Internet Electronic Journal of Molecular Design **2002**, *1*, 1–9 ISSN 1538–6414
BioChem Press http://www.biochempress.com

Inter*net* Electronic Journal of Molecular Design

January 2002, Volume 1, Number 1, Pages 1–9

Editor: Ovidiu Ivanciuc

Special issue dedicated to Professor Alexandru T. Balaban on the occasion of the 70th birthday
Part 1

Guest Editor: Mircea V. Diudea

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Received: May 15, 2001; Accepted: September 10, 2001; Published: January 31, 2002

Citation of the article:
O. Ivanciuc, Building–Block Computation of the Ivanciuc–Balaban Indices for the Virtual Screening of Combinatorial Libraries, *Internet Electron. J. Mol. Des.* **2002**, *1*, 1–9, http://www.biochempress.com.

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Building–Block Computation of the Ivanciuc–Balaban Indices for the Virtual Screening of Combinatorial Libraries[#]

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Abstract

Motivation. The discovery of drug leads is significantly accelerated by *in silico* screening of molecular libraries, that starts from a collection of chemical compounds with a high structural diversity and selects molecules according to their similarity toward specific collections of active compounds. In this process, the molecular similarity/diversity and the drug–like character are characterized with structural descriptors, such as structure keys, fingerprints, graph invariants and various topological indices computed from atomic connectivity or molecular matrices.

Method. In this paper we present an efficient algorithm for the computation of the Ivanciuc–Balaban (**IB**) structural descriptors for large combinatorial libraries using only molecular graph descriptors of the building blocks. The procedure is developed for vertex– and edge–weighted molecular graphs representing organic compounds containing heteroatoms and multiple bonds, and can be easily applied to any combinatorial library.

Results. The new algorithm can be applied for **IB** topological indices derived from the distance **D**, resistance–distance **Ω**, and detour **Δ** matrices, and is significantly faster compared with the usual method for computing **IB** topological indices.

Conclusions. The proposed algorithm is efficient in computing **IB** structural descriptors in combinatorial libraries without actually generating the compounds, because only graph invariants of the building blocks are needed to generate the topological indices of any compound assembled from building blocks.

Keywords. Combinatorial library; drug design; structural descriptor; topological index; virtual screening.

1 INTRODUCTION

In the drug discovery process combinatorial libraries (CL) and high–throughput screening (HTS) are efficiently used to identify biologically active molecules more rapidly than with the conventional approaches [1–4]. An efficient way to reduce the number of compounds that enter the HTS process is the *in silico* screening of CL, a process applied both to diverse and focused libraries with the aim to select for HTS the compounds with potential 'drug–like' characteristics and

[#] Dedicated on the occasion of the 70th birthday to Professor Alexandru T. Balaban.

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sufficient diversity [5–8]. The process of virtual screening of combinatorial libraries (VSCL) starts from a wide selection of reactants that are used to generate *in silico* a huge number of chemical compounds. Then, the structural descriptors relevant for the investigated biological target are identified and computed for all compounds in the virtual library. Finally, the compounds for chemical synthesis and HTS are selected with a statistical algorithm that implements a similarity, diversity, or drug–like paradigm.

In VSCL the chemical structure is translated into a numerical form with the aid of various structural descriptors, many of them traditionally used in QSPR and QSAR. To be efficient, the *in silico* compound screening uses descriptors that require small computational resources, such as counts of atom types, counts of functional groups, fingerprints, constitutional descriptors, graph invariants and topological indices. A recent VSCL method proposes to compute the structural descriptors of reaction products without actually assembling the molecules from the building blocks [9]; this algorithm can be applied to additive or nearly additive descriptors, or for descriptors that can be generated with a simple algorithm from the corresponding descriptors of reactants or building blocks and a proper representation of the chemical reaction that takes place. Considering the high importance of topological indices as structural descriptors used to measure the similarity, diversity, and drug–like character of chemical libraries, we have introduced several algorithms for the computation of the Wiener–type indices of combinatorial molecules, using only distance invariants of the corresponding building blocks [10,11].

In the present paper we extend the building block computation of topological indices for the Ivanciuc–Balaban operator and other descriptors based on the vertex sum and computed from the distance **D**, resistance–distance **Ω**, and detour **Δ** matrices.

