**Maria C. Burguete** *

# The philosophy of computational chemistry II [1]

## (1.1) Introduction

The "pierre de touche" of the scientific world of today is: complexity. This complexity of scientific knowledge demands for interdisciplinary and transdisciplinary approaches.

The actual epistemological and paradigm shift can be very well illustrated by a case study related to the philosophy of computational chemistry based on simulation. For several reasons:

- Because the contemporary world is characterized by the complexity of the diverse scopes: Physical / Biological / Psychological / Social.
- Because it requires holistic thinking to be effective and induces a dynamic iconographic perspective of knowledge: we can no longer look at a scientific subject as if it was «**the one**», what means that by itself the whole conceptualization of that discipline is no longer possible.

## (1.2) Epistemological shift

Let us consider an overview upon epistemological shift:

- In 1950 **Vienna Circle founded Constitutive Epistemology** (where we had a method which allowed scientists to evaluate their scientific research work).
- In 1960 **Thomas Kuhn** emerged with his concept of **Historical Epistemology** promoting the idea of a science evolution through paradigms.
- Later on a **sociological** feature was added to Kuhn' view (Michel Dubois).
- Nowadays we are facing such a scientific diversity that **Regional Epistemology** began to emerge building up a critical thinking (principles, methodologies & conclusions) upon each scientific scope.
- Whenever we have history we also have a philosophical feature: History of Science with its critical analysis of scientific content lead us to Philosophy of Science (**Philosophy of Chemistry**).

## (1.3) Different visions of philosophy of chemistry

- **ENGLISH VISION** (Claus Jacob, University of Exeter, U.K.) – 1999/2002: in this vision we have a more classical approach.
- **GERMAN VISION** (Joachim Schummer, University of Karlsruhe, Germany) – 2000: in this vision we assist to the emergence of bridges between exact sciences and humanistic sciences, therefore bridging the gap between these two fields of knowledge.
- **AMERICAN VISION** (Jody Roberts & Benjamin Cohen, Virginia Polytechnic Institute and State University, USA) – 2002: directed to sociology of science enhancing its empirical features.
- **SPANISH VISION** (Fernando Peral, Maria Dolores Troitino, Maria Cruz Izquierdo, Maria Angeles Plaza, Universidad Nacional de Educacion a Distancia, UNED, SPAIN) – 2002: where interdisciplinarity mainly in the field of physical chemistry is greatly enhanced.
- **FRENCH VISION** (Bernardette Bensaude-Vincent, Université Paris X, FRANCE) – 2003/4: with great Interdisciplinarity & Transdisciplinarity.

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[1] "The Philosophy of Computational Chemistry" I was presented at the 22nd International Congress of Science, in July 2005, Beijing, China.

- **PORTUGUESE VISION** (Maria da Conceição Burguete, Instituto Piaget, PORTUGAL) – 2005/6: Interdisciplinarity & Transdisciplinarity enhancing biochemical features – "*Philosophy of Computational Chemistry: on the way to Epistemology of Interdisciplinarity?*"

Presents a different approach to Chemistry specially to Computational Chemistry where application of systemic paradigm assumes particular relevance, mainly in the field of Receptor Chemistry. It is a different way to think about chemical phenomena considering incertainty and complexity as useful tools of interdisciplinarity.

## (2) Development

**HOLISTIC THINKING:** The field of systems thinking has been developed to provide techniques for studying systems in holistic ways therefore replacing the traditional reducionistic methods.

In this more recent tradition, we can find — **Systems Theory** — considered by some as a humanistic counterpart to the natural sciences. Because it takes in consideration the humanistic side that every natural science should have. We must not forget that science is made **by** human beings and **for** human beings. Systems theory or systemics (focuses on complexity and interdependence) is an interdisciplinary field which studies systems (composed of regularly interacting or interdependent groups of activities) as a whole.

**DYNAMIC ICONOGRAPHIC PERSPECTIVE OF KNOWLEDGE:** Replacement process on the ways of thinking the world induces a vision change of the world perspective pointing out the need of new directions. These new directions deal with concepts such as: uncertainty, instability and ephemerity; such concepts are valid parameters as inquiry instruments to interdisciplinary.

