Systematically Improvable Models From Alchemical Perturbations

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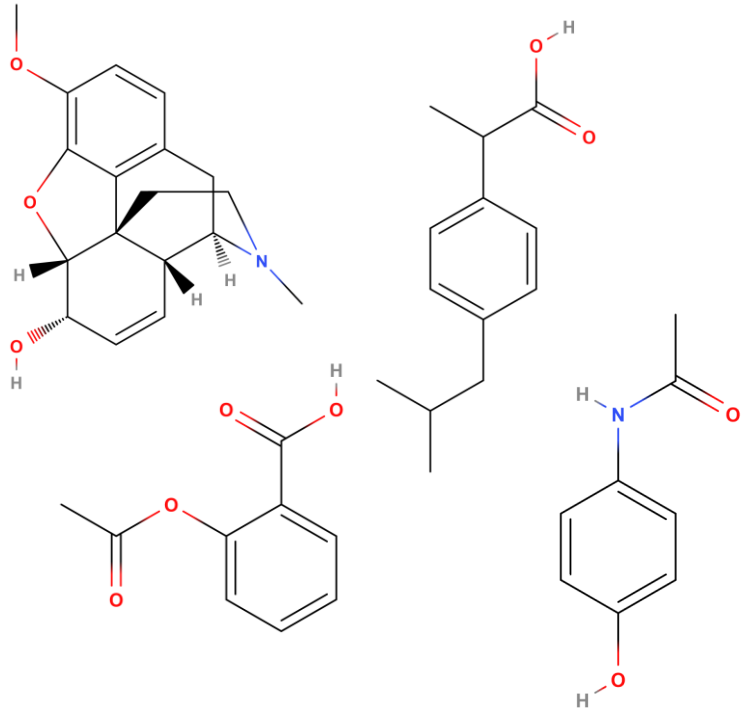
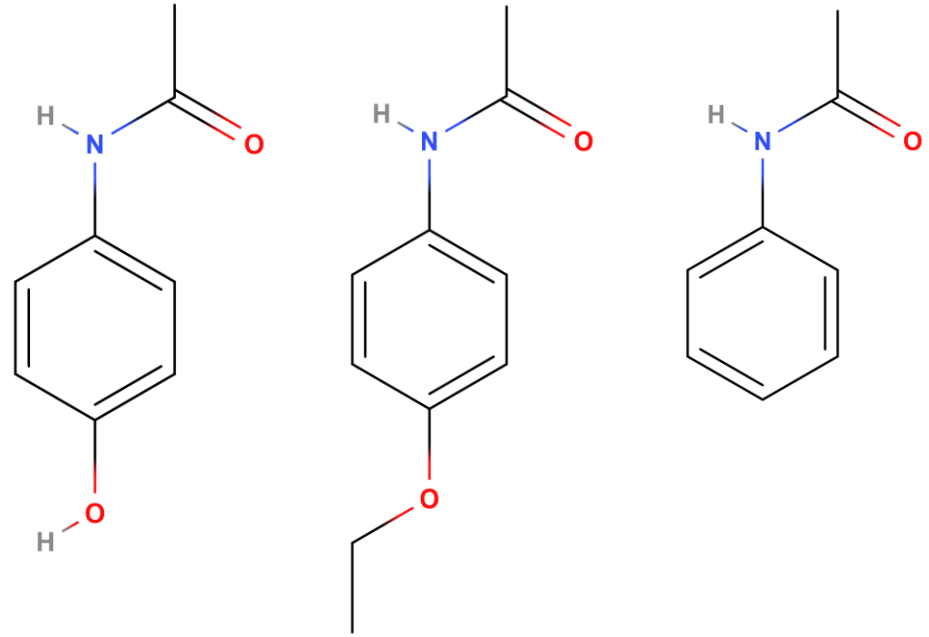
Introduction

Design: sample by guided trial-and-error.



Global Search Problem
Which class of compounds?

Drug-like: 10^{60}



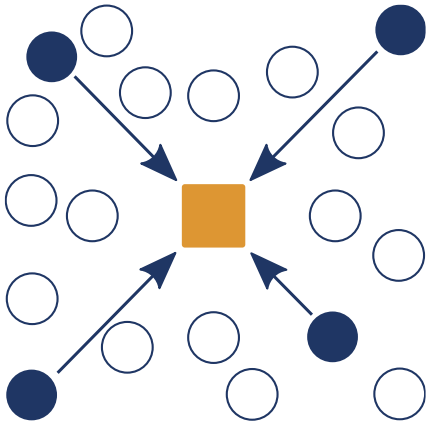
Local Search Problem
Which particular species within that class?

