Growth Algorithms for Lattice Heteropolymers at Low Temperatures

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Two improved versions of the pruned-enriched-Rosenbluth method (PERM) are proposed and tested on simple models of lattice heteropolymers. Both are found to outperform not only the previous version of PERM, but also all other stochastic algorithms which have been employed on this problem, except for the core directed chain growth method (CG) of Beutler & Dill. In nearly all test cases they are faster in finding low-energy states, and in many cases they found new lowest energy states missed in previous papers. The CG method is superior to our method in some cases, but less efficient in others. On the other hand, the CG method uses heavy heuristics based on presumptions about the hydrophobic core and does not give thermodynamic properties, while the present method is a fully blind general purpose algorithm giving correct Boltzmann-Gibbs weights, and can be applied in principle to any stochastic sampling problem.

I. INTRODUCTION

Lattice polymers have been studied intensively to understand phenomena like the globule-coil transition of polymers, protein folding, etc. Protein folding (or, more precisely, protein fold prediction), one of the central problems of computational biology, refers to the determination of the ground state of protein molecules – which grossly modo is also its native state – from their amino acid sequence. Due to rapid advances in DNA analysis the number of known sequences has increased enormously, but progress in understanding their 3-dimensional structure and their functions has lagged behind owing to the difficulty of solving the folding problem.

Simplifying the description of a protein by replacing each amino acid by a simple point particle on a site of a regular lattice implies of course a great reduction of complexity, and one might wonder how much one can learn by this for real proteins. But even if this simplification is too strong, searching for lowest energy states of such models represents a paradigmatic example of combinatorial optimization. This will indeed be our main motivation: Finding algorithms that explore efficiently the low-energy states of a complicated energy landscape with many local minima and in finding the ground state we want these algorithms also to sample excited states correctly, so that they provide a complete thermodynamic description – though we shall restrict ourselves in this paper to presenting results on ground states only.

A popular model used in these studies is the so-called HP model \[ \text{HP} \] where only two types of monomers, H (hydrophobic) and P (polar) ones, are considered. Hydrophobic monomers tend to avoid water which they can only by mutually attracting themselves. The polymer is modeled as a self-avoiding chain on a regular (square or simple cubic) lattice with repulsive or attractive interactions between neighboring non-bonded monomers. Although also other interaction parameters have been used in the literature, almost all examples treated in this paper use energies \( \epsilon_{HH} = -1, \epsilon_{HP} = \epsilon_{PP} = 0 \). The only other model studied here has also two types of monomers, for simplicity also called H and P (although they have identical hydrophobicities), but with \( \epsilon_{HH} = \epsilon_{PP} = -1, \epsilon_{HP} = 0 \). Chain lengths considered in the literature typically are between \( N = 30 \) and \( N = 100 \). Shorter chains do not present any problem, longer ones are too difficult.

A wide variety of computational strategies have been employed to simulate and analyze these models, including conventional (Metropolis) Monte Carlo schemes with various types of moves \[ \text{MC} \], chain growth algorithms without \[ \text{CG} \] and with re-sampling \[ \text{CG-rs} \] (see also \[ \text{CG-rs}\]), genetic algorithms \[ \text{GA} \], parallel tempering \[ \text{PT} \], and generalizations thereof \[ \text{EG} \], \[ \text{ET} \], an ‘evolutionary Monte Carlo’ algorithm \[ \text{EMC} \], and others \[ \text{Perm} \]. In addition, Yue and Dill \[ \text{YD} \] also devised an exact branch-and-bound algorithm specific for HP sequences on cubic lattices which gives all low energy states by exact enumeration, and typically works for \( N < 70 \). If the chain is too long, it does not give wrong output but no output at all. It is the purpose of the present letter to present two new variants of the Pruned-Enriched Rosenbluth Method (PERM) \[ \text{PERM} \] and to apply them to lattice proteins. PERM is a biased chain growth algorithm with re-sampling (“population control”) with depth-first implementation. It has a certain resemblance to genetic algorithms, except that the latter are usually implemented breadth-first and do not allow to obtain correct Gibbs-Boltzmann statistics.

