WEST UNIVERSITY OF TIMIȘOARA

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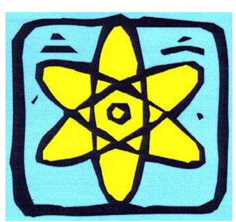
# CHEMICAL ORTHOGONAL SPACES OF ATOMS AND MOLECULES

*Habilitation Thesis*



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# Summary

Since the nowadays and future worldwide need to replace as much as possible the *in vivo* experiments (costly by subjects) as well as those *in vitro* (costly by equipment) with the *in cerebro* (conceptual) and *in silico* (computational) models, the present thesis advances fundamental methods for modeling atoms and molecules within specific orthogonal spaces. The orthogonality concept is here revealed through various paradigms or forms for "covering" the chemical space, namely:

- Orthogonal space of chemical reactivity;
- Orthogonal space of electronic localization function;
- Orthogonal space of bondonic (bosonic) condensation in chemical bond;
- Orthogonal space of enzyme-substrate binding's probability;
- Orthogonal space of chemical structure-biological activity correlations.

For each of these identified types of orthogonality for the chemical space, specific methods were unfolded aiming to provide the equations and the analytical framework for appropriate interpretation and predictivity for the modeling and controlling of the envisaged interactions. In this context, the work contains five basic chapters exposing the analytics and illustrative applications of the above orthogonality schemes, while opening further reliable and sustainable developments of the proposed methods concisely presented in another five chapters, dedicated to current and future research.

**Chapter 1** introduces the orthogonal space of the chemical reactivity by means of the density functional theory definitions for electronegativity

$$\chi \equiv -\left(\frac{\partial E_N}{\partial N}\right)_{V(r)} \cong -\frac{\varepsilon_{LUMO}+\varepsilon_{HOMO}}{2}$$

and for chemical hardness

$$\eta \equiv \frac{1}{2}\left(\frac{\partial^2 E_N}{\partial N^2}\right)_{V(r)} \cong \frac{\varepsilon_{LUMO}-\varepsilon_{HOMO}}{2}$$

essentially interpreted as the *orthogonality* realization of "level $\perp$ interval" (for the semi-sum and the semi-difference of the highest occupied HOMO and the lowest unoccupied LUMO molecular orbitals) around the (global) equilibrium of the total energy ($E_N$) parabolically depending on the system's electrons (or the valence ones). Such "orthogonal" interpretation ($\chi \perp \eta$) is confirmed by the *cutting observable* ($\chi$) *vs. indeterminate observable* ($\eta$) characters as proved by the second quantification approach. This dichotomy justifies the development of the atomic radii scales (without observable

operator in quantum physics) through employing electronegativity as observable chemical quantity, and later implemented for chemical hardness and adjacent quantities (diamagnetic susceptibility and polarizability) as indirect-observable structural properties. Next, the sharing index of electronic delocalization for atoms-in-molecules was formulated, in relation with the chemical softness index (S) being it identified as the driving force of chemical binding, either within the additive or by geometric mean models of the atomic overlap in molecules. Then, through generalizing the working compact finite HOMO & LUMO differences formulas up to the spectral like resolution the systematics of the aromaticity criteria was achieved within the $\chi \perp \eta$ reactive orthogonal space with the help of the equalization electronegativity and of the maximum chemical hardness of atoms-in-molecules principles; in this framework the hard-and-soft-acids-and-bases (HSAB) principle was thoroughly verified as well as the $\chi \perp \eta$ manifested orthogonality on a "trial" yet relevant series of neutral and ionic molecules; finally, a new formulation and classification of the hard-hard, soft-soft and hard-soft reactivity behavior was realized through introducing the maximum chemical hardness index (Y) by the *orthogonal* completion relationship

$$1 = \frac{S}{\eta} + \mathrm{Y}$$

**Chapter 2** introduces and applies at the atomic and molecular levels the electronic localization function defined as the "step" realization of *orthogonality*

$$ELF = \frac{1}{f\left(\dfrac{g(\rho(\mathbf{r}))}{h(\rho(\mathbf{r}))}\right)} \rightarrow \begin{cases} 0, \nabla\rho(\mathbf{r}) >> \rho(\mathbf{r}) \\ 1, \nabla\rho(\mathbf{r}) << \rho(\mathbf{r}) \end{cases}$$

through the gradient and homogeneous competition between the electronic density ($\rho$) related terms – this way generalizing the density indicator, and having the Markovian analytical realizations resulted from combining of the Fokker-Planck (diffusion) path integral formalism with the catastrophe theory of René Thom.

