

## A growth model for DNA evolution

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**Abstract.** – A simple growth model for DNA evolution is introduced which is analytically solvable and reproduces the observed statistical behaviour of real sequences.

The study of fractal structures in DNA chains is a subject of great interest nowadays. Two exciting reports of the existence of long-range correlations, which implies fractal structure, in DNA sequences have been made recently by Li [1] and Peng *et al.* [2], [3].

DNA sequences are formed of four different nucleotides: Adenine, Guanine, Thymine and Cytosine, which are represented by the letters A, G, T, and C, respectively. The first two are called purines and last ones pyrimidines. Roughly, half of the nucleotides in a chromosome are pyrimidines and half are purines.

It is observed that the length of the DNA chain of evolved species, such as mammals, is much longer than the DNA of simple organisms, like bacteria [4]. Thus, DNA sequences are in a dynamical state, with its length increasing during evolution. Often the chain increases by gene duplication. Extra copies of the gene are stored in the same sequence as the original copy. Consequently, DNA sequences of evolved species usually have repetitive patterns [4]. However, the copy is not always identical to the original gene. During the process of duplication a mutation can occur, and more complex functions can appear in the evolving species. In our view, the reason for this is that it causes less disruption to normal functioning to keep a copy of the unmutated gene, because if the mutated gene does not work perfectly, the first copy can continue to function. Sometimes, the repeated segments are next to each other, sometimes

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they are separated. The length of these repeated segments varies greatly; some of them are short, others are as long as the entire gene. A set of genes descended by duplication and variation of some ancestral gene is called a *gene family* [4]. Copy numbers in a given family can vary from two to millions.

It has been found that the content of repetitive DNA tends to increase with increasing chain length. Another important observation is that only a small fraction of the DNA chain is active, namely, codes for protein. The rest of it apparently has no function [4]. In humans the percentage of non-coding DNA can be larger than 90%.

Peng *et al.* [2] analysed the statistical properties of real DNA chains by constructing a graphical representation of the sequence. Starting from the origin, a walker moves either “up” [ $u(i) = +1$ ] if a pyrimidine (C or T) occurs at a position  $i$  or the walker steps “down” [ $u(i) = -1$ ] if a purine (A or G) occurs at position  $i$ . Next, they calculate the cumulative displacement  $y(l)$  of the walker after  $l$  steps, which is the sum of the unit steps  $u(i)$  at each position  $i$ . Thus,  $y(l) = \sum_{i=1,l} u(i)$ . A fractal landscape is constructed by plotting  $y(l)$  vs.  $l$ .

The walk is characterized by the root mean-square fluctuation  $F(l)$  about the average displacement;  $F(l)$  is defined in terms of the difference between the average of the square and the square of the average  $F^2(l) \equiv \overline{[\Delta y(l) - \overline{\Delta y(l)}]^2} = \overline{[\Delta y(l)]^2} - \overline{\Delta y(l)}^2$ , of a quantity  $\Delta y(l)$  defined by  $\Delta y(l) = y(l_0 + l) - y(l_0)$ . Here the bars indicate an average over all positions  $l_0$  in the sequence.

Three possibilities exist for  $F(l)$ : i) if the walk is random, then  $F(l) \sim l^{1/2}$ . ii) If there are local correlations extending up to a characteristic range, then asymptotically  $F(l) \sim l^{1/2}$  would be unchanged from the purely random. iii) If there is no characteristic length (*i.e.*, if the correlation were “infinite range”), then  $F(l) \sim l^\alpha$  with  $\alpha \neq 1/2$ .

In refs. [2], [5], [6] it was found that  $\alpha > 0.5$  for non-coding segments and  $\alpha = 0.5$  for coding segments. On the other hand, in ref. [7] it was reported that in most cases  $\log F(l)$  against  $\log l$  is not a straight line. Non-linear curves were found both for coding segments and those containing non-coding regions with a local slope larger than 0.5. According to these results, a well-defined fractal power exponent  $\alpha$  does not seem to exist for DNA sequences. The behaviour found has been that, for small  $l$ ,  $\alpha$  is approximately 0.5 then increases monotonically to a maximum value. Beyond this, the statistics have not been good enough to allow a conclusion about the asymptotic value of  $\alpha$  in the limit of very large  $l$ . However, there are clear indications in [3] that  $\alpha$  decreases after attaining a maximum, although this behaviour was not investigated in detail for real sequences.

