Bulletin UASVM Horticulture, 66(2)/2009
Print ISSN 1843-5254; Electronic ISSN 1843-5394

Distribution Fitting 3. Analysis under Normality Assumption

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Abstract. Four sets of experimental data were investigated in terms of normal distribution and presence of outliers. The following sets of compound were investigated: blood-brain barrier partitioning (n=105), inhibitory activity of para-substituted aromatic sulfonamides (n=47), inhibition activity of taxoids (n=63), and estrogen receptor binding affinity of triphenilacrylonitriles (n=25). The normality of experimental data was tested using the following tests: Jarque-Bera, Kormogorov-Smirnov, Anderson-Darling, Chi Square and Shapiro-Wilk. The Grubbs' test was applied for identification of outliers. The inhibitory activity of taxoids proved to be single set of compounds normal distributed according to all applied normality tests. A proper structure-activity relationships analysis must be conducted on the sample of 98 blood-brain barrier partitioning compounds, on the sample of 34 para-substituted aromatic sulfonamides, and on the sample of 22 estrogen receptor binding affinity of triphenilacrylonitriles.

Keywords: Normal distribution, Tests, Outlier, Grubbs' test.

INTRODUCTION

Statistical methods and tests work based on a series of assumptions. The normal distribution is assumed by many statistical methods as correlation, least-square regression, factor analysis and related linear techniques (Vasu, 1979). The existence of an erroneous value (an experimental mistake) in the data leads to a sever asymmetry and to misleading results that could lead to non-normal distribution of data. Techniques using maximum likelihood estimation are robust against departure from normality (Steenkamp and van Trijp, 1991). Several methods are used to investigate the normality of experimental data: graphical methods (histogram of standard residuals, normal probability plot) and statistical tests. The following test are most frequent used in testing normal distribution: Shapiro-Wilk (Shapiro and Wilk, 1965; Shapiro and Wilk, 1968; Shapiro et al., 1968), Kolmogorov-Smirnov (Kolmogorov, 1941), chi-square goodness-of-fit (Pearson, 1900), Anderson Darling (Anderson and Darling, 1952), etc. Some tests are sensitive to certain departure from normality and could be applied in special situations (tests based on skewness and kurtosis as Jarque-Bera (Jarque and Bera, 1980; Jarque and Bera, 1981), Z-based statistics) while others are applicable to general cases. Shapiro-Wilk test is the most powerful test of normality with general applicability (Shapiro and Wilk, 1965; Shapiro and Wilk, 1968; Shapiro et al., 1968). Anderson-Darling statistics is another test applicable to general cases but is slightly less powerful that Shapiro-Wilk test (D'Agostino and Stephens, 1986).

The aim of the present research was to analyze if experimental data of four sets of biological active compounds accomplish the normality assumption in order to enter into a multivariate linear regression analysis on structure-activity relationships. An analysis of outliers in experimental data has also been applied using the Grubbs test.

MATERIAL AND METHODS

Four sets of biological active compounds were included in analysis. The following experimental data (see Table 1) were investigated:

1 BBBP (blood-brain barrier partitioning): experimental data obtained in vivo on rats experiments (Young, 1988; Abraham et al., 1994; Salminem et al., 1997; Clark, 1999; Luco, 1999; Yazdanian et al., 1998; Grieg et al., 1995; Lin et al., 1994; Lombardo et al., 1996; Van Belle et al., 1995; Calder et al., 1994; Liu et al., 2001). The following protocol was used: drug was administrated intravenously, subsequently scarification of rats, measurement of drug concentration in blood and brain tissue (BB= $conc_{brain}/conc_{blood}$, where conc = concentration). The experimental data were expressed in logarithmic scale.

2 SASCAII (para-substituted aromatic sulfonamides): carbonic anhydrase II (CAII) inhibitory activity (Melagraki et al., 2006). The measured data are expressed in terms of nano-molar affinity.

3 TaxoIA (inhibitory activity of taxoids): experimental data obtained in vitro with the protocol developed by Skehan and co-authors (Skehan et al., 1990). Six classes of taxoids were included into the study (Zu et al., 1997). The activity was expresses as inhibitory effect (IC_{50}) on human cancer (Barboni et al., 2005; Ojima et al., 1996; Ojima et al., 1997; Ojima et al., 1999a,b).

4 ERBAT (estrogen receptor binding affinity of triphenilacrylonitriles): estrogenic activity was relative binding affinity to the ER (estrogen receptor) vis-à-vis E_2 expressed in logarithmic scale (Mukherjee et al., 2005).

