Molecular docking with Neutral Atoms quantum computing

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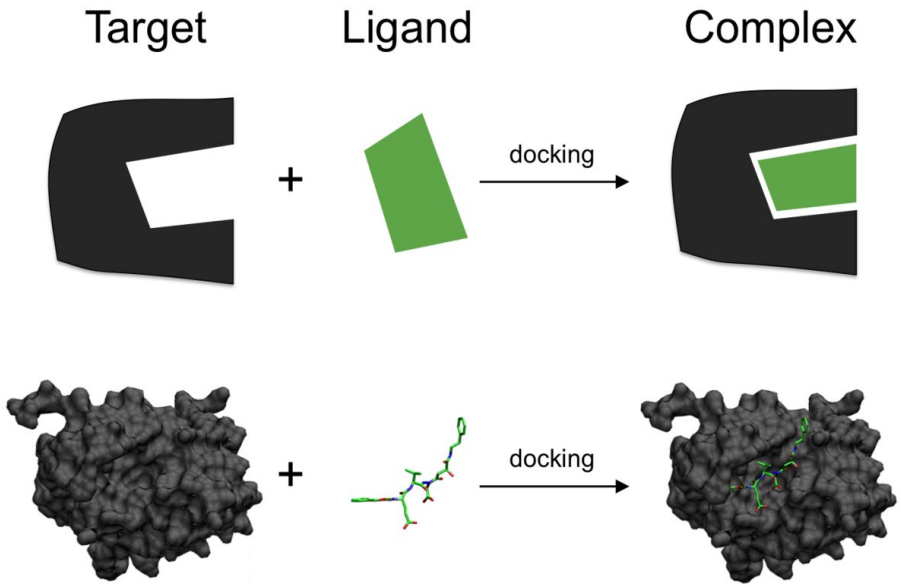
Introduction

- Finding new therapeutic targets for drug discovery is highly important in the pharmaceutical industry.
- Standard methods are **time-consuming and expensive** but new computational strategies are emerging that can speed up process as Virtual screening (VS) .
- VS optimizes drug discovery by **highlighting molecules that fit the target**. To achieve this, two distinct methods are used:
    - Ligand-based
    - Structure-based

90 % of clinical drug development fail to gain approval [6], the pharmaceutical industry needs to improve the drug discovery process

Molecular docking

- Structure-based methods rely on **molecular docking** to demonstrate how likely a particular ligand is to bind to a target protein [1].
- When applied iteratively to a library of small molecules, each member is **docked into the recept**or, assigned a predicted binding energy, and ranked accordingly [3].
- For large chemical libraries, it is desirable to search and score configurations using as **few computational resources as possible** [4].



Molecular docking allows to predict the activity of the candidate molecules at the binding site of the proteins, helping in the selection of those with desirable behavior and reject those with undesirable behavior.

Molecular docking and quantum

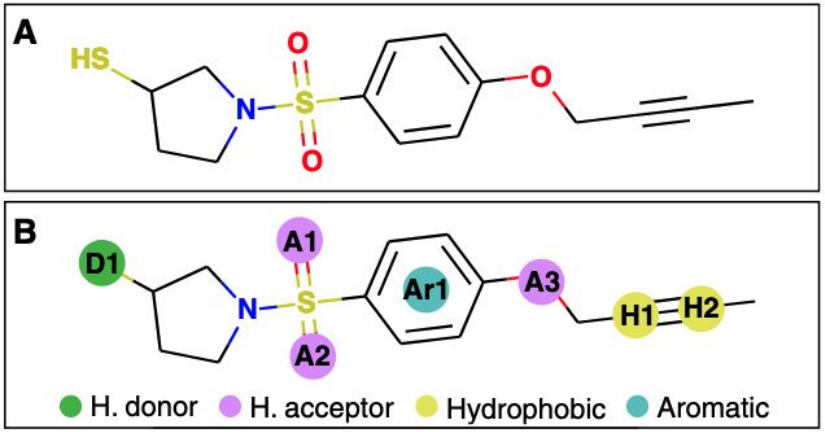
- In the industrial drug design where large numbers of candidate molecules must be screened against a drug target, a fast method for predicting docking configurations is required.
- Gaussian Boson Sampling (GBS), a photonic quantum device, has been used to solve the molecular docking problem [2].
    - The method used was a **vertex-weighted binding interaction graph approach**, where the molecular docking problem is reduced to finding the **maximum weighted clique** in a graph.
    - GBS can be programmed to sample large-weight cliques, with high probability, enhancing the performance of classical algorithms and increasing their success rate of finding the molecular binding pose.

