QUBILS-MIDAS 3D-DESCRIPTORS

1. Mathematical Definition.

The QuBiLS-MIDAS molecular 3D-indices[1, 2] are computed from the atomic contribution of each atom in a molecule. In this way, if a molecule consists of n atoms, then the kth *two-linear, three-linear* and *four-linear* indices for atom *"a"* are calculated as *n-linear algebraic maps*[3, 4] (forms) in $\mathbb{R}^n$, in a canonical basis set, and are expressed by the following equations, respectively:

$$_mL_a = m^{a,k}(\bar{x},\bar{y}) = \sum_{i=1}^{n}\sum_{j=1}^{n} g_{ij}^{a,k}x^iy^j = [X]^T\,\mathbb{G}^{a,k}[Y] \tag{1}$$

$$_{tr}L_a = tr^{a,k}(\bar{x},\bar{y},\bar{z}) = \sum_{i=1}^{n}\sum_{j=1}^{n}\sum_{l=1}^{n} gt_{ijl}^{a,k}x^iy^jz^l = \mathbb{GT}^{a,k}\cdot\bar{x}\cdot\bar{y}\cdot\bar{z} \tag{2}$$

$$_{qu}L_a = qu^{a,k}(\bar{x},\bar{y},\bar{z},\bar{w}) = \sum_{i=1}^{n}\sum_{j=1}^{n}\sum_{l=1}^{n}\sum_{h=1}^{n} gq_{ijl}^{a,k}x^iy^jz^lw^h = \mathbb{GQ}^{a,k}\cdot\bar{x}\cdot\bar{y}\cdot\bar{z}\cdot\bar{w} \tag{3}$$

where, *"a"* indicates the atom ($a = 1,2,\ldots,n$), n is the number of atoms in a molecule, L_a is the entry corresponding to the contribution of the atom *"a"* in the vector of atom-level indices $\bar{L}$ [designated here by the well-known acronym: LOVI (LOcal Vertex Invariant)][5, 6] and $x^1,\ldots,x^n$, $y^1,\ldots,y^n$, $z^1,\ldots,z^n$ and $w^1,\ldots,w^n$ are the coordinates or components of the molecular vectors $\bar{x}$, $\bar{y}$, $\bar{z}$ and $\bar{w}$ in a system of canonical ('natural') basis vectors of $\mathbb{R}^n$.

The use of molecular vectors based on atomic properties as representation of the chemical structures has been used in other works.[7-10] As can be noticed, these molecular vectors are weighted with different "standard" atom- and fragment-based properties (weights) for atoms in a molecule and thus several combinations of algebraic forms are obtained (see Table 1). The weighting schemes (properties) used are the following: 1) atomic mass (M), 2) the van der Waals volume (V), 3) the atomic polarizability (P), 4) atomic electronegativity in Pauling scale (E), 5) atomic Ghose-Crippen LogP (A),[11-13] 6) atomic charge (C) (Gasteiger-Marsili),[14] 7) atomic polar surface area (PSA),[15] 8) atomic refractivity (R),[11-13] 9) atomic hardness (H) and 10) atomic softness (S).

Table 1. N-linear algebraic forms implemented in the QuBiLS program.

1. Two-linear $[m^k(\overline{x}, \overline{y})]$
 	
  - Linear (X, Y = 1)
 	
  - Bilinear (X <> Y)
 	
  - Quadratic (X = Y)
	Used symbols
	1: Using the unitary vector
	<>: Using different properties
	=: Using equal properties

2. Three-linear $[tr^k(\overline{x}, \overline{y}, \overline{z})]$

  - Threelinear (X <> Y <> Z)

  - Threelinear-Quadratic-Bilinear ((X = Y) <> Z)

  - Threelinear-Bilinear (X <> Y, Z = 1)

  - Threelinear-Linear (X, Y = 1, Z = 1)

  - Threelinear-Cubic (X = Y = Z)

3. Four-linear $[qu^k(\overline{x}, \overline{y}, \overline{z}, \overline{w})]$

  - Fourlinear (X <> Y <> Z <> W)

  - Fourlinear-Quadratic-Threelinear ((X = Y) <> Z <> W)

  - Fourlinear-Threelinear (X = 1, Y <> Z <> W)

  - Fourlinear-Cubic-Bilinear ((X = Y = Z) <> W)

  - Fourlinear-Bilinear (X = Y = 1, Z <> W)

  - Fourlinear-Linear (X = Y = Z = 1, W)

  - Fourlinear-Quadruple (X = Y = Z = W)

The coefficients $g_{ij}^{a,k}$, $gt_{ijl}^{a,k}$ and $gq_{ijlh}^{a,k}$ are the elements of the kth *two-tuples*, *three-tuples* and *four-tuples atom-level spatial-(dis)similarity matrices*, $\mathbb{G}^{a,k}$, $\mathbb{GT}^{a,k}$ and $\mathbb{GQ}^{a,k}$ for atom "*a*", respectively. In this way, if each one of the kth *two-tuples [three-tuples*, *four- tuples] atom-level matrices* for a molecule are summed, then is obtained the corresponding k^{th} *two-tuples [three-tuples*, *four-tuples] total spatial-(dis)similarity matrix*, $\mathbb{G}^k$ [$\mathbb{GT}^k$, $\mathbb{GQ}^k$] (see section **2** for mathematical definition). Therefore, each *atom-level matrix* define an *atom-level index* for atom "*a*" (see Eqs. **1-3**). Lastly, the coefficients $g_{ij}^{a,k}$, $gt_{ijl}^{a,k}$ and $gq_{ijlh}^{a,k}$ are obtained from the coefficients g_{ij}^{k} of the $\mathbb{G}^k$, $gt_{ijl}^{a,k}$ of the $\mathbb{GT}^k$ and $gq_{ijlh}^{a,k}$ of the $\mathbb{GQ}^k$, respectively, as follows:

$$
\begin{aligned}
g_{ij}^{a,k} \quad &= g_{ij}^{k} \qquad \textit{if the two atoms are equals atom "a"} \\
&= \frac{1}{2}\, g_{ij}^{k} \quad \textit{if one atom is equal to atom "a"} \\
&= 0 \qquad \textit{otherwise}
\end{aligned}
\tag{4}
$$

$$
\begin{aligned}
gt_{ijl}^{a,k} \quad &= gt_{ijl}^{k} \qquad \textit{if the three atoms are equals to atom "a"} \\
&= \frac{2}{3}\, gt_{ijl}^{k} \quad \textit{if two atoms are equals to atom "a"} \\
&= \frac{1}{3}\, gt_{ijl}^{k} \quad \textit{if one atom is equal to atom "a"} \\
&= 0 \qquad \textit{otherwise}
\end{aligned}
\tag{5}
$$

$$
\begin{aligned}
gq_{ijlh}^{a,k} \quad &= gq_{ijlh}^{k} \qquad \textit{if the four atoms are equals to atom "a"} \\
&= \frac{3}{4}\, gq_{ijlh}^{k} \quad \textit{if three atoms are equals to atom "a"} \\
&= \frac{2}{4}\, gq_{ijlh}^{k} \quad \textit{if two atoms are equals to atom "a"} \\
&= \frac{1}{4}\, gq_{ijlh}^{k} \quad \textit{if one atom is equal to atom "a"} \\
&= 0 \qquad \textit{otherwise}
\end{aligned}
\tag{6}
$$

Finally and right from the previous definitions (see Eqs. **1-3**), the kth *total (whole-molecule) bilinear, quadratic, linear, three-linear* and *four-linear* indices (QuBiLS-MIDAS MDs) can be calculated applying a set of *aggregation operators* (also called *invariants*) defined in the reports[16, 17], to the vector of atomic contributions, $\bar{L}$, for instance: the sum of the atom-level indices (components of $\bar{L}$) to aggregate the information captured by them.

2. N-tuples Spatial-(Dis) Similarity Matrices to Represent 3D-Information of the Chemical Structures.

The codification of 3D information of the chemical structures to compute the proposed indices is performed through the kth *two-tuples, three-tuples and four-tuples spatial-(dis)similarity matrices* [$\mathbb{G}^{k}$, $\mathbb{GT}^{k}$ and $\mathbb{GQ}^{k}$] for the relations among two, three and four atoms respectively (see Eqs. **1-3**). The superscript k indicates the power to which $\mathbb{G}$, $\mathbb{GT}$ and $\mathbb{GQ}$ are raised. In this way, for $k = 0$ all entries of the matrices $\mathbb{G}^{0}$, $\mathbb{GT}^{0}$ and $\mathbb{GQ}^{0}$ have value 1 and for $k = 1$ the coefficients g_{ij}^{1}, gt_{ijl}^{1} and gq_{ijlh}^{1} corresponding to the matrices $\mathbb{G}^{1}$, $\mathbb{GT}^{1}$ and $\mathbb{GQ}^{1}$ represent the information of

the interactions among two, three and four atoms respectively. The definition of the coefficients g_{ij}^1, gt_{ijl}^1 and gq_{ijlh}^1 is shown below:

$$g_{ij}^1 = D_{ij} \quad i \neq j$$
$$= L_{ij} \quad i = j \text{ and lone-pairs are considered } (or \ D_{io})$$
$$= 0 \quad otherwise$$
(7)

$$gt_{ijl}^1 = TT_{ijl} \quad \text{if atoms } i, j \text{ and } l \text{ are not equal}$$
$$= L_{ijl} \quad i = j = l \text{ and lone-pairs are considered } (or \ D_{io})$$
$$= 0 \quad otherwise$$
(8)

$$gq_{ijlh}^1 = QQ_{ijlh} \quad \text{if atoms } i, j, l \text{ and } h \text{ are not equal}$$
$$= L_{ijlh} \quad i = j = l = h \text{ and lone-pairs are considered } (or \ D_{io})$$
$$= 0 \quad otherwise$$
(9)

where, D_{ij} is the (dis)-similarity between atomic nuclei i and j (see Table 1), TT_{ijl} is an measure for ternary relations of atoms and QQ_{ijlh} is an measure for quaternary relations of atoms. The coefficients L_{ij}, L_{ijl} and L_{ijlh} represents the diagonal entries of the matrices $\mathbb{G}^1$, $\mathbb{GT}^1$ and $\mathbb{GQ}^1$ respectively, which for a greater discrimination of the molecular structures could have assigned two different values: 1) the number of lone-pairs electrons for atoms, or 2) the Euclidean spatial distance, D_{io} for each atom i and center of the molecule, o.

Table 1. Metrics used to compute the "distance" between two atoms of a molecule.

Metrics	Formula[a]	Range[b]	Average	Range
Minkowsky (**m1-m7**) $p = 0.25, 0.5, 1, 1.5, 2, 2.5, 3, \text{ and } \infty$ [where, when $p= 1$ it is the Manhattan, city-block or taxi distance (also known as Hamming distance between binary vectors) and $p = 2$ is Euclidean distance)	$d_{XY} = \left(\sum_{j=1}^{h} \lvert x_j - y_j \rvert^p \right)^{\frac{1}{p}}$	$[0, \infty)$	$\bar{d} = \dfrac{d_{XY}}{n^{1/p}}$	$[0, \infty)$
Chebyshev/Lagrange (**m8**) (Minkowsky formula when $p = \infty$)	$d_{XY} = max\{\lvert x_j - y_j \rvert\}$			

