

MODELS THAT TAKE DRUGS

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Biosimulation: Designing drugs in computers is still some way off. But software is starting to change the way drugs are tested.

FIVE years ago, when the first draft of the human genome was unveiled and the dotcom boom was in full swing, hopes were high for the union between biology and computing. The deluge of genomic information would, the theory went, be funnelled into powerful computers, which would then be able to model biological systems, figure out how they went wrong, and design drugs to fix them. Test-tubes would give way to microchips; biology would go from "in vitro" to "in silico".

All of this promised to benefit not just the health of patients, but of drug companies too, by improving the predictability, and hence the economics, of drug development. It would prevent costly—sometimes tragic—surprises late in clinical trials, or worse, long after drugs had reached the market. In other industries, after all, computerized models and simulations of new products are commonplace. Chipmakers simulate new designs before committing them to silicon; non-existent cars can be driven and aircraft flown in virtual reality. But none of this can be said of the drug industry, which may explain why it spends nearly 25% of its revenues on research and development, or about twice as much as most high-tech industries.

Worse, as the industry spends more, it seems to get less. According to an oft-quoted figure from the Tufts Centre for the Study of Drug Development, in Medford, Massachusetts, developing a drug typically costs \$900m and takes 15 years. Only one in 1,000 compounds tested makes it into human trials, and only one in five of those emerges as a drug. Few industries have such a low hit rate. In-silico biology in 1999, PricewaterhouseCoopers, a consultancy, estimated that it could save \$200m and two to three years' development time for each drug. So how is it doing? Alas, the high hopes of a few years ago have yet to be realised. But there are some hopeful signs that the technology might, at last, be starting to prove its worth.

The field is a crowded one. Some firms, such as Gene Network Sciences (GNS), Entelos, and Rosetta Biosoftware (owned by Merck), specialise in modelling biological systems and processes. Others, such as Spotfire, Simulations Plus, Select Biosciences and Lion Bioscience, are more focused on creating three-dimensional images from the resulting data. There is "a lot of confusion, even among scientists" about how to demarcate the field, says Cristiano Migliorini of Roche, a drug giant based in Basel, Switzerland. Drug companies have concluded that so far, no one in-silico firm has all the pieces needed in the drug-development puzzle, so they have contracts with several of them. "Because of the overpromising of genomics, there is still a lot of confusion about where each of us fits into drug development," says Colin Hill, the boss of GNS.

In-silico biology technologies are being applied to a number of drug-development challenges. But the technology that seems most likely to improve the economics and predictability of drug development is software that simulates the workings of biological processes. There are many factors that affect health and disease, so the trick is to find out which matter most and how to influence them. "Biosimulation" can help both to identify promising targets and to determine the degree to which a drug can affect them.

In the April issue of DRUG DISCOVERY AND DEVELOPMENT, an industry journal, several drug companies including Roche, Pfizer, and Johnson & Johnson, offered high praise for this approach. Roche said that biosimulations had helped it to find additional uses for Pegasys, its hepatitis-C drug. Pfizer noted that America's medicines regulator, the Food and Drug Administration (FDA), had specifically mentioned that computer models "provided confirmatory evidence of efficacy" for Neurontin, a drug that treats the pain experienced after a bout of shingles.

YOU WILL BE SIMULATED

Biosimulation software is based on interconnected sets of mathematical equations, calibrated to represent particular biological and physiological behaviours, which respond realistically when their numerical parameters are adjusted to imitate a particular medical condition or the introduction of a drug. It is still not possible to give a virtual drug to a virtual patient and instantly determine whether it will work against a particular disease--but it is possible to draw some useful conclusions from biosimulation.

