Non-linear terms & variational approach in Quantum QSPR

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The theoretical results presented in this work point out that quantitative structure–properties relationslips (QSPR) can be appropriately founded within the theoretical background of quantum mechanics. In this way, the deducible quantum QSPR (QQSPR) framework and the associated fundamental equation, furnish with a causal backup the structure–properties relationships old problem. Moreover, they also provide algorithms to obtain in a general manner, up to any approximation level and even from a variational point of view, unbiased and universal causal QSPR models for any chosen quantum object set.

KEY WORDS: quantum QSPR, molecular similarity, non-linear QQSPR, stochastic similarity matrices, Jacobi rotations, variational QQSPR

1. Introduction

Until now, a good deal of theoretical statements have been set about the foundations of Quantum Quantitative Structure–Properties Relationships (QQSPR) [1], namely the construction of the fundamental QQSPR equation [2] and the generalization of the basic linear formalism based on extended wave functions [3].

Among other advances from the original idea, which essentially was intended to show the origin of empirical QSPR [4] and the setting of a fundamental QQSPR equation [2], there was developed a line of research, based on the stochastic transformation [5] of the similarity matrix [6,7] and, thus, a new fundamental QQSPR equation form was set up. Stochastic based fundamental QQSPR equation [5] among other characteristics has the main structure prepared to hold solutions, supposedly approximate, which as well as the appropriately constructed column or row submatrices of the stochastic similarity matrix can be contained into a vector semispace [8]. The in deep exploration of stochastic fundamental QQSPR equations structure and properties is still to be fully developed.

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In fact, up-to-date, the fundamental QQSPR equations have been mainly treated from the practical point of view as sources of classical QSPR information [9]. Thus, the usual published work on QQSPR has been intended to show that quantum similarity matrices can be used as a sound source of molecular descriptors [10]. Such quantum similarity uses were developed to be employed within the usual classical mathematical treatment, using appropriate statistical procedures for obtaining QSPR linear models [11]. The results of this action so far have provided linear functionals, which are comparable to the usual QSPR ones as obtained from classical statistical manipulation of arbitrary descriptors [9]. QQSPR has thus proved that *unbiased* and *universal* quantum similarity descriptors can be safely employed as a source of classical QSPR models. Moreover, besides the quantum origins of the descriptors, the differences between QQSPR and classical QSPR, can be easily found in the fact that, being the QQSPR models based on the fundamental QQSPR equation, then they can be attached to some causal relationship between molecular structure and properties, which within QQSPR theory are theoretically related by means of the quantum mechanical expectation value concept [12].

Then, it appears that the moment has arrived to find out the path, whenever it exists, to build up a general QQSPR modelling system as independent as possible of classical QSPR procedures.

Among several alternative possibilities for continued research in QQSPR, two of them appear more relevant to the immediate testing grounds and a third one will be left to be discussed after them. Finally, a theoretical setup, based on the variational method, will be presented as a possible structure over which QQSPR can be founded.

The first subject to be analysed of the initial set of two, consists in testing fundamental QQSPR equations based into non-symmetric, rectangular similarity matrices. This matrix structure appears from the study of a molecular quantum object set of M elements, whose density functions are taken as a basis set. Known this M-dimensional basis set, then the quantum similarity measures can be easily computed from it and a probe discrete quantum object set [8] can be constructed by using N known molecular structures as objects. As a result, this procedure provides a $(M \times N)$ similarity matrix, which can subsequently be employed in the setting of QQSPR fundamental equation.

The second research option will consist into the use of higher order terms to construct the operator entering the fundamental QQSPR equation. This choice provides, as a consequence, triple or multiple density quantum similarity measure [13,14] representations which can be used to build up the molecular similarity matrices. Once the similarity matrices known, one can try to construct and solve an attached fundamental QQSPR equation.

A third natural research option can be associated to the study of the stochastic fundamental QQSPR equation and the vector semispace [8] restricted solutions, which can apparently lay within the QQSPR formalism by construction.

After finishing these three preliminary options, taken as a basic discussion, then the framework will be set to seek for a QQSPR method not so connected with the usual classical QSPR procedures. This possibility is left to the end of the present work as encompasses every previous step, while providing a completely different way to obtain structure–properties relationships with fundaments lying exclusively over the quantum mechanical theoretical ground.

2. Fundamental QQSPR equation in $(N \times M)$ similarity matrix spaces

Suppose a quantum object [8] basis set B composed by M quantum systems, whose homogeneous density functions, acting as quantum object tags, are known: $B = \left\{ \rho_I^B \,|\, I = 1, M \right\}$. Suppose also that a probe quantum object set P is well defined and composed by N quantum systems, which have also known density tags: $\left\{ \rho_J^P \right\}$, and at least is also known a set of property values: $\{p_J\}$ attached to every quantum object of the set; in this manner: $P = \left\{ \rho_J^P \wedge p_J \,|\, J = 1, N \right\}$.

A general operator Ω can be associated to the expectation value computation of the observable property π, in such a way that, knowing the appropriate quantum state density function tag ρ for a given quantum system, such quantum object observable property can be evaluated in general by using the integral form [4, 15]:

$$\langle \pi \rangle = \langle \Omega | \rho \rangle = \int_D \Omega\,(\mathbf{r})\,\rho\,(\mathbf{r})\mathrm{d}\mathbf{r}, \tag{1}$$

where D is an appropriate integration domain, where the density and operator variables are defined.

Being the operator Ω, in principle, after the adoption of quantum mechanical rules, a Hermitian operator, without loss of generality it can be supposedly decomposed into a product of two commutative operators

$$\Omega\,(\mathbf{r}) = W\,(\mathbf{r})\,\Theta\,(\mathbf{r}) \wedge [W\,(\mathbf{r})\,;\,\Theta\,(\mathbf{r})] = 0, \tag{2}$$

the operator Θ being a known chosen positive definite one, the remnant Hermitian operator is thus defined as

$$W\,(\mathbf{r}) = \Omega\,(\mathbf{r})\,\Theta^{-1}\,(\mathbf{r})\,. \tag{3}$$

Using equation (1) and the operator composition shown in equation (2), then it can be formally written

$$\langle \pi \rangle = \langle W\Theta | \rho \rangle \equiv \langle W | \Theta\rho \rangle = \langle W | \Theta | \rho \rangle\,, \tag{4}$$

suggesting that the operator W could be approximately obtained, even in the case that it is unknown, due to the nature of the observable attached to the property π.

