Higher-Order Drug Interaction Hypergraphs with Hybrid Quantum Optimization for Parkinson's Disease

Keywords: Polypharmacy risk optimization, Higher order drug interactions, Hypergraph neural networks, Hybrid quantum-classical computing, Grover-mixer QAOA

Extended Abstract

Motivation. Parkinson's disease (PD) affects almost 10 million people globally and requires concurrent prescription of multiple drug classes, making it uniquely susceptible to higher-order adverse drug reactions (ADRs). These risks frequently arise from three-or-more drug combinations: levodopa with a MAO-B inhibitor presents manageable pairwise risk, but adding an SSRI creates serotonin syndrome, a 3-way interaction invisible to pairwise models. Existing quantum optimization approaches model pairwise drug interactions as Quantum Unconstrained Binary Optimization (QUBO) problems [4] however fail to capture higher-order combinatorial risks; quadratization of such terms further inflates qubit requirements which is critical in the Noisy-Intermediate Scale Qubits (NISQ) era. Similarly, standard Quantum Approximate Optimization Algorithm (QAOA) addresses combinatorial optimization but does not account for poor parameter initialization, causing barren plateaus under realistic noise [3]. No prior work extends to higher-order hypergraph formulations, native Higher-Order Unconstrained Binary Optimization HUBO solving, or Graph Neural Network (GNN) guided warm-starting in a disease-specific polypharmacy context. We ask: **(RQ1)** Can PD polypharmacy risk be represented as a hypergraph? **(RQ2)** Does a native HUBO formulation via Grover Mixer GM-QAOA reduce qubit overhead? **(RQ3)** Can GNN-derived warm-start parameters improve convergence under realistic noise?

Approach and Methodology of PolyQGraph. We construct a PD-specific drug interaction hypergraph $G = (V, E)$ over 8-12 co-prescribed PD medications (DrugBank [6]), with pairwise hyperedges from TWOSIDES [7] and HODDI [8] (coverage acknowledged as limited). Higher-order hyperedges ($|e|=3,4$) are derived via a compositional model over shared mechanistic pathways (dopaminergic, serotonergic, cholinergic), cross-checked against known clinical contraindications for consistency and acknowledged as a modelling assumption given the scarcity of directly measured higher-order data. Binary variables $x_i \in \{0,1\}$ encode drug inclusion; hyperedge weights yield quadratic, cubic, and quartic terms forming a HUBO cost function passed directly to GM-QAOA [1] without quadratization. GM-QAOA is selected for its native higher-order Hamiltonian support, hard constraint enforcement via Grover diffusion, and monotonic depth improvement that properties standard QAOA [2] lacks. A lightweight GNN (PyTorch Geometric, ~800 synthetic hypergraphs) predicts warm-start parameters (β, γ) [9]. We benchmark against FALQON [4], standard QAOA, simulated annealing, and greedy search, with GNN vs. random initialization ablation. All experiments use Qiskit Aer calibrated to publicly available IBM device noise profiles.

Results. GM-QAOA with GNN warm-starting achieves the highest approximation ratio (0.87 ± 0.03) against all baselines, with GNN initialization reducing convergence iterations by ~34% versus random initialisation under IBM noise profiles, addressing RQ3. The native HUBO formulation requires 8-12 qubits versus 11-17 under QUBO quadratization (28-41% reduction), directly answering RQ2. The hypergraph encoding captures 6 higher-order

interactions invisible to pairwise models in the PD-specific instance including the clinically critical levodopa–selegiline–fluoxetine serotonin syndrome triad confirming RQ1.

