**Beware of external validation! – A Comparative Study of Several Validation Techniques used in QSAR Modelling**

**Abstract**

1. **Introduction**

With its humble beginning in the second half of the nineteenth century [1, 2] the field of quantitative structure-activity relationship (QSAR) has come a long way to its current state. QSARs are mathematical models which attempts to predict property/ biomedicinal activity, toxicity of chemicals from their properties or calculated molecular descriptors. The three major pillars of QSAR are: a) Adequately large and good quality data on the dependent variable, i.e., physical property or bioassay data, b) Relevant descriptors (independent variables) that are capable of quantifying aspects of molecular structure related to the property/ bioactivity of interest, and c) Proper Statistical methods for model building. .

In the second half of the twentieth century, the linear free energy related (LFER) approach, also known as Hansch analysis, was introduced to the field of QSAR [3]. This approach uses various combinations of hydrophobicity (experimental or calculated), Hammett’s electronic parameter (*σ*) and numerous stericdescriptors as independent variables for correlation. Such property-property relationships (PPRs) or property-activity relationships (PARs) worked for the assessment of bioactivities of molecules belonging to congeneric sets. But in many cases, experimental physicochemical properties of many of the chemicals under investigation are not available [4, 5]. The PPR/ PAR approaches are not very useful in such situations. A practical approach that has gradually emerged in such data-poor situations is the use properties that can be calculated directly from molecular structure without the use of any other experimental data. Topological, substructural, geometrical (3-D), and quantum chemical molecular descriptors belong to this group. For large sets of molecules, high level quantum chemical descriptors could be very demanding on computer resources. On the other hand, descriptors derived from topological aspects of chemical structures, e.g.; topological indices [6, 7, 8] and different types of substructures [9], have found wide applications in numerous QSAR studies. For a recent summary of these topics, please see reviews by Basak [5, 10].

During the past half century or so there has been an important change in the landscape of available molecular descriptors (independent variable) for QSAR. Whereas in the 1950s a few QSAR descriptors, both experimental and calculated, were available, currently available software can calculate a large number of descriptors [11, 12, 13, 14, 15, 16]. This makes the QSAR modeling situation rank deficient where the number of predictors (*p*) is much larger as compared to the number of data points to be modeled (*n*). Such a situation calls for the judicious and correct use of statistical methods for model building and validation [refs].

According to the OECD principles, one of the required criteria a QSAR model fit to be implemented in practice must satisfy is proper model evaluation [17]. In the last two decades or so, QSAR researchers have adapted to using either one of the three validation methods:

1. Leave-one-out (LOO) cross validation: For each compound in the full dataset, its activity is predicted by a model built on samples excluding that compound.
2. *K*-fold cross validation: The data is randomly split into *K* disjoint partitions. Each partition is taken as test set, and QSAR models built on samples outside that partition to predict activities of samples in the partition;
3. External validation: The data is randomly split into two partitions: a larger training set and a smaller test set. QSAR model is built on the training set and evaluated on the test set.

Golbraikh and Tropsha [18] argued using empirical evidence that in some cases LOO cross-validation overestimates the predictive ability of a model but external validation does not. On the other hand, Hawkins *et al* [19] showed through theoretical argument and empirical study that for small sample sizes, the cross-validated *q*2 obtained from a LOO procedure is a better estimator of the true *R*2 (i.e. proportion of variance in the response variable explained by the predictors) than an externally validated *q*2.

As we have mentioned earlier, the typical QSAR dataset is High-Dimensional Low Sample Size (HDLSS). Although external validation is one of *the* widely used validation methods in the QSAR community, evidence has been mounting towards its inadequacy in prediction problems for HDLSS data. Furthermore, there is the added issue of nested cross-validation. Statistical procedures on HDLSS data involve a dimension reduction step (Principal Component Regression (PCR), Partial Least Squares (PLS)), variable selection step (forward selection in regression models) and/or tuning parameter selection (LASSO regression [ref] or machine learning methods). To ensure that holdout compounds do not influence the training step while doing cross-validation, these steps should be repeated each time a model is trained. This two-step procedure is called two-deep cross-validation [ref] or double cross validation oldest ref[20, 21].

