

# Fullqubit alchemist: Quantum algorithm for alchemical free energy calculation

P-W. Huang<sup>1,2</sup>, G. Boyd<sup>1</sup>, G.L.R. Anselmetti<sup>3</sup>, M. Degroote<sup>3</sup>, N. Moll<sup>3</sup>, R. Santagati<sup>3</sup>, M. Streif<sup>3</sup>, B. Ries<sup>3</sup>, D. Marti-Dafcik<sup>1,2</sup>, H. Jnane<sup>1,2</sup>, S. Simon<sup>4</sup>, N. Wiebe<sup>4,5,6</sup>, T.R. Bromley<sup>1</sup>, B. Koczor<sup>1,2</sup>

<sup>1</sup>Quantum Motion, <sup>2</sup>University of Oxford, <sup>3</sup>Boehringer Ingelheim, <sup>4</sup>University of Toronto, <sup>5</sup>PNNL, <sup>6</sup>CIFAR

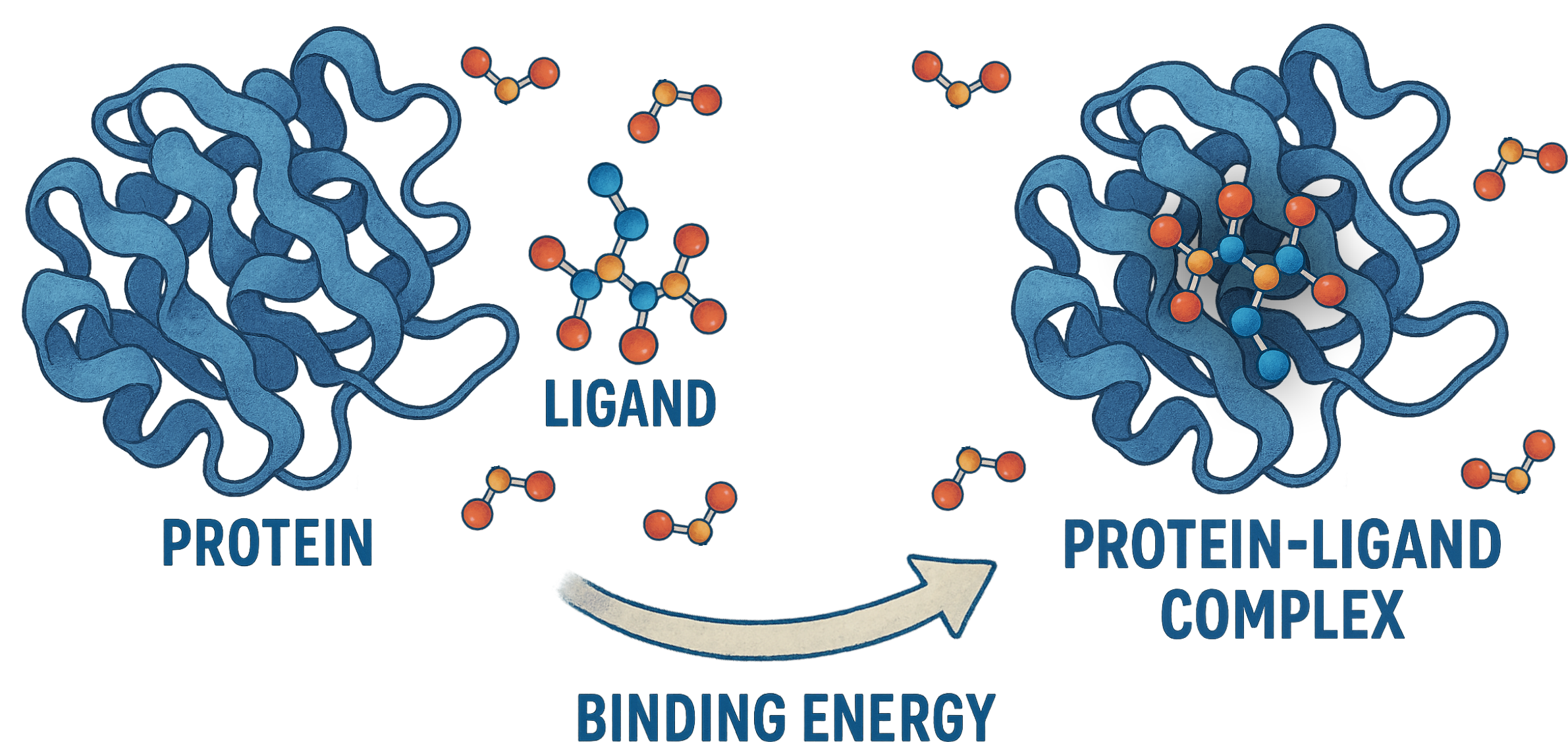


arXiv:2508.

**TL;DR:** We introduce quantum algorithms for molecular dynamics with a logarithmic dependency on precision and alchemical free energy difference calculation without entropy estimation.

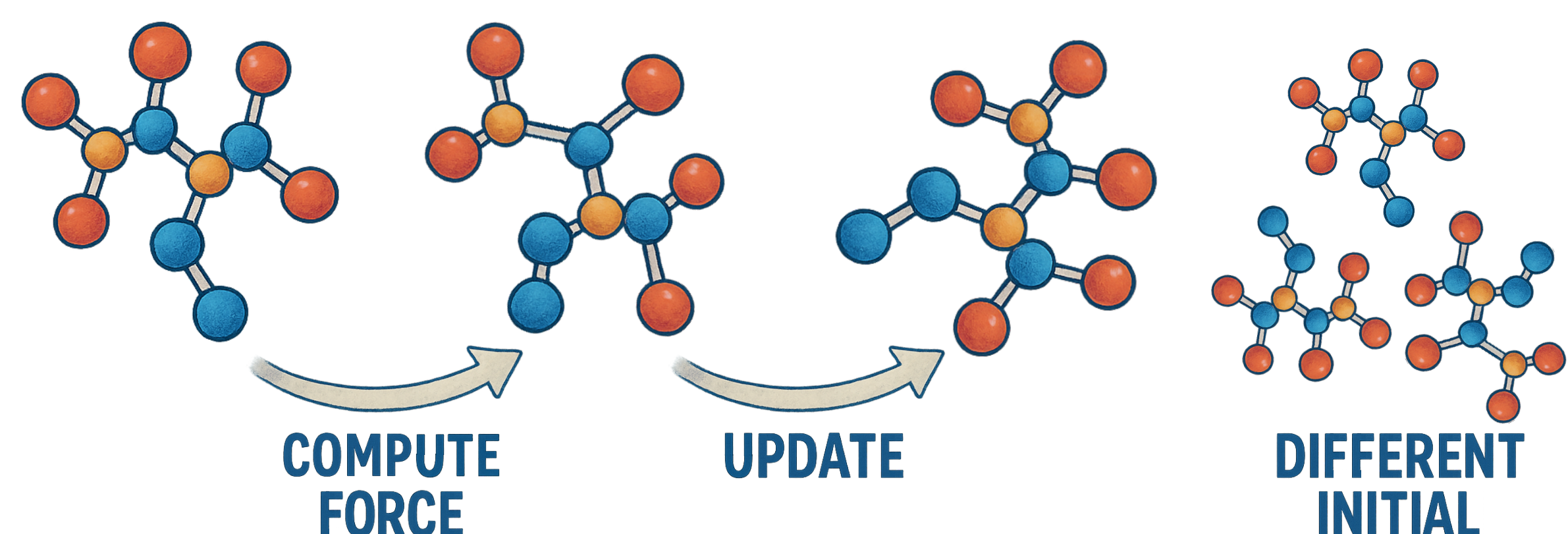
## Drug Design

Modern drug design rely on binding free energy to rank candidates.



## Molecular Dynamics

Molecular dynamics simulate the motion of molecules over time.



