Discrete Mathematical Chemistry: Social Aspects of its Emergence and Reception

Guillermo Restrepo and José L. Villaveces

Abstract: We first show some successes of discrete mathematical chemistry (DMC), a branch of theoretical chemistry born in the 1960s and 1970s. Then we explore the social context in which the emergence of DMC took place, initiated mainly in East European countries. The availability of knowledge, especially of mathematical knowledge, and the lack of research funds were the main conditions that helped get DMC started. We also explore the reception of DMC in the chemical and mathematical circles, being flat rejection in chemistry and slow acceptance in mathematics. Finally, we discuss some definitions of the subject and propose a new one stating that mathematical chemistry is the realization of mathematical thinking in chemistry, understood as functional thinking defined by Felix Klein in the Erlangen Program.

Keywords: *discrete mathematical chemistry, social aspects, emergence, reception, definition*.

> *The perfection of chemistry might be secured and hastened by the training of the minds of chemists in the mathematical spirit [...]. Besides that mathematical study is the necessary foundation of all positive science, it has a special use in chemistry in disciplining the mind to a wise severity in the conduct of analysis: and daily observation shows the evil effects of its absence.*
> (Auguste Comte, 1858, p. 257)

1. Introduction

Currently, based solely on the molecular structure of a chemical substance, it is possible to estimate its environmental impact or its toxicity upon different targets, even when the chemical has not yet been synthesized (Restrepo & Basak 2011). Molecular properties, such as chirality and aromaticity have been addressed with mathematical support (Ruch *et al*. 1970, Ruch 1972, Randić 2003). Unknown substances, such as novel carbon allotropes, have

HYLE – International Journal for Philosophy of Chemistry, Vol. 19 (2013), No. 1, 19-33.

been predicted, along with several of their properties (Balaban *et al*. 1994), and later on have been synthesized. These kinds of predictions have been accomplished by using a novel kind of theoretical chemistry known as Discrete Mathematical Chemistry (DMC).

The formalization of chemical knowledge through discrete mathematical theories is part of DMC's aim. Examples of this sort are the theoretical grounds developed for stereochemistry (Ruch *et al*. 1966, 1967), the mathematical formalization of the chemical concept of chemical structure (Randić 1990), and the interpretation of the periodic law as a topological space (Restrepo *et al*. 2004, Leal *et al*. 2012).

Determining the number of isomers of a given molecular formula, or the number of possible molecular structures as the outcome of a chemical reaction, are traditional questions in chemistry that can be addressed by the assistance of discrete mathematics (Pólya & Read 1987). Mathematics has also been used for predicting synthetic pathways and it is of great help in designing total synthesis (Doemling 2007).

Classification, utterly important for chemistry, as exemplified in the periodic table, in the notion of functional group, and in the Lavoisian nomenclature system (Restrepo & Villaveces 2011), has been addressed by DMC too. Currently, large chemical databases are screened in short time thanks to the advances in chemical similarity, a fundamental part of the chemical classificatory systems. The current IUPAC nomenclature has several instances of application of graph theory as a tool to name substances (Goodson 1980a, 1980b, Panico *et al*. 1993).

The advent of chemometrics and chemo-informatics has allowed making much more sense of the wealth of experimental chemical information. Important algorithms resulting from a combination of chemical with mathematical knowledge are behind the elucidation of spectra and the characterization of molecular fragments in mass spectrometry, to name but a few applications of chemo-mathematical knowledge (Gasteiger 2003).

There are several other successes of DMC, *e.g.* in biochemistry (Randić *et al*. 2000), proteomics (Guo *et al*. 2001), thermodynamics (Ruch 1975), which are worth mentioning, but whose discussion is out of the scope of this paper.[1] To try to show the details of DMC in a single and comprehensive paper, *i.e.* its methods and methodologies, is something difficult to attain due to the different specializations the field has gained. However, trying to trace back the social reasons that have shaped the emergence of this new kind of theoretical chemistry, its reception, and even trying a working definition of the subject, is something we can afford in the current paper.

Before discussing DMC, it is important to define discrete mathematics. A typical definition of the subject, by telling what it is not (Hopkins 2008), is that discrete mathematics studies mathematical structures different to con-

tinuous ones, *e.g.* real numbers that vary 'smoothly'. Hence, objects such as integers, graphs, and statements in logic, which have distinct, separated values, are objects of study in discrete mathematics (Johnsonbaugh 2008). Normally, the objects of interest in discrete mathematics are those that can be enumerated by integers; this is why discrete mathematics has been characterized as the branch of mathematics dealing with countable sets.[2] However, there is no exact, universally agreed, definition of the term 'discrete mathematics'.