Canberra (**m10**)	$d_{XY} = \sum_{j=1}^{h} \dfrac{\|x_j - y_j\|}{\|x_j\| + \|y_j\|}$	$[0,n]$	$\bar{d} = \dfrac{d_{XY}}{n}$ $[0,1]$
Lance - Williams/Bray-Curtis (**m11**)	$d_{XY} = \dfrac{\sum_{j=1}^{h}\|x_j - y_j\|}{\sum_{j=1}^{h}(\|x_j\| + \|y_j\|)}$	$[0,1]$	$\bar{d} = \dfrac{d_{XY}}{n}$ $\left[0,\dfrac{1}{n}\right]$
Clark/Coefficient of Divergence (**m12**)	$d_{XY} = \sqrt{\sum_{j=1}^{h}\left(\dfrac{x_j - y_j}{\|x_j\| + \|y_j\|}\right)^2}$	$[0,n]$	$\bar{d} = \dfrac{d_{XY}}{\sqrt{n}}$ $[0,\sqrt{n}]$
Soergel (**m13**)	$d_{XY} = \dfrac{1}{n}\sum_{j=1}^{h}\dfrac{\|x_j - y_j\|}{max\{x_j, y_j\}}$	$[0,1]$	$\bar{d} = \dfrac{d_{XY}}{n}$ $\left[0,\dfrac{1}{n}\right]$
Bhattacharyya (**m14**)	$d_{XY} = \sqrt{\sum_{j=1}^{h}\left(\sqrt{x_j} - \sqrt{y_j}\right)^2}$	$[0,\infty)$	$\bar{d} = \dfrac{d_{XY}}{\sqrt{n}}$ $[0,\infty)$
Wave – Edges (**m15**)	$d_{XY} = \sum_{j=1}^{h}\left(1 - \dfrac{min\{x_j, y_j\}}{max\{x_j, y_j\}}\right)$	$[0,n]$	$\bar{d} = \dfrac{d_{XY}}{n}$ $[0,1]$
Angular Separation/[1-Cosine (**Ochiai**)] (**m16**)	$d_{XY} = 1 - Cos_{XY}$ where, $Cos_{XY} = \dfrac{XY}{\|\|X\|\|\|\|Y\|\|}$ $= \dfrac{\sum_{j=1}^{h}x_j y_j}{\sqrt{\sum_{j=1}^{h}x_j^2 \ \sum_{j=1}^{h}y_j^2}}$	$[0,2]$	

[a]The variable $x_j(y_j)$ is the value of the coordinate j of the atom s and the atom t, corresponding to the molecule X (Y), respectively. The h value is the Cartesian coordinates (x, y, z) of an atom. The p values in Minkowsky metric are 0.25, 0.5, 1 (Manhattan), 1.5, 2 (Euclidean), 2.5 and 3 (Minkowsky). [b]"*Range*" refers to "range" and not to "rank" and is defined as $Range = max\{x_j\} - min\{x_j\}$.

As can be previously observed, the *two-tuples spatial-(dis)similarity matrix of order 1* ($\mathbb{G}^1$) constitute a generalization of the *geometrical matrix*[18] where each entry only correspond to the Euclidean distance[19-22] between two atoms. On the other hand and as can be analyzed, the sub-indices i, j, l and h belonging to the ternary and quaternary measures (TT_{ijl}, QQ_{ijlh}) represent the atoms of the non-covalent interactions that are codified. Thus, the values of these sub-indices are

not always different whereby the distinct combinations of them are considered. In this way, the *three-tuples (or four-tuples) spatial-(dis)similarity matrices* can be built using only ternary (or quaternary) measures or as from the reducing of ternary (or quaternary) measures to the corresponding inferior measures. Therefore, the following options are into accounted to build the n-tuples matrices:

- Ternary relations:

$$3nC\ (non-complete): TT_{ijl} = \begin{cases} T_{ijl}\ three\ different\ atoms \\ 0\ \ otherwise \end{cases} \tag{10}$$

$$3C\ (complete): TT_{ijl} = \begin{cases} T_{ijl}\ \ three\ different\ atoms \\ D_{ij}\ \ two\ equal\ atoms\ and\ one\ different\ atom \\ 0\ \ otherwise \end{cases} \tag{11}$$

- Quaternary relations:

$$4nC\ (non-complete): QQ_{ijlh} = \begin{cases} Q_{ijlh}\ \ four\ different\ atoms \\ 0\ \ \ \ otherwise \end{cases} \tag{12}$$

$$4C\ (complete): QQ_{ijlh} = \begin{cases} Q_{ijlh}\ four\ different\ atoms \\ T_{ijl}\ \ two\ equal\ atoms\ and\ two\ different\ atoms \\ D_{ij}\ \ three\ equal\ atoms\ and\ one\ different\ atom \\ 0\ \ \ \ otherwise \end{cases} \tag{13}$$

where, $3C$ (or $4C$) and $3nC$ (or $4nC$) is the nomenclature assigned when the ternary (or quaternary) measures can be or not reduced, respectively. In addition, Q_{ijlh} is the measure used to establish the relation among four atoms (see Table 2B), T_{ijl} is the measure used to establish the relation among three atoms (see Table 2A), and D_{ij} is the distance between two atoms (see Table 1). Table 3 shown how the reduction of the ternary and quaternary measures is fulfilled. It is important to highlight, that to compute the ternary and quaternary measures is mandatory to select at least one *(dis)-similarity metric*, except for the calculation of the measures of Volume, Bond Angle and Dihedral Angle. This selected metric is also used when the n-way measures are reduced to considerer relations between two atoms.

Table 2. Measures used to compute the ternary (A) and quaternary (B) relations among atoms of a molecule.

