Profile-Statistical Periodicity of DNA Coding Regions

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Abstract

Novel methods for identifying a new type of DNA latent periodicity, called latent profile periodicity or latent profility, are used to search for periodic structures in genes. These methods reveal two distinct levels of organization of genetic information encoding. It is shown that latent profility in genes may correlate with specific structural features of their encoded proteins.

Key words: latent periodicity; latent profility; spectral–statistical approach; gene structure

1. Introduction

The notion of latent periodicity in nucleotide DNA sequences has arisen from the discovery of various regularity levels in the structural organization of a DNA molecule. For example, a DNA double-helix pitch has been found to equal $\sim 10^{-11}$ bp, a length of $\sim 200$ bp has been found for DNA fragments in nucleosomes, and a loop length of $\sim 2 \times 10^4$–$10^5$ bp has been determined at the higher level of quasi-regular DNA compactization.1 Such particularities are probably due to non-random alternation of bases in the original DNA sequence. Thus, research on both short- and long-range base correlations2 is of great importance for understanding known structural particularities in DNA sequences and for revealing new ones.

Images of various functions demonstrating nucleotide correlations in DNA coding regions show regular peaks with the steps of three bases corresponding to the triplet nature of the genetic code. This has led to the notion of triplet periodicity in the coding regions. It is likely that use of the term ‘latent triplet periodicity’ has also been influenced by the hypothesis on the universal RNY triplet pattern (R, purine; Y, pyrimidine; N, purine or pyrimidine) of codons in ancient genes, because correlations with this pattern can be traced in base distribution over recent coding regions.3

In light of the current understanding of latent periodicity as approximate tandem repeats,4 the occurrence of periodicity has been corroborated by textual ‘consensus pattern’, which is an estimate of a pattern in the original repeat. If alterations in the copies of the pattern account for more than 30% of the pattern, the validity of the revealed consensus pattern is in doubt. Although tandem repeats of tri- and hexa-nucleotides occur in coding regions,5,6 as a rule it is impossible to deduce a reliable consensus pattern of an approximate tandem repeat over the whole length of a coding region.

Weak three-base periodicity in Escherichia coli mRNA with pattern G-non-G-N, complemented by pattern NNC in 16S RNA, has been considered as a mechanism for monitoring translation frames in ribosomes.7 Despite the discovery of a few short tracks of corresponding patterns, this case would be more accurate to consider only as the domination of G and C bases in corresponding triplet positions. The weak preference of a certain type of base in a fixed
position of triplets in the coding region promotes the appearance of a dominant peak in the Fourier spectrum at a frequency of 0.33 corresponding to the three-base period. Nevertheless, this preference is not the key cause behind this observation. It appears that the greater the variance of certain base distributions over period positions, the more impact such a base has on the amplitude of spectral density at the three-period frequency, even when the base is not dominant at triplet positions. Thus, appearance of the peak at the frequency of 0.33 in the Fourier spectrum is due to non-uniform base distribution over the triplet positions.

Use of the Fourier methods for revealing imperfect periodicity has become common. Other statistical methods have also arisen for determining latent periodicity in nucleotide sequences. These methods are based on measuring heterogeneity in base distributions over period positions. In practice, in the absence of weak periodicity in a sequence that is not an approximate tandem repeat, a high index of heterogeneity and a Fourier spectrum with a dominant peak may be observed. It is incorrect in this case to use the term ‘latent periodicity’, until the discovery of a pattern indicating some new type of periodicity, for example, such as the flexible patterns of 11th nucleotide periodicity in the genomes of prokaryotes and low eukaryotes.

