Entropy concepts and DNA investigations

Olga V. Kirillova

Department of Theoretical Physics, St.Petersburg State University
Ulyanovskaya str. 1, St.Petersburg, 198904 Russia
(e-mail:kirill@heps.phys.spbu.ru)

Abstract. Topological and metric entropies of the DNA sequences from different organisms were calculated. Obtained results were compared each other and with ones of corresponding artificial sequences. For all envisaged DNA sequences there is a maximum of heterogeneity. It falls in the block length interval [5,7]. Maximum distinction between natural and artificial sequences is shifted on 1-3 position from the maximum of heterogeneity to the right as for metric as for topological entropy. This point on the specificity of real DNA sequences in the interval.

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1 Introduction

One of the first conceptions of entropy was proposed by C. Shannon in application to the theory of information transmission [1]. Entropy in that context implies the measure of heterogeneity of a set of symbols. In mathematical form it can be written as

\[ H = - \sum_i p_i \log p_i \]

where \( p_i \) is probability of appearance of the \( i \)-th symbol. Then the notion of entropy spread in different fields of science: statistical mechanics, probability theory, computer science etc. Many new conceptions of entropy such as metric entropy, thermodynamic, topological, generalized, Kolmogorov-Sinai, structural spectral entropy have been proposed [2, 3, 4, 5, 6]. But all of them pursues the single aim – description of uncertainty in a large set of objects.

One of the main directions in DNA investigations is search and elaboration of methods for robust structural properties of genome texts extraction. What allows to understand general principles of genetic sequences forming and makes reasonable conclusions in the evolution theories [7, 8]. It is not surprising that entropy and information notions find a wide application in DNA investigations [9, 10, 11]. Indeed in some sense DNA is represented as a long sequence of symbols of the alphabet consisting of just four letters. Eventually letter analysis appears to be insufficient to explain DNA properties or structure. The analysis of letter groups or so called words seems more interesting. But due to exponential growth of the number of possible words of length \( n \), when \( n \) increases, it is considerably more difficult. As a rule in such investigations some additional suggestions as, for example, about an equidistribution of words [12, 13], are taken. On the basis of ones the entropy estimation is performed [14]. But in reality neither a word’s distribution nor even a distribution of letters are not equiprobable. It is essential point if we want to gain an information from and about real DNA. Moreover very often in the analysis short parts of a genome or chromosome have been used [13]. Today available data and computer methods allow to investigate complete genomes and chromosomes. (For example the length of human 22 chromosome is 33476902 bp.) What allows to take the maximum likelihood estimation \( p_i = q_i/N \) (where \( q_i \) is the number of occurrences of the \( i \)-th word in an investigated sample) as enough good approximation for the calculation of the entropy in Shannon’s sense. At least in such respect an investigated
object is not replaced by any artificial set.

So we use the metric and topological definitions of entropy for DNA texts heterogeneity estimation. Some remarks about the possibility of a representation of a DNA sequence by a Markov chain for the calculation of the entropy estimate are also given.

2 Metric entropy

In Shannon’s definition of entropy given above $p_i$ may denote as the probability of a symbol as the probability of a group or a block of symbols. In other words Shannon’s formula can be rewritten as

$$H_n = - \sum_{i=1}^{a^n} p(C_i) \log p(C_i),$$

where $C_i$ is a block of symbols or ‘word’ of length $n$, $a$ – the number of letters in a language and $a^n$ – the number of all possible combinations of length $n$ of the letters in the language. Obviously $H_n$ is non-decreasing function of $n$. The ratio $H_n/n$ tends to a certain limit when $n$ goes to infinity \[2, 9\] and this limit is called the metric entropy \[2\]

$$H_{met} = \lim_{n \to \infty} \frac{H_n}{n}.$$

We have studied the dependence of $h(n) \equiv H_n/n$ for $n \in [1,12]$ for different DNA sequences.

We used the data of the bacteria and yeast *Saccharomyces cerevisiae* complete genomes from GeneBank release No. 114.0 \[13\] and data of 22 human complete chromosome from Sanger Centre \[14\].