In the classical vision, rationality and reality are one and the same thing, what means that, only the rational is real therefore there is only a rational reality.». **Ilya Prigogine**, in opposition to this approach said that *«nowadays we can see a world of instabilities and tolerance is our great challenge because we need to bridge scientific rationality with social and humanistic rationality»***.**

## (2.1) What is the philosophical interest of this research program?

The first approach has an epistemological feature once it is related with the language & classification in chemistry and biochemistry. The second approach has an ontological feature once it is related with the philosophy of chemical bonding.

## HEURISTIC METHODOLOGY (LAKATOS)

The applied methodology follows Lakatos heuristic methodology once there is a central nucleus of concepts surrounded by a protective belt of propositions that support those concepts. Application of Systemic Paradigm to Computational Chemistry allows a new approach to visualize new structures that are created by computer programmes.

### PHILOSOPHY OF COMPUTATIONAL CHEMISTRY

In this Epistemological research project — The Philosophy of Computational Chemistry — computer graphical interfaces overcome a culture based on calculus giving rise to a new culture: "*a culture of simulation*". We simply do not care about what lies behind computers ; we just "*take everything by its interface value*" and this make us feel good. We simply keep on trying computers…

### SYSTEMIC THINKING

Computers encourage a new style of thinking — "***tinkering***"[2] **(**Sherry Turkle) what essentially means EMPIRICISM.

Interactiv mode lead "*bricolage*" to be the *"modus operandi"* of modern computers therefore creating the dominant style of the actual thought: systemic thinking.

A new dynamic vision of Chemical Phenomena had been established as a consequence of the development of three concepts:[3]

– Mobility (simulation),
– Spatiality (conformational analysis),
– Probability (reactional selectivity).

These three characteristics are conducive to a dynamic vision of chemical phenomena and have permitted the emergence of new programmes — specific programmes which allow us to generate molecules with adequate applications in molecular recognition, including the design of synthetic receptors and their agonists and antagonists molecules.

**MOBILITY:**

– The static world of molecules had changed to a dynamic world of molecules.
– The static design of molecular structure was replaced by the simulation of dynamic mouvement of molecules, leading to the conception of Computer Models.

**SPATIALITY:**

– Atoms were considered as physical entities for the first time by Van't Hoff and Le Bel in 1875.
– Nevertheless only in 1973 with Barton's work a new stereochemical thinking was developed with the concept of chirality.
– According to the different positions that the several stereochemical configurations can assume we have different conformational analysis.
Related with conformational analysis we have the emergence of a new phenomena called **Functional Selectivity** in 2004. This concept will be discussed later.

**PROBABILITY:**

– This feature is directly linked to the selectivity of organic reactions, once we can achieve different products from the same raw material.
– Selectivity became more important when studies connected with Host-Guest complexation chemistry took place (1974). Chemical architecture and manipulation of the symmetry properties of molecules had been dominant themes in the research of this field. The generalization of coordination chemistry led to the origin of Supramolecular Chemistry whose foundations are based on three concepts: fixation, recognition and coordination.

## (2.2) Methodologies of computational chemistry

The methodologies of computational chemistry in the architecture of Computer-Aided Ligand Design (CALD) can be visualized in Fig.1.[4]

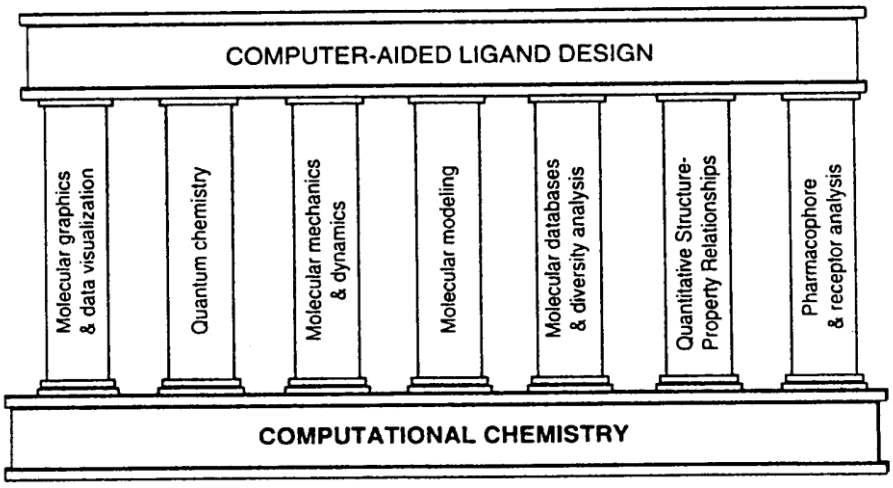
Computational Chemistry is an interdisicplinary area that deals with the broad range of problems and methodologies in computer representation and manipulation in various types of chemical information.