Research in discrete mathematics increased in the latter half of the 20th century partly due to the development of digital computers operating in discrete steps and storing data in discrete bits (Rosen 2000). Topics of discrete mathematics include theoretical computer science, group theory, information theory, formal logic, set theory, combinatorics, graph theory, probability, number theory, algebra, calculus of finite differences, geometry, topology, game theory, decision theory, utility theory, and social choice theory (Rosen 2000).

2. Conditions for the emergence of Discrete Mathematical Chemistry

By the 1970s, theoretical chemistry was making true Charles A. Coulson's warning of a generation of theoretical chemists focusing merely on calculating accurate numbers and energy values, leaving aside the development of chemical concepts (Coulson 1960). The quantum chemistry of those days started to demand computational power to solve its involved equations; therefore, the access to computers was a limiting factor to be active in the field. Several of those theoretical chemists[3] could not attain the computational power and started to look for alternatives to do theoretical chemistry.[4]

Discrete mathematics, particularly graph theory, was the kind of mathematics used in the novel perspective on theoretical chemistry. As most theoreticians grew up as quantum chemists, graph theory was initially applied to address quantum chemical questions such as the resonance phenomenon by using electronic circuits and paths on molecular structures or the Hückel molecular orbital theory. Studies of this sort soon revived new questions, not considered by quantum chemists, as the issue of calculating the number of possible molecules under some conditions, something that Arthur Cayley, a mathematician, had started in the 19th century (Cayley 1857, 1875). Afterwards, these 20th-century chemists addressed other subjects at the core of chemistry, such as the estimation of macroscopic properties of substances. Here, methods based upon the mathematical description of the molecular

structure were applied, which is currently one of the most prolific subjects in the field.

Several of these theoreticians were from Eastern Europe, which makes one ponder on why particularly in this region theoretical chemistry focused on mathematics. A first explanation is given by Alexandru T. Balaban, a leading discrete mathematical chemist from Romania, who claims that the lack of resources for experimental research in those countries was one of the reasons (Balaban 1993). A sharp explanation is given by another figure in the field, Danail Bonchev (Bulgaria), who says that in Bulgaria of the 1970s, „the initial enthusiasm about quantum chemistry soon had to face the hard reality of making science in a small East-block [sic] country lacking the big computers of the leading Western countries" (Bonchev 2005). This shows how, for example, Bonchev wanted to do quantum chemistry but the lack of computers to perform the needed calculations was a limiting factor. Haruo Hosoya, one of the first discrete mathematical chemists of Japan, in spite of living in a country experiencing a rapid economic growth, had to face the lack of resources. As he states: „I was thinking and thinking what can be done for a lonely wolf in a poor university" (Hosoya 2002).

Hence, the lack of funds for research in Eastern Bloc countries and elsewhere did not allow them to be in tune with the theoretical chemistry of economically more developed countries like the USA, mainly devoted to quantum chemical computations using expensive computers. However, this was not a problem just of East European countries; there were several other parts of the globe facing similar situations. Then, why did discrete mathematical chemistry arise in East Europe and not in other parts of the world? We claim that two main requirements were needed to develop DMC: knowledge and lack of research funding. Knowledge in chemistry and mathematics was important. Eastern bloc countries had a strong tradition in mathematical training, strengthened also by the Soviet influence after the Second World War (Wotiz 1973).[5] These countries, in spite of not having access to up-to-date chemical instruments and computers, had updated scientific literature (Wotiz 1973), an important aspect for knowledge generation. Hence, it seems that an early training in mathematics (in high school and later on in chemistry studies), in combination with lack of funds for research, were the ingredients to develop DMC.

3. The reception of mathematical chemistry

3.1. Reception in chemistry and mathematics

3.1.1 Reception by chemical circles

As Milan Randić (2004), a Croatian-American leading discrete mathematical chemist, and Hosoya have stated, the reception by chemists was just *flat rejection*. According to Hosoya, „conservative [chemistry] professors tried to repel new and strange ideas and intruders from their self-perceived closed territory" (Hosoya 2002). Hosoya's case is worth mentioning. He submitted a paper to *Chemical Physics Letters* that framed in discrete mathematics Wiener's work (Wiener 1947) where molecular structure had been related to boiling points. As Hosoya recalls „The comments by the editor (G.J. Hojtink) and an anonymous referee (E. Heilbronner), were as follows: 'I have a definite feeling that these relationships must be known, as they are rather obvious.' 'More work should be done and an attempt should be made to give more depth from a physical chemistry point of view.' 'At the moment it is just an interesting academic exercise'"[6] (Hosoya 2002). It is clear that the idea was understood by the reviewer; however, because of not framing it into the disciplinary language of physical chemistry, the paper was rejected. These kinds of situations happen when different disciplines start to transfer elements of one to the other, when interdisciplinary studies take place (Lattuca 2001).

