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MODELLING ANALYSIS OF AMINO ACIDS HYDROPHOBICITY

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Abstract. The aim of the research was to perform a structural modelling analysis on amino acids hydrophobicity in order to identify, characterize and quantify the relationship between the structure and the property. A sample of twenty essential amino acids (alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine) was investigated by using the Molecular Descriptors Family on the Structure-Activity/Property Relationship approach. The property of interest was the hydrophobic or hydrophilic character measured on twenty-four different scales. The information extracted from the amino acids structure was used in order to generate and to calculate the Molecular Descriptors Family. For each hydrophobicity scale the best performing monovariate model in terms of goodness-of-fit were collected and analyzed. The resulted models have been used in order to predict the hydrophobicity of a sample of eleven non standard amino acids (seleno-L-cysteine, pyrrolysine, lanthionine, 2-aminoisobutyric acid, dehydroalanine, gamma-aminobutyric acid, ornithine, citrulline, homocysteine, hydroxyproline, and dopamine). All identified models were statistically significant ($p < 0.0001$). An internal validation approach was applied for analyzing the validity of the obtained models. The correlation coefficient calculated between the measured and estimated hydrophobicity varied from 0.6649 (hydrophobicity reported by Welling *et al.* 1985) to 0.9504 (hydrophobicity reported by Monera *et al.*, 1995). The obtained results showed that the amino acids hydrophobicity is a property linear related with compounds structure. The amino acids hydrophobicity is strong related with atomic charge through geometry interaction.
Keywords: Amino Acid, quantitative Structure-Property Relationship (qSPR), Molecular Descriptors Family (MDF)

Introduction

Amino acids, the building blocks of proteins, molecule that contains amine and carboxyl functional groups, play an important roles in biology such as: synthesis of proteins [1,2], intermediates of metabolic pathways [3], neurotransmitters [4,5], antibiotics [6,7]. The amino acids known as standard were most investigated. The biochemical, bioinformatics and evolutionary studies of standard amino acids lead also to the development of an online resource, as is for example the Amino Acid Explorer[a].

[a] Amino Acid Explorer. National Center for Biotechnology Information. URL: http://www.ncbi.nlm.nih.gov/Class/Structure/aa/aa_explorer.cgi

The quantitative investigations of the structure-activity relationships of amino acids are important for biological research [8] even if it is applied to the essential amino acids, to the amino acids found in biological systems [9], to the amino acids synthesized abiotically [10,11], or to those engineered by scientists [12]. The quantitative structure-property relationships (qSPRs) methodologies are mathematical approaches of linking chemical structure and compounds activity or property in a quantitative manner [13]. These methods were development due to computers and information technology progresses, offering a less costly and less time consuming determination of activities or properties of chemicals [14,15]. Some properties of amino acids were characterized by using these approaches [16-18].

Hydrophobic or hydrophilic character of an amino acid, very important in protein structure and protein-protein interactions, is one of the most studied properties. To date, many hydrophobicity scales were reported [19-24]. The differences between scales are significant: Janin (1979) and Kyte and Doolittle (1982) classify cistein as the most hydrophobic while Wolfenden *et al.* [25] while Rose *et al.* [24] do not. These differences could be explained by the fundamentally different methods used for constructing the scale.

The aim of the research was to identify and to quantify the interrelation between different hydrophobicity scales of standard amino acids and the structural information of standard amino acids.

Material and Method

Amino Acids Hydrophobicity

Two different samples of amino acids were included into analysis: one for estimation and other for prediction. First sample consisted of twenty standard amino acids was used for generation of the models and consisted of alanine (Ala), arginine (Arg), asparagine (Asn), aspartate (Asp), cysteine (Cys), glutamine (Gln), glutamate (Glu), glycine (Gly), histidine (His), isoleucine (Ile), leucine (Leu), lysine (Lys), methionine (Met), phenylalanine (Phe), proline (Pro), serine (Ser), threonine (Thr), tryptophan (Trp), tyrosine (Tyr), and valine (Val). Second sample consisted of non-standard amino acids (formed through modifications of standard amino acids) was used for prediction and consisted of selenocysteine (Sec), pyrrolysine (Pyl), lanthionine (Lth), 2-aminoisobutyric acid (Aib), dehydroalanine (Dhd), gamma-aminobutyric acid (Gab), ornithine (Oth), citrulline (Ciu), homocysteine (Hcy), hydroxyproline (Hyp), and dopamine (Dop).

