Skin Doctor: Machine Learning Models for Skin Sensitization Prediction that Provide Estimates and Indicators of Prediction Reliability

Anke Wilm [1,2], Conrad Stork [1], Christoph Bauer [3,4], Andreas Schepky [5], Jochen Kühnl [5] and Johannes Kirchmair [1,3,4*]

[1] Center for Bioinformatics, Universität Hamburg, Hamburg, Germany
[2] HITeC e.V, Hamburg, Germany
[3] Department of Chemistry, University of Bergen, Bergen, Norway
[4] Computational Biology Unit (CBU), University of Bergen, Bergen, Norway
[5] Front End Innovation, Beiersdorf AG, Hamburg, Germany

* Correspondence: kirchmair@zbh.uni-hamburg.de; Tel.: +49-40-42838-7303.

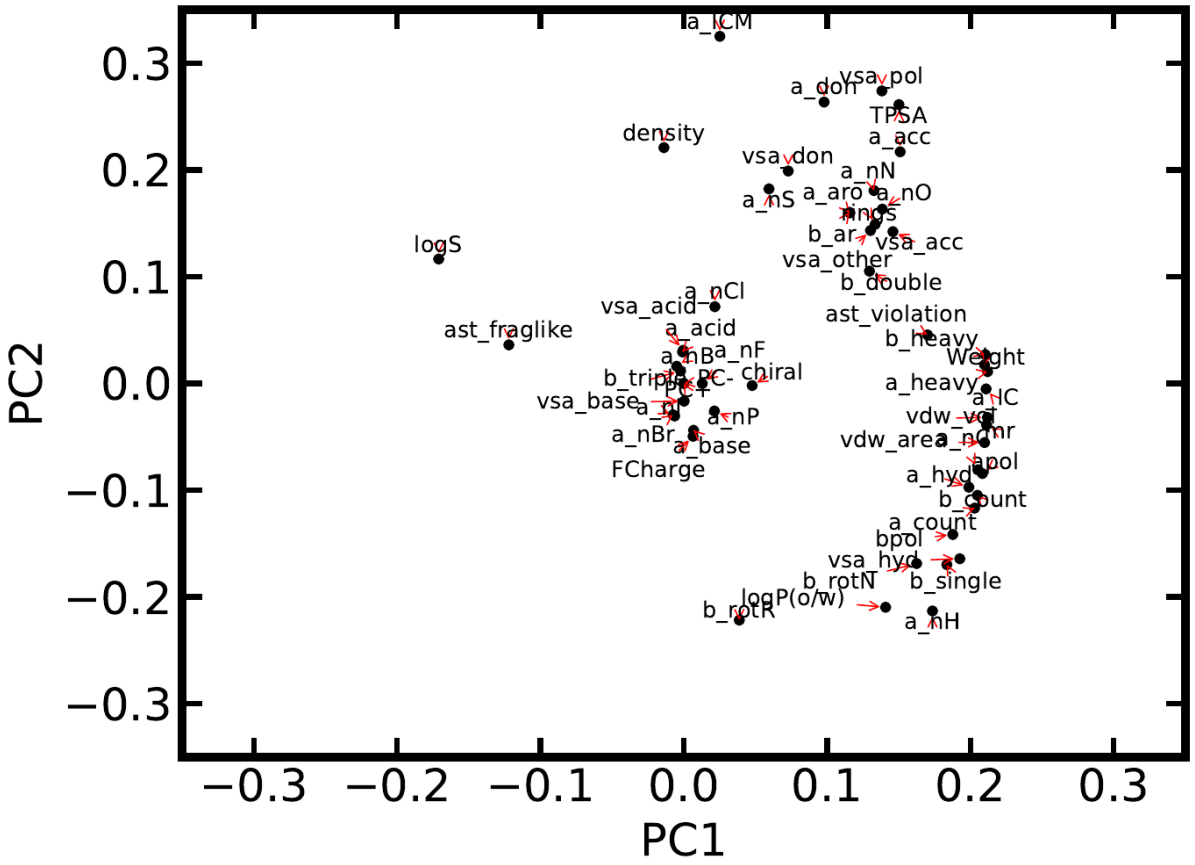


Figure S1. Enlarged version of the loadings plot from Figure 5B. For an explanation of the abbreviations see Table S1.

