



The study of correlation structures of DNA sequences: a critical review

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Abstract—The study of correlation structure in the primary sequences of DNA is reviewed. The issues reviewed include: symmetries among 16 base–base correlation functions; accurate estimation of correlation measures; the relationship between $1/f$ and Lorentzian spectra; heterogeneity in DNA sequences; different modeling strategies of the correlation structure of DNA sequences; the difference of correlation structure between coding and non-coding regions (besides the period-3 pattern); and source of broad distribution of domain sizes. Although some of the results remain controversial, a body of work on this topic constitutes a good starting point for future studies. © 1997 Elsevier Science Ltd

1. INTRODUCTION

There is a long-standing interest in knowing and understanding the correlation between bases in DNA sequences. Before the human genome project era, there were no long, continuous DNA sequences. The study then concerned either the nearest-neighbor base–base correlations (Josse *et al.*, 1961) or the base density heterogeneity in digested DNA segments (Sueoka, 1959). A more complete characterization of correlation between base pairs at both short and long distances became possible only as long DNA sequences became more commonly available.

Not all studies of a complete characterization of correlation structure of DNA sequences were motivated by biology. Rather, many such studies were motivated by the issues of mathematical modeling, dynamical systems, stochastic processes, and noise. Perhaps owing to this reason, this study has not yet become part of the toolbox in the “mainstream” DNA sequence analysis.

This review is an attempt to summarize the current status of this study. There are at least two goals for this review. First, there have been disagreements on the result of correlation structure in DNA sequences. Owing to this uncertainty of what the actual result is, some people still believe that DNA sequences do not exhibit any feature that cannot be explained by the basic stochastic processes such as random sequence or Markov chain—with the first process having no correlation and the second one having only short-range correlations. Resolving this disagreement can be straightforward once everybody agrees to use the same measure of correlation, use the same

estimator, and apply this estimator of the correlation to the same sequence.

The second goal is to promote a more biologically motivated study of the correlation structure of DNA sequences. Although this paper does not accomplish this task, the intention is to at least raise the issue. Most of the current studies of correlation in DNA sequences are based on base–base statistical correlations. This base–base correlation may not be a powerful way to reveal the correlation on a global scale or between larger units. Using an analogy of the natural language texts: statistical correlation between letters in an English text rarely reveals correlations at the syntax level in a sentence, or the correlation between sections, or the overall organization of the text, because the linguistically meaningful units are words, sentences, paragraphs, instead of letters.

Besides the above note that most correlations studied are base–base correlations, another caution is that these are *statistical* correlations. A statistical correlation between two events exists if and only if the joint probability of the two events is not equal to the product of the two probabilities for each event. In other analyses of correlations, such as the one between a risk factor (smoking) and a disease (cancer), the distinction is sometimes made between *causal correlation* and *spurious correlation*. The causal correlation is the correlation between true cause and the effect. The spurious correlation is the non-causal part of the statistical correlation. Without a definition of the causal base–base correlation, it is not clear whether the above distinction is applicable here.

The claim of (base–base, statistical) correlation at long distances in DNA sequences is still a few steps away from finding an organization principle of the genome. The quote from Ohno (1993) for example, “... this would suggest the existence of a ‘grand

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design' in the construction of DNA sequences...”, represents such a misunderstanding. In order to discover a true “organization principle”, one might start from the biologically meaningful units, arrange both the structurally functional regions and the genetically functional regions in place, and see how the organization helps the living of the cell.

There is another confusion related to this study. The term “long-range” in the “long-range (base–base, statistical) correlation” was meant to be longer than (a) 3–6 bases (Li, 1992) or (b) 800 bases (Li and Kaneko, 1992a) or (c) 1–10 kb (1 kb = 1000 bases) (Peng *et al.*, 1992). A recent analysis of complete DNA sequences of budding yeast (*Saccharomyces cerevisiae*) chromosomes also suggested that the correlation exists up to more than 10 kb, but is absent at the 100 kb range (W. Li, unpublished results). On the other hand, the “long-range” in “long-range physical mapping” typically means the range covered by the current physical mapping techniques is as large as 100 kb–1 Mb (1 Mb = 1 000 000 bases). Clearly, what is considered to be long is relative to what is considered to be short. For this reason, the term “long-range” will be used with caution in this review. More often, the term “correlation structure” is used instead to indicate the pattern of correlation at all distances.

This paper is organized as follows: Section 2 describes the original motivation for a complete characterization of correlation structure in DNA sequences; Section 3 reviews both the measures used in characterizing correlation structure (in spatial as well as spectral domains) and some published results on these correlation structures of DNA sequences; two special subsections are included: one on the estimation of correlations (Section 3.2), and another on characterizing heterogeneity of DNA sequences (Section 3.7); Section 4 discusses different approaches to the modeling of the correlation structure of DNA sequences; and finally, Section 5 discusses some biological issues related to the correlation study.

A review of this sort is inevitably biased, in the sense that the material chosen reflects the author's interests and experience, and the opinions expressed are mainly the author's. Nevertheless, I intend to make the review as balanced and as fair as possible. An early review covering the study of this topic before 1993 can be found in Li *et al.* (1994).

2. BACKGROUND

As early as the 1960s, there were attempts to characterize the statistical properties of DNA sequences: for example, the correlations between the nearest-neighbor bases (Josse *et al.*, 1961; Gatlin, 1966) and the heterogeneity of base density in fragmented DNAs (Sueoka, 1959). Statistical regularities were used to detect coding regions, (Shulman *et al.*, 1981; Shepherd, 1981a, 1981b; Staden and McLachlan, 1982; Fickett, 1982), and to study the nucleosome formation (Trifonov and Sussman, 1980). All these studies focus on a particular aspect of the correlation structure of DNA sequences in relation to a particular biological question.

For mathematically oriented researchers, a DNA sequence might be considered as a string of symbols

whose correlation structure can be characterized completely by all possible base–base correlation functions or their corresponding power spectra. For people interested in dynamical systems, there is also a “dynamical” aspect to this otherwise static problem: the change of DNA sequences (even without a reference to the natural selection) can be considered as the updating of the symbolic sequences. This updating, once described by a mathematical model, can be studied easily on a computer. One question is which model will generate what types of correlation structure in a symbolic sequence.

A few years ago, I was studying such a problem. The dynamical system being studied, which updates a symbolic sequence, was the so-called “cellular automata” (Toffoli and Margolus, 1987; Wolfram, 1986). These systems update sequences locally. The question asked was whether these locally operated systems are able to generate global correlations. The answer turned out to be negative for simple cellular automata (Li, 1987).

Two events turned my attention to DNA sequences. One was a publication trying to model the DNA evolution by cellular automata (Burks and Farmer, 1984). Another was the discovery that long-range correlation in a sequence could be easily generated if the sequence is allowed to increase (Li, 1989). In what I called the “expansion–modification system” (Li, 1989, 1991), there are only two processes: “expansion” and “modification”. When the expansion rate far exceeds the modification rate, the sequences generated by the system exhibit a long-range correlation called the “1/f spectrum” (to be discussed more in Section 3.4). It was pointed out to me (K. Kaneko, private communication, 1988–89) that the expansion–modification model I was studying was reminiscence of the biological processes: expansion being the base or oligonucleotide duplication process, and modification being the point mutation. This led us to a study of the correlation structure in DNA sequences (Li, 1992; Li and Kaneko, 1992a).

Other groups interested in studying correlation structure in DNA sequences were probably motivated by different reasons. For example, in Peng *et al.*, 1992, the interest was perhaps to compare power-law functions observed in a representation of DNA sequences to other self-similar phenomena in nature. The interest in Voss (1992) was to compare the 1/f spectra observed in DNA sequences to other 1/f noise in nature such as musical signals (Voss and Clarke, 1975). Voss (1992) also suggested that the information storage in DNA sequences is between efficient (as in random sequences) and redundant (as in repetitive sequences).

