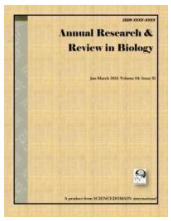

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A Quantum Mechanical Aspect of Enzyme Action: Enzymes as Information Driven Quantal Measurement Engines

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

In this introductory paper we overview existing approaches to enzyme – catalysed reactions. From the Michaelis – Menten kinetics to quantum scatterings several models are considered. We try to introduce our "information – driven measurement engines" (an other model of enzyme action) in relation to existent theories. We conclude that our approach is a special type of quantum mechanical treatment of enzyme catalysed reactions, in its nascent form. It is, we suppose, stands more in relation to a hypothetical gas – phase scattering, maybe even resonance scattering, as a one – dimensional vacuum energy – dependent motion along the reaction path. We are aware that at this time, no realistic gas – phase scattering is available in the area, and our approach is thus similarly hypothetical. Still, it might provide a fresh view on enzyme – catalysed reactions, utilising a somewhat unusual Hamiltonian second – order tensor operator formalism. During arriving at our goal, we give some more extensive review devoted to current catalysed and uncatalysed reaction investigations, of a pure chemical and biochemical nature, exploring both experimental and theoretical procedures.

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1. INTRODUCTION

We have hinted in a previous paper [1], that it is *possible* that the quantum mechanical ''*measurement problem*" derives from (macro)molecular quantum *dynamics*, gradually converging towards a limited (eventually single -) dimensional "out – wave" channel(s) Hilbert space (in an S – matrix formalism). The "measurement constraint" would be an initially randomly coiling, then sterically fixing (freezing) proto – enzyme "measurement device", by a ligase - type "measurement" action on its RNA oligomer as its "object". Pattee (e.g. [2]) advocated a number of attributes in this context, such as that enzymatic behavior is mimicing *projection operators*, they are in a natural way *resettable*, etc.

Chemical reactions, *per se*, are (S – matrix) scatterings theoretically, i.e., they are *second order (perturbational) quantum mechanical processes.* On the other hand, enzyme - catalysed reactions are in a great majority leading to a single outcome (product) as an "out – wave". There are generally no byproducts. This referres to Pattee's measurement "engine" projectional action. They have generally no inverse, a rather general biochemical *experimental fact*, although theoretically there *is* such an inverse.

We must here cite the concept of ''internal measurement" (e.g. [3-5]). The basic idea is that the measurement on relatively large systems, the device/object interaction is not momentary but *takes time*: The *internal* interaction with the "device" propagates internally with at most the velocity of light. Therefore, our enzyme – catalysed "measurement scattering" also *takes time,* a fact well – known in experimental biochemistry (see e.g. fs resolution chemical rate experiments). Disregarding special binding and dissociation rates, on this fact relies a good part of the area of enzyme - catalysed reaction kinetics (the part described traditionally as the unimolecular very fast ''decay" of the enzyme – substrate complex).

Our purpose in this paper is to arrive, finally, to our ''informational measurement engine" concept of enzymes. However, to accomplish it, we intend to review nearly all strictly physical (energetic) approaches available in the literature, to enlighten the (formal) simplicitity of our concepts. Enzymes as ''Maxwell's demons" are known for a long time (e.g. [6-9]. Nonetheless, the concept has not been as pointed as we use it here. Our approach is strictly *quantum mechanical*, but we introduce four – indexed tensor elements as ''Hamiltonians". They serve to distinguish between strictly energetic and informational concepts (the contravariant indices serve as the ''informational" aspects).

We will not use extensively higher mathematics throughout, but we enlighten those mathematical concepts below for the interested reader which play a central role primarily in our own approach, presented in Section 2.2. This distinction from other reviews is important, for example, in quantum scattering resonances, the corresponding formules containing, in a rather complicated way, the repeated occurrences of e. g. band widths. In an overall way, we will keep in mind the general biochemist reader, concentrating on results rather than on the mathematical routes by which they were obtained.

(For those interested in our own research but are non – specialists, we would like to enlighten some physical – mathematical concepts, used primarily in Section 2.2.: an operator is a mathematical object which transforms a function into an other one; in quantum physics, physical quantities are represented by operators of which the most important is the energy operator, the *Hamilton operator*; a projection (operator) selects, in a quantum measurement, specially or by pure chance, a particular function (corresponding to the "collapse of the superposition" of functions to a single component; if a function, upon the action of an operator is only multiplied by a constant, is called the "eigenfunction", the constant the "eigenvalue", of the operator; an affine space is a vector space with non – orthogonal (inclined) basis vectors; the g metric tensor components are the scalar product of these basis vectors; "positive definite metric" spaces are those spaces where the scalar products are always positive; in an affine space a vector has double coordinates values: a "covariant" one, which transforms upon coordinate transformations "approximately" as an orthogonal one, and a

"contravariant" one which does not; there are (orthogonal or affine) function spaces on the analogy of vector spaces, the Hilbert space being a special function space; the "state functions", for historic reasons, in quantum mechanics are termed "wavefunctions", denoted by Ψ; in scatterings, the incoming "in – waves" are usually plane waves, while the post – collision scattered "out – wave" is usually a spherical wave; a tensor is a vector (function) coordinate – transforming object; our "second order difference energy tensor" is a difference of two simple (two – indexed) difference tensor, so it is "second order" (in the differences), having four indexes; "constrained" means "enforcedly limited".)

2. DISCUSSION

In this way, as was noted above, we first survey the essences of the available cornerstones of the study of (energy – driven) enzyme - catalysed reactions. In doing so, we must keep in mind that, whatever the approach is, the fact is that there are reactions up to 10^9 rate enhancement due to enzyme catalysis.

Accordingly, we first investigate the Michaelis – Menten (and Briggs – Haldane) classical kinetics (e. g. Michaelis and Menten [10]; Briggs and Haldane [11]; Morrison [12]; Larsen, and Hansen [13]; for a derivation see e. g. Rhodes and Aflalo [14]); then proceed to more exact (quantum mechanical) frames (e. g. Truhlar et al. [15]; Gao and Truhlar, [16]). However, we are not concerned here with the quantum mechanical *refinements* of the contributing mathematical parametrization, e. g. the more exact calculations of potential energy surfaces (PES) or vibrational modes, rather, we try to introduce a fresh light on the problem (here, rather briefly).

Along this line, thus, finally, we set up our "second order" *difference* dynamical tensor equation, derived from the also ''second order" uncertainty relations, where the enzyme molecules are *active participants* in the quantum dynamics. The difference between the (difference) energy tensors is interpreted as the $(\Delta - \Delta)\ E = E^{\#}$ energy barrier height transition state (TS) *differences* between not catalysed and catalysed reactions. "Information driven" measurement also derives from the "second order" uncertainty relations (*Section 2.2.1*.)

In this way, we try to *formalize the dynamical aspects* of our "information – driven" "measurement engine" concept, introducing positive definite metric Hilbert spaces, with certain kinds of natural "projections" on them, where enzyme action is related to the *coupled,* g^{ij} *geometrical* metric tensors, supposing, as is done usually, that the catalysed TS**'** is under first of all an enforced geometrical constraint upon the reactants (adjusted to the requirements of an induced, somewhat distorted "transition" state of the reaction, the "enzyme – substrate complex", to help the dissociation to product(s) *and* the resetted enzyme molecule). This overall "coordinate measurement" (fixing) of the contributing atoms, as adjusted to the transition complex *coordinate requirements*, may involve high *internal* momenta, which might be one of the reasons of fast enzymatic reactions, internal momenta turning to a resultant *external* one upon the reaction.

This affine projection by the enzyme molecule in fact realizes a difference function between the time dependent wavefunction of the reactant(s) *and* the TS, also that of the product(s), minus the top and slope of the catalysed reaction barrier height (TS**'**). The enzyme molecules act as quantum filters (choice between scattering channels), where the filter is

$$\Delta\Psi = \sum_j \varphi_j - \sum_{j\neq i} \varphi_j = \varphi_i \rightarrow \hat{\mathbf{P}}_i \sum_j \varphi_j = \varphi_i \quad (1)$$

Here $\hat{\mathbf{P}}_i$ is a projection operator.