During the past decade, a variety of technologically-based approaches have been improved as routes to improved discovery of receptor selective drugs. This range from approaches that iomprove physical limitations (e.g. combinatorial chemistry) to those that overcome theoretical issues (e.g. structural biology, molecular modelling and computational approaches).

[2] Sherry Turkle (1999): "Predictions: 30 Great minds on the future", p. 329 (Oxford: Oxford University Press).

[3] Maria. C. Burguete (2003): "Architecture of New Molecules: A Dynamic Approach", p. 43 (ed. by Calouste Gulbenkian Foundation).

[4] *Ibidem*, p. 111.




*Methodologies of computational chemistry in the Architecture of Computer-Aided Ligand Design (CALD).*

**Fig.1. COMPUTATIONAL CHEMISTRY METHODOLOGIES: Computer Aided Ligand Design (CALD)**

The fundamental idea behind CALD research is depicted in the following diagram:

**Functional Selectivity**
↑
**Biological Response**
↑
**Biochemical Change**
↑
**Drug–Receptor Interactions**
↑
**Transport Active Site**
↑
**Chemical & Physical Properties**
↑
**Molecular & Electronic Structure**

In this diagram we realize that the therapeutic effect is based mainly on the molecular and electronic structure of the molecule as well as its chemical and physical structure. Afterwards we have to consider the nature of the active site responsible for interaction drug – receptor, which in turn induces a biochemical change as well as a biological response from the receptor once it is activated.

The concept is that the nuclear and electronic structure underlies all physical and chemical properties of molecules including their biological activity.

However, in recent studies made by Richard Mailman in 2004 we can see the emergence of a new concept — Functional Selectivity — resulting from carefully considering «Function» in the drug discovery process for the first time as «Function Activity Hypothesis» — which explains how a single drug can bind to a single receptor and yet cause a mix of effects (agonists, partial agonists, inverse agonist and/or antagonists).[5]

[5] Richard Mailman (2004): "Functional Selectivity: Novel Mechanism of Drug Action", *Med. Chem. Res.*, vol. 13 (1/2), pp. 115-126.

## (3) EXPERIMENTAL CASE STUDY

Let us consider this experimental case study of dopamine agonists receptors, an example of CALD problematic:

- Why dopamine receptors?
- Dopamine is an important neurotransmitter in both the central and peripheral nervous systems and is implicated in a number of human diseases.

  - 1. Drug design is mainly concerned with the development of new ligands on the basis of structural information about the topological receptor site at which the molecules are expected to show the activity of interest.
  - Alternative methods are for example: Active Analogue Approach.
  - 2. The role of conformation in determining the pharmacological properties of a compound is implicit in the stereospecificity of biological receptors.
  - One possible explanation of similar pharmacological effects for different types of compounds is that *the critical 3D arrangement of electron density is identical in the "active" conformations.*
  - 3. Active Analogue Approach — in this method we seek to rationalise the Ligand-receptor interaction on the basis of structural characteristics of those active molecules that have been identified so far, such as Pramipexole a selective dopamine agonist.

**A Case Study:**

**The Study of Dopamine Agonists in Two Different Conformational States (S-Cis And S- Trans) by Active Analogue Approach**

