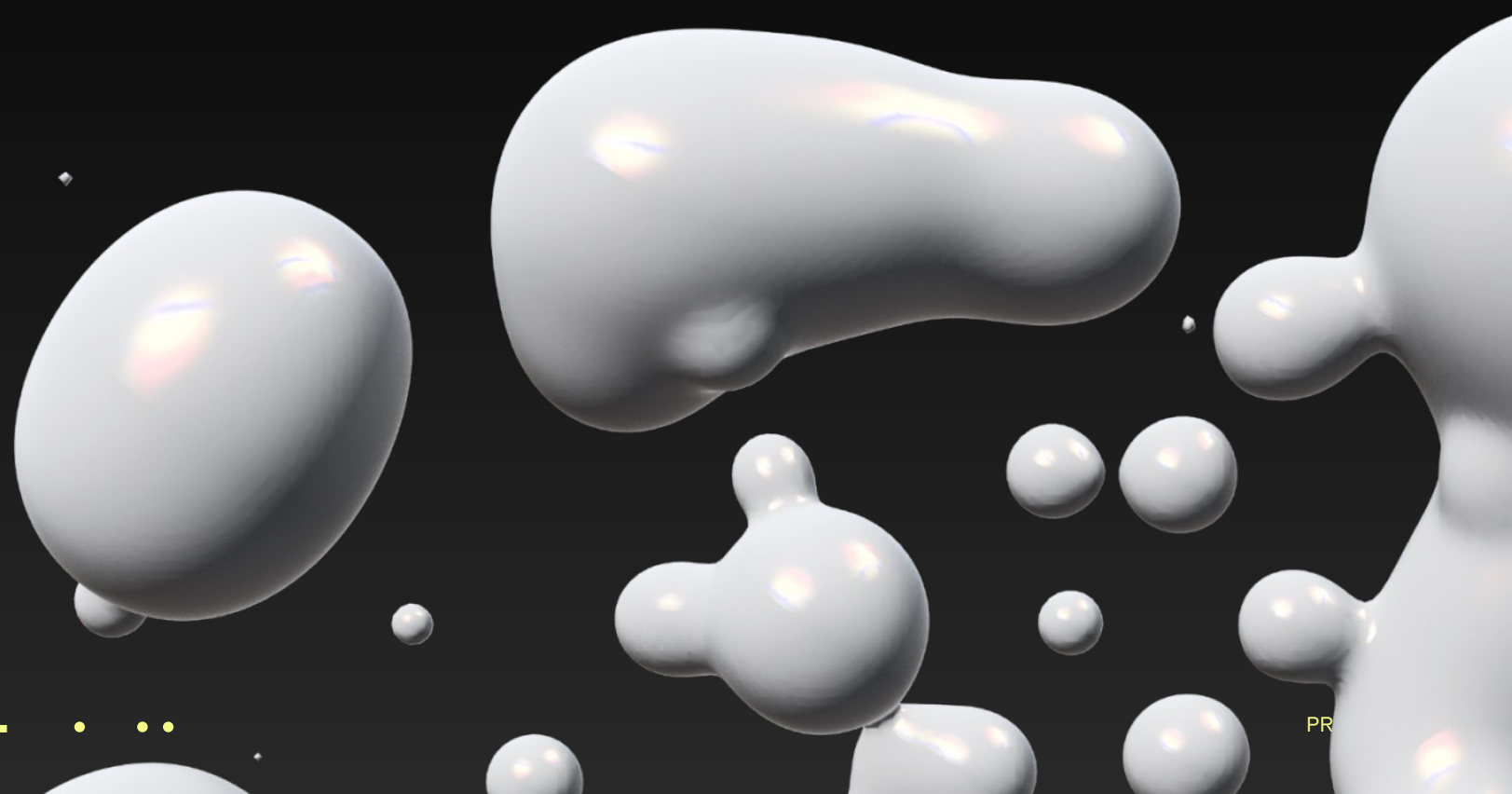
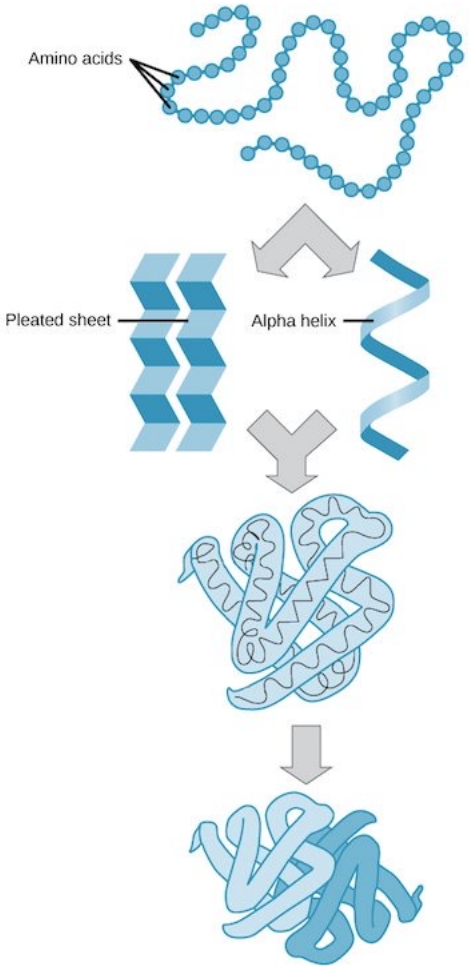
Insights Into the Role of Water in Drug Discovery: A Dual Perspective on Classical & Quantum Approaches

