SANDBOXAQ

AQBioSim

Accelerating the pathway from molecule to medicine

Executive Summary

Unlocking Next-Generation Drug Discovery with Advanced Tech: *The AQ Advantage*

Drug discovery remains a long, costly process that leads to failure more than 80% of the time. SandboxAQ is at the forefront of transforming drug discovery using a combination of molecular simulation and AI. We harness the unmatched capabilities of GPU-driven AI and emerging quantum tools to address the key bottlenecks and failure points in drug discovery and development.

AQBioSim's proprietary approach focuses on:

1. **Molecular Optimization:** Through the use of synthetic quantum data, AQBioSim's machine learning models provide invaluable insights, particularly when confronted with novel targets with limited molecular data. This empowers us to identify potential breakthroughs even for historically "undruggable" targets.
2. **Critical Application:** AQBioSim's groundbreaking method involves ML training with data from quantum physics simulations between molecules. This enhances proprietary absolute free energy perturbation techniques, delivering unparalleled accuracy at the preliminary hit-finding stage.
3. **Target Validation and Clinical Trials:** AQ has introduced a seamless blend of simulation and AI informed by literature and clinical data. This holistic method automatically tests hypotheses, ensuring users are at the cutting edge of potential breakthroughs.

AQBioSim's proprietary solutions scale quantum accuracy to large-scale impact to action upon both traditional and "undruggable" targets with unprecedented efficiency. We combine these with knowledge graph solutions which use simulation and AI to test hypotheses automatically, permitting novel and revolutionary methods of target validation, toxicity prediction, and drug development optimization. We consistently harness the power of GPUs and keep AQBioSim's strategies aligned with quantum hardware advancements, guaranteeing the solutions will evolve and scale exponentially over time.

Challenge Statement

Drug development is slow, expensive, and prone to failure: each new drug is the culmination of a 10+ year process costing more than $2bn per therapy[1]. **The number of drugs released per dollar spent has declined exponentially since the 1950s** - this depressing phenomenon is known as Eroom's Law (which is Moore's law backwards). While the trend has leveled somewhat over the past decade, there remains a clear need to reverse it for patients suffering from thousands of untreated and undertreated illnesses such as Alzheimer's, Parkinson's, and cancers such as glioblastoma multiforme.

[1] *Jama Network 2020*

Challenge: **Bend Eroom's law upwards, converting exponential decline into exponential growth for new medicines.**

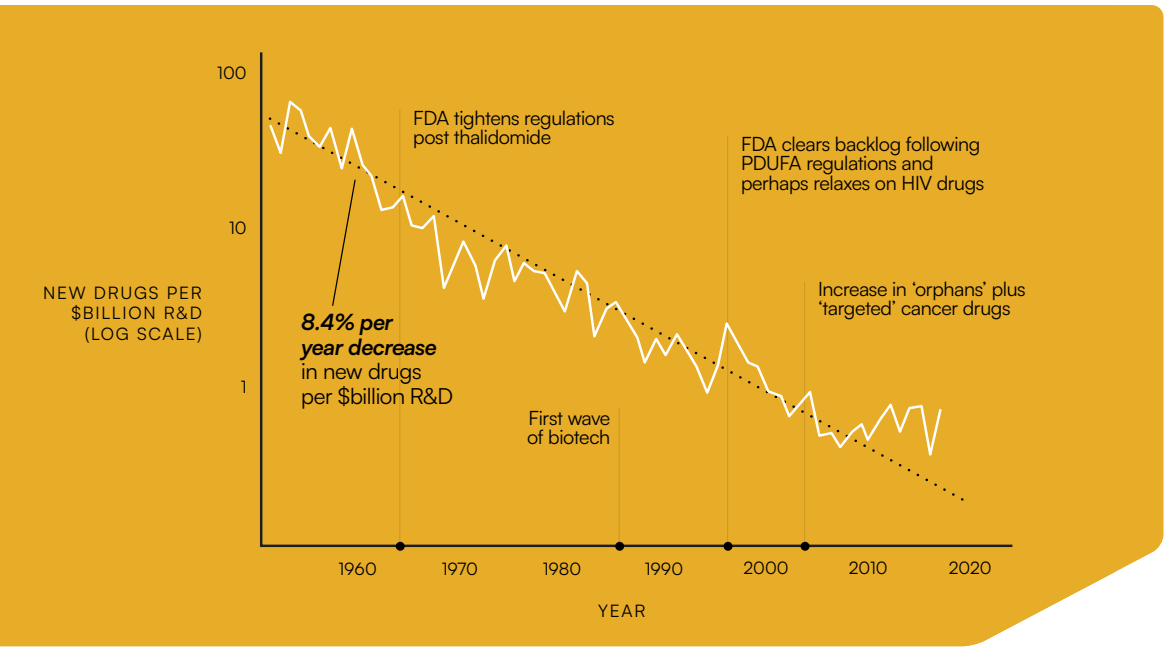

Figure 1: *Eroom's law of exponential decrease in drugs developed per dollar spent. While the trend has flattened somewhat, drugs have nevertheless become orders of magnitude more expensive to develop.*

