**ABSTRACT**

Research in the genomic sciences is confronted with the volume of sequencing and resequencing data increasing at a higher pace than that of data storage and communication resources, shifting a significant part of research budgets from the sequencing component of a project to the computational one. Hence, being able to efficiently store sequencing and resequencing data is a problem of paramount importance. In this article, we describe GReEn (Genome Resequencing Encoding), a tool for compressing genome resequencing data using a reference genome sequence. It overcomes some drawbacks of the recently proposed tool GRS, namely, the possibility of compressing sequences that cannot be handled by GRS, faster running times and compression gains of over 100-fold for some sequences. This tool is freely available for non-commercial use at ftp://ftp.ieeta.pt/~ap/codecs/GReEn1.tar.gz.

**INTRODUCTION**

Inspired by the Biocompress algorithm of Grumbach and Tahi (1), the last two decades have witnessed the proposal of a myriad of algorithms for compressing genomic sequences [(2–16) for a recent review]. The acquired knowledge regarding genome structure that these compression algorithms have been providing, through their representation of genomic sequences using probabilistic models, is likely to surpass in relevance the benefits of the effective storage space reduction provided.

One of the most successful compression algorithms specifically designed for genomic sequences is XM, a statistical method proposed by Cao et al. (14), though other approaches may present competitive or even superior results for some classes of genomes (15,17). XM relies on a mixture of experts for providing symbol by symbol probability estimates that are fed to an arithmetic encoder. The XM algorithm comprises three types of experts: (i) order-2 Markov models; (ii) order-1 context Markov models, i.e. Markov models that rely on statistical information from a recent past (typically, the 512 previous symbols); (iii) the copy expert, which considers the next symbol as part of a copied region from a particular offset. The probability estimates provided by the set of experts are then combined using Bayesian averaging and sent to the arithmetic encoder.

Common practice continues to rely on standard and general purpose data compression methods, e.g. gzip or bzip2. However, this practice may be close to a turning point, as the rate at which genomic data is being produced is clearly overtaking the rate of increase in storage resources and communication bandwidth.

The development of high-throughput sequencing technologies that offer dramatically reduced sequencing costs enables possibilities hardly foreseeable a decade ago (18). Large-scale projects such as the 1000 Genomes Project (http://www.1000genomes.org/) and The Cancer Genome Atlas (http://cancergenome.nih.gov/), as well as, prizes that reward cheaper, faster, less prone to errors and higher-throughput sequencing methodologies (e.g. http://genomics.xprize.org/) are paving the way to individual genomics and personalized medicine (19). As such, huge volumes of genomic data will be produced in the near future. However, as a very significant part of the genome is shared among individuals of the same species, these data will be mostly redundant. Some ideas for storing and communicating redundant genomic data have already been put forward, based on, for example, single nucleotide polymorphism (SNP) databases (20), or insert and delete operations (21).

Recently, Wang et al. (22) proposed a compression tool, GRS, that is able to compress a sequence using another one as reference without requiring any additional information about those sequences, such as, a reference SNPs map. The algorithm proposed by Kuruppu et al. (23) RLZ, is also able to perform relative Lempel–Ziv compression of DNA sequences, though its current implementation cannot fully handle sequences that have characters outside the {a,c,g,t,n} set.

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Other approaches propose encoding sequence reads output by massively parallel sequencing experiments (24–27), which is also a very important problem. The compression of short reads shares some points with the problem being addressed here, though it needs to cope with other requirements, such as, the efficient representation of base calling quality information.

In this article, we describe GReEn (Genome Resequencing Encoding), a new tool for compressing genome resequencing data using a reference genome sequence. As such, it addresses the same problem as GRS (22), RLZ (23) or XM (14). However, as will be demonstrated, GReEn outperforms GRS in storage space requirements and running times, though GRS can handle some sequences in a very effective way, and it overcomes RLZ’s and XM’s lack of support for arbitrary alphabets and inferior performance.

GReEn is a compression tool based on arithmetic coding that handles arbitrary alphabets. Its running time depends only on the size of the sequence being compressed. Moreover, it provides compression gains of over 100-fold for some sequences, when compared to GRS, and even larger gains when compared to RLZ. Finally, GReEn handles without restriction sequences that cannot be compressed with GRS due to excessive difference to the reference sequence.