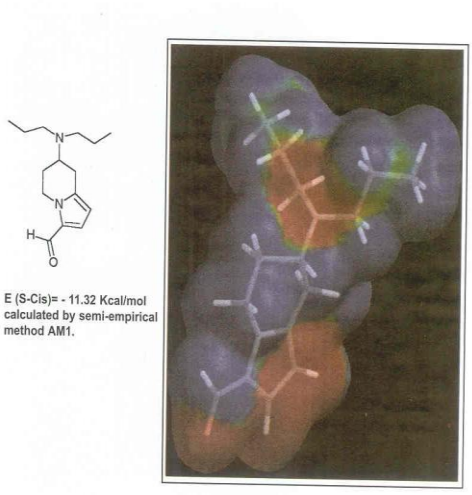



**Fig. A)** S-Cis.CHO

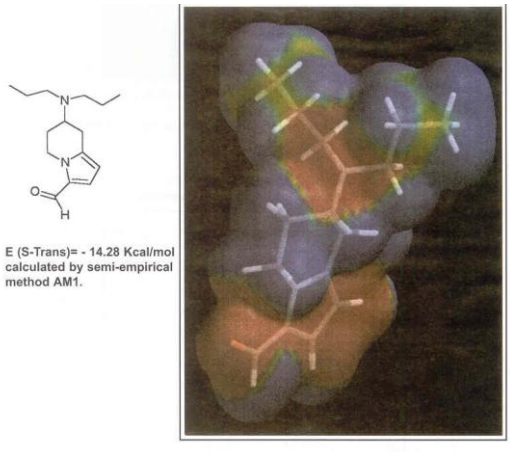



**Fig. B)** S-Trans.CHO

This is a picture of a MOLECULAR SURFACE of dopamine agonists (where molecular electrostatic potentials were used as markers of similarity) and in spite they represent the same molecule when we look at both molecules they seem quite different because they are seen in different conformations (S-Cis & S-Trans). Let us consider a systematic view of this case study:

At a first glance we see a charge distribution in blue (+) and red (-) as a result of the applied molecular electrostatic potentials (MEP) used as markers of similarity (CALD method).

From the Molecular Electrostatic Potentials (MEP) we can see a molecular surface ranging from -2.0 kcal/mol (red) to +3.0 kcal/mol (blue).

## PRAMIPEXOLE: SELECTIVE DOPAMINE AGONIST

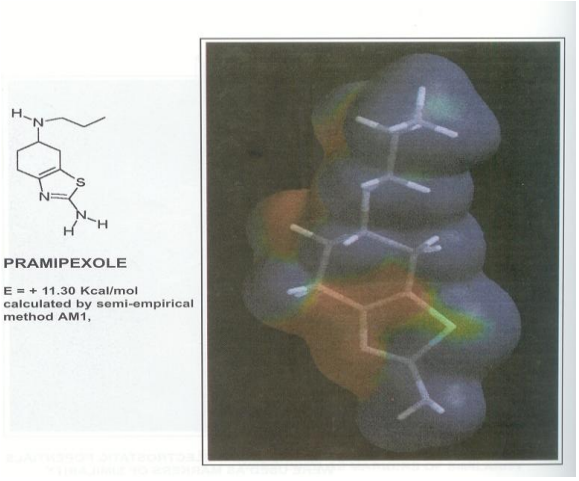



**Fig. C)** Pramipexole selective dopamine antagonist

From the energy values we can say that the form (S-Trans-CHO) is more stable than (S-Cis-CHO); therefore the preferred conformation of the dopamine agonist molecule will be the S-Trans conformation. Comparing fig. a), b) and c) the shapes of the contour maps indicating the distribution of charge show a high similarity between the lead Pramipexole and the S-Trans-CHO.

- Based on these studies we can elaborate a possible location of one pharmacophore site as well as the preferred conformation while binding to a dopamine receptor, thus elucidating about some of the possible features of the dopamine receptor site.
- The resulting structural model suggests:
- Which features contribute to activity.
- What the bioactive conformation may be.

A systematic view upon these models, with the objective of making it possible to come up with new strategies to synthesize new molecules of therapeutic interest, gives us the conscience of the complexity of a fragment of complex reality.

Systemic change was needed because of the paradigm shift that has occurred in chemistry due to the information age.

The passage from Molecular Chemistry to Supramolecular Chemistry, brought about a change from structures & properties to systems & functions.

RICHARD MAILMAN RESEARCH PROJECT — an interdisciplinary project:

- 1) to understand the structural basis that causes ligands to recognize and activate dopamine receptors (see Fig. 2);
- 2) to understand why some ligands cause differential activation of signalling pathways linked to a single receptor (termed “functional selectivity” see Fig. 3).