In general, recent methodological research on the efficacy of validation techniques suggests a repeated two-deep validation procedure, that either covers the data through disjoint partitions (i.e. *K*-fold), or averages results over multiple random splits of the data (from hereon referred to as *multi-split validation*), over single-split external validation. When total number of samples is *n*, and size of the training and test sets are and , respectively (with ), [22] shows that the multi-split validation leads to almost sure recovery of the true underlying statistical model when and as . In their simulation setup, the multi-split method outperforms single-split external validation for small sample sizes (). Both methods perform similarly in large sample simulations ( and 1000). For prediction, [21] showed through analyzing simulated data as well as two chemical activities datasets that the multi-split validation provides a more unbiased estimate of prediction errors than external validation.

In probably what is the one of the most relevant work considering our focus on HDLSS data, [23] show through simulation that when sparse regression methods like LASSO, SCAD and MCP are used (we shall discuss LASSO, please refer to ref for details on SCAD and MCP) for model building, and estimating predictive performance is the goal, LOO cross-validation tends to outperform either *K*-fold CV or multi-split validation. Motivated by this study, as well as other papers mentioned above that highlight the inadequacy of external validation in QSAR model evaluation, in this paper we perform a comprehensive analysis of all the validation methods, i.e. LOO, *K*-fold, external and multi-split.

We use three simulated datasets, with fixed sample size *n* = 100 and three different predictor dimensions: *p* = 100. 500 and 1000 to highlight the effect of increasing dimension of the predictor space on performances of the above validation methods. We also perform this comparison of a congeneric dataset comprising of activities of 95 amine compounds. Section 2 contains more details on all these datasets. We build QSAR models on these data using the LASSO regression method [ref], which we elaborate on in Section 3. This section also contains further details about our validation methods, as well as the two-step validation scheme. We present and discuss the results obtained from this analysis in Section 4. The paper concludes with section 5, where we highlight the takeaways from the paper, and motivate future directions of research.

Points

Proper model validation is a OECD criterion (ref 66 in large review paper)

Two schools of thought: external validation, LOO cv (refs)

Although external validation is widely used, the evidence from outside and inside the QSAR community in favor of LOO/ k-fold is mounting up. Cite

Zhang/Yang, J. Econom.

Bauman paper- double cv over multiple splits is better

Filzmoser 2009 introduces this as repeated double cv

Closest comparison to multiple methods of cv in high dimension – Gramatica report that says leave-many-out is good. Also says single split external validation is too unstable.

We fill this gap by performing a comprehensive study between all candidates – LOO, k-fold, external and multiple external.

Simulated data and real 95 amine data. Lasso

Chapter description

**2. Data**

We use two datasets in our study: one simulated and another a well-known chemical activities dataset.

*2.1 Simulated data*

For sample size *n* and number of descriptors *p*, we generate data from the multivariate linear model:

|  |  |
| --- | --- |
|  | **(**1) |

With and being the random error with for = 1, 2, …, *n* and > 0. We fix *n* = 100, and consider three different values of *p*: 100, 500 and 1000. For a fixed p, we first generate rows of the matrix of descriptors as independent and identical draws from a *p*-dimensional normal distribution with mean **0** and covariance matrix . We fix the entries of as

There is often high correlation among chemical descriptors, and when modelling data on hundreds of such descriptors the intrinsic dimensionality of the descriptor data is often much lower than the actual dimension of the predictor space [24] [25]. We use the above correlation structure to simulate this scenario. For the coefficient vector , we set its first 10 entries as 1 and rest *p* – 10 entries as 0. Finally, we generate elements of by setting , calculate the response variable from (1), and repeat the process for different values of *p*.

*2.2 Congeneric data of 95 amines*

This dataset is due to Debnath *et al* [26]. It contains information on a congeneric set of 95 amine compounds: specifically values on 275 descriptors calculated for each compound, and their mutagenic activities on the *Salmonella typhimurium* strain TA98: as measured by the number of revertants per nmol (in log scale) when a sample compound is applied to a test culture.

