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In Silico Pharmacology: Computer-Aided Methods Could Transform Drug Development

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With the rapidly growing and aging world population comes an urgent and rising demand for new and better drugs. Many observers feel that the pharmaceutical industry seems unable to satisfy this demand. Although the industry's investment in research and development has steadily increased, from about $16 billion in 1993 to nearly $60 billion in 2007, the number of new molecules and biologics approved each year has remained almost unchanged. The past few decades have produced a dazzling array of high-throughput life science technologies such as genomics, proteomics, and mass spectrometry that have dramatically increased the number of "druggable" targets. Unfortunately, this has not yet translated into a flood of new remedies. Indeed, as the US Government Accountability Office points out, until now such technologies have resulted only in "increasing expenses without a commensurate increase in the number of drugs developed."

According to industry estimates, bringing out a new drug typically takes up to 15 years and costs $1 billion or more. Failure rates remain high: only 1 or 2 compounds out of 10,000 tested make it to the market. Many drugs may go through 75–100 clinical trials and often fail at the later stages after considerable resources have already been spent on them. "The efficiency of drug development is low," says Carl Peck, the founding director of the Center for Drug Development Science at the University of California, San Francisco (UCSF). A former director of the Center for Drug Evaluation and Research at the FDA, Peck believes that the wider use of in silico modeling and simulation methods could help improve this situation. Sean Ekins, a clinical pharmacologist and editor of a recent book on computer applications in pharmaceutical research and development, agrees. "The combination of chemistry and biology with informatics has led to advances in silico pharmacology," he says. "In silico methods can now simulate practically every aspect of drug discovery and development."

The use of quantitative methods in pharmacology dates back to the late 19th century, when relations between physical and chemical properties of compounds and their biological activities were first studied. Decades later, in the 1960s, Corwin Hansch and other scientists began to establish so-called quantitative structure-activity relationships (QSARs) tying various molecular descriptors to physical, chemical, and biological properties. This effort still continues, and the public domain "C-QSAR" database, which now contains thousands of such models, has become a valuable resource for drug discovery. In the 1980s and 90s, advances in computer technology led to a number of in silico techniques for modeling ligand-target interactions. Such drug discovery techniques have rapidly grown in speed and power. "You can now run all your molecules of interest simultaneously against different computational models of targets and antitargets," says Ekins. "This was a pipe dream a decade ago, but it is reality now."

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To find new lead compounds, a conventional in vitro high-throughput screening assay will typically test a library of up to a million compounds against the target of interest. Besides being expensive and cumbersome, such large-scale assays sometimes miss valid leads and/or give false matches. Fortunately, many virtual screening techniques have now become available as a complement or alternative. A well-known example is the DOCK software from UCSF, which uses information about molecular structure to predict how well a ligand will bind to a target. In 2002, researchers at Pharmacia Corporation (now part of Pfizer) used this and other computer tools to match a library of 235,000 compounds with protein tyrosine phosphatase-1B, an enzyme implicated in diabetes. The search yielded 365 high-scoring molecules. Subsequent in vitro testing showed that 127 of these inhibited the enzyme effectively – a hit rate of nearly 35%. Traditional high throughput screening, in contrast, gave a hit rate of just over 0.02%. Interestingly, the two "hit lists" differed significantly: the hits from virtual screening appeared more "drug-like" than the ones from real screening (Doman et al., 2002).

Another validation of the in silico approach to drug screening came in 2003. Research groups at two companies had both been on the hunt for a small-molecule inhibitor for the TGFβ-1 receptor kinase, a protein that helps form actin fibers in cells and tissues. Of major interest in cancer research, this protein is also implicated in other fibrotic conditions such as ocular scarring. The first group, at Eli Lilly, found an inhibitor using conventional "wet-lab" assays. The other group, at Biogen Idec, chose to go with an in silico approach. It used software from San Diego-based Accelrys to build a ligand model based on a known weak inhibitor of the kinase and then searched a computer database of 200,000 compounds for similar molecules. The search yielded 87 hits; the most promising of these turned out to be identical to Eli Lilly's molecule (Sawyer et al., 2003; Singh et al., 2003, 2004). "That was a perfect example of how you could come up with a lead molecule without having to synthesize it," says Shikha Varma-O'Brien, an associate director at Accelrys. "This capability is of tremendous importance to chemists."

In parallel with techniques for drug discovery, in silico methods for drug development began to emerge in the 1970s. "Prior to the 70s, much of drug development was empirical and sloppy," recalls Peck. Researchers began to use computational methods to model the interactions between drugs and biological systems: the so-called pharmacokinetic and pharmacodynamic processes. Since then, computational tools relevant to drug development have grown in scope and sophistication. Biological systems that can now be modeled in silico range from a single pathway or disease to entire cells, organs, patients, populations, or even clinical trials. Other tools help researchers navigate and mine the vast amounts of information in the various genetic, genomic, proteomic, and other biology databases to build these models. "Over the years, there has been a paradigm shift at the FDA towards greater use of these technologies," says Peck. "The agency has been encouraging the drug industry to use them as well."

