Lossy Compression of Quality Values via Rate Distortion Theory
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ABSTRACT
Motivation: Next Generation Sequencing technologies revolutionized many fields in biology by enabling the fast and cheap sequencing of large amounts of genomic data. The ever increasing sequencing capacities enabled by current sequencing machines hold a lot of promise as for the future applications of these technologies, but also create increasing computational challenges related to the analysis and storage of these data. A typical sequencing data file may occupy tens or even hundreds of gigabytes of disk space, prohibitively large for many users. Raw sequencing data consists of both the DNA sequences (reads) and per-base quality values that indicate the level of confidence in the readout of these sequences. Quality values account for about half of the required disk space in the commonly used FASTQ format and therefore their compression can significantly reduce storage requirements and speed up analysis and transmission of these data.

Results: In this paper we present a framework for the lossy compression of the quality value sequences of genomic read files. Numerical experiments with reference based alignment using these quality values suggest that we can achieve significant compression with little compromise in performance for several downstream applications of interest, as is consistent with our theoretical analysis. Our framework also allows compression in a regime - below one bit per quality value - for which there are no existing compressors.

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1 INTRODUCTION
1.1 Background and Motivation
It has been more than a decade now since the first draft of the human genome was published (Lander et al., 2001). The Human Genome Project, which required a significant collaborative effort of many scientists for more than 10 years, was completed using the Sanger sequencing technology and is estimated to have cost almost three billion dollars. Just a decade later, many medium and small size laboratories achieve the task of sequencing complete mammalian genomes within a few weeks using the new next generation sequencing (NGS) technologies. Read size is usually smaller for NGS sequencers compared to Sanger sequencing, but sequencing throughput is significantly higher. Current sequencers are capable of generating close to tera-base worth of data that needs to be stored and processed. Several recent studies, such as the cow rumen (Hess et al., 2011) and the MetaHit (Qin et al., 2010) metagenomic projects resulted with hundreds of hundreds of giga-base worth datasets. As project scales will continue to grow, it is expected that the bottleneck of projects involving massive sequencing will move towards the computational aspects, in particular with respect to the analysis and storage of the data. As a result, there is a growing interest in computational tools that can speed up processing and compressing this type of data.

Fig. 1. Essential rubrics of gene-sequencing.

The sequencing process begins with the shearing of the input DNA into many short pieces, which are then prepared for sequencing, loaded onto the sequencer and sequenced. (Figure 1). Different methods are used by the different NGS technologies for the readout of the sequencing signal (also known as base calling). This process may be interfered by various factors, which may lead to wrong readout of the sequencing signal. In order to assess the probability for base calling mistakes, sequencers produce scores that
reflect the level of confidence in the readout of each base. These scores are known as quality values and are part of the standard sequencing output. In the widely accepted FASTQ format, for example, each read is represented by four lines, of which two are for the reads themselves and a string of quality values for the read. The use of quality values depends on the use of the data. Low quality reads and read parts may be removed from the data prior to operations that require high-quality data such as the assembly of genomes or mapping-based single nucleotide polymorphism (SNP) detection. Next we describe in detail the quality value sequences and the FASTQ format.

1.2 FASTQ format

We consider the compression of FASTQ files, because of their wide acceptance as a standard for storing sequencing data. A FASTQ file consists of separate entries for each read, each one consisting of the following four lines (see Figure 2 for example):
- (i) header line, always begins with an @ sign, followed by the name of the read
- (ii) r - the base pair sequence in the read, where $r[i] \in \{A, C, G, T, N\}$ with $N$ representing an unknown base.
- (iii) quality value header, begins with a + sign which may or may not be followed by the read name
- (iv) q - the quality value string for the sequence $r$. $q[i]$ represents the quality value of base $r[i]$.

Quality value $q[i]$ represent the level of confidence in the readout of its corresponding base $r[i]$, with high quality values representing greater confidence. Each quality value is encoded by an ASCII character in the FASTQ format based on one of a few accepted schemes. One such standard is the Sanger scale (Cock et al. 2009).