The 3D structures of standard amino acids were used in order to identify the best model able to characterize the hydrophobic or hydrophilic character.

The hydrophobicity measured on twenty-four scales was the property of interest. The values of the measured hydrophobicity were taken from previously reported researches. Table I presented the abbreviation of the set (Abb.) linked with the reference to the hydrophobicity scale (Ref.).

Table I. Amino acids hydrophobicity scales

Abb.	Ref.	Set abb.	Ref.
Hyd_01	[19]	Hyd_13	[26]
Hyd_02	[20]	Hyd_14	[27]
Hyd_03	[21]	Hyd_15	[28]
Hyd_04	[22]	Hyd_16	[29]
Hyd_05	[30]	Hyd_17	[31]
Hyd_06	[32]	Hyd_18	[33]
Hyd_07	[34]	Hyd_19	[35]
Hyd_08	[36]	Hyd_20	[37]
Hyd_09	[24]	Hyd_21	[38]
Hyd_10	[23]	Hyd_22	[39]
Hyd_11	[40]	Hyd_23	[41]
Hyd_12	[42]	Hyd_24	[43]

Molecular Descriptor Family on Structure-Property Relationships

A qSPR method, called Molecular Descriptors Family on Structure-Property Relationships (MDF-SPR) was introduced [44] and proved its estimated and predictive abilities for different classes of biological active compounds [45-47]. The method used the information extracted from the 2D and 3D structures of compounds in order to identified and quantify the link between compound's structure and property. For each compound a series of molecular descriptors are generated and calculated [44]. The name of the descriptor comprised seven letter and the characters used (all possibilities are presented in Table II, [48]) showed the modality of its construction.

Table II. Characters used by the name of the molecular descriptor

Letter	Characters	No. of all possible characters
First	I-i-A-a-L-l	6
Second	m-M-n-N-S-P-s-A-a-B-b-G-g-F-f-H-h-I-i	19
Third	m-M-D-P	4
Fourth	R-r-M-m-D-d	6
Fifth	D-d-O-o-P-p-Q-q-J-j-K-k-L-l-V-E-W-w-F-f-S-s-T-t	24
Sixth	C-H-M-E-G-Q	6
Seventh	g-t	2

For the set abbreviated as Hyd_24, the model was obtained based on nineteen amino acids, due to the absence of the hydrophobicity of proline on the reference [43].

The models obtained by using the structure of the standard amino acids sample were used in estimation of the hydrophobic or hydrophilic character of the sample of non-standard amino acids.

Results

The interrelation between hydrophobicity of essential amino acids and their structure was investigated. The monovariate model with the best goodness-of-fit was identified for each hydrophobicity scale on the standard amino acids sample. The main characteristics of the models are presented in Table III.

A similarity analysis of the molecular descriptors used by models obtained on the standard amino acids was performed. The obtained frequency of the characters on the name of descriptors is presented in Table IV.

Table IV. Distribution of the character in descriptors name

1st letter		2nd letter		3rd letter		4th letter		5th letter		6th letter		7th letter	
Cha.	f_a	Cha.	f_a	Cha.	f_a	Cha.	f_a	Cha.	f_a	Cha.	f_a	Cha.	f_a
A	4	A	3	D	7	d	4	F	1	E	1	g	19
i	16	B	5	m	11	m	2	K	3	Q	23	t	5
l	4	f	1	P	6	r	18	L	5				
		G	1					O	7				
		H	1					p	5				
		I	1					W	3				
		m	7										
		n	5										

Cha. = character; f_a = absolute frequency

The statistical characteristics of the models presented in Table III expressed for estimation and prediction (leave-one-out analysis) is showed in Table V.

