Data compression and genomes: a two dimensional life domain map

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Abstract

We define the complexity of DNA sequences as the information content per nucleotide, calculated by means of some Lempel-Ziv data compression algorithm. It is possible to use the statistics of the complexity values of the functional regions of different complete genomes to distinguish among genomes of different domains of life (Archaea, Bacteria and Eukarya). We shall focus on the distribution function of the complexity of noncoding regions. We show that the three domains may be plotted in separate regions within the two-dimensional space where the axes are the skewness coefficient and the curtosis coefficient of the aforementioned distribution. Preliminary results on 15 genomes are introduced.

Keywords: DNA sequences, statistical analysis, Lempel-Ziv compression algorithms, evolutionary dynamics

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1 Introduction

As discussed at length in an earlier paper [11], genome evolution is characterised by some very peculiar features deriving from the structure and dynamics of living systems. Life in general is influenced at the same time by the variability generated by internal and external sources and by constraints deriving from self-organisation and adaptation dynamical rules. The interaction between these contrasting processes leads to generalised scale invariant behaviours of many living processes as reviewed by [11] and [12]. Genomes may be considered as the heritable “data-base” of living systems histories and are therefore a useful tool for the study of the dynamical features of the ratio between randomness and constraints throughout evolution. This is particularly relevant in view of the astounding changes in the conceptual framework of evolutionary theories deriving from the new data obtained through genome, transcriptome and proteome analyses in different classes of organisms from prokaryotes to eukaryotes.
Evidence has been recently obtained showing that prokaryotes, eukaryotes and humans differ particularly as far as the sources of variability and homeorhetic processes are concerned. Prokaryotes, due to their short life cycles and to the haploid nature of their genomes, rely on the induction of genetic variability, through mutations, genome re-arrangements, DNA exchange within and between species; eukaryotes have developed throughout evolution very sophisticated and efficient processes leading to phenotypic plasticity; humans, the most “generalist” specie in our Biosphere, adapt themselves through the exploitation of cultural variability. As a consequence of these different behaviours, prokaryote genomes are much smaller and contain a lower amount of regulatory non-coding sequences (12% in bacterium E. Coli) and a correspondingly higher level of coding ones, noncoding presence in multicellular eukaryotes ranging from 76% in Coenorhabditis to 98% in humans [29]. Due to the astounding acceleration of whole genome sequencing, the statistical properties of DNA have been studied extensively in the last fifteen years. The data obtained show that DNA is characterised by short and long range correlations linked to the functional role of different classes of sequences. Coding strings show -especially in eukaryotes- weaker long range correlations than non coding ones (see for instance [28, 13, 23, 24, 32]) and in general deviations from randomness are stronger in eukaryotes than in prokaryotes. Particularly, the authors of [2] used a simple model called “Copying mistake map”, based on the superposition of a pure random choice model and an intermittent generator of homogeneous sequences with the aim of obtaining quantitative estimates of correlation intensities. The results obtained showed that the exponent of the power law was constant in all organisms while the fraction of long correlations increased in eukaryotes. However, it should also be noted that probably all the mentioned methods employed to measure the extent of deviations from randomness in DNA sequences may underestimate the impact of short range correlations and of short, local, low-complexity sequences with possible functional relevance on the basis of specific “hidden conformational codes” [30].

The aim of the present paper is to gain some additional information on the dynamics of the ratio between randomness and constraints and its putative correlation with function, obtaining whole genome pictures on the basis of complexity measures carried out on DNA fragments with different functions, namely coding and non coding (introns and intergenic) in Archaea, Bacteria, Eukarya.

2 Compression algorithms and DNA sequences

We shall analyse the genome sequences from the point of view of data compression in order to obtain a domain classification of genomes by means of their Information Content as symbol sequences. When considered as a single strand sequence of nucleotides, the genomes are interpreted as symbol strings of finite length, drawn by an Information Source (Nature) that remains mainly unknown and emits symbols taken from the alphabet of the four nucleotides \{A, C, G, T\}. Each genome identifies a living organism and we assume that it may be considered as the unique realisation produced by the Source relative to that organism. We recall that, intuitively, an Information Source is a device emitting a sequence of symbols \(x_1x_2x_3\ldots\) where each \(x_i\) is an element of a finite alphabet. DNA sequences are special quaternary symbol sequences. As
discussed in the Introduction, the sequences belonging to a living organism are expected to be nonrandom due to internal and selective constraints. Therefore DNA sequences should be compressible, at least locally.

