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ON THE MINIMAL STERIC DIFFERENCE METHOD (MTD).

1. CRITICAL EVALUATION AND IMPROVEMENT.

IOAN MOȚOC
Chemistry Research Centre
M. Viteazu 24, 1900 Timişoara, Romania

Herrn Prof. Dr. O. E. POLANSKY zu seinem 60.Geburtstag mit allen guten Wünschen gewidmet.

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Summary : The paper is devoted to the minimal steric difference method (MTD) developed by Simon et al. to treat quantitatively the steric effects in the framework of QSAR. Deficiencies of MTD method are discussed, our statements being argued by detailed computations on a series of 15 dihydrofolate reductase inhibitors. Finally, the paper presents the improved algorithm, termed MTD/2, using graphs.

1. Minimal Steric Difference, MTD. Critical Observations.

The minimal steric difference (MTD)[a] method was developed by Simon et al. to account for the steric effects in the framework of chemical structure-biological activity equations (i.e. effector-receptor interactions[1]).

The principles and computing method used in MTD are not discussed here, the reader being referred to refs. 2-4; for computational exemples and a recently published review on MTD work see refs. 5 and 6, respectively.

MTD - general observations :

1) The MTD method uses a topological formalism, the idea of metrics (distance) being introduced via a standard hypermolecule.The method is easy to use but the equations thus obtained apply only to those structures which can be superimpo-

a) The abbreviation MTD is derived from Minimal Topological Difference.

sed over the standard hypermolecule.

2) The manner recommended by Simon et al. to build up the standard hypermolecule is highly subjective. Actually, the condition that molecules are superimposed over the standard hypermolecule so that the steric difference be minimal is not strong enough to remove any possibility of subjective choice.

3) The MTD method has the merit of being the first method which tried to decide which part of the effector molecule lies inside the receptor cavity and which part lies outside.

MTD - critical observations

a) The vertices of the standard hypermolecule act as hidden parameters and usual statistics, Fischer (F) or explained variance (EV), do not account for them. An MTD-type equation log BR = a + b MTD (BR stands for biological response) has one parameter from Fischer statistics viewpoint, but actually there exist n hidden ternary parameters (n is the number of vertices of the standard hypermolecule, each vertex being characterized by a value ε = -1, 0 or +1.

b) The meaning of ε values is as follows : a vertex with ε = -1 is considered to belong to the receptor cavity, ε =+1 to the receptor walls and ε = 0 to a sterically irrelevant space. But, in the computing method developed by Simon et al., the above mentioned meanings cannot be found. In this way, the algorithm sometimes furnishes results as presented in Figure 1, which are extremely difficult to interpret.

FIG. 1. "Islands" : $\varepsilon, \varepsilon' = \{-1, 0 \text{ or } +1\}$, $\varepsilon \neq \varepsilon'$.

Discussion

Observation (a) cannot be avoided without renouncing the basic principles of the MTD formalism.

Observation (b) can be eliminated by completing the MTD algorithm. This is done in the last section of the paper, using graphs.

2. MTD Analysis of Dihydrofolate Reductase Inhibitors

In this section we resume the MTD analysis of a series of dihydrofolate reductase inhibitors originally published

in ref. 2) in order to illustrate the statements of the first section of the present paper.

Table 1 collects - log K_I figures (K_I is the inhibition constant of the compound I) and the substituents R in 2,4-diamino-6-methyl pyrimidine derivatives with the R group in position 5.

The descriptors of the inhibitor structures (i.e. (x_{ij})-matrix) were obtained using the standard hypermolecule shown in Figure 2, which has 25 vertices.

FIG. 2. Hypermolecule of dihydrofolate reductase inhibitors.

The obtained results evidence the high adjustability of the method and the dependence on the starting standard.

i) Adjustability (see Tab.1) : Y_1 are the -log K_I values experimentally determined ; Y_2 are obtained from Y_1's by their partial rearrangement (medium perturbation) ; Y_3 are obtained from Y_1's by their complete rearrangement (strong perturbation). Considering S_1

$$S_1 = \begin{cases} \xi = -1 \text{ , } 1,2,\ldots, 25 \\ \xi = 0 \text{ , none} \\ \xi = +1 \text{ , none} \end{cases}$$

as the starting standard, the following results were obtained:

$\hat{Y}_1(S_1) = 15.463 - 0.686$ MTD ; $r_{init}=0.72$, $r_{final}= 0.97$

S_{opt}: $\bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ 0\ \bar{1}\ \bar{1}\ 0\ \bar{1}\ 0\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ 1\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ 1\ 1\ \bar{1}$ (1)

$\hat{Y}_2(S_1) = 13.319 - 0.763$ MTD ; $r_{init} = 0.23$, $r_{final} = 0.78$

S_{opt}: $1\ \bar{1}\ 0\ 1\ 1\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ 0\ 0\ \bar{1}\ 0\ \bar{1}\ 0\ 0\ \bar{1}\ 1\ \bar{1}\ \bar{1}\ 0\ 0\ 1\ 1\ 1$ (2)

$\hat{Y}_3(S_1) = 10.772 - 0.795$ MTD ; $r_{init} = 0.07$, $r_{final} = 0.84$

S_{opt} :$\bar{1}\ 0\ 0\ 1\ 1\ 0\ 0\ \bar{1}\ 0\ 1\ \bar{1}\ 0\ 0\ \bar{1}\ 0\ 0\ \bar{1}\ \bar{1}\ 1\ 1\ 0\ 0\ 0\ 0\ 1$ (3)

r stands for the correlation coefficient (r_{init} obtained using S_1 and r_{final} by using S_{opt}) and $\bar{1}$ for -1.