Consider a recent example from Entelos, a firm based in Foster City, California. Its technology, called the Metabolism PhysioLab, is based on a mathematical model of the human metabolism. It simulates carbohydrate, lipid and amino-acid metabolism, and models the actions of the gut, the absorption of intestinal nutrients, insulin release, and nutrient cycles in muscle, connective tissue, liver and other tissues. Entelos researchers created 125 unique virtual patients, to represent the variability seen in real-world patients, and then ran a simulation to evaluate an experimental approach to asthma treatment for Pfizer. The simulation determined that while potential drug targets were involved in more than 50 processes in the respiratory system, only three of the 26 known effects and one of the hypothesised effects had a clinically significant impact. The simulation thus determined which physiological processes and drug targets were worth concentrating on. It would have cost Pfizer several years and millions of dollars to get this answer using its standard techniques.

As well as helping in the discovery process--the search for and validation of promising drug candidates--biosimulation can also help with development, when the drug enters clinical trials. Entelos ran another simulation that helped Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) determine the safety limits for a new treatment for type-2 diabetes. The original plan for the trial was to administer different doses to five groups of patients. The biosimulation, again using a group of virtual patients, suggested that the drug would not cause an "adverse event" regardless of the dose. So Entelos recommended that the trial need only test the highest dose. This enabled J&JPRD to eliminate four-fifths of the trial, reducing the total number of recruited patients by 60% and shortening the trial's duration by 40%.

A big limitation of biosimulation, however, is that not all physiological processes are known, so not all are included in the various software models. GNS, based in Ithaca, New York, combines the bottom-up simulation of physiological processes with a top-down "inference modelling" approach based on the analysis of clinical-trial data. Using machine-learning and data-mining techniques, which sort through mountains of data looking for patterns, it is possible both to confirm known behaviours of biological systems, and to predict other, unknown behaviours. The firm's clients include Novartis, Merck and Johnson & Johnson.

Another area where computational modelling can help is in the design of clinical trials--a field in which models developed by Pharsight, of Mountain View, California, have become so useful that the FDA itself is adopting them. Pharsight's "computer-assisted trial design" system models and simulates clinical trials to determine the optimal number of patients, dose amounts, and dosing frequency, all of which have for years mostly been determined through time-consuming and costly trial and error. Pharsight has contracts with big firms including Pfizer and IBM Life Sciences.

GETTING FROM HERE TO THERE

While in-silico biology has come a long way over the past five years, it still has a lot to prove. "Its importance will increase over time," says Henri Theunissen of Organon, a drug firm based in Oss, in the Netherlands. But, he says, "we're currently still in the validation phase of many of these technologies." One problem is that the computer models are still only as good as the data on which they are based, and those data are still incomplete, or are scattered around in scientific journals. Nothing would speed the advancement of biosimulation more than data from clinical trials. Despite public pressure, drug firms and medical journals are reluctant to make such data available.

Dr Hill, the boss of GNS, says his technology delivers to the best of its ability, but needs more information about molecular pathways and mechanisms of action. He reckons that scientists only understand about 5% of the processes involved in drug-cell interaction well enough to model them, create simulations and predict drug behaviour. "The human genome project gave us a parts list for biology, molecular biology taught us how individual parts of the cell work, but 'known biology' is still trailing the 'unknown biology'," he says.

As well as the need for more data, Dr Migliorini of Roche notes that for the field to live up to its promise, the process of drug development will also have to be overhauled. "Without a change in processes," he says, "any large productivity gain is missed." But, he adds, "the industry is certainly now learning how to use these tools intelligently, creating success stories that will pave the way to process changes in the future."

Hans Winkler, senior director of functional genomics at J&JPRD in Beerse, Belgium, says that pathway analysis, better understanding of biological interactions and a greater availability of empirical data all mean that the industry can do a lot better than it could five years ago. But the in-silico biology field is, he says, still 10-20 years from reaching what those in the field say is a key validation point. "We all still have a dream to do something like a gene-expression experiment to analyse how a compound influences apoptosis," he says. This would involve taking a measure of which genes were active in a particular form of cancer, plugging it into a simulation, and then being able to determine which pathways were active, and exactly what the impact of a particular treatment would be. "This is still not possible," laments Dr Winkler. So although in-silico biology is starting to show promise, it still has a long way to go.

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