3. CORRELATION STRUCTURE OF DNA SEQUENCES

3.1. Direct Measure of Correlation

The basic measure of correlation among bases in a DNA sequence are the 16 correlation functions between all 16 possible base-pairs:

$$\{\Gamma_{\beta\beta}(d)\} \equiv \{\Gamma_{AA}(d), \Gamma_{AC}(d), \dots, \Gamma_{GT}(d), \Gamma_{TT}(d)\} \quad (1)$$

each defined as the correlation between nucleotide α and another nucleotide β separated by a distance d :

$$\Gamma_{\alpha\beta}(d) \equiv P_{\alpha\beta}(d) - P_{\alpha} \cdot P_{\beta} \quad \alpha, \beta = \{A, C, G, T\} \quad (2)$$

where $P_{\alpha\beta}(d)$ is the joint probability of observing α and β separated by a distance d , $P_{\alpha} \equiv \sum_{\beta} P_{\alpha\beta}(d)$ and $P_{\cdot\beta} \equiv \sum_{\alpha} P_{\alpha\beta}(d)$ are the density for nucleotide α and β , respectively. Because of the relations $\sum_{\alpha} \Gamma_{\alpha\beta}(d) = \sum_{\beta} \Gamma_{\alpha\beta}(d) = 0$, the number of independent correlation functions (not yet considering any other symmetries) is actually 9 (Herzel and Große, 1995).

Following are comments concerning these correlation functions.

3.1.1. Statistics are taken along a sequence

Suppose $\mathbf{1}_{\alpha}(i)$ is 1 when the nucleotide at position i is α , and 0 otherwise. $N_{\alpha\beta}(d) \equiv \sum_{i=1}^{N-d} \mathbf{1}_{\alpha}(i) \mathbf{1}_{\beta}(i+d)$ is the count of the (α, β) pair separated by a distance d (the sampling is stopped when the second base reaches the end of the sequence). If one uses the periodic boundary condition, $N_{\alpha\beta}(d)^c \equiv \sum_{i=1}^N \mathbf{1}_{\alpha}(i) \mathbf{1}_{\beta}(i+d)$ (where c indicates "circular").

$P_{\alpha\beta}(d)$ is estimated along the sequence, either by $\hat{P}_{\alpha\beta}(d) = N_{\alpha\beta}(d)/(N-d)$ or by $\hat{P}_{\alpha\beta}(d)^c = N_{\alpha\beta}(d)^c/N$. (Note that since the number of counts can either be N or $N-d$, depending on whether the periodic boundary condition is used or not, the symbol N used in equations (4) and (5),(7)–(9),(13),(15) can be either N or $N-d$.) Because statistics are taken along the sequence, all heterogeneity in $P_{\alpha\beta}(d)$ along the sequence will be averaged out. For example, $N_{\alpha\beta}(d)$ counts may come mainly from one region of the sequence, or from throughout the sequence. But from the number $N_{\alpha\beta}(d)$, we do not know which is the case. Consequently, $\{\Gamma_{\alpha\beta}(d)\}$ at a fixed distance d does not contain information on heterogeneity. Nevertheless, $\{\Gamma_{\alpha\beta}(d)\}$ as a function of d does reveal heterogeneity in the sequence.

3.1.2. Strand complementarity

DNA sequences are double-stranded with nucleotides on one strand complementary to those on the other. As a result, $\Gamma_{\alpha\beta}(d)$ on one strand (in the 5'→3' direction) is exactly the same with the $\Gamma_{\bar{\alpha}\bar{\beta}}(d)^{\text{opposite}}$ on the opposite strand in the opposite

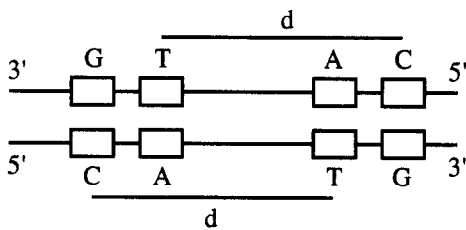


Fig. 1. Illustration of the strand complementary and strand symmetry. If the 5'–C–T–3' correlation on the lower strand is the same with the 5'–C–T–3' correlation on the upper strand, by complementarity, 5'–C–T–3' and 5'–A–G–3' both on the lower strand are the same.

direction (but also in the 5'→3' direction viewed from that strand). For example, in Fig. 1, $\Gamma_{CT} = \Gamma_{AG}^{\text{opposite}}$.

3.1.3. Strand symmetry

It was observed that $\Gamma_{\alpha\beta}(d)$ on one strand is approximately equal to $\Gamma_{\alpha\beta}(d)^{\text{opposite}}$ on the opposite strand in the opposite direction. This idea of "strand symmetry" was suggested in Fickett *et al.* (1992), though they actually suggested the symmetry for base density and density–density correlation, not base–base correlation as explicitly written here. Combining strand symmetry with strand complementarity, we have $\Gamma_{\alpha\beta}(d) \approx \Gamma_{\bar{\alpha}\bar{\beta}}(d)$ on one strand. For example, in Fig. 1, $\Gamma_{CT} \approx \Gamma_{AG}$. This approximate symmetry reduces the number of independent correlation functions from 9 to 6.

There were suggestions of other symmetries. For example, in Teitelman and Eeckman (1996), it was suggested that correlation is almost the same under simultaneous A→T and T→A transformation (e.g. $\Gamma_{AG} \approx \Gamma_{TG}$). This symmetry reduces the number of independent correlation functions from 9 to 5. If the correlation matrix is invariant under simultaneous A→T, T→A, C→G, G→C transformations, the number of independent correlations is reduced from 9 to 3.

Figure 2 shows the 16 correlation functions $\Gamma_{\alpha\beta}(d)$ for d from 1 to 1000, determined from the budding yeast chromosome 1 (using the Bayesian estimator as will be discussed in the next section). It is clearly seen that $\Gamma_{AA}(d) \approx \Gamma_{TT}(d)$ and $\Gamma_{CC}(d) \approx \Gamma_{GG}(d)$, with all other cross-correlations roughly similar to each other.

3.1.4. Relative contribution to the correlation from different pairs

Among the 9 independent correlation functions, some contribute more to the overall correlation than others. In Teitelman and Eeckman (1996), the data showed that $\Gamma_{AA}(d)$ ($\approx \Gamma_{TT}(d)$) is the largest among all correlation functions. $\Gamma_{GG}(d)$ ($\approx \Gamma_{CC}(d)$) is the second largest. The calculation from budding yeast chromosome 1 (Fig. 2) confirms this.

Also note that the correlations between the same nucleotide (e.g. Γ_{AA} , Γ_{GG}) are always positive, and those between different nucleotides (e.g. Γ_{AT} , Γ_{GC}) are usually negative (M. Zhang, unpublished draft, 1992; also see Fig. 2). This can actually be explained in the case of simple domains structure (appendix A of Li *et al.*, 1994).

3.1.5. Average over all correlation functions

Rather than calculate all independent correlation functions, we can define one measure that takes into account all individual correlation functions. For example, the mutual information function (Shannon, 1948; Li, 1990) is defined as (where the base of the log term can also be 4, 10, or e , rather than 2):

$$M(d) \equiv \sum_{\alpha\beta} P_{\alpha\beta}(d) \log_2 \frac{P_{\alpha\beta}(d)}{P_{\alpha} \cdot P_{\beta}} = \sum_{\alpha\beta} P_{\alpha\beta}(d) (\log_2 P_{\alpha\beta}(d) - \log_2 (P_{\alpha} \cdot P_{\beta})) \quad (3)$$

