How to use quantum computers for biomolecular free energies

Matthias Christandl, University of Copenhagen

Collaboration: Copenhagen - ETH - MIT - Novo Nordisk

https://arxiv.org/abs/2506.20587

The Group Leaders

Aram Harrow | Matthias Christandl | Markus Reiher | Troy van Voorhis | Gemma Solomon | Anders Krogh | Kresten Lindorff-Larsen | Jesper Ferkinghoff-Borg

MIT | ETH | MIT | novo nordisk

Quantum Algorithms

Quantum Chemical Simulations

Classical Chemical Simulations

Protein Modeling

Human Health Science

NQCP NIELS BOHR INSTITUTE

Quantum for Life

GEFION

novo nordisk foundation
Benefitting people and society

Quantum for Bio

leap

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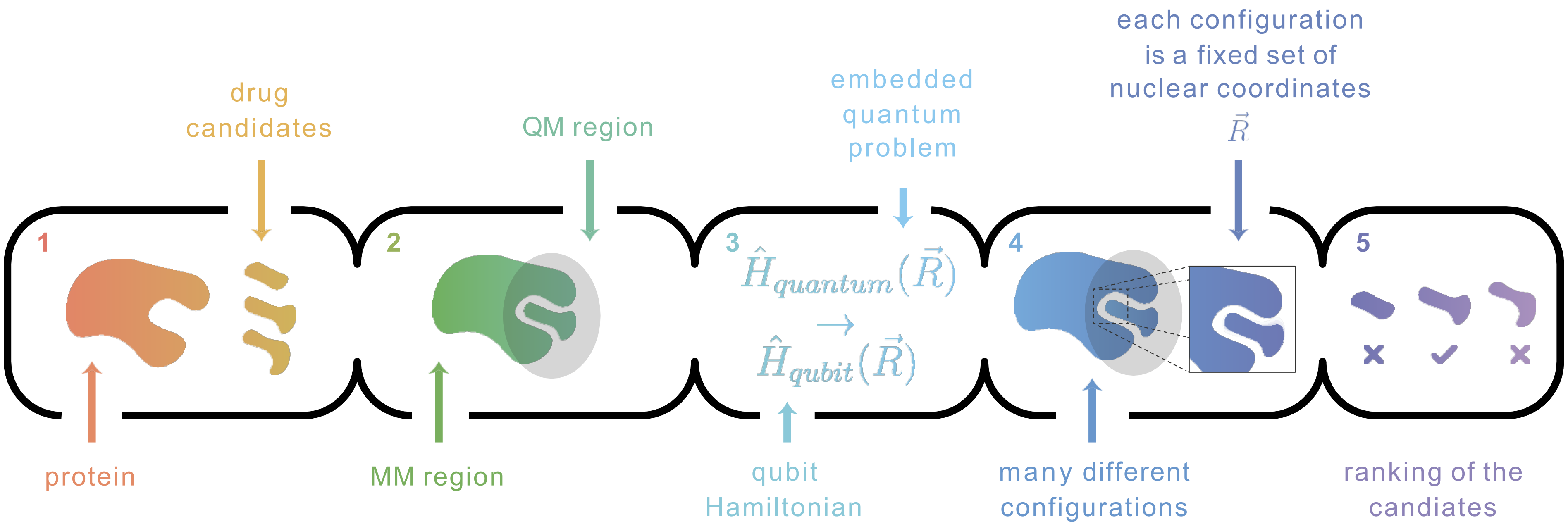
The Project



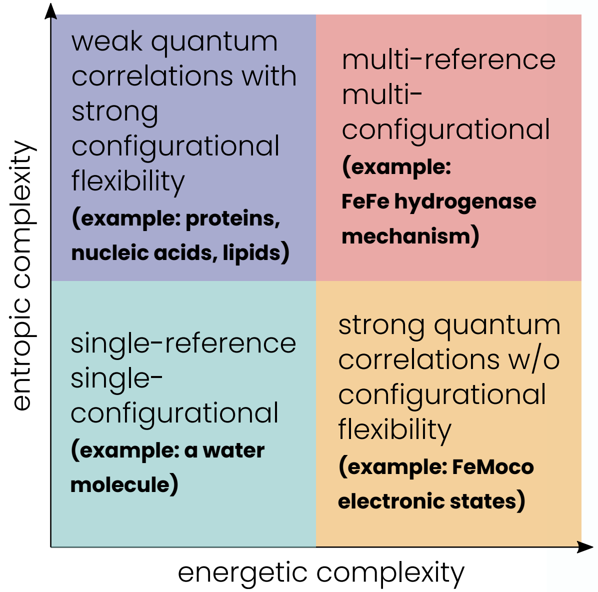
Which candidate binds best?