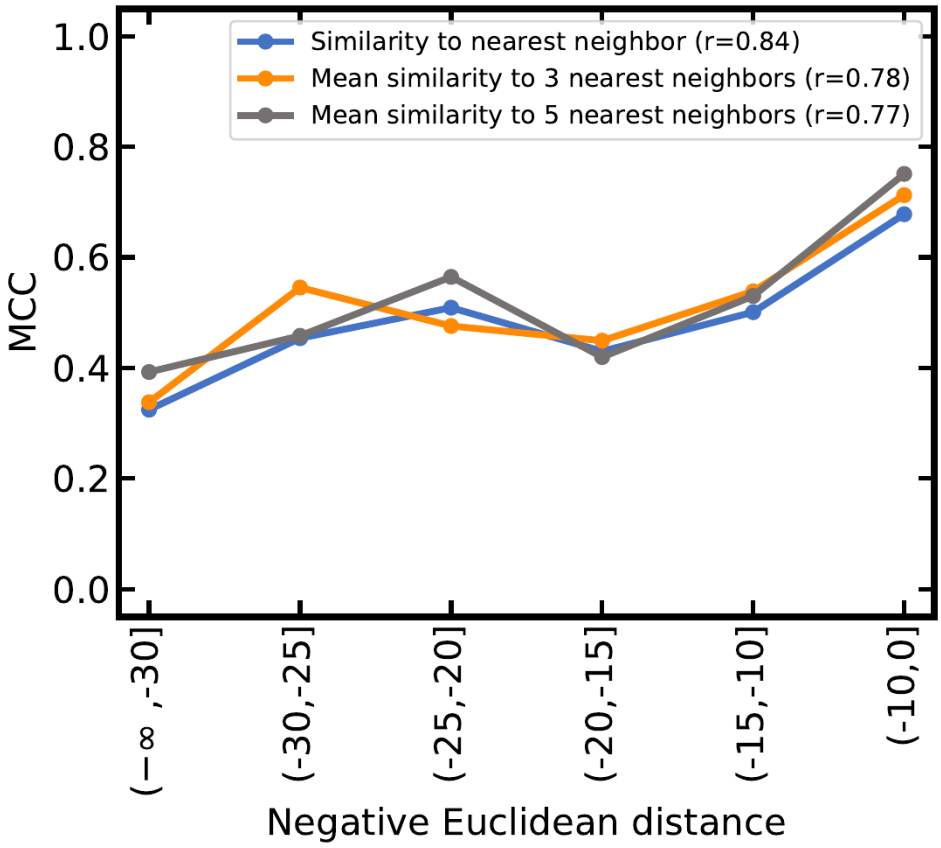


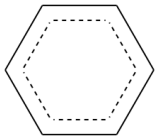
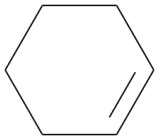
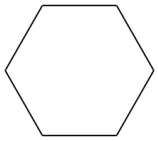
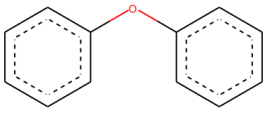
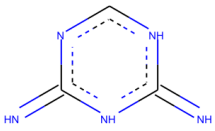
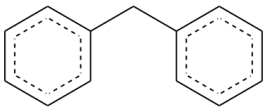
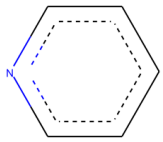
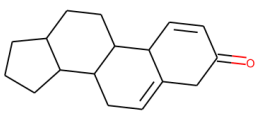
Figure S2. Correlation between molecular similarity measured as negative Euclidean distance in PaDEL space for the SVM_PaDEL model. Number of compounds in each bin are reported in Table S6.

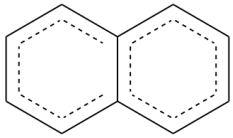
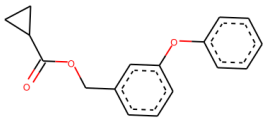
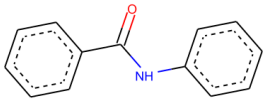
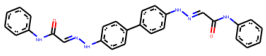
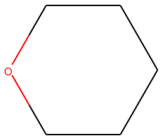
Table S1. Descriptors Used for the PCA and Explanation of the Abbreviations.

Descriptor	Explanation
apol	Polarizabilities of all atoms in molecule (as sum)
ast_fraglike	Binary Astex fragment-likeness
ast_violation	Number of Astex fragment-likeness violations
a_acc	H-bond acceptor atom count
a_acid	Acidic atom count
a_aro	Aromatic atom count
a_base	Basic atom count
a_count	Atom count
a_don	H-bond donor count
a_heavy	Heavy atom count
a_hyd	Hydrophobic atom count
a_IC	Total atom information content
a_ICM	Mean atom information content
a_nB	Boron atom count
a_nBr	Bromine atom count
a_nC	Carbon atom count
a_nCl	Chlorine atom count
a_nF	Fluorine atom count
a_nH	Hydrogen atom count
a_nI	Iodine atom count
a_nN	Nitrogen atom count
a_nO	Oxygen atom count
a_nP	Phosphorus atom count
a_nS	Sulfur atom count
bpol	Bonded atom polarizability difference
b_ar	Number of aromatic bonds
b_count	Number of bonds
b_double	Number of double bonds

