# Main action of proteins and catastrophic bifurcation points: a review

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The design of new pharmaceutical drugs faces the increasing difficulty of locating peptides and proteins in living organisms, as well as the high costs involved in their synthesis and testing. Bioinformatics methods offer viable and practical alternatives, however, it implies the computational modelling of the lipid-aqueous medium where proteins interact. This work presents a bioinformatics method that measures only one physico-chemical property, polarity whose metric represents a promising possibility for the design of new drugs. The algorithm used, is based on the premise that the main function of a protein depends only on the order the amino acids have in its linear sequence. The method has shown high levels of efficiency in multiple tests. However, their main action is not always easy to identify. A protein is usually associated to different pathogen groups by its action i.e., bacteria, fungi, viruses, etc., and its toxicity is a parameter to know it. Previous studies [C. Polanco *et al*., Acta Biochim Pol 60:183-189 (2013)], have shown that the polarity profile of a protein can be an effective identifier of its primary action. The present review shows graphically that the catastrophic bifurcation points of the polarity profile of a protein are characteristic of each protein group.

**Keywords:** physico-chemical properties; proteomics; bioinformatics; polarity; proteins

## 1. General remarks

Proteins are part of the immune system in every living organism, their use to manufacture pharmaceutical drugs has been a common resource to experimentalists for decades [1]. Most of the listed proteins do not show a marked toxicity to some pathogens, however, it is usual to find in databases that the same protein has experimentally shown some degree of toxicity towards different groups e.g., bacteria, fungi, viruses, cancer cells, among others (see APD2 Database [2]). From the bioinformatics perspective, there are different algorithms [3-6], with different degrees of efficiency, to identify the main action of a protein. Some methods use several physico-chemical properties [7], and are aimed to identify a specific toxic action [8]. This paper summarizes the main results that a bioinformatics method called polarity index method (PIM) [9] has to identify the main antimicrobial groups and some structural properties associated with proteins and peptides. The PIM considers in its metrics a single physico-chemical property, polarity. It reads it from the linear sequence of the protein, and takes the relative frequency of every possible polar interaction [9] to be plotted as a smooth curve [10]. In this work the curves are analyzed,and they are used to discriminate between the protein groups.

## 2. New paradigm

In a brief overview of the current methods, the algorithms with greater efficiency are those oriented to identify the "attributes" expressed in the "data training"; however, these algorithms do not produce proteins with high “specificity”, this leads to poor results when they are used for the production of new drugs. How can this be improved? The solution will probably be the design of new algorithms that include in their metrics: (i) a minimum number of physico-chemical properties fundamental to matter e.g., polarity; (ii) the lipid-aqueous medium where proteins interact with each other; and (iii) the use of algebraic structures that consider all possibilities when they "measure" the "attributes" of a protein. Based on these premises, the physico-chemical property polarity was explored, taking the 20 amino acids currently known and classifying them into four polarity groups {acidic, basic, neutral, and non-polar}.

The study of this important structural property of matter goes back to the measurement of the electronegativity between the elements, under the formal definition made by Linus Pauling as "the ability to attract electrons to form a covalent bond", he also “normalized all the elements in the periodic table with hydrogen”, which provides a scale of polarity for the amino acids. The use of polarity to identify the main action of a protein, requires an algebraic structure where all polar interactions between amino acids are recorded. An incident matrix is an *ad doc* structure for this, because it includes the 16 possible polar interactions of the four polarity groups that occur in the amino acids forming the linear sequence of a protein. With this approach a self-learning program named Polarity Index Method (PIM) [9] was built, showing a high discriminative capacity on an extensive group of peptides and proteins from different specialized databases.

## 3. Polarity index method

The core of the PIM is the record of the polar incidents of the amino acids that constitute the linear sequence of a protein. This sequence is an orderly succession of amino acids located in the genome of the cells of every living organism. The PIM reads this sequence from right to left, counting the polar interactions in pairs of amino acids, and

recording them in a polar matrix. This polar matrix has 4 polar groups [P +, P-, N, and NP] in their lines and columns. Then the polar matrix is linearized for its geometric interpretation in a vector of 16 elements with this rule: the first four elements of the vector are placed in the first row of the matrix, the second set of four elements are in the second row, and so forth to the last row of the polar matrix. Finally the vector is normalized and geometrically expressed with a smooth curve (Fig 1a), instead of histogram (Fig 1b) where the 16 possible polar interactions are located in the X-axis, and the relative frequency is located in the Y-axis.

