

# Qualitative Mathematical Concepts, Models and Theories for Computer Assistance in Chemistry

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MORE than 100 years ago Cayley<sup>1,2</sup> introduced the graph theoretical representation and interpretation of the chemical constitution of molecules. This is probably the first qualitative representation of chemistry by mathematics. Meanwhile qualitative mathematical concepts and theories are widely used in chemistry to represent, classify and enumerate molecular systems and their interconversions<sup>3,4</sup>.

In this article a qualitative mathematical approach to chemistry is presented that enables to develop new types of computer programs for the solution of chemical problems<sup>5</sup>. These programs are capable of solving problems whose 'unknown' is a molecular system or a chemical reaction. Since these programs do not rely on detailed empirical data, their results include unprecedented chemistry<sup>6</sup>.

Since three decades computers are applied to chemistry in wide variety of ways that may be classified into the general categories of storage and retrieval of data, numerical computations and problem solving<sup>7</sup>. The many types of chemical documentation, *i.e.* documentation of structures, reactions and properties of the molecular systems as well as the programs that collect experimental data from instruments, but in essence, also the reaction library based synthesis design programs<sup>8</sup>, belong to the storage and retrieval category of computer programs. Some of these programs may include substantial manipulation of data, however their centerpiece is a data base. Numerical computations are of paramount importance to chemistry<sup>9</sup>. Chemical analysis, structure determination by molecular spectroscopy, reaction kinetics, data analysis by statistical methods and pattern recognition, and above all, quantum chemistry are some of the major fields where numerical computations with the aid of computers are utterly indispensable<sup>10</sup>. The third category of computer applications in chemistry is computer assistance in the solution of chemical problems whose 'unknowns' are molecular systems or chemical reactions. Qualitative mathematical theories and models play an important role in the computer assisted solution of such problems<sup>6</sup>. The first system of computer programs in this category was the DENDRAL project, an artificial intelligence type system of programs for the determination of molecular structures from spectroscopic data, *e.g.* MS. A graph theoretical approach to molecular structures is the qualitative mathematical foundation of the DENDRAL system<sup>11</sup>.

## DU-model :

In 1973, Dugundji and Ugi<sup>12</sup> introduced an algebraic representation of the logical structure of constitutional chemistry. It is a global qualitative mathematical model of constitutional chemistry that was designed to provide a general formalistic framework for computer assistance in the solution of chemical problems. This model, the 'DU-model'<sup>12</sup> relies on the extension of isomerism from molecules to ensembles of molecules (EM); its main object is the family of isomeric EM (FIEM), and the imbedding of molecular systems and their reactions within the FIEM.

An FIEM(A), the FIEM of a given collection A of atoms, is the set of all EM that can conceivably be made from the atoms belonging to A, when each atom is used precisely once. One could also say that FIEM(A) consists of all conceivable EM with the empirical formula A. Since A can be any collection of atoms, a theory of the FIEM(A) covers all of chemistry<sup>12</sup>.

Within the framework of the DU-model the EM at the beginning and at the end of a chemical reaction  $EM(B) \rightarrow EM(E)$  are represented by their  $n \times n$  symmetric BE-matrices (bond and electron matrices),  $B = \langle b_{ij} = b_{ji} \rangle$  and  $E = \langle e_{ij} = e_{ji} \rangle$ . In B and E the rows/columns are assigned to the cores of the atoms belonging to the underlying collection A of n atoms. The off-diagonal entries  $b_{ij}$  and  $e_{ij}$  ( $i \neq j$ ) indicate the formal bond orders of the covalent bonds between the atoms  $A_i$  and  $A_j$ , and the diagonal entries  $b_{ii}$  and  $e_{ii}$  are the numbers of lone valence electrons at the atoms  $A_i$ . Since the n atoms in A can be indexed in up to  $n!$  distinct ways, there exist up to  $n!$  equivalent representations by  $n \times n$  BE-matrices for an EM of n atoms. Any two BE-matrices B and B' represent the same EM, if they differ only by a row/column permutation that corresponds to a permutation of the atomic indices<sup>14</sup>. When this permutation of the atomic indices is represented by an  $n \times n$  permutation matrix P, we have

$$B = P \cdot B' \cdot P^{-1} = P \cdot B' \cdot P^t.$$

For documentation purposes one of these is selected to be the canonical representation. The algorithm CANON<sup>15</sup> is particularly suitable for the assignment of canonical indices to the atoms in molecular structures and to thus establish the canonical BE-matrix.

