Statistics of DNA sequences: A low-frequency analysis

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We study statistical properties of DNA chains of thirteen microbial complete genomes. We find that the power spectrum of several of the sequences studied flattens off in the low frequency limit. This implies the correlation length in those sequences is much smaller than the entire DNA chain. Consequently, in contradiction with previous studies, we show that the fractal behavior of DNA chains does not always prevail through the entire DNA molecule. [S1063-651X(99)10211-3]

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I. INTRODUCTION

The statistics of DNA sequences is an active topic of research nowadays. There are studies on the power spectral density, random walker representation, correlation function [1], etc. Although some of the studies are in contradiction with each other, there is a consensus with respect to the reported behavior of the power spectrum of DNA sequences. For high frequencies it is roughly flat, with a sharp peak at $f=1/3$, due to the existence of the codon structure and the nonuniform codon usage [2,3]. There is also much smaller peak around $f\approx 1/11$, which might be related to the DNA folding structure [4]. For smaller frequencies, it has been reported that the power spectrum presents a power-law behavior with exponent approximately equal to -1, that is, $1/f$ noise. Since a cutoff of the power-law exists at high frequencies, it has been called ''partial power-law'' [5]. The presence of ''1/f'' noise in a given frequency interval indicates the presence of a self-similar (fractal) structure in the corresponding range of wavelengths, whereas a flat power spectrum indicates absence of correlations (white noise).

It is an important question to know whether or not the power-law behavior of the power spectrum of a given DNA chain extends up to the smallest frequencies. If this occurs, it would imply that the fractal behavior of that DNA chain spans the entire chain, and that the correlation length of the chain is not smaller than the chain size. Some studies have claimed that the fractal behavior of DNA prevails through the entire DNA molecule [6]. The aim of this paper is to show that this is not generally correct.

We have done statistical analysis of the DNA of thirteen microbial complete genomes [7], that is, *Archaeoglobus fulgidus* (2 178 400 bp), *Aquifex aeolicus* (1 551 335 bp), *Bacillus subtilis* (4 214 814 bp), *Chlamydia trachomatis* (1 042 519 bp), *Escherichia coli*, also known as Ecoli (4 639 221 bp), *Treponema pallidum* (1 138 011 bp), *Haemophilus influenzae Rd* (1 830 138 bp), *Helicobacter pylori 26695* (1 667 867 bp), *Mycoplasma pneumoniae* (816 394 bp), *Mycobacterium tuberculosis H37Rv* (4 411 529 bp), *Pyro-h Pyrococcus horikoshii OT3* (1 738 505 bp), *Synechocystis PCC6803* (3 573 470 bp), and *Mycoplasma genitalium G37* (5 80 073 bp). We have found that the behavior of power spectrum at small frequencies can be different for different organisms. Also, it can be different for different nucleotides in the same organism. Thus, for some organisms, the behavior of the power spectrum (PS) as a function of the frequency shows, in a log-log plot, three different regions, instead of two, reported previously [5,6,8]. That is, as the frequency increases, it changes from (on average) a flat function, a power-law, and then flat again [9], showing that the fractal structure of DNA sequences does not necessarily extend up to the total length of the chain. The flattening of the power spectrum at low frequencies is just a signature of the fact that the correlation length of DNA sequences is, for many sequences, much smaller than the entire length of the DNA chain. We have calculated the autocorrelation function (AF) of the nucleotides in the DNA chains of the organisms mentioned above. We have found that in some of the organisms the correlation length is of the order of a few thousand base-pairs. In others, the correlation length is very large, being not smaller than 100,000 base-pairs. We have also found in nearly all the sequences studied a peak of the autocorrelation function at lengths approximately equal to 100. The corresponding peaks are also present, as expected, in the power spectrum. To the best of our knowledge this has never been reported before.

A DNA chain is represented by a sequence of four letters, corresponding to four different nucleotides: adenine (A), cytosine (C), guanine (G), and thymine (T). The calculation of the power spectrum or the autocorrelation function requires that this symbolic sequence be transformed into a numerical one. Several methods have been proposed for this [5,8,10]. Here we use the method introduced by Voss [8], which has been shown in [11] to be equivalent to the method used in [5]. In Voss's method one associates 0 to the site in which a given symbol is absent and 1 to the location where it is present. So, for a given DNA sequence there will be four different numerical sequences, corresponding to the sequences associated with A, C, G, and T. In his original paper, Voss calculated the PS for each one of these sequences and summed them to find the average PS. Here, we treat them distinctly, because we also want to know about the similarities and differences of the statistical features of different nucleotides in a given DNA sequence.

