# The Metropolized Partial Importance Sampling MCMC mixes slowly on minimal reversal rearrangement paths

István Miklós, Bence Mélykúti, and Krister Swenson

***Abstract*— .**

***Index Terms*— Stochastic programming (G.1.6.k), Markov processes (G.3.e), Analysis of Algorithms and Problem Complexity (F.2.m) Biology and genetics (J.3.a)**

## I. Introduction

THE fact that the gene orders of genomes evolve by inversions were discovered earlier [34] than the DNA double-helix itself [37]. Although the computational problem was clearly stated already in 1941, the first study of the computational complexity of sorting by inversions was published only in the '90s [18]. The first polynomial running time algorithm was given by Hannenhalli and Pevzner [15], which has been subsequently improved [17]. The best algorithm today takes sub-quadratic time to find an optimal soring path [35], and a linear running time algorithm exists that calculates the minimal number of inversions needed to transform one genome into another (without giving a sorting path) [2].

Unfortunately, the problem does not scale well with the number of genomes: the inversion median problem – namely, finding an intermediate genome that minimizes the sum of distances from three input genomes – is known to be NP-complete [9]. Several heuristic approaches have been published on finding the optimal inversion median of three genomes, and some of them are based on considering all optimal sorting paths. Siepel introduced an algorithm for finding all sorting reversals [33], however, it solves neither the counting problem of all optimal sorting scenarios nor the problem of sampling from the uniform distribution of them.

Markov chain Monte Carlo methods [25], [16] for genome rearrangement have been introduced a few years ago, which try to explore the posterior distribution of rearrangement scenarios instead of highlighting a single optimal one. They define different models where genomes can evolve by reversals [19], [36], [20] reversals and translocations [10] or reversals, transpositions and inverted transpositions [26], [28]. The general theory of Markov chain Monte Carlo states that the Markov chain will be in the prescribed distribution after infinite number of random steps, therefore the Markov chain has to mix quickly to achive an almost unbiased distribution in a reasonable time, and hence to be applicable in practice.

We conjectured that the mixing of MCMC methods on genome rearrangement might be slow, since for a related problem we already had a negative result: we showed that sampling protocol of Ajana *et al.* [1] generates a distribution of minimal reversal sorting paths that might be very far from the uniform distribution [24].

We present a negative result in this paper: if we restrict the state space of a special type of MCMC that is used for genome rearrangement problems to the minimal reversal sorting paths, the Markov chain mixes slowly. Although it not proves, it suggests that the same Markov chain might mix slowly on larger spaces containing suboptimal solutions, too.

## II. The graph of desire and reality

The genome rearrangement problem is to transform one genome into another using a set of possible mutations. Genomes are typically described as signed permutations: numbers represent the different genes and the signes represent the reading directions of genes. It is easy to show that the signed permutations with the usual convolution of permutations form a group, and the mutations has a group act on them. Therefore, transfroming a genome $g_1$ into $g_2$ is equivalent with sorting $g_2^{-1}g_1$ into the identical permutation, $+1,\ +2,\ \ldots + n$ (assuming that mutations act from the right).

A signed permutation can be represented as a graph of desire and reliality. In this representation, the signed permutation is transformed into a double-length non-signed permutation replacing $+i$ by $2i-1,\ 2i$ and replacing $-i$ by $2i,\ 2i-1$. This unsigned permutation is framed into $0$ and $2n+1$, where $n$ is the length of the signed permuation. Vertices of the graph of desire and reality are the numbers of the unsigned permutation togather with $0$ and $2n+1$. Starting with $0$, every other vertices are connected in the unsigned permutation with a black line, and they are called *reality edges*, since they show the reality, ie. what is the neighbor of $0$, etc. Also starting with $0$, every node $2i$ and $2i+1$ are connected with a grey arc, and these grey arcs are called *desire edges*, since they show which nodes should be neighbors to get the identical permutation. Since each vertex into the graph of desire and reality has a degree of $2$, the graph falls into cycles. We can distiguish *oriented* and *unoriented* cycles. A cycle is oriented iff there are two reality edges with different directions on a traversing of the cycle, otherwise it is unoriented. Intersecting cycles are called components. A component is oriented if it contains at least one oriented cycle, otherwise it is unoriented. The Hannenhalli-Pevzner theorem says that the minimum number of reversals necessary to sort a permutation $\sigma$ that contains only oriented components is $n+1-c(\sigma)$, where $n$ is the length of the signed permutation and $c(\sigma)$ is the number of cycles. Since a reversal can increase the number of cycles at most by $1$ (see for example [33]), the theorem claims that if a permutation contains only oriented components, there is always a reversal that increases the number of cycles by $1$ and does not create an unoriented component.

