Lecture Notes in Chemistry 112

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Electron Localization-Delocalization Matrices

Springer

Lecture Notes in Chemistry

Volume 112

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ISSN 0342-4901 ISSN 2192-6603 (electronic)
Lecture Notes in Chemistry
ISBN 978-3-031-51432-6 ISBN 978-3-031-51434-0 (eBook)
https://doi.org/10.1007/978-3-031-51434-0

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This book is dedicated to four scientists we admire and whose oeuvre has laid the foundations for the work presented in this monograph:

To the memories of
Richard F. W. Bader (1931–2012) and Robert G. Parr (1921–2017).

and to Todd A. Keith and Ismat Sumar.

Foreword

Quantum chemistry has come a very long way from being restricted to small molecules and specialist applications to the major research tool it is today. In fact tens of thousands of quantum chemists use quantum chemistry every day in academia as well as industry in order to solve real-life chemistry problems, to obtain inspiration for new experiments, or to interpret their experimental data. While a big part of this success is the increasingly accurate numerical predictions offered by contemporary quantum chemistry, one should never forget that obtaining accurate numbers is not synonymous with understanding the chemical problem. Hence, it is a vital and sometimes somewhat neglected part of our profession to turn the results of quantum chemical calculations into chemical context and chemical language. This is the purpose of this monograph. Quantum chemistry and Chemical Graph Theory are two well-developed but disparate branches of theoretical chemistry. This monograph is an enlightening first step for their union taking Richard F. W. Bader's Quantum Theory of Atoms in Molecules (QTAIM) as the bridge between them. The authors provide a concise summary of their contributions to this field over the past decade and have included—especially in the later chapters—several new methods and unpublished results of considerable interest. The examples used in the exposition cover a large range of timely problems with practical solutions where the results of electronic structure calculations are summarized into the electron Localization and Delocalization Matrices (LDMs) which are then analyzed and compared by a whole battery of methods. The predictive power of such LDM analysis is promising. I commend the

authors, Chérif F. Matta, Paul W. Ayers, and Ronald Cook, all three of whom are prominent scientists in their respective lines of research, for pooling their efforts to bring to the light this important monograph.

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Preface

"The molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment *[Todeschini and Consonni, 2000].*

Attention is paid to the term "useful" with its double meaning: it means that the number can give more insight into the interpretation *of the molecular properties* and/or *is able to take part in a model for the* prediction *of some interesting property of other molecules.*

Why must we also accept "or"?

It should not be thought that molecular descriptors are good only if they show an evident link to some information about molecular structure, that is, they are easily interpretable from a structural/ chemical point of view.

It often happens that interpretation of molecular descriptors could be weak, provisional, or completely lacking, but their predictive ability or usefulness in application to actual problems should be a strong motive for their use. On the other hand, descriptors with poor predictive ability may be usefully retained in models when they are theoretically well founded and interpretable due to their ability to encode structural chemical information."

Roberto Todeschini and Viviana Consonni, Molecular Descriptors for Chemoinformatics, Wiley-VCH, Weinheim (2009)

This monograph introduces a new method that converts computational chemistry results into a set of tools to predict the activities and/or properties of a series of compounds. It uses Richard F. W. Bader's Quantum Theory of Atoms in Molecules (QTAIM) starting from a topographical and topological analysis of the molecular electron density to provide a bookkeeping of electrons localized in, and delocalized between, atoms in a molecule, a complex, or a crystal. The method outlined in this monograph extracts molecular descriptors from the QTAIM numerical integration results which are then used to solve concrete experimental chemistry problems.

