External Factor Variable Connectivity Index

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Received January 14, 2003

A new variable index, external factor variable connectivity index (EFVCI), is proposed, in which the atomic attribute is divided into two parts. The innate part is denoted as outer-shell electrons and external part or perturbation by other atoms is represented as summation, multiplied by a variable x, of squared reciprocal matrix of i row (corresponds to atom A_i). The division of atomic attribute in EFVCI is interpreted by using topological structure. In the correlation of boiling point of 149 acyclic alkanes, the optimal values will approach to a constant at -0.29 by using the zero to higher order indices of the same series. The new index, with high regression quality ($R = 0.9986$, $s = 2.26$, and $F = 7088.4$), is compared favorably with variable connectivity index and molecular connectivity index.

INTRODUCTION

Most topological descriptors are characterized by fixed numerical values, which are independent of the property considered.[1] To better describe the property studied, Randić proposed some flexible descriptors[2−5] to improve regression results, with the idea that a variable parameter undergoes change during the regression analysis. Randić also discussed the variable path numbers[6,7] in QSAR. He extended the idea to other distance related matrices[8] to get other variable molecular descriptors, such as variable Harary-Connectivity index H and H^2, the variable Balaban J index, and the "reversed" Balaban index $1/J$ as well as a novel index $1/JJ$ derived from J and $1/J$. The variable indices were, successfully, applied in characterization of amino acids,[9] QSAR study of normal boiling point of smaller alkanes,[1] and QSAR study of toxicity of aliphatic ethers.[10]

The prediction abilities of the variable connectivity index ${}^1\chi^f$ (not included in CODESSA) were compared, favorably, with topological indices available from CODESSA.[4] Unlike molecules with heteroatoms or multiple bonds, one variable parameter is taken into consideration for alkanes without cycle. Variables can be introduced directly when defining an index, and then during the regression analysis optimal variables are sought, which allows construction of "improved" indices.[11]

The different expressions of atomic attributes marked the different stages of the connectivity index. It is interesting to trace developments of the molecular connectivity index. In 1975, Randić introduced the χ index[12] to characterize molecular branching. Soon after, Kier and Hall[13] extended the basic idea to higher order to improve the information contents of the series of indices. To deal with different atoms, the valence connectivity index[14] was defined by using valence electron and atomic number.

More than 10 years later, an extension of the molecular connectivity index, the variable index (${}^1\chi^f$), was introduced,[2,3] also holding one order. Whether the variable index can be extended to other orders is part of our research in this article, and all the acyclic alkanes with 2−10 carbons from ref 15 are chosen, just for considering the simplest situation (only one variable x is taken into consideration). The study of the extension of the variable index shows that the scheme will meet some difficulties, which are shown in the Discussion section. And so another variable scheme is proposed and is extended to higher order to get a better regression quality of modeling the normal boiling point than the "original" molecular connectivity index or the "original" variable method. In later research, improvements are also shown on the studies of molecules with heteroatoms and/or multiple bonds by using the proposed scheme and "chemical distance", which will be described in a subsequent paper.

METHODOLOGY

Molecular Connectivity Index. The general definition of molecular connectivity index is

$$ {}^k\chi_p = \sum_{\substack{all\\ edges}} (V_i V_j \ldots V_k)^{-1/2} \qquad (1)$$

Variable Connectivity Index by Randić. The scheme of refs 1, 4, and 5 is to replace the diagonal elements (zeros) of adjacency matrix with a variable x and use the row sums of the modified adjacency matrix as the atomic attributes in the calculation of the molecular connectivity index. The variable x is determined during regression process and the definition of the variable index is

$$ {}^1\chi^f = \sum_{\substack{all\\ edges}} [(V_i + x)(V_j + x)]^{-1/2} \qquad (2)$$

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10.1021/ci0340052 CCC: $25.00
Published on Web 04/11/2003

Table 1. Three Schemes of Describing Atoms of 2,3-Dimethylpentane and Calculation of Three Different Indices[a]

Scheme of χ Sum(a)