BN-doped 8x8 graphene: 10^{50}

G. Ceder, *Science* **1998**. A. Franceschetti, A. Zunger, *Nature*, **1999**. A. Mullard, *Nature*, **2017**.

Introduction

Machine Learning



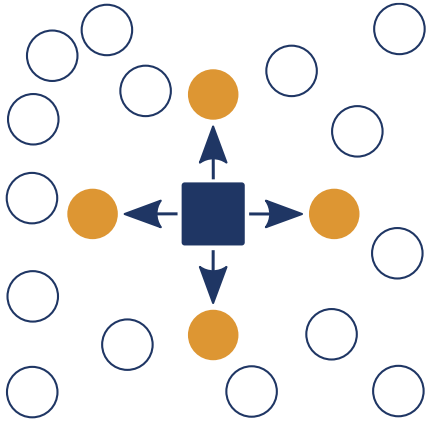
Foundations | Statistical modelling

Accuracy | Systematically improvable through data and training

Specialty | Universal, scale-bridging, data-driven approach

Limitation | Requires training data, no black box

Quantum Alchemy



Foundations | Perturbation theory

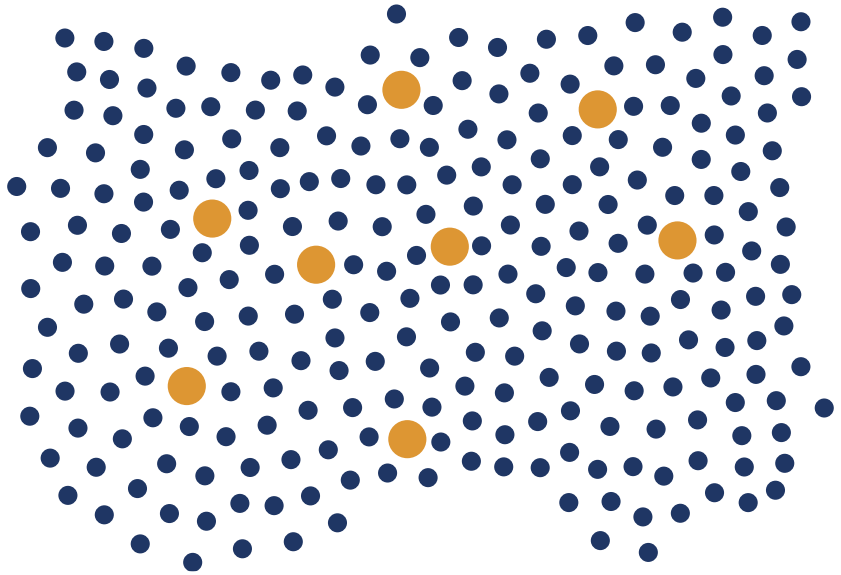
Accuracy | Systematically improvable through higher orders terms

Specialty | Combinatorial scaling with chemical diversity

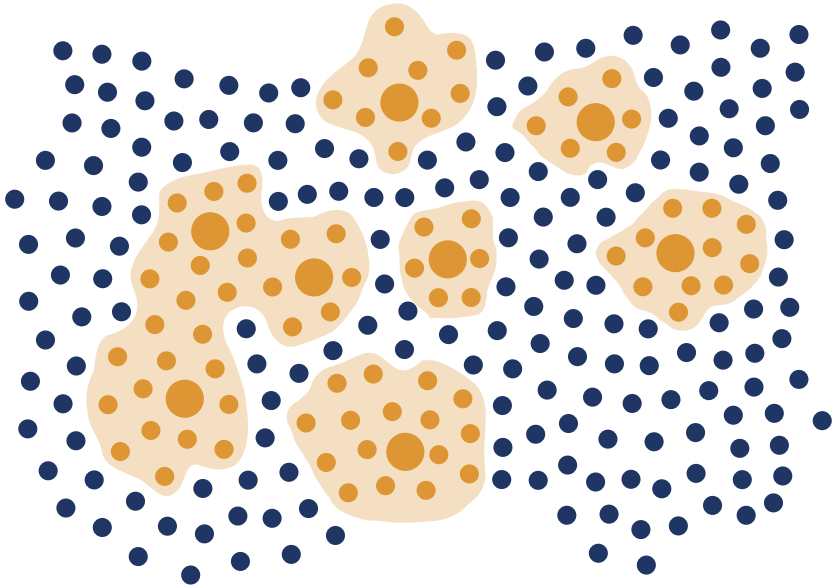
Limitation | Finite range in chemical space

