Electronegativity profile of proteins associated to Ebola virus: a review

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The production of pharmaceutical drugs for the Ebola virus disease, from the physico-chemical analysis of proteins associated to the virus is a prevailing and useful alternative that has provided important results in the bacterial and viral fields. Although the scientific community is now working on the elaboration of vaccines against the disease, it is important to conduct a retrospective study to get a deep understanding of the nature of this virus. The damage Ebola causes to humans has been known for decades. However, with the improvements in the means of transport and communication, the disease is now potentially pandemic. This review addresses the mathematical-computational results found with a metric taken from the electronegativity of the proteins associated to the Ebola virus, and the computational technology that can be used. According to Linus Pauling [L. Pauling, General Chemistry 3rd edition W. H. Freeman & Company Publishers, 1955], electronegativity is the measure of the stability of the valence electrons in a covalent bond. Its metric has a very high discriminative level to identify the main function associated to a protein, as well as its structural properties. This method is now focussed to find the properties in proteins associated to the Ebola virus.

Keywords: Ebola virus outbreak; biosafety; amyloid proteins; electronegativity; bacteria; bioinformatics methods

1. General remarks

From the five species of the Ebola virus proteins (EBOV), currently known, only three of them are classified as bio-safety level 4: Ebola virus (EBOV-S) (Sudan, 1970), Ebola virus (EBOV-Z) (Zaire, 1970), and Ebola virus (EBOV-B) (Uganda, 1970) [1-3].These species cause severe hemorrhagic diseases with considerably high fatality rates (40 - 90%) among human beings [4-6]. There are no specific treatments or vaccines for the Ebola virus at the moment. The treatment consists "of hydrating the patient, maintaining their oxygen status and blood pressure and treating them for any complicating infections" [7]. The most deadly outbreaks were in Zaire (88% of 318 infected people died, 1976) [8], and Sudan-Uganda (53% of 425 infected people died, 2000) [9]. Although diagnostic laboratory testing by real-time polymerase chain reaction is sensitive and specific, in the absence of a vaccine or specific antiviral treatment, only state-of the-art supportive care, will reduce the high fatality rate. While epidemiological genomics research is conducted, the mathematical-computational method Polarity index method (PIM) [10-12], was oriented to calculate the polarity profile of the proteins associated to the EBOV, extracted from UNIPROT Database (UNIPROT) [13]. This profile was compared with three major groups of antimicrobial peptides located in: APD2 Database (APD2) [14], UNIPROT, and the set of selective cationic amphipathic antibacterial peptides (SCAAP), from Del Rio and coworkers [15; Table 2, and Table 2A]. The SCAAPs are characterized by being extremely toxic to bacterial membranes [16, 17], but not to mammalian cells. Additionally the EBOV was also compared with three structural groups: natively unfolded proteins, folded proteins, and the fragments of partially folded proteins [18-20], to determine their structural affinity. These structural groups have been strongly identified as active participants in the chronic neurodegenerative diseases, grouped under the term Amyloidosis [21-23].

Different electronegativity values - first observed by Pauling L. 1955 [24] - show that there is "a bias" in the formation of matter. From this observation it is assumed that this bias is "transmitted" from the elements to the amino acids. Based on this assumption, the polarity profile of EBOV was calculated by the polarity index method, finding that its polarity is mainly bacterial-folded. Since the reader might be interested in conducting the calculation for a large number of proteins, the computer architectures to adapt the polarity index are also introduced, to evaluate proteins massively. For instance, in order to explore 12aa in length proteins, it will be necessary to evaluate 20^{10} proteins. For this large number it will be necessary to use parallel computing [25, 26], as it will not be possible to conduct such a task in a personal computer (PC) in a reasonable time. Therefore, it will be fundamental to use computer technologies to reduce the processing time from hours to milliseconds.

2. Ebola outbreak in numbers

The current Ebola Virus Disease (EVD) outbreak begun in December 2013. The epidemic´s unprecedented scale was a surprise. On August 8, 2014 almost nine months into the longest and most widespread EVD outbreak in history, the World Health Organization (WHO) declared the epidemic to be a public health Emergency of International concern [27]. By August 16, 2014 the cumulative number of EVD cases in Sierra Leone, Liberia, Guinea and Nigeria was 2 240 with 1 229 deaths (fatality rate of 55%), and as of April 26, 2015 a total of 26 312 cases of EVD had been reported in

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two more countries which include two in West Africa (Mali and Senegal) and in The United States, United Kingdom and Spain. with a total death toll of 10 899 patients and a fatality rate of 41 % which represents the largest number of EVD survivors [28]. While the epidemic continues in Sierra Leone an Guinea, on May 09, 2015, forty two days after the burial of the last person to be known to be infected in Liberia (twice de maximum incubation period of the disease), Liberia was the first of the three main countries in Western Africa affected by Ebola to be declared free of the disease by the WHO [29], marking the end of a 15 month epidemic in that country, suggesting that an end of the epidemic in West Africa is in sight.

