SMALL MOLECULE – PROTEIN INTERACTION. A QUANTUM PERSPECTIVE

QUBO-based prioritisation of candidate ligands targeting lipoprotein lipase

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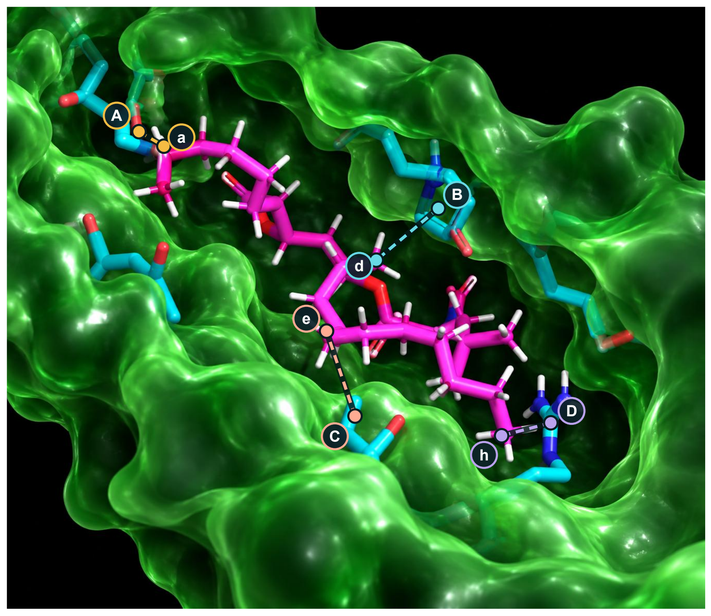
LPL AS A THERAPEUTIC TARGET

Lipoprotein lipase (LPL) plays a central role in the clearance of triglyceride-rich lipoproteins and represents a potential therapeutic target for compounds capable of enhancing or stabilising its activity. This work reformulates a molecular docking approach for identifying favourable interactions between candidate ligands and LPL binding site as a combinatorial optimization problem, enabling the use of quantum computing hardware to address this class of molecular recognition problems.

For each candidate ligand, atomic coordinates, Gasteiger partial charges, electronegativity, and Lennard–Jones-derived steric interactions were used to characterise potential contacts with selected atoms of the LPL binding site. Hence, optimal sets of geometrically compatible ligand–receptor contacts are identified, providing a quantitative interaction score for ligand prioritisation. By encoding the molecular interaction landscape into a Hamiltonian that can be directly processed by quantum annealing hardware, the approach establishes a computational representation that is conceptually closer to the underlying quantum nature of molecular systems than conventional optimisation strategies constrained to purely classical architectures.

Overall, this work demonstrates how molecular docking can be reformulated as a discrete optimisation problem suitable for quantum computing, providing a framework for bridging molecular interaction modelling with quantum architectures.

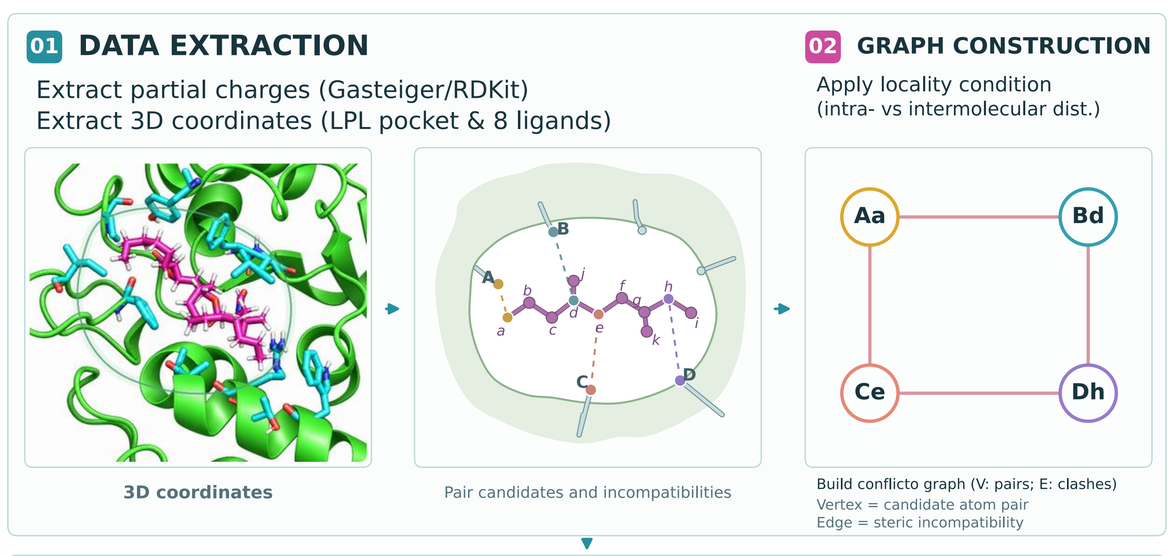


ENCODE CONTACTS AS A CONFLICT GRAPH

Each vertex v=(i,j) is a ligand–LPL atom pair at ≤4.5 Å. Its positive weight, $w_v=-q_iq_j$, is an electrostatic charge-product proxy

Repulsive and zero terms and contacts with $w_v<0.001$ are removed. An edge joins two candidate contacts if their intra- and intermolecular distance patterns cannot be reconciled in one spatial arrangement.

