The Complexity of DNA

The measure of compositional heterogeneity in DNA sequences and measures of complexity

BY WENTIAN LI

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DNA sequences store the complete genetic information of a biological organism. Understanding the "genetic language" in DNA sequences is the ultimate goal of the Human Genome Project, which will have a profound impact on biology, medicine, and human society [1]. In one sense, the genetic language written in DNA sequences is simpler than the English language because it is composed of only four letters—A, C, G, and T—representing the four nucleotides (also referred to as bases). In another sense, DNA sequences are more complex than English because of their length, which allows more combinations of letters, thus more "words." So how complex can a given DNA sequence be?

Besides the question of genome complexity, whose measure ranges from the total length of the DNA sequences to the total number of genes produced in a genome, there is also a question of how complicated the *symbolic text* of a DNA sequence is. This sequence-complexity question requires a measurement of the statistical features in the arrangement of the four nucleotides. We now know that the base composition and correlations among neighboring bases are not the major contributing factors to the sequence-wide pattern. It is the spatial heterogeneity of the base composition [2, 3] or the long-range correlation [4, 5] that largely shapes the complexity of the whole sequence.

At first, it is thought that the heterogeneity in DNA sequences is simple. In the bacteriophage lambda sequence, for example, the spatial difference of base composition is "black and white": The C+G density is higher on the left half of the sequence and lower on the right half. Some people think that the bacteriophage lambda sequence is a good representative of all DNA sequences and that the long-range correlation can be completely explained by this simple heterogeneity [6].

As one of the people who first observed the long-range correlation in DNA sequences [7, 8], it was clear to the author that this proposition was not correct. In fact, the surprise in our first observation of the long-range correlation in DNA sequences was not the long-range *per se*, but a special type of long-range correlation called "1/f spectra" or "1/f noise." Simple heterogeneity could lead to a deviation from the random sequences ("white noise" or "white spectra") but does not automatically lead to "1/f spectra." Extra features besides simple heterogeneity are needed to explain this special type of long-range correlation.

Some recent developments in the study of compositional heterogeneity of DNA sequences enable us to address this issue in a satisfactory fashion [9, 10]. With respect to the base composition, a DNA sequence can be homogeneous, heterogeneous in a simple way, or heterogeneous in a complex way. The complex heterogeneity is characterized

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by the "domains within a domain" phenomenon [4, 5, 9, 10]. For these sequences, whether a region is homogeneous is only relative. Interestingly, the measure of base composition heterogeneity coming out of the study of long-range correlation in DNA sequences is intrinsically related to measures of complexity in the study of complex systems. This connection is the topic to be addressed in this commentary.

PARTITIONING HETEROGENEOUS DNA SEQUENCES

First things first: We need to partition a heterogeneous DNA sequence into two relatively homogeneous subsequences. In the field of information theory, a quantity called Jensen-Shannon distance [11] can be used to measure the distance between two statistical distributions. This Jensen-Shannon distance is defined as the difference between the entropy (another well-known quantity in information theory, as well as in statistical physics) calculated from the whole system and the weighted sum of entropies calculated from the subsystems. The Jensen-Shannon distance is successfully applied to the DNA sequences for the purpose of partitioning the sequence [9, 10].

One first calculates the Jensen-Shannon distance D for each possible partition point i along the DNA sequence. This $D(i)$ function is plotted in Figure 1 for the DNA sequence from the first chromosome of budding yeast (whose academic name is *Saccharomyces cerevisiae*). This sequence contains 230,208 nucleotides. The higher the value of the Jensen-Shannon distance $D(i)$ at a given point i, the bigger the difference of the two subsequences as partitioned at point i, and the more ideal to choose that point to partition the sequence. In Figure 1, the highest point of $D(i)$ is actually reached at one telomere region—the end of the chromosome—and the second highest point at another telomere region. What it tells us is that both telomeric regions are quite different from the rest of the sequence, with respect to base composition.

Besides the two telomeric regions, the third-highest point of $D(i)$ in Figure 1 is near $\approx 189{,}000$. The fourth-highest point is near $i \approx 27{,}000$, etc. Overall, there are several other places where we can partition the sequence and the resulting base composition difference between the two subsequences is large.