Molecular docking to a graph problem- First Approach

Molecular docking to a graph problem

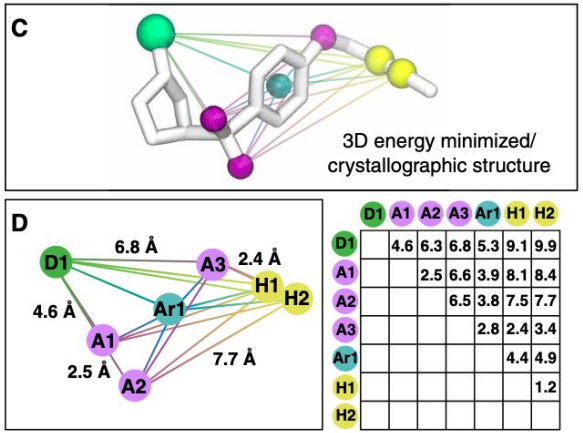
Construction of the labeled distance graph for a ligand molecule.

(**A**) Planar structure of the ligand molecule.



(**B**) Pharmacophore points of the molecule are identified

(**C**) Their pairwise distance is measure using the know three-dimensional (3D) structure.



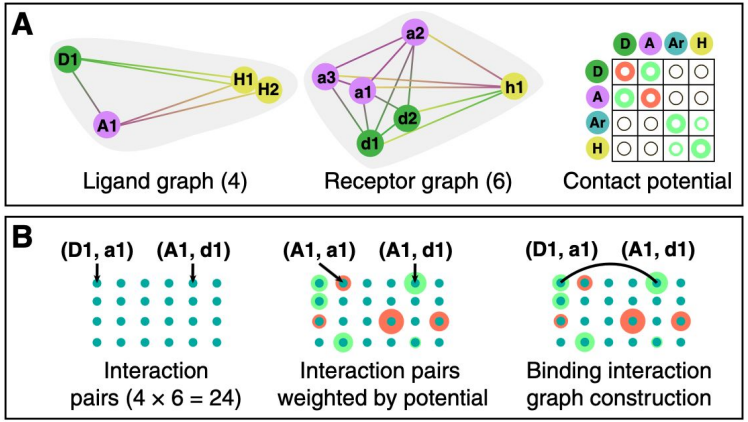
	D1	A1	A2	A3	Ar1	H1	H2
D1		4.6	6.3	6.8	5.3	9.1	9.9
A1			2.5	6.6	3.9	8.1	8.4
A2				6.5	3.8	7.5	7.7
A3					2.8	2.4	3.4
Ar1						4.4	4.9
H1							1.2
H2							

(**D**) Labeled distance graph for the ligand molecule, where vertices represent the pharmacophore points and edge weights of their respective pairwise distance. The complete weight matrix is on the right.

Images and mapping process from [2]