The original version of PERM was used for lattice protein folding in \[ \text{PERM} \] and did extremely well. With one exception, it could find all known lowest energy configurations for all sequences tested in \[ \text{PERM} \] and found a number of new lowest energy states. The one case where it could not find the ground state in an unbiased and blind search was a 64-mer designed in \[ \text{PERM} \] (see Fig. 1), but this is not surprising: Any chain growth algorithm should have problems in finding this configuration, since it has to grow a long arc which at first seems very unnatural and which is stabilized only much later. Indeed, at that time no other Monte Carlo method had been able to find this state either. But a very efficient algorithm, the Core-directed Growth method (CG) \[ \text{CG} \] was overlooked in...
PERM is built on the old idea of Rosenbluth and Rosenbluth (RR)\cite{20} to use a biased growth algorithm for polymers, where the bias is corrected by means of giving a weight to each sample configuration. While the chain grows by adding monomers, this weight (which also includes the Boltzmann weight if the system is thermal) will fluctuate. PERM suppresses these fluctuations by pruning configurations with too low weight, and by “enriching” the sample with copies of high-weight configurations\cite{19}. These copies are made while the chain is growing, and continue to grow independently of each other. PERM has been applied successfully to a wide class of problems, including e.g. the Θ transition in homopolymers\cite{14}, trapping of random walkers on absorbing lattices\cite{21}, and stretching collapsed polymers in a poor solvent\cite{25}. It can be viewed as a special realization of a “go with the winners” strategy\cite{21} which indeed dates back to the beginning of the Monte Carlo simulation era, when it was called “Russian roulette and splitting”\cite{22}. Among statisticians, this approach is also known as sequential importance sampling (SIS) with resampling\cite{23}.

Pruning and enrichment were done in\cite{5, 8, 10} by choosing thresholds $W_{n}^{<}$ and $W_{n}^{>}$ depending on the estimate of the partition sums of $n$-monomer chains. These thresholds are continuously updated as the simulation progresses. If the current weight $W_{n}$ of an $n$-monomer chain is less than $W_{n}^{<}$, a random number $r$ is chosen uniformly in $[0, 1]$. If $r < 1/2$, the chain is discarded, otherwise it is kept and its weight is doubled. Thus low-weight chains are pruned with probability 1/2. Many alternatives to this simple choice are discussed in\cite{22}, but we found that more sophisticated strategies had little influence on the efficiency, and thus we kept the above in the present work. The determination of $W_{n}^{<}$ and $W_{n}^{>}$ will be discussed later. In principle we could use the same as in\cite{5, 8}, but we simplified it since the new variants are more robust, and some of the tricks employed in\cite{5, 8} are not needed.

On the contrary, we found that different strategies in biasing and, most of all, in enrichment had a big effect, and it is here the present variants differ from those in\cite{5, 8}. There, high-weight configurations were simply cloned (with the number of clones determined from the ratio of the actual weight to $W_{n}^{>}$), and the weight was uniformly shared between the clones. For relatively high temperatures this is very efficient\cite{19}, since each clone has so many possibilities to continue that different clones very quickly become independent from each other. This is no longer the case for very low temperatures. There we found that clones often evolved in the same direction, since one continuation has a much higher Boltzmann weight than all others. Thus, cloning is no longer efficient in creating configurational diversity, which was the main reason why it was introduced.

The main modification made in the present paper is thus that we no longer make identical clones. Rather, when we have a configuration with $n-1$ monomers, we first estimate a predicted weight $W_{n}^{\text{pred}}$ for the next step, and we count the number $k_{\text{free}}$ of free sites where the $n$th monomer can be placed. If $W_{n}^{\text{pred}} > W_{n}^{>}$ and $k_{\text{free}} > 1$, we choose $2 \leq k \leq k_{\text{free}}$ different sites among the free ones and continue with $k$ configurations which are forced to be different. Thus we avoid the loss of diversity which limited the success of old PERM. We tried several strategies for selecting $k$ which all gave similar results. Typically, we used $k = \min\{k_{\text{free}}, \lfloor W_{n}^{\text{pred}}/W_{n}^{>}\rfloor\}$.

