

positive predictive value, and negative predictive value, respectively). We remark that the accuracy of our SVM is better than or on par with that of APPNN,⁹ with a simpler, more transparent structure.

In this Article, we make use of this transparent structure of the Budapest Amyloid Predictor. We present numerous patterns related to amyloidicity, such that each of those patterns grasps hundreds or even tens of thousands of individual hexapeptides and gives predictions of their amyloid-forming properties. For example, we show that for all (independent) substitutions of the 20 amino acids for letter “x”, the hexapeptides CxFLFx, FxFLWx, or xxIVIV are all predicted to be amyloids by the Budapest Amyloid Predictor. Note that each of these patterns describes $20^2 = 400$ different hexapeptides. We also note that no amyloid-forming patterns exist with three x’s for the predictor. All 5531 amyloid-forming hexapeptide patterns with two x’s are listed in Table S1.

We also show several patterns, which, by the Budapest Amyloid Predictor, would not form amyloids. For example, the patterns xxDDxx, xxPx Dx, and xxPKxx with any (independently chosen) amino acids for the positions denoted by x are predicted to be nonamyloids by our Budapest Amyloid Predictor. Note that each of these patterns succinctly describes $20^4 = 160\,000$ hexapeptides. We add that nonamyloid patterns with five x positions do not exist for our tool at <https://pitgroup.org/bap>. All of the nonamyloid forming hexapeptide patterns with four x positions are listed in Table 2.

We note that these patterns are succinct representations of the predictions of the Budapest Amyloid Predictor (BAP), whose accuracy rate is 84%;¹⁴ that is, we do not state, for example, that all CxFLFx hexapeptides are amyloids, but we state that all of them are predicted to be amyloids by the BAP tool. The transparent linear structure of the Support Vector Machines makes possible the derivation of these intuitive, useful, and well-applicable patterns from an artificial intelligence (AI) tool, as we clarify in this Article.

We need to add also that today we are living in the era of fast-developing AI methods and tools in numerous fields of science and technology. Most of these tools work as follows.

Suppose the tool needs to compute a value $f(y)$ from another value y . For constructing such an AI tool, the following steps are applied:

- A large set of previously acquired, correct $(y, f(y))$ pairs are partitioned into two classes: the training set A and the test set B.
- The training set A is applied to construct a tool, which assigns the predicted value of $f(y)$, denoted by $f_p(y)$, to each y .
- The test set B is used for evaluating the correctness of the tool: the predicted value, produced by the tool, $f_p(y)$, is compared to the correct, previously known $f(y)$.

The AI tool is deemed “good” if it is correct for a large enough portion of the test values.

In general, however, it is difficult to get insight into the intrinsic decision mechanisms of a typical AI tool; this is especially true for the deep neural networks, which are applied widely today.

In the case of linear Support Vector Machines,¹⁵ the decision mechanism is much more transparent, and one can exploit a highly correct SVM for gaining unprecedented scientific information in certain cases.¹⁹ In this Article, we

show a novel and original method for gaining site-specific amyloid-forming properties of amino acids in hexapeptides and preparing amyloid-forming and nonamyloid forming patterns for the succinct representation of the SVM prediction results for hundreds (cf., Table S1) or even tens of thousands (cf., Table 2) of hexapeptides at the same time.

METHODS

We have introduced the Budapest Amyloid Predictor Web server¹⁴ by applying linear Support Vector Machines as the underlying prediction tool,¹⁵ and the Waltz data set^{16,17} for training and testing purposes. The Waltz data set consists of 1415 hexapeptides, from which 514 peptides are experimentally labeled as “amyloidogenic” and 901 hexapeptides as “nonamyloidogenic”. The Budapest Amyloid Predictor (<https://pitgroup.org/bap>) was constructed as follows:

(i) Each amino acid from the 20 proteinogenic ones was characterized by a 553-dimensional vector, corresponding to its physicochemical properties published in AAindex.¹⁸ Therefore, a hexapeptide was represented by a length $6 \times 553 = 3318$ vector z . We note that this highly redundant representation has given somewhat better predictions than more concise ones¹⁴ and has not caused any difficulties in what follows.

