convex-concave reformulation of the problem based on a duality argument from [23]. Convex-concave programs cannot be solved by standard nonlinear programming approaches which aim to minimize some objective subject to constrains. They can be treated as finite dimensional monotone variational inequalities and they can be solved using the primal-dual interior-point outlined in [19].

The reversible MLE problem is a nonlinear programming problem with a convex objective and non-convex constraints. The number of unknowns in the problem is quadratic in the number of states of the chain. The dual problem has only linear constraints and the number of unknowns grows linearly with the number of states of

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the chain. The reformulation can also be applied in order to solve a number of related MLE problems arising if additional information about the chain is available *a priori*. A broader class of interesting MLE problems for reversible Markov chains can thus be solved.

In [23, 24] the reversible MLE problem has been extended to the discrete transition matrix reweighting analysis method (dTRAM). For dTRAM, simulation data at multiple biasing conditions, also called thermodynamic states, is collected in order to efficiently estimate the stationary vector at the unbiased condition. A positive reweighting transformation relates each stationary vector at a biased condition to the stationary vector at the unbiased condition. This coupling between unbiased and biased condition makes it possible to combine the information from all ensembles into the desired estimate for the unbiased situation.

The dTRAM problem was previously solved through an application of a self consistent iteration procedure to the dual reformulation [23]. This approach can require a large number of iterations to converge. We show that the convex-concave reformulation of the reversible MLE problem can be extended to also cover the dTRAM problem. The resulting convex-concave program can be solved using the algorithm outlined in [19]. The large linear systems arising during the computation of the search direction can be efficiently solved using a Schur complement approach similar to the one outlined in [11, 25]. The resulting algorithm achieves a significant speed-up compared to the self consistent iteration.

2. Markov chain estimation. A Markov chain on a finite state space is completely characterized by a square matrix of conditional probabilities, $P = (p_{ij}) \in \mathbb{R}^{n\times n}$. The entry p_{ij} is the probability for the chain to make a transition to state j given that it currently resides in state i. The matrix P is stochastic, i.e. $\sum_j p_{ij} = 1$ for all i. If P is irreducible then there exists a unique vector, $\pi = (\pi_i) \in \mathbb{R}^n$, of positive probabilities such that π is invariant under the action of P, $\pi^T P = \pi^T$. The vector π is called the stationary vector of the chain.

If there is a vector, π, of probabilities for which P fulfills the following detailed balance condition,

$$\pi_i p_{ij} = \pi_j p_{ji} \tag{2.1}$$

then the chain is a reversible Markov chain with stationary vector π, [12].

In Markov chain estimation one is interested in finding an optimal transition matrix estimate P from a given finite observation $X = \{X_0, X_1, \ldots, X_N\}$ of a Markov chain with unknown transition matrix. The matrix of transition counts $C = (c_{ij})$ together with the initial state $X_0 = x_0$ is a minimal sufficient statistics for the transition matrix [8]. The element c_{ij} denotes the observed number of transitions between state i and state j in X. The matrix P is optimal if it maximizes the following log-likelihood

$$L(C|P) = \sum_{i,j} c_{ij} \log p_{ij}. \tag{2.2}$$

For finite ensembles consisting of finite length observations one can simply add the matrices of transition counts for each observation. The accumulated counts together with the empirical measure of the initial states is then a sufficient statistics for the finite ensemble of observations.

For reversible Markov chain estimation one constrains the general Markov chain MLE problem to the set of all stochastic matrices for which detailed balance with

respect to some vector of probabilities holds. Thus we can find the reversible MLE transition matrix from the following nonlinear program,

$$\begin{aligned} \min_{\pi,P} \quad & -\sum_{i,j} c_{ij} \log p_{ij} \\ \text{subject to} \quad & p_{ij} \geq 0,\ \sum_j p_{ij} = 1,\ \pi_i > 0,\ \sum_i \pi_i = 1,\ \pi_i p_{ij} = \pi_j p_{ji}. \end{aligned} \tag{2.3}$$

In [23, 24] problem (2.3) has been extended to the discrete transition matrix reweighting analysis method (dTRAM). For dTRAM, simulation data at multiple thermodynamic states $\alpha = 0, \ldots, M$ is collected in order to efficiently estimate the stationary vector at the unbiased condition, $\alpha = 0$. A positive reweighting transformation relates the stationary vector at the biased condition, $\alpha > 0$, to the stationary vector at the unbiased condition,

$$\pi_i^{(\alpha)} = U_i^{(\alpha)} \pi_i^{(0)} = \exp(u_i^{(\alpha)}) \pi_i^{(0)}. \tag{2.4}$$

This coupling allows us to combine the information from all ensembles into the estimate for $\pi^{(0)}$.

The dTRAM problem consists of reversible MLE problems for each thermodynamic state coupled via the reweighting transformation (2.4). The desired stationary vector can be obtained as the optimal point of the following nonlinear program,

$$\begin{aligned} \min_{\pi^{(\alpha)},P^{(\alpha)}} \quad & -\sum_{\alpha} \sum_{i,j} c_{ij}^{(\alpha)} \log p_{ij}^{(\alpha)} \\ \text{subject to} \quad & p_{ij}^{(\alpha)} \geq 0,\ \sum_j p_{ij}^{(\alpha)} = 1,\ \pi_i^{(\alpha)} > 0,\ \sum_i \pi_i^{(\alpha)} = 1, \\ & \pi_i^{(\alpha)} p_{ij}^{(\alpha)} = \pi_j^{(\alpha)} p_{ji}^{(\alpha)},\ \pi_i^{(\alpha)} = U_i^{(\alpha)} \pi_i^{(0)}. \end{aligned} \tag{2.5}$$

We show that the convex-concave reformulation of the reversible MLE problem can be extended to derive an efficient numerical algorithm for the solution of the dTRAM problem. Additional structure in the linear systems arising during the primal-dual iteration can be used so that the problem can be solved efficiently for many coupled chains.

