Formal theory of the comparative relations: its application to the study of quantum similarity and dissimilarity measures and indices

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Abstract   The study proposes a formal theory of comparative relations character-ized by a group of abstract definitions and axioms. This abstract characterization allows us to rigorously define in a very general form what a comparative relation is, which can in turn be used as starting point in every case where comparative analysis is used. Some of the consequences of this formalization—when applied to existing results- are analyzed, particularly those related with the consistency of the results of the comparisons. Following, a study was conducted of descriptors of Quantum Quantita-tive Structure–Property Relationships models proposed by Carbó-Dorca et al. Several quantum comparative indices such as: Carbó, Hodgkin–Richards, Petke, Tanimoto, conjugate Petke and conjugate Hodgkin–Richards were also analyzed. The proposed theory gives a solid theoretical basis for comparative analysis that will have a positive

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impact on a broad spectrum of disciplines, where the field of chemistry could be one of the most important beneficiaries.

1 Introduction

Comparison is a frequent task in everyday life. Our first opinions about some particular event are often based on its similarities and differences with respect to other known facts. Since plastic arts [1] to biology [2], comparative analysis has been extraordinarily powerful because when it is correctly done, valuable conclusions are obtained about many different topics and phenomena.

Comparative analysis is regularly used in chemistry with a broad application spectrum: the comparison between chemical elements, which allow the discovery of many relationships among them [3], the classification of organic compounds in classes due to their common performance [4], and so on. The central chemical idea that *similar molecules have similar properties* has been often applied. It is not strange that molecular similarity results have been broadly used in the context of Quantitative Structure-Activity Relationships (QSAR) [5–14]. This justifies the huge interest in the area of molecular similarity, particularly in the problem of how to quantify the degree of similarity among a group of molecules. Numerous elegant approaches have been developed in order to use this idea [5–31].

In different areas a central task has been to bring together several comparative measures inside a common framework. Particularly in the field of molecular similarity we should highlight the works of Carbó-Dorca et al. [11–15,27–29] and Maggiora et al. [26]. Unfortunately, by now it does not exist a general theoretical framework for the comparative analysis. That is because these works do not begin with a general and precise definition of what a comparative relation between objects should be. Instead, they are all based on expressions which presumably could be used to quantify the degree of similarity among different objects of interest; however, in taking such an approach, we are ignoring the general nature of the comparative analysis. Working with an expression that has not been deduced from the general features of the comparative analysis could bring contradictions when their results are interpreted in the context of our intuitive knowledge of comparisons.

In this paper we are presenting a formal study of comparative relations through a set of axioms and definitions that lends their abstract characterization. This allow us to rigorously define what a comparative relation is, which can in a general sense be used as starting point in every case when comparative analysis is used. A theory constructed in this way gives a solid theoretical basis to this thematic, allowing us to increase the advantages drawn from comparative analysis. The application of the developed theory would help us not only in gaining new insights from the uses of similarity measures and indices, but also would become a methodological tool in the development of new ones.

After discussing the formal theory of the comparative relations, some of its consequences are presented as well as a detailed analysis of what we call the consistency

between the results of the comparisons, a new concept, defined in the paper. Additionally we present some results of the application of this theory to the problem of molecular similarity. To do this we lean in the foundational work of Carbó-Dorca and coworkers in which molecular similarity was defined in terms of electronic density functions [21,22]. Descriptors of Quantum Quantitative Structure-Property Relationships (QQSPR) models proposed by Carbó-Dorca et al. [8–15]are studied in detail. There are also analysis of several quantum similarity and difference indices such as: Carbó [15,21], Hodgkin-Richards [23], Petke [24], Tanimoto [25], conjugate Petke and conjugate Hodgkin-Richards [26]. It should be noted that the theory discussed here represents a general framework for the comparative analysis and all its applications. We present the discussions about the problem of molecular similarity only as an example of the application of this theory to a particular situation.

2 Foundations of the formal theory of the comparative relations

2.1 Notation

Comparative relations sets acting over the elements (objects) of some set $M \neq \varnothing$ will be called C_M, C'_M, etc. $C_M = S_M \cup D_M$; S_M: similarity relations, D_M: dissimilarity relations (both over the set M). Similarity relations tell us how similar two objects are; dissimilarity relations show how different they are. The comparison between elements i and j belonging to M with the relation $C \in C_M$ will be written as C_{ij} (correspondingly S_{ij} or D_{ij}). Self comparative relations (result of an object autocomparisson) will be written as C_{ii}, S_{ii} or D_{ii}.

2.2 Axioms

Let us discuss the axioms that formalize the comparative relations.
1st Axiom (of allowed values):
The result of comparing any two objects is always a non negative number.

$$\forall C \in C_M, \quad \forall i, j \in M : C_{ij} \geq 0 \tag{1}$$

This axiom lacks an evident justification that the others possess. The objective of giving the axiom character to the statement (1) is to establish a parallelism between our system of axioms and the distance axioms. Additionally, this axiom facilitates the work with the results of the comparisons.
2nd Axiom (of symmetry):
The result of comparing two objects is independent of the order in which they are selected to carry out the comparison.

$$\forall C \in C_M, \quad \forall i, j \in M : C_{ij} = C_{ji} \tag{2}$$

The results of a comparison are commonly exposed without indicating in which order the objects were considered (e.g. in the amusements where the competitor is compelled to search differences between two similar images, usually there is not an indication

about their order), which indicates that the result of the comparisons does not depend on the order of selection of the objects that will be compared. This offers a strong intuitive justification to the symmetry axiom.

3rd Axiom (of extreme values):

For any set M the result of any self comparative relation of any object of the set is a strict extreme (maximum or minimum) of the set of all the results of comparing the selected element with the elements of M by means of the chosen relation.