(ii) By applying a quadratic programming algorithm for SVM computation from the SciKit-learn Python library,²⁰ we have computed a vector w and a scalar b such that if the sign of $w \cdot z + b$ is positive, then the prediction is “amyloidogenic”; otherwise, it is “nonamyloidogenic”, with 84% accuracy, for any vector z , representing a hexapeptide.

(iii) One can write the dot product $w \cdot z$, with $l = 553$, as

$$w \cdot z = \sum_{i=1}^{6l} w_i z_i = \sum_{j=1}^6 \sum_{i=(j-1)l+1}^{jl} w_i z_i \quad (1)$$

For any given $j = 1, 2, \dots, 6$, the $l z_i$ ’s are determined by the amino acid at position j at the hexapeptide. This means that we have only $6 \times 20 = 120$ sums in eq 1 (for six positions and 20 amino acids), and these 120 values can be precomputed. Table 1 of ref 14 lists these precomputed values. Because we need the same table in the present work, we include it also as Table 1 here.

(iv) Table 1 makes it possible to decide if a hexapeptide is predicted to be amyloidogenic or not, by “hand”; for example, to decide if IVIVIV is amyloidogenic or not, we need to add up the numbers, corresponding to I in the first, to V in the second, to I in the third, to V in the fourth, to I in the fifth, and to V in the sixth column, that is:

$$-0.06 - 0.14 + 0.26 + 0.14 - 0.06 + 0.01 = 0.15$$

and we need to add to this $w \cdot z$ value the scalar $b = 1.083$, which equals 1.233, a positive number, so IVIVIV is predicted to be amyloidogenic.

We refer to Table 1 as the Amyloid Effect Matrix.

As we have demonstrated in paragraph (iv) above, one can simply make the prediction of the SVM by using the values solely from this matrix.

From now on, we would like to exploit the Amyloid Effect Matrix for finding succinct descriptions of amyloidogenic and nonamyloidogenic patterns among the 64 million possible hexapeptides.

Patterns of Amyloidicity. Here, we would like to find very characteristic positions and substitutions, which already

Table 1. Amyloid Effect Matrix, Constructed from the Precomputed Values from Equation 1^a

	1	2	3	4	5	6
A	-0.26	-0.32	-0.27	-0.14	-0.43	-0.22
R	-0.45	-0.41	-0.46	-0.33	-0.52	-0.35
N	-0.40	-0.34	-0.49	-0.27	-0.46	-0.30
D	-0.49	-0.43	-0.56	-0.41	-0.56	-0.36
C	-0.09	-0.21	0.03	-0.05	-0.17	-0.05
Q	-0.37	-0.30	-0.36	-0.34	-0.48	-0.32
E	-0.51	-0.41	-0.43	-0.30	-0.61	-0.39
G	-0.23	-0.37	-0.46	-0.37	-0.30	-0.33
H	-0.32	-0.26	-0.26	-0.30	-0.35	-0.25
I	-0.06	-0.08	0.26	0.09	-0.06	-0.07
L	-0.10	-0.18	0.02	0.04	-0.22	-0.13
K	-0.39	-0.45	-0.51	-0.35	-0.59	-0.32
M	-0.17	-0.25	-0.02	-0.10	-0.19	-0.18
F	-0.13	-0.11	0.05	-0.03	-0.13	-0.11
P	-0.56	-0.38	-0.56	-0.51	-0.42	-0.45
S	-0.37	-0.35	-0.41	-0.30	-0.48	-0.23
T	-0.34	-0.33	-0.28	-0.23	-0.40	-0.23
W	-0.17	-0.17	-0.09	-0.06	-0.12	-0.16
Y	-0.23	-0.11	-0.13	-0.06	-0.18	-0.15
V	-0.05	-0.14	0.19	0.14	-0.19	0.01

^aThe rows correspond to the amino acids, while the columns correspond to the positions. The larger numbers show stronger amyloidogenic properties in the given position. Source: ref 14 (Copyright 2021 the authors). In ref 14, by ordering the columns of this table, a position-dependent amyloidogenicity order of amino acids is given in a subsequent table.