MATERIALS AND METHODS

Dataset

We use the same data as in (22), for ease of comparison with GRS: two versions of the first individual Korean genome sequenced, KOREF_20090131 and KOREF_20090224 (28); two versions of the genome of the thale cress Arabidopsis thaliana, TAIR8 and TAIR9 (29,30); and two versions of the rice Oryza sativa genome, TIGR5.0 and TIGR6.0 (31). We also present results for four additional human genome assemblies, namely, the genome of J. Craig Venter referred to as HuRef (32), the Celera alternate assembly referred to as Celera (33), the genome of a Han Chinese individual referred to as YH (34), and the human genome reference assembly build 37.p2, as made available by the National Center for Biotechnology Information and referred to as NCBI37 (35).

Software availability

The codec (encoder/decoder) is implemented in the C programming language and is freely available for non-commercial purposes. It can be downloaded at ftp://ftp.ieeta.pt/~ap/codecs/GReEn1.tar.gz.

The compression method

As with GRS (22), GReEn relies on a reference sequence for compressing the target sequence. The reference sequence is generally only slightly different from the target sequence, although this is not mandatory. In fact, it is possible to use a sequence from a different species as reference, though, as expected, the compression efficiency depends on the degree of similarity between both reference and target sequences. Moreover, in order to recover the target sequence, the decoder needs access to exactly the same reference sequence as that used by the encoder.

The codec developed in GReEn is able to handle arbitrary alphabets, although it automatically ignores all lines beginning with the ‘>’ character, as well as, all newline characters. We denote by \( \mathcal{C} = \{ c_1, c_2, \ldots, c_m \} \) the set of all different characters, or symbols, that are found in the target sequence, where \( |\mathcal{C}| \) denotes the number of elements in \( \mathcal{C} \), i.e. the alphabet size.

Each character of the target sequence is encoded by an arithmetic encoder (36). As with any arithmetic encoder, besides the symbol to encode, it is necessary to provide the probability distribution of the symbols. One major advantage of arithmetic coding is its ability to adjust the probabilistic model as the encoding proceeds, in response to the changing probability distribution from one encoded symbol to the next.

We denote by \( \theta(c) \) the relative frequency of character \( c \in \mathcal{C} \) in the target sequence, and by \( P_n(c) \) the estimated probability of character \( c \in \mathcal{C} \) when encoding the character at position \( n \) in the target sequence. The set of probabilities \( \{ P_n(c), c \in \mathcal{C} \} \) are passed down to the arithmetic coder. Note that, whereas \( \theta(c) \) values are fixed for a given target sequence, \( P_n(c) \) values usually change along the coding process. For a sequence \( x_N = x_1x_2\ldots x_N \), \( x_i \in \mathcal{C} \), with \( N \) characters, the arithmetic coder produces a bit-stream with

\[
- \sum_{n=1}^{N} \log_2 P_n(x_n)
\]

bits, which demonstrates the importance of providing good probability estimates to the arithmetic coder.

The probability distribution, \( P_n(c) \), can be provided by two different sources: (i) an adaptive model (the copy model) which assumes that the characters of the target sequence are an exact copy of (parts of) the reference sequence; (ii) a static model that relies on the frequencies of the characters in the target sequence, i.e. \( \theta(c) \). The adaptive model is the main statistical model, as it allows a high compression rate of the target sequence, particularly in areas where the target and reference sequences are highly similar. However, this adaptive, or copy, model will at times not be used (the reasons why will be detailed shortly), and the static model will act as a fallback mechanism, feeding the arithmetic coder with the required probability distribution.

The copy model

The copy model is inspired by the copy expert of the XM DNA compression method (14), relying on a pointer to a position in the reference sequence that has a ‘good chance’ of containing a character identical to that being encoded. As encoding of the target sequence proceeds, the pointer associated with the copy model may be repositioned to different locations of the reference sequence. When this repositioning occurs, all parameters of the model are reset. Besides accounting for the number of times, \( t_r \),
that the copy model was used after the previous repositioning, two more counters are maintained: \( h_1^n \) stores the number of times the model guessed the correct character including the correct case (uppercase or lowercase), and \( h_2^n \) records the number of times the model guessed the character but failed the case (for example, it guessed ‘A’ but the correct character was ‘a’).

