Performance Analysis of MEC Approach for Haplotype Assembly

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1 Abstract

The Minimum Error Correction (MEC) approach is used as a metric for reconstruction of haplotypes from NGS reads. In this paper, we show that the MEC may encounter with imprecise reconstructed haplotypes for some NGS devices. Specifically, using mathematical derivations, we evaluate this approach for the SOLiD, Illumina, 454, Ion, Pacific BioSciences, Oxford Nanopore, and 10X Genomics devices. Our results reveal that the MEC yields inexact haplotypes for the Illumina MiniSeq, 454 GS Junior+, Ion PGM 314, and Oxford Nanopore MK 1 MinION.

2 Introduction

It is well-known that all humans are 99.9% the same in their genetic makeup. In all types of genetic variations, the Single Nucleotide Polymorphism (SNP) is the most important one exploited for the genome wide association studies and personalized medicine [1]. The genome of diploids like humans consists of two homologous pairs, i.e., the paternal and maternal chromosomes.

A haplotype is a SNP sequence of a single chromosome which can be reconstructed by either direct experiments or computational modelings. However, due to the high cost of experimental approaches, the modeling techniques have attracted more attention which may be divided into the phasing and assembly approaches. The haplotype phasing should make use of genotypes of multiple individuals to infer the haplotype. However, as opposed to the haplotype assembly, this cannot be performed for a single individual. Moreover, this approach is questioned in the presence of low-frequency and de novo variants [1]. In the haplotype assembly approach, some sets of reads generated by the Next Generation Sequencing (NGS) devices are applied for haplotype reconstruction. The dominant objective function utilized for the haplotype assembly problem is the Minimum Error Correction (MEC) a.k.a the minimum letter flip [2, 3] which is also used for evaluating the performance of different haplotype reconstruction algorithms [4, 5].

Since the MEC function is obtained from the MAXCUT problem [6], it is NP-hard [7, 8]. To minimize the MEC, the HapCUT algorithm iteratively computes max-cuts of the associated graph of reads [9, 10]. The branch-and-bound method solves the problem with genetic algorithms [11]. Also, the integer linear programming [12] generates exact results for the filtered HuRef dataset [13]. In other works, the likelihood function [14], the MaxSAT [15], and the randomized sampling [16] exploit dynamic programming to solve the same problem. Moreover, the fixed-parameter tractability approach [17, 15], self-organizing map method [18], parameterized algorithm [19], and the clustering approach [20] have also been reported. In [21, 10], the weighted MEC function is defined and solved by a heuristic dynamic clustering [22]. The WhatsHap algorithm optimally minimizes the weighted MEC [23] and its multi-core parallelization version is presented in [24]. The k-MEC function has also been defined in which the number of corrections per column of the read matrix is bounded by an integer k [25, 26].

Despite the above long literature for utilizing the MEC for haplotype reconstruction, it is crucial to note that this function may fail to reconstruct the exact haplotype for a high error rate in the reads [11, 27]. Also, a negative correlation between the haplotype accuracy and the MEC has already been reported in [28] which will be discussed later.

In this work, we intend to give a deep insight into the MEC function in order to pave the way for clarifying the above ambiguities as follows. In Section 3 the problem formulation, MEC definition, and analysis of MEC functionality are presented. The functionality curves are discussed in Section 4. Furthermore, some NGS devices are evaluated based on their averaged coverage and the error probability. Section 5 concludes the paper.

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3 Research Method

For diploids, haplotype assembly is the process of reconstructing two haplotypes from overlapped aligned reads and also the non-SNP bases of each read are omitted. Furthermore, those non-informative reads with less than 2 SNPs are removed. The read matrix is then constructed as will be explained next.

3.1 Problem Formulation

We assume that there are $N$ reads obtained from both chromosomes. For a haplotype with the length of $l$, an $N \times l$ read matrix $R$ is constructed whose rows embed the reads and its columns correspond to the heterozygous SNPs loci. Moreover, those SNPs loci not covered by the reads are coded with zero. Then, Bases of reads are converted to $-1$ or $1$ corresponding to the frequency of alleles $[29]$. This modeling is based on bi-allelic nature assumption.