In the present work, a spectral–statistical approach (2S approach) to identifying a new type of latent periodicity, called profile periodicity or profility, is proposed. The notion of latent profility in DNA sequences has been introduced earlier. It expands on the idea of approximate tandem repeat in which textual string (DNA sequence) is presented as a chain of eroded copies (with ~80% identity) of the textual pattern. Latent profile periodicity occurs in DNA regions where nucleotide correlations can be described by hypothesizing on the generation of successive uni-length DNA fragments according to a fixed probability distribution of bases appearance at each fragment position. A pattern of latent profility can be described with the aid of a finite random string consisting of independent random characters with corresponding probability distribution for the textual string as a realization of some profile string. Such a character is a random variable that takes the value of the letter of the alphabet with a probability determined by the frequency column $p_i = (p_1, \ldots, p^K)^T$.

DNA sequences are considered as textual strings in the four-character ($K = 4$) simply ordered alphabet $A = \{a, g, t, c\}$, where $a$ is the adenine, $g$ the guanine, $t$ the thymine and $c$ the cytosine.

Let $\text{Chr}(p)$ be a random character with the frequency column $p = (p_1, \ldots, p^K)^T$. Such a character is a random variable that takes the value of the $i$th character of the alphabet $A = \{a_1, \ldots, a_K\}$ with a probability of $p_i$ ($i = 1, \ldots, K$).

A special random string $\text{Str}_n(\pi) = \text{Chr}(p_1) \cdots \text{Chr}(p_n)$ of $n$ independent random characters is induced by the matrix $\pi = (p_1, \ldots, p_n)$ called an $n$-profile matrix. Let $\text{str} = a_{i_1} \cdots a_{i_n}$ be a textual string, where $i_m$ is the number of a character $a_m$ ($m = 1, \ldots, n$) in alphabet $A$. If the $\text{str}$ is a realization of the random string $\text{Str}_n(\pi)$, then the product $\pi_{i_1}^{1} \cdots \pi_{i_n}^{n}$ determines the probability of such a realization.
The character \( a_i \in A (i = 1, \ldots, K) \) can be identified with a random character for which all components of the frequency column are null, except for the \( i \)th, which is a unity component. Therefore, any textual string in alphabet \( A \) can be identified with the corresponding special random string of the same length.

An integer number \( L \) from the diapason \( 1, \ldots, L_{\text{max}} \), where \( L_{\text{max}} \sim n/5K \), is called the test-period of the string \( \text{Str}_1^L (\pi) \).

Let \( L \) be the test-period of random string \( \text{Str} = \text{Str}_1^L (\pi) \), and \( \text{Str}_n^L (\pi) = \text{Str}_1^L (\pi_1) \cdots \text{Str}_L^L (\pi_m) \) \( \text{Str}_M^L (\pi_{m+1}) \) be a decomposition of string \( \text{Str} \) into sub-strings of length \( L \), where \( 0 \leq M < L \) (if \( M \neq 0 \), sub-string \( \text{Str}_M^L (\pi_{m+1}) \) is not complete; if \( M = 0 \), sub-string \( \text{Str}_M^L (\pi_{m+1}) \) is empty). Then, if \( M = 0 \), the matrix \( \Pi_{\text{Str}}^L (L) = (1/m) \sum_{i=1}^{m} \pi_i \) is called the \( L \)-profile matrix of string \( \text{Str} \). If \( M \neq 0 \), then corrections are made in the \( \Pi_{\text{Str}}^L (L) \) matrix. Thus, the profile-matrix spectrum \( \Pi_{\text{Str}}^L (L) \) defined at each test-period, is introduced for string \( \text{Str} \). The profile-matrix spectrum characterizes the statistical structure of the realizations of random string \( \text{Str} \). If the statistical structures of string \( \text{Str} \) and of analysed textual string \( \text{str} \) are indistinguishable (at a corresponding level of significance), then it can be considered that the string \( \text{str} \) is a realization of random string \( \text{Str} \). Further methods for verifying this will be proposed on the basis of the latent profile periodicity model.