TABLE III. MDF-SPRs models of amino acids hydrophobicity

Amino acid property	Hyd_01	Hyd_02	Hyd_03	Hyd_04
MDF SPR Equation	$\hat{Y} = 0.86 - 0.96 \cdot x$	$\hat{Y} = -7.60 + 19.17 \cdot x$	$\hat{Y} = -3.37 + 7.35 \cdot x$	$\hat{Y} = -0.41 + 7.18 \cdot x$
SPR Determination (%)	88	87	71	85
MDF Descriptor (x)	lAmrLQg	iGPdLQg	iBmrWQt	AmDROQg
Dominant Atomic Property	Charge (Q)	Charge (Q)	Charge (Q)	Charge (Q)
Interaction via	Space (geometry)	Space (geometry)	Bonds (topology)	Space (geometry)
Interaction Model	$d \cdot \sqrt{Q}$	$d \cdot \sqrt{Q}$	Q^2/d	Q
Structure on Property Scale	Proportional	Inversed	Inversed	Proportional
Amino acid property	Hyd_05	Hyd_06	Hyd_07	Hyd_08
MDF SPR Equation	$\hat{Y} = 81.72 + 817.95 \cdot x$	$\hat{Y} = -1.99 + 10.63 \cdot x$	$\hat{Y} = -2.88 - 1.73 \cdot x$	$\hat{Y} = 1.68 - 0.92 \cdot x$
SPR Determination (%)	85	74	69	83
MDF Descriptor (x)	inMrpQg	iMPRoQg	LmDROQg	IAMdKQg
Dominant Atomic Property	Charge (Q)	Charge (Q)	Charge (Q)	Charge (Q)
Interaction via	Space (geometry)	Space (geometry)	Space (geometry)	Space (geometry)
Interaction Model	Q^{-2}	Q^{-1}	Q	$Q^2 \cdot d$
Structure on Property Scale	Inversed	Inversed	Logarithmic	Logarithmic

Amino acid property	Hyd_09	Hyd_10	Hyd_11	Hyd_12
MDF SPR Equation	$\hat{Y} = 0.86 + 1.74 \cdot x$	$\hat{Y} = 0.48 + -137.72 \cdot x$	$\hat{Y} = 1.85 - 753.09 \cdot x$	$\hat{Y} = -3.36 + 3.76 \cdot x$
SPR Determination (%)	81	81	83	81
MDF Descriptor (x)	inMrpQg	IHPrFQt	INPrWQg	iBDdwQg
Dominant Atomic Property	Charge (Q)	Charge (Q)	Charge (Q)	Charge (Q)
Interaction via	Space (geometry)	Bonds (topology)	Space (geometry)	Space (geometry)
Interaction Model	Q^{-2}	Q^2/d^2	Q^2/d	Q^2/d
Structure on Property Scale	Inversed	Logarithmic	Logarithmic	Inversed
Amino acid property	Hyd_13	Hyd_14	Hyd_15	Hyd_16
MDF SPR Equation	$\hat{Y} = 1.36 - 0.20 \cdot x$	$\hat{Y} = 5.30 - 3.78 \cdot x$	$\hat{Y} = -1.23 + 0.39 \cdot x$	$\hat{Y} = 11.05 + 1.85 \cdot x$
SPR Determination (%)	85	85	44	86
MDF Descriptor (x)	iIPmLQt	IAmrLQg	amMRLQt	lfPROQg
Dominant Atomic Property	Charge (Q)	Charge (Q)	Charge (Q)	Charge (Q)
Interaction via	Bonds (topology)	Space (geometry)	Bonds (topology)	Space (geometry)
Interaction Model	Q·d	Q·d	Q·d	Q
Structure on Property Scale	Inversed	Logarithmic	Inversed	Logarithmic
Amino acid property	Hyd_17	Hyd_18	Hyd_19	Hyd_20
MDF SPR Equation	$\hat{Y} = 4.64 - 2.16 \cdot x$	$\hat{Y} = 14.55 + 23.43 \cdot x$	$\hat{Y} = -4.36 + 5.94 \cdot x$	$\hat{Y} = 1.43 - 2.73 \cdot x$
SPR Determination (%)	84	78	78	79
MDF Descriptor (x)	lbmdKQg	inMrpQg	ibDRPQg	AmDROQg
Dominant Atomic Property	Charge (Q)	Charge (Q)	Charge (Q)	Charge (Q)
Interaction via	Space (geometry)	Space (geometry)	Space (geometry)	Space (geometry)
Interaction Model	$Q^2 \cdot d$	Q^{-2}	Q^2	Q
Structure on Property Scale	Logarithmic	Inversed	Inversed	Proportional
Amino acid property	Hyd_21	Hyd_22	Hyd_23	Hyd_24
MDF SPR Equation	$\hat{Y} = 6.55 - 27.79 \cdot x$	$\hat{Y} = 1.47 + -6.57 \cdot x$	$\hat{Y} = -29.73 + -11.96 \cdot x$	$\hat{Y} = 86.05 + 843.88 \cdot x$
SPR Determination (%)	66	75	82	90
MDF Descriptor (x)	immRoQg	AmDROQg	iBDMkEt	inMrpQg
Dominant Atomic Property	Charge (Q)	Charge (Q)	Electronegativity (E)	Charge (Q)
Interaction via	Space (geometry)	Space (geometry)	Bonds (topology)	Space (geometry)
Interaction Model	Q^{-1}	Q	$Q^{-2} \cdot d^{-1}$	Q^{-2}
Structure on Property Scale	Inversed	Absolute	Inversed	Inversed