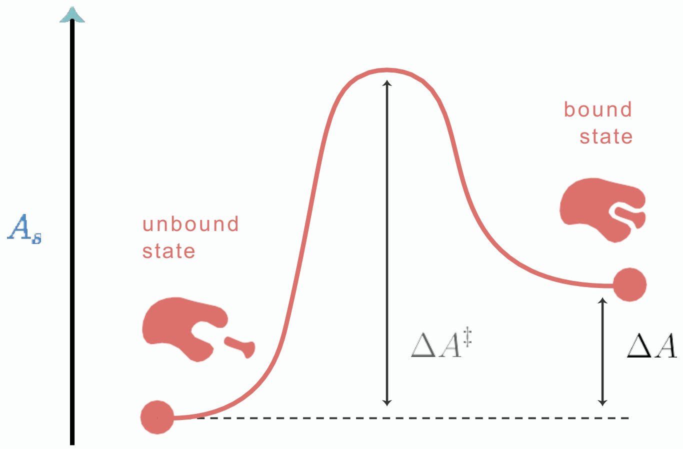
Free energy $\Delta G = ?$

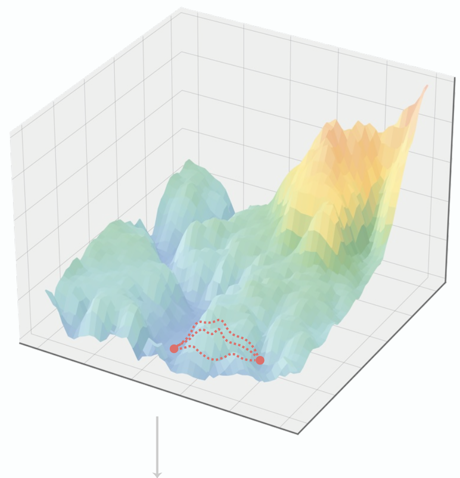
Map the embedded quantum problem to a qubit Hamiltonian

Thermal energy lets the molecules “wiggle” and explore many configurations

Energy versus entropy







$$A_s = -k_B T ln\Big(\int dR^{3N_s-7}\int dP^{3N_s} e^{-\left(\sum_{i=1}^{N_s} \boldsymbol{p}_i^2/(2m_i)+E^{GS}_{quantum}(\boldsymbol{R})\right)/(k_BT)}\Big)$$

Biomolecular simulation quadrangle:

Entropic versus energetic complexity

Free energy: sample from the potential energy surface

Current approach: solve Newton’s equations using heuristic forces

Quantum promise: compute the true forces/energies for electronic interaction

Quantum Computing for Free Energy Sampling?

Challenges

Solutions

1

Calculate energy/force for each configuration?
Way too many points to compute!