In the case, most usual in QQSPR framework, that an approximate construction of the operator W is needed, if an appropriate quantum object set density function tag set, acting as a basis set, B say, is known, as stated at the beginning, that is, $B = \left\{ \rho_I^B \,|\, I = 1, M \right\}$, then the operator W can be written within a first-order linear approach as

$$W \approx \sum_{I=1}^{M} \omega_I \rho_I^B \tag{5}$$

so upon substituting this approximate first-order linear expression into the expectation value in equation (4), it is obtained as

$$\langle \pi \rangle \approx \sum_{I=1}^{M} \omega_I \left\langle \rho_I^B \,\middle|\, \Theta \,\middle|\, \rho \right\rangle, \tag{6}$$

where the integral in equation (6) can be interpreted as a quantum similarity measure [6], that is,

$$\left\langle \rho_I^B \,\middle|\, \Theta \,\middle|\, \rho \right\rangle \equiv \iint_D \rho_I^B (\mathbf{r}_1) \Theta (\mathbf{r}_1; \mathbf{r}_2) \, \rho (\mathbf{r}_2) \, \mathrm{d}\mathbf{r}_1 \, \mathrm{d}\mathbf{r}_2. \tag{7}$$

The unknown coefficient set in equation (6): $|\omega\rangle = \{\omega_I \,|\, I = 1, M\}$, which can be collected into an M-dimensional column (or row) vector, will represent the operator W in terms of the known density function basis set B. This situation, clearly represented by equation (6), still has a set of undetermined parameters, associated now to the vector $|\omega\rangle$ components, instead of the operator W.

Equation (6) can be used to obtain the vector $|\omega\rangle$. As it is usually the case in classical QSPR, it is only necessary to know, a quantum object tag set, associated to some molecular probe set P of cardinality N, $P = \left\{ \rho_J^P \wedge p_J \,|\, J = 1, N \right\}$, where, as previously commented, every quantum object structure in P has also necessarily to be attached to a known value of the involved observable: $|p\rangle = \{p_J \,|\, J = 1, N\}$, which can be also collected in form of a N-dimensional column (or row) vector. Then, equation (6) can be rewritten for every element in P, employing the known property values instead of the expectation observable values, that is,

$$\forall J = 1, N : p_J \approx \sum_{I=1}^{M} \omega_I \left\langle \rho_I^B \,\middle|\, \Theta \,\middle|\, \rho_J^P \right\rangle \tag{8}$$

in this way, the following set of quantum similarity measures is generated:

$$a_{IJ}^{BP} (\Theta) \equiv a_{IJ}^{BP} = \left\langle \rho_I^B \,\middle|\, \Theta \,\middle|\, \rho_J^P \right\rangle, \tag{9}$$

which in turn can be considered, after an appropriate rearrangement, as elements of a $(M \times N)$ similarity matrix, involving the basis and probe quantum object molecular sets, respectively: $\mathbf{A} = \{a_{IJ}^{BP}\}$.

With this matrix definition in mind, then equation (8) can be rewritten as a linear system in matrix form, connecting the already defined vectors in row space form:

$$\langle p| = \langle \omega | \, \mathbf{A}. \tag{10}$$

Such a linear system can be associated to the most common dual problem in column vector space, just defining the transpose of the similarity matrix, using the usual definition

$$\mathbf{Z} = \mathbf{A}^{\mathbf{T}} \to \forall I = 1, N \wedge J = 1, M : z_{JI}^{PB} = a_{IJ}^{BP}, \tag{11}$$

and in this manner, the fundamental QQSPR equation is set up, writing a column equivalent dual expression of the former row equation (10)

$$\mathbf{Z} \, |\omega\rangle = |p\rangle \,. \tag{12}$$

As in classical QSPR, the solutions of equation (12) may provide the knowledge of the coefficient vector $|\omega\rangle$. However, it must be again stressed the fact that equation (12) differs from the classical QSPR setup in the sense that such an equation can be deduced from the quantum mechanical statistical structure, associated to expectation value calculations. In this way, the *causal* connection between molecular structure and molecular properties can be deduced from employing quantum mechanical theoretical fundaments, via the ideas of quantum similarity. The interest of such relationship lies in the fact that fundamental QQSPR equations can be extended to any quantum object structure and properties. So, obviously, these relationships can be applied to molecular systems as well, provided they can be described as quantum objects, making QQSPR *universal* in the sense that it can be applied, under the same conditions, to any submicroscopic quantum object set.

3. Remarks on the structure of the fundamental QQSPR equation

Some remarks may be stated in front of the result given by equation (12) and discussed into the section above. Each of these remarks poses new problems ahead, which will be studied separately in subsequent sections.

3.1. Symmetrical similarity matrices

In the first place, it must be said that the fundamental QQSAR equation has been usually presented in previous literature within the particular case where

the basis and probe molecular quantum object tagged sets coincide, providing a square symmetric similarity matrix, and thus the equality: $\mathbf{A} = \mathbf{Z}$, between the involved similarity matrices holds [6]. This choice has the drawback consisting in that the linear system (12) becomes well defined, with a unique solution, whenever the similarity matrix is non-singular, which shall be the usual case, as far as no quantum object coincides with another within the quantum object set.

But even then, there is quite a wide range of solutions to overcome this apparent limitation. Among other procedures, one can use the symmetric similarity matrix as a source of molecular descriptors and afterwards employ them in classical statistical treatments. This choice, as was already commented, has been studied in many publications of our laboratory with success. In the same way, the similarity matrix can be transformed into a column or row stochastic matrix and, as a consequence, this form suggests several possibilities, which still are far from being exploited. Some analysis of the stochastic issue will be developed in a forthcoming section of the present paper.

