The calculation of molecular similarity: alternative formulas, data manipulation and graphical display

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The use of electrostatic potential comparisons between molecules for the elucidation of structure activity relationships is now a well-established modeling technique. The Carbo and Hodgkin similarity indices are used extensively to make quantitative comparisons of this nature; yet their roots are found in the overlap of electron density distribution, with both formulas utilizing a product-based numerator.

Two new similarity indices are suggested that calculate the electrostatic potential similarity using a difference-based numerator. The form of the new indices allows the creation of additional software functions that enhance the flexibility of similarity calculations and permit the creation of similarity maps.

The general properties of these software functions and all indices are discussed and applied to a series of dopamine D2 receptor agonists.

Keywords: similarity indices, electrostatic potential, graphical analysis, selective optimization, steric differences

ORIGINAL INDICES: GENERAL CHARACTERISTICS

The use of similarity for the quantitative molecular structure comparison of two molecules has been discussed extensively.[1-3] The original formulas utilized in these calculations are nonunique in nature, their functional form influencing behavior during similarity determination.

The index created by Carbo[4-5] is based on the comparison of electron density distributions derived from wavefunction calculations and takes the form

$$R_{AB} = \frac{\int P_A P_B d\nu}{\left(\int P_A^2 d\nu\right)^{1/2} \left(\int P_B^2 d\nu\right)^{1/2}}$$

where P_A and P_B are the electron densities of the two molecules being compared.

The Carbo index is sensitive to the shape of the molecular charge distribution rather than its magnitude. This is highlighted by the fact that when the electron densities of two molecules correlate, the similarity index tends towards unity. Thus if $P_A = nP_B$, $R_{AB} = 1$.

The index can be extended to the calculation of similarity, where P equals electrostatic potential. Similarity is determined via the comparison of electrostatic potentials at the intersections of a rectilinear grid constructed around the two molecules. Consideration of the variation of similarity with electrostatic potential difference at one such intersection (grid point) for the Carbo index further illustrates its low sensitivity to electrostatic potential magnitude (see Figure 1a; for Figures 1a–d, the electrostatic potential difference is P_A–P_B, while *max* refers to the larger electrostatic potential magnitude between P_A and P_B at the grid point in question. For both variables, units are in kcal/mol). The index is seen to behave discontinuously, being sensitive to differences in electrostatic potential sign but not magnitude.

In an attempt to counter this, the Hodgkin index was proposed[6] to increase the magnitude sensitivity of similarity calculations

$$H_{AB} = \frac{2\int P_A P_B d\nu}{\int P_A^2 d\nu + \int P_B^2 d\nu}$$

The behavior of the Hodgkin index at one point in space vs. electrostatic potential difference (Figure 1b) illustrates its increased sensitivity to electrostatic potential disparities over the Carbo index at lower electrostatic potential magnitude. (Compare Figures 1a and b, *max* = 5 kcal/mol plots.) However, both indices sum charge comparisons over all space, with the main contributions to the numerator and denominator terms being made by large magnitude values, which therefore tend to dominate the final similarity result. Since the behavior of the two indices at high magnitude (Figures 1a and b, *max* = 20 kcal/mol plots) is similar except when differences are large, the Hodgkin index will generally function in a similar manner to the Carbo index.

A further feature common to these indices is that there

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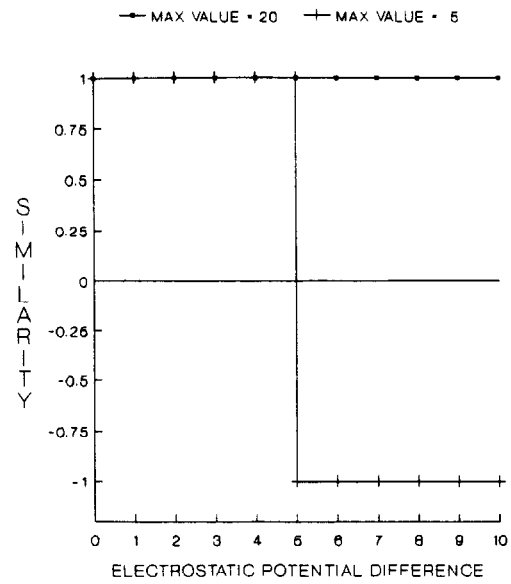