Introduction

Without Perturbation



With Perturbation



Systems/Molecules

- Any
- Known
- Approximated

Paradigm shift

Few highly accurate calculations
instead of many intermediate ones

$$\hat{\mathrm{H}} = \hat{\mathrm{H}}(Z_i, \mathbf{R}_i, N_e, \sigma)$$

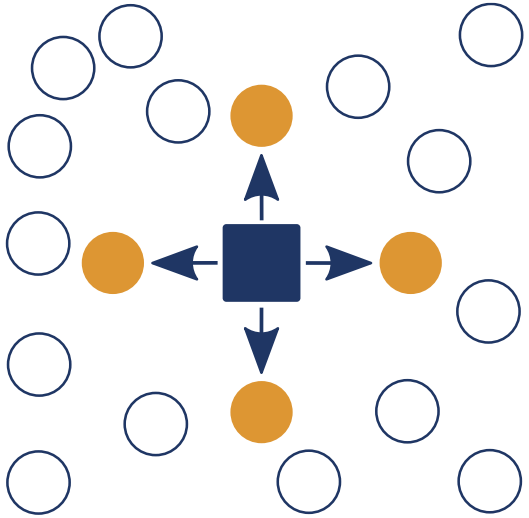
4N

1D, close to $\sum_i Z_i$

1D

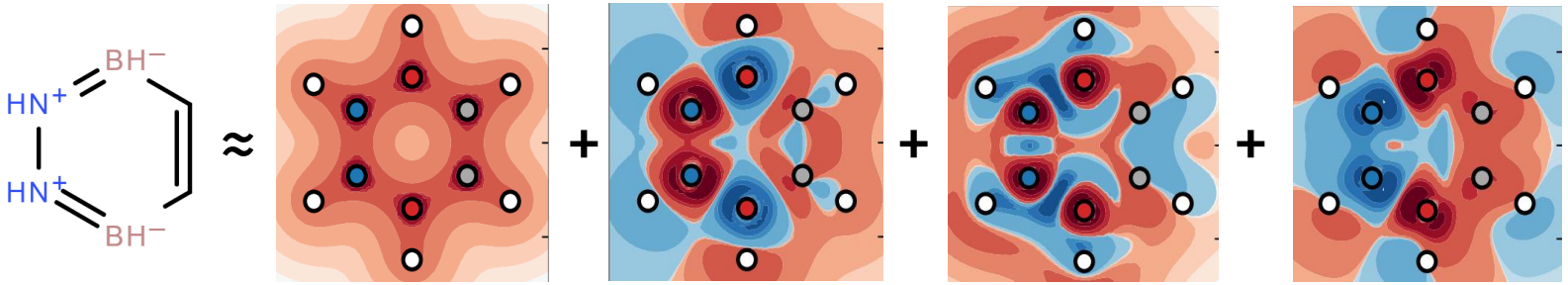
Quantum Alchemy

Quantum Alchemy



Taylor expansion

- Energy function of
  - Geometry — Forces, Vibrations
  - Nuclear charges — Alchemical changes
- Idea: obtain dominant leading derivatives, predict many systems



E. B. Wilson, *J. Chem. Phys.* **1962.**
GFvR, O. A. von Lilienfeld, *Phys. Rev. Res.*, **2020**.

Quantum Alchemy

Interpolate between molecular isoelectronic Hamiltonians

$$\hat{H}(\lambda) \equiv \lambda \hat{H}_\mathrm{t} + (1-\lambda)\hat{H}_\mathrm{r} \qquad \lambda \in [0,1]$$

Taylor expansion around reference molecule

$$E_\mathrm{t} = \sum_{n=0}^{\infty} \frac{1}{n!} \frac{\partial^n}{\partial \lambda^n} \left\langle \psi_\lambda \middle| \hat{H}(\lambda) \middle| \psi_\lambda \right\rangle \Big|_{\lambda=0} = E_\mathrm{r} + \sum_{n=1}^{\infty} \frac{1}{n!} \left. \frac{\partial^n E(\lambda)}{\partial \lambda^n} \right|_{\lambda=0}$$

Hellmann-Feynman theorem

$$\partial_\lambda E = \left\langle \psi_\lambda \middle| \hat{H}_\mathrm{t} - \hat{H}_\mathrm{r} \middle| \psi_\lambda \right\rangle = \Delta E^\mathrm{NN} + \int_\Omega d\mathbf{r} \underbrace{\left(v_\mathrm{t}(\mathbf{r}) - v_\mathrm{r}(\mathbf{r})\right)}_{\equiv \Delta v} \rho_\lambda(\mathbf{r})$$

O. A. von Lilienfeld, *J. Chem. Phys.* **2009**.

Quantum Alchemy

Alchemical Perturbation Density Functional Theory (APDFT)

$$E_\mathrm{t} = E_\mathrm{r} + \Delta E^\mathrm{NN} + \int_\Omega d\mathbf{r} \sum_{n=0}^{\infty} \frac{1}{(n+1)!} \Delta v \frac{\partial^n \rho_\lambda(\mathbf{r})}{\partial \lambda^n}\bigg|_{\lambda=0}$$

$$\rho_t = \sum_{n=0}^{\infty} \frac{1}{n!} \frac{\partial^n \rho}{\partial \lambda^n}\bigg|_{\lambda=0}$$

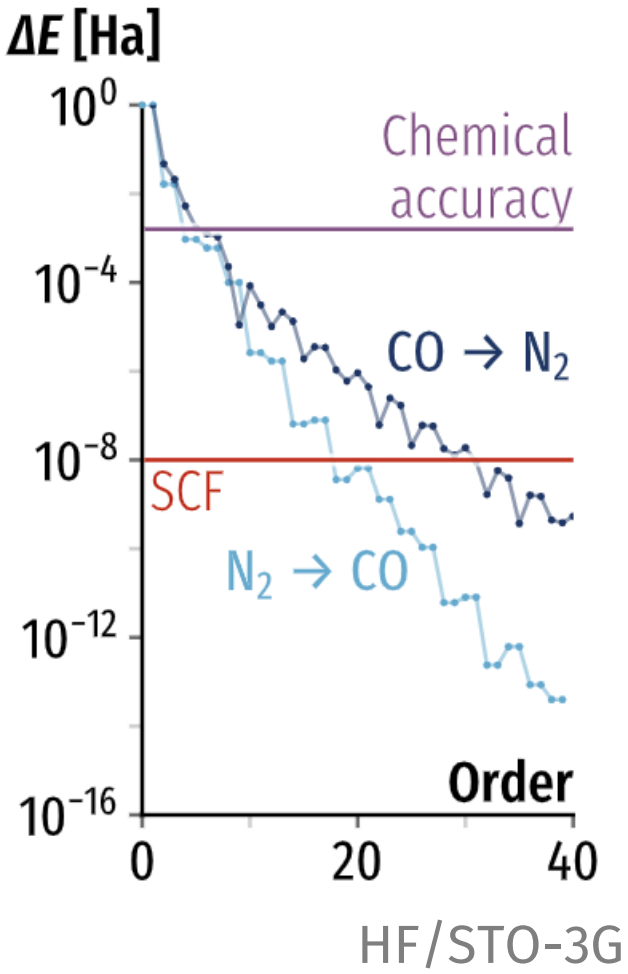
- Gives consistent energies, densities, forces, ...
- Uses the same derivatives for all predictions

ferchault/APDFT

GFvR, O. A. von Lilienfeld, *Phys. Rev. Res.*, **2020**.

