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REVIEW ARTICLE

Chemo informatics: Newer Approach for Drug Development

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ABSTRACT

Chemo informatics is a scientific discipline that has evolved in the last 40 years at the interface between chemistry and computer science. It has been realized that in many areas of chemistry, the huge amount of data and information produced by chemical research can only be processed and analyzed by computer methods. Furthermore, many of the problems faced in chemistry are so complex that novel approaches utilizing solutions that are based on informatics methods are needed. Thus, methods were developed for building databases on chemical compounds and reactions, for the prediction of physical, chemical and biological properties of compounds and materials, for drug design, for structure elucidation, for the prediction of chemical reactions and for the design of organic syntheses.

KEY WORDS Chemi informatics, drug development, structure activity relationship

INTRODUCTION:

Chemical informatics is the application of computer technology to chemistry in all of its manifestations. Much of the current use of cheminformatics techniques is in the drug industry, but chemical informatics is now being applied to problems across the full range of chemistry. Chemical informaticians often work with massive amounts of data. They construct information systems that help chemists make sense of the data, attempting to predict the properties of chemical substances from a sample of data, much as Mendeleyev did many years ago when he accurately predicted the existence and properties of unknown elements in the periodic table. Thus, through the application of information technology, chemical informatics helps chemists organize and analyze known scientific data and extract new information from that data to assist in the development of novel compounds, materials, and processes.[1]

Chemical information: Many people view chemo informatics as an extension of chemical information, which is a well established concept covering many areas that employ chemical structures, data storage and computational methods, such as compound registration databases, on- line chemical literature, SAR analysis and molecule- property calculation.[2]

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Variously known as chemoinformatics, cheminformatics, or even chemiinformatics, chemical informatics is the application of computer technology to chemistry in all of its manifestations. Much of the current use of cheminformatics techniques is in the drug industry. Indeed, one definition of chemical informatics is "the mixing of information resources to transform data into information and information into knowledge, for the intended purpose of making decisions faster in the arena of drug lead identification and optimization." Now chemical informatics is being applied to problems across the full range of chemistry.

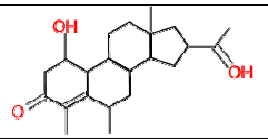
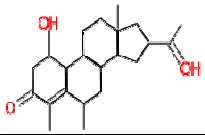
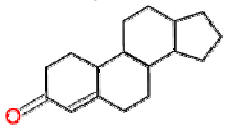
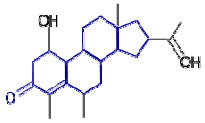
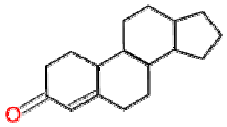
Chemical informaticians often work with massive amounts of data. They construct information systems that help chemists make sense of the data, often attempting to accurately predict the properties of chemical substances from a sample of data. Thus, through the application of information technology, chemical informatics helps chemists organize and analyze known scientific data to assist in the development of novel compounds, materials, and processes. People who work in chemical informatics may concentrate on molecular modeling, chemical structure coding and searching, chemical data visualization, or a number of other areas of specialization. Indeed, the various computer graphics codes for chemical structures that let us both view and search chemical structures via computer were developed by chemical informaticians.

1. Cheminformatics Basics

Cheminformatics is a cross between Computer Science and Chemistry: The process of storing and retrieving information about chemical compounds.

Information Systems are concerned with storing, retrieving, and searching information, and with storing *relationships* between bits of data. For example:

Table 1-Information system and its working

Operation	**Chemical Information System**	
Store		Stores chemical compounds and information about them.
Retrieve	Find: CC(=O)C4CC3C2CC(C)C1=C(C)C(=O)CC(O)C1C2CCC3(C)C4	Retrieves: 
Search	Find molecules containing: 	Retrieves: 
Relationship	What's the logP(o/w) of: 	logP(o/w) = 2.62

How is Cheminformatics Different?