3.2. Origin of Hansch [16] QSAR models

An interesting possibility of the symmetric square representation of the quantum similarity matrices corresponds to its potential to unveil the origin of one parameter classical QSAR models, such as those Hansch has described some years ago. Indeed, under the equivalence of both the basis B and probe P quantum object sets, equation (12) corresponds to a set of N equations with the same number of unknowns, and can be rewritten as

$$\forall J = 1, N : p_J \approx \sum_{I=1}^{N} \omega_I z_{IJ} = \omega_J z_{JJ} + \sum_{I \neq J}^{N} \omega_I z_{IJ}, \tag{13}$$

where there is no need to attach the similarity matrix elements to any specific quantum object set, as all of them are computed over a unique basis of density function tags. Considering the two terms at the end of equation (13), it can be seen that the first one, with a diagonal value of the similarity matrix, is attached to a self-similarity measure z_{JJ}, while the second term in cases of a not so strongly varying family of quantum objects, can be considered almost a constant, that is using

$$\forall J : \alpha = \omega_J \wedge \beta \approx \sum_{I \neq J}^{N} \omega_I z_{IJ} \tag{14}$$

equation (13) takes the final form

$$\forall J = 1, N : p_J \approx \alpha z_{JJ} + \beta \tag{15}$$

which has the required appearance to be considered as possessing a Hansch structure.

Besides of this last deduction, it must be said that self-similarity measures of different kinds have been used to test equation (15) with quite a large series of quantum objects yielding usually good results. Self-similarities can be sound substitutes of the classical Hansch analysis parameters [17]. They constitute for co-generic molecular sets molecular descriptors with the property to be directly attached to a tri-dimensional molecular structure. Self-similarity measures vary slowly with conformational changes [18], so their values for the optimal geometry can be safely used, knowing that the magnitude of the descriptor will differ not very much from the one which is attached to the active conformation associated to the observable property.

4. Non-linear QQSPR equations

4.1. Introduction

In a second remark step, which appears to be sufficiently important as to merit a separate section treatment, the approximate operator linear description (5) may be extended with non-linear terms, which can be easily provided by the nature of the involved quantum object density function tags, which can be founded in turn on the theoretical development of extended wave functions [3, 15].

In this case, equation (5), can be written in a more structured manner as a truncated Taylor series, where only the first two terms are kept for simplicity

$$W \approx \sum_{I=1}^{M} \omega_I \rho_I^B + \sum_{P=1}^{M} \sum_{Q \geqslant P}^{M} \omega_{PQ} \rho_P^B \rho_Q^B + O\,(3)\,, \tag{16}$$

however, with the potential prospect to add terms up to any order. Equation (16) can be perhaps also considered a simplification of a series involving density functions of growing orders, that is,

$$W \approx \sum_{I=1}^{M} \omega_I^{(1)} \rho_I^{(1)B} + \sum_{P=1}^{M} \omega_P^{(2)} \rho_P^{(2)B} + O\,(3)\,. \tag{17}$$

The second order coefficient set $\{\omega_{PQ}\}$ in equation (16), can be also substituted as well, in order to retain a minimal number of unknowns, by products of first-order coefficients, in the following way:

$$\forall P, Q : \omega_{PQ} \approx \omega_P \omega_Q. \tag{18}$$

Then, just if this is the case, equation (8), transforms into a more computationally convenient form:

$$\forall J = 1, N : p_J \approx \sum_{I=1}^{M} \omega_I \left\langle \rho_I^B \middle| \Theta \middle| \rho_J^P \right\rangle + \sum_{P=1}^{M} \sum_{Q \geqslant P}^{M} \omega_P \omega_Q \left\langle \rho_P^B \rho_Q^B \middle| \Theta \middle| \rho_J^P \right\rangle + O(3),$$

(19)

4.2. Triple density quantum similarity integrals

The integrals included into the second-order terms of equation (19) are triple density similarity measures [14], which can have the form chosen, among many other possibilities, in the following way:

$$\left\langle \rho_P^B \rho_Q^B \middle| \Theta \middle| \rho_J^P \right\rangle \equiv \iiint_D \rho_P^B(\mathbf{r}_1) \rho_Q^B(\mathbf{r}_2) \Theta(\mathbf{r}_1; \mathbf{r}_2; \mathbf{r}_3) \rho_J^P(\mathbf{r}_3) \mathrm{d}\mathbf{r}_1 \, \mathrm{d}\mathbf{r}_2 \, \mathrm{d}\mathbf{r}_3.$$

(20)

Moreover, the usual computational form of the triple density measures can be the one, where the operator becomes unit and all the integrand density functions bear the same variable, so the integral in equation (20) acquires a simpler structure, like the triple density overlap integral form:

$$\left\langle \rho_P^B \rho_Q^B \rho_J^P \right\rangle \equiv \int_D \rho_P^B(\mathbf{r}) \rho_Q^B(\mathbf{r}) \rho_J^P(\mathbf{r}) \, \mathrm{d}\mathbf{r},$$

(21)

while, first order similarity measures (7) become, under an equivalent simplification, *overlap-like* integrals [6]

$$\left\langle \rho_I^B \rho_J^P \right\rangle \equiv \int_D \rho_I^B(\mathbf{r}) \rho_J^P(\mathbf{r}) \, \mathrm{d}\mathbf{r}.$$

(22)

