



Molecular Descriptors Family on Structure Activity Relationships

1. Review of the Methodology

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Abstract

This review cumulates the knowledge about the use of Molecular Descriptors Family usage on Structure Activity Relationships. The methodology is augmented through the general Structure Activity Relationships methodology. The obtained models in a series of five papers are quantitatively analyzed by comparing with previous reported results by using of the correlated correlations tests. The scores for a series of 13 data sets unpublished yet results are presented. Two unrestricted online access portals to the Molecular Descriptors Family Structure Activity Relationship models results are given.

Keywords

Structure Activity Relationship Methodology, Online Structure Activity Relationships

Introduction

Modeling, testing and identification of new biological active compounds have impact into agriculture, health and industry, being the main instrument of the economical progress and quality of life improvement. The identification or developing of new biocombustibles, biomaterials and biologically active chemical compounds are the way to the more economical efficiency and decreasing of environment pollution.

Are unanimous recognized now that the objectives of economic efficiency increasing

and environment pollution reducing through new uses for known strains and biocatalysts, optimizing of biotechnological processes, identification and characterization of new enzymes and microorganisms, microbial genomics and bioinformatics, metabolic engineering and modeling, superior proteins and nanocomposite place the research and develop activities through Molecular Descriptors Family (MDF) methodology in the *interdisciplinary research field of chemistry-biology-informatics*.

SAR Methodology

In the last period, the structural indices used on biological active compounds modeling by use of structure-activity integrated studies (SAR – structure-activity relationships) are more frequent computed from steric (geometrical) and/or electrostatic (partial charges) parameters [1] opposing to pure topological parameters [2]. Are preferred semi-empirical and quantum computations with software such as Hondo95, Gaussian94, Gamess, Icon08, Tx90, Polyrate, Unichem/Dgauss, Allinger`s MM3, Mopac93, Mozyme and HyperChem [3].

Regression analysis structure-activity uses classical methods such as linear, multiple linear and un-linear regressions, and also expert systems and neural networks for large databases [4].

The elaboration, implementation and use of molecular models for obtaining of new biological active compounds are referred frequently in the information flux. Here is a review of these preoccupations.

As preliminary analysis method, some authors align the set of molecules. More, CoMFA method introduces a six step algorithm for structure-activity analysis [5]:

1. construct the training set of molecules with known biological activity and generate the 3D structure of the molecules (by use of software such as Mopac, Sybyl [6-7], HyperChem [8-9], Alchemy2000 [6], MolConn [10]);
2. choose a overlapping method (which can be the overlapping of choosed fragments from molecules [5,11,12] or pharmacologically groups [13] and overlap virtually the spatial coordinates;
3. construct a grid which surround the overlapped molecules on step (2) using a standard or modified form [14] and choose a probe atom for the interaction with the grid points [15];

4. use an empirical method (Hint [17]), a specific model (pharmacologically overlapping [18]), classical potential energy (Lennard-Jones, Coulomb), hydrogen bonds energy [19], molecular orbital generated field [20,21] or any other user defined model [15] and calculate the interactions values on grid from step (3) of chosen interaction field with probe atom from step (3);
5. use the computed values of interaction from step (4) between grid points and probe atom to make estimation of known activity by constructing a structure activity relationship;
6. use structure activity relationship obtained at step (5) to make prediction of activity for molecules with same overlapping with training set from step (1).

The CoMFA method are a good tool for predicting varied types of biological activities such as cytotoxicity [22], inhibition [21], or forming properties [23, 24]. More, the method serves in modeling of compounds with pharmaceutical effects [13, 25] and HIV inhibitors [26].

Watching on structural investigations on biological active compounds, a main task is searching of biological active substructures from biological active compounds which produce most of measured biological response [17].

One of the variants to realize the searching of biological active substructures is the identification of the molecular invariants. In this sense, the HWIM method (Weighted Holistic Invariant Molecular) compute a set of statistical indicators derived from steric and electrostatic properties of the molecules [28-30]. A variant of this method, MS-WHIM (from Molecular Surface) serves to molecular surface analysis [31]. MS-WHIM is a collection of 36 statistical indicators derived from steric and electrostatic properties and are oriented to parameterize the molecular surface [32].

