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A Note on Local Molecular Orbitals and Non-linear terms in the Klopman-Peradejordi-Gómez QSAR Method

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Abstract
Local Molecular Orbitals and non-linear terms within the Klopman-Peradejordi-Gómez QSAR (KPG) method are analyzed in detail. This investigation will be helpful in the interpretation of the QSAR equations obtained with the KPG method and to look for some nonlinear terms for their potential future use in the master equation.

Keywords: Molecular interactions, Klopman-Peradejordi-Gómez QSAR method, reactivity indices, superdelocalizabilities, Fukui index, Structure-activity relationships, KPG method.

1. Introduction

The Klopman-Peradejordi-Gómez QSAR method (KPG) began to be developed longtime ago [1-8]. The literature contains the historical steps that led to its current form. The linear equation that follows best describes it is:

$$\begin{aligned}\log(BA)=a+b\log\left(M_D\right)+\sum_{o=1}^{sub}\varphi_o+\sum_{i=1}^{Y}\left[e_iQ_i+f_iS_i^E+s_iS_i^N\right]+\\+\sum_{i=1}^{Y}\sum_{m=(HOMO-2)^*,i}^{(HOMO)^*,i}\left[h_i\left(m\right)F_i(m^*)+j_i\left(m\right)S_i^E\left(m^*\right)\right]+\\+\sum_{i=1}^{Y}\sum_{m'=(LUMO)^*,i}^{(LUMO+2)^*,i}\left[r_i\left(m'\right)F_i(m'^*)+t_i\left(m'\right)S_i^N\left(m'^*\right)\right]+\\+\sum_{i=1}^{Y}\left[g_i\mu_i^*+k_i\eta_i^*+o_i\omega_i^*+z_i\zeta_i^*+w_jQ_i^{*,max}\right]\end{aligned} \quad (1)$$

where BA is a biological activity, M_D is the drug's mass and φ_o is the orientational parameter of the o-th substituent (the summation runs over all the substituents selected for the research). Q_i is the net charge of atom I, and S_i^E and S_i^N are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities (SD) of atom i. F_{i,m^*} is the electron population of atom i in occupied (empty) local MO m* (m'*), $S_i^E(m)^*$ is the orbital electrophilic superdelocalizability of the occupied local MO m* of atom i and $S_i^N(m')^*$ is the orbital nucleophilic

superdelocalizability of the empty local MO m'* of atom i. μ_i^*, η_i^*, ω_i^*, ζ_i^* and $Q_i^{*,max}$ are, respectively, the local atomic electronic chemical potential, the local atomic hardness, the local atomic electrophilicity, the local atomic softness and the maximal amount of electronic charge that atom i may accept. These indices were developed within the Hartree-Fock formalism. The molecular orbitals with an asterisk are the Local Molecular Orbitals (LMO) of each atom (see below). The index Y in the summations runs over all atoms composing the molecule. To solve the liner system of equations 1, we need that the Y value be the same for all molecules. For this purpose, we define a common skeleton for all molecules with the same number of atoms. Highly satisfactory results were obtained for different molecular systems and biological activities [9-19].

In this note, we will examine one of the approximations used to get Eq. 1, to clarify it and determine whether non-linear terms with a physical meaning can be added to the master equation. Also, we shall provide a new analysis of the concept of Local Molecular Orbitals.

The atom-atom interaction.

The KPG method is based on the Klopman & Hudson work. There we found the following two terms corresponding to the interaction of atoms i (of the drug) and j (of the receptor)[20-22]:

$$T_1(i,j)= \sum_{m=1}^{m=HOMO} \sum_{n'=LUMO'}^{n'=N} \frac{F_{m_i} F_{n'_j}}{E_m - E_{n'}} \quad (2)$$

where F_{m_i} is the Fukui index (the number of electrons) of that 'part' of the occupied molecular orbital m localized on atom i of the drug, $F_{n'_j}$ is the Fukui index (the number of electrons) of the empty molecular orbital n' localized on atom j of the receptor, E_m is the energy of the molecular orbital m of atom i and $E_{n'}$ is the energy of the empty molecular orbital n' of the atom j of the receptor. The Fukui indices of all MOs are obtained with any Population Analysis technique. All terms correspond to the isolated systems. N is the size of the basis set of the receptor.