Hosoya accepts that things have softened, but he still thinks that when submitting a paper on DMC to some standard journal in chemistry, the situation turns difficult just because of the subject (Hosoya 2002). Randić claims that there are critics of DMC „who tend to perceive topological indices as frivolous, fraudulent, fortuitous, fiction, fabrication, foreign, fictitious, fallacious, flimsy, folly and foolish" (Randić 2004). A topological index is a mathematical representation (a number or a matrix, mainly) of the molecular structure.[7] Randić continues by saying that detractors of topological indices disregarded them because of a presumed 'lack of interpretability' of the indices, „the 'physical meaning' of which", Randić continues, „appears unclear" (*ibid.*). In defense of DMC, Randić asks, „why should graph theoretical quantities have a 'physical interpretation'?" (*ibid.*). He asks the same questions to other disciplines, *e.g.* „do various quantities of quantum chemistry have a 'physical picture?'" (*ibid.*). For instance, as to molecular orbitals he claims that „only the total molecular wave function has a physical interpretation of the overall electron density, but the individual orbitals […] have no physical meaning, being non-observable quantities. Only observable quantities ought to have a 'physical picture' while non-observables should have an interpretation within the model in which they are used. In that respect, mo-

lecular orbitals […] and graph theoretical indices have a proper interpretation" (*ibid.*) Randić concludes, „some graph theoretical indices [topological indices] describe the molecular shape, chirality, molecular surface or molecular volume," but there is no reason to ask for a realization of all of them (*ibid.*).

Randić explains the possible reasons for that reception of DMC by chemists by taking the case of graph theory: „Graph Theory is deceptively 'simple', which may cause some to have incorrect perceptions of Chemical Graph Theory" (*ibid.*). Another reason for the rejection according by Randić is the rapid growth of the field. As he recalls, about 1973 there were just 20 papers in chemical graph theory, while close to 2000 the count was about 2,000 papers, „which is a factor of hundred compared to the early years of Chemical Graph Theory. This amounts to about a dozen papers per person per year [in 2004], or one paper a month[8]" (*ibid.*). Hosoya thinks that „some repulsive factors from conventional chemists were caused by many of easy-going comrades who just play with such-and-such new topological indices, which is nothing else but the number crunching as I myself was doing more than thirty years ago [when working on computational quantum chemistry]" (Hosoya 2002).[9] In fact, the growth of the subject has been so rapid that in 2000, the first handbook of molecular descriptors (Todeschini & Consonni 2000) appeared and it was recently updated to a new handbook of two volumes (Todeschini *et al*. 2009).

One of the reasons to create the International Academy of Mathematical Chemistry[10] was the fact that some aspects of discrete mathematics in chemistry had not been well received in some circles. However, things have softened and a community of mathematical chemists is currently fostering their growing discipline. Besides the Academy, the community has three scientific journals: *MATCH Communications in Mathematical and in Computer Chemistry*, launched in 1975; the *Journal of Mathematical Chemistry*, initiated in 1987; and the *Iranian Journal of Mathematical Chemistry*, recently launched (2010). There are specialized books on DMC and a wealth of scientific meetings on the subject that gather a growing scientific community.

The simplicity of DMC, which has favored its rejection in the chemical community, is, at the same time, one of the aspects fostering the subject. In a scientific world, where results from complex experiments and expensive computations are common, providing advance estimates of those results based on mathematics are noteworthy. Making predictions by using DMC is not just a matter of mathematical chemists in academia, in fact pharmaceutical companies and environmental agencies are interested in the subject and are currently using DMC's results.[11]

3.1.2 Reception by mathematical circles

The reception by mathematical circles has been slow but favorable. Some early steps in the encounters of mathematics and chemistry were the 1988 and 1996 publications of special issues on DMC by the journal *Discrete Applied Mathematics*. Another case in point is the Workshop on Discrete Mathematical Chemistry organized in 1998 by the journal *Discrete Mathematics & Theoretical Computer Science* (DIMACS). In mathematics meetings, there have also been some sections where DMC is classified as applied mathematics. A discussion whether DMC is applied mathematics or no mathematics at all is given below (Section 5).

To strengthen the chemo-mathematical relationship, however, mathematical chemists could do more; they could attend mathematical meetings to show their results, to meet mathematicians who could bring novel ideas to chemistry and with whom they could start collaborative work. Mathematicians would then be more aware of and interested in DMC. In Colombia, for example, such a relationship has started by common work and by mathematical chemists attending mathematical meetings. In 2009, at the VII Simposio Nororiental de Matemáticas,[12] there was a special session for mathematical chemistry, which was treated for the first time, at least in Colombia, like a traditional mathematical area such as analysis, algebra, combinatorics, and topology, among others. It is worth mentioning the recent 2010 International Conference on Mathematical Chemistry[13] organized by mathematicians at the Xiamen University (China), which is a clear example of the interest of mathematicians in DMC.