In our approach to symbol sequences, the crucial notion is the **Information Content**. Let $A^*$ be the set of finite sequences whose symbols belong to a finite alphabet $A$. Given some sequence $\tau \in A^*$, the meaning of *quantity of information* $I(s)$ contained in $s$ has the following natural connotation:

$$I(\tau) \text{ is the length of the smallest binary message from which you can reconstruct } \tau.$$ 

In his pioneering work, Shannon defined the quantity of information as a statistical notion using the tools of probability theory ([19]). Thus in Shannon framework, the quantity of information which is contained in a string depends on its context. For example the string "pane" contains a certain information when it is considered as a string coming from the English language. The same string "pane" contains much less Shannon information when it is considered as a string coming from the Italian language because it is more frequent in the Italian language (in Italian it means "bread" and, of course, it is very frequent). Roughly speaking, the Shannon information of a string is the absolute value of the logarithm of the probability of its occurrence.

However, there are measures of information which depend intrinsically on the string and not on its probability within a given context. We shall adopt this point of view. An example of these measures of information is the Algorithmic Information Content (AIC). We shall not formally define it (see [19] for rigorous definitions and properties). We limit ourselves to give an intuitive idea which is very close to the formal definition. We can consider a partial recursive function as a computer $C$ which takes a program $p$ (namely a binary string) as an input, performs some computations and gives a string $\tau = C(p)$, written in the given alphabet, as an output. The AIC of a string $\tau$ is defined as the length of the shortest binary program $p$ which gives $\tau$ as its output, namely

$$I_{AIC}(\tau, C) = \min \{|p| : C(p) = \tau\},$$

where $|p|$ means the length in bit of the string which the program $p$ consists of. A theorem due to A. N. Kolmogorov ([20]) implies that the Information Content $AIC$ of $\tau$ with respect to $C$ depends only on $\tau$ up to a fixed constant, therefore its asymptotic behaviour does not depend on the choice of $C$. The shortest program $p$ which outputs the string $\tau$ is a sort of optimal encoding of $\tau$. The information that is necessary to reconstruct the string is contained in the program. Unfortunately, this coding procedure cannot be performed by any algorithm ([22]). That is, the Algorithmic Information Content is not computable by any algorithm.

Our method is focused on another measure: the Information Content of a finite string can also be defined by a lossless data compression algorithm $Z$ ([6]). This turns out to be a Computable Information Content (CIC). In reference [7] quantitative relations among Shannon entropy of the source, the AIC and the CIC of sequences are provided.

We shall therefore investigate whether it is possible to use the CIC of the functional regions of different genomes to distinguish among genomes of different domains of life (Archaea, Bacteria and Eukarya). If the complexity of some
DNA sequence is defined as the information content per nucleotide, then we shall focus on the distribution function of the complexity values relative to noncoding regions. We shall also show that the three domains may be plotted in separate areas within the two-dimensional space where the axes are the skewness coefficient and the kurtosis coefficient of the aforementioned distribution.

In this paper we shall use information content to extract some phylogenetic relationships among complete genomes and identify life domains. Ideas from data compression are not new in genome analysis. Classical studies in compression algorithms on DNA sequences answer the question about the compressibility of DNA with the additional advantage of using compression techniques to capture the properties of DNA, for instance to identify where some linguistic characteristic structures (such as reverse complements and approximate repeats) are located within genomes. Several special-purpose compression algorithms for DNA sequences have been developed (for instance, see [http://www.ebi.ac.uk](http://www.ebi.ac.uk) for an overview of current research groups at the European Bioinformatics Institute). Part of these so-called DNA-oriented algorithms have been also used to study pattern matching problems (e.g. [16]). Moreover, techniques based on the explicit calculation of some information content have been developed to solve gene-finding problems ([14], [26]) and to construct metric distances from which reliable phylogenetic trees may be built (see for instance [21], [8], [27]). In this context, information content’s growth rate is a way to approximate the entropy of the sequence, which is a measure of the complexity of the sequence. In this paper we discuss the application of a variant of Lempel-Ziv compression schemes ([35], [36]). Some other modified algorithms have been used in [17] and [34] for calculating genetic sequence complexity. Of course, this list of references can not be exhaustive.

