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# Role of Glycoinformatics in Biomedical Research: A Review

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## Abstract

Glycans and their physiological receptors – lectins and glycoconjugates, participate in many crucial biological processes such as cell-cell and cell-matrix interactions, adhesion, signaling, differentiation, and development and therefore glycans may serve as identification molecules to the surrounding world. Advancements in the field of glycoinformatics have made it possible to analyze and synthesize glycans, thus helping in production of carbohydrate-based drugs. The results obtained with the use of bioinformatics in the field of study of carbohydrate moieties will be helpful in the treatment of various diseases. Therefore, the present review highlighted the various databases used in the glycoinformatics study and their implications in statistical analysis of glycan databases help to plan glycan synthesis experiments.

**Keywords:** Bioinformatics, Databases, Glycans, Glycoinformatics

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## Introduction

Glycoinformatics is a branch of bioinformatics which deals with the analysis of different glycan structures and their roles in body and to make the role of glycoinformatics more systematic, wide varieties of databases are employed to study various diseases. Glycans are the most abundant and the most diverse biopolymers in nature. Due to their enormous structural diversity, oligosaccharide chains are ideal media for coding biological information. Based on the highly specific interactions between glycans and their physiological receptors – lectins and glycoconjugates participate in many crucial biological processes such as cell-cell and cell-matrix interactions, adhesion, signaling, differentiation, and development and therefore glycans may serve as identification molecules to the surrounding world. They mark cells and tissues as "self" and send signals to the immune system when tissue is injured. On the other hand, tumor cells viruses use glycans on their surfaces to slip past the immune system. Many pathogens use specific glycan structures of the host cell membrane glycoconjugates to stick onto the host cells and to spread themselves to the surrounding cells. Therefore, these functions heterogeneity make the study of glycoinformatics more important in biomedical research. Modern biotechnology and pharmaceutical industries are also progressively adopting geoinformatics in their research and innovation projects. In this paper, we will study about various databases present till date, their functions in glycan analysis, and application of glycans in various biomedical fields such as drug delivery and cancer.

## Role of Glycoinformatics in Drug Designing

Glycoconjugates which include glycoproteins, proteoglycans, glycolipids, and glycosylphosphatidylinositol anchors consist of oligosaccharide chains also referred to as glycans in their structure.[1] Specific interaction between these glycans with their physiological receptors, that is, lectins and glycoconjugates plays an important role in many biological processes such as cell to cell interaction, cell to matrix interaction, signaling, differentiation, and development. These glycans which are present on the surface of cell help the body to recognize self-cells from non-self-cells.[2] Many pathogens to invade our body's cell have specific glycans so that it can interact with host glycoconjugates which cause inflammatory reactions, thus changing the glycan structures.[3] Therefore, carbohydrate-based drugs have therapeutic potential and are increasingly employed as a field of interest in biotechnology and pharmaceutical industries.[4]

Advancements in the field of glycoinformatics have made it possible to analyze and synthesize glycans, thus helping in production of carbohydrate-based drugs. These synthesized carbohydrate-based drugs are much smaller in size than proteins. Although carbohydrates play a very important role in several biological processes, they are still limited in the therapeutic industry. The major reason behind this is their high polarity which makes it unable to passively cross through the enterocyte layer of the small intestine, thus making it unavailable for oral consumption.[5] Even when given through the parenteral route, it gets excreted out very quickly. However, now by eliminating polar groups and metabolic soft spots which are not required for affinity, it is possible to make drugs which can be administered orally.[6] Thus, with the use of glycoinformatic tools, we would be able synthesize these drugs which will be safer and more specific in near future.[7,8]

## Role of Glycoinformatics in Cancer Diagnosis

Recent studies have shown that there is a link between altered protein glycosylation and cancer.[9] As the disease progresses, within the cell, glycans undergo changes. Such kind of changes have been observed in prostate cancer, where in the cancerous cells, composition of glycans is affected.[10]