4. Influence of Discrete Mathematical Chemistry

Several of the seminal papers in DMC have been published in chemistry journals,[14] and still a majority of scientists working in the field are chemists. Therefore, the main influence of DMC has been in and from chemistry.[15] Regarding its influence on mathematics, we think the impact has been quite modest. The reason for this is that DMC is rather young. It would be asking too much of DMC if we expect influential results in mathematics as the product of a very young discipline, which might be different in half a century or so. There are already mathematical chemists publishing in mathematical journals, for example Ernst Ruch, Balaban, Douglas J. Klein, Ivan Gutman, Randić, and some others, which is the first step to make mathematicians aware of the subject. There are also mathematicians and statisticians working in the field, *e.g.* Osvaldo Araujo, Gunnar Brinkmann, Douglas M. Hawkins,

Adalbert Kerber, Héber Mesa, Juan Rada, and Fuji Zhang, among many others.

We have already mentioned in Section 1 some contributions of DMC to chemistry. Regarding mathematics, major contributions have been in the field of graph theory, with the early works by Cayley and James J. Sylvester, and in group actions, as recently shown by Kerber (2010). Balaban's contribution to graph theory is also worth mentioning.[16] Perhaps not a contribution in its own right, but an example of recognition of DMC by mathematicians, is the paper by Béla Bollobás and the influential Paul Erdös (Bollobás & Erdös 1998), in which they called the connectivity index, a DMC product, the Randić weight of a connected graph, recognizing Randić's work in graph theory.

Besides mathematics and chemistry, DMC also influenced other fields, for example, toxicology and drug design, where studies relating molecular structure to activity have had an enormous impact. Two scientists who developed topological indices of hydrocarbons for pharmacology are Lemont B. Kier and Lowell H. Hall, who started to work on the subject in 1967 by making predictions of biological activities using DMC approaches (Kier 2006). More recently, DMC has ventured in proteomics (Randić *et al*. 2002) and in DNA characterization (Randić *et al*. 2000). Important mathematical chemists in these areas are Subhash C. Basak, Ashesh Nandy and Randić.

5. Defining Discrete Mathematical Chemistry

Auguste Comte claimed that „a real definition is the first evidence that a science has attained some consistency: it then measures its own advancement from one epoch to another, and it always keeps inquirers in a right direction, and supports them in a philosophic progress" (Comte 1858, p. 253). DMC already attained such a consistency, since different scientists have defined mathematical chemistry.[17] Denis H. Rouvray (1987), the first editor of the *Journal of Mathematical Chemistry*, states that mathematical chemistry concerns the novel *application* of mathematical methods in the chemical realm, novelty expressed as the development of new chemical theory, and of new mathematical approaches to solve chemical problems. Balaban (2005) considers mathematical chemistry as the „part of theoretical chemistry that *uses* mathematical concepts and tools (including computational ones)". Trinajstić and Gutman (2002) claim that it „is that part of theoretical chemistry which is concerned with *applications* of mathematical methods to chemical problems".

Although there exist definitions for the subject that meet Comte's requirement for consistency, we note that these definitions of mathematical chemistry take mathematics in an instrumental relationship to chemistry, indicated by words like 'use' and 'application'. However, we think mathematical chemistry goes beyond that (Restrepo 2013). We agree with Comte that „the perfection of chemistry might be secured and hastened by the training of the minds of chemists in the mathematical spirit […]. Besides that mathematical study is the necessary foundation of all positive science, it has a special use in chemistry in disciplining the mind to a wise severity in the conduct of analysis: and daily observation shows the evil effects of its absence" (Comte 1893, p. 257). Similarly, Ivar K. Ugi states that the goal of mathematical chemistry is „the mathematization of chemistry without the intermediary of physics and the direct solution of chemical problems by qualitative mathematical methods" (Ugi *et al*. 1993).

We can reframe the Comtean 'mathematical spirit' into the mathematical way of thinking as mentioned by Hermann Weyl (1940), *i.e.* a way of thinking following the functional thinking after Felix Klein's (1872) Erlangen Program. This kind of thinking is based on variables, symbols, and functions. The general idea is to address problems looking for relevant variables, symbolizing them and finding functions that relate the selected variables. We explain this in more detail in Restrepo & Villaveces 2012.

