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# *SYNTHESIS PAPER*

*entitled*

## *QUANTIFICATION OF THE CHEMICAL BOND WITHIN ORTHOGONAL SPACES OF REACTIVITY. APPLICATIONS ON MOLECULES OF BIO-, ECO- AND PHARMACO-LOGICAL INTEREST*

*including the work done and the results obtained in relation to the objectives achieved during the research grant*

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## Abstract

During the international year of Chemistry – 2011, the annually stage of the prezent grant have been elaborated and advanced original methods for modeling the complex molecular systems in interaction, biomolecules and nanosystems. Thus, the consecrated QSAR method was conceptually improved with the Residual-QSAR versions, Alert-QSAR and QSAR-disasters, especially addressing the recursive nature (of feed-back) but also the nonlinear couplings (the form of the universal-elementary polynomials recommended by the catastrophe theory of Thom) for the lidand-receptor interactions, at toxicologic level (carcinogenicity, mutagenicuity) and pharmacological (inhibitors HIV1). The biological activity „in jumps" of „catastrophic" type, in analytically modeled by also by the logistic formulation of the enzymatic reactions of Haldane-Radic type, that involve the non-specific chemical bonds (potentiating the genetic mutations), for which is established the area of applicability reductive to the mono-stratrate kinetics of Menten type, with application to the human cholinesterase. This picture, relatively macroscopic, was completed with fundamental studies in terms of bordering molecular strcuture, especially by involving the priciples and the reactivity indices as electronegativity and chemical hardness, combined in the valence energy (pi) of the total energy Hűckel. The presented analysis are considered as an original achievement of the homologation priciples OECD (Organization for Economic Cooperation and Development) of the models of chemical-biological bond, in general, and of the QSAR type (Quantitative Structure-Activity Relationships) in particular.

## Objectives and Results

**1. Formulation and application of the original orthogonal algorithms Residual-QSAR and Alert-QSAR for modeling the carcinogenity and the mutagenicity. Advanced the idea of an algorithm Double-QSAR to improve the performations of correlation of the classical method (papers [1-4]).**

The desire to obtain significant correlations,, in agreement to the observed reality of the molecular bonds in the biological situs, the QSAR method of classical multilinear correlation is originally amended, specific to the cyclic phenomena (trial-and-error) at the level of the organism toxicity. Thus, is advanced the methods Residual-QSAR and then generalized one Alert_QSAR (when the molecular fragments ar considered as elementary subunits of the chemical-biological interaction) with the algorith:

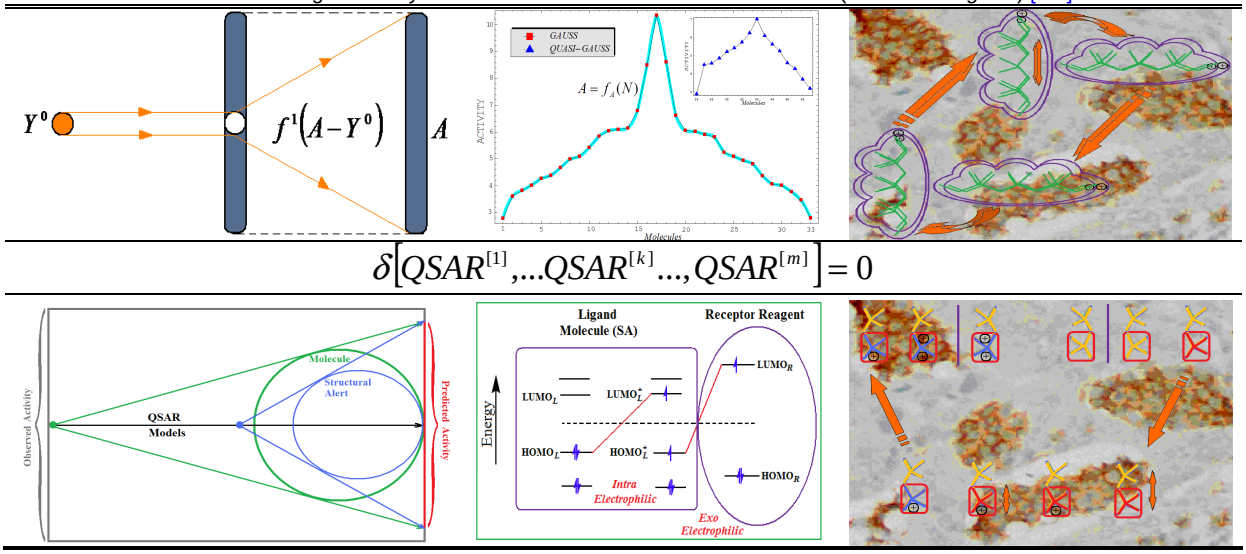
- Is considered a set of variables/molecular descriptors and the observed activities $\left(\{X_i\}_{i=\overline{1,M}}, A\right)$ associated to an organism/species/biological situs;