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*Some databases and their applications*

| *S. No.* | *Databases* | *Application* | *References* |
|---|---|---|---|
| 1. | UniCarbKB | Stores glycan structures of glycoproteins. | [17] |
| 2. | GlycoMod | Provides tools for predicting N- linked and O-linked glycan structures. | [18] |
| 3. | GlycosuiteDB | Provides relation between glycan structures of glycoproteins and their biological sources. | [19] |
| 4. | GlycoDeNovo | Provides algorithm for Accurate *de novo* Glycan Topology Reconstruction from Tandem Mass Spectra. | [20] |
| 5. | Glycoforest | Provides partial *de novo* algorithm for sequencing glycan structures based on MS/MS spectra | [21] |
| 6. | Sweet-II | Provides tools to construct 3D models of saccharides from their sequences using standard nomenclature. | [22] |
| 7. | GlyProt | Provides tools to connect N-glycans *in silico* to a given 3D protein structure. | [23] |
| 8. | PDB CArbohydrate Residue check | Identify and assign carbohydrate structures using atom types and their 3D atom coordinates from PDB files | [24] |
| 9. | Glyco3D | Provides 3D structures of monosaccharides, disaccharides, oligosaccharides, polysaccharides, glycosyltransferases, lectins, monoclonal antibodies against carbohydrates, and glycosaminoglycan-binding proteins | [25] |
| 10 | LiGraph | Provides convert a sugar graph to ASCII IUPAC sugar nomenclature or as a graph | [15] |
| 11. | KEGG Glycan database | Provides database for glycan structures | [26] |
| 12. | GlyTouCan | Provides database for glycan structures | [27] |
| 13. | UniCarb-DB | Provides database for glycomic MS data | [17] |
| 14. | GlycanBuilder, GlycoWorkBench | Provides tool to annotate mass spectra of glycans | [28] |
| 15. | Multiglycan | Provides information provider for glycan profile information from LC–MS spectra. | [29] |
| 16. | GlycoFragment and Distance Mapping | Provides tool to interpret mass spectra of complex carbohydrates | [30] |
| 17. | NGlycPred | Provides server to predict N-linked glycosylation sites | [31] |
| 18. | UNIPEP | Provides human and mouse N-glycosylated proteins and their N-glycosylation sites for biomarker discovery | [32] |
| 19. | GlycoEP | Provides prediction of N-linked, O-linked and C-linked glycosites in eukaryotic glycoproteins | [33] |
| 20. | GlySeq | Provides analyze the sequences around glycosylation sites | [34] |
| 21. | SPRINT-Gly | Provides predicting N- and O-linked glycosylation sites | [35] |
| 22. | DictyOGlyc | Provides prediction of O-glycosylation sites in *Dictyostelium discoideum* proteins | [36] |
| 23. | GlycoMineStruct | Provides highly accurate mapping of the human N-linked and O-linked glycoproteomics. | [37] |
| 24. | GlycoForm | Provides Mathematical model software for N-linked glycosylation | [38] |
| 25. | Glycopep | Provides N-linked glycosylation based on target protein and CID spectra analysis | [39] |
| 26. | Consortium for Functional Glycomics (CFC) | Provides glycomics resources of glycans and glycan-binding protein | [40] |
| 27. | NetNGlyc | Provides N-Glycosylation sites predictor | [41] |
| 28. | NetOGlyc | Provides O-Glycosylation sites predictor | [42] |
| 29. | GPP | Provides N- and O-Glycosylation site predictor | [36] |
| 30. | Big-PI | Provides GPI anchors predictor | [43] |
| 31. | GPI-SOM | Provides GPI anchors predictor | [44] |
| 32. | PredGPI | Provides GPI anchors predictor | [13] |
| 33. | NetCGlyc | Provides C-mannosylation sites prediction | [14] |
| 34. | GlycoCT | Provides tools to convert unifying sequence format for carbohydrates | [15] |
| 35. | SWEET-DB | Provides databank for annotated carbohydrates | [16] |
| 36. | SUgar MOtif search (sumo) | Provides tools to search sugar motif regions from carbohydrate structures | [45] |
| 37. | Bacterial Carbohydrate Structure Database (BCSDB) | Provides glycan structures found in bacteria, plants, and fungi. | [46] |
| 38. | pdb2linucs | Helps in extracting carbohydrate information from pdb files and display it using the LINUCS-Code. | [34] |
| 39. | CCSD | Provides information of carbohydrate science | [47] |
| 40. | Carbohydrate Ramachandran Plot (CARP) | Provides carbohydrate data from PDB files using the pdb2linucs algorithm | [48] |
| 41. | LINUCS | LInear Notation for Unique description of Carbohydrate Sequences | [49] |
| 42. | RESID | Provides database on glycosylation modifications | [50] |
| 43. | GlyGen | Provides informatics resources for glycoscience | [51] |
| 44. | LfDB | Provides a lectin frontier database | [52] |
| 45. | CFG | Provides resources for functional glycomics research | [53] |
| 46. | GlycoStore | Provides databases on glycan retention properties with chromatographic, electrophoretic, and mass spectrometry composition data. | [54] |
| 47. | Galaxy, LipidBank | Provides association for Glycobiology and Glycobiotechnology database | [55] |
| 48. | Glycosylation Network Analysis Toolbox (GNAT) | Provides MATLAB-based environment for systems Glycobiology | [56] |
| 49. | Glycomics@ExPASy | Provides ExPASy resources for glycomic data. | [57] |
| 50. | Monosaccharide DB | Provides resources of monosaccharides | [58] |
| 51. | GlycReSoft | Provides database management program and the project system of CCSD | [59] |
| 52. | CarbBank | Provides softwares for Glycomics and Glycoproteomics | [60] |
| 53. | GlyCosmos | Provides web resource for the glycosciences | [61] |
| 54. | SysPTM | Provides resource for post-translational modification | [62] |

