Diagnostic of a qSPR model: aqueous solubility of drug-like compounds

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Mathematical Chemistry in NANO-era
Dedicated to Professor Mircea V. DIUDEA on the occasion of his 60th birthday
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Aim

- Diagnostic test of a QSPR

Material

- [Duchowicz PR, Talevi A, Bruno-Blanch LE, Castro EA, 2008. New QSPR study for the prediction of aqueous solubility of drug-like compounds. Bioorg Med Chem. 16(17):7944-55]
- qSPR model (modeled using molecular descriptors) able to characterize the aqueous solubility (measured at 298K and expressed in mg/ml - taken from Merck Index 13^{th} ed.) of drug-like compounds (training set of 97 compounds; test set of 69 compounds)

Method

- Statistical parameters, similar with those used in assessment of a diagnostic test in medicine were defined as diagnostic parameters for qSPR model:
  - accuracy (Ac, total fraction of compounds correctly classified)
  - prior proportional probability of a class (PPP, fraction of compounds belonging to class *i*)
  - Sensitivity (Se, percentage of active compounds correctly assigned to the active class)
  - Specificity (Sp, percentage of inactive compounds correctly assigned to the negative class)
  - false-negative rate (under-classification, FNR)
  - false-positive rate (over-classification, FPR)
  - positive (PP) and negative (NP) predictivity;
  - probability of classification as active (PCA) and inactive (PCIC)
  - probability of a wrong classification as active (PWCA) and inactive (PWCI)
  - odds ratio (OR, the odds of correct classification in the group of active compounds divided to the odds of a incorrect classification in the group of inactive compounds)

Results – Signs contingency

Generic	Observed		
Estimated	+	-	Σ
+	TP	FP	
-	FN	TN	
Σ			n

Test	Observed		
Estimated	+	-	Total
+	26	10	36
-	4	29	33
Total	30	39	69

Training	Observed		
Estimated	+	-	Total
+	28	7	35
-	12	48	60
Total	40	55	95

Overall	Observed		
Estimated	+	-	Total
+	54	22	76
-	11	77	88
Total	65	99	164

Results – Diagnostic test

Parameter (Abbreviation)	Formula
Accuracy (AC)	100*(TP+TN)/n
Error Rate (ER)	100* (FP+FN)/n = 1-AC
Prior proportional probability of an active class (PPAC)	(TP+FN)/n
Prior proportional probability of an inactive class (PPIC)	(FP+TN)/n
Sensitivity (Se)	100*TP/(TP+FN)
False-negative rate (under-classification, FNR)	100*FN/(TP+FN) = 1-Se
Specificity (Sp)	100*TN/(TN+FP)
False-positive rate (over-classification, FPR)	100*FP/(FP+TN) = 1-Sp
Positive predictivity (PP)	100*TP/(TP+FP)
Negative predictivity (NP)	100*TN/(TN+FN)
Probability of classification as active (PCA)	(TP+FP)/n
Probability of classification as inactive (PCIC)	(FN+TN)/n
Probability of a wrong classification as active compound (PWCA)	FP/(FP+TP)
Probability of a wrong classification as inactive compound (PWCI)	FN/(FN+TN)
Odds Ratio (OR)	(TP*TN)/(FP*FN)

QSPR Diagnostic

QSPR Diagnostic	Training (95)	Test (69)	Overall (164)
AC	80.00	79.71	79.88
ER	20.00	20.29	20.12
PPAC	0.4211	0.4348	0.3963
PPIC	0.5789	0.5652	0.6037
Se	70.00	86.67	83.08
FNR	30.00	13.33	16.92
Sp	87.27	74.36	77.78
FPR	12.73	25.64	22.22
PP	80.00	72.22	71.05
NP	80.00	87.88	87.50
PCA)	0.3684	0.5217	0.4634
PCIC	0.6316	0.4783	0.5366
PWCA	0.2	0.2778	0.2895
PWCI	0.2	0.1212	0.125
OR	16.00	18.85	17.18