When selecting a $k$-tuple $A = \{\alpha_{1}, \ldots, \alpha_{k}\}$ of mutually different continuations $\alpha_{j}$ with probability $p_{A}$, the corresponding weights $W_{n-1, \alpha_{1}}, \ldots, W_{n-1, \alpha_{k}}$ are (see Appendix)

$$W_{n, \alpha_{j}} = \frac{W_{n-1, \alpha_{j}} k_{\text{free}}}{k_{\text{free}}^{k-1}}.$$  \hspace{1cm} (1)

Here, the importance

$$q_{\alpha_{j}} = \exp(-\beta E_{n, \alpha_{j}})$$  \hspace{1cm} (2)

of choice $\alpha_{j}$ is the Boltzmann-Gibbs factor associated with the energy $E_{n, \alpha_{j}}$ of the newly placed monomer in the potential created by all previous monomers, and the terms in the denominator of Eq. 1 arise from correcting bias and normalization.

For the choice of continuations among the $k_{\text{free}}$ candidates, we used two different strategies:
(1) In the first, called nPERMss for “new PERM with simple sampling”, we chose them randomly and uniformly, with the only restriction that they are mutually different. Accordingly, \( W_n^{\text{pred}} = W_{n-1} k_{\text{free}} \) \cite{26}, and
\[
W_{n,\alpha} = W_{n-1} q_\alpha k_{\text{free}} / k .
\] (3)
This has the advantage of simplicity, but it might at first appear to be inefficient. A priori, we would expect that some bias in favour of continuations with high Boltzmann weights or against continuations which run into dead ends might be necessary for efficiency.

(2) In the second, called nPERMis for “new PERM with importance sampling”, we did just that. For each possible placement \( \alpha \in [1, k_{\text{free}}] \) of the \( n \)-th monomer we calculated its energy \( E_{n,\alpha} \) and its number \( k_{\text{free}}^{(\alpha)} \) of free neighbours, and used modified importances defined by
\[
\tilde{q}_\alpha = (k_{\text{free}}^{(\alpha)} + 1/2) \exp(-\beta E_{n,\alpha})
\] (4)
to choose among them. The predicted weight is now
\[
W_{n,\alpha} = W_{n-1} \sum_{\alpha'} \tilde{q}_{\alpha'} .
\] The replacement of \( q_\alpha \) by \( \tilde{q}_\alpha \) is made since we anticipate that continuations with less free neighbours will contribute less on the long run than continuations with more free neighbours. This is similar to “Markovian anticipation” \cite{27} within the framework of old PERM, where a bias different from the short-sighted stochastic only later when following all possible configurations would become unfeasible. We do not quote the optimal results since they are obtained only for narrow ranges of \( C \) which depend on the specific amino acid sequence, and finding them in each case would require an extensive search.

Since both nPERMss and nPERMis turned out to be much more efficient and robust than old PERM, we did not use special tricks employed in \cite{7} like growing chains from the middle rather than one of the ends, or forbidding contacts between polar monomers.

In the following, when we quote numbers of ground state hits or CPU times between such hits, these are always independent hits. In PERM we work at a fixed temperature (no annealing), and successive “tours” \cite{19} are independent except for the thresholds \( W_n^{\leq,>} \) which use partially the same partition sum estimates. The actual numbers of (dependent) hits are much larger.

For both versions, results are less sensitive to the precise choice of temperature than they were for old PERM. As a rule, optimal results were obtained at somewhat lower temperatures, but in general all temperatures in the range \( 0.25 < T < 0.35 \) gave good results for ground state search.