Q = change; d = distance

The models presented in Table III were used in order to predict the hydrophobicity of the non-standard amino acids. The predicted activity according with the hydrophobicity scale is presented in Table VI. The hydrophobicity of proline on the Monera *et al*. scale was of 96.57.

TABLE V. MDF-SPRs models: statistical characteristics

Abb.	Regression model						Leave-one-out		
	n	r	F (p)	s	$[_{95\%}CI]_{Intercept}$ ($p_{t\text{-}Stat}$)	$[_{95\%}CI]_{Slop}$ ($p_{t\text{-}Stat}$)	r_{loo}	F_{loo}	s_{loo}
Hyd_01	20	0.9376	131 ($1.09 \cdot 10^{-9}$)	0.12	[0.77 – 0.94]*	[-1.14 – -0.78]*	0.9263	109 ($4.73 \cdot 10^{-9}$)*	0.13
Hyd_02	20	0.9327	120 ($2.10 \cdot 10^{-9}$)	1.11	[-9.05 – - 6.14]*	[15.50 - 22.84]*	0.9226	103 ($7.25 \cdot 10^{-9}$)	1.18
Hyd_03	20	0.8434	44 ($3.00 \cdot 10^{-6}$)	0.48	[-4.42 – - 2.32]*	[5.03 – 9.67]*	0.8009	32 ($2.25 \cdot 10^{-5}$)	0.54
Hyd_04	20	0.9238	105 ($6.24 \cdot 10^{-9}$)	0.52	[-0.79 – - 0.02]*	[5.70 – 8.65]*	0.9018	78 ($6.01 \cdot 10^{-8}$)	0.58
Hyd_05	20	0.9232	104 ($6.69 \cdot 10^{-9}$)	20.73	[66.20 – 97.23]*	[649.29-986.61]*	0.9082	85 ($3.16 \cdot 10^{-8}$)	22.58
Hyd_06	20	0.8608	52 ($1.11 \cdot 10^{-6}$)	1.01	[-2.70 – - 1.29]*	[7.52 – 13.75]*	0.8288	39 ($6.49 \cdot 10^{-6}$)	1.11
Hyd_07	20	0.8309	40 ($5.70 \cdot 10^{-6}$)	1.70	[-4.30 – - 1.39]*	[-2.30 – - 1.15]*	0.7936	30 ($3.34 \cdot 10^{-5}$)	1.87
Hyd_08	20	0.9128	90 ($2.02 \cdot 10^{-8}$)	0.42	[1.26 – 2.10]*	[-1.12 – - 0.72]*	0.8935	70 ($1.31 \cdot 10^{-7}$)	0.46
Hyd_09	20	0.8974	74 ($8.21 \cdot 10^{-8}$)	0.05	[0.82 – 0.90]*	[1.32 – 2.17]*	0.8744	58 ($4.73 \cdot 10^{-7}$)	0.06
Hyd_10	20	0.8997	76 ($6.76 \cdot 10^{-8}$)	0.32	[0.29 – 0.70]*	[-172.49 – - 105.66]*	0.8599	56 ($6.37 \cdot 10^{-7}$)	0.36