- Are generated the equations of Table 1, havind as purpose the expression of the residual activities (RA-residual activity) for the entire molecules or for parts of them (molecular fragments) with role of structural alerts (SA-structural alert);
- Ffraction, here on molecular level, when the observed activiy is „diffracted by/on" the usual (direct) QSAR, as illustrated in the first column of Figure 1.

**Table 1.** Comparatibe synopsis of the equations specific to the methods Residual-QSAR and Alert-QSAR [1-3].

| Residual-QSAR | Alert-QSAR |
|---|---|
| $f^0\left(\{X_i\}_{i=\overline{1,M}}\right)=Y^0=a_0+\sum_{i=1}^{M}b_{0i}X_i$ | $A^{SA}_{(m_i,m_j)}=a^{SA}_{0(m_i,m_j)}+\sum_{k=m_i}^{m_j}b^{SA}_{0k}X^{SA}_k$ |
| $f^1\left(A-Y^0\right)=Y^1=a_1+b_1\left(A-Y^0\right)$ | $ARA^{SA}_{\{(m_i,m_j)\}}=a^{SA}_{1\{(m_i,m_j)\}}+\sum_{m_i=1}^{m_{j-1}}\sum_{m_j=m_{i+1}}^{m_k\le M}b^{SA}_{1(m_i,m_j)}RA^{SA}_{(m_i,m_j)}$ |
| $Y_{SC}=a_1-b_1a_0+b_1A-b_1\sum_{i=1}^{M}b_{0i}X_i$ | $1\neq\sum_{m_i=1}^{m_{j-1}}\sum_{m_j=m_{i+1}}^{m_k\le M}b^{SA}_{1(m_i,m_j)}$ |
| $A=Y^1$ | $A=ARA^{SA}_{\{(m_i,m_j)\}}$ |
| $Y_A=\frac{1}{1-b_1}\left[a_1-b_1a_0-b_1\sum_{i=1}^{M}b_{0i}X_i\right]$ | $ARA^{SA}_{\{(m_i,m_j)\}}=\frac{1}{1-\sum_{m_i=1}^{m_{j-1}}\sum_{m_j=m_{i+1}}^{m_k\le M}b^{SA}_{1(m_i,m_j)}}\left[a^{SA}_{1\{(m_i,m_j)\}}-\sum_{m_i=1}^{m_{j-1}}\sum_{m_j=m_{i+1}}^{m_k\le M}b^{SA}_{1(m_i,m_j)}\left(a^{SA}_{0(m_i,m_j)}+\sum_{k=m_i}^{m_j}b^{SA}_{0k}X^{SA}_k\right)\right]$ |

**Figure 1.** The analyze of the genotoxic mechanism with the methods Residual-QSAR (up) and Alert-QSAR (down) for a set of molecules of high diversity toward the intestinal cancerous cells to rats (*Rattus norvegicus*) [1-4].




Essentially, the residual analyze of the strcutural alerts gives multiple benefits, as following:

- avoids the so-called asymptotical limit called QSAR (see the denominator of the final equations of Table Tabelul 1 for when it tends to cancel)
- allows the introduction of the so-called universal *hydrophobicity* in the Alert-QSAR versions, which corresponds to the case when, by the virtue of the action-reaction principle at molecular level, the hydrophobic manifestation can be changed in the hydrophilic one to penetrate the cell walls (lipids) for some structural alerts, in successive cycles of action of the chemical-biological bond;
- allows the introduction of the equal-steric properties (especially energetic) for the molecules with similar carcinogenic potential;
- allows the analyze of the molecular mechanism of action in organism by applying the path principle (Euclidiene for example) minimum in the space of correlation factors (see the equation in the middle of Figure 1 and the model of molecular interation with the cancerous cells of intestinal system at mise – last cclumn of Figure 1);