Thus, we do not deal here in our own scheme with *reaction kinetics*, rather, we try to provide a quantum mechanical *interpretation* of the already widely analyzed molecular level dynamical parameters of the phenomenological Michaelis – Menten kinetics (Sections 2. 1. 2. and 2. 1. 3.), in fact, a possible *en gross description* of the substantial reduction of the energy barrier height in the reaction. This is done by dealing with the corresponding ''transition state" (TS') (here ''enzyme – substrate complex") on a *pure* quantum mechanical basis, trying to transcend in this respect the already existing approaches. We would like to stress that our approach is intended to be a *description*, not a *theory.* Introductorily we intend to do it in its most simple form, disregarding loose - binding case, tight – binding case, multiple binding, allosteric inhibition(s), etc. particular occurrences. As we noted, though, our primary concern is molecular mechanisms, discussed later.

2.1 Strictly Physical Models of Enzyme Action: An Overview

2.1.1 The Michaelis – Menten and Briggs – Haldane kinetics

The basic idea of the description of a *simple* enzyme - catalysed reaction in the Briggs – Haldane derivation of the Michaelis – Menten kinetics is summarised as

$$[\mathrm{S}] + [\mathrm{E}] \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [\mathrm{ES}] \xrightarrow{k_{cat}} [\mathrm{E}] + [\mathrm{S}'](\mathrm{P}). \qquad (2)$$

Here and in what follows in this Section, we will follow the general notation (S = substrate(s), E = enzymes, S ' = P) (''product(s)"). Here [ES] corresponds to the ''transition complex" (enzyme – substrate complex), $k_{on,}$, $k_{off,}$, k_{cat} are the rate constants of the reversible enzyme - substrate reaction and the in practice irreversible, catalytic, reaction rate constant (note that k_{off}, k_{cat} are not equal to k_{on} in dimensions, the latter being a bimolecular reaction rate constant, i. e., referring to two reactant specimen concentrations with dimension concentration^{-1}time $^{-1}$, while k_{off}, together with $k_{cat,}$, has dimension time $^{-1}$,that of a unimolecular (''decay") one. The task is to derive an equation which describes catalytic reaction rates *which contains only measurable quantities.*

We here, as mentioned above, follow the Briggs – Haldane derivation.

Defining the dissociation binding constant of [ES], $K_D = k_{off} / k_{on}$ and K_M (the Michaelis constant) = $(k_{off} + k_{cat}) / k_{on}$, the derivation follows the equations of the rate of change for all the chemical specimens in the system, but the most important is

$$\mathrm{d}[\mathrm{ES}]/\mathrm{d}t = k_{on}[\mathrm{ES}] - (k_{off} + k_{cat})[\mathrm{ES}]. \qquad (3)$$

In most systems, the [ES] concentration will rapidly approach a steady state. This *steady state approximation* is the first important assumption in the Briggs – Haldane derivation. This is also the reason that well – defined experiments measure reaction velocities only in regions where product formation is linear in time. As long as we limit ourselves to study *initial* reaction velocities, we can assume

$$\mathrm{d}[\mathrm{ES}]/\mathrm{d}t = 0 \text{ , from where } k_{on}[\mathrm{E}][\mathrm{S}] = (k_{off} + k_{cat})[\mathrm{ES}]. \qquad (4)$$

To determine the rate of product formation,

$$\mathrm{d}[\mathrm{P}]/\mathrm{d}t = k_{cat}[\mathrm{ES}], \qquad (5)$$

as the free enzyme concentration [E] is equal to the *total* enzyme concentration [E_{total}] – [ES]. Since V_{max} is the reaction rate at saturated substrate concentrations, it is equal to k_{cat} [ES], when [ES] = [E].

So by substitutions and rearrangements, we arrive at k_{cat} [E]; and as $K_M = (k_{off} + k_{cat}) / k_{on}$,we have the familiar Michaelis – Menten equation

$$\mathrm{v} = \mathrm{V}_{max}[\mathrm{S}]/(\mathrm{K}_\mathrm{M} + [\mathrm{S}]). \qquad (6)$$

(Note that [S] here represents the free substrate concentrations, but it is generally supposed to be close to the total substrate concentration. This *second assumption* is the *free ligand approximation,* and is valid as long as the total enzyme concentration is well below K_M of the system. Otherwise (for example with very high affinity substrate), the *quadratic* (or Morrison) *equation* is used instead [8].

Comparing K_M and K_D, it is obvious that K_M must always be greater than K_D.

The third approximation is that Michaelis and Menten assumed, that substrate binding and dissociation occurred much more rapidly than product formation ($k_{cat} << k_{off}$), which is the *rapid equilibrium approximation*, so that K_M would be very close to K_D. The larger the k_{cat} relative to k_{off}, the greater the difference between K_M and K_D. Briggs and Haldane made no such assumptions about the relative values of k_{off} and k_{cat}, and so the Michaelis – Menten kinetics can be regarded *as a special case of the Briggs* – Haldane kinetics.

The opposite extreme, where $k_{cat} >> k_{off}$, is called the Van Slyke – Cullen behavior [17], with

$$\mathrm{v} = k_{cat}[\mathrm{ES}]. \qquad (7)$$

Thus, the derived equation is the Michaelis – Menten dynamics, a kind of ''special case" of the Briggs – Haldane dynamics. Its mathematical form is a rectangular hyperbola, with one paralell to the x – axis is V_{max} (the other has no meaning). The hyperbola expresses the velocity of the enzyme catalysed reaction *versus the substrate concentration.* At K_M we have $V_{max} / 2$. A note is in order to the steady state: it was proven by Schuster and Hilgetag [18] that, mathematically an elementary flux mode can be

defined as a null – space vector, and if all fluxes have fixed signs, all elementary modes are given by the generating vectors of a convex cone. Their formalism is extended to reactions proceeding in either direction. Their example is glycogenesis and glycolysis .

An additional note is in order once more about the *free ligand approximation*. As we hinted above, when a substrate's K_M is lower than the total enzyme concentration, a significant fraction of the substrate will be bound to the enzyme. This is the *tight binding case*, for which the simple Michaelis – Menten equation does not hold. For this case, the *quadratic velocity equation is derived*, but we do not go into its (more involved) details here.

The Michaelis – Menten (Briggs – Haldane) equations are phenomenological equations, at best phenomenological thermodynamic ones. They say nothing about the *molecular mechanisms* of enzyme catalysis.

2.1.2 Quantum mechanical methods included e.g. QM/MM

On a molecular basis, it is quantum mechanics which is the relevant theory. It has been known for a long time that the essence of chemical kinetics is an *energetic barrier* between reactants and products. Quantum mechanics enlighted the situation by discovering that they are, in fact, separated by the converging adjacent walls of (two or more) potential wells, with their internal vibrational energy levels (see Fig. 1.: i^+, $k^{+'}$), forming the barrier(s). Classical and current quantum mechanical theory on the molecular level holds that the primary function of enzymes is to lower (even fully diminish) the barrier *energetically.* (In uncatalysed reactions the determining factor is some kind of externally originated energy supply, increase, such as e. g. collisions in elevated temperatures or photoeffects.) However, the whole system is beyond computational capabilities, thus we note here that most methods use the strategy of calculating quantum mechanically what can be done for single molecules or parts of macromolecules (coenzymes or active centers), also e. g. individual solute molecules, then using a physically reasonable averaging for the whole system, see e. g. the transmission coefficients or the corresponding *reaction paths* (Section 2. 1. 3.). However, before proceeding to the proper *dynamics* in use, we make some account on the more modern applicable quantum mechanical methods available.