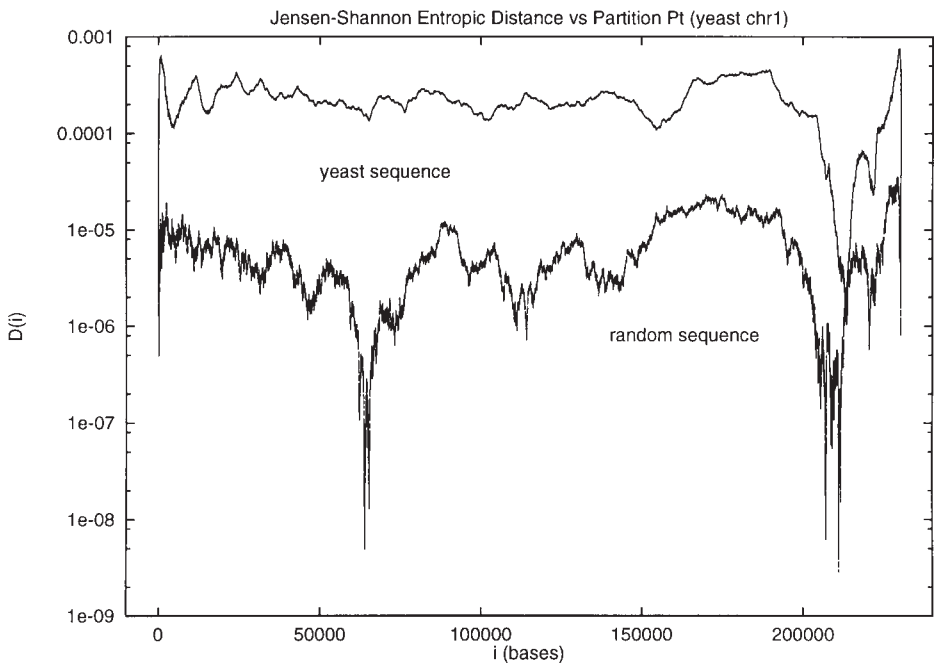
The Jensen-Shannon distance for a random sequence scrambled from the yeast sequence is also calculated (Figure 1). Although there are also ups and downs, the average value of $D(i)$ is at least 10 times lower than that for the yeast sequence. These ups and downs in $D(i)$ for the random sequence are purely random fluctuations.

What about the bacteriophage lambda sequence? Its $D(i)$ function is shown in Figure 2 (again, a random sequence is included for comparison). The sequence length is 48,502 nucleotides. There is an unambiguous optimal partition point around $i \approx 22{,}000$ which maximizes the Jensen-Shannon distance between the two subsequences. Just like the boundary separating a black and a white region, moving away from the boundary gradually mixes some black with the dominantly white region or white with the dominantly black region, and the Jensen-Shannon distance $D(i)$ monotonically decreases. This is exactly what happens in Figure 2, indicating an easily describable heterogeneity structure in the bacteriophage lambda sequence.

DOMAINS WITHIN DOMAINS

When the partitioning process [9] is re-

FIGURE 1



Jensen-Shannon distance $D(i)$ between the subsequence on the two sides as a function of the partition point i for the DNA sequence in budding yeast chromosome 1 and a scrambled random sequence (same length and same base composition). A logarithmic scale is used for the D values.

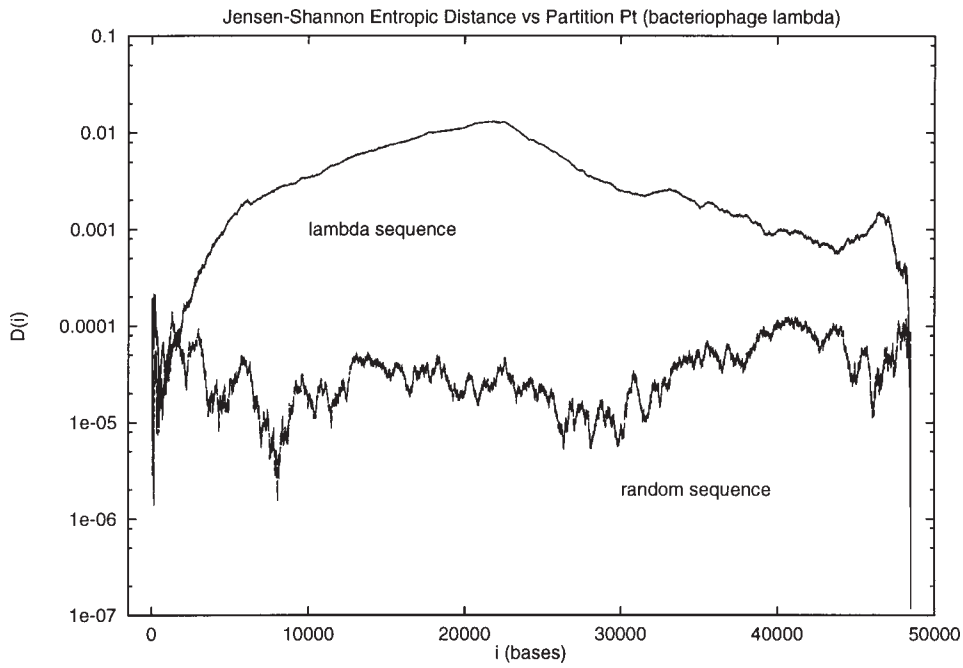
cursively applied to each subsequence of an already-partitioned sequence, sequences with simple heterogeneity are expected to behave differently from sequences with complex heterogeneity. If the sequence is a simple "black and white" type—"black" on one side, "white" on the other—further partitioning is not expected to reveal new structures in the subsequences. On the other hand, if there are sub-domains within a domain, sub-sub-domains within a sub-domain, etc., the recursive partitioning can go on much longer and further down to the smaller-length scales.

