Topological approaches to intermolecular interactions

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Organizing Committee

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1. Proposal

Introduction and motivation

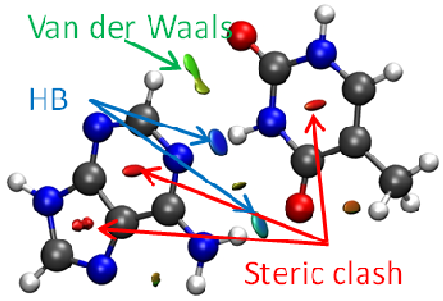
Introduction

Revealing the chemical bonding (structure) and the reorganization of the chemical bonds (reactivity) of any molecular system forms the undisputed foundation of chemistry. Chemical interactions between a protein and a drug, or a catalyst and its substrate, self-assembly of nanomaterials [1], and also many chemical reactions [2] are dominated by noncovalent interactions. This class of interactions spans a wide range of binding energies and encompasses hydrogen bonding, dipole–dipole interactions, steric repulsion, and London dispersion [3]. Molecular structure is governed by covalent, noncovalent, and electrostatic interactions, the latter two of which are the driving force in most biochemical processes. The three-dimensional molecular structure defines covalent bonds; however, noncovalent interactions are hidden within voids in the bonding network. Although there are several ways to view and analyze covalent and electrostatic interactions, an analogously simple method for noncovalent interactions was conspicuously missing. The development of such a method would aid understanding of the complex interactions between biomolecules and the design of self-assembled materials and drugs, among others [4].

One such proposal is the non covalent interaction (NCI) index. It enables visualization and quantification of non covalent theoretical results [5-7]. NCI enables identifying interactions in 3D space from the electron density (Figure 1). Moreover, this approach has the advantage of being transferable to large systems, which are very fast to compute. Consequently, a qualitative NCI analysis is applicable to extremely large systems, including, e.g. proteins and DNA, where describing the interplay of attractive and repulsive interactions is crucial for understanding functionality. This new index, requiring only molecular geometry information, compliments existing methods for covalent and electrostatic interactions, providing a perfect bridge between theoretical chemistry and (in)organic chemistry by means of chemical bonds and their change.

FIGURE 1

Non covalent interactions in the adenine-thymine complex. HBs in blue (2 intermolecular HBs) , steric clashes in red and dispersion in green.



Motivation

This necessity of a CFCAM meeting emerged from two main reasons:

- The first one is to gather the new and growing NCI community and boost the development and exploitation of this new tool. Indeed, this index is now being widely used in the organizing laboratory as well as some others both in France and around the world. It is now crucial to organize this community and promote discussion between people involved.
- The second one is to promote NCI analysis to other communities. Indeed the impact of the method will depend it is perceived and used by people outside NCI community. Indeed both development and application would considerably increase if other communities were to show interest to the approach.
- Finally, the third and last aspect touches the usage and distribution of the NCI analysis and more generally of the topological analyses. Different researcher applying the methods will be invited to talk about how they use it but also what need they have.

Discussions will take place in order to consider new possible type of applications but also new development for applicative purpose (theoretical or experimental).

Moreover, these needs clearly emerged at the RCTF-Marseille. Both organizers, JCG and RC presented their results on this new tool and several people showed their interest in an organized workshop. Given the fact that the RCTF gathers the main representatives of the Theoretical Chemistry community, this CFCAM call perfectly suits the needs of the French community.

However, the organizers will also seek further financial aid in order to bring together the top specialists in theories of bonding and non covalent interactions. This would yield to an incredible source of feedback information that will boost NCI and take the knowledge of non covalent interaction to the next step.

State of the art

Chemical bonds are not directly observables. Since the Hamiltonian of the system is delocalized, additional tools are necessary to: (i) describe the properties of chemically reactive systems, and (ii) extract observable information from the electron density. Covalent bonds are intuitively represented using conventional Lewis structures [8]. They can be visualized from properties of the electron density with modern quantum-mechanical models of bonding, such as the electron localization function (ELF) [9,10] and atoms-in-molecules (AIM) theory [11,12]. Also, purely electrostatic interactions can be analyzed using electrostatic potential maps.[13] Noncovalent interactions are frequently visualized using distance-dependent contacts, generally without consideration of hydrogen atoms [14].Hydrogen bonds can be identified from the molecular geometry [15] and from ELF [16], while grid-based calculations based on force fields are used to model other van der Waals interactions [17].