The quantitative structure-activity relationships QSAR (Q – quantitative) refer a measurable biological activity and the technique which use QSAR are a modern technique used today in many priority domains, including pharmacology, environment, biotechnology and microbiology. The literature of specialty contains today a great number of structure-activity relationships which evaluate the impact of chemicals to the environment [33-37].

The mathematical model used for structure-activity relationships obtaining are most frequently based on linear regression [38] and artificial neural networks [39-41].

MDF SAR Methodology

As are demonstrated above, the methodology of structural investigations for biological active compounds recommend:

1. *Constructing of molecular model* using a molecular modeling software;
2. Validation or applying of the molecular model through *Prediction* (the quantitative evaluation of the link between the topological and topographical structure proposed by the model and measured activity or property, if these are available from experimental data after the synthesizing of the compound) *or Estimation* (computing of the most probable value of the property or activity and quantitative evaluation of the link between obtained or known topological and topographical structure and estimated activity or property, for the case when experimental data are not available or the compounds was not yet synthesized);
3. Establish or choose of the ways of synthesizing (of mechanisms) for the compounds which prove a good biological activity;
4. *Synthesizing* of chemical compounds for which the molecular model recommend good estimated values of desired biological activity;
5. The *Evaluation* of biological activities and properties for the new synthesized compounds.

Proposed methodology for the research *implements the recommended methodology* and *use* for estimating and prediction the *MDF model* (Molecular Descriptors Family) of original design.

The methodology of each biological activity includes:

1. *identification and choosing of structural class* which present the best biological activity selected;
2. *data collecting* about synthesized compounds which belong to the class;
3. *making of the experiments* in order to obtain the values of biological activity for the compounds which are synthesized and are on market available and for which does not exists reported in the literature the values of the selected biological activity;
4. molecular modeling of the every compound from the class and *elaboration of molecular model*;
5. *database generation* with structural descriptors for class members;

6. use of the database for *identification of the best SAR* and of the representative structural descriptors for the biological activity and structural class;
7. *design of new biological active chemical compounds* belonging to the class by applying of obtained SAR for prediction of biological activity;
8. *synthesizing of new compounds and validation of the predictions.*

A set of MDF methodology characteristics must be underlined:

- Computing and integration into the database of structural descriptor values of formulas for descriptors with proved validity in the international flux of information, and of other completely new in a unitary form, formalized and parameterized, called *MDF* (molecular descriptors family) of *original design*;
- Applying of linearizing operators to make passing from the structure (microscopic properties) to the biological activity (macroscopic properties) and bias of obtained descriptors (in number of 787968) to a number of about 100000 descriptors using a *original bias algorithm*;
- System of representative subset selecting of molecular descriptors based on recursive, iterative and heuristic algorithms which identifies the best the structure-activity relationship *projected and implemented by the project team*;
- System of external validation using successive splits in training and test sets using again a *original algorithm*;

The software system process is based on knowledge, learning and cognitive system. The applicative importance of integrated structural investigations on classes of biologically active compounds is revealed because the investigation and *identification of relation between structure and activity of biological active compounds are the tool* of new biologically active chemical compounds identification with better properties which *use accumulated knowledge through learning of behavior* on training sets and *apply the cognitive system* for structure design before synthesizing.

MDF SAR History

First steps begins with *publishing of* [42] which threat the modern investigations from topology point of view of molecular structure and in chapter 9 are enounced the scientific

premises of molecular descriptors family. The *advantages* of use of an integrated system of molecular descriptors, as are MDF, was recognized and published in [43]. The using of the MDF prototype was reported in international flux of information. Here are the results:

- *Biological activity of Mutagenicity and Toxicity* for a set of 15 quinolines using the MDF prototype was modeled and the results are superior to the reported results in a similarly study: $R^2(\text{mutagenicity, subset MDF}) = 0.98$, $R^2(\text{cytotoxicity, subset MDF}) = 0.96$, $\langle \text{subset MDF} \rangle = 2$, relative to 0.87 and respectively 0.80 reported [44]; *the result was the subject of an online international conference* [45];
- *The better results through MDF methodology use* was proved through ability of chromatographic retention index estimation on a set of 10 organophosphoric herbicides; *results using MDF prototype* was reported in [46] and comparatively with the traditionally method of topological descriptors, the following results was: $r^2(\text{ICHR+}, \text{subset MDF}) = 0.999$ relative to 0.900 using *the traditional method of topological descriptors* [47];
- The applications of MDF on environment protection and depollution technologies are shows in [48], where the previous *results obtained* [49] *was surpassed by the MDF prototype MDF in an obvious way: 0.997 relative to 0.658!*
- A more remarkable result through the prism of capabilities which MDF prove to have, are obtained on the complete set of 209 *polychlorinated biphenyls* [50], where prediction ability of relative response factor was remarkable $r = 0.858$.

MDF SAR Model

Starting with our approach, the topological structure of the molecule enters into a fragmentation routine.

Four fragmentation criterions are applied for a given structure. The fragmentation criterions generate fragments of molecule (connected atoms substructures) for all pairs of atoms (carbon and heteroatom atoms type). Minimal fragments criterion applied to a pair (a,b) of atoms produces always a fragment with one atom: {a} (the `a` atom). Maximal fragments criterion on (a,b) pair produce the largest subset of connected atoms from structure which not contain the `b` atom. Szeged fragments criterion for (a,b) pair produces the fragment from molecule of which atoms are closed to `a` then `b` atom. Cluj fragments criterion applies the

Szeged fragments criterion to a substructure of molecule which is obtained by excluding a minimal distance path from molecule. Note that the Cluj fragments criterion differ significant from the previous criterions, and can produce as result a more than one fragment for a given pair (a,b) of atoms. The number of fragments are equal to number of distinct minimal distance paths from `a` to `b`.

The fragmentation procedure produces a list of fragments from molecule (not necessary distinct ones). For a fragmentation criteria and (a,b) pair it result always at least one fragment with at least one atom. In figure 1 are depicted a fictive example of a fragment of (a,b) pair of atoms.

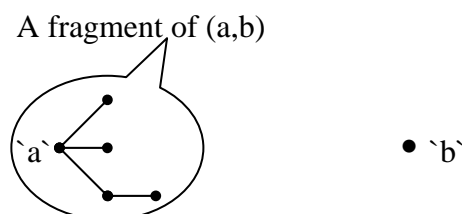


Figure 1. A fragment example

For a molecule fragment the calculations use one of two distance metrics (topological and topographical) and one of six atomic properties (cardinality – it has always value 1, number of directly bonded hydrogen's, atomic relative mass, atomic electronegativity, group electronegativity [51], and atomic partial charge – such as from semi-empirical Extended Hückel model, Single Point approach), when result 12 distinct possibilities.

More, both distance metric and atomic property are used by interaction descriptor. The interaction descriptor formula is one of D (for $I_D = d$), d (for $I_D = 1/d$), O (for $I_D = p_1$), o (for $I_D = 1/p_1$), P (for $I_D = p_1 \cdot p_2$), p (for $I_D = 1/p_1/p_2$), Q (for $I_D = \sqrt{p_1 \cdot \sqrt{p_2}}$), q (for $1/\sqrt{p_1}/\sqrt{p_2}$), J (for $I_D = p_1 \cdot d$), j (for $I_D = 1/p_1/d$), K (for $I_D = p_1 \cdot p_2 \cdot d$), k (for $I_D = 1/p_1/p_2/d$), L (for $I_D = \sqrt{p_1 \cdot \sqrt{p_2} \cdot d}$), l (for $I_D = 1/\sqrt{p_1}/\sqrt{p_2}/d$), V (for $I_D = p_1/d$), E (for $I_D = p_1/d/d$), W (for $I_D = p_1 \cdot p_1/d$), w (for $I_D = p_1 \cdot p_2/d$), F (for $I_D = p_1 \cdot p_1/d/d$), f (for $I_D = p_1 \cdot p_2/d/d$), S (for $I_D = p_1 \cdot p_1/d/d/d$), s (for $I_D = p_1 \cdot p_2/d/d/d$), T (for $I_D = p_1 \cdot p_1/d/d/d/d$), t (for $I_D = p_1 \cdot p_2/d/d/d/d$), and result a number of 288 possibilities.