Since even homogeneous random sequences can have small differences between any two regions, we might want to distinguish the partitioning due to true heterogeneity and that due to a random fluctuation. A significance level *s* can be set as the cutoff point. For example, if *s* is set at 99.9 percent, partitioning is halted when the Jensen-Shannon distance is not as large as would be expected by a 0.1-percent chance due to pure random fluctuation. When recursive partioning is finally halted, all delineated subsequences are true homogeneous regions with a probability of 99.9 percent.

At this point, a final Jensen-Shannon distance can be calculated which adds up the distributional differences between each subsequence pair in each stage of the partitioning (with a certain weight so the partitioning of a shorter subsequences contributes less to the final distance than longer subsequences) [10]. The result thus obtained is called "compositional complexity" $D^*(s)$ in [10]. It is a function of the significance level *s,* and a * is used to indicate that each partition point at each stage is optimally chosen to maximize the Jensen-Shannon distance at that stage of the partition [10]. Also note that $D^*(s)$ is a measure of the distance among many distributions, whereas $D(i)$ is a distance between two distributions.

When the partitioning process is recursively applied to each subsequence of an already-partitioned sequence, sequences with simple heterogeneity are expected to behave differently from sequences with complex heterogeneity.

FIGURE 2



Similar to Figure 1 but for the bacteriophage lambda sequence.

This final Jensen-Shannon distance as a function of the significance level for these four sequences, two DNA sequences and two scrambled random sequences, is plotted in Figure 3. We can see that at the same *s* value, $D^*(s)$ for the yeast sequence is always larger than that of the bacteriophage lambda sequence. This again supports our early conclusion that there is a higher degree of heterogeneity in the yeast sequence than in the bacteriophage lambda sequence. As for the random sequences, these behave as homogeneous sequences when *s* is large—with a very small number of domains. When *s* is reduced, the random fluctuation leads to spurious heterogeneity. The random sequence corresponding to the bacteriophage lambda sequence even overtakes the original sequence as *s* is reduced, meaning that the bacteriophage lambda sequence is very similar to a random sequence once the simple heterogeneity is removed—a point debated so heatedly in the literature and so easily illustrated by this $D^*(s)$ plot!

