A time series model of CDS sequences in complete genome

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Abstract

A time series model of CDS sequences in complete genome is proposed. A map of DNA sequence to integer sequence is given. The correlation dimensions and Hurst exponents of CDS sequences in complete genome of bacteria are calculated. Using the average of correlation dimensions, some interesting results are obtained.

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1 Introduction

In the past decade or so there has been a ground swell of interest in unraveling the mysteries of DNA. With improving of the technique of gene clone and sequences determined, the DNA sequence database become huge rapidly. Doing DNA sequence analysis only use the experimental method does not fit this rapid. Hence it becomes very important to improve new theoretical methods. One approach that has, in just a few years, proven to be particularly fruitful in this regard is statistical analysis of DNA sequences\(^{[1-9]}\) using modern statistical measures, including the works on the correlation properties of coding and noncoding DNA sequences. The second approach is linguistic approach. DNA sequence can be seen as analogous at a number of levels to mechanisms of processing other kinds of languages, such as natural languages and computer languages\(^{[10]}\). Third, using

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nonlinear scales method, such as fractal dimension\cite{11,12,13}, complexity\cite{14,15}. However, DNA sequences are more complicated than these types of analysis can describes. Therefore, it is crucial to develop new tools for analysis with a view toward uncovering mechanisms used to code other types of information.

Since the first complete genome of a free-living bacterium *Mycoplasma genitalium* was sequenced in 1995\cite{16}, an ever-growing number of complete genomes has been deposited in public databases. The availability of complete genomes opens the possibility to ask some global questions on these sequences. Our group also discussed the avoided and under-represented strings in some bacterial complete genomes\cite{13,17,18}. In this paper, we propose a new model to DNA sequences, i.e. the time series model. First we want to compute the correlation dimension and Hurst exponents of each CDS sequence in the complete genome, then consider the distribution of these two quantities on complete genomes of Bacteria. It is a global problem. Last we want to discuss the classification problem of Bacteria using our results.

For the present purpose, a DNA sequence may be regard as a sequence over the alphabet \{A, C, G, T\} representing the four bases from which DNA is assembled, namely adenine, cytosine, guanine, and thymine. For a DNA sequence, we define a map \( f \) as following:

\[
\begin{align*}
A & \rightarrow -2 \\
C & \rightarrow -1 \\
G & \rightarrow 1 \\
T & \rightarrow 2.
\end{align*}
\]  

Then we obtain an data sequence \( \{ x_k : k = 1, 2, \cdots, N \} \), where \( x_k \in \{-2, -1, 1, 2\} \). We formal view this sequence as a time series. According to the definition of \( f \), the four bases \{A, C, G, T\} are mapped to four distinct value. One can also use \{-2, -1, 1, 2\} to replace \{A, G, C, T\} or other orders of A, G, C, T. our main aim is distinguish A and G from purine, C and T from pyrimidine. We expect it to reveal more information than one dimensional DNA walk\cite{14}.

2  Correlation dimension and Hurst exponent

The notion of correlation dimension, introduced by Grassberger and Procaccia\cite{19,20}, suits well experimental situations, when only a single time series is available, it is now being used widely in many branches of physical science. Given a sequence of data from a computer or laboratory experiment

\[
x_1, x_2, x_3, \cdots, x_N
\]  

(2)
where \( N \) is a big enough number. These number are usually sampled at an equal time interval \( \Delta \tau \). We embed the time series into \( \mathbb{R}^m \), choose a time delay \( \tau = p \Delta \tau \), then obtain

\[
y_i = (x_i, x_{i+p}, x_{i+2p}, \cdots, x_{i+(m-1)p}), \quad i = 1, 2, \cdots, N_m
\]

where

\[
N_m = N - (m - 1)p.
\]

In this way we get \( N_m \) vectors of embedding space \( \mathbb{R}^m \).

For any \( y_i, y_j \), we define the distance as

\[
r_{ij} = d(y_i, y_j) = \sum_{l=0}^{m-1} |x_{i+lp} - x_{j+lp}|.
\]

If the distance is less than a present number \( r \), we say that these two vectors are correlated.

The correlation integral is defined as

\[
C_m(r) = \frac{1}{N^2} \sum_{i,j=1}^{N_m} H(r - r_{ij})
\]

where \( H \) is the Heaviside function

\[
H(x) = \begin{cases} 
1, & \text{if } x > 0 \\
0, & \text{if } x \leq 0
\end{cases}
\]

For a proper choice of \( m \) and not too big a value of \( r \), it has been shown by Grassberger and Procaccia\[20\] that the correlation integral \( C_m(r) \) behaves like

\[
C_m(r) \propto r^{D_2(m)}.
\]

Thus one can define correlation dimension as

\[
D_2 = \lim_{m \to \infty} D_2(m) = \lim_{m \to \infty} \lim_{r \to 0} \frac{\ln C_m(r)}{\ln r}.
\]

For more details of \( D_2 \), the reader can refer to ref.[21].

