

Bioinformatics Lab and Diabetes Mellitus: A Review

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ABSTRACT

This Diabetes is a metabolic disorder that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. It is classified into two basic forms Type I and Type II diabetes. Bioinformatics Laboratory comprises of various techniques like sequence similarity, structural analysis, molecular Docking, optimization technique certain advanced algorithms. Computer-assisted drug design approach has contributed to the successful discovery of several novel antidiabetic agents. Molecular Docking continues to be a great promise in the field of computer based drug design. Several simulation models have been proposed to study the physiology and pathophysiology of diabetes. Biological databases and Atlas plays an important role in getting up-to-date global report on diabetes. Like so many other areas of medicine, Bioinformatics has had a profound impact on diabetes research.

Keywords: sequence similarity, Molecular Docking, Diabetes Mellitus, optimization technique, Biological databases.

I. INTRODUCTION

Science of Bioinformatics an interdisciplinary research area, deals with computer science and information technology applied to biology and medicine. It deals with algorithms, databases, artificial intelligence and soft computing, information and computation theory, data mining, image processing, modeling and simulation etc. Biological databases are an important tool in assisting scientists to understand biological phenomena from the structure of macromolecules and their interaction. This knowledge also helps to understand the pathophysiologic aspects against myriad diseases including Diabetes Mellitus. Modelling and Simulation helps in developing a level of understanding of the interaction of the parts of a system, and of the system as a whole. Thus Computer modelling and simulation techniques playing an increasingly central role in medical field. Major research efforts in Bio-informatics include sequence alignment, gene finding, drug design, drugs discovery, protein structure alignment, simulation methods etc. The ultimate goal of the field is to enable the

discovery of new biological insights.

Diabetes Mellitus

Diabetes is a metabolic disorder that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Classic signs and symptoms of diabetes include polyuria, polydipsia, polyphagia, unexplained weight loss; can also be asymptomatic, headache, palpitations, and blurred vision (10). It is classified into two basic forms Type I and Type II diabetes. The main risk factors for diabetes are age, family history, obesity, physical inactivity and sedentary living, insulin resistance, stress etc. Complications of Diabetes mellitus like neuropathy, nephropathy, and retinopathy may develop in prediabetic, diabetic stage of the disease, or many years after the onset of diabetes. Diabetes mellitus is diagnosed when either HbA1c > 6.5, fasting glc > 126 mg/dl, or glc 2 h after OGTT > 200 mg/dl or single random glc > 200 mg/dl. Nearly 45% of all diabetics have peripheral vascular disease may develop Macro and / or Microvascular

complications.

Type I Diabetes Mellitus

Type I Diabetes Mellitus (globally 5-10% cases of all diabetic), is believed to involve a combination of genetic and environmental factors. Risk factors include family member with the condition. The underlying condition of DM1 involves an autoimmune destruction with absolute insulin deficiency. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. The untreated diabetes may result in various complications like early onset that includes diabetic ketoacidosis and nonketotic hyperosmolar coma. Long term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes (retinopathy). However, it is most often diagnosed in children or young adults. Type I Diabetes Mellitus can be diagnosed by plasma sugar level and HBA1C levels (1). Type 1 can be distinguished from type 2 diabetes via a C-peptide assay, which measures endogenous insulin production. Rate of β -cell destruction is quite variable in Type I Diabetes, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Nearly 20 different proteins have been identified as targets for T cells in the NOD mouse, and 12 of these are autoantigens in humans (2).

Type II Diabetes Mellitus

Type 2 diabetes is a long term metabolic disorder characterized by insulin resistance and relative insulin deficiency. Type 2 diabetes is common over 40 years of age. It is characterized by hyperglycemia associated with micro, and macrovascular complications. Type 2 diabetes can be managed by physical exercise, dietary modification and oral anti diabetic/ insulin.

Bioinformatic analysis of diabetic neuropathy using functional protein sequence was reported. Sulfonylurea drugs such as glibenclamide have long

been used clinically for type 2 diabetes (21). More recently, nonsulfonylurea drugs, including glinides such as nateglinide and mitiglinide, have become available for clinical use (26). A number of recent Bioinformatics outcomes have been reported on for use with patients with diabetes (5).

Mature Onset Diabetes of the Young (MODY)

It is an autosomal dominant form of diabetes mellitus due to defects in insulin secretion genes; genetically and clinically heterogeneous (25).

Drug Discovery Methods

Drug discovery is an expensive process due to the high research costs and extensive clinical testing. Two major phases are involved in creating a new drug. They are Discovery phase and clinical Testing Phase. Then the step of obtaining regulatory approval to market the drug was performed.

