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Contribution of Clinical Biochemistry to Structural Bioinformatics

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Abstract

Bioinformatics plays an important role in the study of human diseases with genomic data for drug development and gene therapy. Its applicative arm is clinical biochemistry that focuses on the methodology and interpretation of chemical tests performed to support diagnosis and treatment. Clinical biochemistry is one of the most important parts of laboratory diagnostics tests together with laboratory hematology, immunology, clinical serology and microbiology, clinical toxicology. It possesses the largest number of diagnostic tests that help to understand pathogenesis and etiology of different pathological processes. Clinical biochemistry is based on bioinformatics applications that have been used for tumor marker measurements, stem cell tests, gene expression, and DNA damage repair. Bioinformatics field can be derived from biochemistry. It means that biochemistry has emerged from bioinformatics applications. It is not an overstatement to say that bioinformatics is what biochemistry is evolving to become a distinct guide for quality control. This paper focuses on the point of contemporary clinical biochemistry that tends to support bioinformatics researchers. Integration between biochemistry and bioinformatics would lead to an increase in healthcare performance is thus of increasing importance in future research.

Keywords: Clinical Biochemistry, Bioinformatics, Laboratory Tests, Genomic Data.

1. Introduction

Since the middle of the 20th century, bioinformatics was suggested to be applied for clinical toxicology [1] and cancer [2]. One of the early studies on expressed sequence tags in human stem cells by bioinformatics was performed in 1998 [3], where near 10000 sequences were analyzed. At the beginning of the 21st century, gene expression profiles in 60 human cancer cell lines used in a drug discovery screen were evaluated by cDNA microarrays and corrected with drug activity patterns by combining bioinformatics and chemoinformatics [4]. Clinical bioinformatics was initially proposed to provide biological and medical information for individualized healthcare, enable researchers to search online biological databases and used

bioinformatics in medical practice. It also used to select appropriate software to analysis the genomic data for medical decision-making, optimize the development of disease-specific biomarkers, and supervise drug target identification and clinical validation [5].

While the beginnings of chemistry date to the 17th and 18th centuries, biochemistry emerged in the early 19th century. Clinical biochemistry evolved and consolidated in the 1940s as an autonomous field [6]. Medical biochemistry [7] regarded as biochemistry applied to human organism in health and disease. Molecular biology was commonly regarded as part of biochemistry. Clinical biochemistry was an important applied sub-discipline of medical biochemistry, also known under the names of clinical chemistry, pathological biochemistry or chemical pathology as in Fig. 1. Clinical biochemistry [8] was concerned with methodology and interpretation of biochemical tests performed on body fluids and tissues, to support diagnosis, treatment and monitoring of disease. As a discipline, clinical biochemistry included two main components: methodological and interpretative. The early textbooks were strongly focused on methodology, whereas the majority of contemporary ones emphasize interpretative aspects and bioinformatics correlations, reflecting the close professional relationship between clinical chemists and bioinformaticians.

Clinical biochemistry was a clinical and diagnostics subject, which aims to improve and use standard diagnostic methods, to monitor the disease development and treatment by biochemical methods [9]. Information from biochemical methods used to evaluate the development of pathological process on molecular, cellular and organ level. It was essential for early diagnosis of a disease and assessment of its therapy efficacy. Clinical biochemistry [10] was evolved rapidly during the last ten years; more than a hundred of new analytical methods have appeared including DNA diagnostics, determination of tumor markers, and apoptosis tests. Biochemical tests were of great importance in the diagnosis of endocrine, gastrointestinal, heart and renal diseases as well as in toxicology. Hence, clinical biochemistry closely linked to such theoretical subjects as general and bioorganic chemistry, biochemistry, histology, pathological physiology, pathological anatomy, and bioinformatics. Bioinformatics algorithms combined the advances in biochemistry and molecular biology with the power of computer-based information technology.

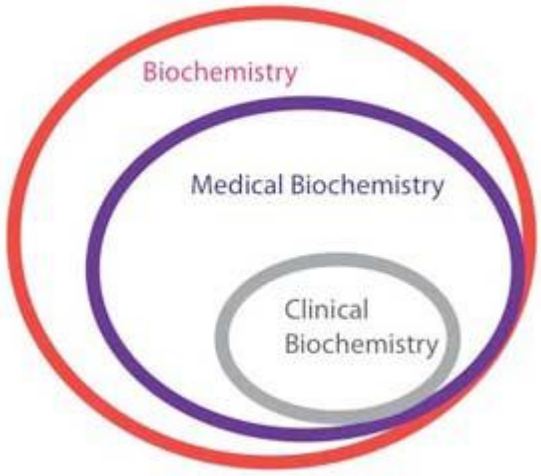

Figure 1. Overlapping between biochemistry, medical biochemistry, and clinical biochemistry

To facilitate the task of learning interesting properties of genomic data, we turn to biochemistry and bioinformatics together, as one field that will take big strides over the next years. Recent advances have made it possible to combine between two sciences like

bioinformatics and biochemistry to understand the genomic analysis. This combination field is one of the life keys of the new century and demand for researchers in this field is strong and growing in the advanced countries.