Fig. 1a

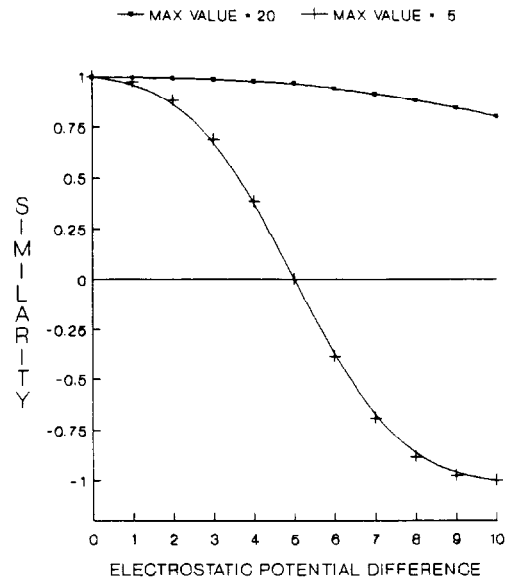

Fig. 1b

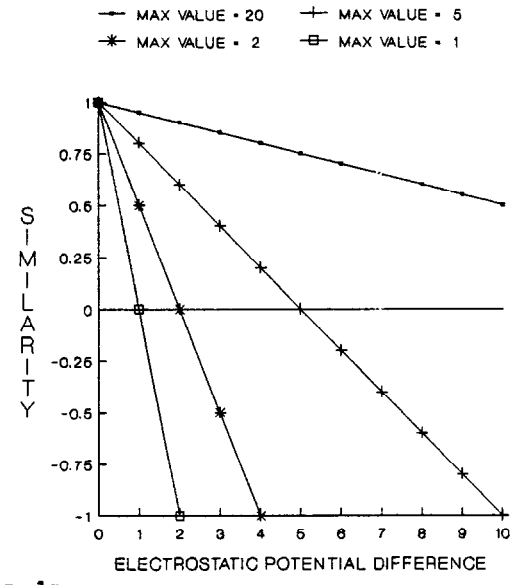

Fig. 1c

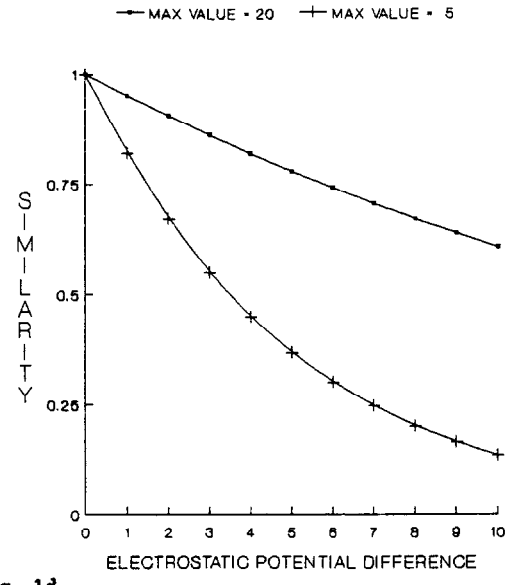

Fig. 1d

Figure 1. a, Carbo index behavior at one point in space; b, Hodgkin index behavior at one point in space; c, linear index behavior in one point in space; d, exponential index behavior at one point in space.

exists no explicit treatment of steric differences between molecules during a similarity calculation. With the current implementation of these indices within the computer software package ASP,[7] whenever a grid point is found to be within the van der Waals surface of a molecule, a zero value is assigned for the electrostatic potential of the molecule at that intersection. This results in no addition to the index numerator totals at that intersection, since the numerator contributions at a grid point are equal or proportional to the product of the electrostatic potentials. The effect this has on the overall similarity for a grid point where steric differences exist (inside the van der Waals surface of one molecule and outside the surface of the second molecule) is variable, since the denominator contributions will depend on the electrostatic potential value of the molecule for which the grid point is outside the van der Waals surface.

