QUANTUM COMPUTING IN DRUG DISCOVERY: A REVIEW OF QUANTUM ANNEALING AND GATE-BASED APPROACHES

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ABSTRACT

Classical computers face significant challenges when dealing with NP problems, especially given the unresolved question of whether NP equals P. These challenges arise due to the computational complexity and resource limitations inherent in solving such problems efficiently. Quantum computing, on the other hand, shows promise in addressing these challenges through principles like superposition and entanglement. By enabling parallel processing and potentially providing exponential speedup, quantum computing holds the potential to tackle problems that are intractable for classical systems. One area where quantum advantage could be clear is drug discovery. This review explores the role of quantum computing in drug discovery, examining the state-of-the-art advancements in both quantum annealing and gate-based approaches. We discuss the current progress, the challenges faced by these technologies, and provide recommendations for future research. By identifying research gaps and potential areas for innovation, this review aims to guide future advancements in applying quantum computing to drug discovery, ultimately contributing to more effective and efficient methods for developing new pharmaceuticals.

1 INTRODUCTION

The trajectory of computing power, as predicted by Moore's Law Schaller (1997), has long fueled advancements in technology. However, as transistors shrink to nanoscale sizes, classical computers encounter inherent limitations due to quantum effects Theis & Wong (2017). These limitations arise from factors Kish (2004); Xiu (2019); Cavin et al. (2012) such as quantum tunneling and interference, which become prominent at smaller scales. Quantum tunneling, for instance, leads to electrons passing through barriers they would classically be unable to overcome, causing errors and instability in computations. Additionally, quantum interference can disrupt the accuracy of computations in classical systems. These quantum phenomena restrict the capacity of classical computers to handle vast datasets and intricate simulations efficiently, highlighting the need for alternative computing paradigms Shanbhag et al. (2008) to address these challenges effectively.

Actually, these quantum effects weren't drawbacks Biswas et al. (2017); Córcoles et al. (2019); Riel (2021). In fact, there was a groundbreaking suggestion by the well-known physicist Richard Feynman to simulate complex quantum systems by using quantum mechanics itself to create computers for doing this task Feynman (1960); Feynman et al. (1982); Feynman (1985). Feynman's insight, proposed in the early 1980s, laid the foundation for a new concept which is the quantum computing, where quantum mechanics could be used to perform computations at a level far beyond the capabilities of classical computers Khrennikov (2021). This shift in perspective from viewing quantum effects as limitations to recognizing them as opportunities marked a pivotal moment in the development of quantum computing.

Quantum superposition arises from Heisenberg's uncertainty principle Hilgevoord & Uffink (2001); Salloum et al. (2024a) , which states that the product of the uncertainties in position (Δx) and momentum (Δp) of a particle is bounded by:

$$\Delta x \cdot \Delta p \geq \frac{\hbar}{2} \tag{1}$$

where $\hbar$ is the reduced Planck constant ($\hbar \approx 1.054 \times 10^{-34}$ Js).

This principle introduces inherent uncertainty into quantum systems, allowing a quantum bit (qubit) to simultaneously represent both zero and one, a fundamental property exploited in quantum computing.

The mathematical representation of superposition is given by Schrödinger's equation McMahon (2007):

$$|\psi\rangle = \alpha|0\rangle + \beta|1\rangle \tag{2}$$

Here, $|\psi\rangle$ is the qubit state, α and β are complex probability amplitudes, and $|0\rangle$ and $|1\rangle$ represent the zero and one states, respectively.

For example, consider a qubit in a superposition state:

$$|\psi\rangle = \frac{1}{\sqrt{2}}(|0\rangle + |1\rangle) \tag{3}$$

Here, $\alpha = \frac{1}{\sqrt{2}}$ and $\beta = \frac{1}{\sqrt{2}}$, representing equal probabilities of measuring zero or one when the qubit is observed.

Entanglement Jozsa & Linden (2003) further enhances computational power in quantum systems. By applying magnetic fields, entangled qubit systems can perform operations in a significantly shorter time frame compared to classical systems. This is due to the correlated nature of entangled qubits, allowing for efficient parallel computations.

The mathematical representation of entanglement is exemplified by the Bell state Horodecki et al. (2009):

$$|\Phi\rangle = \frac{1}{\sqrt{2}}(|00\rangle + |11\rangle) \tag{4}$$

The entangled state $|\Phi\rangle$ is a superposition of states $|00\rangle$ and $|11\rangle$, showcasing the unique correlations created by entanglement.

This entangled state illustrates how measurements on one qubit instantaneously affect the state of the other, demonstrating the efficiency of entanglement for quantum operations.

To understand the superposition and entanglement see the Figure 1.

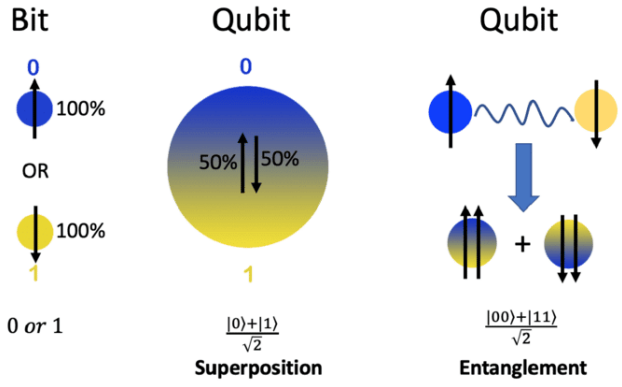

Figure 1: Superposition and Entanglement. Adopted form Steptophysics (2023).

Additionally, a quantum system with n qubits can exhibit 2^n states, showcasing the exponential increase in computational possibilities in quantum computing.

In the context of quantum computing paradigms, there are two primary models to consider Mizuno & Yamaoka (2021): a quantum gate-based computer and a quantum annealer. Quantum annealing Hauke et al. (2020); Salloum et al. is a quantum computing approach aimed at solving optimization problems by finding the lowest energy state of a system, which corresponds to the optimal solution. This process involves initializing a quantum system with the problem's Hamiltonian and gradually modifying it to guide the system towards the optimal solution. One notable leader in quantum annealing is D-Wave Systems Koshka & Novotny (2020), which has demonstrated speedup in solving combinatorial optimization problems using their quantum annealers Mott et al. (2017); Kumar et al. (2018); Neukart et al. (2017); Neven et al. (2012); Von Dollen et al. (2021); Yarkoni et al. (2022).

In contrast, quantum gate-based computing Tiwari & Poonia (2021), also known as universal quantum computing, utilizes quantum gates to manipulate qubits and perform quantum operations. This approach allows for the execution of a wide range of quantum algorithms, including Shor's algorithm Shor (1994; 1999); Proos & Zalka (2003) for integer factorization and Grover's algorithm Grover (1996) for database search. Leaders in gate-based quantum computing include IBM Quantum Alvarez-Rodriguez et al. (2018) and Google Quantum AI Courtland (2017).

