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MOLECULAR INTERACTIONS IN BIOLOGICAL SYSTEMS
II. HYDROPHOBIC INTERACTIONS. THE HIBIS ALGORITHM.

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Abstract. The paper presents a new approach of hydrophobic interactions in biological systems, i.e., the HIBIS algorithm. The aim of HIBIS is to generate bioactive structures using the computer. The algorithm is based on the method of least squares with subsidiary conditions. HIBIS is applied with good results to a series of triazine inhibitors of L. casei dihydropholate reductase.

1. Introduction

The HIBIS (abbreviation for Hydrophobic Interactions in Biological Systems) approach is based upon the enthropic origin of hydrophobic interactions as shown in Figure 1.

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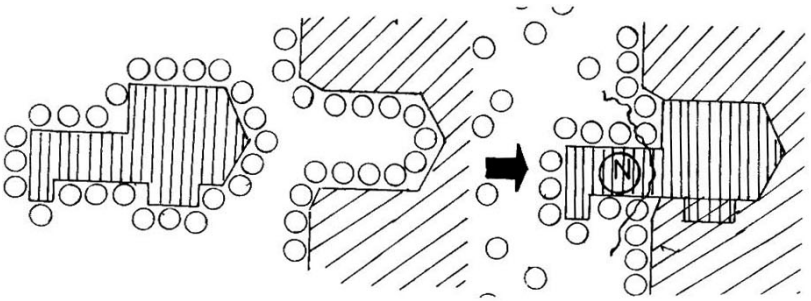


Figure 1. Schematic representation of hydrophobic interaction: R-receptor, D-drug, o-water molecules

The fragment N of the drug molecule (D) does not contribute to the hydrophobic bonding, i.e., this fragment is irrelevant in this context.

HIBIS uses as measure of hydrophobic bonding the log P values, where P is the octanol-water partition coefficient. log P value is computed within the f system[1] as:

$$\log P = \sum_i a_i f_i + (\text{corrections})$$

where f_i is the hydrophobic fragmental constant of the fragment i, and a_i denotes the incidence of this fragment in the considered structure. Tables 1 and 2 collect a few f values useful in applications (for a large collection of f-constants see ref. 4). Table 3 systematizes the corrections used within this system.

2. HIBIS algorithm

We proceed by:

i) superimpose all the S_i structures, i = 1,2,...,n, of the considered series of biomolecules according to the point two of the Steric Difference algorithm[6,7]. The resulted pattern reflects the topology of the receptor space investigated by the effectors which are being considered. This space is termed[5] Investigated Receptor Space, abbreviated by IRS.

Table 1. Fragmental f constants (ref. 2)

Fragment	f	
	aliphatic	aromatic
H	0.167	
CH_3	0.691	
CH_2	0.528	
CH	0.326	
C	0.177	
CH_2=CH	0.906	
COOH	-0.943	-0.076
C(O)H	-1.217	-0.350
$C(O)NH_2$	-1.971	-1.109
C(O)NH	-2.427	-1.560
CN	-1.052	-0.185
CO	-1.673	-0.806
Br	0.255	1.121
Cl	0.058	0.925
F	-0.485	0.382
I	0.563	1.430

Table 2. f constants for fragments in aromatic rings (ref. 3)

Fragment	f	Fragment	f
CH	0.344	C (fused to aromatic C)	0.225
NH	-0.60		
S	0.44	C (fused to heteroatom)	0.44
O	0.10		
N	-0.98		

ii) IRS constitutes a convenient topological frame, namely: the m vertices of the IRS constitute the topological coordinates for the effector fragments. Accordingly, the chemical structure S_i is described by the vector $\underline{X}_{i,H} = [x_{ij}]$, $j = 1,2,\ldots,m$, where $x_{ij} = f_\gamma$ if the vertex j of the IRS

Table 3. Corrections within f-system (ref. 2)

Origin	Correction
a) Proximity effect	
2C - separation	2 x c_M
1C - separation	3 x c_M
b) H attached to a negative group	4 x c_M
c) Ar-Ar conjugation	1 x c_M
d) Cross-conjugation	1 x c_M
e) Condensed aromtic unit	1 x c_M
f) Aromatic-alifatio differences	(3 ± 1) x c_M

(c_M = 0.28)

is occupied by the fragment Y of the effector i, and x_{ij} = 0 otherwise. f is Rekker[1] value associated with the fragment Y. The matrix $\underline{\underline{X}}_H = [x_{ij}]$, i = 1,2,...,n; j = 1,2,...,m, describes the structure of the effector series. The corrections, i.e., n x c_M, are incorporated in the appropriate entry of the $\underline{\underline{X}}$ matrix.

iii) The derived space $<IRS>_H$ is obtained from a given IRS by: one partitions the IRS vertices into receptor (r) and irrelevant (i) ones. $<IRS>_H$ is specified as:

$$<IRS>_H = [r(m_1,...); i(n_1,...)]$$

where $m_1,...; n_1,...$, index the r- and i-type vertices of the IRS. <IRS> is viewed as a connected graph, i.e., the vertices p and q are connected if and only if the edge p-q may represent a chemical bond.

