The Protein Family Classification in Protein Databases via Entropy Measures[*]

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Abstract

In the present work, we review the statistical methods which have been developed in the last few years for classifying into families and clans the distribution of amino acids in protein databases. This is done through functions of random variables, the Entropy Measures of probabilities of the occurrence of the amino acids. An intensive study of the Pfam database is presented with restriction to families which could be represented by rectangular arrays of amino acids with $\boldsymbol{m}$ rows (protein domains) and $\boldsymbol{n}$ columns (amino acids). This work is also an invitation to scientific research groups worldwide to undertake this statistical analysis with arrays of different numbers of rows and columns. We then expect that the mathematical characterization of the distributions of amino acids will be a fundamental insight on the determination of protein structure and evolution.

Resumo

Métodos estatísticos desenvolvidos nos últimos anos para classificar distribuições de aminoácidos em bancos de dados de proteínas em famílias e clãs, são revistos no presente texto. Isto é feito pela introdução de funções de variáveis aleatórias, as medidas de entropia das probabilidades de ocorrência dos aminoácidos. É feito um estudo intensivo do banco de dados Pfam, com restrição a famílias a serem representadas por blocos retangulares de $\boldsymbol{m}$ linhas (domínios de proteína) e $\boldsymbol{n}$ colunas (aminoácidos). A presente contribuição é também um convite a grupos de pesquisa de todo o mundo a empreender análises estatísticas com blocos de diferentes números de linhas e colunas. A expectativa é de que a caracterização matemática das distribuições de aminoácidos seja a motivação fundamental para a previsão da estrutura e evolução das proteínas.

1 Introduction and Motivation

DESIDERATA: "To translate the information contained on protein databases in terms of random variables in order to model a dynamics of folding and unfolding of proteins".

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The information on the planetary motion has been annotated on Astronomical almanacs (Ephemerides) along centuries and can be derived and analyzed by Classical Dynamics and Deterministic Chaos as well as confirmed and corrected by General Relativity. The information which is accumulated on Biological almanacs (Protein databases) on the last decades, is still waiting for its first description to be done by a successful theory of folding and unfolding of proteins. We think that this study should be started from the evolution of protein families and its association into Family clans as a necessary step of their development.

The first fundamental idea to be developed here is that proteins do not evolute independently. We introduce several arguments and we have done many calculations to span the bridge over the facts about protein evolution in order to emphasize the existence of a protein family formation process (PFFP), a successful pattern recognition method and a coarse-grained protein dynamics are driven by optimal control theory [1, 2, 3, 4, 5, 6]. Proteins, or their "intelligent" parts, protein domains, evolute together as a family of protein domains. We then realize that the exclusion of the evolution of an "orphan" protein is guaranteed by the probabilistic approach to be introduced in the present contribution. We think that the elucidation of the nature of intermediate stages of the folding/unfolding dynamics, in order to circumvent the Levinthal "paradox" [7, 8] as well as the determination of initial conditions, should be found from a detailed study of this PFFP process. A byproduct of this approach is the possibility of testing the hypothesis of agglutination of protein families into Clans by rigorous statistical methods like ANOVA [9, 4].

We take many examples of Entropy Measures as the generalized functions of random variables on our modelling. These are the probabilities of occurrence of amino acids in rectangular arrays which are the representatives of families of protein domains. In section 2, the sample space which is adequate for this statistical approach is described in detail. We start from the definition of probabilities of occurrence and the restrictions imposed on the number of feasible families by the structure of this sample space. Section 3 introduces the set of Sharma-Mittal Entropy Measures [10, 4] to be adopted as the functions of probabilities of occurrence in the statistical analysis to be developed. The Mutual Information measures associated with the Sharma-Mittal set, as well as the normalized Jaccard distance measures, are also introduced in this section. In section 4, we present a naive sketch of assessing Protein database, to set the stage for a more efficient approach of the following sections. In section 5, we point out the inconvenience of the Maple computing system for the statistical calculations to be done, by displaying tables with all CPU and real times necessary to perform all necessary calculations. We have also provided in this section, some adaptation of our methods in order to be used with the Perl computing system and we compare the new times of calculation with those by using Maple at the beginning of the section. We also include some comments on the use of Perl, especially on its oddness to calculate with the input data given in arrays and the way of circumventing this. However, we also stress that despite the fact that joint probabilities and their powers could be usually calculated, the output will come randomly distributed and the CPU and real times will increase too much to favour the calculation of the entropy measures. This is due to the intrinsic “Hash” structure [11] of the Perl computing system. We then introduce a modified array structure in order to calculate with Perl.

2 The Sample Space for a Statistical Treatment

We consider a rectangular array of $\boldsymbol{m}$ rows (protein domains) and $\boldsymbol{n}$ columns (amino acids). These arrays are organized from the protein database whose domains are classified into families and clans by the professional expertise of senior biologists [12, 13].

The random variable is the probability of occurrences of amino acids, $p_j(a)$, $j = 1, 2, \dots, n$, $a = A, C, D, \dots, W, Y$ (one-letter code for amino acids), to be given by

$$p_j(a) \equiv \frac{n_j(a)}{m} \tag{1}$$

where $n_j(a)$ is the number of occurrences of the amino acid $\boldsymbol{a}$ in the j-th column. Eq.(1) could be also interpreted as the components of n vectors of 20 components each

$$\begin{pmatrix} p_1(A) \\ \vdots \\ p_1(Y) \end{pmatrix} \begin{pmatrix} p_2(A) \\ \vdots \\ p_2(Y) \end{pmatrix} \cdots \begin{pmatrix} p_n(A) \\ \vdots \\ p_n(Y) \end{pmatrix} \tag{2}$$

and we have

$$\sum_a n_j(a) = m\,, \ \forall j \ \Rightarrow \ \sum_a p_j(a) = 1\,, \ \forall j \tag{3}$$

Analogously, we could also introduce the joint probability of occurrence of a pair of amino acids $\boldsymbol{a}$, $\boldsymbol{b}$ in columns $\boldsymbol{j}$, $\boldsymbol{k}$, respectively $P_{jk}(a, b)$ as the random variables. These are given by

$$P_{jk}(a, b) = \frac{n_{jk}(a, b)}{m} \tag{4}$$

where $n_{jk}(a, b)$ is the number of occurrences of the pair of amino acids $\boldsymbol{a}$, $\boldsymbol{b}$ in columns $\boldsymbol{j}$, $\boldsymbol{k}$, respectively.

A convenient interpretation of these joint probabilities could be the elements of $\frac{n(n-1)}{2}$, square matrices of 20×20 elements, to be written as

$$P_{jk} = \begin{pmatrix} P_{jk}(A, A) & \dots & P_{jk}(A, Y) \\ \vdots & \ddots & \vdots \\ P_{jk}(Y, A) & \dots & P_{jk}(Y, Y) \end{pmatrix} \tag{5}$$

where $j = 1, 2, \dots, (n-1)$; $k = j + 1, \dots, n$.

We can also write,

$$P_{jk}(a,b) = P_{jk}(a|b)p_k(b)\,, \tag{6}$$

This equation can be also taken as another definition of joint probability. $P_{jk}(a|b)$ is the Conditional probability of occurrence of the amino acid $\boldsymbol{a}$ in column $\boldsymbol{j}$ if the amino acid $\boldsymbol{b}$ is already found in column $\boldsymbol{k}$. We then have,

$$\sum_a P_{jk}(a|b) = 1 \tag{7}$$

From eqs.(6), (7), we have:

$$\sum_a P_{jk}(a,b) = p_k(b) \tag{8}$$

and from eq.(8),

$$\sum_a \sum_b P_{jk}(a,b) = 1 \tag{9}$$

which is an identity since $P_{jk}(a,b)$ is also a probability.

Eqs.(8) and (9) can be also derived from

$$\sum_a n_{jk}(a,b) = n_k(b)\,; \quad \sum_a \sum_b n_{jk}(a,b) = m \tag{10}$$

and the definitions, eqs.(1), (4).

We now have from Bayes' law:

$$P_{jk}(a|b)p_k(b) = P_{kj}(b|a)p_j(a) \tag{11}$$

and from eq.(11), the property of symmetry,

$$P_{jk}(a,b) = P_{kj}(b,a) \tag{12}$$

The matrices P_{jk} can be organized in a triangular array:

$$P = \begin{array}{ccccccc} P_{12} & P_{13} & P_{14} & \dots & P_{1\,n-2} & P_{1\,n-1} & P_{1\,n} \\ & P_{23} & P_{24} & \dots & P_{2\,n-2} & P_{2\,n-1} & P_{2\,n} \\ & & P_{34} & \dots & P_{3\,n-2} & P_{3\,n-1} & P_{3\,n} \\ & & & \ddots & \vdots & \vdots & \vdots \\ & & & & P_{n-3\,n-2} & P_{n-3\,n-1} & P_{n-3\,n} \\ & & & & & P_{n-2\,n-1} & P_{n-2\,n} \\ & & & & & & P_{n-1\,n} \end{array} \tag{13}$$

The number of matrices until the P_{jk}-th one is given by

$$C_{jk} = j(n-1) - \frac{j(j-1)}{2} - (n-k) \tag{14}$$

These numbers can be also arranged as a triangular array:

$$C = \begin{array}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & \ldots & (n-3) & (n-2) & (n-1) \\
 & n & (n+1) & (n+2) & (n+3) & (n+4) & \ldots & (2n-5) & (2n-4) & (2n-3) \\
 & & (2n-2) & (2n-1) & 2n & (2n+1) & \ldots & (3n-8) & (3n-7) & (3n-6) \\
 & & & (3n-5) & (3n-4) & (3n-3) & \ldots & (4n-12) & (4n-11) & (4n-10) \\
 & & & & (4n-9) & (4n-8) & \ldots & (5n-17) & (5n-16) & (5n-15) \\
 & & & & & (5n-14) & \ldots & (6n-23) & (6n-22) & (6n-21) \\
 & & & & & & \ddots & \vdots & \vdots & \vdots \\
 & & & & & & & \frac{1}{2}(n^2-n-10) & \frac{1}{2}(n^2-n-8) & \frac{1}{2}(n+2)(n-3) \\
 & & & & & & & & \frac{1}{2}(n^2-n-4) & \frac{1}{2}(n+1)(n-2) \\
 & & & & & & & & & \frac{1}{2}\,n(n-1)
\end{array} \qquad (15)$$

Eq.(13) should be used for the construction of a computational code to perform all necessary calculations. We postpone to other publication the presentation of some interesting results on the analysis of eq.(15).

The calculation of the matrix elements $P_{jk}(a,b)$ from a rectangular array $m \times n$ of amino acids is done by the "concatenation" process which is easily implemented on computational codes. We choose a pair of columns $j = \bar{\jmath}$, $k = \bar{k}$ from the strings, $a = A, C, \ldots, W, Y$, $b = A, C, \ldots, W, Y$ and we look for the occurrence of the combinations $ab = AA, AC, \ldots, AW, AY, CA, CC, \ldots, CW, CY, \ldots, WA, WC, \ldots, WW, WY, \ldots, YA, YC, \ldots, YW, YY$. We then calculate their numbers of occurrences $n_{\bar{\jmath}\bar{k}}(A,A)$, $n_{\bar{\jmath}\bar{k}}(A,C), \ldots, n_{\bar{\jmath}\bar{k}}(Y,W)$, $n_{\bar{\jmath}\bar{k}}(Y,Y)$ and the corresponding probabilities $P_{\bar{\jmath}\bar{k}}(A,A)$, $P_{\bar{\jmath}\bar{k}}(A,C), \ldots,$ $P_{\bar{\jmath}\bar{k}}(Y,W)$, $P_{\bar{\jmath}\bar{k}}(Y,Y)$ from eq.(4). We do the same for the other $\frac{n^2-n-2}{2}$ pairs of columns.

As an example, let us suppose that we have the 3 × 4 array:

A	C	A	D
C	A	D	D
D	A	C	C

Figure 1: An example of a 3 × 4 array with amino acids A, C, D.

