Fullqubit alchemist:

Quantum algorithm for alchemical free energy calculations

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[1]University of Oxford, [2]Quantum Motion, [3]Boehringer Ingelheim, [4]University of Toronto, [5]PNNL, [6]CIFAR

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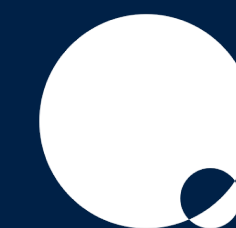
QUANTUM MOTION

Drug design
Motivation and applications

- Working in a complex and warm environment, so need to calculate thermodynamic properties like free energies.

- We care more about differences in free energies between different candidate ligands.

- Need to evaluate molecular dynamics to evolve each configuration in our ensemble to equilibrium.

PROTEIN

LIGAND

BINDING ENERGY

PROTEIN-LIGAND COMPLEX
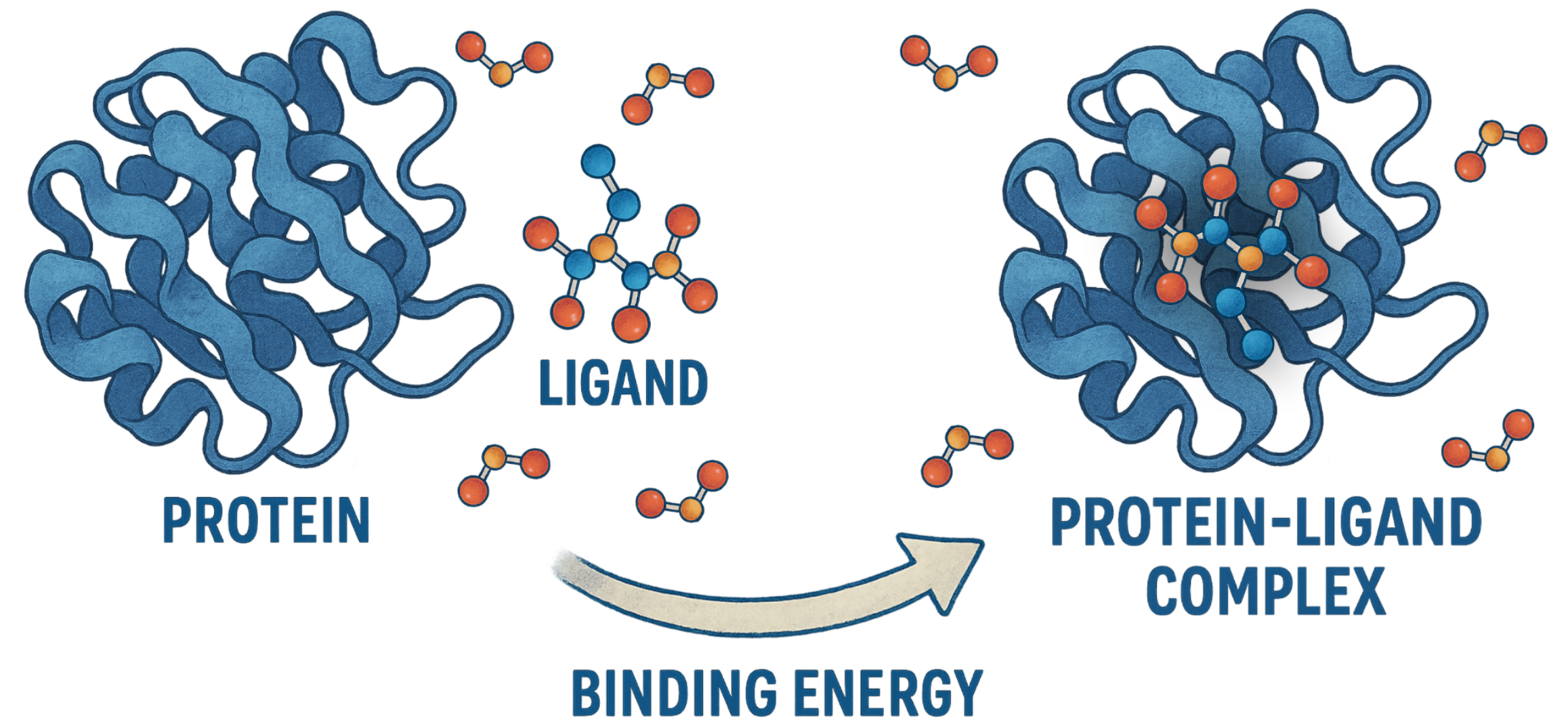
Molecular dynamics

In practice for classical computations

- Propagate particles with Hamiltonian dynamics

- Time average of evolution trajectory to replace ensemble average

  - Lots and lots of compute time!

