Hybrid Quantum-Classical Approach for 3D Protein Folding using the HP Model and QAOA

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***Abstract*—**Protein folding is a computationally challenging problem because the number of possible structures increases rapidly with sequence length. This paper presents a hybrid quantum-classical framework for protein folding using the Hydrophobic-Polar (HP) model in a three-dimensional lattice.

Valid protein structures are generated using a self-avoiding walk, and their energy is evaluated based on hydrophobic interactions. Simulated annealing is used as the classical opti- mization method, while the Quantum Approximate Optimization Algorithm (QAOA) is used for quantum optimization.

Experimental results show that simulated annealing achieves lower energy values (e.g., -5.0 eV) compared to QAOA (-4.45 eV). Although quantum optimization does not yet outperform classical methods, it produces close approximations and shows potential for future improvements.

Index Terms—Protein Folding; QAOA; HP Model; Quantum Computing; Simulated Annealing

I. INTRODUCTION

Proteins are essential biological molecules that must fold into specific three-dimensional structures to function correctly. The folding process is governed by physical interactions between amino acids, but predicting the final structure from a given sequence remains a difficult computational problem.

The difficulty arises because the number of possible config- urations grows exponentially with sequence length. Even for short protein sequences, the search space becomes extremely large, making exhaustive search infeasible.

To simplify this problem, the Hydrophobic-Polar (HP) model is commonly used. In this model, amino acids are grouped into hydrophobic (H) and polar (P) types [1], [4]. Hydrophobic residues tend to cluster together to minimize exposure to the surrounding environment, which drives the folding process.

Quantum computing introduces new approaches for solv- ing such combinatorial optimization problems. The Quantum Approximate Optimization Algorithm (QAOA) is particularly useful because it combines quantum operations with classical optimization techniques [2], [5].

This work investigates whether QAOA can effectively ap- proximate protein folding solutions and compares its per- formance with simulated annealing, a widely used classical method.

PROBLEM DEFINITION

Given a protein sequence $S = (s_1, s_2, \ldots, s_n)$ where each s_i belongs to the set $\{H, P\}$, the objective is to determine a valid three-dimensional structure that minimizes energy.

The problem must satisfy the following constraints:

- **Self-avoidance:** No two residues can occupy the same position in the lattice.
- **Chain continuity:** Consecutive residues must remain connected.

The energy function is defined as:

$$E = -(\text{Number of non-consecutive H-H contacts}) \quad (1)$$

This formulation reflects the tendency of hydrophobic residues to cluster together. Lower energy values correspond to more stable protein structures.

II. LITERATURE REVIEW

Classical optimization techniques such as simulated anneal- ing and Monte Carlo methods have been widely used for protein folding due to their ability to explore large solution spaces effectively [1], [8]. These methods provide reliable results but may struggle with scalability.

The HP model is commonly used because it simplifies protein folding while preserving essential physical behavior [1].

Recent research has explored quantum-based approaches, including QUBO formulations and quantum annealing [3]. Hybrid algorithms such as QAOA have shown promise in solving combinatorial optimization problems [2], [5].

However, current quantum hardware limitations restrict the performance of these methods for large-scale problems.

III. METHODOLOGY

The proposed system follows a hybrid pipeline that inte- grates classical and quantum optimization techniques.

A. Structure Generation

A self-avoiding walk is used to generate valid protein configurations in a three-dimensional lattice. This ensures that no overlapping occurs while maintaining chain continuity.

B. Energy Calculation

The energy of a configuration is calculated based on hy- drophobic interactions. Each valid H-H contact contributes to lowering the total energy, guiding the folding process toward stable structures.

C. Simulated Annealing

Simulated annealing is used as the classical optimization method. It starts with an initial configuration and iteratively improves it by exploring neighboring configurations.