There are four key problems a cheminformatics system solves:

1. Store a Molecule ;
2. Find exact molecule;
3. Substructure search;
4. Similarity search

A sound knowledge of chemistry and excellent facility in computer science are required to be an effective practitioner in the cheminformatics field. Chemical and pharmaceutical companies are in great need of people with such skills. The curriculum for the graduate programs in Chemical Informatics in the Indiana University School of Informatics, developed jointly by IUB and IUPUI, educates students in the following major aspects of chemical informatics:

- **Information Acquisition:** Methods used for generating and collecting data empirically (experimentation) or from theory (molecular simulation)
- **Information Management:** Storage and retrieval of information
- **Information Use:** Data analysis, correlation, and application to problems in the chemical and biochemical sciences. [12]

Information Acquisition

Information acquisition is highly dependent on the computer today. With the integration of modern sensors into chemical instrumentation, the volume of data that can be generated is enormous. Future instrumentation will incorporate information from existing chemical databases, employ modeling techniques, and analyze experimental data as they are generated. Such "smart instruments" will significantly improve the ability of the user to make intelligent decisions about the course of an experiment while the data are being collected and analyzed.

There now exist two complementary pathways for generating and collecting information in the chemical sciences: experimentation and computer simulation. Traditionally, the gathering of data from experiments was done manually, but with the development of computers small enough to be purchased by individual laboratories, the phrase "computers in chemistry" arose to describe their use. Several decades ago this expression meant interfacing a computer to an experiment like a spectrometer or a chromatograph and collecting the data in real time for storage and later manipulation. While this is still being done with microprocessors built into the instruments themselves, a more encompassing label for the wide range of chemical activities involving computers is "computational chemistry."

Computational chemistry seeks to predict quantitatively molecular and biomolecular structures, properties, and reactivity by computational methods alone. It uses modern chemical theory to predict the speed of unknown reactions and the synthetic sequences by which complex new molecules can be made most efficiently. Computational chemistry allows chemists to explore how things work at the atomic and molecular levels and to draw conclusions that are impossible to reach by experimentation alone. Thus, computational chemistry supplements experimentally derived data.

One aspect of computational chemistry is molecular modeling. Molecular modeling involves the investigation of three-dimensional molecular structures using classical and quantum mechanical methods assisted by computer graphics. Other molecular modeling techniques include quantitative structure-property relationships, which find applications in structure-based drug design, similarity searching, and molecular shape prediction. Molecular modeling techniques are utilized extensively in pharmaceutical research, especially to predict pharmacophores--the structural features of molecules required for particular biological activities. Molecular modeling is now used routinely to generate data concerning energetics, dynamics and other information at the molecular scale that is not amenable to experimentation.

Recent advances in combinatorial synthesis and high throughput screening technologies now allow for preparation and analysis of hundreds of thousands of or even millions of molecules in a very short period of time. Combinatorial chemistry techniques grew out of several disciplines, including organic, medicinal, and physical chemistry, engineering and robotics, computational chemistry, informatics, and screening technology. Robotics

as used in combinatorial chemistry provides the drug industry a powerful tool with which to screen millions of potential compounds in a fraction of the time it would have taken to evaluate even a few dozen compounds a decade ago. Now widely employed in the pharmaceutical area, combinatorial chemistry has begun to find applications in materials science. Because so much information is being generated and collected from combinatorial technologies, there is a concomitant problem associated with storing and retrieving those data. That problem is now being addressed by those skilled in chemical informatics. [12]

Information Management

Many of the applications for storing and retrieving chemical data have grown out of the rapid developments in chemical structure coding and searching. The advances in structure-based applications have led to integrated chemical information systems--more and more of which have Web interfaces--and to specialized applications such as Laboratory Information Management Systems (LIMS). The ability to search large secondary databases such as Chemical Abstracts or Medline easily and precisely and to move seamlessly back and forth between the original primary journal literature and the abstracting and indexing databases is one of the truly great achievements of modern chemical informatics research.

Chemists have developed their own communication system (chemical nomenclature and structure systems) that adds a unique dimension to informatics. There is a confluence of activities in chemical informatics that is centered on the chemical structure (both 2-D and 3-D depictions). Two-dimensional chemical structural databases have evolved from traditional chemical structure diagrams into structure searching and substructure searching systems. In the late 1980s, attention turned to 3-D structure searching and representations of chemical structures in three dimensions. Recently, techniques for the full description of the conformational space of flexible molecules and similarity searching techniques have been discovered. These are now being incorporated into chemical information storage and retrieval systems. [12]

Information Use

The computer has enabled chemists to analyze and correlate data from massive chemical and biochemical databanks, and when coupled with chemical visualization and modeling techniques, it is revolutionizing chemical research. Informatics techniques help create an integrated information environment in which all aspects of chemical research and development can be dealt with in a unified system. Not only can chemical structures be used as search keys in such systems, but also unknown properties and spectra can be predicted using chemical informatics tools and techniques that draw on the existing knowledge base of chemistry. Data mining has emerged as a significant factor in the reassessment of data collected over time in an organization. Chemists can now access decades of raw data stored in disparate formats and obtain useful results to build on the research that has taken place in past years. Tying together through Web Services many disparate sources of chemical and life sciences data and information into a usable and useful whole is one of the main activities of the Chemical Informatics and Cyberinfrastructure Collaboratory. [12]