In contrast to the Morgan algorithm<sup>16</sup>, CANON does not rely primarily on the graph of a chemical

formula, but it considers the graph and the chemical nature of the atoms at the same time and with equal emphasis. Thus CANON recognises automatically constitutionally equivalent atoms. Accordingly, it generates an indexing that is also well-suited for stereochemical nomenclature and documentation<sup>18</sup>. Since five years the CAS is testing CANON for its use in large scale chemical documentation. A chemical reaction  $EM(B) \rightarrow EM(E)$  is represented by an additive transformation  $B \rightarrow E$  of the BE-matrices according to



The  $n \times n$  symmetric matrix  $R = \langle r_{ij} = r_{ji} \rangle$  is a so-called reaction matrix that represents the redistribution of the valence electrons during the reaction  $EM(B) \rightarrow EM(E)$ . The off-diagonal integer entries  $r_{ij}$  ( $i \neq j$ ) of  $R$  indicate the bonds which are broken ( $r_{ij} < 0$ ), and made ( $r_{ij} > 0$ ); the diagonal entries  $r_{ii}$  describe changes in the placement of the lone valence electrons.

A reaction matrix  $R$  can be decomposed into its components  $R_k$  according to

$$R = R_1 + \dots + R_k + \dots + R_r.$$

These components may be chosen to represent the basis elements of  $R$  that represent the elementary mechanistic steps of the reaction that is given by  $R$ <sup>18</sup>. A reaction matrix  $R$  may also represent a sequence of chemical reactions, e.g. a multistep syntheses; then the components  $R_k$  may be chosen to represent the individual chemical reactions in the sequence.

The solutions of the fundamental equation of the DU-model are subject to two types of constraints: the mathematical fitting conditions and the valence chemical boundary conditions<sup>18</sup>. Since there exists a mapping of  $n \times n$  matrices onto points or vectors in  $|R^{n^2}$ , an  $n^2$  dimensional euclidean space, an FIEM may be represented by a lattice of points in  $|R^{n^2}$  that correspond to the BE matrices of the isomeric  $EM$ <sup>18</sup>. The chemical reactions that interconvert an  $EM$  correspond then to vectors between the respective points. The  $L_1$ -distance  $d(B,E)$  between two so-called BE-points  $P(B)$  and  $P(E)$  of  $EM(B)$  and  $EM(E)$  is called the chemical distance, because

$$d(B,E) = \sum_{i,j} |b_{ij} - e_{ij}| = \sum_{i,j} |r_{ij}|$$

is (twice) the number of valence electrons that is shifted during the reaction  $EM(B) \rightarrow EM(E)$ . With a given assignment of the atomic indices in  $EM(B)$  the chemical distance  $d(B,E)$  depends on the indexing of the atoms in  $EM(E)$ . According to

$$B + R(P) = PEP^t$$

the reaction matrix  $R(P)$  depends on the permutation matrix  $P$ , and so does the value of  $d(B,PEP^t)$ <sup>12,14</sup>. The minimum of the chemical distance  $\min d(B,PEP^t)$  corresponds to an atom-by-atom bijection with the maximum set of maximum common subgraphs in the formulas of  $EM(B)$  and  $EM(E)$ <sup>14,19,20</sup>.

#### Application of DU-theory :

The DU-model leads to a great variety of applications in computer assisted chemistry.

In the oil industry there are two important types of technical activity: exploration and oil drilling. Computer assistance in chemistry and quantum chemical calculations are in a similar relation. Exploration with the aid of global and detailed maps, satellites and air-planes, navigation aids and geodetic devices corresponds to computer assisted use of qualitative mathematical theories of chemistry, whereas after the deposit has been thus located, drilling for oil, is like doing quantum chemical computations, after the determination of the 'local' individual molecular structure by chemical reasoning or computer assisted search for the system to be treated by quantum chemical methods.

The CANONICAL BE-matrices serve well in the documentation of chemical structures. An indexing of the atoms in a chemical constitution according to the algorithm CANON is not only useful for constitutional documentation, but may also be used with advantage in stereochemistry, because CANON takes automatically into account the constitutional symmetries of molecules<sup>18</sup>.

A computer program CORREL<sup>22</sup> has been implemented for the analysis and correlation of substructures. Its approach to the substructure problem is based on BE-matrices and a network of father-son relations between substructures. Computer programs for screening lists of chemicals for structural analogs of toxic compounds, and a computer program for the bilateral design of syntheses<sup>21</sup> have evolved from the algorithms and concepts of CORREL.