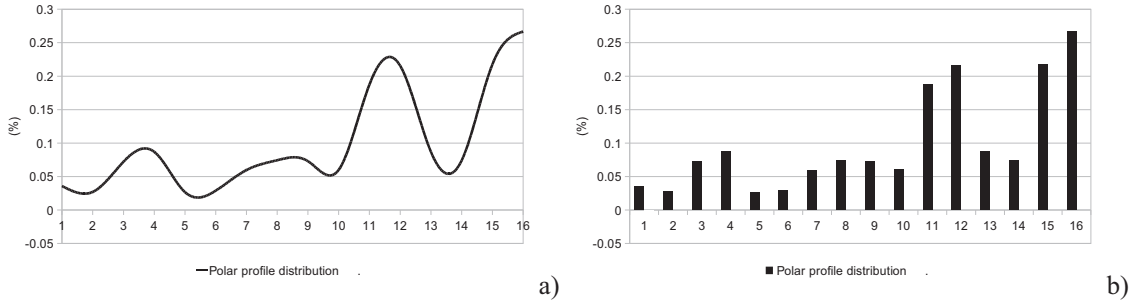



**Fig. 1** Polar frequency distribution a) Smooth curve representation b) Histogram representation.

## 4. Dynamic stochastic models

Dynamic systems have an important role in the design of algorithms for two aspects: (i) stochastic functions can include a high number of variables related to the phenomenon studied, without adding complexity to its computational implementation, and (ii) when the analysis is focused on locating the singularities among the regularities of the system, the catastrophic bifurcation points (CBP) or turning points in the graph of the function, become evident. These CBP points divide the phenomenon in regularity "periods", where the behavior "before" is different than "after".

## 5. Exhaustiveness

The polarity profile has been used in many algorithms related to the identification and/or characterization of the main function of proteins. Algorithms generally take this form $f(x_1,x_2,...,x_n) \rightarrow c$, where c is a number, f is a real function, and $x_i$ are physico-chemical properties. The PIM takes a different approach [9], $F:\mathbb{R} \rightarrow \mathcal{M}$, where the vector function F turns the polarity interactions "x" into a polar matrix $\mathcal{M}$. This is a fundamental difference, as vector functions amplify the characteristics studied. There are two key highlights in this metric:

i. The profile outlined in the polar matrix, becomes more difficult to modify as the process unfolds (Table 1).

**Table 1** Polar matrix distribution.

| | P+ | P- | N | NP |
|---|---|---|---|---|
| P+ | 0.05 | 0.00 | 0.02 | 0.19 |
| P- | 0.00 | 0.00 | 0.00 | 0.02 |
| N | 0.04 | 0.02 | 0.04 | 0.06 |
| NP | 0.14 | 0.00 | 0.10 | 0.26 |

ii. The polar matrix is mathematically interpreted as 16-dimensional space, and not as a figure, as it is usually the case, because a figure does not provide enough information about the phenomenon studied. It is highly possible that the efficiency of the PIM is due to the accurate information these 16 numbers supply.

## 6. Vector functions versus real functions

The family of functions with variable "F", requires a detailed explanation to understand its notations and dynamics. A function is a correspondence rule associating an element of a specific set or space with the element of another. The PIM associates the polar interactions that occur in a protein when the amino acids are read from left to right in pairs i.e. ($a_i$,

$a_j$), and builds an array of incidents (called polar incident matrix) with the rule: "Add 1 to the position ($a_i$, $a_j$) of the matrix, taking $a_i$ as the row and $a_j$ as the column". The vector function F in the PIM, associates the spaces $\mathbb{R}^2$ and $\mathbb{R}^{16}$, this way F: $\mathbb{R}^2 \rightarrow \mathbb{R}^{16}$. Thus the vector function F builds a matrix with the polar incidents. However, it is possible to associate the "v" vector to the matrix in an $\mathbb{R}^{16}$ space (with the properties of the vector functions, instead of the real functions), and that this vector characterizes the matrix. In some cases, this vector can substitute the matrix, as it is geometrically more convenient. The difficulty to illustrate this vector of polar incidents, lies in the fact that the $\mathbb{R}^{16}$ space cannot be plotted; however, it is possible to analytically express it with the notation v=($a_{1,1}$, $a_{1,2}$, $a_{1,3}$, $a_{1,4}$, $a_{2,1}$, $a_{2,2}$, $a_{2,3}$, $a_{2,4}$, $a_{3,1}$, $a_{3,2}$, $a_{3,3}$, $a_{3,4}$, $a_{4,1}$, $a_{4,2}$, $a_{4,3}$, $a_{4,4}$).