- can ne applied on sets of molecules not necessarily congener, by the virtue of the Gaussian-quasiGaussian screen applied to the activities observed (the representation of middle-up of Figure 1);
- allows the introduction of the procedure of reactive-active docking, with the illustrious example of the combination of the electronegativity priciples (equalization of $\chi$) and chemical hardness (the maximum of $\eta$) between the structural alert from the molecule of interest and the binding reagent (from receptor) by the sa-called combined mechanism between intra- & exo- electrophilic, which generates the effect of electrophilic docking (Figure 1, middle-down) [3];
- the extension of the chemical orthogonal space (COS) at the level of tyhe biologic activity, biological ortogonal space (BOS) in terms of electronegativity and chemical hardness ($\chi \perp \eta$).

**2. The establishment of the quantum role of QSAR correlation based on the indices of recativity of density functional theory and of the analyze of the molecular topology. Applications to molecules and nano-molecules of ecological interest: graphene, condensed states and nano materials with biological answer (papers [5-17]).**

The introduction of the orthogonal space of the biological activity in terms of electronegativity and chemical hardness gives the possibility of detainling of the relations of determination between the various phases of reactivity of them (of equalization type... minimum... equalization...maximum)

$$\delta\chi = 0 \rightarrow \delta C_A = 0 \rightarrow \Delta\chi < 0 \rightarrow \delta\eta = 0 \rightarrow \Delta\eta > 0$$

with the intercalation of the optimization of the chemical action

$$C_A = \int \rho(\mathbf{r}) dV(\mathbf{r}) d\mathbf{r}$$

as an observable of the effective potential where the ligand evolves (in receptor field).

**Figure 2.** The representation of fundamental quantum inter-relation characteristic to the first (wavefunction) and second quantification (electronic density) [5].

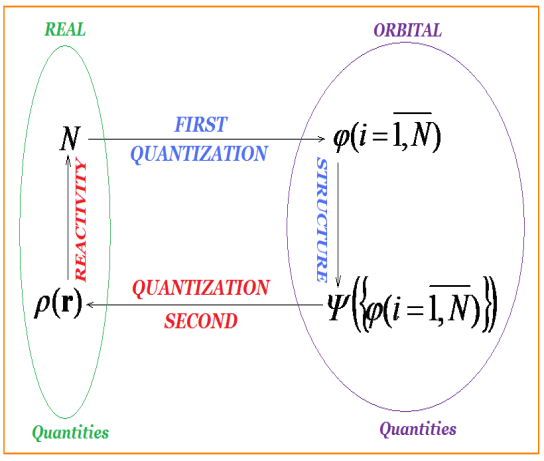
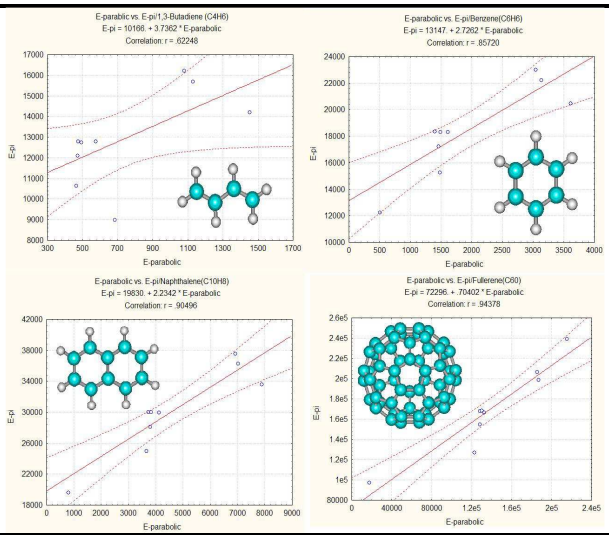
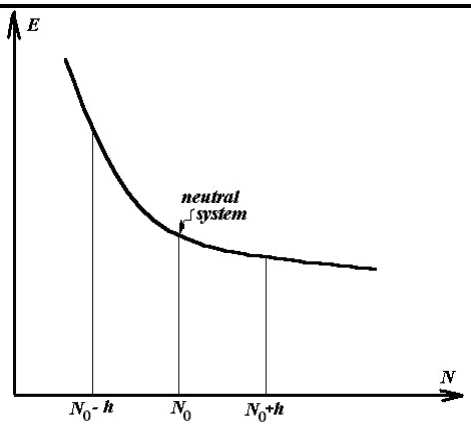