A) Triple Measures (TT_{XYZ})

Measure	Formula
Perimeter (**m19-m20**)	$$T_{XYZ} = d_{xy} + d_{yz} + d_{zx}$$
Triangle Area (**m21-m22**)	$$T_{XYZ} = \sqrt{s(s - d_{XY})(s - d_{YZ})(s - d_{ZX})}$$ $$s = \frac{d_{XY} + d_{YZ} + d_{ZX}}{2}$$
Summation Sides (**m25-m26**)	$$T_{XYZ} = d_{XY} + d_{YZ}$$
Bond angle (Angle between sides) (**m27-m28**)	A_X, A_Y, A_Z *coordinate s of three atoms of a molecule* $$U = A_X - A_Y, V = A_Z - A_Y$$ $$T_{XYZ} = \alpha = \arccos\left(\frac{U * V}{|U| * |V|}\right)$$

B) Quaternary Measures (QQ_{XYZW})

Measure	Formula
Perimeter (**m19-m20**)	$$Q_{XYZW} = d_{XY} + d_{YZ} + d_{ZW} + d_{WX}$$
Volume (**m23-m24**)	A_X, A_Y, A_Z, A_W *coordinat es of four atoms of a molecule* $$Q_{XYZW} = \frac{1}{6}\begin{pmatrix} A_{Y1} - A_{X1} & A_{Z1} - A_{X1} & A_{W1} - A_{X1} \\ A_{Y2} - A_{X2} & A_{Z2} - A_{X2} & A_{W2} - A_{X2} \\ A_{Y3} - A_{X3} & A_{Z3} - A_{X3} & A_{W3} - A_{X3} \end{pmatrix}$$
Summation Sides (**m25-m26**)	$$Q_{XYZW} = d_{XY} + d_{YZ} + d_{ZW}$$

$$A_X, A_Y, A_Z \text{ coordinate s of three atoms of a molecule in the plane A}$$
$$B_W, B_Y, B_Z \text{ coordinate s of three atoms of a molecule in the plane B}$$

Dihedral Angle

(m29-m30)

$$U_A = (A_X - A_Y) \times (A_Z - A_y)$$
$$U_B = (B_W - A_Y) \times (B_Z - A_y)$$
$$Q_{XYZW} = \alpha = \arccos\left(\frac{U_A * U_B}{|U_A| * |U_B|}\right)$$

Table 3. Reduction of the ternary and quaternary measures to compute the n-way relations among atoms of a molecule

Quaternary Measure (Q_{ijlh})		Ternary Measure (T_{ijl})		Distance Metric (D_{ij})
Perimeter (quadrilateral)	→	Perimeter (triangle)	→	Distance between two atoms
Volume	→	Triangle Area	→	Distance between two atoms
Summation Sides (three sides)	→	Summation Sides (two sides)	→	Distance between two atoms
Dihedral Angle	→	Bond Angle	→	0

The matrices $\mathbb{G}^k$, $\mathbb{GT}^k$ and $\mathbb{GQ}^k$ for $k \geq 2$ are calculated multiplying the coefficients g_{ij}^{k-1}, gt_{ijl}^{k-1} and gq_{ijlh}^{k-1} of the matrices $\mathbb{G}^{k-1}$, $\mathbb{GT}^{k-1}$ and $\mathbb{GQ}^{k-1}$, respectively, by the corresponding coefficients g_{ij}^1, gt_{ijl}^1 and gq_{ijlh}^1 of the matrices $\mathbb{G}^1$, $\mathbb{GT}^1$ and $\mathbb{GQ}^1$, respectively. So, the elements of the matrix $\mathbb{G}^k$ will be equal to $\left(g_{ij}^1\right)^k$, the elements of the matrix $\mathbb{GT}^k$ will be equal to $\left(gt_{ijl}^1\right)^k$ and the elements of the matrix $\mathbb{GQ}^k$ will be equal to $\left(gq_{ijlh}^1\right)^k$. When algebraic transformations to normalize the elements of these matrices are not applied, then these are designated as k^{th} *non-stochastic two-tuples spatial-(dis)similarity matrix* (NS-SDSM, $_{ns}\mathbb{G}^k$), k^{th} *non-stochastic three-tuples spatial-(dis)similarity matrix* (NS-T-SDSM, $_{ns}\mathbb{GT}^k$) and k^{th} *non-stochastic four-tuples spatial-(dis)similarity matrix* (NS-Q-SDSM, $_{ns}\mathbb{GQ}^k$).

The proposed matrices $\mathbb{G}^k$, $\mathbb{GT}^k$ and $\mathbb{GQ}^k$ can be considered as ***generalized matrices***.[18] These matrices are computed through the *Hadamard matrix product* and are obtained by raising the matrix elements both to positive or negative exponents. When the exponent k is negative then is computed the reciprocal to each entry of the n-tuples matrices, except for the diagonal elements

when the numbers of lone-pairs is considered. The k values corresponds to non-covalent interactions among atoms of a molecule and its maximum value $(k = -12)$ is related with the Lennard-Jones potential.

3. Normalization Formalisms based on Simple-Stochastic, Double-Stochastic and Mutual Probability Schemes.

With the purpose of normalize the non-stochastic n-tuples matrices [$\mathbb{G}^k$, $\mathbb{GT}^k$ and $\mathbb{GQ}^k$] are applied three probability schemes which are associated with inter-atomic interactions in the chemical structures. The probabilistic transformations have been used in other frameworks with successful results although these are not commonly employed in chemo-informatics studies.[7, 23-26]

In this work are used the kth *simple-stochastic two-tuples spatial-(dis)similarity matrix* (SS-SDSM, $_{ss}\mathbb{G}^k$), k^{th} *simple-stochastic three-tuples spatial-(dis)similarity matrix* (SS-T-SDSM, $_{ss}\mathbb{GT}^k$) and k^{th} *simple-stochastic four-tuples spatial-(dis)similarity matrix* (SS-Q-SDSM, $_{ss}\mathbb{GQ}^k$). The coefficients $_{ss}g_{ij}^k$, $_{ss}gt_{ijl}^k$ and $_{ss}gq_{ijlh}^k$ corresponding to the matrices $_{ss}\mathbb{G}^k$, $_{ss}\mathbb{GT}^k$ and $_{ss}\mathbb{GQ}^k$, respectively, are calculated as follows:

$$_{ss}g_{ij}^k = \frac{g_{ij}^k}{S_j} = \frac{g_{ij}^k}{\sum\limits_{j=1}^{n} g_{ij}^k} \tag{14}$$

$$_{ss}gt_{ijl}^k = \frac{_{ns}gt_{ijl}^k}{S_{jl}} = \frac{_{ns}gt_{ijl}^k}{\sum\limits_{j=1}^{n}\sum\limits_{l=1}^{n} {_{ns}gt_{ijl}^k}} \tag{15}$$