Figure 1 exemplifies the operation of the copy model. Consider the most recent repositioning occurred at position 341 587 of the reference sequence, corresponding to position 327 829 of the target sequence. Since then, it has correctly predicted 5 characters, if the case is considered, and a total of 11 characters if the case is ignored. The dashed arrow indicates a failed prediction. According to this example, the next character to be predicted is ‘G’.

Computing the probabilities. Let us denote by \( p_1^n \) the character predicted by the copy model (‘G’ in the example in Figure 1) and by \( p_2^n \) the case converted \( p_1^n \) (‘g’ according to the example in Figure 1). If \( p_1^n, p_2^n \in \mathcal{C} \) (note that characters of the reference sequence that do not appear in the target sequence do not belong to \( \mathcal{C} \), the probabilities that are passed down to the arithmetic coder are given by

\[
P_n(c) = \begin{cases} 
\frac{h_1^n + 1}{t_n + 3}, & \text{for } c = p_1^n \\
\frac{h_2^n + 1}{t_n + 3}, & \text{for } c = p_2^n \\
1 - P_n(p_1^n) - P_n(p_2^n) \frac{\theta(c)}{1 - \theta(p_1^n) - \theta(p_2^n)}, & \text{for } c \neq p_1^n, p_2^n.
\end{cases}
\tag{2}
\]

The first two branches of Equation (2) correspond to Laplace probability estimators of the form

\[
P(\mathcal{E}_k) = \frac{N_{\mathcal{E}_k} + 1}{\sum_{k=1}^{K} N_{\mathcal{E}_k} + K}, \quad \mathcal{E}_k \subset \mathcal{C},
\tag{3}
\]

where the \( \mathcal{E}_k \) form a set of \( K \) collectively exhaustive and mutually exclusive events, and \( N_{\mathcal{E}_k} \) denotes the number of times that event \( \mathcal{E}_k \) has occurred in the past. In Equation (2) we considered three events, namely, \( \mathcal{E}_1 = \{p_1^n\} \), \( \mathcal{E}_2 = \{p_2^n\} \) and \( \mathcal{E}_3 = \mathcal{C} \setminus \{p_1^n, p_2^n\} \). The third branch of Equation (2) defines how the probability assigned to \( \mathcal{E}_3 \), i.e. \( 1 - P(\mathcal{E}_1) - P(\mathcal{E}_2) \), is distributed among the individual characters of \( \mathcal{E}_3 \). This distribution is proportional to the relative frequencies of the characters, \( \theta(c) \), after discounting the effect of treating \( p_1^n \) and \( p_2^n \) differently.

If only \( p_1^n \) or \( p_2^n \) belongs to \( \mathcal{C} \), the probabilities communicated to the arithmetic coder are the character frequencies of the target sequence, i.e.

\[
P_n(c) = \theta(c).
\tag{5}
\]

Starting and stopping the copy model. Typically, the codec starts by constructing a hash table with the occurrences and corresponding positions in the reference sequence of all \( k \)-mers of a given size (the default size is \( k = 11 \), but it can be changed using a command line option). Figure 2 shows an example where \( k = 8 \) and \( k \)-mers ‘CTNANGTC’ and ‘AAAGTTGG’ have been mapped by the hashing function into the same index (index 4 529 821). As usual in hashing schemes, disambiguation is achieved by direct comparison of the \( k \)-mers that originated the index, which have to be stored in the data structure in order to be compared. Using the hash table, it is easy to find in the reference sequence the characters that come right after all occurrences of a given \( k \)-mer.

Before encoding a new character from the target sequence, the performance of the copy model, if in use, is checked. If \( t_n - h_1^n - h_2^n > m_r \), where \( m_r \) is a parameter that indicates the maximum number of prediction failures allowed, the copy model is stopped. The default value for \( m_r \) is zero, but this may be changed through a command line option.