ALTERNATIVE INDICES

When considering receptor drug binding, the electrostatic interaction energy of the system is proportional to the electrostatic potential exerted by the drug. Drug molecule similarity is related to the difference in binding energies, and this disparity is proportional to the difference in drug electrostatic potentials (ignoring entropy and solvent effects). It is therefore reasonable to assert that a similarity index comparing drug electrostatic potentials also should be based on the calculation of electrostatic potential differences.

Two similarity indices have been formulated based on this premise: the linear index:[8]

$$L_{AB} = \frac{\sum_{i=1}^{N}}{N}\left(1 - \frac{|P_A - P_B|}{max\,(|P_A|, |P_B|)}\right)$$

and the exponential index:

$$E_{AB} = \frac{\sum_{i=1}^{N}}{N}\left(\exp^{-\frac{|P_A - P_B|}{max(|P_A|,|P_B|)}}\right)$$

where $max(|P_A|, |P_B|) = P_{max}$ equals the larger electrostatic potential magnitude (P_A or P_B) at the grid point where the similarity is being calculated.

For both indices the electrostatic potential similarities at each grid point are calculated individually, the values combined and the total divided by the number of grid points involved to determine the average similarity.

A graph of similarity vs. electrostatic potential difference at a single grid point for the linear index (Figure 1c) shows that, as for the Hodgkin index, similarity becomes more sensitive to increasing electrostatic potential difference as the maximum electrostatic potential magnitude (P_{max}) at the grid point is reduced. (Compare the gradients of the plots as *max value* decreases.) In fact, as *max* becomes very small, only small differences in electrostatic potential are required for low similarity values to be produced. This can be seen by considering the following examples

$$(1)\quad L_{AB} = 1 - \frac{(0.1 - (-0.1))}{0.1} = -1$$

$$(2)\quad L_{AB} = 1 - \frac{(20 - 15)}{20} = 0.75$$

In Example (1) the electrostatic potentials found at one grid point are 0.1 and −0.1 kcal/mol. Although both electrostatic potentials are insignificant and the difference between them is very small, the similarity value produced is the lowest value possible for the linear index. In Example (2) the electrostatic potentials are much larger (20 and 15 kcal/mol) and the difference between them is significantly larger than in Example (1). The resulting index value, however, is much higher than in Example (1), showing significant similarity between the two electrostatic potentials.

It is therefore a clear feature of the linear index that in regions of very low electrostatic potential magnitude, small differences produce low (negative) similarity values. These regions will lower the overall similarity value significantly when small disparities exist over an extended area. In essence, it is the size of the electrostatic potential difference relative to P_{max} that is important in determining the resultant similarity value, rather than the size of the difference itself.

The behavior of the exponential index with respect to electrostatic potential difference (Figure 1d) is somewhat different. As with the linear and Hodgkin indices, similarity becomes more sensitive to increasing electrostatic potential differences as the magnitude of P_{max} is reduced. (Compare the gradients of the plots as *max value* decreases.) Small differences in electrostatic potential at low P_{max} values therefore are expected to lower the overall similarity result significantly, as with the linear index. The exponential nature of the index means, however, that similarity never drops below zero, so that even when the electrostatic potential differences are large a positive value for similarity will result. Values for the exponential index are therefore generally significantly higher than for the linear index. The following examples illustrate these points

$$(3)\quad E_{AB} = \exp^{-\frac{(0.1-(-0.1))}{0.1}} = 0.14$$

$$(4)\quad E_{AB} = \exp^{-\frac{(20-15)}{20}} = 0.78$$

In example (3) although the difference in electrostatic potentials is small, the low electrostatic potential magnitudes involved produce a P_{max} value that is small in comparison to the difference, and a low similarity result follows. The resultant similarity values is nonetheless positive, as would be expected. In example (4) the high electrostatic potential magnitudes involved produce a high P_{max} value relative to the electrostatic potential difference, and a high similarity result ensues.

Because each grid point is treated individually, steric differences can be treated explicitly for both of the new indices (described below).

SUPPLEMENTARY SOFTWARE FUNCTIONS

The form of the new indices permits a number of additional software functions to be written that complement the similarity calculations. Index behavior can be altered through control of the denominator P_{max}. Regions of space around the molecules that are to be included in the calculation may be regulated. Graphical analysis is possible through the use of similarity maps. Differences in molecular shape can be taken into account during similarity determinations. These features are described in detail below.