Let us choose the pair of columns 1,2. We look for the occurrence of the combinations AA, AC, AD, CA, CC, CD, DA, DC, DD on the pair of columns 1,2 of the array above and we found $n_{12}(A,C) = 1$, $n_{12}(C,A) = 1$, $n_{12}(D,A) = 1$. The others $n_{12}(a,b) = 0$. From eq.(4) we can write for the matrices P_{jk} of eq.(5):

$$\begin{gathered}
P_{12} = \begin{pmatrix} 0 & 1/3 & 0 \\ 1/3 & 0 & 0 \\ 1/3 & 0 & 0 \end{pmatrix}; P_{13} = \begin{pmatrix} 1/3 & 0 & 0 \\ 0 & 0 & 1/3 \\ 0 & 1/3 & 0 \end{pmatrix}; P_{14} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 0 & 1/3 \\ 0 & 1/3 & 0 \end{pmatrix} \\
P_{23} = \begin{pmatrix} 0 & 1/3 & 1/3 \\ 1/3 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}; P_{24} = \begin{pmatrix} 0 & 1/3 & 1/3 \\ 0 & 0 & 1/3 \\ 0 & 0 & 0 \end{pmatrix}; P_{34} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 1/3 & 0 \\ 0 & 0 & 1/3 \end{pmatrix}
\end{gathered} \tag{16}$$

The Maple computing system "recognizes" the matricial structure through its Linear Algebra package. The Perl computing system "operates" only with "strings". The results above are easily obtained in Maple, but in Perl we have to find alternative ways of calculating the joint probabilities. The first method is to calculate the probabilities per row of the 3 × 4 array. We have for the first row:

$$\begin{gathered}
\Pi_{12}^{(1)} = \begin{pmatrix} 0 & 1/3 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{13}^{(1)} = \begin{pmatrix} 1/3 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{14}^{(1)} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \\
\Pi_{23}^{(1)} = \begin{pmatrix} 0 & 0 & 0 \\ 1/3 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{24}^{(1)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 1/3 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{34}^{(1)} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}
\end{gathered} \tag{17}$$

For the second row:

$$\begin{gathered}
\Pi_{12}^{(2)} = \begin{pmatrix} 0 & 0 & 0 \\ 1/3 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{13}^{(2)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 1/3 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{14}^{(2)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 1/3 \\ 0 & 0 & 0 \end{pmatrix} \\
\Pi_{23}^{(2)} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{24}^{(2)} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{34}^{(2)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1/3 \end{pmatrix}
\end{gathered} \tag{18}$$

For the third row:

$$\begin{gathered}
\Pi_{12}^{(3)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1/3 & 0 & 0 \end{pmatrix};\ \Pi_{13}^{(3)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1/3 & 0 \end{pmatrix};\ \Pi_{14}^{(3)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1/3 & 0 \end{pmatrix} \\
\Pi_{23}^{(3)} = \begin{pmatrix} 0 & 1/3 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{24}^{(3)} = \begin{pmatrix} 0 & 1/3 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix};\ \Pi_{34}^{(3)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 1/3 & 0 \\ 0 & 0 & 0 \end{pmatrix}
\end{gathered} \tag{19}$$

We stress that Perl does not recognize these matrix structures. This is just our arrangement in order to make comparison with Maple calculations. However, Perl "knows" how to sum the calculations done per rows to obtain:

$$\Pi_{12}^{(1)} + \Pi_{12}^{(2)} + \Pi_{12}^{(3)} = \begin{pmatrix} 0 & 1/3 & 0 \\ 1/3 & 0 & 0 \\ 1/3 & 0 & 0 \end{pmatrix} \equiv P_{12} \tag{20}$$

$$\Pi_{13}^{(1)} + \Pi_{13}^{(2)} + \Pi_{13}^{(3)} = \begin{pmatrix} 1/3 & 0 & 0 \\ 0 & 0 & 1/3 \\ 0 & 1/3 & 0 \end{pmatrix} \equiv P_{13} \tag{21}$$

$$\Pi_{14}^{(1)} + \Pi_{14}^{(2)} + \Pi_{14}^{(3)} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 0 & 1/3 \\ 0 & 1/3 & 0 \end{pmatrix} \equiv P_{14} \tag{22}$$

$$\Pi_{23}^{(1)} + \Pi_{23}^{(2)} + \Pi_{23}^{(3)} = \begin{pmatrix} 0 & 1/3 & 1/3 \\ 1/3 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \equiv P_{23} \tag{23}$$

$$\Pi_{24}^{(1)} + \Pi_{24}^{(2)} + \Pi_{24}^{(3)} = \begin{pmatrix} 0 & 1/3 & 1/3 \\ 0 & 0 & 1/3 \\ 0 & 0 & 0 \end{pmatrix} \equiv P_{24} \tag{24}$$

$$\Pi_{34}^{(1)} + \Pi_{34}^{(2)} + \Pi_{34}^{(3)} = \begin{pmatrix} 0 & 0 & 1/3 \\ 0 & 1/3 & 0 \\ 0 & 0 & 1/3 \end{pmatrix} \equiv P_{34} \tag{25}$$

We are then able to translate the Perl output in "matrix language". However, this output does not come as an ordered set of joint probabilities, as we have done by arranging the output in the form of the matrices $\Pi_{jk}^{(l)}$, $j = 1, 2, 3$, $k = 2, 3, 4$, $l = 1, 2, 3$. In order to calculate functions of the probabilities as the entropy measures, it will take too much time for the Perl computing system to collect the necessary probability values. This is due to the "Hash" structure of the Perl as compared to the usual "array" structure of the Maple. A new form of arranging the strings to favour an a priori ordination will circumvent this inconvenience of the "hash" structure. Let us then write the following extended string associated to the $m \times n$ rectangular array:

$$\Big(\underbrace{(\overset{1}{A}\overset{2}{C}\overset{3}{D})}_{1}\underbrace{(\overset{1}{C}\overset{2}{A}\overset{3}{A})}_{2}\underbrace{(\overset{1}{A}\overset{2}{D}\overset{3}{C})}_{3}\underbrace{(\overset{1}{D}\overset{2}{D}\overset{3}{C})}_{4}\Big)$$

We then get

$$\begin{aligned}
&P_{12}(A,C) = 1/3, \quad P_{12}(C,A) = 1/3, \quad P_{12}(D,A) = 1/3 \\
&P_{13}(A,A) = 1/3, \quad P_{13}(C,D) = 1/3, \quad P_{13}(D,C) = 1/3 \\
&P_{14}(A,D) = 1/3, \quad P_{14}(C,D) = 1/3, \quad P_{14}(D,C) = 1/3 \\
&P_{23}(C,A) = 1/3, \quad P_{23}(A,D) = 1/3, \quad P_{23}(A,C) = 1/3 \\
&P_{24}(C,D) = 1/3, \quad P_{24}(A,D) = 1/3, \quad P_{24}(A,C) = 1/3 \\
&P_{34}(A,D) = 1/3, \quad P_{34}(D,D) = 1/3, \quad P_{34}(C,C) = 1/3
\end{aligned} \tag{26}$$

All the other joint probabilities $P_{jk}(a,b)$ are equal to zero.

This is a feasible treatment for the "hash" structure. In the example solved above the probabilities will come already ordered in triads. This will save time in the calculations with the Perl system.

It should be stressed that the Perl computing system does not recognize any formal relations of Linear Algebra. However, it does quite well if these relations are converted into products and sums. In order to give an example of working with the Perl system, we take a calculation with the usual Shannon Entropy measure. The calculation of the Entropy for the columns j,k is done by

$$S_{jk} = -\sum_a \sum_b P_{jk}(a,b) \log P_{jk}(a,b) = -\mathrm{Tr}\Big(P_{jk}(\log P_{jk})^{\mathrm{T}}\Big) \tag{27}$$

where P_{jk} is the matrix given in eq.(5) and Tr, T stands for the operations of taking the trace and transposing a matrix, respectively. The matrix $(\log P_{jk})^{\mathrm{T}}$ is given by

$$(\log P_{jk})^{\mathrm{T}} = \begin{pmatrix} \log P_{jk}(A,A) & \dots & \log P_{jk}(Y,A) \\ \vdots & & \vdots \\ \log P_{jk}(A,Y) & \dots & \log P_{jk}(Y,Y) \end{pmatrix}$$

we also include for a useful reference, the matrix

$$p_j(p_k)^{\mathrm{T}} = \begin{pmatrix} p_j(A)p_k(A) & \dots & p_j(A)p_k(Y) \\ \vdots & & \vdots \\ p_j(Y)p_k(A) & \dots & p_j(Y)p_k(Y) \end{pmatrix}$$

Since from eqs.(20)–(25), we have

$$P_{jk} = \sum_{l=1}^{m} \Pi_{jk}^{(l)} \tag{28}$$

we can write:

$$S_{jk} = -\mathrm{Tr}\left(\left(\sum_{l=1}^{m} \Pi_{jk}^{(l)}\right)(\log P_{jk})^{\mathrm{T}}\right) = -\sum_{l=1}^{m} \mathrm{Tr}\Big(\Pi_{jk}^{(l)}(\log P_{jk})^{\mathrm{T}}\Big) \tag{29}$$

There is no problem for calculating in Perl, if we prepare eq.(28) by expressing previously all the products and sums to be done. The real problem with Perl calculations is the arrangement of the output of values $P_{jk}(a,b)$, due to the "hash" structure as have been stressed above.

3 Entropy Measures. The Sharma-Mittal set and the associated Jaccard Entropy measure

We start this section with the definition of the two-parameter Sharma-Mittal entropies [10, 1, 2]

$$(SM)_{jk}(r,s) = -\frac{1}{1-r}\left(1-\left(\sum_a\sum_b \big(P_{jk}(a,b)\big)^s\right)^{\frac{1-r}{1-s}}\right) \tag{30}$$

$$(SM)_j(r,s) = -\frac{1}{1-r}\left(1-\left(\sum_a \big(p_j(a)\big)^s\right)^{\frac{1-r}{1-s}}\right) \tag{31}$$

where $p_j(a)$ and $P_{jk}(a,b)$ are the simple and joint probabilities of occurrence of amino acids as defined on eqs.(1) and (4), respectively. $\boldsymbol{r}$, $\boldsymbol{s}$ are non-dimensional parameters.

We can associate to the entropy measures above their corresponding one parameter forms to be given by the limits:

$$H_{jk}(s) = \lim_{r\to s}(SM)_{jk}(r,s) = -\frac{1}{1-s}\left(1-\sum_a\sum_b \big(P_{jk}(a,b)\big)^s\right) \tag{32}$$

$$H_j(s) = \lim_{r\to s}(SM)_j(r,s) = -\frac{1}{1-s}\left(1-\sum_a \big(p_j(a)\big)^s\right) \tag{33}$$

These are the Havrda-Charvat Entropy Measures and they will be specially emphasized in the present work. Other alternative proposals for the single parameter entropies are given by

The Renyi's Entropy measures:

$$R_{jk}(s) = \lim_{r\to 1}(SM)_{jk}(r,s) = \frac{1}{1-s}\log\left(\sum_a\sum_b \big(P_{jk}(a,b)\big)^s\right) \tag{34}$$

$$R_j(s) = \lim_{r\to 1}(SM)_j(r,s) = \frac{1}{1-s}\log\left(\sum_a \big(p_j(a)\big)^s\right) \tag{35}$$

The Landsberg-Vedral Entropy measures:

$$
\begin{aligned}
L_{jk}(s) = \quad & \lim_{r\to 2-s} (SM)_{jk}(r,s) = \frac{1}{1-s}\left(1 - \Big(\sum_a \sum_b \big(P_{jk}(a,b)\big)^s\Big)^{-1}\right) && (36)\\
& = \frac{H_{jk}(s)}{\sum_a \sum_b \big(P_{jk}(a,b)\big)^s}\\
L_j(s) = \quad & \lim_{r\to 2-s} (SM)_j(r,s) = \frac{1}{1-s}\left(1 - \Big(\sum_a \big(p_j(a)\big)^s\Big)^{-1}\right) && (37)\\
& = \frac{H_j(s)}{\sum_a \big(p_j(a)\big)^s}
\end{aligned}
$$

All these Entropy measures have the free-parameter Shannon entropy in the limit $s \to 1$.

$$
\begin{aligned}
\lim_{s\to 1} H_{jk}(s) = \lim_{s\to 1} R_{jk}(s) = \lim_{s\to 1} L_{jk}(s) = S_{jk} && (38)\\
\lim_{s\to 1} H_j(s) = \lim_{s\to 1} R_j(s) = \lim_{s\to 1} L_j(s) = S_j && (39)
\end{aligned}
$$

where

$$
\begin{aligned}
S_{jk} &= -\sum_a \sum_b P_{jk}(a,b) \log P_{jk}(a,b) && (27)\\
S_j &= -\sum_a p_j(a) \log p_j(a) && (40)
\end{aligned}
$$

are the Shannon entropy measures [6].