Uses of Chemiinformatics

The application of statistics to the analysis of chemical data (from organic, analytical or medicinal chemistry) and design of chemical experiments and simulations. IUPAC Computational , the science of relating measurements made on a chemical system or process to the state of the system via application of mathematical or statistical methods.[3]

1. Data mining: Nontrivial extraction of implicit, previously unknown and potentially useful information from data, or the search for relationships and global patterns that exist in databases.[4]

2. Data warehouse: (Algorithms and data analysis glossary)

3. Drug design: Includes not only ligand design, but also pharmacokinetics (Pharmacogenomics) toxicity, which are mostly beyond the possibilities of structure- and/ or computer- aided design. Nevertheless, appropriate chemometric (Chemoinformatics) tools, including experimental design and multivariate statistics, can be of value in the planning and evaluation of pharmacokinetic and toxicological experiments and results. Drug design is most often used instead of the correct term "ligand design".[5]

The molecular designing of drugs for specific purposes (such as DNA- binding, enzyme inhibition, anti- cancer efficacy, etc.) based on knowledge of molecular properties such as activity of functional groups, molecular geometry, and electronic structure, and also on information cataloged on analogous molecules. Drug design is generally computer-assisted molecular modeling and does not include pharmacokinetics, dosage analysis, or drug administration analysis.[6]

An iterative process involving drug discovery is lead optimization and chemical synthesis with the aim of maximizing functional activity and minimizing adverse effects.

4. Lipophilicity: Represents the affinity of a molecule or a moiety for a lipophilic environment. It is commonly measured by its distribution behaviour in a biphasic system, either liquid- liquid (e.g., partition coefficient in octan-1-ol/water) or solid/liquid (retention on reversed- phase high performance liquid chromatography (RP-HPLC) or thin-layer chromatography (TLC) system).[6]

5. "Plug and Play" systems: Required for effective chemoinformatics systems. Must be designed backward

from the answer to the data to be captured and systems should be in components where each component has one simple task modular systems that can "plug and play" into other systems.[7]

6. Predictive data mining: Used in structure- function correlations

7. Reducing the investment made in likely drug development failure.

8. Structure Activity Relationship SAR: The relationship between chemical structure and pharmacological activity for a series of compounds[8].

Compounds are often classed together because they have structural characteristics in common including shape, size, stereo chemical arrangement, and distribution of functional groups. Other factors contributing to structure- activity relationship include chemical reactivity, electronic effects, resonance, and inductive effects.[6]

9. Structure based drug design: Structure-based design (SBD) has been in use within the pharmaceutical industry for over twenty-five years. Given the multi-disciplinary nature of drug discovery and development, SBD can hardly be the unique success factor. However, SBD is playing an increasingly important role. SBD of compound properties are still developing and growing in acceptance. In this program, we wish to highlight some recent breakthroughs and successes using SBD, including the accompanying interest in ligand-based.[9]

10. Virtual database assembly: A crucial activity as it enables access to the large number of drug- like molecules that could theoretically be made... can serve several purposes: for example, to generate a maximally diverse virtual library for lead generation, a biased library aimed at a specific target or target family, or a lead optimization library.[10]

11. Virtual library: A library which has no physical existence, being constructed solely in electronic form or on paper. The building blocks required for such a library may not exist, and the chemical steps for such a library may not have been tested. These libraries are used in the design and evaluation of possible libraries.[11]

2. Representing Molecules

One of the greatest achievements in chemistry was the development of the *valence model* of chemistry, where a molecule is represented as *atoms* joined by semi-rigid *bonds* that can be single, double, or triple. This simple mental model has little resemblance to the underlying quantum-mechanical reality of electrons, protons and neutrons, yet it has proved to be a remarkably useful approximation of how atoms behave in close proximity to one another, and has been the foundation of chemical instruction for well over a century.

The valence model is also the foundation of modern chemical information systems. When a Computer Scientist approaches a problem, the first task is to figure out a *datamodel* that represents the problem to be solved as *information*. To the Computer Scientist, the valence model naturally transforms into a *graph*, where the *nodes* are atoms and the *edges* are bonds. Computer Scientists know how to manipulate graphs - mathematical graph theory and computer science have been closely allied since the invention of the digital computer.