(1) Function 1. It is possible to set a user-defined fixed denominator (P_{max}) for the new indices. The value used should be related to the electrostatic potential magnitudes found around the molecules utilized in the calculation. The electrostatic potentials used in the similarity calculations have been converted to units of kcal/mol so that assignments, such as the fixed P_{max} term, can be set to easily definable whole-number values. With a constant P_{max} value, similarity depends only on electrostatic potential differences, since P_{max} can no longer be affected by the magnitude of the electrostatic potential.

In the same vein it is possible to set a minimum value for P_{max} so the user can exert control over the nature of the index when dealing with regions of low electrostatic potential magnitude. This is possible because by setting a minimum cutoff, the maximum sensitivity of the similarity calculation is also defined. This can be seen in Figure 1c, where setting a minimum P_{max} value of 5.0 sets a maximum gradient for similarity vs. electrostatic potential difference, as shown by the max value = 5 plot.

(2) Function 2. User-defined minimum and maximum electrostatic potential cutoffs can be used to control whether a grid point is included in the similarity cal-

culation according to the strength of the electrostatic potential. For example, setting a minimum cutoff of 5 kcal/mol will remove all grid points where the electrostatic potential due to both molecules is less than 5 kcal/mol in magnitude.

This function allows the user to exert a degree of control over which regions in space are included in the similarity calculation, and to remove regions of low electrostatic potential magnitude so as to prevent a possible downward distortion of the overall similarity result.

(3) Function 3. The user can set a fixed grid thickness for use in a similarity calculation. For example, if a fixed thickness of 2 Å is assigned, only grid points 2 Å or less from the van der Waals surface of both molecules will be included in the similarity calculation. This facility allows for the valid inclusion of regions of low electrostatic potential magnitude in the similarity calculations, by removing more distant grid points of low electrostatic potential magnitude found in a standard rectilinear grid.

(4) Function 4. Similarity maps can be calculated for display within software packages like the Chem-X modeling program.[9] The index used in the map creation is user definable. If the exponential index is used, similarity due to regions of negative electrostatic potential can be assigned equivalent negative values so they may be distinguished graphically from similarity due to positive electrostatic potential. This is not possible for the linear index, which can calculate negative similarities by default.

For similarity calculations involving many molecules, the following maps can be generated:

(1) Minimum. The minimum similarity result at each grid point is determined and assigned.
(2) Maximum. The maximum similarity result at each grid point is determined and assigned.
(3) Average. The average similarity result at each grid point is calculated and assigned.
(4) Standard deviation. The standard deviation of the similarity values calculated at each grid point is calculated and assigned.

The results of a single similarity calculation involving one pair of molecules also can be presented in graphical form.

(5) Function 5. When a similarity map is calculated, each grid point within the steric bulk of any of the molecules involved is assigned the value -10.0. (This value is used to differentiate steric information from the electrostatic potential similarity information.) The remaining grid points are allocated electrostatic potential similarity values appropriate to the defined calculation.

This steric and electronic information can be read back into subsequent similarity calculations and a minimum similarity cutoff assigned. Only those grid points for which the similarity value of the map is greater than the defined cutoff are included in the calculation. This allows the user to carry out a similarity calculation only in those regions of space that were found to be similar for all the active molecules used to create the map. Steric difference calculations are made against the map rather than against the lead molecule, allowing the simulation of binding within the steric bulk occupied by the molecules used to create the map (pseudo receptor pocket).

(6) Function 6. For a grid point exhibiting steric differences (inside the van der Waals surface of one molecule and outside the surface of another molecule), a variable similarity penalty can be assigned by the user, the size of the penalty (if any) depending on the importance attached to these disparities. These penalties are added to the other similarity values when determining overall similarity, so a large negative penalty will significantly lower the result when substantial numbers of steric differences exist. Using this feature in conjunction with Function 5 allows the user to force structures to fit into regions occupied by active molecules (receptor site) before maximizing electrostatic potential similarity. This is accomplished because until the number of steric differences is minimized, the penalty terms will dominate the overall similarity result.