ii) Dependence upon the starting standard : let us consi-

der S_2 as starting standard

$$S_2 = \begin{cases} \varepsilon = -1, & 1,2,\ldots, 5, 6, 10 \\ \varepsilon = 0, & 7,8,9,11,12,13,\ldots,22 \\ \varepsilon = +1, & 23,24,25 \end{cases}$$

The corresponding MTD equation is

$\hat{Y}_1(S_2) = 11.740 - 0.896$ MTD ; $r_{init} = 0.79$, $r_{final} = 0.98$

S_{opt} : $\bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ \bar{1}\ 0\ 0\ 0\ \bar{1}\ \bar{1}\ \bar{1}\ 0\ \bar{1}\ \bar{1}\ 0\ 0\ \bar{1}\ 0\ 0\ 0\ 0\ 0\ 1\ 1$ (4)

(compare eqs. 1 and 4).

3. The Improved Version of MTD Algorithm

Let collect the n vertices of the standard hypermolecule in the set M

$$M = \{ m_i \mid \varepsilon(m_i) = -1,\ 0,\ \text{or } +1 \}_{i=1,2,\ldots,n}$$

$\varepsilon(m_i)$ being the ε value attached to the vertex m_i.

M can be partitioned into three sets :

$$\begin{aligned} M_1 &= \{ m_i \mid \varepsilon(m_i) = -1 \}_{i=1,2,\ldots,n_1} \\ M_2 &= \{ m_i \mid \varepsilon(m_i) = 0 \}_{i=n_1+1,n_1+2,\ldots,n_2} \\ M_3 &= \{ m_i \mid \varepsilon(m_i) = +1 \}_{i=n_2+1,n_2+2,\ldots,n} \end{aligned} \qquad (5)$$

One can construct the graph $G = (M, \Gamma)$ in the following way : m_i, $m_j \in M$ are connected if and only if m_i and m_j are nearest neighbours in the considered standard (this statement defines $\Gamma : M \to M$). The subgraphs $G_I = (M_I, \Gamma_I)$, I = 1,2,3, are defined in the same way. It is important to note that G_I are, by definition, connected graphs[7].

Let us denote by P_{m_i} the computing procedure developed by Simon[8] according to which $\varepsilon(m_i) = \varepsilon_{old}$ is changed to $\varepsilon(m_i) = \varepsilon_{new}$. The identical transformation P_{m_i} ($\varepsilon_{old} \to \varepsilon_{old}$) is indicated by $\mathrm{I}P_{m_i}$. With the above notations, our improved

MTD algorithm, termed MTD/2, is as follows :

$\forall m_i \in G_J : P_{m_i}$ if and only if G_J, $\forall J = 1, 2, 3$ is left connected ; if contrary, $\neg P_{m_i}$.

In the MTD/2 algorithm the observation does no longer hold.

The other notes to follow in this series will detail the implementation of the MTD/2 algorithm and MTD/2 - type equations for other series of biologically active compounds by comparing them with MTD equations.

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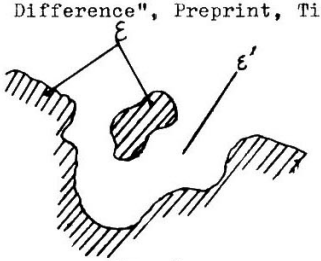

Fig. 1

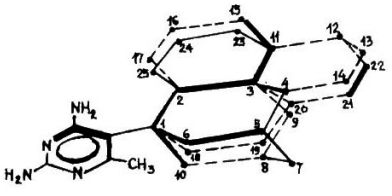

Fig. 2

TABLE 1 . Dihydrofolate reductase inhibitors

i	R	Y_1	Y_2	Y_3	x_{ij}, j=1,..., 25				
					1 5	1o	15	2o	25
1.	CH_3	3.000	6.319	**6.319**	10000	00000	00000	00000	00000
2.	C_2H_5	3.097	6.117	**6.117**	11000	00000	00000	00000	00000
3.	n-C_3H_7	5.127	6.886	6.886	11100	00000	00000	00000	00000
4.	t-C_4H_9	5.495	5.495	5.495	11000	10001	00000	00000	00000
5.	cyclo-C_6H_{11}	6.886	5.127	5.127	11111	10000	00000	00000	00000
6.	n-C_5H_{11}	6.117	3.097	**3.097**	11111	00000	00000	00000	00000
7.	n-C_6H_{13}	6.319	3.000	3.000	11111	01000	00000	00000	00000
8.	Adamanthyl	8.222	8.222	4.252	11111	11111	00000	00000	00000
9.	n-C_7H_{15}	6.658	6.658	7.155	11111	**01100**	00000	00000	00000
1o.	n-C_8H_{17}	6.721	6.721	6.569	10101	11110	10000	00000	00000
11.	n-$C_{1o}H_{11}$	7.222	7.222	6.377	10101	11110	11100	00000	00000
12.	CH_2-cyclo-C_6H_{11}	6.377	6.377	7.222	11100	00000	10001	11000	00000
13.	C_2H_4-cyclo-C_6H_{11}	6.569	6.569	6.721	11110	00000	11110	00000	00000
14.	β-Naphthyl	7.155	7.155	6.658	11100	00000	11000	00111	11000
15.	∝-Naphthyl	4.252	4.252	8.222	11100	00000	10000	00111	00111