A principal theme in this book is the use of "molecular descriptors" in "Quantitative Structure-Activity/Property Relationship (QSAR/QSPR)" modeling. The method introduced here uses computational quantum chemistry to obtain molecular electronic wavefunctions and electron densities which are then analyzed to obtain the QTAIM localization and delocalization indices (LIs and DIs) which, in turn,

are organized to construct the corresponding electron Localization-Delocalization Matrices (LDMs). LDMs are then either compared directly or manipulated to extract matrix invariants as is done in Chemical Graph Theory (CGT) or using statistical methods such as Principal Component Analysis (PCA) to predict molecular activities/properties. The approach outlined in this book can be considered as a bridge between two branches of theoretical chemistry, that is, Chemical Graph Theory (CGT) on one hand and quantum chemistry, in particular QTAIM, on the other. We will term the overall approach presented in this work as *LDM Analysis.*

The *applications* of LDM Analysis are not bound to any specific field. As will be apparent, these applications span physical organic chemistry, corrosion inhibitors research, insect control, enzymology, physicochemical properties, and quantitative molecular comparisons, to name just a few examples. It is hoped that this approach will be of value to those interested in research in such domains as materials science, physical organic chemistry, and drug design, where *in silico* predictions can guide and/or shed light on experiments.

The level of exposition should be accessible to upper-level undergraduate students, graduate students, and researchers in physical chemistry, biophysics, molecular modeling, bioinformatics, and related fields of specialization.

In closing, this book is a *monograph* in the sense that it is a topical review that focuses primarily on the contributions and interests of the authors. It is not at all meant to be a comprehensive all-encompassing review of the literature on molecular descriptors, QSAR/QSPR, or computational quantum chemistry. The exposition is far from complete or comprehensive and can be taken as a "teaser" since the field is young and wide open.

Halifax, NS, Canada — Chérif F. Matta
Hamilton, ON, Canada — Paul W. Ayers
Denver, CO, USA — Ronald Cook

Acknowledgments

R. C. thanks his spouse Diane Cook for her unwavering support. P. W. A. is grateful for his parents and sister. C. F. M. is much indebted to his parents (Farid A. Matta and Nabila N. Abdel-Nour) and to Maged F. Matta, Hebatallah S. Habib, Sara and Nadine Matta, and Sami and Boa Habib.

The authors are indebted to several mentors, colleagues, and students among whom we particularly thank Richard F. W. Bader, Robert G. Parr, Lou Massa, John C. Polanyi, Frank Neese, Claude Lecomte, Russell J. Boyd, Ismat Sumar, Todd A. Keith, André D. Bandrauk, Sason Shaik, Sonja Nikolić, Weitao Yang, Tina A. Harriott, Daniel Majaess, Rafik A. Matta, Ashraf W. El-Miniawy, Federico Rosei, Nagwa El-Badry, Mahmoud Abdel-Aty, Hugo Bohórquez, Eva Knoll, Ángel Martín-Pendás, Labiba K. El-Khordagui, Abdel-Aziz Saleh, Ignacy Cukrowski, Jesús Hernández-Trujillo, Fernando Cortés-Guzmán, Aurora Costales Castro, Olimpia Lombardi, Eric Scerri, James S. M. Anderson, Lázaro A. M. Castanedo, Peyman Fahimi, Ihab Gad, Essam F. Khamis, Islam K. Matar, Halis Seuret, Samir E.-G. Gabrial, Ashraf S. Abousaif, Sherif F. Boutrous (Borgzanno), and Hani B. Maher.

The authors acknowledge with gratitude the Springer's team, its editorial and production offices, and the handling editors for supporting this book.

The completion of this monograph would not have been possible if it wasn't for the financial support of the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), Compute Canada, Mount Saint Vincent University, and Saint Mary's University.

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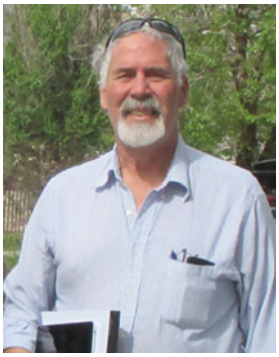
About the Authors

