

Motif-Based RNA Secondary Structure Prediction Using Quantum Computing

Risi Liyanage | Sicheng Zhang | Shi-Jie Chen

Abstract

At thermal equilibrium, RNA molecules populate an ensemble of structures rather than adopting a single conformation. Consequently, RNA structure prediction can be formulated as sampling from the Boltzmann distribution of possible conformations rather than as a deterministic search for the single minimum-free-energy structure. **The RNA folding problem therefore maps naturally on to truly probabilistic sampling methods in quantum computing.** However, this paradigm is hindered by current quantum computers, particularly their limited number of qubits, which restricts representational resolution and may impede accurate prediction. We hypothesize that loop motifs in RNA structures provide a novel representation of

basis and with this formulation, can significantly reduce qubit requirements relative to quartets. Furthermore, the use of loop motif basis has the unique advantage of describing local, distinct

helical discontinuities and allowing broader competing structures for globally viable RNA folds.

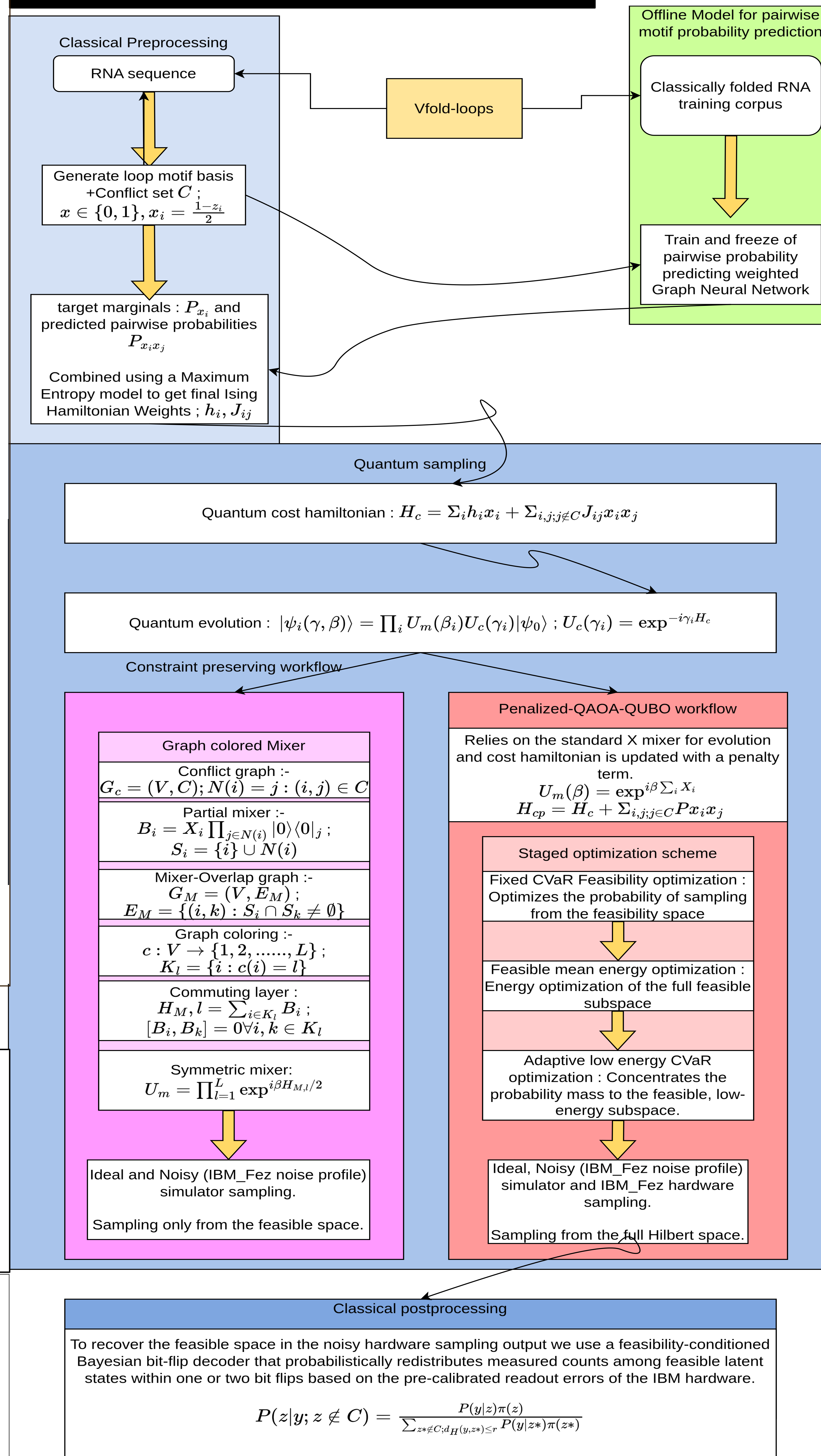
Key Contributions

- Novel motif basis that reduces the Qubit requirement.
- Utilization of true co-occurrence probabilities in the Ising Hamiltonian coupling term.
- Multi-staged optimization procedure targeting specific objectives.