## 7. Linear protein representation

The dimensional space where the main action of a protein was studied is crucial for this and any future analysis. The PIM acts on the linear sequence that is related to the incident matrix, which is read from left to right (or right to left). However, if the space for the matrix were $\mathbb{R}^3$ i.e., 3-dimensional space, the level of complexity in the algorithm would increase significantly, as in this space the protein would have almost an infinite number of possibilities.

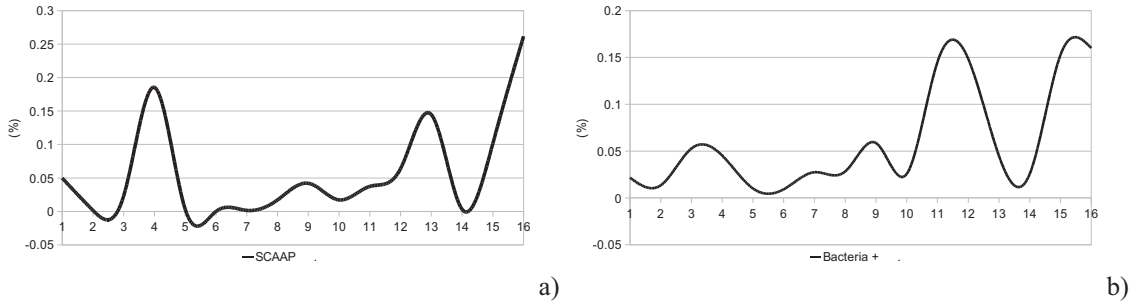
It could be said that the linear representation is not a valid representation, in the sense that it is not yet a protein, and that it would be necessary to wait until the transcription process converts this orderly succession of amino acids in a protein in the 3-dimensional space. However, the major premise in the design of the electronegativity-based PIM, is that the final 3-dimensional conformation of a protein, depends on its linear sequence. This last consideration has important implications in the approach of the computational algorithm, as it is possible to use distributed computational schemes that measure only one physico-chemical property, polarity.

## 8. Catastrophic bifurcation points

There are certain points in a graph (Fig **1a**) that can be identified [11] as characteristic of this representation. They are maximum points located on the horizontal axis of the graph pointing the peak of the curve, and minimum points pointing the trough. However, there are other points where the curve changes from concave to convex, this geometrically means that the curve goes from being concave downward, to be concave upward, or vice versa; these points are called inflection points. All inflection points where the geometrical regularity of the graph marks a turning point, changing the shape of the curve in its regularity, are called catastrophic bifurcation points (CBP) [12]. The CBP (Fig. **2**) are particularly used in the metrics of the PIM, to identify the main action associated with a protein. The PIM locates the irregularities to identify the regularities, this concept is frequently used in dynamical systems [13].

