



## **Interactions between Physics and Biodisciplines within the Framework of Molecular Sciences**

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**Abstract:** In order to be able to study interactions within, between, and among biomolecules, it is highly desirable to use tools of experimental and theoretical physics, or preferably a combination thereof. Very brief comments are presented which concern biochemical reactivity, enzymatic catalysis, origin of life, experimental tools for structure elucidation and quantum chemistry methods. Additional remarks are related to ultrafast processes, experiments with individual molecules, and to symmetry considerations.

**Keywords:** Biochemical reactivity

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### **Introduction**

When I was asked by the chairman of this Workshop to present a banquet address, it soon occurred to me that it would, in a sense, be easier to prepare a few hundreds pages than just a few pages. The field is getting so broad and is connected with numerous challenges that the selection of subjects in a brief remark is rather arbitrary and necessarily reflects interests of the author.

The overlap of sciences indicated in the title of this note will lead, no doubt, to a significant extension and deepening of our knowledge concerning the functioning of living matter. It is beneficial to recall how natural sciences have developed from the 18<sup>th</sup> through 20<sup>th</sup> centuries. The effort of polyhistorians culminated in the 18<sup>th</sup> century; sometimes they were active in not only natural sciences but also in the arts. Their common language was Latin. This language was lost in the 19<sup>th</sup> century and the rapid expansion of the natural sciences encouraged their emancipation. This process of emancipation

was related to the formation of undesirable barriers between the sciences. It is true, however, that before the end of the 19<sup>th</sup> century disciplines like physical chemistry and biochemistry were established: it was an indication of something new. Since approximately the middle of the 20<sup>th</sup> century a strong tendency towards "interdisciplinarity" has been observed. The formation of molecular sciences ranging from physics to medicine, or even anthropology, is a clear-cut example. Those, whose knowledge of several disciplines is sufficiently broad and deep and who have good organizing abilities, could act as leaders of interdisciplinary teams. The individual members of the team should be not only quite professional in their specialization but also rather well informed about related disciplines.

It is the purpose of these introductory remarks to help to create an appropriate atmosphere for this meeting. By way of underscoring the role and beauty of a few carefully selected subjects, which will undoubtedly play a significant role in the topics to be discussed, this introduction is given as nothing more than as an "aperitif".

### **Specific subjects**

Components of living matter, their mutual interactions and general areas of influence have attracted the attention of scientists for years. A subject, which assumes extreme importance is catalysis by biomacromolecules. Moreover, subjects like origin of life, symmetry and its not completely elucidated role in biomolecules and biomolecular reactivity, and the CPT theorem. The role of studying physical properties and reactivity of extensive molecules and clusters thereof will be increasing. Computational methods of quantum and statistical mechanics, together with procedures of molecular dynamics, are exceedingly valuable and powerful tools. We always occupy our minds by thinking how to effectively familiarise the young generation with all the essential classical and modern tools and methods. All the mentioned subjects (and, obviously, numerous other ones) will contribute to the ultimate goal, namely understanding how living matter functions. It is appropriate to stress that strong interactions between theory and experiment are highly desirable. In this connection it should be mentioned that while the theory of the chemical bond assumes a central role in chemistry, the theory of the non-covalent (weak and also van der Waals) bond takes over this role in the realm of biodisciplines.

*Components of living matter and their interactions.* While the attention paid to amino acids peptides, proteins, components of nucleic acids, and models of nucleic acids has been for years rather extensive [1, 2], saccharides, polysaccharides, fatty acids, and membranes deserve significantly more consideration and an appropriate shift of interest is expected in near future.

In a general sense there is no reason to distinguish between "chemical" and "biochemical" processes because both are governed by the same laws of quantum and statistical mechanics. Nonetheless, it is expedient to pay attention to conditions which are for the most part dramatically different for both types of processes (Table 1). It starts with temperature and pressure, which vary in

chemistry in very broad ranges, while biochemical processes are mostly realized at about 310 K and 1 atm. For the reaction environment (cf. Table 1) significantly different media from those mentioned in this table are also topical *in vivo* and *in vitro*, e.g., lipophilic media, or cavities containing a very limited number of water molecules.