The number of grid points exhibiting steric differences is reported in the output file together with the standard electrostatic potential similarity results.

Enhancements to similarity calculation control, the ability to generate maps, regulating facilities for optimizations and calculations using steric difference penalties and map data, are all potentially useful additions to the basic similarity calculations. A number of these facilities were tested in the D2 agonist study and their results are discussed below.

D2 AGONIST STUDY

Preparation and calculation

A series of molecules active at the D2 dopamine receptor (a receptor associated with motor disorders, such as Parkinsons disease[10]) were used for the comparison of the similarity indices. The Cambridge Structural Database[11] was used to search for crystal data relating to the structures of interest. The SYBYL modeling program[12] was used to make functional and stereochemical alterations to the extracted data. Where no crystal data were available the structures were built within SYBYL using standard bond lengths and angles. All the resulting structures were minimized using the SYBYL molecular mechanics force field,[13] and conformational analyses were carried out on all structures containing flexible bonds (other than propyl groups) to determine global torsional minima. The minimized structures were then optimized[14] within Mopac 5 utilizing the PM3 parameter set. Semiempirical molecular electrostatic potentials (MEPs) were then calculated for all structures from the Mopac results without recourse to wavefunction deorthogonalization.[15] Structures containing inherent flexibility (again, other than propyl groups) had MEPs calculated for conformations in each torsional minimum region. These charges were averaged with those for the completely optimized structure so as to lend validity to the MEP point charge scheme used if torsional variation occurred during similarity optimization. The molecules used are listed in Table 1 with D2 receptor activity data, and are displayed in Figure 2.

Table 1. Activity data for D2 dopamine agonists

Molecule label	Molecule name	Log_{10} relative activity[16]†
1	(-)-PPP[17]	Antagonist*
2	SKF 38393	<1.0
3	(+)-PPP[17]	1.0
4	Pergolide[18]	1.3
5	Dp-6,7-ADTN[19]	1.6
6	Quinpirole[20]	1.9
7	CL201-678	1.9
8	N-0434	2.2
9	CH 29-717[18]	3.1
10	Np-Apomorphine[21]	3.4

†*In vivo* data used

*Although not mentioned in the biological data utilized, molecule 1 acts as an antagonist while bound to the D2 receptor site.[22]

The initial structural overlap was carried out within SYBYL in general accordance with a previous D2 agonist SAR study,[23] emphasis being placed on maximizing the fit in regions where binding to the receptor was considered to be strongest. Using molecule 10 as the reference molecule, lone pair vectors were added to the nitrogens marked *a* in Figure 2, with the nitrogen and the lone pair vector then being used as two of the fitting constraints. For molecules containing hydroxyl groups, the hydroxyl oxygen marked *b* in Figure 2 was used as the third fitting constraint, while for the remaining (partial) ergoline structures of 4, 6 and 9, the pyrrole/pyrazole rings were overlayed with the dihydroxy ring of 10 (all marked 1 in Figure 2). No attempt was made to maximize lipophilic group overlap, eg., N-propyl chains.

