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45 Years of the KPG Method: A Tribute to Federico Peradejordi

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ABSTRACT

I present here an historical account of the long conceptual development of the only formal method to study the relationships between electronic structure and biological activity: the Klopman-Peradejordi-Gómez Method (KPG). After a short historical introduction about receptors and linear free energy relationships, some of the first quantum-chemical reactivity indices developed in the 1950-1960 decade are presented. The first article of what can be considered the beginning of formal Quantum Pharmacology is presented and commented. The contribution of Klopman and Hudson concerning the interaction energy is presented. The first paper employing Klopman's results (by Peradejordi et al.) is fully analyzed. After I present my contributions to the development of Peradejordi's work: the analysis of the molecular partition functions, the modification of the mathematical expression for the drug-site interaction energy with the conception of new reactivity indices, the design of the orientational parameter of the substituent from the rotational partition function, the creation of an algorithm to correct anomalous electron populations in Mulliken Population Analysis, the introduction of new local atomic reactivity indices, the use of Local Molecular Orbitals and the extension of the method to any biological activity. The concepts of pharmacophore and common skeleton are briefly commented.

Keywords: Interaction energy, QSAR, DFT, Quantum pharmacology, Mulliken population analysis, Local atomic reactivity indices, Local hardness, Local softness, Local electrophilicity, Local molecular orbitals, KPG model, Receptors, Intermolecular interactions

"He who understands nothing but chemistry doesn't even understand chemistry".
Georg Christoph Lichtenberg.

INTRODUCTION

Historical aspects

The history of chemistry is the history of a series of experiments and interpretations intimately related. The offshoot of modern western chemistry does not come from the European Antiquity due to the 1,000 years of darkness imposed by Christianity. It will be through the Islamic civilization that we shall recover the ancient Greek and roman texts, translated and enlarged. Also we received from Islam the Hindu–Arabic numeral system employed in almost all the world today. In Europe, a special set of exoteric and esoteric system of experimental practices is developed, called Alchemy. During year 1629 David de Planis Campy tries to show the authenticity of the Chemical Art. He stated that all chemical operations can be reduced to only seven: calcination, putrefaction, dissolution, distillation, coagulation, sublimation and fixation. He defined chemistry as having the knowledge of the qualities and virtues of compounds. In 1675 Nicolas Lémery, the King's pharmacist, complains bitterly that the most part of authors of chemistry books have written in so dark ways that it seems that they have made all efforts for not to be understood. This comment can still be fully applied to many of today's undergraduate and graduate chemistry textbooks. During the nineteen century, chemistry builds its solid foundations and become a science in the actual meaning of the term. Those times when problems such as if water was OH or HOH, if OH and HOH were only conventional forms without reference in the microscopic level, when it was finally recognized that carbon has a valence of four, when Kekulé dreamed with the Ouroboros and suggested the structure of benzene, when optical isomerism was discovered or when some scientists held that acids contained preformed water and bases preformed oxides have gone. Today, when some chemists (me

for example) begin to believe that in chemistry *nihil sub sole novum*, always an entirely new field suddenly opens. This is the case, for example, of fullerenes, nanotubes and graphene.

An area of chemistry of the outmost importance is the study of the relationships between the molecular structure and the biological property (or properties). From a philosophical point of view, this approach (and many others) has its roots in Galileo Galilei's statement that, to introduce order in the Universe, we must pay attention to the quantitative aspects of our environment and to the mathematical relationships among them. In 1863, monsieur Cross (it is interesting to mention here that his given name is not known today, see the footnote 13 in [1]), suggested in his Thesis that there was a relationship between the toxicity of primary aliphatic alcohols and their solubility in water. In 1869 Benjamin Ward Richardson concluded that for a series of alcohols toxicity increases with the increase of molecular weight. In 1868 Alexander Crum-Brown and Thomas Fraser suggested that the physiological action of a substance was related to its composition and constitution: It is obvious that there must exist a relation between the chemical constitution and the physiological action of a substance, but as yet scarcely any attempts have been made to discover what this relation is. All that is known is that as a general rule (with some striking exceptions) the compounds of certain elements, such as mercury or arsenic, and of certain radicals, such as cyanogen, possess (when soluble in water, or the fluids of the body) a physiological action which appears to be of the same kind for the whole series of compounds of each element or radical.

In 1870 Antoine Rabuteau studied the toxicity on frogs immersed in ethylic, butyl and amyl alcohols, concluding that the toxicity of these compounds increased as a function of the number of methanediyl groups they have. In 1874 Wilhelm Körner stated the hypothesis about the existence of relationships between the physicochemical properties and the molecular structure. In 1893 Richet proposed that the hypnotic strength of molecules belonging to different chemical families is governed by their solubility in water. During 1899-1901 Charles Ernest Overtone and Hans Horst Mayer stated independently that the anesthetic potency of a large variety of organic non electrolytes was governed by their partition coefficient between water and olive oil. In 1904, Isidor Traube found a linear relationship between surface tension and narcosis. In general terms, the physiological action (Φ) of a substance is a function of its chemical constitution C:

$$\Phi = f(C) \tag{1}$$

It follows that any alteration of chemical composition, ΔC, will be reflected in a change of the biological activity, $\Delta\Phi$. This is the original expression proposed by Crum-Brown and Fraser. From his studies on the action mechanism of curare (name for various plant extract alkaloid arrow poisons), Claude Bernard suggested in 1856 that the ability of this drug to exert its action depends on its access to a very specific place. From the historical point of view, the inquiries of Paul Ehrlich and John Newport Langley led to the concept of receptor. Following the ideas of Balthasar Luchsinger, who suggested that the antagonist effect among two alkaloids depends only upon the relative number of poisonous molecules, Langley suggested that in the nerve terminals existed one or more substances which bind the alkaloids. He also proposed that these compounds formed accordingly to a law involving their relative masses and chemical affinities (1878). During 1905, Langley spoke for the first time about the possible existence of receptive substances as the site of action of some compounds. On his side, and also during year 1878, Ehrlich suggested that there is a definite chemical character of the cell allowing its reaction with a colorant. During year 1897 Ehrlich developed his theory of the side chain, stating that in cells some side chains were able to bind certain toxins and, during year 1900, introduced the term receptor as the designation for the function of the side chain. During the decade of 1930, Nikolai Lazarev showed that the different toxicological and physiological effects (C) of some molecules were related with their water/oil partition coefficients through formal mathematical expressions of the form:

$$\log K_i^B = \text{constant}_1 + \text{constant}_2 \log K_i^A \tag{2}$$

This moment of history could be considered as the birth of the quantitative structure-activity relationships field of research. On the side of organic chemistry, about 1900 most of its key concepts have been formulated, including the steric effect (Víctor Meyer in 1894 and Friedrich Kerhmann in 1888) and the substituent effects. An additional area of research is the one called Linear Free Energy Relationships. Their general form is a linear relationship between the logarithms of the equilibrium or rate constants for a set of reactions $[K^A_i]$, and the logarithms of a second set, $[K^B_i]$, subjected to the same variations of the reactant structure or of the reaction conditions:

$$\log K_i^B = \text{constant}_1 + \text{constant}_2 \log K_i^A \tag{3}$$

The expression *set of reactions* refers to the reaction of a series of substrates, a given substrate with a series of reactants

with the same substrate or to only one reaction under several different conditions (change of solvent for example). The expression free energy comes from the fact that the logarithm of the equilibrium constant is proportional to the change of the standard free energy associated to the reaction and because, following the Transition State Theory, a specific rate constant can be expressed as a function of a standard free energy of activation. Wilhelm Ostwald was one of the first scientists recognizing the existence of a series of regularities within a series of reactions (1885). In 1927 Hixon and Johns published the first comparisons of several sets of acid strengths by employing linear relationships. The first linear free energy was reported by Johannes Nicolaus Bronsted and Kai Julius Pedersen in 1924. The development of Quantum Mechanics during the years 1930 will provide, as we shall see below, entirely new tools for the research in the field of structure-activity relationships.

A primer about receptors

We owe to Alfred Joseph Clark the application of the Law of Mass Action to the drug-receptor interaction concept, providing a quantitative basis for the relationship between dose and effect. Clark's model has been modified and extended several times. Today we know that there is a very large quantity of receptors, that will be understood here as protein molecules that receive chemical signals from outside a cell. Receptor proteins are inserted in all cells' plasma membranes and be classified as cell surface receptors, cytoplasmic receptors, or nuclear receptors. Figure 1 shows an example of membrane receptors.

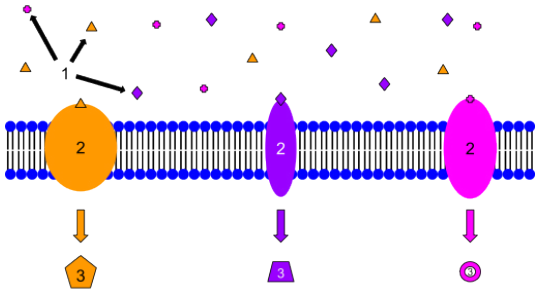

Figure 1: Membrane receptors (1. Ligands, 2. Receptors, 3. Secondary messengers). From Isaac Webb, https://en.wikipedia.org/wiki/Receptor_(biochemistry)#/ media/ File: Membrane_Receptors.svg.