As an example, the first exon of HLA-A on a gene of chromosome 6 (with NCBI reference sequence number NG_029217.2) is considered whose first 40 bases are presented in Fig. 1a. It contains 5 bi-allelic SNP sites (ref-SNP): C/T (rs753601428), C/G (rs529070997), G/T (rs41560714), A/C (rs551138783), and A/G (rs778615037). The procedure of constructing the read matrix is depicted in Fig. 1d. In this example, the exact haplotypes; which should be constructed by the haplotype assembly algorithms, are \{CGTAG\} and \{TCGCA\}.

![Figure 1: First 40 bases of exon 1 of HLA-A gene on chromosome 6 (NCBI Reference Sequence: NG_029217.2) containing 5 bi-allelic SNP sites (refSNP): C/T (rs753601428), C/G (rs529070997), G/T (rs41560714), A/C (rs551138783), and A/G (rs778615037). a) An example of homologous chromosomes in which SNP site came in bold, b) An example of aligned reads, c) Removing non-informative reads and non-SNP bases, and d) Constructing the read matrix.](image-url)

3.2 MEC Definition

If the reads contain no error, the corresponding rows are compatible with each others and haplotypes are extracted using a simple clustering technique. However, in practise, sequencing devices may produce erroneous reads in which case the compatibility of read matrices is lost. To cope with this problem, the MEC approach is developed by inverting the sign of some entries of the read matrix to make it compatible.

- **MEC approach for haplotype assembly** $[11]$:
  1. Find the minimum number of entries of $R$ which should be inverted to make the read matrix compatible.
  2. Cluster the rows of the augmented read matrix and reconstruct the haplotype.

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For the read matrix \( R \) with the dimension of \( N \times l \) and the candidate \( 1 \times l \) vector \( h_c \) as the haplotype, the MEC function is calculated as \([9]\)

\[
\text{MEC}(R, h_c) = \sum_{i=1}^{N} \min\{D(r_i, h_c), D(r_i, -h_c)\},
\]

in which \( r_i \) is the \( i^{th} \) row of \( R \) and the Extended Hamming Distance (EHD) is defined as \( D(a, b) = \sum_{j=1}^{l} d(a(j), b(j)) \) \([12]\). Furthermore, \( d(\cdot, \cdot) \) is a mismatch indicator which penalizes its dissimilar arguments by one:

\[
d(a, b) = \begin{cases} 
1, & \text{if } a \neq 0 \& b \neq 0 \& a \neq b \\
0, & \text{otherwise}. 
\end{cases}
\]

Therefore, the EHD represents the number of mismatches between two vectors. From this point of view, \( \text{MEC}(R, h_c) \) indicates the whole number of mismatches between each row of \( R \) and the vector \( h_c \). It is notable that the function \( D(\cdot, \cdot) \) is not a distance from the mathematical point of view, though it is named as such (See Appendix A).

### 3.3 Analysis of MEC Functionality

Consider \( h_{\text{opt}} \) as an optimal solution resulted from a given method by minimizing the MEC function. The vital question arises here is as how it would be guaranteed to reach the exact haplotype. In Theorem 1, we will show that not only there is no guarantee for this solution, but also due to some conditions this function may not lead to the exact haplotype.

**Theorem 1.** There exists a vector \( h_d \) different from the exact haplotype \( h_{\text{ex}} \) with a lower MEC, when the \( k^{th} \) column of the read matrix, \( R \), contains some erroneous entries whose number \( E^{(k)} \) is greater than half of its coverage. In a mathematical expression:

\[
\text{If } \exists k : E^{(k)} > \frac{c^{(k)}}{2} \text{ then } \exists h_d \neq h_{\text{ex}} : \text{MEC}(R, h_d) < \text{MEC}(R, h_{\text{ex}}),
\]

where \( c^{(k)} \) is the coverage (or the read depth) of the \( k^{th} \) SNP locus. The coverage shows the number of reads which covers the SNP and is equal to the number of known entries of the \( k^{th} \) column of \( R \).