**Table 2.** Fundamental eqautions of the indices of reactivity (electronegativity and chemical hardness) in the context of density functional theory applied to the molecular valence states [6].

| |
|---|
| $\rho(\mathbf{r}) = N\int \Psi^*(\mathbf{r},\mathbf{r}_2,...,\mathbf{r}_N)\Psi(\mathbf{r},\mathbf{r}_2,...,\mathbf{r}_N)d\mathbf{r}_2...d\mathbf{r}_N$ |
| $\int \rho(\mathbf{r})d\mathbf{r} = N$ |
| $f(\mathbf{r}) = \left(\frac{\partial\rho(\mathbf{r})}{\partial N}\right)_{V(\mathbf{r})}$ |
| $\chi = -\int\left(\frac{\delta E[\rho]}{\delta\rho(\mathbf{r})}\right)_{V(\mathbf{r})} f(\mathbf{r})d\mathbf{r} = -\left(\frac{\partial E}{\partial N}\right)_{V(\mathbf{r})}$ |
| $\cong \frac{IP+EA}{2} \cong -\frac{\varepsilon_{LUMO}+\varepsilon_{HOMO}}{2}$ |
| $\eta = \frac{1}{2}\iint\left(\frac{\delta^2 E[\rho]}{\delta\rho(\mathbf{r})\delta\rho(\mathbf{r}')}\right)_{V(\mathbf{r})} f(\mathbf{r})f(\mathbf{r}')d\mathbf{r}d\mathbf{r}'$ |
| $= \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{V(\mathbf{r})} \cong \frac{IP-EA}{2} \cong \frac{\varepsilon_{LUMO}-\varepsilon_{HOMO}}{2}$ |

Substantiation of electronegativity and chemical hardness as quantum sizes is shown if Table 2, in the context of density functional theory [7-11], in turn understood as a method of realization of the second quantification in terms of generation of electronic density (as an observable) associated to the quantum field of the (molecular) wavefunctionc, as illustarted in Figure 2. Remarkable, the two sizes can combine in order to generate the parabolic form of the total energy of valence or border, as in turn proves to be a viable size, and the more appropriate to the extended molecular systems, with the limit at the nanosystems (for example fullerenes and newest graphene [13]) that characterize as the Hűckel energy (pi), Figure 3. But, the approach has the advantage of the global calculation of electronegativity and chemical hardness in an efficient manner related to the border properties (HOMO, LUMO) of the system analyzed, but with implications, for the parabolic approach, at the level of the bonding energy as an energy of molecular formation. Thus was enunciated, demonstarted and applied a new relation of the chemical bond, equivalent to the frontier with the chemical reactivity, further treatable in orthogonal spaces of interaction with the aid of the associated priciples (minimum in electronegativity, maximum for the chemical hardness) for the establishement of the coupled systems (even biological).




$$\min(\Delta E) \cong -\chi\ (\Delta N) + \eta\ (\Delta N)^2$$

$$E_{para(bolic)} \cong -\chi\ N_\pi + \eta\ N_\pi^2$$

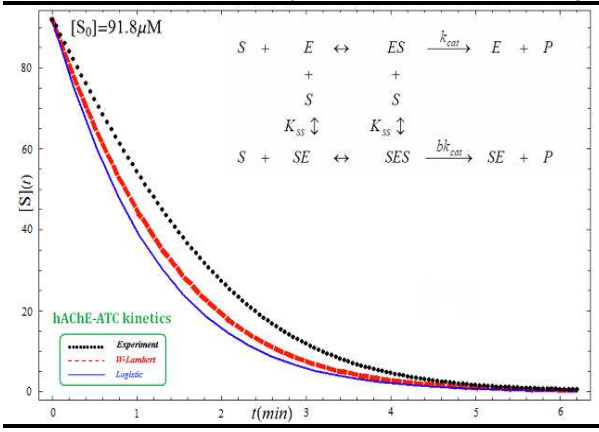
$$E_{pi}(molecule) \cong E_{Total}(molecule) - E_{Bind}(molecule) - E_{Heat}(molecule)$$

**Figure 3.** Realization of the orthogonal space of reactivity at complex systems, of Fullerene type (left), by the correlation of the border energy– pi with the parabolic representation of the indices of reactivity of electronegativity and chemical hardness (right) [5].