3. Dual of the reversible MLE problem. In [23] a duality argument was used to show that finding the MLE of (2.3) for given positive weights π_i is equivalent to the following concave maximization problem,

$$\begin{aligned} \max_{x} \quad & \sum_{i,j} c_{ij} \log(\pi_i x_j + \pi_j x_i) - \sum_{i,j} c_{ij} \log \pi_j - \sum_i x_i \\ \text{subject to} \quad & x_i \geq 0. \end{aligned} \tag{3.1}$$

The x_i correspond to the Lagrange multipliers for the row normalization constraint in the primal problem (2.3). The optimal transition probabilities can be recovered according to

$$p_{ij}^* = \frac{(c_{ij} + c_{ji})\pi_j}{\pi_i x_j^* + \pi_j x_i^*}, \quad j \neq i. \tag{3.2}$$

The vector x^* denotes the optimal point of (3.1) and the diagonal entries p_{ii}^* are determined by the row normalization condition. It is clear that p_{ij}^* is a proper probability

irrespective of the normalization of the weights since any scaling of π_i cancels out in (3.2).

In [23] the inequality constraints on x_i were not made explicit. The non-negativity requirement can be seen from the following splitting of the Lagrangian L_π in [23],

$$\begin{aligned} L_\pi(P,\lambda,\nu) = &- \sum_{i,j\in I} c_{ij}\log p_{ij} + \sum_{i,j\in I}(\pi_i(\lambda_{ij}-\lambda_{ji})+x_i)p_{ij} \\ &+ \sum_{i,j\notin I}(\pi_i(\lambda_{ij}-\lambda_{ji})+x_i)p_{ij} - \sum_i x_i \end{aligned} \tag{3.3}$$

with index set $I = \{(i,j)|c_{ij} > 0\}$ and the constraint $p_{ij} \geq 0$. The value $\min_x L_\pi$ is not bounded from below if $\pi_i(\lambda_{ij}-\lambda_{ji})+x_i < 0$ for some $(i,j) \notin I$. Therefore $x_i \geq 0$ for all $(i,i) \notin I$. It is also not bounded from below if $\pi_i(\lambda_{ij}-\lambda_{ji})+x_i \leq 0$ for some $(i,j) \in I$, so that $x_i > 0$ for all $(i,i) \in I$,

Using the dual function from [23] the reformulation of the reversible MLE problem, (2.3), as a saddle-point problem with constraints is

$$\begin{aligned} \min_\pi \max_x \quad & \sum_{i,j} c_{ij}\log(\pi_i x_j + \pi_j x_i) - \sum_{i,j} c_{ij}\log\pi_j - \sum_i x_i \\ \text{subject to} \quad & x_i \geq 0,\ \ \pi_i > 0,\ \ \sum_i \pi_i = 1. \end{aligned} \tag{3.4}$$

is concave in x but non-convex in π. The problem can however be easily cast into a convex-concave form by the following change of variables,

$$\pi_i \propto e^{y_i}, \tag{3.5}$$

and by replacing the normalization condition with the simpler constraint

$$y_1 = 0. \tag{3.6}$$

The constraint in (3.6) removes the invariance of the objective in (3) with respect to a constant shift of y. Proper stationary probabilities π_i can be obtained from the new variables y_i according to (3.5) followed by straightforward normalization. The variable y_i is the negative free energy of the state i.

The final form of the dual reversible MLE problem is

$$\begin{aligned} \max_y \min_x \quad & -\sum_{i,j} c_{ij}\log\left(x_i e^{y_j} + x_j e^{y_i}\right) + \sum_i x_i + \sum_{i,j} c_{ij} y_j \\ \text{subject to} \quad & x_i \geq 0,\ \ y_1 = 0. \end{aligned} \tag{3.7}$$

The objective in (3.7) is convex in x and concave in y. The feasible set is convex so that (3.7) is a convex-concave program.

For a given state space with n states the original reversible MLE problem (2.3), a non-convex constrained minimization problem in $\mathcal{O}(n^2)$ unknowns, is reduced to a convex-concave programming problem in $\mathcal{O}(n)$ unknowns with simple constraints.

3.1. Scaling. We observe that the number of iterations needed for the solution of (3.7) using the algorithm from [19] can be drastically reduced by scaling the count-matrix by a constant factor γ chosen as

$$\gamma = \left(\max_{i,j} c_{ij}\right)^{-1}. \tag{3.8}$$

With scaled entries $\tilde{c}_{ij} = \gamma c_{ij}$ and scaled variables $\tilde{x} = \gamma x$, $\tilde{y} = y$ we have

$$\tilde{f}_0(\tilde{x}, \tilde{y}) = \gamma f_0(x, y) + \text{const.} \tag{3.9}$$

The constraints in (3.7) are invariant under the scaling so that the optimal point for (3.7) can be obtained from the optimal solution to the scaled problem.

The resulting stationary probabilities as well as the transition probabilities are invariant under the scaling,

$$\tilde{p}_{ij} = \frac{(\tilde{c}_{ij} + \tilde{c}_{ji})e^{\tilde{y}_j}}{\tilde{x}_i e^{\tilde{y}_j} + \tilde{x}_j e^{\tilde{y}_i}} = \frac{(c_{ij} + c_{ji})e^{y_j}}{x_i e^{y_j} + x_j e^{y_i}} = p_{ij}. \tag{3.10}$$

3.2. Special cases and extensions. The reversible estimation problem with fixed stationary vector π

$$\begin{aligned} \min_{P} \quad & -\sum_{i,j} c_{ij} \log p_{ij} \\ \text{subject to} \quad & p_{ij} \geq 0, \ \sum_j p_{ij} = 1, \ \ \pi_i p_{ij} = \pi_j p_{ji} \end{aligned} \tag{3.11}$$

is a convex problem and can efficiently be solved in its dual formulation (3.1) using an interior-point method for convex programming problems.