$(\forall i \in M) \wedge (\forall C \in C_M)$, C_{ii} is a strict extreme of the set $\{C_{ij}\}$, $j \in M$.

$$(\forall i, j \in M) \wedge (\forall S \in S_M) : S_{ii} \geq S_{ij} \tag{3}$$
$$\text{if } j \in M, S_{ii} = S_{ij} \Leftrightarrow i \equiv j$$
$$(\forall i, j \in M) \wedge (\forall D \in D_M) : D_{ii} \leq D_{ij} \tag{4}$$
$$\text{if } j \in M, D_{ii} = D_{ij} \Leftrightarrow i \equiv j$$

Here $\equiv$ indicates an equivalence relationship defined over the elements of M.

This axiom is justified because it is clear that given any object does not exist any other object more similar to it than itself or less different of it than itself.

In the way it is presented herein this axiom is quite restrictive, for that reason it is interesting to analyze the situations in which it can be relaxed. Of course, the relaxation of the axiom cannot introduce incongruities with its intuitive justification: under any conditions we can obtain that for a given object exists other object more similar or less different to it than itself. Taking this into consideration it is clear that the only possibility to relax the axiom lays in the equivalence relationship defined over the elements of M. From the way in which the axiom is presented it turns out that we can define the equivalence relationship in order to work with comparative relations which gives for the comparisons of some pairs of objects conveniently selected the same result as for the self comparisons of any of the elements of the pair. This possibility can be intuitively justified if it is remembered that comparing two objects is nothing more than establishing relations between their characteristics. According to this we can think in the equivalence relationship as defined over the characteristics of the objects. In this sense two objects are equivalent under some features if these features are the same in both of them, and a comparative relation does nothing but reflect this when the objects are compared; therefore, a comparative relation divides M in classes, each of them formed by the objects for which $C_{ij} = C_{ii} = C_{jj}$ (in all cases referred to the chosen relation); this implies that the equivalent objects have some identical characteristics. It is straightforward to prove that these classes are equivalence classes. Further discussions about this topic will be presented in a future work.

We consider that the previously presented axioms are enough to abstractly describe the comparative relations.

In order to show how the given axioms work, let demonstrate a theorem concerning to the comparative relations.

Theorem 1 $\forall C_M, S_M, D_M : S_M \cap D_M = \varnothing$

Proof To prove the theorem is equivalent to demonstrate that any comparative relation C can not be at the same time a similarity and a dissimilarity relation. We will demonstrate this by reduction to the absurdity.

Let

$$C \in C_M : C \in S_M \wedge C \in D_M$$

$$\forall i, j \in M, j \neq i, \left(C \in S_M \Rightarrow C_{ij} < C_{ii}\right) \wedge \left(C \in D_M \Rightarrow C_{ij} > C_{ii}\right) \quad \text{(3rd Axiom)}$$

Combining the last inequalities we will have $C_{ij} < C_{ij}$. This contradiction proves the theorem. The application of the theory confirms an already known result, but now is obtained from a rigorous theoretical framework. □

The previous axioms determine if a given expression can be considered a comparative relation: a measure of the similarity or the difference between objects.

Another important question deals with the possibility to work simultaneously with different comparative relations defined over M. This is interesting because there are cases in which there have been defined diverse comparative relations over one group of objects (for instance in the work with molecular systems there have been defined several quantum similarity and dissimilarity measures and indices). This important question is discussed in the following:

Consistency relationship:

$$\forall i, j, k \in M; \forall S, D \in C_M, \left(S_{ij} - S_{ik}\right) \cdot \left(D_{ij} - D_{ik}\right) \leq 0 \tag{5}$$

Therefore, from the fact that i is more similar/different to j than to k (when compared with any relation S/D belonging to S_M/D_M) it must be deduced that i is less different/similar from j than from k (for every relation D/S belonging to D_M/S_M) and vice versa.

This expresses the interrelation between different comparative relations belonging to a set C_M, ensuring the consistency among them. If a set C_M fulfills the Consistency Relationship, it will be termed a *consistent set*.

In (5) it is impossible to work solely with the strict inequality (even in the case when objects that belong to M were different among them) because we are unable to assure that $j \neq k \Rightarrow C_{ij} \neq C_{ik}, \forall i \in M$. This allows the common assumption of considering the metrics as dissimilarity relations (e.g. in the theory of Fourier series).

Now we present a theorem that clarifies if it is possible to work at the same time with all the comparative relations which could be defined over M. Additionally, it illustrates how important is to guarantee the consistency for any set of comparative relations. It should be noticed that this is a new concept, not related with previous uses of consistency in molecular alignment and molecular similarity.

Theorem 2 *Let* $C_M = S_M \cup D_M$ *be a consistent set, then* $\left(\forall S, S' \in S_M\right) \wedge \left(\forall D, D' \in D_M\right)$ *it is true that:*

$$\left(S_{ij} - S_{ik}\right) \cdot \left(S'_{ij} - S'_{ik}\right) \geq 0 \tag{6}$$

$$\left(D_{ij} - D_{ik}\right) \cdot \left(D'_{ij} - D'_{ik}\right) \geq 0 \tag{7}$$

Proof

$$C_M \text{consistent} \Rightarrow \left((S_{ij} - S_{ik}) \cdot \left(D'_{ij} - D'_{ik} \right) \leq 0 \right) \wedge \left(\left(S'_{ij} - S'_{ik} \right) \cdot \right.$$
$$\left. \times \left(D'_{ij} - D'_{ik} \right) \leq 0 \right) \tag{8}$$

Multiplying the last inequalities:

$$(S_{ij} - S_{ik}) \cdot \left(S'_{ij} - S'_{ik} \right) \cdot \left(D'_{ij} - D'_{ik} \right)^2 \geq 0 \tag{9}$$

but
$$\left(D'_{ij} - D'_{ik} \right)^2 \geq 0$$
then

$$(S_{ij} - S_{ik}) \cdot \left(S'_{ij} - S'_{ik} \right) \geq 0 \tag{10}$$

Following a similar procedure we can prove the inequality (7), which completes the proof of Theorem 2.