## III. MCMC and Partial Importance Sampling

The Metropolis-Hastins algorithm is a general algorithm to create a Markov chain that converges to a prescribed distribution,

$\pi$. It needs a primer Markov chain that is irreducible and aperiodic on the state space $I$ and for any $x, y \in I$, $T(y|x) > 0$ implies $T(x|y) > 0$, where $T(b|a)$ is the transition probability for jumping to $b$ from $a$ in the Markov chain. The Metropolis-Hastings algorithm transforms this chain to another chain in the following two steps:

- (proposal) Draw a random $y$ from the distribution $T(\cdot|x_t)$, where $x_t$ is the state in which the chain is after step $t$.
- (acceptance) Draw a random $u$ from $U[0,1]$. Let $x_{t+1} = y$ if
$$u \leq \frac{\pi(y)T(x_t|y)}{\pi(x_t)T(y|x_t)} \tag{1}$$
and let $x_{t+1} = x_t$ otherwise.

The so obtained Markov chain $(x_t)$ will be reversible, irreducible and aperiodic, and hence, it will converge to $\pi$ since the detailed balance holds [25], [16].

Sometimes each point in the state space $I$ can be represented as a vector, and the primer Markov chain modifies $x_t$ by changing a subset of its coordinates, $w$. Let $w'$ denote the newly drawn coordinates of $y$ proposed from $x_t$. It is easy to show that the acceptance ratio in Eqn. (1) can be replaced by

$$\frac{\pi(y)T(x_t, w'|y)}{\pi(x_t)T(y, w|x_t)} \tag{2}$$

where $T(a, w|b)$ tells the probability of proposing $a$ from $b$ by choosing and modifying the coordinates $w$, without changing the equilibrium distribution, $\pi$, even if $y$ can be proposed by altering a larger set of coordinates of $x_t$ [22]. When the newly drawn coordinates in $y$ does not depend on the old coordinates $x_t$, the algorithm is called Metropolized Partial Importance Sampling.

In case of genome rearrangement, the state space is the allowed transition paths between two genomes. Such a state space can be considered as a vector space, where the coordinates of any point (transition path) are the intermediate genomes leading from one genome to the other. A Metropolized Partial Importance Sampler cuts out a subpath from the current path, which is framed by genomes $g_1$ and $g_2$ and draws a new subpath transforming $g_1$ into $g_2$. This subpath is drawn from distribution that does not depend on the cut out subpath. In published implementations, the new subpath is drawn step by step, drawing a new intermediate genome by considering the list of mutations that act on the current intermediate genome. If the allowed transition paths are the minimal reversal sorting paths, then the next intermediate genome is drawn by applying a random, uniformly distributed sorting reversal on the current intermediate genome. In the next section, we are going to prove that that this kind of MCMC might mixes slowly.

## IV. PARIS MIXES SLOWLY ON MINIMAL REVERSAL PATHS

### A. Convergence of Markov chain Monte Carlo algorithms

The Markov chain Monte Carlo methods provide an algorithm that constructs a Markov chain for any input data. Below $D$ denotes the data, and the convergence is measured as a function of the size of $D$. We would like to measure the convergence of a Markov chain on state space $I_D$ as the maximal variation distance from the equilibrium distribution after step $k$ starting in an arbitrary position $i_D$. We define

$$\tau_{i_d}(\epsilon) := \min\{k_0 : \forall k \geq k_0, d_v(P_D^k \delta_{i_D}, \pi_D) \leq \epsilon\} \tag{3}$$

where $\delta_{i_D}$ is the vector whose coordinates are the possible states of the state space $I_D$ and that contains 1 for the coordinate representing state $i$, and contains 0s for all remaining coordinates, $P_D$ is the transition probability matrix of the Markov chain and $\pi_D$ is the equilibrium distribution. We say that a Markov chain converges quickly if

$$\max_{i_D \in I_D} \tau_{i_D}(\epsilon) \tag{4}$$

is a polynomial function of both $\log(1/\epsilon)$ and $|D|$, and the Markov chain converges slowly if there exist an $\epsilon$ such that for all $l \in \mathbb{N}$,

$$\max_{i_D \in I_D} \tau_{i_D}(\epsilon) = \Omega(|D|^l) \tag{5}$$

Diaconis and Strock showed that

$$\max_{i_D \in I_D} \tau_{i_D}(\epsilon) \geq \frac{\rho_D}{2(1-\rho_D)} \ln\left(\frac{1}{\epsilon}\right) \tag{6}$$

where $\rho_D$ is the second largest eigenvalue modulus, that is $\max\{\lambda_{2,D}, |\lambda_{r,D}|\}$, where $\lambda_{2,D}$ is the second largest eigenvalue of the transition matrix $P_D$, and $\lambda_{r,D}$ is the smallest eigenvalue of $P_D$ (if the Markov chain is reversible, all eigenvalues are real numbers). A consequence of this theorem is that a Markov chain Monte Carlo converges neccessarily slowly if the second larges eigenvalue converges to 1 exponentially with the size of the data.

