FINGERPRINTS OF NON EXTENSIVITY IN DNA FRAGMENT DISTRIBUTION

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ABSTRACT
A formulation of DNA radiation- induced breaking based on Tsallis´s generalized entropy concept is here introduced in order to explain the experimental data of DNA fragment distribution. We explicitly show that the process of breaking can be mathematically described using the most general principles of Physics. In this way, the maximum entropy method leads to an explicit result for the probability density of finding a DNA segment of length l, which agrees very well with the fragment distribution reported in the experiments.

RESUMEN
Una formulación de radiación de ADN basada en el concepto de entropía que generalizó Tsallis´s se introduce aquí para explicar los datos experimentales de ADN, fragmento distribución. Se describe la muestra del proceso de ruptura que usa los principios más generales de Física. De esta manera matemáticamente el método de entropía de máximo lleva a un resultado explícito para la densidad de probabilidad de hallazgo de un segmento de ADN de longitud l en correspondencia con la distribución del fragmento que se informa en los experimentos.

I. INTRODUCTION

Atomic force microscopy (AFM) has revealed itself as an extremely useful device in the analysis of very small structures and specially in DNA fragment analysis [1].

As the ionizing radiation interacting with DNA molecules can influence the properties of living cells up to a lethal extreme, it is of great importance to study the production of fragments in DNA as a result of radiation mediated breaking processes.

A possible effect of the ionizing radiation is related to the production of fragments in DNA. The study of DNA lesion distribution is very important to increase the knowledge of the biological systems, whose more sensitive structures are DNA strands separated by a few nanometers.

On the other hand, DNA fragment analysis may help in the study of the structural properties of genome texts, and then to understand general principles of genetic sequences.

The process of DNA double strand breaking was performed by irradiation of plasmid DNA molecules with electrons and neutrons at different doses (see [1]). Then, the length of the resulting fragments was measured. As a result, the collection of fragments was found to obey a fragment size distribution function (FSDF) with important characteristics from the viewpoint of complexity.

The main fact, which will be focused in this paper, is that the collection of fragments is such that there is not a "characteristic" size of the fragments, i.e. the smaller the fragment, the more abundant is it.

An important feature of the experiments is that the breakage was always performed with thermal neutrons or electrons so that the DNA strand breaking occurred in an indirect way, the radiation exciting the medium where the plasmids were dissolved and suffered breakage due to the molecular impact with the molecules of the solvent. So, there is no way to imagine DNA rupture in this case as the direct action of the radiation on the strands like "scissors cutting a strand". This experiment is in this case a genuine impact breakage, in which it is expected that the global properties of the strand must be expressed somehow in the results of the rupture. The controversial long range correlation in DNA must be expressed in this case, as we shall see. This is the main goal of this paper, in which we report first results of our group in this field.

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II. THE ENTROPIC VIEWPOINT

The FSDF obtained in this case in [1] does not present a definite local maximum, resembling more to an inverse power law, i.e., a distribution function in the basin of attraction of a stable (Levy) distribution [2].

This feature of the FSDF is not new. It has been reported in [3] the occurrence of transition to scaling in FSDF during glass rods breaking, in [4] the power law distribution of fragments was related to self-organized criticality (SOC). Matsushita [5] proposed a fractal representation for a general process of fragmentation.

Our group [6, 7] detected power law behavior in the process of liquid drop fragmentation and we proposed a Bethe lattice representation to interpret FSDF in these experiments.

Some attempts to relate FSDF to first principles in physics like the maximum entropy principle are present in [8, 9] with results that, at the best, do not cover the process in which scaling in FSDF is present. (i.e., when the energy of the fragmentation process is high).

The universal nature and almost unlimited range of applicability of the maximum entropy principle leads us to expect it to be useful in describing scaling in FSDF even at DNA scale.

But the process of fractionating, by its own nature, is a paradigm of phenomena in which interactions are long-range correlated among all parts of the object under fragmentation. Then, though the maximum entropy principle is expected to have an unlimited range of application, in the process of breaking the expression for the entropy in its Shannon form:

$$S = \int p(x) \log p(x) dx \qquad (1)$$

where p(x)dx is the probability of finding the system magnitude x in the interval [x, x+dx], and k is Boltzmann's constant- is not applicable. This is because this formula, based in Boltzmann-Gibbs statistics, is expected to be valid when the effective microscopic interactions are short-ranged, and this gives to this entropy its extensive character. (The entropy of the whole object equals the sum of the entropies of its constituent independent parts)

Since, as we already pointed out, all parts of the fractionating object during the process of violent breakage are correlated, then the entropy of the object being fractionated is smaller tan the sum of the entropies of the parts in which the object divides, defining this way a "superextensivity" in this system. This suggests that it may be necessary to use non-extensive statistics, instead of the Boltzmann-Gibbs one.

