Chemistry of Life

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Understanding Life as Molecules: Reductionism Versus Vitalism

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Chemists have always been fascinated by the molecular nature of life. A living cell can indeed be viewed as just a very small drop of liquid containing thousands of molecules that are accessible to chemical investigations and exchange energy and matter with the environment. A cell, though small, is quite visible and observable, and thus a cell and its molecular content can be studied by modern imaging techniques. Even though the chemical characterization of the large repertoire of natural molecules is not a new science, chemistry will continue to contribute to the understanding of the real nature of life. This is because chemistry is the science of both "informed" and "transformed" matter. Life arises indeed from "informed" matter. Jean-Marie Lehn[1] has studied "informed" matter, which results from the exquisite communication between molecules, through subtle interactions that occur within complex networks and can nevertheless can be described by the laws of physics and chemistry. More than ten years ago, Alberts elegantly pointed out: "Instead of a cell dominated by randomly colliding individual protein molecules we now know that nearly every major process in a cell is carried out by assemblies of ten or more protein molecules".[2] Life also depends on the "transformed" matter derived from a dynamic interconnection of thousands of chemical reactions. These reactions in cells proceed with rates, selectivity, and yields still unsurpassed in chemical laboratories, but nevertheless they are just chemical reactions.

At the same time, however, it is difficult to escape such abrupt statements as: "The era of blind, fervent reductionism, wherein biochemists and biophysicists purified and purified to enable studies of isolated biomolecules, is over".[3] Thus biologists are called upon more and more to shift away from molecular chemistry approaches and mainly concentrate at understanding life at the level of systems. Indeed, an emerging simplistic view of postgenomic biology, partly reflected in the "systems biology" approach, develops the holistic notion that a living organism is essentially a unit and, as a consequence, dissecting an organism through molecular chemistry can throw no real light on its nature. Reductionism is inherent in the scientific approach when dealing with such complex systems as a living organism. It thus obviously applies to almost all disciplines, although to different extents. On one extreme, the molecular and chemical explanation of life, as discussed here, is a reductionist paradigm. At the other extreme, the emerging area of integrated biology, while also reductionist, has its foundations in the notion that reduction should be limited as much as possible and appeals for a change of paradigm.

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"Chemistry is to biology what notation is to music"

It is not the first time that biochemistry has been called upon to re-examine its methods and objectives in the light of new directions in biology. Ironically, biochemistry continuously renews itself, albeit with different names—enzymology, biological chemistry, chemical biology—because its methods rapidly evolve, its tools (microscopy, crystallography, NMR spectroscopy, computational methods, rapid kinetics, etc.) become more and more sophisticated to study larger and larger objects (beautiful recent examples are the ribosome, RNA polymerase, ATP synthase, and complex I). The scope of biochemistry has indeed expanded from an early focus on the chemical, catalytic, and structural properties of individual enzymes to more recent efforts to understand enzyme action in the context of dynamic functional biological systems consisting of many interacting enzymes and proteins. However, no correct interpretation of the chemical properties of these assemblies is possible without the detailed structural, thermodynamic, and kinetic characterization of its components. As the French chemist Pierre Potier (1934–2006) reflected: "chemistry is to biology what notation is to music".

A more balanced view of this new interface between postgenomic systems biology and chemistry, which emphasizes their complementarities, would thus be appropriate. It would imply that biologists indeed continue to study living organisms as dynamic whole units, going from animals and organs (this level, that is, physiology, also needs to be better integrated in biology than it is at present) to cells and cellular compartments (mitochondria, chloroplasts, vesicles), and finally to proteomes, metabolomes, and interactomes, where

collaboration with chemists really can become extremely fruitful. Indeed, there is no other way for the systems biology approach to generate the most accurate models other than coupling their studies of biological systems to in vitro characterization and reconstitution of their chemical components, which provides the required detailed quantitative information on reaction mechanisms, individual reaction rates, and thermodynamic affinity constants as well as tools to image their spatial distribution and dynamics during perturbation. Such an integrated approach has not been greatly developed. A remarkable example of what should be considered as state-of-the-art in this domain is a recently reported study that combines enzyme kinetic data with mathematical models on aspartate metabolism in plants.[4] At the same time, chemists always have to remember that their data gain their full significance only when they take into account that a given protein is part of a complex protein network, can undergo a number of essential post-translational modifications, and interacts within a highly crowded and restricted translational diffusion cellular environment. It is essential that these data are related to the activities of the organism as a whole and are consistent with its overall physiological properties, thus requiring in vivo tests to confirm predictions made by chemistry. This requirement, in my opinion, is the major challenge of biological chemistry but does not make the new era, as is sometimes claimed, a postreductionist one. In fact, it is rather the contrary. To illustrate the type of studies that integrate in vitro chemical and in vivo biological studies of large protein complexes, I would like to use the work on the protein machineries involved in the complex process of assembly of iron–sulfur clusters carried out with Sandrine Ollagnier-de-Choudens in my laboratory, and in collaboration with the microbiology group of Fréderic Barras in Marseille. These machineries contain cluster scaffold proteins, cysteine desulfurases, chaperones, flavoproteins, Fe donor proteins, and ATPases that work together through delicate intermolecular connections to build a cluster with the right stoichiometry at the correct location without release of toxic iron and sulfide ions. Interested readers may refer to selected reports.[5,6] There is no doubt that scientific breakthroughs happen at the interfaces between different disciplines and, even better, when these disciplines complement each other. Herein, I discuss the interface between biology and chemistry but obviously the understanding of the nature of a living organism requires the involvement of other disciplines such as informatics, physics, or technology.