2 MOLECULAR GRAPHS AND TOPOLOGICAL INDICES

In the chemical graph theory [12], an organic compound containing heteroatoms and multiple bonds can be represented as a vertex– and edge–weighted molecular graph [13–16] in which the atom i is represented by the vertex v_i and the covalent bond between atoms i and j corresponds to the edge e_{ij} from the molecular graph. A vertex– and edge–weighted (VEW) molecular graph G consists of a vertex set $V = V(G)$, an edge set $E = E(G)$, a set of chemical symbols of the vertices $Sy = Sy(G)$, a set of topological bond orders of the edges $Bo = Bo(G)$, a vertex weight set $Vw(w) = Vw(w,G)$, and an edge weight set $Ew(w) = Ew(G)$. The number of vertices in the graph G is $|V(G)|$.The elements of the vertex and edge weight sets are computed with the weighting scheme w. Usually, hydrogen atoms are not considered in the molecular graph, and in a VEW graph the weight of a vertex corresponding to a carbon atom is 0, while the weight of an edge corresponding to a carbon–carbon single bond is 1. Also, the topological bond order Bo_{ij} of an edge e_{ij} takes the value 1 for single bonds, 2 for double bonds, 3 for triple bonds and 1.5 for aromatic bonds.

2.1 The Balaban Index J

The Balaban index $J = J(G)$ of the molecular graph G is defined by the formula [17,18]:

$$J(G) = \frac{M}{\mu + 1} \sum_{E(G)} \left[\mathbf{DS}_i(G) \times \mathbf{DS}_j(G) \right]^{-1/2} \tag{1}$$

where $\mathbf{DS}_i$ and $\mathbf{DS}_j$ denote the distance sums of the vertices v_i and v_j that form the edge e_{ij} in the molecular graph G, M is the number of edges in the molecular graph, μ is the cyclomatic number (the number of cycles in G, $\mu = M - N + 1$, where N is the number of atoms in the molecular graph), and the summation goes over the whole set of edges $E(G)$ in the molecular graph. We recall here the distance sum of the vertex v_i, $\mathbf{DS}_i$, defined as the sum of the topological distances between vertex v_i and every vertex in the molecular graph, *i.e.* the sum over row i or column i in the distance matrix **D** [12,19]:

$$\mathbf{DS}_i(G) = \sum_{j=1}^{N} \mathbf{D}_{ij}(G) = \sum_{j=1}^{N} \mathbf{D}_{ji}(G) \tag{2}$$

The Balaban index J was extended for molecular graphs containing heteroatoms and multiple bonds [20,21], and used with success in structure–property and structure–activity studies [13,19] and for the *in silico* screening of combinatorial libraries [8].

2.2 The Ivanciuc–Balaban Operator

The Ivanciuc–Balaban operator **IB** represents an extension of the index J that can be computed with vertex invariants derived from any symmetric molecular matrix [14]:

$$\mathbf{IB}(\mathbf{M}, w, G) = \frac{M}{\mu + 1} \sum_{E(G)} \left[\mathbf{VS}_i(\mathbf{M}, w, G) \times \mathbf{VS}_j(\mathbf{M}, w, G) \right]^{-1/2} \tag{3}$$

where $\mathbf{VS}_i(\mathbf{M},w,G)$ and $\mathbf{VS}_j(\mathbf{M},w,G)$ denote the vertex sums of the two adjacent vertices v_i and v_j that are incident with an edge e_{ij} in the molecular graph G, the summation goes over all edges from the edge set $E(G)$, and w is the weighting scheme. The vertex sum for the atom i, $\mathbf{VS}_i(\mathbf{M},w,G)$, is the sum of the matrix elements $\mathbf{M}_{ij}(w,G)$ between vertex v_i and every vertex in the molecular graph, *i.e.* the sum over row i or column i in the molecular matrix **M** [13]:

$$\mathbf{VS}_i(\mathbf{M}, w, G) = \sum_{j=1}^{N} \mathbf{M}_{ij}(w, G) = \sum_{j=1}^{N} \mathbf{M}_{ji}(w, G) \tag{4}$$

The Ivanciuc–Balaban operator can be applied to any symmetric molecular matrix [22], such as the adjacency **A**, distance **D**, reciprocal distance **RD** [23], resistance–distance Ω [24], path Szeged $\mathbf{Sz_p}$ [25], detour Δ [26], distance–valency **Dval** [27], distance–delta $\mathbf{D_\Delta}$ [28], or distance–path $\mathbf{D_p}$ [28] matrices. When **M** is the distance matrix, **VS** represents the distance sum **DS**, and G is the molecular graph of a hydrocarbon the **IB** operator is identical with the J index.