b_heavy	Number of bonds between heavy atoms
b_rotN	Number of rotatable bonds
b_rotR	Fraction of rotatable bonds
b_single	Number of single bonds
b_triple	Number of triple bonds
chiral	Number of chiral centers
density	Molecular mass density
FCharge	Total charge of the molecule
logP(o/w)	Log of the octanol/water partition coefficient
logS	Log of the aqueous solubility (mol/L)
mr	Molecular refractivity
PC+	Total positive partial charge
PC-	Total negative partial charge
rings	Number of rings
TPSA	Polar surface area (Å^2)
vdw_area	Area of van der Waals surface (Å^2)
vdw_vol	Van der Waals volume (Å^3)
vsa_acc	Approximation to the sum of VDW surface areas (Å^2) of pure hydrogen bond acceptors
vsa_acid	Approximation to the sum of VDW surface areas of acidic atoms (Å^2)
vsa_base	Approximation to the sum of VDW surface areas of basic atoms (Å^2)
vsa_don	Approximation to the sum of VDW surface areas of pure hydrogen bond donors
vsa_hyd	Approximation to the sum of VDW surface areas of hydrophobic atoms (Å^2)
vsa_other	Approximation to the sum of VDW surface areas (Å^2) of atoms typed as "other"
vsa_pol	Approximation to the sum of VDW surface areas (Å^2) of polar atoms
Weight	Molecular weight

Table S2. Ten Most Prevalent Murcko Scaffolds in the LLNA Data Set.[1]

	LLNA of Alves et al.	LLNA of Di et al.	Merged LLNA	Cosmetics	Drugs	Pesticides
	30.12%	23.44%	27.04%	27.50%	10.72%	23.46%
	1.32%	1.85%	1.73%	3.59%	0.21%	
	2.05%	1.56%	2.04%	3.55%	0.54%	0.49%
	0.29%	0.28%	0.20%	0.30%	0.32%	2.75%
	0.15%	0.14%	0.10%	0.07%		1.94%
	1.75%	1.14%	1.53%	1.04%	0.80%	1.62%
	1.90%	1.56%	1.53%	0.85%	0.75%	1.13%
	0.15%	0.14%	0.10%	0.04%	1.39%	

	0.58%	0.28%	0.51%	0.89%	0.38%	1.29%
		0.14%	0.10%	0.07%	0.05%	1.29%
	0.29%	1.28%	0.92%	0.15%	0.05%	1.13%
	1.46%	1.56%	1.12%	0.11%		
	0.29%	0.28%	0.41%	1.04%	0.32%	

[1] Reported are the percentages of compounds based on the indicated Murcko scaffolds among all compounds having a Murcko scaffold.

Table S3. Hyperparameters Selected During Grid Search.[1]

	RF		SVM	
Name	**n_estimators**	**max_features**	**C**	**gamma**
MOE2D	250	0.4	1000	0.0001
MOE2D53	250	0.4	1000	0.001
Padel	250	0.8	1	0.001
MACCS	1000	sqrt	1	0.1
Morgan2	100	0.2	100	0.1
OASIS	10	sqrt	1	0.1
Padel-Est	1000	0.4	10	0.1
Padel-Ext	100	0.4	1	0.01
MOE2D+Padel	500	None	1	0.001
MOE2D+MACCS	500	0.2	10	0.01
MOE2D+Morgan2	500	0.4	10	0.001
MOE2D+OASIS	100	None	100	0.001
MOE2D+Padel-Est	1000	0.4	10	0.01
MOE2D+Padel-Ext	1000	sqrt	10	0.001
Padel+MACCS	500	0.4	1	0.001
Padel+Morgan2	1000	0.2	100	0.001
Padel+OASIS	500	0.6	1	0.001
Padel+Padel-Est	1000	sqrt	1	0.001
Padel+Padel-Ext	50	0.8	1	0.001
MACCS+Morgan2	50	0.8	10	0.01
MACCS+OASIS	50	None	1	0.1
MACCS+Padel-Est	250	sqrt	1	0.1
MACCS+Padel-Ext	50	0.2	1	0.01
Morgan2+OASIS	100	sqrt	100	0.1
Morgan2+Padel-Est	250	sqrt	10	0.01
Morgan2+Padel-Ext	1000	sqrt	1	0.01
OASIS+Padel-Est	50	0.4	10	0.1
OASIS+Padel-Ext	1000	0.6	1	0.01
Padel-Est+Padel-Ext	250	0.6	1	0.01

[1] Definitions of the individual descriptor sets are provided in Table 2.

