Quantum Computational Toxicology

A Paradigm Shift: When Computational Toxicology Intersects with Quantum Chemistry

Safety of chemicals (e.g., environmental pollutants and pharmaceuticals) is of paramount importance. FastCompChem is revolutionizing computational toxicology through a new concept of molecular signature derived explicitly from quantum chemical calculations. Unlike existing approaches, it is possible to cover large swaths of the chemical space since predictions are not tied to known motifs but to the effects on the electronic structure. Pedro Lopes, founder of FastCompChem, explains the company's technologies and describes the options and steps ahead.

Pedro Lopes, FastCompChem, UBIMedical

Personal Profile

Pedro Lopes is the founder of FastCompChem. He holds a chemical engineering degree from Instituto Superior Técnico (IST), Lisbon, Portugal, and a PhD in computational quantum chemistry. He held a faculty position at the University of Maryland, Baltimore, USA, where he developed CHARMM force fields and worked on drug discovery projects. As he became increasingly disillusioned with the current progress of computational tools, he addressed the bottlenecks of quantum methods. Starting with those core technologies, he founded FastCompChem to pursue technologies for quantum-based computer-aided drug design, with initial focus on toxicology.

CHEManager: What was your motivation to start FastCompChem?

Pedro Lopes: I decided to incorporate FastCompChem in 2019 to generalize quantum chemical methods in chemistry and biochemistry. Although I am a quantum chemist by training and vocation, I wanted to learn the art of parameterizing classical force fields. They are crude approximations of physical reality, but they became the de facto standard in molecular simulations. After working many years on CHARMM force fields, I became increasingly disillusioned since force fields have reached a dead end. Only quantum chemistry can sustain the progress of computational chemistry. I made two major contributions to generalize quantum methods. In 2017, I published a very fast approximation to electron repulsion integrals, and, in 2018, the results of an electronic structure optimization algorithm without formal diagonalization. Then FastCompChem was formed to develop solutions to drug discovery. Our current focus is computational toxicology.

Why do you focus on computational toxicology and not on other areas of computational drug discovery?

P. Lopes: Conceptually, it would be easier to develop technologies for virtual screening and molecular simulations. The underlying technologies are similar and much of the work would be replacing the classical with quantum calculations. The impact, however, would also be small since it's a crowded space and companies already have systems with similar functions. Computational toxicology is different. On one hand there is a strong push for new accurate methods. Safety concerns are a major issue in late-stage clinical trials and there is the need of alternatives to animal testing. An in silico solution that accurately predicts toxicity early will save the pharmaceutical industry millions of euros and for environmental effects it is a great way of evaluating chemicals. We have the necessary knowledge to develop the technology.

But there are currently methods for assessing the safety of chemicals, including using quantum descriptors. What differentiates FastCompChem?

P. Lopes: Quantum chemical descriptors are used, for example, in QSAR models, but our technology is radically different. Currently molecular descriptors are derived from molecular structures. Our concept is to develop new descriptors derived from the electronic structure instead. Besides physical observation only possible with quantum methods, the new technology covers the whole chemical space, when quantum calculations are feasible. We don't need to know the effect of each fragment or moiety but merely their combined effects. Although we are developing this technology for computational toxicology, the applications are much broader and can impact chemoinformatics.

What is required to develop the technology?

P. Lopes: Today, nothing is impossible to solve in computational chemistry if there is willingness and the right skills and collaborations. FastCompChem seeks a multidisciplinary approach, with the areas of quantum chemistry and computer science being very relevant. We also need extensive collaborations with the industry and academic groups. Those collaborations are essential to provide expertise in toxicology, to provide experimental data and general guidance to prioritize development. We have a collaboration with a leading quantum chemistry group at the University of Manchester. We are also establishing contacts with leading computer science research institutions. The ultimate goal is to form a large "coalition of the willing" of interested parties to develop the technology.

What is your business model? How do you plan to commercialize the solution?

P. Lopes: At this moment, I can say that it depends on the number of parties joining the project. With a large coalition of multidisciplinary collaborators, and considering the scope of computational toxicology, most likely a different entity will have to be established, for example a consortium. It will always be open to new credible and experienced partners, following a R&D operating model that encourages new partners to join, when needs are identified. Monetization can happen through licensing of the technology or through the execution of specific projects.

What do you expect FastCompChem to be in 10 years?

P. Lopes: Continuing with the best-case scenario I see FastCompChem diversifying into other areas, always with the goal of providing the most accurate solutions based on quantum chemistry. In drug discovery we want to offer complete solutions that also include virtual screening, molecular simulations, ligand-based strategies, etc. I also see great opportunities in other areas such as de novo design of enzymes and catalysis, to name a few.

Business Idea

Quantum Chemistry in Computational Toxicology

Computational methods for drug design are largely based on classical force fields and structure-based chemometrics. They have significant problems:

- The physical models are poor
- They are not easily generalizable to new systems and chemistries
- They cannot be significantly improved
- Only an infinitesimal part of the chemical space is covered

Progress in computational chemistry is possible with: (1) using much better physical models, and (2) reaching larger swaths of the chemical space. Quantum chemistry should underpin the next generation of computational tools as it is the most accurate theory to study matter and its interactions, while dispensing with specific parameterizations. FastCompChem developed very fast solutions that allow generalization of quantum methods: the fastest approximation to electron repulsion integrals and a very competitive electronic structure optimization algorithm. Diagonalization is an area of active research for other applications.