Chérif F. Matta, B.Pharm.Sci. (Alexandria University), Dipl. (Sadat Academy), PhD (McMaster University), HDR (Université de Lorraine), FRSA, FRSB, FInstP, FRSC, FAAS, FAAAS is Professor and Chair/Head of the Department of Chemistry & Physics at Mount Saint Vincent University and an Adjunct (Honorary) Professor at Dalhousie, Laval, and Saint Mary's Universities (all in Canada), and holds frequent Visiting Professorships at Zewail City for Science and Technology (Egypt). After receiving his doctorate from McMaster University under Professor Richard F. W. Bader, Matta has been a Postdoctoral Fellow at the University of Toronto (with Nobel Laureate Professor John C. Polanyi) and later an Izaak W. Killam Postdoctoral Fellow at Dalhousie University (with Professor Russell J. Boyd). Chérif Matta's research ranges from theoretical and computational chemistry to mitochondrial biophysics. He has introduced and developed with the co-authors of this book the concept of the electron Localization-Delocalization Matrices (LDMs) as predictive descriptors in materials and bio-pharmacological research. He discovered an unusual role of the enzyme ATP synthase over and above catalysis as a modulator of the reaction energy itself and not only of the barrier to the reaction. He is also the co-discoverer of the Hydrogen-Hydrogen bonding interaction. Matta has given more than 250 lectures in over 30 countries and has *ca.* 200 publications to his credit including four books. Matta has been named "Distinguished Visiting Professor" by the Polish Ministry of Science and Higher Education 2022–2023, was the

2021–2022 “Science Atlantic Speaker of the Year”, and has been awarded Mount Saint Vincent University’s Award for Research Excellence (2017), the Lady Davis Fellowship (2016–2017), the NSERC-Acfas “Preuve par l’image” Prize for 2016, the Molecular Graphics and Molecular Simulation Society Silver Jubilee Prize for 2009, the John C. Polanyi Prize in Chemistry for 2004, and the Izaak Walton Killam Fellowship in 2002–2004. Prof. Matta is an elected Fellow of the American Association for the Advancement of Science, of the African Academy of Sciences, of the Royal Society of Chemistry, of the Institute of Physics, of the Royal Society of Biology, and of the Royal Society of the Arts. He has served (2021–2022) as Chair/Head of the Interdisciplinary Adjudication Committee of the Canada Research Chairs Programme of the Tri-Council of Canada and is currently serving as Director of Accreditation & Member of the Board of Directors of the Canadian Society for Chemistry. In 2022–2023 he has served as a Member of the Multidisciplinary Selection Board of Canada Excellence Research Chairs of the Tri-Council and is currently serving a second term as an elected Member of the Commission for Quantum Crystallography of the International Union of Crystallography (IUCr) and as a Member of the Canadian National Committee for Crystallography (CNCC).

Paul W. Ayers is the Canada Research Chair in Theoretical Chemistry at McMaster University. Paul’s PhD was supervised by the late Robert G. Parr at the University of North Carolina. After postdoctoral training with Weitao Yang at Duke University, Paul became a (Tier 2) Canada Research Chair at McMaster University. Paul’s research focusses on developing new qualitative and quantitative methods for describing molecular electronic structure and reactivity, focussing on the theory and applications of density (matrix) functional theory. Paul has co-authored more than 350 peer-reviewed publications, with an h-index of 75 and more than 20,000 cumulative citations, has won various awards (including the Dirac Medal, the Rutherford Medal, the Steacie Prize, and the IAQMS medal) and is a Fellow of the Royal Society of Chemistry (U.K.) and a Member of the College of Young Scholars of the Royal Society of Canada. Paul co-founded the QC-Devs international software consortium

for free and open-source software in the computational sciences.



Ronald Cook, PhD was a Principal Scientist at TDA Research, Inc., from 1982 to 2021 and carried and continues to carry out research in computational materials science and materials discovery. He has led numerous modeling efforts, building on previous successful efforts to identify improved corrosion-inhibiting formulations through modeling. This work has included the development of quantum mechanical modeling using the quantum theory of atoms in molecules (QTAIM) computed parameters. Dr. Cook has, in cooperation with Prof. Chérif F. Matta, developed new types of universal descriptors that are generated by computing the Principal Components of, or the GINI indices of the Localization-Delocalization Matrices that are accessible from QTAIM calculations. Dr. Cook has a high level of expertise in converting the descriptors to descriptive/predictive equations using Symbolic Regression (ChaosHunter™), Latent Class Regression, Correlated Component Regression, Self-Organizing Maps, Neural Networks, and Genetic Algorithms. The universal descriptors that are generated by computing the Principal Components of Localization-Delocalization Matrices have been applied to successfully predict corrosion inhibition rates for small molecules that were not predictable through standard Density Functional Theory descriptors. Dr. Cook has extended the use of the universal descriptors described above to successfully predict the inhibition of acetylcholinesterase, the binding of vapor molecules to odorant binding proteins, the prediction of the effectiveness of mosquito repellents and the binding of antifilarial antimycin analogues. Dr. Cook has retired from TDA Research, Inc., and is currently pursuing new developments in QTAIM modeling. Dr. Cook has authored more than 44 peer-reviewed papers and 15 patents.

