Polar Profile of Antiviral Peptides from AVPpred Database

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Abstract Diseases of viral origin in humans are among the most serious threats to health and the global economy. As recent history has shown the virus has a high pandemic potential, among other reasons, due to its ability to spread by air, hence the identification, investigation, containment, and treatment of viral diseases should be considered of paramount importance. In this sense, the bioinformatics research has focused on finding fast and efficient algorithms that can identify highly toxic antiviral peptides and to serve as a first filter, so that trials in the laboratory are substantially reduced. The work presented here contributes to this effort through the use of an algorithm already published by this team, called polarity index method, which identifies with high efficiency antiviral peptides from the exhaustive analysis of the polar profile, using the linear sequence of the peptide. The test carried out included all peptides in APD2 Database and 60 antiviral peptides identified by Kumar and co-workers (Nucleic Acids Res 40:W199–204, 2012), to build its AVPpred algorithm. The validity of the method was focused on its discriminating capacity so we included the 15 sub-classifications of both Databases.

Keywords Polarity index method · Antiviral peptides · AVPpred algorithm

Introduction

Within the antimicrobial peptides there is a group of particular importance, the antiviral peptides. These peptides are potential drugs to face the increased incidence of chronic viral infections caused by HIV and hepatitis [4, 5]; for that reason there is a need to accelerate the development of synthetic antiviral peptides. Inclusive, the testing of vaccines against HIV and hepatitis [6, 7] that are under
development offers no guarantee of success regardless of the millions of infected people. In counterpart, antiviral medications are not oriented to the most acute infections that cause serious diseases, such as hemorrhagic fever and cancer [8–10]; they have limited effectiveness and serious side effects. Perhaps more importantly, the antiviral chemotherapy is producing a rapid development of drug-resistant strains, as a result of the high rate of virus replication, due to the low resistance to replication [11].

In such a scenario, the work in proteomics and bioinformatics should focus on the generation of fast and robust algorithms [12, 13] identifying the antiviral action, from the linear or three-dimensional structure of the peptide. However, the simulation of the three-dimensional structure of the peptide is very complex, without taking into account other factors involved such as: The dynamics of the membrane and toxicity. In this work, we use the Polarity index method [14], already published by our team to identify SCAAP [15–17] and which only uses the linear peptide sequence to identify the same group of antiviral peptides that were identified by AVPpred algorithm [2].

This method [14] generates an exhaustive analysis of the peptide polarity through its polarity matrix. In this sense, the method apparently does not consider other factors, but indirectly it does, because it requires being calibrated by “a set of peptides” that are characteristic of the profile.

Materials and Methods

The identification of antiviral peptides performed by the polarity index method [14] requires the modifications below (Supplementary Material).

Polarity Index method. Updates

1. Replacing the Q[i,j] matrix in the source program [14] by the Table 1, which represents the incidences of antiviral sequences with a unique pathogenic action. Table 1 considers 60 AVPpred antiviral peptides extracted from Kumar and co workers [2], and 1 antiviral peptide extractor from APD2 database [1].

2. Replacing the rule in the source program [14] by P[i,j] + Q[i,j] vector complying with the next rule: polar interactions 15 or 16 are present in the 1st position, polar interaction 14 is not present from 3th to 8th positions, polar interaction 2 is not present in the first seven positions, polar interaction 5 is not present in the first five positions, polar interactions 4 or 8 are not present from 12th to 16th positions, polar interactions 14, 15 or 16 are not present from 11th to 16th positions, polar interaction 9 is not present in the 1st, 4th, 5th or 9th positions, polar interaction 1 is not present in the 10th or 11th positions, polar interaction 11 is not present in the first position, polar interaction 1 is not present in 10th or 11st positions, polar interaction 14 is not present in the 5th position, and polar interaction 4 is not present in the 4th position (Table 2).

APD2 Database Trial Data Preparation

We use 3,636 peptides in the APD2 Database [1] classified by their unique action against: 149 Gram− ONLY, 1711 Gram+/Gram− ONLY, 315 Gram+ ONLY, 141 cancer cells, 9 sperms, 88 HIV, 744 fungi, 21 insects, 244 mammalian cells, 47 parasites, 3 protists, 39 chemotaxis, 0 SCAAP, 125 virus; and also 1,059 by their unique action against: 111 Gram− ONLY, 213 Gram− ONLY, 518 Gram+/Gram− ONLY, 20 cancer cells, 0 HIV, 88 fungi, 35 HIN1, 2 insects, 11 mammalian cells, 9 parasites, 1 protists, 0 chemotaxis, 30 SCAAP, 0 sperms and 21 virus.

