Conformational Searching in ISIS/3D Databases

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Three-dimensional structure databases, and their accompanying searching software, have been available for several years, both from commercial software vendors and by in-house development. Commercially available systems include MACCS-II/3D and ISIS/3D (MDL Information Systems, Inc.), Aladdin (Abbott Laboratories and Daylight Chemical Information Systems, Inc.), ChemDBS-3D (Chemical Design Ltd.), SYBYL/3DB Unity (Tripos Associates), and Catalyst (BioCad Corp.). With the exception of ChemDBS-3D and, most recently, SYBYL/3D Unity, these software products apply geometric searching algorithms to static 3D models. This is acceptable for relatively rigid structures but fails to take into account the inherent flexibility of many molecules of biological interest. Approaches to this problem have included the registration of multiple conformations (all products), conformational analysis at registration and search time (ChemDBS-3D), development of 3D queries that can accommodate limited flexibility in the target structures (MACCS-II/3D, ISIS/3D), and, most recently, application of the directed tweak approach (SYBYL/3DB Unity). This paper will discuss a new approach to the problem, implemented within the ISIS/3D software. The method uses a multilevel screening and constraint-fitting approach, applying torsional optimization with van der Waals energy contributions in the later stages. Methodology and examples are covered.

1. INTRODUCTION

Electronic database systems for the storage, retrieval, and searching of three-dimensional structures are now commonplace. Computer programs for geometric searching have been developed at a number of academic, industrial, and commercial software vendor sites; many of these programs are widely available, and new systems are being developed today.[1-16] The abundance of 3D searching systems is a compelling indication of the interest in the field and of the competitiveness of the commercial market for such products.

With few exceptions, the majority of 3D geometric searching programs operate by storing 3D models as static snapshots of the structural entries. Three-dimensional search queries, often representing pharmacophores derived from modeling studies, are composed of 3D structural templates, topological substructures, geometric objects (planes, lines, points, normal vectors, etc.), and geometric constraints (distances, angles, exclusion volumes). Searches are performed by comparing the pharmacophore geometries to values measured from the candidate models in the database.

Unfortunately, static snapshots of the models do not in general represent the flexibility inherent in real molecules. The failure of a query to match a stored conformation of a structure does not guarantee that the molecule cannot adopt an alternative low-energy conformation that can match the query. This has in fact been demonstrated by Haraki recently, using ChemDBS-3D.[9,27]

This paper describes a system developed for use with ISIS/3D and MACCS-II/3D[6] that performs a *conformationally flexible search* (CFS). This is an approach to 3D substructure searching that considers alternative conformations when matching a geometric query to 3D database structure entries.

The limitations inherent in static 3D searching have been recognized for many years, and a number of approaches have been suggested to address or minimize the problem:

Registration of Multiple, Representative Conformations. This method has been used as a least-effort approach and has been used most successfully with small databases and with relatively rigid structures. Its limitations are increased disk space requirements and longer search times. Also, the conformational space of a reasonably flexible molecule cannot be represented properly by a small number of conformations.

Representing Conformational Flexibility in Queries. Güner *et al.*[17] has demonstrated techniques for building queries that are more tolerant of flexible structures. Its limitation is that it is not applicable to all types of queries.

Conformational Analysis at Registration and Search Time. This is the approach used by ChemDBS-3D.[9] This approach is time consuming for both phases. Also, its coverage of the available conformational space is dependent on the dihedral angle increment used to generate conformations: a small increment will generate more conformations but greatly increases registration and searching times.

Distance Geometry. Clark *et al.*[18] demonstrated that the performance of query fitting by distance geometry is not competitive with other methods, such as torsional optimization (see below).

Torsional Optimization. This method involves turning (tweaking) rotatable bonds in the candidate to fit the constraints of the query, by means of an optimization in torsional space. This is the method adopted for use with ISIS/3D and MACCS-II/3D. In our opinion it represents the best compromise of resources, using commonly available computing hardware.

2. THE CFS PROCESS

Matching a geometric query to candidates in a database is a multistep process. For a given candidate, each successive step is more time consuming; it is expected, however, to be applied to correspondingly fewer candidates. Such an approach is not unusual in structure searching systems. The overall searching scheme is depicted in Figure 1.