### 2.2. A stochastic model of the latent profile periodicity

Occurrence of the latent profile periodicity in the analysed textual string manifests in the statistical string structure observed in the sample profile-matrix spectrum. In fact, if the analysed string is sufficiently long, this sample spectrum takes the form of the profile-matrix spectrum of periodic random string \( \text{Str} \) consisting of independent random characters. In this case, random string \( \text{Str} \) is given by

\[
\text{Str} = \text{Str}_1^L (\pi_1) \cdots \text{Str}_L^L (\pi_m) \text{Str}_M^L (\pi_{m+1}),
\]

where \( L \) is the period of string \( \text{Str} \), \( 0 \leq M < L \), \( \pi_1 = \cdots = \pi_m = \pi_0 \) and \( \text{Str}_1^L (\pi_0) = \text{Str}_M^L (\pi_{m+1}) \text{Str}_L^L (\pi_{10}) \). Such a string \( \text{Str} \) is called the \( L \)-profile string with a random periodicity pattern \( \text{Str}_1^L (\pi_0) \). Moreover, in this case, the designation \( \text{Tdm}_n^L (\pi_0, n) \) is used for the string \( \text{Str}_1^L (\pi_0) \).

Matrix \( \pi_0 \) is called the main profile matrix of the string \( \text{Str} = \text{Tdm}_n^L (\pi_0, n) \) because matrix \( \pi_0 \) initiates the entire profile-matrix spectrum of this string.

Profile string \( \text{Tdm}_n^L (\pi_0, n) \) is a perfect tandem repeat with a random periodicity pattern \( \text{Str}_1^L (\pi_0) \). The profile-matrix spectrum of the string \( \text{Tdm}_n^L (\pi_0, n) \) can be considered as a stochastic model of heterogeneity manifestation in textual strings that are realizations of the string \( \text{Tdm}_n^L (\pi_0, n) \).

### 2.3. Size estimation for pattern of latent profile periodicity in a textual string

To estimate the pattern size of the latent profile periodicity, a characteristic spectrum is established for a textual string. Characteristic spectra of the three approximate tandem repeats from the database TRDB (http://tandem.bu.edu/cgi-bin/trdb/) are shown in Fig. 1a–c. In each of these spectra, the first clear maximum arises at the test-period that is a period of approximate tandem repeat. A similar observation is made for the characteristic spectra of textual strings with latent profile periodicity (Fig. 2a–c). Therefore, the first test-period at which the maximum value of the characteristic spectrum for the analysed textual string is clear is used to estimate the pattern size for the latent profile periodicity, or profile.

The characteristic spectrum for the analysed textual string \( \text{str} \) of length \( n \) in alphabet \( A \) is determined as follows. For every test-period \( \Lambda \) of this string, the profile string \( \text{Tdm}_n^L = \text{Tdm}_n^L (\Pi_{\text{Str}}^L (\Lambda), n) \) is created, and the Pearson statistics14 is introduced:

\[
\psi(\Pi_{\text{Str}}^L (\Lambda), \Pi_{\text{Tdm}}^L (\Lambda), n) = \frac{n}{\lambda} \sum_{j=1}^{\lambda} \sum_{i=1}^{K} \frac{(\pi_{ij}^\Lambda - \pi_{ij}^L)^2}{\pi_{ij}^L (1 - \pi_{ij}^L)} \sim \chi^2_{(K-1)\lambda},
\]

where \( \Pi_{\text{Str}}^L (\Lambda) = (\pi_{ij}^\Lambda)_{K \times \lambda} \) and \( \Pi_{\text{Tdm}}^L (\Lambda) = (\pi_{ij}^L)_{K \times \lambda} \), and \( \chi^2_{\lambda} \) is a \( \chi^2 \) distribution with \( N \) degrees of freedom. When \( \Lambda = 1 \), the value of the characteristic spectrum \( H(\lambda) \) at the test-period \( \lambda \) is calculated by

\[
H(\lambda) = \psi(\Pi_{\text{Str}}^L (\Lambda), \Pi_{\text{Tdm}}^L (\Lambda), n) - E(\chi^2_{(K-1)\lambda}),
\]

where \( E(\chi^2_{\lambda}) \) is the mathematical expectation of \( \chi^2_{\lambda} \).