3. Substructure Searching with Indexes

Indexing is pre-computing the answers to portions of expected questions *before* they're asked, so that when the question comes, it's quick to answer it.

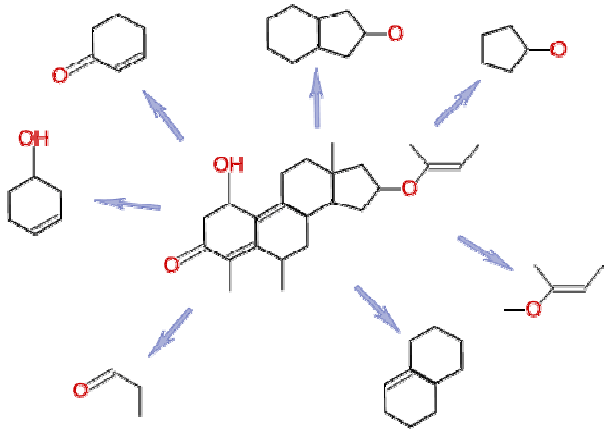
Take your favorite search engine (AOL, Yahoo!, Google, MSN) for example. Without indexing, they might wait until you ask for "John Hartford Bluegrass", then start searching the web, and in a year or two find all the web pages about the deceased banjo/fiddle player and steamboat captain. That would probably not impress you.

Instead, these search engines search the web *before* you ask your question, and build an *index* of the words they find. When you type in "Bluegrass John Hartford", they already know all of the pages that have "John", all of the pages with "Hartford", and all of the pages with "Bluegrass". Instead of searching, they examine their index, and find pages that are on *all three* lists, and quickly find your results. (NB: It's actually a lot more complex, but this illustrates the main idea of indexing.)

Indexes for Chemicals

Instead of indexing words, cheminformatics systems index *substructures*. Although there are many schemes for doing this, cheminformatics systems all use the same fundamental principle: they *decompose the molecule* into smaller bits, and index those.

Figure 1-Indexing of chemical structure.



Decomposing the molecule for indexing

Roughly speaking, a cheminformatics system will index each of the substructures (fragments) above, so that every molecule that contains each fragment is known.

When a query is entered, the cheminformatics system breaks apart the query using the same technique, to find all of the fragments in the query. It then checks its index for each fragment, and combines the lists it finds to get only those molecules that have *all* of those fragments.

This doesn't mean that all molecules returned by the index actually are matches. In the language of databases, we say the index will return *false positives*, candidate molecules that don't actually match the substructure search.

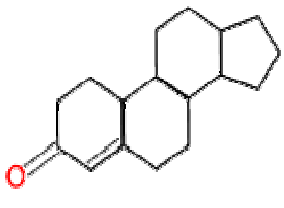
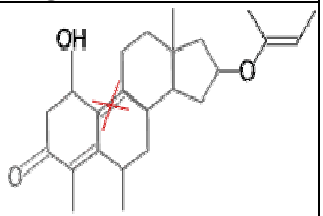
Consider our example of searching for "John Hartford" - the index might return many pages that have both "John" and "Hartford", yet have nothing to do with bluegrass music or steamboats. For example, it might return a page containing, "President John F. Kennedy visited Hartford, Connecticut today...". To confirm that the search system has found something relevant, it must check the pages return from the index to ensure that the specific phrase "John Hartford" is present. However, notice that this is *much* faster than searching every page, since the overwhelming majority of web pages were instantly rejected because they have neither "John" nor "Hartford" on them.

Similarly, a chemical fragment index serves to find only the most *likely* molecules for our substructure match - anything that the index didn't find is definitely not a match. But we still have to examine each of the molecules returned by the indexing system and verify that the complete substructure for which we are searching is present.

4. Molecular Similarity

Substructure searching is a very powerful technique, but sometimes it misses answers for seemingly trivial differences. We saw this earlier with the following:

Table 2.

Query	Target
	
We're looking for steroids...	But we don't find this one because of the double bond.

It is somewhat like searching for "221b Baker Street" and finding nothing because the database contains "221B Baker Street" and the system doesn't consider "b" and "B" a match.

A good similarity search would find the target structure shown above, because even though it is not a substructure match, it is highly similar to our query.

There are many ways to measure similarity.