**Table 1.** Characteristics of Chemical and Biochemical Reactivity.<sup>a</sup>

Conditions	Reactivity	
	chemical	biochemical
Reaction environment	Gaseous, liquid solution, surfaces of solids	Aqueous suspension containing salts and numerous sorts of molecules and macromolecules
Local electric fields	$10^5$ - $10^6$ V/m	$10^7$ - $10^{10}$ V/m (at some reaction sites)
Catalyst	Either noncatalytic or catalytic	Probably always catalytic, frequently extremely powerful specific catalysis
Yields of reactions	From low to high	Very high, frequently almost quantitative
Tunneling	Transfer of lightest particles	The same as for chemical reactivity and perhaps some conformational changes

<sup>a</sup> Based on Ref. 3.

Two more comments on Table 1 are necessary. Firstly, the role of local electric fields (sometimes of enormous strength) is still not sufficiently appreciated. It is of course true that if a high quality model is used in a quantum chemical calculation, then the electric field in a reaction centre is described adequately. However, when the model is not good enough, the electric field has to be incorporated into the Hamiltonian [4] because otherwise the calculation output might be poor, if not completely wrong. We must not forget that fields amounting to  $10^9$ - $10^{10}$  V/m vary dramatically the charge distribution, the ordering of molecular orbitals and other physical properties. Therefore, a forbidden process under low-field conditions can turn into an allowed process – an instance of catalysis without chemical species, but by an electric field.

*Enzymatic catalysis.* This catalysis is no longer connected entirely with biochemical processes taking place *in vivo* and *in vitro*. The importance of this type of catalysis is becoming increasingly broad because it creeps into laboratory and industrial chemistry: one has a feeling that a new era has started. Enzymatic catalysis is frequently due to a metallic ion deposited in a protein molecule. But sometimes the presence of such an ion is not needed and, moreover, the catalytic power is definitely not entirely connected with proteins. This phenomenon is certainly associated with very different macromolecules as well as with supramolecular structures linked with them. Substrate fixed to such a

catalyst, whether located in a cavity or sitting at the surface, is frequently exposed to a strong local electric field, which exerts a significant influence on physical properties and reactivity of the substrate (*vide supra*). Let me add that experts in the realm of enzymology sometimes say that it is hopeless to try to improve enzyme activity and stability (conditioned by evolution) by passing from proteins to other polymers. It is my belief that a brilliant chemist could manage such a task. A recently published paper [5] supports this view. Synthetic polymers which are capable of folding as well as self-assembling might function as biopolymers. They might even assume useful functions which biopolymers do not have.

Great progress has been made with the exploitation of crystalline proteins and with their stabilization by introducing cross-linkages. The number of usable crystalline proteins as industrial catalysts steadily increases. They are also used successfully in enantioselective chromatography. Crystalline proteins and enzymes are frequently less sensitive than chemists believe: stabilized materials can even serve as bioorganic zeolites [6]. Stability may be sometimes enhanced by introducing an enzyme into a hydrogel matrix [7]. From this perspective effort to make progress on the road to synthetic enzymes appears promising [8]. Not only increasing enzyme stability is very topical, but increasing selectivity and catalytic efficiency is as well and can be achieved by that which is called “directed evolution” or “evolution engineering” [9].

In addition to experimentalists, theorists also pass with remarkable rapidity into the realm of big systems. Quantum chemically calculated energies and also Gibbs energies play an essential role for the interpretation of the mechanism of enzymatically catalyzed processes [10]. For the analysis of enzymatic reaction pathways a combined QM/MM method (quantum mechanics, molecular mechanics) represents a real change. A valuable analysis of the applicability of this combined procedure was performed by Monard et al. [11]. The authors paid special attention to the non-bonded interactions between the quantum (internal) and classic (external) parts. A typical static approach relies on the traditional analysis of a potential energy surface and localization of stationary points. In connection with investigating the role of the active-site residues in the catalyzed Claisen rearrangement of chorismate to prephenate, molecular dynamics approach combined with the QM/MM procedure was used [12]. Intensive progress along similar lines is anticipated.

Recently a paper appeared [13] stating that pressure exerting an effect in certain directions may play an important role in the catalytic function of enzymes.

*Origin of life.* This has been a tempting and provocative topic for eighty years [14-16]. Pioneering work concerning formation of building blocks for potential synthesis of amino acids, proteins, and nucleic acids appeared half a century ago [17]. Only about 15 years ago more systematic studies began but there is still a very, very long way to go to reach reliable and convincing ideas concerning the origin of life on Earth [18, 19]. Even seemingly simple questions, such as prebiotic ammonia formation, remains unsettled. Valuable recent reviews are available [20, 21]. One of the fascinating

features, namely the preference for *l*-amino acids and *d*-sugars is mentioned briefly in the section on symmetry.