3. The Polarity Index Method

The metric of the Polarity index method (PIM), evaluates the electronegativity of a protein by reading the amino acids in its linear sequence [24]. The PIM metric generates a matrix of polar incidents, reading the sequence either from left to right (or from right to left) in pairs, sequentially. It takes the 20 amino acids that conform the protein, and classifies them into these groups [30]: acidic-polar P- = {D, E}; basic-polar P+ = {H, K, R}; non-polar NP = {A, F, I, L, M, P, V, W}; and neutral-polar N = {C, G, N, Q, S, T, Y}. With this classification, the amino acids sequence can be translated into a numerical sequence, where {P+, P-, N, NP} → {1, 2, 3, 4}, e.g., if the sequence of a protein is formed with the amino acids MAAEEMHWPVPMKAIGAQN, its numerical equivalent will be 44422414444441443433. With this conversion, a polar incident matrix is built, reading each pair of amino acids in the protein from left to right, where (i,j) = (row, column). In this particular example, the interaction (4,4) occurs seven times, while the interaction (3,2) does not occur at all. At first sight, it could be easy to suppose that each protein will have a different incident matrix; however, proteins with the same function i.e., bacteria, virus, and fungi, among others (Figs. 1-3), have the same group profile [17, 31, 32]. Although this is an approximation method, its level of efficiency is high (> 75%). It evaluates a single physico-chemical property, in an exhaustive way, using a matrix with 16 possible permutations of the four polarity groups. Some algorithms use the polarity property in their metrics, either directly or indirectly; nevertheless, any of them use the property exhaustively [33]. There are other algorithms that use the electronegativity as value, but this approach nullifies the observation of the electronegativity profile.

3.1 Electronegativity profile

The physico-chemical property polarity has been widely described [34-36]. It refers to the electromagnetic balance of the electrons in the valence of the elements and in the amino acids that constitute a protein. The definition of Pauling L. 1955 [24], has been used for this purpose, and the matrix built has been normalized to the electronegativity value of hydrogen. How is the electromagnetic balance used? The main statement of PIM, is that the electromagnetic balance identified in the valence electrons is reproduced by nature at scale as fractal in the amino acids, and it can be identified in the linear sequence of the protein (genome). Thus, when the finite interaction between the elements is stabilized adopting a tertiary structure, it interacts, in turn, with other similar structures to form amino acids. This leads to the assumption that the function of a protein, is closely related to the order the amino acids take in its linear structure. Is it possible to preserve the electromagnetic balance of a protein, when the composition of the amino acids conforming it has been altered? Yes, it is. There are changes that do not affect the balance of a protein; however, in some cases, a single amino acid makes a significant difference. The metric of PIM makes it possible to differentiate what changes alter the electromagnetic balance of a protein and what changes do not affect it.

3.2 Antimicrobial protein groups

Antimicrobial peptides (AP) are the first line of defense in living organisms [37], they featured selective toxicity towards different pathogenic groups, and their average size has 26 amino acids in length [17}. Among the APs, there is a small group of peptides called selective cationic amphipathic antibacterial peptides (SCAAP) [16], which have high toxicity to bacteria and negligible toxicity towards mammal cells. APs have been extensively used to produce pharmaceutical drugs for decades, as they can find pathogenic agents in organisms, or they can attack them with their toxicity. These characteristics have made possible their use as Trojan peptides (TP) [38], as combined with cell penetrating peptides (CPP) [39], the former group locates the membrane while the latter penetrates it and fights the pathogenic agent. One of the main problems this technique faces is that it is increasingly difficult to find APs in nature; and those that exist, exceed the average size (26aa). This has given rise to an emerging discipline called bioinformatics, which develops QSAR algorithms [40], that measure physico-chemical properties identified in the subject peptide or protein.