Of the **QM/MM** (quantum mechanical/molecular mechanical) method [19-20], (modern: e. g. [21-23]), the **QM** side had been for a long time split – valence *ab initio* Hartree – Fock (HF) MO procedures (equations: Roothaan [24]; AO's: [25]), with taking care of static electron correlations by e. g. "Extended" ("Unrestricted") HF methods (e. g. [26]) with analytical first and second partial derivatives with respect to the nuclear coordinates (in the Born – Oppenheimer approximation). This **QM/MM** method became popular for its fortunate combination of the quantal and classical componens (e. g. sp^3 '' ''hybrid" bordering carbon atoms, treated in either ways), to yield relatively good precision. The quantum mechanical (chemical) semiempirical procedures are nowdays largely obsolate for their highly imprecisional nature on the quantal side. Today, however, with the rapid evolution of supercomputers, there are various methods such as the *ab initio* Coupled Cluster (CC) procedure (Čižek, [27]; e g. see [28], MP (Møller – Plesset [29]; modern: e. g. Davidson and Jarzecki, [30]) and other perturbational procedures, intending to go "beyond the HF limit" ("infinite" number of MOs). They can take care for *dynamical* (Coulomb – holes movements) correlations, so for ''electronic unharmonicity" in vibrational – conformational studies. CC e. g. performs pretty well for bond – breaking processes. Though there are again dimensional limits, in combination with **MM** there is again progress to larger systems (e.g. [31]). **MM** methods are also developing with similar rate. Gradients and second derivatives are relatively easy to derive in **QM/MM** procedures.

The above sketched recent development is important for our considerations here, because the potential surface (so also tunneling) and the vibrational modes, the latter mainly in relation to the crucial flat (e.g. large amplitude vibrational torsional, also full rotational) potentials, are sensitive to static and *dynamic* electron correlations in the enzyme *active centers* (also for coenzymes). As for uncatalysed reactions, currently *ab initio* calculations on smaller molecules aim even to compete in precision with experiment, e. g. concerning rate constants (see below).

A note is in order here of the newly introduced "master equation" approach, originating from Bloch's nuclear resonance equations. If we

divide the total Hamiltonian into "system", "environment" and ''their interaction" parts, using the Neumann equation (time evolution of the density operator), in the ''interaction picture", where only it is the ''interaction" which is followed in time, the total density operator and the interaction Hamiltonian remains, and by some mathematical manipulations we arrive at an equation, which describes the time evolution of a probability operator, which dominates (''masters") the probabilistic process. In the ''Born approximation", we separate the fast ''system" and ''environment" parts, so the time evolution is determined by the square of the ''interaction" Hamiltonian.

This is the ''Markovian Master Equation". For an overview of its recent introduction into chemical computations see e. g. ref. [32].

A less frequently used (in chemical reaction kinetics), recently developed method in the *molecular realm* is the Density Functional Theory (DFT). Its essence is introducing a functional (of a scalar, usually the total electronic energy) of the electronic density.

2.1.3 The quantum mechanically supported reaction rate (dynamics)

The *classical* rate equation (dynamics), which we try to refine (and *solve more exactly)* by the introduction of quantum mechanical effects and methods, taking into consideration that enzyme - catalysed reactions are *closed shell ground state processes* (thus theoretically relatively not very involved).

The exact *classical* rate equation is

$$\boldsymbol{K}(\mathrm{T}) = \gamma(\mathrm{T})1/\beta\, h\, exp[-\beta\Delta \mathrm{G}^{\#}(\mathrm{T})] \qquad (8)$$

where T is absolute temperature, β = 1/ **k** T , **k** = Boltzmann's constant, **k** T / *h* = ''pre - exponential factor" , ''frequency factor", ''Arrhenius (''collision") factor A", with approximate value of 10^{-13} sec^{-1} at 300^{0} K; it is sometimes interpreted as a normal mode frequency of dissociation or forming a bond. $\Delta G^{\#}$ (T) = molar free energy of activation, i. e., the exponental is the temperature – dependent Boltzmann distribution of an ensemble of reactants at the *free energy* barrier height, the latter also depending on the temperature. γ(T) = transmission coefficient, the also temperature – dependent fraction of reactants transformed into products over the barrier. Both $\Delta G^{\#}$ (T) and γ (T) depend on the choice of the transition state (TS) . This equation and its approximations were extensively discussed by Gao and Truhlar [15]. Two conditions are generally supposed:

a) the reactants are in local equilibrium along the reaction path ***z*** (''reaction coordinate"), the latter normal to the hypersurface of the free energy;
b) there is no re – cross from the potential energy surface (PES), as they are thermalysed in the reactant or product state.

The two crucial parameters are $\Delta G^{\#}$ (T) and γ (T). For the condensed phase, the problem can be handled by minimizing the rate constant along ***z***. The most important is $\Delta G^{\#}$ (T). For the other important parameter, at enzyme - catalysed reactions, γ (T) ≠ 1. But by optimizing PES , this is minimizing the re – crossing correction (γ (T) ≈ 1.) Concerning coordinates other than ***z*** : we suppose instantenous equilibration along the movement on ***z***.

According to classical mechanics, $\Delta G^{\#}$ (T) is consisting of four parts, we have W_{CM} (T, $\boldsymbol{z}^{\#}$) minus W_{CM} (T, $\boldsymbol{z}_R$), plus G_{CM}^{R} (***z***), plus C(T, ***z***). Here $\boldsymbol{z}_R$ and $\boldsymbol{z}^{\#}$ are reaction coordinates at the reactants and at the transition state TS, G_{CM}^{R} (***z***) is the free energy of the mode in the reactants (R) that correlates with ***z***, C(T, ***z***) is a transformation function (from rectilinear ***z*** to curvilinear ***z***). CM = potential of mean force. For $\Delta G^{\#}$(T), we have thus a potential of mean force, abbreviated here PMF, the corresponding free energy quantity denoted by W_{CM} (T, ***z***). The latter is obtained by averaging over the enzyme and the substrate and solvent configurations along ***z***.

$$\mathrm{W_{CM}}(\mathrm{T}, z) = -\mathrm{RT}\rho_{\mathrm{CM}}(\mathrm{T}, z) + \mathrm{W^0{}_{CM}}, \quad \text{where (9)}$$

ρ_{CM} (T, ***z***) = *classical* mechanical probability as a function of ***z***, calculable by free energy perturbational methods within the framework of **MM.**

The quantum mechanical refinement enters by PMF (or PES) and the free energy of activation is obtained by

a) applying variational perturbation TS theory (VTST) and a variation of PMF; it leads to the calculation of a TS (with PMF) ; the inclusion of discrete vibrational energies makes more exact PMF. Note that the free energy of the reactants and that of the TS

is *critical* for determining the reaction rate. *The vibrational modes are calculated quantum mechanically, e. g. by ab initio VB (Valence Bond) methods.* These are important for PES – sensitive bond – breaking/formation as PMF determines the quantity $W_{CM}(T, z)$. Note that **MM** alone does not perform well for chemical reactions.

b) Nuclear motion, effecting PES (and PMF): vibrational calculations are essential procedures to include into $\Delta G^{\#}(T)$. The best way is to select semiclassical TS points, and perform **QM** vibrational calculations, to estimate re – crossing.

c) Tunneling, first of all H, H^{+}, H^{--}. As the motion along **z** is not separable, we must include multidimensional tunneling, treated semiclassically.

In this way, $\Delta G^{\#}(T)$ results from averaging the PES over an ensemble of structures, so PES *should be accurate*. Here **QM/MM** performs well for the free energy simulation for macromolecules. The **QM** – cal diagonal matrix element ($H_{1,1}$) includes the solvation energy term, the off – diagonal one ($H_{1,2}$) is environment independent. What concerns PMF: supposing ω_0 's , no vibrational mode analysis is performed. We correct for the *classical* vibrational modes in an ensemble average. Note that only those modes are corrected, which are classically orthogonal to ***z*.** In practice, we calculate *not* a single – minimum **QM** normal mode analysis, rather, we calculate instantenous normal modes in a local harmonic approximation. By the similar ω_R correction to G^{R}_{CM}, the free energy barrier decreases by 2 – 4 kcal/mol.