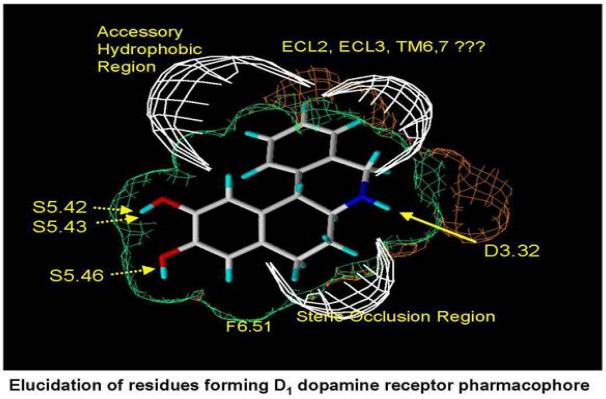



**FIG. 2.** D1 dopamine receptor pharmacophore: elucidation of residues forming d1 dopamine receptor pharmacophore

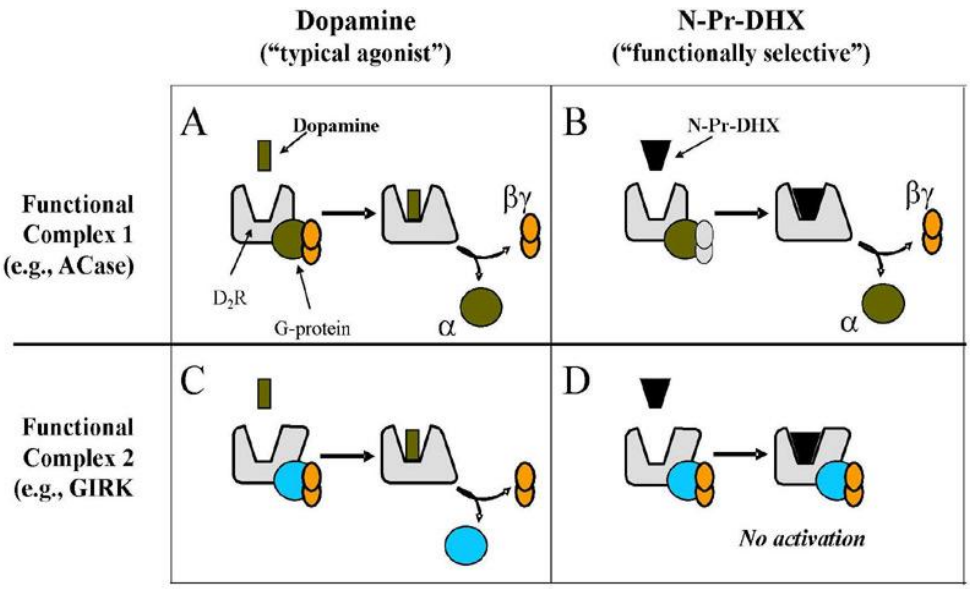



**FIG. 3. Functional selectivity**

## (4) CONCLUSIONS

- Science became epistemic, once the theories say more about the minds that conceive them rather than about the reality processes itself, because every theory is just an approach to reality explanation.
- On the other hand, reality can be seen as a process of information exchange among several levels (biological, physical, psychological & social.
- We are developing a scientific model based in the concept of relationship or interaction, a much broader concept than the concept of analysis still used by normal science.
- The several fragments of reality cannot be put together as before because the more important is their interaction and the way they express themselves in their context.

We have a new conception of the world today:

| | | |
|---|---|---|
| – | Determinism | ---» Uncertainty |
| – | Molecular | ---» Supramolecular |
| – | Structures & Properties | ---» Systems & Functions |
| – | Mechanics | ---» Self-Organization |
| – | Simplicity | ---» Complexity |
| – | Analysis | ---» Interaction |

- While mechanicism presents the world as an enormous deterministic machine, holism besides all those "mechanic" characteristics, understands Nature as a much wider universe made up of a fantastic matrix of dynamic and organic interrelationships.

  "*Computational chemistry is like a game that has changed not only our lives… But also our minds!*"

- There is always a new reality waiting to be discovered… or in other words…

- REALITY IS A PROCESS OF INFORMATION EXCHANGE AMONG ALL THE LIVING BEINGS AT THEIR DIFFERENT LEVELS (biological, physical, psychological and social…).