## Evolution under the NVT Liouvillian

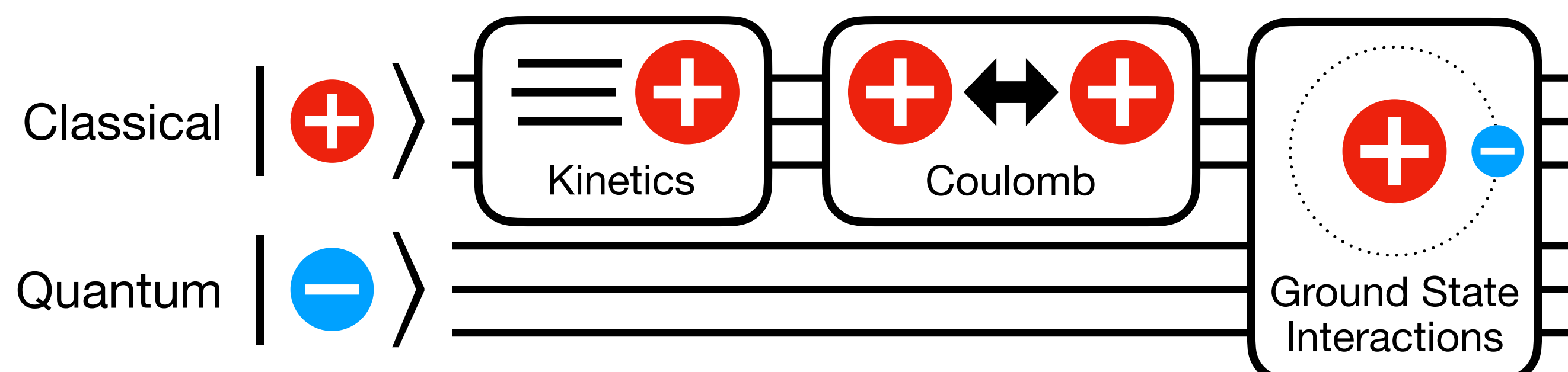
Evolution under the NVT Liouvillian generates thermal states.

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

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

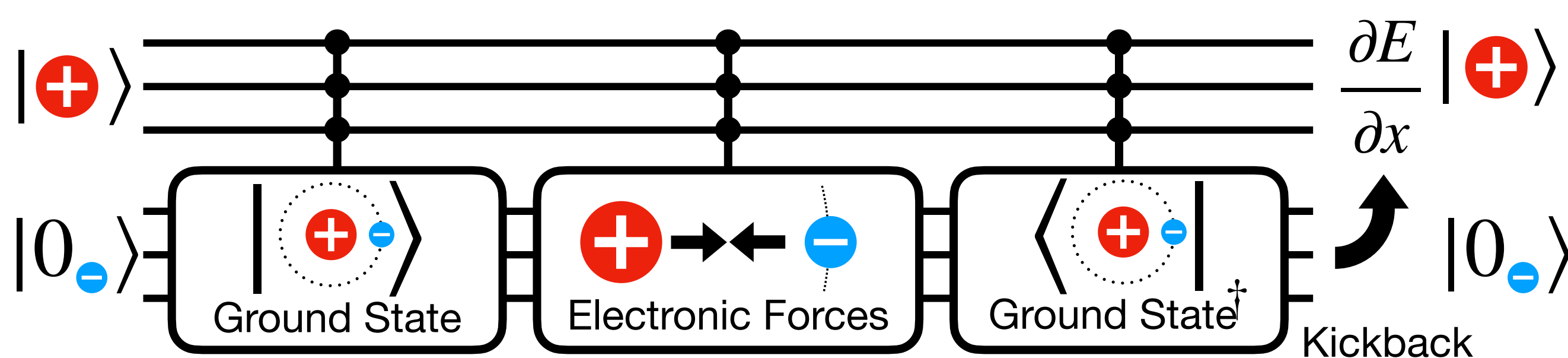
## Modeling Mixed Quantum-Classical Systems

Classical and quantum systems can be modeled separately via the Born-Oppenheimer approximation.



