Transformations for the Compression of FASTQ Quality Scores of Next Generation Sequencing Data

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\section*{ABSTRACT}
\textbf{Motivation:} The growth of next generation sequencing means that more effective and efficient archiving methods are needed to store the generated data for public dissemination and in anticipation of more mature analytical methods later. This paper examines methods for compressing the quality score component of the data to partly address this problem.

\textbf{Results:} We compare several compression policies for quality scores, in terms of both compression effectiveness and overall efficiency. The policies employ lossy and lossless transformations with one of several coding schemes. Experiments show that both lossy and lossless transformations are useful, and that simple coding methods, which consume less computing resources, are highly competitive, especially when random access to reads is needed.

\textbf{Availability and Implementation:} Our C++ implementation, released under the Lesser General Public License, is available for download at http://www.cb.k.u-tokyo.ac.jp/asailab/members/rwan. Contact: r-wan@cb.k.u-tokyo.ac.jp

\textbf{Supplementary Information:} Supplementary data are available at Bioinformatics online.

\section{INTRODUCTION}

Next generation sequencing offers new directions in genome science by allowing entire genomes to be sequenced at lower costs. Given its rapid growth, the problem of economically storing and quickly restoring sequencing data is becoming a concern for both researchers and operators of data centers.

The most notable examples of data repositories is the Sequence Read Archives (SRA) by the International Nucleotide Sequence Database Collaboration (INSDC) at NCBI, EBI, and DDBJ, which helps in disseminating publicly-funded data (Leinonen \textit{et al.}, 2011). While the storing of raw data is infeasible, their hope is to be able to store at least the bases and their corresponding quality scores.

On the other hand, as the amount of data continues to rise, it is conceivable that the burden of storing such data will gradually shift to research laboratories, hospitals, or even individuals. Effective means of storing sequencing data will be needed in these cases as well, even though the resources available will differ greatly.

The above trends suggest that economical representation of sequencing data is important. In response, compression of DNA sequences has been an active research topic for many years. In contrast, relatively little attention has been devoted to quality scores. The set of quality scores is far larger than the four DNA nucleotides; this has the potential to make the problem more difficult than sequence compression. Whenever the economical representation of quality scores was taken into account, the scores were considered together with \textit{all} other components. Hence, it is not clear how well the quality scores component can be compressed.

Note that the little attention given to quality scores does not mean that they are useless. In fact, they are slowly becoming a necessary part of many data analyses. They \textit{can} be used to trim reads at either end (see the Galaxy tool [Blankenberg \textit{et al.}, 2010] for an example) or be used for read mapping, as demonstrated by the MAQ software [Li \textit{et al.}, 2008]. Other future applications may also be possible.

In this paper, we address the issue of economical representation of quality scores as a stand-alone component. This separation allows us to focus on the topic at hand, and does not limit us from combining our results with other works that are devoted to compressing DNA sequences alone. To have a clear understanding, and to supply different levels of economy trade-off, we break the process of economical representation into three independent and optional components: lossy transformation, lossless transformation, and coding (or compression). Rather than advocating a single method for each component, we will explore various options.

\section{BACKGROUND}

Next generation sequencing (NGS) generates raw data as images from which the sequence bases are obtained. In practice, each \textit{read} consists of a sequence of DNA bases, the estimated probabilities $P$ that the respective bases was called incorrectly, plus other supporting information. The probabilities, or \textit{error probabilities}, are stored as quantized integers which are the object of our study.

\textbf{Standard Representation:} Public repositories such as the SRA normally store reads in a human-readable format called FASTQ,
as illustrated in Figure [1]. In this format, an error probability $P$ is first transformed to its respective PHRED quality score $Q$ in a logarithmic manner so as to give more attention to the higher quality bases [Ewing & Green, 1998]:

$$Q = -10 \times \log_{10} P.$$ 

Then, $Q$ is truncated and limited to only integers from 0 to 93 (hence the maximum 93 includes all the values $P$ of $5 \times 10^{-10}$ or less). Lastly, each integer is offsetted by 33 to make it in the range from 33 to 126 which are ASCII codes of printable characters. This final format is referred to as the Sanger-FASTQ format, which is the de facto standard [Cock et al., 2010] for representing the error probabilities. For the clarity of presentation, we use the special term $Q$-scores to refer to the scores in this format, and note that all of our input error probabilities are in this format.

