Prediction of genomic properties and classification of life by protein length distributions

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Much evolutionary information is stored in the fluctuations of protein length distributions. The genome size and non-coding DNA content can be calculated based only on the protein length distributions. So there is intrinsic relationship between the coding DNA size and non-coding DNA size. According to the correlations and quasi-periodicity of protein length distributions, we can classify life into three domains. Strong evidences are found to support the order in the structures of protein length distributions.

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INTRODUCTION

There is an analogy between the current status of particle physics and molecular biology, in each of which there is a theoretical framework to explain the particle world or living world (the Standard Model for the former while the Central Dogma and gene regulation for the latter), but we do not know the dynamical mechanisms that underlie these theoretical frameworks. It is generally believed that the genetic information is stored in DNA sequences. This often results in a misapprehension that all the information about a species is stored in the sequences of its genome. Actually, only a part of the information of life is stored in the sequences, from which we may infer the structures and functions of macromolecules. But there is still other information concerns the underlying mechanism of the evolution of life, which can not be acquired by analyzing the sequences. For example, the mechanism that determines the protein length distribution differs from the mechanism that determines in the protein sequences, which requires new explanation other than the current theoretical framework.

The protein length distribution is an intrinsic properties of a species that concerns the underlying mechanism of molecular evolution. But the nature of the protein length distribution is still unknown. Someone consid-ered it as a result of stochastic process, while others noticed the order in the length distributions [1][2][3][4]. We found that much information of the evolution of life is stored in the fluctuations of protein length distributions. The genome size of a species, even its coding DNA size and non-coding DNA size can be calculated by the protein length distribution of this species. We also found that the three domains of life (Bacteria, Archaea, and Eucarya) can be classified based on the correlations or quasi-periodicity of protein length distributions; furthermore, we can obtain the phylogeny of the three domains [2]. These results shows that the protein length distributions are not random, the fluctuations in the distribution are intrinsic properties and can be taken as the fingerprint of a certain species. We propose a linguistic model to explain the generation of protein sequences and consequently try to explain the nature of protein length distributions. The model indicates that the complexity of the grammars that generate protein sequences is related to the biological complexity of the species. The protein length distributions might be taken as clues to discover the underlying mechanism of molecular evolution.

PREDICTION OF GENOME SIZE AND NON-CODING DNA CONTENT BY PROTEIN LENGTH DISTRIBUTIONS.

The evolution of genome size is one of the central problems in the study of molecular evolution [1][2]. We can write down the experimental formulae of genome size and the ratio of non-coding DNA to coding DNA based on the protein length distributions, which may help us understand the mechanism of genome size evolution.

The protein length distribution of a species $\alpha$ can be denoted by a vector

$$ x(\alpha) = (x_1(\alpha), x_2(\alpha), ..., x_k(\alpha), ...), $$

(1)

where there are $x_k(\alpha)$ proteins in its entire proteome whose lengths are $k$ amino acids (a.a.). Our data of the protein length distributions are obtained from the data of $n = 106$ complete proteomes ($n_b = 85$ bacteria, $n_a = 12$ archaea, $n_e = 7$ eukaryotes and $n_v = 2$ viruses) in the database Predictions for Entire Proteomes (PEP) [3]. The total protein length distribution of all the species in PEP is $X = \sum_{\alpha \in \text{PEP}} x(\alpha)$, from which we found that there are few proteins longer than $m = 3000$ a.a. in the complete proteomes. We can neglect them and set $m$ as the cutoff of protein length in our calculations. Hence the vectors $x(\alpha)$ can be reduced to $m$-dimensional vectors to represent the protein length distributions.

A peak at protein length $l$ in the fluctuations of protein length distribution of species $\alpha$ can be denoted by $x_l(\alpha)$, which is required to be greater than both $x_{l-1}(\alpha)$ and $x_{l+1}(\alpha)$. The number of peaks in the fluctuations of protein length distribution of species $\alpha$ can be denoted
Thus, we found that the genomic properties can be predicted based only on the protein length distributions. The information of genome size $s(\alpha)$, non-coding DNA size $\eta(\alpha)s(\alpha)$ and coding DNA size $(1 - \eta(\alpha))s(\alpha)$ are stored in the fluctuations of protein length distribution of species $\alpha$. More peaks in the fluctuations indicates larger genome size. And the number of peaks in the fluctuations also relates to the non-coding DNA content. The protein length distribution concerns only the coding DNA, but we can deduce the non-coding DNA size by such a distribution. This shows that there must be a universal mechanism to adjust the ratio of coding DNA and non-coding DNA in each species.