Now we even know the atomic composition of many receptors. Figure 2 shows the crystallographic structure in ribbon representation of the 5-HT_{1B} serotonin receptor.

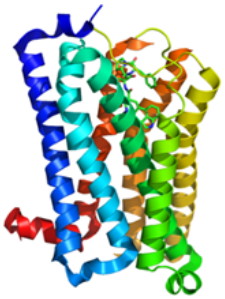

Figure 2: Crystallographic structure in ribbon representation of the 5-HT_{1B} serotonin receptor. From S. Jähnichen, https://commons.wikimedia.org/wiki/File:4IAR.png.

From a conceptual point of view, Ariens proposed to divide the space around receptors in three zones [2]. In Zone I, the drug-receptor interaction occurs through weak intermolecular interactions (for a reversible binding). Zone II is located around Zone I and it is defined as the zone in which long-range and ionic interactions orientate and guide the molecule toward the receptor. Zone III is the remainder of the biophase. Here, thermal agitation provokes sometimes the passing of molecules to Zone II. Ariens' model may look quite primitive but is still useful for its conceptual clarity. Let us consider another simple model of the space around the binding site [3]. The binding site has a 3D structure, may be inside a pocket or exposed to the protein's surface but the following conceptual analysis does not change. We may divide the ligand-site (L-S) interactions in the following four groups: weak (W, d(L-S) $\geq$ 5.0 Å), weak/medium (W/M, 4.0 Å $\geq$ d(L-S)<5.0 Å), medium (M, 3.0 Å $\geq$ d(L-S)<4.0 Å) and strong (S, d(L-S)<3.0Å). Note that this division is based only on the ligand-site distance and that the boundaries are quite arbitrary. Figure 3 displays this division [3].

The continuous thermal agitation (TA) will direct the molecules to the zone of weak interactions (W). Inside this volume, TA may push the molecule outside of this zone or toward the zone of weak/medium (W/M) interactions. Here, we may guess that those molecules having a large number of weak ligand-site interactions are more prone to pass to the zone of W/M interactions. In the zone of weak interactions the orientation and guiding processes probably begins. Next those molecules having a large number of W/M ligand-site interactions will resist the better the action of TA pushing them again toward the W zone. We hypothesize that, when entering the zone of medium (M) interactions these molecules are possibly not more affected by TA and can engage in the final interaction with the site through strong interactions. Now, the number of strong interactions could be related to the time the molecule remains interacting with the site that can be taken as a very simple representation of the affinity for the site. We can modify this analysis and consider that the sum of the weak and weak/medium interactions is enough to overcome the action of TA.

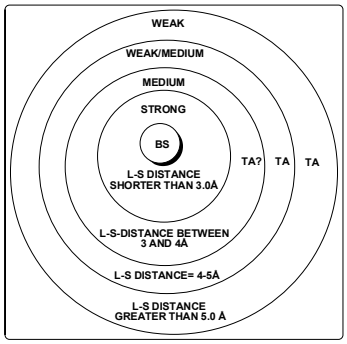

Figure 3: Simplified model of the space around the binding site. The terms weak, weak/medium, medium and strong correspond to the classification of interactions defined above. BS is the binding site and TA is the thermal agitation

Brain or statistics?

Let us consider the following expression:

$$\log A = c_1K_1 + c_2K_2 + c_3K_3 + ... + c_nK_n + \text{constant} \quad (4)$$

where A is a biological activity (affinity constant, antiviral activity, inhibition of cytopathic effects, toxicity, etc.), the c's are constants to be determined and the K's are molecular descriptors, defined as mathematical values describing the structure, the form or a property of the molecule.

It is the way employed to get Equation 4 that makes the difference between QSAR studies. In the first approach, Eq. 4 is simply written without any previous conceptual development (except the guess that there is a relationship between A and the K's). What about the K's? As there are about 4,000 molecular descriptors, it is only question to select a bunch of them, apply any of several statistical techniques and *voilà*! No one doubts that sometimes interesting results are obtained and perhaps some new molecules are discovered and some patents are obtained. My criticism of this methodology is the following. Many descriptors come from different realms: classical chemistry (solubility, ionization constants, experimental dipole moments etc.), quantum chemistry (calculated dipole moments, atomic net charges, reactivity indices, etc.), 2D or 3D geometry, graph theory, etc. When several of these indices coming from different realms are mixed in Equation 4 and a solution satisfying all confidence tests is obtained the problem of the physical interpretation appears (this is called an empirical equation). Surely, any of the molecular descriptors appearing as being significant can be interpreted as such but, what about the whole equation? Of all papers I have referred about this subject, none of their authors was able to answer convincingly this question. But this tsunami of molecular descriptors has an interesting side to be explored that is related to the possibility to redefine some of them in quantum chemical or statistical-mechanical terms (i.e., in the realm in which biological and chemical phenomena occur). Now, let us consider this other approach. A scientist is interested in studying the relationships between electronic structure and receptor binding affinity. First, he builds a model (an idealized representation of reality) of what could be happening. Next, he represents in an algebraic form the many hypothesis contained in the model. Finally, he derives an equation showing the expected relationships among the several descriptors appearing naturally inside his equation. This is Galileo's way. These kinds of equations are called model-based equations [4].

The first reactivity indices

As most biological and chemical processes occur within the microscopic realm, the natural tools to study them are

quantum mechanics and statistical mechanics. During the 1950-1960 decade, Quantum Chemistry begins to provide simpler and faster ways to calculate the electronic wave function of molecules. From this wave function several indices appear from the so-called population analysis (atomic net charges, electron populations of atoms called now the Fukui indices, etc.) and also the set of eigenvalues [5]. Two combinations of indices are extremely important. Let us examine Figure 4. We have a molecular system with a couple of substitutions at different places. We are interested in comparing the reactivity of atom x in both molecules. At that time, only the wave function of small molecules can be calculated and the idea that the two frontier molecular orbitals (MO), the Highest Occupied MO (HOMO) and the Lowest Unoccupied MO (LUMO) were controlling chemical reactions was stated because it was logical for small molecules.

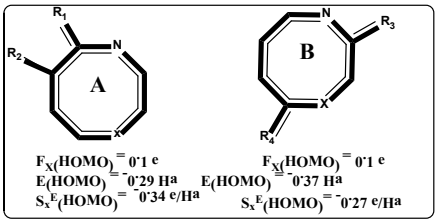

Figure 4: Fukui indices and super delocalizabilities

From the wave function we learn that in molecule A the HOMO has an energy of -0.29 Ha and that atom x has an electron population of 0.1 e in the HOMO and that in molecule B the HOMO has an energy of -0.27 Ha and that atom x has an electron population of 0.1 e in the HOMO. Based only on the HOMO electron populations of x, it is conceptually erroneous to state that x has the same chemical reactivity in both molecules. This is so because this electron population has a different associated eigenvalue: the electrons from atom x in molecule B are more easily "removed" because we need less energy (0.27 Ha) to do this. Then, a better way to represent the chemical reactivity of atom x is by dividing its HOMO electron population by the associated eigenvalue:

$$S_x(\text{HOMO}) = \frac{F_x(\text{HOMO})}{E_{HOMO}} \tag{5}$$

This is called the HOMO superdelocalizability of atom x. The same procedure is carried out for the LUMO and we get:

$$S_x(\text{HOMO}) = \frac{F_x(\text{HOMO})}{E_{HOMO}} \tag{6}$$

This is called the LUMO nucleophilic superdelocalizability of atom x. We can write a similar procedure for all the set of eigenvalues obtained from the wave function, giving origin to the orbital atomic superdelocalizabilities. The terms electrophilic and nucleophilic refer to the electron-donating and electron-accepting properties of atom x. We may also define:

$$S_x^E = \sum_{i=1}^{HOMO} \frac{F_x(i)}{E_i} \tag{7}$$

This index is called the total atomic electrophilic superdelocalizability of atom x. The summation is over all occupied MOs. For empty MOs we may define the total atomic nucleophilic superdelocalizability as:

$$S_x^N = \sum_{j=LUMO}^{N} \frac{F_x(j)}{E_j} \tag{8}$$

where the summation is over all empty MOs.

The work of Agin, Hersh and Holtzman

In 1965 a paper written by Agin et al. entitled '*The action of anesthetics on excitable membranes: a quantum-chemical analysis*' was published [6] (I copied some paragraphs from this article). I must comment it in this section because it is a splendid model of scientific reasoning to follow and because it should be presented and discussed at any teaching lecture on QSAR. This work deals with a study of the anesthetic action over the Sartorius muscle of the frog *Rana pipiens* of molecules with very different structures (some experimental values were taken from the literature). The first assumption these authors made is that they can consider that the partition function for a population of molecules of species A confronted with both the membrane surface and the adjacent extracellular solution is given by:

$$\frac{n}{n^*} = e^{E^*/RT} \tag{9}$$

where n* is the number of molecules adsorbed to the surface, n the number of molecules in solution and E* is some energy difference function. The problem consists in finding a suitable expression for E*. The following step is considering that all molecules are neutral. In this case, they assume that the total interaction energy between a molecule in solution and any molecule embedded in the surface is given mainly by the sum of four contributions (presumed to be independent).

$$E_T = E_K + E_D + E_L - E_R \tag{10}$$

where EK is the Keesom energy (dipole-dipole), ED is the Debye energy (dipole-induced dipole), EL is the London energy (induced dipole-induced dipole) and ER is the energy due to repulsion. Now, the problem of finding an expression for E* has been changed by the problem of finding appropriate expressions for the four components of the right side of Eq. 10.