The proof of Theorem 1 is presented in Appendix B. The core idea of the proof is to consider \( h_d \) equal to \( h_{\text{ex}} \) except its \( k^{th} \) entry whose sign is inverted. This guarantees a lower MEC. In practise, fulfilling the antecedent of Theorem 1 is the major point to be investigated. Specifically, if the antecedent is not satisfied, the MEC approach works properly. In Theorem 2, the probability of occurring the logical complement of the antecedent is presented.

**Theorem 2.** Assume that each non-zero entry of \( R \) is erroneous with the probability of \( p_c \) independent of the other entries. The probability of happening a correct MEC \( (P\{\text{c-MEC}\}) \) is equal to

\[
P\{\text{c-MEC}\} = \prod_{j=1}^{l} \left\{ \sum_{n=0}^{\lfloor \frac{c^{(j)}}{2} \rfloor} \binom{c^{(j)}}{n} p_c^n (1 - p_c)^{c^{(j)} - n} \right\}.
\]

**Proof:** According to Theorem 1, the MEC approach works properly when the number of erroneous entries of each column is lower than half of its corresponding coverage. Based on the above assumption, the number of erroneous entries of each column of \( R \) is independent of the other columns. Then, we have:

\[
P\{\text{c-MEC}\} = \prod_{j=1}^{l} P\left\{ E^{(j)} < \frac{c^{(j)}}{2} \right\}.
\]

When an error happens in an entry due to the bi-allelic assumption, the erroneous entry gets the opposite sign. This is known as the Bernoulli distribution of \( \pm 1 \) with the probability of error \( p_c \). Thus, the number of errors of the \( j^{th} \) column is of Binomial distribution given by \( P\{E^{(j)} = k\} = \binom{c^{(j)}}{k} p_c^k (1 - p_c)^{c^{(j)} - k} \). Therefore, we can write:

\[
P\left\{ E^{(j)} < \frac{c^{(j)}}{2} \right\} = \sum_{k=0}^{\lfloor \frac{c^{(j)}}{2} \rfloor} \binom{c^{(j)}}{k} p_c^k (1 - p_c)^{c^{(j)} - k}.
\]

Then, from (6) and (5), Theorem 2 is proved.
4 Results

4.1 MEC Functionality Curves

The outcome of Theorem 2 is inspected using various scenarios for different probabilities of error and coverage values by introducing the functionality curves of MEC. In Fig. 2a, \( P\{c\text{-MEC}\} \) is presented versus \( p_e = [0.0001, 0.5] \) for different coverage values. In two cases, we consider \( c^{(j)} = 2 \) and 10 for \( j = 1, \ldots, l \), respectively. Next, \( c^{(j)}s \) are defined randomly by the quasi-uniform distribution over two different intervals [1, 2] and [1, 10]. Also, the MEC functionality is investigated for the Poisson distribution with \( \lambda = 2 \) and 10 \([30, 31]\). Accordingly, in Fig. 2b, the histograms of these coverage values are depicted. Furthermore, Fig. 2c shows \( P\{c\text{-MEC}\} \) for different lengths of haplotypes \( l = \{100, 10k, 1M\} \) and coverage values \( c = \{2, 10, 30\} \).