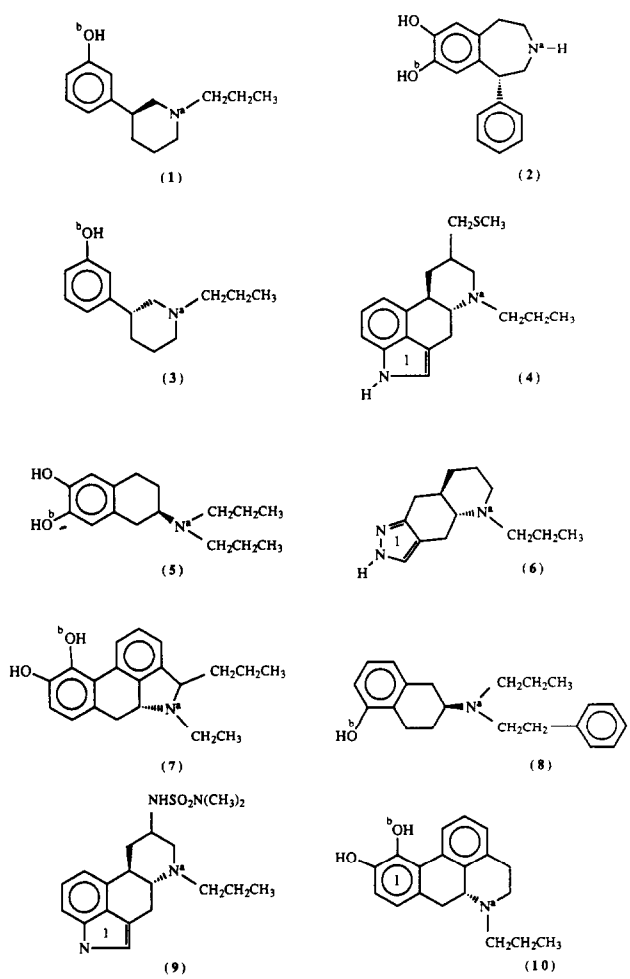

Figure 2. D2 agonist structures.

Once the structures were overlayed, a number of different similarity calculations were undertaken.

The similarity was calculated using the Hodgkin and Carbo indices, plus the linear and exponential indices in their default form.

The linear and exponential indices were calculated with a minimum electrostatic potential cutoff of 5.0 kcal/mol.

The exponential index was calculated with the P_{max} value of the new indices fixed at 2.5 kcal/mol and a minimum electrostatic potential cutoff of 5.0 kcal/mol.

The linear and exponential indices were calculated with a minimum electrostatic potential cutoff of 5.0 kcal/mol for the three most active molecules (8, 9 and 10). An *N* by *N* (similarity determined for all molecules against all others) calculation was used, and Chem-X readable minimum similarity maps were created for both indices. The exponential index map was set up to distinguish similarity due to regions of positive and negative electrostatic potential. Similarity due to positive electrostatic potential was found to be far less significant than that due to negative electrostatic potential (Color Plate 1).

It was decided therefore to determine the minimum similarity value for which no contribution was made by regions of positive electrostatic potential in the linear minimum similarity map. This was done by adjusting the contour levels of the map displayed in Chem-X. The minimum contour value was found to equal 0.50. This value is lower than that displayed in Color Plate 1 because results for the linear index are always smaller than for the exponential index. The shapes of the two maps were virtually identical, however.

This value was then set as a cutoff for a calculation in which the linear map electrostatic potential similarity data was used to regulate the similarity prediction (see Function 5 for further details).

The similarities of molecules 8 and 9 were optimized against molecule 10 in conjunction with the original linear map, and a cutoff of 0.50 assigned. The resulting structural positions were then used to recalculate the linear minimum similarity map.

It was decided that the lipophilic pocket able to accommodate large side chains (possibly the entrance to the active site) described in a previous D2 receptor model[23] should be simulated. To do this, conformers from each of the previously calculated torsional minima of the phenyl/sulphonamide side chains of molecules 8 and 9 were overlaid onto the optimized structures so that the ring systems fitted exactly. These conformations were then run through a dummy similarity calculation with zero charge on all the atoms of each structure. A linear minimum similarity map was calculated that contained information on the combined steric volume occupied by these conformations with the required −10.0 grid point values. This map was then logically associated

through Chem-X with the optimized linear similarity map (using OR logic). The resulting map contained information on the combined steric volume occupied by all conformations involved in the two calculations, plus the minimum electrostatic potential similarity data for molecules 8, 9 and 10 (a pseudo receptor map).

All molecules not involved in map creation (1–7) had their similarity optimized (rigid optimization with no torsional flexibility) against molecule 10, with the pseudo receptor map read in. A steric penalty of −10.0 was set to force the molecules to try and fit into the pseudo receptor before attempting to maximize binding similarity, and a cutoff value (0.56, which is larger than in the original map based calculation due to similarity optimization of molecules 8 and 9) was assigned, which removed all regions of similarity due to regions of positive electrostatic potential. Molecules 1, 3 and 5 also underwent flexible optimization.

Results and discussion

The numerical results determined from these calculations are presented graphically in Figures 3a–f.

The Carbo and Hodgkin indices behaved in an almost identical fashion (Figure 3a), the only significant difference being shown by molecule 9, where large dissimilarities exist (particularly on the sulphonyl side chain) compared to molecule 10.