The notion of complexity of a finite symbol sequence is controversial and basically twofold: it may be defined by paying attention to the regularity of sequences (as in the case of Information-based methods), or - alternatively - by focusing on quantifying the randomness of the same sequences, as in the case of correlation analysis ([23]). In particular, the long-standing interest in understanding the meaning of short-range and long-range correlations in nucleotidic sequences showed that they are bound to several specific features of the DNA code. Statistical analysis of the spatial distribution of nucleotides confirmed the mutual relation between functional requirements and DNA heterogeneity; the presence of differences between coding and noncoding regions were also studied in a phylogenetic setting, in order to relate it to a selection pressure on the DNA structure ([32], [25], [24], [13], [18], [5], [1], [2] and references therein). Recently, also the opposite direction has been investigated: patterns in the short-range statistical correlations in DNA sequences have been shown to serve as evolutionary fingerprints of eukaryotes [12].

Our analysis is set as follows.

The information content (CIC) of any functional region within complete genomes shall be calculated by means of a modified Lempel-Ziv compression algorithm called CASToRe. The complexity of the functional region is the information content per nucleotide. We show that this kind of complexity analysis of complete genomes is an indicator of biological complexity of the organisms, but it is not subtle enough to allow an evolution arrow to be rigorously defined. Furthermore, the linguistic differences among genomes are per se sufficient to allow a precise positioning of the genomes on the two-dimensional map to be
settled. Understanding the reasons of his result may be the starting point of a novel way to apply compression algorithms to DNA sequences. In particular, the applied algorithm and Lempel-ziv schemes in general provide a final dictionary of recurrent words in the analysed sequence, such paving the way to pattern identification.

Finally, as we shall clarify in section 3.1, the choice of CASToRe is motivated by the fact that this algorithm is more suitable than LZ78 to identify regularities. Indeed, it is well-known that a better compression may be reached by using specific DNA-oriented algorithms. Nevertheless, here we are interested in the fact that also a generic-purpose compression scheme may allow a life domain classification to be achieved, such confirming the existence of macroscopic features marking the genomes.

3 Computable Information Content

Formally, a compression algorithm is a reversible coding such that any original finite sequence $\tau$ over a finite alphabet $\mathcal{A}$ may be recovered from the encoded string $Z(\tau)$.

**Definition 1** (Compression Algorithm). A lossless data compression algorithm is any injective function $Z: \mathcal{A}^* \rightarrow \{0,1\}^*$.

Therefore, since the coded string $Z(\tau)$ contains all the information that is necessary to reconstruct and describe the structural features of the original string, we can consider the length of the coded string as an approximate measure of the quantity of information that is contained in the original string.

**Definition 2** (Computable Information Content). The Information Content of a finite string $\tau \in \mathcal{A}^*$ with respect to a compression algorithm $Z$ is defined as

$$CIC_Z(\tau) = |Z(\tau)|. \quad (1)$$

The $CIC$ of a string $\tau$ is the length (in bit units) of the coded string $Z(\tau)$.

The advantage of using a compression algorithm lies in the fact that the Information Content $CIC_Z(\tau)$ is a computable function over the space of finite strings. For this reason we named it Computable Information Content.

Moreover, we define another quantity, the complexity of a finite sequence, providing an estimate for the rate of Information Content contained in it.

**Definition 3** (Complexity of a finite string). The complexity of $\tau$ with respect to $Z$ is the information per symbol

$$C_Z(\tau) = \frac{I_Z(\tau)}{|\tau|}. \quad (2)$$

The complexity value of sequence $\tau$ is related to its compressibility in the sense that the lower is $C_Z(\tau)$, the more compressible $\tau$ is.