As expected and similarly addressed in \([11, 27]\), it is seen in Fig. 2a that \( P\{c\text{-MEC}\} \) is inversely proportional to the sequencing error rate \( p_e \). Also, depending on the coverage distribution, each \( P\{c\text{-MEC}\} \) starts falling down after an individual threshold. As an instance, for the Poisson distribution with \( \lambda = 10 \) and \( l = 1k \), this happens at \( p_e = 2\% \). This reveals that the MEC approach is unable to reconstruct the exact haplotype after the corresponding \( p_e \). The latter problem happens when the number of errors of a column is more than half of its coverage, as expressed in Theorem 1. Existence of such a column is more probable when the error rate increases. In Fig. 2c, we have investigated the haplotype length effect on \( P\{c\text{-MEC}\} \). It is seen that a larger haplotype length \( l \) leads to a lower threshold for the sequencing error rate \( p_e \). Although, this weak point may be compensated by using a moderate coverage value, in practise, this value may not be accessible.

4.2 MEC Functionality for a Reported Experiment

A report on the unsatisfactory performance of MEC has already been addressed in \([28]\). In this report, a whole genome haplotyping has been done for individual NA12878 whose results are reached in the European nucleotide archive with the accession number of ERP000819. This experiment has been performed using the SOLiD sequencing device whose median of reads coverage is 10 and its error rate is about 0.01 \([32]\). In order to inspect the MEC, we incorporated the same error rate and coverage in our analysis and confirmed the same unsatisfactory result as addressed in \([28]\).

4.3 Evaluation of NGS Devices

Here, we analyze the MEC for different NGS devices based on our reasoning. The results are shown in Table 1 for different NGS devices including SOLiD, Illumina, 454, Ion, Pacific BioSciences, Oxford Nanopore, and 10X Genomics. For each device, the number of reads per run, the read length, and the device error rate are selected based on \([33, 34]\). To calculate the averaged coverage for the mentioned specifications, the Lander/Waterman equation is used:

\[ c_a = \frac{l_r \ast N_t}{G}, \]  

(7)

where \( l_r \), \( N_t \), and \( G \) show the read length, the total number of reads, and the genome length, respectively. Here, we take \( \lambda = c_a \).

Furthermore, we calculate the number of informative reads which shows the reconstruction accuracy. The probability of a read to be informative is obtained by

\[ P_i = P\{A \text{ read is informative}\} = 1 - \sum_{i=0}^{1} \binom{l_r}{i} p_i (1 - p_s)^{l_r-i}, \]  

(8)

where \( p_s \approx 0.001 \) is the SNP rate over a genome \([13]\). The number of informative reads calculated approximately using \( N_i = N_t \ast P_i \) are shown for the above devices in Table 1.
Figure 2: Functionality curves of MEC approach: a) Comparison of diverse distribution for the coverage values (Constant $c = \{2, 10\}$, quasi-uniform over $c = \{[1, 2], [1, 10]\}$, and poisson distribution with $\lambda = \{2, 10\}$), b) Histogram of different coverage values, c) Comparison of different haplotype lengths $l = \{100, 10k, 1M\}$ and different constant coverage values $c = \{2, 10, 30\}$. 

(a) 

(b) 

(c)
Table 1: Comparison of sequencing devices for the total number of reads in millions $N_t$, the read length $l_r$, the device error rate $p_e$, and the averaged coverage $c_a$. The MEC functionality is seen in the sixth column from left. Also, the last column is the number of informative reads in millions $N_i$.

| Device                          | $N_t$ | $l_r$ | $p_e$% | $c_a$ | MEC Func. | $N_i$ |
|---------------------------------|-------|-------|--------|-------|-----------|-------|
| SOLiD 550 Wildfire              | 700   | 75    | 0.1    | 17.5  | Yes       | 1.8   |
| SOLiD 550 x1                    | 1400  | 75    | 0.1    | 35    | Yes       | 3.7   |
| SOLiD-4                        | 840   | 85    | 0.06   | 23.8  | Yes       | 2.8   |
| Illumina MiniSeq                | 50    | 150   | 1      | 2.5   | No        | 0.5   |
| Illumina HiSeq2500 v4           | 4000  | 125   | 0.1    | 160   | Yes       | 28.5  |
| Illumina HiSeq X                | 2600  | 150   | 0.1    | 130   | Yes       | 26.3  |
| 454 GS Junior+                  | 0.1   | 700   | 1      | 0.02  | No        | 0.016 |
| Ion PGM 314                     | 0.5   | 400   | 1      | 0.06  | No        | 0.031 |
| Ion S5 540                      | 60    | 200   | 1      | 4     | No        | 1.04  |
| Pacific BioSciences RS II       | 0.055 | 20k   | 13     | 0.36  | No        | 0.055 |
| Oxford Nanopore MK 1 MinION    | 0.1   | 200k  | 12     | 6.6   | No        | 0.1   |
| 10X Genomics                    | 4000  | 100k  | 1      | 133k  | Yes       | 4000  |