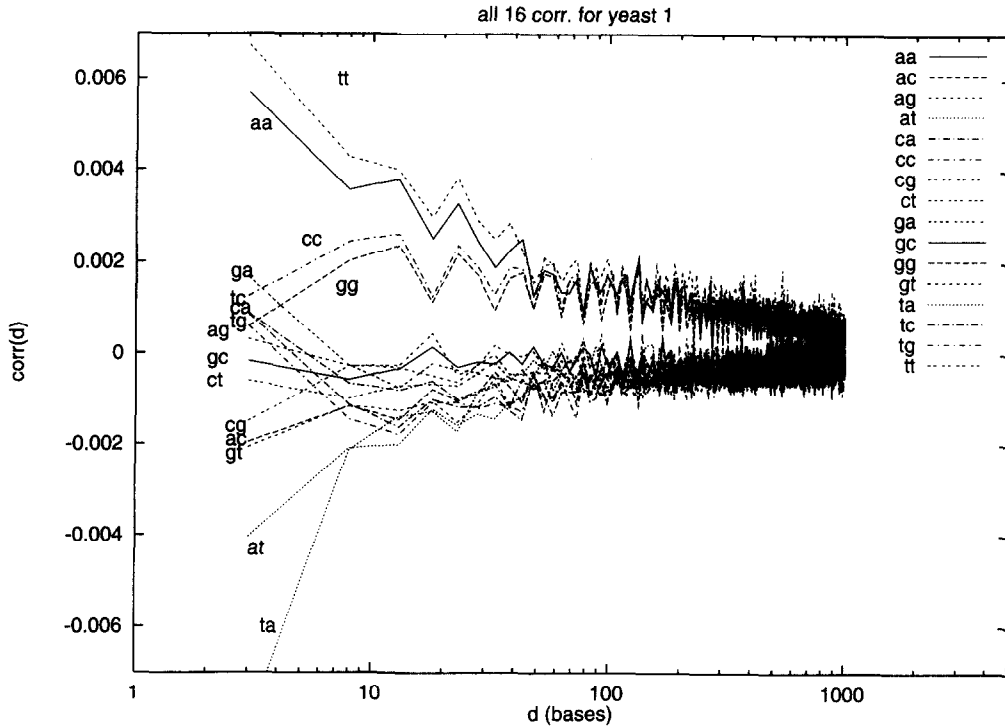


Fig. 2. All 16 correlation functions for budding yeast chromosome 1 sequence. Correlations at five neighboring distances (e.g. $d = 1, 2, 3, 4, 5$) are averaged to smooth the curve. The Bayesian estimator of the correlation function (equation (15)) is used.

or X^2 (see, e.g. section 13.4 of Rice, 1995):

$$X^2(d) = N \sum_{z\beta} \frac{(P_{z\beta}(d) - P_z \cdot P_\beta)^2}{P_z \cdot P_\beta} \quad (4)$$

X^2 should obey the χ^2 distribution with 9 degrees of freedom under the zero-correlation hypothesis (Kullback, 1959).

The sufficient and necessary condition for no correlation between two bases is that all correlation functions are equal to 0. It is equivalent to $M(d) = 0$ or $X^2(d) = 0$. In fact, in a first approximation, $M(d) \approx (1/2N)X^2(d)$ (Li, 1990; Herzel and Große, 1995).

3.2. Estimation of Correlations from a Sequence with Finite Length

Since the correlation at longer distances is typically small, it is important to use the best possible estimator to measure the correlation, otherwise the error due to a finite sample size can be as large as the correlation value itself. We discuss three estimators here.

3.2.1. Frequency-count estimator

It is usually assumed that the best way to estimate the probability of an event a (P_a) is to divide the number of counts for a (N_a) by the total number of count (N), i.e. the frequency-count estimator:

$$(\hat{P}_a)_{\text{freq}} = \frac{N_a}{N} \quad (5)$$

This estimator is obtained by maximizing (here “data” is N_a and “parameter” is P_a)

$$\text{Likelihood} \equiv \text{Prob}(\text{data}|\text{parameter}) \quad (6)$$

to get the parameter. In our case, when $\text{Prob}(N_a|P_a) \sim P_a^{N_a}(1 - P_a)^{N - N_a}$ is maximized with respect to P_a , we obtain equation (5).

Although $(\hat{P}_a)_{\text{freq}}$ is an unbiased estimator of P_a , inserting these estimators to a derived quantity of P_a may not be an unbiased estimator of that quantity. For example, if entropy $H = -\sum_z P_z \log_2(P_z)$ is estimated by $\hat{H} = -\sum_z N_z/N \log_2(N_z/N)$, there is an underestimation (Basharin, 1959; Herzel, 1988; Herzel and Große, 1995; Große, 1995). Similarly,

$$\hat{M}(d)_{\text{freq}} = \sum_{z\beta} \frac{N_{z\beta}(d)}{N} \log_2 \frac{N_{z\beta}(d)N}{N_z \cdot N_\beta} \quad (7)$$

usually overestimates $M(d)$ (Li, 1990; Herzel and Große, 1995; Große, 1995). (Note that equation (5.10) in Li, 1990 should be $(K - 1)^2/2N$ instead of $K(K - 2)/2N$.) The bias in the frequency-count estimator can be corrected when it is approximately calculated. Nevertheless, the variance of the estimator around the true value is not reduced by this correction. The frequency-count estimator for correlation function $\Gamma_{z\beta}(d)$ would be:

$$\hat{\Gamma}_{z\beta}(d)_{\text{freq}} = \frac{N_{z\beta}(d)}{N} - \frac{N_z}{N} \cdot \frac{N_\beta}{N} \quad (8)$$

3.2.2. Indirect Bayesian estimator

A completely different type of estimator is the Bayesian’s estimator (see, e.g. section 15.2.4 of Rice,

1995). The Bayesian estimator of an event out of K possible states is:

$$(\hat{P}_a)_{\text{bayesian}} = \frac{N_a + 1}{N + K} \quad (9)$$

This estimator is obtained by first calculating the posterior probability for the parameter:

$$\text{Posterior} \equiv \text{Prob}(\text{parameter}|\text{data}), \quad (10)$$

then using this probability as the weight to calculate the average value of the parameter. In the case of two possible outcomes,

$$\text{Prob}(P_a|N_a) = \frac{\text{Prob}(N_a|P_a)\text{Prob}(P_a)}{\text{Prob}(N_a)} = \frac{P_a^{N_a}(1 - P_a)^{N - N_a}\text{Prob}(P_a)}{\int_{P_a=0}^1 P_a^{N_a}(1 - P_a)^{N - N_a}\text{Prob}(P_a)dP_a}, \quad (11)$$

and assuming $\text{Prob}(P_a) = \text{const.}$ (i.e. uniform prior distribution), we have

$$(\hat{P}_a)_{\text{bayesian}} = \int_{P_a=0}^1 \text{Prob}(P_a|N_a)P_a dP_a = \frac{\int_{P_a=0}^1 P_a^{N_a+1}(1 - P_a)^{N - N_a} dP_a}{\int_{P_a=0}^1 P_a^{N_a}(1 - P_a)^{N - N_a} dP_a}, \quad (12)$$

which leads to equation (9) (set $K = 2$).

So the second estimator of a derived quantity of the probabilities is obtained by inserting the Bayesian estimator of the probabilities to the function (P. Grassberger, unpublished result, 1994). This ‘‘indirect’’ Bayesian estimator reduces the variance, but there is still a substantial bias (Große, 1996). The indirect Bayesian estimator for correlation function $\Gamma_{x\beta}(d)$ is (for $K = 4$):

$$(\hat{\Gamma}_{x\beta}(d))_{\text{ind_bayesian}} = \frac{N_{x\beta}(d) + 1}{N + 16} - \frac{N_{x\cdot} + 4}{N + 16} \cdot \frac{N_{\cdot\beta} + 4}{N + 16} \quad (13)$$

3.2.3. Direct Bayesian estimator

A direct Bayesian estimator for a quantity does not rely on the Bayesian estimator of the probabilities, but a direct average of the quantity using the posterior probability. For example, the direct Bayesian estimator for correlation function $\Gamma_{x\beta}(d)$ is:

$$(\hat{\Gamma}_{x\beta}(d))_{\text{bayesian}} = \frac{\int_{\{P_{x\beta}\}} \{P_{x\beta} - P_{x\cdot}P_{\cdot\beta}\} \prod_{x'\beta'} P_{x'\beta'}^{N_{x'\beta'}} \text{Prob}(P_{x'\beta'}) d\{P_{x'\beta'}\}}{\int_{\{P_{x'\beta'}\}} \prod_{x'\beta'} P_{x'\beta'}^{N_{x'\beta'}} \text{Prob}(P_{x'\beta'}) d\{P_{x'\beta'}\}} \quad (14)$$

For $K = 4$, the Bayesian estimator can be calculated to be (Wolpert and Wolf, 1995; Große, 1995) (using

the multinomial distribution, and notice $\sum_{x\beta} P_{x\beta} = 1$ and $\sum_{x\beta} N_{x\beta} = N$):

$$(\hat{\Gamma}_{x\beta}(d))_{\text{bayesian}} = \frac{N_{x\beta}(d) + 1}{N + 17} - \frac{N_{x\cdot} + 4}{N + 16} \cdot \frac{N_{\cdot\beta} + 4}{N + 17} \quad (15)$$

Although the direct Bayesian estimator is still biased, the bias is much smaller than the frequency-count estimator and the indirect Bayesian estimator, and the variance is also reduced as compared with the frequency-count estimator (Große, 1996).