Equations (21) and (22), could be obtained defining the respective weighting operators in terms of an integral operator, involving as many products of Dirac's delta functions as density functions appear into the integrand. For instance, in equation (20), the operator $\Theta(\mathbf{r}_1; \mathbf{r}_2; \mathbf{r}_3)$ can be substituted inside the integral in the following manner:

$$\left\langle \rho_P^B \rho_Q^B \rho_J^P \right\rangle \equiv \int_D \left[\iiint_D \rho_P^B(\mathbf{r}_1) \rho_Q^B(\mathbf{r}_2) \left(\delta(\mathbf{r}_1 - \mathbf{r}) \delta(\mathbf{r}_2 - \mathbf{r}) \delta(\mathbf{r}_3 - \mathbf{r}) \right) \rho_J^P(\mathbf{r}_3) \mathrm{d}\mathbf{r}_1 \, \mathrm{d}\mathbf{r}_2 \, \mathrm{d}\mathbf{r}_3 \right] \mathrm{d}\mathbf{r}$$

$$= \int_D \left[\int_D \rho_P^B(\mathbf{r}_1) \delta(\mathbf{r}_1 - \mathbf{r}) \, \mathrm{d}\mathbf{r}_1 \int_D \rho_Q^B(\mathbf{r}_2) \delta(\mathbf{r}_2 - \mathbf{r}) \, \mathrm{d}\mathbf{r}_2 \int_D \rho_J^P(\mathbf{r}_3) \delta(\mathbf{r}_3 - \mathbf{r}) \mathrm{d}\mathbf{r}_3 \right] \mathrm{d}\mathbf{r}$$

$$= \int_D \rho_P^B(\mathbf{r}) \rho_Q^B(\mathbf{r}) \rho_J^P(\mathbf{r}) \, \mathrm{d}\mathbf{r}.$$

(23)

It is, then, straightforward to use the same technique to obtain equations possessing a higher number of density function terms, and so it is easily seen how to take into account and to handle them in the same manner, adding higher order terms within non-linear fundamental QQSPR equations of type (19).

4.3. Hansch type QQSPR quadratic models

In the same manner as done above in the linear case, the fundamental quadratic QQSPR equation (19) can be simplified, so only the diagonal terms of the initial equation remain. First using just a probe set, taking $B = P$ and then supposing that the remnant equation summation terms are constant under the study of some quantum objects, possessing a great deal of homogeneity. In this case one can write

$$\forall J = 1, N : p_J \approx \beta + \alpha \left\langle \rho_J^P \middle| \Theta \middle| \rho_J^P \right\rangle + \alpha^2 \left\langle \rho_J^P \rho_J^P \middle| \Theta \middle| \rho_J^P \right\rangle + O(3), \qquad (24)$$

which constitutes a quadratic extension of the linear Hansch type relationships (15).

4.4. Quadratic fundamental QQSPR equation in matrix form

Having set up in the way outlined above the formal structure of the fundamental QQSPR equations, there is the moment to discuss its matrix implementation, which constitutes the obliged step when seeking for computational algorithms in practical cases. Two possible equivalent modes will be discussed in this section: the first one corresponds to classical matrix product formalism, while a second part will present an equivalent form just employing inward matrix products. The reason for this second formal presentation is the easiness of setting a general framework up to any approximation order.

4.4.1. Classical form

Equation (19) can be easily written in matrix form. For this purpose it is only necessary to define, besides the column vector of the first-order coefficients

$$|\omega\rangle = \{\omega_I \,|I = 1, M\} \qquad (25)$$

also, for every quantum object within the probe set, the first order M-dimensional similarity matrix columns

$$J = 1, N : \left|\mathbf{z}_J^{(1)}\right\rangle = \left\{ z_{IJ}^{(1)} = \left\langle \rho_I^B \middle| \Theta \middle| \rho_J^P \right\rangle |I = 1, M \right\} \qquad (26)$$

as well as the second order $(M \times M)$-dimensional similarity matrices

$$J = 1, N : \mathbf{Z}_J^{(2)} = \left\{ z_{J;PQ}^{(2)} = \langle \rho_J^P | \Theta | \rho_P^B \rho_Q^B \rangle | P, Q = 1, M \right\},$$ (27)

shall be constructed.

Taking the above defined similarity matrices into account, equation (19) can be written as

$$J = 1, N : p_J \approx \langle \mathbf{z}_J^{(1)} | \omega \rangle + \langle \omega | \mathbf{Z}_J^{(2)} | \omega \rangle + O(3),$$ (28)

so, collecting the property observable values into a column vector $|p\rangle = \{p_J | J = 1, N\}$, as already discussed and then, reordering first- and second-order matrix components in the following way:

$$\mathbf{Z}^{(1)} = \left\{ \left| \mathbf{z}_J^{(1)} \right\rangle | J = 1, N \right\}$$ (29)

and

$$\mathbf{Z}^{(2)} = \left\{ \mathbf{Z}_J^{(2)} | J = 1, N \right\}$$ (30)

then the second order fundamental QQSPR equation becomes a quadratic system of equations in matrix form:

$$|p\rangle \approx \left(\mathbf{Z}^{(1)} + \left[\langle \omega | \mathbf{Z}^{(2)} \right] \right) |\omega\rangle + O(3).$$ (31)

4.4.2. Inward matrix product form as a generalization device

Alternatively, there is the possibility to express the equations of the previous description by means of *inward matrix products* [2]. The first-order term in equation (28) can be expressed within inward product formalism at once, as it is a simple scalar product between the involved vectors, so:

$$J = 1, N : \langle \mathbf{z}_J^{(1)} | \omega \rangle \equiv \langle | \mathbf{z}_J^{(1)} \rangle * | \omega \rangle \rangle,$$ (32)

while the second-order term may be expressed in inward product form with the aid of the coefficient vector tensor product, forming a square $(N \times N)$ matrix:

$$\mathbf{W} = |\omega\rangle \otimes |\omega\rangle \equiv \{w_{IJ} = \omega_I \omega_J | \forall I, J = 1, N\}.$$ (33)

so, one can write then the quadratic term of equation (31) as an inward matrix product too

$$J = 1, N : \langle \omega | \mathbf{Z}_J^{(2)} | \omega \rangle \equiv \langle \mathbf{Z}_J^{(2)} * \mathbf{W} \rangle = \langle \mathbf{Z}_J^{(2)} * (|\omega\rangle \otimes |\omega\rangle) \rangle,$$ (34)

and consequently equation (28), can be rewritten as

$$J = 1, N : p_J \approx \langle | \mathbf{z}_J^{(1)} \rangle * | \omega \rangle \rangle + \langle \mathbf{Z}_J^{(2)} * (|\omega\rangle \otimes |\omega\rangle) \rangle + O(3).$$ (35)