2. Integrative Aspects of Clinical Biochemistry

Clinical biochemistry [11] was on the development of methodologies appropriate for measurement of various analyses in a large number of patient samples, the ways of obtaining biological material, the establishment of normal ranges (reference values), and the principles of quality control in clinical laboratories. At that time, the range of the offered diagnostic tests included glucose, non-protein nitrogen to assess the renal function, amino-acid nitrogen to gauge the nutritional status, plasma and urinary proteins, lipids, enzymes, electrolytes (including calcium, magnesium, and phosphorus), and parameters of acid-base balance. Importantly, for practical purposes, tests within this spectrum were grouped into the 'test profiles' that reflect the function of a specific organ such as a particular tissue or muscle. Organ and tissue profiles were established for liver, pancreas, bone, muscle, heart and kidney. There was an increasing understanding of the concept of biological variability, which is one of the most important contributions of clinical biochemistry to medicine. The investigation of inborn errors of metabolism expanded, toxicology and drug monitoring became an important part of the clinical laboratory repertoire. There is also the fast expansion of molecular diagnostics such as the diagnosis of hematological neoplasms, and pharmacogenetics. In recent years, substantial progress has been achieved in genetic applications based on biochemistry tests.

One of the most difficult and central topics in biochemistry is how to best infer systemic properties of cells and organisms from data, model them, and take them into account in data analysis. It has been widely appreciated that most of the earlier biological research has focused on studying only parts of the systems, and understanding how the parts interact will be the next big challenge. The field studying the integration of the parts, and more generally systemic properties of cells and ultimately organisms, has been coined systems biology. Hence, this field needs high-performance computing for statistical modeling, visualization and data mining to provide a suitable ground for bioinformatics applications along with biochemistry demands.

It is often unsuitable to solve biochemistry topics by conventional laboratory tests only due to their enormous amount of computation time and may provide incorrect results. Laboratory errors are classified into random errors and systematic errors. Random errors indicate poor precision while systematic errors indicate poor accuracy. A few examples of random errors are pipetting error, transcription error, wrong sample numbering and labeling, and fluctuating readings on the colorimeter. Systematic errors could occur due to the wrong procedure, incorrect standard, and calibration procedure. Hence, we need other procedures to check on biochemistry results to avoid the laboratory errors. Recently, many chemical laboratories must be equipped with computer clusters and compute farms, and implemented bioinformatics algorithms to pose new challenges for modeling methods and to apply machine learning [12] for visualizing interaction graphs, that applicable in systems-biological analyses of cellular interaction networks.

Many biomedical problems (e.g., microarray gene expression data analysis, image based pattern recognition, genetic and biochemical network analysis, protein -protein interactions, phylogenetic reconstruction, genetic linkage analysis, protein structure prediction, etc.) require more computational challenges on large-scale datasets [13,14]. Therefore, applications of bioinformatics range from clustering of DNA sequences and genes [15], gene regulatory networks, metabolic pathways and data storage. Particularly, the contribution of clinical chemistry to bioinformatics plays a critical role in all genomic processes, which leads to a diagnosis, treatment of an entire range of clinical disorders and the progress in understanding and treatment of genomic data.

In parallel to the expansion of evidence–based medicine, clinical biochemists started to examine systematically the existing evidence for the benefit of bioinformatics, under the banner of evidence-based clinical biochemistry. In other words, efficient bioinformatics algorithms used to analyze and interpret the clinical biochemistry results, in order to guide the physicians to make a right decision for the patient. If bioinformatics is the study of the flow of information in biological sciences, clinical biochemistry is the study of the information in patient care. Fig.2 show the relation between bioinformatics and clinical biochemistry.