5 Conclusion

The reliability of the MEC approach was investigated. It was shown that the MEC is independent of the maternal or paternal chromosome. First, some new properties were proved for the MEC. It was demonstrated that in some practical circumstances, an imprecise haplotype may be reconstructed with a lower MEC than that of the exact haplotype. For this purpose, the functionality curves of MEC were probabilistically obtained for different coverage values and error rates. Using our analyses, some NGS devices were evaluated by the MEC. It was shown that this approach generates misleading results for Illumina MiniSeq, 454 GS Junior+, Ion PGM 314, and Oxford Nanopore MK 1 MinION.

Appendices

A Extended Hamming Distance

The EHD function $D(\cdot, \cdot)$ is defined as

$$D : \{0, 1, -1\}^l \times \{0, 1, -1\} \rightarrow \mathbb{R}^+ \cup \{0\}, D(a, b) = \sum_{j=1}^l d(a(j), b(j)), \quad (A.1)$$

where

$$d : \{0, 1, -1\} \times \{0, 1, -1\} \rightarrow \{0, 1\}, \quad d(a, b) = \begin{cases} 1, & \text{if } a \neq 0 \& b \neq 0 \& a \neq b \\ 0, & \text{otherwise.} \end{cases} \quad (A.2)$$

This function is a distance if the following four conditions are satisfied [35]:

1. $D(a, b) \geq 0$
2. $a = b \Leftrightarrow D(a, b) = 0$
3. $D(a, b) = D(b, a)$ (Symmetric)
4. $D(a, c) \leq D(a, b) + D(b, c)$ (Triangle inequality) \quad (A.3)

However, we show that this is not always the case and the EHD is an improper distance metric.

1. The first condition is always true due to the definition of EHD which is a summation over a series of $\{0, 1\}$ and therefore is always nonnegative.
2. When $a = b$, then for all $j$, $d(a(j), b(j)) = 0$, which leads to the RHS result. However, the reverse is not always true. As an instance, for $a = [010]$ and $b = [-110]$, we have $D(a, b) = 0$, while $a$ and $b$ are unequal. It is concluded that when $D(a, b) = 0$, for the position of zero entries of $a$, the corresponding entries of $b$ can be either 1 or −1. Furthermore, this condition forces the corresponding nonzero entries of the two vectors to be equal. Therefore, this condition is true when all the entries are nonzero.
3. It is obvious that the EHD is symmetric due to the symmetry of $d(\cdot, \cdot)$.
4. The triangle inequality does not hold. A counterpart example is:

$$a = [111], b = [010], c = [-101] \Rightarrow D(a, c) = 1, D(a, b) = 0, D(b, c) = 0,$$
which has led to an unacceptable result $1 \leq 0 + 0$. In fact, this condition holds when the locations of zero entries of $a$, $b$, and $c$ are similar or all the entries are nonzero.

## B Proof of Theorem 1

First, we define the read matrix model and then show in a lemma that changing the origin of each read does not affect the MEC function. Later, the proof of Theorem 1 is given.