Table S4. Matthews Correlation Coefficients for the RF Models.[1]

	MOE2D	PaDEL	Morgan2	PaDEL-Ext	PaDEL-Est	MACCS	OASIS
MOE2D	0.44	0.48	0.46	0.45	0.45	0.44	0.45
PaDEL		0.48	0.49	0.49	0.47	0.49	0.49
Morgan2			0.46	0.44	0.48	0.44	0.44
PaDEL-Ext				0.42	0.43	0.43	0.43
PaDEL-Est					0.43	0.46	0.48
MACCS						0.47	0.47
OASIS							0.27

[1] The diagonal reports MCC values for models based on a single set of descriptors.

Table S5. Matthews Correlation Coefficients for the SVM Models.[1]

	MOE2D	PaDEL	Morgan2	PaDEL-Ext	PaDEL-Est	MACCS	OASIS
MOE2D	0.48	0.5	0.5	0.5	0.5	0.5	0.55
PaDEL		0.5	0.51	0.51	0.5	0.51	0.5
Morgan2			0.39	0.48	0.43	0.46	0.43
PaDEL-Ext				0.47	0.47	0.46	0.47
PaDEL-Est					0.44	0.49	0.47
MACCS						0.47	0.48
OASIS							0.29

[1]The diagonal reports MCC values for models based on a single set of descriptors.

Table S6. Number of Compounds with Specified negative Euclidean distance to 1, 3 and 5 Nearest Neighbors of SVM_PaDEL model in PaDEL space.

	(-∞ ,-30]	(-30,-25]	(-25,-20]	(-20,-15]	(-15,-10]	(-10,0]
Similarity to nearest neighbor	138	112	193	267	259	140
Mean similarity to 3 nearest neighbors	174	148	237	295	207	48
mean similarity to 5 nearest neighbors	200	174	259	288	171	17

Table S7. Number of Compounds with Specified Mean Tanimoto Similarity to 1, 3 and 5 Nearest Neighbors.

		Mean Tanimoto similarity					
Model	**Number of neighbors considered**	**[0 ,0.5]**	**(0.5,0.6]**	**(0.6,0.7]**	**(0.7,0.8]**	**(0.8,0.9]**	**(0.9,1]**
SVM_MOE2D+OASIS	1	24	89	218	327	244	226
	3	38	140	339	334	154	123
	5	53	207	374	289	140	65
SVM_PaDEL+OASIS	1	19	92	198	320	252	228
	3	34	134	317	343	164	117
	5	44	204	362	297	132	70
SVM_PaDEL	1	19	92	198	320	252	228
	3	34	134	317	343	164	117
	5	44	204	362	297	132	70
RF_MACCS	1	25	89	207	335	242	234
	3	38	138	329	344	168	115
	5	56	204	374	296	135	67
SVM_PaDEL+MACCS	1	19	92	198	320	252	228
	3	34	134	317	343	164	117
	5	44	204	362	297	132	70

Table S8. Number of Compounds with Specified Distances Between the Prediction Probability and the Decision Threshold.

	Distance							
Model	**[0 ,0.25]**	**(0.25 - 0.5]**	**(0.5 - 0.75]**	**(0.75 - 1]**	**(1 - 1.25]**	**(1.25 - 1.5]**	**(1.5 - 1.75]**	**(1.75,∞)**
SVM_MOE2D+OASIS	124	159	133	125	121	100	88	278
SVM_PaDEL+OASIS	183	233	198	174	173	91	48	9
SVM_PaDEL	180	238	193	177	172	92	47	10
SVM_PaDEL+MACCS	182	237	198	172	174	90	48	8
	[0 ,0.1]	**(0.1,0.15]**	**(0.15,0.2]**	**(0.2,0.25]**	**(0.25,0.3]**	**(0.3,0.35]**	**(0.35,0.4]**	**(0.4,0.5)**
RF_MACCS	237	134	126	128	126	113	73	195

Table S9. Number of Compounds with Specified Numbers of Consecutive Nearest Neighbors with Same Activity as Predicted.

Model	**0**	**1**	**2**	**3**	**4**	**5 or more**
SVM_MOE2D+OASIS	308	201	142	102	71	304
SVM_PaDEL+OASIS	295	213	124	94	83	300
SVM_PaDELl	295	213	124	94	83	300
RF_MACCS	329	187	135	104	78	299
SVM_PaDEL+MACCS	294	213	124	94	83	301