The concept of chemical distance is part of the DU-theory. It seems reasonable that in general the preferred course of a chemical reaction  $EM(B) \rightarrow EM(E)$  involves the redistribution of a minimum number of valence electrons, i.e. the atoms of  $EM(B)$  and  $EM(E)$  are correlated in such a manner that the formulas of  $EM(B)$  and  $EM(E)$  have in common the largest set of largest substructures. This is the content of the principle of minimal chemical distance (PMCD)<sup>14,19,20</sup>. The PMCD has many applications in chemistry. It is a quantitative measure of chemical similarity and may thus be used in the comparison of molecular systems. The quality of multistep syntheses may be judged by their chemical distances. The elucidation of reaction mechanisms and biosynthetic pathways, as well as the systematic documentation of chemical reactions can take advantage of this approach. The hierarchic classification and rational documentation of chemical reactions is hardly possible without the PMCD, because the unambiguous description of a chemical reaction must comprise a mapping of the educts onto the products and some statement on the underlying pattern of electron redistribution<sup>18</sup>. Our first computer program PMCD for the determination of MCD relied on the assumption that in most relevant

cases the MCD coincides with the minimum of the euclidean distance  $D(B,E)$  between  $P(B)$  and  $P(E)$ <sup>19</sup>.

$$D(B,E) = \sqrt{\sum_{i,j} (b_{ij} - e_{ij})^2}$$

The minimum of  $D(B,E)$  corresponds to the maximum of the scalar product of  $B$  and  $PEP^t$ . Within the framework of the PMCD this maximum is determined by a branch and bound type algorithm<sup>14,19</sup>.

In the meantime a new approach has been taken to the MCD problem. A computer program PEMCD (program for the exact MCD) has been implemented<sup>20</sup>. This program combines the chemical and mathematical aspects of the problem to find the maximum set of maximum common subgraphs in the formulas of  $EM(B)$  and  $EM(E)$ . A hierarchic documentation system for chemical reactions has been developed<sup>13,23</sup>. In this system chemical reactions are classified by MCD, the corresponding minimal reaction matrices in irreducible canonical form<sup>24</sup>, by the chemical elements of their core of the reaction, and the invariant part of the reacting EM.

There exist three categories of solutions to the fundamental equation,  $B+R=E$ . (i) With one given BE-matrix, say  $B$ , those R-matrices are generated which fit mathematically  $B$ , and whose results  $E$  comply with the valence chemical boundary conditions. (ii) With two given BE-matrices,  $B$  and  $E$ , one looks for those R-matrices that are in accordance with certain selection rules, e.g. the PMCD, or some preferred combination of basis elements. (iii) With a given R-matrix the pairs  $(B, E)$  are determined that follow  $B+R=E$  under its constraints. This classification of the solutions of the fundamental equation corresponds to a classification of the chemical problems that can be solved with the aid of computer programs on the basis of the DU-model<sup>5</sup>. The computer programs for the retrosynthetic design of syntheses, e.g. the feasibility study CICLOPS<sup>25</sup>, its offspring EROS<sup>26</sup> and ASSOR<sup>27</sup> belong to category (i), as well as the prediction of the products that are conceivably formed from given educt, and also simulation of mass spectra that arise from fragmentation of a given parent ion<sup>28</sup>. The problems that are solved with the aid of the PMCD, including the documentation of chemical reactions and the bilateral design of syntheses correspond to category (ii)<sup>21</sup>. Computer assisted discovery of unprecedented structures and reactions is an application of category (iii)<sup>6</sup>.

#### *Stereochemistry and theory of the chemical identity group :*

There exists a hierarchy of structural features by which molecules can be classified. Molecules with the same empirical formula are the isomers. The constitutional isomers differ by their chemical constitution. Distinct molecules with the same chemical constitution are stereoisomers<sup>29</sup>. Thus the chemical constitution of a molecule is its

primary structure, whereas its stereochemical features are its 'fine structure'.

The algebra of the BE- and R-matrices and the associated computer programs cover the constitutional aspect of chemistry. The qualitative mathematical treatment of the stereochemical aspect calls for a different kind of approach<sup>17</sup>. The purely geometry oriented concepts and theories of classical stereochemistry have serious shortcomings, because molecules are generally not adequately represented by rigid geometric models. Elementary geometry does not even suffice to interpret the essential properties of rigid molecular objects like the asymmetric carbon atom<sup>31</sup>. A general qualitative theoretical treatment of stereochemistry requires more abstract ideas and models than those of classical stereochemistry<sup>17</sup>.