Tab. 1. Experimental data of investigated sets of biological active compounds

Set	**Activity**	**Experimental values**
BBBP (n=105)	blood-brain barrier partitioning	-2.00; -1.88; -1.82; -1.57; -1.54; -1.42; -1.34; -1.30; -1.30; -1.26; -1.23; -1.17; -1.15; -1.12; -1.10; -1.06; -0.82; -0.75; -0.73; -0.72; -0.70; -0.67; -0.66; -0.52; -0.50; -0.46; -0.43; -0.42; -0.35; -0.31; -0.30; -0.30; -0.29; -0.28; -0.27; -0.24; -0.22; -0.18; -0.18; -0.17; -0.16; -0.16; -0.16; -0.15; -0.15; -0.14; -0.12; -0.10; 0.08; 0.06; -0.06; -0.04; -0.02; 0.00; 0.00; 0.03; 0.03; 0.04; 0.04; 0.08; 0.08; 0.11; 0.12; 0.13; 0.14; 0.22; 0.24; 0.24; 0.25; 0.27; 0.30; 0.34; 0.35; 0.36; 0.36; 0.37; 0.37; 0.39; 0.40; 0.42; 0.44; 0.49; 0.55; 0.60; 0.61; 0.69; 0.76; 0.80; 0.81; 0.89; 0.90; 0.93; 0.97; 1.00; 1.00; 1.01; 1.04; 1.06; 1.07; 1.20; 1.23; 1.44; 0.35; 0.27; -1.82
SASCAII (n=47)	inhibitory activity	2.4116; 2.0934; 1.1139; 1.1761; 0.9542; 0.8633; 1.0414; 1.2553; 1.1761; 1.8261; 1.7324; 0.9912; 0.9777; 0.959; 1.7076; 1.8808; 2.3909; 2.1239; 2.3655; 2.356; 2.4116; 2.3304; 2.3617; 1.7993; 1.5682; 1.2304; 2.3802; 2.0212; 1.8751; 1.1139; 1.6902; 1.6021; 1.4472; 0.9542; 1.8751; 2.4771; 2.5051; 2.2304; 2.2041; 1.7782; 2.0414; 1.6021; 1.8451; 1.4472; 1.8751; 2.0969; 2.0414
TaxoIA (n=63)	inhibitory activity	0.000; 1.021; 1.759; 0.609; 1.224; 0.667; 0.467; 0.609; 0.918; 0.826; 0.103; 0.546; -0.138; 0.095; 0.082; 1.342; 1.319; 1.038; -0.567; 1.291; -0.114; 0.364; 0.516; 0.845; 0.745; 0.101; 2.284; 1.215; 1.210; 1.788; 1.924; 2.160; 0.099; 0.187; -0.346; 0.740; 0.525; 0.166; 0.675; 0.865; 0.669; 0.560; 1.129; -0.473; 0.931; 0.140; 2.170; 1.661; 0.400; -0.126; 1.688; 1.158; -0.276; 0.587; 0.008; 0.886; 0.906; 0.474; 0.529; 1.849; 1.451; 0.793; 0.576
ERBAT (n=25)	receptor binding affinity	-1.046; 1.556; 0.342; 0.519; 1.792; 1.869; 0.785; 2.220; 1.447; 0.398; 1.968; 1.892; 0.959; -0.180; 1.230; -0.444; 0.806; -2.000; 0.531; 2.033; -0.398; -2.000; -1.398; -2.000; -1.398

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The steps applied in statistical analysis of the experimental data were:

1. Graphical representation of the experimental data.

2. Test the normality using the following tests: Jarque-Bera, Chi-Square goodness-of-fit, Kolmogorov-Smirnov, Anderson-Darling, and Shapiro-Wilk (see Table 2). There were included into analysis two tests more affected by the existence of outliers (Chi-Square and Jarque-Bera) and two less affected (Kolmogorov-Smirnov and Anderson-Darling) (Jäntschi and Bolboacă, 2009). The tested null (H_0) and alternative (H_a) hypotheses were: H_0 = Experimental data follow the normal distribution; H_a = Experimental data did not follow the normal distribution. Shapiro-Wilk test is known to be affected by ties but not as bad as Anderson-Darling (Anderson and Darling, 1952).
3. Exclusion of extreme value if the data proved not to be normal distributed and performed the normality tests again until the normal distribution is obtain.
4. Identification of outliers: means and standard deviation (the date that do not belong to the [m ±3·s] interval, where m = sample mean, s = standard deviation of the sample), and Grubbs' test (Grubbs, 1969; Stefansky, 1972). The test is able to detect the presence of a single outlier at an application. The characteristics of the applied Grubbs's test were as follows:
   - H_0= There are not outliers in the data set vs. H_a = There is at least one outlier in the data set.
   - Grubbs' test statistic: $G = [\max|Y_i - Y_m|]/s$ where i = identification number of compound from the data set, Y_m = sample mean, s = standard deviation
   - The hypothesis of no outlier is rejected for two-sided test if $G > \frac{(n-1)}{\sqrt{n}}\sqrt{\frac{t^2_{\alpha/(2n),n-2}}{n-2+t^2_{\alpha/(2n),n-2}}}$ where n = sample size, $t^2_{\alpha/(2n),n-2}$ = critical value of the t-distribution with (n-2) degree of freedom at a significance level of α.

Tab. 2. Summary of tests used to evaluate normality of experimental data

Test	**Statistic**	**H_0 acceptance rule**	**Reference**
Jarque-Bera	$JB = \frac{n}{6}\left(S^2 + \frac{(K-3)^2}{4}\right)$ where S = sample skewness; K = sample kurtosis	H_0: S = 0 & K = 3 $JB < \chi^2_{2,\varepsilon}$ ε = error	(Jarque and Bera, 1980; 1981)
Chi-Square goodness-of-fit	$\chi^2 = \sum_{i=1}^{r}\sum_{j=1}^{c}\frac{(O_{i,j}-E_{i,j})^2}{E_{i,j}}$ df = (k-1), where k = number of groups	$\chi^2 \le \chi^2_{1-\alpha}$	(Pearson, 1900)
Kolmogorov-Smirnov	$D = \max_{1\le i\le n}\left(F(X_i) - \frac{i-1}{n}, \frac{i}{n} - F(X_i)\right)$ $F(X_i)$ = normal distribution function of order experimental data X_i	$D \le D_{crit}$	(Kolmogorov, 1941)
Anderson-Darling*	$A^2 = -N - \sum_{k=1}^{N}\frac{2k-1}{N}\left(\ln(F(X_k)) + \ln(1-F(X_{n+1-k}))\right)$ F = cumulative distribution function of the normal distribution; X_i = ordered experimental data	$A^2 \le A_{crit}$	(Anderson and Darling, 1952)
Shapiro-Wilk	$W^2 = \left(\sum_{i=1}^{N}A_iX_i\right)^2 \Big/ \sum_{i=1}^{N}(X_i - \overline{X})^2$ $A = m^T V^{-1}(m^T V^{-1} V^{-1} m^T)^{-1/2}$	$W^2 \le W_{crit}$	(Shapiro and Wilk, 1968; Shapiro et al., 1968)

* An alternative to the chi-square and Kolmogorov-Smirnov goodness-of-fit;

RESULTS AND DISCUSSION

Descriptive parameters of the experimental data for each set of compounds were calculated and are presented in Table 3. The graphical representations of the investigated data sets are presented in Figure 1 (standard normal deviate).

The BBBP data set is the one with a negative mean. The highest mean of the experimental activity was obtained in investigation of SASCAII data set, which proved to have homogenous compounds according to the value of standard deviation. The ERBAT data set proved to be the most heterogeneous set according to the value of standard deviation. The analysis of the skewness and kurtosis revealed that BBBP data set is far away from a normal kurtosis, followed by the TaxoIA data set. The largest range in experimental data was observed for the BBBP and TaxoIA data sets.

Tab. 3. Descriptive statistics of experimental data

Statistic \ Sample abr.	BBBP	SASCAII	TaxoIA	ERBAT
m	-0.0941	1.7490	0.7437	0.3793
s	0.7656	0.5104	0.6756	1.3856
[m-3*s; m+3*s]	[-2.3908; 2.2026]	[0.2179; 3.2800]	[-1.2832; 2.7705]	[-3.7764; 4.5350]
S	-0.4603	-0.2369	0.3321	-0.4412
K	2.8060	1.7851	2.5960	1.9395
min	-2.0000	0.8633	-0.5670	-2.0000
max	1.4400	2.5051	2.2840	2.2200
n	105	47	63	25

m = arithmetic mean; s = standard deviation;
S = sample skewness; K = sample kurtosis;
Min = minimum; Max = maximum; n = sample size