However, distance-dependant models have to be parametrized, which leads to many transferability problems. An adequate representation of a chemical bond as well as bond breaking/formation processes should be better provided by a physical observable defined in 3D space. The electron density meets these requirements because it is an experimental accessible scalar field, whose relationships with the system's ground-state properties can be understood from the Hohenberg-Kohn theorem [18]. Moreover, since chemical reactions proceed by $\rho(r)$ redistributions, the methods that directly deal with $\rho(r)$ should have a particular appeal for chemists in the understanding of electronic structure and reactivity.

Two main topological methods have followed this philosophy: the electron localization function (ELF)[9,10] and atoms-in-molecules (AIM) theory [11]. Bader's theory of atoms-in-molecules is a model based on quantum mechanics and physical observables, which provides a rigorous and exact definition of bonding within an atomic ensemble in terms of topological properties of its electron density $\rho(r)$. The topology of this scalar field can be decomposed according to its bond critical points (BCP), the zeros of the gradient of this field, and bond paths. Then, it is possible to correlate the topological properties of $\rho(r)$ with elements of the molecular structure and bonding: this renders concepts such as the chemical bond more compatible with the traditional viewpoint of chemists. While these concepts are well-defined, both in theory and in experiment, their chemical meaning has given rise to many criticisms and rather controversial discussions, some of which will be tackled with NCI [5,6].

An alternative way for the representation of the electronic wave function is provided by the use of the electron localization function (ELF) [10] which, as shown by both LCT members B. Silvi and A. Savin [9], provides a division of molecular spaces into nuclear shells, bonding regions and lone pairs. The ELF function is a convenient tool for the analysis of covalent chemical bonding as it reveals regions of molecular space where the probability of finding an electron pair is high. From this point of view, ELF preserves the notion of an electron pair as the central element of the

chemical bonding theory. Silvi and co-workers have developed the bonding evolution theory as a generalization of Bader's work to other scalar fields (e.g. ELF) for reactivity analysis [19].

Within this frame, NCI grows as new source of information, a new approach. The intricate noncovalent interactions cannot be described in an intuitive manner by the above commonly-used topological approaches, and thus distance-dependent methods are usually resorted to. In other words, a real "space method" for the analysis of non-covalent interactions in reactivity was conspicuously missing. The new NCI index provides a new approach to map non-covalent interactions that complements the currently existing methods devoted to covalent and electrostatic interactions [5]. Unlike geometry-based (e.g. radii) methods, the NCI approach is built from the electron density and its derivatives.

It is important to note that join NCI/ELF analysis can be perform and are been shown to be particularly suited for the analysis of the reactivity through the in-depth study of both strong and weal electron pairing regimes along reaction paths.[20]

Objectives

Given the development stage of this new tool, this workshop will have two main types of objectives, scientific and strategic.

Scientific

The scientific objectives of the workshop can be developed in 2 main different axes occupying 3 days of talks and discussions. The first one basically concerns the development of NCI (and other interpretative tools if applicable) and a thorough analysis of the limitations of the methods thanks to the presence of other topological and DFT communities in the discussion. The second one concerns the applications of the topological analysis (and more specifically NCI) to real systems molecular or periodic and how such approaches can be used by people outside the community. This second part will of course lead to a fruitful feedback between the developing and the application/experimental communities, which will be able together to delineate and discern which axes are most urgent to develop.