ensure us that all of the hexapeptides fitting those patterns are homogeneously either amyloidogenic or nonamyloidogenic. Let us see an example:

Example 1. Let us fix the amino acid proline (P) at positions 3 and 4 and leave all four other positions free. Let us consider the pattern

xxPPxx

We state that for all (independent) substitutions for x's, the Budapest Amyloid Predictor (abbreviated as BAP) says that the hexapeptide is not amyloid. Because we have four x's, the pattern xxPPxx describes exactly $20^4 = 160\,000$ hexapeptides, so we state that not one of these 160 000 hexapeptides is predicted to be amyloidogenic.

It is very easy to verify this statement from Table 1. The values corresponding to P's in the third and in the fourth positions (-0.56 and -0.51) add up to -1.07 . Now, even if we take the largest values of columns 1, 2, 5, and 6, that is, -0.05 , -0.08 , -0.06 , and 0.01 , respectively, their sum is -1.25 , and adding $b = 1.083$ to this value, we would still have a result to be a negative number. That is, even the largest values from columns 1, 2, 5, and 6 could not outweigh the large negative sum of -1.07 of the two consecutive proline residues in positions 3 and 4. This means that all hexapeptides, fitting to the pattern of xxPPxx, are predicted to be nonamyloids by BAP.

Example 2. Similarly, one can also find amyloid patterns. For example, we state that all 400 ($=20 \times 20$) hexapeptides, fitting to the pattern FxFLWx, are predicted to be amyloids. One can easily verify this statement from Table 1. The F in position 1 adds -0.13 , in position 3 adds 0.05 , L in position 4 adds 0.04 , and W in position 5 contributes -0.12 ; their sum is -0.16 . Now, if we take the smallest values from columns 2 and

6, that is, -0.45 and -0.45 , and add $b = 1.083$ to their sum, we will get $-0.16 - 0.45 - 0.45 + 1.083 = 0.023$, that is, a positive number, so independently from the choice of the x's, FxFLWx is predicted to be an amyloid-forming hexapeptide.

Minimal Patterns. In what follows, we will find all of the minimal patterns of amyloidicity and nonamyloidicity. These minimal patterns are the most concise representations of the amyloid-forming rules of the BAP predictor.

Here, the "minimal" word means that we cannot decrease the number of the fixed amino acids without invalidating the rule. Our goal is to find the patterns with the minimum number of amino acids fixed. From such minimal patterns, one can easily generate valid but nonminimal ones; for example, the xxPPxx pattern is predicted to be nonamyloidogenic for any substitutions of x's. Therefore, WxPPxx or VIPPxx are also nonamyloid patterns for any substitutions for x, but they are not minimal. It is easy to see by observing Table 1 that neither xxxPxx nor xxPxxx are valid nonamyloid patterns, so xxPPxx is a minimal pattern.

Finding All Minimal Patterns. Our goal is to find every hexapeptide pattern, both the amyloidogenic and the non-amyloidogenic ones, as predicted by BAP.

Finding these patterns is straightforward using the Amyloid Effect Matrix (Table 1). Suppose that we intend to generate the minimal amyloid indicating patterns. Finding the non-amyloid patterns is a similar procedure.

Verifying whether a pattern is a valid amyloid indicator is easy. We need to generalize the steps done in the examples. We substitute the minimal amyloid effective amino acids on the free positions (denoted by s) and check its score. If the score is already positive, then this least amyloidogenic hexapeptide is already amyloid, and then every other hexapeptide from this space is amyloid too.

Finding the rules for hexapeptides could be done by exhaustive search. Let say we want to find all of the rules with k fixed amino acids, where k is between 1 and 6. In what follows, we call the core of the rule the number of fixed amino acids (e.g., the core of rule xxPPxx is 2). The positions s will be referred to as free positions.