*For further details on the subject see the poster attached below.*

II INTERNATIONAL CONFERENCE OF THE EUROPEAN SOCIETY
FOR THE HISTORY OF SCIENCE
Crakow, Polland – September 6-9, 2006

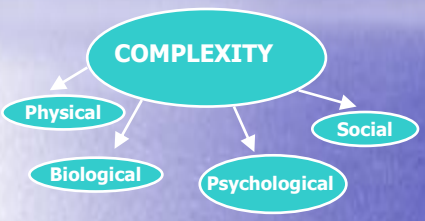
# PHILOSOPHY OF COMPUTATIONAL CHEMISTRY

**M. C. BURGUETE**

Piaget Institute - PORTUGAL

## INTRODUCTION

- The contemporary world is characterized:




- This complexity asks for multiple approaches on specific, interdisciplinary and transdisciplinary aspects that compose the picture of the scientific world.

- Objective science became epistemic – the inside core of the knowledge process.


The actual epistemological and paradigm shift can be very well ilustrated by a case study related to the philosophy of computational chemistry based on simulation. WHY?

- HOLISTIC THINKING:

– The field of systems thinking has been developed to provide techniques for studying systems in holistic ways therefore replacing the traditional reducionistic methods.

In this more recent tradition, we can find - **Systems Theory -** considered by some as a humanistic counterpart to the natural sciences.

- Because we need the organization basic principles which allow the interaction among elements and properties of a system.

**DYNAMIC ICONOGRAPHIC PERSPECTIVE OF KNOWLEDGE:**

the replacement process on the ways of thinking the world, induces a vision change of the world perspective pointing out the need of new directions.

**JAMES LOVELOCK (1919 - )**

- GAYA THEORY (1965):

– The Earth considered as a whole is an auto-regulated living organism or a kind of a living organism of supramolecular architecture. Gaia Theory reminds us that we are, totally dependent of this system.

**ILYA PRIGOGINE (1917- 2003)**

■ *"In the classical vision: rationality and reality are one and the same thing..."*

or:

■ *"...only the rational is real therefore there is only a rational reality."*

## DEVELOPMENT

- A new dynamic vision of Chemical Phenomena had been established as a consequence of the development of three concepts:

**MOBILITY:**

The static design of molecular structure was replaced by the simulation of dynamic mouvement of molecules, leading to the conception of Computer Models.

**SPATIALITY:**

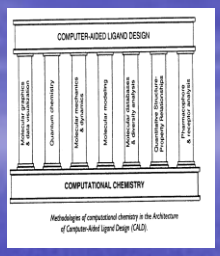
According to the different positions that theseveral stereochemical configurations can assume we have different conformational analysis.

**PROBABILITY:**

This feature is directly linked to the **selectivity** of organic reactions, once we can achieve different products from the same raw material.

Selectivity became more important when studies connected with Host-Guest Complexation Chemistry took place in 1974.

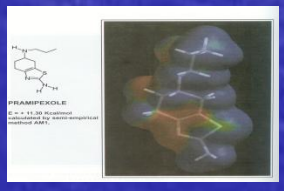
■ The methodologies of computational chemistry in the architecture of computer-aided ligand design (CALD) can be visualized in the following figure:




**Behind CALD research we have:**

Biological Response
↑
Biochemical Change
↑
Drug-Receptor Interactions
↑
Transport Active Site
↑
Chemical & Physical Properties
↑
Molecular Structure & Electronic Structure

**CASE STUDY: PRAMIPEXOLE MOLECULE**




- Active Analogue Approach – in this method we seek to rationalise the ligand-receptor interaction on the basis of structural characteristics of those active molecules that have been identified so far, such as Pramipexole a selective dopamine agonist (used as the lead molecule).

Based on these studies ( we can elaborate an hypothesis concerning a possible location of one pharmacophore site as well as the preferred conformation while binding to a dopamine receptor, thus elucidating about some of the possible features of the dopamine receptor site.

## CONCLUSION

- **The resulting structural model suggests:**

- **Which features contribute to the activity.**
- **What the bioactive conformation may be.**

**We are developing a scientific model based in the concept of relationship or interaction, a much more broad concept than the concept of analysis still used by normal science.**