We introduce here a simple iterative model for gene evolution, which is analytically solvable and reproduces the behaviour of the exponent  $\alpha$  found in [3],[7] for real DNA sequences of intermediate size. The model incorporates basic features of DNA evolution, that is, sequence elongation due to gene duplication and mutations. When very large chains are analysed in our model, the exponent  $\alpha$  is back to the trivial value 0.5. Therefore, our model suggests that the non-trivial value found for  $\alpha$  in [2] is probably due to finite-size effects. We are aware of two other models[1],[8] for DNA evolution, but in both of them the critical exponents do not go back to the trivial values of a random sequence as the chain gets very large.

Our dynamical model for DNA evolution is the following: we start with a coding sequence which consists of  $g$  genes of equal length. Each gene has  $n$  nucleotides, which consists of pyrimidines ( $u = +1$ ) and purines ( $u = -1$ ) randomly distributed in a proportion of 50% each. In the simulated evolutionary process we choose at random a gene of our original sequence and in that gene we choose at random one of its nucleotides. Then, we change (mutate) this nucleotide from a pyrimidine to a purine or vice-versa. In real DNA a mutation in a single nucleotide is called a *point mutation* [4]. A copy of the chosen gene before the mutation is added at the end of the chain. This old gene becomes a non-coding segment, and it is not

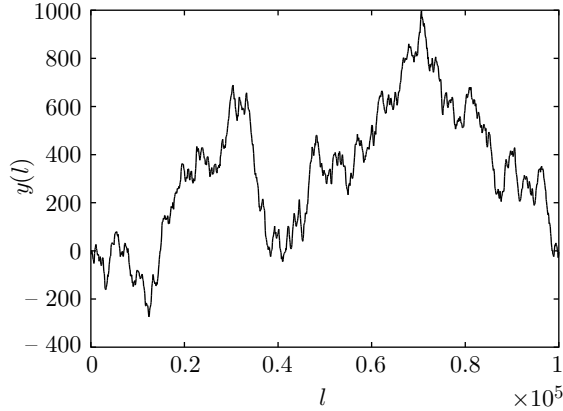


Fig. 1. – Landscape (walk) representation of our model, with  $n = 10$ ,  $g = 3$  and  $N_i = 10^4$ . As in [7], for a more convenient representation, we removed the trend of the landscape in such a way that the end point has the same vertical displacement as the starting point.

further modified. The genes that can mutate are always the first  $g$  genes, which are the coding DNA in our model. We iterate this process  $N_i$  times ( $N_i \gg 1$ ). At the end, our chain will consist of a “head” of  $g$  coding genes and a big “tail” of  $N_i$  non-coding segments. The final length of the chain is  $L = n(g + N_i)$ .

It is clear that our model is a simplified version of what is found in real sequences. Some of the features that our model misses are the following: In real DNA, *a*) the genes do not have the same size; *b*) not all sites of a gene have identical probability of mutation; *c*) the distribution of purines and pyrimidines does not have a random uniform distribution; *d*) a point mutation can be from a purine (pyrimidine) to the other kind of purine (pyrimidine); *e*) non-coding segments are interdispersed with coding ones, and *f*) mutations can also occur via deletions and insertions of genetic material. Our preliminary results show that if we introduce in the model the features *a*) to *e*) the results shown here are changed only quantitatively (this will be reported elsewhere). We have not studied yet feature *f*).

In fig. 1 we show a fractal landscape of our growth model, given by  $y(l)$  vs.  $l$ , for the parameter values  $g = 3$ ,  $n = 10$  and  $N_i = 10^4$ . The landscape presents a jagged contour, as found in real DNA sequences [2], indicating the possible existence of long-range correlations.

