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Review of Quantum Generative Models for Small Molecule Drug Discovery

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Introduction

Background:

- Drug discovery is a lengthy and expensive process, often taking over a decade and costing billions of dollars. This involves searching a vast molecular "chemical space," estimated to have up to 10^{60} possibilities.
- Machine learning models, like GANs, have been applied to this problem, successfully generating molecules with desired chemical and physical properties.

Challenges:

- Classical GANs struggle with the vast chemical space due to limitations in computational capacity and the curse of dimensionality.
- A fully quantum GAN would require over 90 qubits for small molecule datasets like QM9, exceeding current quantum computer capabilities.

Proposed Solution:

- The QGAN-HG (Hybrid Quantum GAN) combines the strengths of quantum computing and classical neural networks:
  1. Quantum Generator: Uses qubits to explore the chemical space efficiently, leveraging quantum parallelism.
  2. Classical Discriminator: Evaluates and refines generated molecules to align with real data distributions.
- This approach reduces the parameters needed while maintaining or improving performance compared to classical models.

Objective

Develop a qubit-efficient hybrid quantum GAN (QGAN-HG) that combines quantum and classical methods to efficiently generate valid drug-like molecules, overcoming the limitations of classical GANs in exploring vast chemical spaces.

Methods

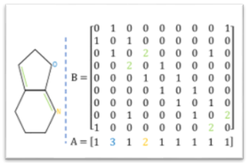
Hybrid Quantum-Classical Architecture:

- The **generator** consists of:
  1. A **quantum circuit** that creates a feature vector by leveraging qubit superposition and entanglement to explore the chemical space efficiently.
  2. A **classical neural network** that transforms the quantum-generated features into atom vectors and bond matrices, representing drug molecules as graphs.
- The **discriminator** is a classical neural network that distinguishes between real molecules from the dataset and synthetic molecules generated by the model.

Molecular Representation:

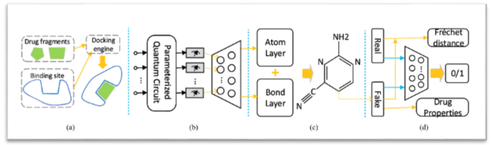
Molecules are encoded as:

- **Atom vectors**: Each entry describes atom types.
- **Bond matrices**: Square matrices with entries representing bond types and properties.



Workflow:

1. **Input Noise**: Quantum circuit takes uniformly sampled noise (e.g., from [−π,π]x[-π, π]) to generate a random quantum state.
2. **Feature Generation**: Quantum circuit processes noise to create a feature superposition using parameterized gates, then the expected value of each feature is approximated and used in the classical neural network.
3. **Molecule Generation**: Classical neural network outputs atom and bond representations.
4. **Validation**: Discriminator evaluates the generated molecules, feeding back error signals to improve the generator.



Training:

- The model optimizes Fréchet Distance (FD) to align generated molecule distributions with real data. Training 85% reduced (Medium Reduced/MR) MolGAN models to measure the effect with and without a hybrid quantum generator.
- Modifications to reduce model instability. Changed parameter initialization, learning rate strategy and quantum circuit design flaws. Experiment reran 8 times for more certainty on results.

Results

Performance Metrics:

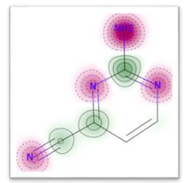
- **Fréchet Distance (FD):** Measures how closely the generated molecule distribution matches the real molecule distribution.
  - QGAN-HG achieved a **lower FD** compared to reduced classical GANs, indicating superior alignment with the real data distribution.
- **Molecule Validity:** Generated molecules were consistently valid, with QGAN-HG outperforming MolGAN in valid score by **~30(/100) points on average**.

Models\Metrics	FD Score	Valid Score	Druglikeliness	Solubility	Synthesizability
MolGAN (MR)	11.42 (± 1.08)	46.71 (± 13.18)	0.47 (± 0.00)	0.66 (± 0.03)	0.12(± 0.05)
QGAN-HG (MR) 10Q	10.71 (± 1.62)	**76.64 (± 9.74)**	0.49 (± 0.01)	0.67 (± 0.05)	0.10 (± 0.06)

Drug Property Evaluation:

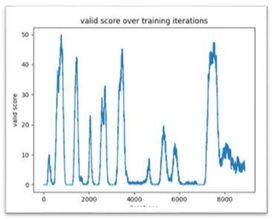
- Metrics like drug-likeness (QED), solubility (logP), and synthesizability (SA) were very similar with and without quantum circuit.
- QGAN-HG with 85% less parameters had a synthesizability score of **~70(/100) points lower on average** than the original MolGAN.

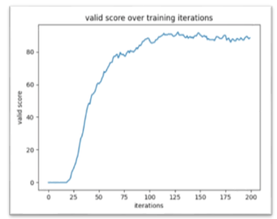
Generated Molecule Example:



Stability and Training:

- Code modifications increased model stability and performance. Converges in substantially less iterations.





Discussion and Future Work

Model Advantages:

- The hybrid quantum-classical architecture demonstrated strong potential for efficiently exploring the vast chemical space. The lower average Fréchet Distance and significantly higher molecule validity scores validate the effectiveness of the QGAN-HG design for molecular graph generation.

Limitations:

- **Instability in Training**: model collapse occurred more often with the quantum circuit included, however this should be less of problem using different GAN variations that address the inherit instability in its design.
- **Scalability Concerns**: Current implementations are limited to small molecules due to qubit constraints and noise in near-term quantum devices. There isn't proof that scaling qubits will retain its significance to bigger datasets.

Comparison with Classical Models:

- While QGAN-HG outperformed reduced classical GANs, full MolGAN models still exceeded QGAN-HG on some metrics like synthesizability.

Future Work:

1. **Training Instability:** Explore variations of the GAN, like the variational autoencoder that are more stable. Test results on real quantum computers
2. **Qubit Scalability:** Incorporate more qubits and leverage future quantum hardware to support larger molecular datasets like ChEMBL.

References

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Resources:

- Used a personal NVIDIA 4090 GPU for training the models for a total time of three days.

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