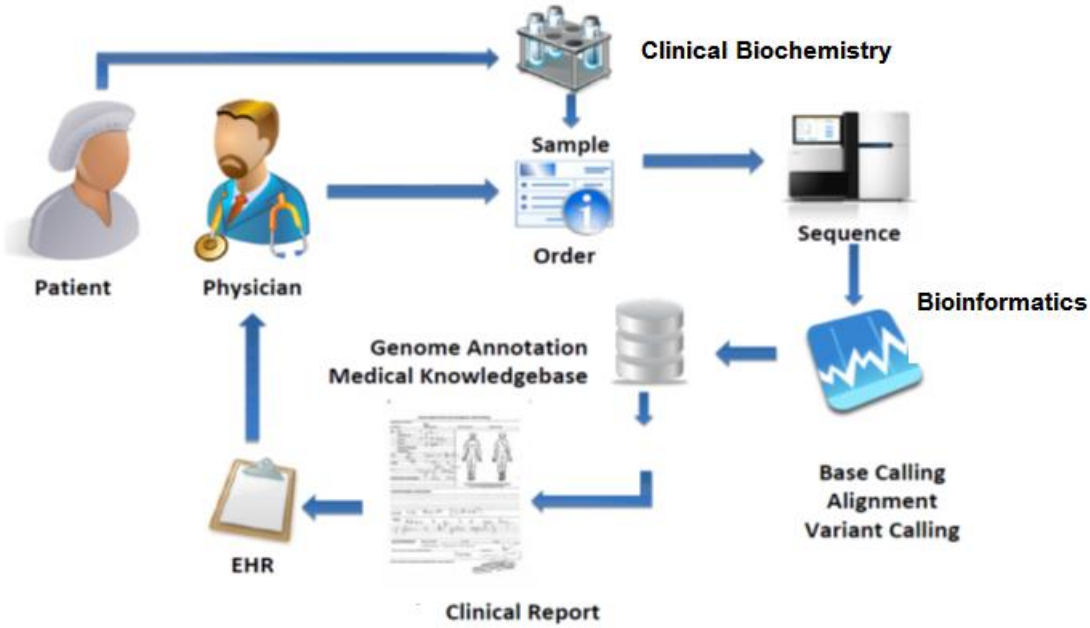

Figure 2. The overview of the cycle of events taking place in a hospital, starting from the physician examining the patient and back to the physician

In general, Science creates new knowledge in a particular way, by employing the scientific method based on experimental verification of hypotheses and rigorous validation of results by peer groups. As bioinformatics is generated [16], new disciplines emerge in science e.g. clinical biochemistry to confirm the importance of bioinformatics and to enhance the accuracy of the bioinformatics results. Therefore, bioinformatics needs to support its further development, to allow validation of specialist knowledge, and to maintain continuity through teaching and research training that based on clinical biochemistry. Clinical biochemistry usually emerges from the convergent experimental results of several bioinformatics researchers. Clinical biochemistry also needs to be disseminated to other disciplines, to develop interdisciplinary research, and to the wider public, to secure political support and funding. This may lead to merging or withering of disciplines, and to the appearance of new applications that help for attribution of scientific discoveries. This happened for both in the case of bioinformatics and clinical biochemistry.

3. Importance of Clinical Biochemistry Laboratory Tests in Bioinformatics Research

Clinical Biochemistry is one of the most rapidly advancing areas of laboratory and clinical medicine. The marked increase in the number and availability of laboratory diagnostic procedures has helped in the solution of clinical problems. Individual laboratory tests are rarely ordered and reported singly; usually combinations of lab tests are used. The physician should be judicious in selecting the tests that really give a clue to the

diagnosis of a disease. Some biochemical investigations that share with bioinformatics researchers are done for most patients e.g. genetic testing, and drug design [17]. A trend is also emerging to conduct certain investigations, which could reveal a predisposition to specific disease processes in healthy individuals [18]. The physician can then suggest preventive measures to the person e.g. test of tumor markers that have family disease history. More than 1,000 genetic tests [19] are currently in use, and more are being developed. Several methods can be used for genetic testing such as:

- Molecular genetic tests (or gene tests) study single gene or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.
- Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.
- Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Genomic changes [20] associated with specific disorders may give rise to a change in the biochemical profile of a particular body fluid. Hence, specific parameters are looked for in a specific body fluid when a disease is suspected. From a clinical point of view, one purpose of performing a test could be corroborating a particular diagnosis or ruling it out. Other tests may be done to assess the severity of a disease process or monitor its progress. Still, others may evaluate or monitor the effectiveness or potential side effects of a particular therapeutic regimen, and certain tests can give a clue about the prognosis or probable outcome of a disease.

To fulfill results accurately, the data generated has to be reliable for which strict quality control (QC) has to be maintained. QC is defined as the procedures used to improve the analytical method. Reliability of the selected method is determined by its accuracy, precision, specificity and sensitivity; with the major emphasis of QC being laid on monitoring the precision and accuracy of the performance of analytical methods [21]. The significant improvement in the quality of laboratory tests in recent years is due the combination of well-designed automated instrumentation with good analytical methods and effective quality assurance programs.

Bioinformatics is a heavy field in programming including database management, statistics, probability, and mathematical modeling [22] that based on a strong understanding of genetics, genomics, and molecular biology [23]. There are some common points between clinical biochemistry and bioinformatics such as:

- Perform sophisticated computational analysis of DNA, RNA and protein sequences, and structures.
- Clone, PCR amplify, analyze sequence DNA molecules.
- Study gene expression at the level of RNA and protein.
- Analyze protein structure and function.
- Culture and study bacteria, viruses and eukaryotic cells.
- Evaluate Immune system function.