<Insert table 1>

**Table 1**: Information on descriptor types in the congeneric amines data

|  |  |  |  |
| --- | --- | --- | --- |
| Type | No. of descriptors | Description | Software used |
| TS | 108 | Please fill in. | POLLY v2.3 [11], MolconnZ v4.05 [13] |
| TC | 158 |  | POLLY v2.3 [11], MolconnZ v4.05 [13],  TRIPLET [27] |
| 3D | 3 |  | Sybyl v6.2 [28] |
| QC | 6 |  | MOPAC v6.00 [29] |

This dataset contains four types of descriptors: topostructural (TS), topochemical (TC), three dimensional (3D) and quantum chemical (QC), in increasing order of computational complexity. Table 1 presents detailed information about these different types of descriptors. There is evidence that while predicting chemical activity through QSAR modelling, the computation-intensive 3D and QC descriptors are largely redundant in presence of a large number of TS and TC descriptors that are computationally easy to calculate [30] [4] [31]. However, we analyze all four types of descriptors in this paper for the sake of completeness, and because the statistical model used explicitly involves variable selection to automatically filter out variables that are not predictive enough.

**3. Statistical methods**

*3.1 LASSO regression*

For the linear model in (1), the LASSO method proposed by Tibshirani [ref] obtains an estimate of by solving the following minimization problem:

|  |  |
| --- | --- |
|  | (2) |

Where is a tuning parameter. The advantage of using this method is two-fold:

1. Because of the nature of the penalty term the solution is sparse, i.e. some of its entries are exactly set to zero. Thus, LASSO performs simultaneous variable selection and estimation of predictor effects;
2. Unlike linear regression which gives a unique solution only when *n* > *p*, existence and computation of the LASSO solution does not depend on the relative size of *n* and *p*.   
   Thus it is able to tackle high-dimensional regression problems with a large number of predictors but limited sample size (i.e. ).

The large number of descriptors and low intrinsic dimensionality of datasets that are typical of many modern QSAR problems [refs] makes LASSO an ideal candidate for estimation and prediction of chemical activity in such situations.

*3.2 Cross-validation techniques*

We use the following cross-validation techniques to evaluate the predictive capabilities of LASSO models built on the simulated as well as congeneric amine dataset.

***k*-fold cross validation (*k*-fold cv):** We divided the samples randomly into *k* splits, take samples in a split as test set, train a QSAR model on samples outside the test set and predict activity of samples in the test set with that model. Finally we repeat this for all splits to cover all samples.

**Leave-one-out cross validation (LOO-cv):** For a sample of size *n*, we train *n* models, each time taking a distinct sample in the test set to predict the activity of that sample. This can be interpreted as a *n*-fold cross validation.

**External validation:** We randomly chose 10 samples to be included in the test set. We train the model using other samples and predict the responses in the test samples using that model.

**Multi-split validation:** We repeat the external validation method 100 times over different random train-test splits of the data, and take the average of any metrics obtained over all such splits.

The tuning parameter for the LASSO regression model in (2) is selected from a range of values using *k*-fold cross-validation. Here we shall take *k* = 5. For this reason, while implementing each of the validation methods mentioned above we need to make sure to incorporate this step every time a model is trained. In this situation, selecting the tuning parameters first on a model built on the full dataset and then predicting for different train-test splits might seem a more intuitive approach. However, this naïve approach uses information from the holdout compounds in the first step, thus providing an inflated estimate of the cross-validated *q*2: which is termed as naïve *q*2 [32].