Too many energies: machine learning of forces, based on accurate quantum data

2

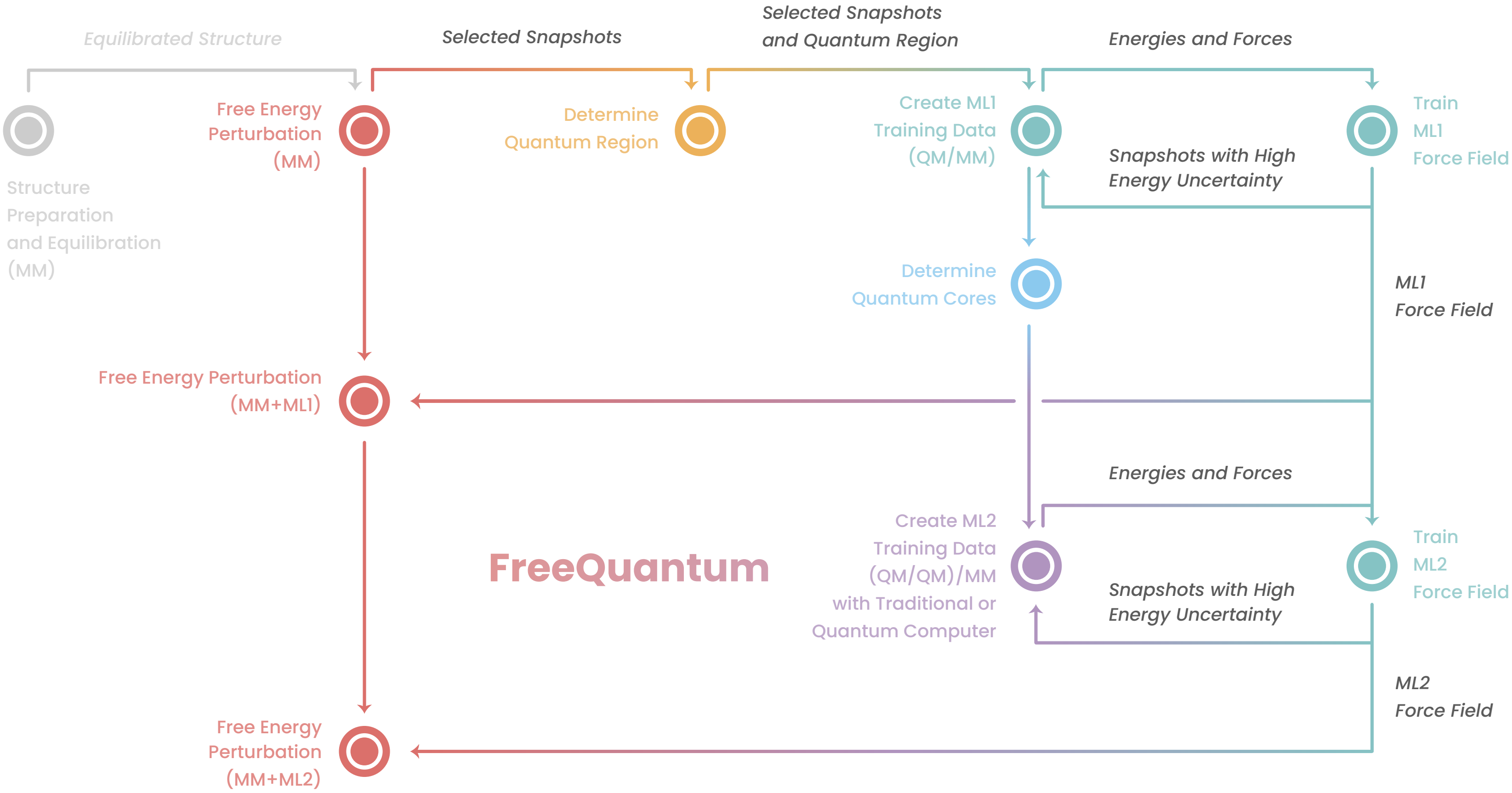
The molecules (e.g. proteins) are too large to be represented on a quantum computer

Too large molecules: multiscale embedding methods

Quantum Computing for Free Energy Sampling?

Challenges		Solutions
Calculate energy/force for each configuration? Way too many points to compute!	1 → 1	Too many energies: machine learning of forces, based on accurate quantum data
The molecules (e.g. proteins) are too large to be represented on a quantum computer	2 → 2	Too large molecules: multiscale embedding methods

Our Computational Pipeline

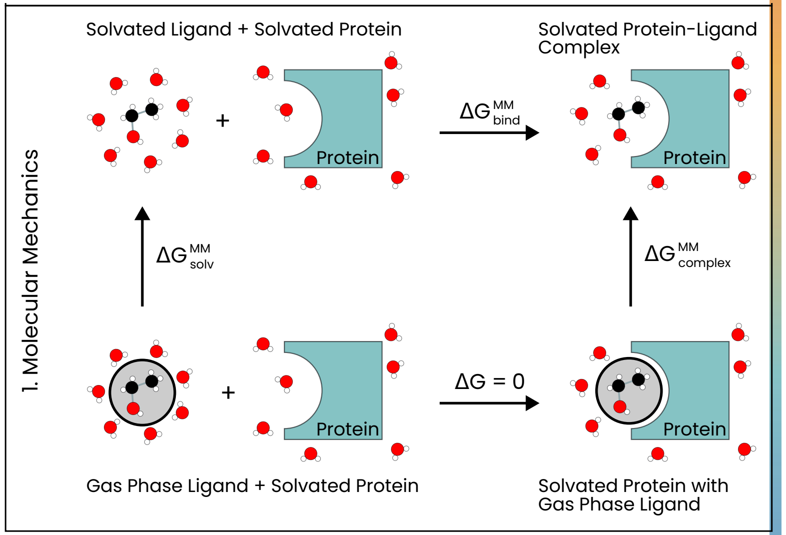


Free Energy Perturbation

- Partition function $$Z = \int d^{3N_{\text{nuc}}} R \,\mathrm{tr} \exp(-\beta H(R))$$

- Free energy difference $$\Delta G_{\text{binding}} = G_{\text{bound}} - G_{\text{unbound}}$$

- Telescoping sum along coordinate to make sampling problems more similar (e.g. reaction coordinate or alchemical) $$= \sum_{k=1}^{s-1} \underbrace{G_{\lambda_k} - G_{\lambda_{k+1}}}_{\Delta G_{\lambda_k}}$$