The overlapping interaction models threatens the interaction between atomic descriptors. The R and r models consider that the distance is far enough to treat all interaction descriptors as scalars. The R model computes the resultant of the fragment's atoms descriptors at position

of atom j . The r model computes the resultant at conventional origin. The M and m models consider all fragmental property cumulated into the property center of the fragment. The property center coordinates are calculated by a formula similarly with well-known mass center coordinates formula. The fragmental descriptor is calculated using property center coordinates and sum of fragmental property as fragmental property. Similarly, the M model refer the atom j and m model refer the origin. The D and d models treat the descriptors as vectors with direction identical to distance vector. The axial projections are summed to obtain the projections of fragmental descriptor. The value of fragmental descriptor is calculated from his projections. The D model refer the j atom and d model refer the origin. Using any of overlapping interaction models, it result a number of 1728 possibilities.

Molecular descriptor value is constructed from fragments descriptors values. A number of nineteen selectors are available and the functions can be grouped as follows. *Conditional group* contains four functions: m (smallest fragmental descriptor value from the array), M (highest value), n (smallest absolute value), and N (highest absolute value). *Average group* contains five functions: S (sum of descriptor values), A (average mean for valid fragments), a (average mean for all fragments), B (average mean by atom), b (average mean by bond). *Geometric group* contains five descriptors: P (multiplication of descriptor values), G (geometric mean for valid fragments), g (geometric mean for all fragments), F (geometric mean by atom), f (geometric mean by bond). *Harmonic group* contains five functions: s (harmonic sum of values), H (harmonic mean for valid fragments), h (harmonic mean for all fragments), I (harmonic mean by atom), i (harmonic mean by bond). The total number of possibilities is now 32832. Considering now the number of fragmentation criterions (four), the total number becomes 131328 possibilities.

Resulted molecular descriptors are almost prepared. Because the structure activity/property model finding is of multiple linear regression type, and measured property usually endure a mathematical transformation such as natural logarithm, a set of six linearization functions are applied also to the resulted molecular descriptors and finally result the complete set of molecular structure descriptors, in number of 787968.

Note that the `sn_tmpx` table produced by our software stores the un-linearized molecular structure descriptors (in number of 131328).

Every MDF member has a name. The name tells about how the descriptor was computed. An example of descriptor name is *lmmRDCg*. The 7-th letter (g in our example)

tells about the distance metric used, and can be *g* (geometrical i.e. topographical) or *t* (topological). The 6-th letter (*C* in our example) is for atomic property. It can be one of *C* (Cardinality), *H* (number of directly bonded hydrogen's), *M* (atomic relative mass), *E* (atomic electronegativity), *G* (group electronegativity), *Q* (the partial charge). The 5-th letter (*D* in our example) tells about the atomic interaction descriptor (I_D) used and are explained above. The 4-th letter (*R* in our example) is for overlapping interaction model, also explained above. The 3-rd letter (*m* in our example) denotes the fragmentation criterion. The *m* letter is for minimal fragments, the *M* letter is for maximal fragments, the *D* letter is for Szeged fragments criterion, and the *P* letter is for Cluj fragments criterion. The second letter (*m* in our example) is for the molecular selector (one of the nineteen selectors explained above). Finally, the first letter (*l* in our example) is for linearization function and is one of: *I* (identity, $f(x)=x$), *i* (inverse, $f(x)=1/x$), *A* (absolute, $f(x)=|x|$), *a* (inverse of absolute, $f(x)=1/|x|$), *L* (natural logarithm of absolute value, $f(x)=\log_e(|x|)$), *l* (simple natural logarithm, $f(x)=\log_e(x)$).

Once that the MDF set is generated, a bias method it reduce the number of descriptors using a significance level of 10^{-9} . The number of resulted biased descriptors depends on the choused molecules set and measured property, and contain about 100000 descriptors.