The reversible estimation problem with partial information about the stationary vector

$$\begin{aligned} \min_{\pi,P} \quad & -\sum_{i,j} c_{ij} \log p_{ij} \\ \text{subject to} \quad & p_{ij} \geq 0, \ \sum_j p_{ij} = 1, \ \ \pi_i > 0, \ \sum_i \pi_i = 1, \\ & \pi_i p_{ij} = \pi_j p_{ji}, \ \ \pi_i = \nu_i \ \ i \in I, \end{aligned} \tag{3.12}$$

with $I \subsetneq \{1, \ldots, n\}$ and given positive weights $(\nu_i)_{i \in I}$ can be solved via its dual

$$\begin{aligned} \max_{y} \min_{x} \quad & -\sum_{i,j} c_{ij} \log (x_i e^{y_j} + x_j e^{y_i}) + \sum_i x_i + \sum_{i,j} c_{ij} y_j \\ \text{subject to} \quad & x_i \geq 0, \ \ y_i = \log \nu_i \ \ i \in I. \end{aligned} \tag{3.13}$$

The reversible estimation problem with bound-constrained information about the stationary vector

$$\begin{aligned} \min_{\pi,P} \quad & -\sum_{i,j} c_{ij} \log p_{ij} \\ \text{subject to} \quad & p_{ij} \geq 0, \ \sum_j p_{ij} = 1, \ \ \pi_i > 0, \ \sum_i \pi_i = 1, \\ & \pi_i p_{ij} = \pi_j p_{ji}, \ \ \eta_i \leq \pi_i \leq \xi_i \ \ i \in I. \end{aligned} \tag{3.14}$$

with $I \subseteq \{1, \ldots, n\}$ and given positive bounds $(\eta_i)_{i \in I}$, $(\xi_i)_{i \in I}$ can be solved via the dual

$$\begin{aligned} \max_{y} \min_{x} \quad & -\sum_{i,j} c_{ij} \log (x_i e^{y_j} + x_j e^{y_i}) + \sum_i x_i + \sum_{i,j} c_{ij} y_j \\ \text{subject to} \quad & x_i \geq 0, \ \ \log \eta_i \leq y_i \leq \log \xi_i \ \ i \in I. \end{aligned} \tag{3.15}$$

The two problems (3.13), (3.15) are convex-concave programming problems. Nonlinear, convex inequality and linear equality constraints possibly coupling x and y can also be treated within the algorithmic framework of [19]. A special case with possible interest for applications are bound constraints on the integrated stationary weights on subsets $S \subseteq \{1, \ldots, n\}$,

$$\sum_{i \in S} \pi_i \leq \nu. \tag{3.16}$$

Equation (3.16) can be expressed in terms of variables y_i as

$$\log \sum_{i \in S} e^{y_i} \leq \log \nu_k, \tag{3.17}$$

The logarithm of a sum of exponentials is a convex function, [5].

3.3. dTRAM. We can apply the duality argument to each thermodynamic state in (2.5) and introduce the coupling between different ensembles, (2.4), through linear equality constraints. The resulting convex-concave programming problem is

$$\begin{aligned} \max_{y^{(\alpha)}} \quad \min_{x^{(\alpha)}} \quad & -\sum_{\alpha} \sum_{i,j} c_{ij} \log \left(x_i^{(\alpha)} e^{y_j^{(\alpha)}} + x_j^{(\alpha)} e^{y_i^{(\alpha)}} \right) + \sum_i x_i^{(\alpha)} + \sum_{i,j} c_{ij} y_j^{(\alpha)} \\ \text{subject to} \quad & x_i^{(\alpha)} \geq 0, \;\; y_i^{(\alpha)} - y_i^{(0)} = u_i^{(\alpha)}, \;\; y_1^{(0)} = 0. \end{aligned} \tag{3.18}$$

The number of iterations required to solve the dTRAM problem is also greatly reduced by scaling each count-matrix according to

$$\tilde{c}_{ij}^{(\alpha)} = \gamma c_{ij}^{(\alpha)} \tag{3.19}$$

with

$$\gamma = \max_{\alpha,i,j} c_{ij}^{(\alpha)} \tag{3.20}$$

As for the reversible MLE problem a larger class of related dTRAM problems can be solved by augmenting the dual problem (3.18) with convex constraints, e.g. dTRAM with partial or bound constrained information about the unbiased stationary vector. It must be ensured that the additional constraints on the biased stationary probabilities do not result in an infeasible problem, i.e. the reweighting condition (2.4) and the constraints cannot be fulfilled simultaneously.

4. Convex-concave programs and variational inequalities. A convex-concave program is the following saddle point problem,

$$\begin{aligned} \max_y \min_x \quad & f(x, y) \\ \text{subject to} \quad & (x, y) \in \mathcal{K} \end{aligned} \tag{4.1}$$

with f convex in x, concave in y, and $\mathcal{K} \subseteq \mathbb{R}^n$ a convex set.

Convex-concave programs can be treated as special cases of finite-dimensional variational inequality (VI) problems, [10]: For a given feasible set $\mathcal{K} \subseteq \mathbb{R}^n$ and a mapping $\Phi : \mathcal{K} \to \mathbb{R}^n$ find a point $z^* \in \mathcal{K}$ such that

$$(z - z^*)^T \Phi(z^*) \geq 0 \quad \forall z \in \mathcal{K}. \tag{4.2}$$

Any point z^* satisfying (4.2) is a solution or optimal point for the VI. The convex-concave program is cast into the VI-form by defining

$$\Phi(z) = \begin{pmatrix} \nabla_x f(x,y) \\ -\nabla_y f(x,y) \end{pmatrix}, \quad z = (x,y). \tag{4.3}$$

A mapping Φ is said to be monotone if

$$(z' - z)^T(\Phi(z') - \Phi(z)) \geq 0 \quad \forall z', z \in \mathcal{K}. \tag{4.4}$$

Monotonicity of (4.3) follows from the convex-concave property of f.