As noted above, the first test-period \( L \) with a clear maximum value of spectrum \( H \) provides an estimate of the latent period of profility in string \( \text{str} \) (Fig. 2a–c).

### 2.4. Estimation of pattern of latent profile periodicity

Let \( L \) be the proposed estimation of pattern size for the latent profile periodicity of analysed textual string \( \text{str} \) of length \( n \) in alphabet \( A \) of \( K \) characters. Then, to estimate the pattern of the latent periodicity in this string, the periodicity pattern of profile string \( \text{Tdm}_L = \text{Tdm}_L (\Pi_{\text{Str}}^L (L), n) \) is proposed. Hence, \( \text{Str}_1^L (\Pi_{\text{Str}}^L (L)) \) is an estimation of the pattern of latent profile periodicity in an analysed string \( \text{str} \). If such an estimation is valid then string \( \text{str} \) is statistically indistinguishable from the profile string \( \text{Tdm}_L \). In this case, string \( \text{str} \) can be considered a realization of the string \( \text{Tdm}_L \).

To check the statistical indistinguishability of strings \( \text{str} \) and \( \text{Tdm}_L \), the \( D_L \) spectrum, called a spectrum of
string str deviation from $L$-profility, is used. At test-period $l$ of string str, the $D_L$ spectrum has the value

$$D_L(l) = \frac{\psi(\Pi_{str}(l), \Pi_{Tdm_L}(l), n)}{\chi^2_{crit}((K-1)\lambda, \alpha)}$$

where $\psi$ statistics has been introduced in Equation (1), and $\chi^2_{crit}(N, \alpha)$ is the left-hand-side critical value of the $\chi^2$ distribution at a significance value $\alpha = 0.05$. When $L = 1$, the $D_1$ spectrum is called a spectrum of string str deviation from homogeneity. At test-period $\lambda$ of string str, the $D_1$ spectrum takes on the value

$$D_1(\lambda) = \frac{\psi(\Pi_{str}(\lambda), \Pi_{Tdm_1}(\lambda), n)}{\chi^2_{crit}((K-1)\lambda, \alpha)}$$

where $Tdm_1 = Tdm_1(\Pi_{str}(1), n)$.

The hypothesis on the statistical indistinguishability of the strings str and $Tdm_L = Tdm_L(\Pi_{str}(L), n)$ is accepted if the condition $N_L/L_{max} < 0.05$ is met, where $L_{max} \sim n/5K$ and $N_L$ is the number of test-periods at which the values of the spectrum $D_L > 1$. For example, as can be seen in Fig. 3, for the coding region of chicken Gallus gallus Apo A-IV mRNA, the hypothesis is accepted if $L = 33$, and it is rejected if $L = 3$.

2.5. Verification of periodicity pattern estimation

To confirm the validity of the $Str_\lambda(\Pi_{str}(L))$ estimation for the latent profility pattern in a textual string str, a reconstruction is built of the $D_1$ spectrum [Equation (4)] of string str deviation from homogeneity. The $D_1$ spectrum has been chosen as the most informative from the spectra pool of str deviation from the profility [Equation (3)].

The reconstruction is realized on the basis of the $Str_\lambda(\Pi_{str}(L))$ pattern inducing the periodic profile string $Tdm_L = Tdm_L(\Pi_{str}(L), n)$. Thus, by analogy with Equation (4), for theoretical reconstruction of...
the $D_1$ spectrum, the $Th_L$ spectrum is chosen that at test-period $\lambda$ of string $str$ takes on the value

$$Th_L(\lambda) = \frac{\psi(\Pi_{Tdm_1}(\lambda), \Pi_{Tdm_1}(\lambda), n)}{\chi^2_{\text{crit}}((K-1)\lambda, \alpha)} \quad (5)$$

If the $Th_L$ spectrum follows the $D_1$ spectrum (Fig. 4a and b), then the $Str_L(\Pi_{str}(L))$ estimation of the pattern of latent $L$-profile periodicity ($L$-profility) in analysed textual string $str$ is correct. Therefore, latent $L$-profile periodicity ($L$-profility) in string $str$ is confirmed.