Concise Representations: Representing each PHRED score in one byte as dictated by the Sanger-FASTQ format is not the best method in terms of storage economy. Data compression can be used to obtain a more space-saving representation.

Compression has been an important component of computational biology, as surveyed by Giancarlo et al. (2009). Generally, short DNA sequences are compressed by encoding them with respect to other data such as a larger genome through “edit operations” – instructions that indicate the mismatches needed to map the short sequences to the genome (see, for example, Daily et al. [2010]).

In recent years, NGS data in FASTQ format has attracted some attention from the compression field. Tembe et al. [2010] encode both the DNA sequences and the $Q$-scores together, treating each distinct pair of DNA base and its respective $Q$-score as a new symbol, and then applying Huffman coding [Huffman, 1952]. Deorowicz & Grabowski [2011] encode all parts of the FASTQ data through a combination of creating independent blocks, LZ77 compression [Ziv & Lempel, 1977], run-length coding, and Huffman coding. These two compression schemes are classified as lossless since the compressed data can be decoded to get back the original data, without any change.

In addition to lossless there exists lossy compression, for which the data can be restored, not as the original, but with some changes that can be regarded as acceptable for applications. Lossy methods can be considered for quality scores – an option that has been advocated by others [Leinonen et al., 2011]. For example, Kozanitis et al. [2011] encodes DNA sequences with respect to a reference genome. The $Q$-scores are compressed using a combination of taking the gaps between adjacent scores and lossy compression. They noted that the gaps between adjacent scores in a sample data set were usually small (often zero). Because of this, they randomly permuted $Q$-scores so that they were either just above or just below the previous score. Amortized over the entire data set, the effect of such randomization balances out. Using SNP calling as an example, they showed that such a lossy transformation has a minimal effect on downstream applications. More recently, Hsi-Yang Fritz et al. [2011] defined “quality budget” as a filter to determine what $Q$-scores are stored. Basically, only the scores associated with sequence bases of interest are retained.

A common theme of the above described methods is that when coding, they treat the $Q$-scores or the gaps between adjacent $Q$-scores as plain symbols, without considering the integral values of the symbols. For Huffman and LZW77 methods, symbols (or sequence of symbols) are processed so that those with higher frequencies will be assigned shorter codewords. We refer to this way of compression as by-symbol; we will also consider by-value compression methods – methods that assign shorter codewords to lower integers, regardless of their frequencies.

3 DATA ANALYSIS

We first analyze some properties of $Q$-scores. Three data sets, summarized in Table I were randomly selected from SRA for that and the subsequent experimentation. The last two columns of the table shows the size of the $Q$-scores and the entire FASTQ data (with both the meta-information and sequences) in MiB. The values in parentheses is their compression ratio as a percentage of the original data when the standard tool gzip is used. Elsewhere in the paper, the compression ratio is defined as the ratio between the size of the compressed data and the size of the original data, expressed in bits per quality score.

Following the lead of Kozanitis et al. [2011], on using score gaps, in addition to statistics for the population of reads and the population of individual $Q$-scores, we also gather additional statistics for another form of $Q$-scores, produced through gap transformation. We transform the sequence $(q_1, q_2, q_3, \ldots q_{n-1}, q_n)$ of $n$ $Q$-scores, in the following manner. First, they are translated to the equivalent form of score gaps $(q_1 - 33, q_2 - q_1, q_3 - q_2, \ldots q_{n} - q_{n-1})$. These gaps are in the range of $[-(\Sigma - 1), \ldots (\Sigma - 1)]$, with $2\Sigma - 1$ different values, where $\Sigma$ is the set of all possible $Q$-scores (hence $\Sigma = 94$). However, we further transform each of the gaps to a positive integer by using the bijection $(0, 1, -1, 2, -2, \ldots 2, 2, 1, -1) \rightarrow (1, 2, 3, \ldots 2, 2, 1)$. Each resulting value will be referred to as a T-gap.

Some important statistics of $Q$-scores and T-gaps are presented in Figure [2]. From the figure we underlined the following three properties, which will be explored in the next section:

Absolute $Q$-score bounds are rarely reached: According to Figure [2a], a large number of reads have their own local minimal $Q$-score different from 0 and 93.