Daniele Loco, R&D Engineer in Quantum Physics & Chemistry



Qubit PHARMACEUTICALS

A small step back: Proteins and Water

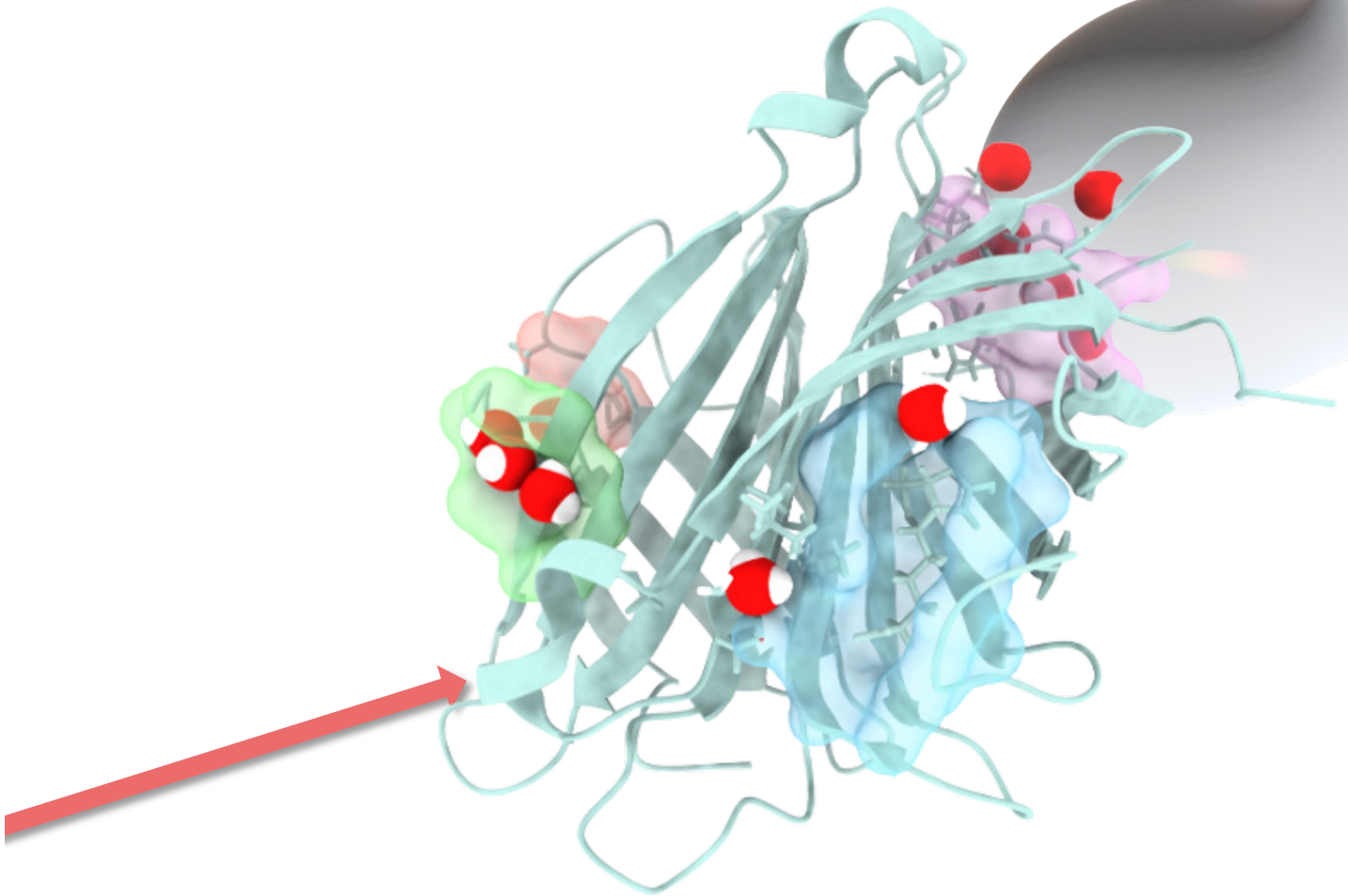


Primary protein structure
sequence of a chain of animo acids

Secondary protein structure
hydrogen bonding of the peptide backbone causes the amino acids to fold into a repeating pattern

Tertiary protein structure
three-dimensional folding pattern of a protein due to side chain interactions

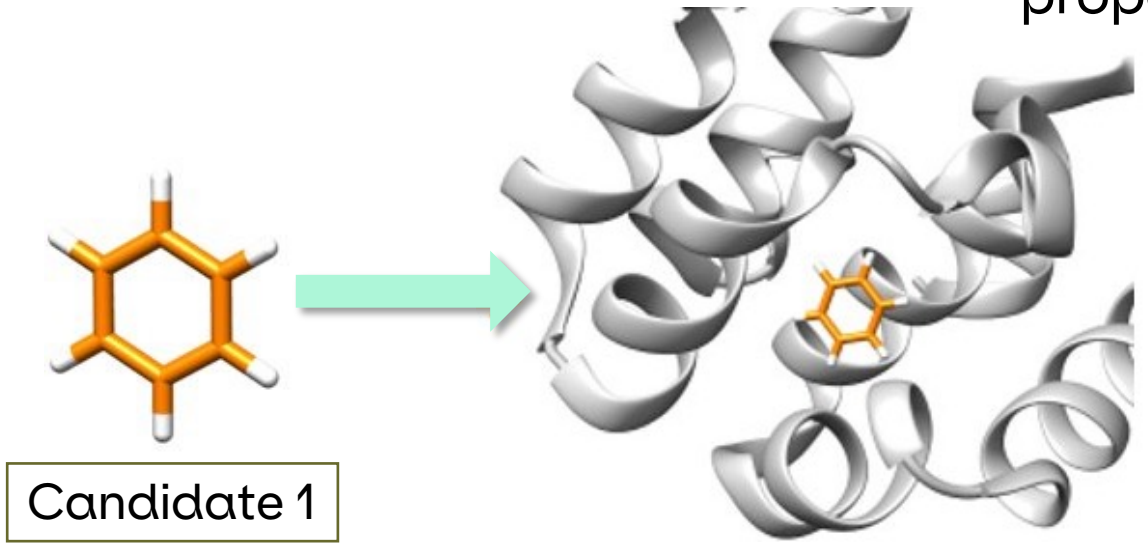
Quaternary protein structure
protein consisting of more than one amino acid chain



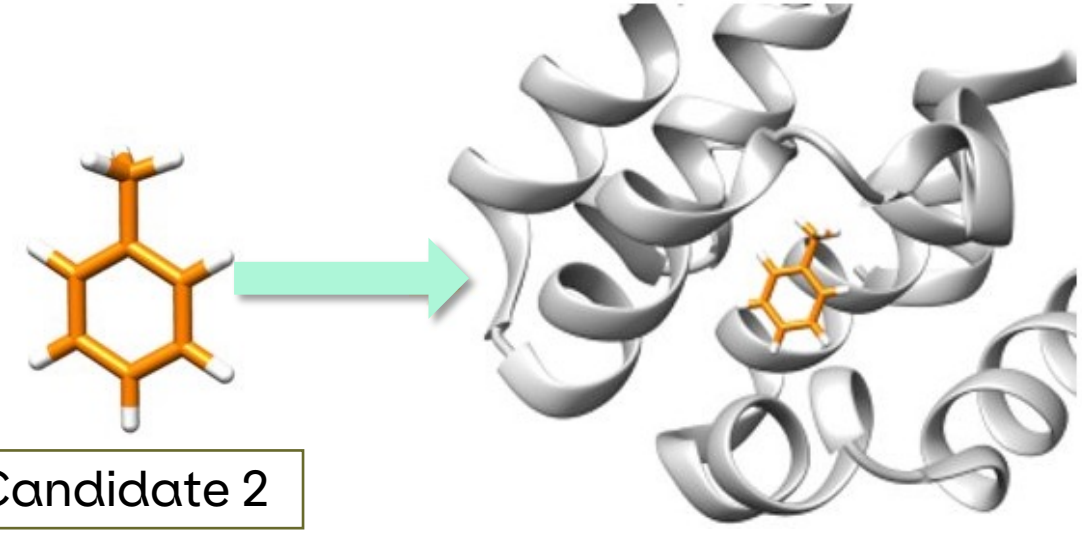
How is this related to Drug Discovery?