To deal with practical problem, one usually choose \( p = 1 \). From Page 346 of ref.[21], if we choose an sequence \( \{r_i : 1 \leq i \leq n\} \) such that \( r_1 < r_2 < r_3 < \cdots < r_n \), then in the \( \ln r - \ln C_m(r) \) plane, we can look for a scaling region. Then the slop of the scaling region is \( D_2(m) \). When \( D_2(m) \) dose not change with \( m \) increasing, we can take this \( D_2(m_0) \) as the estimate value of \( D_2 \). We calculate the correlation dimension of some DNA sequences using the method introduced above. From the \( \ln r - \ln C_m(r) \) figures of these sequences of different value of embedding dimension \( m \), we find that it is suitable to choose \( m = 7 \). For example, we give the \( \ln r - \ln C_m(r) \) figure of Phage’s 5’UTR sequence when \( m = 7, 8 \).
Figure 1: $\ln r - \ln C_m(r)$ figure of phage 5’UTR sequence when $m=7,8$.

(Figure 1). We take the region from the third point to the 17th point (from left to right) as the scaling region.

To study time series, Hurst\cite{22} invented a new statistical method — the rescaled range analysis ($R/S$ analysis), later on B. B. Mandelbrot\cite{23} and J. Feder\cite{24} transplanted $R/S$ analysis into fractal analysis. For any time series $x = \{x_k\}_{k=1}^N$ and any $2 \leq n \leq N$, one can define

$$< x >_n = \frac{1}{n} \sum_{i=1}^{n} x_i$$ \hspace{1cm} (10)

$$X(i, n) = \sum_{u=1}^{i} [x_u - < x >_n]$$ \hspace{1cm} (11)

$$R(n) = \max_{1\leq i\leq n} X(i, n) - \min_{1\leq i\leq n} X(i, n)$$ \hspace{1cm} (12)

$$S(n) = \left[ \frac{1}{n} \sum_{i=1}^{n} (x_i - < x >_n)^2 \right]^{1/2}.$$ \hspace{1cm} (13)

Hurst found that

$$R(n)/S(n) \sim \left( \frac{n}{2} \right)^H.$$ \hspace{1cm} (14)

$H$ is called Hurst exponent.
As $n$ changes from 2 to $N$, we obtain $N - 1$ points in $\ln(n)$ v.s. $\ln(R(n)/S(n))$ plane. Then we can calculate Hurst exponent $H$ of DNA sequence $s$ using the least-square linear fit. As an example, we plot the graph of $R/S$ analysis of an exon segment $s$ of mouse’ DNA sequence (bp 1730–bp 2650 of the record with Accession AF033620 in Genbank) in Figure 2.

The Hurst exponent is usually used as a measure of complexity. From Page 149 of Ref.[22], the trajectory of the record is a curve with a fractal dimension $D = 2 - H$. Hence a smaller $H$ means a more complex system. When applied to fractional Brownian motion, if $H > 1/2$, the system is said to be persistent, which means that if for a given time period $t$, the motion is along one direction, then in the succeeding $t$ time, it’s more likely that the motion will follow the same direction. While for system with $H < 1/2$, the opposite holds, that is, antipersistent. But when $H = 1/2$, the system is Brown motion, and is random.

### 3 Data and results.

More than 18 bacterial complete genomes are now available in public databases. There are four Archaeabacteria: Archaeoglobus fulgidus (aful), Pyrococcus horikoshii (pyro), Methanococcus jannaschii (mjan), and Methanobacterium thermoautotrophicum (mthe);
Table 1: Average of $D_2$ of genes of 18 bacteria.

| Average of $D_2$ | species of Bacterium | Category                        |
|------------------|-----------------------|---------------------------------|
| 2.805            | Mycoplasma genitalium (mgen) | Gram-positive Eubacteria        |
| 2.827            | Methanococcus janaschii (mjan) | Archaeabateria                  |
| 2.872            | Rockettsia prowazekii (rpxx) | Proteobacteria                  |
| 2.883            | Helicobacter pylori 26695 (hpyl) | Proteobacteria                  |
| 2.908            | Helicobacter pylori J99 (hpyl99) | Proteobacteria                  |
| 2.938            | Haemophilus influenzae (hinf) | Proteobacteria                  |
| 2.940            | Mycoplasma pneumoniae (mpneu) | Gram-positive Eubacteria        |
| 2.950            | Mycobacterium tuberculosis (mtub) | Gram-positive Eubacteria        |
| 2.990            | Bacillus subtilis (bsub) | Gram-positive Eubacteria        |
| 3.011            | Aquifex aeolicus (aquae) | hyperthermophilic bacterium     |
| 3.012            | Pyrococcus horikoshii (pyro) | Archaeabateria                  |
| 3.013            | M. thermoautotrophicicum | Archaeabateria (mthe)          |
| 3.016            | Archaeoglobus fulgidus (aful) | Archaeabateria                  |
| 3.020            | Chlamydia trachomatis (ctra) | Chlamydia                       |
| 3.024            | Chlamydia pneumoniae (cpneu) | Chlamydia                       |
| 3.028            | Synechocystis PCC6803 (synecho) | Cyanobacteria                   |
| 3.047            | Rhizobium sp. NGR234 (pNGR234) | Proteobacteria                  |
| 3.060            | Escherichia coli (ecoli) | Proteobacteria                  |