	1	2	3	4	5	6	7	Row sum
1	x	1	0	0	0	0	0	1+x
3	1	x	1	0	0	1	0	3+x
3	0	1	x	1	0	0	1	3+x
2	0	0	1	x	1	0	0	2+x
1	0	0	0	1	x	0	0	1+x
1	0	1	0	0	0	x	0	1+x
1	0	0	1	0	0	0	x	1+x

Scheme of χ^f Sum(a)+x

Scheme of EFVCI 4+Sum(RD.^2)*x

	1	2	3	4	5	6	7	row sum	Ai
1	0	1	1/4	1/9	1/16	1/4	1/9	1.7847	4+1.8747*x
2	1	0	1	1/4	1/9	1	1/4	3.6111	4+3.6111*x
3	1/4	1	0	1	1/4	1/4	1	3.7500	4+3.7500*x
4	1/9	1/4	1	0	1	1/9	1/4	2.7222	4+2.7222*x
5	1/16	1/9	1/4	1	0	1/16	1/9	1.5972	4+1.5972*x
6	1/4	1	1/4	1/9	1/16	0	1/9	1.7847	4+1.7847*x
7	1/9	1/4	1	1/4	1/9	1/9	0	1.8333	4+1.8333*x

bond	χ	χ^f	EFVCI
1−2	1/sqrt(1*3))	1/sqrt((1+x)*(3+x)))	1/sqrt((4+1.7847*x)*(4+3.6111*x)))
2−3	1/sqrt(3*3))	1/sqrt((3+x)*(3+x)))	1/sqrt((4+3.6111*x)*(4+3.7500*x)))
3−4	1/sqrt(3*2))	1/sqrt((3+x)*(2+x)))	1/sqrt((4+3.7500*x)*(4+2.7222*x)))
4−5	1/sqrt(2*1))	1/sqrt((2+x)*(1+x)))	1/sqrt((4+2.7222*x)*(4+1.5972*x)))
2−6	1/sqrt(3*1))	1/sqrt((3+x)*(1+x)))	1/sqrt((4+3.6111*x)*(4+1.8747*x)))
3−7	1/sqrt(3*1))	1/sqrt((3+x)*(1+x)))	1/sqrt((4+3.7500*x)*(4+1.8333*x)))

[a] Three indices for the molecule: $^1\chi$ = 3* 1/sqrt(1*3))+ 1/sqrt(3*3))+ 1/sqrt(3*2))+ 1/sqrt(2*1)); $^1\chi^f$ = 3*1/sqrt((3+x)*(1+x)))+ 1/sqrt((3+x)*(3+x)))+ 1/sqrt((3+x)*(2+x)))+1/sqrt((2+x)*(1+x))); and $^1\chi^{EFVCI}$ = 2*1/sqrt((4+1.7847*x)*(4+3.6111*x)))+1/sqrt((4+3.6111*x)*(4+3.7500*x)))+ 1/sqrt((4+3.7500*x)*(4+2.7222*x)))+1/sqrt((4+3.7500*x)*(4+1.8333*x)))+ 1/sqrt((4+2.7222*x)*(4+1.5972*x))). Note: sqrt denotes square root.

In this article, the variable connectivity index is extended to higher order and holds a general form as

$$ {}^{k}x_p^f = \sum_{\substack{all\\ edges}} [(V_i + x)(V_j + x)....(V_k + x)]^{-1/2} \qquad (3) $$

External Factor Variable Connectivity Index. In developing topological indices, one direction is how to describe atomic attributes. The attributes in the molecule include two factors: one is the innate part and another is the perturbation by other atoms. In graph theory, the perturbation of other molecules, in most cases, is ignored by only considering the influence of atoms in the molecule.

There are some schemes[16−21] to describe the innate attributes. In chemistry, the electron plays an important role in explaining mechanism, reaction, and some other phenomena. In this article, number (4) of outer-shell electrons is used as the innate attribute of a carbon atom for considering only saturated hydrocarbons. After choosing the attribute of a specific atom, the influence of other atoms in the molecule will be considered. In this article, the product of both the sum on a row (which corresponds to a specific atom) of a squared reciprocal matrix and a variable parameter x is used as the influence of other atoms on the atom.