III. RESULTS

(a) We first tested the ten 48-mers from \cite{2}. As with old PERM, we could reach lowest energy states for all of them, but within much shorter CPU times. As seen from Table I nPERMss did slightly better than nPERMms, and both were about one order of magnitude faster than old PERM. For all 10 chains we used the same temperature, \( \exp(1/T) = 18 \), although we could have optimized CPU times by using different temperatures for each chain. In the following we quote in general only results for nPERMss, but results for nPERMms were nearly as good.

The CPU times for nPERMss in Table III are typically one order of magnitude smaller than those in \cite{9}, except for sequence #9 whose lowest energy was not hit in \cite{7}. Since in \cite{2} a SPARC 1 machine was used which is slower by a factor \( \approx 10 \) than the 167 MHz Sun ULTRA I used here, this means that our algorithms have comparable speeds.
TABLE I: Performances for the 3-d binary (HP-) sequences from [4].

| sequence nr. | $-E_{\min}^a$ | PERM$^b$ | nPERMss$^c$ | nPERMIs$^d$ |
|--------------|---------------|-----------|-------------|-------------|
| 1            | 32            | 6.9       | 0.66        | 0.63        |
| 2            | 34            | 40.5      | 4.79        | 3.89        |
| 3            | 34            | 100.2     | 3.94        | 1.99        |
| 4            | 33            | 284.0     | 19.51       | 13.45       |
| 5            | 32            | 74.7      | 6.88        | 5.08        |
| 6            | 32            | 59.2      | 9.48        | 6.60        |
| 7            | 32            | 144.7     | 7.65        | 5.37        |
| 8            | 31            | 26.6      | 2.92        | 2.17        |
| 9            | 34            | 1420.0    | 378.64      | 41.41       |
| 10           | 33            | 18.3      | 0.89        | 0.47        |

$^a$Ground state energies.

$^b$CPU times (minutes) per independent ground state hit, on 167 MHz Sun ULTRA I workstation; from Ref. [8].

$^c$CPU times, same machine

$^d$CPU times, same machine

(b) Next we studied the two 2-d HP-sequences of length $N = 100$ of Ref. [5]. They were originally thought to have ground states fitting into a $10 \times 10$ square with energies $-44$ and $-46$ [5], but in [6] configurations fitting into this square were found with lower energies, and moreover it was found that the configurations with lowest energies ($E = -47$ resp. $E = -49$) did not fit into this square. In the present work we studied only configurations of the latter type.

For the second of these sequences, new lowest energy configurations with $E = -50$ were found later in [14], within 50 h CPU time on a 500 MHz DEC 21164A. We now hit this energy 7 times, with an average CPU time of 5.8 h on a 667 MHz DEC 21264 between any two hits.

For the first sequence of Ref. [5] we now hit several hundred times states with $E = -48$, with ca. 2.6 min CPU time between successive hits. One of these configurations is shown in Fig. 2.

(c) Several 2-d HP-sequences were introduced in [11], where the authors tried to fold them using a genetic algorithm. Except for the shortest chains they were not successful, but putative ground states for all of them were found in [8, 13, 14]. But for the longest of these chains (with $N = 64$, see Fig. 1), the ground state energy $E_{\min} = -42$ was found in [8] only by means of special tricks which amount to non-blind search. With blind search, the lowest energy reached by PERM was -39. We should stress that PERM as used in [8] was blind for all cases except this 64-mer, in contrast to wrong statements made in [10].

We now found putative ground states for all chains of [11] with blind search. For the 64-mer the average CPU time per hit was ca. 30h on the DEC 21264, which seems to be roughly comparable to the CPU times needed in [13, 14], but considerably slower than [8]. As we already said in the introduction, this sequence is particularly difficult for any growth algorithm, and the fact that we now found it easily is particularly noteworthy.