Drug Discovery → Search for new candidate medications (drugs)

Structure Bassed DD → Target bio-system (e.g.: protein, DNA) molecular structure determines drug properties

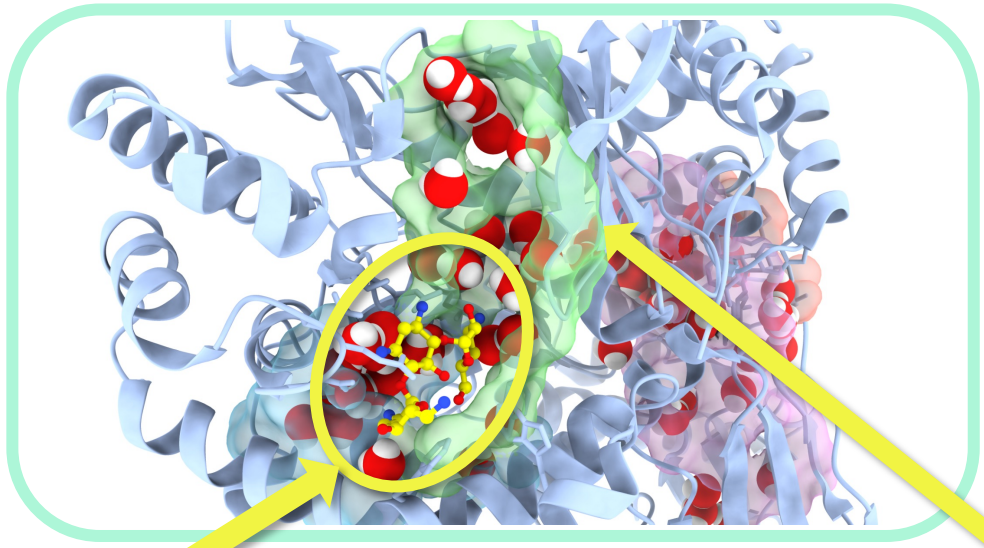


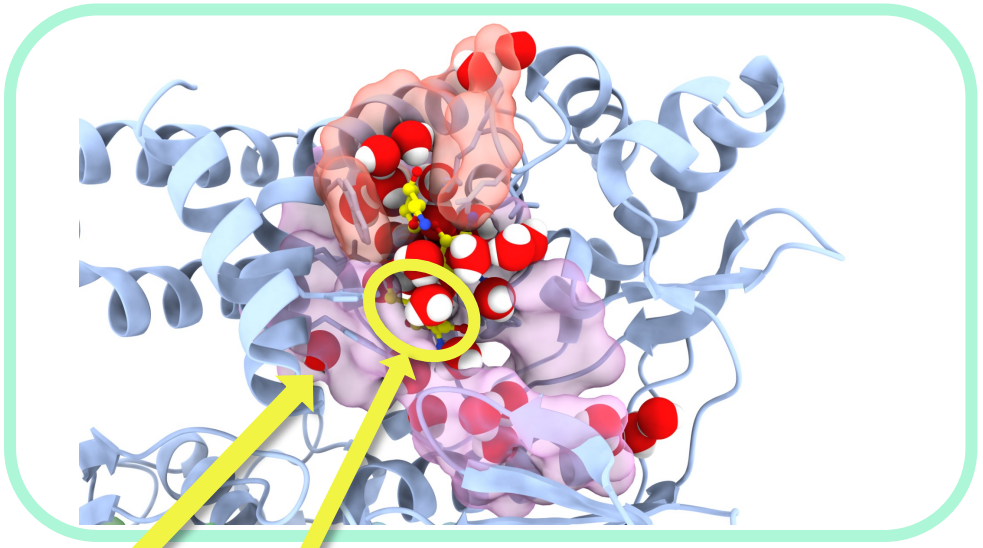
Candidate 1



Candidate 2

Where does water come into play?

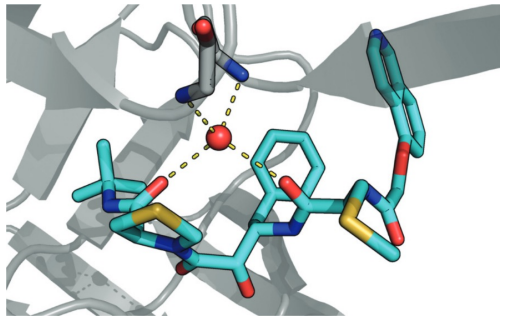




Candidate

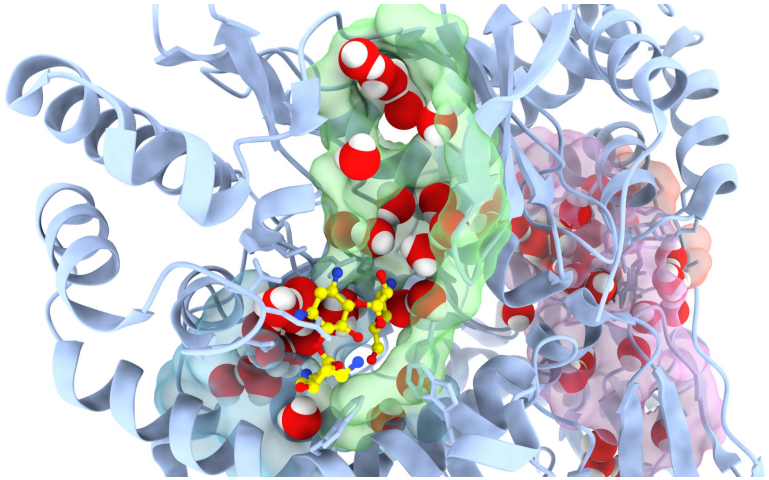
Inside Proteins Pockets
On the protein surface
Can be identified by experiments

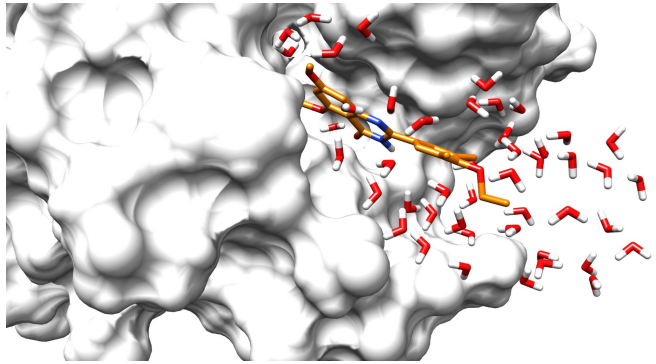
Hydration sites prediction in protein pockets for structure-based drug discovery



Crystal structure of HIV-1 protease in complex with the inhibitor KNI-272 (PDB: 1HPX)

I. Mediating ligand-protein interactions





II. Reorganisation of solvent-protein, solvent-ligand, solvent-solvent interactions

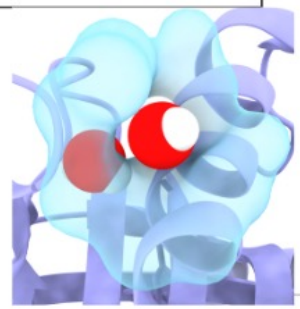
III. Overall complex stabilization through extended interactions network

Essex et al., Chem. Soc. Rev., 2021, 50, 9104

Classical methods: a heterogeneous world

Chem. Soc. Rev., 2021, 50, 9104–9120

Method	Interaction-Based Site Prediction	Free Energy	Ligand Docking	Knowledge-based
Description	Water binding locations based on suitable interaction models and spatial search Water stability evaluated on a number of locations	Binding free energy calculation for each water molecule Often time-consuming	To model the effect of water molecules on ligand binding during the docking to macromolecular targets	To cluster water positions from collection of aligned protein structures with some degree of sequence similarity
Selected Tools	Placevent Dowser++ WATGEN WaterDock GAsol gridSolvate	WATsite GIST WaterMap WaterKit SSTMAP	DeepWATsite DOCK-GIST	PyWATER