Quality values in this scale are computed as $Q = 33 - 10 \log_{10} P^2$, and range typically from 33 – 73. Lossless compression of read files will require, on average, 2 bits/symbol for the base sequence, and 6 bits/symbol for the quality values, i.e., three times as much storage as is required for the reads themselves. Base calling is an inherently noisy process by itself. Based on the amount of noise added by this process, it might be possible to achieve a significant reduction in the representation of these values with only a marginal loss of performance by neglecting a portion of the quality value information that encodes mostly noise. Here we explore the use of lossy compression for achieving this goal.

1.3 Related Work and Our Contribution

The literature abounds in efforts to compress the genomic data. Several approaches exist for compression of whole genomes without

![Fig. 2. Typical FASTQ record. We focus on lossily compressing the fourth line - the quality value string - of every record.](image-url)
bits, etc.) without incurring much loss with respect to a standard distortion criterion and hope that a low distortion would imply little compromise in performance at downstream applications? In other words, does our fidelity criterion correspond well to “physical distortion”?

Towards answering this question, we use mean square error as the distortion criterion for our lossy compression. We choose to work with this particular distortion criterion due to its convenient analytical properties than to our belief that it is canonical to measuring the loss incurred in the downstream applications. Further, we model our source of the quality values in the read file as a multivariate Gaussian. This is justified by both central limit arguments (as the sources of noise in the acquisition of the quality values are incremental and independent) and the fact that, given a vector source with a particular co-variance structure, the Gaussian Multivariate source is the least compressible and, further, a code designed under the Gaussian assumption will perform at least as well on any other source of the same co-variance [Lapidoth, 1995]. We then suggest a tractable scalar quantization algorithm and show numerically that it achieves mean square loss comparable to the optimum (that would be achieved using the optimal vector quantization). We further demonstrate that achieving low mean square error translates to comparable performance in the downstream applications as compared to use of the original (uncompressed) quality values.

Our algorithm operates at any non-zero compression rate, and as far as we know is the first implementation of lossy compression of quality values that can accommodate less than one bit per quality value. We find reasonable performance in the downstream applications even in this low-rate regime.

1.4 Organization of the Paper

The paper is organized as follows. In Section 2, a problem formulation is provided with emphasis on how the quality values are modeled, the class of schemes which are considered, and the performance metrics used. Section 3 provides some background on Rate Distortion theory for memoryless sources. Our primary compression technique is transform coding via singular value decomposition (SVD), which we describe in Section 4. Experiments on real data are presented in Section 5. The paper is concluded in Section 6 with directions for future work.

2 PROBLEM FORMULATION

We now formalize the problem of lossy compression of quality values and describe the general model. As discussed in Section 1.1, quality values represent the reliability of a particular read base. The higher the quality value, the higher the reliability of the corresponding base call, and vice versa. More specifically, quality value is the integer mapping of \( P \) (the probability that the corresponding base call is incorrect) and is represented in (at least) the following different scales/standards:

- **Sanger or Phred scale**: \( Q = -10 \log_{10} P \).
- **Solexa scale**: \( Q = -10 \log_{10} \frac{1}{P} \).

The integer \( Q \) values are encoded in ASCII format, for the purpose of this work, and without loss of generality, we consider the Phred+33 in which the range of quality values is \([0, 40]\). A quality value \( Q \) is represented by the letter whose ASCII value is \( Q + 33 \), resulting with letters in the ASCII range of \([33, 73]\).

### 2.1 Modeling Quality Values

We consider files with fixed read length, \( l \). Denote the number of reads in the file by \( N \). The quality values in a file are denoted by \( \{X_i\}_{i=1}^{N} \), where \( X_i = [X_i(1), \ldots, X_i(l)] \). In real data quality values take integer values in a finite alphabet, \( \mathcal{X} \), for example in Phred+33 scale, \( \mathcal{X} = [33, 34, \ldots, 72, 73] \). However, for the purpose of modeling, we assume \( \mathcal{X} = \mathbb{R} \) (the set of real numbers). Each \( X_i \) is modeled as independent and identically distributed jointly Gaussian random vector distributed as \( \mathcal{N}(\mu_X, \Sigma_X) \). The motivation for modeling the reads as Gaussian is already outlined in Section 1.3, while independence assumption is supported by the fact that reads, in general, are randomly sampled from the genome in gene-sequencing step.