3 FAST ALGORITHM FOR THE IVANCIUC–BALABAN OPERATOR

The scope of the present investigation is to develop a fast and efficient algorithm for computing **IB** topological indices derived from the distance **D**, resistance–distance **Ω**, and detour **Δ** matrices, and therefore it is important to estimate the computational complexity for computing the **IB** indices with Eqs. (3) and (4). We start the computational complexity analysis by considering the distance matrix **D**. For a molecular graph consisting of N atoms and M bonds, and starting from an $N \times N$ matrix with all elements equal to zero, the connection table is translated into the adjacency matrix **A** in $O(M)$ computer operations. Because organic compounds have the maximum degree four, M could not be larger than $2N$, and we can approximate that the adjacency matrix **A** is obtained in $O(N)$ operations. For each molecule the computation of the distance matrix **D** from the adjacency matrix **A** is performed in $O(N^3)$ operations (*i.e.* the computer time is proportional to N^3) indicating that when N increases this part of the algorithm will consume the largest fraction of the computational resources. The computation of the vertex sums **VS** from **D** for all N atoms with Eq. (4) requires $O(N^2)$ steps, and $O(M)$ computer operations are needed in Eq. (3) to obtain the **IB** index. A comparison of the computational cost for obtaining the **IB** indices clearly indicates the most expensive step is the generation of the distance matrix **D** from the adjacency matrix **A**. Because the computation of the resistance–distance matrix **Ω** is performed in $O(N^3)$ operations [11], the above analysis holds true also for **IB**(**Ω**), showing that the computation of the molecular matrix **M** is the most expensive step in obtaining **IB**(**M**). The computation of the detour **Δ** matrix is made by generating all weighted paths in the molecular graph, indicating that this step is the most demanding for obtaining **IB**(**Δ**). Our algorithm for the fast computation of **IB**(**M**,G) indices for combinatorial libraries eliminates the generation of the matrix **M** by computing the vertex sum vector **VS**(**M**,G) from graph invariants of the building blocks that form the molecular graph G.

We present now a formula for computing the vertex sum vector **VS** for a graph G–H obtained from two subgraphs G and H; in Figure 1 we present the structure of the graph G–H. Both subgraphs and the resulting graph G–H are vertex– and edge–weighted graphs, representing organic compounds containing heteroatoms and multiple bonds.

Theorem 1. Let e_{gh} be a cut edge between two subgraphs G and H of G–H such that $g \in G$ and $h \in H$ (see Figure 1). The vertex (atom) and edge (bond) parameters are computed with the weighting scheme w, the vertex sum **VS** is obtained from the molecular matrix **M** (**M** can be the distance **D**, resistance–distance **Ω**, or detour **Δ** matrix), and the matrix element between vertices g and h is $m_{gh}(w)$. Then the vertex sum **VS** for the vertex k, $k \in G$, in the graph G–H computed from the molecular matrix **M**, $\mathbf{VS}_k(\mathbf{M},w,G–H)$, is

$$\mathbf{VS}_k(\mathbf{M},w,G-H) = \mathbf{VS}_k(\mathbf{M},w,G) + |V(H)|\left[\mathbf{M}_{kg}(w,G) + m_{gh}(w)\right] + \mathbf{VS}_h(\mathbf{M},w,H) \qquad (5)$$

Proof. Consider a vertex k from the subgraph G, $k \in G$, and the corresponding vertex sum