**Remark 1.** Under suitable optimality assumptions on the compression algorithm $Z$, we can extend the definition of complexity to infinite symbolic sequences belonging to $\Omega_\mathcal{A}$ and asymptotically obtain the Shannon entropy of the
Information Source from which the sequence has been drawn ([7]). The theoretical work has been extended also to trajectories coming from general dynamical systems and it is supported by application to several complex systems, as to turbulent or intermittent regimes and to weakly chaotic dynamical systems (see [7] and references therein).

3.1 The algorithm CASToRe

We have created and implemented a particular compression algorithm we called CASToRe which is a modification of the Lempel-Ziv compression schemes \textit{LZ77} \cite{35} and \textit{LZ78} \cite{36} and it has been introduced and studied in references \cite{3} and \cite{10}.

First, we describe the internal running of CASToRe. Then, we briefly compare CASToRe to LZ77 and LZ78.

As any Ziv-Lempel schemes, the algorithm CASToRe is based on an adaptive dictionary ([6]). At the beginning of encoding procedure, the dictionary contains only the alphabet. In order to explain the main rules of the encoding, let us consider a step \( h \) within the encoding process, when the dictionary already contains \( h \) phrases \( \{ e_1, \ldots, e_h \} \).

The new phrase is defined as a pair \( (\text{prefix pointer}, \text{suffix pointer}) \). The two pointers are referred to two (not necessarily different) phrases \( \rho_p \) and \( \rho_s \) chosen among the ones contained in the current dictionary as follows. First, the algorithm reads the input stream starting from the current position of the front end, looking for the longest phrase \( \rho_p \) matching the stream. Then, the algorithm looks for the longest phrase \( \rho_s \) such that the joint word \( \rho_p + \rho_s \) matches the stream. The new phrase \( e_{h+1} \) that shall be added to the dictionary is then \( e_{h+1} = \rho_p + \rho_s \). The output file contains an ordered sequence of the binary encoding of the pairs \( (i_p, i_s) \) such that \( i_p \) and \( i_s \) are the dictionary index numbers corresponding to the prefix word \( \rho_p \) and to the suffix word \( \rho_s \), respectively. The pair \( (i_p, i_s) \) is referred to the new encoded phrase \( e_{h+1} \) and has its own index number \( i_{h+1} \).

\textbf{Example.} Consider the following sequence:

\[ \tau = TCTATCTGATTTTCTCTGGATC \]

The starting dictionary is \( \{ A, C, G, T \} \). At the end of the compression, the
dictionary contains 9 new words, built as follows.

| dictionary index | (prefix, suffix) | word  |
|------------------|------------------|-------|
| 0                | −                | A     |
| 1                | −                | C     |
| 2                | −                | G     |
| 3                | −                | T     |
| 4                | (3, 1)           | TC    |
| 5                | (3, 0)           | TA    |
| 6                | (4, 3)           | TCT   |
| 7                | (2, 0)           | GA    |
| 8                | (3, 3)           | TT    |
| 9                | (8, 1)           | TTC   |
| 10               | (4, 1)           | TCC   |
| 11               | (3, 2)           | TG    |
| 12               | (7, 4)           | GATC  |

One of the basic differences in the coding procedure is that the algorithm LZ77 splits the input strings in overlapping phrases, while the algorithm CASToRe (as well as LZ78) parses the input string in non-overlapping phrases. Moreover, CASToRe differs from LZ78 because the new phrase is a pair of two already parsed phrases, while LZ78 couples one already parsed phrase and one symbol from the alphabet.