4.5. Inward matrix product formalism of fundamental QQSPR equation nth order terms

Both, classical and inward product, formalisms are equivalent; however, the inward product equation (35), permits to easily imagine any sequence of corrections into the fundamental QQSPR equation, up to any arbitrarily chosen nth order term. just writing:

$$J = 1, N : p_J \approx \sum_{R=1}^{n} \left\langle \mathbf{Z}_J^{(R)} * \left(\bigotimes_{S=1}^{R} |\omega\rangle \right) \right\rangle + O(n+1), \qquad (36)$$

where the leading equation terms are $\left\{ \mathbf{Z}_J^{(R)} \middle| J = 1, N \right\}$ the Rth order similarity matrices, which can be constructed as

$$J = 1, N : \mathbf{Z}_J^{(R)} = \left\{ z_{J;S(\mathbf{i})}^{(R)} = \left\langle \rho_J^P \middle| \Theta \middle| \rho_{S_1}^B \rho_{S_2}^B \cdots \rho_{S_R}^B \right\rangle \middle| \quad \forall \alpha = 1, R : L_\alpha \in \{1, 2, \ldots, M\} \right\} \qquad (37)$$

with the index set: $S(\mathbf{i}) = \{S_1, S_2, \ldots, S_R\}$ formed by any of the M^R combinations with repetition of R elements chosen within the M integers and, finally, the Rth order tensor products of the coefficient vector are noted as: $\bigotimes_{S=1}^{R} |\omega\rangle$.

5. Stochastic Transformations

It is now the moment to discuss a third remark step, dealing about the stochastic transformation of similarity matrices, because it also merits a separate section. Nowadays, several studies have dealt with stochastic transformations of the fundamental QQSPR equation in linear symmetric form, that is, using $B = P$.

At the light of the previous manipulation presented in this study, the stochastic structure transformation [5] of the fundamental QQSPR equation has to be performed, at any operator-equation approximation level, using the possibility to compute the sum of the elements of the Rth order similarity matrices as have been previously defined in equation (37), that is,

$$\sigma_J^{(R)} = \left\langle \mathbf{Z}_J^{(R)} \right\rangle = \sum (\mathbf{i}) z_{J;S(\mathbf{i})}^{(R)}, \qquad (38)$$

where a nested summation symbol $\sum(\mathbf{i})$ [19] has been employed in order to indicate the nested sums over the R indices, represented by the index sets: $S(\mathbf{i}) = \{S_1, S_2, \ldots, S_R\}$. Using the sum of the similarity matrix elements (38), then the elements of the new matrices scaled by this sum become scaled in turn as follows:

$$\mathbf{S}_J^{(R)} = \left(\sigma_J^{(R)} \right)^{-1} \mathbf{Z}_J^{(R)} \qquad (39)$$

and the new Rth order stochastic similarity matrices [20] behave as a discrete probability distribution, as: $\forall S\,(\mathbf{i}) : z^{(R)}_{J;S(\mathbf{i})} \in \mathbf{R}^+ \rightarrow s^{(R)}_{J;S(\mathbf{i})} \in \mathbf{R}^+$ and besides

$$\left\langle \mathbf{S}^{(R)}_J \right\rangle = 1. \tag{40}$$

Both properties can be cast into a unique *convex condition* symbol [8]:

$$K\left(\mathbf{S}^{(R)}_J\right) = \left\{ \forall S\,(\mathbf{i}) : s^{(R)}_{J;S(\mathbf{i})} \in \mathbf{R}^+ \wedge \left\langle \mathbf{S}^{(R)}_J \right\rangle = 1 \right\}. \tag{41}$$

So, in this way, the stochastic matrix set: $\mathbf{S} = \left\{ \mathbf{S}^{(R)}_J \,|\, R = 1, n \right\}$ can be considered, up to nth order, as a set of M^R-dimensional *unit shell* elements [21], belonging to some *vector semispace* with the same dimensions. In these circumstances one can consider the fundamental QQSPR equation (36) as to be written:

$$J = 1, N : p_J = \sum_{R=1}^{n} \left\langle \mathbf{S}^{(R)}_J * \left(\overset{R}{\underset{S=1}{\otimes}} |\omega\rangle \right) \right\rangle + O\,(n+1), \tag{42}$$

where everything is the same as in the former equation (36), but the similarity matrix set, which has been substituted by the stochastic matrices (39).

The coefficient vector has been left unchanged, but evidently his character could be no longer the same as in equation (36). However, the nature of the coefficient vector can be more precise in this case of the fundamental QQSPR stochastic equations (42). This is due to the characteristic convex conditions properties, which possess the semispace unit shell elements obtained transforming the similarity matrices.

In fact, the stochastic similarity matrix set: $\left\{ \mathbf{S}^{(R)}_J \,|\, R = 1, n \right\}$, so naturally obtained from the original similarity matrix set, can be interpreted as a sequential discrete representation of the continuous normalized density function ρ_J, associated to the involved Jth quantum object. Then, from the quantum mechanical point of view, the whole stochastic matrix set can be viewed as a discrete quantum object tag collection. Thus, in this case, the tensor products of the coefficient vector can be easily considered arrays of convex sets, that is,

$$\mathbf{W}^{(R)} = \overset{R}{\underset{S=1}{\otimes}} |\omega\rangle = \left\{ w^{(R)}_{S(\mathbf{i})} \right\} \rightarrow \left\langle \mathbf{W}^{(R)} \right\rangle = \sum (\mathbf{i}) w^{(R)}_{S(\mathbf{i})} = 1 \wedge \forall S\,(\mathbf{i}) : w^{(R)}_{S(\mathbf{i})} \in \mathbf{R}^+ \tag{43}$$

because, whenever the generating coefficient vector is a convex vector, that is, fulfilling the convex conditions

$$K\left(|\omega\rangle\right) = \left\{ I : \omega_I \in \mathbf{R}^+ \wedge \langle|\omega\rangle\rangle = \sum_I \omega_I = 1 \right\}, \tag{44}$$

then, any tensor product of the convex vector $|\omega\rangle$ fulfils: $K\left(\overset{R}{\underset{S=1}{\otimes}} |\omega\rangle \right)$.

