Targeted Approach

Adopting modelling and simulation technologies for drug discovery and development could help the pharmaceutical industry to overcome the current economic and product pipeline challenge, particularly in the field of CNS research.

Major shifts in the pharmaceutical industry, imposed by drastic reductions in R&D spending and dwindling number of blockbusters, have created the need for innovative improvements in drug discovery strategies. Powerful computer-based approaches are currently in development that simulate the action of drug candidates at intimate levels of nerve cells. This strategy is intended to markedly improve success rates by taking into account complexity and multifactorial features of diseases of the nervous system, two major hallmarks reflected by a broad spectrum of symptoms. Biosimulation-based drug research programmes especially directed towards rare and neglected diseases are expected to profoundly improve the way the next generation of medications are created.

A Healthcare Landscape in Turmoil

All healthcare stakeholders – including patients and their families, caregivers, patient/disease foundations and associations, governments and government organisations, politicians, healthcare professionals, pharma and biotech companies, and insurance providers – are facing increased challenges, particularly in the field of diseases of the central and peripheral nervous systems, and more precisely of neurodegenerative as well as neurodevelopmental diseases.

In particular, medical needs are becoming more acute due in part to an ageing population and the growing costs of R&D in pharmaceutical companies and in academic institutions, while the taxpayer’s concerns and the economic crisis are foreseeing a crisis in the reimbursement of medications.

Following these challenges is the crisis of the pharma industry itself, illustrated by drastic cuts in R&D spending, the shrinking of compound pipelines and a decreased number of blockbusters. Even more dramatically, several of the major pharma companies are slowing their R&D activities in central nervous system (CNS), and in some cases closing entire CNS departments, as seen at Novartis, Basel and AstraZeneca, Wilmington.

The short-term consequences of this disengagement include a drop in the chances of providing treatments for a large population of patients with diseases such as Alzheimer’s, thereby pushing potentially successful disease-modifying therapies to a more distant and uncertain future. Government institutions need to cope with these major challenges and re-think their strategies for supporting and fostering drug research. Ultimately, these government organisations might be forced to find ways to fill the R&D gap. That is the strategy the US National Institute of Health has started to implement by creating centres, such as the National Center for Advancing Translational Sciences, dedicated to advancing drug discovery and development.

Urgent Need for a Shift in DD&D

According to most analysts, the pharma crisis, especially in the field of CNS diseases, is mainly due to the very high attrition rate, leading to enormous increases in R&D costs; the very long time-to-market; little protection time left once drugs are on the market; and only a third of marketed drugs reaching return on investment. Globally, the rate of failure is around 95 per cent for CNS drugs, some 85 per cent of which fail between first-in-man and registration. The major reasons for these failures are a lack of efficacy, the ‘safety issue’, and a lack of differentiation from best in class.
This indicates a real problem with the ‘no go’ decisions taking place along the phases of the DD&D process, from discovery and to preclinical phases where only 10 per cent of drug candidates are discarded. Even in the clinic, Phase 2 trials are not selective enough; 43 per cent of failures are recorded in Phase 3, and another 24 per cent of drugs fail in the registration phase. It appears clear that the filters used during discovery and preclinical stages are not stringent enough. An obvious reason, which is more and more recognised as accounting for the lack of efficacy as well as the occurrence of unexpected side effects, especially with drugs targeting CNS diseases, is that animal models of efficacy are notoriously non-predictive.

Improving the success rate, even by a few per cent, might have a tremendous impact on the overall productivity of the pharma industry. However, to reach such an objective, dramatic changes in the way that we search for new APIs are needed. The most important requirement is to better consider all of the characteristics and features of the disease in question, and thereby the extreme complexity of its underlying biological mechanisms as well as its inherent multifactorial nature. Searching for the ‘magic shotgun’ with multi-agent compounds or drug combinations acting at several molecular targets, biological pathways or networks – instead of the single target/single mechanism ‘magic bullet’ – might provide a true breakthrough innovation in DD&D strategies. This would radically shake-up the strategies applied over the last 30 years, in which DD&D was approached in a very mechanistic way, often leading to oversimplifications driven by the need for high throughput screening of millions of molecules’ quantitative structure-activity relationship assessment, and high performance chemical optimisation.

Further strategy change requires the integration in the DD&D process of all the knowledge generated by basic research as well as data gathered along the value chain, obtained during the discovery or regulatory preclinical stage in the laboratory, accumulated from clinical experience (in terms of treatment regimen, categories of responders and non responders, adverse effects, risks of drug-drug interactions), and obtained as feedback from general practice. In our opinion, despite the fact that a vast amount of knowledge has been accumulated over the last 30 years, proportionally very little is being used in DD&D, mostly because data from basic experimentation and clinical investigation is heterogeneous and therefore cannot be easily integrated.