QSPR Confidence intervals

Training
χ^2 = **30.2305** (p = 0.0000)
Coefficient of correlation Φ = 0.5641
Sensibility = [0.5476, **0.7000**, 0.8239]
Specificity = [0.7639, **0.8727**, 0.9396]
NegativePredictiveValue = [0.6852, **0.8000**, 0.8849]
PositivePredictiveValue = [0.6455, **0.8000**, 0.9044]
FalsePositiveRate = [0.0604, **0.1273**, 0.2361]
FalseNegativeRate = [0.1761, **0.3000**, 0.4524]
Prevalence = [0.3254, **0.4211**, 0.5215]
WrongPositiveTest = [0.0956, **0.2000**, 0.3545]
WrongNegativeTest = [0.1151, **0.2000**, 0.3148]
Accuracy = [0.7107, **0.8000**, 0.8702]
Probability NegativeTest = [0.5318, **0.6316**, 0.7234]
ProbabilityPositiveTest = [0.2766, **0.3684**, 0.4682]
PositiveProbabilityRatio = [2.6613, **5.5000**, 11.1802]
NegativeProbabilityRatio = [0.2130, **0.3438**, 0.5589]
PostTestOdds = [1.8206, **4.0000**, 9.4603]
PreTestOdds = [0.4823, **0.7273**, 1.0897]
PostTestProbability = [1.1182, **1.3333**, 2.2187]
RelativeRisk = [2.3400, **4.0000**, 6.7693]
OddsRatio = [5.7090, **16.0000**, 45.0262]
ExcessRisk = [0.4114, **0.6000**, 0.7404]

QSPR Confidence intervals

Test
χ^2 = **22.9206** (p = 0.0000)
Coefficient of correlation Φ = 0.5764
Sensibility = [0.7096, **0.8667**, 0.9508]
Specificity = [0.5921, **0.7436**, 0.8591]
NegativePredictiveValue = [0.7329, **0.8788**, 0.9552]
PositivePredictiveValue = [0.5625, **0.7222**, 0.8467]
FalsePositiveRate = [0.1409, **0.2564**, 0.4079]
FalseNegativeRate = [0.0492, **0.1333**, 0.2904]
Prevalence = [0.3225, **0.4348**, 0.5524]
WrongPositiveTest = [0.1533, **0.2778**, 0.4375]
WrongNegativeTest = [0.0448, **0.1212**, 0.2671]
Accuracy = [0.6904, **0.7971**, 0.8779]
ProbabilityNegativeTest = [0.3633, **0.4783**, 0.5950]
ProbabilityPositiveTest = [0.4050, **0.5217**, 0.6367]
PositiveProbabilityRatio = [1.9368, **3.3800**, 5.8233]
NegativeProbabilityRatio = [0.0728, **0.1793**, 0.4579]
PostTestOdds = [1.2858, **2.6000**, 5.5231]
PreTestOdds = [0.4760, **0.7692**, 1.2343]
PostTestProbability = [1.2211, **1.6250**, 4.4983]
RelativeRisk = [2.3093, **5.9583**, 14.8392]
OddsRatio = [5.4919, **18.8500**, 64.5994]
ExcessRisk = [0.3876, **0.6010**, 0.7504]

QSPR Confidence intervals

Overall
χ^2 = **83.6385** (p = 0.0000)
Coefficient of correlation Φ = 0.5761
Sensibility = [0.6019, **0.7105**, 0.8030]
Specificity = [0.8194, **0.8750**, 0.9170]
NegativePredictiveValue = [0.8194, **0.8750**, 0.9170]
PositivePredictiveValue = [0.6019, **0.7105**, 0.8030]
FalsePositiveRate = [0.0830, **0.1250**, 0.1806]
FalseNegativeRate = [0.1970, **0.2895**, 0.3981]
Prevalence = [0.2475, **0.3016**, 0.3603]
WrongPositiveTest = [0.1970, **0.2895**, 0.3981]
WrongNegativeTest = [0.0830, **0.1250**, 0.1806]
Accuracy = [0.7746, **0.8254**, 0.8681]
ProbabilityNegativeTest = [0.6397, **0.6984**, 0.7525]
ProbabilityPositiveTest = [0.2475, **0.3016**, 0.3603]
PositiveProbabilityRatio = [3.7431, **5.6842**, 8.6021]
NegativeProbabilityRatio = [0.2320, **0.3308**, 0.4729]
PostTestOdds = [1.5121, **2.4545**, 4.0750]
PreTestOdds = [0.3289, **0.4318**, 0.5633]
PostTestProbability = [1.3252, **1.6875**, 2.9527]
RelativeRisk = [3.7431, **5.6842**, 8.6021]
OddsRatio = [8.8212, **17.1818**, 33.6188]
ExcessRisk = [0.4697, **0.5855**, 0.6836]

Conclusions

- The total fraction of compounds correctly classified of the model proved to be identical for training and test sets as well as for overall set. But, the overall model and the model obtained in test set have a higher ability to correctly assign the inactive compounds to the negative class while the model obtained in training set has a higher ability in correctly assignment of active compounds to the active class.
- QSPR Diagnostic test – useful tool to assess the quality of a QSPR/QSAR