Biochemistry : Past History and looking toward the year 2000

Authored by Burachai Sonthayanon, Ph.D.

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(This article was writtten in 1994 while I worked at the ...)
Department of Biochemistry, Faculty of Science, Mahidol University, Rama VI Rd., Bangkok 10400, Thailand.

This article was written in Aug 1994, originally entitled "**Biochemistry in the information age : Past, Present and beyond the year 2000**", published in the Book commemorating the 30th anniversary of the Biochemistry Department, Faculty of Science, Mahidol University, Bangok, Thailand. The department was the first Biochemistry Department established in Thailand. A minor editing was conducted in November 1998 by the author.

Introduction

On the auspice of the 30th anniversary (1994) of our biochemistry department, it is noteworthy that our local area network (LAN) of computers is finally set up in our department, as well as in 12 other departments in the Faculty of Science, Mahidol University. Just a year ago (1993), our staffs and students still had to either walk to use computer facilities at the Mahidol University Computing Center (MUCC) or use a MODEM to connect a local microcomputer via low speed telephone line to a MUCC server and the Internet. Now that is no longer necessary, with direct and faster physical linking among 14 LANs in the Faculty of Science and the ones in MUCC, one can use a microcomputer in a lab or an office to communicate instantly with other staffs in the department, in the University, even abroad. Various information, data, news, bibliographical lists, library catalogs, as well as computing power of various computers around the world are also now available at just our finger tips. This means that Biochemistry in Thailand has eventually come to the information age. Thus, it is interesting for us to take a brief look at the impact of new technology, especially information technology, on the present status of the discipline. It is, however, worthwhile as well to reconsider the past history of Biochemistry before to discuss the present and later to project on its near future.

Biochemistry was developed with technology.

Biochemistry is a discipline with long history. Its development could be traced back as far as the year 1772 in which the 'chemical revolution' started in Europe after Lavoirsier studied on combustion and Priestley discovered the presence of Oxygen in the air, as well as recognized its importance in respiration of living organisms. To the Thais ' mind, that given year corresponded to the reign of King Taksin the Great of Thonburi era. (Now Thonburi city is a part of the Bangkok Metropolis, on the right (western) side of the Chao Phara River.) Right after studies on gas and combustion in the eighteen century, various chemical concepts have developed : moles, stoichiometry, atomic theory, to name some. With clearer concept of chemistry, together with some knowledge from the age of alchemy, chemical analysis have developed, and followed by organic chemistry and physiological chemistry. As early as 1784, over 200 years ago, Scheele discovered citric acid in lemon juice.

From the year 1800's onward, the research period was called the organic chemistry era, with many studies on various organic substances. Structures of the first amino acid was unraveled in 1820. Also as early as 1822, Alkaptonuria was found as a metabolic disease. Urea was the first organic compound to be synthesized in vitro entirely from inorganic components by Wohler in Germany in 1828. This provided the concept to scientists at the time that organic compounds in living organisms could be derived from inorganic compounds as well as from organic compounds. In 1836, preparation of some fractionated enzymes, e.g. diastase, pepsin, emulsin, from animal and plant samples were already reported. Three years later, Schwann proposed the theory of the cells and explained a number of his ideas about physiological and biochemical aspects of cells which he called 'metabolic phenomena'.

The era of research called physiological chemistry could be seen from 1840-1880. In 1872, Hoppe-Seyler created a first journal in the field of Physiological Chemistry, Zeitschrift fur physiolociasche Chemie. Later, he was the person who coined the word "Biochemie" to describe the subject which "covers all molecular approaches to biology". After 1894, when Buchner brother discovered cell-free fermentation from lysate of yeast cells, the era of enzymology developed. In 1930, Svedberg was the first person who used a newly invented ultracentrifugation to study hemoglobin. Shortly after, ultracentrifugation and electrophoresis became two standard criteria to assess a protein 's purity. During the course of World war II, a number of key metabolic intermediates in glycolysis, TCA and Urea cycles were identified and relevant enzymes studied. After the development and use of atomic weapon at the end of the war in 1948, various isotopes were available for use as biochemical tracers. Meanwhile, progress in bacterial and bacteriophage genetics led to another significant biochemical concept : that DNA, not protein, is a genetic material.

With availability of computer and X-ray crystallographic data, Watson and Crick postulated on double helix structure of DNA in 1953 which, about 20 years later, Molecular Biology based on. Many of enzymes involved in the synthesis of DNA, RNA, and protein have been extensively studied onward. In 1970, the first restriction enzyme was isolated. Two years later, the first recombinant DNA molecules were constructed and cloned into E.coli. In 1977, DNA sequencing methods were available to determine nucleotide sequence of genes which led to a discovery of split genes (exons & introns) in eukaryotes. In 1978, a human hormone, somatostatin, was produced by recombinant DNA technology for the first time. In 1981, Sickle cell anemia became the first genetic disease to become diagnosed prenatally by Southern blot hybridization. In 1982, genetically engineered mice, or supermice was constructed, then followed by a transgenic tobacco. The first human cancer gene was also cloned and studied in that year. In 1983, the complete genome of lambda bacteriophage of 48,502 bp was sequenced. As recent as 1985, polymerase chain reaction (PCR) was invented and found giving the most impact to Molecular Biology and Biochemistry due to its wide applications. It can be clearly seen from this summary of biochemical history that the field has developed significantly from its small origin. The current progress attained today is based mainly on enormous data gathering in different model systems, synthesis of ideas, progress in related disciplines, and available of instrumentation as well as new technology.