Table 1. Three SRA data sets employed in this paper. The last two columns give the size of the $Q$-scores and the original FASTQ data in MiB. Percentages in parentheses indicate the compression ratio when gzip is applied to the data.

<table>
<thead>
<tr>
<th>Accession</th>
<th>Species</th>
<th># reads (x10⁶)</th>
<th>Len</th>
<th>Size (MiB)</th>
<th>Q-scores Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRR032209</td>
<td>M. musculus</td>
<td>18.8</td>
<td>36</td>
<td>662.8</td>
<td>3,488.2</td>
</tr>
<tr>
<td>SRR070788_1</td>
<td>H. sapiens</td>
<td>24.8</td>
<td>100</td>
<td>2,393.2</td>
<td>8,092.1</td>
</tr>
<tr>
<td>SRR089526</td>
<td>H. sapiens</td>
<td>23.9</td>
<td>48</td>
<td>1,115.7</td>
<td>4,814.2</td>
</tr>
</tbody>
</table>
Our investigation follows the diagram in Figure 3. The FASTQ data is first decomposed to separate the Q-scores data from the rest. The Q-scores then can go through the lossy and lossless transformation, and finally the encoding processes to reach point (A), where the compressed representation is attained, and hence compression ratio can be measured. From this point the reverse process can take place. The decoding and lossless untransforming processes are applied to the compressed data to reproduce the Q-scores, which might or might not be the same as the original Q-scores data, depending on whether or not any lossy transformation has been selected. The “Composer” will then recreate the FASTQ-formatted data. After that, at point (B) in the diagram, we can evaluate the effect of lossy transformations (if any) by mapping these data to a reference genome using the MAQ software [Li et al. 2008].

4.1 Blocking

Most of the compression schemes collect some information over the input data before encoding. They normally segment the input stream into non-overlapping blocks and process each block independently in order to limit and optimize peak memory usage. To accommodate that, we explicitly perform the blocking of Q-scores right after they have been produced by the “Decomposer” component, before any of the lossy and lossless transformations. We define the block size $k$ as the number of reads instead of the number of elementary Q-scores to ensure that no read spans across block boundaries, which in turns guarantees that blocks could be compressed or decompressed independently from each other.

In general, block creation incurs only a small cost in the form of local block information at the beginning of each block – the block header. However, as will be seen, some compression schemes might add much more data to the block header, and the relative volume of this data is higher with smaller $k$. To keep these schemes effective, it is essential to set $k$ large enough. On the other hand, smaller $k$ means more flexibility in decoding, and $k = 1$ allows random access to each block in the compressed data – a plus or even a critical feature for some applications. Throughout our investigation, we will consider both small and large block sizes in order to accommodate a potential diversity of applications.

4.2 Lossy Transformation

As stated earlier, Q-scores is an irreversible quantization of some original (floating point) probabilities, and can have $|\Sigma| = 94$ distinct values. The quantization can be viewed as the process of partitioning the probability interval $[0,1]$ into $|\Sigma|$ sub-intervals, or bins, so that the lengths of the bins grow in a logarithmic manner (the closer to the left of $[0,1]$, the shorter the bins). Probabilities falling into the same bin are deemed to share the same quantized Q-score. For clarity we will refer to this method of quantizing the error probabilities as Standard.

As our aim is space saving, it is natural then to think about transformations that are more aggressive than Standard with regard to reducing the number of partitioned bins. For that, we introduce three lossy transformations that are each defined by a unique way to partition the probability interval into bins. We abuse our earlier terminology by unifying their parameters as $|\Sigma|$, which represents the number of distinct bins. After partitioning, each bin is associated with the lowest Q-scores that falls into the bin. Note that since the mapping from bin order to the associated

![Fig. 2. Some statistics for each of the three described data sets: distribution of minimal and maximal Q-scores over the population of reads (top), and distribution of Q-scores (bottom left) and T-gaps (bottom right).](image-url)

![Fig. 3. Workflow of our investigation. Dashed arrows depict a representation of Q-scores alone.](image-url)
4. Lossy Transformation

The lossy transformations benefit compression by means of reducing the number of distinct quantized quality scores. On the other hand, a lossless transformation is a reversible mathematical mapping over the quantized scores so that the scores can be untransformed back without any change. A transformation can potentially improve compression ratio if it yields a distribution of transformed values that is more suited for compression than the untransformed ones. Judging by the analysis in Section 4.2 we investigate the following three lossless transformations.