The underlying principle of quantum annealing lies in leveraging quantum tunneling and superposition to find the lowest energy state of a system, corresponding to the optimal solution of an optimization problem Morita & Nishimori (2008). On the other hand, gate-based quantum computing uses quantum gates, such as Hadamard gates and CNOT gates, to manipulate qubits and perform computations Michielsen et al. (2017). Gate-based quantum computing is versatile, capable of executing various quantum algorithms, and applicable across multiple problem domains, including optimization, cryptography, simulation, and machine learning.

However, both approaches have their limitations. Quantum annealing is specialized for optimization problems and may struggle with general-purpose quantum computing tasks beyond optimization. It also has limited algorithmic flexibility compared to gate-based quantum computing. Connectivity constraints in quantum annealers can restrict the types of optimization problems they can effectively solve.

On the other hand, gate-based quantum computing faces challenges such as gate complexity, error rates, and scalability issues. Implementing complex quantum algorithms on gate-based architectures can be challenging, and gate errors, decoherence, and noise sources can limit the accuracy and reliability of computations.

Therefore, quantum annealing and gate-based quantum computing offer distinct advantages and limitations Karim Eddin et al. (2024), with quantum annealing excelling in optimization problems and gate-based quantum computing showcasing versatility and potential speedup in various quantum algorithms and problem domains. D-Wave Systems is a leader in quantum annealing, while IBM Quantum and Google Quantum AI are leaders in gate-based quantum computing.

Both approaches can solve many problems that a classical computer may struggle with, spanning various domains. One of the interesting and important domains where quantum computers can provide significant help is drug discovery. Therefore, this work aims to provide a review of the state-of-the-art (SOTA) for quantum applications in drug discovery Kumar et al. (2024) for both quantum annealing and quantum gate-based computing.

STRUCTURE OF THE PAPER

This paper is structured as follows: Section 2 provides an overview of drug discovery challenges, while Section 3 discusses the state-of-the-art (SOTA) quantum annealing applications in drug discovery. Following that, Section 4 covers the state-of-the-art (SOTA) quantum gate-based computing applications in drug discovery. Furthermore, Section 5 presents the current advancements, potential, and research gaps in quantum computing for drug discovery. Finally, Section 6 concludes the paper.

Feature	Quantum Annealing	Gate-Based Quantum Computing
Focus	Optimization problems	General-purpose quantum computations
Technique	Quantum tunneling and annealing	Quantum gates and circuits
Strengths	Specialized optimization	Versatile, supports various algorithms
Limitations	Limited algorithm flexibility	Gate complexity, error rates
Hardware	Quantum annealers (e.g., D-Wave)	Quantum processors (e.g., IBM, Google)
Applications	Combinatorial optimization, logistics, finance	Cryptography, quantum simulation, material science
Readiness Level	Commercially available, mature technology	Rapidly evolving, experimental phase
Scalability	Limited by coherence time and noise	Potential for large-scale computations with error correction
Algorithm Examples	QUBO, Ising model	Shor's algorithm, Grover's algorithm
Implementation Difficulty	Easier to implement for specific problems	Requires complex quantum error correction
Current Research	Enhancing precision and scalability	Error correction, fault-tolerant quantum computing
Energy Efficiency	Generally low due to specific hardware design	Higher due to need for maintaining coherence

Table 1: Comparison of Quantum Annealing and Gate-Based Quantum Computing

2 Overview of Challenges and SOTA in Drug Discovery and Computational Chemistry

The drug discovery process is a complex and multi-faceted endeavor that faces numerous challenges across scientific, technical, regulatory, and ethical domains. These challenges significantly impact the efficiency, cost, and success rates of bringing new drugs to market. Below is a comprehensive overview of the key challenges encountered in drug discovery:

1. **Complex Molecular Interactions:** Understanding the interactions between drugs and biological targets Scott et al. (2016); He et al. (2010), such as proteins or enzymes, is inherently complex due to the dynamic and intricate nature of molecular structures. Modeling these interactions accurately often involves solving NP-hard problems, where finding the optimal solution requires exponential time.
2. **Complex Molecular Interactions:** Understanding drug interactions with biological targets, such as proteins or enzymes Scott et al. (2016); He et al. (2010), is complex due to the intricate nature of molecular structures. Accurately modeling these interactions often involves NP-hard problems that require exponential time to solve. Quantum computers have the potential to simulate molecular and atomic interactions with unparalleled detail by using qubits that exist in superposition. This aligns with the quantum nature of molecules, enabling more precise modeling. In drug discovery, quantum computing can improve molecular docking accuracy by addressing quantum mechanical aspects, leading to better predictions of binding affinities and identifying promising drug candidates.
3. **High Dimensionality of Chemical Space:** The vast chemical space containing potential drug compounds presents a formidable challenge von Lilienfeld et al. (2020). Exploring this space comprehensively to identify promising drug candidates is not only time-consuming but also involves combinatorial optimization problems.

4. **Data Complexity:** The vast amount of biological and chemical data available, including genomics, proteomics, metabolomics, and structural data, poses challenges in data integration, analysis, and interpretation Grapov et al. (2018). Handling heterogeneous data sources and extracting meaningful insights while managing data quality and biases is a significant challenge.
5. **Biological Complexity:** Biological systems Hondermarck (2003) exhibit high levels of complexity, including molecular interactions, cellular signaling pathways, and physiological responses. Understanding the multifaceted nature of diseases and their underlying biological mechanisms requires comprehensive modeling and simulation approaches.
6. **Cost and Time Intensive:** Developing a new drug from initial discovery to market approval is a lengthy and costly process Kiriiri et al. (2020); Petrova (2013), often taking up to a decade and requiring substantial financial investments. The computational complexity of analyzing large datasets and conducting extensive simulations further contributes to the time and cost constraints.
7. **Specificity and Efficacy:** Ensuring that drugs are both specific to their intended targets and efficacious in treating specific medical conditions is challenging. Designing drugs with optimal therapeutic profiles requires solving optimization problems that are NP-hard Nicolaou & Brown (2013), such as optimizing molecular structures for enhanced target specificity and therapeutic efficacy.

In addressing these multifaceted challenges, emerging technologies such as quantum computing and quantum machine learning offer promising avenues for innovation and optimization in drug discovery processes. Leveraging the unique capabilities of quantum computing, including its potential to solve NP-hard problems and process vast amounts of data, holds the potential to revolutionize drug discovery workflows and accelerate the development of safe and effective treatments. Integrating quantum machine learning algorithms into drug discovery pipelines can enhance predictive modeling, target identification, and drug optimization processes, paving the way for more efficient and personalized therapeutic interventions.

