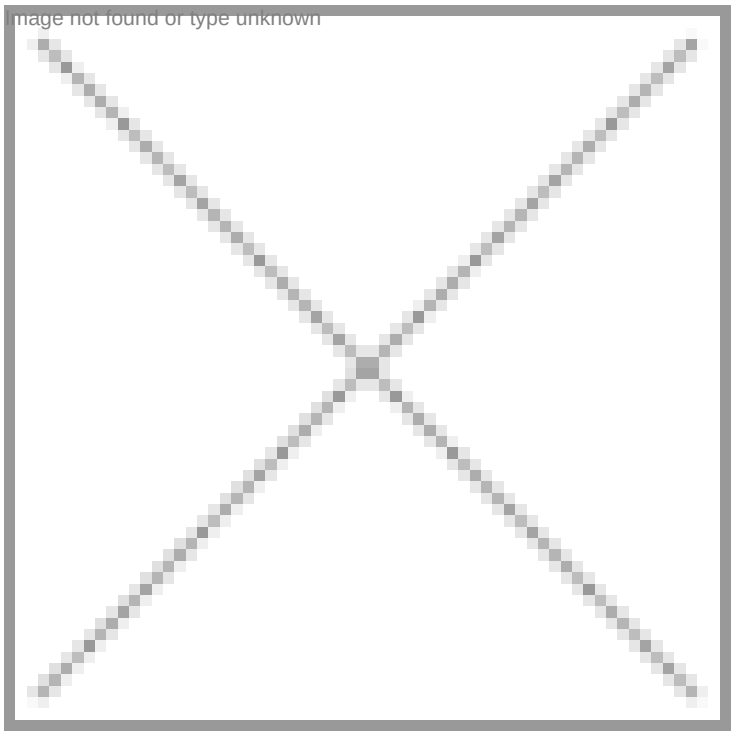
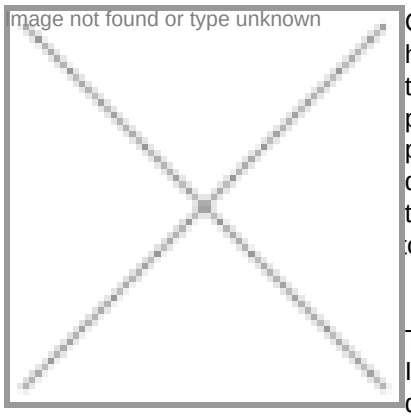
BioSpectrum the business of Bio & Health Sciences

Tracking Trends in Drug Discovery

04 November 2010 | News



The role of computational tools in drug discovery and design is revolutionary. Designing a new drug can be faster and more economical when researchers incorporate computational approaches



Computers have become an integral part of drug discovery process - as rapid advances in hardware and software happening today can help researchers in drug discovery, achieve their goals quickly and more efficiently. Software packages ranging from modeling programs to virtual reality, let scientists explore more structural options, and even make predictions of properties of new compounds. Besides that, the cost and time involved in drug discovery are prohibitively expensive, which is unacceptable, particularly for life-threatening diseases. It is expected that computational tools can save up to 20 percent, if ors.

There has been tremendous change in the field of drug discovery in the past two decades. In the post-genomic era, rational drug discovery is a major approach for discovering and designing new drugs. Generally, experimental techniques are costly, time-consuming, and involve the use of animals for testing. Therefore, computer-based in silico models are alternate to experimental models.

Says Dr GPS Raghava, head, Bioinformatics Center, Institute of Microbial Technology (IMTECH), Chandigarh & head, computational resources for drug discovery (CRDD) initiative of open source drug discovery (OSDD), under Council of Scientific & Industrial Research (CSIR), India, â€œUnlike the traditional approach when drugs were discovered mainly, based on trial-and-error, like plant-based medicines, accidental observations (penicillin) and chemical modification; there have been some major developments in this field. These include the understanding of disease mechanism; designing in silico models;

annotation of genome of pathogen (disease causing agent); annotation of human genome; searching drug targets, understanding structure and function of targets, and designing drug molecules against targets.â€?

Explains Dr B Jayaram, coordinator, Supercomputing facility for Bioinformatics & Computational Biology, IIT Delhi, â€œThe role of the drug molecule is to seek out and bind to the target(s) and only to the target(s), inhibit or activate the target(s), as required by the normal pathway, without itself being chewed up by other pathways before it can act and, make a graceful exit after the action on the target is elicited either as intact molecule, or as harmless pieces. Computers help in designing these molecules.â€?

Overall, computational tools shorten the discovery timeline, rationalize the design and help in decision-making process. Says Dr VN Balaji, director & chief scientific mentor, Jubilant Biosys, â€œWhat is exciting about computational tools is their ability to give atomic level insights into observed molecular interaction and relation to biological data. Dynamic simulations give valuable insights into mobility of molecular interactions for design. These tools are used for molecular design of hits, leads and optimization of leads with better profile as drugs,â€? he adds.

Latest trends

In the present era, drug design is based on disease models. Bioinformaticians are mainly focusing on system biology to understand biological system in totality. Thus, most of the computational tools are designed to understand biological systems, particularly major pathways and disease models. The group under Dr Raghva at, IMTECH, Chandigarh, is particularly focusing on the development of open source in the field of chemo-informatics, in order to attract more academicians to this field.