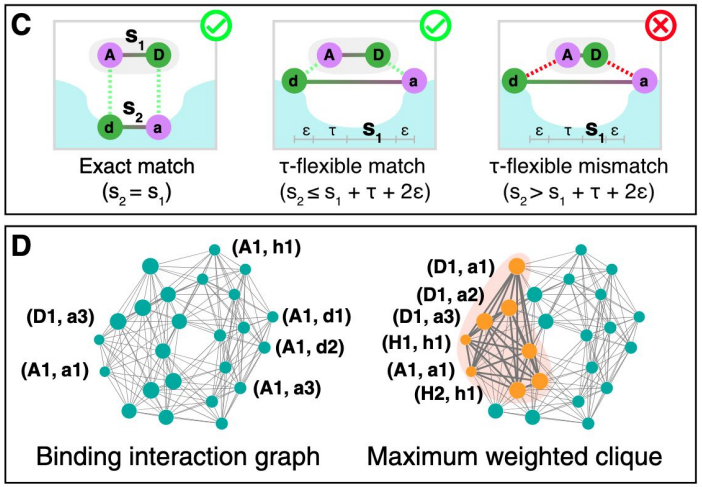
Molecular docking to a graph problem

(**A**) Two labeled graphs (one for the ligand and one for the receptor)



(**B**) The binding interaction graph is constructed by creating a vertex for each possible contact between ligand and the receptor weighted by the contact potential.

(**C**) Various scenarios for pairs of vertices that represent compatible contacts.



(**D**) The resulting graph is then used to search for potential binding poses These are represented as complete subgraphs of the graph, as they form a set of pairwise compatible contacts.

The heaviest vertex-weighted cliques represent the most likely binding poses (maximum vertex-weighted clique depicted in orange in (D))

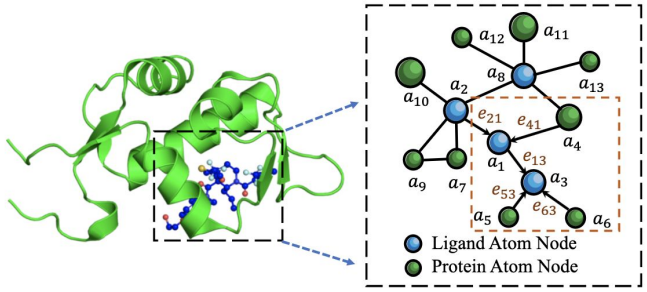
Images and mapping process from [2]

Molecular docking to a graph problem- Second Approach

Molecular docking to a graph problem

Table 1: Mathematical notations.

Notation	Description
$\mathcal{V}^P$,$\mathcal{V}^L$	The atom node sets of protein and ligand
M^P,M^L	The 3D position matrices of protein and ligand
$\mathcal{G}_I$	The complex interaction graph
a_i	The i-th atom node in $\mathcal{G}_I$
e_{ij}	The directed edge from atom a_i to atom a_j
$\mathcal{N}_e(a_i)$	The neighboring edges of atom a_i
$\mathcal{N}_e(e_{ij})$	The neighboring edges of edge e_{ij}
$\boldsymbol{a}_i$, $\boldsymbol{e}_{ij}$	The embedding vectors of atom a_i and edge e_{ij}
$\boldsymbol{d}_{ij}$	The spatial embedding vector between a_i and a_j



(a) 3D Protein-Ligand Complex (b) Complex Interaction Graph

Algorithm 1: Complex Interaction Graph Construction.

Input : The position matrix M^P and node set $\mathcal{V}^P$ of protein
The position matrix M^L and node set $\mathcal{V}^L$ of ligand
The cutoff distance r_θ

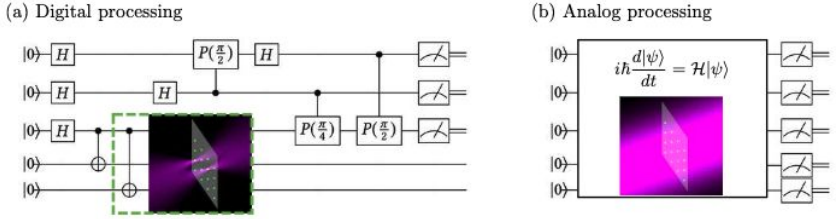
Output: The complex interaction graph $\mathcal{G}_I =< \mathcal{V}, \mathcal{E} >$