The reason for the acronym CASToRe (meaning Compression Algorithm Sensitive To Regularity) is that this scheme provides a sensitive measure of information content in low entropy sequences (see [10]). For instance, consider the case where \( \tau = AAA \cdots A \) is a constant sequence of length \( n \). The theory predicts that the best possible Information Content for a constant sequence of length \( n \) is \( AIC(\tau) = \log(n) + \text{constant} \). If the algorithm \( Z \) is CASToRe, the value of the Information Content is \( I_Z(\tau) = 4 + 2\log(n+1)\log(\log(n+1)) - 1 \). It may be shown that if the algorithm \( Z \) is LZ78, then \( I_Z(\tau) = \text{const} + n^{\frac{4}{3}} \). So, we cannot expect that LZ78 is able to distinguish a sequence whose Information Content grows like \( n^\alpha \) (with \( \alpha < \frac{1}{2} \)) from a constant or periodic string. Furthermore, the running time of CASToRe is also sensibly shorter than that of LZ77 (with infinite window), then any implementation is more efficient. These are the main reasons that motivate the choice of using CASToRe also for these numerical experiments.

**Remark 2.** In the following, the compression algorithm to which we refer for numerical experiments is the algorithm CASToRe. Therefore, we shall omit the subscript \( Z \) everywhere.

### 4 Fragment Analysis

We have calculated the complexity values of coding and noncoding regions within 14 complete genomes\(^1\) of some Archaea, Bacteria and Eukaryotes, together with chromosomes II and IV of *Arabidopsis thaliana*. The complete list is the following.

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\(^1\)The genomes have been downloaded by means of the GenBank sequence libraries [http://www.ncbi.nlm.nih.gov/Genbank/index.html](http://www.ncbi.nlm.nih.gov/Genbank/index.html)
Archaia:
1. Methanococcus jannaschii
2. Archeoglobus fulgidus
3. Methanobacterium thermoautrophicum
4. Pyrococcus abyssi

Bacteria:
1. Aquifex aeolicus
2. Escherichia coli
3. Bacillus subtilis
4. Haemophylus influenzae
5. Mycoplasma genitalium
6. Rickettsia prowazekii
7. Thermotoga maritima

Eukarya:
1. Arabidopsis thaliana (chr. II and IV)
2. Saccharomyces cerevisiae
3. Caenorhabditis elegans
4. Drosophila melanogaster

In order to take into account the biological functional constraints actually existing among the bases within the genome and to highlight new features of coding and noncoding regions, we have exploited a fragment analysis.

Definition 4 (Fragment). We say that any exon, intron or intergenic region is a functional fragment of the genome sequence, according to the prediction as it has been identified via molecular analysis, biological databases and statistical tools.

We shall calculate the complexity $C(f)$ of each fragment $f$ and we shall introduce the following indexes:

- **FC** is the acronym for fragment complexity $C$ calculated via $CIC$.
- **$FC_{ex}/FC_{in}/FC_{inter}$** is the FC only of exon/intron/intergenic fragments, respectively.
- **$AFC(\gamma)$** is the average fragment complexity, obtained as the mean value of the complexity $FC(f)$ over all the fragments $f$, both coding and non-coding, within genome $\gamma$:

$$AFC(\gamma) = \langle FC(f) \rangle$$

- **$AFC_{ex}/AFC_{in}/AFC_{inter}$** is the AFC only of exon/intron/intergenic fragments, respectively.
Table 1: Comparison of AFC vs. AFC - only intergenic regions for the 14 genomes. The values of \( \rho(AFC) \) are the ratios \( AFC_{\text{inter}}/AFC \).

| Genome                        | AFC | AFC_{inter} | \( \rho(AFC) \) |
|-------------------------------|-----|-------------|-----------------|
| Methanococcus jannaschii      | 1.935 | 1.998 | 1.031 |
| Archaeoglobus fulgidus        | 2.024 | 2.101 | 1.042 |
| Methanobacterium thermoautotrophicum | 2.042 | 2.132 | 1.042 |
| Pyrococcus abyssi             | 2.021 | 2.116 | 1.042 |
| Aquifex aeolicus              | 2.003 | 2.081 | 1.031 |
| Escherichia coli              | 2.050 | 2.131 | 1.042 |
| Bacillus subtilis             | 2.035 | 2.110 | 1.042 |
| Haemophilus influenzae        | 1.998 | 2.062 | 1.031 |
| Mycoplasma genitalium         | 1.996 | 2.060 | 1.031 |
| Rickettsia prowazekii         | 1.909 | 1.946 | 1.020 |
| Thermotoga maritima           | 2.040 | 2.147 | 1.053 |
| Arabidopsis thaliana (chr. II and IV) | 2.038 | 1.903 | 0.935 |
| Saccharomyces cerevisiae      | 1.958 | 1.972 | 1.010 |
| Caenorhabditis elegans        | 2.056 | 1.960 | 0.952 |
| Drosophila melanogaster       | 2.051 | 1.948 | 0.952 |