We now introduce a convenient version of a Mutual Information measure:

$$
M_{jk}(r,s) = \frac{1}{1-r}\left(1 - \left(\frac{\sum_a \sum_b \big(P_{jk}(a,b)\big)^s}{\sum_a \sum_b \big(p_j(a)p_k(b)\big)^s}\right)^{\frac{1-r}{1-s}}\right) \qquad (41)
$$

We can see that $M_{jk}(r,0) = 0$ and if $\exists\, \bar{\jmath}, \bar{k}$ such that $P_{\bar{\jmath}\bar{k}}(a,b) = p_{\bar{\jmath}}(a)p_{\bar{k}}(b) \Rightarrow M_{\bar{\jmath}\bar{k}}(r,s) = 0$. We also have,

$$
M_{jk}(1,s) = \lim_{r\to 1} M_{jk}(r,s) = -\frac{1}{1-s} \log \left(\frac{\sum_a \sum_b \big(P_{jk}(a,b)\big)^s}{\sum_a \sum_b \big(p_j(a)p_k(b)\big)^s}\right) \qquad (42)
$$

and in the limit $s \to 1$

$$
\begin{aligned}
M_{jk} = \lim_{s\to 1} M_{jk}(1,s) = & \sum_a \sum_b P_{jk}(a,b) \log P_{jk}(a,b)\\
& - \sum_a \sum_b p_j(a)p_k(b) \log \big(p_j(a)p_k(b)\big) && (43)
\end{aligned}
$$

and from the identities:

$$\sum_a p_j(a) = 1\,,\ \forall j\,; \quad \sum_b p_k(b) = 1\,,\ \forall k$$
$$\sum_a P_{jk}(a,b) = p_k(b)\,,\ \forall j\,; \quad \sum_b P_{jk}(a,b) = p_j(a)\,,\ \forall k$$

obtained from eqs.(3), (4), (6), (7), we can also write instead eq.(43):

$$M_{jk} = \sum_a \sum_b P_{jk}(a,b) \log P_{jk}(a,b) - \sum_a \sum_b P_{jk}(a,b) \log \big(p_j(a) p_k(b)\big) \tag{44}$$

It should be stressed that we are not assuming that $P_{jk}(a,b) \equiv p_j(a)p_k(b)$ above. This equality is assumed to be valid only for $j = \bar{\jmath}$, $k = \bar{k}$.

Eq.(43) or (44) can be also written as:

$$M_{jk} = -S_{jk} + S_j + S_k \tag{45}$$

where S_{jk} and S_j, S_k are the Shannon entropy measures for joint and single probabilities, respectively, eqs.(27), (40).

As an additional topic, we emphasize that the Mutual Information measure can be also derived from the Kullback-Leibler divergence [6] which is written as

$$(KL)_{jk}(b) = \sum_a P_{jk}(a|b) \log \left(\frac{P_{jk}(a|b)}{p_j(a)} \right) \tag{46}$$

where $P_{jk}(a|b)$ is the Conditional probability, eq.(8). We then have,

$$(KL)_{jk}(b) = \sum_a \frac{P_{jk}(a,b)}{p_k(b)} \log \left(\frac{P_{jk}(a,b)}{p_j(a)p_k(b)} \right) \tag{47}$$

and the M_{jk} mutual information measure will be given by

$$M_{jk} = \sum_b p_k(b)(KL)_{jk}(b) = \sum_a \sum_b P_{jk}(a,b) \log \left(\frac{P_{jk}(a,b)}{p_j(a)p_k(b)} \right) \tag{48}$$

which is the same as eq.(44), q.e.d.

As the last topic of this section, we now introduce the concept of Information Distance and we then derive the Jaccard Entropy measure as an obvious consequence. Let us write:

$$d_{jk}(r,s) = H_{jk}(r,s) - M_{jk}(r,s) \tag{49}$$

Since we are working with Entropy measures, we have to satisfy the non-negativeness criteria:

$$H_{jk}(r,s) \geq 0\,; \quad M_{jk}(r,s) \geq 0\,; \quad H_{jk}(r,s) - M_{jk}(r,s) \geq 0 \tag{50}$$

This means that by satisfying the inequalities (50), restrictions on the r, s parameters should be discovered and considered for the description of the protein databases by Entropy measures like $H_{jk}(r,s)$.

From inequalities (50), we can write,

$$0 \leq d_{jk}(r,s) = H_{jk}(r,s) - M_{jk}(r,s) \leq H_{jk}(r,s) \tag{51}$$

and

$$0 \leq J_{jk}(r,s) \leq 1 \tag{52}$$

where

$$J_{jk}(r,s) = 1 - \frac{M_{jk}(r,s)}{H_{jk}(r,s)} \tag{53}$$

is the normalized Jaccard Entropy Measure as obtained from the normalized Information Distance. We then give below the results of checking the inequalities (50) for some families of the Pfam database. We shall take the limit $r \to s$ and we work with the corresponding one-parameter Entropy measures: $H_j(s)$, $H_{jk}(s)$, $M_{jk}(s)$, $J_{jk}(s)$. We then have to check:

$$H_{jk}(s) \geq 0\,, \quad M_{jk}(s) \geq 0\,, \quad H_{jk}(s) - M_{jk}(s) \geq 0\,,$$
$$0 \leq J_{jk}(s) = 1 - \frac{M_{jk}(s)}{H_{jk}(s)} \leq 1$$

Table 1: Study of the non-negativeness of $H_{jk}(s)$, $M_{jk}(s)$ and $d_{jk}(s)$ values for the protein family PF06850.

s	$\mathbf{H_{jk}}$(s)	$\mathbf{M_{jk}}$(s)	$\mathbf{d_{jk}}$(s)
0.1	0	0	0
0.3	0	0	0
0.5	0	0	0
0.7	0	0	0
0.9	0	0	0
1.0	0	0	0
1.2	0	718	16
1.5	0	1708	38
1.7	0	2351	61
1.9	0	2898	192
2.0	0	3139	309

The s-values corresponding to negative $M_{jk}(s)$ values do not lead to a useful characterization of the Jaccard Entropy measure according to the inequality on eq.(51) which is violated in this case and these s-values will not be taken into consideration. Other studies of the Entropy values and specially those of the behaviour of the association of entropies, will give additional restrictions on the feasible s-range. The scope of the present work does not allow an intensive

Table 2: Study of the non-negativeness of $H_{jk}(s)$, $M_{jk}(s)$ and $d_{jk}(s)$ values for the protein family PF00135.

$\mathbf{s}$	$\mathbf{H_{jk}(s)}$	$\mathbf{M_{jk}(s)}$	$\mathbf{d_{jk}(s)}$
0.1	0	0	0
0.3	0	0	0
0.5	0	0	0
0.7	0	0	0
0.9	0	0	0
1.0	0	0	0
1.2	0	0	0
1.5	0	0	467
1.7	0	0	14509
1.9	0	0	19026
2.0	0	0	19451

Table 3: Study of the non-negativeness of $H_{jk}(s)$, $M_{jk}(s)$ and $d_{jk}(s)$ values for the protein family PF00005.

$\mathbf{s}$	$\mathbf{H_{jk}(s)}$	$\mathbf{M_{jk}(s)}$	$\mathbf{d_{jk}(s)}$
0.1	0	0	0
0.3	0	0	0
0.5	0	0	0
0.7	0	0	0
0.9	0	0	0
1.0	0	0	0
1.2	0	8	5
1.5	0	33	4741
1.7	0	55	9679
1.9	0	65	12442
2.0	0	69	13203

study of these techniques of entropy association [2] which will then appear on a forthcoming contribution.

The results on the previous three tables will clarify the idea of restriction of the s-values of entropy measures for obtaining a sound classification of families and clans on the Pfam database. We now announce that the non-negativeness of the values of $H_{jk}(s)$, $M_{jk}(s)$ and $d_{jk}(s)$ is actually guaranteed if we restrict to $s \leq 1$ for all 1069 families which are classified into 68 clans and already characterized at section 2. In figures 2, 3, 4, we present the histograms of the Jaccard Entropy measures for some $s \leq 1$ values of the s-parameter.

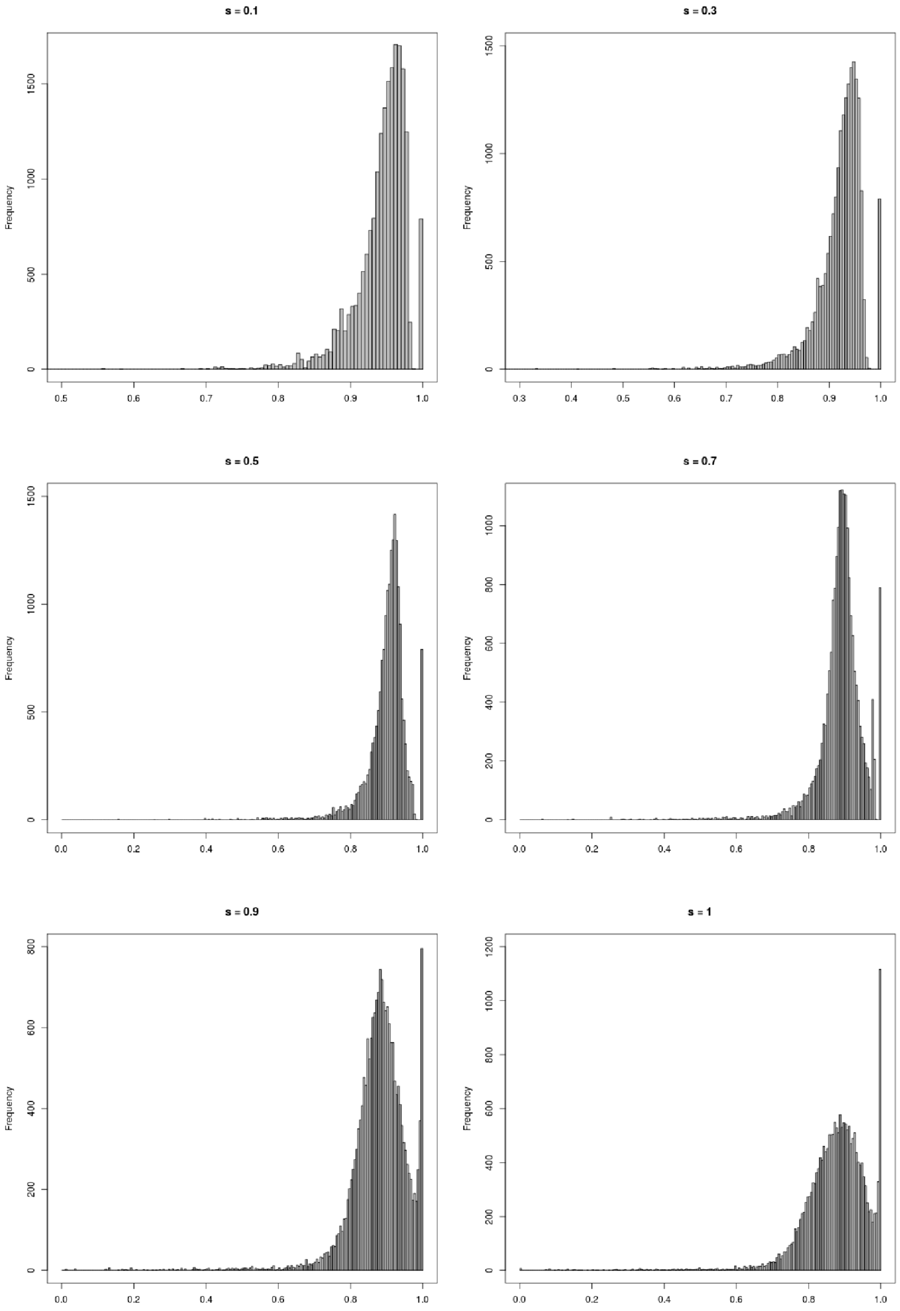


Figure 2: Histograms of Jaccard Entropy for family PF06850.