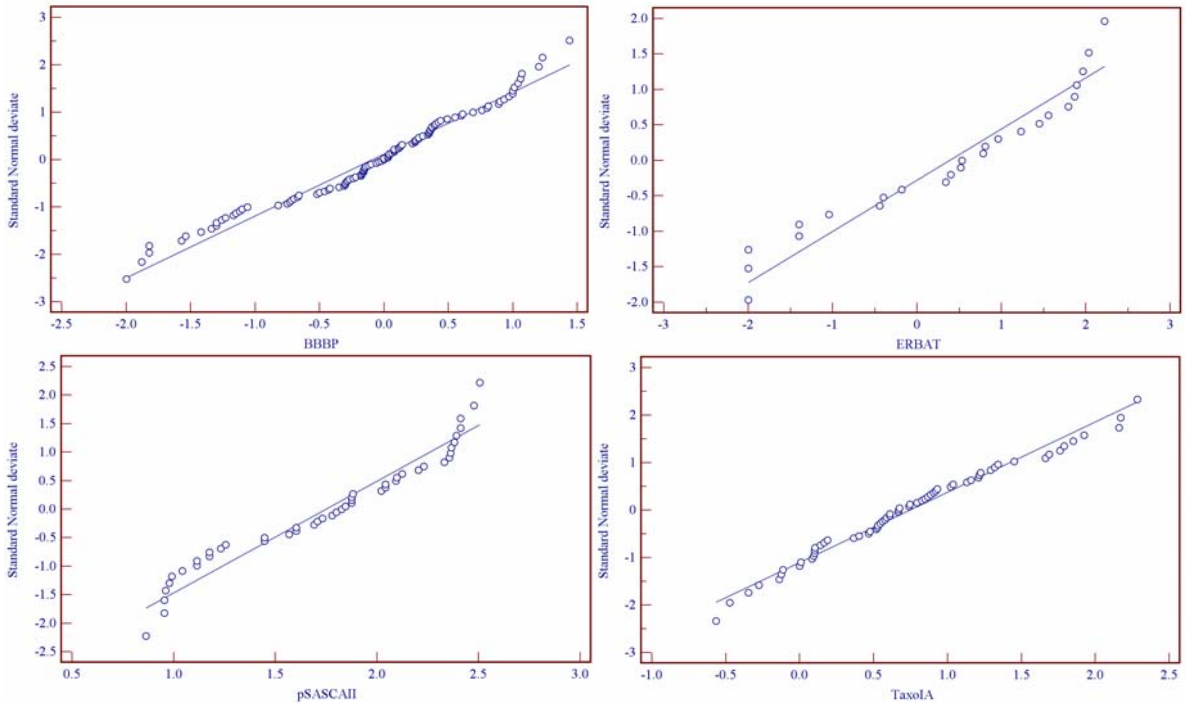

Fig. 1. Standard normal deviate plots: BBBP (upper-left), ERBAT (upper-right), SASCAII (bottom-lest) and TaxoIA (bottom-right)

The analysis of the graphical representation presented in Fig. 1 revealed that with one exception (TaxoIA data set) the investigated experimental data are not quite normal

distributed. One out of five applied normality tests, the Shapiro-Wilks' test identified that these three data sets (BBBP, ERBAT, and SASCAII) are not normal distributed (see Table 4). The Jarque-Bera, Kolmogorov-Smirnov, Anderson-Darling and Chi Square tests applied to al all four investigated sets revealed that these data are normal distributed (see Table 4). Shapiro-Wilks' test identified three sets out of four as not normal.

Tab. 4. Normality tests: results

Set.	Characteristic	JB	KS	AD	CS (df)	SW
BBBP	Statistic	3.8727	0.1033	1.0269	6.7584 (6)	0.9697[a]
	p-value	0.1442	0.1987	n.a.	0.3438	0.0156[a]
	α = 5% - Reject?	No	No	No	No	**Yes**
	α = 2% - Reject?	n.a	No	No	No	n.a.
	Reject=Yes (α =?)	n.a	No	No	No	n.a.
SAACAII	Statistic	3.3301	0.1099	0.9572	6.3654 (4)	0.9290[b]
	p-value	0.1892	0.5831	n.a.	0.17347	0.0069[b]
	α = 5% - Reject?	No	No	No	No	**Yes**
	α = 2% - Reject?	n.a.	No	No	No	n.a.
	Reject = Yes (α =)	n.a.	No	No	**20%**	n.a.
TaxoIA	Statistic	0.2644	0.0733	0.3885	4.3675 (5)	0.9784
	p-value	0.8762	0.8626	n.a.	0.4978	0.3334
	α = 5% - Reject?	No	No	No	No	No
	α = 2% - Reject?	n.a.	No	No	No	n.a.
	α = 1% - Reject?	n.a.	No	No	No	n.a.
ERBAT	Statistic	1.9823	0.1293	0.6314	0.4827 (2)	0.9162[c]
	p-value	0.3711	0.7505	n.a.	0.7856	0.0420[c]
	α = 5% - Reject?	No	No	No	No	**Yes**
	α = 2% - Reject?	n.a.	No	No	No	n.a.
	α = 1% - Reject?	n.a.	No	No	No	n.a.