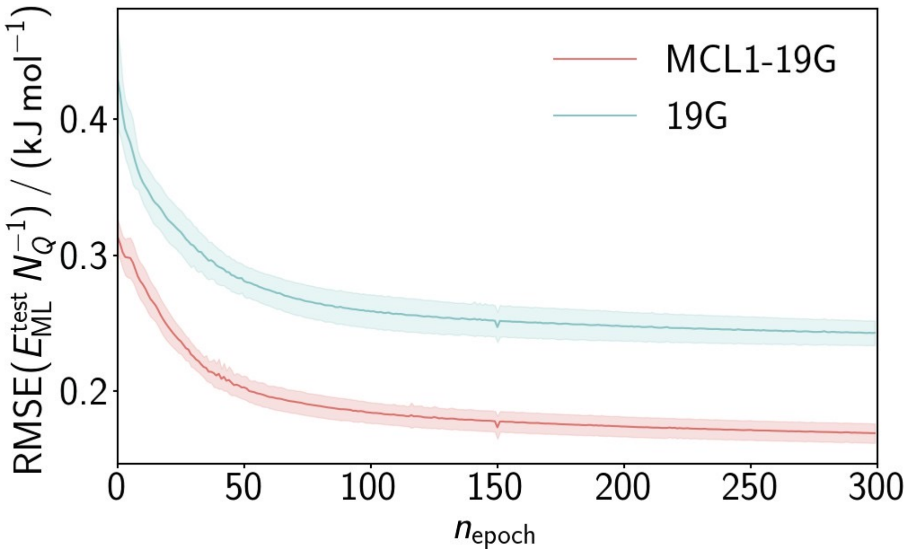
- Alchemical: switch interaction off/on $$H_\lambda = H_{\text{protein}} + H_{\text{ligand}} + \lambda H_{\text{interaction}}.$$

$$\Delta G_{\text{solvated binding}} = \underbrace{G_{\text{solvated complex}} - (G_{\text{solvated protein}} + G_{\text{ligand}})}_{\Delta G_{\text{partially solvated binding}}} + \underbrace{(G_{\text{ligand}} - G_{\text{solvated ligand}})}_{-\Delta G_{\text{ligand solvation}}}$$

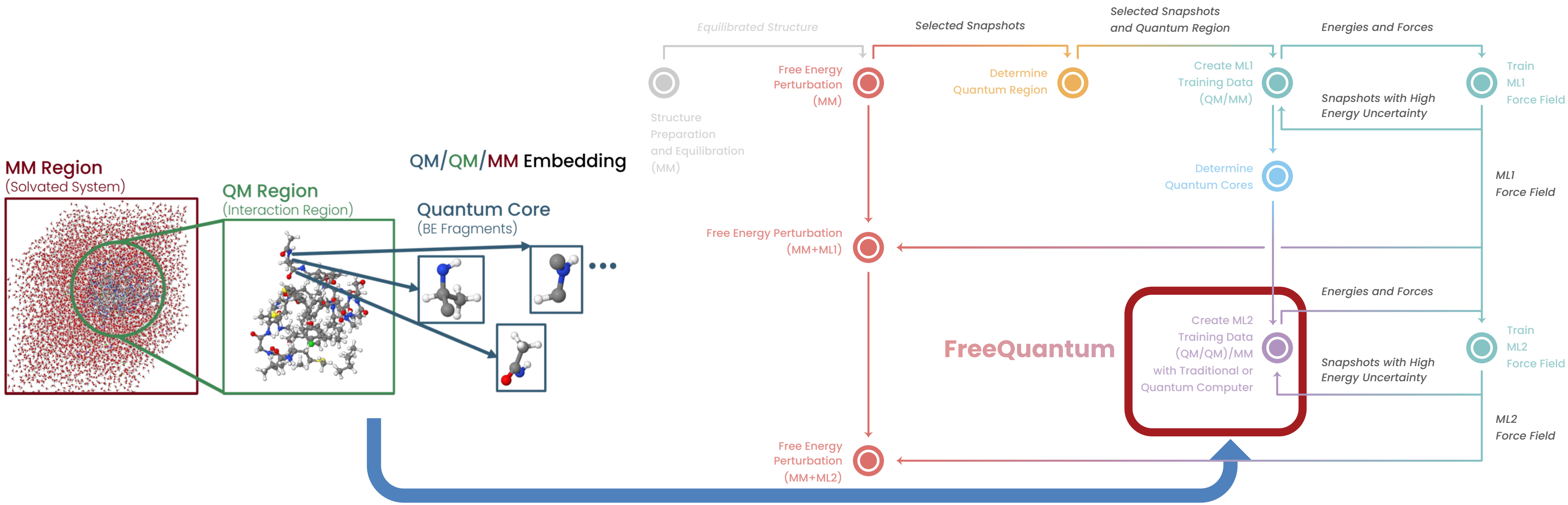
- Then telescoping with reaction coordinate for each part