- Used to compute thermal averages such as free energy

COMPUTE FORCE   UPDATE   DIFFERENT INITIAL
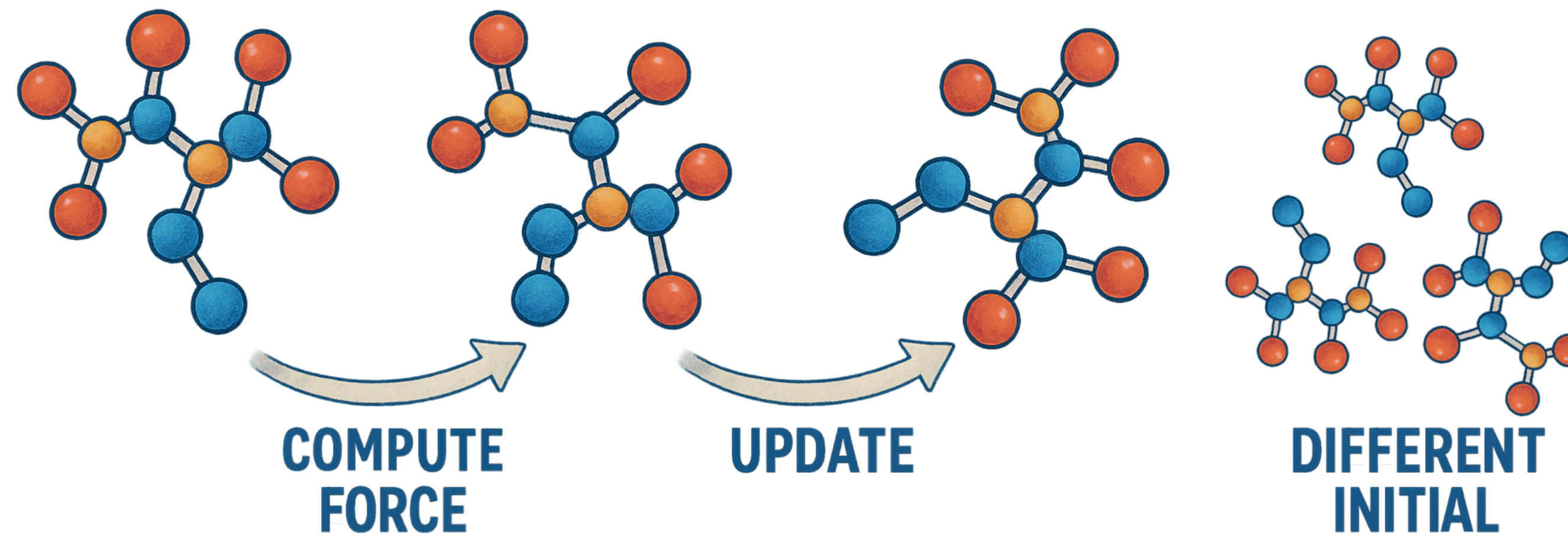