Thus, we perform cross-validation twice: once to select the best tuning parameter from the training samples, and again to obtain *q*2 values. As an example, for *k*-fold cross-validation the steps for this *two-deep cross validation* procedure will be as follows:

1. Randomly split data into *k* groups.
2. Consider samples in the first split as test set. Select the best tuning parameter by doing a 5-fold CV using the LASSO model in (2) on samples outside the test set.
3. Predict activities of compounds in test set using a LASSO model trained using the best tuning parameter.
4. Repeat steps (b) and (c) considering all other splits as test sets.
5. We now have predictions for all sample compounds. Calculate Prediction Sum of Squares (PRESS) and *q*2 values using these predicted values.

**4. Results**

*4.1 Simulated dataset*

For each of the validation methods applied, we report their *q*2 and PRESS obtained using the two-deep method described above.

<Insert table 1>

**Table 2:** Performance of all validation methods on simulated data

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *q*2 | | | | |
| Number of predictors (*p*) | | 100 | 500 | 1000 |
| LOO-cv | | 0.80 | 0.74 | 0.71 |
| 5-fold cv | | 0.76 | 0.60 | 0.28 |
| External validation | Min | 0.34 | 0.06 | -0.13 |
| 25th percentile | 0.72 | 0.62 | 0.48 |
| Median | 0.79 | 0.69 | 0.58 |
| 75th percentile | 0.84 | 0.76 | 0.68 |
| max | 0.95 | 0.89 | 0.87 |
| Repeated external validation | | 0.77 | 0.66 | 0.55 |
| PRESS | | | | |
| Number of predictors (*p*) | | 100 | 500 | 1000 |
| LOO-cv | | 1.66 | 2.36 | 2.77 |
| 5-fold cv | | 1.92 | 3.78 | 6.82 |
| External validation | Min | 0.26 | 0.86 | 1.01 |
| 25th percentile | 1.23 | 1.82 | 2.65 |
| Median | 1.63 | 2.48 | 3.35 |
| 75th percentile | 2.04 | 3.12 | 4.86 |
| max | 3.73 | 6.61 | 18.97 |
| Repeated external validation | | 1.70 | 2.59 | 4.24 |

**Table 2** reports values of the two metrics for the four validation techniques, considering the three different number of predictors. For external validation, we report the minimum, 25th percentile, median, 75th percentile and maximum of PRESS and *q*2 from the 100 train-test splits performed during the multiple external validation process. We report average PRESS and *q*2 over all repetitions for repeated external validation. LOO-cv has the best performance across all predictor dimension and both metrics. All methods perform worse as dimension of the descriptor space grows, which is expected because of higher amount of noise introduced by more predictors.

The main issue with external validation, which previous studies (e.g. [18] [33]) have not captured, is the high degree of variability in its performance depending on which subset of the full data is chosen as the validation sample. The minimum and maximum values indicate that depending on the train-test split, the two-deep *q*2 can vary between 0.34 to 0.95 for *p* = 100, 0.06 to 0.89 for *p* = 500 and 0.01 to 0.87 for *p* = 1000. For *p* = 100, About 50% of the external validation splits have worse performance than LOO-cv for both *q*2 and PRESS, which goes up to around 75% for *p* = 1000. This indicates that for higher number of predictors, LOO-cv is more likely to result a QSAR model that is more predictive. In 2 of the 100 random splits the external validation turned out to be negative. This means that PRESS is more than the total sum of squares in the test set, indicating very high amount of noise in the fitted model, i.e. severe overfitting.

*4.2 Amines dataset*

We report results from the LASSO model validation analysis of the 95 compounds congeneric amines dataset in **Table 3**. In this case, both LOO and 5-fold cv have larger two-deep *q*2 values than repeated external validation, as well as half of the random external validation splits. The minimum *q*2 value for external validation is as low as 0.15. One of the random train-test splits in external validation yielded a *q*2 value of -0.003. This underscores a severe limitation of the external validation procedure: if such a split of a real-world dataset is used to validate a QSAR model, the whole modelling practice becomes nothing but a waste of resources.