JB = Jarque-Bera; KS = Kolmogorov-Smirnov; AD = Anderson-Darling; CS = Chi Square; SW = Shapiro-Wilk; n.a. = not available / not applicable

[a] SW = 0.9781, p = 0.10116 (n = 98, the experimental data equal to -2.00, -1.88, -1.82, -1.82, -1.57, -1.54, and -1.42 were withdrawn)

[b] SW = 0.9495, p = 0.1185 (n = 34, the experimental data equal to 0.8633, 0.9542, 0.9542, 0.959, 0.9777, 2.3617, 2.3655, 2.3802, 2.3909, 2.4116, 2.4116, 2.4771, 2.5051 were withdrawn)

[c] SW = 0.9309, p = 0.1279 (n=22, the experimental data equal to -2.000 were withdrawn)

On the data sets where the normality was not assured for the whole sample size, extreme values were withdrawn (one compound once) and the normality was tested again. The application of this procedure leads to normal distributed according to Shapiro-Wilks' test after withdrawn of 7 compounds from BBBP set, 13 compounds from SAACAII set and 3 compounds from ERBAT set.

The identification of outliers was performed in two steps. The experimental data were first investigated in term of belonging to the m±3s interval. None outlier was identified according to this criterion when all compounds were included into analysis (all four data sets). Grubbs' test was applied in the second step by investigation of all compounds and after exclusion of those compounds to ensure the normality (see Table 4). The analysis of the results leads to the conclusion that the investigated set of compounds did not contain any outlier, even if all compounds were investigated or the samples after assurance of normality according to Shapiro-Wilks's test.

Tab. 5. Grubbs' statistic: results

Set	n	G	G critical value		Reject H_0?	
			α = 5%	α = 1%	α = 5%	α = 1%
BBBP	105	2.4895	3.5654	3.9178	No	No
SAACAII	47	1.7354	3.2616	3.5905	No	No
TaxoIA	63	2.2799	3.3804	3.7204	No	No
ERBAT	23	1.7176	2.9653	3.2513	No	No
BBBP[a]	98	2.1855	3.5420	3.8932	No	No
SAACAII[b]	34	1.8284	3.1176	3.4280	No	No
ERBAT[c]	22	1.8621	2.8968	3.1698	No	No

n = sample size; G = Grubbs' statistic;
The significance of [a, b,] and [c] are given at the bottom of Tab. 3

The normality of investigated sets of compounds is doubtless if all compounds are investigated for three out of four sets of investigated compounds according to Shapiro-Wilks' test that is known to reject the null hypothesis more often than would wish. The normality is a certainty for investigated sets if some certain compounds were withdrawn (see Table 4).

A proper structure-activity relationships analysis must be conducted on the sample of 98 blood-brain barrier partitioning compounds, on the sample of 34 para-substituted aromatic sulfonamides, and on the sample of 22 estrogen receptor binding affinity of triphenilacrylonitriles.

CONCLUSIONS

The inhibitory activity of taxoids proved to be the single experimental data set normal distributed according to all applied normality tests. The normal distribution of blood-brain barrier partitioning (BBBP set), para-substituted aromatic sulfonamides (SASCAII set), and estrogen receptor binding affinity of triphenilacrylonitriles (ERBAT set) were rejected by Shapiro-Wilks' test. In this condition, a proper structure-activity relationships analysis must be conducted on the sample of 98 blood-brain barrier partitioning compounds, on the sample of 34 para-substituted aromatic sulfonamides, and on the sample of 22 estrogen receptor binding affinity of triphenilacrylonitriles.

Acknowledgements. Financial support is gratefully acknowledged to UEFISCSU Romania (ID0458/206/01.10.2007).

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