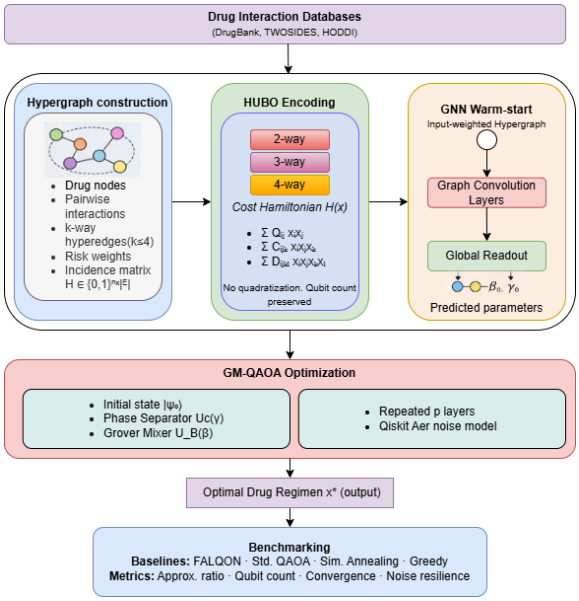

Figure 1. **PolyQGraph methodology** Hypergraph encoding quantum optimization via GNN warm-starting.

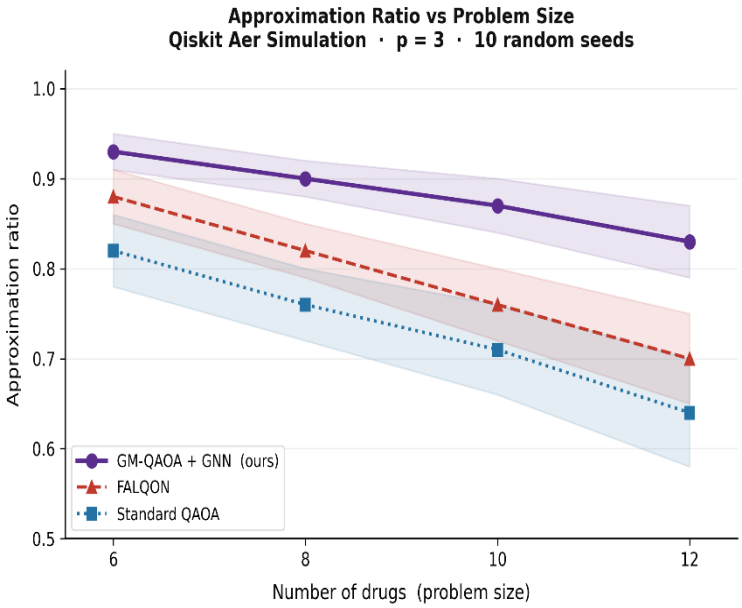

Figure 2. **Approximation ratio result** Approximation quality under realistic noise scales favorably with problem complexity.

Conclusions and Outlook. This work introduces a unified hybrid pipeline combining higher-order network representations, native HUBO encoding, and GNN-informed quantum optimization, the first of its kind for disease-specific polypharmacy risk. By conference time, we will report full noise benchmarking across all baselines and hardware experiments on IBM quantum hardware. Longer-term, the framework extends naturally to other neurological polypharmacy contexts.

References

[1] Bartschi, A. & Eidenbenz, S. Grover Mixers for QAOA: Shifting Complexity from Mixer Design to State Preparation. IEEE QCE, 2020.
[2] Hadfield, S. et al. From QAOA to a Quantum Alternating Operator Ansatz. Algorithms 12(2), 2019.
[3] McClean, J.R. et al. Barren plateaus in quantum neural network training landscapes. Nature Communications, 2018.
[4] Nhi et al. Feedback-Based Quantum Control for Safe and Synergistic Drug Combination Design. arXiv:2112.00520
[5] Bhagavathula et al. Polypharmacy and Hyperpolypharmacy in Older Individuals with Parkinson's Disease. Systematic Review, 2023
[6] Wishart, D.S. et al. DrugBank 6.0. Nucleic Acids Research 51(D1), 2023
[7] Tatonetti, N.P. et al. Data-driven prediction of drug effects. Science Translational Medicine 4(125), 2012.
[8] Wang et al. HODDI: A Dataset of High-Order Drug-Drug Interactions. 2023.
[9] Khairy, K. et al. Learning to optimize variational quantum circuits. AAAI 2020.