3.3. Direct Measure of Correlation in DNA Sequences

It is straightforward to apply the direct measure of correlation to DNA sequences, as was done, for example, in Shepherd (1981a, 1981b), Fickett (1982), Konopka and Smythers (1987), Konopka *et al.* (1987), Arquès and Michel (1987), Li (1992), Li and Kaneko (1992a) and Mani (1992). Besides the well-known period-3 oscillation in coding regions, a calculation of the complete correlation function gives us more information, such as whether the correlation function decays as a power-law function or as an exponential function or in between. Here are some comments.

1. Different sequences may exhibit different correlation functions. When a correlation function is calculated for an individual DNA sequence, its form may be different from one sequence to another. In Li (1992), for example, it is shown clearly that the $M(d)$ s for the 5 human exon sequences are different from the 5 human intron sequences. In another example, the bacteriophage lambda sequence used in Karlin and Brendel (1993) has a $1/f^2$ spectrum (Li *et al.*, 1994) (to be discussed in Section 3.4 and Section 3.5) whereas the budding yeast chromosome 3 sequence exhibits a $1/f$ -like spectrum (Li *et al.*, 1994). As a result, any conclusion from the analysis of one sequence should be taken with care when generalized to another sequence.

2. Correlation function obtained from the whole sequence may be different from that obtained from a sub-sequence. Closely related to the comment in Section 3.1.1, since the statistic is sampled along the sequence, a correlation function based on the statistic sampled from the whole sequence may differ from that based on a statistic sampled from a sub-sequence. There have been statements such as: ‘‘no long-range correlations are found in any of the studied DNA sequences’’ (Azbel, 1995), while the study was only carried out at the sub-sequence level. It is also possible that a correlation is present at the sub-sequence, but will not be extended to longer distances when the whole sequence is analyzed. In fact, no one currently has the sequence of a complete human chromosome and thus the correlation structure at the length-scale of the whole human chromosome is unknown.

3. Correlation function from one sequence may be different from that averaged over many sequences. This is yet another seemingly trivial statement but can be overlooked in a debate on the nature of long-range correlation in DNA sequences. When the correlation functions from many sequences are averaged, the one

with the slowest decay rate dominates at the long distances. If the correlation function in each sequence decays exponentially but with different rates (i.e. different correlation lengths), the averaged correlation function may decay as a non-exponential function, such as a power-law function (it is closely related to the comment 6 in Section 3.4).

3.4. Spectral Analysis

Power spectra via Fourier transform (see, e.g. Percival and Walden, 1993) is widely used in time-series analysis. The estimator of the power spectrum for the (α, β) pair is defined as

$$\hat{S}_{\alpha\beta}(k) \equiv \left(\frac{1}{N} \sum_{j=1}^N \mathbf{1}_{\alpha}(j) e^{2\pi i j k / N} \right) \left(\frac{1}{N} \sum_{j=1}^N \mathbf{1}_{\beta}(j') e^{2\pi i j' k / N} \right)^* \quad (16)$$

where $\mathbf{1}_{\alpha}(j)$ is 1 if the symbol at position j is α and 0 otherwise; the $*$ is the complex conjugate. The frequency f is defined as $f = 2\pi k / N$. Although k can range from 0 to $N - 1$, due to the mirror symmetry around $k = N/2$, typically only the spectrum from $k = 0$ to $k = N/2$ is displayed.

There is a one-to-one correspondence between the power spectrum $\hat{S}_{\alpha\beta}(k)$ and the circular correlation function $\hat{\Gamma}_{\alpha\beta}(d)^c$ (Chechetkin and Turygin, 1994). (Note that strictly speaking, no such relation holds between $\hat{S}_{\alpha\beta}(k)$ and the “non-circular” $\Gamma_{\alpha\beta}(d)$):

$$\hat{S}_{\alpha\beta}(k) = \frac{1}{N} \sum_{d=0}^{N-1} \hat{\Gamma}_{\alpha\beta}(d)^c e^{-i2\pi d k / N} = \frac{\hat{\Gamma}_{\alpha\beta}(0)^c}{N} + \frac{2}{N} \sum_{d=1}^{N/2} \hat{\Gamma}_{\alpha\beta}(d)^c \cos(2\pi d k / N). \quad (17)$$

The second expression is due to the mirror symmetry around $k = N/2$.

Since power spectrum and correlation function are two representations of the same correlation structure, power spectrum does not provide any new information that is not already described by the correlation function. Nevertheless, the visual representation of a power spectrum sometimes can more easily reveal patterns that are harder to discern in the correlation function. The following comments relate to power spectra.

1. Averaged power spectrum. Similar to the case of correlation functions, there are many ways to average or sum power spectra $S_{\alpha\beta}$. For example,

$$S_{\text{ave1}}(k) \equiv \sum_{\alpha\beta} |S_{\alpha\beta}(k)| \quad (18)$$

or (e.g. Voss, 1992; Li *et al.*, 1994)

$$S_{\text{ave2}}(k) \equiv \sum_{\alpha} S_{\alpha\alpha}(k) \quad (19)$$

or, to assign four nucleotides to the four vertices of a tetrahedron, use the three coordinates of a vertex to represent a nucleotide, then calculate the sum of the power spectra of sequences from each coordinate (Silverman and Linsker, 1986; Li and Kaneko, 1992a). It seems that different projections of the

power spectrum do not alter the general shape of the power spectrum.

2. Exponentially decaying correlation functions correspond to a Lorentzian spectrum with a $1/f^2$ tail. In equation (17), if the (circular) correlation function decays exponentially, i.e. $\Gamma(d)^c \sim \lambda^d$, where $0 < \lambda < 1$, it can be shown that in the limit of $N \rightarrow \infty$ (Borštnik *et al.*, 1993) (if N is finite, there are many more terms in the expression, but the main conclusion remains the same):

$$S(k) \sim \text{const.} + \frac{\cos(2\pi k / N) - \lambda}{(1 - \lambda)^2 / 2\lambda + (1 - \cos(2\pi k / N))}. \quad (20)$$

Using the Taylor expansion of $\cos(x) \approx 1 - x^2/2$, the above expression can be approximated as

$$S(f) \sim \frac{\text{const.}}{\text{const.} + f^2} \quad (21)$$

where $f = 2\pi k / N$ is the frequency. This spectral form is called a Lorentzian spectrum. If the correlation function does not decay monotonically, but is oscillatory, the Lorentzian spectrum will be centered around a non-zero frequency due to the periodicity.

3. Step function exhibit $1/f^2$ power spectrum. It is very easy to show that the correlation function of a step function (e.g. $x(i) = 1$ if $1 \leq i \leq N/2$ and $x(i) = 0$ if $N/2 < i \leq N$) decays linearly (see, e.g. appendix A of Li (1991) and appendix A of Li *et al.*, 1994). By using equation (17), the corresponding power spectrum contains a $1/f^2$ term. The implication of this almost trivial result is that for DNA sequences that are C + G-rich on one half but C + G-poor on the other half, the power spectrum is expected to be of the form $S(f) \sim 1/f^2$.