The progress in automated DNA sequencing [24], sequencing of the human genome [25], refinements in mass spectrometry, and improvement in polymerase chain reaction technology has revolutionized the bioinformatics and genetic tests of clinical biochemistry. This has been evident from the work from pioneer institutions and diagnostic laboratories that are provided many tests or able to integrate these tests along with other tests as a bioinformatics service in concert with biochemistry components of central laboratory diagnostic services.

Some advanced researchers proposed to refer to the importance the studying of bioinformatics and biochemistry together. Kloetgen et al. [26] presented the experimental and computational methods for generation and analysis of CLIP data by biochemical and bioinformatics methods. Song et al. [27] suggested that human POLD1 played an important biological role in cell cycle regulation and DNA damage repair. L.L. Chan and P. Jiang [28] discussed bioinformatics analysis as well as clinical applications of the newly developed massively parallel bisulfite

sequencing of cell-free DNA. Further advances in biochemistry that combined with computational bioinformatics, especially in experimental genomics, are predicted to revolutionize the future of healthcare. Tao Wang and Guanghua Xiao [29] discussed the genome-wide CLIP technology from the perspectives of experimental design and bioinformatics analysis. Mak et al. [30] produced free database from extracted data on interactions between transport and metabolism related proteins and chemical compounds. This created data can be used in biochemistry, pharmacology, and bioinformatics.

4. Cancer Diagnosis in Biochemistry and Bioinformatics Research

We introduced an example to used biochemistry and bioinformatics tests for cancer diagnosis. If it's suspected that patients have cancer, physician may order certain cancer blood tests or other laboratory tests, such as an analysis of urine or a biopsy of a suspicious area, to help guide the diagnosis. Samples collected for cancer blood tests are analyzed in a lab for signs of cancer. The samples may show cancer cells, proteins or other substances made by cancer. Examples of biochemistry tests for diagnosing cancer are complete blood count (CBC), blood protein testing, tumor marker tests, and circulating tumor cell tests. Tests that measure the number of cancer cells in a sample of blood (circulating tumors cells) or examine the DNA of such cells are of great interest in cancer medicine because research suggests that levels of these cells might be useful for evaluating response to treatment and detecting cancer recurrence. However, such tests are still being studied in clinical trials and are not routinely used in clinical practice. Tests that determine the sequences of a large number of genes at one time using next generation DNA sequencing methods are being developed to provide gene mutation profiles of solid tumors (e.g., lung cancer).

Therefore, it is a need to share bioinformatics research in biochemistry tests. As a view of bioinformatics, cancer bioinformatics [31] is one of multiple ways to concentrate bioinformatics methods in cancer, according to the specificity of disease metabolisms, signaling, communication, and proliferations. Clinical bioinformatics, an emerging science combining clinical informatics, bioinformatics, information technology, and mathematics together can be considered to be one of critical elements addressing clinical relevant challenges in early diagnosis, efficient therapies, and predictive prognosis of patients with cancer. Many bioinformatics tools used for clustering, classification, prediction and evolutionary biology tree of cancer datasets to improve the life quality of patients with cancer.

The contribution of clinical biochemistry for bioinformatics science [32] is through the use of biomarkers for diagnosis and disease monitoring. We found that challenge is to validate the bioinformatics results in clinical biochemistry. It will assist to develop some topics such as principles of epigenetics, human genome project, genetic variability, pharmacogenetics, and genetic differences in drug targets and transporters.

Finally, bioinformatics tends to describe data analysis, and biochemistry tends to describe the chemistry of the molecules found in living cells. But these two terms are used interchangeably and compatible with each other. For example; a biochemist elucidated the structure and function of the insulin molecule but bioinformaticians figured out how to get yeast or bacterial cells to produce human insulin through genetic analysis and figured out how to grow those cells and purify the insulin. The subject matter of bioinformatics has existed as long as there has been clinical biochemistry, but overlapping between them has emerged the common principles that apply unique features.

5. Conclusion

Laboratory tests play a central function in the evaluation of bioinformatics. This has been driven in part by the recognition of bioinformatics associated with clinical biochemistry. The challenges of analyzing genomic data by using biochemistry and bioinformatics methods together, where improvements are needed. This improvement highlights the need of laboratory quality for

providing patient care without any conflicts and raising the issues of overlapping tests related to bioinformatics and clinical biochemistry. As a result, bioinformatics has not only provided greater depth to genomic investigations but added the dimension of breadth in clinical biochemistry as well. In this way, we are able to examine biochemistry results and compare them with those that are related to computational bioinformatics in order to cover common principles that apply across many systems and highlight unusual features that are unique to some. We would expect that the integration between biochemistry and bioinformatics would lead to an increase in healthcare performance is thus of increasing importance in future research.

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