Instead of the theoretical reconstruction spectrum [Equation (5)], we can use the statistical ($St_L$) reconstruction of the $D_1$ spectrum (Fig. 4a and c). In this case, by using a random number generator and the main $L$-profile matrix $\Pi_{str}(L)$ of the string $Tdm_L$, string $str^*$ is created as a realization of the string $Tdm_L$. Then, by analogy with Equation (4), the value of the $St_L$ spectrum at the test-period $\lambda$ is calculated as follows:

$$St_L(\lambda) = \frac{\psi(\Pi_{str^*}(\lambda), \Pi_{Tdm_1}(\lambda), n)}{\chi^2_{\text{crit}}((K-1)\lambda, \alpha)} \quad (6)$$

where $Tdm^1 = Tdm_1(\Pi_{str^*}(1), n)$. Statistical reconstruction should be used when regular minima in the $D_1$ spectrum clear deviate from null.

3. Results and discussion

Methods of identifying a new type of latent periodicity in DNA called latent profile periodicity, or profility, have been proposed in the present work. A characteristic of this profile periodicity is the random nature of its pattern. The profile matrix of the pattern determines statistical periodicity in the appearance of the characters in textual strings. As a result, latent profile periodicity manifests in the analysed string.

3.1. Profile-statistical basis of structural domains in protein families

Application of the methods proposed in this work enabled us to discover the occurrence of latent profility for the 33 nucleotides (33-profility) in the coding gene regions of the PF01442 apolipoprotein family from the Pfam (http://pfam.sanger.ac.uk/) database of protein families. This family contains the apolipoproteins Apo A, Apo C and Apo E, which are members of a multigene family that probably evolved from a common ancestral gene. Apolipoproteins function in lipid transport as structural components of lipoprotein particles, cofactors for enzymes and ligands for cell-surface receptors. The family contains more than 800 protein sequences from ~100 species. In each position of the family, multiple alignment shows an average identity of amino acids of ~30%. By taking this apolipoprotein family as a case study, we can demonstrate a procedure for identifying latent profility.

The characteristic spectra of coding regions for the apolipoproteins Apo E of house mouse Mus musculus, Apo A-I of gill-head sea bream Sparus aurata and Apo A-IV of chicken G. gallus are shown in Fig. 2a–c. In these spectra, the first clear maximum is found at the test-period of the 33 base pairs (bp). Thus, the estimation of a pattern size equal to the 33 bp is proposed. The maximum values in the spectra of deviation from the 33-profility [Equation (3)] do not exceed a figure of one ($D_{33} < 1$) that illustrated in Fig. 3a for chicken Apo A-IV. Using the result for the considered coding regions, estimates of patterns for the 33-profility periodicity may be proposed. These estimates are determined by a sample 33-profility matrix of the corresponding analysed region. The reasonableness of each pattern estimate is confirmed by similarity between the spectrum of deviation from homogeneity and its theoretical, or statistical, reconstruction for the analysed coding region. An example of verification of pattern estimation for latent 33-profility in the chicken Apo A-IV coding region is shown in Fig. 4. Comparison of Fig. 4a with d disproves the presence of latent 33-profility in the region, though a peak.
at frequency 0.33 corresponding to the test-period of 3 bp dominates in the Fourier spectrum (Fig. 2d).