The idea of adding a variable parameter in the EFVCI index holds some common points of the E-state index[22,23] with regards to the atomic attribute as the combination of the innate part and the perturbation factor (field influence on the intrinsic value) of other atoms. The field influence, called the perturbation, on the intrinsic state takes the form as (I_i-I_j) divided by the squared distance between atom i and j, and $I_i+\Delta I_{ij}$ (sum of influence of other atoms) is the so-called E-state index.

The internal attribute of a carbon atom, in this article, is valence electron 4. In the computing process, we use the squared reciprocal matrix to simplify the calculation and also to express the fact that the role of more distant neighbors will decrease as the distance between atoms in a molecule increases. In the row sums of the squared reciprocal distance matrix, more distant neighbors make smaller contributions. From the above discussion, the attribute of a carbon atom, perturbed by other atoms, can be expressed as

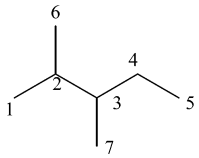

Figure 1. Molecular skeleton and numbering of carbon atoms for 2,3-dimethypentane (from Figure 1 of ref 1).

$$ A_i = 4 + \sum_{j=1}^{n} RD_{ij}\text{•}\text{^}2\text{*}x \qquad (4) $$

After getting the atomic attributes, the form of molecular connectivity index is used to get the external factor variable connectivity index:

$$ {}^{k}x^{EFVCI}{}_p = \sum_{\substack{all\\ edges}} (A_iA_j....A_k)^{-1/2} \qquad (5) $$

This kind of index can be regarded as an extension of the molecular connectivity index by using a new atomic attribute, which makes the index flexible to different properties.

Three Atomic Attributes Used in χ, χ^f, and EFVCI. Different expressions of atomic attributes marked different stages of the connectivity index. An example of different schemes to describe atomic attributes is given in Table 1, with the molecule shown in Figure 1. The sum of the adjacency matrix of atom A_i is used as atomic attributes in the χ index; the sum of the adjacency matrix, whose diagonal elements are replaced by variable x, of atom A_i is applied as atomic attributes in χ^f index; and the sum of both the electron number (4) and the summation, multiplied by a

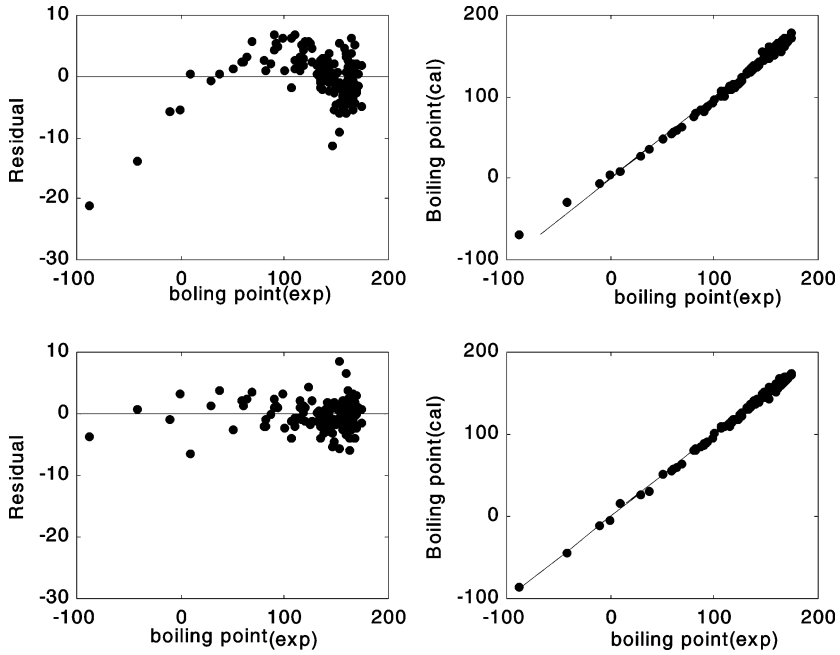

Figure 2. Boiling point regression using chi indices and EFVCI indices.

variable x, of the squared reciprocal matrix of atom A_i is denoted as atomic attributes in the EFVCI index. After the determination of atomic attributes, the three indices can be calculated by using the same general definition (formula 1).