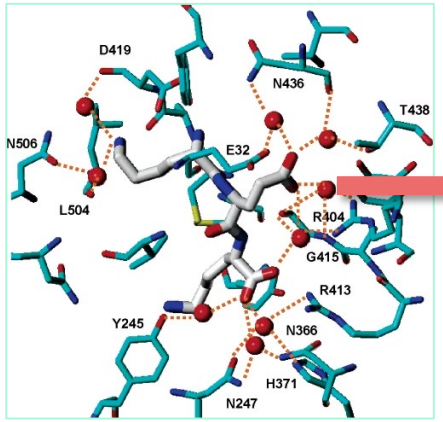


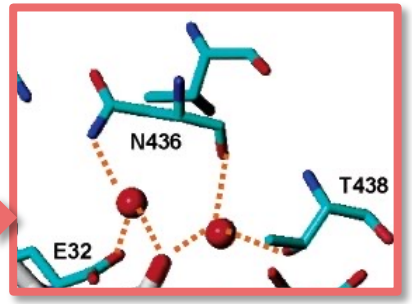
Combination of 3D-RISM; GAsol; WATsite

15 selected methods over ~30 reviewed in literature

Molecular dynamics and water density calculations

Locate water networks interacting with protein:
- Where?
- How many?

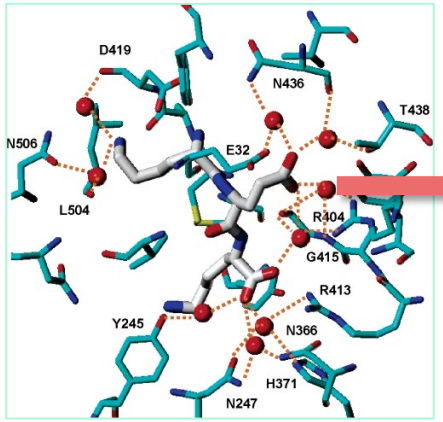


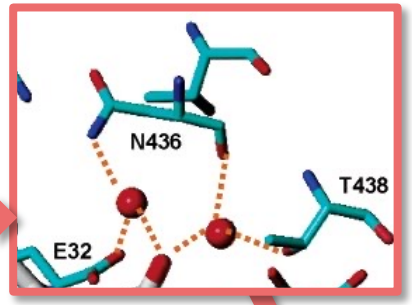


Water and estimated interactions with protein residues

Molecular dynamics and water density calculations

Locate water networks interacting with protein:
- Where?
- How many?





Water and estimated interactions with protein residues

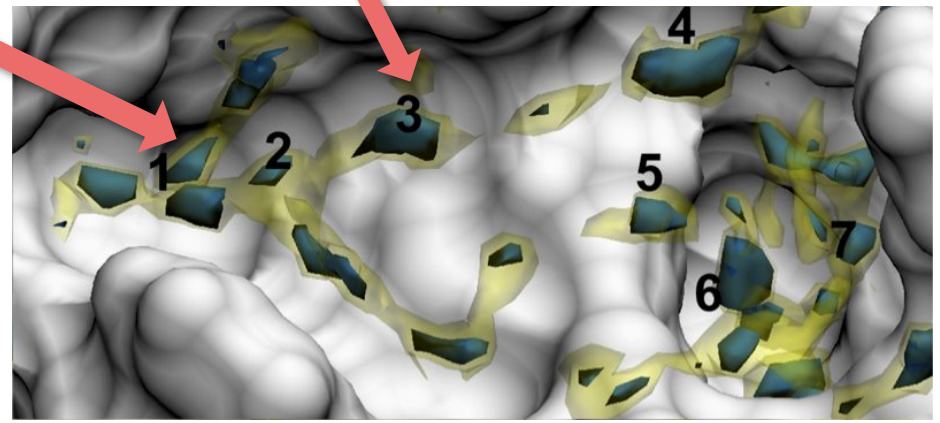
Molecular Dynamics/ Monte Carlo
provide accurate predictions, but they can require extremely long simulation time, which are numerically expensive.

Accurate & Expensive Option

Water density simulation

Continuum-like models computing a continuous distribution of water: 3D-RISM.
Downside: lack of explicit positions of water molecules

Faster but Partial Solution



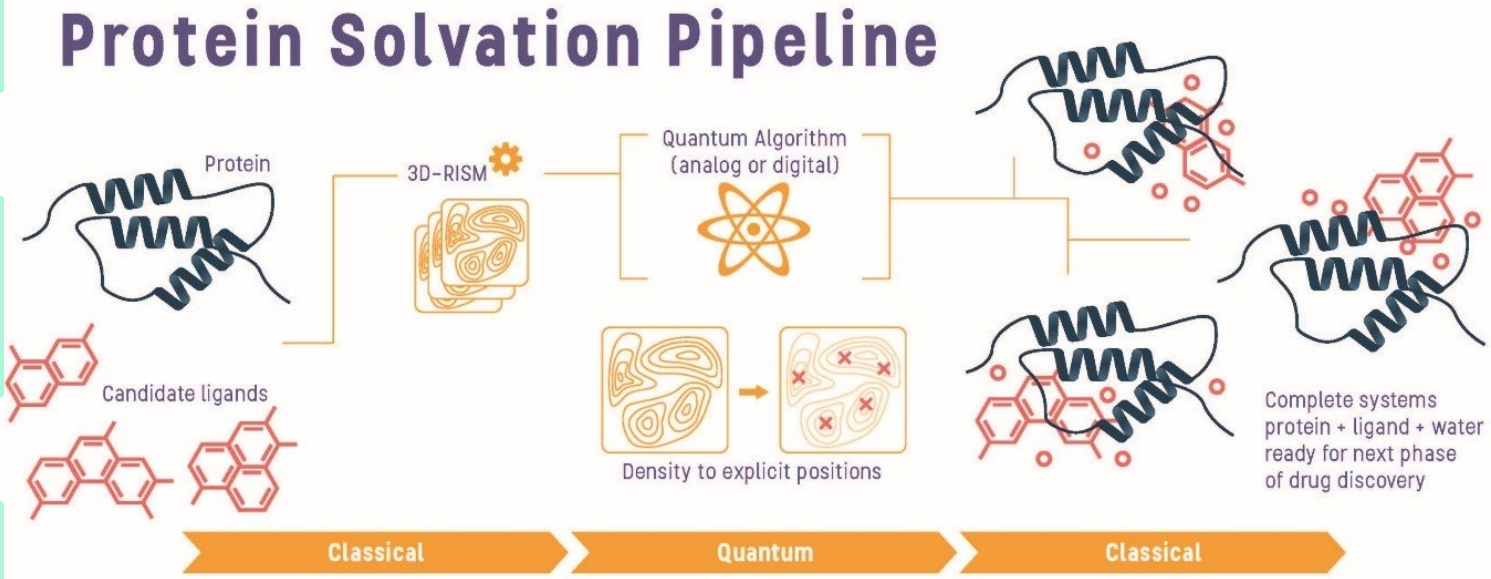
Nguyen et al. https://doi.org/10.1371/journal.pone.0219473

Hydration sites prediction in protein pockets for structure-based drug discovery

Water sampling prohibitive for large biological systems, while experiments can lack accuracy