## 9. Antimicrobial peptides

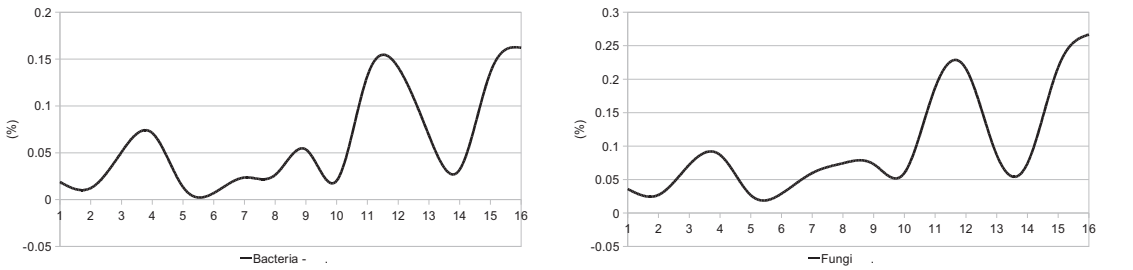
The antimicrobial peptides studied here are those experimentally associated to selective cationic amphipatic antibacterial peptides (SCAAP) [14], bacteria GRAM + [15], bacteria GRAM – [16], fungi [17], cancer cells [18], virus [19], mammalian cells [20], chemotaxis cells [21], and tuberculosis [22]. They were taken from the following databases: APD2 [2], a set of 30 peptides [23,24], and Tuberculist [25]. It is worth mentioning that the main CBP for the groups mentioned above are located in: SCAAP {7,8 and 13,14} (Fig. 2a), bacteria GRAM + {6,7 and 12,13} (Fig 2b), bacteria GRAM – {7,8 and 12,13} (Fig. 3a), fungi {8,9, and 12,13} (Fig. 3b), cancer cells {6,7 and 10,11} (Fig. 4a), virus {5,6 and 12,13} (Fig. 4b), mammalian cells {5,6 and 11,13} (Fig. 5a), chemotaxis cells {4,5 and 12,13} (Fig. 5b), and tuberculosis {6,8 and 12,13} (Fig. 6a). The tuberculosis group did not show any CBP coincidence when it was compared with bacteria GRAM + and bacteria GRAM - in {8,10 and 12,14} (Fig. 6b). In the sperm group [26] the CBP are located in {5,7 and 13,14} (Fig. 7a). The SCAAP group did not show any coincidence of CBP when they were compared with bacteria GRAM + and bacteria GRAM – in {6,8 and 12,14} (Fig. 7b).




a) b)

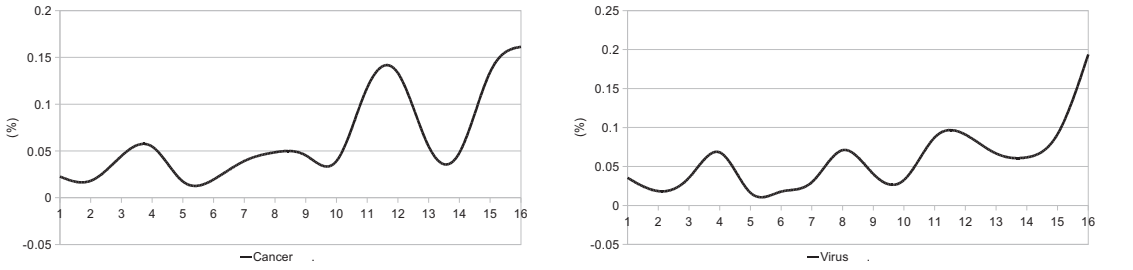
**Fig. 2** Polar frequency distribution a) SCAAP [14] b) Bacteria GRAM + [15].



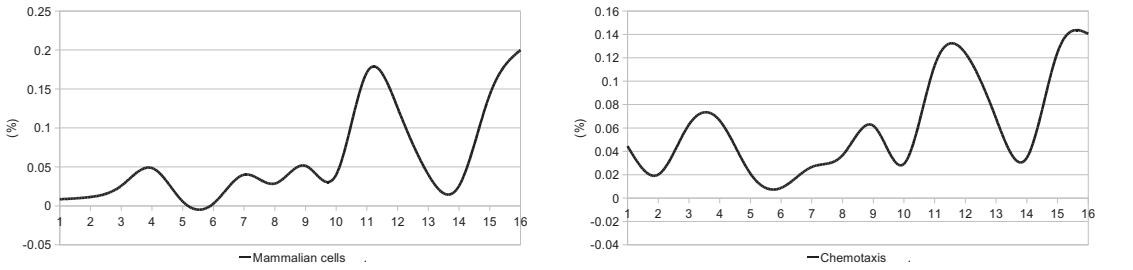

a) b)

**Fig. 3** Polar frequency distribution a) Bacteria GRAM - [16] b) Fungi [17].



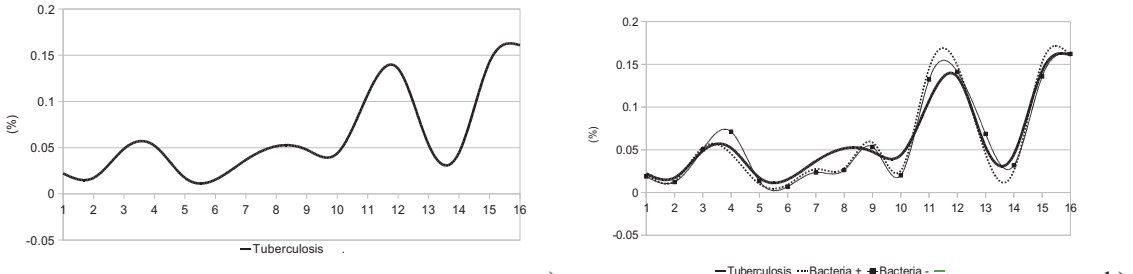

a) b)