From this theorem we can obtain the following:

Corollary *Let $C_M = S_M \cup D_M$ be a consistent set, then:*

$$\left(\forall S, S' \in S_M \right) \wedge \left(\forall D, D' \in D_M \right) : \begin{cases} S_{ij} \geq S_{ik} \Leftrightarrow S'_{ij} \geq S'_{ik} \\ D_{ij} \geq D_{ik} \Leftrightarrow D'_{ij} \geq D'_{ik} \end{cases}$$

Because of (6) and (7), in a consistent set the fact that an object i is more or less similar or different to an object j than to another object k is independent of the relation S or D selected to make the comparison.

The independence in the qualitative result of the comparisons (it means, the relative level of similarity or dissimilarity between the objects, commonly expressed in phrases like: "i is more similar to j than to k", etc.) that comes from this theorem cannot be interpreted as an affirmation of the independence of the degree of similarity or dissimilarity of the objects respect to any set of comparative relations defined over them. It should be possible that different sets of relations fulfilling the above mentioned axioms and the Consistency Relationship lead to different qualitative results over the objects of M. It must be pointed out that the Consistency Relationship concerns only to the interrelation between the comparative relations in each individual set.

From the above-mentioned it is easy to see that in each consistent set C_M the statements "i is more similar/different to j than to k" (a) and "i is more similar/different to k than to j" (b) cannot be true at the same time. It turns out clearly that the second assertion is equivalent to "i is not more similar/different to j than to k" (c). The fact that statements (a) and (c) cannot be obtained simultaneously proves that they fulfill the logical axiom of non contradiction. Then, the results obtained with comparative relations belonging to consistent sets are non contradictory between them. In the case of non consistent sets, comparative relations applied simultaneously could give contradictory results. Though the fact that different relations can give different results

when applied to the same set is known, this problem has never been treated in detail. Here, in the framework of the theory, we analyze the subject through the new concept of consistency, and obtained a way to know when two relations can be used at the same time over the objects of the set *M,* without giving contradictory results, giving extraordinary importance to the concept.

An expression can be considered a comparative relation between the objects of some set *M* if it fulfills all the axioms discussed above. The sole (but important) role that the Consistency Relationship plays is to tell us which comparative relations can be used at the same time over a set *M*.

3 Study of the molecular similarity

Now we will present an example of the application of the discussed theory to a particular situation: the issue of molecular similarity. Although many different and elegant techniques have been developed in order to solve this problem [5–31], the present work will be particularly focused in the study of molecular similarity measures defined in terms of electronic density functions, as in an early work published by Carbó-Dorca et al. [21,22]. We will also study some field-based molecular comparative indices [26] such as Carbó similarity and dissimilarity indices [15,21] and Hodgkin-Richards [23], Petke [24], Tanimoto [25], conjugate Petke and conjugate Hodgkin-Richards [26] similarity indices. We will give special attention to the study of the descriptors of the QQSPR models proposed by Carbó-Dorca et al. [9–15].

3.1 Analysis of the QQSPR based on quantum similarity

The aim of this point is to check if the well-known descriptors of QQSPR models proposed by Carbó-Dorca et al. [9–15] can be taken as similarity relations according to the axioms previously presented. It has been proposed that their descriptors can be considered as quantum similarity measures between molecules [9–15].

It should be pointed out that these comparisons are not made directly over the molecules. Instead, they are carried out working with their respective electronic density functions [8–15,21,22]. This can be done through the existence of a one to one relation between molecules and electronic density functions [14].

To construct such a model as those described in ref [12–15] it is necessary to have a set $M = \{M_i\}_{i=1}^{i=m}$ of quantum objects (called the primary set); also, for each M_i belonging to *M*, it is necessary to know its electronic density function ρ_i and the π_i value of the property π which we want to predict (in the following we are going to talk about quantum objects and not only about molecules since although the principal aim of the creation of these models is their application to molecular systems, it has been pointed out the possibility to use them in any quantum system [15], which offers a great generality to this formalism).

One of the most interesting features of Carbó-Dorca's QQSPR models is that they give a causal explanation to the established relations between the quantum objects and their properties, the so called fundamental QQSPR equation [12–15]. To do that Carbó-Dorca reminds us that the expectation value of a given property π can be

expressed as [13–15]:

$$\langle \pi \rangle = \int_D P_\pi \rho \, dr \tag{11}$$

Where P_π is the hermitian operator associated to π. In the majority of his works Carbó-Dorca takes for P_π the form given below [10–12,15]:

$$P_\pi \approx \sum_{i=1}^{m} \alpha_i g(\rho_i) \; \Omega(r) \tag{12}$$

Herein the α_i are coefficients which can be obtained in different ways [10–12,15] with the help of the information we have of the set M; $\Omega(r)$ is an operator that we need to choose (by now the only restriction that we impose over $\Omega(r)$, sufficient to assure that P_π is hermitian, is that $\Omega(r)$ must be a real function of r, e. g. $\Omega(r) = r^{-1}$) and the $g(\rho_i)$ terms are continuous transformations of the electronic density functions of the objects belonging to M. Although there exists the possibility to construct the operator P_π in different ways, allowing the inclusion of an operator acting as a gauge as well as terms with products of the electronic density functions of the elements of the primary set [13,14], in all cases for its construction are taken the electronic density functions of the objects belonging to the primary set (it is necessary to do that because the complexity of the properties that we want to predict hinders the application of the correspondence principle). Additionally, all terms appearing in (12) are found, this means that the descriptors obtained when working with this form of P_π will be as well obtained working with any other form of P_π. For this reason since now on we will only consider the form of P_π given in (12).