To check a robustness of the latent 33-profility pattern estimation found for the coding regions of apolipoproteins the damages in different consecutive segments of 33 bp have been simulated. Every \( k \)th \((k = 5, 4, 3, 2)\) segment of the coding region has been substituted by a fragment (of the same length) from homogeneous sequence with equally probable distribution of the nucleotides. The example of analysis of gene sequence with such a noise is shown in Fig. 5 for Apo A-IV mRNA of chicken \( G. \) gallus. Spectral–statistical analysis reveals a cutoff in pattern recognition when the sequence damages became equal to 25% \((k = 4)\). In this case, there is a dilemma that what pattern size should be chosen—33 or 66 bp. According to the theoretical reconstructions (Fig. 5c and d) of the spectrum of deviation from homogeneity (Fig. 5b), an estimate of 66 bp appears to be more preferable. Such a preference becomes obvious with 50% of damages when the latent profile periodicity of 66 bp arises naturally. In the analysis done, no

Figure 5. Robustness analysis of pattern estimation for the 33-profility in the coding region of \( G. \) gallus Apo A-IV mRNA (GenBank Y16534, region: 37–1137 bp). See Fig. 2c for the original characteristic spectrum of the region. Upper series: spectral-statistical analysis of the region sequence containing 25% of the destroyed 33-segments. Lower series: analysis of the region sequence containing 50% of the destroyed 33-segments. For the corresponding analysed sequences: (a and e) characteristic spectrum \([\text{Equation (2)}]\), (b and f) the \( D_1 \) spectrum \([\text{Equation (4)}]\) of sequence deviation from homogeneity, (c and g) theoretical reconstruction \([\text{Equation (5)}]\) of the \( D_1 \) spectrum under supposition of the presence of 66-profility in the analysed sequence, (d and h) theoretical reconstruction \([\text{Equation (5)}]\) of the \( D_1 \) spectrum under supposition of the presence of 33-profility in the analysed sequence.

Figure 6. Upper series: verification of pattern estimation for latent profile periodicity of 33 bp (33-profility) in the central part of \( M. \) musculus Apo E mRNA (GenBank M12414, region: 275–604 bp). Lower series: verification of pattern estimation for latent 33-profility in the whole Apo E mRNA (GenBank M12414, region: 1–936 bp). For the corresponding analysed sequences: (a and e) the \( D_1 \) spectrum \([\text{Equation (4)}]\) of sequence deviation from homogeneity, (b and f) theoretical reconstruction \([\text{Equation (5)}]\) of the \( D_1 \) spectrum under supposition of the presence of 33-profility in an analysed sequence, (c and g) theoretical reconstruction \([\text{Equation (5)}]\) of the \( D_1 \) spectrum under supposition of the presence of 11-profility in an analysed sequence, (d and h) the \( D_{11} \) spectrum \([\text{Equation (4)}]\) of sequence deviation from the 11-profility.
essential regions in the apolipoprotein gene sequences were revealed which determine the occurrence of latent profility in the genes. The latent 33-profility of the apolipoprotein genes seems to be a consequence of consistent statistical low of their structural organization.