Machine Learning

- Machine-learning potentials are typically trained on energies and forces
- Energies alone are sufficient using transfer learning
- Transfer learning allows to leverage best the few energy data points available from quantum computing hardware



Quantum Embedding



$$H_{\text{quantum region}} = H_{\text{electronic, quantum region}} + V_{\text{interaction, MM}}$$

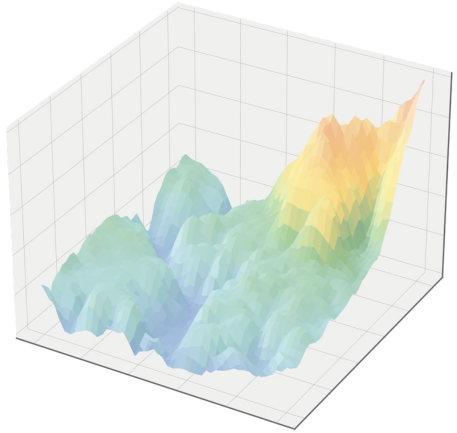
$$H_{\text{quantum core}} = H_{\text{electronic, quantum core}} + V_{\text{interaction, DFT}}$$

Traditional Quantum Engine

Full problem $\hat{H}(t)\Psi(\boldsymbol{r},\boldsymbol{R},t) = \mathrm{i}\hbar\partial_t\Psi(\boldsymbol{r},\boldsymbol{R},t)$

Stationary states $\hat{H}\Psi_n(\boldsymbol{r},\boldsymbol{R}) = E_n\Psi_n(\boldsymbol{r},\boldsymbol{R})$

Born-Oppenheimer $\Psi_{\mathrm{nuc}}(\boldsymbol{R}) \times \Psi_{\mathrm{ele}}^{\boldsymbol{R}}(\boldsymbol{r})$



Exponential explosion

Hierarchy of approximations

DMRG/Tensor Network as proxy for Full-CI

Computationally challenging

No accuracy guarantees

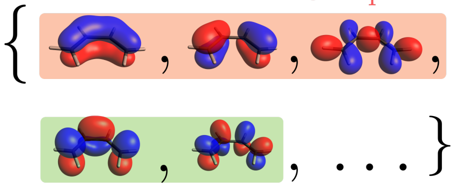
Many-body wave function

$\Psi(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_{N_{\mathrm{ele}}})$

Superposition of configurations

$|\Psi\rangle = C_0|\Psi_0\rangle + \sum_i\sum_a C_i^a|\Psi_i^a\rangle + \sum_{ij}\sum_{ab} C_{ij}^{ab}|\Psi_{i,j}^{a,b}\rangle + \ldots$ **Full CI**

Occupied



Unoccupied

One-particle functions

$\{\varphi_1(\boldsymbol{r}),\varphi_2(\boldsymbol{r}),\ldots,\varphi_{N_{\mathrm{orb}}}(\boldsymbol{r})\}$

$|\varphi_1\cdots\varphi_i\cdots\boxed{\varphi_a}\cdots\boxed{\varphi_b}\cdots\varphi_{N_{\mathrm{ele}}}\rangle = |\Psi_{i,j}^{a,b}\rangle$ **CISD**

Double substitution

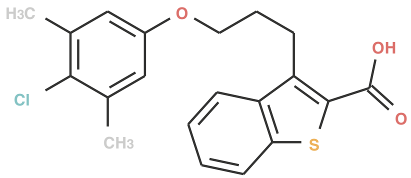
$|\varphi_1\cdots\boxed{\varphi_a}\cdots\varphi_j\cdots\varphi_k\cdots\varphi_{N_{\mathrm{ele}}}\rangle = |\Psi_i^a\rangle$ **CIS**

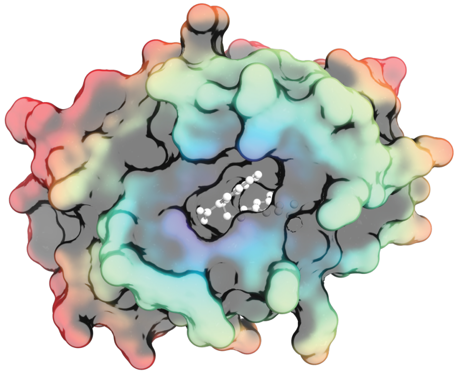
Single substitution

$|\varphi_1\cdots\boxed{\varphi_i}\cdots\boxed{\varphi_j}\cdots\boxed{\varphi_k}\cdots\varphi_{N_{\mathrm{ele}}}\rangle = |\Psi_0\rangle$ **HF**