Following this performance check, if the copy model is not in use, an attempt is made to restart the copy model before compressing the character. This is accomplished by looking for the positions in the reference sequence where the \( k \)-mer composed of the \( k \)-most-recently-encoded characters occurs. If more than one position is found, the one closest to the encoding position is chosen. If none is found, the current character is encoded using the static model and a new attempt for starting a new copy model is performed after advancing one position in the target sequence.
Special case for equal size sequences. When the reference and target sequences have the same size, the codec assumes that both sequences are aligned. Therefore, whenever the copy model is restarted, it is forced to use the current encoding position as reference. This avoids constructing the hash table, hence, increasing the codec speed and generally producing better results. However, this mode of operation may be overridden by a command line option, as it may lead to poor performance for same-sized sequences that are not aligned.

RESULTS

We compare the performance of the method proposed here, GReEn, to the performance of GRS (22), the most recently proposed approach for compressing genome resequencing data that handles sequences drawn from arbitrary alphabets. We also include results of the RLZ algorithm (23) for some sequences, due to its restriction to sequences drawn from the alphabet \{a, c, g, t, n\}.

Tables 1–3 present both the number of bytes produced and the time taken by the respective methods for compressing the sequences used in (22). The results regarding both the GRS and RLZ methods have been obtained using the software publicly provided by the authors. All experimental results were obtained using an Intel Core i7-2620M laptop computer at 2.7 GHz with 8 GB of memory and running Ubuntu 11.04. The best results are highlighted in boldface.

Table 1 displays the compression results for the TAIR9 version of the thale cress genome using the TAIR8 version as reference. Globally, GReEn required 6559 bytes for storing the sequences, whereas GRS needed a little more (6644 bytes). While GReEn took 48 s to encode the data, GRS needed only 28. Therefore, in this case, GRS is equivalent to the proposed method in terms of storage space, but faster.

Table 2 displays the compression results for the TIGR6.0 version of the rice genome using the TIGR5.0 version as reference. In this case, the outcome varies dramatically to the previous results (Table 1). The first significant difference can be observed in both the compressed size and compression time of chromosome 1: 1 502 040 bytes in 708 s using GRS versus 4972 bytes in 18 s (more than a 300-fold improvement) using GReEn. A similarly significant difference can be observed in chromosome 11 (with a gain of over 160-fold). Globally, GRS required 4 901 902 bytes and 2290 s, whereas GReEn was able to store the entire genome in just 125 535 bytes (39-fold improvement) using only 123 s of computing time.

The main conclusion from these results is that, under certain conditions not yet investigated, GRS fails to find large-scale similarities between the two sequences. Therefore, the number of bytes generated is much larger than necessary and, probably as a consequence, the running time explodes. Moreover, when the target sequence is exactly equal to the reference sequence (as in chromosomes 6, 9 and 12), the GRS reports a number of bytes that is essentially zero [in (22) they are shown as zero, although we opted to display the number of bytes effectively used], while GReEn uses a few hundred bytes. However, if critical, this could be easily reduced to almost zero using a sequence comparison before starting encoding.
Table 2. *Oryza sativa* genome: compression of TIGR6.0 using TIGR5.0 as reference

| Chr | Size | RLZ | GRS | GReEn |
|-----|------|-----|-----|-------|
| 1   | 5    | 43 268 879 | 187 715 | 35 | 1 502 040 | 708 | 4 972 | 18 |
| 2   | 5    | 359 380 381 | 210 295 | 28 | 1 400 5 | 1906 | 14 |
| 3   | 6    | 36 406 689 | – | – | 47 764 | 28 | 17 890 | 15 |
| 4   | 5    | 35 278 225 | 175 663 | 27 | 36 145 | 20 | 6 750 | 14 |
| 5   | 5    | 29 894 789 | 120 625 | 21 | 6 177 | 5 | 5 539 | 12 |
| 6   | 5    | 31 246 789 | 61 038 | 23 | 14 | 4 | 482 | 2 |
| 7   | 5    | 29 696 629 | 167 822 | 21 | 4 067 | 8 | 2 448 | 12 |
| 8   | 5    | 28 439 308 | 109 608 | 20 | 118 246 | 43 | 9 507 | 11 |
| 9   | 5    | 23 011 239 | 44 953 | 16 | 14 | 4 | 366 | 2 |
| 10  | 9    | 23 134 759 | – | – | 788 542 | 339 | 60 449 | 9 |
| 11  | 11   | 28 512 666 | – | – | 2 397 470 | 1 122 | 14 797 | 12 |
| 12  | 5    | 27 497 214 | 53 714 | 19 | 14 | 4 | 429 | 2 |