Water prediction at ligand-protein interface can speed-up and enhance drug pipelines

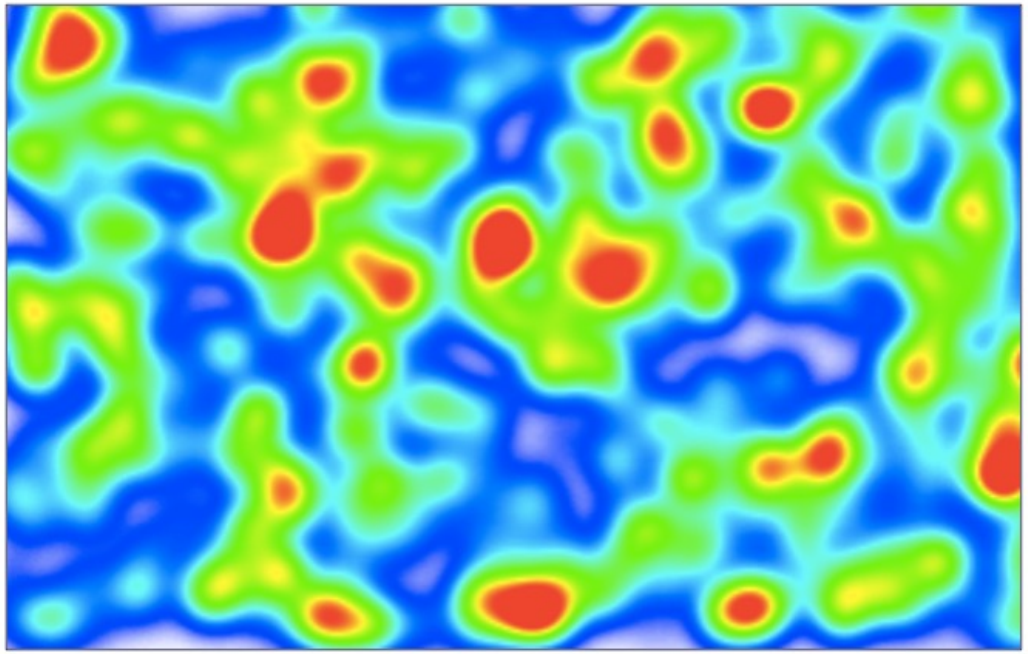
Phase space sampling for highly dimensional problems has high complexity, suitable for a quantum solution



An Analog Quantum Computing Alternative

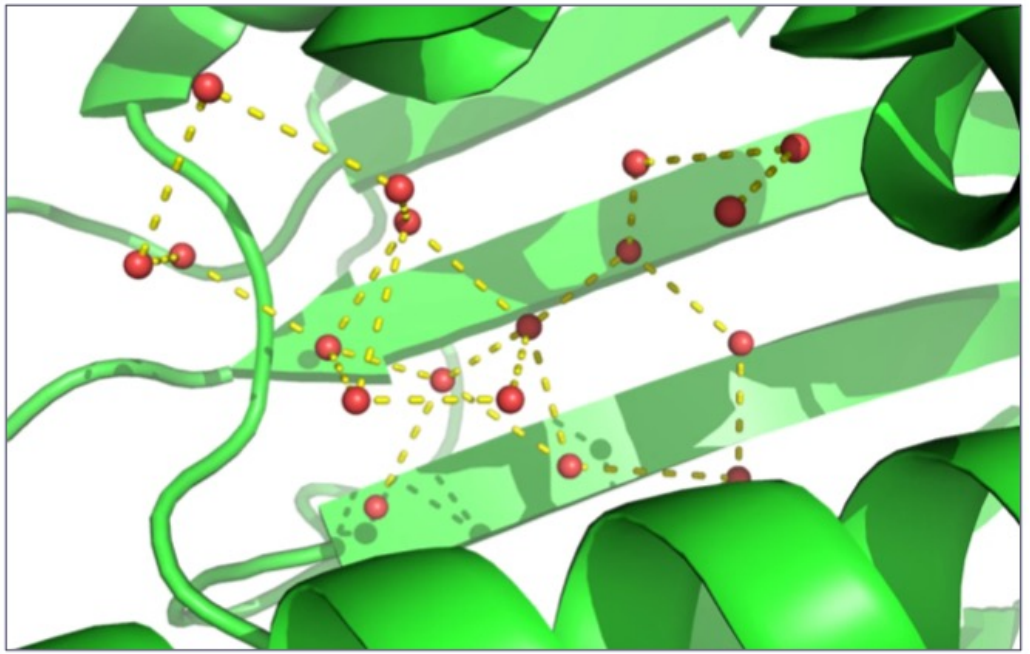
How do we get explicit water positions from a continuous probability density?

What 3D-IRSM gives us



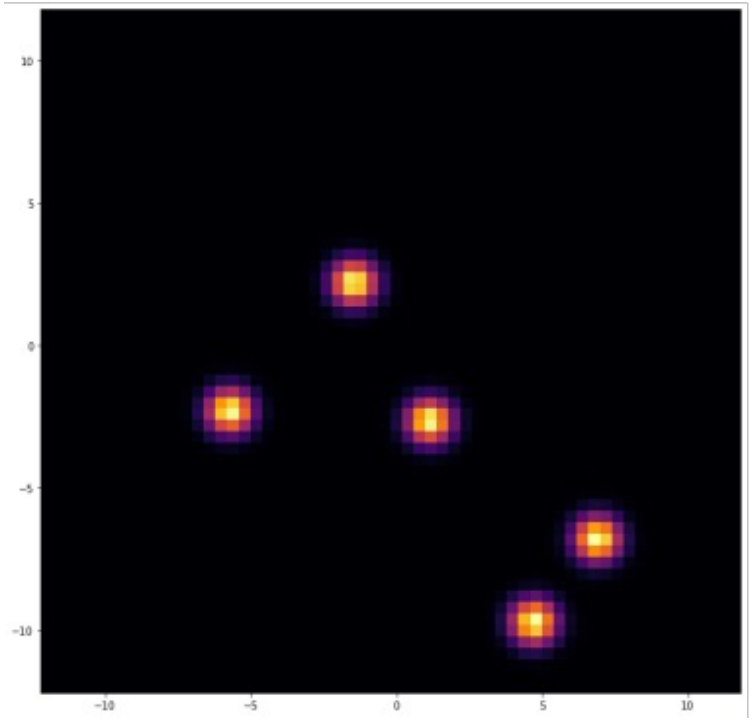
?