Due to altered glycosylation, there occur modifications in structure of glycoproteins in case of cancer cells. These glycoproteins can act as glycan biomarkers for a number of cancer types such as alpha-fetoprotein[11] as well as in case of liver cancer and germ cell tumors.

Studies have now proven that glycans and tumor cells have a relation. The activation of specific oncogenic pathways is because of the crosstalk between glycans and tumor cells.[12] This crosstalk has much clinical importance, as it leads to progression and is also responsible for invasiveness of the disease.

Glycosylation thus has a role in cancer diagnosis as well as in cancer therapy. There are many glycoinformatics resources for glycosylation studies. These resources require few advancements and then can be used for studying aberration in glycosylation in case of cancerous cells.

## Role of Glycoinformatics in Vaccines Formation

Some vaccines based on ganglioside immunogens present on certain types of cancer cells were investigated as well. Technologies for the manufacture of gangliosides for use as active pharmaceutical ingredients in cancer vaccines were developed. One of the cancer vaccine candidates has been tested on patients with melanoma. Another candidate has been developed for the treatment of a variety of other malignant diseases, including colorectal cancer, lymphoma, small cell lung cancer, sarcoma, gastric cancer, and neuroblastoma.[13] All these investigations showed encouraging results, but it is unlikely that cancer vaccines will be able to cure cancer on their own, but they will probably be components of a multitherapeutic approach, adjuvant therapy in early-stage diseases, or combined with adjuvant chemotherapy.[14] Vaccines based on specific glycoconjugates and lectins are of scientific and commercial interest not only against cancer but also as anti-protozoan and anti-viral vaccines. For instance, the galactose-binding lectin of the protozoan Entamoeba histolytica[15] and hyperglycosylated mutants of human immunodeficiency virus (HIV) type 1 monomeric gp120 have emerged as novel antigens for HIV vaccine design.[16]

## Glycoinformatics Databases

The future of current endeavors in glycorelated informatics lies in the consolidation of international consortia. The small size of the glycoscience community has prompted several cooperative initiatives across all continents for representing and collecting glycomics data (as described above). To favor interactions between these complementary initiatives, the International Glycome Informatics Consortium has been founded in 2015 to provide and maintain a centralized software resource enabling cooperative database and tool development. Furthermore, in 2015, a glycomics section was established on the SIB ExPASy proteomics resource portal, and glycoprotein entries in UniProtKB were linked to glycan structural information where known in UniCarbKB. In addition, the National Institutes of Health, USA, as part of the Common Fund Glycoscience Program is now focused on creating new methodologies and resources to study glycans that include the development of data integration and analysis tools.

## Conclusion

The study of glycoinformatics in relation to glycans into the mainstream of evolutionary, molecular, and cellular biology its applications to medicine, materials science, and other fields may benefit humankind in dealing many potent diseases and in the treatment.

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