The Cheeger's inequality gives a lower bound on the second largest eigenvalue. We define the ergodic flow of a set $S_D \in I_D$ as

$$F(S_D) := \sum_{x \in S_D, y \in I_D \setminus S_D} P_D(y|x)\pi_D(x) \tag{7}$$

and the conductance of a Markov chain as

$$\Phi_D := \inf\left\{ \frac{F(S_D)}{\pi_D(S_D)} \middle| 0 < \pi_D(S_D) \leq \frac{1}{2} \right\} \tag{8}$$

It can be shown [23] that

$$1 - 2\Phi_D \leq \lambda_{2,D} \tag{9}$$

It follows that the convergence of a Markov chain is necessarily slow if there are sets $S_D$, for which $F(S_D)/\pi_D(S_D)$ converges to 0 exponentially with $|D|$. Below we construct a series of data with such $S_D$s.

### B. The example

For each $n \in \mathbb{N}$ we construct a $13n - 2$ long permutation. Fig. 1. shows the general structure of the permutation of our example. Its graph of desire and reality can be split into two parts. The first part contains $4n - 2$ rainbow motifes chained into each other with a three long cycle at the right end. The second part contains $n$ repeats of five long cycles being equivalent with the $-1, -2, -3, -4$ permutation. Such permutation exist for all $n$, the general permutation of the first part is shown on Fig. 2, the second part contains the numbers in the identical order, one positive sign is followed by four negative signs, namely, the second part of the permutation is

$$8n-1,\ -(8n),\ -(8n+1),\ -(8n+2),\ -(8n+3),\ 8n+4, \ldots$$

It is easy to show that the first part of the permutaion needs $n$ reversals to get sorted, and it has exactly two optimal sorting paths by reversals. Moreover, these two sorting paths has only the start and end genome in common, all the intermediate genomes of the two sorting paths are different. Each five long cycle in the

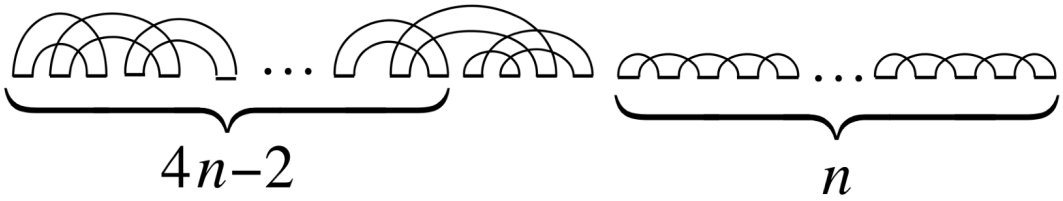


Fig. 1. The graph of desire and reality of the second member of the signed permutation that we generated. For more info, see the text.

$6n$–2, $6n$–3, 1, $6n$–4, $6n$–1, $6n$–5, 2, . . . $k$, $6n$–2$k$–2, $6n$+$k$–2, $6n$–2$k$–3, $k$+1, . . . $2n$–2, $2n$+2, $8n$–4, $2n$+1, $2n$–1, $-(8n-2)$, $2n$, $8n$–3, $8n$–1

Fig. 2. The general form of the signed permutation for the first component on Fig. 1

second part of the permutation needs 4 reversals to get sorted, and each of them has 26 optimal sorting paths. $24 = 4!$ paths revert single numbers, and they form a four-dimensional hypercube, ie. they have 14 common intermediate genomes above the start and end genomes. The remaining two sorting paths reverts the begining and ending three numbers twice, and these two paths are separated both from the hypercube and from each other. The Hannenhalli-Pevzner theorem says that all the sorting paths of the entire permutation are combinations of sorting paths of smaller components, therefore there are

$$2 \times 26^n \times \frac{(8n)!}{(4n)!(4!)^n} \tag{10}$$

sorting paths of the $n$th member of the series. This set of paths can be divided into two, equal size parts based on which path they use for sorting the first component. Let $S_D$ be one of these sets. We are going to show that $F(S_D)/\pi_D(S_D)$ converges to 0 exponentially fast with $n$, and hence, exponentially fast with $|D|$.