AVPpred Algorithm Trial Data Preparation

From Kumar and co workers [2] work about antiviral peptides, we took 60 validated and experimental peptides from 1,245 antiviral peptides. His work evaluated these 60 peptides with 25 physicochemical properties (Table 3) out of 144 properties from the same database and called it AAindex database [3]. These peptides were used to build the SVM AVPpred algorithm [2], and we are using them here to validate the Polarity index method.

Table 1 Q[i,j] Polarity matrix

|       | P+                  | P−                  | N                  | NP                  |
|-------|---------------------|---------------------|--------------------|---------------------|
| P+    | 0.0354861617        | 0.0184528027        | 0.0354861617       | 0.0681334287        |
| P−    | 0.0163236335        | 0.0177430809        | 0.0298083741       | 0.0709723234        |
| N     | 0.0404542238        | 0.0326472670        | 0.0872959569       | 0.0908445716        |
| NP    | 0.0667139813        | 0.0617459193        | 0.0915542915       | 0.1937544346        |

Incidences of 60 AVPpred antiviral peptides extracted from Kumar [2], and one antiviral peptide from APD2 [1].
Table 2  Polarity index method rules

| Position | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   |
|----------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| P[i,j]   | (1,1)| (1,2)| (1,3)| (1,4)| (2,1)| (2,2)| (2,3)| (2,4)| (3,1)| (3,2)| (3,3)| (3,4)| (4,1)| (4,2)| (4,3)| (4,4)|
| Q[i,j]   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

**Rule # 1**

Polar interactions 15 or 16 are present in the 1st position

**Rule # 2**

Polar interaction 14 is not present from 3rd to 8th positions

**Rule # 3**

Polar interaction 2 is not present in the first seven positions

**Rule # 4**

Polar interaction 5 is not present in the first five positions

**Rule # 5**

Polar interactions 4 or 8 are not present from 12th to 16th positions

**Rule # 6**

Polar interactions 14, 15 or 16 are not present from 11th to 16th positions

**Rule # 7**

Polar interaction 9 is not present in the 1st, 4th, 5th or 9th positions

**Rule # 8**

Polar interaction 1 is not present in the 10th or 11th positions

**Rule # 9**

Polar interaction 11 is not present in the 1st position

**Rule # 10**

Polar interaction 1 is not present in 10th or 11th positions

**Rule # 11**

Polar interaction 14 is not present in the 5th position

**Rule # 12**

Polar interaction 4 is not present in the 4th position

Identification Rules in Polarity index method for antiviral peptides. (✔) The polar interaction is present in the position. (✗) The polar interaction is not present in the position.

**Results**

Polarity index method is an algorithm that determines the probable antiviral pathogen action of peptides by using the peptide polarity sequence. It was applied to the APD2 database and the experimental peptides from AVPpred algorithm [2] with the following results.
Table 3  Physicochemical properties from AVPpred

| #  | AAindex ID    | Description                                           | Polarity | Reference |
|----|---------------|-------------------------------------------------------|----------|-----------|
| 1  | BEGF750103    | Conformational parameter of beta-turn                 | ✓        | [18]      |
| 2  | BULH740102    | Apparent partial specific volume                       |          | [19]      |
| 3  | CHAM810101    | Steric parameter                                      | ✓        | [20]      |
| 4  | CHOP780204    | Normalized frequency of N-terminal helix              | ✓        | [21]      |
| 5  | CHOP780206    | Normalized frequency of N-terminal non helical region | ✓        | [21]      |
| 6  | CHOP780215    | Frequency of the 4th residue in turn                   | ✓        | [21]      |
| 7  | CIDH920104    | Normalized hydrophobicity scales for alpha/beta-proteins | ✓    | [21]      |
| 8  | COHE430101    | Partial specific volume                                |          | [22]      |
| 9  | FASG760105    | PK-C                                                  | ✓        | [23]      |
| 10 | FAUJ880104    | STERIMOL length of the side chain                     |          | [24]      |
| 11 | FINA770101    | Helix-coil equilibrium constant                        | ✓        | [25]      |
| 12 | FINA910101    | Helix initiation parameter at position i – 1          |          | [26]      |
| 13 | GEIM800101    | Alpha-helix indices                                    | ✓        | [27]      |
| 14 | GEIM800102    | Alpha-helix indices for alpha-proteins                | ✓        | [27]      |
| 15 | GEIM800104    | Alpha-helix indices for alpha/beta-proteins           | ✓        | [27]      |
| 16 | KARP850101    | Flexibility parameter for no rigid neighbors          | ✓        | [28]      |
| 17 | KARP850102    | Flexibility parameter for one rigid neighbor          | ✓        | [28]      |
| 18 | AURR980101    | Normalized positional residue frequency at helix termini N4
| 19 | AURR980118    | Normalized positional residue frequency at helix termini C" | ✓ | [29] |
| 20 | AURR980120    | Normalized positional residue frequency at helix termini C4
| 21 | AVBF000107    | Slopes tripeptide FDPB PARSE neutral                  | ✓        | [30]      |
| 22 | GEOR030102    | Linker propensity from 1-linker dataset                |          | [31]      |
| 23 | KIDA850101    | Hydrophobicity-related index                           | ✓        | [32]      |
| 24 | GUYH850102    | Apparent partition energies calculated from Wertz-Scheraga index | ✓ | [33] |
| 25 | CASG920101    | Hydrophobicity scale from native protein structures   | ✓        | [34]      |