### 2.2 Scalar Quantization

The compression techniques which are applied and analyzed in this paper, can be modeled as in Fig. 3.

\[
\begin{align*}
S & \xrightarrow{\text{SCALING}} U \\
X & \xrightarrow{\text{ENTROPY CODING}} U \\
R & = H(U) \text{ bits}
\end{align*}
\]

The quality value vectors \( X_i \) are i.i.d. as \( \mathcal{F}_X \sim \mathcal{N}(\mu_X, \Sigma_X) \), and each is mapped into decision regions representable in a finite number of bits. This is the quantization step represented by \( F(X_i) \). Let the mapped (quantized) values so obtained be referred to by \( U_i \). Each \( U_i \) is then losslessly described via a lossless encoder (such as a Huffman encoder, LZ encoder, etc.). The rate \( R \) of compression is the average number of bits per quality value used to describe the reads. This completes the compression step and is lossy in general due to the quantization step. The quantization could be as simple as truncating some entries, or rounding, or more sophisticated, such as transform coding which is the focus of this paper and will be described in Section 3. We refer to this as “scalar quantization” because each read is quantized separately, unlike vector quantization techniques where different reads are collected and jointly quantized. Vector quantization generalizes scalar quantization, but is harder to implement and typically has minor performance improvements.

For reconstructing the quality value sequence, entropy decoding is used to losslessly reconstruct \( U_i \) from its bit description, and
then the mapping \( G(\cdot) \) is used to get a lossy estimate of \( X_i \), as \( \tilde{X}_i \). The normalized distortion satisfies
\[
D = \frac{1}{N} \sum_{i=1}^{N} \frac{1}{T} \left\| X_i - \tilde{X}_i \right\|_2^{N \rightarrow \infty} = \frac{1}{T} E \left[ \left\| X - \tilde{X} \right\|_2^2 \right],
\]
where the limiting behavior as \( N \rightarrow \infty \) is due to the law of large numbers and \( E \) is the expectation over the statistics of source \( X \). There is obviously a tradeoff between rate and distortion, which depends on the source \( X \) and is quantified via the scalar rate-distortion function, \( R(\cdot)(D, X) \) or distortion-rate function \( D^R(\cdot)(R, X) \) (the superscript \( s \) indicates scalar quantization). Henceforth, the compression model in the paper is that of Fig. 3, which is a special case of the general compression architecture that Rate Distortion theory allows, as is briefly reviewed in Section 3. We demonstrate empirically in Section 4 that scalar quantizers for our data work as well as any vector quantizer. Also, from now on the terms ‘quantization’ and ‘compression’ are used interchangeably.

2.3 Performance Metrics

As discussed in Section 2.2, the mean square distortion is mathematically convenient. Of interest in practice is the deterioration in performance when using the lossily reconstructed quality values relative to a file containing the original quality values. A genome sequence read file, i.e., the FASTQ file can be utilized in a variety of applications by a number of downstream analyzers in genomics. However, almost all such downstream applications would eventually depend on the alignment profile of the reads. This alignment may be either de novo or reference based. We consider reference based alignment here and describe two natural performance metrics that will be used for comparison of our scheme with other schemes. They are:

1. Relative Mapping Accuracy: Let us denote a typical base sequence present in the fastq file by \( r \). The position where \( r \) maps to the reference is denoted by \( P(r) \). Let \( A = \{(r, P(r)): r \in \text{FASTQ}(X)\} \) or the file containing the original uncompressed quality values. From now on with some benign abuse of notation we will abbreviate the original fastq file with uncompressed quality values simply as the uncompressed fastq file. Similarly we denote \( \bar{A} = \{(r, P(r)): r \in \text{FASTQ}(\tilde{X})\} \) for the compressed fastq file. The relative mapping accuracy is simply
\[
\frac{|A \cap \bar{A}|}{|A \cap \bar{A}| + |A \setminus \bar{A}|} 
\]
where \( \cap \) stands for intersection and \( A \setminus \bar{B} \) denotes the elements that belong to \( A \) but not to \( B \).