The mean-square fluctuation  $F(l)$  is related to the autocorrelation function  $C(l) = \overline{u(l_0)u(l_0+l)} - \overline{u(l_0)}^2$  through the relation  $F^2(l) = \sum_{i=1,l} \sum_{j=1,l} C(j-i)$ . In our model we can calculate analytically  $C(l)$  and consequently  $F(l)$  and  $\alpha(l)$ . Let us first analyse the term  $\overline{u(l_0)u(l_0+l)}$  that appears in  $C(l)$ . Since in our original random sequence of coding segments the nucleotides are not correlated to each other, this implies that correlations exist only for sites which are at a distance that is a multiple of  $n$ . When this is not the case,  $\overline{u(l_0)u(l_0+l)}$  will be an average of  $L-l$  random terms with values  $\pm 1$ . Because of the central-limit theorem, this term will be a Gaussian random variable with zero mean and variance equal to  $1/\sqrt{L-l}$ . If we consider many realizations of the growth process, the ensemble average of this random variable will be zero. Consequently, in this limit  $\overline{u(l_0)u(l_0+l)} = 0$  for  $l \neq mn$  ( $m = 1, 2, 3, \dots$ ) and  $l \neq 0$ . For  $l = 0$  one obviously has  $\overline{u(l_0)u(l_0)} = 1$ .

To find  $\overline{u(l_0)u(l_0+l)}$  for the case in which  $l = mn$  one will consider first the case of a single gene,  $g = 1$ , with  $n > 1$ . When the gene is duplicated a mutation occurs and we have with probability  $p_1 = 1/n$  that  $u(l_0+n)$  has a different sign from the one of  $u(l_0)$ , and with probability  $1 - p_1$  that their signs are the same. This is valid for any  $l_0$ . Then

$A \equiv \overline{u(l_0)u(l_0+n)} = 1 - 2p_1 = (n-2)/n$ , since  $u(l_0) = \pm 1$ . We have the probability  $p_2 = 2(n-1)/n^2$  for  $u(l_0+2n)$  being different from  $u(l_0)$  and  $1-p_2$  for them being identical. Consequently,  $\overline{u(l_0)u(l_0+2n)} = (n-2)^2/n^2 = A^2$ . We can continue the process and easily find that for the case of a single gene  $\overline{u(l_0)u(l_0+mn)} = A^m$ .

For  $g > 1$  we have to consider that  $u(l_0+n)$  has the probability  $1/g$  of being originated from the same gene as  $u(l_0)$ . Consequently, it has probability  $p_1 = 1/(ng)$  of being different from  $u(l_0)$ , and  $(n-1)/(ng)$  of being identical. Note that here the sum of these two probabilities is not one, since there exists also the probability  $(g-1)/g$  that  $u(l_0+n)$  is originated from a different gene, and this gives on average a vanishing contribution for the term  $\overline{u(l_0)u(l_0+n)}$ . In this way,  $\overline{u(l_0)u(l_0+n)} = A/g$ . Between  $u(l_0+n)$  and  $u(l_0+2n)$  we see the following differences: there are  $g^2$  possible different combinations for the gene that contains  $u(l_0+2n)$ . One of these combinations corresponds to a gene that is mutated twice and  $(1-g)$  possibilities that a gene is mutated once. This will result in  $\overline{u(l_0)u(l_0+2n)} = (A^2 + (g-1)A)/g$ . It is not difficult to find that there are  $g^3$  possible different combinations for the gene that contains  $u(l_0+3n)$ . One of these possibilities corresponds to a gene that is mutated three times,  $2(g-1)$  that a gene is mutated twice and  $(g-1)^2$  that the gene is mutated once. Consequently,  $\overline{u(l_0)u(l_0+3n)} = A[A+g-1]^2/g^3$ . In this way, we can continue the process and find that  $\overline{u(l_0)u(l_0+mn)} = A[A+g-1]^{m-1}/g^m$ . These results are valid for a large number of realizations of the growth process. However, note that the ensemble average is only important if the chain is not very large, because otherwise the spatial average will already give good statistical results.

To determine  $\overline{u(l_0)^2}$  in the expression for  $C(l)$ , we note that even if the number of pyrimidines is different from the number of purines in the initial chain of coding segments, after few iterations the probability of having  $u = -1$  will be identical to the probability of having  $u = +1$ . The easiest way to show this is for the case of a single gene. Consider a nucleotide with  $u(l_0) = +1$ . The probability  $P_+^m$  of having  $u(l_0+mn) = u(l_0+(m-1)n)$  is  $P_+^m = \frac{n-1}{n}P_+^{m-1} + \frac{1}{n}(1-P_+^{m-1})$ , with  $P_+^0 = 1$ . From this recursive relation we find  $P_+^m = (1+A+A^2+\dots+A^m)/n$ . The sum of this geometric series converges to  $1/2$ . Therefore, for large  $m$ , the probability of finding a nucleotide with  $u(l_0+mn) = +1$ , as it was in the beginning of the iteration process, is identical to the probability of finding  $u(l_0+mn) = -1$ . Since by definition  $\overline{u(l)} = \frac{1}{L} \sum_{l_0=1,L} u(l_0)$  and  $u(l_0)$  has probability  $1/2$  of being  $+1$  and  $1/2$  of being  $-1$ , it turns out that  $\sum_{l_0=1,L} u(l_0)$  evolves as a symmetric random walker in one dimension. It is well known that such a walker diffuses away from the origin with average distance of  $\sqrt{L}$ . Consequently,  $\overline{u(l)} \approx 1/\sqrt{L}$ .