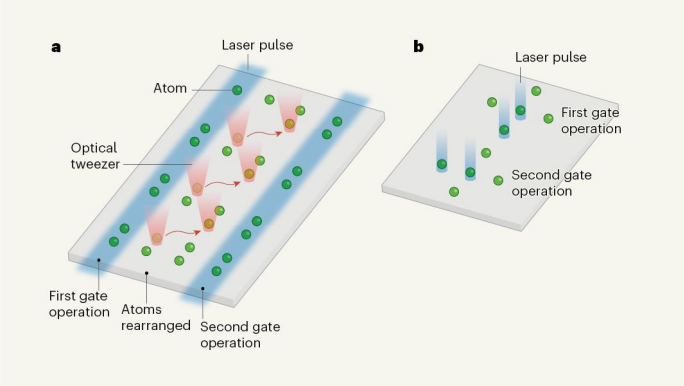
Initialize $\mathcal{V} \leftarrow \mathcal{V}^L$, $\mathcal{E} \leftarrow \{\}$;
for *atom node pair* $(a_i,\ a_j) \in \mathcal{V}^L \times \mathcal{V}^P$ **do**
  Calculate distance $d_{ij} \leftarrow |M^L(a_i) - M^P(a_j)|$;
  if $d_{ij} \le r_\theta$ **then**
    Update node set $\mathcal{V} \leftarrow \mathcal{V} \cup \{a_j\}$;
  end
end
Combined position matrix $M \leftarrow CONCAT(M^L, M^P)$;
for *atom node pair* $(a_i,\ a_j) \in \mathcal{V} \times \mathcal{V}$ **do**
  Calculate distance $d_{ij} \leftarrow |M(a_i) - M(a_j)|$;
  if $d_{ij} \le r_\theta$ **then**
    Update edge set $\mathcal{E} \leftarrow \mathcal{E} \cup \{e_{ij} = (a_i, a_j)\}$;
  end
end
return $\mathcal{V}, \mathcal{E}$

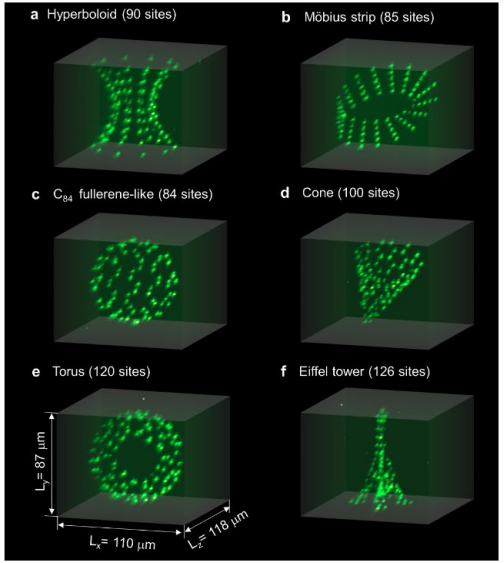
Images and algorithm from [11]

Pasqal's Neutral Atom Quantum Processor

- Based on an analog approach where, as opposed to the case of digital quantum computing, the quantum operations are not divided into discrete consecutive steps (gates), but are rather the result of a time-dependent control of the Hamiltonian acting upon the qubits [14].





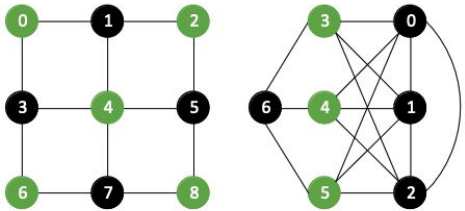


Neutral atoms (green dots) arranged in various configurations. These atoms can be used to encode qubits and carry out quantum computations. Image from [13]

Solution using Neutral Atoms QPU
First approach: Quantum Sampling

Quantum Sampling with Neutral Atoms

- The original computational problem can be mapped onto a maximum- weight independent set (MWIS) problem on a unit-disk graph (UDG).
- In the Physical platform, where each vertex in represents an atom trapped by optical tweezers.
- Sampling of the graph in the Rydberg platform to reduce the search space [8]



(a) Unit disk graph. (b) Non-UD graph.