xkcd.com/2605

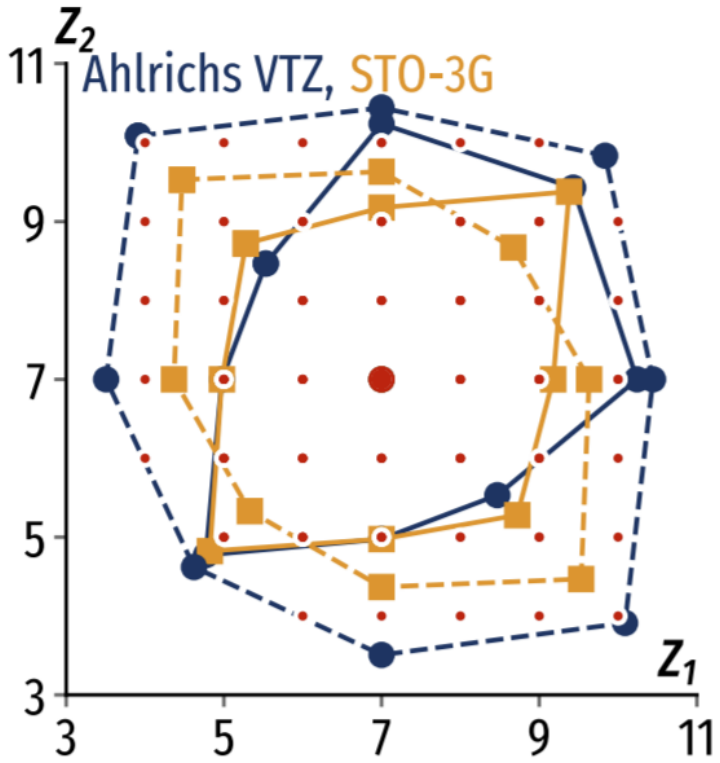
Convergence



HF/STO-3G

Taylor expansion

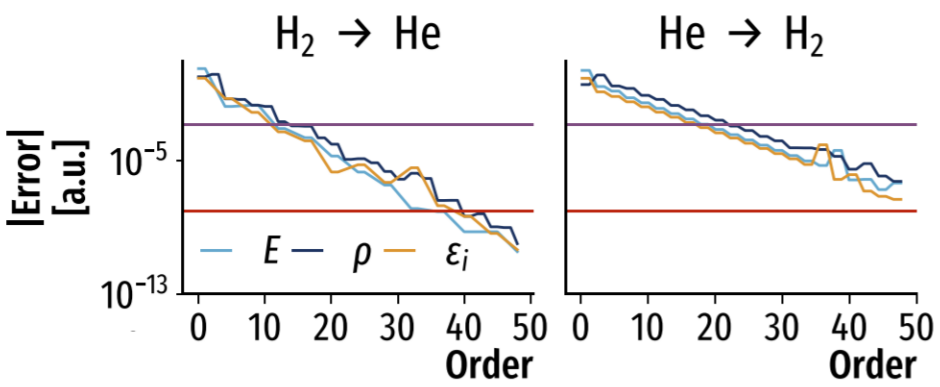
- First terms accurate enough
  - Truncate early
- Converges to the right value
- Large convergence radius
- Scales with chemical space

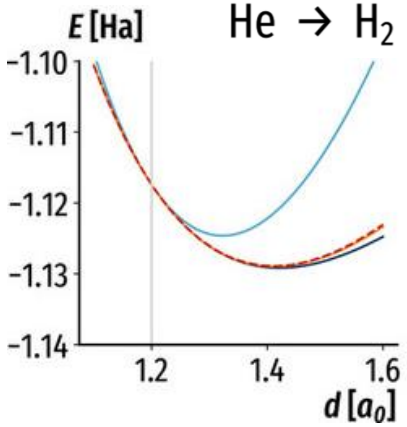


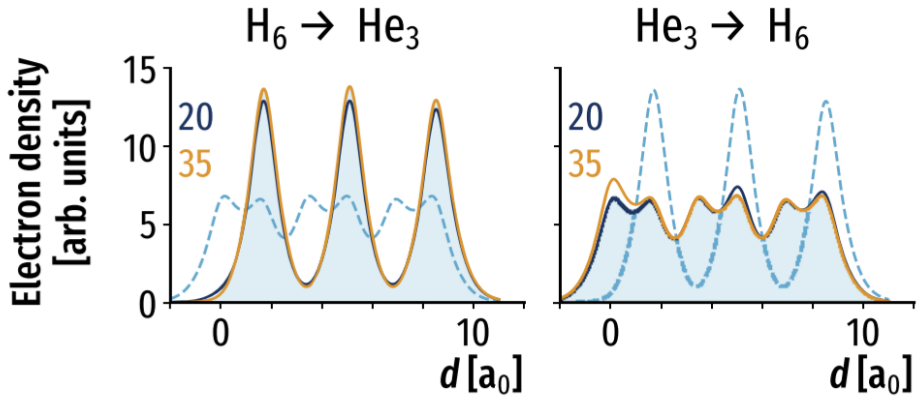
ferchault/APHF

GFvR, *J. Chem. Phys.* 2021.