If $\mathcal{K}$ is a convex polyhedral set, i.e. solely defined in terms of linear equalities and inequalities,

$$\mathcal{K} = \{z \in \mathbb{R}^n | Az - b = 0,\ Gz - h \leq 0\}, \tag{4.5}$$

then z solves the VI (4.2) if and only if there are vectors λ, ν, s, such that the following KKT-conditions are fulfilled [10],

$$\begin{aligned} \Phi(z) + A^T\nu + G^T\lambda &= 0 \\ Az - b &= 0 \\ Gz - h + s &= 0 \\ \lambda^T s &= 0 \\ \lambda, s &\geq 0 \end{aligned} \tag{4.6}$$

The vectors λ and ν are dual variables associated with the inequality and equality constraints. The vector of slack variables, $s = (h - Gz)$, transforms the linear inequality constraints for z into simple non-negativity constraints for s. Optimality conditions for convex $\mathcal{K}$ in standard form, i.e. defined by a finite number of linear equalities and convex inequalities, are also available, cf. [10].

A direct application of a Newton type method to (4.6) ensuring positivity of λ and s is usually unsuccessful since the solution progress rapidly stagnates once the iterates approach the boundary of the feasible set.

A possible strategy to circumvent this problem is numerical path-following. Instead of attempting a direct solution of (4.6) path-following proceeds by solving a sequence of problems with perturbed complementarity condition,

$$\begin{aligned} \Phi(z) + A^T\nu + G^T\lambda &= 0 \\ Az - b &= 0 \\ Gz - h + s &= 0 \\ \lambda^T s &= \mu \\ \lambda, s &\geq 0 \end{aligned} \tag{4.7}$$

tracing the central path of solutions $z^*(\mu)$ towards $z^*(0)$ with $\mu \to 0^+$. Perturbing the complementarity condition ensures that the boundary of the feasible set is not reached prematurely and the iteration makes good progress along the computed search direction.

Interior-point methods ensure the positivity of λ and s at each step of the iteration. If in addition a strictly feasible starting point $Az^{(0)} - b = 0$, $Gz^{(0)} - h + s^{(0)} = 0$

is used then all iterates produced by the algorithm lie in the interior of the feasible region.

Progress towards a solution of the perturbed KKT-conditions (4.7) is usually made by taking steps along the Newton direction computed from the following linear system,

$$\begin{pmatrix} D\Phi(z) & A^T & G^T & 0 \\ A & 0 & 0 & 0 \\ G & 0 & 0 & I \\ 0 & 0 & S & \Lambda \end{pmatrix} \begin{pmatrix} \Delta z \\ \Delta\nu \\ \Delta\lambda \\ \Delta s \end{pmatrix} = - \begin{pmatrix} \Phi(z) + A^T\nu + G^T\lambda \\ Az - b \\ Gz - h + s \\ S\Lambda\mathbf{e} - \mu\mathbf{e} \end{pmatrix}, \tag{4.8}$$

with diagonal matrices $S = \mathrm{diag}(s_1, s_2, \dots)$, $\Lambda = \mathrm{diag}(\lambda_1, \lambda_2, \dots)$, the vector $\mathbf{e} = (1, 1, \dots)$, and the perturbation parameter $\mu > 0$.

We use the following short-hand notation for the dual residuum,

$$r_d = \Phi(z) + A^T\nu + G^T\lambda, \tag{4.9}$$

the primal residuals,

$$\begin{aligned} r_{p,1} &= Az - b, \\ r_{p,2} &= Gz - h + s, \end{aligned} \tag{4.10}$$

and the perturbed complementary slackness,

$$r_c(\mu) = S\Lambda\mathbf{e} - \mu\mathbf{e}. \tag{4.11}$$

Solving the linear system (4.8) is the most expensive part of the algorithm. The sparse block structure of (4.8) can be used to significantly speed up the solution process. Elimination of Δs and $\Delta\lambda$ reduces (4.8) to the *augmented system*

$$\begin{pmatrix} H & A^T \\ A & 0 \end{pmatrix} \begin{pmatrix} \Delta z \\ \Delta\nu \end{pmatrix} = - \begin{pmatrix} r_d + G^T\Sigma r_{p,2} - G^T S^{-1} r_c(\mu) \\ r_{p,1} \end{pmatrix}, \tag{4.12}$$

with diagonal matrix $\Sigma = S^{-1}\Lambda$ and augmented Jacobian $H = D\Phi + G^T\Sigma G$. The increments $\Delta\lambda$ and Δs can be computed from Δz,

$$\begin{aligned} \Delta s &= -r_{p,2} - G\Delta z \\ \Delta\lambda &= -\Sigma\Delta s - S^{-1} r_c(\mu). \end{aligned} \tag{4.13}$$

For nonsingular H further elimination of Δz from (4.12) is possible. The resulting *normal equations* for $\Delta\nu$ are,

$$S\Delta\nu = r_2 - AH^{-1}r_1. \tag{4.14}$$

The vectors r_i are the two components of the RHS of (4.12) and the matrix $S = \left(AH^{-1}A^T\right)$ is the Schur complement of H. The increment Δz can then be computed according to

$$\Delta z = -H^{-1}(r_1 + A^T\Delta\nu). \tag{4.15}$$

A singular matrix H can for example occur for an equality-constrained convex programming problem for which the objective is not strictly convex. Even if the

constraints ensure that the problem has a unique solution, H will be singular so that the normal equations can not be formed.

For convex programming problems a non-singular H can be efficiently factorized using a symmetric positive-definite Cholesky factorization. In the convex-concave case the Jacobian of the mapping Φ is not symmetric,

$$D\Phi(z) = \begin{pmatrix} \nabla_x \nabla_x f(x,y) & \nabla_y \nabla_x f(x,y)^T \\ -\nabla_y \nabla_x f(x,y) & -\nabla_y \nabla_y f(x,y) \end{pmatrix}. \tag{4.16}$$

In that case the augmented system is not symmetric and the Cholesky factorization can not be used.

A further speed-up in the computation of the Newton direction can be achieved through the exploitation of sparse or block-sparse structure possibly present in $D\Phi$, G, A. In this situation solution via an iterative method can be particularly efficient if a good preconditioner is available.