Let us immediately note the following fact. Since the energies of occupied MOs are negative and those of empty MOs are positive, the mathematical condition for the numerical values of these terms to be large is that the values of $(E_m-E_{n'})$ be as small as possible. This condition is realized only when the MOs involved are the higher occupied MOs of the drug's i-atom and the lowest-empty MOs of the receptor's j-atom. For this reason we can approach Eq. 2 as:

$$T_1(i,j)= \sum_{HOMO-10}^{HOMO} \sum_{n'=LUMO'}^{LUMO'+10} \frac{F_{m_i} F_{n'_j}}{E_m - E_{n'}} \quad (3)$$

where HOMO designates the highest occupied MO of atom i of the drug and LUMO' the lowest occupied MO of atom j of the receptor. We have chosen ten molecular orbitals of the drug's i-atom and ten molecular orbitals of the receptor j-atom so as not to miss any important MO-MO interactions.

The second term is:

$$T_2(i,j)= \sum_{m'=HOMO+1}^{m=M} \sum_{n'=1}^{n'=HOMO'} \frac{F_{m'_i} F_{n_j}}{E_{m'} - E_n} \quad (4)$$

where $F_{m'_i}$ is the Fukui index (the number of electrons) of the empty molecular orbital m' at atom i of the drug, F_{n_j} is the Fukui index (the number of electrons) of the occupied molecular orbital n at atom j of the receptor, $E_{m'}$ is the energy of the empty molecular orbital m' of atom i of the drug and E_n is the energy of the occupied molecular orbital n of the receptor. M is the size of the basis set of the drug.

The same reasoning used for the term $T_1(i,j)$ indicates that the most relevant terms are those involving the lowest empty MOs of atom i of the drug and the highest occupied MOs of atom j of the receptor. That is why we can approximate Eq. 2 as:

$$T_2(i,j)=\sum_{m'=LUMO}^{m'=LUMO+10}\sum_{n=HOMO'-10}^{n=HOMO'}\frac{F_{m'_i}F_{n_j}}{E_{m'}-E_n} \quad (5)$$

where LUMO is the lowest empty MO of the drug's atom i and HOMO' is the highest occupied MO of the receptor's atom j.

And why have we so far spoken of the occupied and empty OMs of atom i of the drug and not directly of the occupied and empty OMs of the drug? The next section clarifies this.

Why local molecular orbitals?

We have already discussed the need for employing local molecular orbitals (LMOs), but we feel that it is necessary to reiterate the essential points for the sake of completeness. Let us remember that for atom x, the Local Molecular Orbitals are defined as the subset of the molecule's MOs having an electron population greater than 0.01e on x.

Let us consider an atom Z that is common to molecules I, II and III (i.e., it is part of the common skeleton we have selected). Molecules I, II and III have their own set of occupied and empty molecular MOs. The localization of these OMs on this atom Z is in general different for the three molecules. This is represented in the following figure.

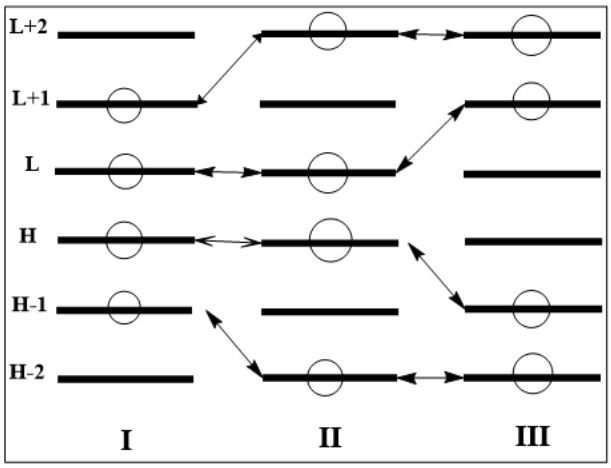

Figure 1: Localization of molecular MOs on a given atom Z, common to molecules I, II and III

We can see that for molecules I and II the **molecular** HOMO is localized on atom Z. On the other hand, we can see that in the case of molecule III, the highest occupied molecular MO is localized on atom Z and corresponds to the second highest occupied molecular MO, (HOMO-1). It is chemically obvious that if atom Z participates in any interaction with another system it will do it through the molecule's HOMO in the case of molecules I and II and through the molecule's (HOMO-1) in the case of molecule III.