What we want

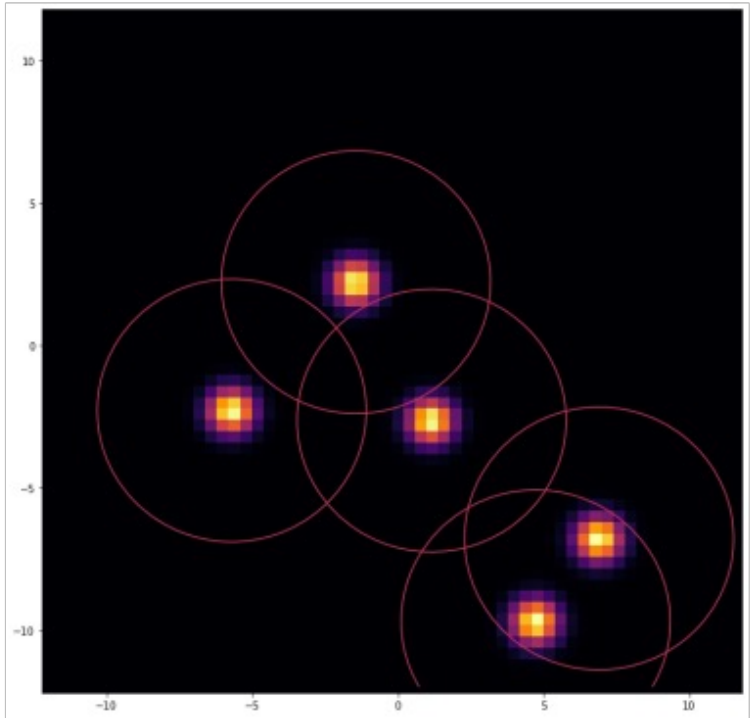


An Analog Quantum Computing Alternative

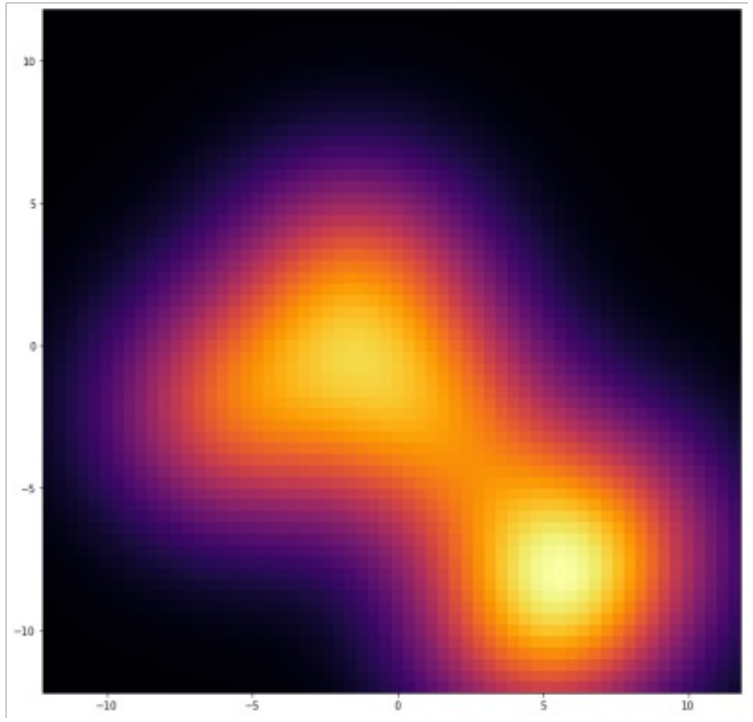
Propose a set of positions



Put a distribution around each

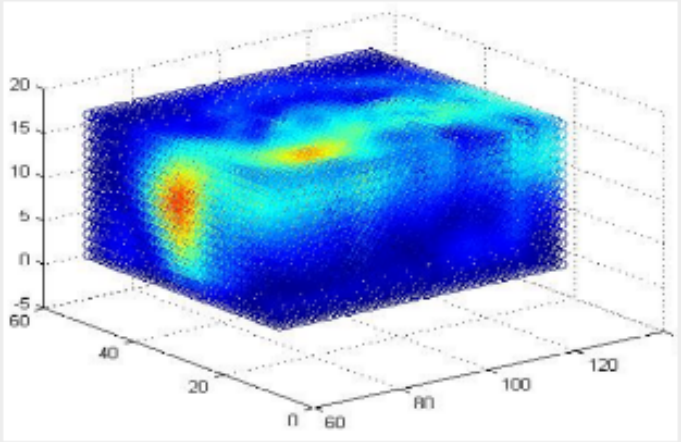


Computing the resulting sum



Analog Quantum Algorithm for Water Location

3D-RISM density



probability of distribution of water in protein cavity

Analog quantum algorithm

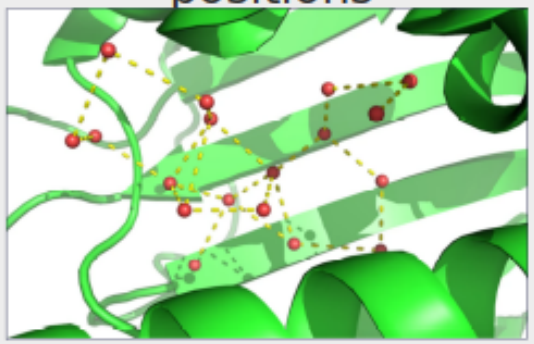
QUBO problem

Base density 2D slice

Functional distance minimization