By artificially linking flank sequences together, Borstnik *et al.* [12] found a behavior for the PS as a function of the

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frequency that was flat, then an exponential decay, then flat again. Our studies of *complete* sequences show that the behavior of the PS does not show any exponential decay in the region of intermediate frequencies. We found instead a power-law. However, for low frequencies we also find a flat PS in several of the sequences studied. A flat PS at high frequencies is observed in all cases.

II. STATISTICAL ANALYSIS

A. Power spectrum

Let us use Voss's method [8] and denote by x_j^A the numerical value associated with the symbol A. Then one has $x_j^A=1$ if symbol A is present at location j and $x_j^A=0$ otherwise. Similar transformation is made for symbols C, G, and T. Consequently, the DNA can be divided into four different binary subsequences of 0's and 1's, associated with the symbols A, C, G, and T.

The Fourier transform of a numerical sequence x_k of length N is by definition,

$$V(f_j)\equiv\frac{1}{N}\sum_{k=0}^{N-1}x_k\exp(-2\pi ikf_j), \tag{1}$$

where the frequency f_j is given by $f\equiv j/N$, and $j=0,\ldots,N-1$. The PS is defined as $S(f_j)=V(f_j)V(f_j)^*=|V(f_j)|^2$. From the definition, we can see that $V(f_0)=\langle x_k\rangle$, where the brackets denote average along the chain. Consequently, this quantity carries no information about the relative positions of the nucleotides. Because of this, we usually neglect this quantity in our calculations, that is, we concentrate only on frequencies with $j>0$.

Since DNA sequences have a large number of base-pairs, and the PS presents considerable fluctuation, some kind of averaging is usually done to plot this quantity as a function of the frequency. The main way of averaging done so far is the following [5,6,8]: the DNA chain of length N is divided into non-overlapping subsequences of length L. Then, the power spectrum of each of these segments is computed and averaged over the N/L subsequences. In this method the smallest frequency for which the PS can be calculated is, of course, $f=1/L$. Consequently, the behavior of frequencies in the range $[1/N,1/L]$ is unknown. An example of such a calculation for Ecoli is shown in Fig. 1(a), where the DNA chain was divided in subsequences of 8192 nucleotides. A clear power law, followed by an approximate flat region with peaks at $f=1/3$ and $f\approx 1/11$, is seen. To avoid overlap of the curves, we have displaced the PS of cytosine, guanine, and thymine by dividing it by 10, 10^2, and 10^3, respectively. Since the power spectrum for sequences of real numbers is symmetric with respect to the axis $f=0.5$, we plot only the PS for frequencies in the interval of 0 to 0.5. A similar figure for adenine is shown in [6].

Another way of averaging the PS, used in [13], is to calculate it for the entire sequence of N points and then plot it by averaging n neighboring points. That is,

$$\overline{S}(f_{j+n/2})=\frac{1}{n}\sum_{l=jn}^{(j+1)n-1}S(f_l) \tag{2}$$

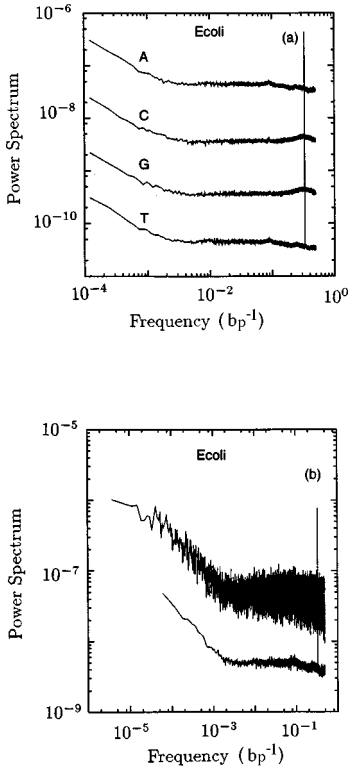

FIG. 1. (a) Power spectrum of Ecoli calculated by dividing the entire DNA chain in subsequences of 8192 nucleotides. The curves for C, G, and T have been multiplied by factors of 10^{-1}, 10^{-2}, and 10^{-3}, respectively, to avoid overlap of the curves. (b) Power spectrum of adenine (A) for Ecoli calculated by averaging 32 (upper curve) and 512 (lower curve) neighboring points. The lower curve has been multiplied by a factor of 10^{-1}.