1. ***Development (Dev)***

   NCI is related to AIM theory since the existence of a BCP in a chemical system has a direct consequence on the s(ρ) diagram. At the critical points, s = 0 due to annihilation of the density gradient. In regions immediately surrounding the critical point, the change in ρ dominates and s(ρ) approaches zero, giving rise to a steep peak. Thus, NCI agrees with Bader's Atoms In Molecules approach in characterizing inter-atomic interactions. However, the NCI representation is not only able to reveal the topological features of the density, but also their effects in the 3D real space as well, by providing chemically intuitive iso-surfaces. Furthermore, NCI is able to recover chemical features to which AIM is blind [7]. One of the basic aims of this workshop will be to compare previously existing topological analysis of the chemical bond (AIM and ELF) with NCI, in search for (in)-consistencies. The appearance of NCI features in the absence of AIM ones will also be analyzed in order to set their relationships to (non)bonding features.

   Recently other interesting topological functions have been developed. They propose alternative and complementary views to analyze electronic density of chemical systems. The

workshop will gather all these new communities and explore their possibilities of interactions.

The limitations of the topological analysis and more specifically of the NCI approach will be discussed. The presence of members of the DFT and energetics community will enable us to delimit which problems should be tackled to understand the relationship between density and energetic properties.

Applications to real systems: molecules, biosystems and solids (Apps)

Weak interactions play a major importance in complex systems and reactivity, often explaining the route for a given reaction mechanism.

The application of interpretative analysis such as NCI is a major issue in the method development. Indeed such approaches are intrinsically developed to help the understanding of structures and reactivity. In the workshop we will review different recent application of NCI and of the other methods to complex systems. Three different subjects presenting particular difficulties will be addressed in the framework of the molecular and biologic systems: i) Study of reaction mechanism; ii) Study of chiral systems; iii) Study of dynamic systems.

Recently the NCI analysis has been generalized to periodic systems opening new areas of applications. The approach will be presented together with some first applications. The importance and relevance of the method for different system will be discussed.

2. Strategical

This workshop will follow a bottom-up approach in order give to NCI as much visibility as possible. First, it aims at organizing the growing of NCI in an ordered manner by gathering together the various communities which might be concerned by NCI.

On the one hand, the community of NCI is rapidly growing with people all over the world using or developing new tools. A meeting to discuss their goals, expectations and ideas on the method would be a real boost and would prevent overlap in the research fields.

On the other hand, the workshop will aim at presenting this new community of NCI users to the much larger one of people using and developing other topological approaches. This would allow developing crosschecking between the different methods and should help improving existing tools and developing new ones. Finally the workshop will be used to discuss the application of the analysis to complex systems (biological, reactive, periodic…). The practical issues as well as the expectation from experimental researchers will be debated in order to find the best and easiest way to use and develop these tools.

Participant List

Participants will be invited from the topological communities. The following preliminary list has been elaborated:

International-invited

1. **Erin Johnson** (ejohnson29@ucmerced.edu) **[ORGANIZER]**
2. **Weitao Yang** (weitao.yang@duke.edu)
3. Paul Popelier (paul.popelier@manchester.ac.uk)
4. Miroslav Kohout (kohout@cpfs.mpg.de)
5. Ángel Pendás (angel@fluor.quimica.uniovi.es)
6. Manuel Yañez (manuel.yanez@uam.es)
7. José Manuel Recio (jmrecio@uniovi.es)
8. G. Andres Cisneros (andres@chem.wayne.edu)
9. Russell Boyd (russell.boyd@dal.ca)

10. Juan Andres (andres@qfa.uji.es)
11. Mauro Causa (mauro.causa@unina.it)
12. Carlo Gatti (carlo.gatti@istm.cnr.it)
13. Slawomir Berski (slawekbe@o2.pl)
14. Patrick Bultinck (Patrick.Bultinck@ugent.be)
15. Paul Ayers (ayers@mcmaster.ca)
16. Henry Rzepa (h.rzepa@imperial.ac.uk)

National

17. Bernard Silvi (silvi@lct.jussieu.fr)
18. Anthony Schemama (scemama@irsamc.ups-tlse.fr)
19. Michel Caffarel (caffarel@irsamc.ups-tlse.fr)
20. Odile Eisenstein (odile.eisenstein@univ-montp2.fr)
21. Michel Mons (michel.mons@cea.fr)
22. Anne Zehnacker (anne.zehnacker-rentien@u-psud.fr)
23. Benoit de Courcy (Benoit.de.Courcy@lct.jussieu.fr)
24. Marie-Laure Bonnet (marie-laure.bonnet@lct.jussieu.fr)
25. Michael Devereux (Michael.Devereux@unibas.ch)
26. Monica Calatayud (calatayud@lct.jussieu.fr)

Organization details

Schedule

The workshop will be organized on three days. Contributions will be separated into the two main topics (1.5 days each): development (Dev) and applications (Apps).
Each day will be divided into morning and afternoon contributions (called hereafter workshop slots, WS). Each WS will start with a plenary lecture (1h). All of them will be given by international experts in the field.