5. Implementation details. In order to apply the algorithm in [19] to the reversible MLE problem (3.7) we transform the convex-concave program into the VI form using the mapping $\Phi = (\nabla_x f, -\nabla_y f)$ in (4.3). The gradient of the objective in (3.7) is given by

$$\begin{aligned} \partial_{x_k} f &= -\sum_j \frac{(c_{kj} + c_{jk}) e^{y_j}}{x_k e^{y_j} + x_j e^{y_k}} + 1 \\ \partial_{y_k} f &= -\sum_j \frac{(c_{kj} + c_{jk}) x_j e^{y_k}}{x_k e^{y_j} + x_j e^{y_k}} + \sum_i c_{ik}. \end{aligned} \tag{5.1}$$

For the computation of the Newton direction we also need the Jacobian $D\Phi$. The diagonal blocks are given by

$$\begin{aligned} \partial_{x_k} \partial_{x_l} f &= \sum_j \frac{(c_{kj} + c_{jk}) e^{y_j} e^{y_j}}{(x_k e^{y_j} + x_j e^{y_k})^2} \delta_{k,l} + \frac{(c_{kl} + c_{lk}) e^{y_k} e^{y_l}}{(x_k e^{y_l} + x_l e^{y_k})^2}, \\ \partial_{y_k} \partial_{y_l} f &= -\sum_j \frac{(c_{kj} + c_{jk}) x_k e^{y_j} x_j e^{y_k}}{(x_k e^{y_j} + x_j e^{y_k})^2} \delta_{k,l} + \frac{(c_{kl} + c_{lk}) x_k e^{y_l} x_l e^{y_k}}{(x_k e^{y_l} + x_l e^{y_k})^2}, \end{aligned} \tag{5.2}$$

and off-diagonal blocks are given by

$$\begin{aligned} \partial_{y_k} \partial x_l f &= \sum_j \frac{(c_{kj} + c_{jk}) e^{y_k} x_j e^{y_j}}{(x_k e^{y_j} + x_j e^{y_k})^2} \delta_{k,l} - \frac{(c_{kl} + c_{lk}) x_k e^{y_k} e^{y_l}}{(x_k e^{y_l} + x_l e^{y_k})^2}, \\ \partial_{x_k} \partial_{y_l} f &= \partial_{y_l} \partial x_k f. \end{aligned} \tag{5.3}$$

It is straightforward to encode the equality and inequality constraints in (3.7) into matrices A, G and vectors b, h.

$$A = (\underbrace{0, \ldots, 0}_{n}, \underbrace{1, 0, \ldots, 0}_{n}), \tag{5.4}$$

$$b = 0, \tag{5.5}$$

$$G = (-I_n, 0_n), \tag{5.6}$$

$$h = (0, \ldots, 0)^T \tag{5.7}$$

with I_n the identity and 0_n the zero matrix in $\mathbb{R}^{n\times n}$.

The Jacobian $D\Phi$ is singular because of the invariance of the objective f under a constant shift of y; this is also true for the augmented Jacobian H since the inequalities act only on x. Therefore the normal equations (4.14) cannot be formed and the search direction has to be computed from the augmented system (4.12).

The blocks of $D\Phi$ have the same sparsity pattern as the matrix $C_s = C + C^T$. This matrix is usually sparse. The augmented Jacobian differs from the original Jacobian only on the diagonal so that it is also sparse in a situation in which C_s is sparse. The equality constraints for the reversible MLE problem do only affect the y variables, i.e. $A = (0, A_y)$. The augmented system, (4.12), can be cast into the following symmetric form,

$$\begin{pmatrix} H_{xx} & H_{yx} & 0 \\ H_{yx}^T & -H_{yy} & -A_y^T \\ 0 & -A_y & 0 \end{pmatrix} \begin{pmatrix} \Delta x \\ \Delta y \\ \Delta \nu \end{pmatrix} = \begin{pmatrix} b_x \\ -b_y \\ -b_\nu \end{pmatrix}. \tag{5.8}$$

The augmented system matrix, W, on the left-hand side of (5.8) is indefinite so that a symmetric indefinite factorization, [6], or the minimum residual (MINRES) method, [17], can be used to solve (5.8). If an iterative method is used, a suitable preconditioner needs to remove the ill-conditioning due to the $\Sigma = S^{-1}\Lambda$ term in H. MINRES requires a positive definite preconditioner. We use a positive definite diagonal preconditioning matrix, T, with diagonal entries,

$$t_{ii} = \begin{cases} |w_{ii}| & \text{if } |w_{ii}| > 0 \\ 1 & \text{else} \end{cases}. \tag{5.9}$$

5.1. dTRAM. We can also apply the primal-dual interior-point method to the convex-concave reformulation of the dTRAM problem, (3.18). The dTRAM problem consists of a reversible MLE problem for each thermodynamic state coupled via an equality constraint. The resulting VI-mapping for dTRAM is given by the vector

$$\Phi = (\Phi_0, \ldots, \Phi_m).$$

The entry Φ_α is the mapping for the reversible MLE problem at thermodynamic state α. Since Φ_α depends only on variables $(x^{(\alpha)}, y^{(\alpha)})$ the Jacobian of Φ_α has a block-diagonal structure

$$D\Phi = \begin{pmatrix} D\Phi_0 & & \\ & \ddots & \\ & & D\Phi_m \end{pmatrix}$$

The matrix $D\Phi_\alpha$ is the mapping for the reversible MLE problem at thermodynamic state α. The linear inequality constraints at different α are decoupled so that G is also block diagonal,

$$G = \begin{pmatrix} G_0 & & \\ & \ddots & \\ & & G_m \end{pmatrix}.$$

The block $G^{(\alpha)}$ is the matrix of inequality constraints at thermodynamic state α,

$$G_\alpha = (-I_n, 0_n)\,,$$

and $h = 0$ is the corresponding RHS. The matrix for the equality constraints has the following form,

$$A = \begin{pmatrix} A_0 & 0 & \dots & 0 \\ A_{1,0} & A_1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ A_{m,0} & 0 & \dots & A_m \end{pmatrix}$$

with $A_0 = (0, \dots, 0, 1, \dots, 0)$ the constraint matrix for the unbiased ensemble, $\alpha = 0$, and $A_\alpha = (0_n, I_n)$ the constraint matrix at condition $\alpha \neq 0$. The matrix $A_{\alpha,0} = (0_n, -I_n)$ is the coupling matrix between biased and unbiased ensemble. The corresponding RHS is

$$b = \begin{pmatrix} b_0 \\ \vdots \\ b_m \end{pmatrix}$$

with $b_0 = 0$, and $b_\alpha = (u_i^{(\alpha)})$ the vector of energy differences with respect to the unbiased condition.