MinShifting This method converts each Q-score $q$ to $q - q_{\text{min}}$, where $q_{\text{min}}$ is the minimal score in the respective block. This requires $q_{\text{min}}$ to be stored in the block header.

FreqOrdering This technique remaps the Q-scores that appear in the block to the set of contiguous positive integers starting from 1 in order of decreasing frequency. The reverse mapping needs to be stored in the header.

GapTranslating For a block of $n$ quantized scores, this transformation is the combination of taking gaps between adjacent scores and translating these gaps to positive integers, exactly as described earlier in Section 4.2.

It is clear that all the three lossless transformations have a common theme – to map the quantized scores to lower values. Naturally, they will mainly benefit the by-value compression schemes. However, as a special case, the GapTranslating transformation can potentially affect the by-symbol schemes, since it dramatically changes the symbol set as well as the distribution curves. Based on these definitions and the distribution curves of Figure 4, it seems unnecessary to apply more than one lossless transformation at any one time.

4.4 Compression

For clarity of presentation, we assume that the input block of the coding process, that is, the encoding stream is $X = x_1 x_2 \ldots x_n$. These integers, or symbols, do not necessarily have to be standard Q-scores due to the lossy and lossless transformations. More generally, they are drawn from a known set of $\ell$ distinct integers $\Omega = \{\omega_1, \omega_2, \ldots, \omega_\ell\}$, which can be easily computed for each combination of lossy and lossless transformations.

Four groups of compression methods are considered, which differ in the level of lossy and lossless transformations. More generally, they are derived from a known set of $\ell$ distinct integers $\Omega = \{\omega_1, \omega_2, \ldots, \omega_\ell\}$, which can be easily computed for each combination of lossy and lossless transformations.

Static codes: A code of this group associates each positive number with a distinguished and fixed codeword. Hence the codeword for a symbol $\omega \in \Omega$ is fixed in advance, regardless of neighboring symbols or the overall frequency of that symbol in the encoding stream. Each static code is designed for a particular distribution of the integer numbers, and in fact a minimum-redundancy code for that distribution. The simplest code is unary, which encodes a value $\omega \geq 1$ as a sequence of $\omega - 1$ one-bits followed by a single zero-bit. Another code, gamma, which is more effective than unary for large numbers, codes a value $\omega \geq 1$ in two parts: the value of $v = \lceil \log_2 \omega \rceil$ in unary, and $v$-bit binary representation of $\omega - 2^v$. For larger numbers, a reasonable code is delta, which is similar to gamma, but with $v$ coded using gamma rather than unary.

Parameterized codes: These codes are not context-free, as they each employ a parameter which is derived from making a pass over the encoding.
stream. The simplest code of this family is binary, that employs the parameter $b = \max(x_1, x_2, \ldots, x_n)$. It uses the binary representation of $x = 1$, in either $[\log_2 b]$ or $[\log_3 b]$ bits, as the codeword for $x \in X$.

One interesting code of this group is golomb (Golomb, 1966), which uses the parameter $b$, computed from $n$ and $N = \sum_{i=1}^n x_i$. It codes a value $x \in X$ as the pair $(x/b, x \mod b)$. Gallager & van Voorhis (1975) show that golomb is a minimum redundancy code when the distribution of the alphabet $f(x)$ is geometric. That makes golomb attractive for compressing T-gaps. A related coding scheme that we also considered is rice (Rice, 1979), that differs from golomb only by forcing $b$ to be a power of 2.

When the input stream has some sort of clustering, interpolative coding (interp) by Moffat & Snir (2006) is a good choice. It first converts the input stream $X$ to the equivalent sequence of cumulative sums $X'$, and separately codes the first and last elements of the later. Then, it codes the middle element of $X'$ using binary, whose parameter is computed from the values of the first and last elements. It continues recursively to the left and right halves of $X'$.

