[Interview] The Rise of Quantum Physics in Drug Discovery

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Computer-aided drug design (CADD) is a central part of so-called "rational drug design", pioneered in the last century by companies like Vertex. Over the last decades, CADD had great influence on the way new therapeutics are discovered, however, it also showed limitations due to modest accuracy of computational tools.

The majority of software tools used for computational chemistry and biology rely on molecular mechanics -- a simplified representation of molecules, essentially reducing them down to "balls and sticks": atoms and bonds between them. In this way it is easier to compute, but accuracy suffers greatly.

In order to gain adequate accuracy, one has to account for the electronic behavior of atoms and molecules, i.e. consider subatomic particles -- electrons and protons. This is what quantum mechanical (QM) methods are all about -- and the theory is not new, dating back to the early decades of the 20th century.

However, quantum methods are extremely computationally costly -- so much that it was a prohibitive barrier for the quantum theory to really influence the practical side of things until very recently.

Nowadays, due to an exponential growth of available computing power, quantum methods are finally becoming valuable tools in scientists' hands.

Recently I did a brief research and gathered a list of computational startup applying quantum theory to drug discovery to tackle practical use cases. One prominent example is Barcelona-based computational startup Pharmacelera, which develops disruptive solutions for computer-aided drug design.

I talked to Dr. Enric Gibert, CEO and Co-founder of Pharmacelera to get a better understanding of how quantum methods can boost modern pharmaceutical research:

The "Two Enrics": Dr. Enric Gibert (CEO) and Dr. Enric Herrero (CTO)

Enric, can you tell a story behind Pharmacelera, how has everything started?

The company was founded in 2015 by Enric Herrero (CTO) and myself – known as the two Enrics. The two of us have a background on High-Performance Computing, machine learning and software development. Early in the project we involved Professor Javier Luque from the University of Barcelona, who is a highly-cited expert on Quantum-Mechanics (h-index of 70), and Manel López, who worked for more than 20 years at the Molecular Modeling group at Almirall. Bringing together this team allowed us to leverage personal industry connections, expertise and multi-disciplinary know-how for the benefit of the company development.

We raised around a million Euro of capital from public grants and business angels with substantial track record in the pharmaceutical industry, which allowed us to engage "smart money" for the early phase. We then spent around 2 years developing a platform's core components and shaping the future product, which is now ready to use.

What kind of products and services does your company offer?

Our technology is based on a novel and accurate 3D representation of molecules derived from Quantum-Mechanics (QM) calculations and we have developed two products around it. PharmScreen is a state-of-the-art virtual screening software package to find candidate molecules with larger chemical diversity from compound libraries. PharmQSAR is a 3D Quantitative Structure-Activity Relationship (QSAR) software package that builds predictive models based on data from experimental assays. Our goal is to offer both products on a licensing basis: a cloud-based Software-as-a-Service monthly subscription or a yearly license for companies willing to execute our technology on their own IT infrastructure. As experts in computational chemistry, we also provide a wide range of contract research services in computer aided drug design. We have published several scientific papers (including a recent one in the Journal of Chemical Information and Modeling (JCIM) last year), some co-signed with GSK, explaining a bit of science behind our technology. This technology has already raised the interest of several top-notch institutions and we have recently signed a partnership collaboration with the Cambridge Crystallographic Data Center.

Then, what would be a typical use case for your customers, and how would quantum theory/calculations factor in to add value here?

Both PharmScreen and PharmQSAR use a unique 3D representation of molecules based on electrostatic, steric and hydrophobic interaction fields derived from QM calculations, achieving higher accuracy compared to alternative approaches. I would like to reinforce the importance of the hydrophobic / lipophilic profile of compounds as (de)solvation is often disregarded by most software packages and it plays a key role in determining the interactions between a ligand and the binding pocket.

Using this technology, we can tackle a wide range of problems in drug discovery. For instance, we can create an ad-hoc library of commercially available compounds based on certain structural properties specified by a customer and perform an accurate virtual screening of the library to identify diverse hits from an initial suggested scaffold. And when talking about virtual screening, we can extend it to fragment screening and scaffold hopping, as these are slightly different approximations to the same problem of identifying novel molecular skeletons. We can also enhance the screening results of a molecular docking

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campaign by using our QM methods to accurately compare molecules. We are presenting our latest work in this regard at GRC CADD meeting in July, showing synergy and getting the best of both structure-based and our ligand-based methodologies. Regarding QSAR, we can build a regression model based on experimental data, derived insights about what parts of the molecules are contributing positively / negatively to the interaction and predict the activity of compounds that have not been tested experimentally. I can think of many other examples and case studies in which our technology and our expertise on computational chemistry can help identify and optimize

Speculations about potential of quantum theory in chemistry and drug discovery has been going on for a long time. In 2013 there was even a Nobel Prize awarded for that kind of stuff. However, it seemed like a lot of quantum methods used to be more of a theoretical value, rather than having a real practical impact. Now I can see that new startups emerge to offer quantum theory to tackle real-life drug discovery problems. Does it mean the era of quantum theory has finally arrived in the pharmaceutical industry? Thanks to what?

I would distinguish here two concepts that share some characteristics but that refer to different things that are often confused. Quantum-Mechanics (QM) and Quantum Computing (QC). QM, on the one hand, is a fundamental theory in physics which describes nature at the smallest scales of atoms and subatomic particles. These algorithms represent the reality more accurately than traditional methodologies at larger computing costs (these algorithms are executed in traditional computing systems). However, computing resources are now ubiquitous, and commodity and the industry is looking for new methodologies to find a new wave of New Molecular Entities. Hence, there is definitively an increase in the applicability of this fine grain theory in drug discovery.

On the other hand, QC refers to a new set of computing devices that are built around quantum-mechanical phenomena. As opposed to current computers that represent states as binary 0/1 values and operate on logical binary operations of those, QC computers represent values in Qubits, which can be 0, 1 or a superposition of the two. A Quantum Computer of n Qubits can be in any superposition state out of $2n$ possibilities and quantum algorithms are often labeled as probabilistic computing. It is a totally different theory that is expected to solve problems that current computers can't. All big technology companies (IBM, Microsoft, Google, to name a few) are working on QC and the first low scale prototypes

are available. However, it is still an immature technology and a massive use is not expected in the short-term.

To wrap it all up, what do you think will be a role, ultimately, of quantum theory and some related computational technologies, such as machine learning, in the future drug discovery workflow? Will those tools become central in the pharmaceutical research? What about human creativity?

Yes. I think that we have seen and will continue seeing an increasing interest in Quantum-Mechanics and Quantum Computing. Developing a new drug is extremely expensive and the costs are not declining yet the opposite. Hence, the ecosystem is looking to new technologies that can help revert this situation. In our field (computer-aided drug design), researchers are embracing machine learning, and quantum-mechanics as new leaps to accelerate and improve drug discovery. Human intervention, expertise and creativity will still play a key role, no doubt about it. But there will be a huge difference between teams working in drug discovery embracing these technologies and teams that get stuck with traditional methodologies only.

Enric, thank you very much for your time!

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If you have more questions about Pharmacelera and their products, please, reach out to contact@pharmacelera.com. You may also follow their activity in LinkedIn.