$$_{ss}gq_{ijlh}^k = \frac{_{ns}gq_{ijlh}^k}{S_{jlh}} = \frac{_{ns}gq_{ijlh}^k}{\sum\limits_{j=1}^{n}\sum\limits_{l=1}^{n}\sum\limits_{h=1}^{n} {_{ns}gq_{ijlh}^k}} \tag{16}$$

where, $_{ns}g_{ij}^k$, $_{ns}gt_{ijl}^k$ and $_{ns}gq_{ijlh}^k$ are the elements of the matrices $_{ns}\mathbb{G}^k$, $_{ns}\mathbb{GT}^k$ and $_{ns}\mathbb{GQ}^k$ respectively, S_j is the summation of the coefficients of the row i in the matrix $_{ns}\mathbb{G}^k$ or the *spatial (dis)similarity vertex degree of order k* for the atom i, and S_{jl} and S_{jlh} is the summation of all entries of the two- and three-tuples matrices corresponding to each atom i in the non-stochastic n-tuples matrices $_{ns}\mathbb{GT}^k$ and $_{ns}\mathbb{GQ}^k$, respectively.

From these simple-stochastic algebraic transformations are obtained non-symmetric matrices and thus other approach to considerer is a double-stochastic scaling where the sum of the elements of each row and column is equal to 1. However, for the n-tuples matrices $(n > 2)$ does not exist reported algorithms to perform this transformation. Therefore, only have been employed the kth *double-stochastic two-tuples spatial-(dis)similarity matrix* (DS-SDSM, $_{ds}\mathbb{G}^k$) which is computed through the *Sinkhorn and Knopp algorithm*.[27]

Lastly, the kth *mutual-probability two-tuples spatial-(dis)similarity matrix* (MP-SDSM, $_{mp}\mathbb{G}^k$), k^{th} *mutual-probability three-tuples spatial-(dis)similarity matrix* (MP-T-SDSM, $_{mp}\mathbb{G}\mathbb{T}^k$) and k^{th} *mutual-probability four-tuples spatial-(dis)similarity matrix* (MP-Q-SDSM, $_{mp}\mathbb{G}\mathbb{Q}^k$) are used. With the mutual-probability transformation are obtained matrices where the summation of all entries is equal to 1. The coefficients $_{mp}g_{ij}^k$, $_{mp}gt_{ijl}^k$ and $_{mp}gq_{ijlh}^k$ corresponding to $_{mp}\mathbb{G}^k$, $_{mp}\mathbb{G}\mathbb{T}^k$ and $_{mp}\mathbb{G}\mathbb{Q}^k$, respectively, are computed as follows:

$$_{mp}g_{ij}^k = \frac{g_{ij}^k}{S} = \frac{g_{ij}^k}{\sum\limits_{i=1}^{n}\sum\limits_{j=1}^{n} g_{ij}^k} \tag{17}$$

$$_{mp}gt_{ijl}^k = \frac{_{ns}gt_{ijl}^k}{S_{ijl}} = \frac{_{ns}gt_{ijl}^k}{\sum\limits_{i=1}^{n}\sum\limits_{j=1}^{n}\sum\limits_{l=1}^{n} {}_{ns}gt_{ijl}^k} \tag{18}$$

$$_{mp}gq_{ijlh}^k = \frac{_{ns}gq_{ijlh}^k}{S_{ijlh}} = \frac{_{ns}gq_{ijlh}^k}{\sum\limits_{i=1}^{n}\sum\limits_{j=1}^{n}\sum\limits_{l=1}^{n}\sum\limits_{h=1}^{n} {}_{ns}gq_{ijlh}^k} \tag{19}$$

where, S_{ij}, S_{ijl} and S_{ijlh} are the sample spaces belonging to the matrices $_{ns}\mathbb{G}^k$, $_{ns}\mathbb{G}\mathbb{T}^k$ and $_{ns}\mathbb{G}\mathbb{Q}^k$ respectively. The three sample spaces are computed by summing all elements of their respective matrices.

4. Local-Fragment (group, atom-type) *N*-tuples Spatial-(Dis)Similarity Matrices.

The previous n-tuples matrices used to represent the relations among two, three and four atoms $(_{ns[ss,ds,mp]}\mathbb{G}^k$, $_{ns[ss,mp]}\mathbb{G}\mathbb{T}^k$, $_{ns[ss,mp]}\mathbb{G}\mathbb{Q}^k)$ can be also employed to codify information related with groups or atom-types belonging to a specific molecular fragment *F*. In this way, are utilized the kth *local-fragment two-tuples, three-tuples and four-tuples spatial-(dis)similarity matrices*,

$_{ns[ss,mp]}\mathbb{GT}_F^k$, $_{ns[ss,mp]}\mathbb{GT}_F^k$ and $_{ns[ss,mp]}\mathbb{GQ}_F^k$, respectively. The elements of these local-fragment matrices are computed as shown below:

$$
\begin{aligned}
_{ns[ss,ds,mp]}g_{ijF}^k &= {}_{ns[ss,ds,mp]}g_{ij}^k && \text{if the two atoms belongs to fragment } F \\
&= \frac{1}{2}{}_{ns[ss,ds,mp]}g_{ij}^k && \text{if one atom belongs to fragment } F \\
&= 0 && \text{otherwise}
\end{aligned}
\tag{20}
$$

$$
\begin{aligned}
_{ns[ss,mp]}gt_{ijlF}^k &= {}_{ns[ss,mp]}gt_{ijl}^k && \text{if the three atoms belongs to fragment } F \\
&= \frac{2}{3}{}_{ns[ss,mp]}gt_{ijl}^k && \text{if two atoms belongs to fragment } F \\
&= \frac{1}{3}{}_{ns[ss,mp]}gt_{ijl}^k && \text{if one atom belongs to fragment } F \\
&= 0 && \text{otherwise}
\end{aligned}
\tag{21}
$$