## 3. The study of the role of the enzymatic kinetics for the ligand-receptor interactions of nonspecific/in jumps/catastrofic type. The formulation and the application of the original orthogonal algorithms QSInAR and QSAR-disasters for modeling the inhibitive actions of steroids in human cells and of HIV inhibitors of reverse type of non-nucleotide transcriptase (papers [18-27]).

Although subject to the quantum superposition principle, at nano-scopic level [9], the natural phenomena at mezo-scopic level rarely evolve after multi-linear laws, rather being characterize by quantum jumps, by interactions and nonlinear couplings. Thus, the genetic mutations of the effects related to the cellular proliferation, especially the viral one, are subject to some logarithmic lwas, or polynomial of high order. A paradigmatic case are sunt nonspecific enzymatic reactions, with inhibition and competitiveness, as the reaction of type Haldane-Radic, Figure 4 (left). These, not only have a polinomial-exponential behavior but also reduce hard and on levels of concentration of substrat-ligand in general small (of micro-Molar) to the mono-substrat kinetics of Menten type, particularly manifesting by jumps of the activity (engendering the product), of catastrophic type.

**Figure 4**. Curves of temporal progression (left) for the enzymatic reaction hAChE-ATC, modeled after the kinetics scheme of Haldane-Radic, comparative between the experimental observations, and the equations W-Lambert and respectively toward the logistic transformation (right) [19,20] for the kinetics values: $K_S$ = 160 μM (Menten constant); $K_{SS}$ = 8700 μM; $V_{max}$ = 162.45 μM/min; $b$ = 0.12, for an intial given concentration of substrate [18-20].




$$f_1 W\left(f_2 e^{f_2} e^{-f_3 t}\right) \to f_1 \ln\left(1 + \left(e^{f_2} - 1\right) e^{-f_3 t}\right)$$

$$[S]_L^{HR}(t) = \frac{K_{SS}}{1 - b + K_{SS}/K_S} \ln\left(1 + \left(e^{\left(\frac{1}{K_S} + \frac{1-b}{K_{SS}}\right)[S_0]} - 1\right) e^{-\frac{V_{max}}{K_S} t}\right)$$

$$[S]_L^{HR}(t) = \begin{cases} [S_0], & t \to 0 \\ 0, & t \to \infty \end{cases}$$

$$\frac{d[P]_L^{HR}}{dt} = -\frac{d[S]_L^{HR}}{dt} = v_L^{HR} = \frac{V_{max}}{K_S} \frac{\left(e^{\lambda S_0} - 1\right)}{\lambda \cdot e^{\lambda S_0}} = \frac{V_{max}}{K_S} \frac{\left(1 - e^{-\lambda S_0}\right)}{\lambda}$$

$$\lambda = \frac{1}{K_S} + \frac{(1-b)}{K_{SS}}$$

This is the point (even final, in the sense of the activity observed by the quantity of product generated by nonspecific kinetics reactions) from where, again returning to the QSAR modeling, there can be considered a correction of (delta) Dirac type, approximative through a Gaussian form of the variables of the molecular space of the characters (the so-called “the behavior space”),ie [23]:

$$Y_{i=\overline{1,N}}^{\Gamma/QSAR}\left(X_1,...X_M\right)=Y_{i=\overline{1,N}}^{QSAR}\left(X_1,...X_M\right)\pm Y_{i=\overline{1,N}}^{M/\Gamma/QSAR}\left(X_2,...X_M\right)$$

with

$$Y_{i=\overline{1,N}}^{M/\Gamma/QSAR}\left(X_2,...X_M\right)=\sum_{j=2}^{M}\frac{1}{\sqrt{\pi}}\exp\left(-\frac{X_j^2}{4\sigma_{i=\overline{1,N}}}\right)$$

In these conditions, for a general dispersion of the observed activity

$$\sigma_A=\sum_{i=1}^{N}\left(A_i-\overline{A}\right)^2$$

the calculation of the coefficient of correlation corresponding to the catastrophic correction (exponential)

$$R_\Gamma=\sqrt{1-\frac{1}{\sigma_A}\sum_{i=1}^{N}\left(A_i-Y_i^{\Gamma/QSAR}\right)^2}$$

relatively to the consacrated Pearson coefficient (of the classical QSAR)