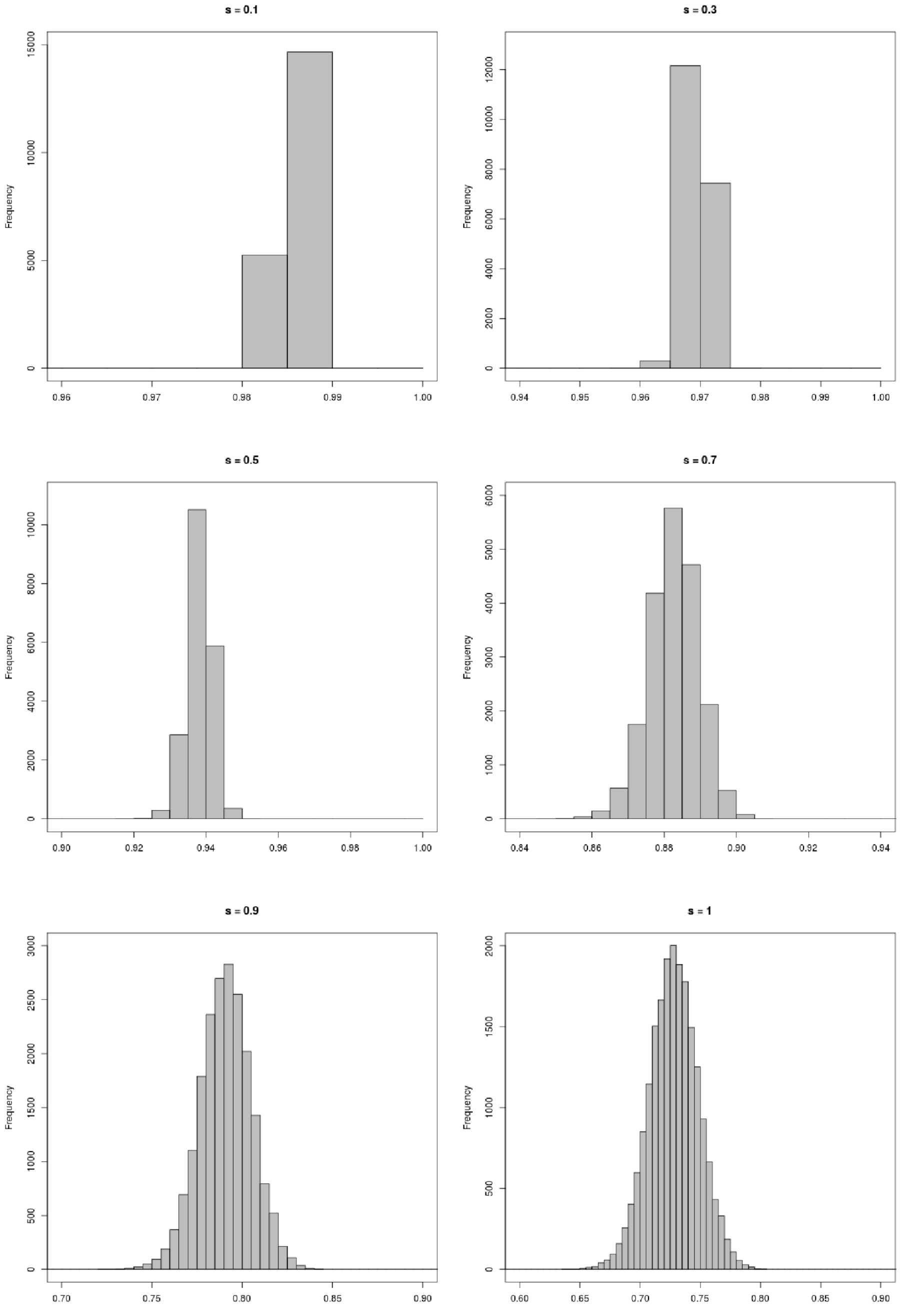


Figure 3: Histograms of Jaccard Entropy for family PF00135.

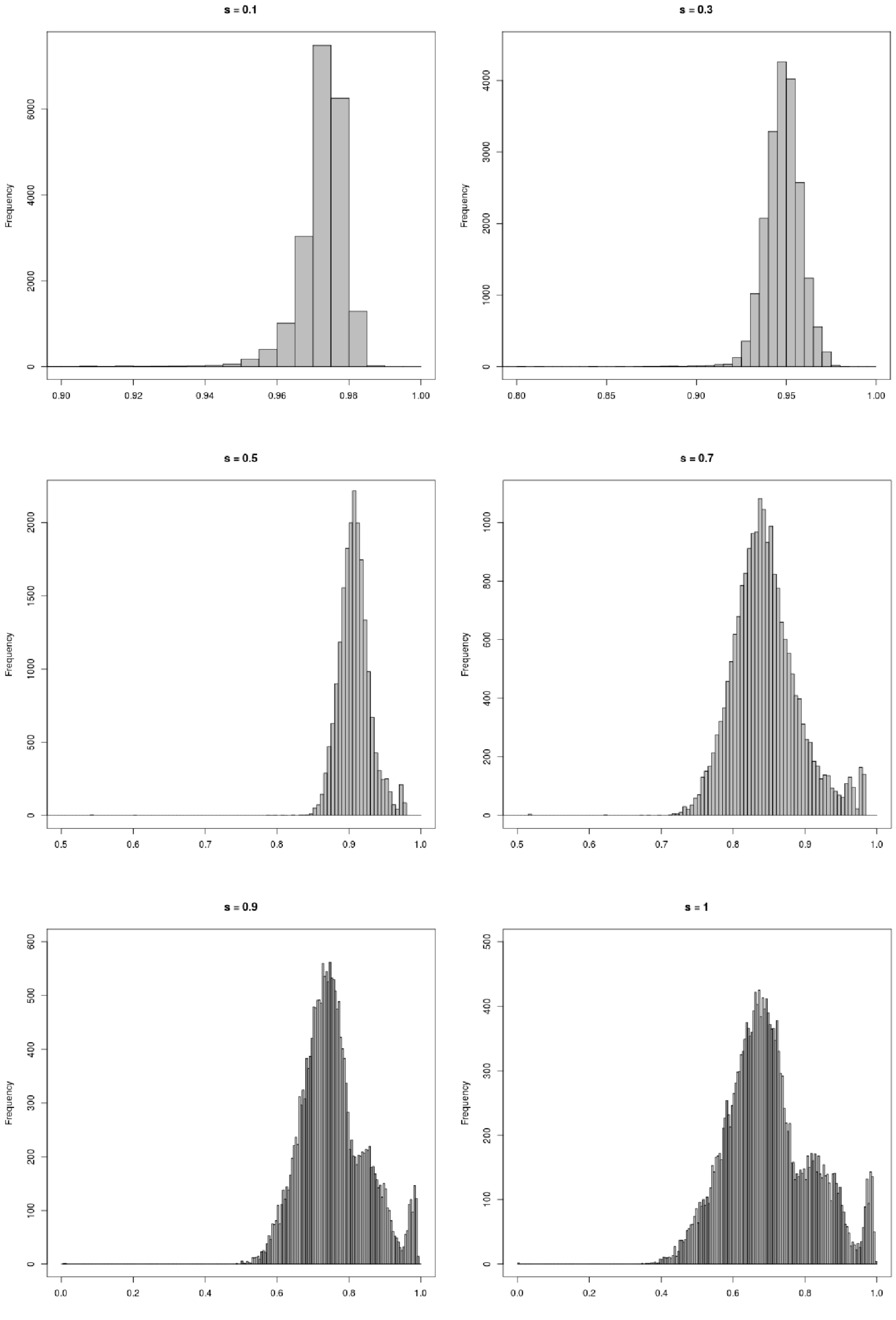


Figure 4: Histograms of Jaccard Entropy for family PF00005.

We also present the curves corresponding to the Average Jaccard Entropy Measure (formula) for 09 families, a well-posed measure, with the restriction $s \leq 1$, which is given by

$$J(s, f) = \frac{2}{n(n-1)} \sum_j \sum_k J_{jk}(s, f)$$

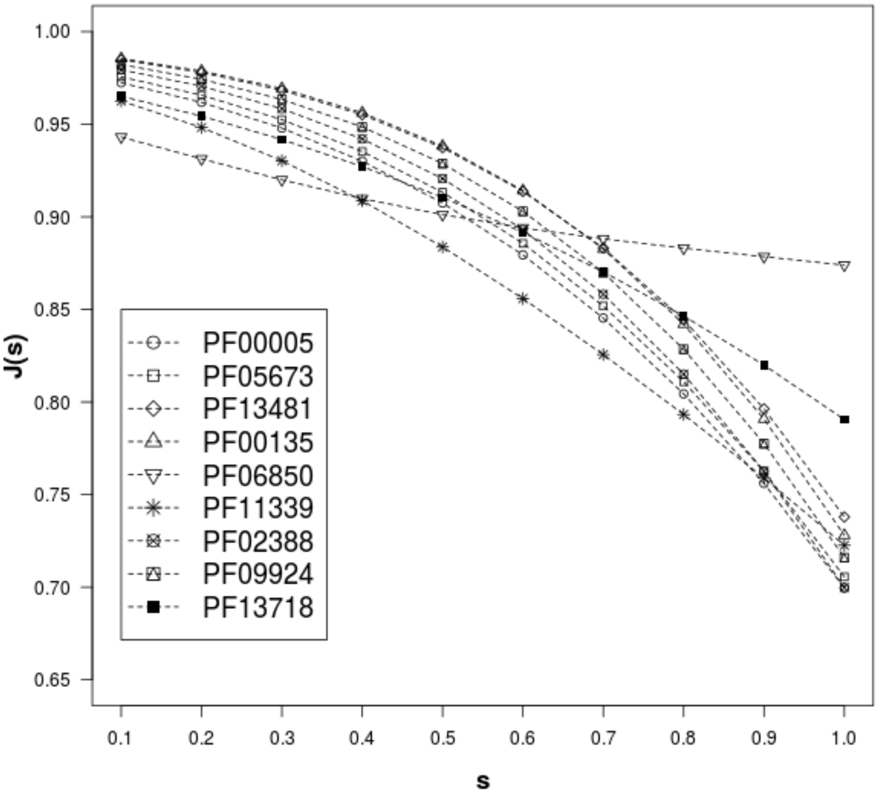


Figure 5: Curves of the Average Jaccard Entropy measures for families PF00005, PF05673, PF13481, PF00135, PF06850, PF11339, PF02388, PF09924, PF13718.

4 A First Assessment of Protein Databases with Entropy Measures

As a motivation for future research to be developed in sections 6, 7, we now introduce the first application of the formulae derived on the previous sections in terms of a naive analysis of averages and standard deviations of Entropy measure distributions. This will be also the first attempt at classifying the distribution of amino acids in a generic protein database. A robust approach to this research topic will be introduced and intensively analyzed on sections 6, 7 with the introduction of ANOVA statistics and the corresponding Hypothesis testing.

We then consider a Clan with $\boldsymbol{F}$ families. The Havrda-Charvat entropy measure associated to a pair of columns on the representative $m \times n$ array of each family with a specified value of the $\boldsymbol{s}$ parameter is given by

$$H_{jk}(s;f) = -\frac{1}{1-s}\left(1 - \sum_a \sum_b \big(P_{jk}(a,b;f)\big)^s\right) \tag{54}$$

We can then define an average of these entropy measures for each family by

$$\langle H(s;f)\rangle = \frac{2}{n(n-1)} \sum_j \sum_k H_{jk}(s;f) \tag{55}$$

We also consider the average value of the averages over the set of F families:

$$\langle H(s)\rangle_F = \frac{1}{F}\sum_{f=1}^{F} \langle H(s;f)\rangle \tag{56}$$

The Standard deviation of the Entropy measures $H_{jk}(s;f)$ with relation to the given average in eq.(55) can be written as:

$$\sigma(s;f) = \left(\frac{1}{\frac{n(n-1)}{2}-1}\sum_j\sum_k \big(H_{jk}(s;f) - \langle H(s;f)\rangle\big)^2\right)^{1/2} \tag{57}$$

and finally, the Standard deviation of the average $\langle H(s;f)\rangle$ with respect to the average $\langle H(s)\rangle_F$:

$$\sigma_F(s) = \left(\frac{1}{F-1}\sum_{f=1}^{F}\big(\langle H(s;f)\rangle - \langle H(s)\rangle_F\big)^2\right)^{1/2} \tag{58}$$

We present in figs.6, 7 below the diagrams corresponding to formulae (55) and (57). We should stress that only Clans with a minimum of five families are considered.