The results for calculations involving the new indices in their default form (Figure 3b) show marked differences from the Carbo and Hodgkin indices, with significantly lower similarity values obtained for molecules 4 and 7.

When a minimum electrostatic potential cutoff was incorporated into the similarity calculation, the behavior of the new indices mirrored the Carbo and Hodgkin indices much more closely, with significant increases in the value of the similarity results for molecules 4 and 7 (Figure 3c).

Use of a fixed P_{max} value lowered overall similarity but appeared to have little effect on the relative molecular similarities (Figure 3c).

For all these calculations the similarities of molecules 8 and 9 were seriously underestimated. This is because side chain electrostatic potential differences compared with molecule 10 lower the overall similarity result, overshadowing the similarity in regions purported to be involved in primary binding.

When the minimum similarity map was used as the basis for the determination of similarity, very different results were obtained (Figure 3d). As expected, the similarities of molecules 8 and 9 were much higher, as were the similarities of all other molecules. The similarities of the molecules with lower activity (1–4) were higher than would be expected. However, the number of grid points exhibiting steric differences for these molecules against the pseudo receptor map (with the exception of molecule 4) was significantly higher than for the more active molecules (Figure 3e).

When molecules 1–7 underwent similarity optimization with a large steric penalty so as to force them to fit into the pseudo receptor, the number of steric differences for the highly active molecules dropped to near zero in all cases (Figure 3e), while the similarity increased (Figure 3f). Molecule 4 also fitted perfectly into the pseudo receptor map, and exhibited the highest similarity of all molecules not used in the pseudo receptor map calculation. (It should be noted that although the activity rating for molecule 4 in the biological data used[16] is low, other biological data[24] show molecule 4 to be almost as active as molecule 10.) Molecules 1–3 still showed significant steric differences from the receptor map, with molecules 2 and 3 having decreased in similarity.

It should be noted that for molecule 1 to maximize electrostatic potential similarity, its N-propyl group must point away from the N-propyl groups of all other molecules. Since it is postulated that the N-propyl group is very important in lipophilic binding to the receptor,[23] this probably accounts for its antagonistic properties.

When molecules 1, 3 and 5 underwent flexible similarity optimization, differing results were obtained. Molecule 5 remained virtually unchanged, but the steric differences of molecules 1 and 3 dropped significantly while their similarities increased (compare the starred points on Figures 3e-f with the results for rigid optimization). In line with previous studies,[22,23] however, the energies of the resulting conformations were significantly higher than the global minima for these molecules (4 kcal/mol for molecule 1, and 6 kcal/mol for molecule 3, according to van der Waals energy calculations carried out in Chem-X).

In all cases the relative behavior of the linear and exponential indices was virtually identical from molecule to molecule, with the linear index generally showing a higher resolution (relative similarity difference between molecules).

CONCLUSION

Although the optimum methodology for the use of the new indices is not completely defined, previous work done with the default form of the linear index[25] suggests that there are problems in the similarity values obtained. Similarity data variance resolution using principal component analysis requires a larger number of principal components for the linear index than for the Carbo and Hodgkin indices. The low similarity values obtained for molecules 4 and 7 in the current study are almost certainly symptoms of this problem, which relates to the previously mentioned property of large (dis)similarity contributions made by regions of low electrostatic potential. The exponential index also appears to be distorted in a similar manner by regions of low electrostatic potential magnitude. The use of an electrostatic potential cutoff seems to overcome this problem by excluding regions of low electrostatic potential magnitude from the calculation.

It would be valuable to assert which indices are best employed in the various applications in which similarity is utilized; however, until the formulations have been applied to a number of diverse biological problems, no firm conclusions can be drawn. The functions available for the comparison of low electrostatic potential magnitude regions also require further investigation.

The utility of the new indices is nonetheless clear from the flexibility in the way similarity can be calculated, and the new tools available for both graphical analysis and similarity optimization.