An illustrative example of the mathematical way of thinking is the prediction of the properties of substances based upon their molecular structure. Here, the variables may be molecular fragments and the target property the boiling point, for instance. The symbols for the variables are mf_1, mf_2, …, mf_n for the n molecular fragments and bp for the boiling point. Functional thinking is realized when a function of the form $bp = f(mf_1, mf_2, \ldots, mf_n)$ is found.

Based on Comte's idea of the mathematical spirit and Weyl's idea of the mathematical way of thinking, we propose the following definition: *mathematical chemistry is the realization of the mathematical way of thinking in chemistry*. For the particular case of DMC, the mathematical way of thinking implies studying discrete sets of chemical interest, *e.g.* molecules, chemical reactions, to name but a few; and applying the three steps mentioned before. Mathematical chemistry is not just using mathematical tools.[18] Certainly, chemistry has benefited to a large extent by using mathematics, but the benefits would be immense if mathematics were in the minds of chemists and not just in their hands.

6. Conclusion

Discrete mathematical chemistry mainly started in Eastern European countries, particularly in Bulgaria, Yugoslavia, and Romania at the beginning of the second half of the 20th century. Considering the social panorama of science in these countries at the time, we found two main aspects that we argue are the reasons for the development there, both the availability of knowledge and the lack of research funds. Eastern European countries had a tradition in mathematical training, which, in addition to the chemical knowledge of their scientists, shaped the conditions for starting interdisciplinary work in discrete mathematical chemistry. The lack of research funds for scientists trained in quantum chemistry and with a strong mathematical background was the second factor. It is interesting to note that this lack of funds restricting the use of computers was circumvented by using mathematics further developed for optimizing computers.

There are open questions: Why was graph theory the first kind of discrete mathematics developed? Is this related to the mathematical training of Eastern European countries at that time, or to the mathematics taught in chemistry programs? These questions, and several others, need to be addressed by historians and curriculum specialists.

When DMC started to be noticed by the chemical community, the reaction was flat rejection, mainly because this new kind of theoretical chemistry did not fit into quantum chemistry, the mainstream theoretical chemistry of the second half of the 20th century. The same situation currently occurs when DMC is used to estimate biological activities or properties of chemicals substances; in this case traditional chemists look for mechanistic explanations and, as DMC models fail in that, the models are often not well accepted. As Randić argues (see above), there is no reason to ask for a physical explanation, not even in quantum chemistry, where there are no physical explanation for all its concepts. After all, why should there be a physical explanation for something chemical?

There is no doubt that chemical knowledge has advanced thanks to DMC; the prediction of new substances and their properties is possible thanks to DMC results, chemical knowledge has started to be formalized and this has happened in just a few decades. The methods developed in DMC have started to be applied in other fields, like biochemistry and molecular biology. Regarding the contribution of DMC to mathematics, it is still incipient but not absent as there are already discrete mathematical chemists generating mathematical knowledge. However, the contribution to mathematics could be more. DMC should not make the mistake of *using* mathematics only as a tool for chemistry, which would lead DMC to be dependent on mathematics and to avoid exploring problems of chemistry that may not fit in the mathematics

of the time. Such use of mathematics may lead to the indiscriminate use of mathematical algorithms found in commercial packages to produce results devoid of mathematical and chemical knowledge.

Acknowledgements

The authors thanks A. T. Balaban (Texas A&M University at Galveston, USA), A. Bernal (Universidad Nacional de Colombia, Colombia), D. Bonchev (Virginia Commonwealth University, USA), R. Brüggemann (Leibniz-Institute of Freshwater Ecology and Inland Fishery, Germany), A. Kerber (University of Bayreuth, Germany), D. J. Klein (Texas A&M University at Galveston, USA), Wilmer O. Leal (Universidad de Pamplona, Colombia), E. J. Llanos (Corporación Scio, Colombia), M. Randić (National Institute of Chemistry, Slovenia), A. Rocke (Case Western Reserve University), J. Schummer (University of Karlsruhe, Germany), R. Todeschini (University of Milano-Bicocca, Italy), and N. Trinajstić (Ruđer Bošković Institute, Croatia) for their valuable comments, ideas, and suggestions, which have been included in this manuscript.

Notes

[1] For a broad account of DMC and, in general, of mathematical chemistry in these and other areas, see Klein 2013 (in this issue).

[2] Sets that have a positive integer number of elements.

[3] Haruo Hosoya has claimed that before entering the field of DMC he "had grown up as a kind of number crunching chemist trained by a huge pile of semi-empirical MO [Molecular Orbital] calculations" (Hosoya 2002).

[4] The mentioned computational complexity of quantum chemistry was also the motivation for developing Density Functional Theory (DFT). As it was too complicated to obtain the wave function, DFT's founders became interested in the electronic density (Kohn, 1999).