$\mathbf{VS}_k(\mathbf{M},w,G–H)$ computed from the molecular matrix **M**. The vertex descriptor $\mathbf{VS}_k(\mathbf{M},w,G–H)$ is the sum of two types of matrix elements from $\mathbf{M}(w,G–H)$, namely between k and all vertices from G, including k, as one can see from Eq. (4), and between k and all vertices from H. When the molecular matrix **M** is the distance **D**, resistance–distance **Ω**, or detour **Δ** matrix, the matrix element $\mathbf{M}_{kj}$ between the vertex k from G and another vertex j from H can be partitioned into three contributions: $\mathbf{M}_{kg}$, between vertex k and the cut vertex g; $\mathbf{M}_{gh} = m_{gh}$, between cut vertices g and h; $\mathbf{M}_{hj}$, between cut vertex h and the vertex j from H. The substitution of Eq. (4) in Eq. (6) completes the demonstration of Theorem 1:

$$\begin{aligned}\mathbf{VS}_k(\mathbf{M},w,G-H) &= \sum_{i\in V(G)}\mathbf{M}_{ki}(w,G)+\sum_{j\in V(H)}\left[\mathbf{M}_{kg}(w,G)+m_{gh}(w)+\mathbf{M}_{hj}(w,H)\right] \\ &= \sum_{i\in V(G)}\mathbf{M}_{ki}(w,G)+|V(H)|\left[\mathbf{M}_{kg}(w,G)+m_{gh}(w)\right]+\sum_{j\in V(H)}\mathbf{M}_{hj}(w,H)\end{aligned} \tag{6}$$

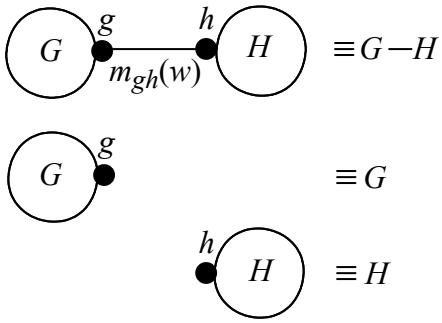

Figure 1. The molecular graph $G–H$ with a cut edge between the subgraphs G and H; the matrix element of the edge e_{gh}, computed with the weighting scheme w and the molecular matrix **M**, is $m_{gh}(w)$.

The practical importance of Eq. (5) comes from the possibility to compute the vertex sum vector $\mathbf{VS}(\mathbf{M},w,G–H)$, and the corresponding **IB** indices, without generating the molecular matrix for the composed graph $G–H$; instead, $\mathbf{VS}(\mathbf{M},w,G–H)$ is obtained from the molecular matrices **M** and vertex sum vectors **VS** of the subgraphs G and H. The great saving in computer time comes from the much smaller dimension of the matrices $\mathbf{M}(w,G)$ and $\mathbf{M}(w,H)$, compared with $\mathbf{M}(w,G–H)$. Therefore, Eq. (5) is the core of an efficient algorithm for the fast computation of the **IB** indices for compounds from combinatorial libraries. Besides the **IB** indices, this procedure can be applied to speed–up the computation of any other structural descriptors obtained from the vertex sum vector. However, the method presented above can be applied only to the distance **D**, resistance–distance **Ω**, or detour **Δ** matrices; with small modifications, the algorithm can be extended to other molecular matrices.

The description of the fast algorithm for computing the Ivanciuc–Balaban indices from building blocks is presented for the general case when a chemical compound $AB_1…B_n$ is generated from a core structure A and n substituents B_1, B_2,…, B_n, as presented in Figure 2.