In some studies, the protein length are considered as random variable of a stochastic process. If so, there should not be close relationship between the number of peaks $p(\alpha)$ and the genome size $s(\alpha)$; and the outline of the protein length distribution would be more smooth when the genome size increases. Our results show that the protein length is not a random variable of stochastic process and the fluctuations are intrinsic properties.

The number of peaks of the fluctuations in the protein length distribution $p(\alpha)$ is an intrinsic property of a species $\alpha$. We also found that the correlation between $p(\alpha)$ and $s(\alpha)$ is closer than the correlation between $p(\alpha)$ and $l(\alpha)$ (Fig 1b and Fig 2c). It is suggested that the biological complexity is related to the non-coding DNA content, and the biological complexity is also related to the genome size for prokaryotes [11][12][13]. The number of peaks $p(\alpha)$ can be interpreted as the complexity of structures of protein length distribution. The linguistics plays significant roles in the organization of protein or DNA sequences [14][15]. We proposed a linguistic mechanism to account for the generation of protein sequences [16]. The bell-shaped outline and the fluctuations of the protein length distribution can be simulated by a linguistic model. The number of peaks of the fluctuations in the protein length distribution is determined by the complexity of grammars. The correlation between $p(\alpha)$ and $s(\alpha)$ indicates a relationship between the complexity of the structure of protein length distribution and the biological complexity of that species, both of which may result from the complexity of grammars in the sequences.

**CLASSIFICATION OF LIFE BY CORRELATION AND QUASI-PERIODICITY OF PROTEIN LENGTH DISTRIBUTIONS.**

Molecular sequence analysis provides a more precise and profound method in classification of life than classical taxonomy. Based upon rRNA sequence comparisons, life on this planet can be divided into three domains: the Bacteria, the Archaea, and the Eucarya [3]. The differences that separate the three domains are of a more profound nature than the differences that separate clas-
The correlation coefficient of protein length distributions between species $\alpha$ and $\beta$ is defined by
\[
r(\alpha, \beta) = \frac{\sum_{k=1}^{m} (x_k(\alpha) - \bar{x}(\alpha))(x_k(\beta) - \bar{x}(\beta))}{\sqrt{\sum_{k=1}^{m} (x_k(\alpha) - \bar{x}(\alpha))^2 \sqrt{\sum_{k=1}^{m} (x_k(\beta) - \bar{x}(\beta))^2}}.
\] (5)

where $\bar{x}(\alpha) = \frac{1}{m} \sum_{k=1}^{m} x_k(\alpha)$. And the average correlation coefficient of species $\alpha$ can be defined by
\[
R(\alpha) = \frac{1}{106} \sum_{\beta \in PEP} r(\alpha, \beta).
\] (6)

We can also define the Minkowski distance between species $\alpha$ and $\beta$ as
\[
d(\alpha, \beta) = \left( \sum_{k=1}^{m} \frac{|x_k(\alpha)|^q}{||x(\alpha)||^q} \frac{|x_k(\beta)|^q}{||x(\beta)||^q} \right)^{1/q},
\] (7)
where we chose the parameter $q = 1/4$ in the calculation. And the average Minkowski distance of species $\alpha$ can be defined by
\[
D(\alpha) = \frac{1}{106} \sum_{\beta \in PEP} d(\alpha, \beta).
\] (8)

The average correlation coefficient $R(\alpha)$ and the average Minkowski distance $D(\alpha)$ represent the evolutionary relationship between species $\alpha$ and all the other species. The more the average correlation coefficient is (or inversely the less the average Minkowski distance is), the closer the evolutionary relationship is.