Now the authors reasoned as follows. For nonpolar molecules or for molecules with only small permanent moments, EK << EL, ED << EL and usually both are counterbalanced by ER. If this is correct, then it is not necessary to consider EK, ED and ER. After this point, the authors wrote what I may call an avoidable statement: "*it will be seen that the results suggest this is justified*". This was not necessary. Now the problem consists only in using the mathematical form for ED:

$$E_L = \frac{3}{2}\frac{\alpha_1\alpha_2}{r^6}\frac{I_1 I_2}{I_1+I_2} \tag{11}$$

where r is interaction distance (center-center) in Å, α is the electronic polarizability in cc, and I is the ionization potential in eV. On the other hand they make use of a formula, derived by Casimir and Polder, for the interaction of a neutral molecule with a conducting wall (a model for the surface):

$$E_L = \frac{\alpha I}{8r^3} \tag{12}$$

where the polarizability and ionization potential refer to the neutral molecule. At this moment, and after some considerations about the use of I and the exact meaning of the interaction distance r, the authors have a mathematical form for E*:

$$\ln(n) = \ln(n^*) - \frac{1}{2RT}\alpha I\left\{\frac{1}{4r_1^3} - \frac{3\alpha_\omega I_\omega}{r_2^6(I+I_\omega)}\right\} \tag{13}$$

Where ω refers to water. Now, the authors stated that "since the variation of I is small, the expression within the braces remains relatively constant if rl and r2 are constant. After, they consider that a more convenient parameter than n is the minimum blocking concentration, MBC, defined as the minimum concentration in the external solution necessary for complete block of excitability". In this way, Equation 13 becomes:

$$\ln(\text{MBC}) = \ln C_s - K\alpha I \tag{14}$$

where Cs is the minimum blocking concentration of molecules at the surface and

$$K = -\frac{1}{2RT}\left\{\frac{1}{4r_1^3} - \frac{3\alpha_\omega I_\omega}{r_2^6(I+I_\omega)}\right\} \tag{15}$$

Now, and assuming that all the approximations made are right, and that the minimum surface concentration, C_s, necessary for complete block is about the same for all molecules, Equation 14 shows that there is a linear relationship between log(MBC) and αI. The procedures to obtain values for I and α were a mixture of experimental data and hand-made calculations (remember: no computers at that moment!). The results are shown in Figure 5.

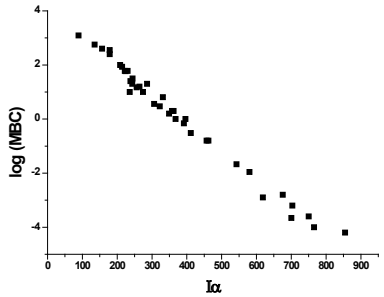

Figure 5: Plot of Iα vs. log (MBC) from Equation 14

As we can see, the results are extremely good and pleasant. This is what is expected to be the work of a serious Quantum Pharmacologist: first the working hypotheses and after the numbers to test them.

The contribution of Klopman and Hudson

The understanding of almost but not all chemical phenomena can be obtained with a model based on the interaction among molecular orbitals. The historical roots of this method can be traced to the works of Coulson and Longuet-Higgins, works continued, enlarged and perfected later. As we shall present below a model for weak interactions, we shall center our attention of the perturbation treatment of MO-MO interactions. In 1967 Klopman and Hudson presented a general perturbation model for chemical reactivity including ionic interactions and not restricted only to π electrons [7-9]. In their model, the electronic energy change, ΔE, associated with the interaction of atom i of molecule A with atom j of molecule B is given by:

$$\Delta E=\sum_{p}\left[\begin{array}{l} Q_i Q_j/R_{ij} + (1/2)(\beta_{ij}^2)\sum_{m}\sum_{n} F_{mi}F_{n'j}/(E_m-E_{n'}) - \\ - (1/2)(\beta_{ij}^2)\sum_{m'}\sum_{n} F_{m'i}F_{nj}/(E_{m'}-E_n) \end{array}\right] \quad (16)$$

where Q_i is the net charge of atom i, F_{mi} is the Fukui index of OM m of atom i, β_{ij} is the resonance integral (assumed to be independent of the kind of atomic orbitals (OA) because the A-B complex does not involve covalent bonds), E_m ($E_{m'}$) is the energy of the m-th occupied MO (m' for the empty MOs) of molecule A. n and n' refer to molecule B. The summation on p is over all interacting atom pairs. The first term of the right side of Equation 16 represents the electrostatic interaction between atom with net charges Q_i and Q_j. The next two terms introduce the interactions between occupied MOs of one molecule with the empty MOs of the other molecule and vice versa. As this model represents the interaction energy in terms of atom-atom interactions, it was only a matter of time that someone applied it for pharmacological/biological problems.

The paper of Peradejordi, Martin and Cammarata

This happened when, in 1971, an article written by Peradejordi et al. was published [10]. The authors presented the results of a quantum-chemical study of the structure-activity relationships of tetracycline antibiotics (Figure 6).

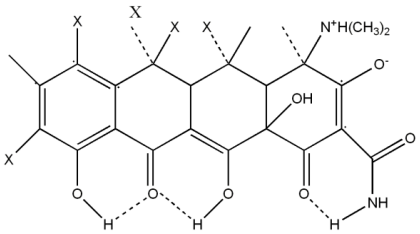

Figure 6: General structure of tetracyclines studied by Peradejordi et al. [10]

After an analysis of a possible mechanism of action Peradejordi et al. [10] proposed that the inhibitory rate constants, K_i^I, can be expressed as:

$$\log K_i^I = \text{constant} + \log K_i^c \quad (17)$$

where K_i^c is the ribosome-tetracycline equilibrium constant. Now, let us consider the following equilibrium:

$$D_i + R \leftrightarrow D_i R \quad (18)$$

where D_i is the drug, R the receptor and D_iR the drug-receptor complex. Accordingly to statistical thermodynamics we may write the corresponding equilibrium constant as:

$$K_i = \frac{Q_{D_iR}}{Q_{D_i}Q_R}\exp(-\Delta\varepsilon_0^i / kT) \quad (19)$$

where Q_{D_iR}, Q_{D_i} and Q_R are, respectively, the total partition functions of the drug-receptor complex, the drug and the receptor, and k and T stand for Boltzmann's constant and the absolute temperature. $\Delta\varepsilon_0^i$ is the difference in ground-state energies between the drug-receptor complex and the reactants:

$$\Delta\varepsilon_0^i = \varepsilon_{D_iR} - (\varepsilon_{D_i} + \varepsilon_R) \quad (20)$$

To dispose of the partition function terms, Peradejordi et al. [10] held that the partition function terms are constant

in the set of molecules analyzed. In their case this was almost correct. Next, they stated that the solvation energy is constant in the series because each of the two compound series, the ribosome-tetracycline complex and the tetracyclines are composed of molecules of the same size, having similar structure and a similar charge distribution in their zwitterionic moieties. After other considerations, and making use of Equation 16, they arrived to the expression:

$$\log K_i^I = c + d\sum_p \left\{ Q_{i_{t_p}} Q_{r_p} \langle tt|rr\rangle_p + \sum_{k_i}\sum_m \frac{2c_{k_i t_p}^2}{\varepsilon_{k_i} - \varepsilon_m} c_{mr_p}^2 \beta_{t_p r_p} - \sum_{l_i}\sum_n \frac{2c_{l_i t_p}^2}{\varepsilon_{l_i} - \varepsilon_n} c_{nr_p}^2 \beta_{t_p r_p} \right\}, \quad i=1,.,n \tag{21}$$

Where the summation of p is over all interacting pair of atoms. The Q's are atomic net charges, $\langle tt|rr\rangle_p$ is the coulombic electron-repulsion energy, the c's are the atomic orbital coefficients in the molecular orbital development, e_{ki} and e_{li} are, respectively, the energies of the occupied and empty molecular orbitals of Ti; e_m and e_n have the same meaning for the ribosome; and β_{tr} represents the resonance integral associated with the t_p-r_p bond. Note the important fact that the ribosome structure is not known. For this reason Equation 21 needs to be simplified in some way. *The first important point to consider is that we are working with a family of molecules interacting with the same site*. Therefore, all terms related to the ribosome can be considered as being constants. But the problem of terms like $1/(\varepsilon_{l_i} - \varepsilon_n)$ remains because the eigenvalues of the ribosome are not known. To solve this problem, Peradejordi et al. [10] held that "*the differences ε_{ki}-ε_n and ε_{li}–ε_m, for all pairs of orbitals will be large, with very little transfer of charge. The small differences between the various ε_m and between the various ε_n values can then be neglected*". This allowed them to obtain the following expression for ΔE:

$$\Delta E_{b,e} = A\, Q_b + B \sum_m^{occupied} \frac{F_{m,b}}{\varepsilon_m - \overline{\varepsilon}_{n'}} + C \sum_{m'}^{empty} \frac{F_{m',b}}{\varepsilon_{m'} - \overline{\varepsilon}_n} \tag{22}$$