REFERENCES

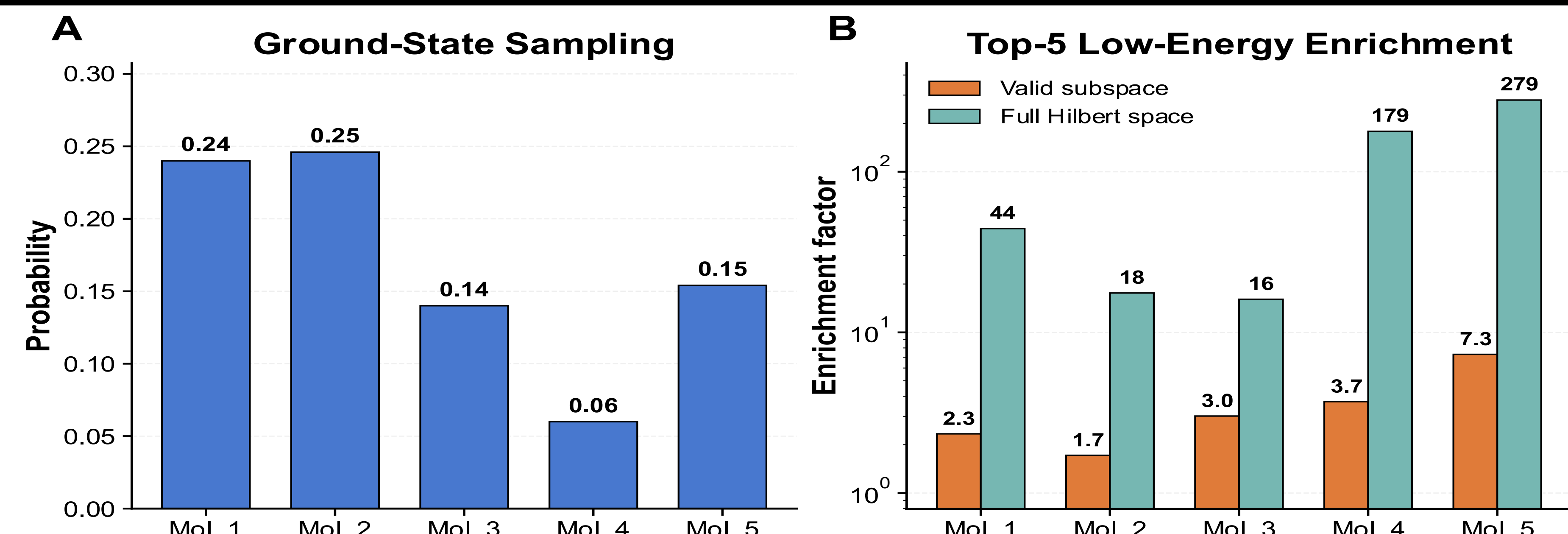
- [1] Alevras et al., IEEE QCE, 2024. 10.1109/QCE60285.2024.00064
- [2] Kumar et al., IEEE QCE, 2025. 10.1109/QCE65121.2025.00254
- [3] Alevras et al., IEEE QCE, 2025. 10.1109/QCE65121.2025.00255
- [4] Fox et al., PLOS Comput. Biol., 2022, 18:e1010032.

Computational workflow



Constraint preserving Mixer

Excellent Ideal performance – Excessive depth in hardware mapping



80 – 100% top 5 recall @ 20 for ideal simulator. However, when the noise is introduced, the high gate demand due to MCRX gate decomposition causes signal suppression. The valid substate sampling is limited to 1x - 3.5x with respect to the baseline valid fraction.

Penalized-QUBO-QAOA

Single objectives optimize either feasibility or energy ; staged method is balanced

Optimization method	Normalized Method Performance				
	Ground state sampling %	Feasible state sampling %	Low-energy (top-10%) %	Feasible energy gap	Rate of ground state being mode
Staged optimization	12.425	64.076	22.475	0.587	100.000
Feasibility-aware CVaR	12.046	66.651	20.745	0.605	80.000
Expected QUBO energy	11.327	62.859	19.954	0.608	80.000
Conditional feasible mean	10.901	56.535	19.332	0.566	62.000
Ascending CVaR	10.559	53.732	16.379	0.615	60.000
Fixed feasible CVaR	9.813	55.429	17.548	0.612	80.000
Fixed penalized CVaR	7.911	54.461	17.918	0.609	80.000

Postprocessing recovers valid sampling while keeping the learned low energy bias