On the other hand, nPERMIs was much faster than [8] for the sequence with $N = 60$ of [11]. It needed $\approx 10$ seconds on the DEC 21264 to hit $E_{\min} = -36$, and $\approx 0.1$ second to hit $E = -35$. In contrast, $E = -36$ was never hit in [8], while it took 97 minutes to hit $E = -35$.

(d) A 85-mer 2-d HP sequence was given in [25], where it was claimed to have $E_{\min} = -52$. Using a genetic algorithm, the authors could find only conformations with $E \geq -47$. In Ref. [10], using a newly developed evolutionary Monte Carlo (EMC) method, the authors found the putative ground state when assuming large parts of its known structure as constraints. This amounts of course to non-blind search. Without these constraints, the putative ground state was not hit in [10] either, although the authors claimed their algorithm to be more efficient than all previous ones.

Both with nPERMss and with nPERMIs we easily found states with $E = -52$, but we also found many conformations with $E = -53$. For nPERMIs at $\exp(1/T) = 90$ it took ca. 10 min CPU time between successive hits on the Sun ULTRA 1. One of those conformations is shown in Fig. 3.

(e) As two easy cases we studied the two longest sequences from [12], since we can compare there with CPU times given in [12] for three versions of a supposedly very efficient genetic algorithm. These 2-d HP sequences with lengths $N = 33$ and 48 have ground state energies -14 and -23, respectively. In [12], the most efficient version needed on average $\approx 45$ min CPU (on an unspecified machine) to reach a ground state of the 33-mer. For the 48-mer only energy -22 could be reached, within $\approx 2.5$ h per hit. Using $\exp(1/T) = 40$, it took the Sun ULTRA 1 just 0.4 sec to hit one ground state of the 33-mer, 7 sec to hit $E = -22$ for the 48-mer, and 16 min to hit a ground state of the 48-mer. Thus the present algorithm is roughly 1000 times faster than that of [12].

(f) Four 3D HP sequences with $N = 58$, 103, 124, and
FIG. 3: New putative ground state configuration with $E = -53$ of the 2-d $N = 85$ chain taken from [10, 28].

FIG. 4: Configuration with $E = -44$ of the $N = 58$ HP sequence modeling protein BPTI from Ref. [16, 29].

136 were proposed in [29, 30] as models for actual proteins or protein fragments. Low energy states for these sequences were searched in [16] using a newly developed and supposedly very efficient algorithm. The energies reached in [16] were $E = -42$, $-49$, $-58$ and $-65$, respectively. With nPERMIs, we now found lower energy states after only few minutes CPU time, for all four chains. For the longer ones, the true ground state energies are indeed much lower than those found in [16], see Table II. Examples of the putative ground state configurations are shown in Figs. 4 to Fig. 7.

Note the very low temperatures needed to fold the very longest chains in an optimal time. If we would be interested in excited states, higher temperatures would be better. For instance, to find $E = -66$ for the 136-mer (which is one unit below the lowest energy reached in [16]), it took just 2.7 seconds/hit on the DEC 21264 when using $\exp(1/T) = 40$.

(g) Several 3-d HP sequences were studied in [18], where also their exact ground state energies were calculated using the ‘constrained hydrophobic core construction’ (CHCC) which is essentially an exact enumeration method tailored specifically to HP sequences on the cubic lattice. According to [18], CHCC can be used to find all exact ground state configurations for chains of length $N \approx 70$ to 88, depending on their degeneracies.

The longest chains given explicitly in [18] together with their native configurations are a four helix bundle with $N = 64$ and $E_{\text{min}} = -56$, and a chain with $N = 67$ folding into a configuration resembling an $\alpha/\beta$ barrel with $E_{\text{min}} = -56$, too. Both have low degeneracy.

| $N$ | $E_{\text{min}}^a$ | $E_{\text{min}}^b$ | $\exp(1/T)$ | CPU time $^c$ |
|-----|------------------|------------------|-------------|-------------|
| 58  | -42              | -44              | 30          | 0.19        |
| 103 | -49              | -54              | 60          | 3.12        |
| 124 | -58              | -71              | 90          | 12.3        |
| 136 | -65              | -80              | 120         | 110.        |