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The sometimes exclusive reliance in current biological research on intact cells and organisms to fathom the nature of life has a hint of vitalism. Vitalists believe in the existence of a "vital force", which is different from and superior to the physical forces, explains the order of life, and is opposed to death. For several centuries, this vital force was the common and simple explanation for the formation and the transformation of the complex chemical compounds present in living organisms. At the end of the 18th century, the French physiologist Marie François Xavier Bichat (1771–1802) claimed: "The science of the organized bodies should not be treated in the same way that of inorganic bodies…Physical and chemical phenomena follow the same laws; but a huge gap exists between these laws and those of life".[7] In contrast, reductionists, such as Justus Von Liebig (1803–1873) in Germany or Marcelin Berthelot (1827–1907) and Claude Bernard (1813–1878) in France, whose theories began to be developed and debated already in the 19th century, and with whom a number of brilliant chemists and biochemists agreed with later on, believe in the molecular nature of the living world and rely on the laws of physics and chemistry to understand it.

The history of biological chemistry has been profoundly shaped by the dispute between vitalists and reductionists. In the brief historical perspective given below I would like to bring up some well-known major milestones in biological chemistry which illustrate the power of the reductionist approach.

During the 17th century, and until the end of the 18th century, there was no clear frontier, that is, no division, between the inert and the living matter, essentially because the only solid science at that time was mechanics and there was no reason to exclude the fact that living organisms are just machines that can be described in terms of gravity, affinity and motion, which follow the laws of mechanics. As shown by the English physiologist William Harvey (1578–1657), the heart is a pump and blood circulation a hydraulic system. At the same time, it also appears obvious that the mechanical sciences of the classical age are not sufficient to explain the complexity of the living organisms and this materialism is thus opposed by animistic philosophical and moral positions. Indeed the perfection of beings, as compared to things, can only be justified and explained by a spiritual force, which is present to execute God's wills. This mysterious force has different names, such as the soul, the intelligence, and finally, at the end of the 18th century, the vital force. Vitalism then becomes a true operator of knowledge and, playing a decisive role in the separation between the inert things and the living organisms, it was an essential step in the advent of a sound biological science, not only for physiologists and physicians but also for chemists.

At the end of the 18th century and beginning of the 19th century, chemists concentrated on the analysis and character-

ization of the molecular components of living organisms. In 1783, the great Swedish chemist Scheele (1742–1786), under the direction of Bergman (1735–1784), discovered citric acid and isolated glycerine by boiling olive oil in the presence of lead oxide. These compounds, which are derived from animals or plants, are qualified as "organic " to distinguish them from the "inorganic" compounds, which lack carbon. Their laboratory synthesis was regarded as impossible, and the vital force was the only explanation for their biosynthesis and transformations.

The first breakthrough was achieved in 1828 by the German chemist Friedrich Wöhler (1800–1882; Figure 1). In order to generate ammonium isocyanate, Wöhler heated a

Figure 1. Friedrich Wöhler (1800–1882).

mixture of silver isocyanate and ammonium chloride and discovered that the product was urea, a compound known since 1773 as a mammalian organic residue excreted in urine.[8] This result demonstrated for the first time that a biological molecule could be made without the assistance of vital functions. In 1837, Justus von Liebig declared: "the extraordinary and unaccountable production of urea without any assistance of vital functions, due to Wöhler, should be considered as one of the discoveries upon which a new scientific era can start". However Wöhler's finding did not yet fully establish the unity between the organic and inorganic worlds, that is, between the living world and the inert matter, since silver isocyanate is not an inorganic substance. Similarly, in 1845, another German chemist, Hermann Kolbe (1818–1884), achieved a remarkable reaction, which implied the formation of C–C and C–H bonds starting from carbon and very simple inorganic precursors. Reaction of elemental carbon with dihydrogen and water as a source of oxygen, in the presence of iron sulfide and chlorine, generated acetic acid, a natural compound. Kolbe's synthetic reaction is a beautiful illustration of the basic hypothesis of prebiotic chemistry, namely that life has resulted from the accumulation of fairly complex organic compounds, which are formed during reactions of simple forms of carbon with mineral compounds catalyzed by iron sulfide species. Prebiotic chemistry became a major field in chemical sciences much later, with the seminal work of Stanley Miller (1930–2007) in 1953.[9] Wöhler's and Kolbe's results gave the real start to biological chemistry, and from then on, generations of chemists have achieved the identification and synthesis of natural compounds of increasing complexity. The final demonstration of the unity of the organic and mineral worlds was provided by M. Berthelot (1827–1907), when he succeeded in generating acetylene when carbon black and hydrogen were submitted to an electric arc: "One can establish, in contrast to long-standing opinions, that the chemical effects of life are due to ordinary chemical forces".[10] During that thriving period, reductionism was not the privilege of chemists. The cellular theory, which states that a living organism can be resolved in a collection of cells to which the unique properties of life have to be assigned and was generalized by the German physiologist Schwann (1810–1882) and botanist Schleiden (1804–1881), also strongly contributed to the decline of vitalist theories.