In Equation 22 all terms are related to the tetracyclines, and A, B and C are constants. Now, as the second and third terms of the right side of Eq. 22 are similar (but not equal) to Fukui's superdelocalizabilities, Peradejordi et al. [10] arrived to the following final equation:

$$\Delta E = a + \sum_i \left[e_i Q_i + f_i S_i^E + s_i S_i^N \right] \tag{23}$$

Where Q_i is the net charge of atom i, S_i^E is the total atomic electrophilic superdelocalizability of atom i (equation 7) and S_i^N is the total atomic nuleophilic superdelocalizability of atom i (Equation 8). With all this analysis the following system of simultaneous linear equations is obtained:

$$\log K_i^I = A + \sum_p \left\{ a_p\, Q_{b,p} + b_p S_{b,p}^E + c_p S_{b,p}^N \right\} \qquad i=1,2,...,n \tag{24}$$

where A, a_p, b_p and c_p are constants to be determined. The net charges and the total atomic superdelocalizabilities were calculated with the current available methods for a previously defined set of atoms, called today the common skeleton (see below). As it happens even today, there were no data of enough molecules to solve system of equations 24. Therefore, linear multiple regression analysis techniques (LMRA) are employed to find a set of reactivity indices whose numerical variation gives the best account of the variation of $\log(K_i^I)$ values through the series. The plot of observed vs. calculated $\log(k_i^I)$ values is shown in Figure 7.

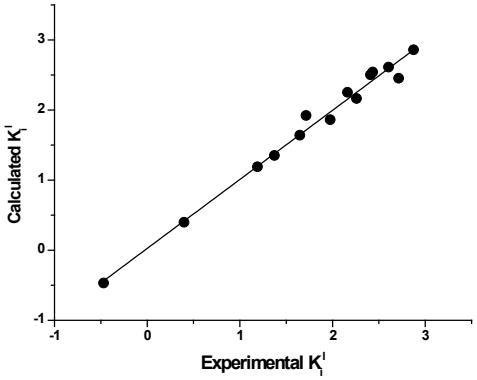

Figure 7: Graphic representation of actual *versus* estimated $\log(k_i^I)$ values

We can see that the agreement between observed and calculated values is excellent.

What about the author of this paper?

The above situation existed when this author arrived from Chile, at that time (1977) a small country localized at the end of the world, to the Centre de Mécanique Ondulatoire Appliquée du CNRS in Paris (CMOA). I was received by Professor Raymond Daudel, a gentlemen in the full extent of the word. He was a disciple of Louis de Broglie and one of the founders of French quantum chemistry. One day he invited me to a Vietnamese restaurant, just around the corner of CMOA to talk about Chile and my studies. Professor Daudel visited Chile one or two times, remembering with pleasure the *empanadas* (a kind of pastry baked or fried stuffed with onions, meat, hard-boiled egg, black olives and some spices) and the *cazuela de ave* (a kind of chicken casserole with vegetables). I was nervous because I was expecting an interrogation about quantum mechanics, quantum chemistry and related topics. At the end, when we were drinking water, he told me: "*I will tell you a phrase in Romanian to see if you can translate it*". Romanian keeps an important number of features of old Latin and also has words taken from the neighboring Slavic languages, as well as from French, German, Greek and Turkish. After a couple of minutes I did it correctly. It was all. He told me to talk with all the researchers to see if I can find something interesting me. After perambulating the CMOA, listening offers of work and promises of publishing in top journals, I selected Dr. Federico Peradejordi because he promised me nothing but an entirely new work. It consisted in employing the method of his above mentioned paper to study the relationships between electronic structure and the IC_{50} values of a series of morphine derivatives. After accepting, he told me: *Go and study all about opiates and return only when you think you know enough about this subject*. I must find the libraries, some of them outside of Paris, get reprints or photocopies, etc. I returned two months after! I called his method "*the swimming pool*" because you learn to swim or you drown yourself (sometimes I use it today to test the academic commitment of some students). At that time the first results about opiates interacting with their receptors were reported as IC_{50} (IC_{50} is the concentration of competing ligand which displaces 50% of the specific binding of the radioligand). While working in the problem I visited London, Amsterdam, Barcelona, Andorra, many museums (almost all weekends); and carried out many other different ludic activities (I was in Paris and not inside a convent). When the results began to appear, no significant statistical results could be obtained. After several hot discussions, sometimes using an unpleasant Spanish, I suggested that one problem was that, as the opiates have two rings in some cases and four in others, the partition functions were not constants and must be included in the model (because the differences in the masses and moments of inertia). My proposal was plainly rejected. Geometries were all revised again (they were hand-made at that time!), calculations were repeated but nothing relevant was obtained. Summarizing: I returned to Chile without degree, enraged and with the will of solving the problem at all cost. But my life in Paris never will be forgotten. Before finishing this section, I must add that I followed many authentically boring lectures. The only one impressing me up today was Professor Daudel's exposition: without notes and with only chalk, he started from the convex sets, traveled through all quantum mechanics and quantum chemistry and stopped when he wrote the equations of the semiempirical methods. This is the only case of teaching excellence I personally know. The following anecdote deserves to be told. In the CMOA there was a person charged of programming the needs of the scientists: you go to his office with your idea and you get a FORTRAN IV program. I was interested in writing a program to draw the molecular orbitals on the wide papers of the old IBM printers. As the programmer had a lot of jobs, I wrote the program myself (I still do these pleasant programming tasks). When I told Federico what I intended to do, I must listen a long diatribe despite my explanation that I know programming because in my country we must know a little about all aspects of our work. When I finished writing it, Federico accompanied me to punch the cards and read them to execute the program to draw the HOMO of benzene. The printed result was a large white paper sheet with only the six carbon and the six hydrogen atoms printed and resembling C_6H_6. I listened again a diatribe but this time it was very, very long. After returning to my desk and thinking a little, I run the program again, returned to Federico's office an told him: *Dear professor, the drawing was empty because the HOMO has zero electron density in the molecular plane. Here you have the HOMO density al 0.5 Å from the molecule's plane* and I showed him a beautiful HOMO. I received no comments. But I must recognize that Federico transferred to me something of what he inherited from his academic family tree (https://academictree.org/chemistry/tree.php?pid=71132): patience and the need of examining several times the results from different angles. The passage of time has shown that these abilities are extremely valuable.

The partition functions

Once in Chile, I began the analysis of the partition functions (PF, see Equation 19). The total partition function, Q, may be written as:

$$Q = Q^{tras}\left[g_0^{(e)} Q^{(\upsilon,r)_0} + \sum_{p=1} g_j^{(e)} Q^{(v,r)_j} \exp(\frac{-\Delta\varepsilon_j}{kT}) \right] \quad (25)$$

Where $\ddot{A}\mathring{a}_j = \mathring{a}_j - \mathring{a}_0$, Q^{tras} is the translational PF, $Q^{(v,r)}$ is the rovibrational PF and the g's are the degeneracies of the different levels. Now, and considering that the Boltzmann factors of the excited electronic states are negligible regarding the ground state (there are exceptions), we may use only the later:

$$Q = Q^{tras} Q^{(v,r)_0} \quad (26)$$

Regarding the translational PF's we may consider that the masses of the receptor and the molecule-receptor are similar (this occurs when the receptor is a macromolecule), we may write:

$$\log\left(\frac{Q^{tras}_{D_iR}}{Q^{tras}_{D_i} Q^{tras}_{R}} \right) \approx \log(M_{D_i}) \quad (27)$$

where MD is the mass of the drug molecule. I found the first possible reason why I could not get good results in

Paris (pethidine has two rings while morphine has five). In the meantime I got a book in which the full mathematical relationship between the equilibrium constant and IC_{50} was presented [11]. The essential result of the analysis of this relationships is that the IC_{50} values need to be measured in the same experimental setting (the same radioligand and quantity, the same quantity of tissue, etc.). When I was in Paris, I employed the first published experimental results (the IC_{50} technique was new) that come from different experimental settings: this was the main problem preventing me to get significant results.

For the rovibrational PF I employed the approximation:

$$Q^{(v,r)} = Q^{(v)} Q^{(r)} \quad (28)$$

and after some reasoning I was able to obtain the following expression:

$$\log\left(\frac{Q^{(r)_0}_{D_iR}}{Q^{(r)_0}_{D_i} Q^{(r)_0}_{R}} \right) = \text{constant} + \log\left(\frac{\sigma_{D_i}}{(ABC)^{1/2}} \right) \quad (29)$$

where ABC is the product of the moments of inertia along the three principal axis of rotation of the drug and $\acute{o}_{D_i}$ is its symmetry number. Again, only terms belonging to the drug appear in the right side of Equation 29. These results were published in due time [12].