An independent set contains no adjacent vertices. The MWIS therefore selects the largest summed weight among geometrically compatible contacts, converting the docking question into combinatorial optimisation.



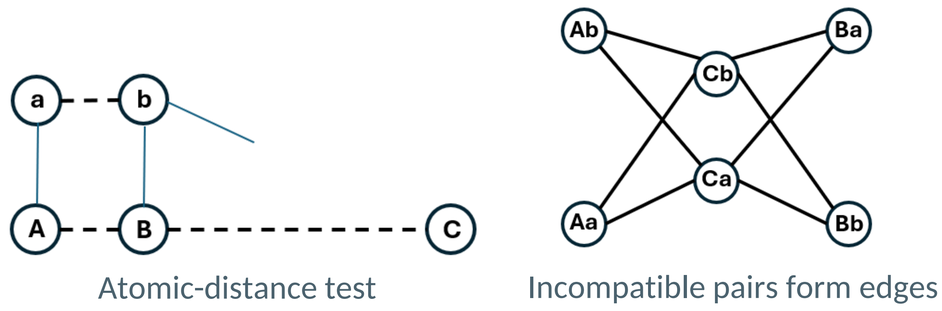


Figure1: Conflict graph construction and MWIS formulation. The locality condition (left) compares intermolecular (solid lines) and intramolecular (dashed lines) distances for vertices 'Aa'/'Bb' (compliant) and 'Aa'/'Cb' (non-compliant) against a 4.5 Å interaction threshold; non-compliant pairs form adjacent edges. The resulting conflict graph (right) represents potential interacting atom pairs for the ligand (ab) and receptor (ABC), grouped into independent sets (e.g., {Aa, Ab, Ba, Bb} and {Ca, Cb}). Solid lines denote steric conflicts. The optimal binding configuration corresponds to the Maximum Weighted Independent Set (MWIS), which maximises the cumulative interaction energy while strictly respecting spatial constraints.

QUANTUM DOCKING RESULTS ACROSS LIGANDS

Selected interaction score

Table 1: Massive reduction of the combinatorial search space (2^n) by filtering weak interactions, Cumulative weights of the MWIS representing the interaction energy between the receptor and ligands.

Ligand	Atoms	Initial N_0	Retained N	Cut	MWIS weight	Interaction profile
1	52	4,992	2,197	56%	19.18	Baseline
2	69	6,624	2,894	56%	21.67	Standard
3	**72**	**6,912**	**3,212**	**54%**	**29.66**	**High energy, low conflict density**
4	79	7,584	3,477	54%	25.04	Stantard
5	84	8,064	3,461	57%	26.87	Standard
6	86	8,256	3,709	55%	33.41	High energy (largest size)
7	**88**	**8,448**	**3,429**	**59%**	**13.86**	**Low energy, high conflict density**
8	91	8,736	3,958	55%	37.30	Highest energy

Key Findings:

- **Size–energy correlation:** Generally, larger ligands present higher interaction energies.
- **Outliers:** Ligand 3 shows anomalously high energy (fewer steric conflicts), suggesting an optimal spatial fit. Ligand 7 shows the lowest energy despite its size, indicating a highly dense conflict graph.

CONCLUSIONS

Successful formulation: Molecular docking was successfully mapped to a QUBO/MWIS problem using the concept of steric impedance.

Scalability: Resolved conflict graphs of up to $N = 3958$ **vertices** using quantum-inspired Digital Annealing.

Ligand ranking: Established a clear classification of molecules with **favourable** interaction capabilities with the LPL enzyme.

VALIDATION FOR DRUG DISCOVERY

Spatial reconstruction: Post-processing to map the MWIS solution back to 3D space to reconstruct poses and compare with classical docking and molecular dynamics.

Pharmacophore grouping: Reducing variables by grouping atoms into pharmacophores and validate accuracy of the simplified system.

Quantum hardware: Execution on D-Wave Quantum Annealers (LeapHybridBQMSampler).

Digital Quantum Algorithms: Implementing techniques like Pauli Correlation Encoding to compress variables.

Experimental validation.

Steric Impedance: The resistance to molecular interaction due to spatial repulsion between bulky functional groups.

Conflict Graph (G):

- **Vertices (V):** Potential interacting atom pairs (Ligand-Receptor).
- **Edges (E):** Steric conflicts (pairs that cannot coexist due to violating the *locality condition*).
- **Weights (ω_v):** Coulombic interaction energy $\omega_v = -q_{L,v}q_{R,v}$.

MWIS (Maximum Weighted Independent Set): Finding the set of non-adjacent vertices that maximises the total interaction energy.

REFERENCES

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