In other words, the relative mapping accuracy measures what percentage of original (uncompressed) reads have mapped to the same position on the reference sequence with the lossily compressed quality values.

2. Symmetric Difference: This is simply
\[
\frac{|A \setminus \bar{A}| + |\bar{A} \setminus A|}{|A \cap \bar{A}| + |A \setminus \bar{A}|} 
\]
This measures the percentage of reads that align to different positions on the reference sequence with the uncompresed and the lossily compressed quality values.

Ideally, we would want our read file containing compressed quality values to give an alignment profile identical to that of the read file with the uncompressed quality values. In other words, we want a high relative mapping accuracy and a low symmetric difference.

3 RATE DISTORTION THEORY : SOME PRELIMINARIES

In this section, we provide a brief background on Rate Distortion theory for memoryless sources. For detailed description and proofs please refer to [Cover and Thomas, 1991]). We consider fixed rate schemes which are as follows. Referring to Fig. 4 our goal is to encode a source sequence of block length \( n, X^n \), using only \( nR \) bits, in order to minimize the distortion between the original source sequence and the reconstruction sequence, \( \tilde{X}^n \), chosen by the decoder. We assume that our given distortion function \( d : (X, \tilde{X}) \rightarrow R_+ \) operates symbol by symbol (as opposed to block by block) and that the distortion \( D \) is given by \( D = \frac{1}{n} \sum_{i=1}^n d(X_i, \tilde{X}_i) \).

**Definition 1.** A rate-distortion scheme of rate \( R \) consists of the following:

1. An encoder, \( f_n : X^n \rightarrow \{1, \ldots, 2^{nR}\} \).
2. A decoder, \( g_n : \{1, \ldots, 2^{nR}\} \rightarrow \tilde{X}^n \).
3. A reconstruction sequence, \( \tilde{X}^n = g_n(f_n(X^n)) \).

**Definition 2.** The pair \((R, D)\) is said to be achievable if \( \forall \epsilon > 0, \exists n \) and a rate-distortion scheme at rate \( R \leq R + \epsilon \) and (expected) distortion \( \leq D + \epsilon \).

**Definition 3.** The rate-distortion function is defined as \( R(D, X) = \inf \{D' : (R', D') \text{ is achievable} \} \). Similarly, we define the distortion-rate function as \( D(R, X) = \inf \{D : (R, D') \text{ is achievable} \} \).

**Theorem 1.** Gaussian Memoryless Scalar Source [Cover and Thomas, 1991]: For an i.i.d. Gaussian scalar source \( X \sim \mathcal{N}(\mu, \sigma) \), the rate-distortion and the distortion-rate functions are:
\[
R(D, X) = \frac{1}{2} \log \left( \frac{\sigma^2}{D} \right) \mathbf{1}_{\{D < \sigma^2\}} 
\]
(4)
\[
D(R, X) = \sigma^2 e^{-2R},
\]
(5)
where \( \mathbf{1}_{\{A\}} \) is the indicator function that takes the value one when the event \( A \) is true and zero otherwise.

**Theorem 2.** Gaussian Memoryless Vector Source with independent components [Cover and Thomas, 1991]: For an i.i.d. Gaussian vector source \( X \sim \mathcal{N}(\mu, \Sigma_X) \), with \( \Sigma_X = \text{diag}(\sigma_1^2, \ldots, \sigma_t^2) \) (i.e., independent components), the optimal
distortion-rate tradeoff is given as the solution to the following optimization problem:

\[
D(R, X) = \min_{\rho = [\rho_1, \ldots, \rho_l]} \sum_{i=1}^{l} \sigma_i^2 2^{-2\rho_i} \quad \text{s.t.} \sum_{i=1}^{l} \rho_i \leq R.
\]