Simultaneously with the bias algorithm, the mono-varied correlation between descriptors and measured property are dons and the descriptors are sorted by accordingly.

Bi-varied correlations are applied in order to find the best bi-varied MDF SAR models by use of all possible combinations between pairs of descriptors. Upper than bi-varied (tri-, four-, ... varied) correlations are possible and made only by use of a set of heuristic algorithm, that reduces the finding time to a real time. As result, the best found MDF SARs are collected.

On all MDF SAR found models a set of prediction capability tests are applied. First test is for leave one out prediction capability and it shows the best models for every variation rank. By combining the results of estimation capability with the prediction capability, only a reduced set of MDF SAR models are selected, as a rule no more than one for every variation rank. Finally, a random routine stripes out a arbitrary number of molecules from the whole set and rebuild the model using the remaining set (which act as *training set*). By use of the stripped out molecules (*test set*) the models are validated.

MDF SAR Software

The MDF SAR software uses a database on the entire process of SAR findings.

A first molecules set table is created and named using the set name and `_tmpx` suffix (as example, ``sn_tmpx``). The table has as columns the molecules names (from molecules files names) and as rows the molecular descriptors. The table always contains 131328 records (each record for a descriptor). First of our programs (*mdf_prepare.php*) create the table. The second of our programs (*mdf_generate.php*) for every file from HIN folder read the molecule from the file, generate the molecular descriptors for the molecule and fill the corresponding column in the molecules set table (``sn_tmpx`` table).

The current implementation of our original software requires that the molecules from set to be saved in separate files in HyperChem HIN format. A label is required here: set name. The set name is a given name for the molecules set; this name will be used further for set folder name and set tables naming. The set preparation procedure requires construction of a new folder: the set folder. The *sn* is our exemplification set name. The molecules structures (as HIN files) are stored (temporarily) in a subfolder (of *sn* folder) called for convenience HIN. The measured activity or property is stored (temporarily) in a subfolder (of *sn* folder) called for convenience DATA as text file. Is essentially for the programs to run correctly that the measured values (of activity or property) to be putted in the file in separate rows in alphabetical order of molecules files names.

Many quantum mechanics models are available for molecules models constructing by use of software (such as HyperChem). Than Molecular Descriptors Family (MDF) to be generated is essentially to choose a model that compute also the partial charges on atoms. Once the quantum mechanics model was choused, all molecules from set must be constructed according with the selected model.

At the end of MDF generating, the ``sn_tmpx`` table are fully prepared. The third of our programs (*mdf_linearize.php*) generate the rest of tables set, as follows:

- Read the activity/property file from DATA subfolder of set folder and create the ``sn_data`` table with measured values on separate rows. It has only one column;
- Copy the structure of ``sn_tmpx`` table (with molecules names as columns) into a new table called ``sn_xval`` wich will contain the linearized values of molecular descriptors. In order to increase the speed of further data processing's, another table, ``sn_yval`` are created also.

The `sn_yval` table is created for storing supplemental information relative to every descriptor from `sn_xval` table. It has columns for molecular descriptor family member name, squared correlation coefficient (of his values for all molecules with measured values of activity/property for all molecules), average of descriptor values (all molecules from set), average of squared values, and covariance with measured values;

- Using every one of the linearization methods, a record from `sn_tmpx` table will produce six records in `sn_xval` table (and another six corresponding records in `sn_yval` table). Both tables are simultaneously filled by *mdf_bias.php* program;
- Is possible that the descriptor value construction to have, in one point, an undetermined operation to do, and the final value is stored then as infinite (INF). If a descriptor has INF values, it can be used in correlations and is deleted;
- Almost always not all (of remaining from 787968) descriptors are distinct. More, even if it exist a small difference, may be not enough that to consider the descriptors significantly different. Sorting the descriptors by squared correlation coefficient allow to apply a significantly different criteria. Our program considers two descriptors significantly different if squared correlation coefficient differs with more than 10^{-9} . All not significantly different descriptors are deleted now; this is the last task of *mdf_bias.php* program;
- In order to help the multiple linear regression structure activity/property relationship findings, the *mdf_order.php* program rearrange records in `sn_xval` and `sn_yval` tables by squared correlation coefficient score;

Molecules set tables set preparation is now completed. A database server store and manage the `MDF` database (figure 2). The `MDF` database contain two management tables (`sar` and `ready`) and more set tables.