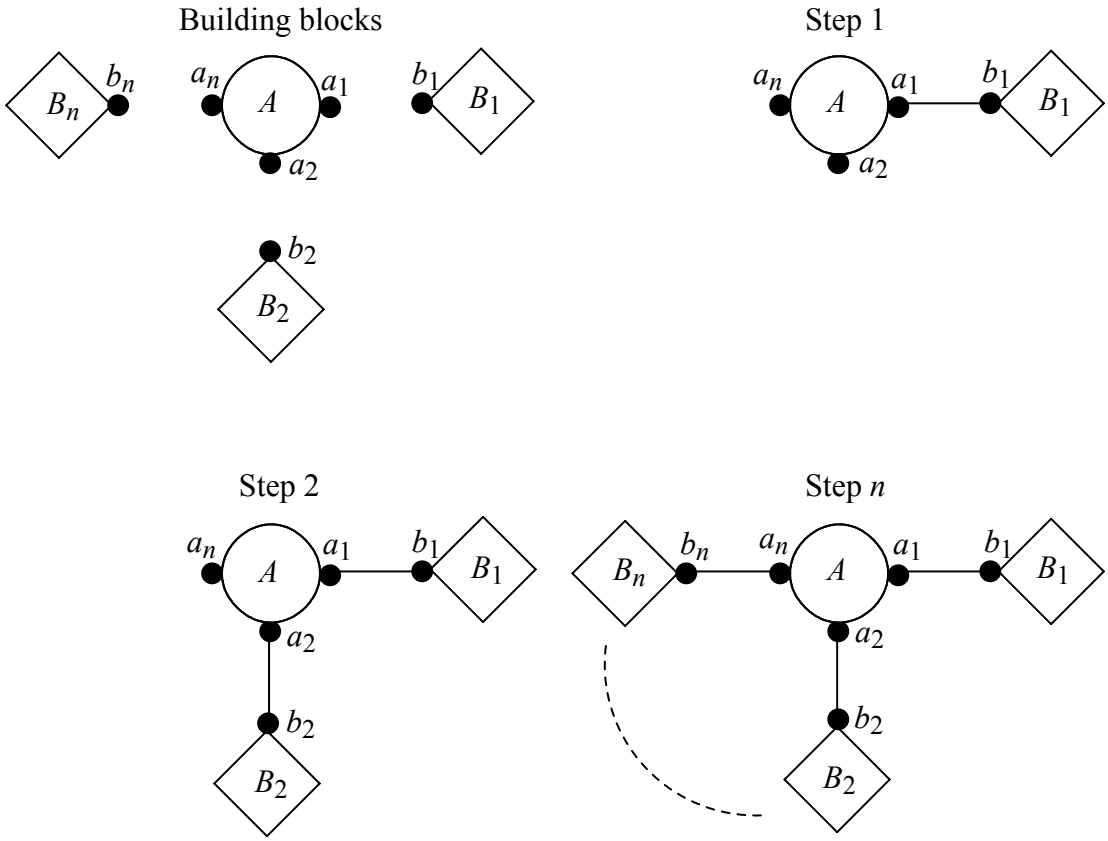

Figure 2. Generation of combinatorial compounds from a core structure A and n substituents B_1, B_2,…, B_n.

Algorithm 1

1. Consider a core structure A with n substitution atoms a_1, a_2,…, a_n and n substituents B_1, B_2,…, B_n, each having one substitution atom b_1, b_2,…, b_n, respectively. The final molecular graph is presented in Figure 2.

2. Compute the matrix **M** (where **M** can be the distance **D**, resistance–distance **Ω**, or detour **Δ** matrix) with the weighting scheme w for the core structure A and the n substituents B_1, B_2,…, B_n, *i.e.* **M**(w,A), **M**(w,B_1), **M**(w,B_2),…, **M**(w,B_n).

3. Compute the vertex sum vectors for all atoms in the molecular graphs A, B_1, B_2,…, B_n, *i.e.* **VS**(**M**,w,A), **VS**(**M**,w,B_1), **VS**(**M**,w,B_2),…, **VS**(**M**,w,B_n).

4. Compute the edge elements $m_{a_i b_i}(w)$ between all pairs of vertices $\{a_i, b_i\}$, for i from 1 to n.

5. For all atoms k from the core structure A, $k \in V(A)$, compute the vertex sum vector in the final compound $AB_1 \ldots B_n$:

$$\mathbf{VS}_k(\mathbf{M}, w, AB_1 \ldots B_n) = \mathbf{VS}_k(\mathbf{M}, w, A) + \sum_{i=1}^{n} \left\{ |V(B_i)| \left[\mathbf{M}_{ka_i}(w, A) + m_{a_i b_i}(w) \right] + \mathbf{VS}_{b_i}(\mathbf{M}, w, B_i) \right\} \quad (7)$$

6. For all atoms l from the substituent structure B_i, $l \in V(B_i)$, compute the vertex sum in the final compound $AB_1 \ldots B_n$:

$$\mathbf{VS}_l(\mathbf{M}, w, AB_1 \ldots B_n) = \mathbf{VS}_l(\mathbf{M}, w, B_i) + |V(A)|\left[\mathbf{M}_{lb_i}(w, B_i) + m_{b_i a_i}(w)\right] + \mathbf{VS}_{a_i}(\mathbf{M}, w, A)$$
$$+ \sum_{\substack{j=1 \\ j \neq i}}^{n} \left\{ |V(B_j)|\left[\mathbf{M}_{lb_i}(w, B_i) + m_{b_i a_i}(w) + \mathbf{M}_{a_i a_j}(w, A) + m_{a_j b_j}(w)\right] + \mathbf{VS}_{b_j}(\mathbf{M}, w, B_j) \right\} \quad (8)$$