$$R_0=\sqrt{1-\frac{1}{\sigma_A}\sum_{i=1}^{N}\left(A_i-Y_i^{QSAR}\right)^2}$$

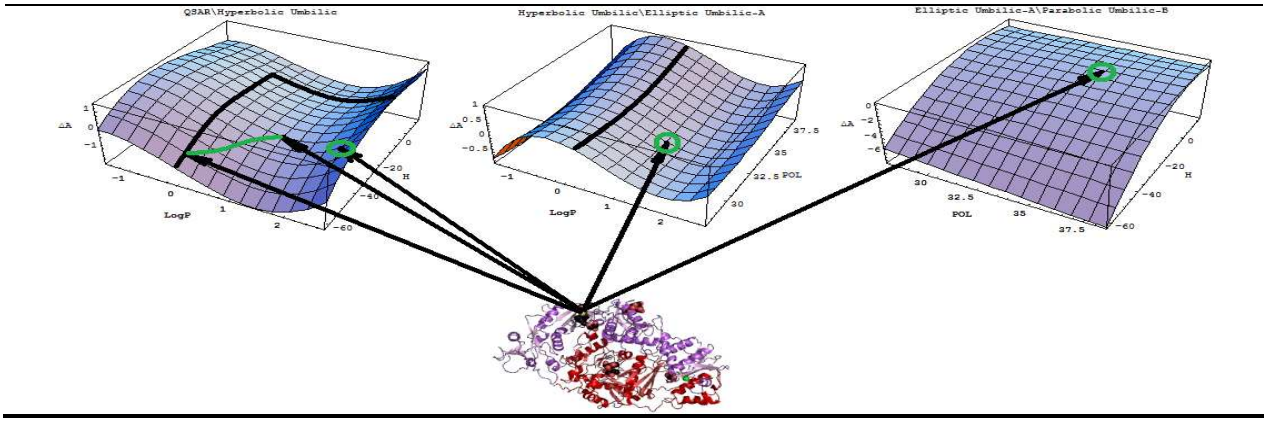
generates the remarkable result of the superiority of any catastrophic correlation toward any classical multi-regresional correlation

$$R_{M/\Gamma}\to 1\geq\forall R_0$$

This fact allows the advancement of the catastrophic-QSAR equations, as those illustrated in Table 3 [23,24].

**Tabel 3**. The realization of the QSAR-Catastrophes based on the universal Thom polynomials, adapted for the space of the structural variables as the comportamental space of the molecular characters; down in the illustration of the determinations of the activities anti-HIV on the surphases of the QSAR-Catastrophes optimum for the derivatives typical of pyridinones [23,24].

| Model | QSAR equation |
|---|---|
| | **GROUP I**: one single descriptor, $\left\|X_1\right\rangle$ |
| QSAR-(I) | $\left\|Y_I\right\rangle=a_0\left\|1\right\rangle+a_{11}\left\|X_1\right\rangle$ |
| Fold | $\left\|Y_F\right\rangle=f_0\left\|1\right\rangle+f_{11}\left\|X_1\right\rangle+f_{13}\left\|X_1^3\right\rangle$ |
| Cusp | $\left\|Y_C\right\rangle=c_0\left\|1\right\rangle+c_{11}\left\|X_1\right\rangle+c_{12}\left\|X_1^2\right\rangle+c_{14}\left\|X_1^4\right\rangle$ |
| Swallow tail | $\left\|Y_{ST}\right\rangle=s_0\left\|1\right\rangle+s_{11}\left\|X_1\right\rangle+s_{12}\left\|X_1^2\right\rangle+s_{13}\left\|X_1^3\right\rangle+s_{15}\left\|X_1^5\right\rangle$ |
| Butterfly | $\left\|Y_B\right\rangle=b_0\left\|1\right\rangle+b_{11}\left\|X_1\right\rangle+b_{12}\left\|X_1^2\right\rangle+b_{13}\left\|X_1^3\right\rangle+b_{14}\left\|X_1^4\right\rangle+b_{16}\left\|X_1^6\right\rangle$ |
| | **GROUP II**: two descriptors, $\left\|X_1\right\rangle$, $\left\|X_2\right\rangle$ |
| QSAR- (II) | $\left\|Y_{II}\right\rangle=q_0\left\|1\right\rangle+q_{11}\left\|X_1\right\rangle+q_{21}\left\|X_2\right\rangle$ |
| Hyperbolic umbilic | $\left\|Y_{HU}\right\rangle=h_0\left\|1\right\rangle+h_1\left\|X_1\right\rangle+h_2\left\|X_2\right\rangle+h_{1122}\left\|X_1X_2\right\rangle+h_{13}\left\|X_1^3\right\rangle+h_{23}\left\|X_2^3\right\rangle$ |
| Elliptic Umbilic | $\left\|Y_{EU}\right\rangle=e_0\left\|1\right\rangle+e_{11}\left\|X_1\right\rangle+e_{21}\left\|X_2\right\rangle+e_{12}\left\|X_1^2\right\rangle+e_{22}\left\|X_2^2\right\rangle+e_{1122}\left\|X_1X_2^2\right\rangle+e_{13}\left\|X_1^3\right\rangle$ |
| Parabolic umbilic | $\left\|Y_{PU}\right\rangle=p_0\left\|1\right\rangle+p_{11}\left\|X_1\right\rangle+p_{21}\left\|X_2\right\rangle+p_{12}\left\|X_1^2\right\rangle+p_{22}\left\|X_2^2\right\rangle+p_{1221}\left\|X_1^2X_2\right\rangle+p_{24}\left\|X_2^4\right\rangle$ |