Reference configuration

The Biological Systems

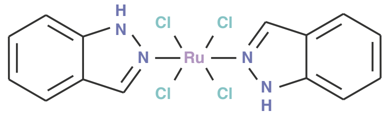


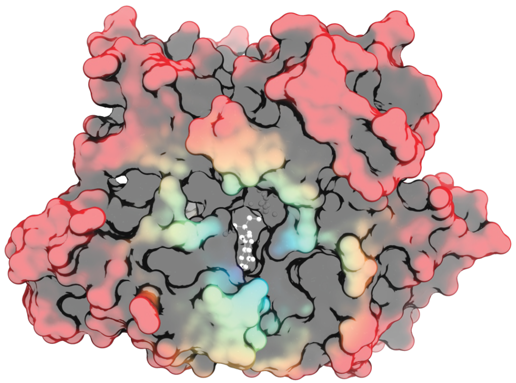


The MCL1-19G complex
(the “model complex”)

Benchmark data available

Used for testing purposes





The GRP78-NKP1339 complex
(the “Ruthenium complex”)

No benchmark data available

Electronic structure challenge

Full Computational Run

- The FreeQuantum pipeline is based on first principles
- Benchmarking: The MCL1-19G model complex (protein MCL1 and small molecule 19G) demonstrates that our pipeline yields reliable results

arXiv > physics > arXiv:2503.03955

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Physics > Chemical Physics

[Submitted on 5 Mar 2025]

Machine Learning Enhanced Calculation of Quantum-Classical Binding Free Energies

Moritz Bensberg, Marco Eckhoff, F. Emil Thomasen, William Bro-Jørgensen, Matthew S. Teynor, Valentina Sora, Thomas Weymuth, Raphael T. Husistein, Frederik E. Knudsen, Anders Krogh, Kresten Lindorff-Larsen, Markus Reiher, Gemma C. Solomon

arXiv > physics > arXiv:2503.03928

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[Submitted on 5 Mar 2025]

Hierarchical quantum embedding by machine learning for large molecular assemblies

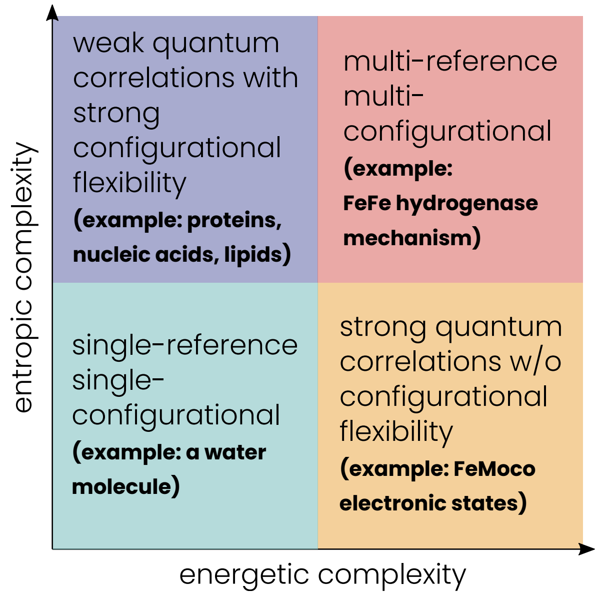
Moritz Bensberg, Marco Eckhoff, Raphael T. Husistein, Matthew S. Teynor, Valentina Sora, William Bro-Jørgensen, F. Emil Thomasen, Anders Krogh, Kresten Lindorff-Larsen, Gemma C. Solomon, Thomas Weymuth, Markus Reiher

- It can be applied in cases where standard MM models are not available
- For this, the GRP78-NKP1339 complex (protein GRP78 and small molecule NKP1339) serves as an example

Method	MCL-1/19G
MM	-37.5 ± 0.4 [20]
PBE/MM	-35.3 ± 1.8 [20]
UMP2/PBE/MM	—
LCCSD(T)/PBE/MM	-37.2 ± 1.0 [21]
UCCSD(T)/PBE/MM	—
NEVPT2/PBE/MM	—
Experiment	-37.3 ± 0.1 [43]

The potential of quantum computing

- Energy computation of quantum cores carried out by quantum computers
- Advantages: accurary guarantees, more precise for larger and more correlated systems
- With the FreeQuantum pipeline we built a computational framework that allows to slot-in the quantum computer
- Ready for quantum advantage, when quantum hardware is



Biomolecular simulation quadrangle:

Entropic versus energetic complexity

Quantum Phase Estimation


arXiv > quant-ph > arXiv:2503.05647

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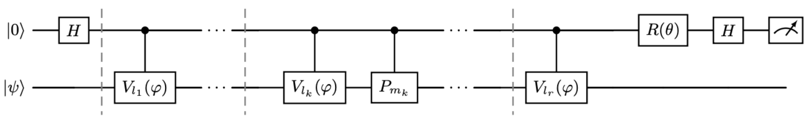
Quantum Physics