The block-diagonal form of $D\Phi$ and G can be exploited for the solution of the augmented system. The block diagonal structure of $D\Phi$ and G implies a block diagonal structure for H,

$$H = \begin{pmatrix} H_1 & & \\ & \ddots & \\ & & H_m, \end{pmatrix}. \tag{5.10}$$

The block $H_\alpha = D\Phi_\alpha + G_\alpha^T \Sigma_\alpha G_\alpha$ is the augmented Jacobian at thermodynamic state α. Using the block structure of H and A, the augmented system (4.12) can be reordered resulting in the following linear system,

$$\begin{pmatrix} W_0 & B_{1,0}^T & \dots & B_{m,0}^T \\ B_{1,0} & W_1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ B_{m,0} & 0 & \dots & W_m \end{pmatrix} \begin{pmatrix} \Delta\xi_0 \\ \Delta\xi_1 \\ \vdots \\ \Delta\xi_m \end{pmatrix} = - \begin{pmatrix} \tilde{b}_0 \\ \tilde{b}_1 \\ \vdots \\ \tilde{b}_m \end{pmatrix} \tag{5.11}$$

The augmented system matrix at condition α is

$$W_\alpha = \begin{pmatrix} H_\alpha & A_\alpha^T \\ A_\alpha & 0 \end{pmatrix}. \tag{5.12}$$

The coupling between the biased condition and the unbiased condition is encoded in the matrix

$$B_{\alpha,0} = \begin{pmatrix} 0 & 0 \\ A_{\alpha,0} & 0 \end{pmatrix} \quad \alpha \neq 0. \tag{5.13}$$

The vector $\Delta\xi_\alpha = (\Delta z_\alpha, \Delta\nu_\alpha)$ is the resulting increment for the augmented system at condition α. The vector b_α in (5.11) is given by the RHS of the augmented system at condition α,

$$\tilde{b}_\alpha = \begin{pmatrix} r_d^{(\alpha)} + G_\alpha^T \Sigma_\alpha r_{p,2}^{(\alpha)} - G_\alpha^T S_\alpha^{-1} r_c^{(\alpha)}(\mu) \\ r_{p,1}^{(\alpha)} \end{pmatrix}. \tag{5.14}$$

The arrow-shaped structure of the linear system in (5.11) allows us to apply the Schur complement method, [11,25], to eliminate $\Delta\xi_1, \ldots, \Delta\xi_m$ and solve the following condensed system for $\Delta\xi_0$,

$$S\Delta\xi_0 = -\left(\tilde{b}_0 - \sum_{\alpha=1}^{m} B_{\alpha,0}^T W_\alpha^{-1} \tilde{b}_\alpha\right) \tag{5.15}$$

The Schur complement matrix is

$$S = \left(W_0 - \sum_{\alpha=1}^{m} B_{\alpha,0}^T W_\alpha^{-1} B_{\alpha,0}\right). \tag{5.16}$$

All other increments can be computed from $\Delta\xi_0$ via

$$\Delta\xi_\alpha = -W_\alpha^{-1}\left(\tilde{b}_\alpha + B_{\alpha,0}\Delta\xi_0\right) \tag{5.17}$$

For a system with n states at m thermodynamic conditions the complexity for a direct factorization of the Newton system (4.8) is $\mathcal{O}(m^3n^3)$. The Schur complement approach reduces complexity to $\mathcal{O}(mn^3)$. In addition, assembly of the Schur complement in (5.16) and solution of (5.17) can be easily paralellized.

As for the reversible MLE case, the blocks of $D\Phi_\alpha$ have the same sparsity pattern as the matrix $C_s^{(\alpha)} = C^{(\alpha)} + C^{(\alpha)T}$. The same is true for the augmented Jacobian H_α except for the diagonal. Since $C_s^{(\alpha)}$ is usually sparse we use a sparse LU method to factor the augmented system matrices W_α for $\alpha > 0$. The direct assembly of the Schur complement in (5.16) is expensive since the computation of $W_\alpha^{-1}B_{\alpha,0}$ requires $\mathcal{O}(n)$ solves.

If an iterative method is used to solve the condensed system (5.15) one would like to avoid assembly of the Schur complement S in (5.16) all together. Instead only few matrix-vector products involving S should be computed. As for the reversible MLE case, we can transform the condensed system into a symmetric indefinite form and use MINRES to obtain a solution. Obtaining a good preconditioner without explicit assembly of S is difficult. We use the probing method outlined in [7] to obtain an approximation of the diagonal of S using only few matrix-vector products. We then construct a positive definite diagonal preconditioning matrix T with entries

$$t_{ii} = \begin{cases} |\tilde{s}_{ii}| & \text{if } |\tilde{s}_{ii}| > 0 \\ 1 & \text{else} \end{cases}.$$

The entry $\tilde{s}_{ii}$ denotes the diagonal entry estimated by the probing approach.

The Schur complement based solution can also be applied to the dTRAM problem with additional constraints whenever those constraints do not couple different biasing conditions.

TABLE 1

Reversible MLE problem. Newton-IP algorithm vs. SC-iteration. We report the number of states N, the growth factor for states N/n (n is the number of states in the previous row), the total algorithm run time T (in seconds), the growth factor for run time T/t (t is the run time in the previous row), the scaling exponent for run time with increasing number of states p, ($T \propto N^p$), and the speedup of the Newton-IP method over the SC-iteration SC/IP. The scaling is subquadratic for both methods. The Newton-IP algorithm achieves a significant speed-up over the SC-iteration for all examples except the pentapeptide.