3 State-of-the-Art (SOTA) Quantum Annealing Applications in Drug Discovery

In this section, we review the state-of-the-art (SOTA) applications of quantum annealing in drug discovery, highlighting its potential and current achievements.

1. **Sampling Rare Protein Transitions Using Quantum Annealing:** This study Ghamari et al. (2024) demonstrates the potential of quantum annealing in simulating spontaneous structural rearrangements in macromolecules, a task challenging for classical supercomputers due to time scale limitations. By employing a hybrid path-sampling paradigm that combines classical exploration with quantum annealing for generating trial transition paths, the study achieves significant progress in simulating complex protein transitions.
2. **Designing Lattice Proteins with Quantum Annealing:** Quantum annealing shows promise in solving optimization problems related to protein folding and design Irbäck et al. (2024). The study successfully identifies ground states in a coarse-grained lattice model and optimizes sequences for protein structures, showcasing the effectiveness of quantum annealing in biophysical challenges like protein design.
3. **Ligand Modeling and Molecular Docking**: Quantum annealing has been leveraged to model ligand interactions with target proteins in drug discovery Shetty et al. (2023). By employing quantum-inspired algorithms combined with deep learning techniques, researchers have achieved improvements in blind docking accuracy. This approach enables more efficient exploration of molecular conformations and binding sites, leading to enhanced drug design processes.
4. **Molecular Unfolding and Docking Optimization**: Quantum annealing has been applied to optimize molecular docking processes, specifically in the phase of molecular unfolding (SMU) Mato et al. (2022). By formulating the optimization problem as a High-order

Unconstrained Binary Optimization (HUBO) and transforming it into a Quadratic Unconstrained Binary Optimization (QUBO), quantum annealing algorithms can efficiently explore the conformational space of molecules, improving docking accuracy and reliability.

5. **Target Identification by Enzymes (TIE) Problem**: Quantum optimization techniques have been developed to address the NP-hard problem of target identification by enzymes in metabolic networks. The QuTIE Ngo et al. (2023) (Quantum Optimization for Target Identification by Enzymes) approach demonstrates optimal or near-optimal solutions for identifying enzyme targets associated with specific diseases, showcasing the potential of quantum annealing in complex biological network analysis.
6. **Molecular Conformation Generation**: Quantum-inspired algorithms have been utilized to generate molecular conformations efficiently, a crucial step in structure-based drug design Li et al. (2024). By employing compact phase encoding methods and optimizing internal distances within molecules, quantum-inspired approaches outperform traditional methods like simulated annealing, offering faster and more accurate conformation generation for drug discovery purposes.
7. **Machine Learning for Biomolecular Simulations**: Quantum annealing has been explored for machine learning tasks in computational biology Li et al. (2018), such as classifying and ranking transcription factor binding affinities. While still in its early stages, quantum machine learning approaches show promise in enhancing classification performance for biological data sets, indicating a potential avenue for future advancements in drug discovery research.
8. **Multi-Objective Optimization in Drug Design**: Quantum annealing approaches have been applied to multi-objective optimization problems in drug design Tucs et al. (2023). By considering multiple criteria, such as drug potency, selectivity, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) Lin et al. (2003) properties, quantum optimization techniques can guide the design of multi-functional and optimized drug candidates.

4 State-of-the-Art (SOTA) Quantum Gate-Based Computing Applications in Drug Discovery

Quantum gate-based approaches have shown tremendous promise in drug discovery, offering innovative solutions for molecular modeling, simulation, and analysis. Some key applications of quantum gate-based methods in drug discovery include:

1. **Quantum-Inspired Molecular Docking:** Recent developments in quantum-inspired algorithms, such as the digitized-counterdiabatic quantum approximate optimization algorithm (DC-QAOA) Chandarana et al. (2022), have demonstrated remarkable accuracy in predicting protein-ligand binding affinities Ding et al. (2024). These algorithms leverage quantum principles to explore complex molecular interactions, offering unprecedented insights into drug-target interactions crucial for designing highly specific and effective drugs.
2. **Quantum-Based Biomolecular Simulations:** Quantum computing enables high-fidelity simulations of biomolecular systems Kim et al. (2022); Khatami et al. (2023), providing detailed insights into molecular dynamics, conformational changes, and protein folding. These simulations aid in understanding disease mechanisms, predicting drug efficacy, and optimizing drug candidates for improved therapeutic outcomes.
3. **Quantum Machine Learning (QML) for Drug Design:** Quantum machine learning techniques Batra et al. (2021); Vitz et al. (2024), including quantum-enhanced neural networks and support vector machines, are being increasingly utilized for drug design and optimization. These algorithms leverage quantum computing's parallel processing capabilities to analyze large datasets, identify molecular patterns, and predict pharmacological properties with enhanced accuracy.
4. **Hybrid Quantum-Classical Approaches:** Hybrid quantum-classical algorithms, such as the Variational Quantum Eigensolver (VQE) and Quantum Approximate Optimization Algorithm (QAOA), offer scalable solutions for electronic structure calculations and energy

minimization in drug molecules Innan et al. (2024). These approaches combine the computational power of quantum circuits with classical optimization techniques, achieving higher accuracy and efficiency in modeling molecular properties.

5. **Quantum-Assisted Virtual Screening:** Quantum computing accelerates virtual screening Mensa et al. (2023) processes by efficiently searching chemical databases and identifying potential drug candidates with desired pharmacological profiles. Quantum-enhanced algorithms streamline the screening pipeline, reducing time and resources required for identifying lead compounds and accelerating drug discovery timelines.
6. **Quantum-Based Biomolecular Structure Prediction:** Gate-based quantum algorithms facilitate biomolecular structure prediction, aiding in understanding protein folding mechanisms and ligand binding modes. These simulations contribute to the rational design of therapeutically relevant molecules and optimize drug-target interactions Harris & Kendon (2010); Wong & Chang (2022).
7. **Quantum-Simulated Drug Design:** Quantum simulations enable the design of novel drug candidates by simulating chemical reactions, molecular transformations, and drug-target interactions at the quantum level. These simulations facilitate rational drug design, optimization of drug properties, and prediction of drug efficacy, leading to the development of tailored therapeutics for diverse medical needs Andersson et al. (2022); Harris & Kendon (2010).
8. **Generative Design of Small Molecules:** Quantum gate-based methods are employed in generative design of small molecules, leveraging quantum algorithms to explore chemical space and generate novel molecular structures with desired pharmacological properties. These techniques enable the discovery of innovative drug candidates and accelerate drug development pipelines. Examples include quantum generative adversarial networks Kao et al. (2023) and quantum computing-enhanced algorithms Vakili et al. (2024).
9. **Quantum Algorithms for Genomic Analysis:** Quantum algorithms applied to genomic data analysis expedite the identification of disease-related genetic variations, biomarkers, and therapeutic targets Marchetti et al. (2022); Bhuvaneswari et al. (2023). Quantum-enhanced genomic analysis tools enhance precision medicine initiatives by enabling personalized treatment strategies based on individual genetic profiles and disease mechanisms.