Total 372 317 567 | 4 901 902 | 2 290 125 535 123

Size of the compressed target sequences (in bytes) and corresponding compression time (in seconds). The original sequence alphabets have been preserved. The [C] column indicates the size of the alphabet of the target sequence. The missing RLZ values correspond to sequences with characters that cannot be handled by the current implementation of this algorithm.

(note that, due to the requirement that the probabilities communicated to the arithmetic coder should be represented as integers, a lower bound exists in the minimum number of bits that can be generated in each coding step).

Table 3 displays the compression results for the KOREF_20090224 version of the human genome using the KOREF_20090131 version as reference. In this case, GReEn gives consistently better results, both in terms of storage requirements and computing time. In fact, this latter aspect deserves a special note because contrarily to GRS, the running time of GReEn varies linearly with the size of the sequence. Therefore, GReEn allows for an *a priori* good estimate of the time that is required to compress a given sequence.

Besides considering the datasets in (22), we also investigate four human genome assemblies, in order to provide a more comprehensive comparison of both GRS and GReEn compression approaches. However, our intention fell short because GRS failed to compress most of the sequences due to an excessive difference between the reference and target sequences. Table 4 displays the results obtained when the YH genome was compressed using KOREF_20090224 as reference. It is clear that GRS gave unacceptable results, both regarding the size of the compressed sequences and the time required to compress them, for the few chromosomes that could be compressed with GRS.

Table 5 displays the compression results, using GReEn, for four different human genome assemblies (HuRef, Celera, YH and KOREF_20090224) using the NCBI37 version as reference. As this article is about sequence compression, not sequence analysis, we refrain from elaborating too much on the differences observed. Nevertheless, we hint at what we believe may be possible explanations. First, the HuRef and Celera assemblies are not resequencing assemblies and this, *per se*, accounts for greater compression differences with respect to the reference assembly.

The HuRef assembly is an individual genome sequenced with capillary-based whole-genome shotgun technologies and *de novo* assembled with the Celera Assembler. Hence, this assembly is the farthest apart (i.e. with a larger number of bytes required for its compression) from the reference NCBI37 assembly.

The Celera assembly represents one of the two pioneering efforts in sequencing a human genome. Its consensus sequence is derived from the genomes of five individuals using a capillary-based whole-genome shotgun sequencing approach. Unlike the reference assembly generated by the International Human Genome Sequencing Consortium (here represented in the NCBI37 assembly), which used a clone-based hierarchical shotgun strategy that is more likely to output a high-quality finished genome sequence as the sequence assembly is local and anchored to the genome, the Celera Genomics Sequencing Team opted for a whole-genome shotgun strategy where sequence contigs and scaffolds must be individually anchored to the genome, rendering assembly more complex and more prone to long-range misassembly. Moreover, this whole-genome shotgun assembly resulted from a combined analysis of the genomic data generated by the Celera Genomics Sequencing Team and some data generated by the International Human Genome Sequencing Consortium using the KOREF_20090131 as reference.

Table 3. *Homo sapiens* genome: compression of KOREF_20090224 using KOREF_20090131 as reference