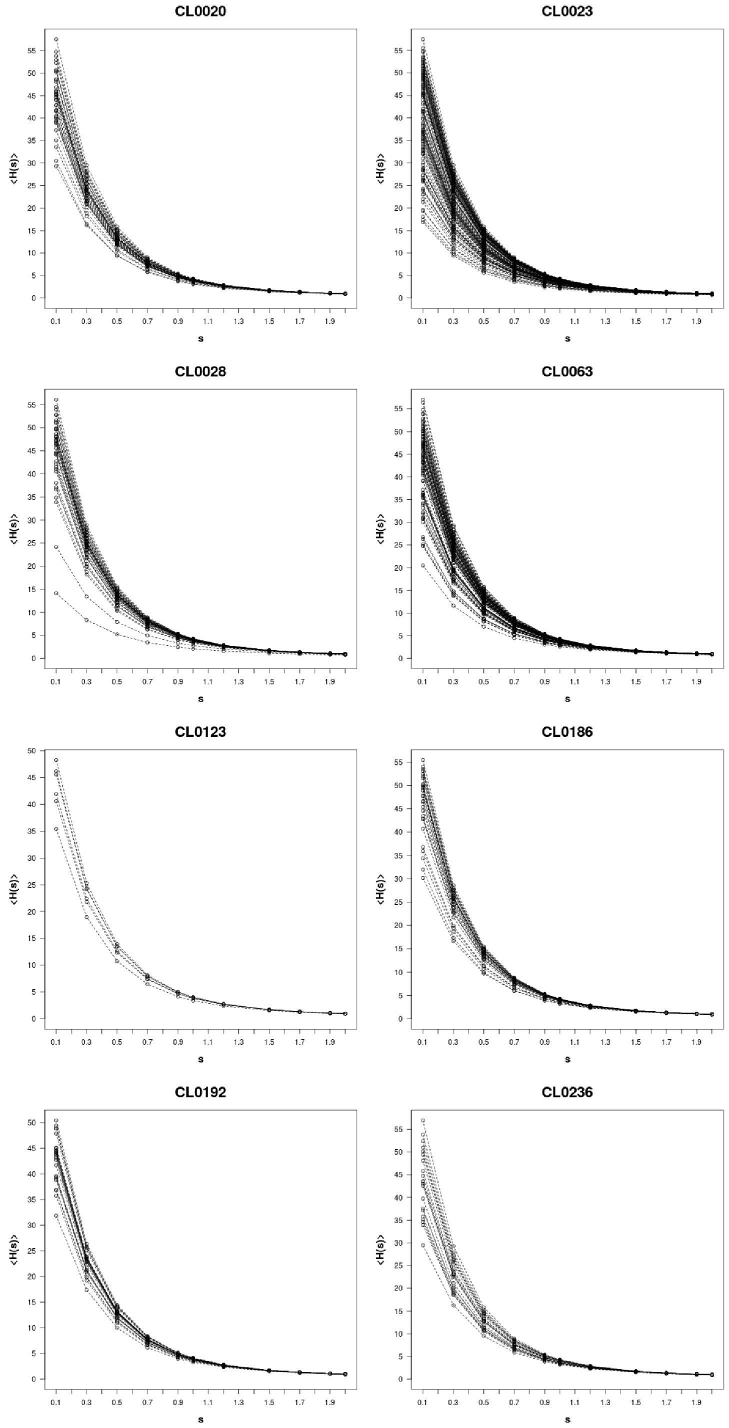
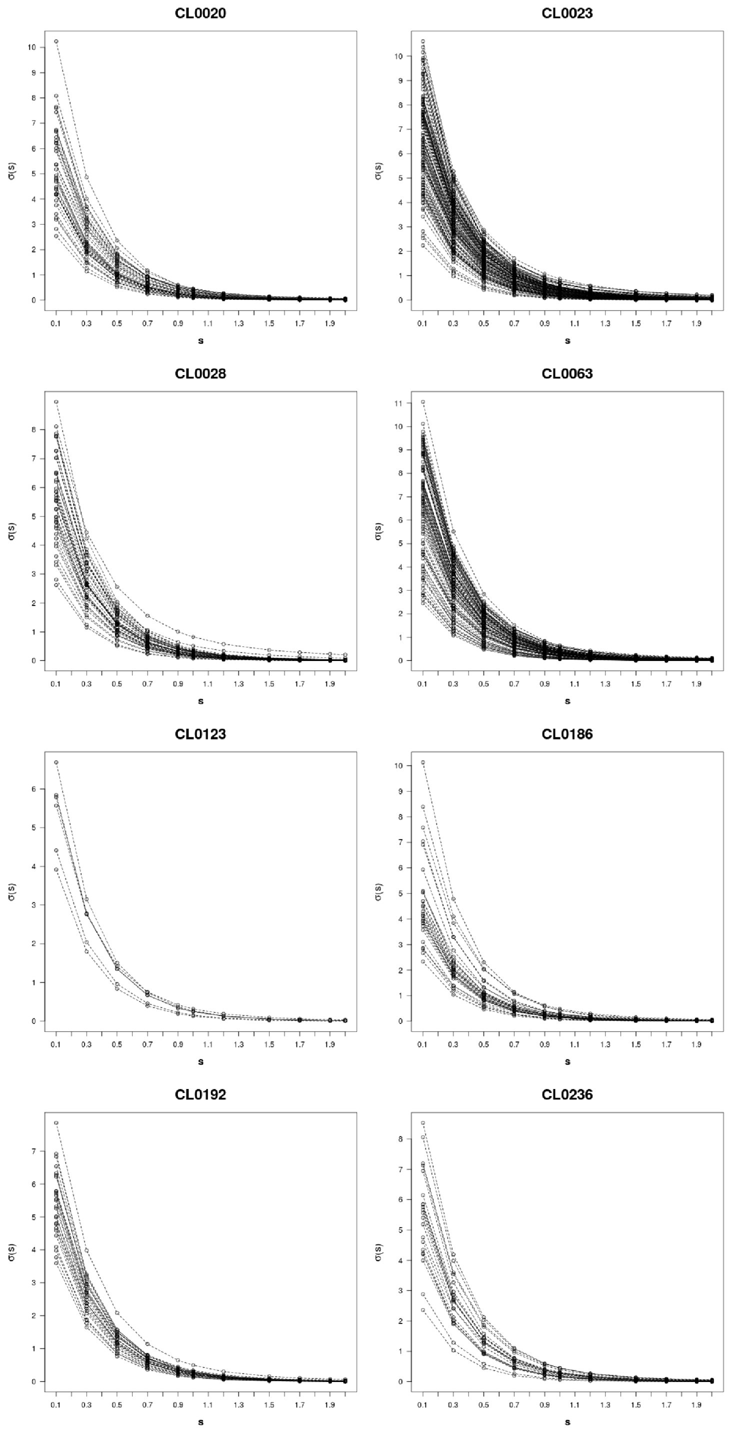


Figure 6: The Average values of the Havrda-Charvat Entropy measures for the families of a selected set of Clans and eleven values of the s-parameter, eq.(55).



CL0020 CL0023 CL0028 CL0063 CL0123 CL0186 CL0192 CL0236

Figure 7: The standard deviation of the Havrda-Charvat Entropy measures with relation to the averages of these entropies for each family and eleven values of the s-parameter, eq.(57).

We now present the values of $\langle H(s)\rangle_F$ and $\sigma_F(s)$ for a selected number of Clans and eleven values of the s-parameter, according to eqs.(56) and (58).

Table 4: The average values and the standard deviation of the Average Havrda-Charvat Entropy measures for eleven values of the s-parameter and a selected set of 8 Clans.

Clans from Pfam 27.0 — Havrda-Charvat Entropies							
Clan number	s	$\langle H(s)\rangle_F$	$\sigma(s)_F$	Clan number	s	$\langle H(s)\rangle_F$	$\sigma(s)_F$
CL0020 (38 families)	0.1	44.212	6.396	CL0123 (06 families)	0.1	43.001	4.667
	0.3	23.375	3.057		0.3	22.851	2.295
	0.5	12.992	1.492		0.5	12.765	1.161
	0.7	7.645	0.746		0.7	7.546	0.605
	0.9	4.784	0.384		0.9	4.741	0.326
	1.0	3.875	0.278		1.0	3.846	0.242
	1.2	2.661	0.150		1.2	2.648	0.137
	1.5	1.680	0.063		1.5	1.676	0.062
	1.7	1.311	0.038		1.7	1.309	0.038
	1.9	1.062	0.023		1.9	1.061	0.024
	2.0	0.967	0.018		2.0	0.966	0.019
CL0023 (119 families)	0.1	39.235	10.175	CL0186 (29 families)	0.1	46.084	6.790
	0.3	20.908	4.984		0.3	24.260	3.224
	0.5	11.733	2.510		0.5	13.417	1.561
	0.7	6.982	1.305		0.7	7.853	0.772
	0.9	4.422	0.704		0.9	4.886	0.392
	1.0	3.604	0.525		1.0	3.949	0.282
	1.2	2.504	0.302		1.2	2.701	0.149
	1.5	1.606	0.144		1.5	1.696	0.060
	1.7	1.263	0.093		1.7	1.320	0.035
	1.9	1.030	0.063		1.9	1.067	0.020
	2.0	0.940	0.053		2.0	0.970	0.016
CL0028 (41 families)	0.1	44.906	7.996	CL0192 (26 families)	0.1	42.862	4.566
	0.3	23.671	3.906		0.3	22.791	2.190
	0.5	13.114	1.961		0.5	12.741	1.072
	0.7	7.692	1.015		0.7	7.538	0.537
	0.9	4.799	0.545		0.9	4.739	0.275
	1.0	3.882	0.406		1.0	3.847	0.199
	1.2	2.660	0.232		1.2	2.650	0.107
	1.5	1.676	0.109		1.5	1.678	0.044
	1.7	1.307	0.070		1.7	1.311	0.026
	1.9	1.058	0.047		1.9	1.062	0.015
	2.0	0.963	0.039		2.0	0.967	0.012
CL0063 (92 families)	0.1	42.312	8.023	CL0236 (21 families)	0.1	43.251	7.469
	0.3	22.454	3.857		0.3	22.905	3.564
	0.5	12.534	1.896		0.5	12.757	1.734
	0.7	7.411	0.956		0.7	7.524	0.863
	0.9	4.660	0.496		0.9	4.719	0.440
	1.0	3.784	0.362		1.0	3.828	0.317
	1.2	2.611	0.198		1.2	2.636	0.169
	1.5	1.658	0.086		1.5	1.669	0.069
	1.7	1.297	0.051		1.7	1.304	0.040
	1.9	1.053	0.032		1.9	1.058	0.024
	2.0	0.960	0.026		2.0	0.964	0.019

In figs.8a and 8b below, we present the graphs corresponding to Table 4. These results just point out a more elaborate formulation of the problem.

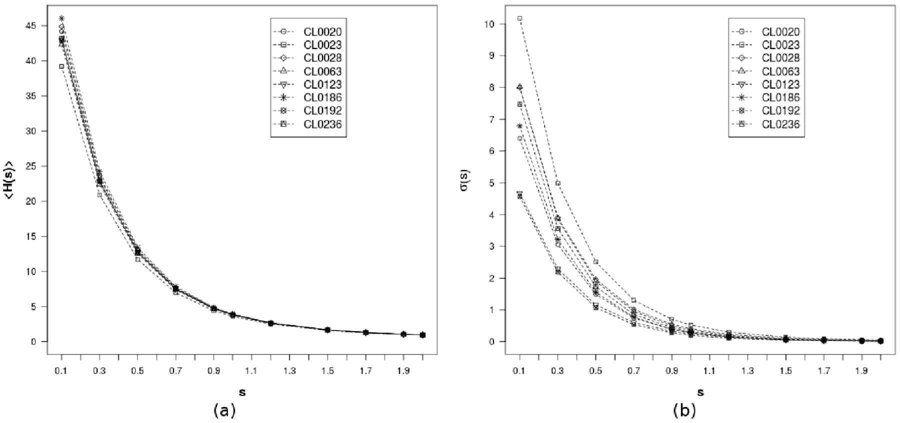


Figure 8: (a) The average values of Havrda-Charvat Entropies for a set of 08 Clans. (b) The Standard Deviation of the averages for Havrda-Charvat Entropies for a set of 08 Clans.