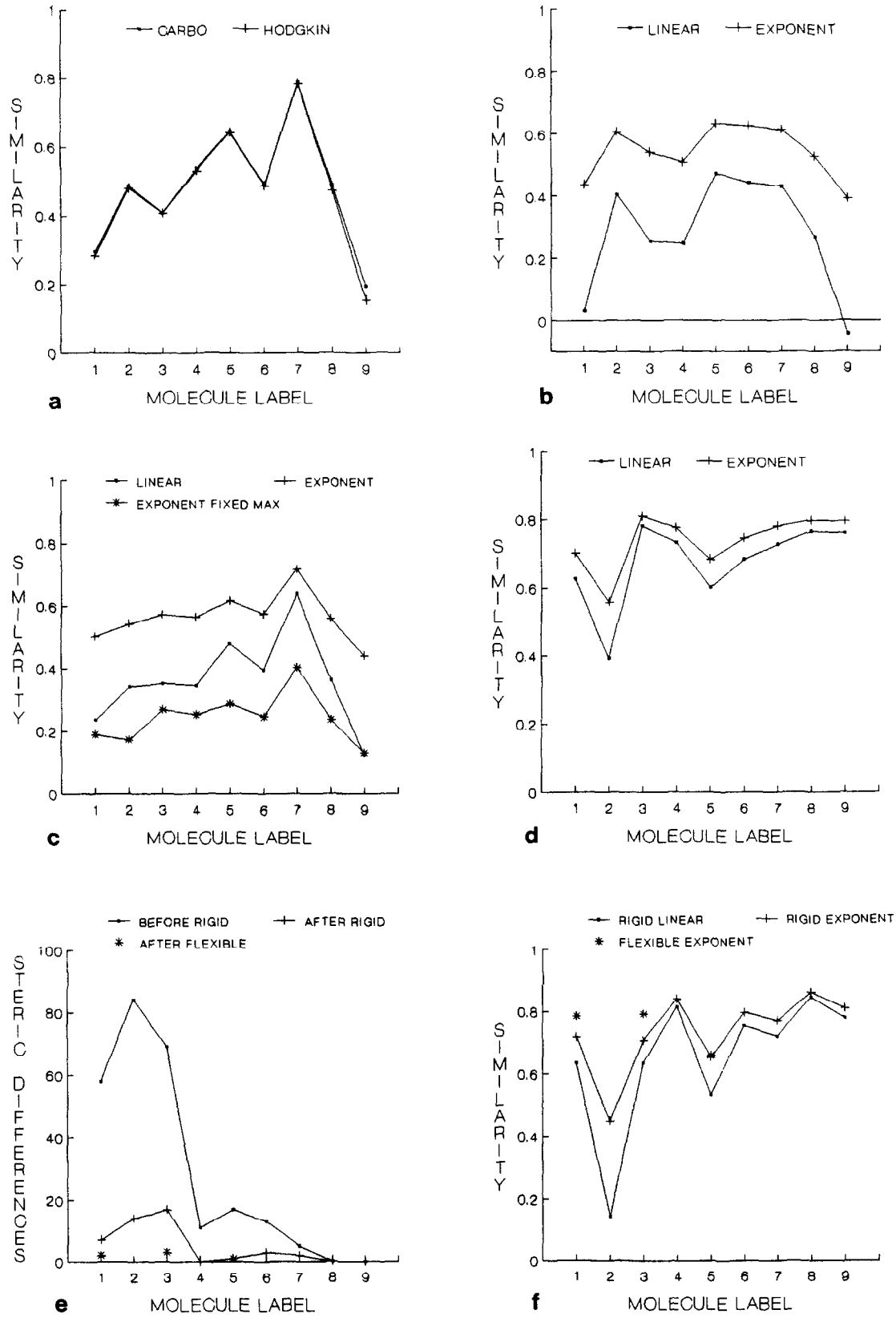

Figure 3. a, Similarity vs. molecule 10 for the Carbo and Hodgkin indices; b, similarity vs. molecule 10 for the new indices in their default form; c, similarity vs. molecule 10 for the new indices, with a minimum electrostatic potential cutoff/fixed max value set; d, similarity vs. molecule 10 for the new indices with pseudo receptor map cutoff before similarity optimization; e, number of grid points exhibiting steric differences before and after similarity optimization; f, similarity vs. molecule 10 for the new indices with pseudo receptor map cutoff after similarity optimization.

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