Hyd_11	20	0.9116	89 ($2.26 \cdot 10^{-8}$)	2.07	[0.64 – 3.06]*	[-921.24 – - 584.95]*	0.8731	51 ($1.13 \cdot 10^{-6}$)	2.56
Hyd_12	20	0.8986	75 ($7.42 \cdot 10^{-8}$)	0.45	[-4.22 – - 2.50]*	[2.85 – 4.67]*	0.8812	62 ($2.93 \cdot 10^{-7}$)	0.48
Hyd_13	20	0.9252	107 ($5.30 \cdot 10^{-9}$)	0.36	[1.02 – 1.70]*	[-0.25 – - 0.16]*	0.9003	75 ($8.02 \cdot 10^{-8}$)	0.42
Hyd_14	20	0.9208	100 ($8.69 \cdot 10^{-9}$)	0.80	[4.07 – 6.54]	[-4.58 – - 2.99]*	0.9073	84 ($3.48 \cdot 10^{-8}$)	0.86
Hyd_15	20	0.6649	14 ($1.38 \cdot 10^{-3}$)	1.21	[-1.99 – - 0.48]+	[0.17 – 0.61]+	0.5961	7 ($1.44 \cdot 10^{-2}$)	1.37
Hyd_16	20	0.9259	108 ($4.88 \cdot 10^{-9}$)	2.46	[8.71 – 13.39]*	[1.48 – 2.22]*	0.8935	69 ($4.91 \cdot 10^{-8}$)	2.97

Hyd_17	20	0.9182	97 ($1.15\cdot10^{-8}$)	0.52	[3.63 – 5.65]*	[-2.62 – - 1.70]*	0.8984	75 ($7.94\cdot10^{-8}$)	0.58
Hyd_18	20	0.8814	63 ($2.84\cdot10^{-7}$)	0.76	[13.98 – 15.13]*	[17.22 – 29.65]*	0.8546	49 ($1.65\cdot10^{-6}$)	0.84
Hyd_19	20	0.8832	65 ($2.50\cdot10^{-7}$)	0.50	[-5.65 – - 3.06]*	[4.38 – 7.50]*	0.8611	51 ($1.13\cdot10^{-6}$)	0.54
Hyd_20	20	0.8901	69 ($1.48\cdot10^{-7}$)	0.24	[1.25 – 1.61]*	[-3.42 – - 2.04]*	0.8545	48 ($1.78\cdot10^{-6}$)	0.28
Hyd_21	20	0.8163	36 ($1.14\cdot10^{-5}$)	2.19	[4.66 – 8.44]*	[-37.53 – - 18.06]*	0.7740	27 ($6.50\cdot10^{-5}$)	2.41
Hyd_22	20	0.8661	54 ($7.99\cdot10^{-7}$)	0.66	[0.97 – 1.96]*	[-8.45 – - 4.69]*	0.8344	41 ($4.89\cdot10^{-6}$)	0.73
Hyd_23	20	0.9046	81 ($4.40\cdot10^{-8}$)	1.07	[-36.23 – - 23.23]*	[-14.76 – - 9.17]*	0.8819	63 ($2.85\cdot10^{-7}$)	1.18
Hyd_24	19	0.9504	159 ($4.77\cdot10^{-10}$)	16.49	[73.60 – 98.50]*	[702.55 – 985.21]*	0.9382	125 ($3.00\cdot10^{-9}$)	18.37

