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STRUCTURAL METRIC INDUCED BY THE STERIC DIFFERENCE (SD^*) METHOD

Ioan Moţoc[a] and Ioan Muşcutariu[b]

a) Chemistry Research Centre
B-dul M.Viteazul 24, 1900 Timişoara

b) Department of Physics, University of Timişoara
B-dul V.Pârvan 4, 1900 Timişoara Romania

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Summary: The paper shows that the SD^* version of our Steric Difference method defines a partial ordering of bioactive structures. The SD^* approach has better discriminating ability than the initial version (SD) of the Steric Difference method. The SD^* function induces a structural distance (i.e., a metric) on the effector series.

1. SD^* Method

The SD version[1,2] of the Steric Difference method uses the non-occupancy of the receptor cavity and the occupancy of the receptor walls as measure of the attractive and repulsive steric potentials respectively. The non-occupancy of the receptor cavity implies to consider that all non-hydrogen atoms have same volume. We removed this shortcoming of the method within the SD^* version[3] of the Steric Difference method (for review and applications see refs. 4 and 9).

We define the SD^* function as :

$$SD^* : \{S\} \times \{S_i\}_{i=1,\ldots,n} \longrightarrow R_+ \times R_+ \qquad (1)$$

where S is a structure complementary to the receptor cavity, S_i is the structure of the effector i, $1 \leqslant i \leqslant n$, and R_+ is the real positive semiaxis.

The n considered effectors elicit the biological response BR interacting with the same biological receptor, via

the same mechanism.

Thus, $SD^{*}(S, S_i)$ results in a pair of real numbers, $SD^{*}(S,S_i) = \left[SD^{*}_c ; SD^{*}_w\right]$, and in general $SD^{*}(S,S_i) \neq SD^{*}(S_i,S)$.

The values of the SD^{*} function are computed according to the following algorithm:

1) If other alternatives are not available, the structure of the most potent drug of the studied series is considered complementary to the receptor cavity. This structure, denoted by S, is termed standard.

2) Superimpose S_i over S. The hydrogen atoms are neglected and the superposition is performed according to the rule that one superimposes the pharmacophor of S and S_i. In order to obtain an easy to use method for performing the geometrical congruences, one may neglect differences lower than ± 0.2 Å and $\pm 20^{o}$ in the bond lengths and bond angles of the effectors.

3) Count the suporposable atoms 1,2,...,p of S_i over S. Compute:

$$SD^{*}_c = \sum_{j=1}^{p} k_j$$

SD^{*}_c expresses the occupancy of the receptor cavity. k_j characterizes the size of the atom j: k=o for hydrogen;

k=1 for the second row elements, except F, k_F = o.8; k=1.2, 1.3, 1.7 for the 3-rd, 4-th and 5-th row elements, respetively (Austel et al.[5]).

4) Count the unsuperposable atoms 1,2,...,q of S_i over S. Compute:

$$SD^{*}_w = \sum_{j=1}^{q} k_j$$

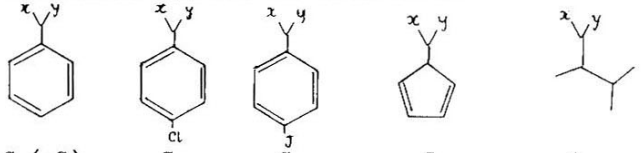
SD^{*}_w expresses the occupancy of the receptor walls.

The SD^{*} steric parameters are used in QSAR in the usual manner, namely:

$$BR = a + bSD^{*}_c + cSD^{*}_w \quad , \quad b > o, \quad c < o \ .$$

$SD^{*}(S,S_i)$ expresses with better accurancy than $SD(S,S_i)$ the steric dissimilarity between S and S_i.

Illustratively, for the structures:



$S_1(=S)$ S_2 S_3 S_4 S_5

($\overset{x}{y}>$— stands for the pharmacophoric group).

The SD and SD^* functions have the following values:

S_i	$SD(S,S_i)=[SD_c;SD_w]$	$SD^*(S,S_i)=[SD^*_c\ ;\ SD^*_w]$
S_1	o; o	6.o ; o.o
S_2	o ;1	6.o ; 1.2
S_3	o ; 1	6.o ; 1.7
S_4	1 ; o	5.o ; o.o
S_5	2 ; 1	4.o ; 1.o

(The pharmacophore atoms are not considered).

2. SD^* for Ordering of Bioactive Structures

Using the SD^* method we can characterize each bioactive structure of a series of effectors by the pair of real numbers $[SD^*_c\ ;\ SD^*_w]$. Accordingly, the biostructures can be represented as points on a grid. The rule for ordering specifies that two structures (denoted by 1 and 2) can be compared if $SD^*_{c,1} \geq SD^*_{c,2}$ and $SD^*_{w,1} \leq SD^*_{w,2}$. If this condition holds, the structure 1 dominates the structure 2, and we connect the corresponding points on the grid. The grid diagram may be used to estimate qualitatively missing data.