| Chr | Size | GRS | GReEn |
|-----|------|-----|-------|
| 1   | 247 249 719 | 1 336 626 | 222 | 1 225 767 | 32 |
| 2   | 242 951 149 | 1 354 059 | 230 | 1 272 105 | 31 |
| 3   | 199 501 827 | 1 011 124 | 165 | 971 527 | 26 |
| 4   | 191 273 063 | 1 139 225 | 193 | 1 074 357 | 25 |
| 5   | 180 857 866 | 988 070 | 173 | 947 378 | 23 |
| 6   | 170 899 992 | 906 116 | 146 | 865 448 | 22 |
| 7   | 158 821 424 | 1 096 646 | 167 | 998 482 | 20 |
| 8   | 146 274 826 | 764 313 | 125 | 729 362 | 19 |
| 9   | 140 273 252 | 864 222 | 134 | 773 716 | 18 |
| 10  | 135 374 737 | 768 364 | 122 | 717 305 | 17 |
| 11  | 134 452 384 | 755 708 | 119 | 716 301 | 17 |
| 12  | 132 349 534 | 702 040 | 114 | 686 455 | 17 |
| 13  | 114 142 980 | 520 598 | 87 | 490 888 | 15 |
| 14  | 106 368 585 | 484 791 | 81 | 451 018 | 14 |
| 15  | 100 338 915 | 496 215 | 79 | 453 301 | 13 |
| 16  | 88 827 254 | 567 899 | 91 | 510 254 | 11 |
| 17  | 78 774 742 | 505 979 | 81 | 464 324 | 10 |
| 18  | 76 117 153 | 409 529 | 71 | 378 420 | 10 |
| 19  | 63 811 651 | 399 807 | 62 | 360 388 | 8 |
| 20  | 62 435 964 | 282 628 | 48 | 266 562 | 8 |
| 21  | 46 944 323 | 226 549 | 40 | 203 036 | 6 |
| 22  | 49 091 432 | 262 443 | 41 | 230 049 | 6 |
| M   | 1 6 571 | 183 | 1 | 127 | 1 |
| X   | 154 913 754 | 3 231 776 | 500 | 2 712 153 | 20 |
| Y   | 57 772 954 | 592 791 | 96 | 481 307 | 7 |

Total 3 080 436 051 | 19 666 791 348 | 3 188 | 17 971 030 396

Size of the compressed target sequences (in bytes) and corresponding compression time (in seconds). The original sequence alphabets have been preserved. The size of the alphabet in the target sequence is 21 for the M chromosome where it is 11.
Table 4. Homo sapiens genome: compression of YH using KOREF_20090224 as reference

| Chr | Size (Bytes) | GRS (Secs) | GReEn (Secs) |
|-----|--------------|------------|--------------|
| 1   | 247 249 719  | --         | 2 349 124    | 22           |
| 2   | 242 951 149  | --         | 2 420 007    | 22           |
| 3   | 199 501 827  | 17 410 946 | 2 879        | 18           |
| 4   | 191 273 063  | --         | 1 877 056    | 17           |
| 5   | 180 857 866  | --         | 1 792 278    | 16           |
| 6   | 170 899 992  | 25 815 446 | 7 526        | 15           |
| 7   | 158 821 424  | --         | 1 820 425    | 14           |
| 8   | 146 274 826  | --         | 1 358 770    | 13           |
| 9   | 140 273 252  | --         | 1 476 495    | 13           |
| 10  | 135 374 737  | --         | 1 353 193    | 12           |
| 11  | 134 452 384  | --         | 1 274 433    | 12           |
| 12  | 132 349 534  | 16 136 610 | 2 120        | 11           |
| 13  | 114 142 980  | 11 227 954 | 3 181        | 10           |
| 14  | 106 368 585  | --         | 8 627 670    | 10           |
| 15  | 100 338 915  | --         | 8 924 429    | 9            |
| 16  | 88 827 254   | --         | 1 015 246    | 8            |
| 17  | 78 774 742   | --         | 8 640 710    | 7            |
| 18  | 76 117 153   | 13 187 892 | 4 061        | 7            |
| 19  | 63 811 651   | --         | 8 589 422    | 6            |
| 20  | 62 435 964   | 8 409 776  | 1 449        | 6            |
| 21  | 46 944 332   | 7 269 666  | 6 664        | 6            |
| 22  | 49 691 432   | --         | 4 444 932    | 5            |
|M    | 16 571      | 321        | 127          | 1            |
|X    | 154 913 754  | --         | 3 258 188    | 11           |
|Y    | 57 772 954   | --         | 859 688      | 4            |

The compression values for chromosome 19 in the YH and KOREF_20090224 assemblies are unexpectedly high. This chromosome has the highest GC content (48.4%) and the lowest (median) sequence depth (28-fold) in the YH genome (34), hence constraining the quality of the final sequence. Not surprisingly, chromosome 19 in the YH genome has a very large number (more than twice those of the reference NCBI37 assembly) of unsequenced bases (‘N’ symbols in our encoding). Chromosome 19 in the KOREF_20090224 assembly faces the same hurdles, which we assume to be a consequence of the similar sequencing methodology.