Paradigm Shifts Need Breakthrough Innovative Approaches and Technologies

Innovative approaches and appropriate technologies have to be developed to integrate the complexity of pathophysiological dysfunctions and their underlying biological mechanisms in order to identify new drug targets, search for lead compounds with better efficacy/side effect profiles, and to optimise already existing drug candidates in clinical development or on the market. The complexity that has to be taken into account appears at many levels: molecular (the binding of a molecule to the many sites of a protein receptor, enzyme or transporter); cellular (adaptation, compensation, topological features); and temporal (long-term modifications of drug effects). Indeed, complex interactions at the molecular level regulate activity at the level of neurons, while interactions between multiple populations of neurons ultimately give rise to complex neural system function and behaviour. This spatial complexity takes place in the context of a composite temporal integration of multiple scales, ranging from microseconds, to hours or even longer. This organisation, spanning many spatial and temporal dimensions is extremely difficult to grasp experimentally and thereby, renders the interpretation of the drug effects obtained in vitro and even more in vivo very hazardous. Therefore, innovative technologies capable of assembling all the pieces of this gigantic puzzle are required to search for, test and develop this huge diversity of parameters.

Biosimulation: a Technology of Choice

The modelling and simulation (M&S) approach is directly aimed at assembling the puzzle, by creating well-suited architectures, developing the most appropriate and efficacious tools and algorithms and taking advantage of the prodigious development of computational instruments. Ultimately, the objective is to simulate on the computer the path and fate of an active molecule and potential drug candidate and to determine its effects on reconstituted/reconstructed neurons that incorporate known pathological features.

Modelling is used in most industrial branches and the creation of simulators is an almost obligatory passage for technological innovation that may endanger human beings. In the health domain, and by extension human diseases, M&S has been applied to identify better treatment in most therapeutic fields, including cardiovascular, respiratory (asthma), inflammatory-related diseases, as well as oncology or virology. M&S is currently applied by most pharmaceutical companies to predict pharmacokinetic profiles of drugs, risks of side effects, skin permeability, or blood-brain barrier penetration. But in the field of CNS diseases, the M&S approach has rarely been used to simulate disease states or drug efficacy and safety profile, essentially because of the complexity of these diseases.

Reconstructing neurons on the computer and simulating mechanisms of signal transduction in order to test drug candidates under pathological conditions necessitate the integration of events taking place at the molecular level and up to higher levels of cellular complexity in order to perform multi-scale testing and profiling of drug candidates. Basically, modelling is a process which consists of representing basic molecular and subcellular constituents of the nerve cell by mathematic equations describing kinetic models of physico-chemical reactions. In a ‘bottom up’ approach these basic
elementary models are assembled in increasing levels of complexity by incorporating cell connections and geometries, circuits and larger neuronal networks. The functional input/outputs between elementary models and higher levels of complexity constitute multi-scale simulation engines. Constructing M&S platforms is an iterative process necessitating a permanent dialogue and mutual cross-fertilization between bench experimentalists and modellers involving neurobiologists and engineers in informatics, mathematics, physics and chemistry (see Figure 1).

**Multi-Scale Biosimulation Technology to Foster Drug Discovery in Rare Diseases**

The immense complexity of rare diseases, such as Huntington’s disease – a fatal, inherited neurodegenerative disease, characterized by a broad spectrum of quite often contradictory symptoms – is probably the biggest hurdle for finding the most appropriate treatment. This makes the biosimulation approach particularly well suited for identifying drugs that could target the optimal nodes that connect a large number of molecular and subcellular events, and could address any of these symptoms. The triad of motor dysfunction, mental disorders and cognitive deficits in Huntington’s disease reflects the disruption of numerous and different signaling cascades. Thus, an M&S approach is particularly appropriate, as it dissects the roles of different biological mechanisms in the occurrence of each of these symptom groups, and to simulate the effect of drug intervention on the balance between hyper- or hypo-active activity of various signal transduction mechanisms present in neuronal populations that are progressively dying during the course of Huntington’s disease.

The significant advances that could be provided by simulating deficits of rare diseases will also help to shed new light on neurodevelopmental (such as autism), neurodegenerative (such as Alzheimer’s) and psychiatric (such as depression and schizophrenia) diseases affecting broader patient populations.