Quantum gate-based methods demonstrate significant potential in enhancing drug discovery workflows, from molecular docking and simulations to machine learning-driven drug design and virtual screening.

5 Current Advancements, Potential, and Research Gaps in Quantum Computing for Drug Discovery

While significant advancements have been made, it's important to note that quantum computing has not yet achieved widespread adoption or a major breakthrough in drug discovery. However, the field shows immense potential for transformative impacts. Some notable progress includes improved molecular modeling and simulation, enhanced drug design and optimization, accelerated virtual screening, quantum machine learning for pharmacological predictions, precise biomolecular structure prediction, quantum-assisted genomic analysis, and the development of hybrid quantum-classical approaches. These advancements have contributed to a deeper understanding of complex biological systems, faster identification of potential drug candidates, and more efficient drug design processes.

However, several research gaps and challenges persist in harnessing quantum computing for drug discovery:

1. **Quantum Algorithm Optimization:** Further optimization of quantum algorithms is needed for specific drug discovery tasks, enhancing efficiency, accuracy, and scalability for large-scale simulations.
2. **Hardware Advancements:** Improvements in quantum computing hardware are crucial to overcome limitations such as qubit coherence, gate error rates, and scalability issues for reliable computations.

3. **Data Integration and Validation:** Developing frameworks for seamless integration of diverse data sources into quantum platforms and establishing validation protocols against experimental data are essential for reliable predictions.
4. **Resource Optimization:** Exploring methods to optimize resource utilization and reduce computational costs in quantum simulations is necessary for practical applications.
5. **Interpretability and Transparency:** Ensuring clear explanations of quantum-derived results is crucial for gaining trust and acceptance in the pharmaceutical industry, especially in machine learning-driven drug design.
6. **Ethical and Regulatory Considerations:** Addressing ethical and regulatory challenges related to quantum computing in drug discovery is paramount for transparency, fairness, and accountability.

By addressing these gaps, the intersection of quantum technology and pharmaceutical science can achieve further exploration and innovation, leading to transformative advancements in drug discovery and development.

6 Conclusion and Outlook

Quantum computing presents a promising frontier in drug discovery, addressing challenges in molecular modeling, optimization, and biomolecular simulations. Despite significant progress in leveraging quantum technologies for tasks like ligand modeling and molecular docking, a considerable gap remains between theoretical potential and practical implementation in the pharmaceutical industry. Advancements in quantum annealing systems, such as those from D-Wave Systems, and gate-based quantum computing platforms like IBM Quantum and Google Quantum AI, enable researchers to explore complex molecular interactions, predict drug responses, and optimize chemical reactions with unprecedented accuracy and efficiency. However, challenges persist, including optimizing quantum algorithms for specific tasks, advancing quantum hardware, integrating heterogeneous data sources, and ensuring interpretability and transparency. Ethical and regulatory considerations also play a crucial role, necessitating frameworks for accountability and fairness.

In the short term, incremental improvements in quantum hardware and algorithms are expected, leading to more practical applications in molecular modeling and simulation. The development of specialized quantum algorithms may improve the accuracy and speed of drug candidate optimization. Medium-term prospects include the integration of quantum and classical computing methods, enhancing scalability and applicability to more complex biological systems and larger datasets. Collaborative efforts between academia, industry, and governmental bodies will be crucial in advancing these technologies and addressing ethical and regulatory frameworks.

In the long term, as quantum computing technologies mature and become more accessible, they are likely to lead to transformative changes in the pharmaceutical industry. Quantum computing could become a standard tool in drug discovery, enabling highly targeted and personalized treatments. Breakthroughs in quantum error correction and fault-tolerant quantum computing will enhance reliability and efficiency, solidifying their role in pharmaceutical research and development. The future of quantum computing in drug discovery holds significant promise. By addressing current challenges and fostering a collaborative ecosystem, the potential of quantum technologies to revolutionize drug discovery and development is immense. This progression will ultimately contribute to more effective, timely, and personalized therapeutic solutions, transforming modern medicine. Continued research, collaboration, and innovation in this field will pave the way for groundbreaking advancements in pharmaceutical science.

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A Quantum Gate-based and Quantum Annealing in nutshell

Quantum computing employs sophisticated methodologies such as Quantum Gate-based computing and Quantum Annealing for advanced computational tasks.

A.1 Quantum Annealing

Quantum Annealing Rajak et al. (2023); Hen & Spedalieri (2016); Salloum et al. (2024b); Yulianti & Surendro (2022); Das & Chakrabarti (2005) tackles optimization problems by minimizing a cost function $E(\mathbf{s})$ using the annealing Hamiltonian $H(\mathbf{s}, t) = A(\mathbf{s}) + B(t)C(\mathbf{s})$. The Ising model is frequently employed in Quantum Annealing for tasks like graph partitioning and clustering.

$$H = -\sum_{i,j} J_{ij}\sigma_i^z\sigma_j^z - \sum_i h_i\sigma_i^z \tag{5}$$

Quantum Annealing techniques are pivotal in solving NP-hard problems and optimization challenges with exponential search spaces Rajak et al. (2023).

The Quantum Annealing process can be mathematically described using the Schrödinger equation for a time-dependent Hamiltonian:

$$i\hbar\frac{\partial}{\partial t}|\Psi(t)\rangle = H(t)|\Psi(t)\rangle \tag{6}$$

where $|\Psi(t)\rangle$ is the quantum state at time t, $\hbar$ is the reduced Planck constant, and $H(t)$ is the time-dependent Hamiltonian.

Quantum annealing is a metaheuristic tool considered a special and enhanced variant of simulated annealing as shown in Figure 2. The core idea of simulated annealing is to probabilistically explore different configurations of a system as the temperature decreases. The probability of transitioning from one state to another depends on the energy difference between the states and is given by the Boltzmann distribution:

$$P(E) = \frac{e^{-\beta E}}{Z}, \tag{7}$$

where:

$P(E)$ is the probability of the system being in state E,

β is the inverse temperature, $\beta = \dfrac{1}{k_B T}$, where k_B is the Boltzmann constant and T is the temperature,

E is the energy of the state,

Z is the partition function, a normalization factor.