**Fig. 4** Polar frequency distribution a) Cancer cells [18] b) Virus [19].



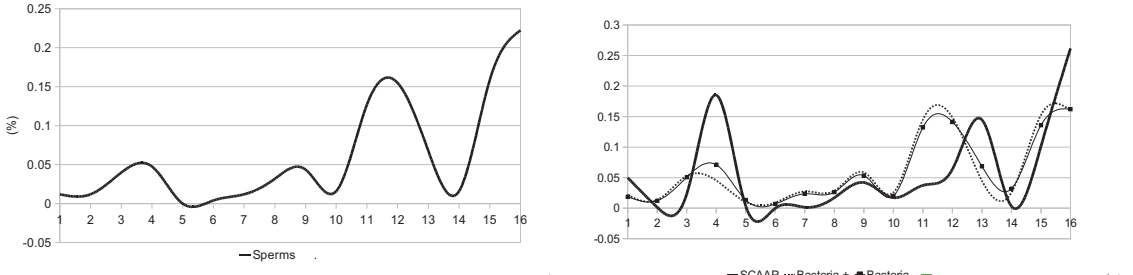

a) b)

**Fig. 5** Polar frequency distribution a) Mammalian cells [20] b) Chemotaxis cells [21].




a) b)

**Fig. 6** Polar frequency distribution a) Tuberculosis [22] b) Tuberculosis [22], bacteria GRAM+ [15], and bacteria GRAM- [16].




a) b)

**Fig. 7** Polar frequency distribution a) Sperms [26] b) SCAAP [14], bacteria GRAM + [15], and bacteria GRAM - [16].

## 10. Cell penetrating peptides

Cell penetrating peptides (CPP) [27] are a group of peptides characterized by their penetration mechanism to the membrane of the microorganism and the destruction of pathogens. They are classified into two groups: endocytic pathway, which have restrictions for penetration, and non-endocytic pathway, with no restrictions for penetration. The remaining group that does not belong to any of these groups is called unknown pathway peptide group. The databases used were: CPPsite [28], and SCAAP-CPP [14,5]. It is important to note that the main CBP for the groups mentioned are located in: CPP endocytic pathway {4,5 and 9,10} (Fig. 8a); CPP non-endocytic pathway {4,5 and 11,13} (Fig 8b); CPP unknown pathway {4,5 and 7,8} (Fig. 9a); and SCAAP-CPP {4,5 and 8,10} (Fig. 9b). There is no coincidence of CBP in the SCAAP group when it was compared with the SCAAP-CPP and CPP endocytic pathway in {10-12} (Fig. 10a). And there is no CBP coincidence in the CPP endocytic pathway group, when it was compared with the CPP non-endocytic and unknown pathways in {10,14} (Fig. 10b).

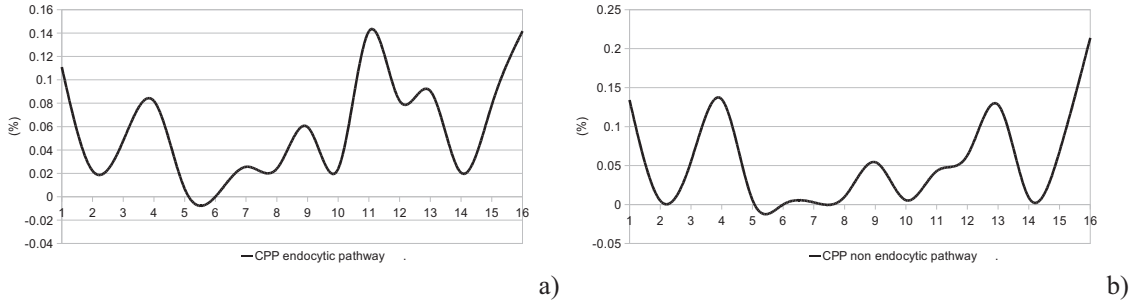



**Fig. 8** Polar frequency distribution a) Cell penetrating peptides (CPP) endocytic pathway [28] b) Cell penetrating peptides non-endocytic pathway [28].

