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Computational technologies in drug discovery

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Computational technologies are more than exotic play tools, impacting research productivity in a discovery program and more.

Supreet Deshpande
The author is currently the CEO of Vlife Sciences Pvt Ltd. He has over 17 years of experience in business development and has worked with large multinational companies in the past. He can be contacted at supreet@vlifescieces.com

Deciphering of human genome and advancements in proteomics have each been watershed events for drug discoverers. These dramatic advancements have left a world target-rich but drug-poor. Computational technologies prophesying to make best use of this rich target information have remained focused on creating "Awe" in the minds of users but have been often found short of creating a "Wow" for the patients. In the not too past, unrealistic expectations set by vested interests created a bioinformatics bubble. Subsequent bursting of the bubble cast doubts in the minds of serious researchers about the utility of computational technologies. Does this mean computational technologies remain only exotic play tools and no more? The answer is an emphatic no.

Impact of computational technologies

Computational technologies significantly impact Research Productivity in a discovery program. Taking example of the Pharmaceutical Sector where a drug takes 12-15 years to move from an "Idea" to "Market" involving an expense of over $1 billion (Source: Tuft's University, USA), computational technologies have become an integral part of any discovery program. Majority of the expenditure in early stage drug research goes towards failures, lost forever. The use of advanced computational technologies in drug discovery leads to better designed, comprehensively studied pre-clinical candidates, which have better chance of success in the subsequent laboratory experimentation. An artist's representation of the aforesaid is given below:

Computational technologies can help a drug researcher in multiple ways. They enable expansion of the initial chemical exploration space manifold, which is not feasible in a time and cost intensive laboratory-centric effort. They help the development of a robust molecule design criteria taking cognizance of the needs of protein target and information of known active compounds against that protein from historical research. They enable multiple 'what if' scenario try-outs before even entering a laboratory. They allow pursuit of a structure based research program even when the three dimensional protein structure is not available. Finally, they enable virtual screening of a chemical space on various aspects thus preempting later stage failures on account of efficacy, toxicity and bio-availability.

The successful application of computational technologies in a discovery research program significantly depends on three factors. The first factor is the selection of the RIGHT technology, second is knowledge of the researcher about the limitations of the technology in addition to its strengths and the third and most important factor is establishing CORRECT expectations from that technology.

The differentiators among various computational technologies

One computational technology differs from the other primarily due to the mathematical algorithms underlying each research function that it allows to do. These mathematical algorithms are expected to reproduce known experimental results obtained through historical experiments. The accuracy and the speed of computational study and the technology's ability to handle complex biological and chemical structures depend largely on the underlying mathematical algorithm.

The second critical differentiator is the number of various ways, the technology presents to do a particular work. E.g. If one needs to perform a QSAR study, a technology which incorporates more statistical methods for predictive model building, the more options the user has to arrive at a closer to reality model or utilize a Consensus approach for Go-No go decisions based on the output of multiple methods.

The third differentiating aspect is the quality of the graphical representation that a computational technology can achieve for complex proteins and alien chemistries. This aspect becomes particularly critical when the out of the computational technology is to be used for scientific publications and when a researcher has to use a technology for long durations. This holds true also for various analytical graphs that the technology can generate to enable user correct interpretation of the results of computational study.

The fourth important aspect is the Graphic User Interface. Simpler and more intuitive the interface, the shorter is the learning curve for a new user. It is a critical consideration when a company chooses to move from one computational technology to another. Also, in an industrial environment where time is critical, an intuitive GUI helps the user to complete the experiment faster than a command line based instruction submission.

Selecting the RIGHT technology

There is no technology for computer aided drug discovery which can be BEST for all types of biological and chemical universe, given that it is extremely large. Therefore often, companies having significant cash out-lay for technology acquisition acquire multiple technologies and utilize them for their specific strengths.

To choose the right technology it is important to benchmark various available options against each other on 'Accuracy', 'Speed' and 'Complexity handling' parameters and thus identify the better technology. Such benchmarking studies play a significant role in helping to make the crucial buying decision.

Benchmarking studies compare the output from multiple technologies for a specific functionality; say 'Docking', on a common data-set. While making their buying decision based on benchmarking studies, the purchaser must establish that the data-set is unbiased for a specific technology. The benchmarking study ideally must include comparison of competing technologies on. A technology vendor who presents benchmarking results on the main competitor's data-set is most believable and credible.

An important consideration in selecting a computational technology is the after sale support that a vendor is able to provide. A technology provider who has full access and ownership of the underlying code must be preferred, as they can provide customization of the technology to suite your specific needs.

It is important however to remember while making a buying decision that the price of a computational technology license is not directly indicative of its superiority. Often, there are drivers other than a technology edge that drive a cost, which may not be of direct scientific relevance to your research requirement.

Additionally, caution must be exercised in getting swayed by the brand perception. Older the technology brand in the market does not necessarily mean that the technology continues to retain competitive superiority. Often new technology vendors with significant focus on in-house innovation present a more advanced technology.

How to make best use of computational technologies?

Any technology is ultimately a tool and no tool delivers by itself. For exploiting the capabilities of a tool, in this case being computational technologies, the user of the technology must be knowledgeable not only in use of technology but strong in fundamentals of science as well. Thus the user ought to:

- Know the limitations of technology as much as its strengths
- Set RIGHT expectations
- Purchase the best technology based on criteria of Accuracy, Speed and ability to better handle biological and chemical complexities
- Recruit scientific talent that is familiar with the use of advanced technologies and with strong domain knowledge
- Choose a vendor who provides strong after sale support and has capability to undertake training workshops within your organization to help conventional researchers overcome their inhibitions in using advanced technologies

Knowing the capabilities and limitations of computational technology can thus enable its user to make its optimal use for improving their research productivity. With such an insight into the technology scientists can equip themselves with the correct criteria on which the technology can be evaluated and compared and help themselves in making the best choice.

This combination of scientific know-how and the power of computational technologies can bring to fruition the promises held out by modern genomics and proteomics and significantly expedite the process of bringing new drugs for the benefit of the mankind.