Quantum annealing, in contrast, operates with quantum states and relies on the Schrödinger equation:

$$H(t)|\psi(t)\rangle = E(t)|\psi(t)\rangle, \tag{8}$$

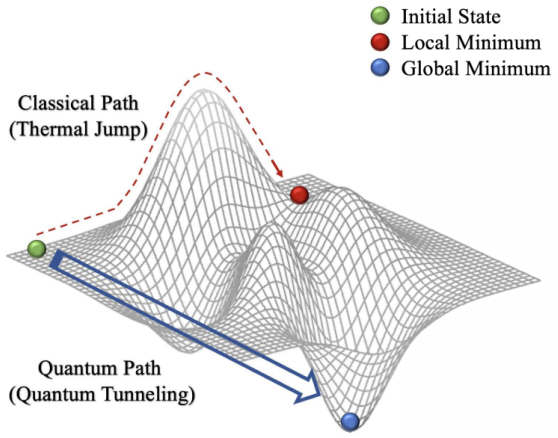

Figure 2: Quatnum annealing vs simulated annealing. Adapted from Heng et al. (2022).

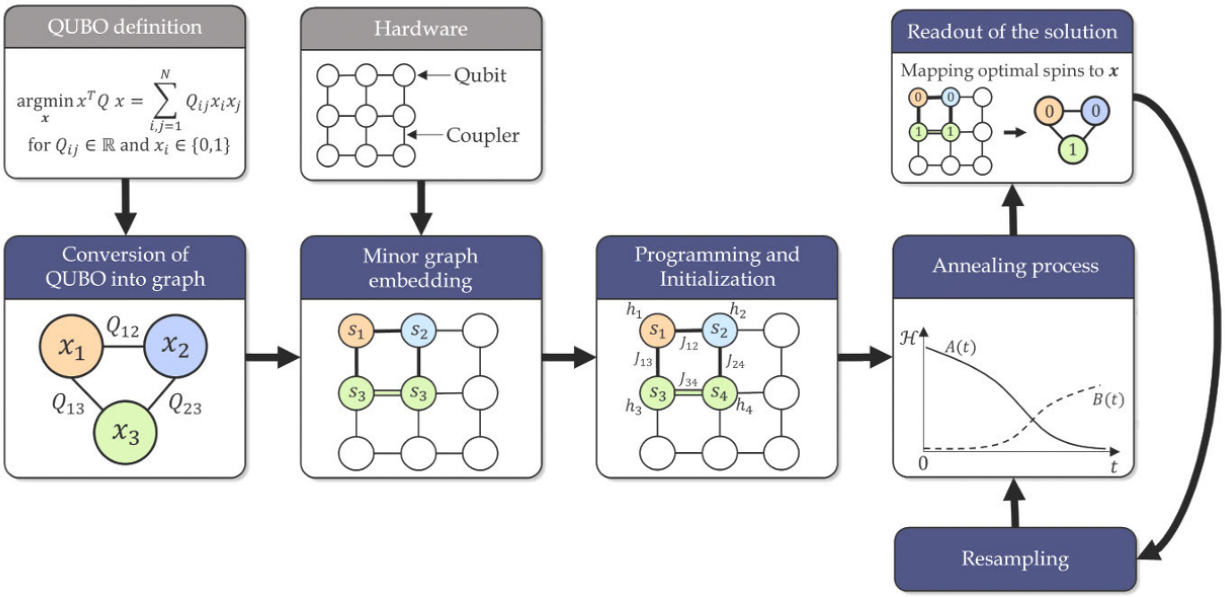

Figure 3: Quatnum annealing workflow. Adapted from Yarkoni et al. (2022).

where:

$H(t)$ is the time-dependent Hamiltonian operator, $|\psi(t)\rangle$ is the quantum state of the system at time t, $E(t)$ is the corresponding energy.

In drug discovery, quantum annealing has shown significant potential in addressing complex optimization problems. By mapping the problem onto an Ising model, which is equivalent to a QUBO (Quadratic Unconstrained Binary Optimization) problem, quantum annealing can efficiently explore the vast search space to identify optimal configurations that minimize the system's energy.

Algorithm 1 and Figure 3 outline and show the process of solving a problem using quantum annealing. First, the problem is defined and a cost function that quantifies the objective is constructed. The cost function is then translated into a QUBO matrix, which is embedded onto a quantum annealer.

The quantum annealer samples solutions to find the minimum energy states, which represent the optimal solution to the problem.

A.2 Quantum Gate-Based Computing in a Nutshell

Quantum gate-based computing utilizes the unique properties of quantum gates to manipulate qubits, enabling sophisticated computational processes that transcend classical computing capabilities. The evolution of quantum states under the action of quantum gates is governed by unitary transformations, typically represented by the expression

$$U = e^{-iHt/\hbar}$$

where H denotes the Hamiltonian operator, t represents time, and $\hbar$ is the reduced Planck constant.

Key quantum gates such as the controlled-phase gate (CP) and the Toffoli gate ($CCNOT$) facilitate complex multi-qubit operations, crucial for implementing quantum algorithms. The controlled-phase gate (CP) can be expressed as:

$$CP = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & e^{i\phi} \end{pmatrix},$$

where ϕ is the phase angle. The Toffoli gate ($CCNOT$), a three-qubit gate, is represented by:

$$CCNOT = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{pmatrix}.$$

These gates are instrumental in the execution of pivotal quantum algorithms, such as the Quantum Fourier Transform (QFT) and the Quantum Phase Estimation (QPE). The QFT is essential for decomposing quantum states into their frequency components, while QPE is utilized to estimate the eigenvalues of unitary operators. These algorithms have profound implications for fields like cryptography, where they underlie quantum factoring algorithms (e.g., Shor's algorithm), and quantum chemistry, where they facilitate the simulation of molecular systems.

In the realm of drug discovery, several quantum algorithms and circuits are of paramount importance due to their ability to simulate molecular interactions and predict chemical reactions with high precision. These include the Variational Quantum Eigensolver (VQE), Quantum Approximate Optimization Algorithm (QAOA), and Quantum Machine Learning Algorithms such as Quantum Support Vector Machines (QSVM) and Quantum Neural Networks (QNN). These advanced quantum computing methods pave the way for revolutionary advancements in computational science and problem-solving paradigms. By utilizing these gates and circuits, researchers can achieve unprecedented accuracy in molecular simulations, accelerating the drug discovery process and enabling the development of new therapeutics with greater efficiency and effectiveness.

B Case Studies of Industry Applications of Quantum Computing in Drug Discovery

In this section, we present several case studies that illustrate the application of quantum computing technologies in the drug discovery industry. These case studies provide insights into how leading companies are using quantum computing to address complex challenges in drug development.