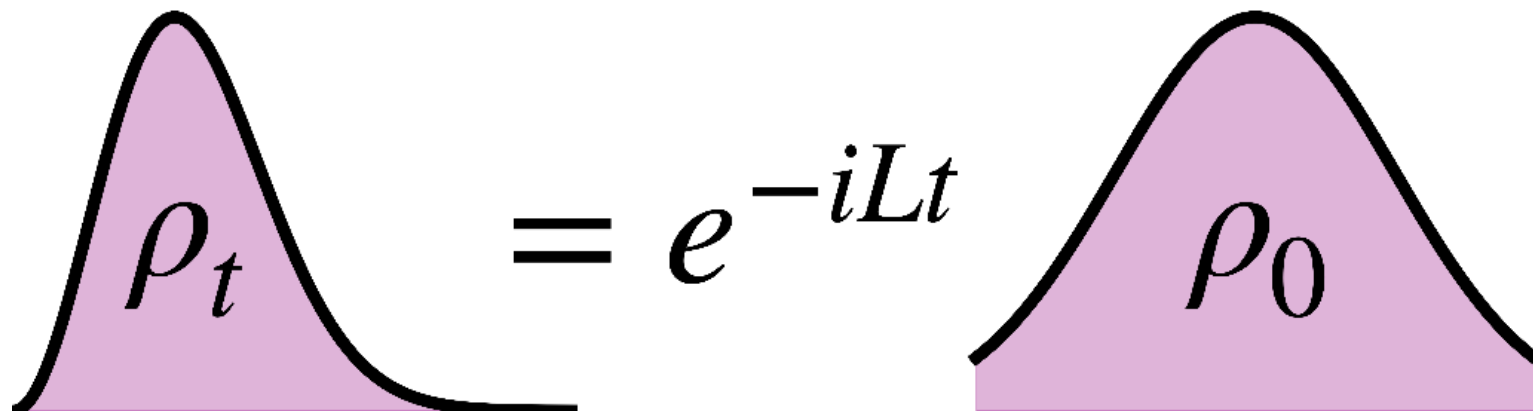
Hybrid quantum solution
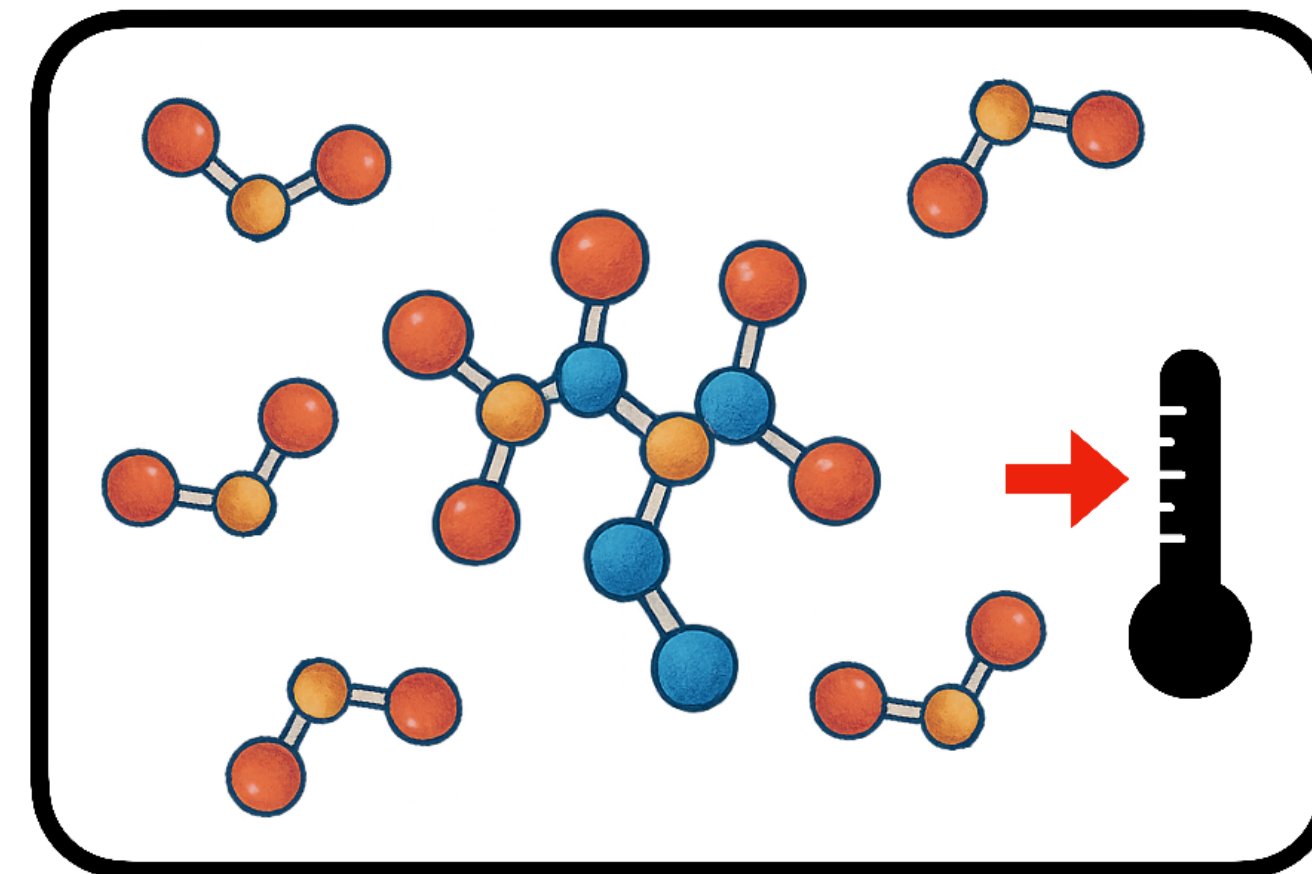## *Classical MD + QPE*