7. Use in Eq. (3) the vertex sum values computed in steps 5 and 6 to compute the corresponding **IB** index.

We will now estimate the computational complexity of the Algorithm 1. The computational expenses of the above algorithm are shared between steps 1–4, in which the molecular matrices and vertex sum vectors for the building blocks A, B_1, B_2,…, B_n are computed, and a second phase (steps 5 and 6) in which the vertex sum of the final compound $AB_1 \ldots B_n$ is obtained with Eqs. (7) and (8). Finally, in step 7, the **IB** index is computed from the **VS** vector. Similarly with the analysis of the standard procedure of computing the **IB** indices, we start the computational complexity estimation by considering the distance matrix **D**. The generation of the distance matrix **D** for the building blocks A, B_1, B_2,…, B_n, followed by the calculation of the vertex sum values for all atoms in the building blocks is the most computational demanding phase, because for a molecular graph G with $|V(G)|$ vertices (atoms) the distance matrix $\mathbf{D}(G)$ is obtained in $O(|V(G)|^3)$ computer operations. However, we have to consider that the size of the building blocks is much smaller than that of the final compound $AB_1 \ldots B_n$, and this computation is performed only once for the whole combinatorial library. We have to mention that for all building blocks A, B_1, B_2,…, B_n the molecular matrices $\mathbf{M}(w,A)$, $\mathbf{M}(w,B_1)$, $\mathbf{M}(w,B_2)$,…, $\mathbf{M}(w,B_n)$ and vertex sum vectors $\mathbf{VS}(\mathbf{M},w,A)$, $\mathbf{VS}(\mathbf{M},w,B_1)$, $\mathbf{VS}(\mathbf{M},w,B_2)$,…, $\mathbf{VS}(\mathbf{M},w,B_n)$ must be stored in the memory during the computation of the **IB** indices for a combinatorial library. The computation of the **VS** values for all atoms in the final compound $AB_1 \ldots B_n$ is performed in steps 5 and 6, in which Eq. (7) is computed for all atoms in A and Eq. (8) is applied for all atoms in the substituens B_1, B_2,…, B_n; if we denote with N the total number of vertices in the final molecular graph $AB_1 \ldots B_n$, this step has a computational complexity of $O(nN)$, where n, in general, is not larger than 5. Finally, the computation of the **IB** index in step 7 is performed in $O(N)$ operations. It is now clear that the usual algorithm for computing the $\mathbf{IB}(\mathbf{D})$ index with Eqs. (3) and (4), which involves $O(N^3)$ operations per compound, is much less efficient than the algorithm that uses Eqs. (7) and (8) to obtain the vertex sum values and involves $O(nN)$ operations per compound. Also, the larger is the combinatorial library the greater the relative efficiency of our algorithm that uses Eqs. (7) and (8) compared with the standard one. The above complexity analysis holds true also for computation of the **IB** index from $\mathbf{\Omega}$ and $\mathbf{\Delta}$ matrices.

4 CONCLUSIONS

Graph decomposition algorithms represent an efficient method for generating molecular graph invariants, which can be applied to speed-up the calculation of graph descriptors for the virtual

screening of combinatorial libraries. Using a graph algorithm for decomposing the Wiener index *W* in additive contributions of the building blocks that form a molecular graph, we have proposed a very efficient method for obtaining *W* for combinatorial libraries [10,11]. In this paper we have extended the building block computation of topological indices for the Ivanciuc–Balaban operator **IB** computed from the distance **D**, resistance–distance **Ω**, and detour **Δ** matrices. The procedure is developed for vertex– and edge–weighted molecular graphs representing organic compounds containing heteroatoms and multiple bonds, and can be easily applied to any combinatorial library. Also, the algorithm can be adapted for computing other descriptors based on the vertex sum vector, such as the **Chi** operator **Chi**(**VS**,**M**,*w*,*G*) [29], and for other molecular matrices, such as the even/odd molecular matrices [30,31].

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