Indeed, technological development has played a major role in the development of Biochemistry. Weren't it because of the development of chemistry, organic chemistry, analytical chemistry, instrumentation, the discipline would not have been thriving like this today. Without the extensive knowledge of organic analysis, structural determination of cellular metabolites would not be possible and earlier biochemists would not be able to trace conversions of one chemical compound in a cell to another. Without the introduction of isotopes, it would be impossible to trace the fate of various atoms along the webs of complex metabolic pathways. Without the development of high speed centrifuges and ultracentrifuges, people would not be able to fractionate cellular organelles and various macromolecules. Without computers, X-ray crystal data of proteins, nucleic acids, and their complexes, would not be solvable by hand. Nor does string sequences of DNA would be easily amenable for scrutiny by bare human eyes and brains.

What is a general status of biochemistry today (1994) ?

The presence of Biochemistry in various life-science disciplines has made this subject one of the most important fundamental subjects. Biochemistry today has out grown into other disciplines, and it is still growing and branching. It has played important integral role in development of various life-science disciplines such as Microbiology, Genetics, Molecular Biology, Molecular Genetics, etc. Molecular systematics and molecular evolutions are just few examples of new disciplines arisen which make use of enormous biochemical data available (notably protein and nucleotide sequences). With newly described quantitative procedures, together with numerous computer softwares available, biological and paleontological questions could now be addressed using the live 'molecular fossils'.

Molecular Biology has become a major subject in the discipline of Biochemistry. Availability of cloning technology allow ones to study genes whose products were expressed at very low level inside some specific cells or tissues and thus otherwise nearly impossible with conventional biochemical isolation and purification. Cloning of such genes in another simpler organism (such as E.coli, yeasts) using highly-expressed vectors allow ones to prepare their desired proteins in sufficiently large amount, usually for enzymological characterizations and biophysical studies. Site-directed mutagenesis also becomes a useful way to generate a number of well-defined mutant proteins thus allow biochemists to study protein function in relation to the protein structure in a systematic way. Genetic Engineering techniques also allow gene transfer and construction of transgenic organisms. This approach is now a very useful approach in the study of genes of unknown function such as creation of knock-out mice. Nucleotide sequence determination and computer comparison has become a standard procedure in characterizing gene functions, based on information already available from related genes in other (heterologous) organisms. Prediction on the presence of exons, introns, regulatory elements, can now be conducted with a degree of accuracy. The new mode of biological study, namely the study of a gene sequence first, analyse mode of gene expression next, then identify possible functions and eventually isolate the respective protein last , is now commonly conducted and widely known as the reversed genetics' approach. This is in opposite to the traditional study approach in classical genetics which starts from phenotypes, proteins, and lastly the genes.

Biochemical applications are now so numerous and can be witnessed in various fields, ranging from medicine, biotech and pharaceutical industry, and agriculture. Its potential applications will undoubtedly grow in the near future, but perhaps with more commercial refinements. Many industrial enzymes in use today, for example, amylases, may be replaced by genetically improved enzymes in the next few years. Crops in the fields may be soon mainly transgenic by next decade : with the number of transgenes grow steadily. (Barring the opposition by consummers, of course.) Number of cases of human with transgenes,now over a hundred cases (in 1994 as reported by TIME), will continue to muliply.

What are impacts of computer and information technology on biochemistry ?

Computer has played increasingly important role in Biochemical research for the past five decades. Nowadays, computers can be found in almost every laboratory and office of researchers. Its importance to biochemical research work may now be well comparable to that of a pH meter or an electronic balance. Apart from word-processing, statistical analysis and hypothesis testing are among the common computer applications in a laboratory. This kind of jobs can be analysed by various application softwares, ranging from less expensive spreadsheet programs to specialized and expensive statistical programs. Researchers studying enzyme kinetics, for example, can use any programs of those catagory to fit their results with curves or lines. Meanwhile, Biochemists interested in fluxes of metabolites in biochemical pathways may find computer simulations highly informative. This kind of work, in fact, can be modeled by a simple spreadsheet program, although it is done better by custom-written programs. Some Biochemists working on 2 dimensional gel electrophoresis or Molecular Biologists working with retriction patterns or DNA sequence ladders of many DNA clones may be quite familiar with a more sophisticated computer (workstation) with image processing facility for their works. However, all Molecular Biologists now can not work without networked computers : they are always needed to analyze their nucleotide and protein sequence data. This last type of application will eventually require more powerful computers (server) in the near future due to the exponentially increasing volume of DNA and protein sequence data, especially those from the human genome project expected to around by 2003. Protein chemists may find that inspecting a 3 dimensional structure of a protein-ligand complex very important for their understanding of protein structure and function. Pharmacologists alike would find that molecular modeling study of interactions between drugs and proteins would also facilitate molecular design of new drugs targeting new gene products.