Before computational drug discovery was introduced, drugs were discovered by chance in a trial and-error manner. High-Throughput Screening method helps to quickly conduct millions of chemical, genetic or pharmacological tests in order to identify active compounds, antibodies or genes which modulate a particular biomolecular pathway. But the use of HTS is very expensive. The HTS field continues to be dynamic and very competitive. The methods of HTS are applied to the screening of combinatorial chemistry, genomics, protein, and peptide libraries. A Novel High-Throughput Screening Assay for Putative Antidiabetic Agents through PPAR α Interactions was reported (15).

Animal Studies

Alloxan is a toxic glucose analogue, which selectively destroys insulin-producing cells in the pancreas (that is beta cells) when administered to rodents and many other animal species. Alloxan (2,4,5,6-tetraoxypyrimidine; 2,4,5,6-pyrimidinetrione) is an oxygenated pyrimidine derivative. It causes insulin-

dependent diabetes mellitus (called "Alloxan Diabetes"). Hence alloxan is used to induce diabetes in laboratory animals. Alloxan can be prepared by oxidation of uric acid by nitric acid. Alloxan monohydrate is used to induce Type II Diabetes Mellitus in experimental animals. Alloxan monohydrate is prepared by oxidation of barbituric acid by chromium trioxide. Alloxan monohydrate 150mg/kg body weight was dissolved in normal saline and injected intraperitoneally after 18 hours fasting to induce hyperglycemia in experimental rats (39).

Streptozotocin (STZ) is the most commonly used drug for induction of diabetes in rats (3). This drugs exert their diabetogenic action when they are administered parenterally (intravenously, intraperitoneally or subcutaneously). The dose of these agents required for inducing diabetes depends on the animal species, route of administration and nutritional status (11).

Computational Methods

Computational methods can be used to predict or simulate how a particular compound interacts with a given protein target. Virtual Screening is a general term for computational methods that use computers for quick search of large libraries of chemical structures in order to identify those structures which are most likely to bind to a drug target. Virtual screening is defined in terms of finding new scaffolds rather than many of these hits.

There are two broad categories of screening techniques: ligand-based and structure-based (22). In Ligand based method, Ligand is compared with pharmacophore model to determine that the ligand will bind with it (37). Structure-based virtual screening involves docking of candidate ligands into a protein target followed by applying a scoring function to estimate the likelihood that the ligand will bind to the protein with high affinity (8). The main

advantages of computational methods compared to laboratory experiments are i) Low costs ii) Huge chemical search space iii) Can investigate compounds that is not yet synthesized.

Docking Studies

Molecular docking is used to predict how a drug candidate binds to a protein target without performing a laboratory experiment i.e on simulation based. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex (19). Docking plays an important role in the rational design of drugs (16). There are two approaches within the molecular docking method. One approach uses a matching technique that describes the protein and the ligand as complementary surfaces (24) The second approach simulates the actual docking process in which the ligand-protein pair wise interaction energies are calculated (12).

Molecular docking software consists of two core components i) Search algorithm ii) Score function.

Search algorithm (Optimization algorithm): It is used to find the best conformations of the ligand and protein system.

Score function: This is a function providing a measure of how strongly a given ligand will interact with a particular protein.

Hex is a molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. Hex will run on most Windows-XP, Linux and Mac OS X PCs. it is one of the few docking programs which has built-in graphics to view the results (30). Types of docking program used for determining protein-ligand interaction were listed in Table I.

Table 1. Types of Docking Program

Program	Algorithm	URL
3D-Dock	Global: FFT; rescoring: residue potentials; refinement: mean-field sidechain multicopy	www.bmm.icnet.uk/docking/
HEX	Global: Fourier correlation of spherical harmonics	www.biochem.abdn.ac.uk/hex/
GRAMM	Global: FFT clustering and rescoring decoys also available	reco3.ams.sunysb.edu/gramm/
PPD	Global: geometric hashing; rescoring: multiple filters	ftp://flash62.bioc.columbia.edu/pub/other
DOT	Global: FFT for shape complementarity and approximate Poisson–Boltzmann electrostatics	www.sdsc.edu/CCMS/DOT
BIGGER (Chimera)	Global: bit mapping; rescoring: multiple filters	www.dq.fct.unl.pt/bioin/chemera/
DOCK	Global: grid-based energy function; flexible docking; random search plus incremental construction	www.cmpharm.ucsf.edu/kuntz/dock.html
AutoDock	Grid-based empirical potential flexible docking via Monte Carlo search and incremental construction	www.scripps.edu/pub/olson-web/download.html

(Source: Smith and Sternberg, 2002)

Many researchers are trying to find out correct target for the treatment of diabetes. One of the ways is by molecular docking studies. The targets which was used by many Scientist were **Glycogen phasphorylase**, **Protein Tyrosine Phosphatase 1-Beta(PTP-1B)**, **Dipeptidyl peptidase IV (DPP IV)**, **Glucokinase**, **Peroxisome Proliferator-activated Receptor (PPAR)- γ** etc. **Protein – Ligand** docking studies has been done by many researchers for structural based drug designing for Diabetes mellitus (14). Docking studies of green tea flavonoids were carried out using Auto

Dock 4.0 and Argus lab 4.0.1. Analysis of the results shows that epicatechin can act as a potent insulin receptor activator (13).