For finding all of the rules with core k , our approach is

- (i) generating all of the $\binom{6}{k}$ index subsets;
- (ii) for each index subset, we generate all of the 20^k rule candidates by assigning all of the possible amino acids to the k core positions; and
- (iii) verify the validity of the pattern by checking each of them as already described.

We remark that this exact exhaustive search is not fast computationally, but it perfectly works for hexapeptides. The number of verifications is

$$\sum_{k=1}^{k=6} \binom{6}{k} 20^k = 21^6 - 1$$

less than 86 million, and its running time is several hours in today's low-end computers.

The amyloid patterns are listed in Table S1, while the nonamyloid patterns are in Table 2.

The Case of Restricted Amino Acid Classes. Amino acids are frequently characterized and classified by their chemical properties, like polarity, nonpolarity, hydrophobicity, hydrophilicity, etc. If we want to find patterns of amyloidicity for the free positions, denoted by x, one can choose

substitutions only from a given restricted class, and then one can have stronger, more specific patterns than in the general case, when x can be substituted by any of the 20 amino acids.

Finding those patterns in the restricted classes can be done analogously to the general case. The minimum values of Table 1 from the given class need to be considered.

Statistical Analysis. We refer to the work¹⁴ for the statistical accuracy estimations of the Budapest Amyloid Predictor. There we have shown that the predictor has ACC = 0.84, TPR = 0.75, TNR = 0.9, PPV = 0.8, and NPV = 0.86 (that is, accuracy, true positive ratio, true negative ratio, positive predictive value, and negative predictive value, respectively). Figure 1 of ref 14 also gives the ROC (receiver operating characteristics) curve of the tool, with the AUC (area under curve) value as 0.89.

RESULTS AND DISCUSSION

Figure 1 visualizes the substitutions into a nonamyloid and an amyloid pattern.

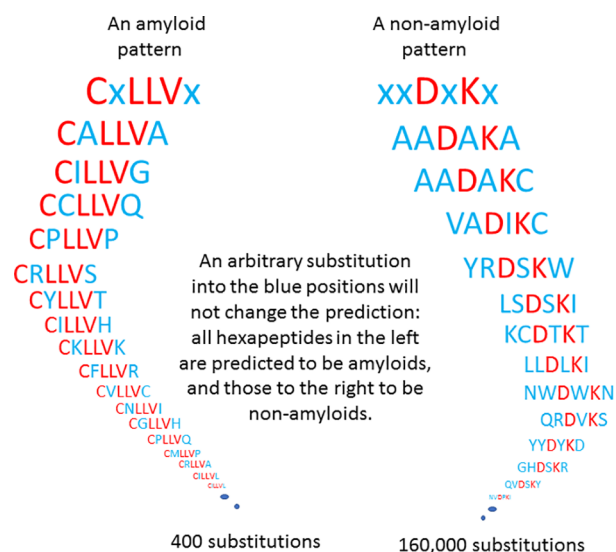


Figure 1. Examples of amyloid and nonamyloid patterns.

We have successfully identified all 5531 minimal amyloid patterns (Table S1) using BAP. For example, xxIYCI, IFIYxx, and CxVVxC are amyloid patterns from Table S1.

We have found that almost all amyloidogenic hexapeptide patterns contain valine (V) and/or isoleucine (I) residues, both of branched and hydrophobic side chains. Among the 5531 patterns identified (Table S1), only 16 patterns are free of both V and I: CxFLWx, CxFLFx, CxCLWx, CxCLFx, CxLLWx, CxLLFx, LxFLWx, LxFLFx, LxCLWx, LxCLFx, LxLLWx, LxLLFx, FxFLWx, FxFLFx, FxCLWx, and CxFLCx.

Furthermore, leucine, L, the third branched and hydrophobic side chain, is represented one or more times in the above listed 16 patterns. In conclusion, V, I, and L residues make hexapeptides intrinsically amyloidogenic.

We remark that no amyloid pattern with three free positions (i.e., x) exists, by the results of the exhaustive search.

Table 2 lists the 24 nonamyloid patterns, each with four free positions. No other nonamyloid patterns exist with four free positions, and no nonamyloid pattern exists with five free positions by the results of the exhaustive search, described in the Methods.