Selected physicochemical properties to build the AVPpred algorithm by Kumar [2]. AAindex amino acid index database [3]. Polarity (✓) physicochemical properties are directly or indirectly related to the polarity.

Table 4  Polarity index matches by linear sequence in virus

| No  | Code       | ID PUBMED   | Sequence                      | #1 | #2 | References |
|-----|------------|-------------|-------------------------------|----|----|------------|
| 1   | AVP_0618   | 6096849     | GPPISLERDLVGTNLGNAIAKLEAKELLESDQI |   |    | [35]       |
| 2   | AVP_0629   | 3788062     | KVLHLEGVEVNIALLSTNKAIVSVSANGVSVLTS |   |    | [36]       |
| 3   | AVP_0607   | 2893293     | DFLEENITALLEEAQIQQEKNMYELQKLNSWDVFG |   |    | [37]       |
| 4   | AVP_0168   | 8382405     | EGPTLGNAWAREIWATLFGKA          | N  |    | [38]       |
| 5   | AVP_0179   | 8382405     | NWAREIWATLFGKA                 | N  |    | [38]       |
| 6   | AVP_0467   | 10390360    | FAIKWEYVLILFLL                 |    |    | [39]       |
| 7   | AVP_0512   | 1848704     | SWLRDIWDLCEVLSDFK              |    |    | [40]       |
| 8   | AVP_0514   | 1848704     | SWLRDIWDLCEVLSDFK              |    |    | [40]       |
| 9   | AVP_0373   | 1848704     | SWLRDIWDLCEVLSDFK              |    |    | [40]       |
| 10  | AVP_0372   | 52472831    | SWLRDIWDLCEVLSDFK              |    |    | [41]       |
| 11  | AVP_0387   | 9223423     | TWLRAIWDWCTALTDFK              |    |    | [42]       |
| 12  | AVP_0323   | 8822631     | PPVYTKDVISSQISSMNQSLQSSKDYKEA  |    |    | [43]       |
| 13  | AVP_0328   | 3012869     | VANDPIDILNKKASKDLLEESKEWRRNQKLDSD | N  |    | [44]       |
| 14  | AVP_0210   | 11118300    | ANTAVFSSHNTQKIPAGPFNRRNLRMADLRQNAAFAG |    |    | [45]       |
| 15  | AVP_0024   | 1695254     | CGGNNLLRRAIEAQQHLLLQLTWGVKQLQQARILAVEYLKDQ | N  |    | [46]       |
| 16  | AVP_0312   | 16667080    | EQCREEEDDR                     | N  |    | [47]       |
| 17  | AVP_0358   | 15893660    | GGTIFDCGETCFLGTCYTPGSCGNYGFCYGTN | N  |    | [48]       |
### Table 4