DATA AND DESCRIPTORS

To demonstrate the performance of the external factor variable connectivity index, we studied the correlation of the normal boiling point of 149 acyclic alkanes (because there should, under many cases as shown by Randić,[24] be special considerations for cycles), ranging from 2 to 10 carbons, taken from ref 15. The three series of indices used are as follows: ${}^0\chi$, ${}^1\chi$, ${}^2\chi$, ${}^3\chi_{path}$, ${}^3\chi_{cluster}$, ${}^4\chi$, ${}^5\chi$; ${}^0\chi^f$, ${}^1\chi^f$, ${}^2\chi^f$, ${}^3\chi^f_{path}$, ${}^3\chi^f_{cluster}$, ${}^4\chi^f$, ${}^5\chi^f$; and ${}^0\chi^{efvci}$, ${}^1\chi^{efvci}$, ${}^2\chi^{efvci}$, ${}^3\chi^{efvci}_{path}$, ${}^3\chi^{efvci}_{cluster}$, ${}^4\chi^{efvci}$, ${}^5\chi^{efvci}$.

RESULTS AND DISCUSSION

Correlation with the Boiling Point by χ, χ^f, and EFVCI. The regression results of the boiling point by seven χ indices are $s = 3.97$, $F = 2294.9$, and $R = 0.9956$. The regression residual is shown in the upper left plot in Figure 2. There are three alkanes (n2, n3, 33en5) of absolute residual above 10 °C. The maximum absolute residual is 20.9 °C (n2). The upper right plot is the comparison of calculated boiling points and experimental boiling points.

To improve the information content of χ^f and also to compare the χ^f and EFVCI, we extend the variable connectivity index to more orders (0−5). By the same searching process in ref 1, the optimal value for seven χ^f indices are obtained at $x = 19$. The standard error of optimal χ^f variables is 3.65, which is just below that (3.97) of seven simple molecular connectivity indices. Using the optimal EFVCI index at $x = -0.29$, the regression results are $s = 2.265$, $F = 7088.4$, and $R = 0.9986$, which is a good regression by indices from the same series. The regression residual is shown in the low left plot in Figure 2. The maximum absolute residual is 8.6 °C (2244mn6). There are only six alkanes (22mn3, 2244mn6, 22344mn5, 246mn7, 24mn8, 34en6) with absolute residual above 5 °C. The low right plot in Figure 2 is the comparison of calculated boiling points and the experimental boiling points.

From the comparison of modeling boiling points by χ, χ^f, and EFVCI, the regression results by EFVCI are the best, and the results by χ^f are better than these by χ.

Searching Optimal Values for χ^f and Optimal EFVCI. Multilinear regression and varying the variable parameter show the plot of standard error and the variable x for χ^f in Figure 3. The optimal values for two to seven χ^f indices are as follows: −0.1500 for ${}^0\chi^f$ and ${}^1\chi^f$; 2.4000 for ${}^0\chi^f$, ${}^1\chi^f$, and ${}^2\chi^f$; 0.7500 for ${}^0\chi^f$, ${}^1\chi^f$, ${}^2\chi^f$, and ${}^3\chi^f_{path}$; 2.2000 for ${}^0\chi^f$, ${}^1\chi^f$, ${}^2\chi^f$, ${}^3\chi^f_{path}$, and ${}^3\chi^f_{cluster}$; −0.1500 for ${}^0\chi^f$, ${}^1\chi^f$, ${}^2\chi^f$, ${}^3\chi^f_{path}$, ${}^3\chi^f_{cluster}$, and ${}^4\chi^f$; and 19 for ${}^0\chi^f$, ${}^1\chi^f$, ${}^2\chi^f$, ${}^3\chi^f_{path}$, ${}^3\chi^f_{cluster}$, ${}^4\chi^f$, and ${}^5\chi^f$. The variable x fluctuates in a wide range, having no tendency to approach a constant. When searching for the optimal value for two to seven indices of EFVCI by observing the variation of standard error as x ranging from −0.6 to 1 with a step length of 0.01, the optimal values for two to seven EFVCI indices are as follows: 0.8 for ${}^0\chi^{efvci}$ and ${}^1\chi^{efvci}$; −0.65 for ${}^0\chi^{efvci}$, ${}^1\chi^{efvci}$, and ${}^2\chi^{efvci}$; −0.05 for ${}^0\chi^{efvci}$, ${}^1\chi^{efvci}$, ${}^2\chi^{efvci}$, and ${}^3\chi^{efvci}_{path}$; −0.32 for ${}^0\chi^{efvci}$, ${}^1\chi^{efvci}$, ${}^2\chi^{efvci}$, ${}^3\chi^{efvci}_{path}$, and ${}^3\chi^{efvci}_{cluster}$; −0.27 for ${}^0\chi^{efvci}$, ${}^1\chi^{efvci}$, ${}^2\chi^{efvci}$, ${}^3\chi^{efvci}_{path}$, ${}^3\chi^{efvci}_{cluster}$, and ${}^4\chi^{efvci}$; and −0.29 for ${}^0\chi^{efvci}$, ${}^1\chi^{efvci}$, ${}^2\chi^{efvci}$, ${}^3\chi^{efvci}_{path}$, ${}^3\chi^{efvci}_{cluster}$, ${}^4\chi^{efvci}$, and ${}^5\chi^{efvci}$. The process is shown in the Figure 4. From the plot, when x equal to zero, the standard error is very high. The reason is that because when x is equal to zero, the atomic attributes are regarded as the same, which will surely make the regression bad. The optimal values of χ^f and EFVCI for a different number of variables are plotted in the Figure 5.