with $j=0,1,\ldots,N/n$. This can be translated by saying that this is an average in sliding windows of n points, where there is no overlapping between one window and the next. In this method, the smallest frequency that is calculated is $n/2N$. We show in Fig. 1(b) the PS for adenine in Ecoli using this method, with $n=32$ (upper curve) and $n=512$ (lower curve). In the case of few points per bin ($n=32$) we see hints that the PS flattens off in the low frequency limit. This does not occur when $n=512$, which shows only the power-law at intermediate frequencies and the flat region at high frequencies. We will see, however, that the method we use below, which is a standard one in statistics, gives better results in the low frequency region than this and the other method discussed above.

In the method we use, we calculate the mean PS in a sliding window of n points, with adjacent windows having an overlap of $n-1$ points. The average PS in each window will determine the values of the smoothed resulting sequence. In mathematical terms we can express this as

$$\overline{S}(f_j)=\frac{1}{n}\sum_{m=j-\Delta}^{j+\Delta}S(f_m) \tag{3}$$

where $\Delta=(n-1)/2$, n is taken an odd number, and j varies from $\Delta+1$ to $N-\Delta-1$. Although the new sequence in this method is smoother than the original one, its length is only smaller than it by 2Δ points. We have found that this method

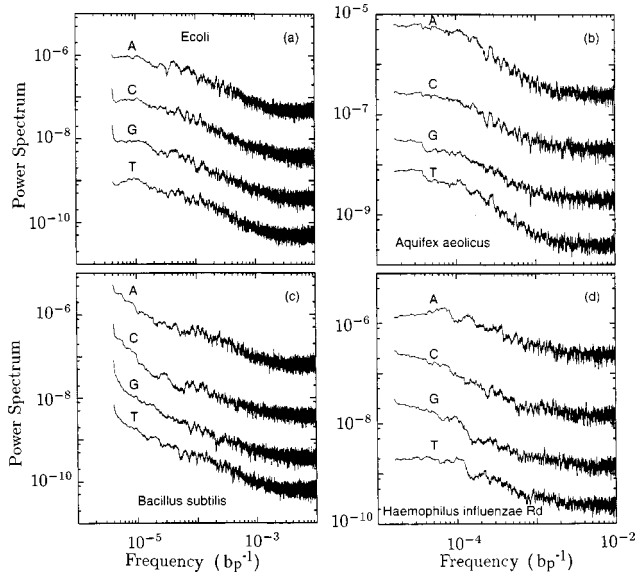

FIG. 2. Power spectrum of (a) Ecoli, (b) *Aquifex Aeolicus*, (c) *Bacilus subtilis*, and (d) *Haemophilus influenzae Rd*. The curves for C, G, and T have been multiplied by factors of 10^{-1}, 10^{-2}, and 10^{-3}, respectively, to avoid overlap of the curves.

shows the same behavior for moderate and high frequencies as the two other methods discussed above. However, it is superior for studies at low frequencies.

To speed up the calculations of the PS we have used, as it is normally done, the Fast Fourier Transform algorithm [14]. This algorithm speeds up the calculation of the PS by a factor of $N/\log_\alpha N$, but it requires that length of the sequence analyzed be an integer power of the integer α, which usually is taken to be two. Since the length of DNA sequences are not generally equal to an integer power of two, we take in our computation the largest subsequence, starting from the beginning of the chain, that fulfills this requirement. More specifically, we take the first $N'=2^K$ nucleotides, where K is the largest power of 2 satisfying the requirement that $N' \leqslant N$, with N being the total size of the DNA chain. In this way, the number of nucleotides not included in the calculation is always smaller, and in many cases much smaller, than $N/2$. We have also done calculations considering the entire length of the DNA and zero padding the sequence to the next integer power of 2, as described in [14]. The results remain essentially the same as the ones we show here.