Table 2. List of All Nonamyloid Patterns with Four Free Positions^a

PxPxxx	PxDxxx	xxPPxx	xxPDxx	xxPGxx	xxPKxx
xxPQxx	xxDPxx	xxDDxx	xxDGxx	xxDKxx	xxDQxx
xxKPxx	xxKDxx	xxNPxx	xxGPxx	xxRPxx	xxPxEx
xxPxKx	xxPxDx	xxDxEx	xxDxKx	xxDxDx	xxKxEx

^aIt contains 24 patterns. Note that each pattern describes $20^4 = 160\,000$ hexapeptides succinctly, all of which are predicted to be nonamyloids by the Budapest Amyloid Predictor.¹⁴ From the 24 patterns, only nine do not contain proline in a fixed position.

Results for Amino Acid Subsets. In this subsection, we find amyloid patterns when the x positions can be substituted only by the members of some specific amino acid classes. The amino acid classes we examine are small nonpolar, hydrophobic, and polar amino acids, as classified by ref 21, and listed in the second column of Table 3.

Table 3. Amino Acid Subsets Examined^a

class name	class elements listing	no. of free positions	no. of patterns
small nonpolar	GAST	3	411
hydrophobic	CVLIMPFYW	3	43
polar	DENQHQR	3	4
hydrophobic-{P}	CVLIMFYW	5	38
amino acids-{P}	QFYESNCMLIAHGWRKVT	3	4

^aThe classification of the residues in the first three rows is as in ref 21. The last two rows correspond to the classes where we left out proline, a well-known structure-breaker from the hydrophobic set or from all of the amino acids. The third column shows the number of free positions we get in the special substitutions, and the fourth column shows the number of patterns found for these special substitutions for "x".

When the substitutions to the free positions, denoted by x, can be done only from special subsets, listed in Table 3, we can get amyloid rules with three free positions, in contrast with the unrestricted case, when our rules have two free positions (Table S1).

When x is allowed to be substituted from the small nonpolar set, then 411 patterns can be found with three free positions, for example, VIIxxx, IIIxxx, VxIVxx, VxIIxx, VxILxx, VxIFxx, VxICxx, VxIWxx, VxVVxx, and VxVIxx. All of the existing 411 patterns are listed in Table S2. No such pattern exists with four free positions.

If x is chosen from the hydrophobic set, then 43 patterns exist with three free positions, listed in Table 4. No such pattern exists with four free positions, by the results of the exhaustive search.

When x is chosen from polar amino acids, then the only four patterns with three free positions are xxIVIx, xxIVWx, xxIIIx, and xxVVIx.

We note that no pattern exists in these three cases without V and I amino acids; that is, all of the patterns in these three restricted substitutions contain either valine or isoleucine in fixed positions.

If proline is not allowed to be substituted for any x, but otherwise the remaining 19 amino acids can be chosen for the x positions, then we have exactly four amyloid patterns with three x positions: xxIVIx, xxIVWx, xxIIIx, and xxVVIx; note

Table 4. List of All 43 Amyloidogenic Patterns with Three Free Positions When x Is Hydrophobic, Chosen from CVLIMPFYW^a

VxIVxx	VxIIxx	VxILxx	VxIFxx	VxVVxx	VxVLxx	VxVLxx	IxIVxx
IxIIxx	IxILxx	IxVVxx	IxVIxx	CxIVxx	CxIIxx	CxILxx	CxVVxx
CxVIxx	LxIVxx	LxIIxx	LxILxx	LxVVxx	LxVIxx	FxIVxx	FxIIxx
FxVVxx	MxIVxx	MxIIxx	MxVVxx	WxIVxx	WxIIxx	GxIVxx	YxIVxx
xxIVLx	xxIVxV	xxIVxC	xxIVxI	xxIVxF	xxIIxV	xxIIxC	xxIIxV
xxVVxV	xxVVxC	xxVIxV					

^aEach pattern describes $9^3 = 729$ hexapeptides.