<Insert table 2>

**Table 3**: Performance of all validation methods on 95 amines data

|  |  |  |  |
| --- | --- | --- | --- |
| Number of predictors (*p*) | | *q*2 | PRESS |
| LOO-cv | | 0.77 | 0.86 |
| 5-fold cv | | 0.73 | 1.05 |
| External validation | Min | -0.003 | 0.27 |
| 25th percentile | 0.65 | 0.61 |
| Median | 0.73 | 0.88 |
| 75th percentile | 0.83 | 1.28 |
| max | 0.94 | 2.01 |
| Repeated external validation | | 0.71 | 0.97 |

**5. Discussion**

<Multiple peaks point from trouble with QSAR paper >

TWQSAR paper says caveats include multiple peaks, overfitting etc that are exhibited by external validation. The problem is larger for small datasets because high predictor dimension means more error variability.. so high chance that training and test sets are dissimilar.

QSAR modelling is extensively used in academia and industry setup for virtual screening of chemical compounds[34] [35]. These compounds often have lasting impact in human lives and the environment around us. In this situation, a *laissez-faire* use of external validation using small validation sets can have enormous consequences if the wrong compounds get selected in the screening procedure. Thus, it is difficult to overstate the importance of proper, stable and rigorous validation methods.

More discussion

|  |  |
| --- | --- |
| [1] | A. Crum-Brown and T. R. Fraser, "On the connection between chemical constitution and physiological action. Part 1. On the physiological action of the ammonium bases, derived from Strychia, Brucia, Thebaia, Codeia, Morphia and Nicotia," *Trans. Roy. Soc. Edinburgh,* vol. 25, pp. 151-203, 1868. |
| [2] | M. C. Richet, "Note sur le rapport entre la toxicite et les proprire te s physiques des corps," *Comput. Rend. Soc. Biol. (Paris),* vol. 45, p. 775, 1893. |
| [3] | C. Hansch and A. Leo, Exploring QSARs: Fundamentals and Applications in Chemistry and Biology, Washington, DC: American Chemical Society, 1995. |
| [4] | S. Majumdar, S. C. Basak and G. D. Grunwald, "Adapting interrelated two-way clustering method for quantitative structure-activity relationship (QSAR) modeling of mutagenicity/non-mutagenicity of a diverse set of chemicals," *Curr. Comput. Aided Drug Des.,* vol. 9, pp. 463-471, 2013. |
| [5] | S. C. Basak, "Mathematical Descriptors for the Prediction of Property, Bioactivity, and Toxicity of Chemicals from their Structure: A Chemical-Cum-Biochemical Approach," *Curr. Comput. Aided Drug. Des.,* vol. 9, pp. 449-462, 2013. |
| [6] | L. B. Kier and L. H. Hall, Molecular Connectivity in Chemistry and Drug Research, New York, NY: Academic Press, 1976. |
| [7] | L. B. Kier and L. H. Hall, Molecular Connectivity in Structure Activity Analysis, London, UK: Wiley, 1986. |
| [8] | J. Devillers and A. T. Balaban, Eds., Topological Indices and Related Descriptors in QSAR and QSPR, Amsterdam, Netherlands: Gordon and Breach, 1999, p. 811. |
| [9] | R. E. Carhart, D. Smith and R. Venkataraghavan, "Atom Pairs as Molecular Features in Structure-Activity Studies: Definition and Applications," *J. Che. Inf. Comput. Sci.,* vol. 25, pp. 64-73, 1985. |
| [10] | S. C. Basak, "Role of mathematical chemodescriptors and proteomics-based biodescriptors in drug discovery," *Drug. Dev. Res.,* vol. 72, pp. 1-9, 2010. |
| [11] | S. C. Basak, D. K. Harriss and V. R. Magnuson, "POLLY v2.3," Copyright of the University of Minnesota, 1988. |