Convergence







Taylor expansion

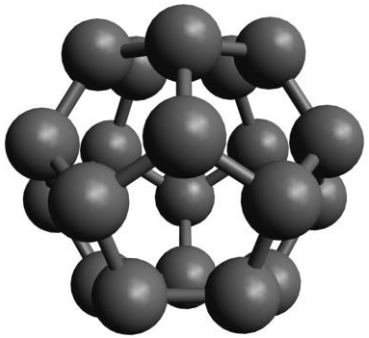
- Large changes still converge (more slowly)
- Geometric response can be recovered

GFvR, *J. Chem. Phys.* 2021.

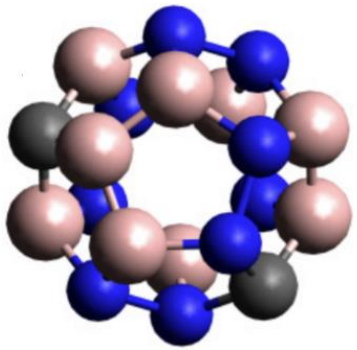
Covalent interactions

Scaling with chemical space

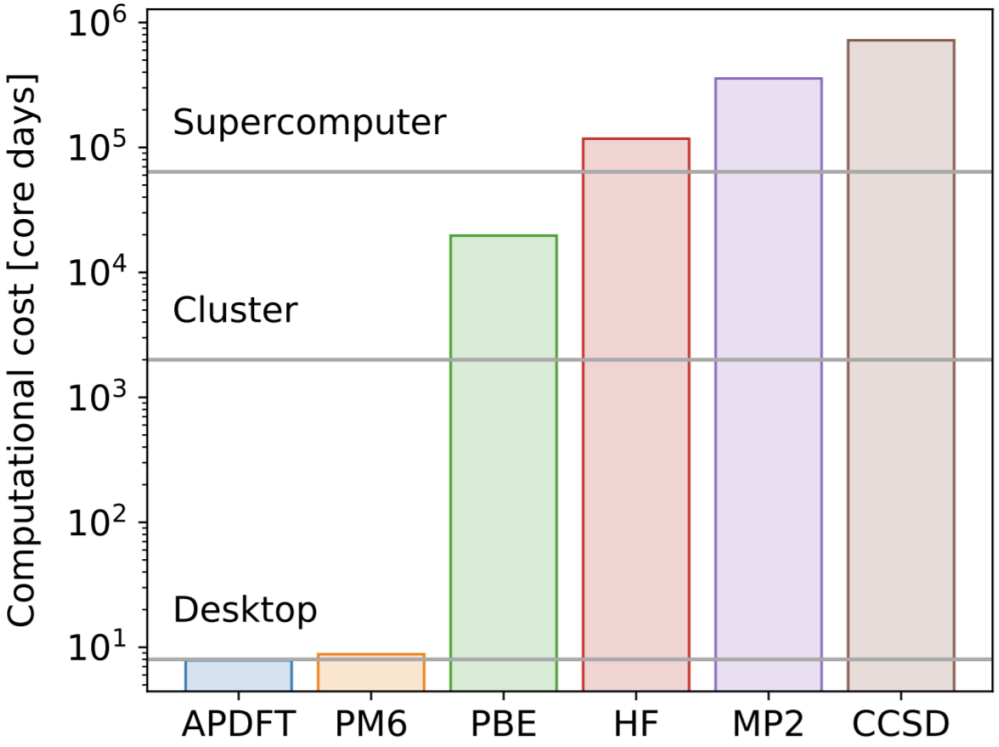
- 1 derivative for second order
- 5 derivatives for third order