Combining the results found above, we have the following expression for the autocorrelation function

$$C(l, L) = \begin{cases} 1 - 1/L, & \text{if } l = 0, \\ A[A+g-1]^{m-1}/g^m - 1/L, & \text{if } l = mn, \\ -1/L, & \text{otherwise.} \end{cases} \quad (1)$$

This shows that the autocorrelation function is a function of  $l$  and of the length  $L$  of the chain. The above equation does not apply when  $n = 1$  and  $g = 1$ , where  $C(l, L)$  is a period-two function. Also, for the case  $n = 1$  and  $g > 1$  all sites are uncorrelated to each other, which results in  $\overline{u(l_0)u(l_0+l)} = 0$  when  $l \neq 0$ . Finally, the case  $n = 2$  is not interesting since it results in  $A = 0$ . Therefore, we will concentrate our attention to cases in which  $n > 2$ .

From eq. (1) we can obtain the correlation length  $\tilde{l}$ , which is determined by the smallest value of  $l$ , with  $l = mn$ , satisfying  $C(l, L) = 0$ . Namely,  $\tilde{l} = \tilde{m}n$ , where  $\tilde{m}$  is given by

$$\tilde{m} = \log \left[ \frac{A+g-1}{LA} \right] / \log \left[ \frac{A+g-1}{g} \right]. \quad (2)$$

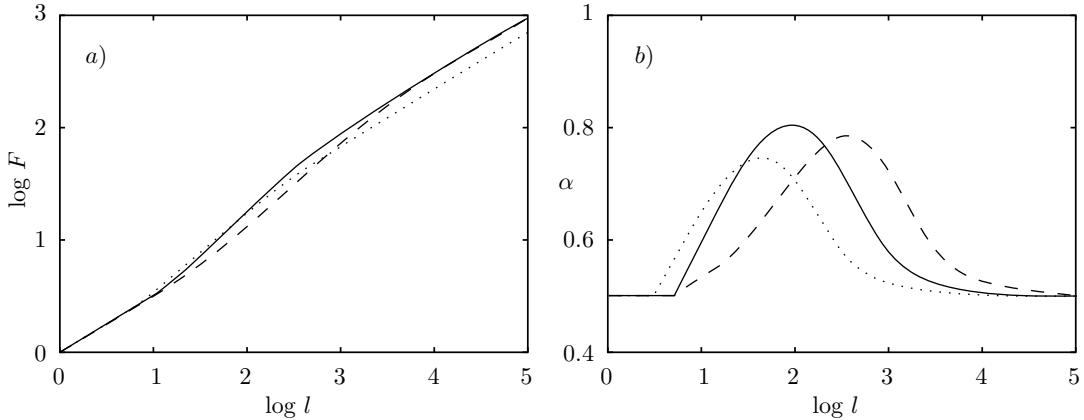


Fig. 2. – a)  $\log F(l, L)$  vs.  $\log l$ . b)  $\alpha(l, L)$  vs.  $\log l$ , for  $n = 10$ ,  $g = 3$  (solid),  $n = 10$ ,  $g = 10$  (dashed) and  $n = 6$ ,  $g = 3$  (dotted) with  $N_i = 10^4$ .