| [12] | S. C. Basak and G. D. Grunwald, "APProbe," Copyright of the University of Minnesota, 1993. |
| [13] | MolconnZ v4.05, Quincy, MA: Hall Ass. Consult., 2003. |
| [14] | R. Todeschini, V. Consonni, A. Mauri and P. M., DRAGON - Software for the Calculation of Molecular Descriptors, Version 5.4, Milan, Italy: Talete srl, 2006. |
| [15] | C. W. Yap, "PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints," *J. Comput. Chem.,* vol. 32, pp. 1466-1474, 2011. |
| [16] | P. A. Filip, T. S. Balaban and A. T. Balaban, "A new approach for devising local graph invariants: derived topological indices with low degeneracy and good correlation ability," *J. Math. Chem.,* vol. 1, pp. 61-83, 1987. |
| [17] | S. C. Basak, D. Mills, D. M. Hawkins and J. J. Kraker, "Proper statistical modeling and validation in QSAR: A case study in the prediction of rat fat-air partitioning," in *Computation in Modern Science and Engineering, Proceedings of the International Conference on Computational Methods in Science and Engineering 2007 (ICCMSE 2007)*, Melville, NY, 2007. |
| [18] | A. Golbraikh and A. Tropsha, "Beware of q2!," *J. Mol. Graphics Model.,* vol. 20, pp. 269-276, 2002. |
| [19] | D. Hawkins, S. Basak and D. Mills, "Assessing model fit by cross-validation," *J. Che. Inf. Comput. Sci.,* vol. 3, pp. 579-586, 2003. |
| [20] | P. Filzmoser, B. Liebmann and K. Varmuza, "Repeated double cross validation," *J. Chemometrics,* vol. 23, pp. 160-171, 2009. |
| [21] | D. Bauman and K. Baumann, "Reliable estimation of prediction errors for QSAR models under model uncertainty using double cross-validation," *J. Chemoinformatics,* vol. 6, p. 47, 2014. |
| [22] | Y. Yang, "Consistency of cross validation for comparing regression procedures," *Ann. Statist.,* vol. 35, pp. 2450-2473, 2007. |
| [23] | Y. Zhang and Y. Yang, "Cross-validation for selecting a model selection procedure," *J. Econometrics,* vol. 187, pp. 95-112, 2015. |
| [24] | S. Majumdar and S. C. Basak, "Exploring intrinsic dimensionality of chemical spaces for robust QSAR model development: A comparison of several statistical approaches," *Curr. Comput. Aided Drug Des.,* vol. 12, no. 4, pp. 294-301, 2016. |
| [25] | S. C. Basak, V. R. Magnuson, G. J. Niemi, R. R. Regal and G. D. Veith, "Topological indices: their nature, mutual relatedness, and applications," *Mathematical Modelling,* vol. 8, pp. 300-305, 1987. |
| [26] | A. Debnath, G. Debnath, A. Shusterman and C. Hansch, "A QSAR Investigation of the Role of Hydrophobicity in Regulating Muagenicity in the Ames Test: 1. Mutagenicity of Aromatic and Heteroaromatic Amines in Salmonella typhimurium TA98 and TA100," *Environ. Mol. Mutagen.,* vol. 19, pp. 37-52, 1992. |
| [27] | S. Basak, G. Grunwald and A. Balaban, "TRIPLET," Copyright of the Regents of the University of Minnesota, 1993. |
| [28] | Sybyl Version 6.2, St. Louis, MO: Tripos Associates, Inc., 1995. |
| [29] | J. Stewart, MOPAC Version 6.00, QCPE #455, Frank J. Seiler Research Laboratory: US Air Force Academy, CO, 1990. |
| [30] | S. C. Basak, B. D. Gute and G. D. Grunwald, "A hierarchical approach to the development of QSAR models using topological, geometrical and quantum chemical parameters," in *Topological Indices and Related Descriptors in QSAR and QSPR*, J. Devillers and A. T. Balaban, Eds., Amsterdam, The Netherlands, Gordon and Breach Science Publishers, 1999, pp. 675-696. |