In 1970 permutational isomerism was defined and the relations of permutational isomerism to other types of isomerism were clarified<sup>32</sup>. Since then permutational isomerism has become a standard notion, and it is now an indispensable part of chemical terminology<sup>17,33</sup>. The permutational treatment of molecules requires their conceptual dissection into a skeleton and a set of ligands. When more than one mode of dissection is conceivable, the one that suits best the given problem<sup>34</sup> is chosen. The skeleton can be rigid or non-rigid, and no precise geometry, or symmetry needs be defined. Thus rigid and flexible molecules can both be treated uniformly. According to earlier procedures, the ligand carrying sites of the skeleton are indexed, and these skeletal indices are also given to the ligands in a reference isomer<sup>32,35</sup>. In a more modern treatment no double indexing is used. The ligands are indexed according to their chemical nature by the CIP rules<sup>35</sup> or the algorithm CANON<sup>15,18</sup>, while the skeletal sites are left unindexed<sup>17,37,38</sup>. Although they may differ greatly in shape, and are representable by different geometric models, any two molecules that belong to the same pure chemical compound are said to be chemically identical, they are spontaneously interconverted under given observation conditions. In chemistry the most fundamental observable property of molecules is their chemical identity. Since the chemical identity of a molecule comprises its chemistry as well as the union of all of its geometries, it is well-suited to be the central issue of a general theory of stereochemistry.

In a recent monograph<sup>17</sup> a general theoretical treatment of stereochemistry is described, with chemical identity as the unifying element. When a molecule of given compound is treated by this theory, first, its set of ligands  $L$  is identified and its family of permutation isomers is established. By the family  $J_x(L)$  of  $X$  relative to  $L$  is meant the set of all distinct isomers that can be obtained from  $X$  by permutation of the ligands on the skeleton. Within this family one of the permutation isomers, say  $X$ , is chosen to be the reference isomer. Let us select one molecular individual from compound  $X$

as a characteristic model E and define its skeleton and ligands. This characteristic model is called the reference model. We assume that E has  $n$  ligands that are all chemically distinguishable from one another. Each permutation of the ligands gives a molecule representing some chemical compound, not necessarily X. The chemical identity group of X is determined by those permutations of the ligands of E that do in fact represent a molecule of the chemical compound X. These permutations form a group  $S_x$ , the chemical identity group of X. It is a subgroup of  $Sym L$ , the symmetric group on  $|L|$  objects. The distinct permutation isomers of X are represented by the left cosets of  $S_x$  in  $Sym L$ . A great variety of stereochemical problems can be solved by an analysis of the imbedding of the chemical identity groups in their  $Sym L$ .

Note that we are relying on the unambiguous definition of chemical identity, rather than on any purely geometric concept, such as skeletal symmetry. In fact, for molecules with chemically distinct ligands, the ligand interactions always cause the skeletons to deviate from their idealised geometries, and there is no such thing as an approximate symmetry. Thus a chemical identity preserving ligand permutation does not necessarily bring a skeleton into self-coincidence, as is required in the conventional representation of skeletal point group symmetries and dynamic symmetries by permutations of skeletal sites of idealised ligands<sup>8,9</sup>.

The main mathematical objects of the theory of the chemical identity group that are useful for stereochemistry are the subgroups and normalisers of  $S_x$  in  $Sym L$ , the Dieter group which represents the chemical identity of a complete ensemble of inter-converting permutation isomers, and the various types of mappings between the partitions and coverings of  $Sym L$  including the diverse set-valued mappings of the coset spaces of  $S_x$  in  $Sym L$ <sup>17,38,40</sup>. These mathematical entities and structures may be used for the classification and enumeration of molecular systems and their interactions as well as conformational analysis. They may also serve to follow pathways of stereochemical transformations, and to generate graphs that represent isomerisations according to a given mechanism or mode.

Since computer programs for the mathematical operations that belong to the theory of the chemical identity groups are easy to implement, this theory will enhance computer assistance in stereochemistry.

#### Conclusion :

The algebra of the BE- and R-matrices and the theory of the chemical identity group represent together the essential aspects of the logical structure of chemistry. This qualitative mathematical approach to chemistry has already led to a variety of mathematically based computer programs for the solution of chemical problems. It is foreseeable that in the future most computer programs for chemistry will rely to a varying degree on these

and other qualitative mathematical ideas, theories and formalisms, even the programs that are essentially information based, because the advantages of a mathematical approach will become more and more obvious in the whole field of computer chemistry.

Such quantitative mathematical models do not only have advantages for the design of chemistry oriented algorithms. Since they are associated with many new concepts and logical methods, qualitative mathematical models of the logical structure of chemistry will become more and more a natural ingredient of chemical reasoning. Some such notions are already in use, like constitutional symmetry<sup>15</sup>, basis reaction<sup>6</sup> and constitutional equivalency<sup>16,17</sup> permutational isomerism<sup>17</sup>, chemical chirality (in contrast to geometric chirality), chiral genus and its use to define asymmetric induction<sup>41</sup>; more will follow as mathematics proceeds to penetrate chemistry.

#### Acknowledgement

The financial support of our work by Deutsche Forschungsgemeinschaft und Fonds der chemischen Industrie is gratefully acknowledged.

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