2.1. Key Screening. The first step is a topological screening step, where substructures and atom types in the query are used to set keys. For this step MDL software uses 962 keys, arranged in an inverted format. It is especially useful for identifying functional groups and ring system screening in the query.

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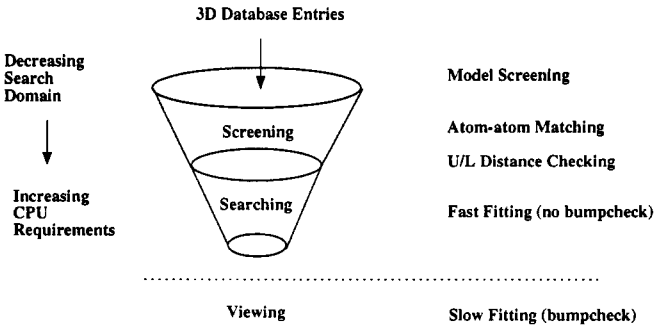

Figure 1. Approach to CFS, involving several steps. Models are screened using topological keys. An atom–atom matching step is next, and distance range calculations are made for some constraints. Finally, a torsional fitting of the candidate to the query is made, either with or without a bumpchecking term. During viewing, the procss is repeated for each hit, where the slow (bumpchecking) fitting is normally done. Throughout the process, steps requiring greater CPU requirements are performed on a correspondingly smaller number of candidates.

ISIS/3D and MACCS-II/3D databases also contain 3D key screens for static 3D search,[7] representing 20 000 atom/distance/angle combinations. This keying system is not used for CFS, since it assigns keys based on fixed distances and angles.

The authors also investigated the use of a 3D *range-based* key file. However, timing tests showed that only about 10% savings in overall search time was obtained. It was determined that range-based keying was redundant with other screening levels in the process (see below). For this reason the use of a range-based key file was abandoned pending further research.

2.2. Atom-by-Atom Match, Distance Range Calculation. The next step is the atom-by atom match of the query atoms and substructures and verification of the geometric constraints. As with static searching in MACCS-II/3D and ISIS/3D, geometric constraints are checked as soon as the component atoms are matched; a failure of the constraint causes backtracking in the atom matches. For distance constraints in CFS, a fast atom-pair distance range calculation is performed. Figure 2 illustrates the process. For each distance constraint, the shortest path between the component atoms (the most restricted path, or MRP), and the set of rotatable bonds between them, is determined. Then the reduced flexible path (RFP) is determined, by combining contiguous nonrotatable bonds into single nonrotatable vectors. The maximum of the distance range is calculated by assigning each rotatable bond to 180°. The minimum distance calculation is more complicated and involves a quick depth-first conformational search of the rotatable bonds in the RFP. This search is terminated if the atoms can come within the sum of their van der Waals radii. The entire calculation is sufficiently fast that the distance ranges can be calculated on the fly and need not be precalculated and stored in the database.

2.3. Torsional Optimization. For a geometric query with only one distance constraint, verifying that the constraint falls within the interatomic distance range of the matching atoms in the candidate is sufficient to assign the candidate as a hit. However, if two or more constraints are present in the query, it is necessary to verify that all constraints can be satisfied simultaneously in a single conformation.

After all atoms in the query are successfully matched, the rotatable bonds between the matched atoms are discovered. We define rotatable bonds as acyclic single bonds, except amide bonds and bonds between two unsaturated atom centers (e.g., single bonds in 1,3-butadiene, biphenyl, and benzaldehyde). This definition does not consider the flexibility of non-