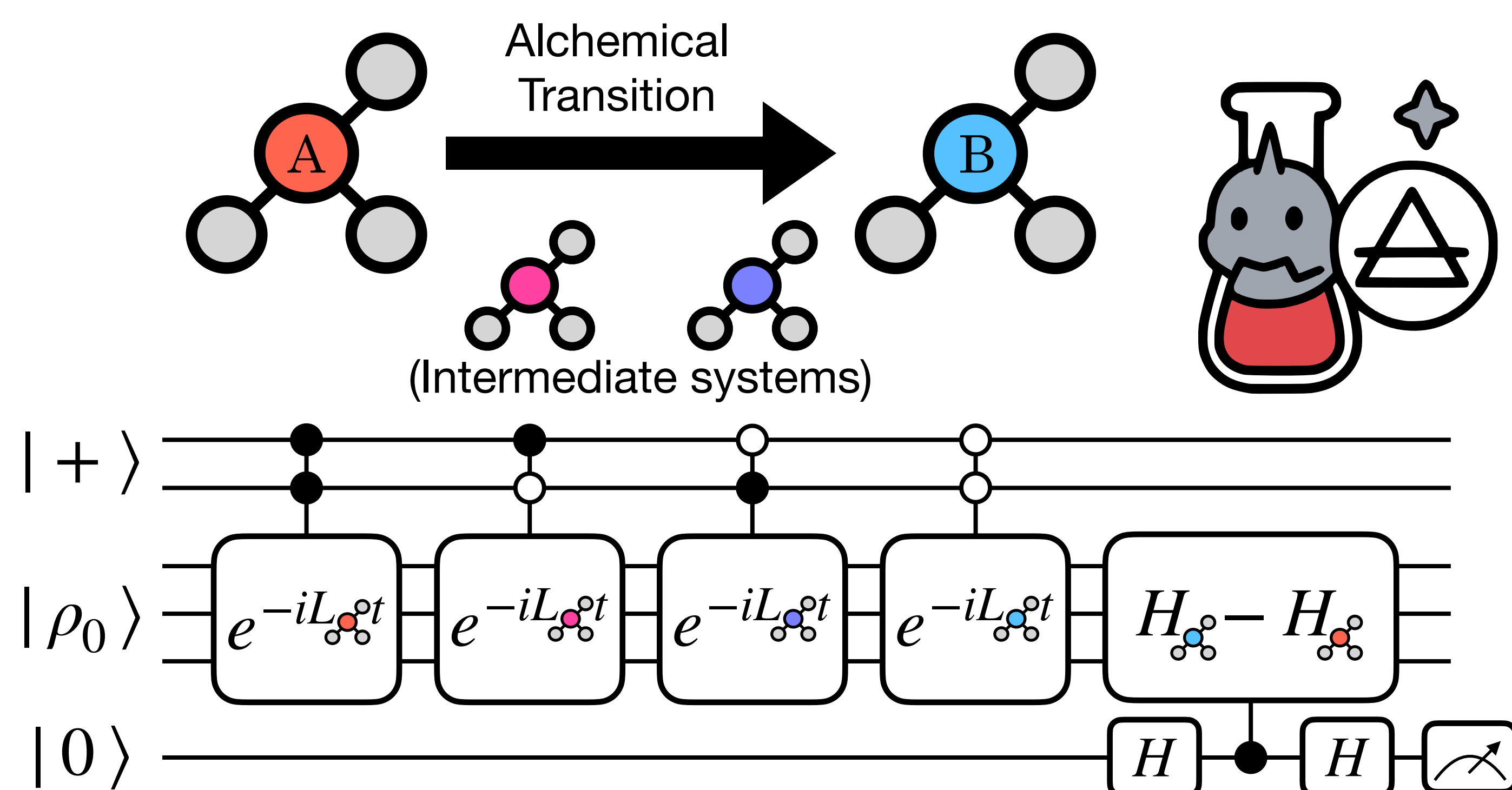
## Electronic Register Kickback

Electronic forces are “kicked-back” into the nuclear register after computation via Hellmann-Feynman theorem.