$$
\begin{aligned}
_{ns[ss,mp]}gq_{ijlhF}^k &= {}_{ns[ss,mp]}gq_{ijlh}^k && \text{if the four atoms belongs to fragment } F \\
&= \frac{3}{4}{}_{ns[ss,mp]}gq_{ijlh}^k && \text{if three atoms belongs to fragment } F \\
&= \frac{2}{4}{}_{ns[ss,mp]}gq_{ijlh}^k && \text{if two atoms belongs to fragment } F \\
&= \frac{1}{4}{}_{ns[ss,mp]}gq_{ijlh}^k && \text{if one atom belongs to fragment } F \\
&= 0 && \text{otherwise}
\end{aligned}
\tag{22}
$$

where, the coefficients $_{ns[ss,ds,mp]}g_{ijF}^k$, $_{ns[ss,mp]}gt_{ijlF}^k$ and $_{ns[ss,mp]}gq_{ijlhF}^k$ are the values of the *local-fragment matrices* $_{ns[ss,mp]}\mathbb{GT}_F^k$, $_{ns[ss,mp]}\mathbb{GT}_F^k$ and $_{ns[ss,mp]}\mathbb{GQ}_F^k$, respectively, and the elements $_{ns[ss,ds,mp]}g_{ij}^k$, $_{ns[ss,mp]}gt_{ijl}^k$ and $_{ns[ss,mp]}gq_{ijlh}^k$ are the (dis)similarity values represented in the total matrices $_{ns[ss,ds,mp]}\mathbb{G}^k$, $_{ns[ss,mp]}\mathbb{GT}^k$, $_{ns[ss,mp]}\mathbb{GQ}^k$, respectively.

It is important highlight that to the local-fragment matrices can be applied the algorithms specified in the Eqs. **4-6** and in this way determine the kth *atom-level local-fragment matrices*, $_{ns[ss,mp]}\mathbb{GT}_F^{a,k}$, $_{ns[ss,mp]}\mathbb{GT}_F^{a,k}$ and $_{ns[ss,mp]}\mathbb{GQ}_F^{a,k}$. Therefore, these matrices can be used to compute the atom-level molecular indices for each atom *"a"* of a molecule, which are represented in the local-fragment LOVIs vector, $_FL_a$. In this way, the kth *local-fragment bilinear, quadratic, linear, three-linear* and *four-linear indices* are calculated applying the aggregation operators over the atom-level local-fragment vector $_F\bar{L}$.

In this software, the local-fragment MDs can be calculated by seven chemical (or functional) groups in the molecule, these are: hydrogen bond acceptors (A), carbon atoms in aliphatic chains (C), hydrogen bond donors (D), halogens (G), terminal methyl groups (M), carbon atoms in aromatic portion (P) and heteroatoms (O, N and S in all valence states, denoted as X).

5. *N*-tuples Constraints to Consider Interactions According to Topological and/or Euclidean Geometric Distances.

With the purpose of establishing a relation between the topological and geometrical aspects for each group of *"N"* atoms considered and in this way take into account some short-, middle- and large-relations, two procedures are defined:

- *N-tuple Graph-theoretical cutoff* (*P*) known as "*path cutoff*", based on the topological distance. These cutoffs are denoted as: ***lag P*** for $N = 2$, ***lag 3P*** for $N = 3$ and ***lag 4P*** for $N = 4$.

- *N-tuple Euclidean-geometric cutoff* (*L*) known as "*length cutoff*", based on the Euclidean distance. These cutoffs are denoted as: ***lag L*** for $N = 2$, ***lag 3L*** for $N = 3$ and ***lag 4L*** for $N = 4$.

The application of one or both molecular cutoffs on the matrices $\mathbb{G}^1_{(F)}$, $\mathbb{GT}^1_{(F)}$ and $\mathbb{GQ}^1_{(F)}$ permits to compute the *two-, three- and four-tuple topological and geometric neighborhood quotient total (or local-fragment) spatial-(dis)similarity matrices*, $\mathbb{NQG}^1_{(F)}$, $\mathbb{NQGT}^1_{(F)}$ and $\mathbb{NQGQ}^1_{(F)}$, respectively. The coefficients of these novel matrix approaches are computed by multiplying the elements of the matrices $\mathbb{G}^1_{(F)}$, $\mathbb{GT}^1_{(F)}$ and $\mathbb{GQ}^1_{(F)}$ by a ratio obtained as the number of relations between the *N* considered atoms that present a topological and/or Euclidean-geometric distance smaller or equal to a predefined *p* and/or *l* thresholds. Then, the entries ${}^{NQ}g^1_{ij(F)}$, ${}^{NQ}gt^1_{ijl(F)}$ and ${}^{NQ}gq^1_{ijlh(F)}$ of the matrices $\mathbb{NQG}^1_{(F)}$, $\mathbb{NQGT}^1_{(F)}$ and $\mathbb{NQGQ}^1_{(F)}$ are mathematically defined as follows:

$$
{}^{NQ}g^1_{ij(F)} = g^1_{ij(F)} \text{ if } p_{min} \leq p_{ij} \leq p_{max} \quad and \, / \, or \quad l_{min} \leq l_{ij} \leq l_{max}
$$
$$
= 0 \text{ otherwise}
$$