- Offload ground state energy calculations to quantum computer

- Feed ground state energy calculations to MD step

- More accurate calculations for energy and potential to find energies for cases where classical simulation is hard.

- Main process is still classical MD, so large simulation time is still required

- Can we do better if we implement MD on the quantum computer as well?

- Are there algorithmic speedups if we do so?

Molecular dynamics
Under the Liouvillian picture

- Liouvillian dynamics with fixed volume and temperature

- Born Oppenheimer approximation – classical nuclei and quantum electrons

- Generate discretized phase space on logarithmic number of qubits

- Electronic dynamics determined by ground state energy calculations

$$\rho_t = e^{-iLt} \rho_0$$

$$L = -i\left(\frac{\partial H}{\partial p}\frac{\partial}{\partial x} - \frac{\partial H}{\partial x}\frac{\partial}{\partial p}\right)$$

Molecular dynamics on a quantum computer
Or, Liouvillian block-encodings and Liouvillian simulation

- Two register sets on quantum computer to implement the Liouvillian operator:

  - "Classical" nuclear register – Corresponds to classical MD in Liouvillian formalism on exponential sized grid

  - "Quantum" electronic register – Corresponds to ground state energy/forces calculations

- Arithmetic to calculate kinetic and Coulomb forces/momentum

- Apply Hamiltonian simulation as Liouvillian is self-adjoint
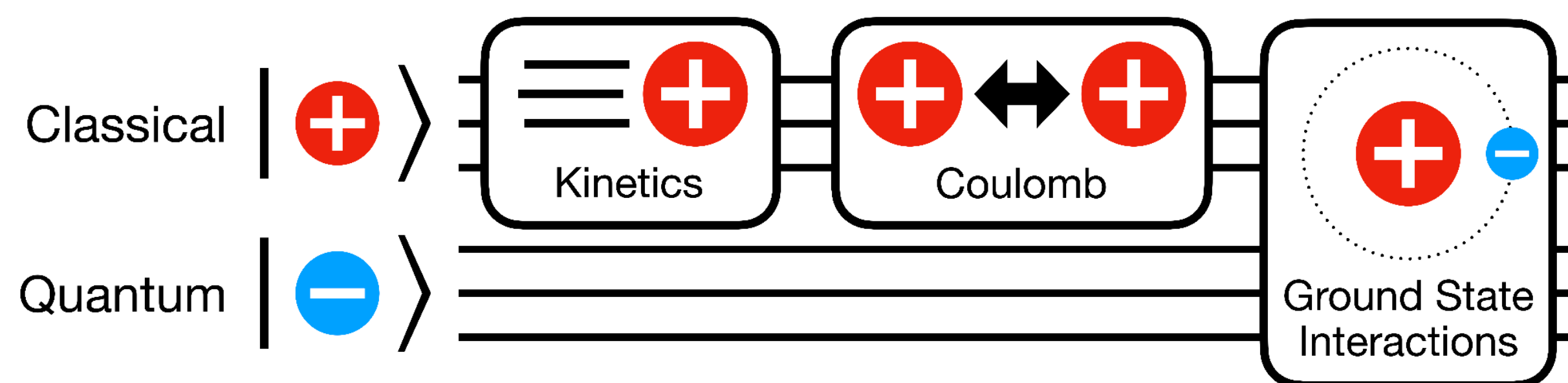
Block-encoding energies without QPE
*Another way to obtain ground state energies/forces*

- Obtain quantum mechanical electronic forces via kicking back results from electronic register to nuclear register

- Compute ground state energy by preparing ground state, applying the Hamiltonian, then unpreparing the ground state