Concerning γ (T), there is classically treated re – cross *and* **QM** – ally treatable effects, such as tunneling (in general, nuclear motion) on **z** (these are missing in the above noted calculations) on PMF. There is a general way out: „Quantum Transition State Theory" (Quantum TST). Its essence is to *extend the spatial enzyme - catalysed reaction TS along* **z**. The point is to treat **z** *classically,* the other degrees of freedom by **QM**. This is what leads to classical dynamical *and quantum effects as treated γ (T).* The method is ensemble averaged variational TST with multidimensional tunneling. The ensemble average is calculated by **MM**, e. g. by a diabatical energy – gap coordinate, representing collective solvent motion. (E. g. ΔE = bond forming/breaking). *For each configuration in the TS ensemble, it is partitioned into primary (**QM**) and secondary (**MM**) region.*

If the **MM** region is kept rigid, we have isoinertial Minimum Energy Path, ("s_i") (MEP). It yields a generalized free energy of activation $\Delta G^{GT}(T, s_i)$ (in the general theory Δ G), so $s_i = s_i^{\#}$. As a result, the classical equilibrium flux is reduced relative to the dividing surface, and we have a *quasiclassical free energy of activitation.* When ***z*** $(s_i) = \boldsymbol{z}^{\#}$, there is a quasiclassical transition factor Γ_i, with a classical positive exponential free energy term, depending on $s_i^{\#}$, and a negative quasiclassical free energy term, with reference to the TS.

The MEP approximation is a good example of **QM/MM**: the secondary (**MM**) zone is equilibrated, it yields thermal and entropic contributions, by calculating them averaging the TS configuration ensemble and doing the same along the minimum energy path.. An advanced method is to be mentioned: ***z*** is taken as the vectorial sum of all the internal coordinates.

Note that month by month, more refined methods are tested, and introduced to account for the above noted quantum effects involved.

2.1.4 Computer simulations

The above model calculations are in general termed as *computer simulations*. Garcia Viloca et al. [33] discussed several model calculations in detail, by inclusion e.g. of H – bond formation, charge transfer, etc. on specific enzyme - catalysed reactions. The results are in general encouraging. They were able to separate the individual [TS]' barrier decreasing values due to the different effects in a numerically acceptable way.

As Gao and Truhlar [15], Truhlar et al. [16] and Garcia Viloca et al. [33] summarised to some extent more modern experimental and theoretical results on enzyme - catalysed reactions, a briefer discussion is in order here on current quantum mechanical calculations (and, to a smaller extent, experimental results) on the chemical reaction kinetics of smaller molecules (however, including bioplymers and their interactions with smaller compounds).

What concerns *environmental* experiments, e. g. Lee et al. [34] studied the oxidation of nitrosodimethylamine (NDMA) precursors with ozone and chlorine dioxide. They eastablished

both their kinetics and their effect on the NDMA formation potential. Hammes et al. [35] used mechanistic and kinetic methods to evaluate the organic disinfection byproducts in drinking ozonated water. Hu et al. [36] revealed the mechanism and reaction kinetics of oxidation of carbamazepine by Mn(VII) and Fe(VI). Sharma [37] studied the one – and two – electron steps in the oxidation steps by Ferrate (VI) and Ferrate (V) of inorganic compounds. As the most interesting of all similar works, Neta et al. [38] presented (somewhat older) experimental rate constants for reactions of inorganic radicals in aqueous solutions.

An other interesting area is *atmospheric, oceanic and space* chemical research, as conducted e. g. in the University of Michigan, *Ann Arbor.* These (and similarly interested) researchers frequently use *ab initio* and master equation calculations, too.

Robinson and Lindtstedt used an *ab initio* study devoted to describe the abstraction of hydrogene from n – propyl benzene [39]. Georgievskii et al. [40] reformulated the master equation for the study of multiple – well chemical reactions [40]. Somers et al. [41] discussed by experimental and computer simulations of the 2,5 dimethylfuran pyrolysis and oxidation. Simmie et al. [42] used quantum mechanical methods to reveal the abnormal reactivity of 2 – methoxifuran. Also Simmie et al. [43] performed modern *ab initio* procedures to establish the substituent effects in the thermochemistry of furans. Weston et al. [44] used a master equation model with sophisticated *ab initio* SCTST rate constants for reaction rates and H/D kinetic isotope effects. Wu et al. [45] also used a theoretical method to study the CH_3 - $CH{=}CH_2$ + O(D-1) reaction. Lam et al. [46] used experimental and theoretical procedures to derive the gas – phase reactions of aryl radicals with 2-butyne. One of the most interesting method in theoretical terms were performed by Glowacki et al. [47] on a modified master equation for the study of multi energy – well reactions. Also, Feller and Simmie adopted high – level *ab initio* studies to explore various reaction enthalpies. This latter study is a good example of the precision which can be obtained by sophisticated current theoretical procedures [48]. Barker et al. [49] similarly used high – level *ab initio* study in context with semiclassical TST theory, exploring certain isotope effects. Altarawneh et al. [50] studied theoretically of the thermochemical and structural parameters of chlorinated isomers of aniline. Da Silva et al. [51] investigated both theoretically and experimentally the pyrolysis of fulvenallene and fulvenallenyl. Again Simmie et al. [52] used *ab initio* methods to investigate the decomposition of 2,5 dimethylfuran. An also *ab initio* study of Thanh et al. [53] in connection with semiclassical TST theory was carried out for certain chemical rate constants. FitzPatrick et al. [54] used a modified (Statistical TST) theory of modeling of the chemical dynamics and adopted an *ab initio* procedure for calculating critical points. Vasu et al. [55] used experimentally Shock Tube/Laser Absorption measurements of the reaction rates of OH with ethylene and propene. Bozkaya et al. [56] studied theoretically different quantum mechanical parameters (barrier, lifetime, etc.) for the dissociation of HN_2.

Concerning theoretical methods, these frequently adopt fotoeffects and, to a smaller extent, the variance of temperature (we do not deal here with the latter).

Gustafsson et al. [57] compared the rate constants of the radiative association of HF molecules as obtained by **QM** – cal and classical dynamics. Li et al. [58] studied tunnelling effects with an effective quantum force. Nyman and Yu [59] overviewed the available quantum approaches to polyatomic reaction dynamics. In our view, the most important for practical reasons was that Wakelam et al. [60] who provided a kinetic database for astrochemistry. Again Gustafsson et al. [61] studied, by refined theoretical methods, radiative associations.

Keeping in mind the biochemist reader, finally we list here a number of current research works, not exactly those of enzyme kinetics, but generally the *interactions* of biopolymers with smaller molecules, giving not much comment. The pecularity of these studies is that they use the phenomena of the stabilizing effects of *electronic polarisations*, and they adopt extensively *refined molecular force fields*. While this field can not, naturally, studied by **QM** methods, they can adopt e. g. quantum mechanical force fields, transferred from smaller molecules and, generally, theoretical considerations e. g. of electronic polarisations, are frequently used. In physical terms, the main problem is not so much the largeness of biopolymers, rather, their (physically) disordered nature.

Concerning adapted (''calibrated") force fields, those of the zinc – protein complex [62] and the molecular dynamics of the INT-DBD binding of

DNA [63] is mentioned here. Effects of charge polarisation stabilization is very favored. Its theory was exposed by Zeng et al. [64]. Its critical effect in stabilization of the dynamical structure of guanine quadruplex DNA was studied by Song et al. [65]. Electronic stabilizing as crucial factor in the native structure of proteins was put forth by Ji and Zhang [66]. An other theoretical (numerical) study, calculating also polarising electric fields, was carried out by Mei and Zhang [67]. The critical stabilizing effect of electronic polarization concerning the Mg^{2+} complex in the catalytic core of the HIV-1 integrase was studied by Lu et al. [68]. Helix (protein) folding is also critically depends (at room temperature) on the electronic polarization of intraprotein H – bonds, as discussed by Duan et al. [69]. That electronic polarization is crucial for enzymatic catalytic function, has been known for a long time, but Xiang et al. provided new evidences [70].