System	N	N/n	Newton-IP			SC-iteration			SC/IP
			T	T/t	p	T	T/t	p	
Three-well	361		1.1			4.6			4.0
	2134	5.9	7.3	6.4	1.0	75.1	16.2	1.6	10.2
	8190	3.8	56.8	7.7	1.5	400.3	5.3	1.2	7.0
	29618	3.6	286.8	5.0	1.3	1076.9	2.7	0.8	3.8
Alanine	292		0.7			4.2			6.3
	1059	3.6	4.2	6.4	1.4	32.3	7.8	1.6	7.6
	3835	3.6	32.2	7.6	1.6	214.0	6.6	1.5	6.6
	5826	1.5	61.8	1.9	1.6	347.7	1.6	1.2	5.6
Pentapeptide	250		0.6			0.2			0.4
	500	2.0	1.2	1.9	0.9	0.6	2.4	1.3	0.5
	1000	2.0	3.6	3.0	1.6	1.0	1.8	0.9	0.3
	2000	2.0	5.4	1.5	0.6	1.3	1.3	0.4	0.2
Birth death	100		1.0			10.4			10.6
	200	2.0	2.1	2.1	1.1	34.1	3.3	1.7	16.3
	500	2.5	5.8	2.8	1.1	185.3	5.4	1.8	31.7
	1000	2.0	13.9	2.4	1.3	338.7	1.8	0.9	24.3

6. Results. Below we report results for the primal-dual interior-point (Newton-IP) and the self consistent iteration (SC-iteration) approach to solving the reversible MLE and dTRAM problem. We compare the efficiency of both algorithms for a number of examples. Using iterative methods for the solution of the linear systems arising in the Newton-IP approach we achieve a similar scaling behavior as for the SC-iteration. We demonstrate that the Newton-IP approach offers a significant speedup for nearly all examples.

6.1. Reversible MLE. In Table 1 we compare the performance of the algorithm for different example data-sets. The count matrix was estimated from the full data set using the sliding-window method [18]. The tolerance indicating convergence was $\mathrm{tol} = 10^{-12}$ for both algorithms. Both methods exhibit a subquadratic scaling in the number of states. The Newton-IP method is able to achieve a significant speed-up over the SC-iteration for all examples except for the pentapeptide data.

In Figure 1 we show the performance of both methods for the alanine dipeptide system with 361 states. For the SC-iteration the number of iterations required to converge to a given tolerance is very variable across different data sets. The total number of iterations required to converge deteriorates with increasing amount of input data. For the Newton-IP method the required number of iterations is consistent across all data sets. Both methods exhibit subquadratic scaling in the number of observed states.

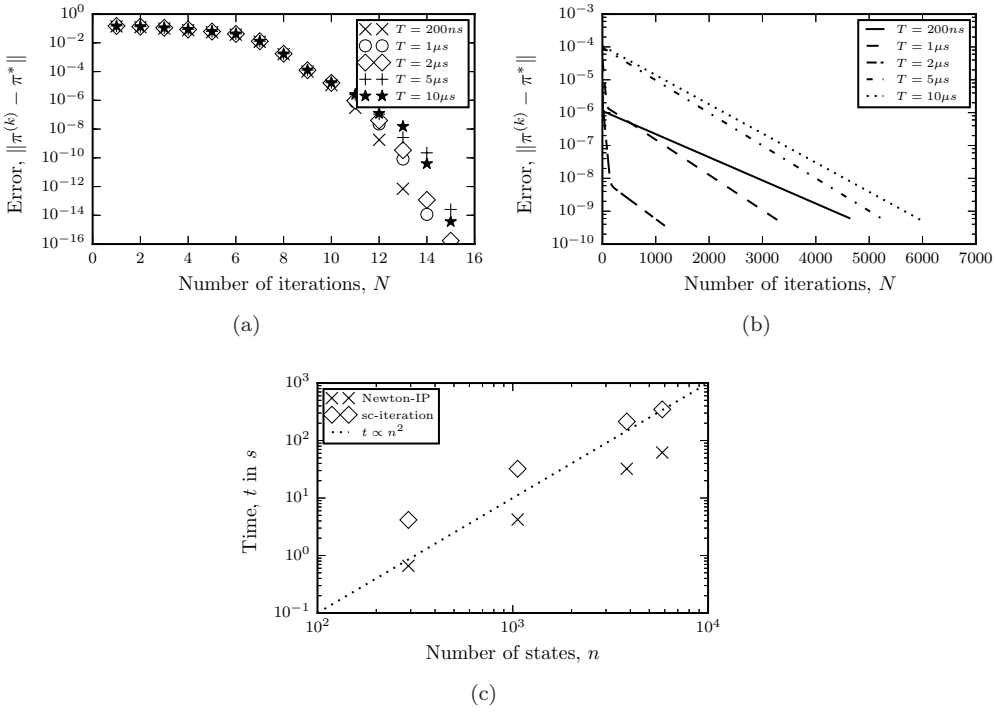


FIGURE 1. *Comparison of Newton interior-point method, a), and self-consistent iteration, b) for the alanine dipeptide example. Convergence is plotted for different data sets corresponding to different amounts of total simulation time. The vector π^* is a reference stationary distribution obtained from the converged Newton interior-point method. The Newton interior-point method converges superlinearly, the self-consistent iteration converges linearly. The number of required iterations is very sensitive to the input data set for the SC-iteration while the Newton-IP method is only mildly affected. c) Both methods exhibit a subquadratic scaling in the number of states. The Newton-IP method achieves a significant speed-up over the SC-iteration.*

6.2. dTRAM . In Table 2 we compare the performance of the Newton-IP and the SC-iteration for different examples. The count matrix was estimated from the full data set using the sliding-window method [18]. The tolerance indicating convergence was tol $= 10^{-10}$ for both algorithms. The Newton-IP method is more efficient for all three examples and achieves a dramatic speed-up (orders of magnitude). The Schur complement probing approach is successful for the alanine and the doublewell umbrella sampling example. For the multi-temperature example the Schur complement was assembled and the condensed system was solved using a direct method. For the SC-iteration method the required time to solve the multi-temperature example was very large so that computations were only carried out for two examples with a small number of states.