$^a$Lowest energies found in Ref. [16]  
$^b$Present work, using nPERMIs  
$^c$CPU times (hours) per independent lowest state hit, on 667 MHz DEC ALPHA 21264
TABLE III: Newly found lowest energy states for binary sequences with interactions \( \bar{\epsilon} = (\epsilon_{HH}, \epsilon_{HP}, \epsilon_{PP}) \).

| N  | d  | \( \bar{\epsilon} \) | Sequence | \( \text{old } E_{\text{min}} \) | \( \text{new } E_{\text{min}} \) | Ref. |
|----|----|----------------------|----------|----------------|----------------|-----|
| 100| 2  | -(1,0,0)             | \( P_5H PH_2P_5H_3PH_5PH_2(P_2H_2)_{12}PH_5P_2PH_7P_11H_7P_2PHPH_5PH_2 \) | -47 \[7\] | -48 \[7\] |     |
| 85 | 2  | -(1,0,0)             | \( H_4P_3H_2P_5H_4H_6P_5P_3H_2P_3PH_2P_6PH \) | -52 \[10\] | -53 \[10\] |     |
| 58 | 3  | -(1,0,0)             | \( PHPH_5PH_2P_5PH_2PH_3PH_2PHP_2H_3P_2H_3PHPH_2P_2H_2P_2PH \) | -42 \[16\] | -44 \[16\] |     |
| 103| 3  | -(1,0,0)             | \( P_2H_2P_3H_2P_4P_3H_2P_6P_2PHP_2P_3H_2P_4PHPH_2P_2H_2P_3PHPH_2P_2H_2PHPH_2P_2H_2PHPH \) | -49 \[16\] | -54 \[16\] |     |
| 124| 3  | -(1,0,0)             | \( P_3H_2PHPH_2P_3P_2H_2PHPH_2P_2H_2PHPH_2P_2H_2PHPH_2P_2H_2PHPH_2P_2H_2PHPH_2P_2H_2PHPH \) | -58 \[16\] | -71 \[16\] |     |
| 136| 3  | -(1,0,0)             | \( PHP_2PHPH_2P_3PHPH_2P_3PHPH_2P_2PHPH_2P_2PHPH \) | -65 \[16\] | -80 \[16\] |     |

Finding ground states for the 64-mer was no problem for nPERMIs. For \( \exp(1/T) = 50 \), the DEC ALPHA 21264 machine needed on average 26.8 min CPU time to hit one of them. Things are a bit more interesting for the 67-mer. One of its ground states is shown in Fig. 8. Assume we want to let this grow, starting from the \( \beta \) sheet end (monomer \#67). Then we see that we always can form immediately stabilizing H-H bonds, and that we would be never seriously misled if we would place monomers greedily, at positions where they have low energies. Indeed, starting from this end we had no problems with nPERMIs: It took on average 67 min to hit a native state on the DEC ALPHA 21264.

On the other hand, when starting with monomer \#1, we were unsuccessful and the lowest energy reached was \( E = -53 \), even after much longer CPU times. This is easily understood from Fig. 8 starting from this end we have to go repeatedly into directions which seem very unnatural at first sight, and which get stabilized much later.

Notice that the difference between the two growth directions is not that there is a folding nucleus when starting from \#67, and no folding nucleus when starting from \#1. After the first quarter is built up, both give the same \( \alpha/\beta \) pair. Building this first quarter is no problem even when starting from \#1, at least when we use \( C \ll 1 \) (in which case it is built essentially by complete enumeration). Thus the existence of a nucleus in the traditional sense is not sufficient. Instead it is crucial that further growth from this nucleus does not lead into false minima of the energy landscape.