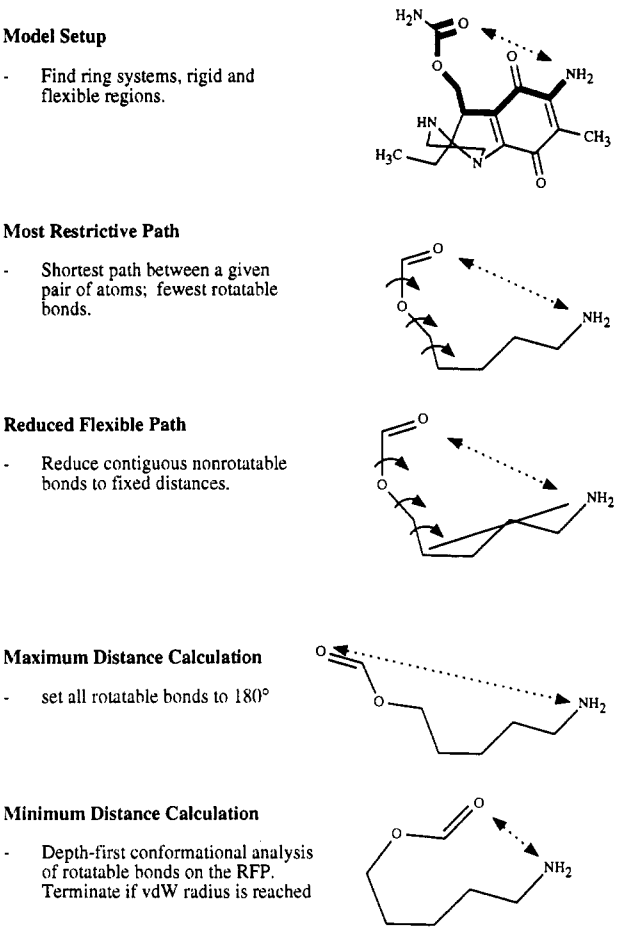

Figure 2. Upper/lower distance range calculation.

aromatic rings. Results included in this article were obtained by keeping all rings conformationally rigid during searching and browsing.

After identification of rotatable bonds, a torsional optimization is executed on the candidate model. In this process, the objective is to minimize the root mean square (RMS) deviation between the constraint values and the fitted-model measured values. This is formally an unconstrained nonlinear optimization. MACCS-II/3D and ISIS/3D use two methods of performing this optimization: a *search* of the space of available torsional angles, using a sequential simplex optimization, and a derivative-based optimization. If the optimization fails, search backtracking is used to find an alternative atom-by-atom match.

2.3.1. Sequential Simplex Optimization. The modified sequential simplex method of Nelder and Mead[19] is a nonderivative optimization technique. A standard implementation of the algorithm is used.[20,25] Optimization takes place in torsional space, while the RMS calculation takes place in the Cartesian space of the atomic coordinates. Initial parameters include a rotation increment (0.5 rad), mirroring factor (1.0), expansion factor (2.0), and contraction factor (0.5).

Optimization takes place in torsional space, while the objective function calculation (i.e. sum of RMS deviations) takes place in Cartesian space. It uses variable rotation increments to approach a minimum in the objective function (see below). For a wide variety of queries and models, this method converges in 10's to 100's of iterations.

The simplex method has the advantage of generality. The objective function need not be continuously differentiable, and the method is easily engineered to accommodate new

Table 1. Timing Tests of CFS, Compared with Static Geometric SSS[a]

query	static 3D SSS		CFS			
			without bumpcheck		with bumpcheck	
	hits	CPU	hits	CPU	hits	CPU
thromboxane synthetase inhibitor	71	2	n/a	n/a	153 (141)	15 (17)
antiarrhythmic	73	9	449 (442)	58 (45)	365 (408)	188 (135)
dopamine	10	1	141 (125)	8 (7)	116 (120)	30 (36)
antihistamine	208	13	556 (533)	45 (40)	463 (503)	162 (166)
ACE inhibitor	104	4	265 (258)	29 (27)	230 (244)	93 (92)
central nervous system	400	11	1903	235	1419	699

[a] The searches were performed over the Comprehensive Medicinal Chemistry database, release 92.1, consisting of 5374 models of pharmacological interest. The machine used was a DEC VAX 6610. CPU times are in seconds. Numbers of hits and CPU times for CFS are for simplex and derivative (in parentheses) fitters. The thromboxane synthetase inhibitor query was not subjected to nonbumpcheck fitting since it contains only a single distance constraint (see section 2.3).