Building the operator P_π according to (12) for a given molecule M_A it is found that:

$$\langle \pi_A \rangle = \int_D P_\pi \rho_A dr \tag{13}$$

$$\langle \pi_A \rangle = \int_D \left[\sum_{i=1}^{m} \alpha_i g(\rho_i) \; \Omega(r) \right] \rho_A dr \tag{14}$$

$$\langle \pi_A \rangle = \sum_{i=1}^{m} \alpha_i \left[\int_D g(\rho_i) \; \Omega(r) \rho_A dr \right] \tag{15}$$

Therefore, it is possible to write:

$$\langle \pi_A \rangle = \sum_{i=1}^{m} \alpha_i C_{iA} \tag{16}$$

which is similar to the fundamental QQSPR equation [12–15]. Here:

$$C_{iA} = \int_D g(\rho_i) \ \Omega(r)\rho_A dr \tag{17}$$

A similar procedure can be used in order to express $<\pi_i>$ for all the objects of the primary set M^I, obtained from M substituting each time the object M_A for M_i. Keeping in mind that the transformation g appearing in the structure of P_π is independent of the starting primary set, it follows that:

$$\forall i, \ C_{Ai} = \int_D g(\rho_A) \ \Omega(r)\rho_i dr \tag{18}$$

As priorly stated, we are studying these models because it has been proposed that their descriptors, the C_{iA}'s, can be considered as quantum similarity measures between the quantum objects [8–15]. Let us see if they fulfill the axioms of the previously presented theory.

For C to be a comparative relation it must be, in accordance with the symmetry axiom, that $C_{iA} = C_{Ai}$, that is:

$$\int_D g(\rho_i) \ \Omega(r)\rho_A dr = \int_D g(\rho_A) \ \Omega(r)\rho_i dr \tag{19}$$

Keeping in mind that (19) must be true for any considered primary set and/or objects M_A, M_i, it must be:

$$g(\rho) = s\rho, \quad s \in \Re \tag{20}$$

Now it is possible to see (in accordance with the 1st Axiom) that, in order to consider C as a comparative relation, $\Omega_0(r) = s\Omega(r)$ must be a positive defined operator. In refs [8,15] they assume that $g(\rho) = \rho$ (equivalent to take $s = 1$) and for that reason they only use positive defined operators $\Omega(r)$. Here we have demonstrated that this is only one of the possible results if the descriptors of the model are to be interpreted as comparative relations. From now on we will work under these assumptions, as is usually done, because it would not affect any of the results or deductions presented below. Also, these considerations allow obtaining the well known fundamental QQSPR equation [12–15].

From this it is set that in this formalism the only allowed "comparative measures" are those given by the expression:

$$C_{ij} = \int_D \rho_i \Omega(r)\rho_j dr \tag{21}$$

This is the general form of the Quantum Similarity Measure (QSM) defined by Carbó-Dorca in his works [8–15,21,22]. The next step is to check if it fulfils the axioms here presented.

The first two axioms are immediately fulfilled since Eq. (21) was obtained under the assumption that these axioms are true for these "measures". For the validation of the measure under the 3rd Axiom, it is necessary to consider three density functions that guaranty:

$$\int_D \rho_j dr \le \int_D \rho_i dr \le \int_D \rho_k dr \tag{22}$$

So $\int_D (\rho_i - \rho_k) dr \le 0$

$\rho_k(r)$ and $\rho_i(r)$ are continuous functions, so there must exist $D_1 \subset D$ where $\rho_k(r) \ge \rho_i(r)$.

Now, evaluating $C_{ii} - C_{ik}$:

$$C_{ii} - C_{ik} = \int_D \rho_i \Omega(r)\rho_i dr - \int_D \rho_i \Omega(r)\rho_k dr = \int_D \rho_i \Omega(r)(\rho_i - \rho_k) dr \tag{23}$$

$$C_{ii} - C_{ik} = \int_{D_1} \rho_i \Omega(r)(\rho_i - \rho_k) dr + \int_{D_2} \rho_i \Omega(r)(\rho_i - \rho_k) dr \tag{24}$$

where $D_2 = D \backslash D_1$. The first integral is negative, and in any case where the addition of the two integrals gives a negative number

$$C_{ii} \le C_{ik} \tag{25}$$

So C can not be used as a similarity relation in these cases, because it violates the 3rd Axiom. Repeating this reasoning with ρ_j and ρ_i it is easy to demonstrate that

$$C_{ij} \le C_{ii} \tag{26}$$

So, C could not be used as a dissimilarity relation.

It can be noticed that violations of such type can be easily found when working with sets constituted by independent atoms. For example, inequality (25) is evident if $i = H$ and $k = Br$. A similar situation can be obtained when working with molecular systems. In a recent work [32] we observed these violations when comparing, using the Coulomb operator in (21) [15], different structural patterns found in acetamide polymorphs. Taking in consideration that the compared structures were constituted by the same atoms (they only differ in the position in the space of the atoms that form them) we can expect to find similar situations when working with molecules formed by different atoms. This shows that the above mentioned violations are not exclusive of the atomic systems.

It must be noticed that these problems in the performance of the 3rd axiom are given by violations of our intuitive knowledge of the comparative relations, so they are inde-

pendent of the equivalence relationship established over the elements of any quantum objects set. Therefore, in some situations, we can find quantum objects sets in which expressions (21) can not be considered as comparative relations.

3.2 Study of some field-based molecular comparative indices

For quantifying the degree of similarity between molecules many field-based molecular comparative indices have been proposed [15,21,23–26]. In this work we are going to study, using the formal theory here presented, some of them: Carbó similarity and dissimilarity indices [15,21], Hodgkin-Richards [23], Petke [24], Tanimoto [25], conjugate Petke and conjugate Hodgkin-Richards [26] similarity indices. Although different studies have been carried out over these indices establishing many relations among them (for instance, a work of Maggiora et al. in which it is created a formalism who incorporates many of the above mentioned indices [26]) we decided to present each index separately in order show how the above discussed formalism can be applied to each individual case for obtaining valuable conclusions. In doing so firstly we are going to study the performance of the previously presented axioms. Due to their particular characteristics we will work first with Carbó indices, leaving for a second paragraph the discussions relating to the other indices. Finally, we will analyze the consistency among them.