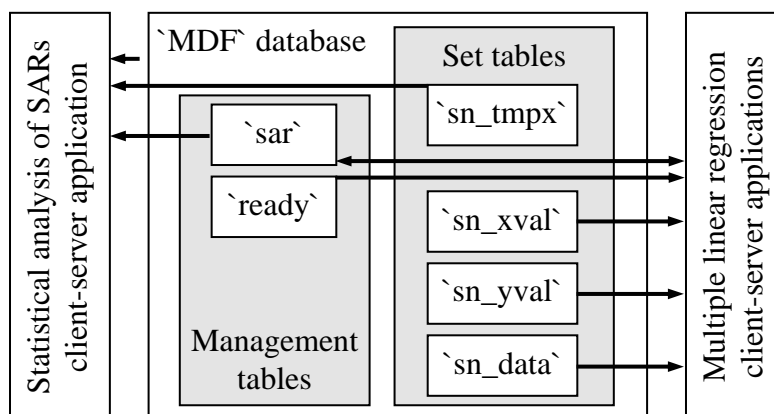


Figure 2. Model of MDF set tables management

Now a client program can connect to the `MDF` database, query the `ready` table to obtain the set name which are currently set for structure activity/property relationship findings, fetch the measured data from `sn_data` table, MDF members values from `sn_xval` table and pre-prepared statistical parameters from `sn_yval` table and proceed to QSAR findings. Because the findings are very consuming of time (about $5 \cdot 10^9$ pairs of MDF members in bi-varied MLR model) the client programs use statically memory allocation management and for multi-varied models (more than two) use heuristic algorithms for QSAR findings. Until now, we develop seventeen heuristic programs to serves us to find QSAR models with more than two linearized descriptors. Every new better QSAR model (greater squared correlation coefficient score) are inserted into `sar` table. Client-server applications communicates together through `sar` table and a new record is putted into `sar` table if does not exists a better one already.

Any time, and especially at the end of structure activity relationships findings, the *mdf_query.php* running produces a report with complete statistical analysis of the best QSAR models from `MDF` database. The program use as entry data the original values of molecular structure descriptors from all `sn_tmpx` sets tables which have records into `sar` table and select from `sar` table only the best found models on every set and number of molecular structure descriptors from structure activity relationship.

A user is recommended and was created to have the aright rights to the database. Table 1 contains a set of prescriptions, which was specified and saved on server.

Table 1. MySQL user definition

User overview				
User	Host	Password	Global privileges	Grant
mdf	%	Yes	CREATE TEMPORARY TABLES, LOCK TABLES	No
Database-specific privileges				
	Database	Privileges	Grant	Table-specific privileges
	MDF	SELECT	No	Yes
Table-specific privileges				
	Table	Privileges	Grant	Column-specific privileges
	sar	INSERT	No	No
	ready	UPDATE	No	No

A client program, which uses the *mdf* user to identify itself, will get SELECT privilege on all tables from `MDF` database (including sets tables). On `sar` table will get a specific privilege to INSERT and on `ready` table will get a specific privilege to UPDATE.

The original program which was developed, called MDF2, connect to the database server using the IP address, user name and password. First, query the `ready` table to know which table set are prepared for structure – activity/property findings are prepared. The program looks for '2' value in `v` field (make bi-varied regressions) and get the corresponding `set` and `r2` values.

The second step is to fetch data from set tables for the ready set. Once the data are completely fetched, the routine for quantitative relationships starts. When a multiple linear regression equation which correlates with a squared correlation coefficient bigger than the current value of `r2` are found, the equation are saved into `sar` table and the `r2` value from `ready` table are updated correspondingly. Thus, any time the program can be stopped and restarted without waste time to find something that is already into the `sar` table. More, many client programs can run in same time on same molecules set, including here the multi-varied ones (MDF3, MDF4, and so on).