4. When both the correlation function and the power spectrum are power-law functions. Since the Fourier transform of a power-law function is still a power-law function, we have (using equation (17) in the $N \rightarrow \infty$ limit and approximate the sum by an integral)

$$(S(f) \sim) \frac{1}{f^b} \sim \int_{x=1}^{\infty} \frac{1}{x^a} \cos(xf) dx \left(\sim \int_{x=1}^{\infty} \Gamma(x) \cos(xf) dx \right). \quad (22)$$

Suppose we change f to kf

$$\frac{1}{(kf)^b} \sim \int_1^{\infty} \frac{1}{x^a} \cos(xkf) dx = \frac{k^a}{k} \int_1^{\infty} \frac{1}{(kx)^a} \cos((kx)f) d(kx) \sim \frac{1}{k^{1-a}} \frac{1}{f^b}. \quad (23)$$

In other words, $b \approx 1 - a$. This “scaling argument” or “dimension analysis” has been frequently used in physics. The step function discussed in comment 3 above confirms this relationship since $a = -1$ and $b = 2$.

Caution should be taken for many real situations. For example, there can be cutoffs of the power-law function at both high and low frequencies (Theiler, 1991). It is also possible that the power spectrum is only a stepwise power-law function.

5. **1/f spectra (1/f noise, 1/f fluctuation, flicker noise).** A particularly interesting situation is when $b \approx 1$, which implies $a \approx 0$, or the correlation function decays to zero very slowly. What makes “1/f spectra” or “1/f noise” interesting is that this type of fluctuation is very common in nature (Press, 1978). 1/f noise was perhaps first observed and studied in the noise of electronic systems (Johnson, 1925; Schottky, 1926), but it appears in numerous other phenomena, ranging from star luminosity to traffic flow.*

6. **1/f spectra as a superposition of Lorentzian spectra.** A natural and popular explanation of 1/f noise is that these are superpositions of many series with exponentially decaying correlation function. Each is sampled from a broad distribution of the correlation length τ (in $\Gamma(x) \sim e^{-x/\tau}$). One specific probability density function of the correlation length τ that leads to 1/f spectra is

$$g(\tau)d\tau = \begin{cases} \frac{1}{\ln(\tau_{\max}/\tau_{\min})} \frac{1}{\tau} d\tau & \text{if } \tau_{\min} < \tau < \tau_{\max} \\ 0 & \text{otherwise} \end{cases} \quad (24)$$

(van der Ziel, 1950). The log-normal distribution can approximately lead to the $1/\tau$ distribution (Montroll and Shlesinger, 1982).

Since many so-called 1/f noises are only “1/f-like”, meaning these spectra are not perfect power-law functions, it is very likely that the requirement in equation (24) is too strong. A reasonably broad distribution of correlation lengths might explain the data equally well. This point made here is very important to the understanding of the long-range correlation in DNA sequences. There is nothing magic about the long-range correlation or 1/f spectra: these could in principle be explained by the co-existence of many different length scales. What is essentially needed is a broad distribution of these different length scales (to be discussed more in Section 5.3). Although this fact is well known in the 1/f-noise community, its relevance to the correlation structure in DNA sequences should be emphasized here.

3.5. Spectral Analysis of DNA Sequences

Similar to the direct calculation of the correlation function of DNA sequences, the application of spectral analysis to DNA is straightforward. As mentioned in the previous section, the advantage of spectral analysis is to reveal patterns hidden in a direct correlation function. But the early applications of spectral analysis were mainly focused on revealing periodic signals (McLachlan and Karn, 1983; Tavaré and Giddings, 1989 and the references therein). Only recently, attention turned to the functional shape of the power spectrum at all frequency ranges (Li, 1992; Li and Kaneko, 1992a; Voss, 1992; Buldyrev *et al.*, 1995). The following two comments are related to this topic.

1. **1/f-like power spectra were observed in DNA sequences.** 1/f-like power spectra were indeed

observed in DNA sequences (Li and Kaneko, 1992a; Voss, 1992; Li *et al.*, 1994). These are not white noise, indicating the existence of correlation. These are not Lorentzian spectra either, indicating that there is a broad distribution for the correlation lengths in these sequences. It was questioned in Borštnik *et al.* (1993) whether the “apparent” 1/f^a spectra are actually Lorentzian spectra. By comment 6 in the Section 3.4, we see that superposition of Lorentzian spectra can lead to a 1/f-like spectrum. The question is whether there is a single length scale (as in the case of Lorentzian spectrum) or multi-length scales (as in the case of 1/f spectra).

2. **The quality of the 1/f spectra differs greatly among sequences.** By the “quality” of a 1/f spectrum, the meaning is a measure of how closely the observed spectrum is to a perfect 1/f^a ($a \approx 1$) spectrum. As mentioned in comment 1 of Section 3.3, different DNA sequences do not necessarily exhibit the same power spectrum. Comment 3 in Section 3.3 says that the spectrum obtained by averaging many sequences (e.g. such as Voss, 1992; Buldyrev *et al.*, 1995) may have a different spectral form from that obtained in an individual sequence. The exponent a in 1/f^a in Voss (1992) is very close to 1 (note that the flat spectrum was subtracted from the overall spectral shape), whereas the a in Buldyrev *et al.* (1995) is much smaller: another indication of the wide variation of the quality of 1/f spectra. The power spectra of all 16 budding yeast chromosomes are strikingly similar, all 1/f-like (W. Li, unpublished results and paper in preparation). The question still remains to what extent the spectra of different DNA sequences are similar to or different from each other.

3.6. Other Measures of the Correlation Structure

3.6.1. DNA walk

In a controversial paper (Peng *et al.*, 1992) (controversial because some results could not be reproduced on the same data set by two other groups, Prabhu and Claverie, 1992; Chatzidimitriou-Dreisermann and Larhammar, 1992), a DNA sequence is first converted to a binary sequence (for example, G or C is converted to 1, A and T converted to 0), then the binary sequence is converted to a walk (1 for moving up, 0 for moving down). A random binary sequence leads to a random walk. The variance of this walk at certain distance N is related to the correlation function of the original binary sequence (Peng *et al.*, 1992; Karlin and Brendel, 1993):

$$\text{Var}(N) = N\Gamma_{\text{binary}}(d=0) + 2 \sum_{d=1}^{N-1} (N-d)\Gamma_{\text{binary}}(d). \quad (25)$$

For random sequences, $\Gamma_{\text{binary}}(d) = 0$ when $d > 1$, so only the first term is non-zero. It leads to $\text{Var}(N) \sim N$. Any deviation from the linear relationship indicates a deviation from the random sequence.

One might be curious about whether the above relationship can be generalized to cross-correlation functions $\Gamma_{\alpha\beta}$ ($\alpha \neq \beta$). Indeed, using the identity

* An on-line bibliography on 1/f noise can be found at <http://linkage.rockefeller.edu/wli/1fnoise>.

$\Gamma_{\alpha\beta}(-d) = \Gamma_{\beta\alpha}(d)$, we have:

$$\text{Cov}(N)_{\alpha\beta} = N\Gamma_{\alpha\beta}(d=0) + \sum_{d=1}^{N-1} (N-d)[\Gamma_{\alpha\beta}(d) + \Gamma_{\beta\alpha}(d)] \quad (26)$$

where $\text{Cov}_{\alpha\beta}$ should be the covariance of two such converted walks, one for symbol α and another for symbol β . When $\alpha \neq \beta$, $\Gamma_{\alpha\beta}(d=0) = -P_{\alpha}P_{\beta}$ is negative. Instead of a linear increase, we have the case of linear decrease.

Converting a binary sequence to a walk is equivalent to carrying out an integral or summation. Consequently, the statistics obtained from the walk (such as the variance) are related to the integral (summation) of the statistics from the original binary sequence (such as the correlation function). The integral (summation) makes the statistics from the walk smoother. Whether it is an advantage or disadvantage depends on the purpose of the study. Actually, by using a better estimator or by averaging many sequences, the direct calculation of correlation function can also be very smooth.