The process gave us some insights: (1) the EFVCI index in this case varies in a narrow range and will approach a constant. (2) In QSAR research, five former EFVCI indices give the regression standard about 3.17, while seven indices give the standard error about 2.265. The information contained in the last two indices is, to some extent, rich,

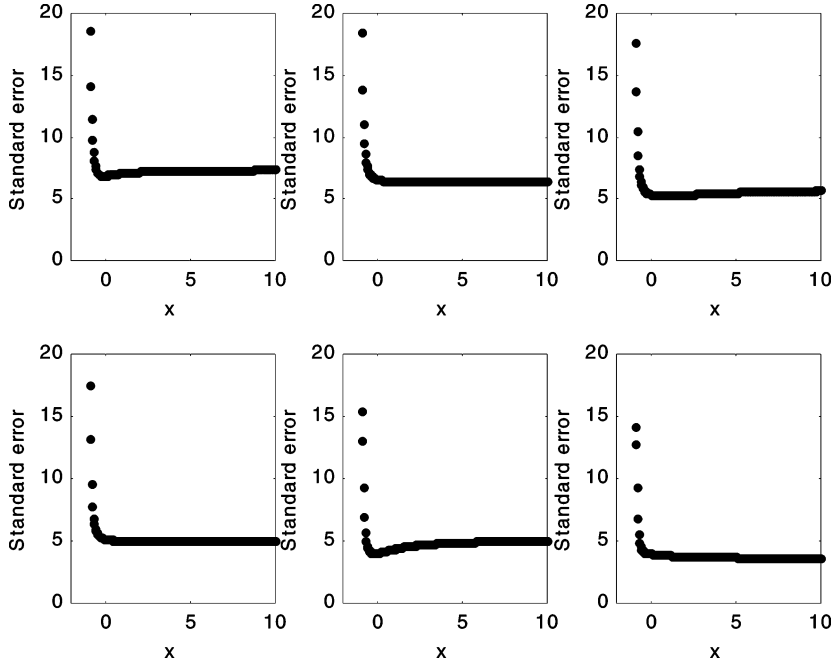

Figure 3. Variation of the standard error of estimate with change of the diagonal entry x of the adjacency matrices and process for searching optimal value by using χ^f.