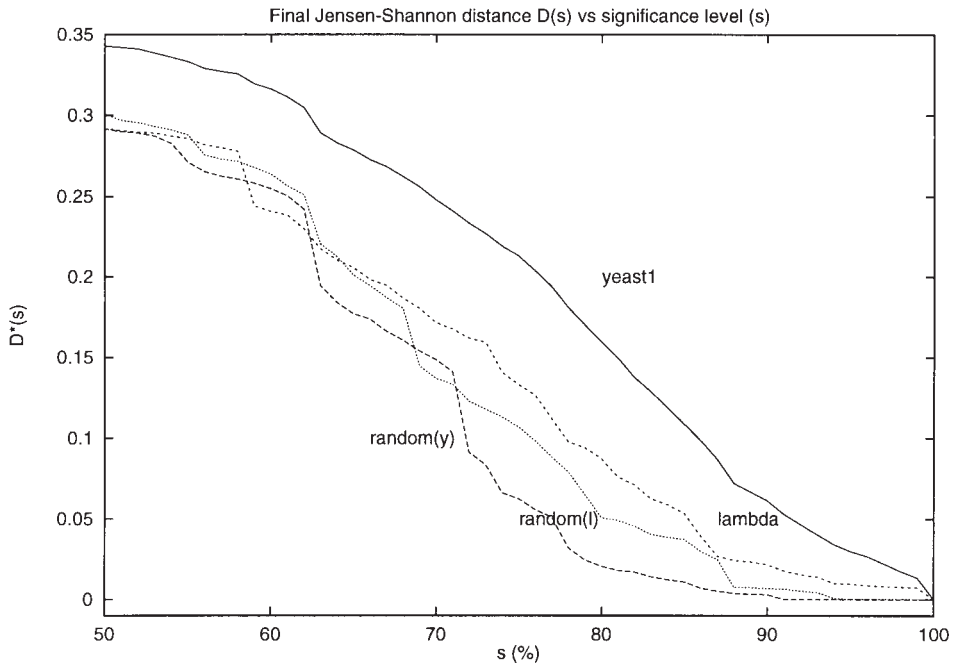
THE PERSPECTIVE OF SPECTRAL ANALYSIS

The difference between DNA sequences being homogeneous, heterogeneous in a simple way, and heterogeneous in a complex way can be elegantly shown by the D^*(s) plot. Here I want to comment that these differences can also be shown (though not so elegantly) by the traditional spectral analysis.

Power spectrum is a technique used to represent the correlation structure in a sequence according to wavelength (or frequency *f* which is the inverse of the wavelength). The power at a given frequency, *P(f)*, is the contribution from that frequency component to the total variance of the fluctuation in the sequence.

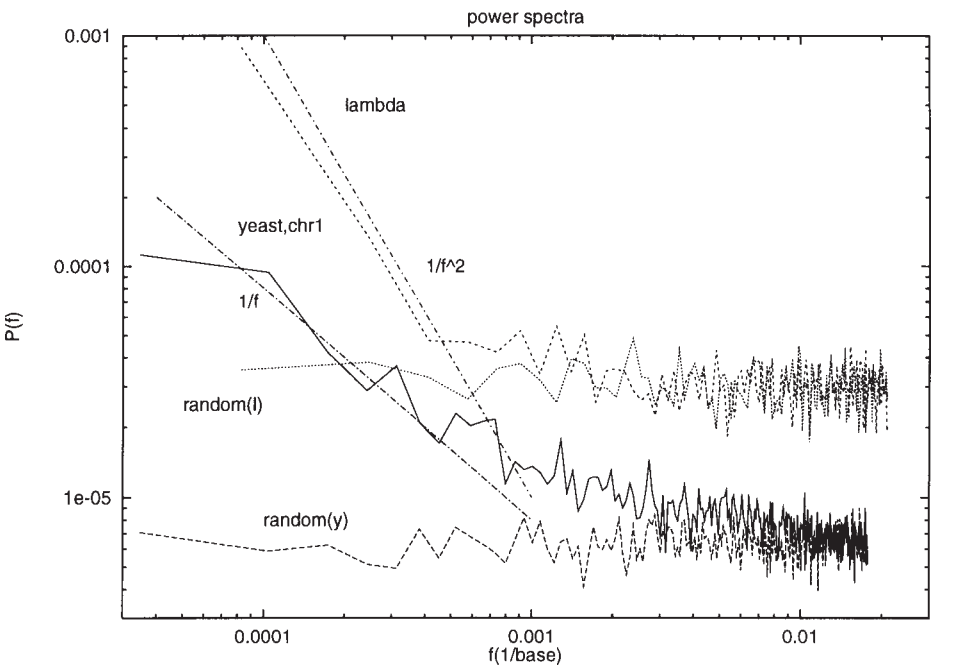
A random sequence lacks correlation at any length scale, and the contribution to the total variance of fluctuation in the sequence from each frequency

FIGURE 3



Final Jensen-Shannon distance *D*(s)* ("compositional complexity") as a function of the significance level s for yeast chromosome 1 sequence, bacteriophage lambda dequence, and the two corresponding random sequences. The larger the value of *s*, the more difficult to partition a sequence and the more likely that the resulting partition reflects true heterogeneity rather than a random fluctuation.

FIGURE 4



Power spectra *P(f)* of the DNA sequence from the yeast chromosome 1, the bacteriophage lambda sequence, and two corresponding random sequences. The power *P* is plotted as a function of the freqeuncy *f* (both in the logarithmic scale). These power spectra are smoothed. Two reference lines are also shown: One represents a $1/f$ spectrum, and the other a $1/f^2$ spectrum.

compodom sequence is plotted, it is flat. Using an analogy to visible light, since the color white takes equal contribution from colors of all frequencies, a random sequence with a flat power spectrum is also known as "white noise" (see, e.g., [12]).