In the meantime Francisco Tomás and José Aulló published a paper dealing with monoamine oxidase inhibition by β-carbolines using the same approach that Peradejordi et al. At home, I began to apply the work on the inhibition of acetylcholinesterase by carbamates [13], I showed that the numerical values of the total atomic nucleophilic superdelocalizability calculated with the CNDO/2 method were very sensitive to conformational changes [14] and I worked on other problems interesting me [15-17]. Finally, because of personal interest and because experimental data not involving IC_{50} was being published, my attention turned to the interaction of phenetylamines and indolealkylamines with the rat fundus serotonin receptor. My first paper showed that the molecular electrostatic potential (MEP) of mescaline analogues was very different in the neutral forms but very similar in the protonated ones (the ones existing at physiological pH) [18]. MEP is considered important during the earlier stages of the drug-site interaction, allowing the orientation and guidance of the molecule toward the receptor. The next step was the application of the expanded model of Peradejordi et al. to the mode of binding of phenylalkylamines to the (rat fundus) serotonergic receptor and a quantum chemical study of the relationships between molecular structure and (rat fundus) serotonin receptor binding affinity in serotonin analogues [19,20]. Also Cassels and I published a paper about the reevaluation of psychotomimetic amphetamine derivatives in humans [21] and another showing the relationship between the equilibrium constant and IC_{50} [22]. My work continued by analyzing the relationships between electronic structure and pA_2 in a series of 5-substituted and 7-substituted tryptamines [23,24]. The culmination of these studies was achieved when I and my collaborators were able to make a fully successful prediction. There was experimental evidence that DON ((±)-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane) could have hallucinogenic activity despite that the 4–nitro substituent has a different chemical nature than the usual 4-substituents (Br, Me, Et, OMe). The ensuing step was to employ one of my earlier equations relating pA_2 and electronic structure in phenylalkylamines [20]. Our predicted pA_2 value was 7.52 while the experimental pA_2 value for the R-(-) isomer is 7.49 [25]. The next step was to employ the correlation between pA_2 and total hallucinogenic dose (THD) in humans developed by Glennon et al., obtaining

a THD value of 0.6 mg for the nitrate [25]. The experiments in humans have shown that a dose of about 3.5 mg of DON nitrate (as racemate) produces strong LSD-like effects in some individuals (not in all subjects because of their biological differences), including the classical hexagonal grid in the sky (numerous reports about this grid can be found in Internet). This successful prediction was enough stimulating to continue working with the KPG model.

The drug-receptor interaction energy

I continued working the drug-site interaction energy (Equation 21), trying to find a more elegant way to deal with the eigenvalues of the site. One day I noticed that the term like $1/(E_m-E_n)$ can be written as a series expansion [26]:

$$\frac{1}{1-x}=1+x+x^2+x^3+.... \qquad |x|<1 \tag{30}$$

This led to the following equation:

$$\Delta E=a+\sum_i\left[e_iQ_i+f_iS_i^E+s_iS_i^N\right]+\sum_i\sum_m\left[h_i(m)F_i(m)+j_i(m)S_i^E(m)\right]+$$
$$+\sum_i\sum_{m'}\left[r_i(m')F_i(m')+t_i(m')S_i^N(m')\right]+\Phi \tag{31}$$

where $F_i(m)$ is the Fukui index (the electron population) of atom i in MO m [5], $S_i^E(m)$ is the electrophilic superdelocalizability of OM m, at atom i (i.e., the electron population of atom i in MO m divided by the MO energy), m' stands for the vacant MOs and Φ is the remnant of the series expansion. Now, we have local atomic reactivity indices concerning any MO and any atom. Now, allow me a disquisition. During years the 80s the calculation of the molecular wave function was done using a computer (an IBM-370 if I remember well) but full geometry optimizations take a long time, even with CNDO/2. Therefore, as I was convinced that the states of consciousness must have neural correlates, I decided to see what it can be done about this matter. With a very good friend and skilled neurologist, Juan Carlos Saavedra-Aguilar (MD) we began to study the so-called "near-death experiences" (NDE). The product of our work was the first proposed full neurobiological model of NDE, and it was published in a special issue [27,28]. Later we made other contributions [29-31]. Still today I think about this and related problems [32,33].

The orientational parameter of the substituent

Another problem I was attacking was how modify the rotational partition function in order to obtain terms related to the substituents. We started by expressing the rotational kinetic energy in terms of the $\hat{H}(p,q)$ operator (with the Euler angles):

$$\hat{H}(p,q)=\frac{\sin^2\delta}{2A}\left[P_\theta-\frac{\cos\delta}{\sin\theta\sin\delta}(P_\phi-P_\delta\cos\phi\right]^2+$$
$$+\frac{\cos^2\delta}{2B}\left[P_\theta+\frac{\sin\delta}{\sin_\theta\cos\delta}(P_\phi-P_\delta\cos\theta)\right]^2+\frac{1}{2C}P_\delta^2 \tag{32}$$

where A, B and C are the moments of inertia around the principal axis of rotation and used the classical expression for the rotational partition function

$$Q_r=\frac{1}{h^3}\int_0^\pi\int_0^{2\pi}\int_0^{2\pi}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}e^{-\hat{H}(p,q)/kT}d\theta d\phi d\delta dP_\theta dP_\phi dP_\delta \tag{33}$$

With this we obtained the following expression:

$$Q_r=\frac{8\pi^2(2\pi kT)^{3/2}(ABC)^{1/2}}{h^3\sigma} \tag{34}$$

where σ is the symmetry number.

The analysis of the moments of inertia with the consideration that we are dealing with a family of drugs interacting with the same receptor led to the following approximate expression:

$$\ln(ABC)\approx k\sum_i m_{i,j}r_{i,j}^2=\sum_i O_i \tag{35}$$

where k is a constant, the summation on i is over all substituents of a common skeleton, $m_{i,j}$ is the mass of atom j of substituent i and $r_{i,j}^2$ is the distance of atom j of substituent i to the molecule's center of mass. We interpreted these

new indices as giving an account of the substituent's influence on the percentage of molecules achieving the correct orientation to interact with the site [34]. For this reason we called them "orientational parameters". As this way of calculating them was complicated we simple proceeded as follows. We built a benzene ring, we attached a given substituent to it, we optimize the geometry, and we calculate the corresponding OP using as the coordinate origin the carbon to which the substituent was attached. Recently we have published standard tables of OP values for some substituents [35-37]. Table 1 summarizes all studies carried out until the next theoretical stage was incorporated.

Table 1: Summary of formal structure-activity studies (1982-2010)

Paper	Title	Ref.
1	Quantum-chemical studies on acetylcholinesterase inhibition. I. Carbamates	[13]
2	The mode of binding of phenylalkylamines to the Serotonergic Receptor	[20]
3	Quantum chemical approach to the relationship between molecular structure and serotonin receptor binding affinity	[19]
4	Quantum-chemical study of the relation between electronic structure and pA2 in a series of 5-substituted tryptamines	[24]
5	Electronic structure and serotonin receptor binding affinity of 7-substituted tryptamines	[23]
6	A quantum-chemical and experimental study of the hallucinogen (±)-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON)	[25]
7	Quantum chemical study of electronic structure and receptor binding in opiates	[38]
8	Electrostatic medium effects and formal quantum structure-activity relationships in apomorphines interacting with D1 and D2 dopamine receptors	[39]
9	Quantum-chemical Structure-Activity Relationships in carbamate insecticides	[40]
10	Quantum-chemical structure-affinity studies on kynurenic acid derivatives as Gly/NMDA receptor ligands	[41]
11	Theoretical study of the opioid receptor selectivity of some 7-arylidenenaltrexones	[42]
12	A Zindo/1 Study of the Cannabinoid-Mediated Inhibition of Adenylyl Cyclase	[43]
13	A structure-affinity study of the opioid binding of some 3-substituted morphinans	[44]
14	A theoretical study of the inhibition of wild-type and drug-resistant HTV-1 reverse transcriptase by some thiazolidenebenzenesulfonamide derivatives	[45]
15	A theoretical structure-affinity relationship study of some cannabinoid derivatives	[46]
16	A DFT study of the relationships between electronic structure and peripheral benzodiazepine receptor affinity in a group of N,N-dialkyl-2- phenylindol-3-ylglyoxylamides	[47]

A survey of the papers presented in Table 1 will show that almost all but one were carried out calculating the molecular wave function with the semiempirical CNDO/2 and ZINDO/1 methods. Today they look very primitive but they were really successful. ZINDO/1 is designed in such a way that the eigenvalues of empty MOs are always positive, eliminating the arithmetical cancellation of terms in Eq. 8. Paper 15 of Table 1 was the first one using density functional theory (DFT). Its existence is due to the use of a computational cluster in Dr. Boris Weiss' Laboratory (I am still obliged to him). This paper opened the following new research line.