At each step, a new configuration is accepted based on the probability:

VI. Results and Discussion

A. 3D Structure

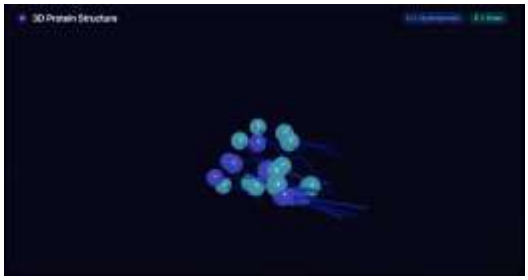


Fig. 1. 3D Protein Folding Visualization

$$P = e^{-(E_{new} - E_{old})/T} \quad (2)$$

where T is the temperature parameter. Initially, higher temperatures allow exploration of the search space, while lower temperatures encourage convergence toward optimal solutions.

D. Quantum Optimization

The folding problem is converted into a QUBO formulation:

$$E(x) = \sum a_i x_i + \sum b_{ij} x_i x_j \quad (3)$$ This is then mapped to an Ising Hamiltonian:

$$H = \sum h_i Z_i + \sum J_{ij} Z_i Z_j \quad (4)$$

QAOA is applied to approximate the ground state of this Hamiltonian. It alternates between problem-specific and mixing operations, with parameters optimized using classical methods.

E. Fallback Mechanism

If QAOA produces unstable or invalid results, a classical eigenvalue-based solver is used to ensure reliable outputs.

IV. Experimental Setup

Experiments were conducted on protein sequences of length 8–22.

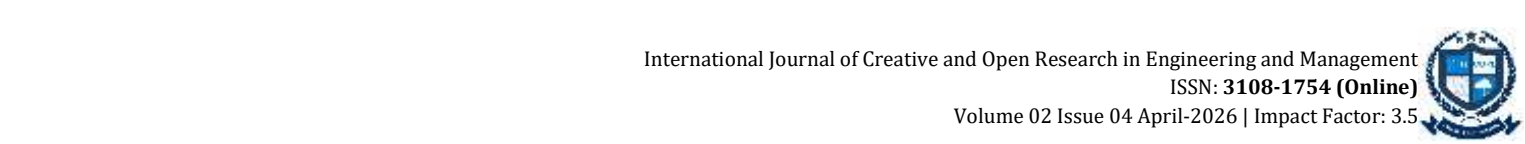
Simulated Annealing:

- Iterations: 1000
- Cooling factor: 0.95

QAOA:

- Circuit depth: 2
- Optimizer: COBYLA

All experiments were executed using a Python-based back- end.



The generated structure shows clustering of hydrophobic residues, indicating correct folding behavior.

B. Energy Convergence

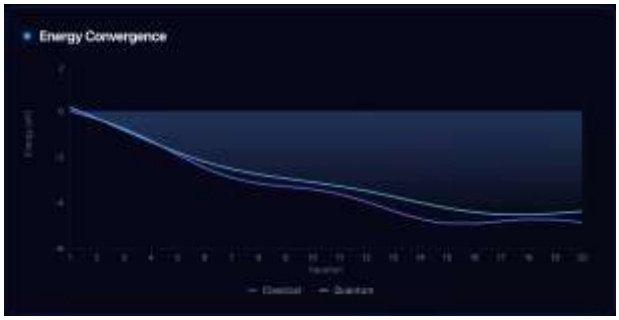


Fig. 2. Energy Convergence

Simulated annealing converges faster and achieves lower energy values compared to QAOA.

C. Energy Comparison

TABLE I
ENERGY COMPARISON

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Method	Energy (eV)
Classical	-5.0000
Quantum	-4.4521

D. Discussion

The results indicate that simulated annealing performs better in terms of energy minimization. QAOA, however, produces reasonably close results, especially for shorter sequences.

The performance gap increases with sequence length due to limitations such as circuit depth, optimization complexity, and hardware constraints.

VII. CONCLUSION

This paper presents a hybrid quantum-classical approach for protein folding using the HP model. While classical methods currently achieve better results, quantum approaches demonstrate promising potential.

Future improvements in quantum hardware and algorithm design may enable better scalability and performance for complex protein folding problems.

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