3.6.2. Graphical representation of DNA sequences

Similar to the "DNA walk", there have been many other proposals to map a DNA sequence to a graph, making visualization of the base density or correlation easier (Hamori and Ruskin, 1983; Hamori, 1985; Gate, 1986; Hamori, 1989; Hamori *et al.*, 1989; Jeffrey, 1990; Berthelsen *et al.*, 1992; Pickover, 1992; Wu *et al.*, 1993; Zhang and Zhang, 1994).

Another type of graphical representation concerns the sequence-dependent bending/curving (Calladine and Drew, 1990). These graphical representations of a DNA sequence require some biochemical modeling of the spatial bending of the double helix of the DNA molecule (e.g. Tung and Harvey, 1986; Shpigelman *et al.*, 1993; Tung and Carter, 1994). A review of this topic is outside the scope of this paper.

3.6.3. Wavelet analysis

The wavelet transformation (Daubechies, 1988, 1992) is a new type of transformation where localized "wavelets" replace the sine/cosine functions in the Fourier transform as the basis. This new method is ideal for studying heterogeneity in DNA sequences, a topic to be discussed in the Section 3.7. For references on wavelet transformation applied to DNA sequences, see Zhang (1995); Arneodo *et al.* (1995, 1996).

3.7. Study of Heterogeneity

As pointed out in Section 3.1.1, statistics are sampled along DNA sequences. If there is heterogeneity along the sequence, it is averaged out during the sampling process. This heterogeneity is intrinsically related to the slow decay of the correlation function: in order to have a significant correlation at longer distances, the correlated units should be larger than a few bases. These larger units, relatively homogeneous sub-sequences, can be called "domains".

Heterogeneity of base density in DNA sequences was observed in preparations of DNA fragments (e.g. Sueoka, 1959; Filipinski *et al.*, 1973; Thiery *et al.*, 1976;

Macaya *et al.*, 1976; Cuny *et al.*, 1981). There were limitations in this experimental determination of the heterogeneity. First, only the C + G density of DNA fragments is determined. The spatial variation of C + G density within a fragment cannot be detected. Second, though a C + G-rich fragment is usually followed by a C + G-poor fragment, it is not known exactly how these fragments are assembled to the original long DNA sequences, so the correlation among these fragments is not well known.

These experimental studies inspired a few theoretical studies (Elton, 1974; Churchill, 1989; Kozhukhin and Pevzner, 1991; Fickett *et al.*, 1992). The modeling of sequence heterogeneity will be discussed in the next section. Here, let me address the issue on how to characterize the heterogeneity in a DNA sequence.

Consider the simplest situation of heterogeneity in a DNA sequence: the left half of the sequence is highly C + G-rich and the right half is C + G-poor. A characterization of the heterogeneity includes the information on the boundary between the two homogeneous halves, the difference of C + G density (or in general base densities) between them, the size of each domain etc. Some potential problems can be seen immediately: what if the C + G density on the left half is only slightly different from that on the right half—do we still consider the sequence to consist of two domains? What if the left half can be decomposed to sub-domains itself? The problem is that we may not always have a clear-cut domain structure.

Methods that identify and partition the whole sequence into homogeneous domains are *segmentation algorithms*, a term used in image processing. The basic idea in a segmentation algorithm is to use a measure of the degree of fluctuation (such as variance), find a partition point that minimizes the fluctuation in either partition as compared with the degree of fluctuation in the original unpartitioned sequence.

One conceptually simple segmentation algorithm was proposed and applied to DNA sequences (Bernaola-Galván *et al.*, 1996). In this segmentation algorithm, the single-base entropy, $H_1 \equiv -\sum_{\alpha \in \{A,C,G,T\}} P_{\alpha} \log_2 P_{\alpha}$, is used to measure the fluctuation (H_1 measures the randomness at the base level). The weighted sum of the two entropies from both partitions is compared with the overall entropy from the original sequence. A partition point is determined when the difference between the two (called "Jensen-Shannon divergence" in Lin, 1991) is maximized.

An extension to the above approach is to use high-order entropies (e.g. $H_2 \equiv -\sum_{\alpha\beta} P_{\alpha\beta} \log_2 P_{\alpha\beta}$ for two-base entropy, H_N for N -base entropy, and the source entropy $h \equiv \lim_{N \rightarrow \infty} H_N/N$ (Shannon, 1951)). Typically, high-order entropies are difficult to calculate owing to the lack of sample size. One approach to extrapolate to the infinite-size limit is to use the regression analysis (Konopka, 1994). Another alternative is to use some measure of compressibility (Ziv and Lempel, 1977), which is intrinsically related to the source entropy. Both approaches are subject to finite-sample-size effect and may not give a reliable estimation of the source entropy. In the case of DNA sequences it has indeed been suggested (Konopka,

1994) that extrapolated source entropy carries a high sampling error and thereby is not a useful criterion to discriminate between introns and exons.

There is an important parameter to be decided in a segmentation algorithm, which is the threshold of the divergence. In essence, the question is how different the two domains should be before we distinguish the two. A low threshold value makes it easier to partition, even for random sequences. A high threshold value leads to no partition at all. Changing the threshold value, we may change the size distribution of the partitioned domains. In Bernaola-Galván *et al.* (1996), the size distributions of different DNA sequences are compared and quantitative differences were observed. For future studies, such comparison might be carried out at each of the possible threshold values. A family of the size distributions is then compared with another family of distributions.

A crucial question concerning the heterogeneity of a DNA sequence can be answered by these segmentation algorithms—whether there are domains within a domain. For simple heterogeneity, there are no domains within a homogeneous domain. For complex heterogeneity, the concept of heterogeneity is only relative: a domain which is homogeneous under one threshold value can be heterogeneous under another slightly lower threshold value. This phenomenon was indeed observed in Bernaola-Galván *et al.* (1996) for one sequence, and not in another sequence. The claim that “the mosaic character of DNA consisting of domains of different composition can fully account for apparent long-range correlations in DNA” (Karlin and Brendel, 1993) underestimates the true complexity of the heterogeneity problem in DNA sequences.

4. MODELING DNA SEQUENCES

Characterizing the correlation structure of DNA sequences does not involve any modeling of the sequence. The observation of the slower-than-exponential decay of correlation function and the $1/f$ -like power spectra in DNA sequences does not require any assumption about the sequence. We notice a comment in Karlin and Brendel (1993): “Recent papers proffer the asymptotically weakly independent stationary process as a model to describe apparent long-range dependencies inherent to many DNA sequences. However, the assumption of stochastic stationarity is problematic...” This comment confuses the two: by calculating the correlation function or the power spectrum, we only extract information from the DNA sequence and summarize this information in a compact form; we do not automatically assume the DNA sequences to be homogeneous (stationary). Four different modeling strategies of DNA sequences are reviewed below.

4.1. One-step Markov Chains were Known to be a Poor Model for DNA Sequences

One of the earliest attempts to model DNA sequences was to use the one-step Markov chain (Gatlin, 1966, 1972; Elton, 1974). It was then realized that one-step Markov chains are not good models for DNA sequences. One reason is that in coding regions,

the position within a codon is important, thus the Markov transition probabilities depend on this position (Borodovskii *et al.*, 1986a, 1986b; Tavaré and Song, 1989). This problem is relatively easier to fix: one might use Markov models with cyclic, position-dependent, transition probabilities. Another reason is due to heterogeneity: on the global scale the Markov transition probabilities depend on which homogeneous domain the position falls in (Borodovskii *et al.*, 1986a, 1986b). This problem cannot be solved within the framework of a Markov model.

The correlation structure of DNA sequences gives another confirmation that one-step Markov chains are not good models for DNA sequences. The correlation function for a one-step Markov chain decays exponentially. This can be easily proved: the joint probability $P_{xp}(d)$ can be obtained by calculating the d th power of the Markov transition matrix, which is dominated by the d th power of the largest eigenvalue of the matrix; this leads to an exponential decay for $P_{xp}(d)$ (see, e.g. Feller, 1968). Since we know from Section 3.3 that the correlation function in DNA sequences does not usually decay exponentially, then a one-step Markov chain does not characterize the observed correlation functions.