3.3 Structural protein groups

The conformational study of peptides and proteins is related with the form they adopt in three dimensional spaces, and the similarity this form has with other proteins that have the same function. Thus, the bacteria group will have a particular form, different from the fungi or virus groups. This function-structure [41] paradigm has prevailed for

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decades; however, there is a group of peptides and proteins that do not adopt a known structure and are characterized by clumping on neurons, causing important neurodegenerative disorders. This group is called natively unfolded proteins [42]. It was the lack of regular structure, what made possible the identification of two additional groups: partially folded proteins, and folded proteins. The former, is a group with a medium structural level; while the latter is a group with a known structure such as: bacteria, fungi, virus etc.

4. Results

The polarity index method discriminates more efficiently the groups located in APD2, and UNIPROT databases (Table 1). It is worth noting that the reduction of false positives substantially reduces the efficiency of PIM (Table 1). The PIM shows that EBOV proteins are associated with the Bacteria Gram+/−, cancer (Table 2) and to the natively folded protein groups (Table 3). It also shows that EBOV proteins are not associated with the SCAAP group (Table 2).

Table 1 Main antibacterial groups

UNIPROT	APD2	APD2	APD2	UNIPROT	UNIPROT	UNIPROT
Ebola	**Fungi**	**Cancer**	**Viruses**	**Fungi**	**Cancer**	**Viruses**
100	10	35	29	**66**	**70**	**63**
77	6	**25**	10	29	31	23

Table 2 Secondary antibacterial groups

UNIPROT	APD2	APD2	APD2	del Rio
Ebola	**Gram +**	**Gram -**	**Gram+/-**	**SCAAP**
100	34	16	**50**	0
77	19	13	**15**	0

Table 3 Structural groups

Ebola	Folded	Partially folded	Unfolded
100	**64**	10	22
73	**20**	5	11

5. Clustering approach

In previous sections, the difficult solutions landscape that is shaped by physico-chemical characteristics of 10 amino acids proteins was explained. Therefore, bioinformatics algorithms must be approached from a hardware architectural perspective in order to accelerate finding suitable solutions previous to experimental testing. More specifically, calculating the polarity index for every possible protein combination is a highly expensive computational task. In this section, two alternatives of massively parallel processing platforms to accelerate PIM calculation are discussed: on the one hand, Field Reconfigurable Gate Arrays (FPGAs) that offer a flexible fabric where tailored processing units can be defined according to specific algorithmic requirements [43]. On the other hand, Graphics Processing Units (GPU) where hundreds of processing cores follow the SPMD (Single Program Multiple Data) execution model [44].

Designing hardware architectures for FPGAs requires longer design cycles but different performance metrics can be targeted such as processing time reduction, power consumption or resources usage [45, 46]. In contrast, a parallel computational model for a GPU requires shorter design times and algorithmic acceleration is implicitly the main targeted performance metric [47].

In order to find suitable solutions, the PIM model needs to be calculated for each protein combination. Different algorithmic searching techniques can be used to find possible solutions; this discussion does not focus on any specific technique but on searching schemes where independence of solutions exists. FPGAs provide a fine grained fabric where an array of processor elements (PEs) can be defined. Each PE implements the same logic for PIM assessment and each PE deals with a single or a number of possible solutions.

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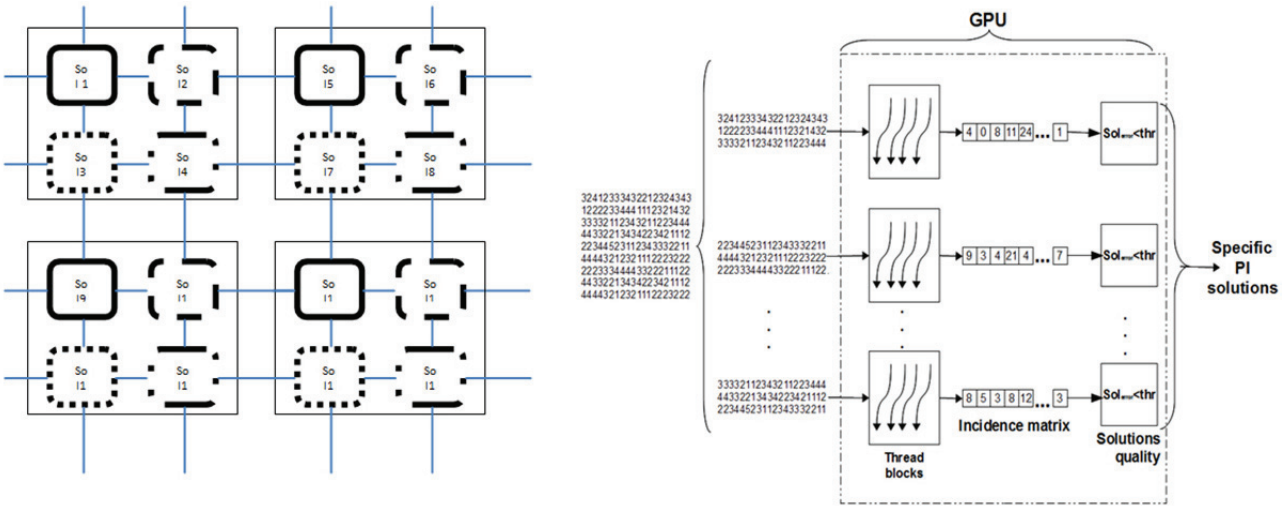