The first observation is that

$$\frac{F(S_D)}{\pi_D(S_D)} = \frac{1}{|S_D|} \sum_{x \in S_D, y \in I_D \setminus S_D} P_D(y|x) \tag{11}$$

since $\pi_D$ is the equilibrium distribution. We cut $S_D$ into three parts, the first two parts are negligebly small, and the third contains too small ergodic flow towards the complement of $S_D$. Let $S_{D,1}$ be the subset of $S_D$ which contains the paths in which there are less than $7\frac{9}{11}n$ intermediate genomes between the first and last sorting reversals of the first component of the permutation. Since each sorting path contains $8n$ reversals and $4n$ reversals sorts the first component, there exists a $c_1 > 1$ for which

$$\frac{|S_{D,1}|}{|S_D|} = O\left(\frac{1}{c_1^n}\right) \tag{12}$$

The remaining set, $S_D \setminus S_{D,1}$ contains sorting paths in which the complete sorting of at least $\frac{9}{11}n$ five-long cycles are between the first and the last sorting reversals of the large component of the permutation. Let $S_{D,2}$ be the subset of $S_D \setminus S_{D,1}$ that contains paths in which at most $\frac{3}{4}n$ five-long cycles are sorted with single number reverting mutations between the first and the last sorting reversals of the large component. It is obvious that there exists a $c_2 > 1$ for which

$$\frac{|S_{D,2}|}{|S_D|} = O\left(\frac{1}{c_2^n}\right) \tag{13}$$

since the number of five long cycles that are sorted with single number of reverting mutations are binomially distributed with expectation $\frac{12}{13}k$, and $k \geq \frac{9}{11}n$.

Let $S_{D,3}$ be $S_D \setminus \left(S_{D,1} \cup S_{D,2}\right)$. We have

$$\begin{aligned}\frac{F(S_D)}{\pi_D(S_D)} = \frac{1}{|S_D|} \quad & \Big(\textstyle\sum_{x \in S_{D,1}, y \in I_D \setminus S_D} P_D(y|x) + \\ & \textstyle\sum_{x \in S_{D,2}, y \in I_D \setminus S_D} P_D(y|x) + \\ & \textstyle\sum_{x \in S_{D,3}, y \in I_D \setminus S_D} P_D(y|x)\Big)\end{aligned} \tag{14}$$

$|S_{D,1}|$ and $|S_{D,2}|$ are upper bounds for the first and the second sum, hence

$$\frac{F(S_D)}{\pi_D(S_D)} = O\left(\frac{1}{\min\{c_1, c_2\}^n}\right) + \frac{1}{|S_D|} \sum_{x \in S_{D,3}, y \in I_D \setminus S_D} P_D(y|x) \tag{15}$$

Recall that

$$P_D(y|x) = \sum_w T_D(y, w|x) \min\left\{1, \frac{\pi_D(y) T_D(x, w'|y)}{\pi_D(x) T_D(y, w|x)}\right\} \tag{16}$$

$$P_D(y|x) = \sum_w \min\left\{T_D(y, w|x), T_D(x, w'|y)\right\} \tag{17}$$

and hence, we can approximate $P_D(y|x)$ as

$$P_D(y|x) \leq \sum_w T_D(x, w'|y) \tag{18}$$

Let $c = \min\{c_1, c_2\}$, and we have

$$P_D(y|x) \leq O\left(\frac{1}{c^n}\right) + \frac{1}{|S_D|} \sum_w \sum_{\substack{x \in S_{D,3}, \\ y \in I_D \setminus S_D}} P_D(x, w'|y) \tag{19}$$

where the first sum runs only on windowses $w$ that contains at least the first and the last reversal sorting the large component. The inner sum sums for all $y$ the probability that such a subpath is proposed in the $w'$ window that transforms $y$ into in the $S_{D,3}$ set. For a particular $y$, there is a $c_3$ such that the probability of the transformation is $O\left(\frac{1}{c_3^n}\right)$, since for a successfull transition, at least $\frac{3}{4}n$ five long cycle should be sorted by single number reversing mutations, however, in the proposal distribution, the number of five long cycles that are sorted by single number reversing mutations is binomially distributed with expectation $\frac{2}{3}k$, and $k \leq n$. The number of $y$s in the subset $I_D \setminus S_D$ is exactly $|S_D|$ hence