Foot ulcers are a very common complication of type I and type II diabetes. Individuals with diabetes have at least a 10-fold greater risk of being hospitalised for soft tissue and bone infections of the foot than the individuals without diabetes (17). A clinico-bioinformative study was conducted for infected foot ulcers in male and female diabetic patients. From the study it was concluded that Male diabetic patients

with MDRGNB-infected foot ulcers have poor glycemic control and hence they might have higher mortality rates compared to their female counterparts. Further Amino acid residues Asn132, Glu166, Pro167, Val172, Lys234 and Thr235 of CTX-M-15 (enzyme) make important contacts with cefotaxime (drug) in the 'enzyme-drug complex', researchers are expected to duly utilize this information for designing more potent and versatile CTX-M-inhibitors (32).

Simulation models

The ability to simulate the glucose-insulin system in normal life conditions can be very useful in diabetes research. Several simulation models have been proposed and proven to be useful in tackling various aspects of normal physiology and pathophysiology of diabetes. The mostly used and also the simplest model is the minimal model of Bergman (6) for type 1 diabetes patients under intensive care. The minimal model is based on an Intravenous Glucose Tolerance Test (IVGTT), where glucose and insulin concentrations in plasma are sampled after an intravenous glucose injection. Recently, a new meal simulation model has been proposed (10). Scope of this is to develop a new simulation model of the glucose-insulin system in the normal human capable of describing the physiological events which occur during a standard mixed meal.

Sequence Alignment

Sequence alignment is a way of arranging the primary sequences of **DNA**, **RNA**, or **protein** to identify regions of similarity that may be a consequence of functional, structural, or evolutionary relationships between the sequences. Pairwise sequence alignment and multiple sequence alignment techniques are often used by researchers in Bio informatics. Using bioinformatics techniques and sequence analyses algorithms, a comparative study between human and rodents revealed similarity in the behavior of genes involved in the control of energy homeostasis. The Study it was inferred that brain-derived neurotrophic

factor (BDNF) controls the actions of several proteins including insulin, leptin, and gherlin and is significant to the pathobiology of type2 diabetes and obesity (28).

Basic Local Alignment Search Tool is the most widely used bioinformatics tool. It is optimized for speed but sacrifices only minimal sensitivity in searching databases. Relationship between altered calcium homeostasis and diabetic cardiomyopathy was found by constructing a Phylogenetic tree using Neighbour-Joining Algorithm in bioinformatics approach (29). Role of several genes/proteins that are believed to be involved in the evolution of obesity associated diabetes by employing multiple sequence alignment using ClustalW tool was studied (by constructing a phylogram tree using functional protein sequences extracted from NCBI) (27). Genomics has become a major source of drug targets, and knowledge on bioinformatics is crucial for finding and validating novel targets so as to minimize investment in laboratory resources.

Databases for Diabetes

Biological databases are an important tool to explain a host of biological phenomena from the structure of biomolecules and their interaction, to the whole metabolism of organisms and to understanding the evolution of species. This knowledge helps facilitate the fight against diseases, and in the development of drug.

DrugBank is a freely available, fully downloadable drug interaction and drug metabolism database. It contains detailed information about 250 of the most frequently prescribed FDA-approved drugs (chemical structure, common and chemical names, 3D structure coordinates, drug/chemical class, solubility, pharmacology, etc.), along with detailed information about their known protein, expected or measured toxicity and known metabolizing enzymes. A user-friendly database of type 2 diabetes genetic association of manually curated information was

constructed (20). This database can be used for research purposes, such as an association and functional study of type 2 diabetes related genes, and to construct a diabetes risk test in the preparation of personalized medicine in the future.

A database named Phyto-Mellitus with information on plants traditionally used for diabetes with their chemical constituents was present (23). The database can be accessed alphabetically using genus name for information on specific plants. From the data, 36% were whole plants, 30% leaves, 13% seeds, 11% roots, and 10% fruits. MEDLINE, the world's largest database of medical abstracts, including thousands of journal articles dealing with diabetes. MEDLINE is a service of the U.S. Government's National Library of Medicine (NLM) in Bethesda, Maryland.