We now proceed to analyze a proposal (naive) for testing the robustness of the Clan concept. We will check if Pseudo-Clans which have the same number of families (a minimum of 05 families) of the corresponding Clans will have essentially different values of $\langle H(s)\rangle_F$ and $\sigma_F(s)$. The families to be associated with a Pseudo-Clan are obtained by sorting on the set of 1069 families and by withdrawal of the families already sorted. In Table 5 below we present the values $\langle H(s)\rangle_F$ and $\sigma_F(s)$ for the Pseudo-Clans obtained by the procedure described above.

The Figures 9a, 9b, do correspond to the comparison of data of Table 4 (Clans) with those of Table 5 (Pseudo-Clans). Clans are in red, Pseudo-Clans in blue.

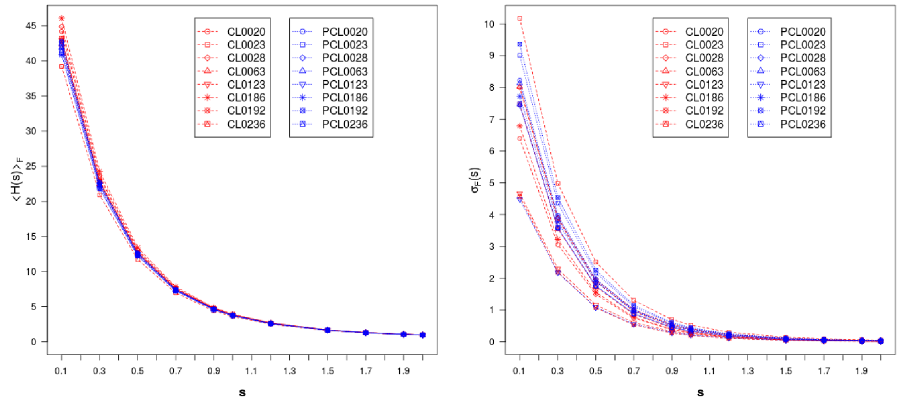


Figure 9: (a) The comparison of Clans and Pseudo-Clans average values. (b) The comparison of Clans and Pseudo-Clans standard deviation values.

Table 5: The average values and the standard deviation of the Average Havrda-Charvat Entropy measures for eleven values of the s-parameter and a selected set of 8 Pseudo-Clans.

Pseudo-Clans / Pfam 27.0 — Havrda-Charvat Entropies							
Pseudo-Clan number	s	$\langle H(s)\rangle_F$	$\sigma(s)_F$	Pseudo-Clan number	s	$\langle H(s)\rangle_F$	$\sigma(s)_F$
PCL0020 (38 families)	0.1	42.381	8.224	PCL0123 (06 families)	0.1	42.042	4.484
	0.3	22.480	3.979		0.3	22.359	2.175
	0.5	12.542	1.972		0.5	12.508	1.082
	0.7	7.410	1.005		0.7	7.409	0.555
	0.9	4.657	0.528		0.9	4.667	0.293
	1.0	3.781	0.389		1.0	3.791	0.216
	1.2	2.607	0.216		1.2	2.618	0.120
	1.5	1.655	0.096		1.5	1.663	0.053
	1.7	1.295	0.059		1.7	1.301	0.032
	1.9	1.051	0.037		1.9	1.056	0.020
	2.0	0.958	0.030		2.0	0.962	0.016
PCL0023 (119 families)	0.1	41.023	9.007	PCL0186 (29 families)	0.1	40.888	7.719
	0.3	21.825	4.360		0.3	21.790	3.768
	0.5	12.219	2.163		0.5	12.220	1.891
	0.7	7.247	1.104		0.7	7.258	0.981
	0.9	4.573	0.582		0.9	4.585	0.529
	1.0	3.714	0.427		1.0	3.730	0.394
	1.2	2.573	0.240		1.2	2.582	0.227
	1.5	1.640	0.109		1.5	1.646	0.109
	1.7	1.286	0.068		1.7	1.290	0.071
	1.9	1.046	0.044		1.9	1.048	0.049
	2.0	0.954	0.037		2.0	0.956	0.041
PCL0028 (41 families)	0.1	42.716	7.435	PCL0192 (26 families)	0.1	42.756	9.361
	0.3	23.658	3.573		0.3	22.666	4.535
	0.5	12.641	1.756		0.5	12.635	2.253
	0.7	7.468	0.886		0.7	7.458	1.151
	0.9	4.692	0.460		0.9	4.681	0.608
	1.0	3.808	0.335		1.0	3.797	0.448
	1.2	2.625	0.183		1.2	2.615	0.250
	1.5	1.664	0.079		1.5	1.657	0.113
	1.7	1.302	0.048		1.7	1.296	0.070
	1.9	1.056	0.030		1.9	1.051	0.046
	2.0	0.962	0.024		2.0	0.958	0.037
PCL0063 (92 families)	0.1	41.870	8.134	PCL0236 (21 families)	0.1	41.551	7.476
	0.3	22.252	3.914		0.3	22.090	3.591
	0.5	12.440	1.929		0.5	12.357	1.763
	0.7	7.366	0.977		0.7	7.322	0.887
	0.9	4.638	0.510		0.9	4.614	0.459
	1.0	3.771	0.375		1.0	3.752	0.334
	1.2	2.603	0.207		1.2	2.595	0.181
	1.5	1.654	0.092		1.5	1.652	0.077
	1.7	1.295	0.057		1.7	1.294	0.046
	1.9	1.052	0.036		1.9	1.051	0.028
	2.0	0.959	0.030		2.0	0.959	0.022

From the figures and tables above we can see that the region $s \leq 1$ leads to a better characterization of the Entropy measures distributions on protein databases.

For completeness, we list some useful formulae obtained from eqs.(55), (56),

(58) which help to predict the profile of the curves above:

$$\langle H(s;f)\rangle = -\frac{1}{1-s}\left(1 - \frac{2}{n(n-1)}\sum_{a,b,j,k} e^{-s|\log P_{jk}(a,b;f)|}\right) \tag{59}$$

$$\langle H(s)\rangle_F = -\frac{1}{1-s}\left(1 - \frac{2}{Fn(n-1)}\sum_{f,a,b,j,k} e^{-s|\log P_{jk}(a,b;f)|}\right) \tag{60}$$

$$\sigma_F(s) = \frac{2(F-1)^{1/2}}{Fn(n-1)}\left(\sum_{f=1}^{F}\left(\sum_{a,b,j,k} e^{-s|\log P_{jk}(a,b;f)|}\right)^2\right)^{1/2} \tag{61}$$

5 The treatment of data with the Maple Computing system and its inadequacy for calculating Joint probabilities of occurrence. Alternative systems.

In this section, we specifically study the performance of the Maple system and an example of alternative computing system, the Perl system, for calculating the simple and joint probabilities of occurrences of amino acids. We also use these two systems for calculating 19 s-power values of these probabilities. We now select the family PF06850 in order to get an idea of the CPU and real times which are necessary for calculating the probabilities and their powers for the set of 1069 families. We start the calculation by adopting the Maple system version 18. There are some comments to be made on the construction of a computational code for calculating joint probabilities. This will be done in detail at the end of CPU and real times for the calculation of the simple and joint probabilities by using the developed code. The table below will repeat the times for calculating $200\times 20 = 4\times 10^3$ and $200\times \frac{200-1}{2}\times 20\times 20 = 7.96\times 10^6$ of simple and joint probability values, respectively, for the PF06850 Pfam family.

Table 6: CPU time and real times for the calculation of the simple and joint probabilities of occurrence associated with the protein family PF06850.

Maple System, version 18	t_{CPU} (sec)	t_R (sec)
Simple probabilities	0.527	0.530
Joint probabilities	5073.049	4650.697

After calculating all values of the probabilities $p_j(a)$ and $P_{jk}(a,b)$, we can proceed to evaluate the powers $\big(p_j(a)\big)^s$ and $\big(P_jk(a,b)\big)^s$ for 19 s-values. Our aim will be to use these values for calculating the Entropy Measures according to eqs.(32), (33). It should be noticed that the values of $p_j(a)$ and $P_{jk}(a,b)$, have to be calculated only once by using a specific computational code already referred on this work. Nevertheless, the use of the code for calculating the joint probabilities associated to 1069 protein families is the hardest of all calculations to be undertaken and it takes too much time. These probabilities once calculated should be grouped in sets of 400 values each corresponding to a pair of columns j, k among the $\frac{n(n-1)}{2}$ feasible ones and the calculating of entropy value associated to this pair of columns j, k. Given a s-value and after calculating the entropy of this first pair $H_{1\,2}$ as a function of the 400 variables $\big(P_{jk}(a,b)\big)^s$, $j \neq 1$, $k \neq 2$ and he/she will proceeds to calculate again all values of $\frac{n(n-1)}{2} \times (20)^2$ in order to extract another value of joint probability for calculating the corresponding entropy value. This seems to be associated to the unknowing of the concepts of a function of several variables, unfortunately. After circumventing these mistakes coming from a bad educational formation, we succeed at keeping all calculated values of the probabilities and we then proceed to the calculation of the powers $\big(p_j(a)\big)^s$, $\big(P_{jk}(a,b)\big)^s$ of these values and the corresponding entropy measures. In tables 7, 8, 9, 10 below, we report all these calculations for 19 values of the s-parameter.

Table 7: CPU and real times for the calculation of 19 s-powers of simple probabilities of occurrence associated with the protein family PF06850.

Maple System, version 18, s-powers of probability $\big(p_j(a)\big)^s$		
s	t_{CPU} (sec)	t_R (sec)
0.1	0.263	0.358
0.2	0.137	0.145
0.3	0.268	0.277
0.4	0.139	0.153
0.5	0.240	0.219
0.6	0.144	0.157
0.7	0.276	0.254
0.8	0.144	0.157
0.9	0.264	0.235
1.0	0.088/0.151	0.095/0.307
2.0	0.153	0.095
3.0	0.128	0.131
4.0	0.148	0.141
5.0	0.096	0.144
6.0	0.148	0.167
7.0	0.148	0.155
8.0	0.181	0.094
9.0	0.104	0.092
10.0	0.104	0.100
Total	3.173	3.164

The last row in tables 7, 8, includes the times necessary for calculating the probabilities of table 6.

Table 8: CPU and real times for the calculation of 19 s-powers of joint probabilities of occurrence associated with the protein family PF06850.

Maple System, version 18, s-powers of probability $\big(P_{jk}(a,b)\big)^s$		
s	t_{CPU} (sec)	t_R (sec)
0.1	390.432	206.646
0.2	382.887	202.282
0.3	401.269	210.791
0.4	416.168	216.993
0.5	427.572	221.541
0.6	430.604	223.227
0.7	421.904	218.484
0.8	434.888	224.267
0.9	431.948	223.023
1.0	442.933/482.612	224.731/259.301
2.0	176.212	147.455
3.0	234.100	174.853
4.0	289.184	181.552
5.0	327.740	178.117
6.0	334.800	194.691
7.0	349.064	195.258
8.0	361.304	195.437
9.0	386.217	197.150
10.0	397.276	197.868
Total	7036.502	3834.366

We are then able to proceed to the calculation of the corresponding Havrda-Charvat entropy measures, $H_j(s)$, $H_{jk}(s)$: The results for 19 s-values are given in tables 9, 10 below.

The total time for calculating all the Havrda-Charvat Entropy measure content of probabilities of occurrence of amino acids on a specific family is given in table 11 below.

From inspections of table 11, we realize that the Total CPU and real times for calculating the Havrda-Charvat entropies $H_j(s)$, of simple probabilities of occurrence $p_j(a)$ are obtained by summing up the total time results from tables 6, 7 and 9. For the Havrda-Charvat entropies $H_{jk}(s)$, we have to sum up the total times at table 6, 8 and 10. We take for granted that the times for calculating the Entropy Measure content of each family will not differ too much and the results 3rd and 5th rows of table 11 are obtained by multiplying by 1069 — the number of families in the sample space.

The results of table 11 suggest the inadequacy of the Maple computing system for analyzing the Entropy measure content of an example of protein database. We have restricted ourselves to operate with usual operating sys-

Table 9: CPU and real times for the calculation of the Entropy measures $H_j(s)$ for the protein family PF06850.