4.2. High-order Markov Chains are Penalized by Having Too Many Free Parameters

High-order Markov chains certainly have more degrees of freedom to characterize a wider variety of correlation structures than the one-step Markov chains. In particular, with multiple eigenvalues for the transition matrix (each related to a different decay rate of the exponential function), it is not impossible (though practically unlikely) to have such a distribution for these eigenvalues that the resulting mixture of exponential functions lead to a $1/f$ -like power spectrum (Li, 1987).

Nevertheless, there is a major drawback in using high-order Markov chains: the number of free parameters increases with the square of the order of the Markov chain. In the Bayesian framework of model selection, models with more free parameters are penalized (see, e.g. Sivia, 1996), in the spirit of the “Ockham principle”. If one has to use a model with many parameters, it must fit the data comparatively much better to compensate for this penalty. In Raffery and Tavaré (1994), a certain assumption is made concerning relationship among the parameters in the model, thus reducing the number of independent parameters. But this assumption might not be justified.

The fundamental reason that casts doubt on one-step Markov model also negates the high-order Markov chains: as long as the order of the Markov chain is finite, it will not characterize the heterogeneity at the length scale larger than its order.

4.3. Hidden Markov Chains are Ideal Models for Simple Heterogeneity

The obvious heterogeneity in DNA sequences motivated the introduction of other mechanisms that possibly describe the phenomenon. One powerful model is the hidden Markov chain or hidden Markov model (Baum and Petrie, 1966; Rabiner, 1989). There

are two layers of variables in a hidden Markov model. When it is applied to DNA sequences (Churchill, 1989, 1992), these two layers of variables are: (1) the observed variable, which is the four nucleotides along a sequence $\{O(i)\}$ ($i = 1, \dots, N$); and (2) the state variable $\{S(i)\}$ (unobserved), which is related to a description of the domain.

The state variable sequence can be produced by a Markov chain. Thus, a hidden Markov model is characterized by two sets of transition probabilities: one is the state transition probability $\text{Prob}(S(i) \rightarrow S(i+1))$ (suppose the Markov chain is one-step); another is the mapping probability from the state variable to the observable $\text{Prob}(S(i) \rightarrow O(i))$.

The state variable can be discrete or continuous. For an example of the discrete state variable, consider three possible values for $\{S(i)\}$: H , M , L , for high, moderate, and low $C + G$ density. The mapping probabilities are different for different state variables. For example, when $S(i) = H$, then $\text{Prob}(H \rightarrow G)$ and $\text{Prob}(H \rightarrow C)$ are higher than $\text{Prob}(H \rightarrow A)$ and $\text{Prob}(H \rightarrow T)$.

For an example of the continuous state variable, consider $S(i)$ being the $C + G$ density at the site i , which can take any real number between 0 and 1 [In practice, the lower and upper limits can be $1/3$ and $2/3$ (Fickett *et al.*, 1992).] With a given value of $S(i)$, say, s , the mapping probability can be chosen as $\text{Prob}(S(i) \rightarrow C) = \text{Prob}(S(i) \rightarrow G) = s/2$, $\text{Prob}(S(i) \rightarrow A) = \text{Prob}(S(i) \rightarrow T) = (1-s)/2$. The continuous state variable version of the hidden Markov chain was called "walking Markov chain" in Fickett *et al.* (1992). Comparing the continuous state variable version with the discrete version, the former does not necessarily lead to a sharp boundary between domains.

Similar to the case of the high-order Markov chain, there is also an issue of estimating many parameters in the hidden Markov chains. Thus the fitting of the data must be very good in order to compensate the penalty for using too many parameters. But overall, hidden Markov chains are a much better choice for characterizing heterogeneity in DNA sequences than the high-order Markov chains.

4.4. Rewriting Systems and Complex Heterogeneity

Hidden Markov chain represents a major improvement over the regular Markov chain in characterizing DNA sequences because it is able to describe the heterogeneity well. But as discussed in Section 3.7, when the heterogeneity becomes complex, a seemingly homogeneous region can be heterogeneous when the criterion for being heterogeneous is relaxed. The same phenomenon may reappear at a sub-domain level. In other words, there can be sub-domains within a domain, sub-sub-domains within a sub-domain, etc.

Rewriting systems are able to generate such hierarchical organization of domains and self-similarity. Being rediscovered and renamed a few times, such as the context-free language (Chomsky, 1956) (if the distinction between non-terminal symbols and terminal symbols is removed), L-systems (Lindenmayer, 1968; Rozenberg and Salomaa, 1980; Prusinkiewicz and Lindenmayer, 1990), development systems (Węgrzyn *et al.*, 1990), and substitutional

sequences (Cheng and Savit, 1990), a rewriting system updates a sequence by replacing a symbol (or a string) by another string of symbols.

For example, the famous Fibonacci sequence is generated by repeated use of the following "rewriting rule" (replacing a symbol at t with a string of symbols at $t+1$):

$$0_t \rightarrow 1_{t+1} \quad 1_t \rightarrow (10)_{t+1} \quad (27)$$

The expansion-modification system (Li, 1989, 1991) is a probabilistic rewriting system:

$$0_t \xrightarrow{1-p} (00)_{t+1} \quad 0_t \xrightarrow{p} (1)_{t+1} \quad 1_t \xrightarrow{1-p} (11)_{t+1} \quad 1_t \xrightarrow{p} (0)_{t+1} \quad (28)$$

with the probability attached to each rule. One might easily generalize this model to a model of duplication and point mutation in DNA sequences, such as

$$T_t \rightarrow A_{t+1}(ACC)_{t+1} \rightarrow (ACCACC)_{t+1} \dots, \text{ etc.} \quad (29)$$

If there is conflict among different rewriting rules, we might choose each one with certain probability.

Rewriting systems operate quite differently from Markov chain and its variants. Markov chain moves along a sequence and generates new symbols sequentially. Rewriting systems not only update symbols *parallelly*, but also *repeatedly*. These two features give rewriting systems certain advantages over Markov chains in modeling long DNA sequences that might result from a long evolutionary process involving repeated duplications.

There are also several parameters to be determined in a rewriting system. For example, the initial sequences, the number of times the rule is applied, and the probability of applying certain rules when there is a conflict. It would be interesting to use a more rigorous model selection procedure to choose the type of rewriting system that might characterize DNA sequences well, and to compare the rewriting system models with the hidden Markov models.

5. SOME BIOLOGICAL ISSUES

Is the study of the correlation structure of DNA sequences useful for working biologists? Since most of the current DNA sequence analyses are based on the knowledge of local signals (e.g. consensus pattern of regulatory regions), the global view of DNA sequences takes a back seat. Let me use an analogy of natural language texts. Understanding local signals is similar to the construction of a dictionary of words. The interaction among different regulatory regions is perhaps analogous to syntax of sentences. The evolutionary history of the DNA sequences is analogous to the writing of a text (with repeated redrafting). And the resulting genome organization is analogous to a style of the text. If a dictionary has already been constructed, the next goal should be an understanding of the whole text.

The following sections describe some biological issues related to the study of the correlation structure of DNA sequences.

5.1. Concentration of Genes and the $C + G$ Density

It was shown that the concentration of genes is correlated with the $C + G$ density (Bernardi *et al.*, 1985; Bernardi, 1989, 1995; Zoubak *et al.*, 1996; Mouchiroud *et al.*, 1991). The concentration of genes

in the C + G-richest region of human genome can be 5–10 (Bernardi, 1989) or 15 times (Zoubak *et al.*, 1996) higher than those of the C + G-poorer regions. If the connection between C + G density and the concentration of genes is proven general, spatial distribution of C + G density can be used to give an indication of the locations of genes.

The base–base correlation structure reviewed here can be extended easily to the density–density correlation. One can partition a sequence into *non-overlapping* windows, and calculate the C + G density in each window. Similarly, the spatial distribution of genes can be characterized by the binary sequence which assigns a 1 to a base in the gene and 0 to a base in the intergenic region. The cross-correlation between the density sequence and the binary sequence can answer quantitatively the question of whether the spatial distribution of genes is related to the spatial variation of C + G density.