3.2.1 Analysis of the performance of the extreme values axiom for Carbó similarity and dissimilarity indices

It can be proven that the expression (21) fulfils all the axioms of the scalar product [33]. Is for this reason that is introduced the nomenclature:

$$C_{ij} \overset{\text{def}}{=} (i, j) \tag{27}$$

Using (21) and (27), Carbó similarity index can be written as:

$$B_{ij} = \frac{(i, j)}{\sqrt{(i, i)(j, j)}} \tag{28}$$

And Carbó dissimilarity index is:

$$D_{ij} = \sqrt{(i, i) + (j, j) - 2(i, j)} \tag{29}$$

It is easy to note that (28) is the expression of the cosine of the angle subtended by i and j; and that (29) is the Euclidean distance between two vectors.
Remembering that $(i, i) = \int_D \rho_i^2 \Omega(r) \, dr$, as well as the properties of electronic density functions it is evident that:

$$\forall M_i \in M : (i, i) > 0 \tag{30}$$

This is a very important result, meaning that it is always possible to calculate these indices for any two molecules (this is also true for the indices that will be discussed below).

Keeping this in mind here will be analysed if Carbó indices fulfil the comparative relations axioms. From the structure of these indices it is evident that they fulfil the allowed values and the symmetry axioms, for this reason only the proof of the extreme values axiom will be given.

Carbó similarity index:

It is necessary to prove that $\forall M_i, M_j \in M : B_{ij} \leq B_{ii}$.
$\forall M_i$ it is true that $B_{ii} = 1$.
$\forall M_i, M_j \in M : \frac{(i,j)}{\sqrt{(i,i) \cdot (j,j)}} \leq 1$ (Cauchy-Schwarz's inequality [33])

$$\Rightarrow \forall M_i, M_j \in M : B_{ij} \leq B_{ii} \tag{31}$$

It can be easily proved that when $M_i \neq M_j$, $B_{ij} = 1 \Leftrightarrow \rho_i = k\rho_j$, $k \in \Re_+, k \neq 1$. But, although such a condition can be perhaps considered as a possibility in the abstract mathematical analysis, the situation described by the above relation of densities is physically impossible. Then, $B_{ij} = 1 \Leftrightarrow M_i = M_j$. We have then proved that, $\forall M_i \in M$, B_{ii} is a strict maximum of the set $\{B_{ij}\}$, $M_j \in M$. This means that Carbó index can be effectively considered as a similarity relation among the objects of any quantum objects set.

Carbó dissimilarity index:

As it was noticed previously, this index is the Euclidean distance among vectors i and j. In accordance with the axioms of the metrics [33], $D_{ij} \geq 0$. Besides, $D_{ij} = 0 \Leftrightarrow i = j$, then, $\forall i, j \in M, i \neq j : D_{ii} < D_{ij}$. So, Carbó dissimilarity index fulfils the comparative relations axioms. In this case we do not refer to the explicit correspondence between the Carbó dissimilarity index and a certain group of molecules and we work with this index operating over two arbitrary vectors. We prefer to make this exception since it allows us to notice that any metric can be taken as a measure of the differences among the elements of the corresponding metric space (it can be seen that we have used the metric's axioms without referring to an explicit one, for that reason we can assure that the previous demonstration is valid for any metric).

3.2.2 Analysis of the performance of the extreme values axiom for Hodgkin–Richards, Petke, Tanimoto, conjugate Petke and conjugate Hodgkin–Richards similarity indices

Using the same nomenclature as before these indices can be written as:
Hodgkin–Richards index:

$$H_{ij} = \frac{2(i,j)}{(i,i) + (j,j)} \tag{32}$$

Conjugate Hodgkin–Richards index:

$$H_{ij}^* = \frac{(i, j)\{1/(i, i) + 1/(j, j)\}}{2} \qquad (33)$$

Petke index:

$$P_{ij} = \frac{(i, j)}{\max\{(i, i), (j, j)\}} \qquad (34)$$

Conjugate Petke index:

$$P_{ij}^* = \frac{(i, j)}{\min\{(i, i), (j, j)\}} \qquad (35)$$

Tanimoto index:

$$T_{ij} = \frac{(i, j)}{(i, i) + (j, j) - (i, j)} \qquad (36)$$

For the previous indices the demonstration of the fulfilling of the first two axioms of the comparative relations is also trivial. We will use the following equivalence relationship in the following: $M_i \equiv M_j \Leftrightarrow \rho_i = \rho_j$.

Hodgkin–Richards index:

$\forall M_i \in M \, H_{ii} = 1$, which can be easily proven. According to (30) (i, i) and (j, j) are positive numbers, for that reason it can be used the well known inequality [33]:

$$\sqrt{(i, i) \cdot (j, j)} \leq \frac{(i, i) + (j, j)}{2} \qquad (37)$$

using the Cauchy–Shcwarz's inequality

$$(i, j) \leq \sqrt{(i, i) \cdot (j, j)} \qquad (38)$$

we obtain

$$2(i, j) \leq (i, i) + (j, j) \qquad (39)$$

and:

$$\frac{2(i, j)}{(i, i) + (j, j)} \leq 1 \qquad (40)$$

Meaning that:

$$H_{ij} \leq 1 \qquad (41)$$

Resulting finally that, $\forall M_i, M_j \in M, H_{ij} \leq H_{ii}$

To demonstrate that (41) is a strict inequality when $M_i \neq M_j$ the expressions of the integrals corresponding to the notations (27) and (21) will be used.