Quite surprisingly, the Frenchman Louis Pasteur (1822–1895) revived the vitalistic point of view at the end of the 19th century through his discoveries of the molecular dissymmetry[11] and fermentation.[12] For him, these two fascinating properties were intimately dependent on the living nature of an organism and could only be explained by an unknown vital force that specifically introduces them into living systems. The situation is thus highly paradoxical, and can be translated into passionate controversies: on one hand the analysis of chemical reactions excludes any peculiarity of the chemistry of life, and on the other hand unique crystallographic and microbiological properties can arise from living organisms.

The victory of reductionism over vitalism was obtained during the 20th century and resulted from two major discoveries that were milestones in the advent of biological chemistry. The first milestone is the discovery of the enzymes that provide the explanation for molecular dissymmetry and for fermentation, and more generally opened the way to the chemistry of transformed living matter. The second milestone is the determination of the structure of DNA, which later revealed the mechanisms of cell replication and heredity, thus opening the way to the chemistry of the informed living matter.

The revolution started with studies by the German chemist Eduard Buchner (1860–1917), who was awarded the Nobel Prize in 1907. Buchner discovered that filtrated yeast extracts, which were devoid of living cells, were still able to convert glucose into alcohol and carbon dioxide, thus disqualifying the vitalistic theory of fermentation.[13,14] These results thus demonstrated for the first time that living organisms contain very special molecules, since named enzymes, which provide them with a tremendous power of chemical transformation of matter in general. These enzymes explain the fantastic rates of cellular reactions and their exquisite (stereo)selectivities, they determine the shape, the

function, and the fate of cells and organisms, and thus enzyme catalysis is one of the keys of life. With the emerging dogma "one reaction–one enzyme" a huge research field arose for the chemist who became an enzymologist/biochemist and not only continued to isolate and characterize natural molecules but also started to understand the mechanisms by which they are transported, synthesized, and transformed by proteins and enzymes.

The second discovery is that of the structure of DNA by Crick and Watson in 1953.[15] Their model beautifully explains at the molecular level how cellular DNA can be replicated, thus allowing a cell to generate two daughter cells that contain the same genetic content. This discovery is a remarkable illustration of the power of the reductionist process which, in this particular case, started with the isolation of the biological molecule in pure form (by Miescher in 1869) and finished with its chemical and structural characterization. In their discovery of the double helix, Crick and Watson not only accounted for the multitude of physical and chemical properties of DNA, but also provided compelling mechanisms for the replication of DNA, its mutability, the expression of its genetic information, and tools to develop tremendous applications from biotechnologies to treatments of genetic diseases.

Many later historical events could have been selected for demonstrating the power of the reductionist approach. However, the famous scientific breakthroughs discussed above are particularly illustrative since they were achieved at a time when the technologies to study a complex living organism were not as developed and powerful as they are today. As a more recent successful illustration of the reductionist approach, the field of therapy is an interesting example. Indeed, whereas gene and cell therapy strategies still require practical validation, thus indicating that the majority of drugs will still be chemicals in the near future, rational drug design, which relys on the molecular characterization of a single biological target and its interactions with small compounds, coupled to high-throughput screening methods, has succeeded in providing bioactive molecules for clinical use, including compounds that act against such complex and multifactorial pathologies as cancer. One of such prototypic molecules is Imatinib, currently marketed by Novartis as Gleevec, which is an inhibitor of tyrosine kinase and has potent anticancer properties.[16] Interestingly, it is the combination of molecular (reductionist) and clinical (integrative by its nature) approaches that later allowed use of Gleevec in broader anticancer clinical applications, for the benefit of an increased number of patients.

Conclusions

The conflict between vitalist and reductionist views of life still exists today. There are indeed various and subtle, political, or unconscious, forms of vitalism. For a major part, vitalism comes from the revitalization of antiscientific religious fundamentalism everywhere in the world, including in developed countries. Fundamentalism is also present in some extreme stands taken by ecological associations who would like us to believe that natural compounds are not chemicals. These ideologies will be better limited if physiologists, biologists, and chemists collaborate even more than they do today, both in education and research.

The discovery that the human genome contains no more than 30 000 genes and the end of the central dogma of biology ("one gene, one protein") indeed seems to support the notion that the complexity of a living organism resides in more than the sum of its molecular components. However this additional property of life is neither a soul, an intelligence, or a vital force, but is a complex organization of molecular matter. The reductionist chemical approach, greatly helped by the fantastic development of experimental technological tools that allow quantitative molecular analysis of supramolecular complexes, metabolic networks, cells, and animals, will continue to play an important role in the novel integrative postgenomic era.

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