Maple System, version 18, Entropy Measures $H_j(s)$		
s	t_{CPU} (sec)	t_R (sec)
0.1	0.148	0.261
0.2	0.084	0.153
0.3	0.120	0.189
0.4	0.124	0.198
0.5	0.160	0.299
0.6	0.092	0.139
0.7	0.159	0.199
0.8	0.137	0.175
0.9	0.120	0.166
1.0	0.192/0.175	0.339/0.159
2.0	0.144	0.099
3.0	0.147	0.105
4.0	0.084	0.101
5.0	0.136	0.070
6.0	0.096	0.119
7.0	0.115	0.078
8.0	0.120	0.109
9.0	0.133	0.080
10.0	0.132	0.133
Total	2.443	3.012

tems, Linux or OSX, on laptops. We have also worked with the alternative Perl computing system. The Maple computing system has an "array" structure which is very effective for doing calculations which require a knowledge of mathematical methods. On the contrary, the alternative Perl computing system has a "hash" structure as was emphasized in the 2nd section and it operates very well elementary operations with very large numbers. It is essential the comparison of a senior erudite which is largely conversant with a large amount of mathematical methods versus a "genius" brought to fame by media, who is able only to multiply in a very fast way, numbers of many digits.

In order to specify the probabilities of computational configurations with the usual desktops and laptops, we list below some of them which have been used in the present work. The computing systems were the Maple (M) and Perl (P), the operating systems, the Linux (L) and Mac OSX (O) and the structures: The Array I (A_I), Array II (A_{II}) and Hash (H) (page 8, section 2). The available computational configurations to undertake the task of assessment of protein databases with Entropy measures could be listed as:

1. MLA_I — Maple, Linux, Array I

2. POH — Perl, OSX, Hash
3. PLA_{II} — Perl, Linux, Array II
4. POA_{II} — Perl, OSX, Array II

Table 10: CPU and real times for the calculation of the Entropy measures $H_{jk}(s)$ for the protein family PF06850.

Maple System, version 18, Entropy Measures $H_{jk}(s)$		
s	t_{CPU} (sec)	t_R (sec)
0.1	156.332	133.242
0.2	160.797	136.706
0.3	169.024	140.960
0.4	176.824	147.853
0.5	184.120	150.163
0.6	190.304	154.058
0.7	196.633	157.750
0.8	205.940	164.101
0.9	215.559	169.549
1.0	253.648/124.501	204.634/148.993
2.0	141.148	184.030
3.0	158.536	167.173
4.0	173.136	181.282
5.0	197.680	238.723
6.0	215.000	111.476
7.0	145.257	115.221
8.0	156.848	122.957
9.0	157.300	126.233
10.0	166.399	135.080
Total	3420.485	2941.791

Table 11: Total CPU and real times for calculating the Entropy measure content of a family PF06850 and approximations for Grand Total of all sample space.

Maple System, version 18	Entropy Measures $H_j(s)$ — 19 s-values	Entropy Measures $H_{jk}(s)$ — 19 s-values
Total CPU time (family PF06850)	0.527+3.173+2.443 =6.143 sec	5,073.049+7,036.502+ 3,420.485=15,530.036 sec
Grand Total CPU time (1069 families)	6,566.867 sec =1.824 hs	16,601,608.484 sec =192.148 days
Total Real time (family PF06850)	0.530+3.164+3.012 =6.706 sec	4,650.697+3,834.366+ 2,941.791=11,426.854 sec
Grand Total Real time (1069 families)	7,168.714 sec =1.991 hs	12,215,306.926 sec =141.381 days

The following table will display a comparison of the CPU and real times for the calculation of 19 s-values of the joint probabilities $\big(P_{jk}(a,b)^s\big)$ for the protein family PF06850 by the four configurations nominated above. It should be stressed that we are here comparing the times for calculating the s-power with the values of the probabilities themselves previously calculated and kept on a file.

We can check that the times on table 12 seem to be generically ordered as

$$t_{MLA_I} > t_{POA_{II}} > t_{PLA_{II}} > t_{POH} \tag{62}$$

From this ordering of computing times, we are then able to consider that the inconvenience of using the "hash" structure which has been emphasized on section 2, was not circumvented by working with a modified array structure (A_{II} instead of H), at least for the Mac Pro machine used in these calculations. We do not also know if this machine has been even used with an "overload" of programs from the assumed part-time job of the experimenter (maybe 99.99% time job!). Anyhow, the usual Hash structure of Perl computing system has delayed the calculation of the Entropy Measures and even with the help of the modified A_{II} structure, it does not succeed at computing with this structure if operated on a OSX computing system.

On the other hand, the configuration MLA_I could be chosen for parallelizing the respective adopted code in a work to be done with supercomputer facilities. If we try to avoid this kind of computational facility, in the belief that the problem of classifying the distribution of amino acids of a protein database in terms of Entropy Measures could be treated with less powerful but very objective "weapons", we should try to look for very fast laptop machines instead, by working with a Linux operating system, a Perl computing system and a modified array structure. This means that it would be worthwhile the continuation of the present work with the PLA_{II} configuration. This is now in progress and will be published elsewhere.

We summarize the conclusions commented above on tables 13–16 below for the calculation of CPU and Real times of 19 s-powers of joint probabilities $\big(P_{jk}(a,b)\big)^s$ and the corresponding values of Havrda-Charvat entropy measures. The necessary times for calculating the joint probabilities themselves has not been taken into consideration. It would be very useful to make a comparison of the results of table 10 with those on tables 14, 16, and table 12 with tables 13, 15 as well.

As a last remark of this section, we shall take into consideration, the restrictions of $s \leq 1$ for working with Jaccard Entropy measures and we calculate the total CPU and real times for the set of s-values: $s = 0.1$, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0. The results are presented in table 17 below for the PLA_{II} configuration and the calculation of the Havrda-Charvat entropies.

Table 12: A comparison of calculation times (CPU and real) for 19 s-powers of joint probabilities only of PF06850 protein family, using the four configurations MLA_I, POA_{II}, PLA_{II}, POH.

$\mathbf{s}$	$\mathbf{t_{CPU}}$ (sec)				$\mathbf{t_R}$ (sec)			
	MLA_I	POA_{II}	PLA_{II}	POH	MLA_I	POA_{II}	PLA_{II}	POH
0.1	390.432	33.478	**41.633**	24.849	206.646	88.527	83.139	26.862
0.2	382.887	31.711	26.483	25.093	202.282	80.624	53.384	26.904
0.3	401.269	31.726	25.286	24.751	210.791	80.519	50.689	27.305
0.4	416.168	31.448	26.138	26.345	216.993	79.032	51.409	27.687
0.5	427.572	32.860	**25.822**	26.726	221.541	93.048	51.334	27.528
0.6	430.604	33.444	27.013	25.021	223.227	102.317	52.889	25.408
0.7	421.904	31.053	25.814	25.011	218.484	79.255	51.466	26.414
0.8	434.888	31.526	26.725	25.183	224.267	80.469	53.388	25.668
0.9	431.948	31.482	26.895	25.409	223.023	80.002	53.579	25.536
1.0	442.933	32.056	25.990	25.096	224.731	80.917	51.687	25.640
2.0	176.212	32.638	27.089	26.012	147.454	80.751	54.384	26.960
3.0	234.100	31.892	25.766	24.498	174.853	85.853	51.843	24.717
4.0	284.184	31.662	26.515	25.251	181.552	91.837	52.636	25.718
5.0	327.740	32.295	27.516	24.925	178.117	87.486	54.908	25.814
6.0	334.800	32.674	28.126	25.440	194.691	86.569	54.611	25.847
7.0	349.064	31.674	23.908	26.389	195.258	86.215	49.262	27.745
8.0	361.304	33.105	26.020	25.106	195.437	116.601	51.889	26.735
9.0	386.217	31.881	26.208	24.783	197.150	81.372	53.114	25.155
10.0	397.276	32.269	26.125	24.979	197.868	87.963	52.541	26.504
Total	7036.502	611.374	515.072	480.867	3834.365	1649.357	1028.655	500.147
Total (1069) families	7,522,020.640 =87.067 days	653,588.806 =7.565 days	550,611.968 =6.373 days	514,046.813 =5.950 days	4,098,936.190 =47.441 days	1,763,162.630 =20.407 days	1,099,632.200 =12.727 days	534,157.143 =6.188 days

Table 13: Calculation of CPU and Real times of 19 s-powers of joint probabilities $\left(P_{jk}(a,b)\right)^s$ measures for 06 families from 03 Clans with the POA_{II} configuration.

s	CL0028				CL0023				CL0257			
	PF06850		PF00135		PF00005		PF13481		PF02388		PF09924	
	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)
0.1	33.478	88.527	46.747	130.014	41.475	169.679	44.187	171.636	44.716	242.376	46.177	288.259
0.2	31.711	80.624	42.157	90.687	36.893	78.893	38.567	88.754	37.088	88.091	40.709	148.371
0.3	31.726	80.519	39.957	82.240	36.929	97.270	38.800	81.613	37.350	88.664	38.986	119.781
0.4	31.448	79.032	41.737	87.934	36.252	80.428	38.500	78.757	35.592	80.337	36.773	87.217
0.5	32.860	93.048	41.130	89.997	38.203	93.595	37.618	80.179	35.117	78.476	35.534	82.528
0.6	33.944	102.317	41.417	120.420	37.143	81.289	38.387	81.667	45.900	501.222	35.830	83.439
0.7	31.053	79.255	40.422	78.531	36.386	84.421	43.216	562.659	43.452	259.861	35.261	72.605
0.8	31.526	80.469	41.556	118.519	36.955	79.543	41.862	148.028	35.047	78.469	35.718	85.142
0.9	31.482	80.002	41.386	81.747	36.811	81.025	35.518	78.547	35.540	74.570	40.534	204.673
1.0	32.056	80.917	40.724	80.958	37.234	80.587	36.610	87.848	36.353	78.767	39.095	125.292
2.0	32.638	80.751	40.701	79.667	38.452	79.336	36.916	111.199	36.658	81.415	40.415	182.552
3.0	31.892	85.853	40.822	79.293	38.223	80.688	37.356	84.312	36.658	81.415	39.774	157.090
4.0	31.662	91.837	41.208	79.825	37.936	98.905	37.000	86.906	36.012	77.741	38.794	140.857
5.0	32.295	87.486	41.059	82.191	38.293	83.289	36.245	80.873	35.308	77.225	39.927	147.368
6.0	32.674	86.569	41.215	86.311	37.601	82.375	36.395	97.307	35.748	76.573	39.327	154.829
7.0	31.674	86.215	41.290	88.714	38.341	80.991	36.724	95.148	36.194	75.341	39.826	153.204
8.0	33.105	116.601	40.984	83.157	37.756	81.073	40.524	105.466	36.716	82.921	41.056	175.943
9.0	31.881	81.372	41.469	113.561	38.748	82.499	37.874	94.981	40.341	121.311	39.847	144.595
10.0	32.269	87.963	41.466	89.366	37.807	81.043	37.134	88.005	40.053	136.243	40.333	171.395
Total	611.374	1649.357	787.447	1743.132	717.438	1676.929	729.433	2303.885	719.843	2381.018	743.916	2725.140

Table 14: Calculation of CPU and Real times of Havrda-Charvat Entropy measures for 06 families from 03 Clans with the POA_{II} configuration.