Since  $F(l, L)$  can be obtained from  $C(l, L)$ , and if we take into consideration that  $C(-l, L) = C(l, L)$ , we find

$$F(l, L) = \sqrt{l \left[ 1 + 2 \sum_{j=1, l} C(j, L) \right] - 2 \sum_{j=1, l} j C(j, L)}. \quad (3)$$

As in [3], we calculate the local slope  $\alpha(l_i, L)$  of  $\log F(l_i, L)$  vs.  $\log l_i$ , given by

$$\alpha(l_i, L) = \frac{\log F(l_{i+1}, L) - \log F(l_i, L)}{\log l_{i+1} - \log l_i}. \quad (4)$$

If we take  $l_{i+1} = l_i + k$ , then

$$\alpha(l_i, L) = \frac{\log \left\{ 1 + \frac{k \left[ 1 + 2 \sum_{j=1}^{l_i+k} C(j, L) \right] + 2 \sum_{j=l_i+1}^{l_i+k} (l_i - j) C(j, L)}{l_i + 2 \sum_{j=1}^{l_i} (l_i - j) C(j, L)} \right\}}{2 \log \left\{ 1 + \frac{k}{l_i} \right\}}. \quad (5)$$

For  $l < ng$  or large  $l$ , we have  $C(l, L)$  of the order of  $-1/L$ , this implies that for very large chains eq. (5) gives  $\alpha \approx 0.5$ . For intermediate values of  $l$  we have that  $\alpha$  presents a spiked behaviour at  $l = mn$ , as a consequence of the spikes present in the correlation function (see eq. (1)). We observe that if we average  $\alpha(l, L)$  for  $n$  consecutive values of  $l$ , with  $l \geq ng$ , the curve  $\alpha$  vs.  $\log l$  becomes smooth. Another equivalent way to smooth  $\alpha(l, L)$  is to take  $k = n$  and  $l_i$  a multiple of  $n/2$ . This is the method we use here.

We show in fig. 2a)  $\log F(l, L)$  vs.  $\log l$  for  $n = 10$ ,  $g = 3$  (solid),  $n = 10$ ,  $g = 10$  (dashed) and  $n = 6$ ,  $g = 3$  (dotted). In all the three cases,  $N_i = 10^4$ . As in real DNA sequences [3], [7] we do not find a straight line. Therefore, also in our growth model a well-defined fractal power exponent  $\alpha$  does not exist. In fig. 2b) we show  $\alpha$  vs.  $\log l$  associated with the curves shown in fig. 2a). We see that the local slope  $\alpha$  starts from  $1/2$ , then increases to a maximum value, and for large  $l$  decreases again to  $1/2$ . For these parameters values we find from eq. (2)  $\log \tilde{l} \approx 3.17$ ,  $3.64$ ,  $2.69$ , respectively, which correctly mark the region in which  $\alpha(l, L)$  returns to the trivial value  $1/2$ . We see that, for small and large  $l$  the exponent  $\alpha$  is the one of a random sequence. Our results for  $n = 10$ ,  $g = 10$  and  $n = 10$ ,  $g = 3$  are in good agreement with figs. 4 and 8 of [3]. However, in those figures the statistics for large  $l$  are not as good as

in our case, and  $\alpha$  presents considerable fluctuations. The results obtained from our analytical expressions were compared with the ones obtained by direct simulation of the growth process, and they were in excellent agreement with each other. Our picture indicates that for large  $l$ ,  $\alpha(l, L) = 1/2$  in real DNA sequences if chains sufficiently big were analysed in [3].

We also analysed the Fourier spectrum of the numerical sequence obtained through the random walk method described above. We see at large frequencies a white-noise component (with peaks located at  $f = 1/n$  and its respective harmonics, reflecting the presence of the spikes at  $l = mn$  in the autocorrelation function). For intermediate frequencies we find  $1/f$  noise and at small frequencies the power spectrum again flattens off. This can be observed only if the chain is very large. If this is not the case, only the  $1/f$  and the white-noise regions (at large frequencies) are observed (more details will be published elsewhere). This is exactly what has been seen in real DNA sequences [1], [9]. By studying very large sequences, we are able to show that the  $1/f$  noise in real DNA chains is apparently only a transient behaviour observed in chains that are not sufficiently large.

In conclusion, we have introduced a growth model for DNA evolution which incorporates basic features of a DNA growth process, that is, sequence elongation due to gene duplication and mutations. Our model gives the same statistical results of real sequences investigated in the literature, that is, the apparent existence of long-range correlations. However, when larger chains are studied, we see that this is only a transient behaviour valid for chains not sufficiently big. From our studies we suggest that a possible way to find the asymptotic value of  $\alpha$  in real sequences, eliminating the statistical fluctuations, is to divide the chain into big segments and study the ensemble average of this exponent.

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