In earlier work, after diagonal dot matrix analysis of internal homology within *M. musculus* Apo E mRNA, it was concluded that gene evolution took place by duplication of an 11-bp ancestral sequence. The supposition was also made that, before the genes of Apo E, Apo A-I and Apo A-IV were formed by duplication of the general 33-bp unit, copies of the ancient 11-‘pattern’ in the tandem 33-repeat underwent essential mutational alterations. In mouse Apo E mRNA fragment (GenBank M12414, 275–604 bp), 3-, 11- and 33-profility were examined in the present work. It is this fragment for which an ancestral 11-bp sequence was derived previously. Using the methods proposed here, only 33-profility has been revealed and confirmed for the fragment. The same conclusion is made for the entire mouse Apo E mRNA sequence. Fig. 6 illustrates the performed analysis. Theoretical reconstructions of the $D_1$ spectra of deviation from homogeneity (Fig. 6a and e) were undertaken with the assumption of the occurrence of latent 33-profility in both the particular fragment and the entire Apo E mRNA (Fig. 6b and f, respectively), follow the corresponding $D_1$ spectra. Theoretical reconstructions (Fig. 6c and g) of the same $D_1$ spectra, undertaken with the assumption of the presence of latent 11-profility in the analysed sequences, are not similar to the corresponding $D_1$ spectra. Moreover, the $D_{11}$ spectra of deviation from 11-profility (Fig. 6d and h) at numerous test-periods exceed the threshold ($D_{11} > 1$), indicating the absence of 11-profility in the analysed sequences. Domination of some nucleotides (more than 50%), revealed earlier in four positions (the 2nd, 3rd, 7th and 9th) of the quasi-pattern of the 11 bp, is probably due to structural particularity of textual 33-repeat from the central part (275–604 bp) of mouse Apo E mRNA. In contrast, 33-profility undoubtedly settles a fixed periodicity of appearance for the nucleotides both in the central part and over the whole analysed Apo E mRNA.

The known secondary structure of the apolipoprotein family PF01442 contains several pairs of α-helices of the 11 and 22 amino acid residues. Such a spatial organization correlates with the 33-bp profile periodicity of the apolipoprotein genes. The generic size of the pattern of latent profile periodicity in the PF01442 family genes possibly influences the formation of the typical secondary structure for the protein family and agrees well with the hypothesis on family origin from a common ancestral gene.

A generic size of ~290 bp for the latent profile periodicity pattern is observed in the genes of fibronectin type III domain-containing protein, which is a protein of an intercellular matrix. It is a glycoprotein that many cells synthesize and secrete into intercellular space. The fibronectin consists of two identical polypeptide chains joined by disulfide bridges near the C-terminuses. Each polypeptide chain contains ~10 domains, each of which holds the specific sites binding the various substances. The proposed spatial structure of the domain contains seven antiparallel β-strands.

Orthologous genes of the fibronectin type III domain family that have been analysed in the present work are listed in Table 1. Table 2, using data from the KEGG database (http://www.genome.jp/kegg/), shows an identity percentage between pairs of the protein family. In characteristic spectra (e.g. see Fig. 7a) of genes from this family, the generic pattern size of latent profile periodicity is found to be 291 bp. Statistical reconstruction (Fig. 7c) corresponding to the pattern size of 291 bp reconstitutes the spectrum of deviation from homogeneity (Fig. 7b), which verifies latent profile periodicity with this period. The pattern size of 291 bp is in good agreement with the size of repeated domains (~90–100 amino acids) in the proteins of the family.

### Table 1. Analysed orthologous genes of the fibronectin type III domain family

| Organism            | KEGG entry | CDS (bp) | Protein                              | Number of domains |
|---------------------|------------|----------|--------------------------------------|-------------------|
| *Homo sapiens*      | hsa:22862  | 3597     | Fibronectin type III domain containing protein 3A, 1198 amino acids | 9                 |
| *Mus musculus*      | mmu:319448 | 3597     | Fibronectin type III domain containing protein 3A, 1198 amino acids | 9                 |
| *Gallus gallus*     | gga:418863 | 3600     | Fibronectin type III domain containing protein 3A, 1199 amino acids | 9                 |
| *Xenopus laevis*    | xla:446899 | 3600     | Fibronectin type III domain containing protein 3A, 1199 amino acids | 9                 |
3.2. Manifestation of levels of organization of genetic information encoding

Regularity of the peaks at 3 bp is observed in the characteristic spectra of the coding regions (Figs 2a–c, 7a and 8). Thus, an encoding organization level caused by the genetic triplet code is manifested. This regularity of a characteristic spectrum is called further as 3-regular heterogeneity, or 3-regularity. As in the Fourier spectra, 3-regular heterogeneity of a characteristic spectrum can be observed in the absence of latent periodicity of 3 bp (see Fig. 2, for example). If 3-regularity exists in the characteristic spectrum of a coding region, then revealing latent profility (different from 3-profility) in the spectrum determines the second level of the encoding organization. For example, Fig. 2a–c shows the characteristic spectra in which, as discussed above (Figs 3 and 4), latent 33-profility is revealed against the background of 3-regularity.