We can classify life by clustering analysis based only on the protein length distributions. In the $R - \log D$ plane, we found that the species in the three domains cluster together respectively (Fig 2a). The similar results can also be obtained by other methods. The average protein length in the proteome of species $\alpha$ can be calculated by protein length distribution:
\[
\bar{l}(\alpha) = \frac{\sum_{k=1}^{m} k x_k(\alpha)}{\sum_{k=1}^{m} x_k(\alpha)}.
\] (9)

According to the distributions of species in the plots of $\bar{l} - R$, $\bar{l} - \log D$ and $\bar{l} - p$, we found that the species in the three domains also cluster together in the corresponding plots respectively.

We can also classify life according to the quasi-periodicity of protein length distributions. There are underlying orders in the organization of protein sequences, so we can observe the quasi-periodic structures in the protein length distributions. According to Fourier analysis,
we can also observe the clustering of species for different domains.

The abstract discrete fourier transformation of the protein length distribution \( x(\alpha) \) is:

\[
y_f(\alpha) = \frac{1}{\sqrt{m}} \left| \sum_{k=1}^{m} x_k(\alpha) e^{2\pi i(k-1)(f-1)/m} \right|.
\] (10)

The frequency of the highest peak in the fluctuations of the spectrum \( y(\alpha) \) can be denoted by \( f_h(\alpha) \). The maximum frequency for the top 10 highest peaks in the fluctuations of the spectrum \( y(\alpha) \) can be denoted by \( f_{max}(\alpha) \).

We found that there is an interesting relationship between the highest peak frequency \( f_h(\alpha) \) and the average protein length \( \bar{l} \) of species (Fig. 3 in Ref. [16]). The distribution of species in \( f_h - \bar{l} \) plane shows a regular pattern: the species in the three domains gathered in three rainbow-like arches respectively. This pattern strongly indicates the intrinsic correlation among the protein length distributions, which cannot achieve if the protein length distributions are stochastic. The periodicity of the protein length distributions can be inferred by the correlations between \( f_h \) and \( f_{max} \). The regular distribution of species in Fig. 2d indicates the correlation between the short period \( m/f_h \) and the long period \( m/f_{max} \). Therefore, the quasi-periodic structures of the spectra indicate the correlations between long proteins and short proteins in a proteome.

The total spectra for three domains Bacteria, Archaea and Eucarya are \( B = \frac{1}{n_b} \sum_{\alpha \in \text{Bacteria}} y(\alpha) \), \( A = \frac{1}{n_a} \sum_{\alpha \in \text{Archaea}} y(\alpha) \) and \( E = \frac{1}{n_e} \sum_{\alpha \in \text{Eucarya}} y(\alpha) \) respectively. So the average spectra for the three domains are defined as follows respectively:

\[
B(s) = \frac{1}{2s+1} \sum_{k=-s}^{f+s} b_k 
\] (11)

\[
A(s) = \frac{1}{2s+1} \sum_{k=-s}^{f+s} a_k 
\] (12)

\[
E(s) = \frac{1}{2s+1} \sum_{k=-s}^{f+s} e_k, 
\] (13)

where \( f = 1 + s, ..., m - s \) and we chose \( s1 = 100 \) and \( s2 = 300 \) as the ranges for averaging in calculations. We found that the outlines of \( A \) and \( E \) are similar, both of which have convex bottoms (Fig 3a, b), but they are dissimilar with the outline of \( B \), which has a concave bottom (Fig 3c). According to the phylogeny of the three domains, the relationship between Archaea and Eucarya is more closer than the relationship between Archaea and Bacteria. So the outlines of the average spectra of the three domains reveal the phylogeny of the three domains.

**CONCLUSION AND DISCUSSION**

We can conclude that much evolutionary information is stored in the protein length distributions, according to which we can calculate the genome size and non-coding DNA content. The mechanism that determines the protein length distribution concerns not only coding DNA but also non-coding DNA. So we demonstrated the intrinsic relationship between coding DNA size and non-coding DNA size. New methods are proposed to classify life into three domains based only on the protein length distributions. We confirm that there are quasi-periodic structures in the protein length distributions, and we found the relationship between average protein length and the frequencies of Fourier transformation of protein length distributions.

The protein length distributions can not be considered as random fluctuations. We found strong evidences of the...
underlying mechanism in the organization of amino acids in protein sequences, which indicates the languages in the protein sequences. We proposed a linguistic model to accord for the protein length distribution, which suggested that there is a close relationship between the complexity of grammars of the protein sequences and the biological complexity of the species.

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