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Displaying 3D fields on raster devices

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A system is being implemented at the IBM UK Scientific Centre to display 3D fields. The system generates output intended for raster devices, both displays and printers.
System outline. At present the system deals only with potential fields, where a single scalar quantity is given at each point in space. The scalar quantities might represent electrostatic potentials, electron densities or even temperatures. The system is not aware of the physical meaning of the data. In the current implementation, the field is given as a set of sample values on a uniform rectangular grid. Fields can be represented using one or more of the methods described below. The system renders the requested images into a pixel array, and this can be displayed on the various raster devices at the Scientific Centre.
Equipotential surfaces. The system allows objects to be defined which have a surface corresponding to a given potential level of a given field. Equipotential surfaces are rendered in the same way as are geometrically defined objects, their surface colour and characteristics can be defined and they are lit similarly. The shading gives a strong impression of the 3D shape of the surface.
Density clouds. The most direct way to display a quantity such as an electron density is to render it directly as if it were a physical cloud of electrons. When generating a cloud, control can be exercised over its 'optical depth'. This is the distance that a light ray could travel through the densest part and influences the solidity of resulting shape.
Colour mapped field values. Field values are represented using colour. The system allows any surface to be coloured from the value of a field. This includes surfaces produced by geometric construction and those from contouring fields. The technique is best suited to cases when the field value is of most interest on a particular geometric surface, for example a van der Waals or solvent-accessible surface.
Field direction. Field direction is indicated using solid arrows. When rendered with hidden surfaces removed, the arrows give some indication of the direction of the field not only in the plane of the display, but also into and out of this plane. Arrows can be placed in a regular grid over the surface of any geometric object. As a further feature, each arrow can be considered as the start of a field line and further arrows added along this field line. The field lines are followed until a local maximum or minimum in the field is reached.

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Graphics computer-generated receptor mapping as a predictive tool for drug design

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Computer graphics technology has proven particularly useful in the determination of crystallographic structures and for theoretical mechanistic studies of the interaction between a substrate and a receptor of known or partially elucidated structure. On the other hand, when the receptor structure is totally unknown, the graphics computer has generally been used *a posteriori* to account for structure–activity relationships. *De novo* generated receptor maps have not yet been shown to be a *predictive* tool, probably for two reasons: (i) the method relies on the lock–key model for receptor–substrate interaction and generally neglects the receptor flexibility and the induced fit phenomenon; (ii) it is difficult to ensure that the substrates which are to be compared to perform the mapping actually bind at the same site. An example of where graphics computer-aided receptor mapping technology has led to the *a priori* design of highly optimized ligands is presented here. Our target was the putative 5-HT_{1A} receptor which has been recently characterized in the CNS using the specific radioligand [^{3}H]-8-hydroxy-*N*-di-n-propyl amino tetralin ([^{3}H]-8-OH-DPAT)[1]. A VAX 750/PS 300/Sybyl system was used. The starting point for the development of potent and selective *antagonist* ligands was the comparison of four structurally diverse antagonists having moderate affinities ($pIC_{50} < 7$) and no selectivity for the 5-HT_{1A} recognition site. Using this model, we have designed several original molecules structurally unrelated to the reference compounds; as predicted, all were highly active. For example, 8-[4-(1,4-benzodioxan-2-yl-methyl-amino) butyl]-8-azaspiro[4,5]decane-7,9-dione (MDL 72832) has nanomolar affinity ($pIC_{50} = 9.14$) for the 5-HT_{1A} binding site in rat frontal cortex. Moreover, were successfully predicted the stereochemistry of the interaction and optimized the selectivity of substrates. We have also compared several active 5-HT_{1A} receptor *agonists* to provide a steric map of the 5-HT_{1A} agonist site. The resultant pharmacophore differed significantly from the antagonist site map. It accounted for: (i) the affinity of all the agonists, (ii) the weak differentiation between *R* and *S* enantiomers of 8-OH-DPAT, (iii) the positive contribution of lipophilic substitution on the basic N atom of substrates, (iv) the positive contribution of the electronegativity or of the H acceptor properties of substituents in a precise region corresponding to the carbon 8 of 8-OH-DPAT, (v) the negative contribution of substitution in positions 5,6 or 7 of 8-OH-DPAT. Our study demonstrates that graphics computer-generated receptor maps can constitute a predictive tool which can help the chemist to design totally original molecules from different chemical classes with optimized affinity and selectivity for the target receptor.