$$P = \sum_i w_d |d_i^2 - d_0^2| \quad \text{Distances}$$

$$+ \sum_i w_{a3} |\cos(\theta)_i - \cos(\theta)_{0i}| \quad \text{Angles (3-point)}$$

$$+ \sum_i w_{a4} |\cos(\Omega)_i - \cos(\Omega)_{0i}| \quad \text{Dihedral Angles (4-point)}$$

$$+ \sum_i w_l (\mathrm{RMS}_{\text{line } i}) \quad \text{Line constraint}$$

$$+ \sum_i w_p (\mathrm{RMS}_{\text{plane } i}) \quad \text{Plane constraint}$$

$$+ \sum_i w_e (N_i) \quad \text{Exclusion Sphere (N= no. of atoms in sphere i)}$$

$$+ w_f (\mathrm{RMS}_{\text{fixed atoms}}) \quad \text{Fixed atoms}$$

$$+ \text{BumpCheck Penalty}$$

Figure 3. Objective function for the simplex torsional optimization technique.

$$P = \sum_i w_i (d-d_i)^2 + \sum_j w_j (\theta-\theta_j)^2 + \text{Bump Check Penalty}$$

(distances) (angles) (nonbonded interactions)

Figure 4. Objective function for the derivative torsional optimization technique.

types of constraints and evaluation functions. The simplex fitter can be used with queries containing any of the entire MACCS-II/3D and ISIS/3D constraint set.

2.3.2. Derivative-Based Optimization. For geometric queries containing only distances and angles, a potentially more efficient alternative to the simplex method exists: a derivative-based optimization.

The derivative-based fitter[26] uses a two-stage fitting process. In the first stage, the steepest descent method[21] is used to rapidly approach the neighborhood of the minimum. First derivatives (gradients) of the penalty function are evaluated analytically in torsional space by the use of chain rule:

$$\frac{dP}{d\Omega} = \frac{dP}{dx}\frac{dx}{d\Omega}$$

where dP/dx is the first derivative of the penalty function, P, with respect to an atomic Cartesian coordinate, x, and $dx/d\Omega$ describes the transformation between Cartesian and torsional coordinates.

Simplex Fitter:

$$\text{Bumpcheck Penalty} = \sum_m w_m \frac{r_{0,i} + r_{0,j}}{r_{i,j}}$$

Derivative Fitter:

$$\text{Bumpcheck Penalty} = \sum_m \left(a_{i,j} \frac{A_{i,j}}{r^{12}} + b_{i,j} \frac{B_{i,j}}{r^6} \right)$$

Where:

$w_{i,j}$, $a_{i,j}$, and $b_{i,j}$ are empirical scaling factors

$r_{0,i}$ is the default van der Waals radius of atom i

$r_{i,j}$ is the measured distance between atoms i and j

$A_{i,j}$ and $B_{i,j}$ are standard van der Waals constants

Figure 5. Nonbonded interactions (bumpchecking) in CFS.

When the gradient falls below a threshold, and the steepest descent method becomes inefficient, the BFGS method is used to complete the optimization.[22] This method utilizes first and second derivatives (gradients and Hessians) to accelerate the convergence and uses cubic interpolation to find the minimum in the direction of descent.

Since the input molecule is not likely to be situated in a local minimum with respect to a penalty function based on an external pharmacophore, no "tweak" of the bonds is performed by either the simplex or the derivative fitter.[23] In the case of the simplex fitter, a new initial simplex is formed at the last point, and a second pass is performed, if the first optimization fails.

2.3.3. Objective Function. Figure 3 describes the objective function for the simplex method, and Figure 4 shows the corresponding function for the derivative method. The objective function for the simplex fitter includes several more terms, reflecting its ability to handle a much richer set of geometric constraints. The weighting factors for the terms in the simplex method were derived empirically.

The torsional optimization can optionally include a term for nonbonded interactions. For display of fitted models, this term is required to avoid creating models with close atom contacts. For a proper compromise of efficiency and accuracy, a combination of close-contact ratio values and Lennard-Jones 6–12 potential values are used during the fitting process (Figure 5). The nonbonded interaction calculation is invoked by default at view time. It can optionally be invoked at search time, with considerable increase in CPU time for the search. In addition, hydrogen atoms and electron lone pairs can be