3. Structural Metric Induced by SD^* Function

The SD^* function defines a structural distance within an effector series. One proceeds as follows:

for any two structures S_I, S_J belonging to a given effector series one may compute the values of the SD^* function, namely $SD^*(S, S_I) = \left[SD^*_{c,I} ; SD^*_{w,I} \right]$ and $SD^*(S,S_J) = \left[SD^*_{c,J} ; SD^*_{w,J} \right]$. The function $\delta(S_I,S_J)$ defined as :

$$\delta(S_I,S_J) = \left[(SD^*_{c,I}-SD^*_{c,J})^2+(SD^*_{w,I} - SD^*_{w,J})^2 \right]^{1/2} \qquad (2)$$

is a structural metric on the considered effector series. Indeed, it is easily observed that $\delta(S_I, S_J)$ verifies the conditions:

$$\text{i)}\ \delta(S_I, S_J) \geq o \qquad (3a)$$

$$\text{ii)}\ \delta(S_I, S_I) = o \qquad (3b)$$

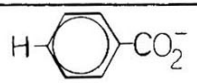
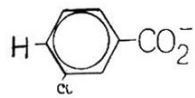
$$\text{iii)}\ \delta(S_I,S_J) = \delta(S_J,S_I) \qquad (3c)$$

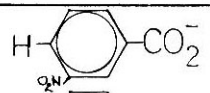
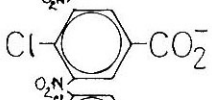
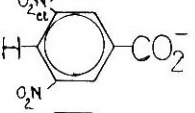
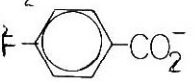
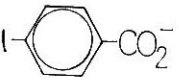
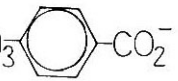
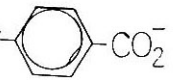
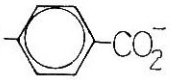
$$\text{iv)}\ \delta(S_I,S_L) \leq \delta(S_I,S_J) + \delta(S_J,S_L) \qquad (3d)$$

One calls δ as dissimilarity coefficient[6] if it satisfies conditions (3a - c); if δ satisfies also the property (3d) of the triangle then δ is a metric[7].

For the haptens collected in Table 1 the computed structural distances δ are displyes in Table 2. The values of δ clearly evidence the structural differences between the considered haptens.

Table 1. Hapten - antibody interactions : K_{rel} values and SD^* steric parameters [a)]

No.	Hapten	$K_{rel}(I)$	$SD^*_c(I)$	$SD^*_w(I)$
1.		1.oo	9.o	o.o
2.		o.43	9.o	1.2

No.	Hapten	K_{rel}(I)	SD^{*}_{c}(I)	SD^{*}_{w}(I)
3.		o.12	9.o	3.o
4.		o.41	1o.2	3.o
5.		o.o7	9.o	4.2
6.		3.6	9.8	o.o
7.		5.8	1o.2	o.o
8.		1.8	1o.o	o.o
9.		5.4	1o.3	o.o
1o.		9.8	1o.7	o.o

a) K_{rel} values are taken from ref. 8 SD^{*} parameters are computed against the standard shown in Figure 1.

Table 2. The structural distances $\delta(S_I,S_J)$ between the haptens of Table 1.

$\delta(S_I,S_J)$ J=1	2	3	4	5	6	7	8	9	10
I=1	0.00	1.20	3.00	3.23	4.20	0.80	1.20	1.00	1.30	1.70
2	1.20	0.00	1.80	2.16	2.00	1.44	1.70	1.56	1.77	2.08
3	3.00	1.80	0.00	1.20	1.20	3.10	3.23	3.16	3.27	3.45
4	3.23	2.16	1.20	0.00	1.70	3.03	3.00	3.01	3.00	3.04
5	4.20	3.00	1.20	1.70	0.00	4.28	4.37	4.32	4.40	4.53
6	0.80	1.44	3.10	3.03	4.28	0.00	0.40	0.20	0.50	0.90
7	1.20	1.70	3.23	3.00	4.37	0.40	0.00	0.20	0.10	0.50
8	1.00	1.56	3.16	3.01	4.32	0.20	0.20	0.00	0.30	0.70
9	1.30	1.77	3.27	3.00	4.40	0.50	0.10	0.30	0.00	0.40
10	1.70	2.08	3.45	3.04	4.53	0.90	0.50	0.70	0.40	0.00

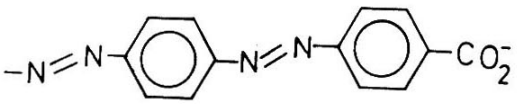


Figure 1. The standard used to compute the SD* steric parameters (the pharmacophore is $-C\lesssim^{O}_{O}\ominus$).

*

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