[Submitted on 7 Mar 2025]

Phase estimation with partially randomized time evolution

Jakob Günther, Freek Witteveen, Alexander Schmidhuber, Marek Miller, Matthias Christandl, Aram Harrow

- The main cost of phase estimation derives from the cost of Hamiltonian simulation
- Chemistry: an unstructured Hamiltonian with many terms which leads to deep circuits
- We use single-ancilla quantum phase estimation (QPE)



- Partially randomized product formulas (Trotter) need no ancillas and reduce circuit depth

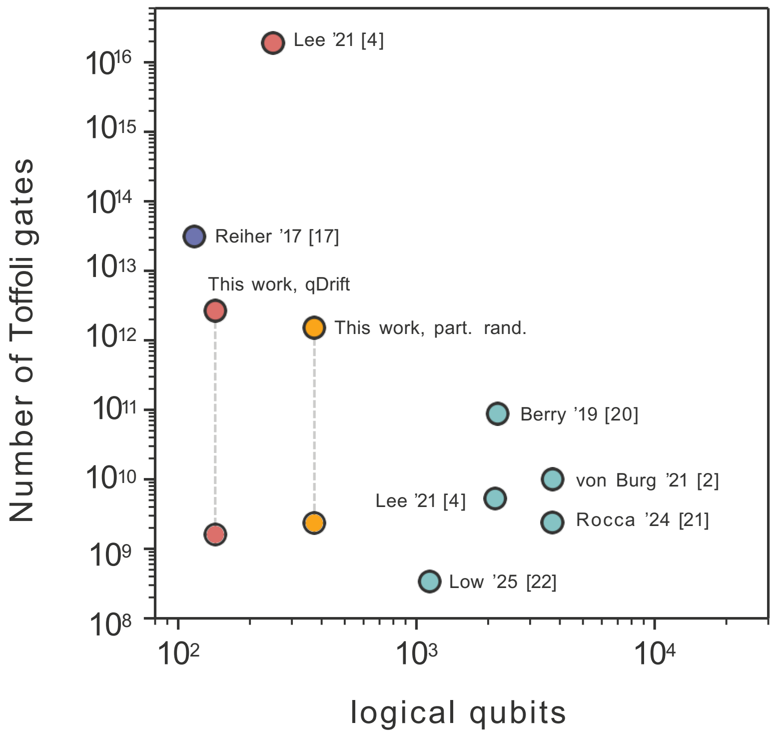


Figure: FeMoCo benchmark

$$|\Psi(t)\rangle \approx \prod_{i=1}^{N}\left(e^{-i\hat{H}_1 t/\hbar}e^{-i\hat{H}_2 t/\hbar}\right)|\Psi(0)\rangle$$

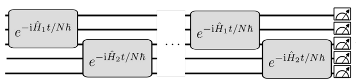


Figure: Trotter reminder

Quantum Resources

- Partially randomized product formulas need no ancillas and reduce circuit depth

- Runtime (Trotter constant) estimate using novel software on large GPU cluster

arXiv > quant-ph > arXiv:2504.17881

Quantum Physics

[Submitted on 24 Apr 2025]

phase2: Full-State Vector Simulation of Quantum Time Evolution at Scale

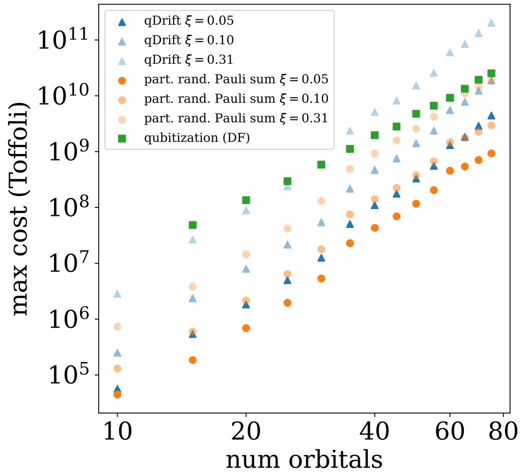
Marek Miller, Jakob Günther, Freek Witteveen, Matthew S. Teynor, Mihael Erakovic, Markus Reiher, Gemma C. Solomon, Matthias Christandl