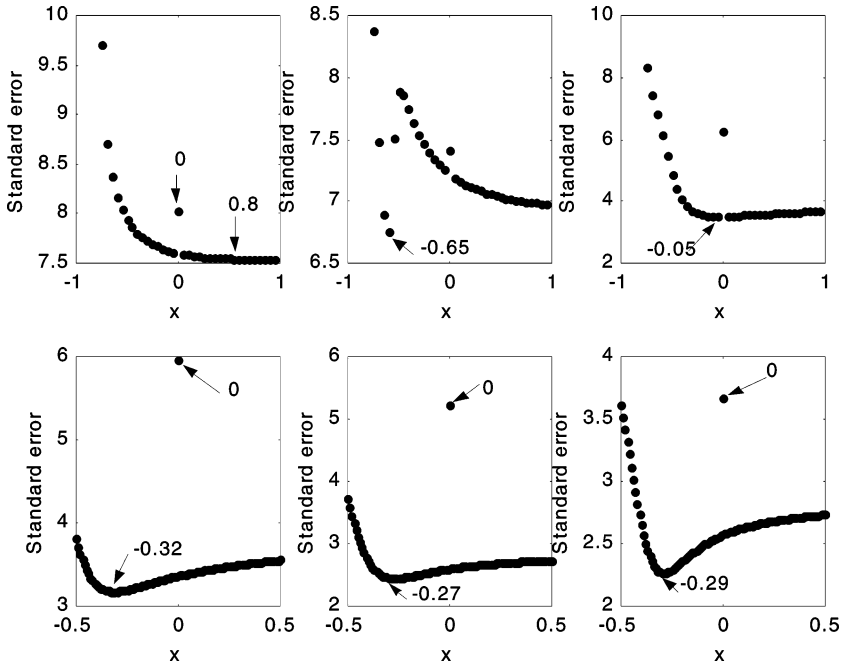

Figure 4. Variation of the standard error of estimate with change of x in EFVCI and process for searching optimal value by using EFVCI.

which should not be ignored. (3) The change of the variable parameter is little, which is, from a view of perturbation, rational and acceptable. Whether the optimal value holds some chemical nature should be studied further, maybe, from quantum chemistry.

Topological Structural Interpretation of EFVCI. The interpretation includes three aspects: (1) structural interpretation of the EFVCI; (2) structural interpretation of the variable scheme used in EFVCI; and (3) interpretation of the innate and external division of atomic attributes in EFVCI.

The apparent disadvantage of topological indices is due to a lack of research on their structural interpretation. Randić et al.[25,11] initiated efforts for interpretation of topological indices. They discovered the bond additive properties of the molecular connectivity index. The EFVCI indices are derived from the molecular connectivity index, and they should share some common structure information. The bond additive properties can also be used to interpret the EFVCI index as shown in Table 1, in which three schemes of describing atomic attributes are compared.

Consider molecule 223mn4, the atomic attributes in EFVCI are $4+1.9722*x$, $4+4.5000*x$, $4+3.7500*x$, $4+1.8333*x$, $4+1.9722*x$, $4+1.9722*x$, and $4+1.8333*x$, for atoms 1, 2, 3, 4, 5, 6, and 7, respectively. The atom having more atoms surrounding with it will be influenced more than the atom with fewer atoms. Having four atoms with distance one, and two atoms with distance two to it, the no. 2 atom, in general, is influenced most. From the point