For this reason, if a comparison of reactivities is to be made in terms of the possible donation of electrons by atom Z, we need to consider **molecular** HOMO in the case of molecules I and II, and **molecular** (HOMO-1) in the case of molecule III. So, for the case of this atom you have to:

1) In molecule I, the LMOs of Z atom are the molecule's (HOMO-1), (HOMO), (LUMO) and (LUMO+1). Using the nomenclature for the local MOs of atom Z, they are labeled (HOMO-1)Z*, (HOMO)Z*, (LUMO)Z*, (LUMO+1)Z*.
2) In molecule II, the LMOs of Z atom are the molecule's (HOMO-2), (HOMO), (LUMO) and (LUMO+2). Using the nomenclature for the local MOs of atom Z, they are labelled (HOMO-1)Z*, (HOMO)Z*, (LUMO)Z*, (LUMO+1)Z*.
3) In molecule III, the LMOs of atom Z are the molecule's (HOMO-2), (HOMO-1), (LUMO+1) and (LUMO+2). Using the nomenclature for the local MOs of atom Z, they are labelled (HOMO-1)Z*, (HOMO)Z*, (LUMO)Z*, (LUMO+1)Z*.

The relationship between these two nomenclatures is depicted in Figure 2. This matrix also demonstrates how to organize and use the data *properly*. In the case of our research, we developed a computer algorithm that can identify LMOs in every atom of a molecule.

$$\left\{\begin{array}{ccc} \text{I} & \text{II} & \text{III} \\ (\text{LUMO+1})^* & (\text{LUMO+1})^* & (\text{LUMO+1})^* \\ (\text{LUMO})^* & (\text{LUMO})^* & (\text{LUMO})^* \\ (\text{HOMO})^* & (\text{HOMO})^* & (\text{HOMO})^* \\ (\text{HOMO-1})^* & (\text{HOMO-1})^* & (\text{HOMO-1})^* \end{array}\right\} \Leftrightarrow \left\{\begin{array}{ccc} \text{I} & \text{II} & \text{III} \\ (\text{LUMO+1}) & (\text{LUMO+2}) & (\text{LUMO+2}) \\ (\text{LUMO}) & (\text{LUMO}) & (\text{LUMO+1}) \\ (\text{HOMO}) & (\text{HOMO}) & (\text{HOMO-1}) \\ (\text{HOMO-1}) & (\text{HOMO-2}) & (\text{HOMO-2}) \end{array}\right\}$$

Figure 2: Left. Local Molecular Orbitals. Right. Molecule's molecular orbitals from Fig 1.

This analysis is especially necessary when dealing with large molecules. Within this analysis it is clear that all terms in equations 2 and 3 refer only to local molecular orbitals, occupied and empty, of atoms i and j. Another way to come to this same conclusion is by noticing that when any of the Fukui indices is zero the corresponding terms disappear from the equations.

The analysis.

Now we shall analyze terms T_1 and T_2 to try to rewrite them as the product of separate terms exclusively related to the drug or to the receptor. *We may treat terms associated with the receptor as constants because the receptor or other biological structures are the same for the series of compounds employed in any investigation.* To keep a comprehensible nomenclature it must be understood from here that we are dealing only with local molecular orbitals (the asterisk was omitted in some cases for the sake of clarity).

The following expression serves as the basis for the separation:

$$\frac{1}{1-x} = 1+x+x^2+x^3+.... \quad -1<x<1 \text{ or } |x|<1 \tag{6}$$

where x will be, for example, a term of the form $|E_m/E_{n'}|<1$ or $|E_{n'}/E_m|<1$ accordingly to the condition imposed on x. This series is convergent.

The T_1 term.

- For T1 we have two possibilities for a certain energy Em of the occupied MO m of the drug.
- If -1< Em/En' <1 we have this series expansion keeping the first two terms:

$$\frac{1}{1-\frac{E_m}{E_{n'}}} = 1+\left(\frac{E_m}{E_{n'}}\right) \tag{7}$$

- If -1< En'/Em< 1 we have this series expansion:

$$\frac{1}{1-\frac{E_{n'}}{E_m}} = 1+\left(\frac{E_{n'}}{E_m}\right) \tag{8}$$

It is possible to notice that these expansions provide an immediate separation between the terms belonging exclusively to the drug from those that belong only to the receptor (see Eq. 3). To better appreciate what we could obtain, we will consider two cases:

Case 1. In all cases we have $-1< E_m/E_{n'} <1$. Then, Eq. 3 can be written as:

$$T_1(i,j) = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{E_m - E_{n'}} = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{-E_{n'}} \left(\frac{1}{1-\frac{E_m}{E_{n'}}}\right) \tag{9}$$

$$T_1(i,j) = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{-E_{n'}} \left(1+\left(\frac{E_m}{E_{n'}}\right)\right) = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{-E_{n'}} + \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{-E_{n'}} \left(\frac{E_m}{E_{n'}}\right) \quad (10)$$

$$T_1(i,j) = -\sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \left(\frac{F_{n'_j}}{E_{n'}}\right) F_{m_i} - \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \left(\frac{F_{n'_j}}{(E_{n'})^2}\right) F_{m_i} E_m \quad (11)$$

$$T_1(i,j) = -\sum_{m=HOMO-10}^{m=HOMO} F_{m_i} \sum_{n'=LUMO'}^{n'=LUMO'+10} S^N_{n'_j} - \sum_{m=HOMO-10}^{m=HOMO} LDOS_i(m) \sum_{n'=LUMO'}^{n'=LUMO'+10} S^{N(2)}_{n'_j} \quad (12)$$

where we have defined a second-order orbital nucleophilic superdelocalizability, $S^N_{n'_j}/E_{n'} = S^{N(2)}_{n'_j}$, and a local atomic density of states of atom i/MO m as $LDOS_i(m) = F_i(m)E_m$. Employing Ξ(receptor) and Φ(receptor) for the receptor terms we have:

$$T_1(i,j) = -\Xi(receptor) \sum_{m=HOMO-10}^{m=HOMO} F_{m_i} - \Phi(receptor) \sum_{m=HOMO-10}^{m=HOMO} LDOS_i(m) \quad (13)$$

Therefore, it seems appropriate to include the Fukui indices individually for the first 10 occupied local molecular orbitals and their local state density of states, which has not been included until now. We have usually employed the first 3 highest occupied local molecular orbitals. An important point is this one. We need to keep in mind that, when one or more Fukui indies appear in the results, we need to know that they are accompanied by nucleophilic superdelocalizabilities of an atom of the receptor. If local density of states appear, then we must be aware that they are accompanied by second-order orbital nucleophilic superdelocalizabilities.

Case 2. In all cases we have $-1 < E_{n'}/E_m < 1$. Then, Eq. 3 can be written as:

$$T_1(i,j) = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{E_m - E_{n'}} = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{E_m} \left(\frac{1}{1-\frac{E_{n'}}{E_m}}\right) \quad (14)$$

$$T_1(i,j) = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{E_m} \left(1+\left(\frac{E_{n'}}{E_m}\right)\right) = \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} \frac{F_{m_i} F_{n'_j}}{E_m} + \sum_{m=HOMO-10}^{m=HOMO} \sum_{n'=LUMO'}^{n'=LUMO'+10} F_{m_i} F_{n'_j} \left(\frac{E_{n'}}{(E_m)^2}\right) \quad (15)$$

$$T_1(i,j) = \sum_{m=HOMO-10}^{m=HOMO} S^E_m \sum_{n'=LUMO'}^{n'=LUMO'+10} F_{n'_j} + \sum_{m=HOMO-10}^{m=HOMO} \frac{F_{m_i}}{(E_m)^2} \sum_{n'=LUMO'}^{n'=LUMO'+10} F_{n'_j} E_{n'} \quad (16)$$

$$T_1(i,j) = \Xi(receptor) \sum_{m=HOMO-10}^{m=HOMO} S^E_m + \Phi(receptor) \sum_{m=HOMO-10}^{m=HOMO} S^{E(2)}_{m_i} \quad (17)$$

Note that when an orbital electrophilic superdelocalizability of an atom of the drug appears, it is connected to a Fukui index of the atom of the receptor. When a second-order orbital electrophilic superdelocalizability of an atom of the drug appears, it is connected to a LDOS of atom j of the receptor.

Now let us look at $T_2(i,j)$:

$$T_2(i,j)=\sum_{m'=LUMO}^{m'=LUMO+10}\sum_{n=HOMO-10}^{n=HOMO'}\frac{F_{m'_i}F_{n_j}}{E_{m'}-E_n} \quad (18)$$