| No | Code   | ID PUBMED  | Sequence                          | #1 | #2 | References |
|----|--------|------------|-----------------------------------|----|----|------------|
| 18 | AVP_0019 | 7841460    | GICRCICGKICRCICGKICRCICGKR       |    |    | [49]       |
| 19 | AVP_0284 | 21685289   | GICRCICGKRGCRCICGKR              |    |    | [50]       |
| 20 | AVP_0397 | 7529412    | GIKEWKRIVR1KDFLRN1V              | N  |    | [51]       |
| 21 | AVP_0361 | 16872274   | GLPVCGTECHGGTNGTGCNSWPSWVTN      | N  |    | [52]       |
| 22 | AVP_0286 | 10521339   | GVCRCICRGGVCRCICRR               |    |    | [53]       |
| 23 | AVP_0304 | 15949629   | KTCENLADTY                       |    |    | [54]       |
| 24 | AVP_0684 | 7031661    | LEAIPCSIPFPCLGKFIPv              |    |    | [55]       |
| 25 | AVP_0692 | 7031661    | LEAIPSIPELFALFIPv               |    |    | [55]       |
| 26 | AVP_0703 | 7031661    | LEAIPMISPEVFPPGKFIPv           |    |    | [55]       |
| 27 | AVP_0155 | 9777331    | LSYRCPCR                         | N  |    | [56]       |
| 28 | AVP_0409 | 1433527    | WMEDWREIELAKKAEELAKKAEELAKKAWSLWNWF |    |    | [57]       |
| 29 | AVP_0222 | 3031048    | YALLIRMAYKNI                     |    |    | [58]       |
| 30 | AVP_0224 | 19469303   | YQALLASMAYKNI                    |    |    | [59]       |
| 31 | AVP_0225 | 9504927    | YQLIAMYKNI                       |    |    | [60]       |
| 32 | AVP_0584 | 2578615    | YTSIHLISLEESQNQQKEQNEQELDFKWASLWNWF | N  |    | [61]       |
| 33 | AVP_0591 | 3040505    | YTSIHLISLEESQNQQKEQNEQELNFLNWASLWNWF | N  |    | [62]       |
| 34 | AVP_0310 | 9516047    | GLFGVLGSAHAVLPHYPVPAEIKL         | N  |    | [63]       |
| 35 | AVP_0183 | 782699     | DWHLGQGSAMEWKR                   |    |    | [64]       |
| 36 | AVP_0444 | 9784389    | FLFLPHTFLSKVL                     |    |    | [65]       |
| 37 | AVP_0452 | 10951191   | GLFDIICKIAESW                    |    |    | [66]       |
| 38 | AVP_0459 | 12089438   | GWWLKKIESIDAF                    |    |    | [67]       |
| 39 | AVP_0460 | 11053427   | HVDKVKAVKLKQQLRIMRLT            | N  |    | [68]       |
| 40 | AVP_0348 | 782699     | TTEAWDRAEAYARIEARIAAEAAQEEQKNEAILREL |    |    | [64]       |
| 41 | AVP_0354 | 782699     | TTEAWDRAEAYARIEARISQEQQKNEAILREL |    |    | [64]       |
| 42 | AVP_0612 | 3012869    | ELNKAADSEKESWIRRSNQKLDNSGNHQSTS  | N  |    | [44]       |
| 43 | AVP_0623 | 3012869    | IELNKAADSEKESWIRRSNQKLDNSGNHQSTS | N  |    | [44]       |
| 44 | AVP_0390 | 3012465    | AADLALAYAEFLGGRVLTT             |    |    | [69]       |
| 45 | AVP_0068 | 10077657   | HRWRRKRHRWRRHKWRRWRRWKR          |    |    | [70]       |
| 46 | AVP_0061 | 10077657   | KRWRRKRHRWRRHKWRRWRRWKR          |    |    | [70]       |
| 47 | AVP_0055 | 15095345   | RTRKGDGGKRTKRKRGRK              |    |    | [71]       |
| 48 | AVP_0191 | 14648299   | RGKIAAKIAAKIAAKIAAKIAAKIAIAKIA  |    |    | [72]       |
| 49 | AVP_0134 | 3012869    | ISIELNKAADSEKESWIRRSNQKLDNSGNHQQS | N  |    | [44]       |
| 50 | AVP_0482 | 2959959    | RKRKAVALLPAVLLA                  |    |    | [73]       |
| 51 | AVP_0483 | 2959959    | RKRKAVALLPAVLLA                  |    |    | [73]       |
| 52 | AVP_0302 | 2661722    | KDLFDK                           | N  |    | [74]       |
| 53 | AVP_0113 | 3788062    | GPPISLERLDVGTNLGNIAKLEDAKELLESSQDI |    |    | [35]       |
| 54 | AVP_0114 | 3788062    | HRIDLPPISLERLDVGTNLGNIAKLEDAKELLE |    |    | [35]       |
| 55 | AVP_0116 | 3788062    | ISLERLDVGTNLGNIAKLEDAKELLESSQDLRS |    |    | [35]       |
| 56 | AVP_0288 | 12810954   | CGECGGHIVGFRCMVRFLRLFVI          |    |    | [75]       |
| 57 | AVP_0289 | 9634230    | CRCCCELKSLCPFLTRVRLGLVL          | N  |    | [76]       |
| 58 | AVP_0138 | 6096849    | LVFPSDEFDASIQVNEKINQLAFIRKSDELHNN |    |    | [77]       |
| 59 | AVP_0278 | 2833514    | KWKLFKKIGIKFLHVAKKKF            |    |    | [78]       |
| 60 | AVP_0335 | 12886019   | CDVIALLCHLNT                    |    |    | [79]       |
| 61 | APD2_01209 | 7744961 | RICRCICGRRRICRCICGR               |    |    | [80]       |