Bending the Curve

Eroom's law may be surprising, given that Moore's law for exponential growth of computational efficiency has played over roughly the same time frame. This growth has not been realized in pharmaceutical development, due to integration difficulties based on:

1. **Complexity:** Many tasks in drug development (e.g. confirming a therapeutic hypothesis, modeling novel biochemistry, identifying promising molecular targets) are too complex and involve too many unknowns for explicit programming.
2. **Cost:** The quantum physics relevant to drug-drug interactions are too expensive for routine simulation by present methods.

Novel, emerging, and future technologies in AI, which can handle complex tasks without explicit programming, and quantum modeling, which can model quantum and other physics with high accuracy, promise to address both issues. Their synergistic combination, called "AQ", forms the basis of SandboxAQ's vision to fully computerized drug discovery and turn Eroom's law around to greater efficiency.

Solutions

SandboxAQ's strategy is to progressively connect pharmaceutical R&D to the exponential scaling of GPUs via novel technologies as they emerge. Specifically, we work on molecular optimization, target validation, and clinical development.

Molecular Optimization

AQBioSim produces an optimal drug molecule given a target as follows:

1. **Generation of quantum-accurate synthetic data** via GPU-enhanced large-scale quantum chemistry simulations unknown for explicit programming.
2. **Training of AI models** over these for consumption by AQBioSim's "AQ-FEP" absolute free-energy perturbation methods.
3. **Multi-objective optimization** over these and other models to move efficiently towards clinical candidates.

AQBioSim's active-learning-enhanced AQ-FEP solution is a unique absolute free energy perturbation workflow able to efficiently explore the chemical space to identify small molecules with optimal binding affinity to the target system. It represents the optimal balance between speed and accuracy able to screen thousands of ligands efficiently. In parallel it unlocks the possibility of training an ML model surrogate function to efficiently expand the search to billions of compounds. This approach maximizes the probability of success in finding potential game-changing clinical candidates, minimizing the risk of false positives and false negatives.

Approach

- Profiled ~30k unique ligands with AQ-FEP
- Greedy D-MPNN surrogate compared to internal controls: Random and Top Dockers

Search Strategy	#Ligands with AQFEP<-20 kcal/mol
Random	16
Top Dockers	46
Tranche 3 (D-MPNN)	305
Tranche 4 (D-MPNN)	351
Tranche 5 (D-MPNN)	267

Result: Across active learning iterations, a greedy D-MPNN surrogate model selects lower scoring compounds than other search strategies

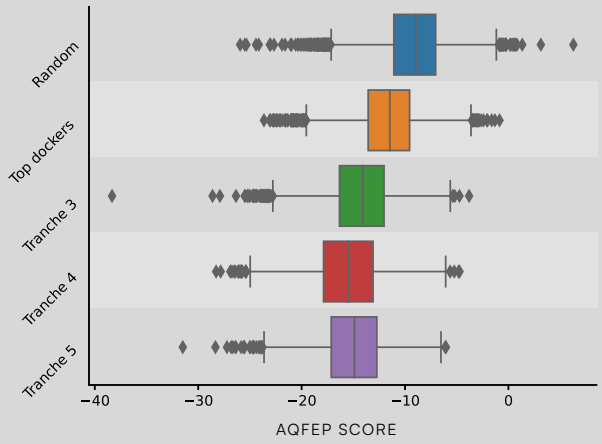

Figure 2: *Comparison of AQBioSim's ML-enhanced AQ-FEP approach showing superior performance to random and scoring-function-based strategies.*

Because the above process does not require elaborate training data, we are able to apply it to a wide variety of targets in a virtual screening process. The flexibility of AQBioSim's tools also allows them to operate upon first-in-class drugs acting upon previously undruggable targets such as those involved in neurodegenerative disease.