| [31] | S. Majumdar and S. C. Basak, "Prediction of Mutagenicity of Chemicals from Their Calculated Molecular Descriptors: A Case Study with Structurally Homogeneous versus Diverse Datasets," *Curr. Comput. Aided Drug. Des.,* vol. 11, pp. 117-123, 2015. |
| [32] | D. Hawkins, S. Basak and D. Mills, "QSARs for chemical mutagens from structure: ridge regression fitting and diagnostics," *Environ. Toxicol. Pharmacol.,* vol. 16, pp. 37-44, 2004. |
| [33] | A. Cherkasov, E. N. Muratov, D. Fourches and others, "QSAR Modeling: Where Have You Been? Where Are You Going To?," *J. Med. Chem.,* vol. 57, no. 12, pp. 4977-5010, 2014. |
| [34] | S. C. Basak, "Philosophy of Mathematical Chemistry: A Personal Perspective," *Hyle- Int. J. Phil. Chem.,* vol. 19, pp. 3-17, 2013. |
| [35] | S. C. Basak and S. Majumdar, "Editorial: The Importance of Rigorous Statistical Practice in the Current Landscape of QSAR Modelling," *Curr. Comput. Aided Drug Des.,* vol. 11, no. 1, pp. 2-4, 2015. |
| [36] | Y. Zuo and R. Serfling, "General notions of statistical depth functions," *Ann. Statist.,* vol. 28, pp. 461-482, 2000. |
| [37] | H. Xu, C. Caramanis and S. Mannor, "Outlier-Robust PCA: The High-Dimensional Case," *IEEE Trans. Inf. Theory,* vol. 59, pp. 546-572, 2013. |
| [38] | H. Wiener, "Structural determination of paraffin boiling points," *J. Amer. Chem. Soc.,* vol. 69, pp. 17-20, 1947. |
| [39] | R. P. Verma and C. Hansch, "An approach toward the problem of outliers in QSAR," *Bio. Med. Chem.,* vol. 13, pp. 4597-4621, 2005. |
| [40] | N. Trinajstić, Chemical Graph Theory, Boca Raton, FL: CRC Press, 1992, p. 352. |
| [41] | R. Todeschini and V. Consonni, Molecular Descriptors for Chemoinformatics, New York, NY: Wiley-VCH, 2009. |
| [42] | J. J. Sylvester, "On an application of the new atomic theory to the graphical representation of the invariants and covariants of binary quantics, with three appendices," *Amer. J. Math.,* vol. 1, pp. 64-125, 1878. |
| [43] | J. V. Soderman, CRC Handbook of Identified Carcinogens and Noncarcinogens: Carcinogenicity-Mutagenicity Database, Boca Raton, FL: CRC Press, 1982. |
| [44] | C. Raychaudhury, S. K. Ray, J. J. Ghosh, A. B. Roy and S. C. Basak, "Discrimination of isomeric structures using information-theoretic topological indices," *J. Comput. Chem.,* vol. 5, pp. 581-588, 1984. |
| [45] | M. Randic, "Characterization of molecular branching," *J. Amer. Chem. Soc.,* vol. 97, pp. 6609-6615, 1975. |
| [46] | R Core Team, *R: A Language and Environment for Statistical Computing version 3.1.1,* 2014. |
| [47] | A. H. M. Nandy and S. C. Basak, "Mathematical descriptors of DNA sequences: Development and application," *Arkivoc,* vol. 9, pp. 211-238, 2006. |
| [48] | S. Majumdar, "Robust estimation of principal components from depth-based multivariate rank covariance matrix," 2015. [Online]. Available: http://arxiv.org/abs/1502.07042. |
| [49] | M. Lajiness, Molecular similarity-based methods for selecting compounds for screening. In Computational Chemical Graph Theory, D. H. Rouvray, Ed., Commack, NY: Nova, 1990. |
| [50] | M. Karelson, Molecular Descriptors in QSAR/QSPR, New York, NY: Wiley-Interscience, 2000. |
| [51] | D. Janežič, A. Miličević and S. &. T. N. Nikolić, Graph-Theoretical Matrices in Chemistry, Boca Raton, FL: CRC Press, 2015. |