(b) Next we studied the two-species 80-mer with interactions \((-1,0,-1)\) that was introduced in [3]. It was constructed in [3] such as to fold into a four helix bundle with \( E = -95 \), but two configurations with \( E = -98 \) were found in [7] which essentially are \( \beta \) sheet dominated.
IV. DISCUSSION

In the present paper we presented two new versions of PERM which is a depth-first implementation of the ‘go-with-the-winners’ strategy (or sequential importance sampling with re-sampling). The main improvement is that we now do not make identical clones of high weight (partial) configurations, but we branch such that each continuation is forced to be different. We do not expect this to have much influence for systems at high temperatures, but as we showed, it leads to substantial improvement at very low temperatures. The two versions differ in using simple sampling (nPERMss) resp. importance sampling (nPERMis) when choosing among possible branches.

Although the method could be used for a much wider range of applications (see [31] for applications of PERM), we applied it here only to lattice heteropolymers with two types of monomers. These represent toy models of proteins, and we hope that our results will also foster applications to more realistic protein models. We showed only results for lowest energy configurations, but we should stress that PERM and its new variants are not only optimization algorithms. They also give information on the full thermodynamic behaviour. We skipped this here since finding ground states is the most difficult problem in general, and sampling excited states is easy compared to it.

Comparing our results to previous work, we see that we found the known lowest energy states in all cases but one. Moreover, whenever we could compare with previous CPU times, the comparison was favourable for our new algorithms, except for the CG method of Beutler and Dill [8]. But we should stress that the latter is very specific to HP chains, uses strong heuristics regarding the formation of a hydrophobic core, and does not give correct Boltzmann weights for excited states. All that is not true for our method. In general nPERMss did slightly better than nPERMis, although the difference was much less than a priori expected.

In principle, essentially the same algorithms can also be used for off-lattice systems. This was already true for the original version of PERM which performed well for Lennard-Jones polymers at temperatures around the Θ-transition [32], but rather badly for collapsed heteropolymers at temperatures much below the Θ temperature [32]. Work is presently in progress to see whether the new versions of PERM perform better, and whether they can be used efficiently to study protein folding with realistic interactions.

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Appendix

In this appendix we shall collect some basic facts about random sampling, when tuples of instances are selected instead of individual instances. The discussion will be very general. On the other hand, we will not deal with problems specific to sequential sampling, i.e. we will assume that we sample only for the choice of a single item (e.g. for the placement of a single monomer).

Our central aim is thus to estimate a partition sum

\[ Z = \sum_{i=1}^{N} q_i \]  

where the importances \( q_i \) might e.g. be Boltzmann-Gibbs factors, and where \( N \) is assumed to be finite (the generalization to infinite \( N \) and to integrals instead of sums is straightforward). A conventional Monte Carlo (MC) procedure consists in choosing ‘instances’ \( i(\alpha) \), \( \alpha = 1, 2, \ldots \) with probabilities \( p_{i(\alpha)} \) such that each instance gives an unbiased estimate \( \hat{Z}_1(\alpha) \) (the index “1” will be explained in a minute). Thus, given \( M \) such instances and letting \( M \) tend to infinity, we have

\[ Z = \lim_{M \to \infty} \frac{1}{M} \sum_{\alpha=1}^{M} \hat{Z}_1(\alpha). \]  

One easily sees that

\[ \hat{Z}_1(\alpha) = \frac{q_{i(\alpha)}}{p_{i(\alpha)}} \]  

does the job. Indeed,

\[ \lim_{M \to \infty} \frac{1}{M} \sum_{\alpha=1}^{M} \frac{q_{i(\alpha)}}{p_{i(\alpha)}} = \sum_{i=1}^{N} \frac{q_i}{p_i} = Z. \]  

At the same time we can also estimate the variance of \( \hat{Z}_1 \). We have

\[ \text{Var} \hat{Z}_1 = \langle \hat{Z}_1^2 \rangle - \langle \hat{Z}_1 \rangle^2 = \sum_{i=1}^{N} \left( \frac{q_i}{p_i} \right)^2 - Z^2 = \sum_{i=1}^{N} \frac{q_i^2}{p_i} - Z^2. \]

Up to now everything is correct for any choice of the probabilities \( p_i \). They get fixed e.g. by \( p_i = 1/N \) (uniform sampling) or by demanding \( \text{Var} \hat{Z}_1 \) to be minimal, under the constraint \( \sum_i p_i = 1 \). This simple variational problem gives \( p_{i^{\text{opt}}} \propto q_i \), which is known as importance sampling. For perfect importance sampling one finds furthermore that \( \text{Var} \hat{Z}_1 = 0 \).