Target validation and clinical development

After a drug has entered the clinic, a long process begins of developing proof points for consumption by regulatory authorities. Similarly before a drug program has even started, there is a need to demonstrate that its target is causally related to the unmet need in the first place. Both operations reduce the need for efficient testing and demonstration of hypotheses. AQBioSim narrows hypotheses by first selecting them with AI and validating them with simulation.

This technique applies in three contexts. By direct application to therapeutic hypotheses, it can be used to identify and validate new targets. By connecting between molecules, targets, and observed adverse reactions, we can also use it to predict and explain toxicity throughout the drug discovery and development process, both in order to help design better molecules and to explain the behavior of existing ones.

Case Study

Solving for "Undruggable" Neurodegenerative Disease

AQBioSim's PrionDock platform, for example, is a custom solution optimized to predict the functional activity of small molecules acting with an unprecedented innovative mode of action. The custom solution was able to result in unprecedented impact where other state-of-the-art computational tools failed. PrionDock unlocked for the first time rational structure-based drug discovery for this uniquely challenging class of proteins. Virtual screening based on this innovative technology resulted in an unprecedented hit rate, 10 times superior to prior high-throughput screening campaigns.

> We are confident that this platform will continue to help us revolutionize the way we develop drugs across our other disease focus areas.

Stanley Prusiner
NOBEL PRIZE WINNER

Finally, during clinical development, the technique can be used to identify mechanisms behind observed late-stage toxicity, or to produce arguments in advance that said toxicity will not be observed. This allows for selection of patient cohorts which will not experience the toxicity and improved speed of regulatory filing, thus enhancing the success rate of drug programs at their most critical point.

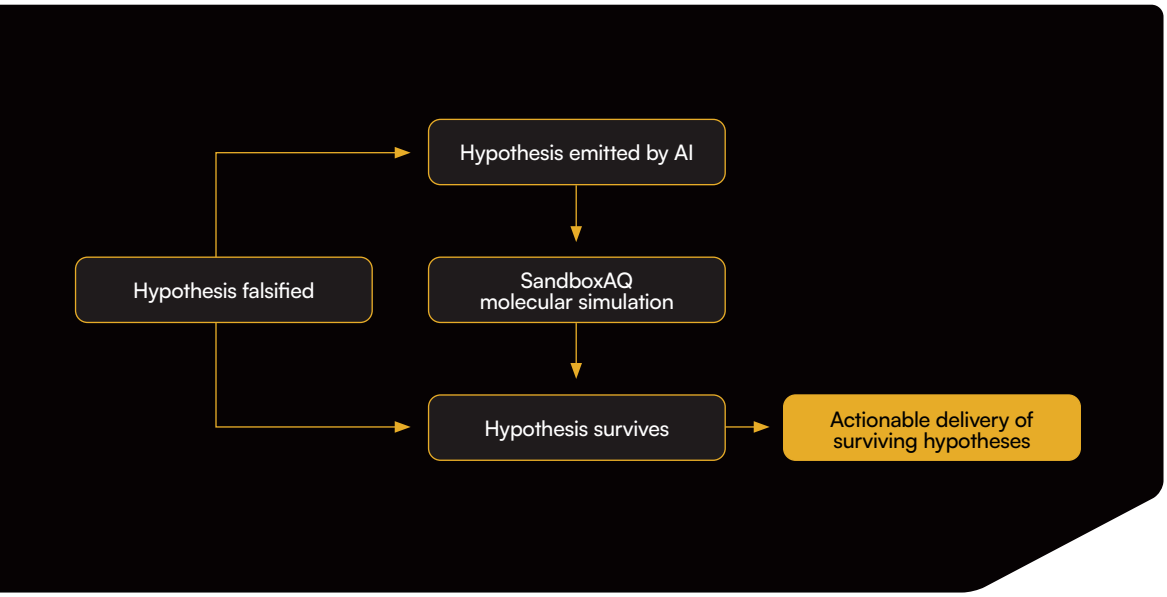

Figure 3: *Illustration of AQBioSim's hypothesis filtration procedure combining AI with simulation to produce actionable insights*

Summary

AQBioSim accelerates the scaling of R&D efficiency by identifying critical industry needs and connecting them to breakthrough technologies as they emerge.

Its proprietary solutions scale quantum accuracy to large-scale impact to action upon both traditional and previously undruggable targets with unprecedented efficiency. AI hypothesis testing solutions go on to enable novel and revolutionary methods of target validation, toxicity prediction, and drug development optimization.

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