4.1 Results

We have compared the average fragment complexity of the above collection of genomes. The results are shown in Table 1.

First of all, we have to point out that frequently the values of both coding and noncoding fragment complexity and of the associated AFC are slightly bigger than 2 bit per symbol and this is much more evident in Prokaryotic noncoding regions (see their AFC_{inter}). This is due to the presence of several regions that are shorter than 200 bp. This short length causes a disadvantage in the compression: the statistics of words over 4 symbols is very poor and the compression is definitely worse than in case of long sequences. Any Lempel-Ziv scheme looks for recurrent words and in the case of poor statistics it is more likely to find many short words than a few longer word, which leads to lower compressibility. Nevertheless, length constraints do not bias the possibility to develop a reliable method for coding sequences identification based on how does the information content grow within each fragment: in [26], it is shown that around 92% of genes were correctly predicted in Prokaryotic genomes. Applications to Eukaryotes are in progress. Anyway, since we are not interested in achieving the best compression, but a complete overview of the features of FC distribution, we think that such an investigation should comprehend fragments of any length.

It should also be stressed that AFC does not represent the average complexity of the different genomes as the relative length of coding and non-coding fragments is very different in eukaryotes and prokaryotes in the sense that one fragment represents a different percentage of the whole genome in the two domains. This is also why, at a first glance to Table 1, the averages AFC and AFC_{inter} do not reveal any immediate meaningful difference among the genomes. It is by comparing those values (we used the ratio \( \rho(AFC) = AFC_{\text{inter}}/AFC \)) that
Figure 1: The normalised distribution of the Fragment Complexity FC for the different functional fragments: coding, intergenic and intron (when present). The pictures show the value of FC vs. the frequency of fragments with that FC. In particular, only the subregion \( \{FC \in [0.6, 2.8]\} \) is drawn since the remaining part does not contain values different from zero. The plots are relative to (a) archaea Archaeoglobus fulgidus, bacteria (b) Escherichia coli and (c) Thermotoga maritima, (d) monocellular eukaryote Saccharomyces cerevisiae and (e) plant Arabidopsis thaliana. Thick solid lines are relative to coding regions, while crossed-dashed lines are relative to intergenic regions and – only in plots (d) and (e) – dashed lines refer to introns.

an evidence for the higher compressibility of Eukaryotic genomes is provided: the lower value of \( \rho(AFC) \) is determined by the stronger regularity and greater extent of noncoding regions in Eukaryotes (see also results in [15]).

Still, a clearer distinction between Prokaryotes and Eukaryotes should be found in a more profound analysis of fragment complexity. Therefore, we shall study the distribution of the fragment complexity following the functional type and separately for each genome.

Figure 1 shows some normalised distributions of the FC of fragments. Plots (a), (b) and (c) are relative to Prokaryotes Archaeoglobus fulgidus and Escherichia coli: thick solid line refer to coding fragments, while crossed-dashed lines refer to noncoding fragments. Plots (d) and (e) are relative to Eukaryotes Arabidopsis thaliana and Saccharomyces cerevisiae: thick solid line refer to exons, crossed-dashed lines refer to intergenic fragments and dashed lines refer to introns.