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Simplified formulae for inter- and intramolecular interactions related with quantum theory

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The availability of simple analytical formulae for expressing the intermolecular interaction energies and/or the intramolecular conformational energies is essential for a number of applications. A possible way for deriving and/or improving such formulae consists in using the quantum theory of intermolecular interactions, and more specifically its perturbation–theory version[1]. In this framework, the interaction energy between two molecules may be expressed as a series of terms: 1st order, electrostatic and exchange (short-range repulsion) terms; 2nd order, induction and dispersion terms (2nd order exchange and higher-order terms are usually neglected). Then each term is expressed through some simplified expression, the essential idea being to introduce a sum of local contributions, namely elementary interactions between sites (atoms and/or bonds), expressed in terms of suitable molecular properties[2,3]. Thus, the electrostatic term is obtained as a sum of interactions between molecular charge distributions represented by sets of multipoles (charges, dipoles, quadrupoles) located at the atoms and the middles of the bonds. The (long-range) induction terms are obtained from the electric fields created by these same multipoles and from bond and/or atom polarizabilities. The (long-range) dispersion term is expressed as a sum of atom–atom terms $-(C_6/R^6 + C_8/R^8 + C_{10}/R^{10})$ and the short-range repulsion term as a sum of atom–atom or bond–bond terms (with exponential dependence with respect to interatomic distances). Recently an explicit charge-transfer term (corresponding to the short-range behaviour of the induction energy) has been introduced: it involves atom–atom terms with *nonisotropic* behaviour, i.e. with a dependence upon the orientation of the bonds pertaining to the atoms under consideration. The elaboration of simplified formulae (such as those used in molecular mechanics) from basic quantum theory, for the intramolecular (conformational) energy, and more precisely its dependence upon the torsional angles (with bond lengths and valence angles kept fixed) is much less advanced that it is for intermolecular interactions. It is tempting to use formulae of the intermolecular type for evaluating intramolecular interaction terms between nonbonded atoms, and we did so in our recently proposed procedure SIBFA (Sum of Interactions Between Fragments computed *ab initio*)[4]. Noticeably, the evaluation of the short-range repulsion is refined by introducing, besides the genuine chemical bonds, fictitious bonds associated with the lone-pairs. The results obtained so far are encouraging.

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Computer graphics applications of electron deformation densities and electrostatic potentials in coordination chemistry

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Computer programs have been developed in order to display on a raster scan device electron deformation densities (EDD) and electrostatic potentials (EP), both as 2D colour-filled contour maps and as coloured 3D solid models. In the latter case, we represent isovalue surfaces obtained from a triangulation algorithm based on the connection of contours lying in successive planes are given. The combined use of these molecular properties calculated by the multiple scattering Xα quantum chemical model and such graphics is expected to be of value in rationalizing and interpreting the reactivity of coordination and organometallic compounds. Indeed, several important reaction mechanisms of inorganic chemistry, such as ligand substitution or rearrangement, proceed generally by nucleophilic (or electrophilic) attack and may therefore be described in first approximation by simple arguments based on the EDD or EP of model compounds. As an example the case of $[Cr(O_2)_4]^{3-}$, $[Mo(O_2)_4]^{2-}$ and $[Nb(O_2)_4]^{3-}$ complexes are discussed in an attempt to understand the differences in metal–ligand bonding and chemical behaviour exhibited by parent metal dioxygen complexes. Investigations by the authors, which reveal that the main features of EDD and EP maps are strongly correlated, provide a simple interpretation of the unique catalytic properties of Mo(VI) dioxygen complexes for the epoxidation of alkenes.

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A new approach of drug design based on the determination of a minimum set of common parameters in terms of molecular surface electrostatic potentials for compounds with the same therapeutic activities: case of neuroactive agents

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It has been shown[1,2] that molecular electrostatic potentials can be considered as a reactivity index in terms of quantum mechanics. The main idea is that the recognition step can be described in a fixed nuclei modelization and is essentially determined by two factors: the molecular surfaces and the molecular electrostatic potentials on these surfaces. These entities must form complementary pairs, if their interaction is to lead to the formation of a stable or a metastable complex. The structures of the drug receptors are rarely known, while lots of molecules with the same therapeutic activity are perfectly defined. This common activity indicates that these drugs probably act on the same biological receptors; from the concept previously defined, these molecules must present some identical parameters characteristic of the molecular electrostatic potential. The determination[4] and the analysis of such parameters on tricyclic neuroleptic and antidepressant drugs (41