As for more ''theoretical" studies, a **QM/MM** study (with an *ab initio* method on the quantal side) on the peptide bond formation in the ribosome which helps to form the eight – membered ring formation, was carried out by Xu et al. [71]. A similar calculation was performed by Zhu et al. on the amide proton chemical shifts in proteins (in a definite solvent) [72]. A straightforward quantum mechanical calculation on the solvation and protein – ligand free energy was performed by Tong et al. [73]. Other ''computer simulations" of similar nature were carried out by Han and Zhang [74], Wu et al. [75], Zhang et al. [76] and others.

As it can be seen from the above brief overview, and as we noted above, theoretical (specially, quantum mechanical) calculations are thus currently frequently used in combination with classical (or "semiclassical") theories and, mainly, with *experiments* in chemical reaction kinetics. However, as noted also above, on the chemical kinetics of *small molecules*, at least concerning current pure **QM** calculations, can *compete in precision* with experimental results.

2.1.5 Fractal kinetic theory

Here the supposition is that if the kinetics is dimensionally constrained (to two or a single dimension), e. g. in a membrane channel, they do not follow the mass – action kinetics, rather, *fractal kinetics* (Savageau, [77]). The power – law formalism is used to introduce fractals for a simple pathway and reversible reactions. Simple bimolecular rates are considered, and extended to the Michaelis – Menten kinetics. The fractal kinetic rate law is established for the examination of the steady – state equation. The result is that by fractal kinetics the temporal response along a pathway, characterized by both fundamental and quasi – steady – state equations (based on traditional mass – action kinetics), is shown that the equilibrium ratio is a function of the amount of material in a closed system, and microscopic reversibility imposes severe constraints on the set of the fractal kinetic orders.

In a biochemical pathway, fractal kinetics allow an increase in flux to occur with faster temporal response and with less accumulation of pathway intermediates than traditional kinetics. Therefore, the primary aim is to find novel ways to achieve important features of biochemical pathway design.

2.1.6 Chemical reactions as quantum scatterings

Chemical reactions as second order quantum mechanical perturbational processes are first of all cross – beam *gas phase scatterings*, so our own considerations (see Section 2. 2.) are to a large part *''gedanken experiments"*. However, it is *possible* that one day such enzyme – catalysed reactions will be able to be studied by gas phase processes. There do not seem to be *in principle* obstacles to its possibility, in particular in view of the different modern versions (e. g. statistical conformational distributions, compare [78]) of Koshland's original ''induced fit" hypothesis [79-81]. It is *possible,* in the spirit of the paper, that *"fortunate"* (complementing) collisions would lead to single energetic radial ones, as corresponding to ''selective measurements" by the enzyme molecules, as a single barrier – top resonance scattering.

This hypothetical approach is important for us, for our approach *resembles* enzymatic activation of reactants *in vacuo.* We will move in the quoted Section within the general framework of the time – dependent Schrödinger equation, but now and then refer to the original second order S – matrix scatterings, similarly to the below cited authors.

Bowman and Schatz [82] and Althrope and Clary [83] discussed in detail the problem of chemical reactions as gas – phase scatterings by quantum mechanical variational (and hyperspherical) methods, procedures and calculations on bimolecular collisions.

In general terms, the incoming waves are plane waves, the outgoing one a spherical one:

$$\Psi(\mathbf{r}) \sim exp(i\mathbf{kr}) + f(\mathbf{k},\theta)[exp(i\mathbf{kr})/r] \quad (r \to \infty) \quad (10)$$

Here f (**k**, θ), the scattering amplitude = (1/ 2 *i* **k**)$\sum^{\infty}_{i=0}$ (2 i 1) (s $_i$ - 1) P_i (cos θ), the S – function: s $_i$ = *exp* (2*iσ* $_i$). The differential cross section: d σ = $|$ f (**k**, θ) $|^2$. The integral for full space:

$\int |$ f (**k**, θ) $|^2$ d Ω = 2 π $\int_0^{\pi}$ $|$ f (**k**, θ) $|^2$ sin θ dθ. Different coordinate systems are used: Jacobi transformed, reaction path, hyperspace ones. The crucial state – to – state reaction probability:

$$\rho_{\alpha,t;\alpha',t'} = \left|S_{\alpha,t;\alpha',t'}\right|^2, \quad (11)$$

where α denotes reagents or products, t denotes the electronic structure. Concerning approximations, we have the ''reduced dimension" (RD) or ''rotating bond" theories.

Considering the time dependent Schrödinger equation, from the point of view of available efficiency the basis set and the propagation method is important.

$$\Psi(t) = \left[exp\left(-i\,\hat{\mathbf{H}}\,t/\hbar\right)\right]\ \Psi(t=0), \quad (12)$$

where the first factor is the time evolution operator, computed by certain propagation algorithms, Ψ (t), the time dependent wavefunction is represented by grid. The propagation algorithm can be chosen to be a split – operator method: *exp* {- *i* Δ t $\hat{\mathbf{H}}$/ ħ } = { } { } … , so that Ψ (t + Δ t) = { } { } Ψ (t), or e. g. the so – called Cheybichev series is used. These methods have different advantages and disadvantages.

There is a notable further approximation: the reactant/product decoupling (RPD) approximation, in which we avoid the coordinate problem by splitting the *exact* Schrödinger equation, concerning wavefunctions, into χ $_r$ (t) + χ $_p$ (t) = χ (t), so instead of the equation

$$i\,\hbar\{\partial\chi(t)/\partial t\} = \hat{\mathbf{H}}\chi(t), \quad (13)$$

with

$$i\,\hbar\{\partial\chi_r(t)/\partial t\} = \hat{H}\chi_r(t) - iV_p\chi_r(t)$$

$$i\,\hbar\{\partial\chi_p(t)/\partial t\} = \hat{H}\chi_p(t) + iV_p\chi_r(t) \quad (14)\ !!!$$

we have two equations (χ denotes reactants and products). The first usable scattering equations were set up by Liu in 1975; Liu et al. [84] in the late 80s obtained good PES, converged integrals and differential cross sections (H + H_2 → H_2 + H). (Note that the study was critically discussed by Truhlar and Horowitz). It resulted in the Liu – Siegbahn – Truhlar – Horowitz (LSTH) PES in the 80s. Real quantum scattering calculations are available since 1995. What is important is the overall behavior of the cross section using quantum *and* classical trajectories treated together (QCT). Using it, t*here is a time delay in forward scattering*. The concrete calculation was F + H_2 → HF + H.

The first accurate *ab initio* calculation on PES was performed by Stark and Werner [85]. It

a) correctly predicted a bent TS, provided a realistic barrier height, with the inclusion of spin – orbit coupling. Since then, numerous calculations were performed on insertion – type, heavy – light – heavy atom, metal atom inclusion, etc. types of reactions, involving ion – molecule reactions, with deep wells, long – range potentials, nonabatiatic effects, etc. Scattering near – resonances were studied, with lifetime investigations, showing that resonances may take part in the collisions, providing adiabatic potential wells. Feschbach resonances occurred: quasi bound states were found that were associated with PES, containing no local minima. (Notably, Feschbach resonances were originally introduced in nuclear physics.) In general, *it was found that chemical scatterings are very sensitive to the concrete form of PES*. In this respect, we note that theory and experiment are in a way complementary.

An alternative approach is following the one – dimensional reaction path ***z*** along the above noted minimal PES of the reduced mass μ:

$$\partial^2\Psi/\partial\boldsymbol{z}^2 + 2\mu/\hbar^2[E - V_{MEP}(\boldsymbol{z})]\Psi = 0. \quad (15)$$

Here E is the total energy, μ is the reduced mass, V $_{MEP}$ is the minimum potential energy path. Concerning Ψ,

$$\Psi(\boldsymbol{z} = -\infty) = exp\, i\,k\,\boldsymbol{z} + S_R\, exp - i\,k\,\boldsymbol{z}$$
$$\boldsymbol{z}(S = \infty) = S_T\, exp\, i\,k\,\boldsymbol{z}. \quad (16)$$

Here S_R and S_T are the energy – dependent (complex) reflexion and transmission amplitudes. S_T is the reaction probability, determinable by calculating $\left| S_T \right|^2$.