Let ρ_j be: $\rho_j = \rho_i + \delta_R$. Then:

$$H_{ij} = \frac{2\left(\int_D \rho_I^2 \Omega(r)dr + \int_D \rho_I \Omega(r)\delta_R dr\right)}{2\int_D \rho_I^2 \Omega(r)dr + 2\int_D \rho_I \Omega(r)\delta_R \, dr + \int_D \delta_R^2 \Omega(r)dr} \tag{42}$$

From (42) it is clear that $H_{ij} = 1 \Leftrightarrow \int_D \delta_R^2 \Omega(r)dr = 0$
Remembering that ρ_j and ρ_i are continuous functions, δ_R will be also continuous [33]. With this and the properties of the L_2 [33] space it is clear that $\forall r \in D, \delta_R(r) \equiv 0$. Then $\rho_i = \rho_j \forall r \in D$.
Keeping this in mind we can affirm that $H_{ij} = 1 \Leftrightarrow M_i = M_j$. This proves that, $\forall M_i \in M, H_{ii}$ is a strict maximum of the set $\{H_{ij}\}, M_j \in M$.

Conjugate Hodgkin–Richards index:
It can be easily shown that $\forall M_i \in M : H_{ii}^* = 1$. But it has been already demonstrated that this index is unbounded from above [26]. That means that we can find situations in which H_{ii}^* is not a strict maximum of the set $\{H_{ij}^*\}, M_j \in M$. One of those situations is the following: we know that $\forall M_i, M_j \in M : (i, j) > 0$; then we can write: $(j, j) = p^2(i, i); \ (i, j) = q^2(i, i)$. It is important to realize that these are relations between positive numbers, not between density functions. From here and in accordance with (33) we will have that:

$$H_{ij}^* = \frac{q^2(i, i)\{1/(i, i) + p^{-2}/(i, i)\}}{2} = \frac{q^2}{2}\left(1 + \frac{1}{p^2}\right) \tag{43}$$

From here it is obvious that $q^2 \geq 2 \Rightarrow H_{ij}^* > 1$.
This proves that in some occasions the conjugate Hodgkin-Richards index cannot be used as a similarity index.

Petke index:
It can be proven without difficulty that, $\forall M_i \in M : P_{ii} = 1$.
Supposing that $\max\{(i, i), (j, j)\} = (i, i)$, then:

$$P_{ij} = \frac{(i, j)}{(i, i)} \tag{44}$$

knowing that:

$$(i, j) = B_{ij}\sqrt{(i, i) \cdot (j, j)} \tag{45}$$

Then:

$$P_{ij} = \frac{B_{ij}\sqrt{(i,i)\cdot(j,j)}}{(i,i)} = B_{ij}\sqrt{\frac{(j,j)}{(i,i)}} \tag{46}$$

It was already demonstrated that $B_{ij} \le 1$ besides, since $\max\{(i,i),(j,j)\} = (i,i)$: $\sqrt{\frac{(j,j)}{(i,i)}} \le 1$. Keeping this in mind:

$$P_{ij} \le 1 \tag{47}$$

Finally $\forall M_i, M_j \in M$, $P_{ij} \le P_{ii}$

To prove that $P_{ij} = 1 \Leftrightarrow M_i = M_j$ we can remember that it was already shown that $M_i \ne M_j \Leftrightarrow B_{ij} < 1$. Then, because $\sqrt{\frac{(j,j)}{(i,i)}} \le 1$, we will have that $P_{ij} = B_{ij}\sqrt{\frac{(j,j)}{(i,i)}} < 1$.

The previous result ends up proving that $\forall M_i \in M$, P_{ii} is a strict maximum of the set $\{P_{ij}\}$, $M_j \in M$. (It should be noticed that we would arrived to the same result if we had supposed that $\max\{(i,i),(j,j)\} = (j,j)$).

Conjugate Petke index:

It is evident that $\forall M_i \in M : P_{ii}^* = 1$. But it has been already demonstrated that this index is unbounded from above [26]. That means that situations could be found in which P_{ii}^* is not a strict maximum of the set $\left\{P_{ij}^*\right\}$, $M_j \in M$. In order to show cases when this happens let us write $(i,j) = q^2(i,i)$, again a relation between numbers. Doing so:

$$P_{ij}^* = \frac{q^2(i,i)}{(i,i)} = q^2 \tag{48}$$

where it was supposed that $\min\{(i,i),(j,j)\} = (i,i)$. From here it is obvious that $q^2 > 1 \Rightarrow P_{ij}^* > 1$. This shows the possibility of situations in which the conjugate Petke index cannot be interpreted as a similarity index.

Tanimoto index:

Firstly it is important to prove that the calculation of this index can be carried out for any two molecules M_i, M_j. The last is equivalent to prove that is impossible that the denominator of this index could be 0. It is equivalent to prove that, $\forall M_i, M_j \in M$: $(i,j) \ne (i,i) + (j,j)$.

As it was already discussed:

$$2(i,j) \le (i,i) + (j,j)$$

According to the properties of the electronic density function, $(i, j) \neq 0 \Rightarrow (i, j) > 0$, then:

$$(i, j) < 2 (i, j) \leq (i, i) + (j, j) \tag{49}$$

Besides, if $(i, j) = 0$ it is easy to see that $T_{ij} = 0$. The previous result proves that it is always possible to calculate the Tanimoto index for any two molecules.
It can be easily shown that, $\forall M_i \in M : T_{ii} = 1$. Since we want to prove that $T_{ij} \leq 1$ it is enough to demonstrate that, in the cases when $T_{ij} \neq 0 : T_{ij}^{-1} \geq 1$.
Since:

$$T_{ij} = \frac{(i, j)}{(i, i) + (j, j) - (i, j)} \tag{50}$$

$$T_{ij}^{-1} = \frac{(i, i) + (j, j)}{(i, j)} - 1 \tag{51}$$

In accordance with (39):