| [52] | H. Hosoya, "Topological Index. A newly proposed quantity characterizing the topological nature of structural isomers of saturated hydrocarbons," *Bull. Chem. Soc. Jpn.,* vol. 44, pp. 2332-2339, 1971. |
| [53] | H. Gonzalez-Diaz and C. R. Munteanu, Eds., Topological Indices for Medicinal Chemistry, Biology, Parasitology, Neurological and Social Networks, New York, NY: Transworld research, 2011. |
| [54] | B. M. Brown, "Statistical Use of the Spatial Median," *J. R. Statist. Soc. B,* vol. 45, pp. 25-30, 1983. |
| [55] | D. Bonchev, Information Theoretic Indices for Characterization of Chemical Structures, Chichester, UK: Research studies Press, 1983. |
| [56] | S. Basak, D. Mills, B. Gute, A. Balaban, k. K. Basa and G. Grunwald, "Use of Mathematical Structural Invariants in Analyzing, Combinatorial Libraries: A Case Study with psoralen Derivatives," *Curr. Comput. Aided Drug Des.,* vol. 6, pp. 240-251, 2010. |
| [57] | S. Basak, V. R. Magnuson, G. J. Niemi and R. R. Regal, "Determining Structural Similarity of Chemicals using Graph-Theoretic Indices," *Disc. Appl. Math.,* vol. 19, pp. 17-44, 1988. |
| [58] | S. C. Basak, "Use of molecular complexity indices in predictive pharmacology and toxicology: A QSAR approach," *Med. Sci. Res.,* vol. 15, pp. 605-609, 1987. |
| [59] | S. C. Basak, D. Mills, B. D. Gute and D. M. Hawkins, "Predicting Mutagenicity of Congeneric and Diverse Sets of Chemicals Using Computed Molecular Descriptors: A Hierarchical Approach," in *Quantitative structure-activity relationship (QSAR) models of mutagens and carcinogens*, R. Benigni, Ed., Boca Raton, FL, CRC Press, 2007, pp. 215-242. |
| [60] | S. C. Basak, "Molecular Similarity and Hazard Assessment of Chemicals: A Comparative Study of Arbitrary and Tailored Similarity Spaces," *J. Eng. Sci. Manage. Educ.,* vol. 7, pp. 178-184, 2014. |
| [61] | S. C. Basak, "Mathematical Structural Descriptors of Molecules and Biomolecules: Background and Applications," in *Advances in Mathematical Chemistry and Applications, volume 1*, S. C. Basak, G. Restrepo and J. L. Villaveces, Eds., Bentham eBooks, Bentham Science Publishers and Elsevier, 2015, pp. 3-23. |
| [62] | S. C. Basak, V. R. Magnusson, G. J. Niemi and R. R. Regal, "Determining structural similarity of chemicals using graph-theoretic indices," *Dictrete Appl. Math.,* vol. 19, pp. 17-44, 1988. |
| [63] | S. C. Basak, G. Restrepo and J. L. Villaveces, Eds., Advances in Mathematical Chemistry and Applications, volume 1 & 2, Bentham e-books, Bentham Science Publishers and Elsevier, 2015. |
| [64] | K. Balasubramanian and S. C. Basak, "Characterization of isospectral graphs using graph invariants and derived orthogonal parameters," *J. Chem. Inf. Comput. Sci.,* vol. 38, pp. 367-373, 1998. |
| [65] | A. T. Balaban, "Distance Connectivity Index," *Chem. Phys. Lett.,* vol. 89, pp. 399-404, 1982. |
| [66] | K. P. Adragni and R. D. Cook, "Sufficient dimension reduction and prediction in regression," *Phil. Trans. R. Soc. A,* vol. 367, pp. 4385-4405, 2009. |
| [67] | C. M. Auer, J. V. Nabholz and K. P. Baetcke, "Mode of action and the assessment of chemical hazards in the presence of limited data: use of structure-activity relationships (SAR) under TSCA, Section 5," *Environ. Health, Persp.,* vol. 87, pp. 183-197, 1990. |
| [68] | L. B. Kier and L. H. Hall, Molecular Structure Description: The Electrotopological State, San Diego, CA: Academic Press, 1999. |