DISCUSSION

The GRS tool recently introduced by Wang et al. (22) for compressing DNA resequencing data using a reference sequence allows to significantly reduce data storage space requirements. However, this tool seems to be effective only when the target sequence is very similar to the reference sequence, preventing the compression of many sequences of interest. Moreover, as we have shown, for example, in chromosomes 1 and 11 of the TIGR6.0 version of the rice genome, it may fail to give reasonable results even for similar sequences. Another drawback of GRS is that the encoding time does not depend only on
In this article, we described a computational tool, GReEn, aiming at compressing genome resequencing data using another sequence as reference. This tool is able to handle arbitrary alphabets and does not pose any restrictions or requirements on the sequences to compress. Several examples of its efficiency in compressing genomic data and its improvements with respect to other recently proposed tools have been included, rendering evident the practical interest of the tool here proposed.

With the generation of increasingly larger volumes of genome sequencing and resequencing data, and the increasing costs associated to storing and transmitting those data, compression tools that efficiently recognize redundancies are in demand. However, the interest in such compression methodologies goes beyond data storage and communication. By being a probabilistic model of the underlying genomic sequence(s), compression tools reveal similarities and differences that are paramount for studies of human genomic variation between individuals, hence, key for progress in personal medicine efforts.

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Table 6. *Homo sapiens* genome: compression of KOREF_20090224 using KOREF_20090131 as reference

| Chr | RLZ | GRS | GReEn |
|-----|-----|-----|-------|
| 1   | 591 629 | 152 388 | 90 555 |
| 2   | 576 769 | 146 754 | 89 440 |
| 3   | 472 814 | 117 544 | 72 708 |
| 4   | 471 157 | 134 628 | 83 611 |
| 5   | 428 287 | 108 407 | 66 597 |
| 6   | 411 404 | 109 866 | 67 264 |
| 7   | 395 524 | 119 223 | 71 898 |
| 8   | 350 337 | 94 139  | 56 650 |
| 9   | 357 584 | 119 647 | 68 607 |
| 10  | 335 464 | 101 486 | 60 303 |
| 11  | 326 836 | 91 380  | 54 966 |
| 12  | 320 444 | 89 170   | 55 408 |
| 13  | 266 378 | 64 313   | 36 962 |
| 14  | 248 165 | 58 865   | 34 245 |
| 15  | 235 094 | 56 569   | 32 693 |
| 16  | 217 748 | 60 580   | 35 315 |
| 17  | 193 700 | 55 582   | 33 836 |
| 18  | 182 604 | 48 098   | 29 191 |
| 19  | 162 826 | 53 355   | 30 505 |
| 20  | 149 403 | 38 114   | 22 969 |
| 21  | 112 822 | 29 048   | 16 620 |
| 22  | 119 791 | 32 562   | 18 423 |
| M   | 94 56  | 75      | 54     |
| X   | 428 878 | 224 997  | 129 497 |
| Y   | 150 901 | 61 306   | 33 312 |

Number of bytes after compressing each sequence. For allowing the comparison to RLZ and GRS, all characters were transformed to lowercase before compression and all unknown nucleotides were mapped to 'n'. Therefore, after this transformation, all sequences were composed only of characters from set [a,c,g,t,n].

The compression tool has two control parameters, namely, the size of the $k$-mer that is used for searching copies (with a default value of $k = 11$), and the number of prediction failures that are tolerated by the copy model before it is restarted (with a default value of 0). Changing these parameters may change the performance of the codec, degrading the performance for some sequences while improving it for others. It is left to the user the decision of trying to optimize these parameters or, as we have done when producing the experimental results included in this article, to use the default values.

**CONCLUSION**

In this article, we described a computational tool, GReEn, aiming at compressing genome resequencing data using another sequence as reference. This tool is able to handle arbitrary alphabets and does not pose any
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