$$T_{ij}^{-1} \geq \frac{2 (i, j)}{(i, j)} - 1 = 1 \tag{52}$$

Since $T_{ij} = 0$ implies that $T_{ij} < 1$ it has been demonstrated that $\forall M_i, M_j \in M : T_{ij} \leq T_{ii}$.
Now it will be proven that $M_i \neq M_j \Leftrightarrow T_{ij} < 1$. If $T_{ij} = 1$:

$$\frac{(i, j)}{(i, i) + (j, j) - (i, j)} = 1 \tag{53}$$

$$(i, j) = (i, i) + (j, j) - (i, j)$$

$$(i, i) - 2 (i, j) + (j, j) = 0$$

$$(i - j, i - j) = 0 \tag{54}$$

Making explicit the integral in (54):

$$\int_D [\rho_i - \rho_j] \, \Omega(r) [\rho_i - \rho_j] \, dr = 0 \tag{55}$$

and remembering that ρ_i and ρ_j are continuous, in accordance with the properties of the L_2 space [33], it implies that $\forall r \in D, \rho_i = \rho_j$. This proves that $\forall M_i \in M, T_{ii}$ is a strict maximum of the set $\{T_{ij}\}, M_j \in M$.
We have demonstrated that Hodgkin–Richards, Petke and Tanimoto similarity indices fulfil the axioms of the comparative relations independently of the considered quantum object set M. Then, all of them can be used to carry out comparisons among the objects of any quantum objects set. This shows how the comparative relations character of these indices can be derived directly from the previously discussed axioms. This is a

very important result, since it implies that there are no contradictions among expressions that have been used during long time in the study of the quantum similarity, and the formalism presented here. It was also shown that situations exist in which the conjugate Hodgkin-Richards and the conjugate Petke indices cannot be interpreted as similarity indices. It must be stated again that these violations in the performance of the 3rd Axiom are given by violations of our intuitive knowledge of the comparative relations, so they are independent of the equivalence relationship established over the elements of any quantum objects set.

3.2.3 Analysis of the consistency between Carbó, Hodgkin–Richards, Petke and Tanimoto indices

It is of interest to know if the results obtained by means of the application of the previously discussed indices do not present discrepancies among them; so we will investigate the consistency of the studied indices. The fact that some comparative relations fulfil the Consistency Relationship implies that the qualitative information obtained by means of them will be the same, being therefore concordant the obtained results. According to how the Consistency Relationship was presented, to analyse its fulfilling means to work with comparative relations of different types, so we will work separately with each of the similarity indices, discussing in detail for every particular case its consistency referred to Carbó dissimilarity index (we exclude the analysis related to conjugate Hodgkin-Richards and conjugate Petke indices since it was already shown that there are situations in which they cannot be interpreted as similarity indices). Though it is also necessary to know when the results obtained with a group of comparative relations of the same type are consistent among them, in this work we will limit to analyse the fulfilling of the Consistency Relationship in the form that it has been presented here, leaving for a future paper the analysis of the consistency of comparative relations sets of the same type.

Carbó similarity index:
Let it be three objects $i, j, k \in M : D_{ij} \geq D_{ik}$. According to the Consistency Relationship:

$$B_{ij} \leq B_{ik} \Leftrightarrow D_{ij} \geq D_{ik} \tag{56}$$

To investigate if the relation is fulfilled the following relations are used:

$$\begin{aligned}
D_{ij} &= \sqrt{(i,i) + (j,j) - 2(i,j)}; \quad (i,j) = B_{ij}\sqrt{(i,i)(j,j)} \\
D_{ik} &= \sqrt{(i,i) + (k,k) - 2(i,k)}; \quad (i,k) = B_{ik}\sqrt{(i,i)(k,k)},
\end{aligned} \tag{57}$$

then

$$\begin{aligned}
D_{ij} &= \sqrt{(i,i) + (j,j) - 2B_{ij}\sqrt{(i,i)(j,j)}} \\
D_{ik} &= \sqrt{(i,i) + (k,k) - 2B_{ik}\sqrt{(i,i)(k,k)}}
\end{aligned} \tag{58}$$

$$D_{ij}^2 - D_{ik}^2 = (j, j) - (k, k) + 2 \left\{ B_{ik}\sqrt{(k, k)} - B_{ij}\sqrt{(j, j)} \right\} \sqrt{(i, i)}$$

Supposing that $D_{ij} \geq D_{ik}$

$$(j, j) - (k, k) + 2 \left\{ B_{ik}\sqrt{(k, k)} - B_{ij}\sqrt{(j, j)} \right\} \sqrt{(i, i)} \geq 0 \qquad (59)$$

Let $(k, k) = p_1^2 (i, i)$, and $(j, j) = p_2^2 (i, i)$
Then

$$p_1 B_{ik} - p_2 B_{ij} \geq \frac{p_1^2 - p_2^2}{2} \qquad (60)$$

Case a:

$$p_1 = p_2 \Rightarrow B_{ij} \leq B_{ik} \qquad (61)$$

In this case the indices are consistent. (This is the case when $(k, k) = (j, j)$)

Case b:

$$p_1 < p_2; \quad p_2 = p \cdot p_1; \quad p > 1 \qquad (62)$$

$$p_1 B_{ik} - p \, p_1 B_{ij} \geq \frac{p_1^2 - p^2 p_1^2}{2}$$

$$B_{ik} \geq p B_{ij} - \frac{p_1 \left(p^2 - 1 \right)}{2} \qquad (63)$$

The last expression does not imply that $B_{ik} \geq B_{ij}$. Only if $p \approx 1$ $((k, k) \approx (j, j))$ it can be conclusively affirmed that the indices are consistent.

Case c:

$$p_2 < p_1; \quad p_1 = p \cdot p_2; \quad p > 1 \qquad (64)$$

$$p B_{ik} - B_{ij} \geq \frac{p_2 \left(p^2 - 1 \right)}{2}$$

$$p B_{ik} - B_{ij} \geq 0 \qquad (65)$$

which is conclusive only if $p \approx 1$.