Since our method shows the same behavior for the PS in the range of intermediate and large frequencies as the other averaging method, and also due to the large size of the DNA chains, we plot the PS only in the frequency range $[1/N,0.01]$. We show in Fig. 2 the results of our calculation for $n=33$ for four representative cases of the thirteen ones studied. For clarity, we have displaced the PS of C, G and T by dividing it by 10, 10^2, and 10^3, respectively. In this way, an overlap of the curves is avoided. Our results show that the low frequency PS associated with each of the nucleotides in the organisms studied fall into one of the following cases:

(a) All the four PS associated with the four different nucleotides flattens off at low frequencies. In these cases there are three regions in the PS versus frequency curve. At both low and high frequencies the PS is of white noise type and the middle region is characterized approximately by a power-law behavior, that is, in a log-log plot the PS satisfy $S\sim f^{-\gamma}$, with $\gamma>0$. This is for example the case of Ecoli, shown in Fig. 2(a). When compared with Fig. 1 or with Fig. 1 of [6] we see that the averaging methods of [5,6,8] and [9] do not show the true behavior of the PS at low frequencies. In this calculation we used the first 2^{22} nucleotides, which corresponds to 90% of the Ecoli DNA. We show another case with the same behavior in Fig. 2(b), which is the PS of *Aquifex aeolicus*. For the PS of *Aquifex aeolicus* we used the first 10^{20} sites, which corresponds to 68% of the chain length. The other organisms, among the ones studied, that show the same PS behavior are *Archaeoglobus fulgidus*, *Synechocystis PCC6803*, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*.

(b) The second type of behavior is the one in which the PS at small frequencies of all the nucleotides presents a power-law behavior, which is approximately an extension of the PS behavior at intermediate frequencies. For these organisms, the PS presents only two regions: a flat one at high frequencies, and a power-law behavior for intermediate and low frequencies. A typical case for this kind of behavior is shown in Fig. 2(c), which is the PS of *Bacillus subtilis*. In the calculation of the PS in this case we have used the first 10^{22} sites, which corresponds to 99% of the total length of the chain. The other organisms studied that have similar PS are: *Treponema pallidum*, *Pyro-h Pyrococcus horikoshii OT3*, and *Mycoplasma genitalium*.

(c) The third, and last, type of behavior we have seen is the one in which, for a given organism, different nucleotides present different asymptotic behavior for the PS at low frequencies. That is, the PS flattens off for some of the nucleotide sequences, and for the others it remains approximately a power-law. An example of such a behavior is shown in Fig. 2(d), which is the PS of *Haemophilus influenzae Rd*. We see that different behavior for the PS are grouped in pairs. In all the cases studied we found that the PS of A is qualitatively similar to the PS of T and the one of C is similar to the one of G. This kind pairing of the statistical features of nucleotides has been reported for yeast chromosomes in [1]. This is consistent with the strand symmetry of DNA sequences, reported in [15]. A possible explanation for the single-base strand symmetry is provided in [16] and [17]. In the calculation of the PS we have used the first 10^{20} sites of the DNA chain, which corresponds to 57% of the total number of nucleotides. Since a large number of sites are left out of the calculation, we have also analyzed the PS of the central and final region of the chain. We verified that the results remain essentially the same as the ones shown in Fig. 2(d). The other organisms that have similar statistical features for the PS are *Chlamydia trachomatis* and *Helicobacter pylori 26695*.

For very large DNA sequences, such as the ones of much more complex organisms than microbes, all the three methods discussed above for the calculation of the PS may be impractical, due to computer limitations. In this case, an approach such as the one used in [13], in which the density sequence rather than the original base sequence is used in the Fast Fourier Transform, will certainly be more appropriate.