Table 5. List of All 38 Amyloidogenic Patterns with Five Free Positions When x Is Hydrophobic, but Cannot Be Proline, Chosen from CVLIMFYW^a

Vxxxx	Ixxxx	Cxxxx	Lxxxx	Fxxxx	Mxxxx	Wxxxx	xIxxxx
xFxxxx	xYxxxx	xVxxxx	xWxxxx	xLxxxx	xCxxxx	xxIxxx	xxVxxx
xxFxxx	xxCxxx	xxLxxx	xxMxxx	xxWxxx	xxxVxx	xxxLxx	xxxLxx
xxxFxx	xxxCxx	xxxWxx	xxxYxx	xxxIx	xxxWx	xxxFx	xxxCx
xxxxYx	xxxxV	xxxxC	xxxxI	xxxxF	xxxxL		

^aEach pattern describes $8^5 = 32\,768$ hexapeptides.

that without the restriction to proline, no amyloid pattern exists with three free positions.

These four patterns are exactly the same as in the case of polar residue substitutions, but the set of hexapeptides they represent differs: in the case of polar substitutions, each of the four patterns represent $7^3 = 343$ hexapeptides, while for the nonproline substitutions, $19^3 = 6859$ hexamers.

If x could be chosen from hydrophobic amino acids, except proline, the “structure breaker”, then we have the “largest” patterns of amyloidogenicity: 38 patterns exist with just one fixed position, listed in Table 5. Note that each of those patterns describes $8^5 = 32\,768$ hexapeptides, such that all of them are predicted to be amyloidogenic.

CONCLUSIONS

Here, we established the patterns of amyloidogenicity and nonamyloidogenicity in the case of hexapeptides, based on a Support Vector Machine-based predictor, available at <https://pitgroup.org/bap>. Because there are 20^6 , that is, 64 million hexapeptides, formed from the 20 proteinogenic amino acids, it is worthwhile to show succinct patterns of both amyloid-forming and nonforming hexapeptides, based on the BAP predictor. First, in the literature, we have introduced hexapeptide patterns with free-to-choose positions, denoted by “x”, describing hundreds, or even tens of thousands of hexapeptides with the same predicted amyloidogenicity, each with only six characters. In Table S1, we list 5531 amyloid patterns (e.g., CxLLVx), where for the positions, denoted by “x”, we can substitute any of the 20 amino acids, and the resulting hexapeptide will be predicted as “amyloidogenic” by BAP. Note that each of the patterns in Table S1 describes 400 hexapeptides. Similarly, we have found succinct representations of the BAP-predicted nonamyloidogenic hexapeptides (Table 2), each with four free positions. Therefore, each entry of Table 2 represents $20^4 = 160\,000$ hexapeptides. We have also examined restricted substitutions for the x positions, like small nonpolar, or hydrophobic or polar amino acids, and described succinct patterns for those hexamers in Tables 3, 4, 5, and S2.

To our knowledge, no machine learning tool was used before to derive succinct chemical knowledge through simple patterns for deep structural properties.

ASSOCIATED CONTENT

Data Availability Statement

The Budapest Amyloid Predictor webserver is available freely at <https://pitgroup.org/bap>. The hexapeptide patterns identified in this work are enclosed in the text or in the Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c02513>.

Table S1 lists all of the existing minimal patterns of amyloid-forming hexapeptides, computed from the SVM model of the Budapest Amyloid Predictor; Table S2 lists all of the existing minimal patterns of amyloid-forming hexapeptides, computed from the SVM model of the Budapest Amyloid Predictor, when the substitutions for the positions, denoted by “x”, are allowed by small, nonpolar residues, G, A, S, and T (PDF)

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Author Contributions

A.P., V.F., and V.G. initiated the study and evaluated the results, L.K. and E.S. constructed the SVM for the prediction, B.V. constructed the webserver, V.G. oversaw the work and wrote the paper, and A.P., V.F., and V.G. secured the funding.

Author Contributions

[†]L.K. and E.S. contributed equally.

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Notes

The authors declare no competing financial interest.

DEDICATION

Dedicated to the memory of Imre G. Csizmadia.

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