Chapter 1
An Introduction to Electron Localization-Delocalization Matrices

Give us insight not numbers [1] (see also [2]).

Charles A. Coulson (1910–1974)—(1959)

Give us insight and *numbers* [1].

Frank Neese, Mihail Atanasov, Giovanni Bistoni, Dimitrios Maganas, and Shengfa Ye—(2019)

This book has been written with the practicing chemist in sight. It is *not* a book on theoretical chemistry but rather one that is primarily focused on making practical predictions starting from theoretical chemistry calculations. It is true that predicting and explaining is not "the same thing", as argued along the length of a book that René Thom[1] titles: "*Prédire n'est pas expliquer*" (Predicting is Not Explaining) [3]. However, as it is hoped it will become apparent in the following pages that, in making numerical predictions, one can, in fact, gain insight. In other words, by exploiting the panoply of existing tools from quantum chemistry, to graph theory, and ending up with modern statistics one can, in many cases, go beyond Coulson's wish and indeed get "*insight* and *numbers*" out of electronic structure calculations as the modern revision of this wish formulated six decades later by Neese, Atanasov, Bistoni, Maganas, and Ye in 2019 [1].

What will be explored in detail in this book is a new method to extract, summarize, and use the information obtained from quantum chemical (electronic structure) calculations for a series of molecules to uncover trends in sought-for properties for the purpose of making useful predictions. Sometimes such predictions can also give us mechanistic insights into the chemistry of the problem. The core of the method

[1] René Thom (1923–2002) was an eminent French mathematician and 1958 Fields Medalist credited for several noted contributions to topology including being the principal developer of Catastrophe Theory (along with British Mathematician Prof. Sir E. Christopher Zeeman (1925–2016)) who widely popularized the theory).

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C. F. Matta et al., *Electron Localization-Delocalization Matrices*, Lecture Notes in Chemistry 112, https://doi.org/10.1007/978-3-031-51434-0_1

that will be expanded on the pages of this book is the abstract linear algebraic representation of a molecular electronic structure in terms of an electron Localization-Delocalization Matrix, or LDM—which is the subject of analysis as a powerful molecular descriptor.

In performing such an LDM analysis, one starts from electronic structure calculations, typically of the Density Functional Theory type [4–6] (with a moderate-to-relatively-large basis set as much as the compromise of speed and accuracy allows). The resulting electronic structure is then summarized at an atomic/atomic pair level of "coarseness" [7] using Bader's Quantum Theory of Atoms in Molecules (QTAIM) [8, 9] by extracting the so-called localization and delocalization indices (LIs and DIs, respectively) [10]. These indices describe the electronic structure in terms of the number of electrons that are, on average, localized within atomic basins and those that are shared (delocalized) between every atomic pair in the molecule whether chemically bonded or not. The sharing is naturally more significant when there exists a bonding interaction linking the two atoms but it is not zero otherwise. One can describe the bond path (lines of maximal electron density that link bonded atoms in real space) as "privileged exchange channels" [11] since electron sharing is mediated by the exchange symmetry of the wavefunction.

These LIs and DIs can clearly be arranged in matrix format not dissimilar to the *charge and bond order matrix*, an archaic name to what is now more commonly known as the *density matrix*, listing the bond orders as its off-diagonal elements leaving the diagonal ones for atomic populations [12–15]. The arrangement of the LIs and DIs of a given molecule in matrix format yields what we term the electron Localization-Delocalization Matrix (LDM). LDMs are rich in coded chemical information since they capture and summarize elegantly the electron distribution reflecting, at once, aspects of both the molecular electron density (e.g., atomic electron populations, atomic charges, atomic contributions to higher molecular multipoles) and of the electron *pair* density distributions (e.g., the delocalization/sharing of electrons between atoms through the mechanism of exchange) at an atomic-diatomic resolution.