The fragment complexity FC distribution appears to significantly vary in coding and in noncoding regions: in the first case, the distribution is generally more concentrated around the mean value, while in the latter case the values of FC are dispersed and the oscillations have a smaller extent. Furthermore, especially in the case of intergenic fragments, the distribution may present multiple peaks and the decay from the maximum to zero (the so-called tail of the distribution) may be not as fast as in the case of coding regions. Finally, as also Table 1 suggests, in Prokaryotes coding regions tend to have lower complexity than noncoding regions, while this feature is inverted in Eukaryotes. Again, this has two main motivations: regularities and periodicities are stronger in noncoding regions of Eukaryotic genomes, where moreover Prokaryotic noncoding fragments are shorter and less correlated.

The particular features that characterise the shape of the distribution of FC in the intergenic regions of all the genomes led us to the idea of studying some statistical indexes referred to the distribution and measuring the “spread” of the distribution shape: we focused on the curtosis coefficient and on the skewness coefficient.

As we have previously pointed out, the distributions of FC of intergenic regions have long tails that are usually asymmetric with respect to the mean value, so we may conclude that mean value and standard deviation do not finely describe the core of the distribution. Furthermore, the degree of convexity of the distribution curve may be a discriminant value to identify the distribution. These two features (convexity and asymmetry) are measured by the curtosis
Figure 2: Statistical 2D-map for several genomes from the life domains. The statistical coefficients Skewness and Curtosis are referred to the distribution of only intergenic fragment complexity. Prokaryotes: Stars (☆) = Archaea; diagonal crosses (×) = Bacteria. Eukaryotes: vertical crosses (+). Numbers and letters are referred to the following genomes. Archaea: a) Methanobacterium thermoaerotrophicum, b) Archaeoglobus fulgidus, c) Pyrococcus abyssi, d) Methanococcus jannaschii. Bacteria: 1) Thermotoga maritima, 2) Aquifex aeolicus, 3) Haemophilus influenzae, 4) Mycoplasma genitalium, 5) Escherichia coli, 6) Bacillus subtilis, 7) Rickettsia prowazekii. Eukaryotes: A) Saccharomyces cerevisiae, B) Caenorhabditis elegans, C) Arabidopsis thaliana, D) Drosophila melanogaster.

Figure 3: Same picture as Figure 2, now highlighting the boundaries among life domains. Stars (☆): Archaea. Diagonal crosses (×): Bacteria. Vertical crosses (+): Eukaryotes.

coefficient and by the skewness coefficient, respectively, and they determine the “distance in shape” of the current distribution with respect to a Gaussian distribution.

Let us define them. Let \( X = (X_i)_{i \in I} \) be the finite data set of the distribution of the fragment complexity \( FC_{inter} \) of intergenic fragments over the collection of the 14 genomes.

The standard deviation \( \sigma \) is, by definition, such that
\[
\sigma^2 = \mathbb{E}[(X - \mathbb{E}[X])^2],
\]
where \( \mathbb{E}[X] \) is the mean value of the distribution, which we denoted by \( AFC_{inter} \).

The curtosis coefficient is calculated by means of the fourth moment:
\[
c = \frac{\mathbb{E}[(X - \mathbb{E}[X])^4]}{\sigma^4}.
\]
The higher the curtosis \( c \) is, the flatter and more convex the distribution is.

The skewness coefficient is calculated by means of the third moment:
\[
s = \frac{\mathbb{E}[(X - \mathbb{E}[X])^3]}{\sigma^3}.
\]
The greater the skewness \( s \) is, the more asymmetric the distribution is. If the skewness is positive the asymmetry prevails on the left tail, otherwise on the right tail.

Figure 2 shows a two-dimensional picture that is a snapshot in the space skewness \( \times \) curtosis where the values \( (s, c) \) for several genomes are plotted. The stars (☆) are referred to the Archaeal genomes, diagonal crosses (×) are relative to Bacterial genomes, while vertical crosses (+) make reference to Eukaryotic genomes. Numbers and letters on the picture identify the genomes, as listed in the caption of Figure 2.

The three domains of life may be identified as three well separated areas in the picture. The boundaries among Archaea, Bacteria and Eukaryotes are plotted in Figure 3.

