Commentary: Jarryl D'Oyley and Catherine Stace

Redefining drug discovery using quantum physics

The world of pharmaceutical research is characterised by high budgets and decade-long timelines. But this may be on the cusp of change. Quantum physics, or the study of matter and energy at the most fundamental level, has the potential to deliver outcomes for drug discovery that are both more efficient and less costly than current methods. The application of this technology across all drug types is potentially profound. In this article, we describe how our company Kuano Ltd of the UK[1] is taking advantage of this opportunity.

In recent years, computer-based methods have made huge progress in drug design and development. Artificial intelligence plays a big role, with tools like AlphaFold and RoseTTAFold, by transforming how we predict protein structures. But despite their sophistication, these methods still rely on simplified models of chemistry and may not fully capture the real physical behaviour of the biological system.

One way to visualise this is to think about classic ball-and-stick diagrams – atoms fixed at points in space where only distance and position seem to matter. Most of today's advances in computer-based drug design, even the most powerful AI-driven tools, are built on this same picture of the world. But if we keep feeding our models the same kind of information, we'll keep running into the same limitations irrespective of how sophisticated the algorithms have become. By moving beyond the rigid classical descriptions and adopting quantum mechanical ones when they matter, we can reveal what was once hidden. Suddenly, what looked like an unsolvable problem becomes an opportunity for discovery.

Quantum-enhanced insight

Consider an enzyme and the reaction it drives. If we want to design the most potent and truly selective inhibitors, we have to go beyond a simple picture of shape and coordinates because many proteins in the same family can look almost identical. Instead, we need to understand the possibilities and probabilities of how that specific reaction unfolds, and how we might influence it. This requires stepping into the realm of quantum physics. This quantum-enhanced insight allows for the prediction of molecular behaviour with unprecedented accuracy, simulating complex chemical interactions before costly laboratory experiments begin, and identifying promising compounds that conventional screening might overlook.

When it comes to understanding covalent ligand reactivity, conventional approaches typically focus only on what happens between a single amino acid and the reactive chemical group, or warhead. In reality, the outcome depends on a system-wide interplay in which the protein, its environment, the warhead, and the ligand all influence each other. To capture this complexity and uncover a solution across the wider system, we need the tools of quantum physics.

Quantum physics throws the classical rule book out of the window. It is an alternative view of the world in which probabilities are considered. Parts of this realm are interconnected by non-local entanglement, enabling us to calculate outcomes that defy conventional expectations. It reveals what is normally invisible, such as transition states, and allows us to predict behaviours that might seem counterintuitive. The local world of classical models becomes more holistic and interactive, turning mysteries into explainable phenomena.

But here is the challenge: when a large number of alternatives in a quantum picture of the world need to be tracked simultaneously, the amount of data explodes and the computational demands quickly become impractical. How can we harness this quantum viewpoint? How can we organise such vast data and make simulations of complex systems truly scalable?

At Kuano we believe that this can be achieved through quantum-computing inspired algorithms that run on existing digital infrastructure; no quantum computer is needed. As quantum hardware matures however, our technology is ready to scale up seamlessly, harnessing even greater computational power.

This platform has been able to deliver accurate, scalable, quantum-level simulations in biologically relevant systems on existing infrastructure. At the same time, it is positioned to leverage quantum hardware when it becomes viable. This is the result of a fusion of quantum computing principles with AI and machine learning, to create what we believe to be something that exceeds the scale, accuracy and resolution of other physics-based approaches, such as Density Functional Theory (DFT), a computational method for predicting the electronic structure of molecules that is becoming increasingly commonplace. However, the next generation of these methods, such as Kuano's technology, blends DFT and other familiar tools with advanced theoretical concepts and cutting-edge techniques. For example, the company has been able to deploy specialised metrics to measure entanglement, and automated orbital selection to focus on aspects where quantum matters. Tensor networks, which are a mathematical framework for understanding complex data, are also used to exploit insights from quantum computing. These add up to providing Kuano with a sophisticated filtering and property optimisation system which integrates with generative AI for compound design. As a result, we have a platform that enables us to look at the biological world differently, unbounded by what went before. This enables us to explore new chemical space where quantum simulations can replace the absolute need for pre-existing experimental datasets.

Unlocking drug programmes

Conventional approaches often falter when faced with targets that are under-researched, structurally complex, or biologically obscure. Fragment screening, docking, and structure-based design typically focus on stable, well-characterised biomedical targets, leaving a vast array of promising targets unexplored. One such target is an enzyme called Notum which is linked to Alzheimer's disease and colorectal cancer[2]. Despite its therapeutic promise, this enzyme has never reached clinical development. Repeated attempts using traditional methods such as advanced medicinal chemistry and fragment screening techniques, have failed to generate viable leads. As a result, Notum has been largely dismissed by the pharmaceutical industry as too difficult or obscure to pursue. Kuano however saw the enzyme as a way to demonstrate how quantum physics, fused with artificial intelligence, could turn targets that were thought to be undruggable into druggable ones.