Minimum redundancy codes: Minimum redundancy coders employ the minimum number of bits to encode the data stream based on the actual distribution of the input symbols. More frequent symbols are assigned shorter codewords in an optimized manner. Huffman code (huffman), invented by Huffman (1952), is an excellent representative of this family due to its simplicity and efficiency.

Complex codes: Under “complex codes” we refer to compression systems (as opposed to single codes) which do not generate codewords for single symbols, but for sequences of symbols instead. They normally spend a considerable amount of time to build the set of symbol sequences and then apply some form of minimum redundancy coding as the final stage. Representatives include zlib (http://www.zlib.net/) - the library version of the widely-available compression system gzip, and libbzip2 - the library version of bzip2 (http://www.bzip.org/).

It can be easily seen that the above four coding families were presented in increasing order of algorithmic complexity, at least in terms of the encoding process. Moreover, the first two families have the by-value nature, while the other two are by-symbol. It can be expected that as we move down the above list of four families, we can get better compression ratios, and get poorer encoding times. And it is no doubt that the further we progress down this list, the method will request more memory to perform their work.

5 RESULTS

This section reports the main experiment results for the data set SRR032209. Additional results, including those for the data set SRR070788_1 are provided in the supplement. All experiments were conducted on a set of 2.53 GHz 8-Core Intel Xeon E5540 with 12 GB of RAM and hyper-threading.

5.1 Space

Effects of lossless transformations: Figure 5 demonstrates the compression effectiveness, as compression ratios, achieved by the described lossless transformations with various block sizes.

The most noticeable feature in the figure is the near immobility of the by-symbol curves, and the variability of the by-value curves across the four graphs. As anticipated, in general, the lossless transformations improve compression ratio for the by-value methods, and have almost no effects on the by-symbol compression schemes. Moreover, all the by-symbol compression schemes are not effective when the block size $k$ is small.

The effect of lossless transformation on the by-value compression schemes is tremendous. In fact, these compression schemes are unsuitable for the original Q-scores, as shown in box (a) of the figure. It is understandable, as the minimal Q-scores of 33 is already a large value for these methods which reserve short codewords to small values. While we can take off 33 from all Q-scores before encoding to improve compression effectiveness, that simple operation is not considered here because it cannot do better than the MinShifting transformation.

Panels (b) and (c) of Figure 5 clearly show the difference in performance between MinShifting andFreqOrdering. The former has a very low cost in terms of block headers, and performs well when $k = 1$, but gets worse when $k$ grows since the impact of the minimal value lessens. On the contrary, while FreqOrdering spends more for the block headers, the absolute cost is stabilized when $k$ is large enough, making FreqOrdering the clear winner. It should be noted, however, that the combination ($k = 1$, MinShifting, binary) is the simplest from panels (b) and (c), but achieves a very impressive compression ratio. This combination can be a good choice when random access is a need.

Finally, Figure 5(d) shows that GapTranslating is the best overall lossless transformation for the by-value coding schemes, with the only exception of binary. It is interesting to see that the compression ratio is almost stable across different $k$. Moreover, the compression ratio attained by interp is very close to that achieved by the by-symbol compression schemes with large $k$. The solid black lines indicate the zero-order self-information for each transformed data set – a limit that can be improved upon through block creation or more complex models.

Based on Figure 5, we will further consider four representative coding schemes: gamma, interp, huffman, and libbzip2.
Effects of lossy transformations: Compression ratio achieved with different levels of granularity of the lossy transformation LogBinning for the data set SRR032209 is shown in Figure 6. As one would expect, the more stringent the lossy transformation, the better the compression ratio. With \( k = 1 \), the combination of (GapTranslating, interp) is the clear winner. With \( k = 256 \) or 16384, although libbzip2 with no lossless transformation is the best, interp and gamma with GapTranslating can achieve fairly close compression ratios.

In general, when a relative mapping accuracy of 99% is acceptable, the lossy transformation LogBinning with \( |\Sigma| = 5 \) can be applied. At this setting, various combinations of lossless transformations and coding methods can achieve compression ratios of around 1 bit per quality score – a dramatic progress in comparison to the level of 2.5 bits per quality score achieved in the absence of any lossy transformation.