Prokaryotes are strictly localised, almost collinear, at the bottom horizontal strip. In fact, the flatness of their distributions is more accentuated than in Eukaryotes, which are grouped at the top of the picture. Therefore, a preliminary
analysis suggests that the crucial parameter in distinguishing between Prokaryotes (Archaea and Bacteria) and Eukaryotes is the curtosis coefficient, which is significantly higher in the Eukaryotes than in Prokaryotes. This coefficient may be useful as a “primitive” evolutionary index.

For what concerns the separation between Archaea and Bacteria, even if it is evident that the skewness coefficient plays a crucial role in ordering the genomes, it is also clear that there is not a neat boundary, because of the presence of a bacterium in half-strip that contained all the results relative to the Archaeal genomes (i.e. the genome labelled by 1 in the plots). This Bacterium, whose skewness and curtosis coefficients are both the lowest ($s = 0.180$, $c = 0.137$), is *Thermotoga maritima*. However, it should be stressed that it was originally classified as an Archaea and now it is known as one of the deepest and most slowly evolving lineages in thermophilic Eubacteria. Presumably, this fact may motivate the tendency of the distribution of the $FC$ of intergenic regions of *Thermotoga maritima* to become similar to an archael distribution: Figure 1 shows that the similarity is not only qualitative (multiple peaked and widespread), but also quantitative. Moreover, evidences have been showed (33) for massive lateral gene transfer between *Thermotoga maritima* and bacterial genomes (especially Pyrococcus horikoshii). Figure 3 supports the idea that also intergenic parts of *T. maritima* are Archaea-like.

5 Concluding remarks

The results previously discussed show that compression algorithms may indeed be a useful tool for the study of the evolutionary dynamics of the randomness/constraints ratio in genomes. The fragment complexity is a measure of the relative impact of constraints on genome structure and it differs from other traditional approaches based on long and short-range correlations, periodicities, local DNA structures, etc basically in two points. First, it is a self-contained measure and gives a description of DNA sequences independently of the context they belong to. Second, it is not directly connected to any statistical quantity (for instance, the occurrence of some specific oligonucleotides or other patterns), therefore may be used to compare coding and non coding fragments even considering that they have different lengths in different domains. On the other hand through the study of functionally different fragments , the presence of local low or high complexity sub-sequences can be evaluated and eventually correlated with its effects on DNA local conformational landscapes and eventually with functional and structural differences between the fragments studied [2]. In our case we show that eukaryotic fragments are on the average more compressible than prokaryotic ones coherently with the experimental finding of a higher number of low complexity sequences particularly in non coding strings of eukaryotes and with the vast literature on the effects on gene expression of such strings (see for instance [11]). Moreover, the distribution of fragment complexity values was found to be rather different in prokaryotes and eukaryotes and to be a feature capable of discriminating between and within the two groups of organisms. Particularly, it has been possible to distinguish between Bacteria and Archaea through the skewness of their distributions, Archaea curves being more near to a Gaussian than those of Bacteria. Moreover both Prokaryote groups differ from Eukaryotes for the parameter curtosis whose values are higher in
more complex organisms than in then unicellular Saccharomyces. According to [4], higher values of curtosis mean slow decay of the power law in correlated systems. In other words we could infer from these data that in eukaryotes there is a divergence between two groups of sequences showing different complexity values. This is again coherent with experimental data showing than in eukaryotes coding and non coding sequences do indeed diverge in the number of low complexity sequences while this kind of heterogeneity is much weaker in the case of prokaryotes. Most probably, this is the result of selection forces acting differently on prokaryotes and eukaryotes: while in prokaryotes’evolution selection acts mainly on genes (coding sequences), in eukaryotes it is more effective on non coding regulatory DNA (where adaptation relies, as discussed before, on regulatory plasticity during life cycles). One striking example of this behaviour is the fact that while genes -with very few exceptions- are very similar in humans and chimpanzees, gene expression is differently regulated. Different regulation therefore may have required the fixation throughout evolution of more constraints in non coding sequences and in general a wider divergence from coding ones.

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Curtosis coefficient vs. Skewness coefficient

Points labeled A, B, C, D, a, b, c, d with corresponding coordinates.
Curtosis coefficient vs. Skewness coefficient