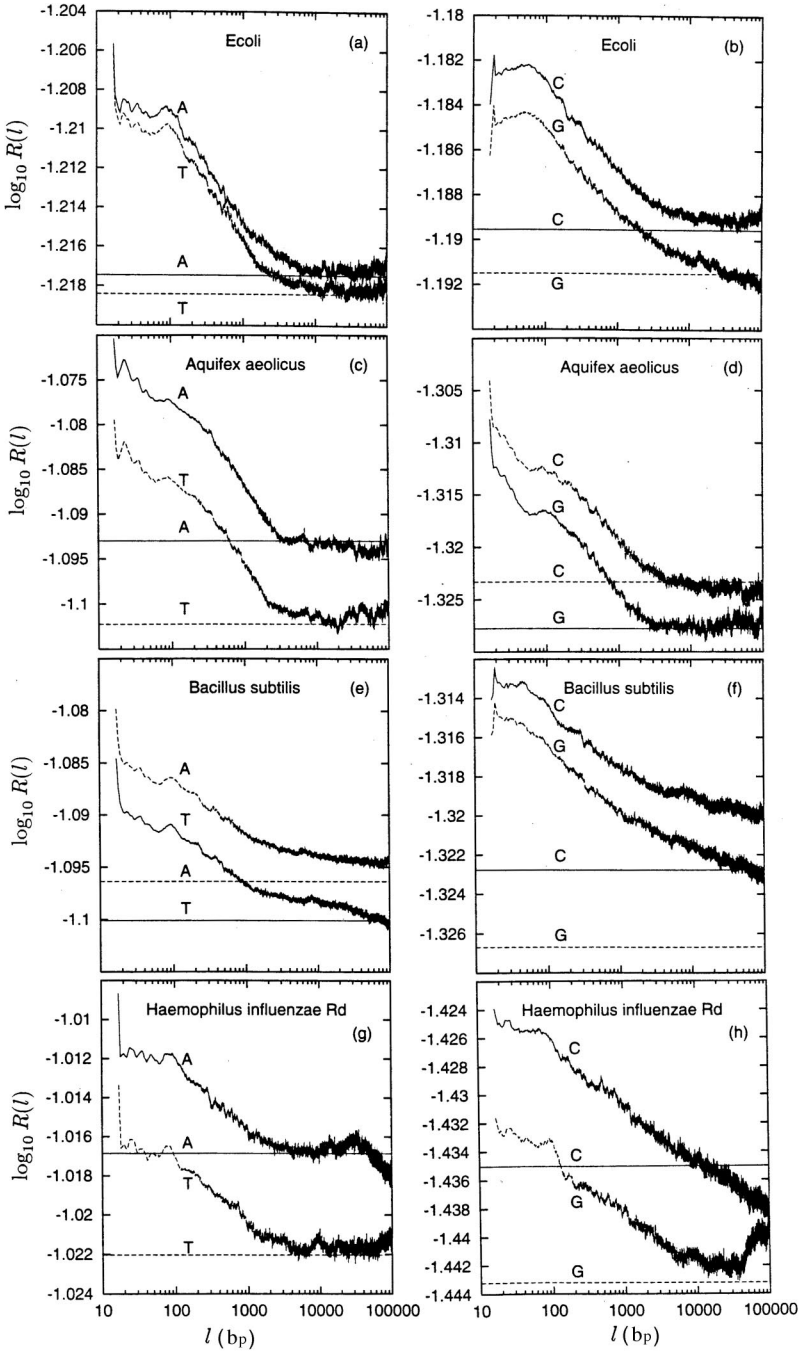

FIG. 3. Autocorrelation function of Ecoli for (a) A and T, (b) C and G, *Aquifex Aeolicus* for (c) A and T, (d) C and G, *Bacilus subtilis* for (e) A and T, (f) C and G, and *Haemophilus influenzae Rd* for (g) A and T, (h) C and G. The horizontal lines are $\langle x_k \rangle^2$. Statistical linear independence between the nucleotides in a given sequence occurs when $R \equiv \langle x_k x_{k+l} \rangle = \langle x_k \rangle^2$.

B. Autocorrelation function

The autocorrelation function $R(l)$ of a numerical sequence is, by definition,

$$R(l) \equiv \langle x_k x_{k+l} \rangle, \tag{4}$$

where the brackets denote average over the sites along the chain. For $l=0$, Eq. (4) implies $R(0)=\langle x_k^2 \rangle$, which is a quantity carrying no information about the relative position of the nucleotides. As in the case of the power spectrum for $S(0)$, this quantity will be neglected in our calculations. There are two reasons why we do not use the more traditional definition of AF, that is, $R(l) \equiv \langle x_k x_{k+l} \rangle - \langle x_k^2 \rangle$. The first, and most important one, is that there is no simple relationship between the traditional definition and the PS. The PS and the AF are Fourier transform pairs, as discussed in [18], only when the AF is given by Eq. (4). Also, the analytical connections between these two quantities discussed below, such as power-law in the PS implying power-law in the AF, are valid only with the definition we use, not with the traditional definition. The other reason is that the traditional definition can result in negative values for the AF, as we see below, and this does not allow us to plot it a logarithmic scale.