- Compute electronic forces with Hellmann-Feynman theorem and analytical derivative of first-quantized Hamiltonian

$$\frac{\partial E_n}{\partial \lambda} = \langle \psi_n | \frac{\partial H}{\partial \lambda} | \psi_n \rangle$$
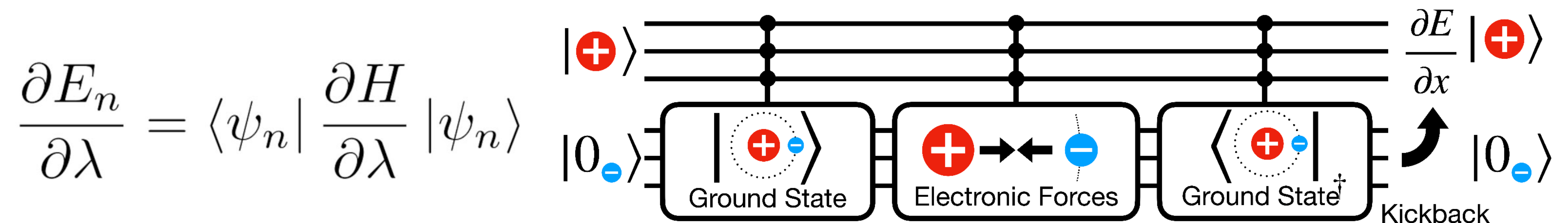
Calculating free-energy differences
## *Thermodynamic integration on a quantum computer*

- Free energy differences can be expressed as an integral that interpolates the molecular dynamics between initial and final configurations.

- Sum over interpolated Liouvillian simulation prepared states over nuclear Hamiltonian

Controlled Liouvillian simulations
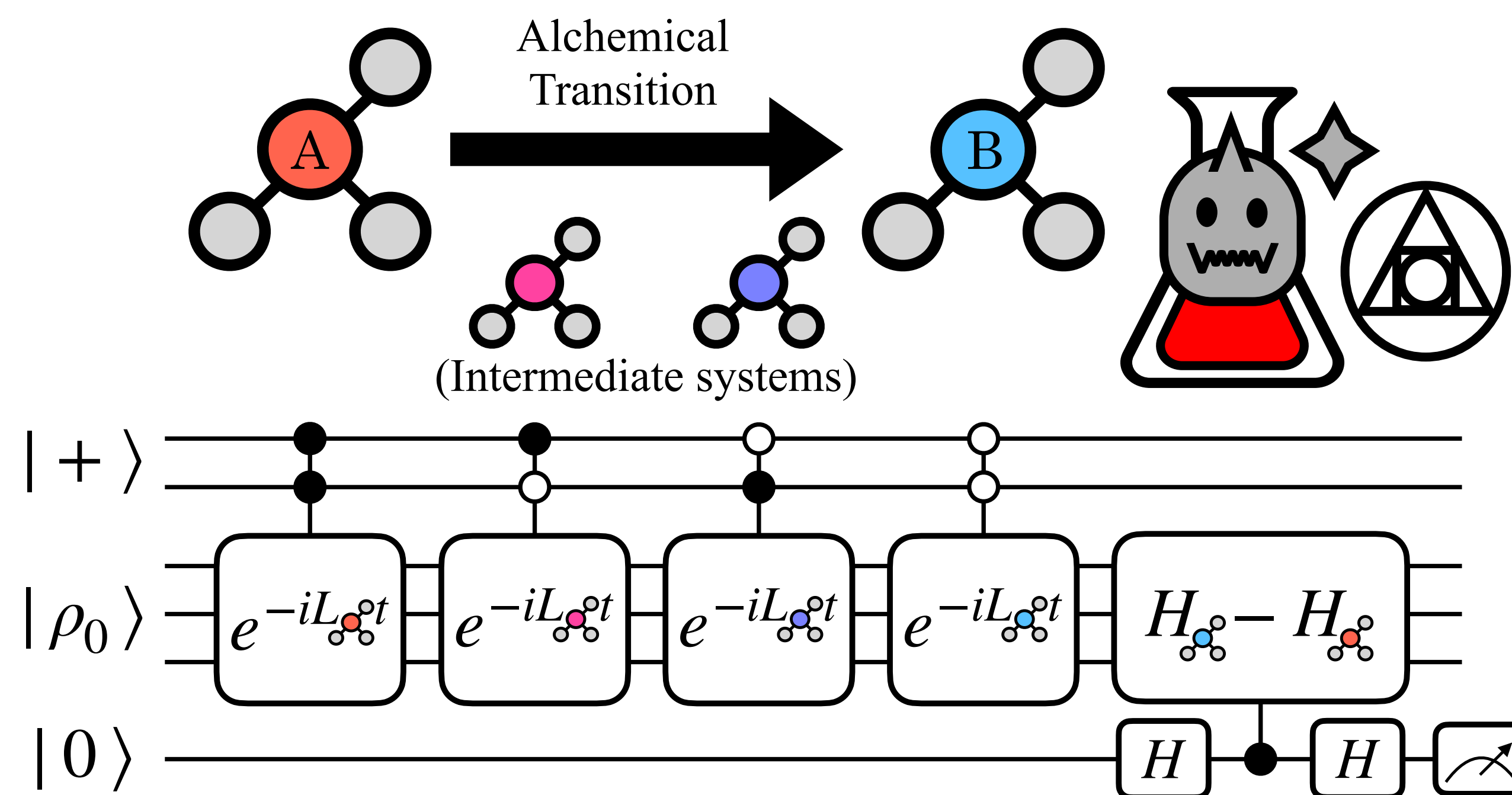
How the algorithm doesn't scale linear to the interpolation points