Resonance scattering more closely

Resonance scatterings are of special interest for us, for reasons what has been said above. Though contemporarily available (experimental and theoretical) methods are not appropriate to test our suppositions, it is well worth to overview current research in the field. For the interested biochemist, we recommend Sakurai's updated book as an introduction to the resonance phenomena [86].

Scattering resonances were extensively studied by Fernández – Alonso and Zare [87], as associated with *poles* in the S – matrix, e. g. $E = E_0 - i\Gamma / 2$ in the last propagation equation; this contribution of the denominator of the proper resonance equation to σ vanishes (here Γ is the resonance width). Theoretically, we search for such poles in the complex plane. As the S – matrix is a complex analytical function, the poles completely define it.

Friedman and Truhler examined *barrier resonances* [88]. They showed, that symmetric energy barriers are also associated with a short – lived pole in the S – matrix, far from the real axis. They also concluded that this holds also for asymmeric potential barriers, too; in fact, $E_0 - i\hbar\omega(2n + 1)$, where E_0 is the position on the potenential barrier, and ω is the frequency. The first pole occurs at E_0 ; similar localisation effects were found for the usual resonance phenomena. The resonance types found:

a) conventional resonances (Feschbach resonances),
b) barrier resonances,
c) Wigner cusps (threshold anomalies).

The first two are associated with true metastable states. *Semiclassically*, they are associated with maxima in the vibrational adiabatic potential curves, i. e., the repulsive periodic orbit dividing surface (RPDS), in contrast to the RPOs, is related to conventional resonances. Ten barrier states dominated the low energy spectrum, and formed two progressions along the reactant and product states. Their stability is similar to Feschbach resonances, they increase with energy.

Considering Feschbach resonances, we introduce into the one – dimensional propagation equation $V_{eff}(z)$:

$$V_{eff}(z) = V_{\mathrm{MEP}}(z) + \hbar\omega(z)(n + 1) + \hbar^2/16\mu(n^2 + n + 1)\left\{\left[\left(d \ln \omega(z)\right)^2\right]/d z\right\}^2 \quad (17)$$

The first term is the original V_{MEP} along ***z***; n are running integer quantum numbers and ω is the frequency. The second and third term in their *interaction* greatly effect the *shape* of the potential. Thus we have both *shape and barrier* resonances. The investigation can be extended to adiabatic potential curves taking into account J (the total angular momentum), adding rotational energy vs. **z.** Geometric phase (orientation of incoming waves) also can be considered, initially in a $H + H_2$ scattering, and it is a very *sensitive function* of the collision energy *and PES*. Additionally, we have the two – vector (**k** – **k**') correlation approach in the usual cross – beam experiments.

For current research on shape resonances, see e.g. ref. [89]. As for a current experimental investigation on chemical scattering resonances at ultra cold (a few Kelvin), low angle and ultrasonic cross – beam molecular collisions, obtaining shape and Feschbach resonances, see [90].

2.2 The Author's Scheme: The Information Driven Measurement Engine

2.2.1 The basic concepts: the ''loose'' uncertainty relations and the secondary differences Hamiltonian tensor operator

We arrived to the point of the discussion, that the author's frame of the *information driven* quantal measurement action as supposedly *(at least one of the*) driving force of enzyme catalysis can be discussed. We think that it was necessary to some existent theories (and, in some cases, practice) to present above, for the comprehensibility of our scheme.

In our own approach, the primary effect of enzyme action is to decrease the quantum uncertainties of the substrate(s), to obtain a ''skewed" probability field. The way to attain this is to decrease the quantum uncertainties of the substrates (*i)* by a part of the quantum uncertainties of the enzyme molecule (*j*) (the

difference of differences) of the *complex systems*' *resultant vectors*, yielding a kind of ''secondary" uncertainty relations. This realizes the *in principle quantum specificity*. In the coordinate – momentum picture, with reference to the *internal* specific interactions:

$$\left(\Delta\mathbf{q}_i - \Delta\mathbf{Q}_j\right)\left(\Delta\mathbf{p}_i - \Delta\mathbf{P}_j\right) \sim 2\hbar_{ii} - 2\hbar_{ij} \quad (18)$$

The summands in eq. (18) *define* operator (matrix) *differences*, in a compressed form as a *secondary physical (energy) quantity.* As a corollary result,

$$\Delta\mathbf{q}_i = C_{ji}\,\Delta\mathbf{Q}_j, \quad \text{i.e.,} \quad (19)$$

an informational -, *quasi – deterministic* relation follows from eqs. (18-19) . Here $\Delta\,\mathbf{Q}_j$, so $\Delta\,\mathbf{P}_j$ corresponds to an *a priori resultant effect of enzymatic uncertainty*, with reference to a set of steric configurational/conformational (so also electronic) and linear momentum of the enzyme molecule in the *transition complex,* with *quasiclassical* alternatives, the internal *choice* describable as a *quantum information content*. The crucial geometrical (and electronic) information content of the enzyme molecule is derivable from eq. (19), with certain considerations of [79-81] :

$$\mathbf{I}_{enzyme\ conformation,\ electronic\ fitting} = \log_2\left|C_{ji}\right|^2 \quad (20)$$

The $\hbar_{ij}$ coupling constants, in fact, as noted above, express this (induced, [79-81]) *spatial (geometric) specificity*:

$$\hbar_{ij} = \hbar_{ji} = \Delta\mathbf{q}_i\Delta\mathbf{P}_j = \Delta\mathbf{p}_i\Delta\mathbf{Q}_j \longrightarrow \Delta\mathbf{q}_i = C_{ji}\Delta\mathbf{Q}_j. \quad (21)$$

Starting again from the phenomenological eq. (18), with some considerations on the fundamental principles of quantum mechanics, we can set up the dynamical equation, with *i, k* = *incoming waves* of *A* (reactants) + B^0' (the quantum catalyst) (*i*), *outgoing wave of C* (products) + B^0 (resetted quantum catalyst) (*k*), and, most important, the intermediate transition complex (enzyme – substrate complex) (*j* **'**).

The 2 $\hbar_{ii}$ **-** 2 $\hbar_{ij}$ constant in the second order relation points to *contrary* to the *usual wide total energy level difference (the difference between the bottom and top of the barrier, the latter (the barrier) involving Coulomb and exchange repulsions of overlapping many dimensional potential wells,* generally needing some energetic activations*)* of uncatalysed interactions of complex molecules*, versus* the intervening enzymatic conformational and electronic fittings*, the also wide difference of differences*, maybe extending to being even a *''global resonant" barrier heights difference one.*

Introducing the second order mathematical objects (the difference of differences),

$$\hat{\bar{\mathbf{H}}}^{jj'}_{ik}\ def = \hat{\bar{\mathbf{H}}}_{ik}\ def = \bar{\mathbf{H}}^{j}_{i} - \bar{\mathbf{H}}^{j'}_{k} \quad (22)$$

where we denoted tensor elements (operators), the covariant indices denoting initial, wheras contravariant ones final individual quantum states (interpretable, however, in the condense phase also as ensembles) along the reaction path (coordinate) ***z***, with ($\Delta_k{}^{,j}$ - $\Delta_j{}^{,j}$) E = $E^{\#}$ referring to the difference of the uncatalysed dividing barrier height of PES and the barrier height with the crucial enzymatic activation component *of the total energy of the complex molecules*, so, in an ''interaction picture",

$$\hat{\bar{\mathbf{H}}}_{j'k}(\tau)\,\tilde{\mathbf{\Psi}}^{j'}_{k}(\tau) = \left(\Delta^{j}_{k'}(\tau) - \Delta^{j}_{j'}(\tau)\right)\mathrm{E}\tilde{\mathbf{\Psi}}^{j'}_{k}(\tau) = \mathrm{E}^{\#}\tilde{\mathbf{\Psi}}^{j'}_{k} \quad (23)$$