Microprocessor technology born with computers also for some time have turned up in various new laboratory equipments, which oftenly allow more precise measurement and some are suitable for micro-scale analytical work. Those new equipments are inevitable in the modern day 's science which requires higher and higher standard of analytical precision. In addition, new scientific equipment are increasingly more dependent on computer controls. In many cases, result of an automatic analysis controlled by such an equipment could be ported directly into another computer sitting nearby for online data collection and analysis. Modern machines are now mainly seen sitting together with a PC and all the controls are often solely through the computer graphic-based softwares. More automation and microscaling will likely come to more general biochemical instrumentations in the near future.

Starting just few years ago, another important scientific use of computer is now in telecommunication, data and information retrieval as well as execution of programs in remote host computers. Today, with thousands of scientific literature coming out daily, computer is also needed for a scientist to keep abreast of new publications of their interest. Databases are now widely accessible for data download. A number of bibliographical softwares also play a significant role in indexing and editing the information. Many of the data and information are quite accessible through Internet.

Internet has proven to be crucial for the development of every scientific discipline, including Biochemistry. The Net, with a current (1994) estimated Worldwide users of around 25 millions, is the source of all information available to mankind. A number of automatic servers have been put into service by various institutions which provide computer access to international scholastic users. Most of the time the service is free of charge although there are some cases where there are some service charge but the cost charged are quite minimal. Examples of databanks which are of our interest include GenBank, Protein databank, etc. Users can send an E-mail with keywords to retrieve relevant information or DNA and amino acid sequences from such databases. Some servers also have powerful computers liked to it for automatic execution of some installed programs. A well known example is 'blast' servers at NCBI,NIH which allow users to submit a sequence (protein or nucleic acids) to compare against various databases. Results of the comparison would normally be automatically E-mailed to sender in just few minutes after a querry mail was sent. A lot of computer programs, documents, or other files are also widely avaialble online for file transfer from hundred of thousand servers linking throughout the Internet. More interesting and useful features of the Internet are still much more. Unfortunately, it is beyond the scope of this article to describe the benefits of Internet in details.

The presence of the Internet also allow rapid communication via E-mail among research scientists and scholars. With just few keystrokes, answers to E-mails are quite convenient, cheap, and fast. Collaborating workers now find FAX machines a little obsolete since they could communicate via E-mails almost free and exchange their edited manuscripts conveniently. Also, the documents would be ready for word processing immediately, which is usually not the case for fax-trasmitted documents. Scientists or scholars can send E-mails to consult experts they might not personally know for some quick comments. On the other hand, with several thousand discussion forums on various topics available (called USENET newsgroups), one can post a relevant question to the public and some comments or advises ususally come in a matter of days. E-mail also open another mode of scientific communication, electronic journals. Current content lists have been avialable in a USENET newsgroup. Some scientific Journals have already offered electronic version of the journals via E-mail for previews by their subscribers, which usually means few months ahead of the arrival of the journals via postal service. Thus, for 'Netters', the slower postal service is referred to by the slang 'snail mail'. Some important (hot) scientific papers, plus pictures, have been put in computers for remote retrieval through the Internet by FTP (file transfer protocol).

WWW is a new emerging computer interface competing with e-mail. Using a browser program, one can look up information pages from hundred thousands of computer across the networks. Now even main frame computers start to have software interface in the www format.

Biochemistry has become integral part of many subjects. Biochemical basis has been and will remain foundation of biotechnology. On the other hand, information technology will be a key factor which sustain the growth of the subject as well as all other scientific disciplines. Internet will play an even more important role in the development of all scientific disciplines, Biochemistry included, for years to come.

What Biochemists should look up to the year 2000 ?

As indicated above, one definite situation Biochemists will soon face is more widespread use of computers in instrumental analysis as well as in data analysis. Computers will also serve as the most necessary communication tool for each lab, in order to keep close collaboration with distant laboratories having mutual interest in a research area. Biochemists, as well as other life-scientists, now have to be computer-literate. Aquaintance with computers will also speed up their office works. Scientists now start to face a faster throughput of scientific literature publihed due to faster mode of electronic communication. The pace may then be quicken in the near future. This means ones have to work faster in order to be competitive in their fields. For instrumentation and tool kits, new superiors ones will surely be developed to give more luxury (i.e. fast, accurate or sensitive, and simple to use) to researchers, although not necessarily at a cheper price. They will be necessary in order to keep productivity in the lab up to the international level. This translates into higher budget requirements for such lab equipments and tools. However, in my opinion, the main concern for

Biochemists in a developing country in the next few years is probably not the research budget, but the man-power. With hundreds of research fields which are highly competitive around the World like this how could we compete with the World, esp. the large pharmaceutical and biotechnology companies. For us in a developing country, one of the most challenging questions we should thus ask ourselves now is, 'What can we do to build new teams of new generation of Biochemists to conduct competitive research work in academic institutions in the next decade ?'