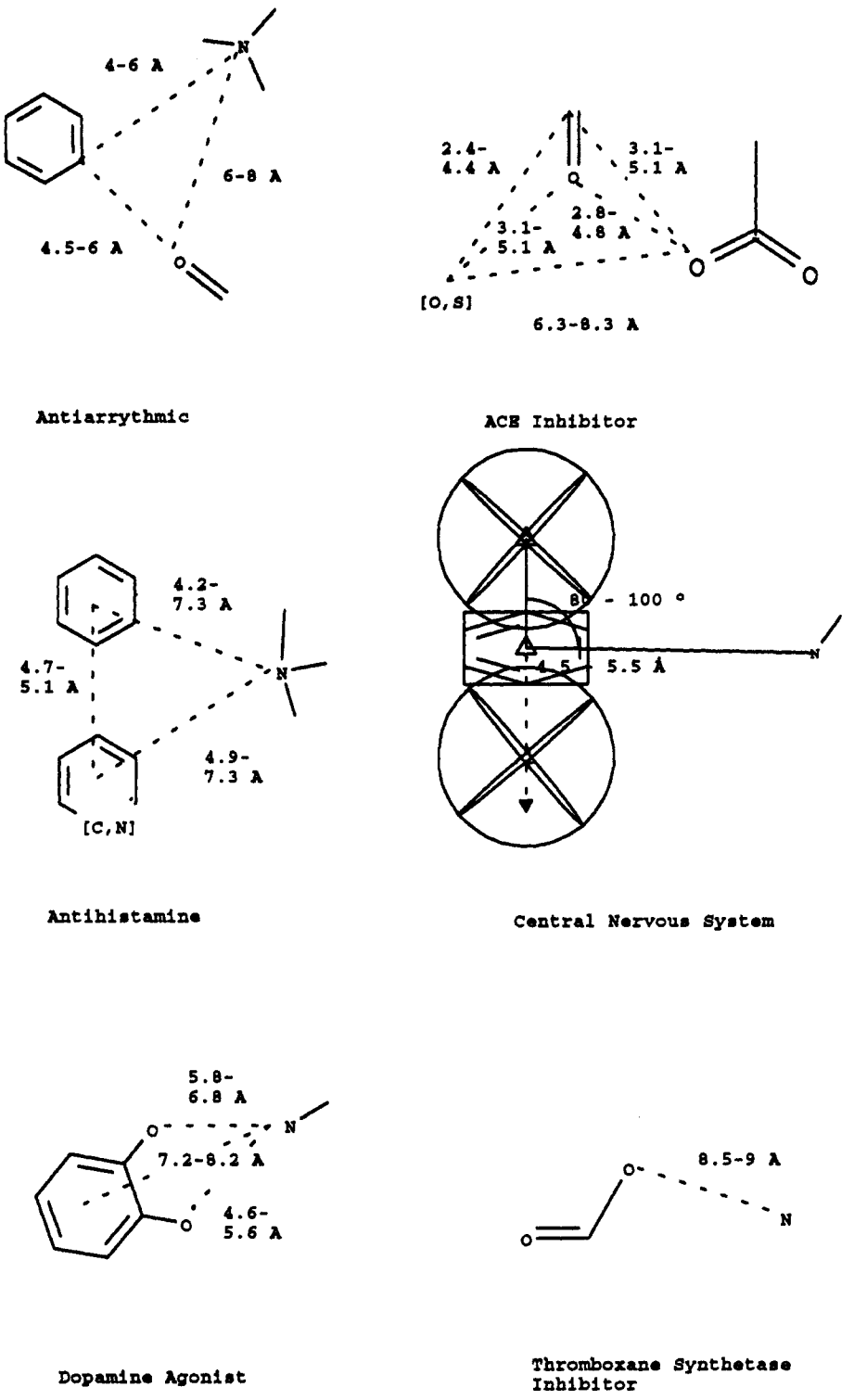

Figure 6. Graphical representation of queries used for performance measurements.

omitted from the calculation, included, or sprouted on atoms mapped in the query, or sprouted on all atoms in the structure.

3. PERFORMANCE MEASUREMENTS

3.1. Comparison with Static 3D Searching. Table 1 includes timing tests of database searches for a variety of queries. The tests were performed on a DEC VAX 6610 computer over the Comprehensive Medicinal Chemistry database (Revision 92.1) of 5374 models. The queries used are displayed graphically in Figure 6.