C_{20}



$3.1 \cdot 10^6$ targets



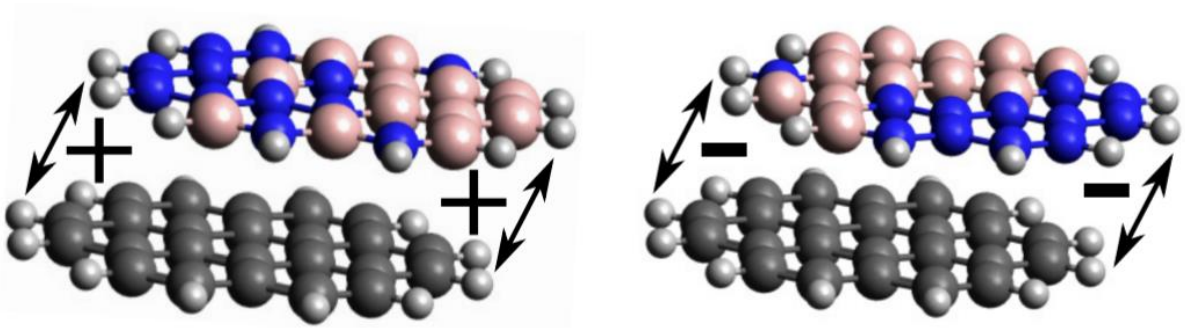
QA: 80.000x faster

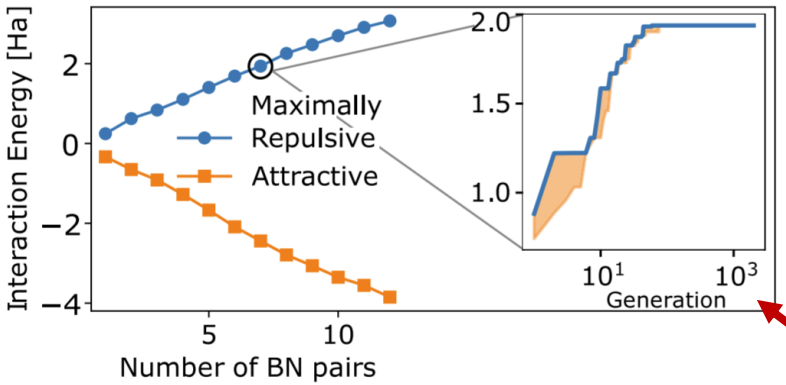
GFvR, O. A. von Lilienfeld, *Phys. Rev. Res.*, **2020**.