Dr Balaji believes chemo-informatics, involving the analysis of chemical information, developing and using specialized tools to process large amounts of information, has emerged as an extremely important area. Talking about latest trends, he opines, â€œMolecular docking, dynamics, pharmacophore modeling and virtual screening approaches are important in drug design. Tools to predict specificity, metabolites, pharmocodynamicâ€“pharmacokinetic profile, bio-availability,

> Image not found or type unknown ditional approach when drugs were mainly discovered, based on trial-and-error, there have been some major developments in computational biologyâ€?
> ***-Dr GPS Raghava**, head, Bioinformatics Center, IMTECH, Chandigarh & head, CRDD, CSIR*

to

> Image not found or type unknown asons for considerable optimism in anticipating that we may reach out farther in the years to come, than has been possible thus far, in reducing cost and time in drug discoveryâ€?
> ***-Dr B Jayaram**,coordinator, Supercomputing Facility for Bioinformatics & Computational Biology, IIT Delhi*

> Image not found or type unknown ng about computational tools is their ability to give atomic level insights into observed molecular interaction and relation to biological dataâ€?
> ***-Dr VN Balaji**, director & chief scientific mentor, Jubilant Biosys*

m ends.

Many commercial drug design tools are available. Some of the established packages are by US-based companies Schrodinger, Tripos, Accelrys and Canada's Chemical Computing Group. Many machine learning tools are being used for quantitative modeling of structure-activity relationships (QSAR). Incremental improvement in accuracy of scoring functions, many new tools for analyzing SAR, development of shape-based techniques, improved efficiency of

ne nome analysis programs (Chemgenome), protein structure prediction programs (Bhageerath) and co for drug design (Sanjeevini). Chemgenome is a novel successful step towards deciphering the language of DNA from an energetic perspective. The accuracies realized by Sanjeevini in docking candidate molecules to targets, and in estimating binding affinities to target, are comparable to the best in the business. Intense efforts are continuing in the lab (SCFBio, IITD) to make the software faster, more user-friendly, and as good as it can get. Concurrently, efforts are also in progress in the lab, to design novel anti-malarials with Sanjeevini.

The Gene-to-Drug software suite developed at the Supercomputing Facility for Bioinformatics, IIT New Delhi, accessible freely over the

â€œIt was more of a personal dream to develop an in-house drug design software suite that is freely accessible to the user community, particularly to tackle diseases in developing countries where investments are relatively low.â€? says Dr Jayaram.

Joint initiatives

Drug design being a complex process, needs immense expertise, resources and systematic work. Therefore, sharing of information becomes important to make progress. Companies generate huge data like failed drugs, molecules that have failed in different phases of clinical trials, resources and software. These resources are very important for computer scientists to develop in silico models for drug discovery. Ultimately, companies that design new drug molecules can use these models.

Dr Balaji, while endorsing the role of academic institutes says, â€œAlmost all molecular design software we see today, were

originally developed and/or prototyped in an academic environment. The molecular design software houses give enhanced user-friendly features, validation and training modules. Academic institutions are continuously contributing to advancing the methods used in drug design and test out hypotheses. Industry needs tools to mine data and design new molecular entities. Science from academics and knowledge from industry can together lead to quality tools, and optimize drug discovery process.â€?

Academic institutes are invaluable sources of new therapeutic targets for diseases, biological assay techniques, new chemical synthetic routes, catalysts, and so on. Commercial establishments bring in among other factors, efficiency, affordability, knowledge and experience, skilled person power, practical solutions, project management experience, swift decision making. A symbiotic blend of these go a long way in accelerating the discovery process.

As Dr Raghava says, â€œBoth academic institutes and companies should work in collaboration, in the interest of better health for everyone. We need to understand that drugs are required for everyone, as we all are disease-prone. Besides business, we should think about human beings suffering from dreaded diseases like cancer, HIV, tuberculosis.â€?

Agreeing to Dr Raghava's statements, Dr Jayaram says â€œThere is hardly an academician who is not excited about seeing his/her research benefiting society; while the industry has no escape from market forces and balance sheets. This scenario provides a natural link between academia and industry.â€?

â€œMore specifically, the industry could take the in silico suggestions forward through synthesis and in vitro/in vivo testing. Also, knowledge of the failed candidate molecules from pharmaceutical companies can be pumped into academic labs in an iterative way, to produce good candidates.â€? Dr Jayaram says, while suggesting ways to boost partnerships.

In the Indian context, drug discovery in academic labs today, is mostly driven by government-sponsored R&D projects. Given the infrastructure and advances made in these labs, and considering the strengths in information technology (IT) and synthetic organic chemistry available in the country, the time is ripe for industry and academia to create a win-win situation for all. In India, many academic industry collaborations have resulted in new technology development. Packages such as EduSAR from V-life Sciences, Pune and Biosuite from Tata Consultancy Services (TCS), are promising examples. Computational platform AVADIS from India's Strand Life Sciences for target and biomarker identification is well-known.

Another example is of Dr Raghava. His group, in collaboration with private company Biomantra, New Delhi, developed a software package VaxiPred.

As rightly said by Dr Jayaram, while the exact numbers are arguable, it takes on an average, $1.4 billion (62,000 crore) and 10 years, to see a new drug in the market - 20 percent of these numbers as investment into academia, is a reasonable proposition to doubly ensure success.

Rahul Koul in New Delhi