(23)

$$^{NQ}gt^1_{ijl(F)} = gt^1_{ijl(F)} \quad if \; p_{min} \le p_{ij}, p_{jl}, p_{li} \le p_{max} \quad and/or \quad l_{min} \le l_{ij}, l_{jl}, l_{li} \le l_{max}$$

$$= \frac{2}{3} gt^1_{ijl(F)} \begin{cases} if \; p_{min} \le p_{ij}, p_{jl\,(li)} \le p_{max} \quad and/or \quad l_{min} \le l_{ij}, l_{jl\,(li)} \le l_{max} \\ if \; p_{min} \le p_{jl}, p_{li} \le p_{max} \quad and/or \quad l_{min} \le l_{jl}, l_{li} \le l_{max} \end{cases}$$

$$= \frac{1}{3} gt^1_{ijl(F)} \quad if \; p_{min} \le p_{ij\,(jl,li)} \le p_{max} \quad and/or \quad l_{min} \le l_{ij\,(jl,\,li)} \le l_{max} \tag{24}$$

$$= 0 \qquad otherwise$$

$$^{NQ}gq^1_{ijlh(F)} = gq^1_{ijlh(F)} \quad if \; p_{min} \le p_{ij}, p_{jl}, p_{lh}, p_{hi} \le p_{max} \quad and/or \quad l_{min} \le l_{ij}, l_{jl}, l_{lh}, l_{hi} \le l_{max}$$

$$= \frac{3}{4} gq^1_{ijlh(F)} \begin{cases} if \; p_{min} \le p_{ij}, p_{jl\,(lh)}, p_{lh\,(hi)} \le p_{max} \quad and/or \quad l_{min} \le l_{ij}, l_{jl\,(lh)}, l_{lh\,(hi)} \le l_{max} \\ if \; p_{min} \le p_{jl}, p_{lh}, p_{hi} \le p_{max} \quad and/or \quad l_{min} \le l_{jl}, l_{lh}, l_{hi} \le l_{max} \end{cases}$$

$$= \frac{2}{4} gq^1_{ijlh(F)} \begin{cases} if \; p_{min} \le p_{ij}, p_{jl\,(lh,\,hi)} \le p_{max} \quad and/or \quad l_{min} \le l_{ij}, l_{jl\,(lh,\,hi)} \le l_{max} \\ if \; p_{min} \le p_{jl}, p_{lh\,(hi)} \le p_{max} \quad and/or \quad l_{min} \le l_{jl}, l_{lh\,(hi)} \le l_{max} \\ if \; p_{min} \le p_{lh}, p_{hi} \le p_{max} \quad and/or \quad l_{min} \le l_{lh}, l_{hi} \le l_{max} \end{cases} \tag{25}$$

$$= \frac{1}{4} gq^1_{ijlh(F)} \quad if \; p_{min} \le p_{ij\,(jl,\,li,\,hi)} \le p_{max} \quad and/or \quad l_{min} \le l_{ij\,(jl,\,lh,\,hi)} \le l_{max}$$

$$= 0 \qquad otherwise$$

where, the coefficients g^1_{ij}, gt^1_{ijl}, gq^1_{ijlh} represents the relations between two, three and four atoms of a molecule and correspond to the total (or local-fragment) matrices $\mathbb{G}^1_{(F)}$, $\mathbb{GT}^1_{(F)}$ and $\mathbb{GQ}^1_{(F)}$, respectively. In addition, p_{XY} and l_{XY} represent the topological and Euclidean-geometric distance between two atoms of a molecule, while $[p_{min}, p_{max}]$ and $[l_{min}, l_{max}]$ constitute the used-defined topological and Euclidean-geometric intervals, respectively.

Also, other molecular cutoff procedures are proposed in order to only consider the ternary $(N = 3)$ and quaternary $(N = 4)$ relations between atoms of a molecule whose values are consistent with a specific multi-metric. These procedures are denominated as *N-tuple Geometric cutoff based on Multi-metrics* and its mathematical definition is as follows:

$$^{NQ}gt^1_{ijl(F)} = gt^1_{ijl(F)} \; if \; tv_{min} \le tv_{ijl} \le tv_{max}$$
$$= 0 \qquad otherwise \tag{26}$$

$$^{NQ}gq^1_{ijlh(F)} = gq^1_{ijlh(F)} \; if \; qv_{min} \le qv_{ijlh} \le qv_{max}$$
$$= 0 \qquad otherwise \tag{27}$$

where, tv_{ijl} and qv_{ijlh} are the values corresponding to the calculation of a ternary and quaternary multi-metric, respectively. In addition, $[tv_{\min}, tv_{\max}]$ and $[qv_{\min}, qv_{\max}]$ are the predefined intervals when cutoffs based on relations between three and four atoms are applied, respectively. Specifically, the ternary multi-metrics that may be used include the Triangle Area (*lag A*), Bond Angle (*lag BA*) and Ternary (or Triangle) Perimeter (*lag TP*); while the quaternary multi-metrics that may be used include Volume (*lag V*), Dihedral Angle (*lag DA*) and Quaternary (or Quadrilateral) Perimeter (*lag QP*).

It is important to highlight that the molecular cutoffs defined for a same number of atoms could be simultaneously applied, *e.g.*: in a relation between three distinct atoms $(i \neq j \neq l)$ if any permutation of *three-tuple cutoffs* (*lag 3P*, *lag 3L*, *lag A*, *lag BA* and *lag TP*) is used, then all the considered criteria must be fulfilled. On the other hand, also the molecular cutoffs for relations between two, three and four atoms can be concurrently applied on the same matrix representation. Therefore, on *four-tuple matrix approaches* when four distinct atoms are analyzed $(i \neq j \neq k \neq l)$ then *four-tuple cutoffs* can be applied, if three distinct atoms are analyzed $[(i = j) \neq l \neq h]$ then *three-tuple cutoffs* can be applied, and if two distinct atoms are analyzed $[(i = j = l) \neq h]$ then *two-tuple cutoffs* can be applied. Likewise, this previous strategy is employed on *three-tuple matrix approaches* when *three-tuple cutoffs* and *two-tuple cutoffs* are computed for relations between three $(i \neq j \neq l)$ and two $[(i = j) \neq l]$ distinct atoms, respectively.