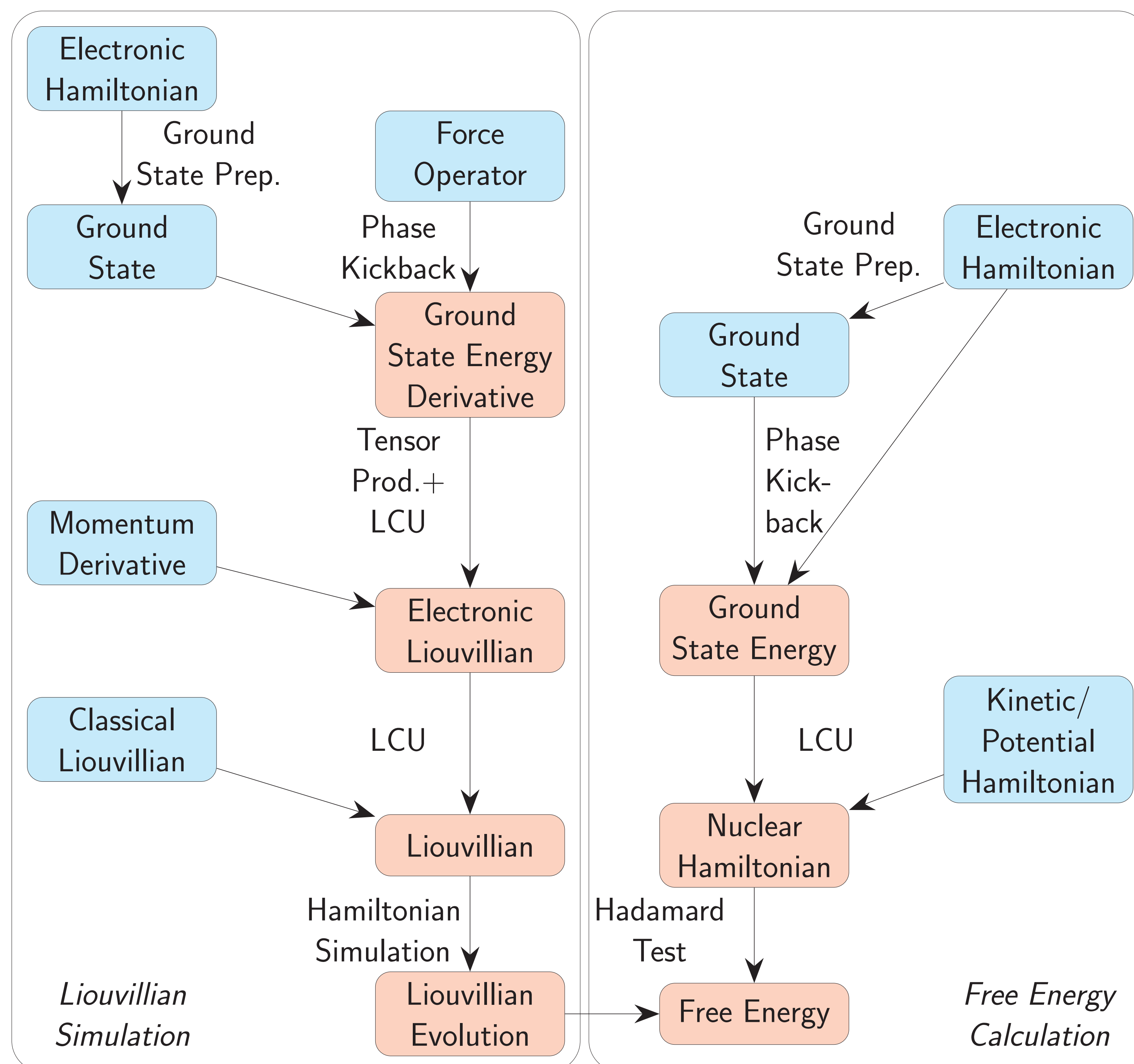
## Alchemical Free Energy Calculation

Alchemical methods calculate free energy differences by integrating across different thermal states without explicit entropy estimation.



## Algorithm Design

We recursively construct block encodings to obtain the final result.



## Performance Comparison

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

## References

- [1] T. E. O'Brien et al., *Phys. Rev. Res.* **2022**, 4, 043210.
- [2] S. Simon et al., *PRX Quantum* **2024**, 5, 010343.