Indeed, if convex conditions (44) hold, then it is easy to see that convex conditions are present within any arbitrary order tensor product of the coefficient vector, as shown in the following deduction:

$$
\mathbf{W}^{(R)} = \overset{R}{\underset{S=1}{\otimes}} |\omega\rangle = \left\{ w_{S(\mathbf{i})}^{(R)} = \omega_{S_1}\omega_{S_2}\ldots\omega_{S_R} \in \mathbf{R}^+ \right\} \wedge \langle \mathbf{W}^{(R)} | = \sum (\mathbf{i}) \, w_{S(\mathbf{i})}^{(R)}
$$

$$
= \left(\sum_I \omega_I \right)^R = \left(\langle |\omega\rangle \rangle \right)^R = (1)^R = 1 \rightarrow K \left(\overset{R}{\underset{S=1}{\otimes}} |\omega\rangle \right) \equiv K \left(\mathbf{W}^{(R)} \right). \quad (45)
$$

6. Variational QQSPR

So far the fundamental QQSPR equation has been solved by means of the usual strategy associated to classical QSPR. Equations (12) and (31) or (42) as in classical terms, can be solved for the coefficient vector $|\omega\rangle$. As has been previously commented this is done, by substituting in the expectation value expression (19) the vector $|\pi\rangle$ by an experimental property vector $|p\rangle$, associated to the probe quantum object set P. The result will be obtained in the same way as in classical QSPR, but using the quantum similarity matrices as molecular descriptors. However, fundamental QQSPR equation may be proven that it can be solved within the usual quantum variational procedures.

6.1. Similarity matrix unrestricted variational treatment

For such a purpose it is sufficient to rewrite the second order expectation value equation (19) as

$$
\forall J = 1, N : \langle \pi_J \rangle \approx \sum_{P=1}^{M} \omega_P z_{J;P}^{(1)} + \sum_{P=1}^{M} \sum_{Q \geqslant P}^{M} \omega_P \omega_Q z_{J;PQ}^{(2)} + O(3) \quad (46)
$$

then, considering every quantum object expectation value as a variational function of the parameters within the coefficient vector $|\omega\rangle$, the resulting expression can be varied, taking into account that the density functions, supposedly obtained by quantum mechanical procedures, no longer need variation. In this way, every Jth quantum object will have to possess a specific coefficient vector $|\omega\rangle$, which can be thus named as $|\omega_J\rangle$. That is,

$$
\forall J = 1, N : \delta \langle \pi_J \rangle \approx \sum_{P=1}^{M} \delta\omega_P z_{J;P}^{(1)} + 2 \sum_{P=1}^{M} \sum_{Q \geqslant P}^{M} \delta\omega_P \omega_Q z_{J;PQ}^{(2)} + O(3), \quad (47)
$$

then, using the variation condition for the Jth quantum object

$$
\delta \langle \pi_J \rangle = 0 \quad (48)
$$

it is obtained

$$\forall J = 1, N : 0 \approx \sum_{P=1}^{M} \delta\omega_P z_{J;P}^{(1)} + 2 \sum_{P=1}^{M} \sum_{Q \geqslant P}^{M} \delta\omega_P \omega_Q z_{J;PQ}^{(2)} + O(3), \tag{49}$$

which can be rewritten as

$$\forall J = 1, N \wedge P = 1, M : 0 \approx z_{J;P}^{(1)} + 2 \sum_{Q=1}^{M} \omega_Q z_{J;PQ}^{(2)} + O(3). \tag{50}$$

This last equation can be expressed in matrix form, using the appropriate similarity matrices as previously defined in equations (26) and (27)

$$\forall J = 1, N : \mathbf{z}_J^{(1)} + 2\mathbf{Z}_J^{(2)} |\omega_J\rangle = 0, \tag{51}$$

thus, the specific coefficients for each quantum object may be computed as

$$\forall J = 1, N : |\omega_J\rangle = -\frac{1}{2} \left[\mathbf{Z}_J^{(2)} \right]^{-1} \mathbf{z}_J^{(1)}. \tag{52}$$

This is the same as to associate a particular operator W to each quantum object, constituting such a result not a too surprising feature, as the operator W can be easily supposed to vary from one quantum object to another, in the same way as Hamilton operators do. The variational expectation value for the Jth object could be obtained in this case as

$$\langle \pi_J \rangle \approx \left\langle \omega_J | \mathbf{z}_J^{(1)} \right\rangle + \left\langle \omega_J | \mathbf{Z}_J^{(2)} | \omega_J \right\rangle + O(3). \tag{53}$$

Using equation (52) into equation (53), the following expectation value final optimal form will result:

$$\langle \pi_J \rangle \approx -\frac{1}{4} \left\langle \mathbf{z}_J^{(1)} \left| \left[\mathbf{Z}_J^{(2)} \right]^{-1} \right| \mathbf{z}_J^{(1)} \right\rangle + O(3). \tag{54}$$

6.2. Expectation vs. experimental values

Then, the set of stationary expectation values $|\pi\rangle$ can be compared with the experimental value vector $|p\rangle$, in such a way as to have

$$|p\rangle = a + b |\pi\rangle, \tag{55}$$

being $\{a, b\}$ some origin and scale parameters, respectively. They can be obtained by the usual well known regression techniques [20].

6.3. Algorithm for unrestricted variational QQSPR

Once the set of coefficients $\{a, b\}$ is obtained by using equation (55) for a given probe quantum object set, the property expectation value $\langle \pi_K \rangle$ of any new quantum object K, say, with known density function ρ_K, can be employed to estimate the experimental value p_K of the quantum object studied property, by using the following steps:

(a) Compute: $\left\{ \mathbf{z}_K^{(1)}; \mathbf{Z}_K^{(2)} \right\}$ using the basis set B.

(b) Evaluate: $\langle \pi_K \rangle \approx -\frac{1}{4} \left\langle \mathbf{z}_K^{(1)} \left| \left[\mathbf{Z}_K^{(2)} \right]^{-1} \right| \mathbf{z}_K^{(1)} \right\rangle + O\,(3)$.