*Ultrafast processes.* During the last 50 years chemical physics has passed from millisecond to femtosecond spectroscopy ( $1 \text{ fs} = 10^{-15} \text{ s}$ ). By contrast to classical studies of kinetics, femtochemistry allows to depict truly elementary processes of chemical transformations, the formation and the decay of covalent bonds [22]. This dramatic development was culminated with awarding to A. H. Zewail the Nobel price for chemistry in 1999.

Now it is indeed possible to directly investigate the mechanism of processes in chemistry and biology [23]. High-resolution infrared spectroscopy in combination with solving the time-dependent Schrödinger equation make it possible to efficiently investigate such processes [24]. Further progress in the area of femtochemistry is expected in near future.

Two questions are really tempting in this connection. In what way is the resolution of femtosecond spectroscopy influenced by the Uncertainty principle [25] and how realistic are the attempts to pass to attochemistry ( $1 \text{ as} = 10^{-18} \text{ s}$ ).

*Experiments with individual molecules.* Researches in the area of molecular sciences in the last decade of the 20<sup>th</sup> century entered robustly into another frontier section. The number of properties investigations associated with single molecules has been increasing so rapidly that Wiley Interscience has started publishing a journal entitled "Single Molecules".

A pioneering work [26] focussed on the relationship between applied force and resulting distortion was analyzed with a single DNA molecule in terms of classical physics. A whole ensemble of tools including a scanning force microscopy, SFM, is now available for related studies [27]. A disturbing feature, a kind of handicap of the scanning tunneling microscopy, STM, that is, an undesirable contact between a tip and the surface of a solid, has become extremely valuable for chemical manipulations with and within single molecules [28]. Rapid development of various sorts of scanning microscopies suggests great expansion and applicability growth of this technique.

*Symmetry and the CPT theorem.* Symmetry considerations based on the exploitation of group theory have played an overwhelming role in molecular sciences for many years. This is, however, not the case in biodisciplines, with some exception; this situation should be changed. Invariance of a physical law with respect to various symmetry operations is associated with the existence of a conservation law. Hamiltonian invariance with respect to the space symmetry operation requires orbital or state symmetry conservation during the course of a chemical transformation. This is equivalent to that which is well-known under the name the Woodward-Hoffmann Rules.

Symmetry considerations represent a valuable tool for analyzing quaternary structures of proteins. Reasons were clarified as to why these structures cannot contain mirror reflections or inversion symmetry. In an excellent published account it was shown that the only symmetry operations for

proteins clusters (quaternary structures) are rotations [29]. In accordance with this, three classes of point groups are possible, corresponding to cyclic, dihedral, and cubic symmetry.

Since the revolutionary Pasteur discovery which is related to chirality, it has been known that optical antipodes assume different physical properties and reactivity. By contrast, there was no doubt about the energy of these antipodes, which was deemed absolutely identical. It turned out, however, that this was not true. Within the framework of the CPT theorem [30] (C, P, and T stand for charge operator, parity, and time inversion operator) it can easily be shown that weak forces are discriminative and distinguish between *d*- and *l*-forms [31, 32]. The energy difference is, no doubt, real but always very small and by means of contemporary techniques not measurable. According to fair estimates, it could be measurable within ten or twenty years. Invariance with respect to the combined CP operation is satisfied; it has been shown that  $\Delta E$  associated with passing from a right- to left-handed system is identical with  $\Delta E$  connected with the transition of a right-handed molecule to the respective right-handed antimolecule [31]. A point, which is still open, concerns the possibility that in a prebiotic soup the one-to-one mixtures of optical antipodes of biomolecules passed to mixtures in which one form overweighted the other by interactions with chiral surfaces of solids (*e.g.*, silica). This is one of the tentative explanations for existence of *l*-amino acids and *d*-sugars in living matter.

Recently, the case of a large parity-violation effect was announced [33]. I would like to close these remarks by expressing astonishment at the high symmetry of various supra-supramolecular systems, *e.g.*, viruses. Obviously a lot has to be done in order to understand it.

*Experimental tools for structure elucidation.* Although classical procedures are still valuable in specific connections, at present three techniques do clearly play a central role: X-ray analysis, NMR, and mass spectrometry. The about 90 percent success in this area is due to these powerful methods, which have made amazing progress during the last twenty years. Their common feature is that they are capable of dealing with very extensive systems, *i.e.*, with molecules which are of fundamental biological relevance. Time limitation permits commenting on this only very briefly.