s	CL0028				CL0023				CL0257			
	PF06850		PF00135		PF00005		PF13481		PF02388		PF09924	
	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)
0.1	19.451	26.196	22.620	56.287	25.411	121.508	18.968	32.706	23.380	80.826	22.502	77.826
0.2	19.245	24.901	22.851	69.992	23.362	65.508	18.810	26.835	23.366	87.098	23.330	60.684
0.3	19.582	26.001	23.963	60.960	22.598	72.363	18.602	26.028	20.012	43.734	21.929	48.947
0.4	20.194	31.418	22.211	54.562	23.448	63.369	19.176	30.482	21.218	67.817	22.182	45.480
0.5	20.162	31.653	23.163	67.391	22.153	55.173	19.281	34.495	21.037	55.237	23.200	62.384
0.6	20.941	34.979	23.961	62.158	22.342	57.081	20.794	44.558	21.087	54.900	22.477	62.421
0.7	20.805	34.057	23.679	82.669	19.587	35.750	19.982	41.314	20.375	32.699	22.398	66.438
0.8	20.900	34.146	22.787	60.924	19.081	34.116	18.890	28.054	20.167	32.685	23.056	61.376
0.9	20.909	34.568	22.808	54.890	19.030	33.258	18.894	29.712	19.422	26.934	23.543	65.099
1.0	21.353	35.024	22.860	51.308	19.789	32.218	19.869	37.922	21.076	35.774	22.528	52.209
2.0	20.505	32.920	21.085	46.921	19.672	33.778	19.083	62.081	22.530	82.336	21.783	51.656
3.0	23.923	58.898	22.020	47.298	18.788	31.926	19.097	35.399	24.210	83.371	21.636	69.905
4.0	24.622	68.692	21.954	50.909	18.556	26.512	19.208	32.014	24.300	112.613	21.458	49.931
5.0	24.221	60.107	22.131	58.975	19.424	33.185	18.231	25.898	24.199	95.807	22.011	55.109
6.0	24.475	64.843	22.911	72.004	20.582	38.006	18.330	25.959	22.741	61.516	21.857	67.976
7.0	24.593	70.336	22.779	51.309	20.564	38.390	19.583	30.719	23.222	88.997	23.018	85.054
8.0	25.613	83.423	20.058	34.861	20.460	35.589	19.977	37.130	23.825	110.933	24.474	90.322
9.0	24.139	73.873	21.418	44.709	19.274	32.129	18.871	29.089	24.207	106.471	23.349	74.724
10.0	25.785	101.370	22.183	46.878	23.625	87.442	22.652	64.895	23.779	86.225	21.802	57.444
Total	421.418	927.405	427.442	1075.005	397.746	927.301	368.298	675.290	424.153	1345.973	428.533	1204.985

Table 15: Calculation of CPU and Real times of 19 s-powers of joint probabilities $\left(P_{jk}(a,b)\right)^s$ measures for 06 families from 03 Clans with the PLA_{II} configuration.

s	CL0028				CL0023				CL0257			
	PF06850		PF00135		PF00005		PF13481		PF02388		PF09924	
	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)
0.1	41.633	83.139	43.135	83.901	44.003	84.655	26.613	52.365	27.452	53.350	43.132	83.249
0.2	26.483	53.384	26.373	50.442	26.610	52.904	26.599	51.822	43.199	83.497	25.762	50.203
0.3	25.286	50.689	26.644	50.992	29.965	53.250	24.946	48.846	25.498	50.303	25.904	50.737
0.4	26.138	51.409	25.255	48.576	26.696	52.482	27.769	53.837	25.753	51.013	25.684	50.371
0.5	25.822	51.837	26.041	50.492	26.648	52.171	25.026	48.927	25.727	49.887	25.513	48.793
0.6	27.013	52.889	25.778	50.324	24.912	49.340	26.062	51.312	26.066	51.417	25.435	49.686
0.7	25.814	51.466	25.496	49.954	25.284	50.268	23.698	48.134	25.723	50.760	25.822	51.122
0.8	26.725	53.388	26.254	50.865	25.456	50.870	25.816	51.196	26.883	52.511	29.837	57.367
0.9	26.895	53.579	23.740	47.296	26.237	51.725	28.441	54.743	25.237	50.532	27.951	54.289
1.0	25.990	51.687	27.225	54.384	26.014	51.969	27.148	52.701	23.672	48.547	26.314	51.932
2.0	27.089	54.384	26.237	50.335	27.756	54.761	26.424	52.503	24.811	49.859	25.846	51.125
3.0	25.766	51.843	27.342	52.508	25.135	50.954	27.753	53.650	25.072	49.142	25.727	50.990
4.0	26.515	52.636	25.716	50.531	25.106	50.449	24.871	50.279	25.674	51.536	26.897	52.227
5.0	27.516	54.908	26.002	50.390	24.666	49.463	23.973	47.554	25.675	51.032	27.810	53.820
6.0	28.126	54.611	27.441	53.032	26.014	52.209	25.676	50.426	26.235	51.375	26.180	51.346
7.0	23.908	49.262	26.812	51.556	24.696	49.783	25.519	50.741	25.863	50.995	25.593	50.611
8.0	26.020	51.889	25.431	49.135	26.757	52.518	26.369	49.668	26.401	52.682	25.084	50.596
9.0	26.208	53.114	25.856	50.090	25.803	51.253	24.628	47.880	25.379	51.014	27.049	52.891
10.0	26.125	52.541	24.963	47.402	24.369	48.065	42.270	83.281	24.878	49.926	24.563	48.616
Total	515.072	1028.655	511.741	992.205	509.127	1009.089	509.601	999.865	505.198	999.378	516.103	1009.971

Table 16: Calculation of CPU and Real times of Havrda-Charvat Entropy measures for 06 families from 03 Clans with the PLA_{II} configuration.

s	CL0028				CL0023				CL0257			
	PF06850		PF00135		PF00005		PF13481		PF02388		PF09924	
	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)
0.1	21.219	26.895	18.698	23.442	19.383	24.675	21.351	26.966	19.059	24.560	21.451	26.829
0.2	22.604	28.014	21.109	26.536	20.336	25.665	19.555	24.562	19.370	24.681	22.504	27.855
0.3	19.056	24.130	20.692	25.663	21.934	27.466	21.084	26.236	19.317	24.934	19.681	24.732
0.4	21.552	27.442	19.981	25.021	18.794	24.142	21.065	26.485	20.878	26.291	21.947	26.979
0.5	31.952	88.406	21.161	26.374	19.123	24.309	22.534	27.851	19.729	25.011	21.888	27.168
0.6	20.195	25.362	21.006	26.371	21.426	30.303	20.640	26.050	19.424	24.279	20.750	26.175
0.7	19.168	23.924	20.989	26.482	21.440	27.129	19.370	24.287	19.274	24.779	21.545	26.830
0.8	21.982	27.362	19.760	24.681	20.662	25.948	21.324	26.648	21.685	26.964	21.644	27.160
0.9	21.356	27.235	21.251	26.550	19.518	24.880	21.276	26.736	21.283	26.981	19.217	23.910
1.0	20.206	25.608	20.914	26.173	20.726	25.877	21.430	26.625	20.102	25.198	19.810	25.348
2.0	19.435	24.882	20.660	25.675	20.798	26.326	20.301	25.481	19.588	24.837	20.446	25.755
3.0	20.549	25.646	19.988	25.479	20.629	25.516	19.914	25.230	20.438	25.648	19.393	24.815
4.0	19.528	24.693	20.649	25.610	19.428	24.637	20.505	26.001	20.868	26.009	20.060	25.643
5.0	19.698	24.824	21.076	26.468	19.865	24.753	19.120	24.267	19.466	24.423	21.760	27.244
6.0	20.809	26.319	20.352	25.914	19.507	24.362	20.110	25.587	20.708	25.961	21.240	26.665
7.0	20.287	25.951	21.073	26.459	19.482	24.861	18.272	23.535	19.015	24.460	20.646	25.964
8.0	21.427	26.885	19.494	24.421	20.107	25.228	20.645	26.095	21.039	26.222	20.014	25.155
9.0	21.623	27.335	21.554	26.517	19.239	24.529	20.629	25.929	21.035	26.450	21.086	26.526
10.0	20.815	26.379	21.127	26.630	19.927	25.340	19.781	25.063	21.438	27.019	17.286	22.390
Total	403.461	557.294	391.524	490.466	382.324	485.946	388.906	489.634	383.716	484.707	392.368	493.143

Table 17: Calculation of CPU and Real times of Havrda-Charvat Entropy measures for 06 families from 03 Clans with parameters $0 < s \leq 1$ and the PLA_{II} configuration.

s	CL0028				CL0023				CL0257			
	PF06850		PF00135		PF00005		PF13481		PF02388		PF09924	
	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)	t_{CPU} (sec)	t_R (sec)
0.1	21.219	26.895	18.698	23.442	19.383	24.675	21.351	26.966	19.059	24.560	21.451	26.829
0.2	22.604	28.014	21.109	26.536	20.336	25.665	19.555	24.562	19.370	24.681	22.504	27.855
0.3	19.056	24.130	20.692	25.663	21.934	27.466	21.084	26.236	19.317	24.934	19.681	24.732
0.4	21.552	27.442	19.981	25.021	18.794	24.142	21.065	26.485	20.878	26.291	21.947	26.979
0.5	31.952	88.406	21.161	26.374	19.123	24.309	22.534	27.851	19.729	25.011	21.888	27.168
0.6	20.195	25.362	21.006	26.371	21.426	30.303	20.640	26.050	19.424	24.279	20.750	26.175
0.7	19.168	23.924	20.989	26.482	21.440	27.129	19.370	24.287	19.274	24.779	21.545	26.830
0.8	21.982	27.362	19.760	24.681	20.662	25.948	21.324	26.648	21.685	26.964	21.644	27.160
0.9	21.356	27.235	21.251	26.550	19.518	24.880	21.276	26.736	21.283	26.981	19.217	23.910
1.0	20.206	25.608	20.914	26.173	20.726	25.877	21.430	26.625	20.102	25.198	19.810	25.348
Total	219.290	324.380	205.561	257.293	203.342	260.394	209.629	262.446	200.121	253.678	210.437	262.986
Grand Total	1284.343	1895.873	1199.098	1727.300	1131.878	1693.572	1066.375	1511.927	1124.465	1681.087	1211.808	1772.106

The corresponding times for calculating the joint probabilities and s-powers of these have been added up to report the results for the Havrda-Charvat entropies of the Grand total row.

Table 18: Total CPU and real times for calculating the Entropy measure content of a family PF06850 and approximations for Grand Total of all sample space.

POA_{II}	Entropy Measures	Entropy Measures
	$H_j(s)$ — 19 s-values	$H_{jk}(s)$ — 19 s-values
Total CPU time (family PF06850)	$0.358 + 2.562 + 0.292$ $= 3.212$ sec	$550.129 + 611.374$ $+421.418 = 1,582.921$ sec
Grand Total CPU time (1069 families)	$3,433.628$ sec $= 0.954$ hs	$1,692,142.549$ sec $= 19.585$ days
Total Real time (family PF06850)	$1.062 + 9.300 + 0.332$ $= 10.694$ sec	$593.848 + 1,649.357+$ $927.405 = 3.170.61$ sec
Grand Total Real time (1069 families)	$11,431.886$ sec $= 3.175$ hs	$3,389,382.090$ sec $= 39.229$ days

Table 19: Total CPU and real times for calculating the Entropy measure content of a family PF06850 and approximations for Grand Total of all sample space.

PLA_{II}	Entropy Measures	Entropy Measures
	$H_j(s)$ — 19 s-values	$H_{jk}(s)$ — 19 s-values
Total CPU time (family PF06850)	$0.291 + 1.801 + 0.640$ $= 2.732$ sec	$787.254 + 515.072$ $+403.461 = 1,705.787$ sec
Grand Total CPU time (1069 families)	$2,920.508$ sec $= 0.811$ hs	$1,823,486.303$ sec $= 21.105$ days
Total Real time (family PF06850)	$0.642 + 7.261 + 1.291$ $= 9.194$ sec	$1,068.026 + 1,028.655$ $+557.294 = 2,603.975$ sec
Grand Total Real time (1069 families)	$9,828.386$ sec $= 2.730$ hs	$2,783,649.275$ sec $= 32.218$ days

6 Concluding Remarks and Suggestions for Future Work

The treatment of the distributions of probability of occur in protein databases is a twofold procedure. We intend to find a way of characterizing the protein database by values of Entropy Measures in order to provide a sound discussion to be centered on the maximization of a convenient average Entropy Measure to represent the entire protein database. We also intend to derive a partition function in order to derive a thermodynamical theory associated to the temporal evolution of the database. If the corresponding evolution of the protein families is assumed to be registered on the subsequent versions of the database (Table

17), we will then be able to describe the sought thermodynamical evolution from this theory as well as to obtain from it the convenient description of all intermediate Levinthal's stages which seem to be necessary for describing the folding/unfolding dynamical process.

We summarize this approach by the need of starting from a thermodynamical theory of the evolution of protein databases via Entropy measures to the construction of a successful dynamical theory of protein families. In other words, from the thermodynamics of evolution of a protein database, we will derive a statistical mechanics to give us physical insight on the construction of a successful dynamics of protein families.

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