T2D-Db is a database of all molecular factors reported to be involved in the pathogenesis of Type 2 diabetes in human, mouse and rat. It provides information on candidate genes, gene description, genomic loci, aliases, gene and protein sequences and the corresponding literature, gene ontology, homologus/orthologus genes, microarray expression and tissue specific expression analyses, protein-protein interaction information, SNP markers etc. It also caters information on genes candidates for the risk factors/complications reported to be associated with Type 2 diabetes (1).

Atlas on Diabetes

The Diabetes Atlas will be used by the World Diabetes Foundation, the International Diabetes Federation and the World Health Organization to communicate the global impact of diabetes and underline the need for immediate intervention from governments, healthcare professionals, international health organisations and other bodies.

According to the World Health Organisation estimates, India had 32 million diabetic subjects in the

year 2000 and this number would increase to 80 million by the year 2030 (38). The first Edition of Diabetes Atlas was published in 2000. The 5th edition of the IDF Diabetes Atlas was officially released on World Diabetes Day 14 November 2011. The Atlas is the most up-to-date global report on diabetes, covering all aspects of the disease from epidemiology to health economics and education.

Advances in Information Technology

Information Technology now plays an increasingly important role in diabetes healthcare and is continuing to revolutionize day-to-day management for millions of people.

Telemedicine is the use of telecommunication and information technologies in order to provide clinical health care at a distance. The Informatics for Diabetes and Education Telemedicine (IDEATel) Project has been performed by Steven Shea in 2007. It was found that diabetes case management delivered using telemedicine improved hemoglobin, blood pressure and cholesterol levels in older patients with diabetes mellitus at one year of follow-up, compared to usual care. The IDEATel study provides evidence that medical informatics and telemedicine technology can help to translate advances in treatment of chronic diseases into effective health care.

A system that provides real-time individualized medical treatments that are easily accessible using Internet and wireless technology is called as ubiquitous healthcare (u-healthcare) system. The u-healthcare system can potentially provide disease prevention and early treatment, as well as continuous follow-up that are available whenever and wherever they are needed. Appropriate self-care, is essential in diabetes care but is difficult to monitor. Hence a new health care delivery model with the u-healthcare system has been introduced to induce effective glucose control. A glucometer with a mobile system and Zigbee communication protocol, which is a specification for a suite of high-level communication

protocols using small, low-power digital radios for wireless home area networks, showed that diabetic patients could be more autonomous in controlling their glucose levels (17). To improve quality and efficiency of care for elderly patients with type II diabetes, Clinical Decision Support System (CDSS)-based ubiquitous healthcare (u-healthcare) service, which is an individualized health management system using advanced medical information technology have been introduced by many researchers.

AIDA is a freeware computer program that allows the interactive simulation of plasma insulin and blood glucose (BG) profiles for demonstration, self-learning and research purposes (18). A web-based version of the program, called AIDA online, has been available on the World Wide Web since 1997/1998 for diabetes education. AIDA online includes a standard Web-browser interface. Input parameters include carbohydrate ingestion and insulin dosing. The output of the program is the simulated BG, with supplemental information regarding the simulated plasma insulin values.

Computer-Prompted Diabetes Care (CPDC) is a multifaceted software program designed to allow the physicians of the Maccabi Health Care Services, for diabetes care through the use of real-time, on-screen, situation -specific messages (36). The CPDC software was developed relatively inexpensively by Maccabi Health Care Service. Novel approach for diagnosing diabetes illness using pervasive healthcare computing and artificial neural networks on small mobile and wireless devices have been reported on 2010 (4). All over the world scientists are using nanotechnology to create new treatments for diabetes. The future possibilities on the latest technological advancement in treating Diabetes is too firm to ignore.

II. CONCLUSION

Rapid urbanization and industrialization have resulted in dramatic lifestyle changes leading to lifestyle related diseases. The design of new drug is based on the requirement of active binding site present in a protein. Bio-informatics has been applied effectively in the management of chronic diseases such as Diabetes, Cancer and Cardiovascular Disorders. Biological Databases are key to both bioinformatics and Drug Discovery.

Computer- assisted drug design approach has contributed to the successful discovery of several antidiabetic agents. There are various tools, which can be used for Computer aided drug design such as QSAR, Docking, Homology modeling etc. CADD is dependent on Bioinformatics Databases, Application, Softwares and tools. As such, there is considerable overlap in CADD research and Bioinformatics. Various computer programs, visualizer, analyser medicinal chemistry tools and computer aided drug design, were used by many researchers, students to design novel potential drug candidates for diabetes (31). Bio informatics plays a central role in diabetes research.

III. REFERENCES

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