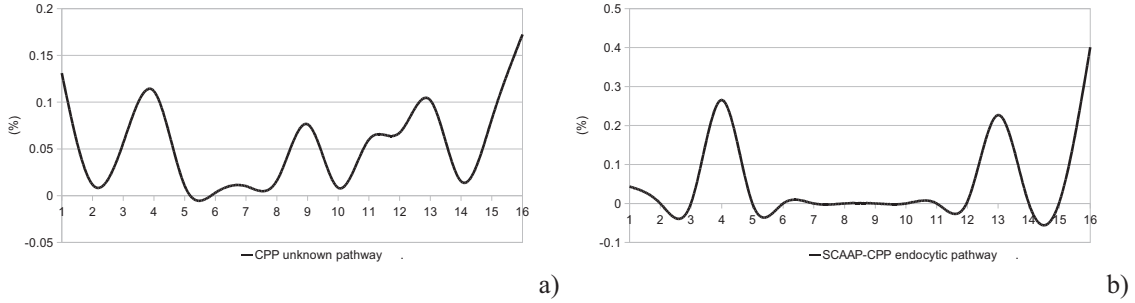



**Fig. 9** Polar frequency distribution a) Cell penetrating peptides (CPP) unknown pathway [28] b) SCAAP-CPP selective cationic amphipathic antibacterial peptides (SCAAP) [29], and cell penetrating peptides (CPP) endocytic pathway [28].

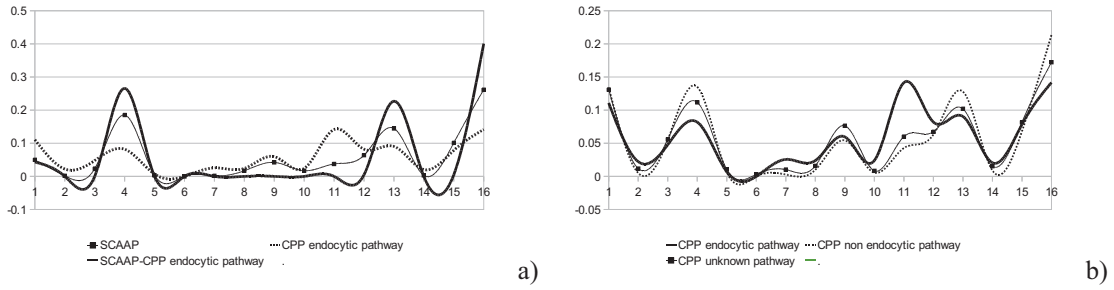



**Fig. 10** Polar frequency distribution a) Selective cationic amphipathic antibacterial peptides (SCAAP) [14], cell penetrating peptides (CPP) endocytic pathway [28], and SCAAP-CPP endocytic pathway [28] b) Cell penetrating peptides endocytic pathway [28], CPP non-endocytic pathway [28], and CPP unknown pathway [28].

## 11. Disorder proteins

The family of disordered proteins do not have any known structural order [29,30]. They are classified, according to their degree of disorder, into three groups [31]: unfolded proteins [32], partially folded proteins [33], and folded proteins [32] or functional proteins. The level of disorder of a protein is associated to protein clumping, when the disorder proteins clump to neurons, they lead to particularly serious chronical neurodegenerative problems [34]. The database used for the extraction of disordered proteins was AmyPDB [35]. Note that the main CBP for this group are located in: natively

unfolded proteins {6-8} (Fig. 11a), partially folded proteins {6,8} (Fig. 11b), and unfolded proteins {6,8} (Fig. 12a). These groups were compared to each other, showing no CBP coincidence in {6,8} (Fig. 12b).