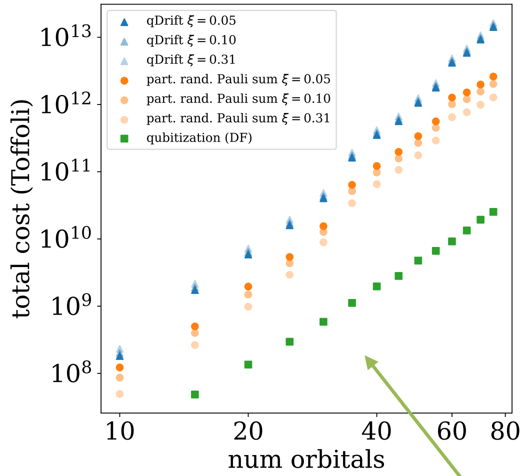
- It is possible to prepare initial states with high ground state overlap

PRX LIFE **3**, 013003 (2025)

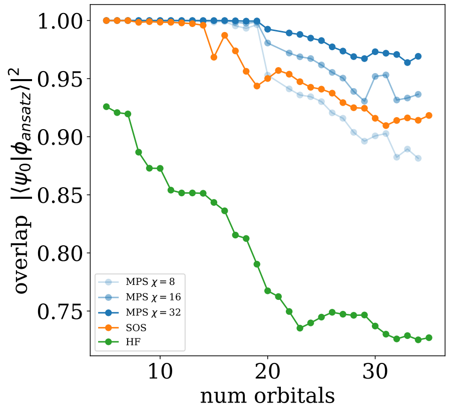
High Ground State Overlap via Quantum Embedding Methods

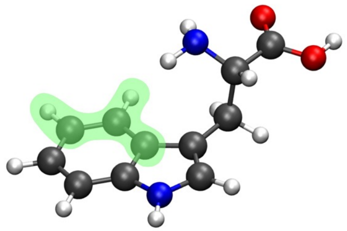
Mihael Erakovic,[1,*] Freek Witteveen,[2,†] Dylan Harley,[2] Jakob Günther,[2] Moritz Bensberg,[1] Oinam Romesh Meitei,[3] Minsik Cho,[3] Troy Van Voorhis,[3] Markus Reiher,[1,‡] and Matthias Christandl[2,§]



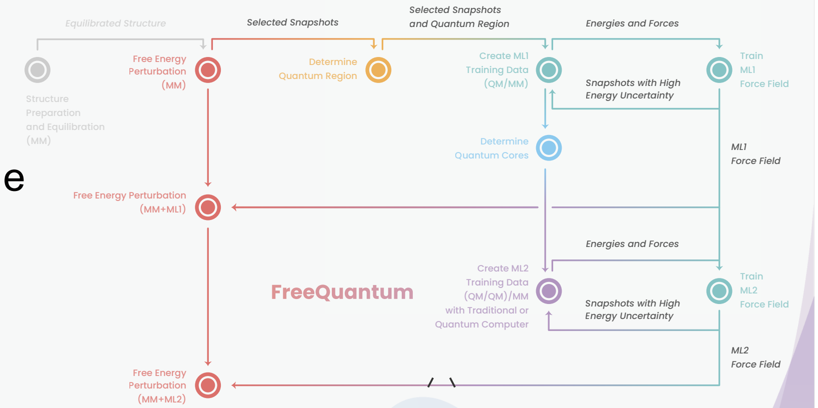


substantial #ancilla qubits





Conclusion

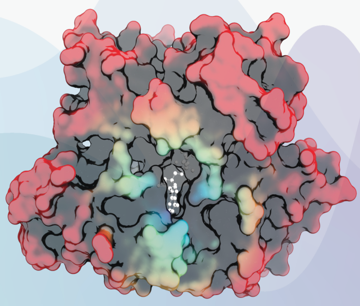


Developed a complete, modular, and autonomous computational pipeline for free energy calculations.

Compatible with traditional quantum chemistry and future fault-tolerant quantum computers.

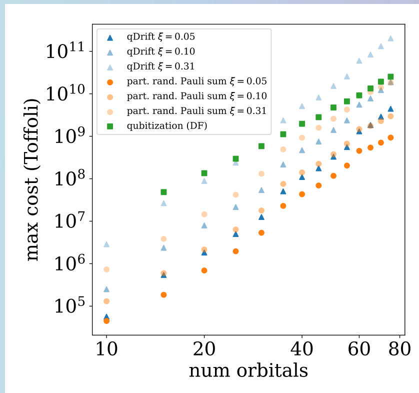
Adapts to computational resources; modules can be exchanged or upgraded.

Ruthenium drug–protein complex (open-shell spin doublet) demonstrated feasibility with HPC.



Impact: Multilayer embedding + ML reduces quantum region size → makes quantum computing for free energy feasible.

Opens path toward quantum advantage in biology; FreeQuantum is open source and free.



How to use quantum computers
for biomolecular free energies https://arxiv.org/abs/2506.20587