**Advantages Available**

Adopting M&S technology offers a number of advantages for improving efficiency, including:

- **Improve the Success Rate of DD&D**
  One of the main interests for implementing an M&S approach is its capability to address one of the major challenges facing the pharma industry: to improve success rate. Thus, applications of the biosimulation could provide clues to identify and thereby anticipate risks of failures in drug effectiveness or foresee potential and initially unexpected side effects, as illustrated in the following examples:

  - The apparent effects of drugs might be highly dependent on the experimental conditions, leading to interpretations and hypotheses that might prove to be wrong at later stages of the DD&D process; the biosimulation approach, by performing try-and-fail tests on the computer under a broad spectrum of experimental conditions.
been repeatedly observed that drug candidates with clear-cut efficacy in _in vitro_ and/or _in vivo_ animal models are ineffective in humans. Therefore, preceding bench experiments by simulation and taking into account as many pathological features as possible in the model may considerably reduce the risks of failures, and at the same time the number of bench experiments, and the number of laboratory animals required, thereby decreasing the R&D costs and optimising the time-to-market.

### Generate New Knowledge

One criticism of the M&S approach is that modelling can only be as good as the experimental data used. However, by creating _in silico_ models that require optimisation of a certain number of experimental parameters and the identification of new experimental conditions, information obtained using the biosimulation process provides new directions for bench experimental testing.

### Some Challenges of the Biosimulation Approach

In order to establish the widespread adoption of the biosimulation approach for DD&D in CNS, a number of challenges needs to be overcome.

### Need for Standardisation of Experimental Data

The power of the biosimulation approach is its ability to integrate a wealth of experimental data from multiple domains of research ranging from physiology and pharmacology, molecular and cell biology, human genome and resulting genomic and proteomic data, metabolomic data, to clinical experience, including...

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For standardised experiments and data sets, less predictive ones, and to establish rules, it is necessary to harmonise all of these data, to filter out those that are predictive from the rest. Many results are not usable because of the restricted ‘faith validity’ due to the experimental conditions. Therefore, there is a need to harmonise all of these data to filter out those that are predictive from the less predictive ones, and to establish rules for standardised experiments and data sets.

**Need for More Validations and Proofs of Concept**

The biosimulation approach applied to DD&D in CNS is in an early stage, and its acceptance rests on extensive validation by: providing simulation results that can reproduce the experimental results under any condition; making predictions that are confirmed by bench experiments; and ultimately, by clinical applications. There are already such validations, as well as proof-of-concept studies. A recent achievement is the uncovering of new mechanisms of action of a drug candidate to treat Huntington’s disease, which would have been very difficult using only bench experiments.

**Acceptance from All Stakeholders**

Although most of the major pharma and biotech companies have embraced the ‘systems biology’ approach and are building up their biosimulation approach in various therapeutic areas, its application to DD&D for the treatment of diseases of the central and peripheral nervous system is still at an embryonic stage. As a consequence, stakeholders in the global healthcare era remain relatively skeptical and suspicious. In contrast, health institutions, such as the US National Institute of Health or the FDA, are seeing biosimulation as promising and worth pursuing its evaluation. In a recent NIH white paper, the panel recommended ‘the establishment of multi-faceted research programmes that combine experimental and computational studies and span biochemical, genetic, animal and clinical approaches’. Likewise, the FDA has initiated and supported several programmes involving computer simulation technologies to ‘simulate the activity of experimental medications so the agency can get an earlier read on the safety and efficacy of drugs in the pipeline.’

**Conclusion**

The biosimulation approach might certainly be one of the future directions required by paradigm shifts in the search of better medications. Considering that the actual low success rate of DD&D underscores weaknesses of the predictive value of animal models and of the single target/single mechanism approach, the famous quote “all models are wrong but some are useful” amply justifies expanding and generalising the biosimulation approach, especially, but not only, for the rare, orphan and neglected diseases for which medical need is even more urgent.

Learning from the experience of using biosimulation in many non-CNS therapeutic areas and bringing together multidisciplinary teams of researchers, business developers and executives from the pharma and biotech industry, as well as experts from government organisations, would tremendously boost the biosimulation approach.

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**About the author**

Serge Bischoff is the President, CEO and co-founder of Rhenovia Pharma, which provides services to optimise the drug discovery process of pharma and biotech companies. Having completed a PhD in neurobiology, Serge moved to the big pharmaceutical industry. For five years, he was a research scientist at Synthelabo-Sanofi in Bagnieux before spending 24 years at Ciba and Novartis in Basel, Switzerland. Here he was heading drug discovery programmes in psychiatric and neurological diseases. Email: serge.bischoff@rhenovia.com