References

1. Marrero-Ponce, Y.; García-Jacas, C. R.; Barigye, S. J.; Valdés-Martiní, J. R.; Rivera-Borroto, O. M.; Pino-Urias, R. W.; Cubillán, N.; Alvarado, Y. J., Optimum Search Strategies or Novel 3D Molecular Descriptors: is there a Stalemate? *Current Bioinformatics* **2013**, 10, 533-564.
2. García-Jacas, C. R.; Marrero-Ponce, Y.; Barigye, S. J.; Valdés-Martiní, J. R.; Rivera-Borroto, O. M.; Verbel, J. O., N-Linear Algebraic Maps to Codify Chemical Structures: is a suitable generalization to the atom-pairs approaches? *Current Drug Metabolism* **2013**, 15, 441-469.
3. Johnson, R. W.; Huang, C. H.; Johnson, J. R., Multilinear algebra and parallel programming. *J Supercomput* **1991**, 5, 189-217.
4. Hestenes, D.; Sobczyk, G., *Linear and Multilinear Functions*. Vol. 5.
5. Balaban, A., T., Local versus Global (i.e. Atomic versus Molecular) Numerical Modeling of Molecular Graphs. *J. Chem. Inf. Comput. Sci.* **1994**, 34, 398.
6. Todeschini, R., Consonni V., New Local Vertex Invariants and Molecular Descriptors Based on Functions of the Vertex Degrees. *MATCH Commun. Math. Comput. Chem* **2010**, 64, 359-372.

7. Marrero-Ponce, Y.; Torrens, F.; García-Domenech, R.; Ortega-Broche, S. E.; Romero Zaldivar, V., Novel 2D TOMOCOMD-CARDD molecular descriptors: atom-based stochastic and non-stochastic bilinear indices and their QSPR applications. *J Math Chem* **2008**, 44, 650-673.

8. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Torrens, F., Atom-based 3D-chiral quadratic indices. Part 2: Prediction of the corticosteroid-binding globulinbinding affinity of the 31 benchmark steroids data set. *Bioorg. Med. Chem.* **2006**, 14, 2398-2408.

9. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Torrens, F.; Rotondo, R., Atom-based stochastic and non-stochastic 3D-chiral bilinear indices and their applications to central chirality codification. *Journal of Molecular Graphics and Modelling* **2007**, 26, 32-47.

10. Castillo-Garit, J. A.; Martinez-Santiago, O.; Marrero-Ponce, Y.; Casañola-Martín, G. M.; Torrens, F., Atom-based non-stochastic and stochastic bilinear indices: Application to QSPR/QSAR studies of organic compounds. *Chemical Physics Letters* **2008**, 464, 107-112.

11. Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J., Prediction of Hydrophobic (Lipophilic) Properties of Small Organic Molecules Using Fragmental Methods: An Analysis of ALOGP and CLOGP Methods. *J. Phys. Chem. A* **1998**, 102, 3762–3772.

12. Balaban, A. T., *From Chemical Topology to Three-Dimensional Geometry*. Plenum Press: New York, 1997.

13. Balaban, A. T., *Steric fit in quantitative structure-activity relations*. Springer-Verlag: 1980; p 178.

14. Gasteiger, J.; Marsili, M., Iterative partial equalization of orbital electronegativity - a rapid access to atomic charges. *Tetrahedron* **1980**, 36, 3219-3288.

15. Ertl, P.; Rohde, B.; Selzer, P., Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties. *J. Med. Chem.* **2000**, 43, 3714-3717.

16. Barigye, S. J.; Marrero-Ponce, Y.; Martínez López, Y.; Artiles Martínez, L. M.; Pino-Urias, R. W.; Martínez Santiago, O.; Torrens, F., Relations Frequency Hypermatrices in Mutual, Conditional and Joint Entropy-Based Information Indices. *J. Comput. Chem.* **2013**, 34, 259-274.

17. Barigye, S. J.; Marrero-Ponce, Y.; Santiago, O. M.; López, Y. M.; Torrens, F., Shannon's, Mutual, Conditional and Joint Entropy-Based Information Indices. Generalization of Global Indices Defined from Local Vertex Invariants *Curr. Comput.-Aided Drug Des.* **2013**, 9.

18. Todeschini, R.; Consonni, V., *Molecular Descriptors for Chemoinformatics. Vol. 1. Alphabetical Listing; Vol. 2. Appendices, References*. Wiley-VCH: Weinheim, 2009; p 2125.

19. Andrew C. Good, S. S. S., W. Graham Richards, Structure-activity relationships from molecular similarity matrices. *Journal of Medicinal Chemistry* **1993**, 433-438.

20. Gasteiger, G.; Sadowski, J.; Schuur, J.; Selzer, P.; Steinhauer, L.; Steinhauer, V., Chemical Information in 3D Space. *J. Chem. Inf. Comput. Sci.* **1996**, 36, 1030-1037.

21. Todeschini, R.; Consonni, V., *Molecular Descriptors for Chemoinformatics*. 1st ed.; WILEY-VCH: Weinheim, 2009; Vol. 1, p 667.

22. Bogdanov, B.; Nikolic, S.; Trinajstic, N., On the Three-Dimensional Wiener Number *J. Math. Chem.* **1989**, 3, 299-309.

23. Marrero-Ponce, Y.; Huesca-Guillén, A.; Ibarra-Velarde, F., Quadratic indices of the molecular pseudograph's atom adjacency matrix and their stochastic forms: a novel approach for virtual screening and in silico discovery of new lead paramphistomicide drugs-like compounds. *J. Mol. Struct.(THEOCHEM)* **2005**, 717, 67-79.

24. González-Díaz, H.; Uriarte, E., Proteins QSAR with Markov average electrostatic potentials. *Bioorg. Med. Chem. Lett.* **2005**, 15, 5088-5094.

25. Ramos de Armas, R.; González Díaz, H.; Molina, R.; Uriarte, E., Markovian Backbone Negentropies: Molecular Descriptors for Protein Research. I. Predicting Protein Stability in Arc Repressor Mutants. *PROTEINS: Struc. Funct. Bioinform.* **2004**, 56, 715–723.

26. Carbo-Dorca, R., Stochastic Transformation of Quantum Similarity Matrixes and Their Use in Quantum QSAR (QQSAR) Models. *Int. J. Quantum Chem.* **2000**, 79, 163-177.
27. Sinkhorn, R.; Knopp, P., Concerning nonnegative matrices and doubly stochastic matrices. *Pacific J. Math.* **1967**, 21, 343-348.