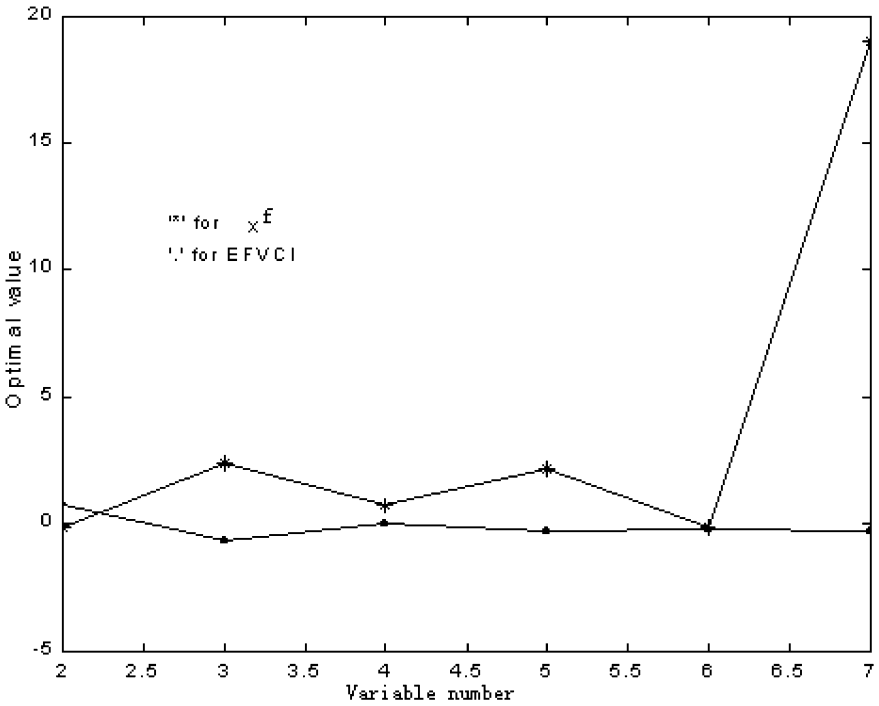

Figure 5. Comparison of process for searching optimal values by different number of variable for χ^f and EFVCI.

Table 2. Three Atomic Attributes of 2,3-Dimethypentane Used in χ, χ^f, and EFVCI

	attributes in χ^f			attributes in EFVCI	
attributes in χ sum(a)	sum(a) + x*	$x =$ −0.1500	$x =$ 19	4+sum(RD.^2)*x^a	$x =$ −0.29
1	1+x	0.85	20	4+1.8747*x	3.4563
3	3+x	2.85	22	4+3.6111*x	2.9528
3	3+x	2.85	22	4+3.7500*x	2.9125
2	2+x	1.85	21	4+2.7222*x	3.2106
1	1+x	0.85	20	4+1.5972*x	3.5368
1	1+x	0.85	20	4+1.8747*x	3.4563
1	1+x	0.85	20	4+1.8333*x	3.4683

[a] *x in χ^f is −0.1500 for six indices and 19 for seven indices.

of graph center, the atom is the center of the molecule by the IVEC method proposed by Bonchev.[26] The center sequence of 223mn4 by IVEC is (2), (3), (1,5,6), and (4,7). Examining the atomic attributes for different atoms (4+4.5000*x for no. 2 atom; 4+3.7500*x for no. 3 atom; 4+1.9722*x for no. 1, 5, and 6 atoms; and 4+1.8333*x for no. 4 and 7 atoms), the atomic attributes in EFVCI reflect, to some extent, the center sequence. Studies on other molecules also result in the same conclusions. That is, the more central[27] the atom is, the bigger the influence the atom will have.

The good performance of EFVCI drives us to ponder why the scheme of EFVCI can improve the regression significantly. It is known that the atomic attribute is composed of two parts: the innate factor and the external perturbation. In most cases, the innate attribute domains the property of an atom, and other atoms are the factors that perturb the atom. The external perturbation is changing and the innate attribute is relatively stable. The atomic attributes for χ, χ^f, and EFVCI for 2,3-dimethypentane are listed in Table 2. From the table, the atomic attributes in χ are fixed numbers as vertex degree; the atomic attributes for atoms (2, and 3; or 1, 5, 6, and 7) in χ^f are identical; the atomic attributes are 3.4563, 2.9528, 2.9125, 3.2106, 3.5368, 3.4563, and 3.4683 for 1, 2, 3, 4, 5, 6, and 7 atoms, respectively. The attributes for no. 1 and 6 atoms, which are recognized as the same center sequence by IVEC,[26] are equal. The atomic attributes with different kinds of sequences can be distinguished by EFVCI, which, in the long run, helps make improvements on regression.

CONCLUDING REMARKS

The new scheme regards the topological structure as the environment that influences the atoms and thus divides the attribute of atoms into two parts: internal and external attributes. This method is compared favorably with the variable connectivity index and the molecular connectivity index.

ACKNOWLEDGMENT

This project is financially supported by National Nature Foundation Committee (NNFC) of P. R. China (no. 20235020, and 20175036). And the authors also appreciate the hospitality of Hong Kong Baptist University, when the authors attend "Workshop on Data Mining in Traditional Chinese Medicines".

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CI0340052