As the first criterium of the texts heterogeneity let us consider C plus G content (C+G) of the DNA sequences. It has been obtained that all yeast chromosomes have % C+G close to 38.42 ± 0.85. In the case of 20 complete bacteria genomes C+G content varies from 29% *rickettsia prowazekii* (rpxx) genome to 65.61% *mycobacterium tuberculosis* (mtub).

It have been obtained that for different DNA sequences reduction rate of $h(n)$ ($\Delta h(n) = h(n) - h(n+1)$) differs, moreover $\Delta h(n)^{hum} < \Delta h(n)^{bact} < \Delta h(n)^{yeast}$. The values of $h(n)$ for yeast different chromosomes are more close each other than those for the bacteria genomes. The chromosome IV of yeast and *mtub* bacteria genome have minimal difference between $h(1)$
and $h(12)$. First yeast chromosome and *mycoplasma pneumoniae* (*mpneu*) bacteria genome have maximal difference between $h(1)$ and $h(12)$. Let us notice that the chromosome I is the shortest with maximum % C+G (its length is 230204 bp). The chromosome IV has minimal % C+G and it is the longest (its length is 1531930 bp). The value of $h(1)$ is maximal for the chromosome I and minimal for the chromosome IV and vice versa in case of $h(12)$. In Fig. 1 one can see $h(n)$ for I, IV, VI and XV yeast chromosomes.

The bacteria genomes with greater content C+G, contrary to the case of yeast, have minimal difference between the levels 1 and 12. The bacteria *rpex* genome with the smallest value of % C+G (29%) has the smallest $h(n)$ up to $n = 5$. *Treponema pallidum* (*tpal*) genome has maximal value of $h(n)$ for $n \in [2, 7]$ but it does not hold for $n > 7$. In Fig. 2 the graphs of $h(n)$ for different bacteria genomes: (*rpex*, *ecoli* (*escherichia coli K-12 MG1655*), *tpal*, *mtub*, *mpneu*, *mgen* (*mycoplasma genitalium G37*)) are shown.

It was obtained also that genomes/chromosomes having approximately equal values of $h(1)$ and % C+G become fairly far from each other when the block’s length increases (see Fig. 3). What points on the genomes have distinct heterogeneity in the ‘word’ context for different word’s length and this can not be found from only the letter analysis. It is possible to pick out three such sets from the envisaged sequences. The first one consists of the human 22 chromosome (% C+G 47.8; $h(1)$ 1.9986) and the genomes of bacteria: *synechocystis PCC6803* (*synecho*) (% C+G 47.72; $h(1)$ 1.9985), *archaeoglobus fulgidus* (*aful*) (% C+G 48.58; $h(1)$1.9994). *Haemophilus influenzae Rd* (*hinf*) bacteria genome (% C+G 38.15; $h(1)$ 1.959) and XV (% C+G 38.16; $h(1)$ 1.9591) and XIII (%C+G 38.2; $h(1)$ 1.9594) yeast chromosomes form the second; the third set is presented by *helicobacter pylori 26695* (*hpyl*) bacteria genome (% C+G 38.87; $h(1)$ 1.964), VI (% C+G 38.73; $h(1)$ 1.963) and IX (% C+G 38.9; $h(1)$ 1.9642) yeast chromosomes. The longer a sequence the slower $h(n)$ decreases. In some aspect this observation can has a simple explanation – the more length of a sequence the more chances to meet there different subsequences, in other words here the finite sample effect presents. But one can see that for $n < 6(7)$ the values of $h(n)$ for some shorter sequences are greater than for longer ones. This fact can not be explained just statistically.


## 3 Topological entropy

The topological entropy is defined as

\[ k(n) = \log_2\frac{N(n)}{n}, \]

where \( N(n) \) is the number of distinct blocks of length \( n \) in a sequence under attention [2]. We calculated \( k(n) \) for \( n \leq 12 \).