(c) Obtain the estimated property: $p_K = a + b \langle \pi_K \rangle$.

6.4. Stochastic similarity matrices restricted variational treatment

Of course, all of which has been said up to now in this section remain valid for stochastic similarity matrices: $\left\{ \mathbf{s}_K^{(1)}; \mathbf{S}_K^{(2)} \right\}$, they just have to be used instead of the similarity matrix pair: $\left\{ \mathbf{z}_K^{(1)}; \mathbf{Z}_K^{(2)} \right\}$ in the above algorithm. However, in the stochastic case may be interesting if the coefficient set $|\omega\rangle$ can to be obtained obeying convex conditions as a restriction, so the previous unrestricted variation algorithm may be no longer applicable.

6.5. Expectation value Jacobi rotations variational form

To obtain the desired restricted variation over the coefficient vector involved into expectation value expressions, a similar procedure as the one employed in developing the ASA technique [22] could be easily set up to perform the variational computation over equation (46), but taking into account the additional restriction of obtaining a convex vector, as a result of the optimization process.

6.5.1. Preliminary considerations

When this option as discussed above is chosen, it is only necessary to express the operator W variational coefficients with the aid of a new free normalized auxiliary vector; in order to ensure the convex conditions $K(|\omega\rangle)$ hold throughout the entire optimization process, that is,

$$|\omega\rangle = |x\rangle * |x\rangle \wedge \langle x|x\rangle = 1 \rightarrow \langle|\omega\rangle\rangle = \sum_I \omega_I = \sum_I x_I^2 = 1 \wedge \forall I : \omega_I = x_I^2 \in \mathbf{R}^+.$$

$$(56)$$

After this consideration, it is only necessary to obtain the variation of equation (46), by applying norm conserving, orthogonal elementary Jacobi rotations

[23] into the auxiliary vector $|x\rangle$ element pairs, in order to arrive to an expression, depending of the elementary Jacobi rotation angle, which could be easily optimized later on.

The interesting point to remark at this stage is to realize that such a restricted variational procedure can be applied to higher order equations, with orders larger than the ones studied up to now. This is due to the fact that Jacobi rotations over the auxiliary vector just change a couple of the coefficient auxiliary vector elements each time an elementary Jacobi rotation is performed, and the same occurs with the coefficient vector. This knowledge of the coefficient vector variation can be easily brought into the tensor products and worked out up to any tensor order.

The rest becomes a procedure with somehow a growing technical computational complexity, but defined within a well structured theoretical background algorithm.

6.5.2. Elementary Jacobi rotations algorithm scheme

Elementary Jacobi rotations need the cosine c, and the sine s, of a rotation angle. These involved trigonometric functions fulfil the usual convex relationship: $c^2 + s^2 = 1$. When acting over a vector, the Jacobi rotations will change two vector components, the Kth and Lth, say, leaving the remaining components as they are

$$|x\rangle = \begin{pmatrix} \cdots \\ x_K \\ \cdots \\ x_L \\ \cdots \end{pmatrix} \rightarrow \begin{pmatrix} \cdots \\ cx_K - sx_L \\ \cdots \\ sx_K + cx_L \\ \cdots \end{pmatrix} \Rightarrow |w\rangle = \begin{pmatrix} \cdots \\ x_K^2 \\ \cdots \\ x_L^2 \\ \cdots \end{pmatrix} \rightarrow \begin{pmatrix} \cdots \\ (cx_K - sx_L)^2 \\ \cdots \\ (sx_K + cx_L)^2 \\ \cdots \end{pmatrix} \quad (57)$$

It is easy to obtain the variation in the coefficient vector due to an elementary Jacobi rotation as

$$|\delta\omega\rangle = v_{KL} \begin{pmatrix} \cdots \\ -1 \\ \cdots \\ +1 \\ \cdots \end{pmatrix} = v_{KL}\Big(|e_L\rangle - |e_K\rangle\Big), \quad (58)$$

where $\{|e_K\rangle, |e_L\rangle\}$ are the corresponding canonical basis set vectors. The scalar coefficient v_{KL} possess the form:

$$v_{KL} = s^2\left(x_K^2 - x_L^2\right) + 2cs x_K x_L. \quad (59)$$

Then, employing this result into the equivalent expression of equation (28), but written in expectation value matrix form, it can be deduced

$$\langle\delta\pi\rangle = \langle\delta\omega|\left(\,|z^{(1)}\rangle + 2Z^{(2)}\,|\omega\rangle\,\right) + \langle\delta\omega|\,Z^{(2)}\,|\delta\omega\rangle, \quad (60)$$

where the quantum object subindex has been taken out to simplify the notation. Then, upon substituting the coefficient vector variation

$$\langle \delta \pi \rangle = v_{KL} \left[\left(z_L^{(1)} - z_K^{(1)} \right) + 2 \sum_I \omega_I \left(Z_{IL}^{(2)} - Z_{IK}^{(2)} \right) \right] + v_{KL}^2 \left(Z_{KK}^{(2)} + Z_{LL}^{(2)} - 2Z_{KL}^{(2)} \right) \tag{61}$$

which, upon equalization to zero and terms rearrangement, can be expressed as a second-order equation on the elementary Jacobi rotation sine and cosine

$$As^2 + Bsc + \beta = 0, \tag{62}$$

with the coefficients A and B defined as

$$\begin{aligned} A &= \alpha \left(\omega_K - \omega_L \right), \\ B &= 2\alpha x_K x_L, \end{aligned} \tag{63}$$

and, besides, the parameters α and β are constructed by the elements of the similarity matrices in the following way:

$$\begin{aligned} \alpha &= Z_{KK}^{(2)} + Z_{LL}^{(2)} - 2Z_{KL}^{(2)}, \\ \beta &= \left(z_L^{(1)} - z_K^{(1)} \right) + 2 \sum_I \omega_I \left(Z_{IL}^{(2)} - Z_{IK}^{(2)} \right). \end{aligned} \tag{64}$$