Search performance varies widely with the query. The search times for nonbumpcheck fitting takes 3–20 times as long as a comparable static 3D search, returning from 4 to 30 times as many hits. When the bumpcheck term is included, the CPU time again increases, up to 7 times as long as a nonbumpcheck fit, but up to 20% of the hits are lost. This loss is due to either close atom contacts in the fitted structure or to the optimization being trapped in a local minimum, preventing the fitter from finding a low-energy solution. In the case of the simplex fitter, if the fitting process fails, the torsional angles are perturbed and the fitting is restarted.

3.2. Comparison of Range Calculation vs Fitting: Maximizing Interactivity. In a typical user scenario, a query is constructed and CFS is invoked, resulting in a list of hits. The chemist then browses the hits one at a time. During this final viewing stage, the program retrieves the stored model from

Table 2. Comparison of Hits and Timings of Distance Range Calculations to Those from the Results of Bumpcheck and Nonbumpcheck Fittings[a]

	CFS			
	nonbumpcheck		bumpcheck	
query	hits, %	CPU, %	hits, %	CPU, %
thromboxane synthetase inhibitor	n/a	n/a	95	150
antiarrhythmic	87	175	71	569
dopamine	87	160	72	600
antihistamine	92	180	77	648
ACE inhibitor	96	132	83	420

[a] Hits and CPU are displayed as a percentage of the distance range values, where the distance range values are 100%. Data are based on searches of the Comprehensive Medicinal Chemistry database of 5374 models, run on a DEC VAX 6610. The simplex fitter was used.

the database, uses the current query, and re-executes the matching and fitting process. It is possible in ISIS/3D and MACCS-II/3D, however, to execute a more exhaustive analysis at the final viewing stage, rather than during the search time. How this is managed can have a large effect on the user's perception of interactivity.

Table 2 provides performance statistics for the different phases of the search. The searching times and hits were normalized to 100% for the combined atom–atom match and distance range verification. The table shows that in general a very high percentage (>85%) of hits that survive the range verification also survive a nonbumpcheck fitting but that the cost of the fitting is low, averaging an extra 60% in searching time.

For the case of a bumpcheck fitting, a smaller, but still large, percentage (80%) survive the fitting process. However, a much larger amount of time is necessary (4–6 times as long).

For the above user scenario, the time a chemist must wait for the program to respond is of two types: the time required for the search to complete, and the time required to view the next hit during browsing. A given operation (e.g. a bumpcheck fitting) must be executed many hundreds or thousands of times in the former case but only once in the latter case. To maximize the interactivity of the system, the best compromise would be to perform during searching only those operations required to verify that a correct conformer *could* be found, to a reasonable degree of confidence. The final building of the conformation via a bumpcheck fit could be left to the browsing (viewing) step, with the caveat that a small percentage would not survive the final fitting process. For that reason, ISIS/3D and MACCS-II/3D have default options set to perform only the range checking and/or nonbumpcheck fitting at search time, and optionally a full bumpcheck fitting at view time.

4. SORTING AND SEARCH CUTOFFS

The demand for conformationally flexible searching is based on the assumption that static geometric searching misses valid hits to 3D geometric queries. This assumption is correct: CFS typically returns five times as many hits as a static search. But in solving the missed hits problem, CFS introduces instead a new problem: *too many* hits for a chemist to browse or manage conveniently. For that reason, ISIS/3D and MACCS-II/3D include options for sorting hits or assigning cutoffs, based on data generated as part of the fitting process. These include the following.

RMS: The RMS Deviation of the Measured Values from the Fitted Structure, Relative to the Constraint Values. For interatomic distance and angle ranges, this is the deviation from the center of the range.