Let us now assume that we select each time not one instance but \( K \) instances, all of which are different. This requires of course \( K < N \). Moreover we will assume \( K < N \), since otherwise this would amount to an exact summation of \( Z \). An advantage of such a strategy should be that we obtain a more widely and uniformly spread sample. When \( N \gg K \), this should not have a big effect, but in our applications both \( N \) and \( K \) are small and the effect is substantial.

Thus each event consists in choosing a \( K \)-tuple \( \{i_1, i_2, \ldots, i_K\} \), with the \( i_j \) mutually different, from some probability distribution \( p_{i_1, i_2, \ldots, i_K} \). We consider tuples related by permutations as identical, i.e. without loss of generality we can assume that \( i_1 < i_2 < \ldots < i_K \). Each choice \( \alpha \) of a tuple \( \{i_1(\alpha), i_2(\alpha), \ldots, i_K(\alpha)\} \) will lead to an estimate \( \hat{Z}_K(\alpha) \). Instead of Eq. (8) we have now

\[ \hat{Z}_K(\alpha) = \frac{N \sum_{i=1}^{K} q_{i_1(\alpha)} \ldots q_{i_K(\alpha)}}{K p_{i_1(\alpha) \ldots i_K(\alpha)}}, \]  

since one verifies easily that \( \langle \hat{Z}_K(\alpha) \rangle = Z \).

The variance of \( \hat{Z}_K(\alpha) \) is calculated just like that of \( \hat{Z}_1(\alpha) \),

\[ \text{Var} \hat{Z}_K = \left( \frac{N-1}{K-1} \right) \sum_{i_1 < \ldots < i_K} \frac{(\sum_{k=1}^{K} q_{i_k})^2}{p_{i_1 \ldots i_K}} - Z^2. \]

Importance sampling is again obtained by minimizing it with respect to \( p_{i_1 \ldots i_K} \), giving the result

\[ p_{i_1 \ldots i_K}^{\text{opt}} = \left( \frac{N-1}{K-1} \right) \frac{\sum_{k=1}^{K} q_{i_k}}{\sum_{j=1}^{N} q_j}. \]  

The variance of \( \hat{Z}_K \) vanishes again for this choice.

On the other hand, for uniform (or “simple”) sampling, with

\[ p_{i_1 \ldots i_K}^{\text{ss}} = \left( \frac{N}{K} \right)^{-1}, \]

we obtain

\[ \text{Var} \hat{Z}_K = \frac{(N-K)N^2}{K(N-1)} \text{Var} q. \]  

For \( K = 1 \) this is the obvious result \( \text{Var} \hat{Z}_1 = N^2 \text{Var} q \), while for \( K = N \) it gives \( \text{Var} \hat{Z}_N = 0 \) as it should. For general \( 1 < K < N \) the factor \( 1/K \) is trivial and results from the fact that each event corresponds to \( K \) instances, while the factor \( (N-K)/(N-1) \) gives the non-trivial improvement due to the fact that only different instances are chosen in each event.

Finally, when using Eq.(10) for sequential sampling, one has to attribute weights to each individual instance, instead of giving a weight only to the entire tuple. The obvious solution is

\[ W_{i_k(\alpha)} = \frac{q_{i_k(\alpha)} N}{K^{(N-K)} p_{i_1(\alpha) \ldots i_K(\alpha)}}. \]
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