Abb. = abbreviation of hydrophobicity scale; n = sample size; r = correlation coefficient;
F = Fisher parameter and associated type I error values (p); s = standard error of estimated;
$_{95\%}$CI = 95% confidence interval; Intercept = the intercept for the regression model;
$p_{t\text{-}Stat}$ = the type I error for the intercept and slop on regression model (Student t test);
r_{loo} = correlation coefficient obtained in leave-one-out analysis; F_{loo} = Fisher parameter obtained in leave one out analysis;
s_{loo} = standard error of estimated in leave-one-out analysis; * $p < 0.05$; + $p > 0.05$

Table VI. Non-standard amino acids: predicted hydrophobicity

Abb.	Non-standard amino acid										
	Aib	Ciu	Dhd	Dop	Gab	Hcy	Hyp	Lth	Oth	Pyl	Sec
Hyd_01	0.71	-0.07	0.51	0.79	0.50	0.54	0.33	-0.21	0.38	0.25	0.18
Hyd_02	-9.91	-19.45	-11.39	-14.31	-10.67	-11.47	-11.88	-23.87	-13.92	-33.21	-12.87
Hyd_03	-0.22	-0.81	-0.16	5.04	0.14	0.06	-0.42	-1.04	0.07	-0.78	-1.14
Hyd_04	0.14	2.95	0.78	1.09	0.22	-0.29	0.20	3.19	2.35	2.98	10.97
Hyd_05	143.07	105.51	232.95	98.01	93.32	96.35	159.64	353.92	98.86	119.29	145.69
Hyd_06	-1.20	2.98	-0.23	-0.99	-1.07	-1.83	-1.66	3.33	2.09	0.63	5.19
Hyd_07	1.56	-1.57	0.22	-0.18	1.33	4.30	1.38	-1.69	-1.23	-1.59	-3.68
Hyd_08	0.68	-2.50	0.72	0.15	0.16	0.39	-0.07	-3.54	-0.61	-4.71	-2.03
Hyd_09	0.99	0.91	1.18	0.90	0.89	0.89	1.03	1.44	0.90	0.94	1.00
Hyd_10	0.45	-0.83	-0.07	0.17	0.46	0.49	0.49	-1.32	-1.33	-0.72	-13.33
Hyd_11	1.69	-8.25	-0.30	1.38	1.67	1.85	1.84	-15.63	-5.84	-5.70	-67.94
Hyd_12	0.46	-0.73	0.21	3.94	0.85	0.84	-0.09	-1.31	0.31	-2.42	-1.32
Hyd_13	-0.27	0.56	0.64	0.07	0.41	0.22	0.70	0.60	0.40	0.53	0.58
Hyd_14	0.90	-4.59	-0.13	1.25	-0.18	0.03	-1.23	-6.18	-0.92	-1.78	-2.37
Hyd_15	3.58	-1.02	-0.80	-0.97	3.27	-1.20	-1.10	-1.14	-0.53	-1.17	-0.59
Hyd_16	-1.77	6.16	4.04	1.36	4.53	1.12	1.63	7.63	5.57	17.39	10.79
Hyd_17	0.94	-2.38	0.73	1.19	0.33	0.44	-0.37	-2.89	-0.35	-2.05	-0.87
Hyd_18	16.31	15.23	18.89	15.02	14.89	14.97	16.79	22.35	15.04	15.63	16.39
Hyd_19	0.63	-0.74	0.38	2.23	0.46	1.10	1.63	-0.57	0.34	-3.58	-2.86
Hyd_20	1.22	0.15	0.98	0.86	1.19	1.39	1.20	0.06	0.38	0.14	-2.90
Hyd_21	-2.82	0.38	-2.76	5.66	0.14	5.78	0.53	4.56	0.11	1.25	5.18
Hyd_22	0.96	-1.61	0.38	0.09	0.89	1.36	0.91	-1.83	-1.06	-1.64	-8.96
Hyd_23	-1.87	0.88	-1.33	-5.41	0.00	-1.48	-3.27	-0.17	-0.96	-2.66	-0.39
Hyd_24	149.34	110.59	242.07	102.85	98.02	101.15	166.44	366.88	103.74	124.81	152.04