Examples of (a) an easy and (b) a hard graph for a neutral atom platform. The MIS is indicated in green. Image from [5]

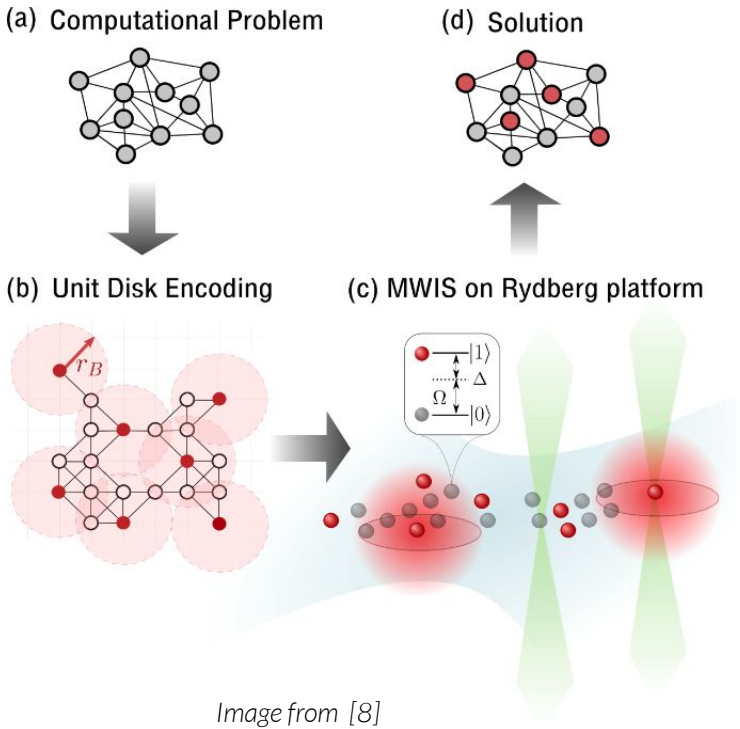
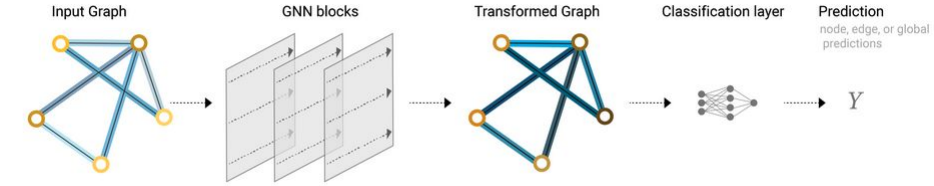


Image from [8]

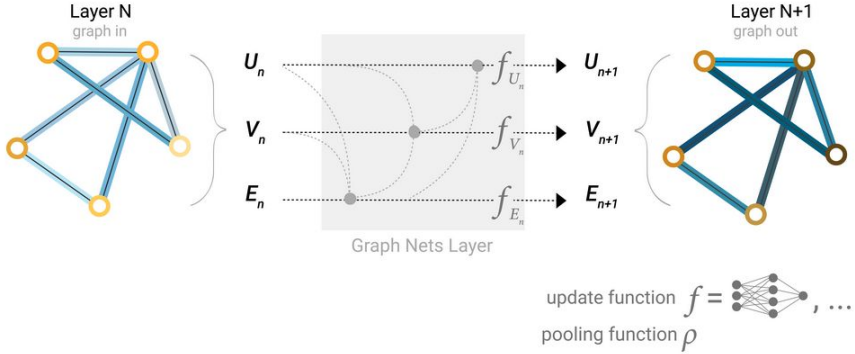
Solution using Neutral Atoms QPU
Second approach: Quantum Graph Neural Network

Graph Neural Networks (GNNs)

- A GNN is an optimizable transformation on all attributes of the graph (nodes, edges, global-context) that preserves graph symmetries (permutation invariances).
- GNNs adopt a “graph-in, graph-out” architecture meaning that these model types accept a graph as input, with information loaded into its nodes, edges and global-context, and progressively transform these embeddings, without changing the connectivity of the input graph.