This kind of theory has already been proposed by Tsallis [10], who postulated a generalized form of entropy, given by

$$S_q = k \frac{1 - \int p(x) dx}{q - 1} \qquad (2)$$

where q is a real number.

This entropy can also be expressed as:

$$S_q = -k \int p(x) \, l_q \, p(x) dx \qquad (3)$$

where the generalized logarithm $l_q p(x)$ is defined as (see [11]):

$$l_q p = \frac{p^{1-q} - 1}{1 - q} \qquad (4)$$

It is straightforward to see that $S_q \to S$ when $q \to 1$, recovering Boltzmann-Gibbs statistics.

It is our goal to derive, starting from first principles, a functional dependence to describe the DNA FSDF obtained in [1].

Starting from equation \ref{eq:2} we may follow the method of Lagrange multipliers to apply the maximum entropy principle to the fragmentation of DNA. To do this, we impose two constraints: The first is the trivial one of normalization of the probability:

$$\int p(l) \, dl = 1 \qquad (5)$$

i.e., the sum of the probabilities of finding a fragment of any length is equal to unity.

As a second constraint we may choose to adopt a ``q-mean value'' as:

$$\int p^q(l) \, l dl = 1 \qquad (6)$$

Which reduces to the classical mean value when $q \to 1$. In this formulation the length l of the fragments has been referred to a unit adequately chosen as to choose the "q-mean value" equal to one.

It may seem strange to introduce a "q-mean value", also known as "unnormalized mean value" in this formulation. Really, this choice is not unique but for our purposes and for simplicity reasons we will choose this formulation. In [11] a detailed discussion of the possible choices for the second constraint can be found. The one here chosen showed to be particularly useful in describing anomalous diffusion and was also employed by us in [12,13] dealing with problems of fragmentation.

Now we use the method of Lagrange multipliers by means of the construction of the functional:

$$L(p,\alpha,\beta) = \frac{S_q}{k} + \alpha_{\dot{O}}\, p(l)dl - \beta_{\dot{O}}\, p^q(l)ldl \qquad (7)$$

being α and β the Lagrange multipliers. The extremization of this functional leads to:

$$p(l)dl = \beta(2-q)dl / [1 + \beta(q-1)l]^{\frac{1}{q-1}} \qquad (8)$$

III. COMPARISON WITH THE EXPERIMENTAL RESULTS

Equation 8 is the expression for the probability of finding a fragment of length l and depends on two coefficients to adjust. In this case we can apply this expression to fit it to the experimental data reported in [1], where methods of atomic force microscopy were applied to measure FSDF of irradiated DNA.

Figure 1 shown the experimental results for DNA breaking with electrons at doses of 5000 (e5000) and 7000 (e7000) Gy. Both are fitted with Equation 8.

Figure 2 represents FSDF for DNA breaking with neutrons at the same doses.

In both cases the length of the fragments was normalized to the length of the largest one, and the number of fragments was normalized to their total number. As can be seen, the agreement is very good. It is remarkable to see that the values of q in all cases are very similar. This fact reveals that the use of Tsallis's entropy is not a mere fitting tool.

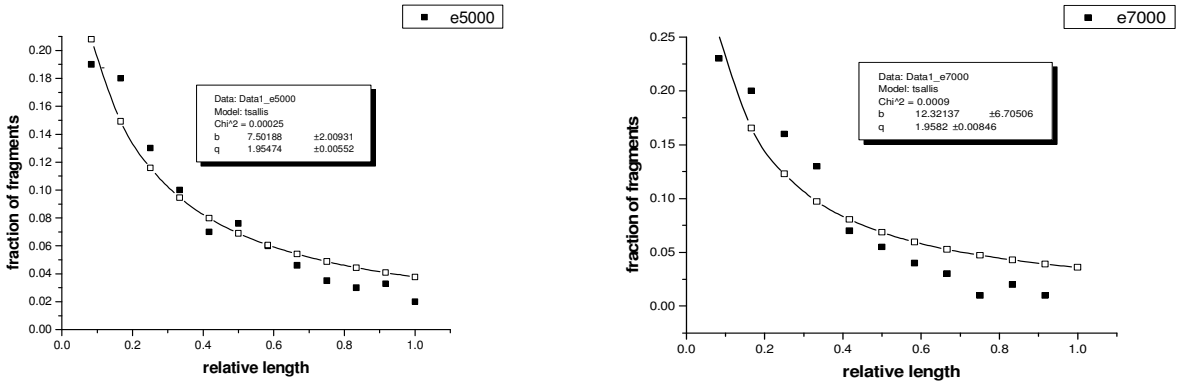

Figure 1.