(6)

(7)

4 COMPRESSION VIA SINGULAR VALUE DECOMPOSITION (SVD)

The general transform coding paradigm is shown in Fig. 5. If the source/signal is “compressible” in a particular domain, intuitively one should transform the source/signal to that domain. First the read vector \( X \) (vector of length \( l \)), is decorrelated by a unitary operation matrix \( V (VV^T = I) \) computed from the empirical statistics of \( X \). The Bit Allocation block then allocates bits to each read position. This allocation is precomputed by using the statistics of the quality value file. Thus for each read, \( Y = VX \) is quantized by a scalar quantizer, to obtain bits \( U \) which are then finally compressed into bits by an entropy encoder. To obtain the “quantized” read vector \( \tilde{X} \), the compressed bit description is first entropy decoded and then demapped by the quantizer into decisions for each bit sequence followed by inverse transform through \( V^T \).

SVD-BitAllocate: Here we perform transform coding as in Fig. 5 with \( V = V_{svd} \).

The rate of bits allotted per quality value sequence is a user specified parameter. The source would be compressed accordingly. Thus we can formulate the bit allocation problem as a convex optimization problem:

\[
\text{minimize } \frac{1}{l} \sum_{i=1}^{l} \sigma_i^2 2^{-2\rho_i} \quad \text{subject to } \sum_{i=1}^{l} \rho_i \leq R.
\]

(8)

The objective function here is the mean squared error per quality value. Hence the rate \( R = \sum_{i=1}^{l} \rho_i \), where \( \rho_i \) is the number of bits allocated to the \( i^{th} \) component of \( Y \). Since \( Y \) has independent Gaussian components under our modeling assumption, the optimal value of the above Problem 8 is exactly equal to the optimal distortion rate function for a Gaussian source as outlined in Section 3. The solution to Problem 8 dictates the number of bits that needs to be allocated to store \( Y \). Ideally this allocation should be done by vector quantization for the whole block \( Y \) together. However, due to ease of implementation and negligible performance loss, we use a scalar quantizer. Thus the component \( Y \) is normalized to a unit variance Gaussian (the variances of each component are either known from the statistics of the read file or are estimated) and then it is mapped to decision regions representable in \( \rho_i \) bits. The decision regions and their representative values (stored in \( D_{map}(\rho_i) \)) for all possible \( \rho_i \) are found from a Lloyd Max procedure on a scalar Gaussian distribution, i.e., for \( \rho_i \) bits the \( D_{map}(\rho_i) \) will store \( 2^{\rho_i} \) regions (boundary points and representative value for each region) which would give the minimum mean squared error for a unit variance Gaussian.

Algorithm 1 SVD-BitAllocate(\( X_{svd}^{N}, R \))

\[
\mu_X, \Sigma_X \leftarrow \text{Empirical mean and covariance of } X_{svd}^{N} \\
\text{Compute } \text{SVD } \Sigma_X = V_{svd} S V_{svd}^T, S = \text{diag}(\sigma_1^2, \ldots, \sigma_l^2) \\
\text{Precompute Lloyd Max quantizer } D_{map} \text{ for gaussians} \\
\text{for } i = 1 \rightarrow N \text{ do} \\
\quad Y_i \leftarrow F_{svd} X_i \\
\quad \rho_i \leftarrow \text{BitAllocate}(S, R) \\
\quad U_i \leftarrow \text{Scalar-Quantization}(D_{map}, Y_i, \rho) \\
\text{end for} \\
\text{function } \text{BitAllocate}(S, R) \\
\quad \min_{\rho} \frac{1}{l} \sum_{i=1}^{l} \sigma_i^2 2^{-2\rho_i} \\
\quad \text{such that } \sum_{i=1}^{l} \rho_i \leq R \\
\text{end function} \\
\text{function } \text{Scalar-Quantization}(D_{map}, Y_i, S, \rho) \\
\quad \text{for } j = 1 \rightarrow l \text{ do} \\
\quad \quad \hat{Y}_i(j) \leftarrow \sigma_j Y_i \\
\quad \quad \hat{U}_i(j) \leftarrow \text{Quantize } \hat{Y}_i(j) \text{ using } D_{map}(\rho_j) \\
\quad \text{end for} \\
\text{end function}
\]

Once we get \( U_i^{N} \), we may perform lossless compression using standard universal entropy coders. However, this was found to achieve negligible compression improvements over \( R \) bits per read, and hence was not considered in the numerical results, to which we now turn.