[5] Kozliak (2000) found that chemistry curricula in countries that had Soviet influence still have a strong mathematical component.

[6] Hosoya continues, "I had to fight for my graph-theoretical papers against invisible enemies, *i.e.*, ignorant and offensive referees and editors, inside and outside of the country. I recall the comment of my boss, which was directed to me after I gave my lecture [on my work relating molecular structure and macroscopic properties] in the seminar which his staff and students attended. 'I think I've got your theory. I put two points on this blackboard, one for MO [Molecular Orbital] and the other for VB [Valence Bond] worlds. It is generally known that the truth is

somewhere in between these two points, but your theory is located somewhere far off this segment'" (Hosoya 2002).

[7] A customary molecular representation in DMC is by using graphs. A graph G is a collection made of two sets: vertices V and edges E. For a molecular graph, vertices correspond to atoms and edges to pairs of bonded atoms. Based upon such graphs it is possible to derive topological indices.

[8] Randić (2004) refers to six authors, including himself.

[9] Being aware of this situation, Randić, between 1993 and 1996, published papers (Randić 1993, 1996) in which he drafted some rules to actually claim the existence of a new molecular descriptor.

[10] The International Academy of Mathematical Chemistry was created in 2005. Its first president (2005-2007) was Alexandru T. Balaban and since 2008 has been Roberto Todeschini. The website of the academy is http://www.iamc-online.org/.

[11] The United States Environmental Protection Agency as well as Bayer Schering Pharma AG, are instances of these companies and agencies.

[12] http://matematicas.uis.edu.co/7simposio/.

[13] http://math.xmu.edu.cn/icm2010/ICMC2010.htm.

[14] Although a wealth of important DMC papers have been published in chemistry journals, there are also some exceptions, *e.g.* Kier *et al*.'s (1975) famous paper on molecular connectivity, published in the *Journal of Pharmaceutical Sciences*, a journal belonging to the Pharmacology & Pharmacy category of the ISI Web of Knowledge (Restrepo *et al*. 2013).

[15] But the influence of DMC has not exclusively been in chemistry. Restrepo *et al*. (2013) have found that some DMC results are applied in computer science, pharmacology & pharmacy, environmental sciences, physics, crystallography, and automation & control systems, to name but a few.

[16] In graph theory a cage is the minimal highly symmetrical regular graph of degree three whose minimal circuit has a certain number of points; Balaban discovered the trivalent cages with minimal circuits 10 and 11, which are called the Balaban cages (Ghiriviga 2005).

[17] Regarding the term 'mathematical chemistry', Nenad Trinajstić (1997) states that he coined it in a 1978 paper (Horvatić & Trinajstić 1978). However, Mikhail V. Lomonosov (1711-1765) wrote a manuscript in Latin with the title *Elementa Chimiae Mathematicae* (Lomonosov 1741). Balaban (2005) states that Lomonosov aimed at presenting axiomatically all chemistry known at that time, however not succeeding in his task. Anyhow, the manuscript needs further analysis by historians, mathematicians, and chemists, to try to grasp, with current knowledge, more ideas on the relationship between mathematics and chemistry.

[18] In the case of DMC, of using just discrete mathematical tools.

References

Balaban, A.T.: 1993, 'Confessions and reflections of a graph-theoretical chemist', *MATCH Communications in Mathematical and in Computer Chemistry*, **29**, 3-18.

