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PERSPECTIVE

Gazing into the crystal ball; the future of computer-aided drug design

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There is nothing new under the sun

Twenty-five years is almost a full career for a scientist, but before looking to the future, we should ask what is really new in the last 25 years, i.e. since 1986? Surprisingly little! Here is a partial but still fairly good list of techniques routinely used by modellers: high throughput docking, high precision docking, free-energy calculations, quantum mechanics, molecular mechanics, distance geometry, molecular dynamics, statistical thermodynamics, conformational searching, scaffold morphing, solvation, QSPR, QSAR, bioavailability predictions, pharmacophores, protein modeling, de novo design, library design, chemical databases and searching, data analysis and visualization, virtual screening, chemometrics, interaction analysis using small molecule and protein x-rays, and FBDD. The majority of these techniques were introduced in the early to mid 1980s, and we think everything on the list except FBDD was introduced by the early 1990s (many techniques have been re-invented since; the collective memory of the literature seems to be under 10 years and falling). The biggest revolution in computational chemistry over the last 25 years was not a new computational technique, but rather the introduction of Beowulf clusters around 2000, which in just a few years increased processing power by about 100× beyond Moore's Law for many problems, i.e., it skipped at least a decade. This "suddenly" enabled application of a large number of the techniques from the 1980s to real systems.

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Speed and size matters

So what about the next 25 years? If Moore's Law holds, doubling compute power every 1.5–2 years predicts something like a 10,000X–100,000X increase in computer power. Approximations in sampling, conformational analysis, and the level of theory can no longer be justified by the expediencies created by slow hardware. However, it can be argued that fundamentally we have not advanced a great deal in physics-based scoring methods, especially with respect to the treatment of solvent in the calculation of free energies of binding. In future, we should be able to treat even protein systems using QM at a high level of theory. That alone will let us solve many problems interactively in minutes that today need an expert to devote weeks or months to. The increased computer power might finally improve the ability to predict ligand–protein binding, but this will not be a game changer. Medicinal chemistry is already very good at engineering tight binding ligands. If only we understood water. Perhaps that too will come into scope as force fields are developed that can truly handle multipoles efficiently and accurately.

Trust but verify

A key advance over recent years has been the creation of open-access databases that are becoming increasing well

curated. For a decade the only larger freely available molecular database was the famous NCI dataset. In the last 5 years or so the amount of well-validated free molecular data, including also bioactivity information, has exploded (PubChem, ZINC, ChEMBL…). This has allowed academic researchers to validate their models and theories with robust data. Not only has the quantity of data increased but also the quality, to include experimental conditions, underlying metadata, and annotation. Robust data sets should lead to robust models. In the future, we may be able to see similar advances in the modelling of ADME phenomena, if the Pharma companies can be persuaded to release more of their studies. At some stage, models could become so robust that they are used to detect outliers and anomalies in new data as part of the curation procedure. These anomalies could be used to investigate the experimental procedure, or to highlight the need for a new model to be built. While much of this process could be automated, human intervention would still be necessary to distinguish whether the data is telling us something new, or something erroneous. Database searches will routinely return a combination of experimental and predicted results. This is a true "knowledge base", in which the experience of millions of previous experiments is combined to make reliable estimates for new cases.

Share the wealth

There is an increasing number of high quality, free or open source tools for molecular modelling and cheminformatics. Our fields are catching up slowly with the traditionally more open bioinformatics arena. This means that we are moving slowly towards common standards, allowing niche software vendors to concentrate on their particular expertise, without having to support a very large number of tools needed for a vertically-integrated suite. Those tools are now freely available and can support most of the common formats. This, combined with the increased number of cpu's, also means that we have to move away from the traditional modes of software licensing, that is, one modeller, one cpu, one token. If we do not, then we cannot take full advantage of the hardware that will be at our disposal, and progress will be limited. It will be interesting to see which vendor is the first to realise the opportunity.

Say what you mean, mean what you say

As modelling has become a standard part of medicinal chemistry, we need to take especial care over how we present our results to semi-naive interpreters. There is a very common trend to overquote the number of figures of significance, giving a false impression of precision, or to applying generalised, blurred conclusions to the context of particular problems. This has been to misunderstand the chemists and managers in drug discovery, who take these estimates at full face value. In the near future, we would hope that all models return not a single figure, but an error estimate, derived from the experimental error, the local neighbourhood and other factors, to give a much better idea of the value of the prediction. There have been great leaps in QSAR from an understanding of statistical artefacts, to domain applicability, SAR landscape modelling and model aging, but there is still much further to go. This will become more important as the use of Pareto-based multi-objective methods spreads; then the output of many models will be used simultaneously, and we will need to be confident about every link in the chain. We should also be humble and acknowledge that some of the best contributions of modelling to drug discovery have not been dependent on numerical modelling.

Trimming the sails

Skilled modellers often adjust default parameters in programs to reflect local knowledge and experience, with a view to obtaining the best enrichment or similar. The best performance in docking and scoring is still obtained by a modeller reranking the list by eye If however the metric to be optimised can be defined clearly from prior experiments on analogous systems, then, with the increased computing power at our disposal, we could conduct exhaustive parameter scanning to optimise enrichment in the training system before applying to the test system. This could even include the parameters used to create the underlying databases!

Integrate and assimilate

We believe that a true paradigm shift will come from the integration of increasingly accurate computational chemistry models with emerging models from other fields. Unlike computer-aided drug design, the biological fields have seen many new technologies in the last 25 years, and have produced many models that rely on chemical insight. This field will extend beyond genomics and pathways to modelling cells, organs and even to modelling whole animals as foreshadowed by current PBPK models. Thus, molecular design will advance from predicting general molecular interactions to modelling local cellular functions of interest to discovery project teams, then to PBPK and animal efficacy. This last might be most important, since the inability to predict human effects based on animal

models is the most costly part of drug discovery. We can currently cure almost any disease in a rat model, but most compounds fail in expensive clinical testing. Real progress in predicting human results based on animal testing would be the biggest game changer. This sounds farfetched, but it is a perturbation problem, which gives us optimism; we can already do it on a single compound basis, with the support of a lot of hard-won experimental data.

We also see an increased need to front-load development-like activities into the pre-clinical phase, whether through regulatory requirements or through management 'fail-fast' strategies. In this respect, the ability to predict crystallinity/polymorph forms, and therefore solubility, will finally arrive, as will models for ADME, PK/PD and the like, rolled into single multiobjective models. We will need to be able to translate our results (plus errors) into risks, to drive proper decision-making.

Conclusion

We have deliberately painted a slightly bleak picture, but this is intended to give hope to young researchers. There are still many interesting and challenging problems in our field waiting for the prepared mind. There are still many unconquered diseases and aspects of drug discovery that could be greatly assisted by improved modelling techniques and better informatics.