Productivity of X-ray analysis has increased dramatically and it may be used with systems of molecular mass up to a few hundreds of kDa. Recently, in connection with ribosomes, molecular mass over 2500 kDa was reached [34] with resolution of 5.5 Å. Preparation of appropriate monocrystals represents sometimes an involved task. In spite of that, experts intend to prepare the majority of enzymes of a human body in crystalline form and to establish their structure. A great and ambitious goal, indeed!

Nuclear magnetic resonance is on the road leading to a 1000 MHz apparatus. The increase in price is at present quite dramatic and, therefore, in the near future just a few pieces will be available. Fortunately, even smaller fields permit, especially in the form of two-dimensional methods, routine structure elucidation of peptides and proteins of up to 50 kDa [35]. Recently, a membrane protein with

molecular mass of nearly 900 kDa was analyzed [36]. Passing to high resolution NMR with solids represents essential progress [37].

Mass spectrometry is amazingly successful with huge systems, *e.g.*, in characterizing intact microorganisms [38] or in the realm of proteomics [39, 40].

*Molecular quantum mechanics and related methods.* This region reminds us of an ocean: it is huge and offers numerous possibilities, which are in some instances otherwise not attainable [41]. Also here a strong tendency to pass to very extensive systems represents a very significant attribute. Rapid development is carried out along two lines: the classical quantum chemistry approach, occasionally combined with molecular mechanics (empirical potentials) and with methods of the physics of a continuum (Table 2). The other direction has been developed for years and is connected with computer experiments (of Monte Carlo, MC, and molecular dynamics, MD, types). In this area progress now proceeds very rapidly. Computer facilities make it possible to follow, *e.g.*, aggregation of molecules leading to membranes, and peptide or protein folding [42]. These processes require between 10 ns to 1  $\mu$ s. It is possible, when using 1 fs steps, to follow trajectories with systems having ten thousands atoms (or at least thousands of atoms) for 10 ns (100 ns, *i.e.*, 0.1  $\mu$ s). Sophisticated papers dealing with the folding of proteins have appeared [43, 44]. An amazing step forward was made recently by utilising thousands of personal computers to study the folding of the  $\alpha$ -helical protein. Simulation was carried out for (the nearly unbelievable) 300  $\mu$ s [45].

**Table 2.** How do the individual computational methods consider electrons, atoms, and continuum (liquids or solids): explicitly, e; explicitly in a part of the system under study, (e); implicitly, i. Methods considered: quantum chemistry, QM; molecular mechanics, MM; the physics of a continuum, PC.  $n_{at}$  stands for attainable number of atoms.

Method	$n_{at}$	Electrons	Atoms	(s) (l)
QM	hundreds	e	e	e
QM/MM	thousands up to tenthousands	(e)	e	e
MM <sup>a</sup>	tenthousands	i	e	e
PC	$\infty$	i	i	e
QM/MM/PC	$\infty$	(e)	(e)	e

<sup>a</sup> Frequently used in connection with the Monte Carlo and molecular dynamics methods.

Back to quantum chemistry. Semiempirical methods are passing into history: there is a trend toward using nonempirical methods throughout the quantum chemistry community. Even more: with small- and medium-sized systems extrapolations to infinite basis sets are becoming popular [46, 47]. The density functional theory (DFT) represents in various connections a valuable and efficient tool. It must not be used, however, in instances where interaction energy is essentially given by electron correlation.

*Consequences for teaching.* In order to make interactions between physicists, biologists and biochemists of various specialisations more extensive and more sophisticated, changes in educational systems are desirable. An introduction to biodisciplines for physics students should be prepared and delivered by first class biologists with broad knowledge and a warm attitude to mathematics and physics.

For biochemists a specific difficulty exists, which can be taken as a warning for young aspiring scientists: if they not like math and physics, it is unreasonable to expect an effortless progress in the biodisciplines. To overcome, at least partially, this potential barrier, it seems very useful that introductory courses in mathematics and physics for biology students be delivered by distinguished bio-experts who have established their professional and productive interactions with experimental and theoretical physicists.

## Conclusion

If we succeeded in accomplishing the above mentioned requirements, I am persuaded that a significant step forward in understanding the functioning of living matter could be achieved within the next 20 to 30 years.

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