B.1 Discovery of Novel KRAS Inhibitors Using a Quantum Computing-Enhanced Algorithm

The discovery and development of small molecule inhibitors for KRAS, a crucial oncogene in cancer therapy, have traditionally faced significant challenges. Researchers have begun to adopt innovative

Algorithm 1 Quantum Annealing Pseudocode Example

function DefineProblem() {Define the problem's variables and constraints.}
Problem.variables ← ["x1", "x2", "x3"]
Problem.constraints ← ["x1 + x2 ≤ 1", "x2 + x3 ≤ 1"]
return Problem
end function

function CostFunction(Variables) {Create a cost function to minimize.}
Cost ← Variables["x1"] + Variables["x2"] + 2 * Variables["x3"]
return Cost
end function

function ConstructQUBOMatrix(Problem) {Translate cost function and constraints into a QUBO matrix.}

Q ← zeros matrix of appropriate size {Populate Q with coefficients from the cost function and constraints.}
$Q[0][0] \leftarrow 1$ {x1 coefficient}
$Q[1][1] \leftarrow 1$ {x2 coefficient}
$Q[2][2] \leftarrow 2$ {x3 coefficient}
$Q[0][1] \leftarrow 2$ {constraint: x1 + x2 ≤ 1}
$Q[1][2] \leftarrow 2$ {constraint: x2 + x3 ≤ 1}
return Q
end function

function InitializeSampler() {Initialize the D-Wave sampler.}
sampler ← EmbeddingComposite(DWaveSampler())
return sampler
end function

function EmbedProblem($Q, sampler$) {Embed the QUBO matrix onto the quantum annealer.}
embedded_problem ← sampler.sample_qubo(Q)
return embedded_problem
end function

function SampleSolutions($embedded\_problem, sampler, num\_reads$) {Sample solutions from the quantum annealer.}
solutions ← sampler.sample($embedded\_problem, num\_reads$)
return solutions
end function

function CalculateEnergy($sample, Q$) {Calculate the energy of a given sample based on the QUBO matrix.}
$energy \leftarrow 0$
for $(i, j), value \in Q$ **do**
  if $i \neq$ bias & $j \neq$ bias **then**
    $energy \leftarrow energy + value \cdot sample[i] \cdot sample[j]$
  else if $i ==$ bias **then**
    $energy \leftarrow energy + value \cdot sample[j]$
  else if $j ==$ bias **then**
    $energy \leftarrow energy + value \cdot sample[i]$
  end if
end for
return $energy$
end function

$problem \leftarrow$ DefineProblem()
$Q \leftarrow$ ConstructQUBOMatrix($problem$)
$sampler \leftarrow$ InitializeSampler()
$embedded\_problem \leftarrow$ EmbedProblem($Q, sampler$)
$response \leftarrow$ SampleSolutions($embedded\_problem, sampler, 100$)
$min\_energy \leftarrow \infty$
$optimal\_sample \leftarrow$ None
for $sample$ in $response$ **do**
  $energy \leftarrow$ CalculateEnergy($sample, Q$)
  if $energy < min\_energy$ **then**
    $min\_energy \leftarrow energy$
    $optimal\_sample \leftarrow sample$
  end if
end for
Output: "Optimal Sample: ", $optimal\_sample$
Output: "Minimum Energy: ", min_energy

computational techniques to enhance the drug discovery process, aiming to increase hit rates and decrease costs. This study introduced a hybrid quantum-classical generative model to design new KRAS inhibitors, illustrated by a schematic representation of the hybrid framework for KRAS ligand development Vakili et al. (2024).

In the initial phase, a curated set of 650 experimentally verified inhibitors targeting the KRAS protein was extracted from the literature. The STONED-SELFIES algorithm was then applied to generate analogs for each identified compound, expanding the collection to approximately 850,000 compounds. An additional 250,000 top candidates were identified through a virtual screening process using the REAL ligand library against the KRAS protein, culminating in a dataset of over 1 million molecules for training the generative model.

The generative model training involved two key components: a classical Long Short-Term Memory (LSTM) network and a Quantum Circuit Born Machine (QCBM). The LSTM network processed sequential data encapsulating the chemical structures of ligands, while the QCBM, trained based on the quality of LSTM-generated samples, created complex, high-dimensional probability distributions. Chemistry42 was used as a reward function to incentivize the creation of structurally diverse and synthesizable molecules.

The workflow proceeded as follows:

1. Train the LSTM network on the compiled dataset.
2. Generate initial molecule candidates using the LSTM network.
3. Train the QCBM using the LSTM-generated samples.
4. Generate new molecules targeting KRAS using the QCBM.
5. Evaluate and refine the generated molecules using Chemistry42.

The pseudocode for this workflow is outlined below:

Algorithm 2 Hybrid Quantum-Classical Workflow for KRAS Ligand Development

```
Train LSTM network on training_data
Generate initial_molecules using LSTM model
Train QCBM on initial_molecules
Generate quantum_molecules using QCBM model
Initialize refined_molecules as an empty list
for each molecule in quantum_molecules do
    score ← evaluate molecule using Chemistry42
    if score > threshold then
        add molecule to refined_molecules
    end if
end for
return refined_molecules
```

Fifteen promising molecules were synthesized and subjected to experimental testing to assess their ability to engage with the KRAS target. Among these candidates, two molecules, ISM061-018-2 and ISM061-22, demonstrated effective engagement with KRAS. ISM061-018-2 was identified as a broad-spectrum KRAS inhibitor, exhibiting a binding affinity to KRAS-G12D at 1.4 μM, while ISM061-22 exhibited specific mutant selectivity, displaying heightened activity against KRAS G12R and Q61H mutants.

Comparative analysis with existing classical generative models indicated that integrating quantum computing enhances distribution learning from established datasets, suggesting a potential advantage for quantum generative models over their classical counterparts. The efficacy of distribution learning was found to correlate with the number of qubits utilized, underlining the scalability potential of quantum computing resources.