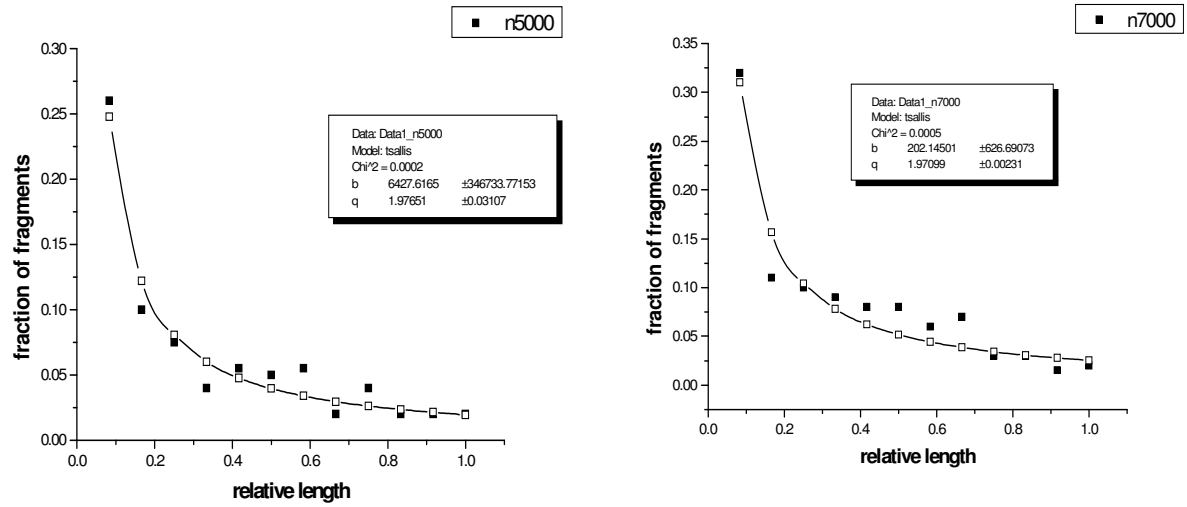

Figure 2.

The differences in the values of β are, nevertheless, remarkable specially between electrons and neutrons.

More experimental data for electrons from 50 to 200 Gy and neutrons at doses of 900, 7 500, 2 000 and 10 000 Gy were also fitted with good results. The wide range of variation for β and the narrow one for q is revealed in all cases. In this paper we are reporting the results of the coincident doses of electrons and neutrons of 5 000 and 7 000 Gy to illustrate the application of this viewpoint. Only in the cases of very low doses of electrons (50 and 100 Gy, where fluctuations in FSDF are important) the results are not as good looking as before.

The variation of β and, conversely, the almost constant value of q in all cases may lead to conclude that the effective temperature of the breaking processes is strongly influenced by the doses and masses of the radiating particles, whereas the non extensive nature of the process (measured by q) is independent of the nature of the radiation and is more related with intrinsic properties of the system under breakage. It is perhaps not unworthy to warn the reader that this is but a possible (though plausible) scenario which remains to be proved.

IV. CONCLUSIONS

This fact reveals the non extensive nature of breaking in DNA, as was revealed for macroscopic objects in [12, 13]. So, this characteristic of breaking is not exclusive of macroscopic bodies.

The relation of non extensivity in breaking with long range correlation in the structure of DNA is, thus, an open question that can be treated by this way. Indeed, it is tempting to induce structural long range correlation in DNA from the non extensivity observed in its FSDF.

Use of Boltzmann's entropy to describe FSDF obtained in these experiments leads to incorrect results (i.e., Eq. 9) impossible to fit with the data, which shows power law behavior.

The reported presence of 1/f spectrum in sequences and long-range correlations in the DNA sequences [14] supports the assertion that the observed FSDF reflects intrinsic properties of the DNA molecule. Further work on the relation between non extensivity and sequence correlations is in progress.

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