The catastrofic QSAR-equations, besides the considerable improvement that bring to the multi-linear QSAR correlations have the advantage of the indication od the complexe interactions at molecular level (by synergistic coupling) in the considerated structural variables and, moreover, allow, by generating the 3D afferent surfaces the identification of the areas of valability of the correlations produced, with the identification of the molecules with optimum action on biologic sense by solving the systems resulted from the retainer of the first best multilinear models, with the physicochemical constraints associated to the principles that characterize the structural variables considered: minimum of polarizability- as being proportional with the inverse of the chemical hardness, the area of hydrofobicity (positive-negative for the hydrofob-hydrophilic character), or the negative area for the energy of formation ecc. In Table 3 (down) is exposed such a selection of the domain of applycability for the molecules that specifically act as inhibitors in the hydrofobic pocket of the non-nucleotide ensembles of the reverse-transcriptase of the HIV viruses [23,24]. The method is evinced in order to be completed with further studies QSAR of correlation, vy systematic developments in sets of powers on the space of the molecular characters.

## Conclusion and Perspectives

The 2011 stage of the present project was a major step for the generalization of the chemical bond from the orthogonal spaces of chemical reactivity (COS) to those orthogonal of biological activity (BOS), through the algorithms of linear (quantum) modeling and nonlinear (statistical) in agreement to the OECD principles [25,26] recommended for the adjudication of the creditworthiness of a molecular model in the complex interaction with the environment (ecotoxicological, pharmacological):

- ***Principle 1: A final point well definedt:*** the biological activity, generalized to the rate of final product in the ligand-receptor interactions, having as paradigm the enzyme kinetics substrate Michaelis-Menten and its generalization Haldane-Radic;
- ***Principle 2: An un-ambiguous algorithm:*** the version Residual-, Alert- and Catastrophes-QSAR;
- ***Principle 3: A defined area of applicability:*** mutagenicity & carcinogenicity with series of non-congener molecules; HIV inhibitors with congener molecular series;
- ***Principle 4: A proper size for the otimum correlation, robustness and predictability :*** the principle of minimum action, spectral paths, reactivity priciples (minimum of electronegativity, maximum of chemical hardness, minimum of polarizability ecc), the Gaussian-quasiGaussian screen of the molecular distribution ofr the school series (trial) and of testing;
- ***Principle 5: A mechanistic interpretation (deterministic)***: the hierarchy of the paths of minimum action identify the specific influences of the molecular descriptors in the space of the structural character, and its weight.

Further studies of this project will promote the exposed results and methods to extended nano-systems (nano-surfaces, PAH, endofullerenes ecc.) modeling the pahses transitions netween the periodical ideal systems and those with defects, exploiting the concenpt of bondone and the Heisenberg principle extended in the quantum observability of the chemical bonds (developed in the first year of the project, 2010), the extracting of the molecular-causal information from the spectra of composite materials, bio-inorganic, bio-active ecc.

## Written and communicated papers (the members of the grant are in bold)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8. **Putz M.V.** On Relationship between Electronic Sharing in Bonding and Electronegativity Equalization of Atoms in Molecules, *International Journal of Chemical Modeling*, 3(4) (**2011**) 371-384; URL: https://www.novapublishers.com/catalog/product_info.php?products_id=28877
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