### B.1 Read Matrix Model

The read matrix model is given by

$$ R = P_\Omega(M) + E, \quad (B.1) $$

where $P_\Omega$ is an operator defined as

$$ [P_\Omega(M)]_{ij} = \begin{cases} M_{ij}, & (i, j) \in \Omega, \\ 0, & \text{o.w.,} \end{cases} \quad (B.2) $$

$\Omega$ is the set of indices of known entries, and $M$ is expressed as

$$ M = u^T h_{ex}. \quad (B.3) $$

Each entry of the $1 \times N$ vector $u$ shows the origin of each read which can be either $+1$ or $-1$ corresponding to the paternal or maternal haplotype, respectively. Since, in the bi-allelic haplotype model, the error corresponds to a sign change in the entries of $P_\Omega(M)$ from $1$ to $-1$ (or vice versa), the entries of the error matrix $E$ are defined as $E_{ij} = -2M_{ij}$.

### B.2 Independency of MEC from Origin of Read

**Lemma:** Consider two different origin vectors $u_a$ and $u_b$, and a given haplotype $h_t$. We claim that

$$ \forall h_t \quad \text{MEC}(R_a, h_t) = \text{MEC}(R_b, h_t), \quad (B.4) $$

where

$$ R_a = P_\Omega(u_a^T h) + E_a, \quad (B.5) $$

$$ R_b = P_\Omega(u_b^T h) + E_b, \quad (B.6) $$

in which $E_a$ and $E_b$ are the error matrices whose error positions are identical.

**Proof.** Since, each row of the read matrix affects the MEC independently, it is enough to prove the lemma only for the $n$th arbitrary row. To do so, we should prove that

$$ \min\{D(r_a, h_t), D(r_a, -h_t)\} = \min\{D(r_b, h_t), D(r_b, -h_t)\}, \quad (B.7) $$

in which $r_a$ and $r_b$ are the $n$th rows of $R_a$ and $R_b$, respectively defined as

$$ r_a = P_\Omega(u_a(n) h) + e_a, \quad (B.8) $$

$$ r_b = P_\Omega(u_b(n) h) + e_b, \quad (B.9) $$

where $u_a(n)$ and $u_b(n)$ show the $n$th entries of $u_a$ and $u_b$, and $e_a$ and $e_b$ are the $n$th rows of $E_a$ and $E_b$, respectively. Also, $P_\Omega(\cdot)$ is a sub-operator of $P_\Omega(\cdot)$ dedicated to the $n$th row of a given matrix. Clearly, for $u_a(n) = u_b(n)$, we have $r_a = r_b$ and (B.7) is held. Otherwise, for $u_a(n) \neq u_b(n)$, without loss of generality, we assume that $u_a(n) = 1$ and $u_b(n) = -1$. Then, (B.8) and (B.9) reduce to

$$ r_a = P_\Omega(h) + e_a \quad (B.10) $$

$$ r_b = P_\Omega(-h) + e_b \quad (B.11) $$

Considering that the error positions of $r_a$ and $r_b$ are identical and exploiting the model of (B.3), it can be shown that $e_a = -e_b$. Using this result in (B.10) and (B.11), we get $r_a = -r_b$. Using the first property of MEC (as shown in Appendix C), we get

$$ D(r_a, -h_t) = l_n - D(r_a, h_t) = l_n - D(r_b, -h_t) = D(r_b, h_t), \quad (B.12) $$

where $l_n$ shows the number of nonzero entries of the $n$th row. By using (B.12) in the left side of (B.7), the lemma is proved as

$$ \min\{D(r_a, h_t), D(r_a, -h_t)\} = \min\{D(r_b, h_t), l_n - D(r_a, h_t)\} = \min\{D(r_b, -h_t), D(r_b, h_t)\}. \quad (B.13) $$

This shows that the MEC function is not sensitive to the changes of entries of $u$. 