This case study underscores the potential of quantum computing in enhancing drug discovery processes. The integration of quantum algorithms with classical methods offers a promising approach to developing effective therapeutics. The success of this study highlights the scalability potential of

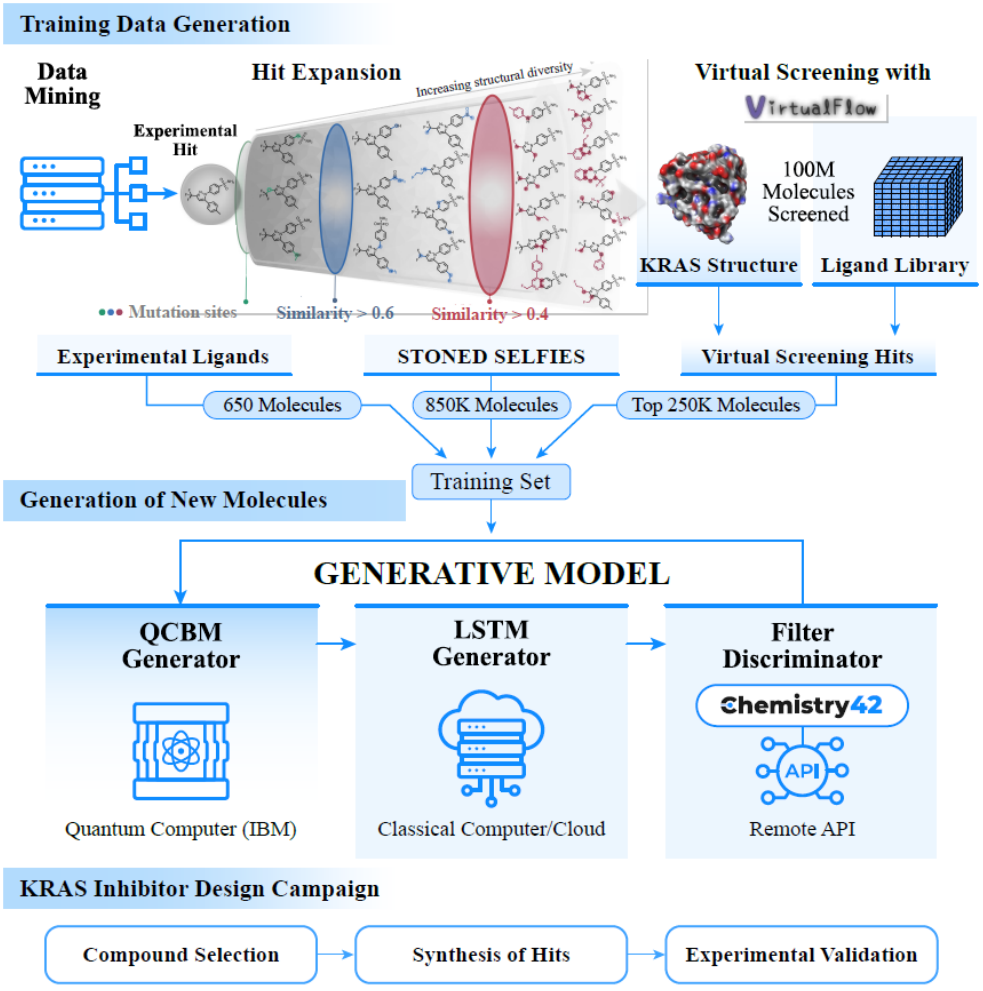

Figure 4: Representation of the KRAS Ligand Development Hybrid Framework. Adapted from Vakili et al. (2024).

quantum computing resources, suggesting that future models could further improve drug discovery efficiency and effectiveness.

B.2 Hybrid Quantum Graph Neural Network for Molecular Property Prediction

The integration of quantum computing and machine learning has led to the development of a hybrid quantum-classical convoluted graph neural network (HyQCGNN) for predicting the formation energies of perovskite materials. This study utilized a gradient-free optimization approach and compared the performance of HyQCGNN with classical models such as GENConv and XGBoost Vitz et al. (2024).

The HyQCGNN model was implemented using PyTorch and PyTorch-Geometric for defining the classical components and Qiskit for the quantum circuits. The GENConv layer performed dimensionality reduction on the input graph, which was then processed by a quantum circuit using amplitude encoding. Observables from the quantum circuit were measured and compared to the target values. The optimization was performed using the NGOpt algorithm from Nevergrad.

Training, evaluation, and software implementation details include:

Algorithm 3 Hybrid Quantum-Classical Workflow for Molecular Property Prediction

1: Initialize optimizer with model parameters
2: Load classical parameters into GENConv layer
3: Transform input graph to intermediate graph using GENConv
4: Unroll intermediate graph into vector $\vec{x}$
5: Load $\vec{x}$ into quantum circuit with quantum parameters
6: Measure observables, scale, and compare to target values
7: Report difference to optimizer for parameter update
8: Request updated parameters from optimizer

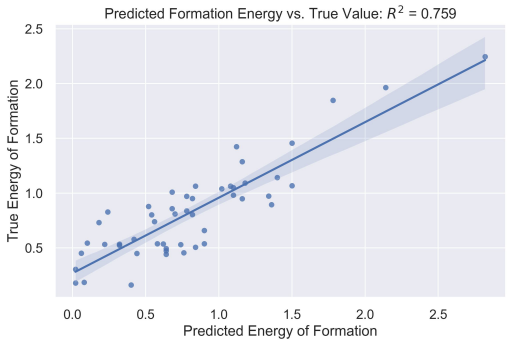

Figure 5: Performance of GENConv model

- The neural networks were defined using PyTorch and PyTorch-Geometric.
- Quantum circuits were defined using Qiskit and integrated with PyTorch through Qiskit's TorchConnector.
- Models were trained on an internal cluster with 64 CPU cores and simulated on the Qiskit QASM simulator.
- The best models were selected based on performance on a validation set with 25 samples, and final evaluation was done on a test set with 25 samples.

Both classical and hybrid models were trained for 2000 iterations using the NGOpt algorithm of Nevergrad. The performance of HyQCGNN was competitive with the results obtained from GENConv and XGBoost models. Despite the advanced methods in GENConv, the hybrid model's R2 score was only slightly lower, suggesting that hybrid quantum-classical models are viable for predicting complex molecular properties.

The results for both classical and hybrid methods are illustrated in the figures below:

- **Figure 5:** Plot and associated R2 value for the true formation energy vs. GENConv model prediction.
- **Figure 6:** Plot and associated R2 value for the true formation energy vs. Hybrid model prediction.
- **Figure 7:** Plot and associated R2 value for the true formation energy vs. XGBoost model prediction.

The feature importance analysis performed using XGBoost highlighted that the most relevant feature affecting the formation energy is the first ionization energy of site A in a perovskite material.

B.3 Quantum Annealing in Molecular Docking

Drug discovery is a multi-phase process that includes virtual *in silico* simulations, *in vitro*, and *in vivo* experimentation. Molecular docking, a critical step in this process, simulates the atomic interactions of a ligand inside a protein binding site, predicting whether a stable complex can form.