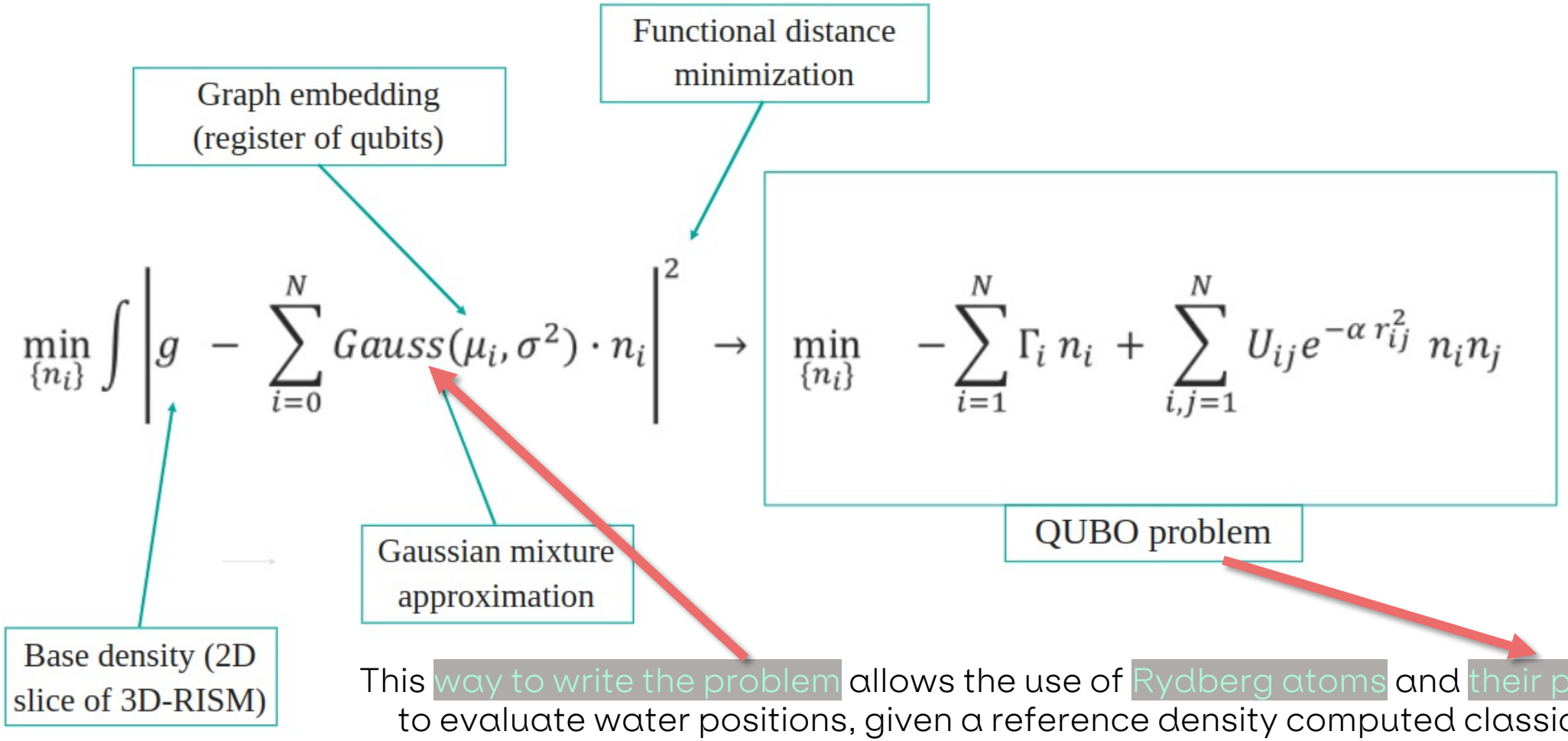
Gaussian mixture approximation

Water molecule positions



finite set of points in protein cavity

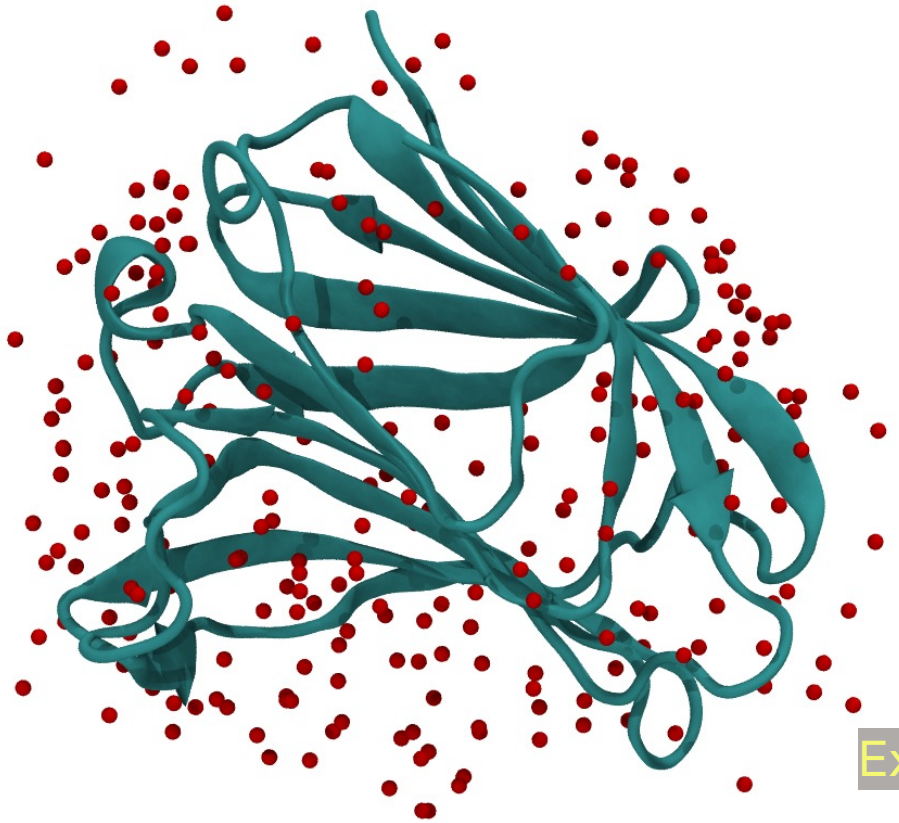
Optimization as a bridge between water location and the Quantum Machine



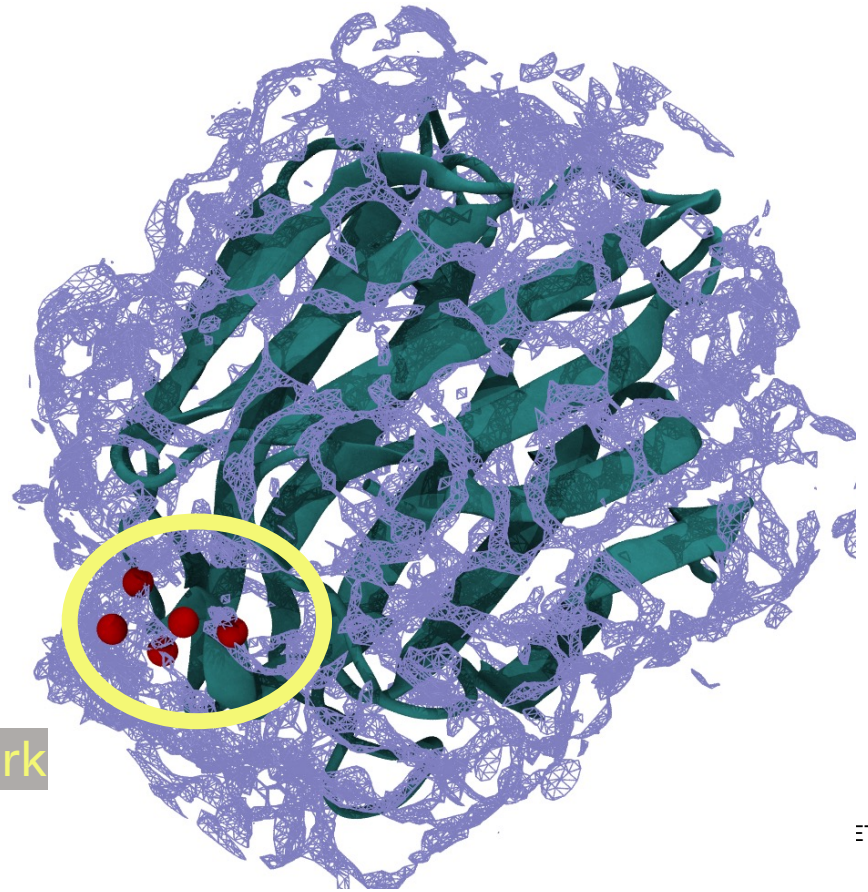
This way to write the problem allows the use of Rydberg atoms and their physics to evaluate water positions, given a reference density computed classically

WIP: Resources estimation and evaluation for advanced applications

Galectin protein (4wvv.pdb)