The temporarily results of the MDF SAR findings are a subject of an unrestricted online access. The portal to the access of this results produced by the *i_mdf_query.php* program is http://vl.academicdirect.org/molecular_topology/mdf_findings/.

The evaluation software, which splits randomly the whole set into the training and test sets are also of an unrestricted online access and the portal of the finally MDF SAR models are: http://vl.academicdirect.org/molecular_topology/qsar_qspr_s/.

MDF SAR Results

The MDF methodology was applied on the activities of molecules which was previous discuss by other scientists as well as on the activities of molecules which never were the subject of any related researches.

The following table (table 2) contains the obtained MDF SAR scored compared with the previous obtained results where *Set name* column is the given name of the set used by our software *Previous reported SAR* columns are for the reference of the reported results (where

r^2 is the r-squared coefficient, n is the number of molecules, v is the number of variables included in the previous reported model, and *Ref* is the reference to the paper where the model was published). The *MDF SAR* columns contain the obtained scores by use of the MDF methodology (r^2 is the r^2 estimation score, r^2_{cv} is the r^2 prediction score, n is the number of molecules included in the model, v is number of variables in the model, and *Ref* the reference to the paper).

Table 2. MDF SAR Results

No	Set name	Previous reported SAR				MDF SAR				
		r^2	n	v	Ref	r^2	r^2_{cv}	n	v	Ref
1	IChr10	0.9	10	2	[47]	0.999	0.999	10	2	[46]
2	PCB_rrf	-	-	-	[52]	0.628 0.693 0.737	0.619 0.682 0.717	209	1 2 4	[50]
3	36638	0.967	16	?	[49]	0.994	0.991	16	3	[48]
4	23159	0.388 0.839	18 18	1 3	[53]	0.755 0.982	0.684 0.974	18 18	1 2	[54]
5	23159e	-	-	-		0.899 0.968	0.758 0.898	8 8	1 2	
6	Ta395	0.87	13	2	[44]	0.977	0.961	15	2	[45]
7	Tox395	0.8	13	2		0.957	0.934	14	2	
8	41521	0.913 0.985	8 8	3 5	[55]	0.999	0.998	8	2	[56]
9	23151	0.741 0.985	16 13	4 4	[57]	0.997	0.995	16	3	-
10	26449	0.9911 0.9982 0.9929	25	1 2 4	[58]	0.961 0.99 0.998	0.954 0.988 0.997	25	1 2 4	-
11	Triazines	0.97	30	3	[59]	0.951 0.975 0.983 0.989	0.946 0.971 0.976 0.985	30	1 2 3 4	-
12	23167	0.366 0.861 0.93	31 31 27	1 4 3	[60]	0.724 0.862 0.939	0.697 0.842 0.924	31	1 2 3	-
13	40846_1	0.700 0.753 0.909 0.917	36 40 20 20	5 6 5 7	[61]	0.628 0.806 0.918	0.606 0.789 0.891	40	1 2 4	-
14	40846_2	0.719 0.876 0.902	40 36 20	7 7 6		0.551 0.785 0.904	0.516 0.756 0.88	40	1 2 4	-
15	40846_4	0.632 0.760 0.769 0.822	40 20 36 20	4 3 5 4		0.556 0.752 0.92	0.523 0.728 0.903	40	1 2 4	-

16	23158	0.8	40	5	[62]	0.951	0.945	40	2	-
17	22583	0.883	57	5	[63]	0.783	0.766	57	2	-
		0.885	20	5		0.835	0.809		3	
		0.888	37	5		0.9	0.884		4	
						0.918	0.9		5	
18	Dipeptides	0.782	58	2	[64]	0.85	0.836	58	2	-
						0.879	0.867		3	
						0.904	0.883		4	
						0.925	0.910		5	
19	23110	0.898	44	5	[65]	0.683	0.666	69	1	-
			69			0.871	0.859		2	
			25			0.904	0.890		3	
						0.923	0.913		4	
	0.936	0.928	5							
20	PCB_lkow	-	-	-	[52]	0.873	0.870	206	1	-
						0.890	0.885		2	
						0.917	0.909		4	
21	PCB_rrt	-	-	-		0.984	0.984	209	1	-
						0.997	0.997		2	

A very important characteristic of MDF SAR is that allow making of important remarks about the structural causality of the measured activity. For the published results of MDF SAR models, more details available in papers [45, 46, 48, 50, 54, 56].