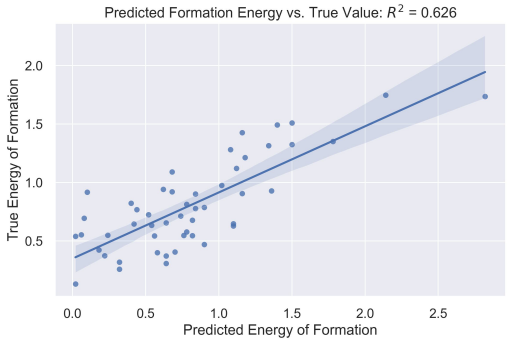

Figure 6: Performance of hybrid model

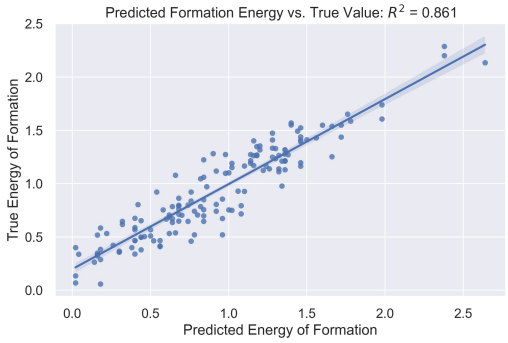

Figure 7: Performance of XGBoost model

This process involves significant computational resources due to the multiple degrees of freedom and high dimensionality. Recent advancements in quantum computing have introduced potential methods to enhance this computational process. Specifically, QA to support molecular docking, focusing on the molecular unfolding (MU) process, which is the first step in geometric molecular docking techniques Mato et al. (2022). MU aims to find the molecular configuration that maximizes its volume by maximizing the internal distances between atoms within the molecule. The molecular docking process involves detecting three-dimensional poses of the ligand within the active site of the protein and ranking these poses using a scoring function. The initial ligand pose can introduce shape bias, affecting docking quality. Molecular unfolding (MU) is used to remove this bias by expanding the ligand to an unfolded shape. The MU problem's objective is to maximize the molecular volume, expressed as the total sum of internal distances between pairs of atoms in the ligand. Given a molecule, the torsional configuration that maximizes this quantity is sought. The mathematical formulation of the objective function for MU is given by:

$$D(t) = \sum_{\substack{a,b \in M \\ a \neq b}} D_{ab}(\Theta)^2 \tag{9}$$

where $D_{ab}(\Theta)$ denotes the distance between two different atoms a and b within the molecule M, and Θ represents the set of torsional angles. Each torsion around a bond's axis can assume values within $[0, 2\pi)$. The goal is to maximize $D(t)$.

The process begins with identifying rotatable bonds, which are the problem parameters. These discrete rotations are rewritten using one-hot encoding, introducing binary variables. The total sum of internal atomic distances is expressed as a HUBO, transformed into a QUBO through distance simplification, coarse-grained rotations, and threshold approximation. This reduction in complexity enables embedding and running complex instances on QPUs.

Algorithm 4 Molecular Unfolding Using Quantum Annealing

1: Identify rotatable bonds and initialize torsional angles.
2: Encode torsional angles using one-hot encoding to introduce binary variables.
3: Define the objective function $D(t)$ as a HUBO.
4: Convert the HUBO to a QUBO.
5: Embed the QUBO on the quantum annealer.
6: Run quantum annealing and retrieve the solution.
7: Decode the solution to obtain the unfolded molecular configuration.

The quantum MU model was executed on D-Wave's Advantage and 2000Q hardware. Performances were compared with parallel random optimization, simulated annealing (SA), and the GeoDock greedy algorithm. Advantage outperformed 2000Q in terms of qubits used and chain lengths. While classical techniques excelled in larger problems, the quantum annealer yielded superior results for medium-small problems, surpassing the GeoDock approach.

This study explored the potential of using a quantum annealer to enhance the drug discovery process, specifically within the molecular unfolding phase of geometric molecular docking. By formulating the MU problem as a high-order unconstrained binary optimization and solving it on D-Wave hardware, we demonstrated the capabilities and limitations of current QA devices. Future work may involve alternative encoding strategies, dynamic thresholds, and solution refinement techniques like reverse annealing. Extending the QA approach to the entire docking process could further validate the application of QC in computational sciences.

B.4 Quantum Computing Applied to Protein Folding Using the Lattice-Based HP Model

In the work Irbäck et al. (2024), the authors applied quantum computing technology to protein folding using the lattice-based HP model. This model simplifies amino acids into hydrophobic (H) and polar (P) groups. Previous studies on quantum computing methods for protein folding have primarily relied on chain growth or turn-based algorithms. These approaches faced challenges with nonlocal interactions unless the chain length was very short. Our novel approach employed a scalable field-like representation with qubits at all lattice sites, enabling the study of chains up to 64 amino acids long using the D-Wave hybrid solver. The work focused on the minimal two-dimensional (2D) lattice-based HP model, where proteins are represented as self-avoiding chains of H or P beads. These beads interact via a pairwise contact potential, and the energy function E_{HP} is defined as:

$$E_{HP} = -N_{HH} \tag{10}$$

where N_{HH} denotes the number of HH contacts. This model favors the formation of a hydrophobic core and serves as a useful test bed for novel computational approaches due to the availability of exact results for all sequences with $N \leq 30$. The design problem involves finding a sequence $s = (s_1, \ldots, s_N)$ that folds into a given target structure C_t. the work aims to minimize the energy $E_{HP}(C_t, s)$ over sequence s using the D-Wave quantum annealer. This problem is recast in quadratic unconstrained binary optimization (QUBO) form, with an auxiliary energy term to control the number of H beads N_H in the sequence. The total energy $E(s)$ to minimize is given by:

$$E(s) = -\sum_{1 \leq i < j \leq N} w_{ij} s_i s_j + \lambda \left(\sum_{i=1}^{N} s_i - N_H \right)^2 \tag{11}$$

where s_i indicates whether bead i is of type P ($s_i = 0$) or H ($s_i = 1$). The parameter λ balances the two terms to ensure the desired composition of H beads.

The D-Wave Advantage system provides a hybrid quantum-classical solver that combines classical solvers with QPU queries to enhance performance on challenging QUBO problems. by utilizing this solver to optimize sequences for target structures with $N = 30$, $N = 50$, and $N = 64$. For each structure and composition, the authors performed multiple runs to generate optimized sequences. Folding computations were then conducted using the D-Wave hybrid solver to verify that the sequences folded into the intended structures.

The hybrid D-Wave annealer efficiently handled both steps of the sequence optimization and filtering process, providing a robust approach to the HP design problem. Pure QPU computations were limited by the problem size, showing decreased success rates for larger chains. Our time-dependent Schrödinger equation simulations suggested that control errors in the Hamiltonian could explain this limitation, as the added control noise qualitatively reproduced the modest QPU results.

The methods developed in this study are applicable to any quantum annealer and represent a significant step towards practical applications of quantum annealing (QA) in protein design and other biophysical challenges.