Fig. 1 Left: PEs array on FPGA architecture. Right: Parallel computational model on GPU.

In Fig. 1 (left) an array of PEs is presented with toroidal connections among them, in this architectural scheme, solutions are exchanged among PEs in order to improve the search. The processing bottleneck is the PIM calculation but only combinatorial logic is required which means latency is kept to the minimum. The array size can vary depending on availability of hardware resources. Distributing solutions among PEs together with the searching technique's robustness define the overall processing performance.

A parallel computational model for GPUs to calculate the PIM model depends also on the algorithmic searching technique. NVIDIA GPUs' streaming processors consists of several CUDA cores with independent processing units [47]. An important aspect for GPUs' development is taking advantage of their memory hierarchy. Each block of CUDA cores has its own shared memory block and a set of CUDA cores' blocks has access to the GPU's global memory. Each CUDA core evaluates a protein combination to obtain its associated electronegativity profile, depending on the search's criterion; optimal solutions can be returned to local or global memory to start processing another solutions batch, see Fig. 1 (right). Reducing accesses to global memory improves overall processing performances.

Taking advantage of mathematical-computational tools together with currently available parallel processing platforms to accelerate the calculation of proteins' electronegativity profile, impact the amount of physical and human resources required for experimental testing.

6. Discussion

The use of PIM to identify EBOV proteins, made possible the observation of two main characteristics: (i) their polar profile is very similar to the antibacterial peptide group, and (ii) they are associated with the structural folded protein group. The first characteristic has already been observed in the effective application of antibacterial agents for the treatment of patients with EBOV [48]. The second characteristic is very likely, due to the presence of folded fragments in the EBOV proteins [49]. In this sense, the PIM can contribute in the understanding of the nature of the virus, from two aspects: i) its metric depends on the polarity of a peptide, and it does not require any other property associated with the EBOV proteins; and ii) the lower the number of physico-chemical properties studied, the greater the opportunity to identify regularities in the proteins. Additionally, the metrics of PIM can be used in any probabilistic predictive model oriented to epidemic scenarios, because it can be added to other programs that consider non-clinical variables such as climate change, deforestation, and the invasion of forests by humans. As in the case of the influenza virus, it is possible to design computer systems to generate early warnings of the outbreaks, based on clinical and non-clinical parameters. This effort should be shared by different health care organizations to promote the implementation of computational applications to monitor severe infectious disease outbreaks with epidemic potential.

7. Future trends

The application of the proteins associated with the Ebola virus to develop antiviral drugs will certainly lead to new treatments. However, the methods used in the last four decades, focused on the location of these proteins in living organisms and their experimental testing, are not practical because of the increasing costs in the supplies. This factor has prompted the development of bioinformatics algorithms, capable to evaluate the physico-chemical characteristics of 20^{10} proteins of 10 amino acids in length, in a period of 5 days of continuous processing time in a conventional computer. Nevertheless, it is not sufficient to measure one or several attributes to select a small group of peptides,

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because the resulting group might not even be suitable for evaluation (20^{10} x 1% = 10 240 000 000 peptides). It would be necessary to develop computational simulations of the peptides as well as the testing. This represents a great challenge if we consider that currently, there are more than 60 computational algorithms that assess different peptide properties in the linear and tertiary representation. Therefore to simulate the combination of all possible conditions and mechanisms where peptides interact in the organism, would be an enormous task, however all efforts must be directed to achieve that aim.

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