Discussions

Most of the previous reported SAR models were investigate the activities of molecules starting from the whole set of compounds but frequently the best results were obtained after the exclusion from the SAR models of one or more than one compounds. The MDF SAR original methodology have been applied on whole sets of compounds and had been obtained better results comparing with the previous reported models most of the time using a number of variables lower than previous reported models (see table 2).

The Hotelling's t test [66] and the Steiger's Z-test [67] were applied in order to determine whether there were significant differences between the coefficient of correlation from the previous reported models with the MDF SAR models (see table 3).

The Hotelling's t test was proposed by Harald Hotelling in 1940 and Steiger's Z-test was proposed by James H. Steiger in 1980. The differences between p scores obtained through Hotelling's t and Steiger's Z and is why the traditional Hotelling's t test for

comparing correlations is generally not appropriate in practice can be found in [68] and [69]. Detailed several aspects of the correlated correlations can be found in [70-72].

The measured activities of the set of molecules, the estimated activities previous reported and the estimated activities obtained after applying the MDF SAR methodology were used to obtain the correlation coefficients (r_{y1} , r_{y2} , r_{12}). The results are in table 3. The statistical tests were applied just for the MDF SAR published sets of molecules, by using of the formulas:

$$t = \sqrt{\frac{n-3}{2}} \frac{(r_{y1} - r_{y2})\sqrt{1+r_{12}}}{\sqrt{1+2r_{12}r_{y1}r_{y2} - r_{12}^2 - r_{y1}^2 - r_{y2}^2}}$$

$$Z = \sqrt{\frac{n-3}{2}} \frac{(2 - r_{y1}^2 - r_{y2}^2)/\sqrt{1-r_{12}}}{\sqrt{4 - (r_{y1}^2 + r_{y2}^2)(3 - r_{12})}} \ln \sqrt{\frac{(1+r_{y1})(1-r_{y2})}{(1-r_{y1})(1+r_{y2})}}$$

Table 3. Comparison of MDF SAR models vs. other methods scores

Set	n	r_{y1}	r_{y2}	r_{12}	t	Z	p_t (%)	p_Z (%)
Ta395	15	0.9882	0.8368	0.8451	6.159	4.380	4.87792E-03	5.95150E-04
Tox395	14	0.9782	0.7738	0.7602	4.837	3.630	5.21148E-02	1.41641E-02
23159	18	0.9908	0.5422	0.5396	13.401	6.554	9.42167E-08	2.80620E-09
36638	16	0.9972	0.8157	0.8163	14.521	7.087	2.05978E-07	6.91447E-11
IChr10	10	0.9996	0.8249	0.8256	27.680	7.511	2.06208E-06	2.95319E-12
41521	8	0.9996	0.9556	0.9591	12.467	5.098	5.88865E-03	1.71629E-05

Legend:

r_{y1} is the r score obtained by MDF;

r_{y2} is the r score obtained by other method previously reported

r_{12} is the r score between calculated MDF values and previously reported method values;

t is the Hotelling's t-test value for "correlated correlations" within a population;

Z is the Steiger's Z-test value for "correlated correlations" within a population;

df is degree of freedom for the t and Z values, $df = n-3$;

p_t is the two tailed probability associated with the t value;

p_Z is the one tailed probability associated with Z normal distribution value.

The Hotelling's t test and the Steiger's Z-test have been applied on whole set of molecules not just for the molecules included into the previous reported models; these is the reason for that exists differences between r^2 from table 2 and r squared values from table 3.

The values of t, p_t (%), Z, and p_Z (%) sustain that the MDF SAR models allows significantly better prediction of compounds activities compared with other published models.

The p values from both t and Z tests give us for all cases from the table 3 an up to 99.999% probability that the MDF model is significantly better than the previous reported models.

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