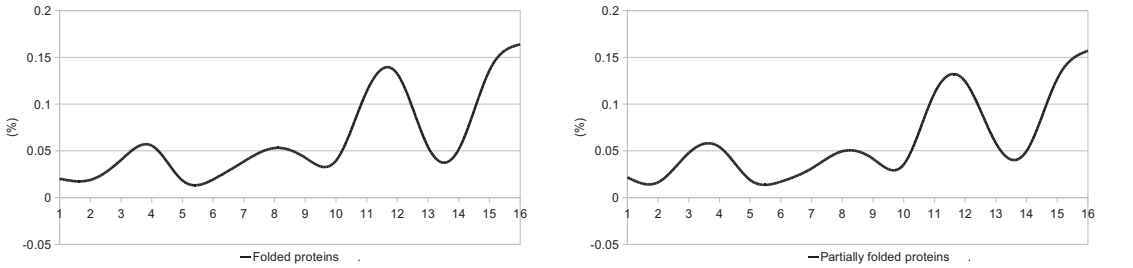



**Fig. 11** Polar frequency distribution a) Folded proteins [32] b) Partially folded proteins [33].

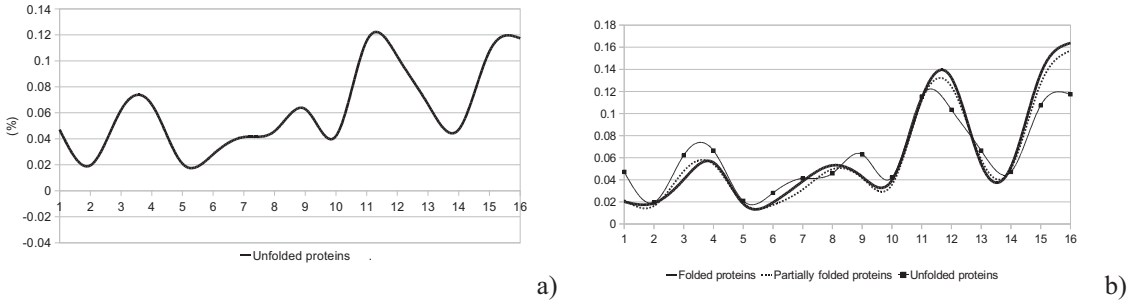



**Fig. 12** Polar frequency distribution a) Natively unfolded proteins [32] b) Folded proteins [32], partially folded proteins [33], and natively unfolded proteins [32].

## 12. Lipoproteins

Lipoproteins [36] are proteins that transport lipids (fats) throughout the body, there is a classification based on the density of the lipids transported: Chylomicrons [37], very low density lipoproteins (VLDL) [38], intermediate density lipoproteins (IDL) [39], low density lipoproteins (LDL) [40], and high density lipoproteins (HDL) [41]. The database used for the extraction of lipoproteins was Uniprot [42]. Note that the main CBP for these groups are located in: HDL {6,8} (Fig. 13a), LDL {6,8} (Fig 13b), VLDL {6,8} (Fig. 14a), and IDL {6-8} (Fig. 14b). The HDL and LDL groups were compared to each other, showing they have no coincidence of CBP in {7,8} (Fig. 15a). The VLDL and Chylomicrons groups were compared to each other, showing they have no coincidence of CBP in {7,8} (Fig. 15b).