An end-to-end prediction task with a GNN model.

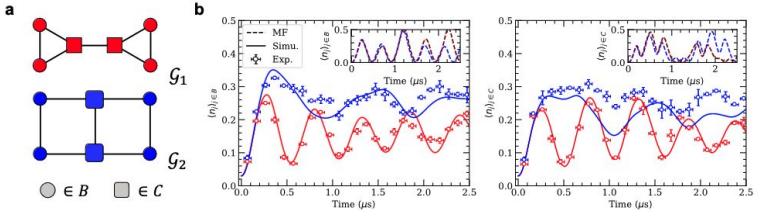


Schematic of a Graph Nets architecture leveraging global representations.

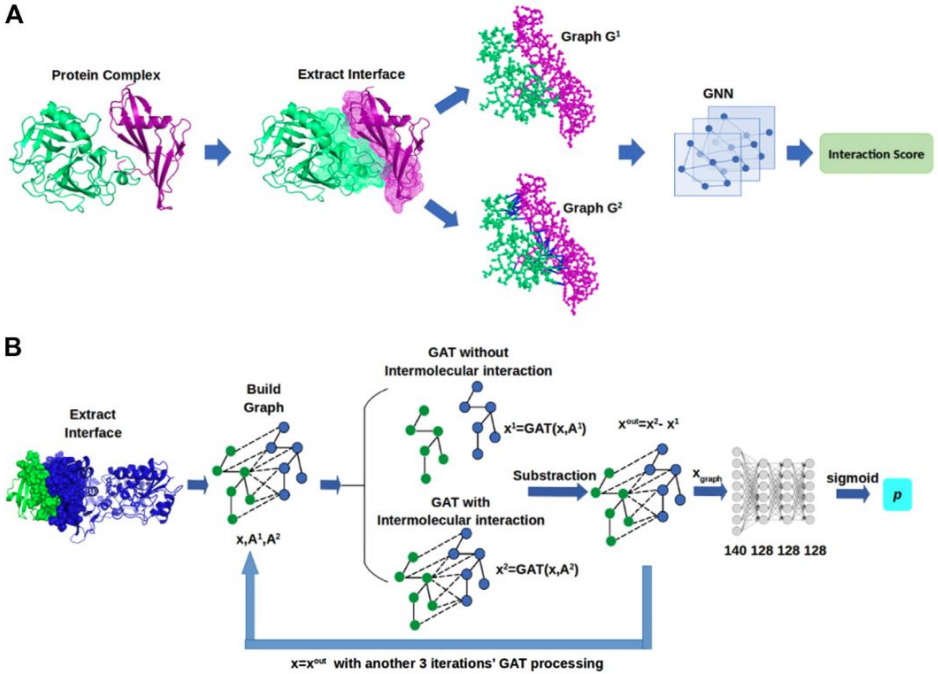
Images from [18]

Quantum GNN for Molecular Docking

- Given the natural encoding of graphs with neutral atoms. We can create a quantum GNN layer [16, 17] to solve the molecular docking problem [10,11,12]
- In [7], Pascal explore the use of Neutral Atom Quantum Processor for Graph Machine Learning



Simulation with Neutral atoms of two different graphs with identical local structure [7]



(A) Overall logical steps of the pipeline of GNN for Molecular docking. (B) Architecture of the GNN network with gated graph attention mechanism [9]

Challenges on quantum solutions

- Mapping of the molecular docking problem to a graph problem
- Lack of literature on Quantum GNN for Neutral Atom Quantum Processor
- Encoding of the problem
- Can we use error mitigation techniques with a Neutral Atom Quantum Processor?
- Sampling using a Neutral Atom Quantum Processor
- Choose cases for benchmarking against classical solutions

Conclusions and next steps

- The Quantum GNN approach can be use for other type of problems
- Sampling of graphs with Neutral Atom Quantum Processor has many applications
- Explore the use of a Neutral Atom Quantum Processor for drug discovery

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