An investigation of different levels in the organization of genetic information encoding has been carried out on a sample of 18 140 human coding regions (CDS) from the KEGG GENES-54.1 database (http://www.genome.jp/kegg/genes.html). Only those coding regions were chosen for which there is experimental evidence of protein translation. Open reading frames, hypothetical proteins, tRNA and rRNA, and genes assumed by their sequences to show similarity to other known genes were excluded from the sample. It appears that 3-regularity in the characteristic spectra is fixed for 93% of the sample (16 786 CDS). Against the background of 3-regular heterogeneity, latent 3-profility is revealed for 62% (11 200 CDS) of the original sample. For the 11% of the sample (1953 CDS), two levels of organization of the encoding are manifested (3-regular heterogeneity and the latent profility different from 3-profility).

Taking into account the inaccuracy of the statistical methods, the following conclusions can be made from the results obtained. Owing to amino acids triplet encoding, the 3-regular heterogeneity of the characteristic spectra is generic for human genes. However, such regularity is not due to latent periodicity of 3 bp. Thus, it is essential to differentiate between the phenomena of regular heterogeneity and latent periodicity in the genetic sequences. In order to verify the existence of latent periodicity of some type, it is necessary to observe a pattern inducing the periodicity.

3.3. Local profile periodicity

In the coding regions, the manifestation of the local two-level organization of genetic information encoding is possible. Thus, for the whole coding region, 3-regular heterogeneity only is observed (see Fig. 8, for example). Regions with local profile periodicity (local profility) can be revealed by scanning the sequence with a small window. For example, regarding local profility in the coding region of the cya gene
from the bacterium Bordetella pertussis (GenBank Y00545, region: 981–6101 bp), in the entire coding region, 3-regular heterogeneity only is revealed (Fig. 8), and there is no latent profility. Latent profile periodicity is observed solely in local areas of the coding regions. Three local areas of latent profile periodicity with a period of 27 bp (Figs 9a–c and 10) can be distinguished in the coding region of the cya gene of bacterium B. pertussis.

Let us note again that the first level of encoding is manifested in the 3-regularity of characteristic spectrum (Fig. 9a–c) and in existence of dominant peak at frequency equal to 0.33 in the Fourier spectrum (see, for example, Fig. 9d). The second level of encoding organization—the 27-profile periodicity—in the local areas of the cya gene is pointed at by dominant peaks of characteristic spectra. Such a profile periodicity is proved by reconstruction of the spectrum of deviation from homogeneity in every local area (see, for example, Fig. 10a and b). In contrast to the characteristic spectra, the second level of encoding organization is not manifested in the Fourier spectra (see, for example, Fig. 9d).

The cya gene encodes bifunctional hemolysin/adenylate cyclase (UniProtKB P15318) in which the areas corresponding to the gene local 27-profility hold the hemolysin-type calcium-binding sites. These sites have a periodic structure of 18 amino acid residues (Fig. 11) corresponding to 54 bp (2 × 27 bp) in the gene.

### 3.4. Conclusions

Methods for identifying a new type of latent periodicity—latent profility in DNA—have been proposed. For DNA coding regions, latent profility enables us to distinguish two levels of organization of genetic information encoding. The first level (the triplet level of encoding), revealed via the Fourier analysis techniques, indicates the phenomenon of regular heterogeneity in the DNA coding regions. The second level of organization in the encoding is due to latent profile periodicity of the DNA sequence. It has been shown that latent profile periodicity in genes of the same family may correlate with the structural features of encoded proteins. Such an effect may manifest in the local areas of coding regions where latent profile periodicity is observed.
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