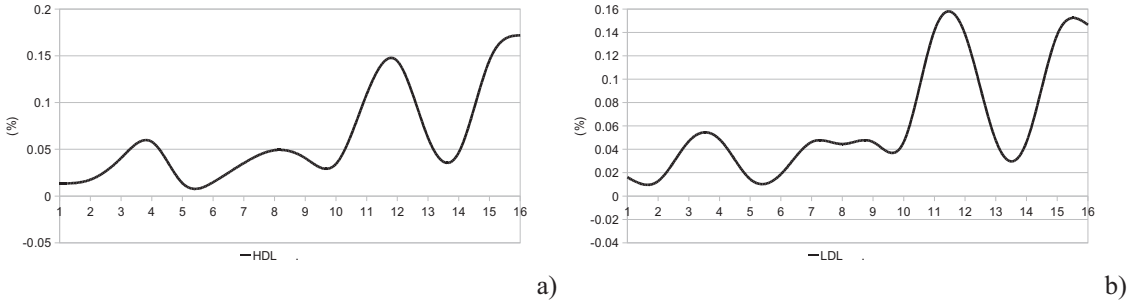



**Fig. 13** Polar frequency distribution a) High density lipoproteins (HDL) [41] b) Low density lipoproteins (LDL) [40].

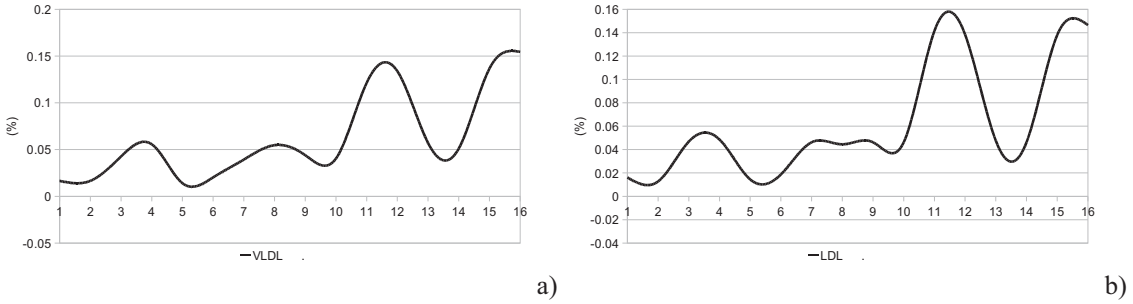



**Fig. 14** Polar frequency distribution a) Very low density lipoproteins (VLDL) [38] b) Intermediate density lipoproteins (IDL) [39].

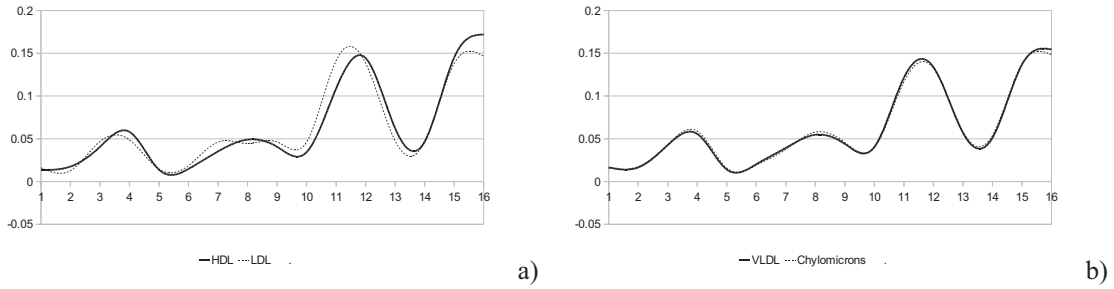



**Fig. 15** Polar frequency distribution a) High density lipoproteins (HDL) [41] and low density lipoproteins (LDL) [40] b) Very low density lipoproteins (VLDL) [38] and chylomicrons lipoproteins (Chylomicrons) [37].

## 13. Discussion

The evaluation of polarity in a peptide to identify its main function, is not an exclusive technique of the PIM, in fact this property is evaluated by more than 75% of the known bioinformatics algorithms. What is new is the extensive way the polarity profile of a peptide is displayed, using a matrix that considers 16 possible polar interactions between amino acids. As this method is an unsupervised learning method that compares its polar arrays, there are multiple possibilities for the training peptides. The polar matrix displays 16 interactions, if the peptide or protein is short, it will probably contain zeros in most of its elements. However, the notation of peptides and proteins in databases are always increasing, this makes possible the generation of representative training sets that will produce polar arrays with no zeros. It is worth noting that the 16 polar interactions from the polar matrix definitely give much more information about the peptide studied, than the figure resulting from a single evaluation. In the last four decades, more than 85 bioinformatics algorithms have been developed to the construction or identification of proteins and peptides. Now more than ever, the computational structure is above the quality of the bioinformatics results. The quality of these results does not depend on the computational capacity, but on the granularity of the algorithms designed.

In my view, it would be necessary to redesign the metrics, taking the fundamental properties of matter and making them exhaustive, as most of the bioinformatics programs do not have high efficiency levels. Another aspect to bear in mind, would be the exploration of different peptide regions with experimental and bioinformatics techniques, since only a small protein spectrum has been experimentally tested.

## 14. Future trends

If this new paradigm is considered, it will be possible to build algorithms with higher level of efficiency, where the granularity will be the entire protein and not only fragments of it, and taking into account their interaction with the medium and other proteins. With this approach, it will be likely to have new drugs with fewer adverse effects. The research with this method has been mainly oriented to three objectives: (i) to identify "Trojan peptides" in fixed length peptides i.e., antibacterial peptides that penetrate the membrane of pathogen agents without the intermediation of any other factor; (ii) to obtain a computational classification of the databases previously mentioned; and (iii) to model lipid-aqueous scenarios, where the proteins produced coexist with other proteins.

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