Now, to build the data matrix for LMRA, we shall employ Equation 31 and 35 and consider a common skeleton composed by ten atoms. In the data matrix, the first row is composed by the biological activity of molecule 1 (in the first column), the three reactivity indices of Eq, 24 corresponding to atom 1, plus the MO-dependent indices of Equation 31 (if we consider only the three highest occupied and the three lowest vacant MOs, we get 12 local indices per atom), plus the orientational parameters of the substituents (if there are). Therefore, each atom is described now by 15 local atomic reactivity indices. At this point it is clear that never we shall find a paper with enough molecules to solve the linear system of equations (the extended version of Equation 24).

FIXING MULLIKEN POPULATION ANALYSIS

As it is well known, Mulliken Population Analysis (MPA) has some drawbacks. Sometimes it produces negative electron populations and sometimes MO populations greater than 2. When calculating biologically active molecules we began to notice the appearance of these anomalous populations. Interestingly these problems are dependent on the size of the molecules and the basis set. As I was employing MPA and I still do it, I designed an empirical way to solve this problem [48]. The procedure consisted simply in distributing the anomalous populations of an atom between the atoms bonded to it. It is probably an approximate method but, considering that for the medium-sized molecules we usually study the anomalous populations are small, it worked without problems (up to this date).

The generation of new local atomic reactivity indices

The line of research was based on my dislike for some results of conceptual DFT. Let us consider the example of molecular hardness, η. In principle η is simply the HOMO-LUMO energy gap. η is expressed in eV (or analogous units). When we need to calculate the HOMO "local" hardness of atom i, we simply multiply η by the Fukui index of the HOMO at this atom. The problem is that this DFT "local" hardness has units of eV×e, creating serious conceptual doubts about its meaning. I remember that one colleague told me one day something like *there is a theorem in DFT not allowing to calculate…* and that I answered *I don't care, I will create this index with or without theorems* (a Feyerabend-like approach).

This research was running in parallel with a conceptual analysis of the data matrix for LMRA. As all quantum chemists know, in enough larger molecules, the HOMO or any other MO is not always localized on the whole molecule. Figure 8 shows some examples (from [49]).

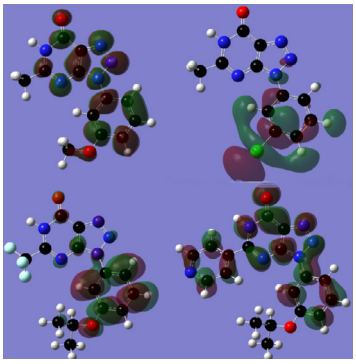

Figure 8: Some molecular orbitals of a [1,2,3]Triazolo[4,5−d]pyrimidin-7(6H)−one derivative (from [49])

The history runs as follows. I was considering how to build the LRMA data matrix for atoms having zero electron population when I suddenly had a kind of enlightenment experience (Aufklärung). As internal experiences cannot be explained to others, I show in Figure 9 the results.

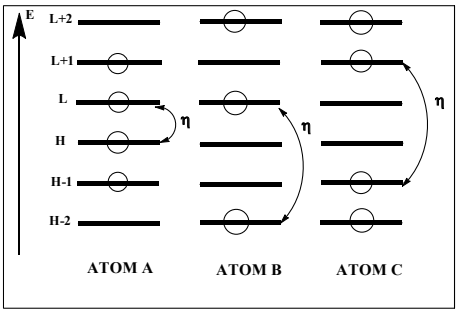

Figure 9: Local atomic reactivity indices and local molecular orbitals (H stands for the HOMO, H-1 for the second highest occupied MO, H-2 for the third highest occupied MO, L for the LUMO, L+1 for the second lowest empty MO and L+2 for the third lowest empty MO)

In Figure 9 we have three atoms A, B and C. The MOs carrying a circle are those with a non-zero electron population, i.e., the ones localized on these atoms. In the case of atom A the molecular HOMO and LUMO are localized on it. I called them $HOMO_A$* and $LUMO_A$*. This allowed me to define the *local atomic hardness* of atom A as the $HOMO_A$*- $LUMO_A$* gap (η_A). In this case the local MOs coincide with the molecules' frontier MOs. In the case of atom B, its *local* HOMO corresponds to the third highest occupied MO of the molecule and its *local* LUMO to the molecule's LUMO. Here, η_B corresponds to the molecular (HOMO-2)-LUMO gap and the molecular (HOMO-2) is called the *local* HOMO of atom B and is written as $(HOMO)_B$*. For atom C we have that η_C is the molecular (HOMO-1)- (LUMO+1) gap. In this case, (HOMO-1) is written $HOMO_C$* and (LUMO+1) as $LUMO_C$*. The most important fact of these definitions is that this local atomic hardness is expressed in eV, exactly as the global hardness. This was intellectually satisfactory. Also, this approach introduces naturally the concept of Local Frontier Molecular Orbitals. The role in chemistry of molecular orbitals other that the frontier ones has been suggested many times. The data matrix for LMRA is built now with these considerations. Figure 9 shows that the following new local atomic reactivity indices are defined as:

Local atomic electronic chemical potential:

$$\mu_i=(\varepsilon_{HOMO^*,i}+\varepsilon_{LUMO^*,i})/2 \quad (36)$$

Local atomic hardness:

$$\eta_i=(\varepsilon_{HOMO^*,i}-\varepsilon_{LUMO^*,i}) \quad (37)$$

Local electrophilic superdelocalizability of the HOMO* of atom i and local nucleophilic superdelocalizability of the LUMO* of atom i:

$$S_i^{E^*}=\frac{F_{i,HOMO^*}}{\mathring{a}_{HOMO^*}} \quad (38)$$

$$S_i^{N^*}=\frac{F_{i,LUMO^*}}{\varepsilon_{LUMO^*}} \quad (39)$$

Local atomic softness of atom i:

$$S_i=\kappa_i=\frac{1}{\eta_i} \quad (40)$$

Local atomic electrophilicity of atom i:

$$\omega_i=\frac{\mu_i^2}{2\eta_i} \quad (41)$$

The maximal amount of charge atom i may receive:

$$Q_i^{max}=-\frac{\mu_i}{\eta_i} \quad (42)$$

The physical meaning of these indices is: μi is a measure of the tendency of a system to gain or lose electrons; a large negative value indicates a good electron acceptor while a small negative value implies a good electron donor. The local atomic hardness can be interpreted as the resistance to exchange electrons with the environment. The local electrophilic index is associated with the electrophilic power and includes the tendency of the electrophile to receive extra electronic charge together with its resistance to exchange charge with the medium. These results were published in 2013 [50].

Now, the original Equation 24 becomes:

$$\log K_i = a + bM_{D_i} + c\log\left[\sigma_{D_i}/(ABC)^{1/2}\right] + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N\right] +$$
$$+ \sum_j \sum_m \left[h_j(m)F_j(m) + x_j(m)S_j^E(m)\right] + + \sum_j \sum_{m'} \left[r_j(m')F_j(m') + t_j(m')S_j^N(m')\right] +$$
$$+ \sum_j \left[g_j\mu_j + k_j\eta_j + o_j\omega_j + z_j\varsigma_j + w_jQ_j^{max}\right] \quad (43)$$

Table 2 shows the application of these results to several molecular systems with the new local atomic reactivity indices (the article's title was included to give an idea of the activities analyzed) and the new form of the data matrix. Figure 10 shows the new form of the data matrix.

Table 2: Formal structure-activity studies (2010-2016, affinity constants, IC_{50}, pA_2)

Paper	Title	Ref.
17	A DFT and Semiempirical Model-Based Study of Opioid Receptor Affinity and Selectivity in a Group of Molecules with a Morphine Structural Core	[51,52]
18	A quantum-chemical analysis of the relationships between hCB2 cannabinoid receptor binding affinity and electronic structure in a family of 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives	[53]
19	A quantum chemical analysis of the relationships between electronic structure, PAK1 inhibition and MEK phosphorylation in a series of 2-arylamino-4-aryl-pyrimidines	[54]
20	A Preliminary Formal Quantitative Structure-Activity Relationship Study of some 1,7-Bis-(amino alkyl)diazachrysene Derivatives as Inhibitors of Botulinum Neurotoxin Serotype A Light Chain and Three P. falciparum Malaria Strains ***	[55]
21	A DFT Study of the Inhibition of the Papain-like Protease (PLpro) from the SARS Coronavirus by a Group of 4-Piperidinecarboxamide Derivatives	[56]
22	A Density Functional Study of the Inhibition of the Anthrax Lethal Factor Toxin by Quinoline-based small Molecules related to Aminoquinuride (NSC 12155)	[57]
23	A Short Note on the Relationships between Electronic Structure and S-Nitrosoglutathione Reductase Inhibition by 3-[1-(4-carbamoylphenyl)-5-phenyl-1H-pyrrol-2-yl]propanoic acids	[58]