Balaban, A.T.; Klein, D.J. & Folden, C.A.: 1994, 'Diamond-graphite hybrids', *Chemical Physics Letters*, **217**, 266-70.
Balaban, A.T.: 2005, 'Reflections about mathematical chemistry', *Foundations of Chemistry*, **7**, 289-306.
Bollobás, B. & Erdös, P.: 1998, 'Graphs of extremal weights', *Ars Combinatoria*, **50**, 225-33.
Bonchev, D.: 2005, 'My life-long journey in mathematical chemistry', *Internet Electronic Journal of Molecular Design*, **4**, 434-90.
Cayley, A.: 1857, 'On the theory of the analytical forms called trees', *Philosophical Magazine*, **13**, 172-6.
Cayley, A.: 1875, 'Ueber die analytischen Figuren, welche in der Mathematik Bäume genannt werden und ihre Anwendung auf die Theorie chemischer Verbindungen', *Berichte der deutschen chemischen Gesellschaft*, **8**, 1056-9. [English version: 'On the analytical forms called trees, with application to the theory of chemical combinations', *Report of the British Association for the Advancement of Science*, 257-05 [online available at: http://www.archive.org/stream/collectedmathema09cayl#page/426/mode/2up, accessed 6 Sept. 2012].
Comte, A.: 1858, *The positive philosophy of Auguste Comte*, trans. H. Martineau, New York: Calvin Blanchard. [Published originally in French as *Discours sur l'Esprit positif*, 1844].
Coulson, C.A.: 1960, 'Present state of molecular structure calculations', *Reviews in Modern Physics*, **32**, 169-77.
Doemling, A.: 2007, 'Ivar Ugi: an exceptional scientist and human being. In memorial Ivar Ugi', *Heterocycles*, **73**, 1-11.
Gasteiger, J.: 2003, *Handbook of chemoinformatics: from data to knowledge*, New York: Wiley.
Ghiriviga, I.: 2005, 'Professor Alexandru T. Balaban, a tribute', *Arkivoc*, **x**, 1-8.
Gillispie, C.C.: 1960, *The edge of objectivity*, Princeton: Princeton University Press.
Goodson, A.L.: 1980a, 'Graph-based chemical nomenclature. 1. Historical background and discussion', *Journal of Chemical Information and Computer Sciences*, **20**, 167-72.
Goodson, A.L.: 1980b, 'Graph-based chemical nomenclature. 2. Incorporation of graph-theoretical principles into Taylor's nomenclature proposal', *Journal of Chemical Information and Computer Sciences*, **20**, 172-6.
Guo, X.; Randić, M. & Basak, S.C.: 2001, 'A novel 2-D graphical representation of DNA sequences of low degeneracy', *Chemical Physics Letters*, **350**, 106-12.
Hopkins, B.: 2008, *Resources for teaching discrete mathematics*, Washington: Mathematical Association of America.
Horvatić, K. & Trinajstić, N.: 1978, 'Matematicka kemija. Primjena teorije skupova u kemiji', *Kemija u Industriji*, **27**, 127-35.
Hosoya, H.: 2002, 'The topological index Z before and after 1971', *Internet Electronic Journal of Molecular Design*, **1**, 428-42.
Johnsonbaugh, R.: 2008, *Discrete mathematics*, Upper Saddle River: Prentice Hall.
Kerber, A.: 2010, *Applied finite group actions*, Berlin: Springer.
Kier, L.B.: 2006, 'My journey through structure: the structure of my journey', *Internet Electronic Journal of Molecular Design*, **5**, 181-91.
Kier, L.B.; Hall, L.H.; Murray, W.J. & Randić, M.: 1975, 'Molecular connectivity. I: relationship to nonspecific local anesthesia', *Journal of Pharmaceutical Sciences*, **64**, 1971-4.
Klein, F.: 1872, *Vergleichende Betrachtungen über neuere geometrische Forschungen*, Erlangen: A. Deichert.

Klein, D.J.: 2013, 'Mathematical Chemistry! Is It? And if so, what is it?', *Hyle: International Journal for Philosophy of Chemistry*, **19**, 35-85 (this issue).
Kohn, W.: 1999, 'Electronic structure of matter – wave functions and density functionals', Nobel lecture, January 28, 1999 [online available at: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1998/kohn-lecture.pdf, accessed 6 May 2013].
Kozliak, E.I.: 2000, 'Chemical education in countries of the former Soviet Union', *Journal of Chemical Education*, **77**, 870-5.
Lattuca, L.R.: 2001, *Creating interdisciplinarity*, Nashville: Vanderbilt University Press.
Leal, W.; Restrepo, G. & Bernal, A.: 2012, 'A network study of chemical elements: from binary compounds to chemical trends', *MATCH Communications in Mathematical and in Computer Chemistry*, **68**, 411-36.
Lomonosov, M.: 1741, *Elementa chimiae mathematicae* [online available at: http://feb-web.ru/feb/lomonos/texts/lo0/lo1/lo1-065-.htm, accessed 10 Sept. 2012].
Panico, R.; Powell, W.H. & Richer, J.-C.: 1993, *IUPAC nomenclature of organic compounds*, London: Blackwell.
Pólya, G. & Read, R.C.: 1987, *Combinatorial enumeration of groups, graphs, and chemical compounds*, New York: Springer.
Randić, M.: 1990, 'The nature of chemical structure', *Journal of Mathematical Chemistry*, **4**, 157-84.
Randić, M.: 1993, 'Novel molecular descriptor for structure-property studies', *Chemical Physics Letters*, **211**, 478-83.
Randić, M.: 1996, 'Molecular bonding profiles', *Journal of Mathematical Chemistry*, **19**, 375-92.
Randić, M.; Vracko, M.; Nandy, A. & Basak, S.C.: 2000, 'On 3-D graphical representation of DNA primary sequences and their numerical characterization', *Journal of Chemical Information and Computer Sciences*, **40**, 1235-44.
Randić, M.; Basak, S.C.: 2002, 'A comparative study of proteomics maps using graph theoretical descriptors', *Journal of Chemical Information and Computer Sciences*, **42**, 983-92.
Randić, M.: 2003, 'Aromaticity of polycyclic conjugated hydrocarbons', *Chemical Reviews*, **103**, 3449-606.
Randić, M.: 2004, 'Nenad Trinajstić – pioneer of chemical graph theory', *Croatica Chemica Acta*, **77**, 1-15.
Restrepo, G.: 2013, 'To mathematize, or not to mathematize chemistry', *Foundations of Chemistry*, **15**, 185-197.
Restrepo, G. & Basak, S.C.: 2011, 'Editorial', *Current Computer-Aided Drug Design*, **7**, 81-2.
Restrepo, G.; Llanos, E.J. & Silva, A.E.: 2013, 'Lemont B. Kier: a bibliometric exploration of his scientific production and its use', *Current Computer-Aided Drug Design*, in press.
Restrepo, G.; Mesa, H.; Llanos, E.J. & Villaveces, J.L.: 2004, 'Topological study of the periodic system', *Journal of Chemical Information and Computer Sciences*, **44**, 68-75.
Restrepo, G. & Villaveces, J.L.: 2011, 'Chemistry, a lingua philosophica', *Foundations of Chemistry*, **13**, 233-49.
Restrepo, G. & Villaveces, J.L.: 2012, 'Mathematical thinking in chemistry', *Hyle: International Journal for Philosophy of Chemistry*, **18**, 3-22.
Rosen, K.H.: 2000, *Handbook of Discrete Mathematics*, Boca Raton: CRC Press.
Rouvray, D.H.: 1987, 'Editorial foreword', *Journal of Mathematical Chemistry*, **1**, i-iv.