Case 1. In all cases we have $-1< E_{m'}/E_n <1$. Then, Eq. 18 can be written as:

$$T_2(i,j)=\sum_{m'=LUMO}^{m'=LUMO+10}\sum_{n=HOMO-10}^{n=HOMO'}-\frac{F_{m'_i}F_{n_j}}{E_n}\frac{1}{\left(1-\frac{E_{m'}}{E_n}\right)}=-\sum_{m'=LUMO}^{m'=LUMO+10}\sum_{n=HOMO-10}^{n=HOMO'}\frac{F_{m'_i}F_{n_j}}{E_n}\left(1+\left(\frac{E_{m'}}{E_n}\right)\right) \quad (19)$$

$$T_2(i,j)=-\sum_{m'=LUMO}^{m'=LUMO+10}F_{m'_i}\sum_{n=HOMO-10}^{n=HOMO'}S^E_{n_j}-\sum_{m'=LUMO}^{m'=LUMO+10}F_{m'_i}E_{m'}\sum_{n=HOMO-10}^{n=HOMO'}S^{E(2)}_{n_j} \quad (20)$$

$$T_2(i,j)=-\Xi(\text{receptor})\sum_{m'=LUMO}^{m'=LUMO+10}F_{m'_i}-\Phi(\text{receptor})\sum_{m'=LUMO}^{m'=LUMO+10}F_{m'_i}E_{m'} \quad (21)$$

Note that when a Fukui index of an empty MO of the atom of the drug appears, it is connected to the electrophilic superdelocalizability of the atom of the receptor. When a local density of states of an atom of the drug appears, it is connected to a second-order electrophilic superdelocalizability of a MO of atom j of the receptor.

Case 2. In all cases we have $-1< E_n/E_{m'}< 1$. Then, Eq. 18 can be written as:

$$T_2(i,j)=\sum_{m'=LUMO}^{m'=LUMO+10}\sum_{n=HOMO-10}^{n=HOMO'}\frac{F_{m'_i}F_{n_j}}{E_{m'}}\left(\frac{1}{1-\frac{E_n}{E_{m'}}}\right)=\sum_{m'=LUMO}^{m'=LUMO+10}\sum_{n=HOMO-10}^{n=HOMO'}\frac{F_{m'_i}F_{n_j}}{E_{m'}}\left(1+\left(\frac{E_n}{E_{m'}}\right)\right) \quad (22)$$

finally we obtain:

$$T_2(i,j)=\sum_{m'=LUMO}^{m'=LUMO+10}S^N_{m'_j}\sum_{n=HOMO-10}^{n=HOMO'}F_{n_j}+\sum_{m'=LUMO}^{m'=LUMO+10}S^{N(2)}_{m'_j}\sum_{n=HOMO-10}^{n=HOMO'}F_{n_j}E_n \quad (23)$$

$$T_2(i,j)=\Xi(\text{receptor})\sum_{m'=LUMO}^{m'=LUMO+10}S^N_{m'_j}+\Phi(\text{receptor})\sum_{m'=LUMO}^{m'=LUMO+10}S^{N(2)}_{m'_j} \quad (24)$$

Note that when an orbital nucleophilic superdelocalizability of an atom of the drug appears, it is connected to a Fukui index of the atom of the receptor. When a second-order orbital nucleophilic superdelocalizability of an atom of the drug appears, it is connected to a LDOS of atom j of the receptor.

It is possible to write an algorithm that detect what is the relationship between the drug's and receptor's MO energies (Eq. 7 or 8) and select the appropriate indices to use in QSAR studies. An empirical way to work is simply to calculate all the indices appearing in Eq. 12, 16, 20 and 23 and using them in the KPG model. This should be done at least for the three highest occupied and three empty local MOs of the common skeleton atoms. These new suggestions will be implemented in the D-CENT-QSAR software[23-25] during March 2024.

For the interpretation of the indices appearing in the final SAR equation(s) we present the relationships between the reactivity indices of an atom of the drug with an atom of the receptor.

Table 1.: Atom-atom drug-receptor interactions.

Equation	Drug-associated term	Receptor-associated term
12	Fukui index occupied MO	Nucleophilic SD empty MO
12	LDOS occupied MO	2nd order Nucleophilic SD empty MO
16	Occupied MO Electrophilic SD	Fukui index empty MO
16	2nd order Electrophilic SD occupied MO	LDOS empty MO
20	Fukui index empty MO	Occupied MO Electrophilic SD
20	LDOS empty MO	2nd order Electrophilic SD occupied MO
23	Nucleophilic SD empty MO	Fukui index occupied MO
23	2nd order Nucleophilic SD empty MO	LDOS occupied MO

On the other hand, it is important to note that calculations of the electronic structure produce empty MOs that possess negative energies. This fact produces problems in the calculation of total nucleophilic superdelocalizability due to the algebraic subtraction between positive and negative orbital superdelocalizabilities values. That is why it is suggested not to include this reactivity index but to include the orbital superdelocalizabilities of the three lowest empty OMs. This will be also implemented during March 2024.

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