5 RESULTS

We present the results of numerical experiments with our algorithm on real read data. The data was downloaded from the NCBI human genome sequence read archive [NCBI 2012] (reads with identifier ERR005351 are used). The total number of quality value sequences considered for the data presented is about 20 million, each sequence length (i.e., read length) being 46. We tested the mean squared error performance of the quantized quality values from our algorithm against other algorithms [Wan et al. 2011] Figure 6. The results
Fig. 6. Mean squared error plots as a function of the number of bits allocated per position. The optimal here refers to the solution of Problem \(\text{\cite{Wan et al.}}\). Log Binning is proposed in \(\text{\cite{Wan et al.}}\).

Fig. 7. Percentage of reads which have been aligned to the same positions as the original unquantized reads. Log Binning has been proposed in \(\text{\cite{Wan et al.}}\).

Fig. 8. Fraction of size of symmetric difference over size of mapped reads with unquantized values. Log Binning has been proposed in \(\text{\cite{Wan et al.}}\).

show that for low number of bits per quality value position, our algorithm achieves much lower mean squared error compared to existing implementations (binning based quantizers \(\text{\cite{Wan et al.}}\)). At higher values, the degradation in mean squared error (MSE) comes from the fact that our modelling assumption works with continuous real numbers, hence the “optimal” mean square value does not vanish even with increasingly many bits. Thus, the log binning curve (which works with the integers directly) performs better and actually goes below the “optimal” MSE curve for sufficiently high number of bits. Note that with 6 bits per position, we can code for the quality values losslessly.

We also show the alignment performance by a sequence read aligner (bowtie) with our quality value sequences. Figure 7 and 8 show the performance of the relative mapping accuracy and symmetric difference (defined in Equations 3 and 2) between reference based alignment using the quantized files as a function of the bits allocated per quality value position. This can influence several downstream applications like variant calling/SNP detection (Figure 7). The plots show little performance loss even with very small number of bits per position. This also corroborates our overall claim that lower distortion with respect to mean square loss translates to comparable performance in the downstream applications. Further our framework allows us to work with less than one bit per quality value, which may prove invaluable in future applications where the number of reads and their lengths will be increased manyfold. Also note that for zero rate, we are using just the mean of the quality values over all the reads. Since this needs a constant storage cost, the amortized number of bits required to store this information for large numbers of reads is zero. The curves in Figure 8 suggest that even with this information, we can achieve performances much better than by discarding quality values altogether.

The plots, as expected, show increasingly better match with higher rates, with reconstructions using the original quality value sequence. This is due to the fact that the alignment performance has been compared to the uncompressed values. However, in accordance with our conjecture to be studied in future work, the curve measuring the ‘true’ performance with respect to the yet unknown ‘ground’ truth may not be monotone with increasing rate, as limiting the rate may denoise the data and hence enhance the accuracy.

6 DISCUSSION

We have presented a scheme for lossy compression of the quality value sequences arising in genomic data. By directly allocating bits to the most significant variations, our scheme simply and effectively captures the information in the quality value sequence given limited storage resources. While refinements such as the use of clustering ideas to learn the statistics of the reads more finely would likely
result in improved performance in the downstream applications (as compared to using the original quality value sequence), we suspect, based on preliminary observations, that our scheme may also achieve some form of denoising. Our thesis is that appropriate lossy compression of the quality values may result not only in improved compression ratios, but also in improved performance in the downstream applications, such as improved accuracy in sequence assembly that would be based on the lossy rather than the original version of the quality values. This prospect and its applications in high volume read sequencing is an exciting direction for future investigations.

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