1. **2D topology:** The best-known and most widely used similarity metrics compare the two-dimensional topology, that is, they only use the molecule's atoms and bonds without considering its shape.
2. **3D configuration:** One of the most important uses of similarity is in the discovery of new drugs, and a molecule's shape is critical to it's medicinal value

3D similarity searches are uncommon, for two reasons: It's difficult and it's slow. The difficulty comes from the complexity of molecular interactions - a molecule is not a fixed shape, but rather a dynamic object that changes according to its environment. And the slowness comes from the difficulty: To get better results, scientists employ more and more complex programs.

3. **Physical Properties:** The above 2D and 3D similarity are based on the molecule's structure. Another technique compares the properties - either computed or measured or both - and declares that molecules with many properties in common are likely to have similar structure. It is the idea of QSAR taken to the database.

4. Clustering: "Clustering" is the process of differentiating a set of things into groups where each group has common features. Molecules can be clustered using a variety of techniques, such as common 2D and/or 3D features.

Many cheminformatics databases have one or more similarity searches available.

5. Chemical Registration Systems

Chemical Registration is the "big brother" of cheminformatics.

A cheminformatics system is primarily devoted to recording chemical structure. Chemical Registration systems are additionally concerned with:

- Structural novelty - ensure that each compound is only registered once
- Structural normalization - ensure that structures with alternative representations (such as nitro groups, ferrocenes, and tautomers) are entered in a uniform way.
- Structure drawing - ensure that compounds are drawn in a uniform fashion, so that they can be quickly recognized "by eye".

- Maintaining relationships among related compounds. For example, all salt forms of a compound should be recognized as being related to one another, and compounds in different solvates are also related.
- Registering mixtures, formulations and alternative structures.
- Registering compounds the structure of which is unknown.
- Roles, responsibilities, security, and company workflow.
- Updates, amendments and corrections, and controlling propagation of changes (e.g. does changing a compound change a mixture containing that compound?)

Introductory Resources in Cheminformatics

Online Resources

- The Obernai Declaration (from the Workshop Cheminformatics in Europe: Research and Teaching, 2006)
- Bibliography - Chemical Information Retrieval and 3D Searching - Greg Paris
- Software links - from the QSAR and Modelling Society
- Daylight SMILES Tutorial
- ChemIH Forum - a discussion forum with SMILES-based structure drawing enabled
- ChemIH Forum - how to post SMILES on ChemIH Forum
- QSAR World
- SMILES PowerPoint 1 (ppt)
- Chemoinf.com - The Chemoinformatics Hub
- QSAR [and other] Software
- Vigyaan - a self-contained suite of chemoinformatics software
- ChemTK Evaluation Package
- Cheminformatics Virtual Classroom
- Molecular Docking Web (Garrett M. Morris)
- Molecular Descriptors
- Molecular Conceptor
- Cheminformatics 101 (eMolecules)
- Chemical Informatics Undergraduate Course at Indiana University (1 credit hour)
- An (Opinionated) Guide to Microarray Data Analysis (Mark Reimers)
- BioMolecular Explorer 3D
- Dalke Scientific (Cheminformatics Python programming)
- JOELib - cheminformatics library
- The Chemistry Development Kit
- OpenBabel
- iBabel
- E-BABEL Interactive Molecular Structure Formats Interconversion Program (part of the Virtual Computational Chemistry Laboratory)
- VCCLAB - Virtual Computational Chemistry Laboratory
- Frowns ChemoInformatics System
- cheminfo.org
- CML (Chemical Markup Language) Discussion Forum
- MQL – Molecular Query Language
- Unofficial InChI FAQ

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DISCUSSION

From above survey, Chemoinformatics is the application of informatics tools to solve discovery chemistry problems. From library shaping to ADME-Tox prediction via virtual screening, computational chemistry is an integral component of hit and lead generation. Coverage this year will include case studies of several approaches and tools that helped to identify compounds with a balanced ADME-Tox profile together with high potency and selectivity. Creation of large in silico virtual libraries of compounds vastly increase the efficiency in mining the chemical space and considerably reduces time and costs in drug discovery.

By using chemoinformatics in the drug development, drug development process is very easy and sophisticated. But in Indian drug industries, application of chemoinformatics is still in child stage. To increase efficiency and accuracy in new drug development, we must implement the newer and newer technologies and for that chemiinformatics is the best option.

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20. Virtual Computational Chemistry Laboratory http://www.vcclab.org