24	A DFT Study of the Relationships between the Electronic Structures of a series of 2,4,5- Trisubstituted Pyrimidines and their Inhibition of four Cyclin-dependent Kinases and their Anti-Proliferative Action against HCT-116 and MCF-7 Cell Lines ***	[59]
25	A Theoretical Study of the Relationships between Electronic Structure and CB1 and CB2 Cannabinoid Receptor Binding Affinity in a Group of 1-Aryl-5-(1-H-pyrrol-1-yl)-1-H-pyrazole-3-carboxamides	[60]
26	A Density Functional Theory study of the relationships between electronic structure and metabotropic glutamate receptor subtype 5 affinity of 2-amino- and 2-halothiazole derivatives	[61]
27	Quantum-Chemical and Docking Studies of 8-Hydroxy-Quinolines as Inhibitors of the Botulinum Neurotoxin A Light Chain (BoNT/A LC)	[3]
28	A Density Functional Theory and Docking study of the Relationships between Electronic Structure and 5-HT_{2B} Receptor Binding Affinity in N-Benzyl Phenethylamines	[62]
29	A Quantum Chemical Analysis of the Inactivation Rate Constant of the BoNT/A LC Neurotoxin by some 1,4-Benzoquinone and 1,4-Naphthoquinone derivatives	[63]
30	DFT and Docking Studies of the Relationships between Electronic Structure and 5-HT_{2A} Receptor Binding Affinity in N-Benzylphenethylamines	[64]
31	A Quantum Chemical Study of the Relationships between Electronic Structure and cloned rat 5-HT_{2C} Receptor Binding Affinity in N-Benzylphenethylamines	[65]
32	A DFT analysis of the Inhibition of Carbonic Anhydrase Isoforms I, II, IX and XII by a Series of Benzenesulfonamides and Tetrafluorobenzenesulfonamides	[66]
33	A Quantum-chemical and Docking study of the inhibitory activity of a family of Thienopyrimidine derivatives bearing a chromone moiety against mTOR Kinase	[67]
34	Electronic structure and docking studies of the Dopamine D3 receptor binding affinity of a series of [4-(4-Carboxamidobutyl)]-1-arylpiperazines	[68]
35	A Density Functional Study of the Relationships between Electronic Structure and Dopamine D2 receptor binding affinity of a series of [4-(4-Carboxamidobutyl)]-1-arylpiperazines	[69]
36	A Density Functional Study of the Inhibition of Microsomal Prostaglandin E2 Synthase-1 by 2-aryl substituted quinazolin-4(3H)-one, pyrido[4,3-d]pyrimidin-4(3H)-one and pyrido[2,3-d]pyrimidin-4(3H)-one derivatives	[70]
37	A Theoretical Analysis of the Relationships between Electronic Structure and HIV-1 Integrase Inhibition, Antiviral Activity and Protein Binding Effects of a series of Naphthyridinone derivatives ***	[71]
38	A DFT study of the inhibition of human phosphodiesterases PDE3A and PDE3B by a group of 2-(4-(1H-tetrazol-5-yl)-1H-pyrazol-1-yl)-4-(4-phenyl)thiazole derivatives	[72]
39	A quantum chemical study of the inhibition of α-glucosidase by a group of oxadiazole benzohydrazone derivatives	[73]
40	A note on the inhibition of steroid 11β-hydroxylase, aldosterone synthase and aromatase by a series of coumarin derivatives	[74]
41	A quantum chemical analysis of the inhibition of protein kinase A (PKA) and Rho-associated protein kinase-2 (ROCK2) by a series of urea-based molecules	[75]
42	A theoretical study of the inhibition of human 4-hydroxyphenylpyruvate dioxygenase by a series of pyrazalone-quinazolone hybrids	[76]
43	A theoretical analysis of the inhibition of the VEGFR-2 vascular endothelial growth factor and the anti-proliferative activity against the HepG2 hepatocellular carcinoma cell line by a series of 1-(4-((2-oxoindolin-3-ylidene)amino) phenyl)-3-arylureas ***	[77]
44	A DFT study of the inhibition of FMS-like tyrosine kinase 3 and the antiproliferative activity against MV4-11 cells by N-(5-(tert-butyl)isoxazol-3-yl)-N'-phenylurea analogs ***	[78]
45	A Quantum-Chemical Analysis of the Relationships between Electronic Structure and Cytotoxicity, GyrB inhibition, DNA Supercoiling inhibition and anti-tubercular activity of a series of quinoline–aminopiperidine hybrid analogues ***	[79]

This method was called the Klopman-Peradejordi-Gómez method for the main contributors to its development and because the KPG abbreviation looks good. If somebody feels that his/her contribution is also fundamental, we have no problem in changing the name.

On the other hand I was thinking in a way to apply this method to biological activities different from equilibrium constants (K_i, pA_2, IC_{50}, etc.). I was influenced by the results of several works of Cammarata and Rogers (and maybe others). They found the following results: the partition coefficients are correlated by a model equation including the charge density and the induced polarization of thirty aromatic molecules, a correlation between the partition coefficients of 19 molecules and their charge density and total electrophilic superdelocalizability, a correlation of the lipophilic parameter (π) values for benzoic acid substituents with appropriate electronic indices calculated for the same substituents, and that some electronic indices were suitable for correlating the π values derived for phenoxyacetic acids. Looking back with our actual knowledge, all these results were pointing to the fact that the abovementioned reactivity indices existing at that time were exceptionally useful. Moreover, the fact that the lipophilic parameter could be expressed in terms of electronic indices allows it to appear in Equation 43. In this moment I began to test the model

for other biological activities. I worked with some undergraduate students on the relationships between accumulation capacity and molecular structure in a group of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and polychlorinated biphenyls in some zucchini subspecies [80] and in structure-biological activity relationships for two different sets of molecules presenting inhibitory activity against some effects of HIV-1 (inhibition of HIV-induced cytopathicity and cytostatic effects) and H1N1 virus (decrease of H1N1-induced cytopathic effects) [81]. The excellent results obtained led me to the next step.

I stated the following general hypothesis: *all biological processes occurring, from the moment of the entry of a drug molecule into the biological system* (*in vitro* or *in vivo*) *until the manifestation of any biological activity, are controlled by the local atomic reactivity indices appearing in Equation 43*. Therefore, if this hypothesis is correct, a preliminary representation of the final biological action can be obtained simply by replacing log K_i by log (BA), where BA is any biological in vitro or in vivo activity [51]. But this hypothesis is true if and only if it fulfills the following condition. The drug molecules may undergo a multi-step (for example, in the n-th step molecules must cross a pore) and/or a multimechanistic (for example, to cross the pore molecules must interact consecutively with j unknown sites) processes. *Therefore it seems logical to state that a necessary condition to obtain good structure-activity relationships is that all the steps and all the mechanisms inside each step must be the same for all the group of molecules under study* [51]. This opened an entirely new territory for research. The resulting papers are shown in Table 3.

Table 3: Formal structure-activity studies for biological activities (2010-2016)

Paper	Title	Ref.
46	Model-based quantum-chemical study of the uptake of some polychlorinated pollutant compounds by Zucchini subspecies	[52]
47	Modeling the relationships between molecular structure and inhibition of virus-induced cytopathic effects. Anti-HIV and anti-H1N1 (Influenza) activities as examples	[81]
48	Quantum-chemical modeling of the relationships between molecular structure and in vitro multi-step, multimechanistic drug effects. HIV-1 replication inhibition and inhibition of cell proliferation as examples.	[51]
49	Quantum Chemical Study of the Relationships between Electronic Structure and Pharmacokinetic Profile, Inhibitory Strength toward Hepatitis C virus NS5B Polymerase and HCV replicons of indole-based compounds	[82]
50	Quantum-chemical modeling of the hepatitis C virus replicon inhibitory potency and cytotoxicity of some pyrido[2,3-d] pyrimidine analogues	[83]
51	A Theoretical Study of the Relationships between Electronic Structure and Cytotoxicity of a group of N2-alkylated Quaternary β-Carbolines against nine Tumoral Cell Lines	[84]
52	A theoretical study of the relationships between electronic structure and anti-inflammatory and anti-cancer activities of a series of 6,7-substituted-5,8-quinolinequinones	[85]
53	An Analysis of the Electronic Structure of an Imidazo[1,2-a]Pyrrolo[2,3-c]Pyridine series and their anti-Bovine Viral Diarrhea Virus Activity	[86]
54	Toward Understanding the Inhibition of Vesicular Stomatitis Virus Replication in MDCK Cells by 4-Quinolinecarboxylic acid Analogues. A Density Functional Study	[87]
55	A Note on the Relationships between Electronic Structure and Inhibition of Chikungunya Virus Replication by a group of [1,2,3]Triazolo[4,5-d]pyrimidin-7(6H)-ones Derivatives	[49]
56	Quantum-chemical study of the relationships between electronic structure and anti-influenza activity. 1. The inhibition of cytophatic effects produced by the influenza A/Guangdong Luohu/219/2006 (H1N1) strain in MDCK cells by substituted bisaryl amide compounds	[88]
57	Quantum-chemical study of the relationships between electronic structure and anti-influenza activity. 2. The inhibition by 1H-1,2,3-triazole-4-carboxamide derivatives of the cytopathic effects produced by the influenza A/WSN/33 (H1N1) and A/HK/8/68 (H3N2) strains in MDCK cells	[89]
58	A Quantum-chemical study of the in vitro cytotoxicity of a series of (Z)-1-aryl-3-arylamino-2-propen-1-ones against human tumor DU145 and K562 cell lines	[90]
59	A Theoretical Study of the Relationships between Electronic Structure and Antifungal Activity against Botrytis cinerea and Colletotrichum lagenarium of a Group of Carabrone Hydrazone Derivatives	[91]
60	A Preliminary Quantum-Chemical Study of the anti-HIV-1 IIIB Activity of a series of Etravirine-VRX-480773 Hybrids	[92]
61	A theoretical study of the relationships between electronic structure and inhibition of tumor necrosis factor by cyclopentenone oximes	[93]
62	Quantum-chemical study of the cytotoxic activity of pyrimidine–benzimidazol hybrids against MCF-7, MGC-803, EC-9706 and SMMC-7721 human cancer cell lines	[94]
63	A quantum-chemical analysis of the antiproliferative activity of N-3-benzimidazolephenylbisamide derivatives against MGC803, HT29, MKN45 and SW620 cancer cell lines	[95]
64	A theoretical analysis of the relationship between the electronic structure of indole derivatives and their phytotoxicity against Lactuca Sativa seeds	[96]