The approach was to simulate the transition state, which is the fleeting, high-energy intermediate where reactions occur. This state is the key fingerprint of enzyme function which can only be simulated using quantum. It is the key to unlocking the potency, selectivity, and mechanism of action of a molecule. It also revealed chemical interactions that were invisible to conventional simulations, and enabled the company to identify potent inhibitors and demonstrate early *in vivo* efficacy. This was achieved with fewer than 100 compounds and demonstrated a potential for a new generation of precision therapies, even against the most elusive targets[3]. Another example is DNMT1, a methyltransferase which is implicated in multiple cancers and is known to present significant challenges. DNMT1 shares its natural substrate with its close relatives DNMT3a and DNMT3b, making the design of selective inhibitors difficult. Current drugs circumvent this by avoiding the active site and binding the DNA substrate instead. But this causes unwanted side effects. By contrast, in just two months, we were able to demonstrate selectivity for DNMT1 over DNMT3a/3b with only 40 synthesised compounds. This unveiled a totally new type of chemistry that avoided the nucleoside analogues that had blighted earlier therapies for this target[4].

While comparable projects typically require budgets exceeding £1 million and large teams, the Notum inhibitor progressed with just £350,000 and a lean, highly skilled team, achieving faster timelines than industry standards. This was particularly impressive given Notum's largely uncharted scientific territory. In the case of DNMT1, a longstanding, industry-wide conundrum was solved in a number of weeks. By comparison, the nearest reported alternative took months, if not years, of screening. Where traditional methods struggled, Kuano's platform generated viable inhibitors. It achieved this objective through systemic, data-driven analysis rather than brute-force experimentation. The platform, with quantum simulation at its core, extends from hit identification to lead optimisation. At every step it reveals new insights which are made possible by the quantum physics that underpins our technology. For us, breakthrough therapies emerge not from massive budgets, but from deep scientific insight enhanced by quantum intelligence.

We believe this technology is a new paradigm for drug discovery by integrating computational chemistry, AI, and quantum physics into a mature end-to-end design engine. We start with a quantum simulation, deploy a range of methods from our quantum toolbox, and translate this into putative chemical matter with our AI design engine. This isn't just another piece of modelling software, it is a revolutionary lens that reveals molecules as dynamic, reactive entities operating within a quantum web of forces.

This approach has been deployed in two of the industry's most sought-after advances: understanding the selectivity for phosphatases, and the elucidation of covalent ligand reactivity. Kuano's study of SHP1 and SHP2, two well-known and structurally similar phosphatases, revealed the determinants of selectivity observed for existing ligands. The quantum lens is not limited to the handful of residues in the active site. It was able therefore to reveal a key peripheral residue that, for the first time, explained the observed selectivity. This picture was further enhanced by the technology's ability to quantify both favourable and unfavourable interactions, whereas existing methods would only reveal one side of this picture[5].

For covalent ligands in two well-known use cases, we created 'quantum fingerprints' of known ligands and were able to distinguish between the influence of the different ligand chemistries and environment in describing the observed reactivity. This went beyond the usual 'residue+warhead' perspective. Importantly, Kuano's approach is transferable to residues other than cysteine. This has important implications for the rational design of covalently-reactive ligands in context.

As we expand our capabilities to model covalent reactivity, peptides, allosteric modulators, and protein-protein interfaces, the platform is poised for broad, cross-target scalability. And when quantum computers become viable, we believe that Kuano's quantum-native algorithms will unlock unprecedented accuracy, further pushing the frontiers of medical science.

Conclusion

The success with our initial targets is just the beginning. There is still plenty more work to be done. Today our approach can tackle a huge range of systems, but the largest and most complex may require the eventual arrival of quantum hardware to unlock at scale. Nevertheless, the potential of Kuano's current platform extends far beyond small-molecule inhibitors, enabling enzyme engineering for industrial biotech, biologics design, and mechanistic analyses that clarify structure-activity relationships for clinical compounds. This scalable approach applies across diverse target classes including enzymes, transporters, and receptors and unlocking therapeutic opportunities previously considered out of reach.

References: 1. https://www.kuano.ai. 2. van Driel MS, Linssen JDG, van Neerven SM, et al, (2023) Pleiotropic role of NOTUM in colorectal cancer, *Gut* 72 p2222-2223. 3. Bayle ED, Svensson F, Atkinson BN, Steadman D, Willis NJ, Woodward HL, Whiting P, Vincent JP, Fish PV, (2021) Carboxylesterase Notum Is a Druggable Target to Modulate Wnt Signaling. *J Med Chem*. 64(8) p4289-4311. 4. Zhang Zhixiong, Wang Guan, Li Yuyan, Lei Dongsheng, Xiang Jin, Ouyang Liang, Wang Yanyan, Yang Jinliang. (2022) Recent progress in DNA methyltransferase inhibitors as anticancer agents. *Frontiers in Pharmacology* 13:1072651. 5. Kuano Ltd, 2025 (unpublished data). Available at: https://www.kuano.ai/case-studies.

This article was written by Jarryl D'Oyley, PhD, Project Manager and Co-Founder at Kuano Ltd, and Catherine Stace, PhD, MBA, EVP of Business Development at Kuano Ltd. Email: Catherine.stace@kuano.ai.