$$e^{-iL_\Lambda t_{\mathrm{eq}}} : \times \tilde{\mathcal{O}}(\alpha_{\max} t_{\mathrm{eq}} + \log \tfrac{1}{\varepsilon})$$

Algorithm breakdown
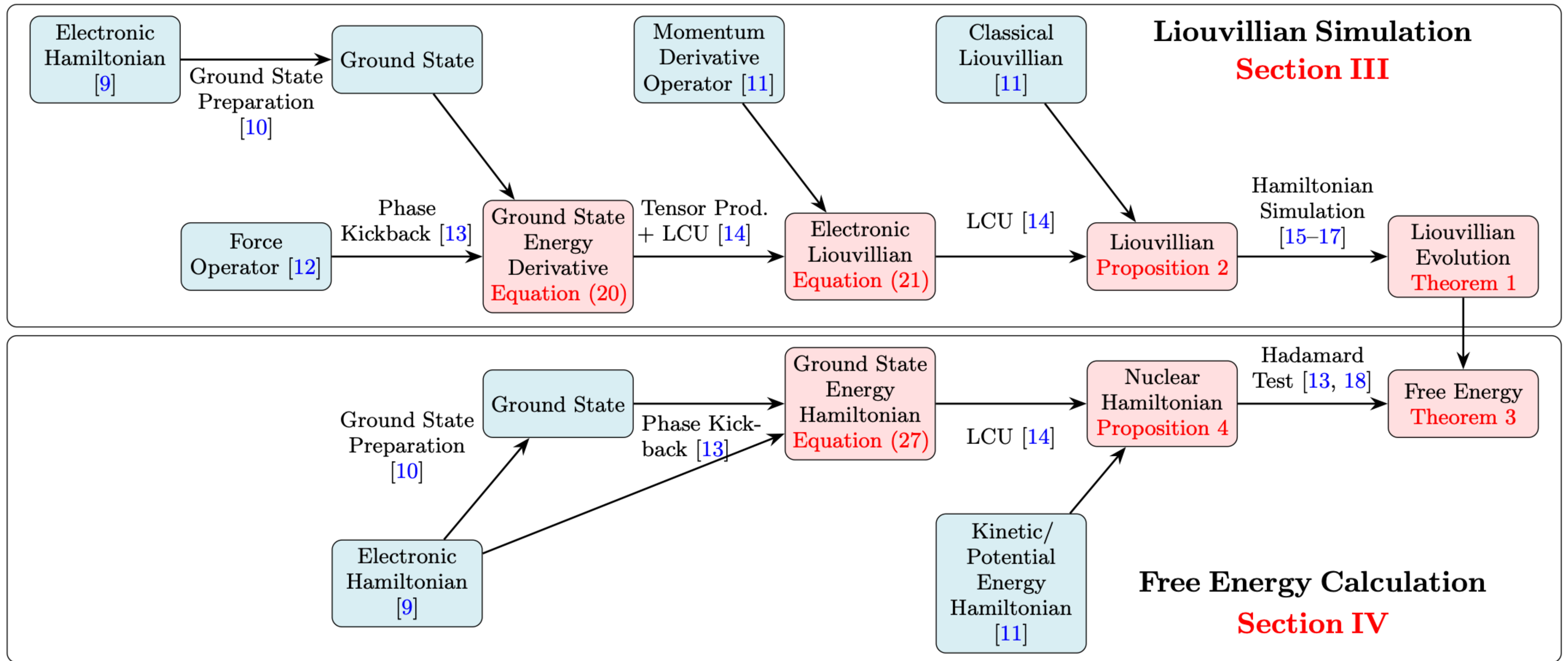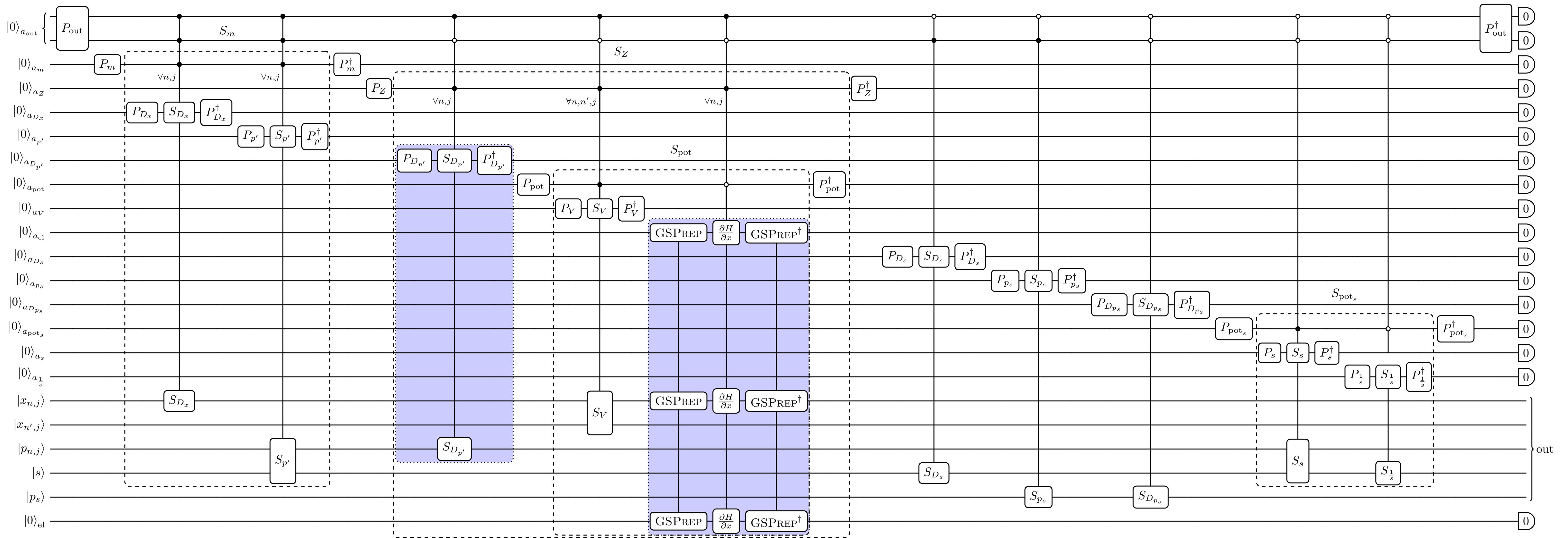
Performance comparison
With other quantum algorithms and advantages over classical

- Exponential improvements in precision over iterating between MD time step and electronic structure calculations (with both classical and quantum computing methods)

- Superpolynomial improvements over previous Trotterized Liouvillian approach

- Bypass entropy estimation via relative free energy calculations (no sampling over exponential phase-space)

	MD simulation	Free energy calculation
QPE + Euler Int. [1]	$\tilde{\mathcal{O}}(\varepsilon^{-1})$	—
Liouville + Trott. [2]	$\tilde{\mathcal{O}}(\varepsilon^{-o(1)})$	$\tilde{\mathcal{O}}(\eta^{1+o(1)}\varepsilon^{-1.5} + \varepsilon^{-2})$
Our work	$\mathcal{O}(\log^3 \varepsilon^{-1})$	$\tilde{\mathcal{O}}(\varepsilon^{-1})$