This is a certain kind of ''pseudo" – eigenvalue (in fact, extremal value) problem**.**

2.2.2 The affine projections

For the sake of the comprehensibility of what follows, we quote here the basic affine relations in *two composite* affine Hilbert spaces. As for one of them, for brevity, $\tilde{\mathbf{\Phi}}_j >= \chi_j * \chi_i >$,

$$\begin{aligned}\left\langle\tilde{\mathbf{\Phi}}_i\middle|\tilde{\mathbf{\Phi}}_j\right\rangle &= \mathrm{g}_{ij}\\ \left\langle\tilde{\mathbf{\Phi}}^i\middle|\tilde{\mathbf{\Phi}}^j\right\rangle &= \mathrm{g}^{ij}\\ \left\langle\tilde{\mathbf{\Phi}}^i\middle|\tilde{\mathbf{\Phi}}_j\right\rangle &= \delta^i_j\\ \left\langle\tilde{\mathbf{\Phi}}^i\middle|\tilde{\mathbf{\Phi}}_{j'}\right\rangle &= \mathrm{g}^i_j,\end{aligned} \quad (24)$$

(here * is ''product"; *i* and *j* corresponds, in a scattering context, to the *special scattering channel* (incoming/outgoing wave components) as the associated *special wavefunction components*. $\tilde{\mathbf{\Phi}}_j$ **'** denotes the function (vector) component in an other (affine) coordinate system. (We do not, in general, deal here with the $e^{i\mathbf{kr}}$, $e^{i\mathbf{kr}}$ */* r incoming – outgoing plane and spherical wavefunctions, rather, we move within the frame of the time – dependent Schrödinger

equation, so they are but *internal* time dependent *amplitude functions*.) Our projectional equations then become, denoting the wavefunction (vector) of the working enzyme molecule by $\chi^{E'}$ (''device") and that of the substrate molecules (''objects") by χ^{S} , and we introduce the two composite affine Hilbert space coordinate systems, one for the *active* enzyme E ' and the S activated (substrate) molecules, together expressed as enzyme – substrate complex [ES]' (TS)' , *and* for the dissociated product(s), S' (+ < E free, resetted) .

The *other affine Hilbert space* is defined for ($S^{\dagger}$, $S^{\dagger}$), i. e., the ''self – interacting" substrate molecule(s) and the uncatalysed transition state (TS). The loaded enzyme (the enzyme - substrate complex) will be referred to as being in a ''virtual" state, emphasizing its special existence, distinguishing it by the enzyme's contravariant, the other components as covariant, ''strictly material" state(s). The prime on „ *j* ' " in eqs. (19, 22, 23) superscripts/subscripts refer to the (lower) value on an orthogonal energy scale, the enzyme catalysed (TS)' , the scale beginning at '' k ' '' in Fig. 1. ; the unprimed ones (*" j "*) refer to the the upper (not catalysed) reaction transition state (TS) (see also Fig. 1.). This notation referres primarily to the Δ E - s and the $\widetilde{\mathbf{\Phi}}$ ' - s. The initial states of the $\widetilde{\mathbf{\Phi}}$ functions are referred to by ''*i*" , the final state by ''*k".* (We do this to spare superfluous letters. *We deal here only with the second and first half of the functions*.) Using some properties of dual spaces,

$$C_j(\tau)\, C^{j''}(\tau)\, C_j(\tau)\, C^{j''}(\tau) < \sum_i g^{ij} \chi_j^{E'} \mid \chi_{j''}^{S}{}_{\text{activated}} > < \chi^{jE'*} \chi_{j''}^{S}{}_{\text{activated}} \rightarrow C'(\tau) < \chi_j^{E*} \chi_{j''}^{S} = C_{(\tau)} < \widetilde{\mathbf{\Phi}}^{j'}{}_{((j',k),S'} \text{))) [ES] (TS') ; } (+ < \chi^{E}_{j\ resetted}) \rightarrow C^{\dagger i}(\tau)\, C^{\dagger j}(\tau)\, \chi_j^{\dagger S\dagger} > < \chi_i^{\dagger S\dagger} \rightarrow (C^{\dagger i}(\tau))^2\, C^{\dagger j}(\tau)\, g\ddagger_{ii}\, \chi_j^{\dagger S\dagger} > < \chi_i^{\dagger S\dagger} \mid \chi_i^{\dagger S\dagger} > \rightarrow [TS] \rightarrow C^{+}\widetilde{\Phi}_{ij(S^{\dagger}S^{\dagger})+(TS)} - C < \widetilde{\Phi}^{j'}_{(j',k)(S')[ES](TS')};\ \left(+ < \chi_j^{E}\right) = (\Psi - \Delta\Psi) \qquad (25)$$

(Here τ is the time parameter, g i i ‡ is the metric tensor component in the other affine coordinate system (square of the length of the *i* th basis vector), double prime referres to the *other component* of the vector (function) in the same composite Hilbert space.) Ψ– ΔΨ *is the full wavefunction of the system, including the proper TS - s.*

As noted above, in these affine equations, showing half of the functions, the g^{ij} *metric tensor components* fix the *sterically constrained* individual *scattering channel* (''*i*") and the associated *specific wavefunction components* of E' , S activated (and [TS]' , as „ *j* '"). The enzymatic contravariant state $\chi^{j}{}_{E}$ is ''virtual" (informationally ruled) state, as it becomes charged with the substrat(s), dominating above the ''strictly material" states, fixing both the scattering channel *and* the transition complex [TS]' wavefunction. It fixes also the wavefunctions of E' and S . $C^{+}\widetilde{\mathbf{\Phi}}_{i}{}^{j}$ - $C\widetilde{\mathbf{\Phi}}^{j'}{}_{(j',k)([ES](TS)',S')}$ is half of the difference function between the initial states ($S^{\dagger}$ $S^{\dagger}$), (*i*) and the also ''strictly material" final states (products) ($S^{\dagger}$ '), (*k*), *were there no enzyme action*. Substructed from it the catalysed reaction half function, the enzyme catalysed [TS] ' barrier height half function, we can write (this is, in a sense, the rewriting of eq. (23)):

$$\left(\bar{\mathrm{H}}^{j}_{k'}(\tau) - \bar{\mathrm{H}}^{j}_{j'}(\tau)\right)(\Psi - \Delta\Psi)(\tau) = \left(\Delta^{j}_{k'}(\tau) - \Delta^{j}_{j'}(\tau)\right)\mathrm{E}(\Psi - \Delta\Psi) = \mathrm{E}^{\#}(\Psi - \Delta\Psi). \qquad (26)$$

Here $E^{\#}$ is the difference in the maxima of the potential energy barrier heights half - wavefunctions between *i* ($S^{\dagger}$ $S^{\dagger}$), E' + S (activated) and final state(s) (k) ($S^{\dagger}$ '), S' + E, *through intermediate states j*, *j* ' , (TS) , (TS)' (see Fig. 1. for an endergonic reaction), the problem also essentially being the ''pseudo" - eigenvalue (in fact, extremal value) problem of the previous kind. In pure letters,

$$i \rightarrow (j),\ j' \rightarrow k \qquad (27)$$

j ', *j* here refers to the TS (barrier heights) with and without enzyme action. *k'*, as noted above, is the initial coordinate of the orthogonal energy scale. The outcome of the first affine projection is $C\widetilde{\mathbf{\Phi}}^{j'}{}_{(j'k)((ES\ (TS)')}$ *and* the resetted enzyme molecule ($< \chi_j^{E}$), i. e., from the ''virtual" state *j* ' ([ES]' , TS'), to ''strictly material state(s)" E + S' *k* (*j* ') ; the second projection shows the route from a kind of ''self – interaction" ($S^{\dagger}$ $S^{\dagger}$), substrate state *i* , (eq. (25)) to state *j* ((TS) $\mathbf{C^{+}}$ $\widetilde{\mathbf{\Phi}}_{i}{}^{j}$) . In scattering terms, (Ψ - Δ Ψ) **= c⁺** $\widetilde{\mathbf{\Phi}}_{i}{}^{j}$

- $\mathbf{C}\widetilde{\mathbf{\Phi}}^{j'}{}_{(j',k)}{}_{((ES\ (TS'}{}_{+}\mathbf{S}'{}_{)))}(+<\chi^{E})$ which *practically coincides with* $S_T{}^{++}$: *i* ($S^{\dagger}$), (E **'** + S $_{activated}$) → (*j* , *j*') → k (S**')** (E + S'). (E' + S $_{activated}$ is *purely hypothetical*) (The technical point is that the ''virtual" state *j* **'** at $\mathbf{C}\widetilde{\mathbf{\Phi}}^{j'}{}_{(j',k)}{}_{((ES\ (TS'))}$ for consistency must be an *initial coordinates* ending at ''*k*", by a *final interchange* of indices *j* **'** ↔ *k*).