four Gram-positive Eubacteria: Mycobacterium tuberculosis (mtub), Mycoplasma pneumoniae (mpneu), Mycoplasma genitalium (mgen), and Bacillus subtilis (bsub). The others are Gram-negative Eubacteria: one hyperthermophilic bacterium Aquifex aeolicus (aquae); six proteobacteria: Rhizobium sp. NGR234 (pNGR234), Escherichia coli (ecoli), Haemophilus influenzae (hinf), Helicobacter pylori J99 (hpyl99), Helicobacter pylori 26695 (hpyl) and Rockettsia prowazekii (rpxx); two chlamydia Chlamydia trachomatis (ctra) and Chlamydia pneumoniae (cpneu), and one cyanobacterium Synechocystis PCC6803 (synecho).

For a given bacterium, we calculate the correlation dimension and Hurst exponent of each CDS sequence (i.e. the coding sequence) in its complete genome first (the results is shown in Figure 3 and Figure 4), then calculate the average of these two quantities. We find that the average of Hurst exponents of 18 bacteria are almost equal (range being from 0.538 to 0.590). But the differences among the values of average of correlation dimensions of these bacteria are larger. One can see Table 1 (from top to bottom, the value of $D_2$
become larger).

4 Discussion and conclusions

Although the existence of the archaebacterial urkingdom has been accepted by many biologists, the classification of bacteria is still a matter of controversy\cite{25}. The evolutionary relationship of the three primary kingdoms (i.e. archaebacteria, eubacteria and eukaryote) is another crucial problem that remains unresolved\cite{25}.

From Table 1, we can roughly divide bacteria into two classes first, the average of $D_2$ of one class is less than 3.0, that of another class is greater than 3.0. We can see that the classification of bacteria using the average of $D_2$ is almost coincide with the original classification of bacteria. Archaebacteria gather with each other except mjan. Gram-positive bacteria get together except mgen. Chlamydia also gather with each other. Proteobacteria is divided into two sub-category: rpxx, hpyl, hpyl99 and hinf belong to one sub-category; pNGR234 and ecoli belong another sub-category.

A surprising feature shown in Table 1 is that Aquifex aeolicus is linked closely with the Archaebacteria. We noticed that Aquifex, like most Archaebacteria, is hyperthermophilic. It has previously been shown that Aquifex has close relationship with Archaebacteria from the gene comparison of an enzyme needed for the synthesis of the amino acid trytophan\cite{26}. Our result, from the comparison of the complete genome, shows that the case is even more worse. Such strong correlation on the level of complete genome between Aquifex and Archaebacteria is not easily accounted for by lateral transfer and other accidental events\cite{26}.

We calculate the average of correlation dimensions and Hurst exponents of genes in all 16 chromosome of Saccharomyces cerevisiae (yeast), they are 3.018 and 0.579 respectively. From Table 1, one can see that Archaebacteria and Chlamydia are linked more closely with yeast which belongs to eukaryote than other category of bacteria. There are several reports (such as Ref. \cite{27}), in some RNA and protein species, archeabacteria are much more similar in sequences to eukaryotes than to eubacteria. Our present result supports this point of view.

We also randomly produce a sequence of length 3000 consisting of symbols from the alphabet \{A, T, G, C\}. The correlation dimension is 1.02883. From Table 1, Fig. 3, we can conclude that all CDS sequences are far from random sequences. Since the Hurst exponent of random sequence is 0.5. From Fig. 4, we can see that correlation dimension is well than Hurst exponent when we compare real DNA sequence with a random sequence on the alphabet \{A, T, G, C\}.

In Ref. \cite{14}, we find the Hurst exponent is a good exponent to distinct different
functional regions, but now we only consider the same kind of functional region (i.e. they are all genes), it is reasonable that the average of Hurst exponent do not change much. Fortunately, now we can use the average of correlation dimension to distinguish different species.

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Figure 3: The correlation dimensions of CDS sequences in the complete genome of 18 bacteria.
Figure 4: The Hurst exponents of CDS sequences in the complete genome of 18 bacteria.