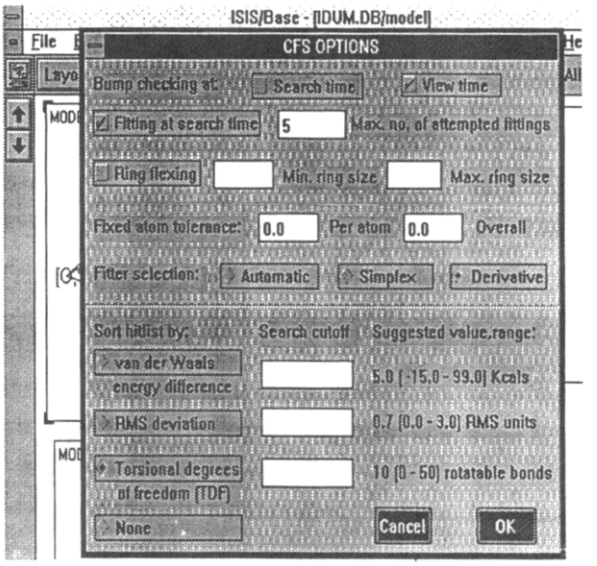

Figure 7. CFS options dialog box. This sets the fitting parameters for CFS, both for searching and for viewing.

vdW: Nonbonded-Interaction Penalty Function. The reported value is the difference in energy between the stored conformation and the fitted model. It is not a real energy function; for instance, only 1–5, and higher interactions are considered.

TDF: Torsional Degrees of Freedom. This is a count of the number of rotatable bonds used in the fitting. It measures the level of flexibility of the region of the molecule where the query matches. It is anticipated that a match to a rigid model, or a match to a rigid portion of a model, might be more interesting under some circumstances than a match on a very flexible structure.

5. USER INTERFACE

The ISIS and MACCS-II systems have been described previously.[24] Figure 7 shows the dialog box that appears when the CFS option is selected. It includes the user-accessible options for CFS; default values exist for all options; inexperienced users can click "OK" and immediately execute a search.

Inclusion of the bumpcheck term in the objective function can be optionally performed at either search or view time. For interactive use, bumpchecking is normally turned off at search time.

Fitting at search time can also be turned off; in that case only a distance-range check is performed at search time. However, the data in Table 2 indicate that for many queries the range check alone is a powerful indicator that the final bumpcheck fitting will be successful.

In order to avoid runaway search times, an option to limit the number of attempted mappings (and fittings) was included. This was to avoid the case where a few large and highly functionalized structures in the database would dominate the overall search time.

At the time of this writing, rings of all sizes are held rigid during the fitting process. Efforts to include ring perturbations are in progress and will be described in future papers.

The user can direct ISIS/3D to perform the fitting process with either the simplex or derivative fitters, or ISIS/3D can make the choice automatically, based on the types of constraints in the query. The derivative fitter is more efficient for full bumpcheck fittings; however, it can process queries

containing only distance and angle constraints. The simplex fitter is slower but is more general and can process queries containing any of the geometric constraints supported for static 3D searches.

The CFS dialog box includes options for sorting hit lists, or assigning search cutoffs, based on data returned from the fitting process. This includes sorting by van der Waals energy difference (the difference between the stored and fitted models), RMS deviation of measured values to constraint values, and torsional degrees of freedom. A list of ranges of suggested values is supplied as well.

6. CONCLUSIONS

Geometric 3D searches of static conformations of structures can be of great benefit but cannot retrieve flexible structures if the incorrect conformer is stored in the database. We have found that torsional optimization is a viable means of searching the conformational space of molecules as part of a database search and can often be fast enough to do so interactively.

It was found that range-based keys did not in general provide an adequate return in enhancing the searching speed of the program. Further, storage of a precalculated distance range matrix was not able to sufficiently increase the efficiency of the search to justify the support of the extra data file.

Two optimization techniques were found to be useful for CFS. A Nelder–Mead type simplex method is general and could be adapted to support all ISIS/3D and MACCS-II/3D objects and constraints. A derivative-based method is potentially more efficient but at this time is limited to distance and three-point angle constraints.

Using either fitter, nonbumpcheck fitting typically is several times slower than a comparable static geometric search, but returns several times as many hits. Inclusion of the bumpcheck term increases the time required again, around seven times as long as for a nonbumpcheck search. For interactive use, it is best to perform the search without the bumpcheck term but include the term for display of fitted structures; approximately 10–20% of the nonbumpcheck hits are expected to fail during viewing using the above scenario.

For management of large hit lists, ISIS/3D provides sorting and cutoff options for CFS-generated data: RMS fit-to-query, energy of nonbonded interactions, and torsional degrees of freedom.

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