In **chapter 3** new approach of chemical bonding is exposed with the help of the *bondon* concept (the quantum particle of the chemical bond), having its mass quantified by the bonding distance and energy

$$m_B = \frac{\hbar^2}{2} \frac{(2\pi n + 1)^2}{E_{bond} X_{bond}^2}, \; n = 0,1,2$$

It allows the reinterpretation of the molecular Hamiltonian as being composed by fermionic and bosonic condensation components within an *orthogonal* fermionic-bosonic/bondonic space (FB)

$$\left\langle \hat{H}_{FB} \right\rangle = \left\langle \hat{H}_{F} \right\rangle_{\substack{FERMIONIC \\ SIDE}} + \left\langle \hat{H}_{B} \right\rangle_{\substack{BOSONIC \\ SIDE}}$$

This model produces a generalization of the molecular orbitals' theory, here illustrated for homopolar interaction; it is based on the similar context the (fermionic) density functional theory and the (bosonic) Bose-Einstein condensation are grounded on the same quantum normalization relationship of the systems' particle number

$$N = \int \rho(\mathbf{r}) d\mathbf{r} = \int |\psi(\mathbf{r})|^2 d\mathbf{r}$$

**Chapter 4** provides complete analytical temporal solutions for enzyme kinetics of Michaelis-Menten (specific for some mutant enzymes) and Haldane-Radić (specific for cholinesterase kinetics) types through the logistic transformation

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

with functions $f_1, f_2, f_3$ depending on specific kinetics parameters, within the *orthogonal* completion of the substrate probability binding space within the enzymic complexes

$$1 = P_{\mathrm{REACT}}([S]_{bind}) + P_{\mathrm{UNREACT}}([S]_{bind})$$

**Chapter 5** exposes the algebraic reformulation of the structure-activity correlations (QSAR) through replacing the statistical errors' minimization of predicted data ($Y_{PRED}$) respecting those observed ($Y_{OBS}$) by the orthogonal condition

$$\left\langle Y_{PRED} \middle| prediction \ \ error \right\rangle = 0$$

It generates the Spectral-SAR determinant solution

$$\begin{vmatrix} |Y_{PRED}\rangle & \omega_0 & \omega_1 & \cdots & \omega_k & \cdots & \omega_M \\ |X_0\rangle & 1 & 0 & \cdots & 0 & \cdots & 0 \\ |X_1\rangle & r_0^1 & 1 & \cdots & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & & \vdots & \\ |X_k\rangle & r_0^k & r_1^k & \cdots & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & & \vdots & \\ |X_M\rangle & r_0^M & r_1^M & \cdots & r_k^M & \cdots & 1 \end{vmatrix} = 0$$

where the (ω & r) components are computed with the *orthogonal* Gram-Schmidt formalism. The algebraic correlation factor was accordingly introduced

$$RA \equiv \frac{\left\| Y_{PRED} \right\rangle\|}{\left\| Y_{OBS} \right\rangle\|}$$

and proved being always superior to the Pearson statistical one (*Timişoara Theorem*). Moreover, the Spectral-SAR minimal action principle

$$0 = \delta[l, l'] = \delta\sqrt{\left(\left\| Y_l \right\rangle\| - \left\| Y_{l'} \right\rangle\|\right)^2 + \left(R_l - R_{l'}\right)^2} \text{, } l, l'\text{: } ENDPOINTS \quad MODELS$$

was also advanced to consistently model the mechanistic ligand-receptor interaction, in accordance with the OECD (Organization for Economic Cooperation and Development) principles, having as primary applications the ecotoxicological studies (here on the acute toxicity of *Daphnia magna*).

These studies and models of orthogonality are further completed with fertile developments' directions, separately and combined: the atomic universal periodicity by gold ratio and Bohmian mechanics or through the elemental strength factor of the Bose-Einstein condensation, "coloring" of the molecular topology with the chemical reactivity by Timişoara-Parma rules (**Chapter 6**); electronic localization and aromaticity reformulation by orbital density variation (**Chapter 7**); employing the bondonic concept for studying the phase transitions in nanosystems and extended systems (**Chapter 8**); considering the tunneling effects and entanglement phenomena in enzyme kinetics with the aid of density functional of chemical action (**Chapter 9**); generalizing of QSAR correlations by means of the nonlinear functions in general and by Thom catastrophic polynomials in special, with validation of the chemical reactivity principles (**Chapter 10**).