5.2. Besides the Period-3 Structure in Coding Region, are the Correlation Structures in Coding and Non-coding Regions Different?

Owing to the codon structure, the correlation function for coding sequences exhibits period-3 structure with a high–low–low pattern (Fickett, 1982). Eukaryotic intron sequences do not exhibit this period-3 pattern, but occasionally, they exhibit a period-2 pattern (Konopka and Smythers, 1987; Konopka *et al.*, 1987; Arquès and Michel, 1987; Li, 1992) (unlike nuclear DNA sequences, the non-coding regions in viral or mitochondrial sequences may still have period-3 patterns; see Arquès and Michel, 1987; Konopka, 1994).

Besides this well-known pattern, how does the correlation function decay with distances in either coding or non-coding sequences, and how do the correlation structures differ in the two types of sequences? Despite several studies, this remains an open question. Intuitively, because of the specific constraints imposed by the function of the coding region, i.e. the three-nucleotide to one-amino-acid translation as well as the ability for the translated amino acid sequence to fold successfully, evolutionary tinkering is mostly prohibited in the coding region. On the other hand, non-coding regions (both intron and the intergenic regions) are open to changes, because these changes typically do not lead to fatal damage of the cell and the organism.

One of the most important changes in DNA sequences is duplication (Bridge, 1919; chapter 17 of Morgan *et al.*, 1925), either the oligonucleotide duplication or gene duplication. The gene duplication, in particular, is considered to be crucial for the generation of complexity and the acquisition of new functions in higher organisms (Ohno, 1970; Market *et al.*, 1974; MacIntyre, 1975; Doolittle, 1981). To quote from Doolittle (1981): "... it is simpler to duplicate and modify proteins genetically than it is to assemble appropriate amino acid combinations de novo from random beginning".

If the changes in non-coding sequences are mainly duplications, the non-coding regions should be less random, or more redundant. This would predict a longer-ranged correlation in non-coding sequences. Indeed, Li (1992) showed that this is true for a few

human DNA sequences. But Voss (1993, 1994 did not observe significant difference in power spectra between coding and non-coding sequences. More recently, another study shows that after the period-3 structure is subtracted, the mutual information functions for coding and non-coding regions are very similar to each other, both decay as an approximate power-law function in the 1–1000 bases range (I. Große, private communication, 1996). This study paid particular attention to correcting the bias in the estimation due to finite sequence length to make sure the small correlation at long distances is estimated accurately.

So which study is correct? In light of the fact that the currently available DNA sequences are biased towards coding sequences and the flanking sequences, I would like to caution that once the intergenic sequences are represented in the sample with a larger proportion, the conclusion might be modified accordingly. Intergenic sequences may expose to a lesser degree of constraints as compared to the intron sequences (with perhaps the exception of structural constraints), thus exhibiting different statistical features. Indeed, intergenic sequences are analyzed separately from the intron sequence in, for example, Guigó and Fickett (1995).

Human intergenic sequences, in particular, have more "room" to accumulate changes owing to their sheer size. With the combination of the two (less constraint and larger size), one can imagine that duplication, insertion and point mutation can play a major role in shaping the intergenic sequences. (This speculation is already supported by a study of intergenic sequences in the maize genome; see SanMiguel *et al.*, 1996.) Thus, human intergenic sequences may more easily exhibit long-range correlation than other types of sequences.

5.3. Broad Distribution of Domain Sizes as the Origin of Power-law Decay of the Correlation Function

There have been many papers discussing the "biological origin" of long-range correlations. But what was mostly discussed was the known fact that the base density may be different at different regions, i.e. the heterogeneity. What is non-trivial about the correlation structure in many DNA sequences should be discussed along the line of "complex heterogeneity versus simple heterogeneity", " $1/f$ spectra versus $1/f^2$ spectra", and "broad versus narrow distribution of domain sizes".

For example, for the DNA sequence of a complete chromosome, the sequence can be partitioned into coding and non-coding domains. Assuming coding and non-coding domains are distinct in base density, the size distribution of coding as well as non-coding domains determines the correlation structure of the whole sequence. A study along this line was presented in Herzel and Große (1997) for budding yeast chromosomes, and a broad distribution for coding domains (actually it is the distribution of the "open reading frames", i.e. the potential or putative coding regions). Note that this discussion does not apply to the correlation structure in intergenic sequences, and the assumption that a clear distinction between the

base densities in coding and non-coding domains may not always hold.

One can attribute the broad distribution to either internal or external factors. For external factors, it was shown that the size distribution of insertions and deletions of pseudogenes are approximately power-law functions (Gu and Li, 1995). If these insertions are distinct base-density-wise from the hosting DNA sequence, the power-law distribution of the sizes is enough to lead to a complex heterogeneity. The power-law distribution of insertion sizes was used in Buldyrev *et al.* (1993) by the assumption that the insertion is accomplished by a loop formation, and the size distribution of the loop length in a long polymer should be a power-law function (des Cloizeaux, 1980). But it has not been examined whether this argument is correct.

Duplication is a best example of the internal factors for broad distributions. The intuition can be again derived from the expansion-modification system (Li, 1989, 1991). Since a mutation followed by the repeated duplication of that mutated base generates a distinct domain whose size is proportional to the number of duplications, in order to have a broad distribution of sizes, one simply needs different duplication events to start at different times. Then the broad distribution is just a historical profile of these duplication events. For a more realistic modeling of the (gene) duplication events, see Ohta (1987a, 1987b, 1988a, 1988b, 1989, 1990).

Using oligonucleotide repeats as an explanation of the $1/f$ -like spectra in DNA sequences (Li and Kaneko, 1992b) does not mean that a single simple repeat can explain the correlation structure in DNA sequences—it will not, because such a repeat manifests itself as a peak in the power spectrum instead of a broad band $1/f$ spectrum. Rather, what we suggested in Li and Kaneko (1992b) was a series of duplications each occurring at a different historical period, and repeating a variety of times.

Finally, it is also possible that both external and internal factors contribute to the broad distribution of domain sizes.

5.4. Correlation Between Other Units

There can be many variations to the average correlation between two bases calculated along a sequence. One example is the statistical correlation between two specific sites. The statistic in this case is no longer sampled along a sequence, but from a set of aligned sequences at these two specific sites. For example, the mutual information between two specific sites in HIV proteins was calculated to detect the co-varying mutation spots (Korber *et al.*, 1993). In this example, a set of similar sequences is made possible by the high variability of the HIV.

If there are only a few copies of a biologically meaningful unit on a DNA sequence, it is difficult to obtain a statistic. Take the replication origins on budding yeast chromosomes for example (Newlon *et al.*, 1993). The replication origins could be determined through a sequence analysis by searching the 10- or 11-base consensus pattern (Palzkill *et al.*, 1986). (This might be called a putative replication origin because of the possibility of false positives and the possibility of inactivation of the origin.) One yeast

chromosome may have only a limited number of replication origins (around the order of 10). Thus, a proposition concerning these origins may be simply studied by an exhaustive listing without using any statistics. For example, in order to test the proposition that replication origins are always located inside a non-coding region (Murakami *et al.*, 1995), we might just count how many replication origins are indeed located in the non-coding region.

6. CONCLUSION

Determining a correlation structure of DNA sequences on a more global scale reveals that the picture of simple heterogeneity is not enough to explain features of many sequences. A key to the understanding of the complexity of correlation structure in DNA sequences is the broad distribution of domain sizes. More quantitative measurement is necessary to characterize this feature more accurately. With even longer stretches of continuous DNA sequences to be available in the future, it is conceivable that correlation structure at even larger scales can be studied. Blurring the details at the base level might be necessary in order to detect any significant correlation at these larger scales. Our grand goal is to eventually learn the “genome organization” principles, and explain this organization using our knowledge about evolution. On the latter aspect, this study may look similar to the study of molecular evolution and population biology (see, e.g. Kimura, 1983; Gillespie, 1991), but with more emphasis on spatial correlation in DNA sequences.*

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