Ruch, E. & Ugi, I.: 1966, 'Das stereochemische Strukturmodell, ein mathematisches Modell zur gruppentheoretischen Behandlung der dynamischen Stereochemie', *Theoretica Chemica Acta*, **4**, 287-304.
Ruch, E.; Schönhofer, A. & Ugi, I.: 1967, 'Die Vandermondesche Determinante als Näherungsansatz für eine Chiralitätsbeobachtung, ihre Verwendung in der Stereochemie und zur Berechnung der optischen Aktivität', *Theoretica Chimica Acta*, **7**, 420-32.
Ruch, E.; Schönhofer, A.: 1970, 'Theorie der Chiralitätsfunktionen', *Theoretica Chimica Acta*, **19**, 225-87.
Ruch, E.: 1972, 'Algebraic aspects of the chirality phenomenon in chemistry'. *Accounts of Chemical Research*, **5**, 49-6.
Ruch, E.: 1975, 'The diagram lattice as structural principle' *Theoretica Chimica Acta*, **38**, 167-83.
Todeschini, R. & Consonni, V.: 2000, *Handbook of molecular descriptors*, Weinheim: Wiley-VCH.
Todeschini, R.; Consonni, V.; Mannhold, R. & Kubinyi, H.: 2009, *Molecular descriptors for chemoinformatics*, 2 vols., Weinheim: Wiley-VCH.
Trinajstić, N.: 1997, 'Mathematics and chemistry – the unlikely partners', in: D.H. Rouvray (ed.), *Concepts in chemistry: a contemporary challenge*, Somerset: Research Studies Press.
Trinajstić, N.; Gutman, I.: 2002, 'Mathematical chemistry', *Croatica Chemica Acta*, **75**, 329-56.
Ugi, I.; Bauer, J.; Bley, K.; Dengler, A.; Dietz, E.; Fontain, E.; Gruber, B.; Herges, R.; Knauer, M.; Reitsam, K. & Stein, N.: 1993, 'Computer-assisted solution of chemical problems: a new discipline in chemistry', *Angewandte Chemie International Edition*, **32**, 201-27.
Weyl, H.: 1940, 'The mathematical way of thinking', *Science*, **92**, 437-46.
Wiener, H.: 1947, 'Structural determination of paraffin boiling points', *Journal of the American Chemical Society*, **69**, 17-20.
Wotiz, J.H.: 1973, 'Higher education in chemistry in Bulgaria, Hungary, Poland, Romania, and Yugoslavia', *Journal of Chemical Education*, **50**, 520-25.

Guillermo Restrepo:
Laboratorio de Química Teórica, Universidad de Pamplona, Pamplona, Colombia; grestrepo@unipamplona.edu.co, guillermorestrepo@gmail.com

José L. Villaveces:
Grupo de Química Teórica, CEIBA, Complex Systems Research Center, Universidad de los Andes, Bogotá, Colombia