5.2 Speed

When our main goal is space economy, processing (transformation and coding) time is also important. Both compression and decompression times are of concern – throughout the day, compression is initiated by a data archiver many times, while decompression is performed just a few times, but by many users.

Figure 7 samples the time for the four representative cases across block sizes and coding methods, with either the lossless transformation set at GapTranslating or the lossy transformation fixed at LogBinning. The figure shows that when \( k = 1 \) the order of both compression and decompression time reflect well the algorithmic complexity of the coding methods. However, while it takes less time to compress than to decompress with the by-value methods, the order is reversed for the by-symbol methods. In particular, the compression time of libbzip2 is dramatically higher than that of all other.

When \( k \) changes from 1 to 256, all running times improve with the times for libbzip2 improving the most due to the higher running times for \( k = 1 \). With \( k = 256 \) and the LogBinning lossy transformation, the by-symbol methods clearly outperform the by-value methods in terms of both compression and decompression times. This is explained partly by the reduction of the alphabet size. While this reduction has little meaning to the by-value methods since they do not rely on either symbol frequencies or pattern of symbols, it does help the by-symbol methods in reducing the size of the frequency table and creating more and longer repeated patterns.

6 CONCLUSION

In this work, we have considered how to economically represent quality scores in NGS data as a combination of three main components: lossy transformation, lossless transformation, and coding. Of them, the first two are optional, but they can considerably affect the whole process. By separating these components, we were able to see the effects each of them can bring, and also to identify the best settings in order to achieve good system performance.

In our study, we proposed three lossy transformations, introduced or made use of three lossless transformations, investigated several by-value coding schemes, and considered more conventional by-symbol methods. Moreover, we demonstrated how data blocking can affect both compression ratios and running times. Finally, we also proposed a method to assess the usability, or worthiness, of any lossy transformation by employing the read mapping tool MAQ.

We found that while full-fledged compression systems such as libbzip2 are widely accepted for economical representation of NGS, they are not the best choice for quality scores. Here, simple codes such as the static code gamma and parameterized codes interp and golomb, when accompanied by the lossless transformation GapTranslating, are highly competitive: they can achieve similar levels of compression while using less time.
In particular, unlike their counterparts which are effective only with large block sizes, the simple codes have the distinguished feature of being unaffected by this factor. This is an important point because it essentially removes the block size parameter from the process, and allows simple codes to greatly outperform their counterparts when small block sizes are in use. Note that small block sizes offer a number of advantages which we have not explored. First, peak memory usage is reduced. Second, since blocks are coded independently, errors in the compressed data stream can be isolated easily. Third, random access in compressed data can be supported at the additional low cost of an index before each block. Finally, independent blocks mean that our findings would apply to higher coverage data sets.

As expected for the lossy transformations, compression ratios positively correlate with the number of distinct quality scores. Of the three proposed transformations, LogBinning is the most effective – it achieves excellent relative mapping performance even when employing only a few distinct quality scores. With this choice, compression ratio is improved by around six times, while processing time, when coupled with by-symbol coding schemes, is reduced significantly – all suggesting that lossy transformations are useful.

Our results for SRR032209 are supported by those of SRR0707881, which appear in the supplementary document. Even though the reads are longer, the relative performance of the transformation and compression methods remain the same.

Our view is that as NGS data continues to grow, lossy and lossless transformations can work in tandem. For example, NGS data can be compressed losslessly and kept in off-line storage (such as tape backup) while lossy versions of the data can be shared between users and research laboratories for daily use. Employing lossy transformations requires consideration since such changes are more easily noticeable and difficult to assess compared to images and video data (Witten et al. 1994) – our evaluation with MAQ is meant to address this issue.

In the future, we plan to reorder the reads, as was done by Wan & Asai (2010) for the sequence bases, so that each block possesses reads that have similar quality score patterns. With respect to running time, we intend to parallelize some of our methods across blocks. Furthermore, the effect of lossy transformations on other applications of NGS data, such as RNA-Seq and SNP calling, also need to be evaluated.

Our implementation, dubbed QScores-Archiver, is available from http://www.ch.k.u-tokyo.ac.jp/asailab/members/rwan under the Lesser General Public License version 3 or later to allow users to combine it with their FASTQ compression systems.

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REFERENCES