$$P_D(y|x) = O\left(\frac{1}{\min\{c_1, c_2, c_3\}}\right) \tag{20}$$

□

## V. Discussion and Conclusion

In this paper we showed that the Metropolized Partial Importance Sampler might mix slowly on minimal reversal paths. The source of the slow mixing are the big gaps in the optimal sorting

paths, like the gaps between the two optimal sorting paths of the large component in our example. Due to these big gaps, large portion of the actual sorting path should be replaced in the proposal to get an irreducible chain. The large changes cause small acceptance ratios, and eventually slow mixing. One might argue that the Metropolozed Partial Importance Sampling could be improved on the above mentioned example if it resampled mutations only on one component (which mutations might not be consecutive on the current path). However, big gaps are common in genome rearrangements paths, for example, it can be shown that hurdle-cutting and hurdle merging [15] sorting paths are disjunt except the start and the end genome. Both the gurdle-cutting and the hurdle-merging paths might be numerous, and we conjecture that the Metropolized Partial Importance Sampler might mix slowly even on two hurdles.

Our result does not prove but suggests that the similar MCMC methods on the Bayesian distribution of all sorting paths [10], [19], [20], [26], [28], [36] might also mix slowly. However, this proof does not imply in any sense that no fast mixing Markov chain exists for sampling from the uniform distribution of minimal reversal sorting paths or Bayesian distributions of genome rearrangement paths. Indeed, there are at least two possible ways to improve the mixing of Markov chains: with novel proposals that might destroy bottlenecks and with paralel chains that change information. We show an example for both of them.

- Let a reversal be described as a double cut-and-joy (DCJ) mutation [6]. The DCJ representation of a reversal tells which adjacencies are changed in the signed permutation. Let sorting paths be described by their series of reversals in DCJ representation. For example, the sorting path:
  $+3,+4,-1,-2 \rightarrow +1,-4,-3,-2 \rightarrow +1,+2,+3,+4$
  is represented by $(0,b3|b1,e2)\ \ (e1,e4|b2,5)$. This means that before the first reversal, the begining of gene $3$ was at the begining of the permutation (represented as $0$), the begining of gene $1$ was in adjacency with the end of gene $2$, and the first reversal swapped the positions $b3$ and $b1$. Similarly, the second reversals breaks the adjacencies between $e1$ and $e4$ and between $b2$ and the end of the permutation by swapping $e4$ and $b2$. Note that $(a,b|c,d)$ means the same reversal than $(d,c|b,a)$, but differs from, for example, $(b,a|c,d)$.
  Let the verteces of a graph be the minimal reversal paths of a signed permutation. Let two points of this graph be connected iff at most four-four, not necessarily consecutive reversals can be removed from their DCJ representations such that the remaining patterns will be the same (note that the remaining representations of DCJ mutations might not represent valid DCJ operations). Our conjecture is that the graph will always be connected if the signed permutation contains only oriented components. Above this conjecture, it is an open question if such fixed number of removals holds for all signed permutations, and if so, the so-obtained Markov chain (namely, remove a fixed number of not necessarly consecutive reversals and put back reversals not neccesarily to the same place) can be transformed into a quickly mixing MCMC.
- For an $n$ long, signed permutation that can be sorted in $k$ step, we create a $k+1$ dymensional vector space. The first coordinate of any element in the state space contains the signed permutation, and the $l$th coordinate contains a transformation path from the given signed permutation to an other sigend permutation that can be sorted in $l-1$ step.
  We define a Markov chain on this vector space that changes two consecutive coordinates, the $l$th and $l+1$st in the following way. The new $l$th coordinate is the shortened path in the old $l+1$st coordinate, and the new $l+1$st coordinate is a random extension of the old $l$th coordinate. Applying the appropriate Metropolis-Hastings ratio, the Markov chain will converge to the uniform distribution. The open question is that if this MCMC converges quickly for any signed permutation.

We also would like to highlight that a commonly used method, Paralel Tempering [12], also known as $(MC)^3$ [32] will not work. Indeed, we showed that an MCMC might mixes slowly even if the target distribution is the uniform one, and the uniform distribution cannot be further heated.

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**István Miklós** got his PhD in Theoretical Biology and Ecology at the Eötvös Loránd Unviersity, Budapest in 2002. He was a postdoc in the Bioinformatics group, Department of Statistics at the University of Oxford from 2002 until 2004 and at the Eötvös Loránd Unviersity from 2004 until 2006. He got a young researcher position at the Rényi Institute in 2006, and he is a visitor in the Bioinformatics group in Oxford in the 2007/2008 academic year.

**Bence Mélykúti** Biography text here.

**Krister Swenson** Biography text here.