The biological response, BR_i, elicited by the effector i is computed accordingly to equation:

$$BR_i = a + b f_i + c f_i^2 \qquad (1)$$

where f_i is given by:

$$f_i = \sum_{\substack{\text{all j of} \\ \text{r-type}}} x_{ij}$$

The HIBIS algorithm consists of the following steps:

1) consider the starting $\langle IRS \rangle_H$ denoted by $\langle IRS \rangle_{H,\ init}$. Compute the corresponding equation (1) and its correlation coefficient.

2) change the attribute of the vertex j of the IRS (i.e., r → i, or i → r) if the following two conditions hold:

   i) the resulting equation (1) has a better correlation coefficient; and

   ii) the sugraphs of r- and i-type vertices, respectively, are left connected.

The changes are performed until further improvements are not possible.

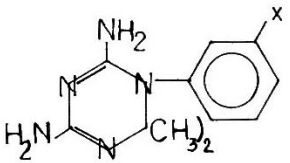
3) the resulting $\langle IRS \rangle_H$ is considered as $\langle IRS \rangle_{init}$ and step 2 is carried out for all vertices j = 1,2,...,m.

4) continue steps 2 and 3 until no change of the vertex attribute occurs. The resulted $\langle IRS \rangle_H$ is optimal, denoted by $\langle IRS \rangle_{opt}$. The congruting procedure is stopped.

We note that HIBIS and SIBIS algorithm are useful to map both flexible and rigid biological receptors. Details concerning the HIBIS program (FORTRAN) are given in ref. 9.

3. Applications

Illustratively, we apply HIBIS to study the inhibition of Lactobacillus casei dihydrofolate reductase by 4,6-diamino-1,2-dihydro-2,2-di-methyl-1-(3-x-phenyl)-s-triazines (I):



(I)

The inhibition constants collected in Table 4 are taken from ref. 8. The standard, S, is compound no. 20.

$\langle IRS \rangle_{H,\ init}$ is shown in Figure 1B. Within this $\langle IRS \rangle$, the $\underline{\underline{X}}_{i,H}$ matrices are:

$$\underline{\underline{X}}_{i,H} = [f_{SO_2NH_2} \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \ldots 0] =$$

$$= [-1.480 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \ldots 0]$$

$$\underline{\underline{X}}_{3,H} = [f_{H} \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \ldots 0] =$$

$$= [0.167 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \ldots 0]$$

$$\underline{\underline{X}}_{18,H} = [f_{OCH_2} \quad f_{CH} \quad f_{CH} \quad f_{CH} \quad f_{CH} \quad f_{CH} \quad f_{CH} \quad 0 \ldots 0] =$$

$$= [-1.864 \quad 0.344 \quad 0.344 \quad 0.344 \quad 0.344 \quad 0.344 \quad 0.344 \quad 0 \ldots 0]$$

Table 4. Inhibition constants for triazines (I)

No.	X	log $1/I_{50}$
1.	SO_2NH_2	1.82
2.	$CONH_2$	2.47
3.	H	2.64
4.	$COCH_3$	2.87
5.	CH_3	3.07
6.	OCH_3	3.12
7.	OH	3.19
8.	$C(CH_3)_3$	3.20
9.	$COOC_2H_5$	3.21
10.	SO_2F	3.21
11.	F	3.29
12.	CF_3	3.29
13.	Cl	3.45
14.	NO_2	3.56
15.	Br	3.69
16.	I	3.73
17.	$O(CH_3)_2OC_6H_5$	3.74
18.	$OCH_2C_6H_5$	4.20
19.	$O(CH_2)_3CH_3$	4.20
20.	$(CH_2)_5CH_3$	4.96

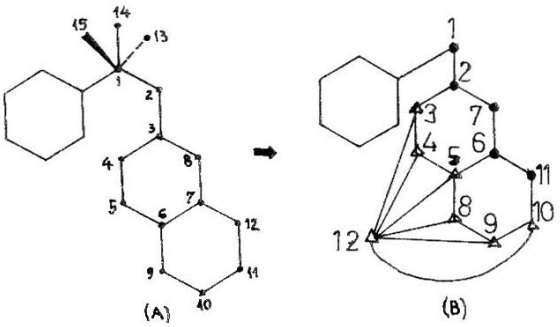


Figure 1. (A) <IRS> resulted from atom per atom superposition. (B) $<IRS>_H$ used in the HIBIS computations (·: r-vertex; △: i-vertex; the vertices 1,2, 13,14 and 15 of <IRS> shown in (A) are contracted into the vertex 1 of $<IRS>_H$).

The $<IRS>_{H,init}$ = [r(1,2,6,7,11); i(3,4,5,8,9,10,12)] provides the equation:

$$\log 1/I_{50} = 3.049\ (\pm 0.099) + 0.401(\pm 0.077)f + 0.035(\pm 0.036)f^2 \qquad (2)$$

($r = 0.779$, $x = 0.421$, $F = 8.274$)

Using the HIBIS algorithm one gets:

$$\log 1/I_{50} = 3.017(\pm 0.088) + 0.368(\pm 0.060)f + 0.031(\pm 0.023)f^2 \qquad (3)$$

($r = 0.832$, $x = 0.373$, $F = 11.987$), with

$<IRS>_{H,opt}$ = [r(1÷7, 10, 11); i(8, 9, 12)]

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