Now what about sequences with simple or complex heterogeneity? The answer is not obvious. Let me calculate the *P(f)*s for our four sequences and show these in Figure 4. The two random sequences have flat power spectra as expected. Both yeast chromosome 1 and the bacteriophage lambda sequence deviate from the flat spectrum. But can we distinguish simple and complex heterogeneity by the power spectra?

We actually can. More discussion can be found in [4, 5]. The proposition is that DNA sequences with simple heterogeneity exhibit $1/f^2$ power spectra, whereas those with complex heterogeneity frequently exhibit $1/f$ power spectra (for a readable account of $1/f$ and $1/f^2$ power spectra, see [12, 13]). Power spectra of other shapes are of course possible but not common in DNA sequences. Also, the grouping of all possible spectra into only $1/f$ and a $1/f^2$ is a simplification, considering the case of a $1/f^{1.5}$ power spectrum, for example. The reason that such simplified picture is presented is to emphasize the importance of the difference between $1/f$ and a $1/f^2$ power spectra.

In Figure 4, a $1/f^2$ and a $1/f$ function (these are straight lines in the double-logarithmic plot) are shown as reference functions that can be compared with the power spectra from the two DNA sequences. Indeed, the bacteriophage lambda sequence and the yeast chromosome exhibit different spectra: $1/f^2$ spectrum for the former and $1/f$ spectrum for the latter.

MEASURE OF HETEROGENEITY COMPLEXITY

Our original goal was to distinguish DNA sequences with simple and complex heterogeneity, and the introduction of $D^*(s)$ seems to be able to accomplish this task. Does $D^*(s)$ have anything to do with measures of complexity in the field of complex systems studies?

We first need to clarify what is meant by a measure of complexity. In the most general framework, a measure of complexity of a task is *any measure that characterizes the difficulty in accomplishing that task* (e.g.,[14]). A measure of complexity of an object is *a measure of complexity of a task performed on that object*. Describing an object using a specific language with a specific set of vocabularies, for example, is a task performed on that object. All the following examples can be considered a measure of complexity of a symbolic sequence: the length of the shortest description of a sequence (algorithmic complexity [15]); the length of the shortest description of the regularities in a sequence (effective complexity [16]); the time required to reproduce a sequence from a short, if not the shortest, description, or the time consumed in finding this short description (logical depth [17]), etc.

When describing an object, one can describe every detail (a strong description) or only the nonrandom regularities of the object (a weak description). Correspondingly, there can be strong and weak versions of a measure of complexity. In describing the heterogeneity of base composition in a DNA sequence, we clearly describe a specific regularity, thus the weak version. If we use the length of a description of the heterogeneity in a DNA sequence as the measure of complexity, the question is: is $D^*(s)$ such a measure?

$D^*(s)$ mainly contains two pieces of information: (1) the total number of homogeneous domains and (2) the magnitude of base composition differences among these domains. Increasing either one of these, $D^*(s)$ is also increased. With some exceptions, the length of a description of the heterogeneity in a sequence increases with the total number of domains. One exception is the case of perfectly periodic domain structures, which nevertheless is rarely applicable to DNA sequences.

The magnitude of the differences among domains does not necessarily contribute to the length of a description of the heterogeneity. However, a stronger difference between domains makes the domain structure more convincing. We might consider a larger difference among domains a better assurance that the number of domains obtained is correct. So the magnitude of the differences indirectly contributes to the length of a description of the heterogeneity.

The most interesting common feature between $D^*(s)$ and the measure of complexity is that they both increase with the level of details in the description. Intuitively, details not visible to the naked eye could be revealed by a magnifying glass. Similarly, a presumably homogeneous domain with a higher significance level can be partitioned to more domains when the significance level is reduced. Also, a description working at a crude level does not describe the details at a finer level. All these arguments point out that $D^*(s)$ and measures of complexity are monotonic functions with the level of description: the smaller the s, the higher the $D^*(s)$; the finer the detail, the larger the measure of complexity.

In general, the measure of complexity must take into account at what level one wants to describe the object [16]. Random sequences require a long description if all details are to be described, but a very short one if only a rough picture is required. A measure of complexity for a random sequence is thus unstable with respect to the level of detail in the description. To my knowledge, very few, if any, proposed measures of complexity actually address the issue of the level of detail in the description. The $D^*(s)$, however, is explicitly a function of the level s. Perhaps we can learn a lesson or two from the measure of heterogeneity, $D^*(s)$, and introduce level-dependence explicitly to the measure of complexity.

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