The rest of the WS will be enriched by shorter oral presentations (20-30 min), selected from the list of the rest of the expected attendee list provided above. Contributions from students and postdocs will also be taken into account for oral presentations. Bourses will be granted to ca. 4 students, which will be chosen in terms of their CVs and financial possibilities. These will be advertised through a direct link on the home workshop wiki/webpage.

At the end of the afternoon WS, a round table will take place for discussion. It is at this moment that ideas suggested and enlightened during the day's contribution will converge for the development of the topological analysis of non covalent interactions. Specific thematics will be given to each discussion set depending on the speaker of the day. In addition, the different interventions will be followed by discussions on the possible new applications and the consequences on the methods development and association.

Due to their relevance both in NCI development and in the analysis of non covalent interactions in general, the attendance of the first two participants (i.e. E. Johnson and W Yang) has been confirmed in the case of funding. A call upon registration will be made for oral contributions. Given the nature of the workshop, these will be mainly attributed to experts (14/18), but contributions from outstanding students will be considered and funded accordingly.
The organizing and local scientific committees will meet upon closure of the registration deadline in order to choose the name and type of contributions.

Social program
From the social point of view, each WS will be divided into two parts by a break in order to promote interaction and informal discussion between participants. Coffee, tea and snacks will be provided by the organizers.
Depending on the available funding, the social program will be expanded to include lunches (at the *Ardoise*, restaurant on the *Jussieu* Campus).
Similarly, one dinner will be organized on day 2 which, upon funding, will be covered by the organization.
A poster session will be organized at the end of the first date to allow PhD student and postdoc that wouldn't have talked to present their results. This session should allow socialization and discussion between the different people. Refreshment and food will be served depending on the available funding.

Location
As far as the placing is concerned, a room at the UPMC will be booked in order to avoid charges for room renting. Depending on their availability, the renting of a room elsewhere will be envisaged. The coffee break and the lunches will be served on the campus close to the meeting room.

	Day 1: DEV	**Day 2: DEV+APPS**	**Day 3: APPS**
9:00-10:00	Plenary	Plenary	Plenary
10:00-10:30	Coffee break	Coffee break	Coffee break
10:30-12:00	Oral contributions	Oral contributions	Oral contributions
12:00-14:00	Lunch	Lunch	Lunch
14:00-15:00	Plenary	Plenary	Plenary
15:00-15:30	Coffee break	Coffee break	Coffee break
15:30-17:00	Oral contributions	Oral contributions	Oral contributions
17:00-18:00	Discussion	Discussion	Discussion
	Poster session	Dinner	

2. Financial Support

Financial support will cover:

- The travel of two invited speakers (flight+hotel)
- Refreshments served at the coffee break, lunches (upon financial aid received)
- Travelling grants for 4 students
- Dinner for participants (upon financial aid received)
- Logistics: communication materials, location of a room if necessary

The following chart gives an approximate estimation of costs:

Budget

International travel	3000 (1500x2)
Lodging of invited speakers	800 (100x2x4)
Coffee breaks / Poster session	500

Dinner	1000
Student grants	3000
Logistics	1500
TOTAL	9800

A total of 6000 euros would be provided by the CFCAM (2000x3days). In order to cover the rest of the charges, further funding will be requested from individuals and organizations at the local/regional/national levels:

- SMART (LCT belong to this research federation:FR 2622, UPMC/CNRS)
- RCTF (French network for theoretical chemists)
- Mérimée project (bilateral cotutelle doctoral project)
- Others

The amount requested will depend on each organization availability and rules.

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