So, cases could exist when these two indices are not consistent. Only in a very few number of cases it can be unambiguously concluded that they give the same qualitative information.

This last result shows that under certain conditions it cannot be assured that Carbó indices are consistent between them; therefore, it has to be taken into account when working at the same time with the results they give.

Hodgkin–Richards index:

In this case:

$$H_{ij} \geq H_{ik} \tag{66}$$

Remembering (29) and (32)

$$\frac{(i,i) + (j,j) - D_{ij}^2}{(i,i) + (j,j)} \geq \frac{(i,i) + (k,k) - D_{ik}^2}{(i,i) + (k,k)} \tag{67}$$

$$\frac{[(i,i) + (k,k)] \cdot \left[(i,i) + (j,j) - D_{ij}^2\right] - [(i,i) + (j,j)] \cdot \left[(i,i) + (k,k) - D_{ik}^2\right]}{[(i,i) + (j,j)] \cdot [(i,i) + (k,k)]} \geq 0$$

$$D_{ik}^2 [(i,i) + (j,j)] \geq D_{ij}^2 [(i,i) + (k,k)] \tag{68}$$

$$D_{ik}^2 \frac{[(i,i) + (j,j)]}{[(i,i) + (k,k)]} \geq D_{ij}^2 \tag{69}$$

If $(j,j) \leq (k,k) \Rightarrow D_{ik} \geq D_{ij}$, then the indices are consistent.
Now, when: $(j,j) > (k,k) \Rightarrow \frac{(i,i)+(j,j)}{(i,i)+(k,k)} = r^2 > 1$
Then:

$$r^2 \cdot D_{ik}^2 \geq D_{ij}^2 \tag{70}$$

$$|r| \cdot D_{ik} \geq D_{ij} \tag{71}$$

But from this it is not possible to assure that $D_{ij} \leq D_{ik}$ (because $|r| > 1$). As in the previous case, this means that in certain cases the results from Hodgkin-Richards index and from Carbó dissimilarity index could not be consistent between them.

Petke index:

Supposing:

$$P_{ij} \geq P_{ik} \tag{72}$$

and remembering expressions (29) and (34), under the assumption that $\max\{(i,i), (j,j)\} = \max\{(i,i), (k,k)\} = (i,i)$

$$\frac{(i,i) + (j,j) - D_{ij}^2}{2\,(i,i)} \geq \frac{(i,i) + (k,k) - D_{ik}^2}{2\,(i,i)} \tag{73}$$

$$(j,j) - D_{ij}^2 \geq (k,k) - D_{ik}^2$$

$$(j,j) - (k,k) \geq D_{ij}^2 - D_{ik}^2 \tag{74}$$

When $(j,j) > (k,k)$ it is possible that $D_{ij} > D_{ik}$, therefore, cases could exist in which it is not possible to assure that Petke index is consistent with Carbó dissimilarity index.

Tanimoto index:

Let:

$$T_{ij} \geq T_{ik} \tag{75}$$

Remembering (36)

$$\frac{(i, j)}{(i, i) + (j, j) - (i, j)} \geq \frac{(i, k)}{(i, i) + (k, k) - (i, k)} \tag{76}$$

$$(i, j) \cdot [(i, i) + (k, k) - (i, k)] \geq (i, k) \cdot [(i, i) + (j, j) - (i, j)] \tag{77}$$

Working with (29) in the left hand side of (77) (for the right hand side the work is exactly the same changing the correspondent sub indexes) it is obtained:

$$\frac{1}{2} \left[(i, i) + (j, j) - D_{ij}^2 \right] \cdot \left[(i, i) + (k, k) - \frac{1}{2} \left[(i, i) + (k, k) - D_{ik}^2 \right] \right]$$
$$= \frac{1}{4} \left[(i, i) + (j, j) - D_{ij}^2 \right] \cdot \left[(i, i) + (k, k) + D_{ik}^2 \right] \tag{78}$$

From (77) and (78):

$$\left[(i, i) + (j, j) - D_{ij}^2 \right] \cdot \left[(i, i) + (k, k) + D_{ik}^2 \right]$$
$$\geq \left[(i, i) + (k, k) - D_{ik}^2 \right] \cdot \left[(i, i) + (j, j) + D_{ij}^2 \right] \tag{79}$$

Working with (79):

$$D_{ik}^2 [(i, i) + (j, j)] \geq D_{ij}^2 [(i, i) + (k, k)] \tag{80}$$

This last expression is identical to (68) then, in the case of the Tanimoto index, it is not possible to assure the consistency of its results with those obtained by means of the Carbó dissimilarity index in some particular cases.

The previous results are extremely important since they show that cases can be found when the results obtained with the studied similarity indices could not be consistent with those obtained from the Carbó dissimilarity index. This does not mean that it is impossible to work with these indices as comparative relations because, as it was already discussed, in all the cases they fulfil the axioms of these relations. The fact that in some occasions the indices here presented do not fulfil the Consistency Relationship only implies that under some conditions the results they provide could be contradictory. The above-mentioned prevents us against possible incongruities that could appear in the work with these indices, but it does not deny the possibility of consider the results that we obtain by means of them as comparative relations among the elements of any quantum objects set M. Any way, an interesting idea is to construct indices based in a procedure that guaranties their consistency. It will be presented in a future work.

4 Conclusions

In this paper a formal theory of the comparative relations is proposed with their abstract characterization through a group of definitions and axioms. Special attention was given to the justification of each axiom as well as the description of its principal consequences. Additionally, several quantum similarity and dissimilarity measures and indices were analyzed following the introduced formal theory. It must be remarked that we are providing the natural interpretation of comparative relations for Carbó, Hodgkin–Richards, Petke and Tanimoto indices through the presented axioms, though some times they could be non consistent among them. This is a very important result, since it implies that there are no contradictions among expressions that have been used during long time in the study of the molecular quantum similarity and the formalism presented here.

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