Both methods scale linearly in the number of thermodynamic states. The Newton-IP method with Schur complement probing scales at most quadratic in the number of states. If the Schur complement is assembled and factored by a direct method the scaling is between quadratic and cubic. The SC-iteration exhibits quadratic scaling in the number of states. The Newton-IP method achieves orders of magnitude speed-up compared to the SC-iteration for all examples.

In Figure 2 we show performance of the Newton-IP and SC-iteration for the dou-

TABLE 2

Newton-IP algorithm vs. SC-iteration for the dTRAM problem. We report the number of states N, the number of thermodynamic state M, the growth factor for states N/n (n is the number of states in the previous row), the total algorithm run time T (in seconds), the growth factor for run time T/t (t is the run time in the previous row), the scaling exponent for run time with increasing number of states p, ($T \propto N^p$), and the speedup of the Newton IP method over the SC method SC/IP. In one case we report instead the growth factor of the number of thermodynamic states M/m (m is the number of states in the previous row) and the scaling exponent for run time with increasing number of thermodynamic states ($T \propto M^p$). Both method scale linearly in the number of thermodynamic states. The Newton-IP method with Schur complement probing (alanine, doublewell with umbrella sampling) scales at most quadratic in the number of states. If the Schur complement is assembled and factored by a direct method (doublewell with independent temperature sampling) the scaling is between quadratic and cubic. The SC-iteration exhibits quadratic scaling in the number of states. The Newton-IP method achieves orders of magnitude speed-up compared to the SC-iteration for all examples.

System	N	M	N/n	Newton-IP			SC-iteration			SC/IP
				T	T/t	p	T	T/t	p	
Alanine	292	40		34.0			1263.9			37.2
	1521	40	5.2	202.4	6.0	1.1	66018.4	52.2	2.4	326.2
Doublewell, umbrella	100	20		5.1			115.5			22.7
	199	20	2.0	6.4	1.3	0.3	492.9	4.3	2.1	77.1
	497	20	2.5	17.3	2.7	1.1	3258.4	6.6	2.1	188.7
	990	20	2.0	48.3	2.8	1.5	13729.7	4.2	2.1	284.4
	1978	20	2.0	193.1	4.0	2.0	59890.5	4.4	2.1	310.1
Doublewell, umbrella	100	20		5.1			115.5			22.7
	100	40	2.0	8.3	1.6	0.7	244.5	2.1	1.1	29.3
	100	80	2.0	16.5	2.0	1.0	721.1	2.9	1.6	43.8
	100	100	1.2	20.9	1.3	1.1	1110.6	1.5	1.9	53.1
Doublewell, multi-temperature	100	16		3.7			12223.2			3285.8
	200	16	2.0	10.7	2.9	1.5	50446.2	4.1	2.0	4705.8
	500	16	2.5	79.8	7.4	2.2				
	1000	16	2.0	544.5	6.8	2.8				

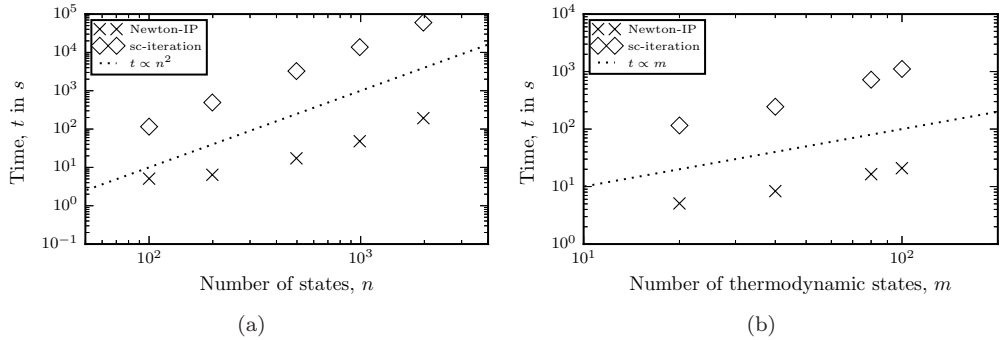
blewell umbrella-sampling example. The Newton-IP method achieves a significant speed-up (up to two orders of magnitude) over the SC-iteration.

7. Conclusion. We show that the problem of finding the maximum likelihood reversible transition matrix on a finite state space is equivalent to a convex-concave programming problem with a much smaller number of unknowns and constraints.

The primal-dual interior-point method for monotone variational inequalities outlined in [19] can be used to efficiently solve the arising convex-concave program. For a number of examples the proposed algorithm significantly speeds up the computation of the reversible MLE compared to a previously proposed fixed-point iteration.

The convex-concave reformulation makes it possible to efficiently solve a number of related problems arising in the context of reversible Markov chain estimation.

One application of special interest is statistical reweighting of data from multiple ensembles via the dTRAM method [23]. We extend the convex-concave reformulation to the dTRAM problem so that it can also be solved by a primal-dual interior-point method. We show that the arising linear systems can be efficiently solved using a



(a) (b)

FIGURE 2. *Comparison of the Newton-IP method and the SC-iteration for the dTRAM problem. We show results for the doublewell potential with harmonic umbrella forcing. a) Both methods exhibit quadratic scaling in the number of states, but the Newton method is up to two orders of magnitude faster then the sc iteration. b) Scaling is linear in the number of thermodynamic states for both methods.*

Schur complement approach. The outlined algorithm is shown to significantly speed up the solution process compared to a previously proposed fixed-point iteration.

Similar to the reversible MLE problem a number of related dTRAM problems can be solved using our method. The efficient linear solution of the arising Newton systems using the Schur-complement method can be retained no additional coupling between the different thermodynamic ensembles is introduced.

The investigation of efficient preconditioning techniques for the presented problems remains a topic for future research. Obtaining a good preconditioner for the Schur complement without direct assembly is of special interest for the dTRAM problem.

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