Statistical independence between sites separated by a distance l implies that $\langle x_k x_{k+l} \rangle = \langle x_k \rangle^2$. The value of l above which this condition is satisfied (on average) is called the correlation length. DNA molecules, depending on the organism, can form an open or a closed loop. Bacterial DNA usually forms a closed loop [19]. For circular chains, the auto-

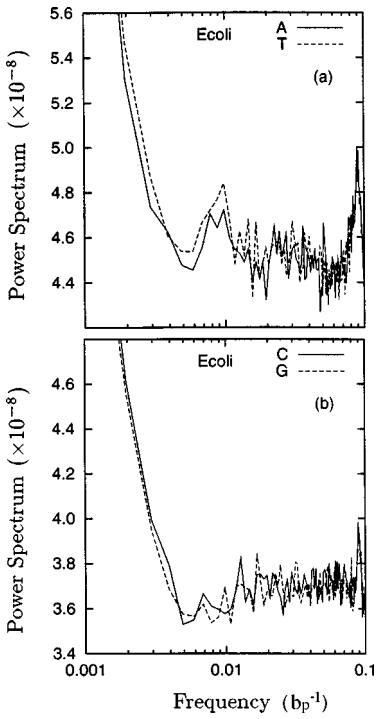

FIG. 4. Power spectrum of Ecoli, in the range of frequencies from 0.001 to 0.1, in which the averaging is done by dividing the entire DNA chain in subsequences of 1024 nucleotides for (a) A and T, and (b) C and G. The *y*-axis has a linear scale.

correlation function and the PS form Fourier transform pairs (this is the Wiener-Khintchine theorem) [18]. In order to consider the entire DNA sequence (without having the constrains of the Fast Fourier algorithm) we calculate the AF using its plain definition, that is, Eq. (4), and not via Fourier transforming of the PS [20]. We present results for l in the interval $[1,10^5]$. This is a much larger interval than the ones considered in previous publications [1,21], which took l in $[1,10^3]$. It is obvious that when $l \ll N$, as it occurs here, it does not matter if we consider open or closed boundary conditions. Since we find it computationally easier to consider open boundary conditions, we present the results of the AF for this case. It is beyond the scope of this paper to study cross-correlation between two different kinds of nucleotides. Such a kind of study can be found for example in [1,2].

We show in Fig. 3 the AF versus l for the sequences whose PS we displayed in Fig. 2. Since the AF presents a strong oscillation of period 3 [2], we chose n to be a multiple of 3 in order to smooth it out. Here we have used $n=33$ (there was no particular reason for choosing n a multiple of 3 in the calculation of the PS). In Fig. 3 the horizontal lines are the corresponding values of $\langle x_k \rangle^2$. When $R(l) \equiv \langle x_k x_{k+l} \rangle \approx \langle x_k \rangle^2$ statistical independence between the nucleotides of a given type holds. As Fig. 3 shows, when $l \lesssim 100$ the AF is roughly flat for some sequences, and for others it is approximately a power-law. Then, as l increases we see a regime of a power-law in all cases. For the interval of l studied, we observe that the AF can get flat again as l increases even more (with $R(l) \approx \langle x_k \rangle^2$), or not reach a plateau. For the sequences where the PS flattens off at low frequencies, we expect that the AF will get flat for larger l, with statistical independence holding. However, for most of the cases studied, this happens when $l \gg 10^5$. Only the AF of *Aquifex aeolicus* seems to reach a plateau for l in the interval $[1,10^5]$ for all the nucleotides. This is shown in Fig. 3(c) and Fig. 3(d), where we observe that the correlation lengths for this organism appear to be between 10^3 and 10^4. For the other organisms studied, we see a wide variety of behaviors for the AF in the region of $l \in [10^3, 10^5]$. As Fig. 3 shows, we find cases in which the AF reaches a plateau with statistical independence between the nucleotides, in others we see a slow decrease of the AF, such as the AF of A for *Bacillus subtilis*. We also find an abrupt change of slope in a plateau region, like the AF for A and of G in *Haemophilus influenzae Rd*. And most interestingly, we find the presence of anticorrelations, that is, $\langle x_k x_{k+l} \rangle$ being smaller than $\langle x_k \rangle^2$. This implies that sites separated by a given distance tend to be occupied by different nucleotides. The case in which this appears more strongly is in the AF of C for *Haemophilus influenzae Rd*. We have also observed that most of the sequences present a peak in the AF at $l \approx 100$. We have found that the corresponding peaks are also seen in the PS. We will show this for Ecoli. In order to significantly reduce fluctuations, we divided the DNA sequence of Ecoli in reasonable short segments of 1024 bp and applied the averaging method used in [5,6,8], which was described above. The results, with a linear scale in the *y*-axis, are plotted in Fig. 4(a) for A and T and in Fig. 4(b) for C and G. In the PS the peaks of A and T are broader and higher than the ones of C and G. Due to the properties of the Fourier Transform, the wider peaks in the PS are narrower in the AF, and vice-versa, as we see in Fig. 4. Also, the location of the peaks are not the same for all the nucleotides. For A,T they are at $l \approx 100$ bp, but for C and G they are at $l \approx 80$ and $l \approx 60$ bp, respectively. To the best of our knowledge, this kind of periodicity has never been reported before, and the reason for it is unknown to us.