7
B.3 Proof of Theorem 1

To prove Theorem 1, we propose a specific haplotype vector like \( h_d \) which leads to a lower MEC than the exact haplotype, meaning that minimizing the MEC function does not necessarily lead to the exact haplotype. To do so, first we suppose that the antecedent of Theorem 1 is held for the \( k^{th} \) column, i.e., \( E^{(k)} > c^{(k)}/2 \) and \( h_d \)

is constructed as

\[
h_d = [h_{ex}(1), \ldots, h_{ex}(k-1), -h_{ex}(k), h_{ex}(k+1), \ldots, h_{ex}(l)],
\]

(B.14)
in which \( h_d(k) \) is equal to \(-h_{ex}(k)\). To prove that \( MEC(R, h_d) < MEC(R, h_{ex}) \), without loss of generality, based on Section B.2, we may consider \( u = [1, \ldots, 1] \). Due to the definition of MEC in (1), there is no difference for \( u \) to count the mismatches for either the rows or columns of \( R \). In this way, we can conclude that

\[
MEC(R, h) = MEC(R^{(\sim k)}, h^{(\sim k)}) + MEC(r^{(k)}, h(k)),
\]

(B.15)
in which \( r^{(k)} \) is the \( k^{th} \) column of \( R \) and \( R^{(\sim k)} \) shows a matrix whose \( k^{th} \) column has been omitted. Furthermore, based on the properties of the MEC function, as shown in Appendix C, it can be seen that

\[
MEC(r^{(k)}, h(k)) = E^{(k)},
\]

(B.16)

\[
MEC(r^{(k)}, -h(k)) = c^{(k)} - E^{(k)}.
\]

(B.17)

Therefore, using (B.16) and (B.17) in (B.15) for \( h_d \) and \( h_{ex} \), we get

\[
MEC(R, h_d) = MEC(R^{(\sim k)}, h_{ex}) + c^{(k)} - E^{(k)},
\]

(B.18)

\[
MEC(R, h_{ex}) = MEC(R^{(\sim k)}, h_{ex}) + E^{(k)}.
\]

(B.19)

According to the antecedent of Theorem 1, we get \( c^{(k)} - E^{(k)} < E^{(k)} \) which accomplishes the proof.

C Properties of MEC

The MEC function is calculated for the read matrix \( R \) with the dimension of \( N \times l \) and the haplotype \( h \) as:

\[
MEC : \{0, 1, -1\}^{N \times l} \times \{1, -1\}^l \rightarrow \mathbb{R}^+ \cup \{0\}, \quad MEC(R, h) = \sum_{i=1}^{N} \min\{D(r_i, h), D(r_i, -h)\}
\]

(C.1)

where \( D(\cdot, \cdot) \) is defined by (1) and (2) and \( r_i \) shows the \( i^{th} \) row of \( R \). The following properties can be shown for the MEC function.

1. For \( r_i \), with \( l_i \) known nonzero entries, by supposing \( D(r_i, h) = D_i \), we get

\[
D(r_i, -h) = l_i - D_i,
\]

\[
D(-r_i, h) = l_i - D_i,
\]

\[
D(-r_i, -h) = D_i,
\]

(C.2)

2. For every \( r_i \) and \( h \), we have

\[
D(r_i, h) = \begin{cases} k, & \text{if the } i^{th} \text{ read came from parental haplotype}, \\ l_i - k, & \text{if the } i^{th} \text{ read came from maternal haplotype}, \end{cases}
\]

(C.3)

where \( k \in \mathbb{N} \). For the exact haplotype \( h_{ex} \), \( k \) is equal to the number of error entries of \( r_i \) denoted by \( e_i \). Then, the MEC for the exact haplotype is

\[
MEC(R, h_{ex}) = \sum_{i=1}^{N} \min\{e_i, l_i - e_i\} = \sum_{i=1}^{N} \min e_i = E,
\]

(C.4)

in which \( E \) is the total number of error in the read matrix. Note that the next-to-last equality in (C.4) is based on the assumption that the error rate \( e_i/l_i < 0.5 \). For the error-free read matrix and the paternal exact haplotype \( h_{ex} \), (C.4) reduces to \( MEC(R, h_{ex}) = 0 \).
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