It has been obtained that for \( n \leq 4 \) \( k(n) \) is maximal and equal 2 for all genomes/chromosomes, i.e. all possible \( n \)-letters’ combinations are present in even from the investigated DNA texts. On the fifth level just the shortest bacteria \( mgen \) genome (its length is 580074 bp) has no some words. On the 6 level a half of bacteria genomes and 7 yeast chromosomes have all possible words. (Let us notice they are not the longer.) On the 7 level all bacteria and yeast DNA sequences have no some words. From the 8 level no all words are present even in human 22 chromosome. Though the number of all possible words \( 4^8 = 65536 \) is essentially less of any investigated sample. Further the \( n \) increases the \( k(n) \) decreases for all sequences. For yeast chromosomes reduction takes place monotonously according to the length, the shorter a chromosome the faster reduction. As for the bacteria genomes, although here reduction also almost follows to genome length change, it is not precisely (Fig. 4). Thus one can say that \( k(n) \) strongly correlates with length of a sequence.

Due to check the finite size effect we generated artificial DNA sequences of the same size and with the same nucleotides fractions for human 22 chromosome, \( mgen \) - the shortest bacteria genome, \( ecoli \) – the longest (4639221 bp) bacteria genome, \( mtub \) and \( tpal \) bacteria genomes as well as for the longest (IV) and the shortest (I) yeast chromosomes and compare the results obtained from the artificial and natural sequences.

Due to clarify the picture we have considered the differences of \( k(n) \) and \( h(n) \) for artificial and natural sequences: \( \Delta_{\text{top}}^n = k(n)^{\text{art}} - k(n)^{\text{nat}} \), \( \Delta_{\text{met}}^n = h(n)^{\text{art}} - h(n)^{\text{nat}} \). Besides we have paid attention to the difference between \( k(n)^{\text{nat}} \) and \( h(n)^{\text{nat}} \) (\( \Delta_n = k(n)^{\text{nat}} - h(n)^{\text{nat}} \)). As it is easy to see the latter value reflects heterogeneity of elements’ distribution. If only some fraction of all possible elements is realized in an envisaged sequence and all of them are equally probable hence \( k(n) = h(n) \).

As one can see the differences at beginning increase then achieve maximum value (in the interval [7,11] for the first and second cases and [5,9] for the third) and drop (Fig. 5, Fig. 6, Fig. 7). Characteristically that maxi-
mums of the first and second cases almost coincide, the third is shifted to the left on 1-3 positions. For the latter from envisaged $n$ values all differences are very small and close each other (except the human chromosome). This can be related just with the finite sample effect.

4 A DNA sequence and Markov processes

One of the first attempts of modelling DNA sequences and obtaining appropriate statistical characteristics based on the application of Markov processes \[9, 17\]. Under the term Markov process or Markov chain it is usually assumed the stochastic process where a state of a system depends on its previous state. It is so called one step Markov chain (a process with memory equal 1). In general case the memory (dependence) may be greater than 1 but necessarily finite. In the critical review [18] W. Li showed that a one step Markov chain does not characterize observed correlation functions of DNA sequences. We checked how considerable is supposition of Markovity for $H_n$ entropy estimation. It is essential point because for $n > 12$ natural calculation (requiring $4^n$ values of $p(C_i)$) of $H_n$ becomes fairly difficult. At the same time if a process one can consider as a one step Markov chain, $p(C_i)$ can be represented as

$$p(C) = p_{i_1}p_{i_2}p_{i_3}p_{i_4}...p_{i_{n-1}i_n},$$

and for $H_n$ we have

$$H_n = \sum_{i_1} \sum_{i_2} ... \sum_{i_n} p_{i_1}p_{i_2}p_{i_3}p_{i_4}...p_{i_{n-1}i_n} \log[p_{i_1}p_{i_2}p_{i_3}p_{i_4}...p_{i_{n-1}i_n}].$$

Thus for calculation of $H_n$ for any $n$ we have to know only the transition probability matrix $\{p_{ij}\}_{i,j=1}^a$ and the letter distribution $\{p_i\}_{i=1}^a$ (in our case $a = 4$). As it has been revealed the greater $n$ the greater divergence of the $H_n$ estimates obtained by the means of natural calculation and ones for the Markov process. The differences of this values for bacteria \textit{ecoli, mgen, mtub, tpal} genomes, human 22 and yeast chromosomes IV and I for different $n$ are presented in Table 1.

So approximation DNA by the one step Markov process for $H_n$ entropy estimation when $n > 12$ seems not to be quite correct. At first because of progressive increase of distinctions.