In terms of business development, FastCompChems's easiest move would be targeting technologies for virtual screening and molecular simulations. This is a crowded space and adoption of the new technology would face significant barriers. Computational toxicology offers greater opportunities and was chosen instead. Specific reasons for developing quantum-based computational tools for toxicology are:

- Reduction of time and costs of drug design processes by bringing safety testing earlier
- Provision of an effective alternative to animal models
- Extension of the same technology to chemoinformatics

Besides the significant impact of the quantum computational toxicology tools there are additional benefits. The technology will work as a Trojan Horse in driving acceptance of quantum technologies initially in drug discovery and in other areas of chemistry and biochemistry. The general adoption of quantal technologies by the industry is a crucial step in ensuring the continued development of computational chemistry and of its applications.

- FastCompChem, Covilhã, Portugal
www.fastcompchem.pt

Elevator Pitch

Changing Computational Chemistry

FastCompChem was founded to develop new quantum methods for drug discovery. Development is prioritized in terms of the perceived need and estimated impact. At FastCompChem computer science assumes an equal footing to quantum chemistry to allow fast prototyping of new concepts.

Milestones

2017

- Fastest approximation of electron-electron repulsion integrals (ERIs) is published. The proof of concept used 3-center integrals. The technology was subsequently extended to 4-center ERIs.

2018

- Results from a competitive alternative to formal diagonalization were published. It was based on an Extended Hückel Hamiltonian complemented with toy electron-electron repulsion functions. The future molecular dynamics software will likely be based on the tight-binding approximation.

2019

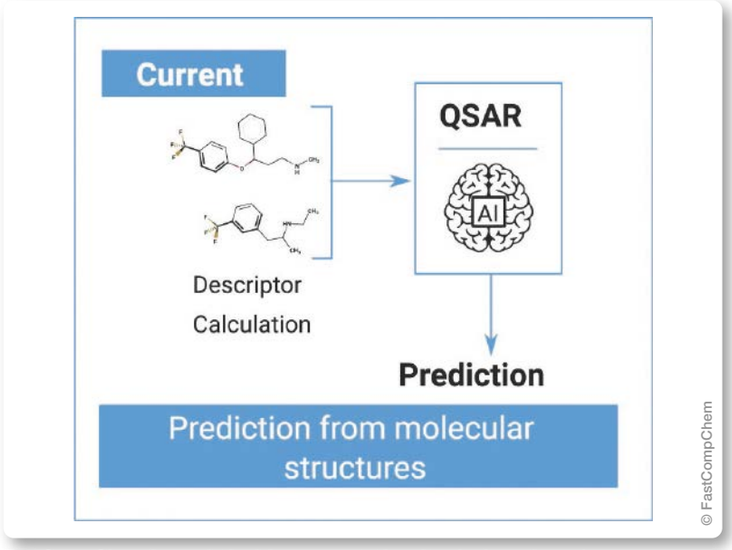
- Foundation of FastCompChem

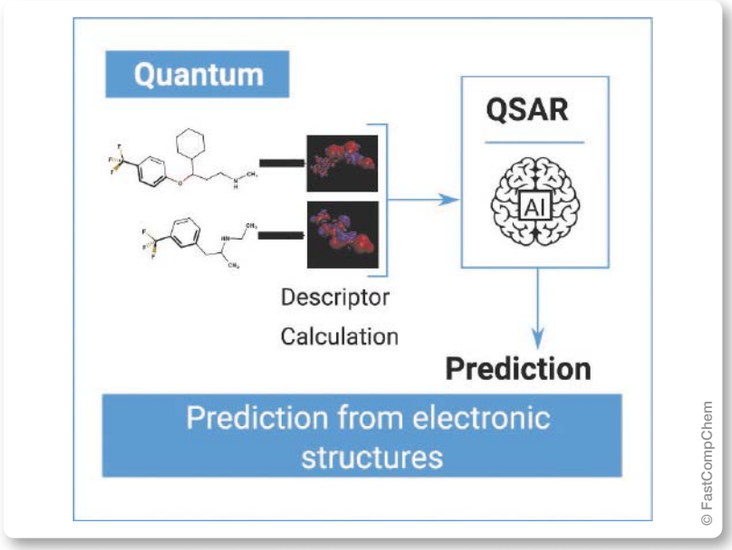
2020

- With the onset of the Covid-19 pandemic, FastCompChem was funded by the PT2020 program (€500,000) to develop novel diagnosis for the infection because of its expertise in AI, computer graphics/vision and scientific software development. Medical diagnosis became a totally separate R&D program of FastCompChem.
- FastCompChem received an investment from Portugal Ventures (€100,000). Work began on the concepts of the new quantum-based computational tools for toxicology.

Roadmap

FastCompChem is currently building collaborations. The development of new computational toxicology tools requires the active involvement of leading partners from the industry and academia. Development will be accelerated with the active participation of leading computer science institutions. FastCompChem already has a collaboration with the University of Manchester to advance the quantum chemical component.





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