65	A theoretical analysis of the cytotoxicity of a series of β-carboline-dithiocarbamate derivatives against prostatic cancer (DU-145), breast cancer (MCF-7), human lung adenocarcinoma (A549) and cervical cancer (HeLa) cell lines	[97]
66	A preliminary DFT analysis of phenolic acids in connection with their phytotoxic activity	[98]
67	Quantum Chemical Analysis of the Relationships between Electronic Structure and Antiviral Activity against HIV-1 of some Pyrazine-1,3-thiazine Hybrid Analogues	[99]
68	On the relationship between electronic structure and carcinogenic activity in substituted Benz[a]anthracene derivatives	[100]
69	A Quantum-Chemical study of the Relationships between Electronic Structure and Trypanocidal Activity against Trypanosoma Brucei Brucei of a series of Thiosemicarbazone derivatives	[101]
70	A quantum-chemical study of the relationships between electronic structure and anti-HIV-1 activity of a series of HEPT derivatives	[102]

Table 3 shows that the application of Eq. 43 to many different biological activities give very good results. The most gratifying paper of 2016 was the one entitled "*On the relationship between electronic structure and carcinogenic activity in substituted Benz[a]anthracene derivatives*" [100]. From about 1945 many researchers are trying to obtain a formal relationship between molecular structure and carcinogenic activity without success (two or three purely statistically structure-activity relationships have been published). In this paper we did it and we found that a specific atom, never mentioned in all previous studies, appears as being important for carcinogenic activity. We still work on this topic. Another important matter to deal with is the interpretation of the results. If the action mechanism is unknown, then we have no way to assign the reactivity indices appearing in the resulting equations to a specific site of the chain of events leading to the appearance of the biological effect.

$$\left\{\begin{array}{ccc} A & B & C \\ F_A(L) & .... F_B(L) & .... F_C(L) \\ F_A(H) & .... F_B(H) & .... F_C(H) \end{array}\right\} \rightarrow \left\{\begin{array}{ccc} A & B & C \\ F_A(L) & .... F_B(L+1) & .... F_C(L+2) \\ F_A(H) & .... F_B(H) & ..... F_C(H-2) \end{array}\right\} \rightarrow \left\{\begin{array}{ccc} A & B & C \\ F_A(L)^* & .... F_B(L)^* & .... F_C(L)^* \\ F_A(H)^* & .... F_B(H)^* & .... F_C(H)^* \end{array}\right\}$$

Figure 10: From left to right: molecular frontier MOs, atomic frontier MOs and local nomenclature (from [51])

The problem of the common skeleton

As we said before, the KPG method makes use of the concept of common skeleton. This skeleton is defined as a definite collection of atoms, common to all molecules selected for a study, which accounts for nearly all the biological activity. Nevertheless, the selection of the set of atoms is not easy in some cases. Let us consider the molecular system depicted in Figure 11 (taken from [103]).

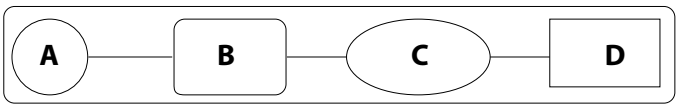

Figure 11: A molecular system

This system is arbitrarily divided in regions A, B, C and D that are common to all molecules studied. The common skeleton contains atoms belonging to all of them. The standard KPG procedure employs this skeleton. Now, let us consider a case in which all molecules have regions A, B and C in common (set X), but region D is present only in some (set Y). In these cases the KPG method should be applied to two sets of molecules: the one corresponding to set X and the one composed by set Y. In the first case we use atoms of regions A, B and C to compose the common skeleton and in the second we employ atoms of the four regions. The analysis of the statistically significant results should provide more information about some of the atoms participating in the drug-site interaction or in the process leading to the appearance of a biological effect. A good example is the interaction of phenylalkylamines with the serotonin receptors. The usual common skeleton will include the carbon atoms of the phenyl ring, the atoms of the side C-C-N chain and the proton. But we have found that, if we enlarge the common skeleton by adding the first atom of the substituents attached to the phenyl ring, the results are significantly better [103,104]. Therefore the researcher should try to study, if possible, more than one common skeleton to get more useful information.

Table 4: Intermolecular interactions

Interactions		
Hydrogen Bonds	Classical	Hydrogen-bond between strong donor and acceptor atoms.
	Non Classical	Interactions between a carbon donor atom and an acceptor, or a π group and a donor atom.
	Water	Hydrogen bonds formed with water molecules.
	Salt Bridge	Hydrogen bonds between charged groups.

Electrostatic	Charge	Interactions between pairs of oppositely charged groups.
	π-Charge	Interactions between a positively charged atom and the electrons of a delocalized π system: π-cation
Hydrophobic	π-Hydrophobic	Hydrophobic interactions with delocalized π systems (such as π-π).
	Alkyl Hydrophobic	Hydrophobic interactions with alkyl groups.
	Mixed π/Alkyl Hydrophobic	Weak π-σ interactions between a C-H and a π ring system, or interactions of other alkyl groups and π rings.
Halogen	Fluorine	Interactions with fluorine atoms.
	Cl, Br, I	Interactions with chlorine, bromine, or iodine atoms.
Miscellaneous	Metal	Metal interactions between metal cations and hydrogen bond acceptors.
	Sulfur	Interaction with sulfur atoms.
	Lone Pairs	Lone pair interaction with positively polarized π rings.

About the pharmacophore

The IUPAC defines the pharmacophore as "*the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response*". "*A pharmacophore does not represent a real molecule or a real association of functional groups, but a purely abstract concept that accounts for the common molecular interaction capacities of a group of compounds towards their target structure. The pharmacophore can be considered as the largest common denominator shared by a set of active molecules*" [105]. As the equations provided by the KPG method include only those reactivity indices whose variation gives an account of the variation of the biological activity, we have called them *partial* pharmacophores. An interesting line of research, not yet followed for this model, is to analyze several results involving different sets of molecules acting in the same way to try to create a unique updated or refined pharmacophore.

Interpreting results and intermolecular interactions

The analysis of the resulting equations and the nature of involved MOs may help to suggest some possible interactions with the receptor. Table 4 shows some kinds of interactions. It was copied from a table found in the Help section of the Discovery Studio Visualizer software [106]. This free software is highly recommended because of its high quality and multiple options.

This table has proven to be very useful in our own studies. If the nature of the resulting equations allows it, the researcher may propose interactions such as: π-cation, π-anion, π-donor, π-σ, π-lone pair, π-sulfur, stacked and T-shaped π-π, π-amide, alkyl-alkyl, π-alkyl, etc. A tip for interpretation: it is very important to examine how distant are the Local Atomic Frontier MOs from the molecule's ones.

Formal equations and docking studies

We expect that if a resulting equation involving certain is correct, then a docking study of the molecules with a site will show at least that these atoms dock to the site. This has not been the case of our studies. We employed Autodock (http://autodock.scripps.edu/) that is a very good software. This only means that more options for the conformational freedom of the site are needed together with a more refined representation of the ligand molecule. Probably this will employ more computing time but today this is not a problem.

A personal comment. Most of the works leading to publications were carried out with undergraduate students and a few ones following studies leading to a Master or Doctorate degree. I think that all the process was extremely pleasing along these years because you can mix teaching with a practical introduction to research and you do not spend your life repeating the last edition of a textbook. The most gratifying experience you may have in your work is when you notice the sudden brightness of a student's eyes when he fully integrates the previous knowledge with was he is doing. At this moment you know that you are doing your job well.

This paper ends citing some words of Georg Christoph Lichtenberg: "*In Nature we see not words but only the first letters of words, and when we wish to read we find that the new so-called words are once again mere first letters of other words*".

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