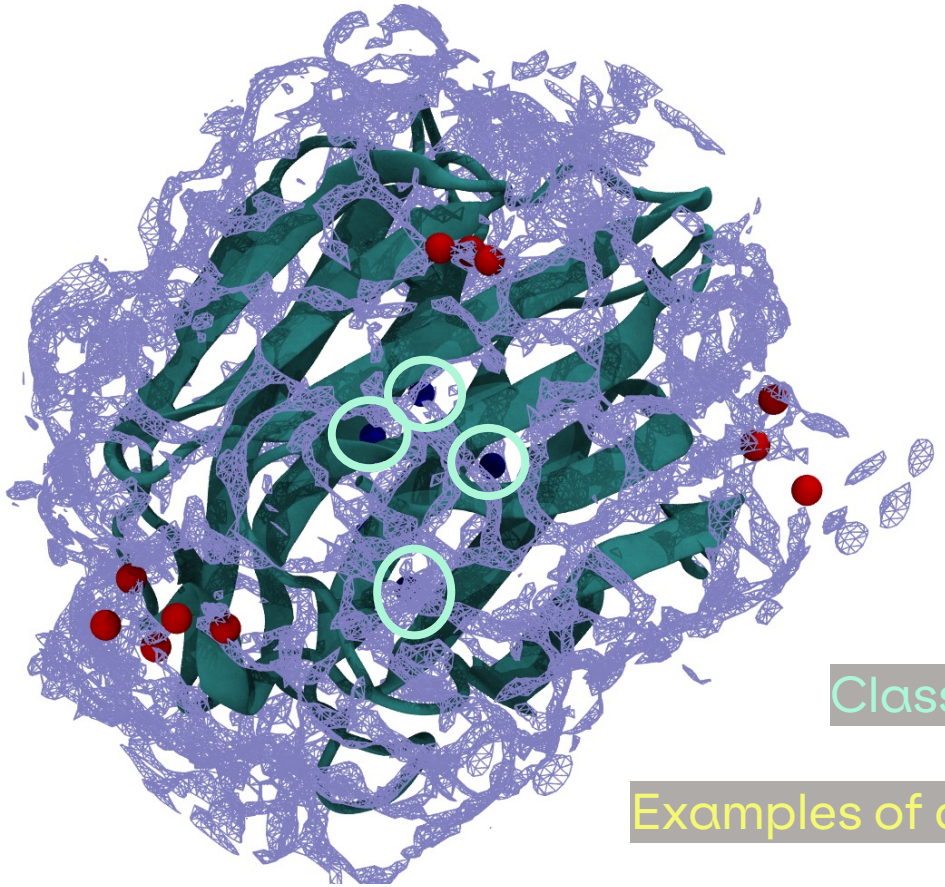
3D-RISM density



Example water network

WIP: Resources estimation and evaluation for advanced applications

Example classical water placement



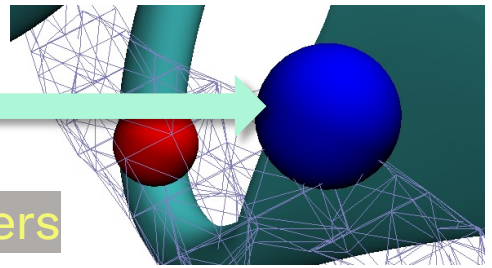
Analog equivalent for a real-life application

Map 3D space to qubit array:
1 qubit = 1 potential water molecule
Metric: assess simulation vs experimental measures

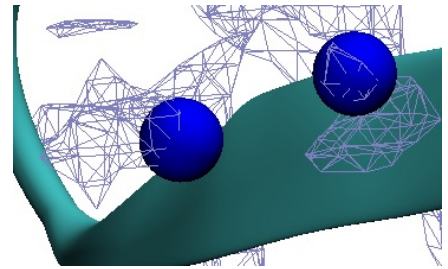
Estimate resources:
~20 Ang cube size x 2 qubits/Ang = 16000 qubits grid

Classical solution vs crystal clusters:
- relatively accurate = ~1.5 Ang distance
- adding missing crystal water
- limited in space.

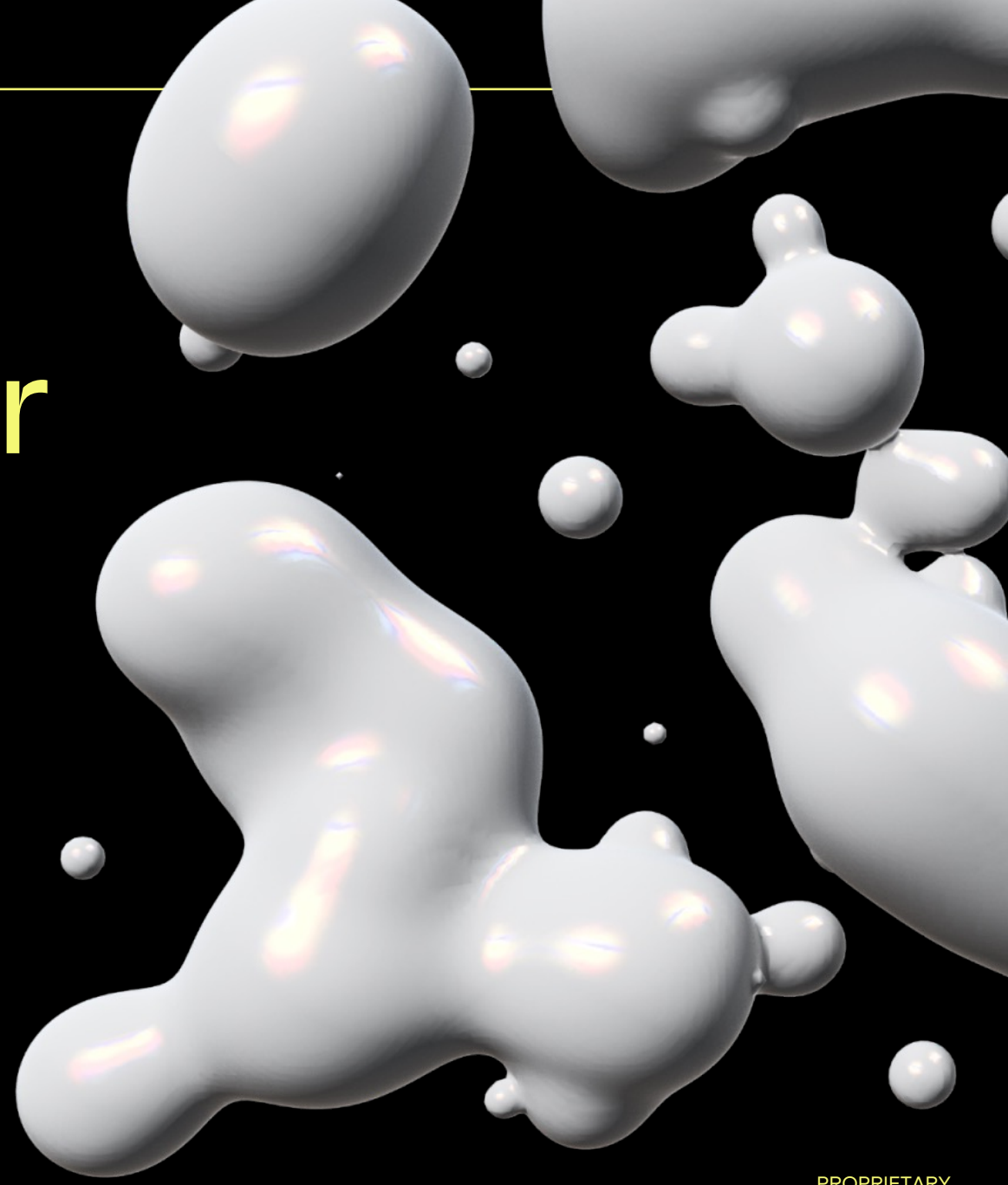
Classical solution



Examples of crystal water clusters



Thank you for your kind attention



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