Several companies now specialize in developing innovative computational tools for drug development. Adding new meaning to the term "computer mouse," Foster City, California, based Entelos offers researchers in type 1 diabetes their favorite tool, the immune system of a non-obese diabetic mouse—built entirely in silico. Developed in collaboration with the American Diabetes Association, the virtual mouse immune system is far easier to manipulate than its flesh-and-blood counterpart. As a versatile and inexhaustible resource, this in silico animal model could open new avenues for diabetes research, says Richard Kahn, the diabetes association's chief scientific and medical officer. "There are many questions in diabetes that we may never resolve using clinical trials," says Kahn. "Maybe mathematical models could provide effective and accurate answers."

Entelos uses a top-down approach to construct disease platforms and virtual patient populations, drawing from clinical trial results, pathway databases, and other results from the literature. "We build mechanistic models in a compartmental way and then add granularity to those compartments and integrate them according to the question being asked" says Mikhail Gishizky, the company's chief scientific officer. "We don't need to take the modeling down to the gene level in every area." Richard Ho, a principal at La Jolla, California, based Rosa, supports this principle. "Stuff that happens at the cellular level often doesn't make it to clinical significance," he says. In his previous tenure as a diabetes researcher at Johnson & Johnson, Ho used software from Entelos to show that an experimental diabetes drug, which another company had successfully tested on animal models, would fail in humans. Meanwhile, the other company went ahead with clinical trials for this drug. Two years later the results of the trial were in: the drug was ineffective. "The results looked exactly like what we'd predicted with our models," says Ho. "That's lots of time, effort, and expense we saved with four months of computer modeling."

Taking a different tack, Cambridge, Massachusetts, based Gene Network Sciences uses massively parallel computers to "reverse-engineer" disease models directly from gene chip and other high-throughput data. This data-driven approach is particularly effective at capturing the effect of genetic and genomic variations, says the company's executive vice president and co-founder Iya Khalil. She mentions results of unpublished study where researchers used the company's software to reverse-engineer and simulate the action of a cancer drug; among the genes that the simulation detected as being important for the drug's efficacy were several that were not previously known to affect the drug's pathway (Pitluk and Khalil, 2007). "Using this system, you can test millions of hypotheses and then go back and see where these predictions fall in the context of the literature," says Khalil. "Often you end up discovering new biology relevant for the efficacy of the drug."

The list of companies developing in silico tools for pharmacology has steadily grown during the past two decades. This proliferation of tools and vendors has brought its own challenges, such as incompatible data formats, which some newer platforms are trying to address. Meanwhile, at the big pharmaceutical firms, the intended clients for these products, interest in in silico methods is growing. Most of these companies are now either developing such methods in house or working with partners that provide them. The FDA, too, is collaborating with many in silico tool developers including Entelos, UK-based SymCyp, and Mountain View, California, based Pharsight. "In silico methods are having an increasingly important role in different areas of pharmaceutical research and development," says Ekins.

Will computational methods ever be able to completely replace in vitro and in vivo testing? "The answer here can only be a clear and resounding 'no', at least in the near future," says Ekins, along with coauthors Jordi Mestres and Bernard Testa in a pair of recent review articles (Ekins et al., 2007a, 2007b). They point out that biological systems have a highly nonlinear, even chaotic nature, whereby even tiny changes in initial conditions could make them behave in a dramatically different manner. "No computer program will ever be able to fully model their complexity," they argue. Peck is more optimistic. "There may come a time, perhaps 50 or 100 years in the future, when drugs will be discovered in silico, tested in silico, optimized in silico, and made available to patients for clinical use with little or no confirmatory testing," he says. "This is a bold and even somewhat frightening vision, but someday we'll know enough about biology to go a long way towards this goal."

REFERENCES

Doman, T.N., McGovern, S.L., Witherbee, B.J., Kasten, T.P., Kurumbail, R., Stallings, W.C., Connolly, D.T., and Shoichet, B.K. (2002). J. Med. Chem. *45*, 2213–2221.

Ekins, S., Mestres, J., and Testa, B. (2007a). Br. J. Pharmacol. *152*, 9–20.

Ekins, S., Mestres, J., and Testa, B. (2007b). Br. J. Pharmacol. *152*, 21–37.

Pitluk, Z., and Khalil, I. (2007). Drug Discov. Today *12*, 924–930.

Sawyer, J.S., Anderson, B.D., Beight, D.W., Campbell, R.M., Jones, M.L., Herron, D.K., Lampe, J.W., McCowan, J.R., McMillen, W.T., Mort, N., et al. (2003). J. Med. Chem. *46*, 3953–3956.

Singh, J., Chuaqui, C.E., Boriack-Sjodin, P.A., Lee, W.C., Pontz, T., Corbley, M.J., Cheung, H.K., Arduini, R.M., Mead, J.N., Newman, M.N., et al. (2003). Bioorg. Med. Chem. Lett. *13*, 4355–4359.

Singh, J., Ling, L.E., Sawyer, J.S., Lee, W.C., Zhang, F., and Yingling, J.M. (2004). Curr. Opin. Drug Discov. Devel. *7*, 437–445.

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