Let us note, for small $n$ for the bacteria genomes the differences are equal. For the sequences from distinct species the results differ even for small $n$. As one can see here the finite sample effect is also present.
5 Conclusion

The effect of finiteness of a sequence seems to be considerable for large \( n \) in entropy estimation. In average as \( h(n) \) as \( k(n) \) reductions correlate with length of a sequence. For \( n \) of order 11, 12 the differences of \( h(n) \) and \( k(n) \) very small (for yeast chromosomes and the bacteria genomes) as well as the distinctions of the natural and artificial sequences. For the human chromosome these distinctions are greater.

Reduction rate of \( h(n) \) for different organisms differs. In general it is not follow to the length. Although for yeast chromosomes for \( n > 8 \) exactly, the longer a sequence the greater \( h(n) \). For all envisaged DNA sequences maximum of heterogeneity has been revealed in the interval of length \( n = [5,7] \). Maximum of distinction between natural and artificial sequences is shifted on 1-3 position from the maximum of heterogeneity to the right as for metric as for topological entropy. This also points on the specificity of natural DNA sequences in the interval \( n = [7,11] \).

One step Markov chain is not a good approximation for the metric entropy estimation. It is not the means to obtain a satisfactory estimate of \( H_n \) when \( n > 12 \).

Presented work confirms the fact of existence of the characteristic lengths set revealed by spectral methods [6]. This can be related with the DNA texts segmentation. The work is also in accordance with the block organization principle of nucleic asids, that reflects the block-hierarchical mechanisms of evolution [19].

Possibly the investigation of a long genome (consisting of many chromosomes) as a single sequence allows to achieve greater accuracy in entropy estimation and reduce the finite sample effect.

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FIGURES

Fig. 1 In this figure one can see $H_n/n$ versus $n$ for I, IV, VI and XV yeast chromosomes.

Fig. 2 In this figure one can see $H_n/n$ versus $n$ for rpzx, ecoli, tpal, mtub, mpneu, mgen bacteria genomes.

Fig. 3 In this figure one can see $H_n/n$ versus $n$ for human 22 chromosome, genomes of bacteria: synecho, aful, hinf, hpyl and XV, XIII, VI, IX yeast chromosomes.

Fig. 4 In this figure one can see $K_n$ versus $n$ for human 22 chromosome, genomes of bacteria: ecoli, mgen, mtub, tpal and IV, I yeast chromosomes.

Fig. 5 In this figure one can see $\Delta_n$ (denoted D), $\Delta_{met}^n$ (denoted Dm) and $\Delta_{top}^n$ (denoted Dt) versus $n$ for bacteria ecoli, mgen, mtub genomes.

Fig. 6 In this figure one can see $\Delta_n$ (denoted D), $\Delta_{met}^n$ (denoted Dm) and $\Delta_{top}^n$ (denoted Dt) versus $n$ for yeast chromosomes I and IV.

Fig. 7 In this figure one can see $\Delta_n$ (denoted D), $\Delta_{met}^n$ (denoted Dm) and $\Delta_{top}^n$ (denoted Dt) versus $n$ for human 22 chromosome.
Table 1: In this table one can see the differences of $h(n)$ estimates obtained by the means of natural calculation and approximation of the sequences by the one step Markov chains for bacteria *coli, mgen, mtub, tpal* genomes, human 22 and yeast I and IV chromosomes for different $n$.

| n  | mgen | ecoli | mtub | tpal | I    | IV   | hum  |
|----|------|-------|------|------|------|------|------|
| 3  | 0.3% | 0.3%  | 0.3% | 0.3% | 0.1% | 0.1% | 0.2% |
| 4  | 0.6% | 0.6%  | 0.6% | 0.6% | 0.25%| 0.15%| 0.47%|
| 5  | 0.9% | 0.9%  | 0.9% | 0.8% | 0.46%| 0.25%| 0.74%|
| 10 | 16.96%| 8.38% | 7.46%| 16.45%| 26%  | 13.14%| 5.06%|
fig. 3

H/n

0 2 4 6 8 10 12

n

1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2

hum
 synecho
 aful
 hinf
 hpyl
 XV Chr.
 XIII Chr.
 VI Chr.
 IX Chr.
fig. 7

D hum
Dt hum
Dm hum