Subject sequences identified by polarity index method in APD2 database [1] and by AVPpred [2], where peptides have action only on virus. #1: (N) rejected peptide by SVM AVPpred algorithm. #2: (N) rejected peptide by polarity index method. Source: National Center for Biotechnology Information, US National Library of Medicine [http://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins](http://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins) in database: Swiss-Prot (swissprot), accessed March 20, 2013
From the 25 physicochemical properties used to design the SVM AVPpred algorithm [2], 21 are directly or indirectly \((18/25 = 84\%)\) related to the polarity (Table 3, column Polarity with entries with figure \(\checkmark\)).

Polarity index method had over \(43/60 = 71\%\) efficiency detecting the 60 validated and experimental antiviral peptides from Kumar and coworkers [2] (Table 4, entries 1–60 and Table 5 column AVPpred), and \(1/1 = 100\%\) detecting the antiviral peptides from APD2 database (Table 4, entry 61 and Table 5, column Virus). There are no coincidences between both excluding sets (Table 4, columns #1 and #2).

### Discussion

When reviewing different databases of antimicrobial peptides, we detected a peptide with predominantly toxic action toward a pathogenic group; this allows us to assume that nature considers only small changes in the primary structure of the peptide to induce its possible pathogenic action. In that sense, the peptide linear structure plays an important role in the identification of its pathogenic action, when we use algorithms that use “training sets” with the desired profile.

Although the physicochemical property called polarity is involved in most of the algorithms that predict anti-virus peptides, this method has an innovative aspect as it expresses the metric through a polarity matrix that includes 16 interactions. We see this matrix as a picture of the polar dynamics of the peptide. The polarity matrix clearly shows a pattern that led us to achieve an identification efficiency of 70% on the AVPpred database. The same pattern also rejected other groups of peptides in APD2 database, with the exception of the anti-virus set. We assume that if we built the matrix with one digit, perhaps we did not have enough information to focus the method correctly.

We believe the effectiveness of the polarity index method in terms of the computing resources required makes it suitable candidate for a more detailed analysis related to the subdomains of peptides. In this regards, we have initiated a comprehensive classification of the APD2 database gathering, from published manuscripts, the toxicity values of antimicrobial peptides and thus explore peptide sub-domains with specific and very toxic pathogenic action. Our team is working on this as we consider it of vital importance to strongly support basic scientific research. We have also published work where the same method is used to understand the profile of the “first proteins” from 4 billion years ago. For this task, we are using clusters of GPU coprocessors, which will allow the analysis of 15 amino acids in length peptides.

Finally, within the antiviral peptide group, there are two sub-groups not approached in this work as they constitute by themselves an independent topic for the importance they
have and the degree of subject matter expertise required: the influenza A type H1N1 and HIV peptides. Given their potential to provoke a world pandemic, these two groups of peptides concentrate the efforts of several research groups, as they can undoubtedly become a problem of enormous proportions. Our team is now directing the method toward the identification of these two sub-groups.

Conclusions

In summary, we report an implementation of a polarity index method in the exhaustive prediction of antiviral peptides from AVPpred and APD2 databases, with high level of discriminative efficiency (44/61 = 72), from the reading of its linear sequence.

Availability

The test files and source code are given as “Supplementary Material”

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Conflict of Interest

We declare that we do not have any financial and personal interest with other people or organizations that could inappropriately influence (bias) our work.

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