Chemical Graph Theory has a long tradition of summarizing molecular topology into topological (connectivity) matrices [16–29]. Meanwhile, any matrix representing a set of connected objects—is numbering/labeling dependent since there exist $n!$ way to arrange n distinguishable objects (except when symmetry reduces this number). Chemical graph theorists extract matrix invariants from these matrices as a means to uniquely describe molecules [16–29]. Instead of re-inventing the wheel, we follow the chemical graph theorists' footsteps to extract invariants from the LDMs, albeit by introducing new ways to do so such as the Frobenius distance between matrices or using statistical methods such as Principal Component Analysis.

Balasubramanian, in a far-sighted article [23], proposed three decades ago the "[*i*]*ntegration of graph theory and quantum chemistry"* and underscored the correspondence of graph-theoretical graphs whether within Chemical Graph Theory or as the complete set bond paths defined within QTAIM [8, 30]. This book is an attempt to fulfill Balasubramanian's vision by extending and expanding the now decade-old

proposal to achieve such a merger [31]. The antecedents of this book have appeared in the following key references: [31–39].

The book starts with a review of the physical description of electron localization and delocalization in molecular quantum mechanics (Chapter 2). The exposition then moves to review, in Chapter 3, the basic tenets of Bader's QTAIM, especially with regard to how it defines LIs and DIs in terms of the six-dimensional integrals of the Fermi hole density. The chapter emphasizes the strong connection between these 2-electron mathematical indices and several experimentally measured quantities. This connection reinforces the idea that these indices condense much chemical information. Chapter 4 defines the LDMs and related matrices and explores methods to define molecular similarity or proximity in this context. The chapter then discusses briefly some of the challenges to this kind of representation of molecular structure and proposes some possible solutions. The chapter shows how solutions to these challenges can lead to the modeling of molecular behavior in terms of the LDMs by predicting properties such as boiling points, pK_a's of weak acids, and λ_{max} of substituted benzoic acids. Chapter 5, discusses the approach to molecular fingerprinting using LDMs and several technical and programming details to automate the implementation of this type of analysis by introducing the programme AIMDELOC with examples of application. In anticipation of the following application-centered chapters, Chapter 6 reviews the basics of Principal Component Analysis (PCA) since this analysis is applied in subsequent chapters to extract invariant descriptors from the LDMs. A general protocol for how to apply PCA to LDMs in property modeling is introduced in this chapter. The following chapters (Chapters 7–9) are all about the use of PCA to extract invariant molecular descriptors from the LDMs. Chapter 7 outlines a PCA of the LDMs of corrosion inhibitors. The analysis results in robust predictive modeling of corrosion inhibitors' efficiency and, further, provides valuable insight into the *mechanism* of some of the studied corrosion inhibitors pinpointing what may have been overlooked in the literature as the *active species* of (at least) three stress corrosion cracking inhibitors containing sulfhydryl groups (R−SH). Chapter 8 applies this analysis to mosquito repellency showing how it can be used to *classify* odorants and in shedding light into the modes of action of the repellents. Chapter 9 demonstrates the usefulness of the LDM-PC analysis in predicting enzyme–substrate interaction, for example, the action of acetylcholine esterase inhibitors as Alzheimer's Disease retarding drugs. LDM-PC analysis is also shown of value in the predictive modeling of the bioremediation approach to clean organophosphorous environmental toxicants and chemical warfare agents. Chapter 10 explores the extension of LDM Analysis to very large molecules *via* the two fragmentation approaches aiming at increasing the speed of the calculation by recombining the LDMs of small fragments to approximate the LDM of the large molecule. Chapter 11 concludes this book by summarizing the main points to be retained and possible future developments.

In closing, it is stressed that the topic of this book is *a work in progress*. The field is still young but certainly appears promising in providing "insight *and* numbers". The LDMs, in themselves, are elegant mathematical summaries of complex molecular electronic structures.

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