Discussions

Twenty-four hydrophobicity scales of standard amino acids were investigated by using the Molecular Descriptor family on the Structure-Property Relationship approach. A linear monovariate regression model was obtained for each hydrophobicity scale and the best model in terms of goodness-of-fit was analyzed. All regression models were statistically significant at a significance level of 5% (see Fisher parameter and significance, Table V). The power of determination, expressed as the determination coefficient, varied from 44% to 88% within the set of twenty standard amino acids. The lowest performance was obtained for Welling *et al.* scale. The hydrophobicity is proved to be weakly related to atomic charge through topological interaction according to this model (see Table III, sample abbreviated as Hyd_15). The

highest estimation power was obtained by the model on Black *et al.* scale; eighty-eight percent in variation of hydrophobicity proved to be linearly related with the variation of the *lAmrLQg* molecular descriptor. This model showed that the hydrophobicity is on strong relationship with atomic charge through geometry interaction.

The analysis of the character distribution in the descriptors name revealed that not all possible characters are found in the descriptors name of the best performing models (the proportion varied from 25% - for the fifth letter to 100% - for the seventh letter). Seventy-nine percent of investigated scales showed that the hydrophobicity is related (in various degree) to atomic charge through geometry interaction. This observation supports the existence of a relationship between amino acids structure and their hydrophobicity and the similarities of these scales as well.

The empirical analysis of a correlation coefficient (Colton rules [49]) showed that with a single exception (the model for hydrophobicity on the Welling *et al.* scale) very good correlation were obtained between the measured hydrophobicity and that estimated by the MDF SPR models.

A previously reported investigation of the ability of MDF SPR approach in the modelling the amino acids hydrophobicity showed similar results. A set of fifteen standard amino acids was investigated on two scales and it was revealed that the hydrophobicity is strongly related to atomic charge through geometry interaction [50]. The comparison of the correlation coefficient of previously reported models and the obtained in the present study ($p = 0.5244$ for Hessa *et al.* scale, and $p = 0.2586$ for Kyte & Doolitle scale) showed no statistically significant difference.

The internal validation analysis of the obtained models showed that the models were stable and valid. The difference between the correlation coefficient obtained by the regression model and the correlation coefficient obtained in leave-one-out analysis varied from 0.01 to 0.07, the highest difference being obtained for the Welling *et al.* scale.

In conclusion, it could be say that the MDF SPR models with one variable provided good performance in investigated hydrophobicity of standard amino acids.

The hydrophobicity of each investigated non-standard amino acids was predicted based on the MDF SPR models obtained on standard amino acids (see Table VI). The impossibility to assess the reliability of the predicted values is the main limitation of the study. Due to limited resources, the measured hydrophobicity of non-standard amino acids, on

the investigated scales was not available. The reliability analysis could be easily done once the hydrophobicity of non-standard amino acids is measured on each of twenty-four hydrophobicity scales.

A question arises during the investigation of the relationships between amino acids structures and their hydrophobicity by using the MDF SPR approach: “Is it possible to rescale the hydrophobicity scales?” This could be investigated by taking into consideration the scale that gave the minimum value for the most standard amino acids (Sereda *et al.*, 1994), the scale that gave the maximum value for most amino acids (Manavalan & Ponnuswamy, 1978), a middle scale, and considering the MDF SPR models obtained in the present investigation (the confidence values for intercept and slop associated to the regression model). This will be investigated in further research.

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