(Here ++ is to distinguish the quantity from pure (uncatalysed) scatterings). The pecularity of our introductory method is that we calculate only *halves* of both barrier wavefunctions along the ''reaction coordinate" (path) ***z***, from the initial state $S^{\dagger}$ to the [TS], and from the [ES]' (TS)**'** to the final state E + S'. This is supposed to work, except for very asymmetric barrier shapes.

Changing to scattering, the arrows in Fig. 1, show the $S^{\dagger}$ → (TS) **;** [ES]' (TS)**'** → E + S' routes. The transition complex is a very shallow but finite multidimensional minimum (in a saddle point context) on PES, and is a state (TS), (''virtual" for (TS)'). If we interpret the processes in a condensed phase as an ensemble, subject to equilibration, we change to free energy.

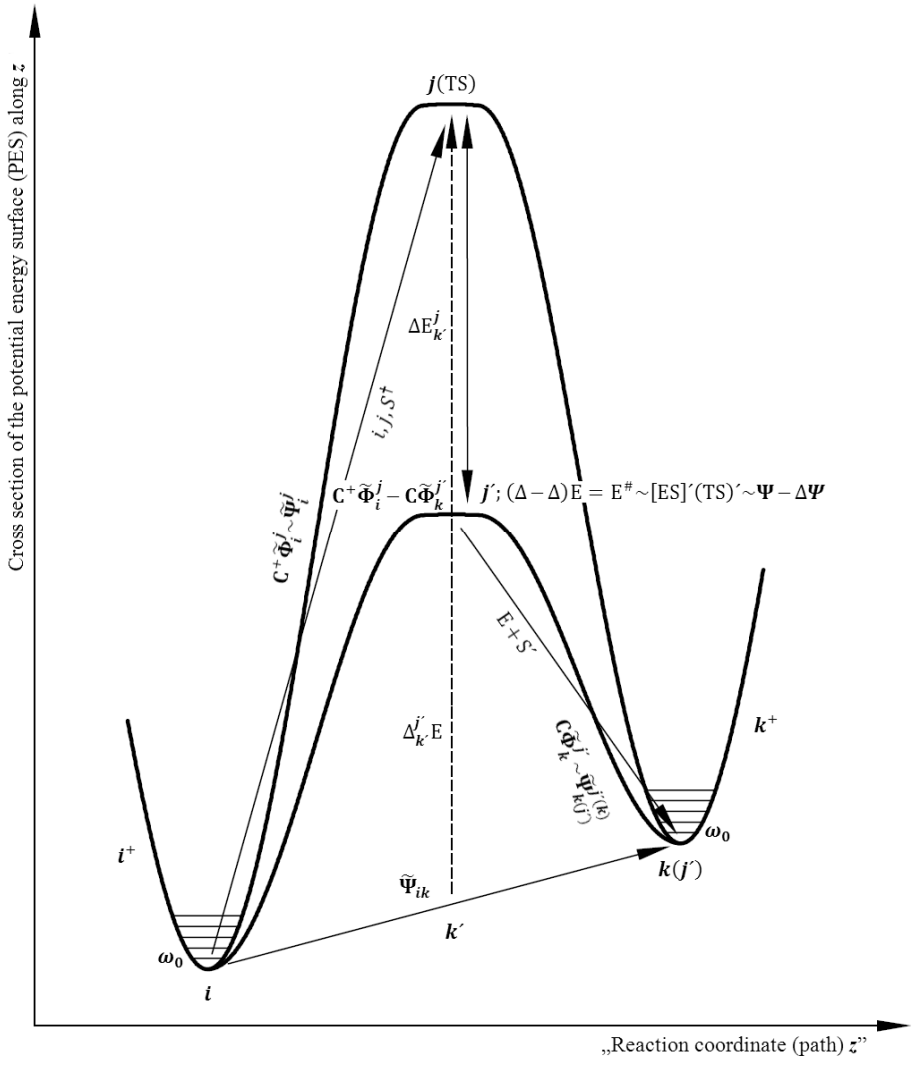

Fig. 1. Cross section section of PES along z for and endergonic reaction. For the symbols, see text

(Note, however, that Mayer showed [91] that the statistical distribution in simple uncatalysed TS should be treated by *quantum statistics*, rather than by Boltzmann's. In this light, the above kinetic equations of Section 2.1.3., and their generalizations (e. g. Garcia – Viloca et al. [33]), are not entirely "exact".

3. CONCLUDING REMARKS

We have overviewed the the available enzyme - catalysed reaction kinetics theories (occasionally practices), from the Michaelis – Menten (and Briggs – Haldane) kinetics to a (hypothetical) quantum scattering, to provide a reasonable background for our information – driven quantum formalism. It has been shown that our ''*second order*" frame is in practice consistent with certain condensed phase ensemble approaches, if the word "state" is substituted for (equilibrated) "states" and change to free energy.

More important, our formal treatment is consistent with a (*hypothetical*) gas phase quantum scattering as a second order perturbational process, and the *individual states* are treated as in – and out - going *individual waves*, propagating in the *proper scattering channel.* In fact, changing to this scattering picture, the formalism presented might *resemble* a gas phase *generalized* barrier *resonance scattering,* due to the *(at present yet purely formal)* tensorial secondary approach, following from the .*"second order" uncertainty relations.*

Our above argument is highly introductory, an *in principle one*, rather than practical. We can not, as at the present stage of the investigation, to provide examples of any outstanding practical usefullnes. However, it might help to rethinking of the enzyme – catalysed reactions in a *fully* quantal way, with the note that we must evidently take into account the geometrical – electronic complementation *informations, so effective in face of a rather individual „black box" approach*, in which physical parameters are calculated *a posteriory,* knowing the exact steric complementations.. Our kind of research, we think, can be approached in a molecular evolutional way, where also chance has its determining role. Nonetheless, the "Maxwell – demon" aspect of the enzymatic process, emphasised by Monod [6], and theoretically discussed by Brillouin [7] (see also e. g. Collier [8], also Barato and Seifert [9]) calls our attention to the fact that *information* in this sense might be a very strong complementing factor besides pure energetic considerations. We here only introductorily have put forth the "virtual" (not strictly "material") nature of the action of enzymes in the [ES] complex. $\hat{\tilde{\mathbf{H}}}_{i\,k}{}^{j\,j'}$ in fact referres to the *highly (informationally) selective (selectively projected) quantum transitions,* based on *space complementations* in the sense of Pattee (e.g. [2]) and Balázs (e.g. [1]) which we called above, in lack of a better expression, *individual resonance scatterings* involving highly selective (individual, selected, ''measurement") quantum states.

Though nowdays ''brute force" approximations are in use in general, our study might perhaps provide an additional, fresh view on enzyme kinetics, emphasizing *molecular information* and the corresponding "*internal measurement*" aspect of enzyme action.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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