The final point we discuss is with respect to the functional form of the PS and AF. For analytical studies the easiest way to derive relationship between these two quantities is to transform the sum of Eq. (1) into an integral [22]. There are three typical cases that are well studied and understood.

(a) When the AF obeys a power-law in the entire range of lengths, that is, $R(l) \sim l^{-\gamma}$ (with $0 < \gamma < 1$) results in $S(f) \sim f^{\gamma-1}$, which is also a power-law. For γ close to zero, this implies $S(f) \sim 1/f$, that is, a fractal behavior.

(b) In the case that the AF decays exponentially, that is, $R(l) \sim \exp(-l/l_c)$, where l_c is a characteristic length, results in $S(f) \sim 1/(1+f^2 l_c^2)$. Here, when $f \ll 1/l_c$ implies in $S(f)$ being constant in this frequency range (white noise). When $f \gg 1/l_c$ one has $S(f) \sim 1/f^2$.

(c) When the AF is described by a function that is a product of an exponential decay and a power-law, that is, $R(l) \sim l^{-\gamma} \exp(-l/l_c)$, results in $S(f) \sim (1+f^2 l_c^2)^{(\gamma-1)/2}$. For $f \ll 1/l_c$ implies in $S(f)$ being constant in this frequency range. When $f \gg 1/l_c$ one has $S(f) \sim f^{\gamma-1}$.

Thus, for cases (b) and (c) there is flattening of the PS at low frequencies only. In case (a) there is no flattening at all. This is not exactly what happens in DNA sequences. There we see flattening of the PS at *high* frequency, and in some cases also at low frequencies. For the AF there are cases in which flattening occurs for large l and in most cases flattening also occurs for small l. An intermediate power-law region is found for both the PS and the AF. Our preliminary

studies indicate that there are not many typical functions that would reproduce the behavior of the AF and PS for DNA sequences. Note that the non-triviality of this point comes from the fact that these functions are linked by the sum given in Eq. (1). So far, the best candidate we have found is

$$R(l)=\frac{A\exp(-l/l_c)}{(B+l)^{\gamma}}+C. \tag{5}$$

Qualitatively we have found that this function correctly describes what we have seen for the PS and AF of DNA sequences. In a future study, we plan to further investigate this question, and if this function proves to be the most appropriate one, we will use methods of minimization to find the parameters A, B, C, l_c, and γ that best fits the AF and PS of the sequences studied.

III. CONCLUSION

In summary, we have studied statistical properties of the complete DNA of 13 microbial genomes and shown that its fractal behavior not always prevails through the entire chain. For some sequences the power spectrum gets flat at low frequencies, and for others it remains a power law. In the study of the autocorrelation function we have found a rich variety of behaviors, including the presence of anti-correlations.

ACKNOWLEDGMENT

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