We have been frustrated by the amount of time it takes to build a 3D model of a compound even with the most modern computer equipment. This frustration increases when we also want to apply to the model the information that we have gained from modelling previous members of the series or other compounds of similar structure and biological properties. At the time we started this project we had a Maccs database of all Abbott compounds and a state-of-the-art molecular graphics and modelling facility (Interact/CMD/Gramps). However, each new structure had to be built interactively from parts or templates previously entered. The objective of the work reported here was to increase the rate and reliability with which we could build a 3D structure of the active conformation of a molecule. Specifically we wanted to build a 3D model of the active conformation of compounds that was accurate enough to be used as a starting structure for a molecular or quantum mechanics minimizer. The other requirement for the system was that the expert could supply and modify the structures included and the rules to be applied to them without the involvement of a computer programmer. Aimm (Abbott intelligent molecular modeller) was developed to meet these goals. The heart of Aimm is Genie and the Genie control language, GCL. Substructure search targets are linear descriptions specified in Genie, of which Smiles is a subset. Atoms in the substructure can be specified to be exact matches, any atom, or of a particular user-defined type (hydrogen bond acceptor atom, for example). Bonds may also be specified by very flexible rules. Expressions and defined atom environments further expand the power of the specification of the search target. GCL processes an input structure and initiates actions based on the targets found within it. Typical actions might be to call a subroutine, to write to a file, or to print information to the screen. Because it is so simple to program in GCL, the expert system can be programmed by the expert directly. We have assembled the rigid compounds carefully modelled at Abbott and noted in them substructures to be used as templates for further use. Additionally, from our previous receptor mapping of dopaminergic and adrenergic agents we have assembled the templates to be used to build the active conformation of flexible compounds of this class. A structure enters Aimm as a Smiles string generated from Maccs MOL files or by hand. An identifier field carries the Abbott number or other information. Aimm uses GCL to recognize the parts for which it has structural information and then writes an Interact macro that contains the commands to display these parts and build the target molecule. The application of Aimm to dopaminergic aminotetralins and isoquinolines will be used as an illustration.

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Modelling of molecules and solvent access surfaces by means of quadric surfaces: an algorithm for shaded display

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Several methods for solid modelling of molecules are based on quadric surfaces. In CPK models the atoms are represented as spheres and the bonds as cylinders. Solvent access surfaces are formed by spherical patches and torical patches which can be approximated by hyperboloidal patches. Helix and β-sheets can be modelled respectively by cylinders and volumes limited by planes. Any usual geometric transformation (rotation, translation, symmetry, scaling, including perspective projection) applied to a quadric yields to another quadric. An algorithm for displaying shaded pictures of an object which is the union of volumes limited by a quadric surface and planes is used here. The use of quadric surfaces yields to second order equations which can be analytically solved. The algorithm does not require an explicit calculation of the intersections between the quadric surfaces and planes. Using coherence between two adjacent pixels, the amount of computations is drastically reduced. The computing time is roughly proportional to the number of the atoms.

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Struct — a triangulation algorithm to visualize molecular quantities

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It is very helpful for many problems in chemistry to visualize the 3D structure of a molecule in a way which allows the evaluation of strategies for further investigations of intramolecular rearrangements, substitution of molecular groups, or bimolecular reactions. The program system Struct generates molecular images on a Colour Raster Display unit with medium resolution (640 × 400, 512 × 512 pixel or similar). Struct is based on a fast algorithm which is designed for the use on high performance low cost graphical workstations. In a first step Struct generates the image of a 3D wire model indicating the chemical bonds and different atoms by different colours. This image can be manipulated interactively, it can be moved, zoomed and rotated in order to find the best viewpoint for a specific representation. The van der Waals 'surface' of the molecule can be drawn in the chosen projection in two different ways. The most common technique is to display the smoothed surface. A more sophisticated way is to construct a 'chicken wire' network by triangles. The triangles are based on an hexagonal topology on the surface of a sphere surrounding each atom in the distance of the van der Waals radius. This topology of the atomic surface points allows the generation of a closed molecular surface in a unique manner. The details of the surface generation and shading algorithm are published elsewhere[1-3]. Finally the shading of the triangles can be used to visualize different surface qualities. The colour reflects the value of the Coulomb potential affecting a positive charge moving along the van der Waals surface.