6.6. Higher order stochastic expectation value variational treatment

6.6.1. General comments

Whenever equation (42) is studied, after being conveniently modified for the expectation values form,

$$\forall J = 1, N : \langle \pi_J \rangle = \sum_{R=1}^n \left\langle \mathbf{S}_J^{(R)} * \mathbf{W}^{(R)} \right\rangle + O(n+1) \tag{65}$$

it appears the obvious fact consisting into that the variation will affect just the Rth order tensor products $\mathbf{W}^{(R)}$ of the coefficient vector. So it can be written, dropping the quantum object subindex J just for convenience, as done before:

$$\langle \delta \pi \rangle = \sum_{R=1}^n \left\langle \mathbf{S}^{(R)} * \delta \mathbf{W}^{(R)} \right\rangle + O(n+1) \tag{66}$$

so the relevant variation will be associated to the terms $\delta \mathbf{W}^{(R)}$, which can be easily written, using a tensor notation as

$$\delta \mathbf{W}^{(R)} = \delta \left(\overset{R}{\underset{S=1}{\otimes}} |\omega\rangle \right) = \sum_{S=1}^R \binom{R}{S} \left[\left(\overset{R-S}{\underset{P=1}{\otimes}} |\omega\rangle \right) \otimes \left(\overset{S}{\underset{Q=1}{\otimes}} |\delta\omega\rangle \right) \right] \tag{67}$$

but being the definition of the coefficient vector variation, upon Jacobi rotations, well known from equation (58), it can be written:

$$\delta \mathbf{W}^{(R)} = \sum_{S=1}^{R} \binom{R}{S} (v_{KL})^S \left[\left(\overset{R-S}{\underset{P=1}{\otimes}} |\omega\rangle \right) \otimes \left(\overset{S}{\underset{Q=1}{\otimes}} \left[\left(|e_L\rangle - |e_K\rangle \right) \right] \right) \right]. \tag{68}$$

So in this way, the restricted variation of the expectation value QQSPR equations, using elementary Jacobi rotations, is clearly defined up to any order.

6.6.2. A computational detail concerning tensor products of the difference of two canonical vectors

The tensor product of the difference between the pair of canonical basis set vectors:

$$|e_L\rangle - |e_K\rangle = \begin{pmatrix} \cdots \\ -1 \\ \cdots \\ +1 \\ \cdots \end{pmatrix} \equiv |L\rangle - |K\rangle \equiv |L - K\rangle, \tag{69}$$

which appears in equation (68), may be expressed in terms of a nested summation symbol. For example, up to second order the sum of the four tensor terms is readily written as

$$|L - K\rangle \otimes |L - K\rangle = |L \otimes L\rangle - |L \otimes K\rangle - |K \otimes L\rangle + |K \otimes K\rangle \tag{70}$$

with the obvious meaning for the involved tensors

$$|L \otimes L\rangle \equiv |e_L\rangle \otimes |e_L\rangle = \mathbf{E}_{LL} = \left\{ e_{LL;PQ} = \delta_{LP}\delta_{LQ} \right\} \tag{71}$$

and so on.

In general, up to Sth order

$$\overset{S}{\underset{Q=1}{\otimes}} \left| L - K \right\rangle = \sum (\mathbf{i})\, \sigma\left(Q\,(\mathbf{i}) \right) |Q\,(\mathbf{i})\rangle, \tag{72}$$

where $Q\,(\mathbf{i}) = \{Q_1 \otimes Q_2 \otimes \cdots \otimes Q_S\}$ is any of the possible 2^n combinations with repetition of the indices K and L, the symbol $|Q\,(\mathbf{i})\rangle$ meaning a tensor product of the initial canonical basis set vectors with such an index repetition. That is, an object equivalent to a canonical hypermatrix, whose elements are all zero, except the one with indices associated to those entering the set $Q\,(\mathbf{i})$. Also $\sigma\,(Q\,(\mathbf{i}))$ corresponds to the sign, associated to the fact that the index K appears in $Q\,(\mathbf{i})$ an even, $\sigma\,(Q\,(\mathbf{i})) = +1$, or odd, $\sigma\,(Q\,(\mathbf{i})) = -1$, number of times.

7.   Conclusions

Quantum similarity provides QSPR theory with a general framework, where a set of computational procedures can be well described from the mathematical point of view leading to the possibility to set up well defined algorithms. Such algorithms lead in turn to models very similar to the classical QSPR linear functional forms. Moreover, in the QQSPR case, the models possess the power of creating universal and unbiased quantum object descriptors, which can be used to construct causal relationships between quantum object structure and properties.

In order to obtain the desired theoretical QQSPR construction, a basis and a probe quantum object sets are needed. Both quantum object sets shall have known density function tags and, in addition, the probe set has to contain a known set of property tags. Moreover, non-linear terms are easily introduced into the theoretical models, just at the expense of needing more quantum similarity measure integrals to be computed. From the background of the theoretical QQSPR description, classical QSPR structures with multilinear models or even simpler, like those proposed by Hansch, can be easily deduced.

The main difference between classical and quantum QSPR model construction consists into the fact the QQSPR equations could be considered causal, even if the procedure needs statistical tools to obtain the desired relationship, as QQSPR model functionals can always be considered originated from the fundamental QQSPR equation. Stochastic transformations of the initial QQSPR framework can be easily imagined up to any order and provide quantum objects of a discrete mathematical tag structure, resembling the density function behaviour.

The same fundamental QQSPR equation can be set up theoretically and varied afterwards in order to obtain an optimal quantum mechanical description of the QQSPR unknown operator representation. Then, every quantum object expectation value can be optimally computed in terms of first and second order, or up to higher orders, similarity measures, if necessary. These variational expectation values can be related to known experimental values by finally setting an appropriate origin and scaling factor. The complete QQSPR variational procedure permits to easily obtain approximate experimental property values for new quantum objects, not included into the initial probe quantum object set.

Resuming every theoretical aspect discussed here, one can state that the present theoretical results point out that QSPR can be well founded within the background of quantum mechanics. In this way, the deducible QQSPR framework and the associated fundamental equation, not only provide with a causal backup the structure–properties relationships old problem, but furnishes a way to obtain in a general manner, up to any approximation level, unbiased and universal causal models for any chosen quantum object set.

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