Non-covalent interactions

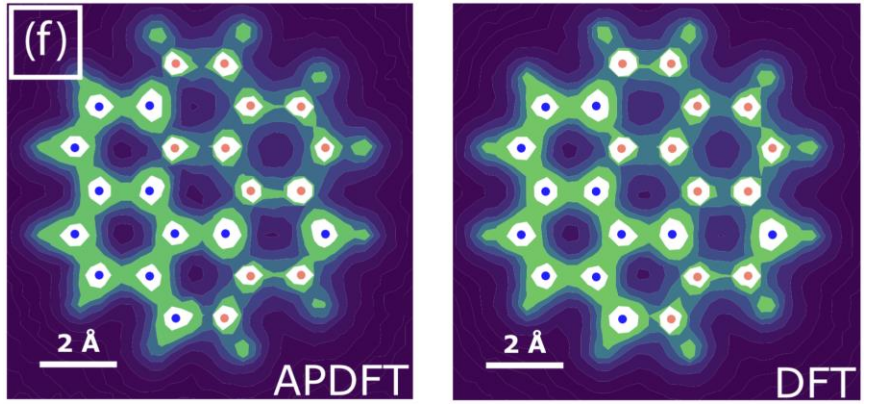
BN-doped coronene dimer

- Identify most/least attractive doping pattern
- Design case





QA: 20.000x faster

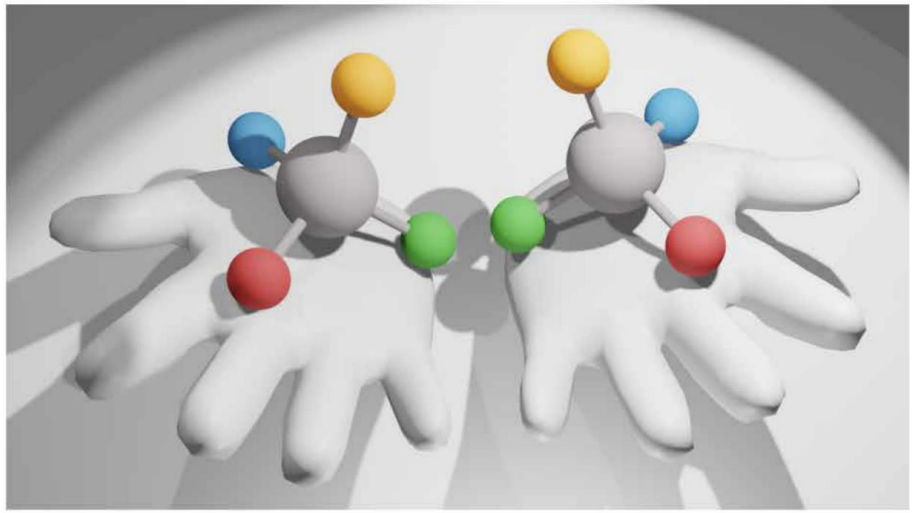


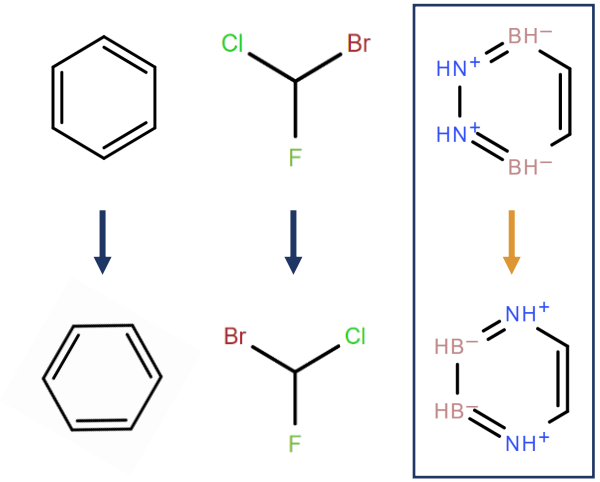
$2.8 \cdot 10^{10}$ targets

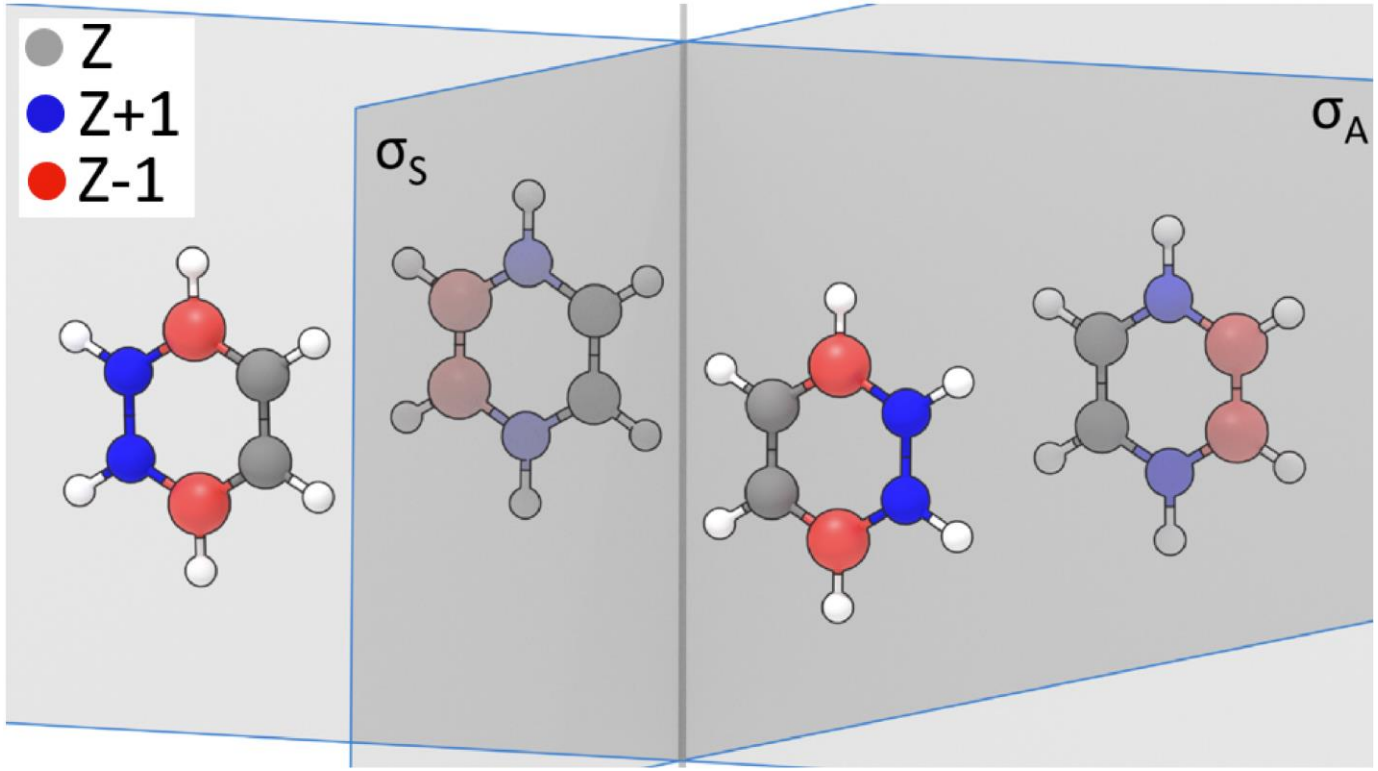
GFvR, O. A. von Lilienfeld, *Phys. Rev. Res.*, **2020**.

Alchemical enantiomers

Quasi-degeneracy for systems if this symmetry applies to them.





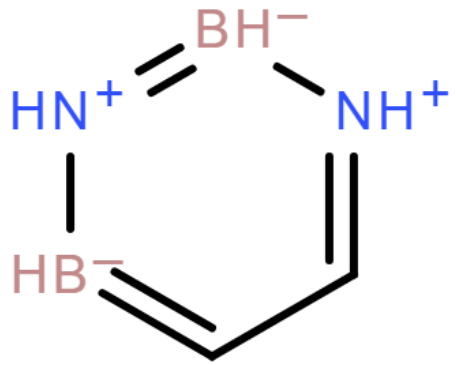


GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

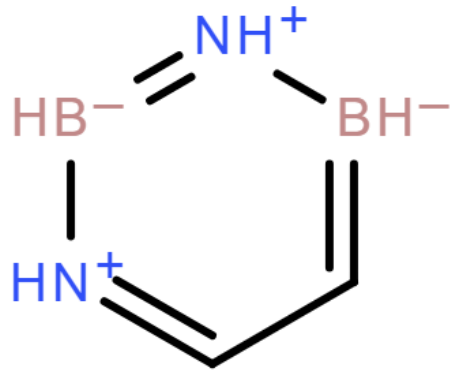
Alchemical enantiomers

Alchemical enantiomers are

- **two spatially non-superimposable,**
- alchemically coupled,
- and iso-electronic compounds with the same formal charge,
- where each transmutating atom is assigned to exactly one subset within each of which averaging of nuclear charges results in identical chemical environments.



These are no alchemical enantiomers!



GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

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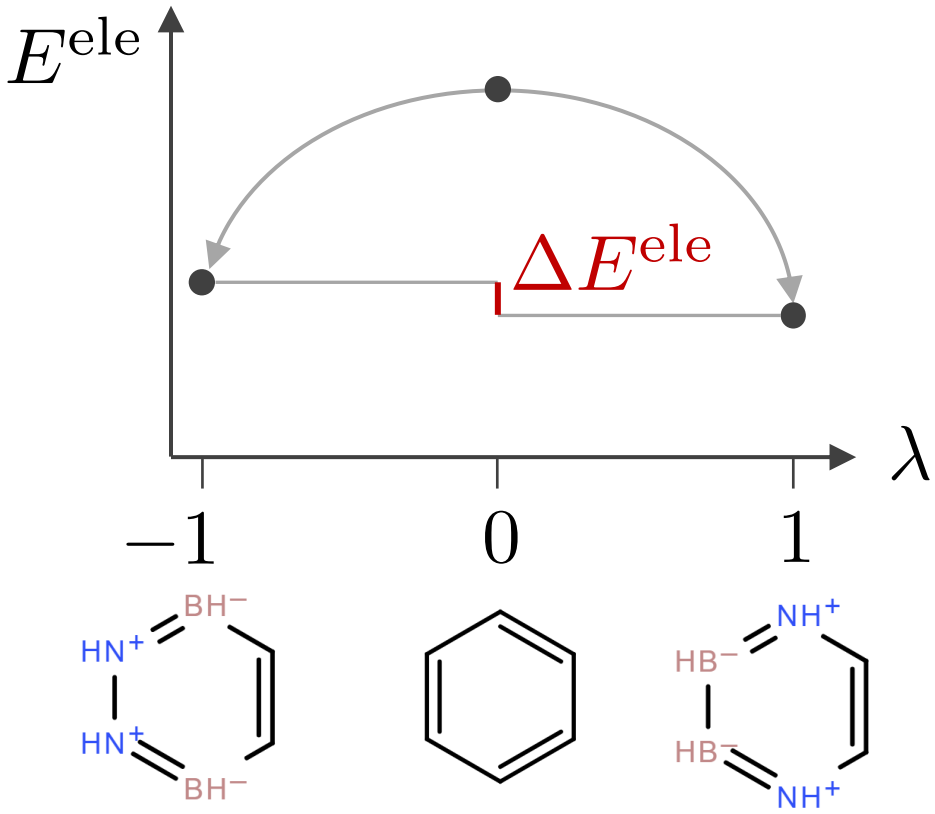

GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

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GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

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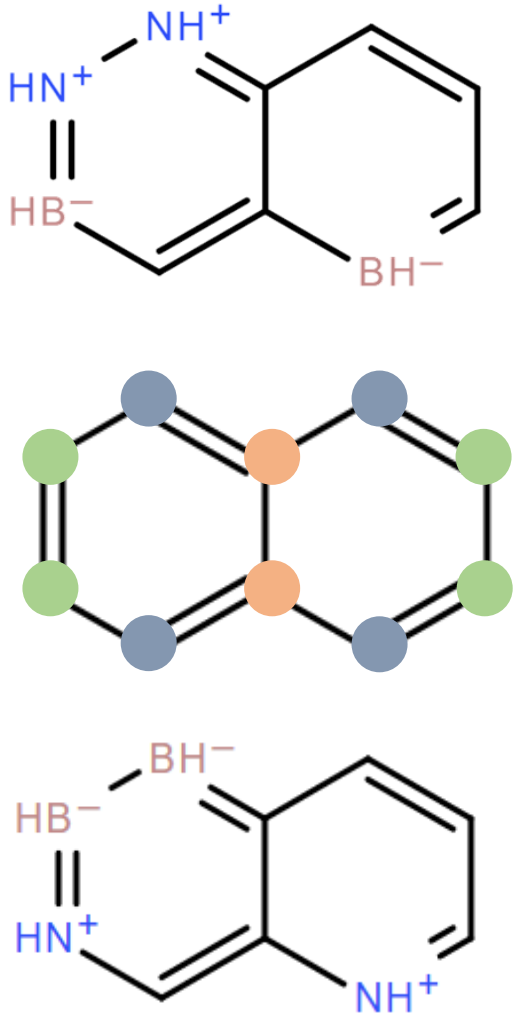
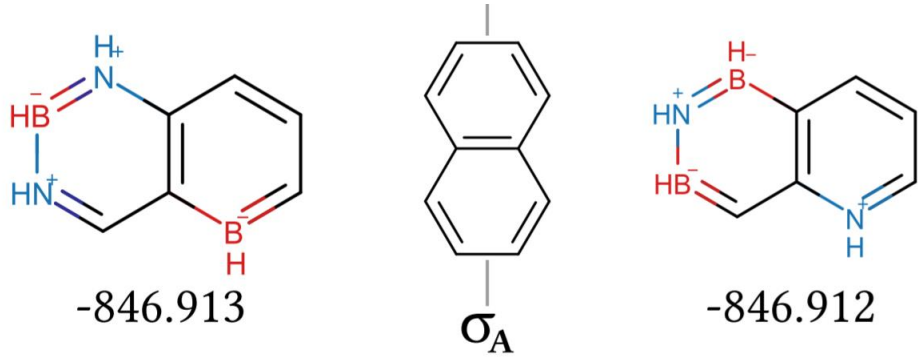


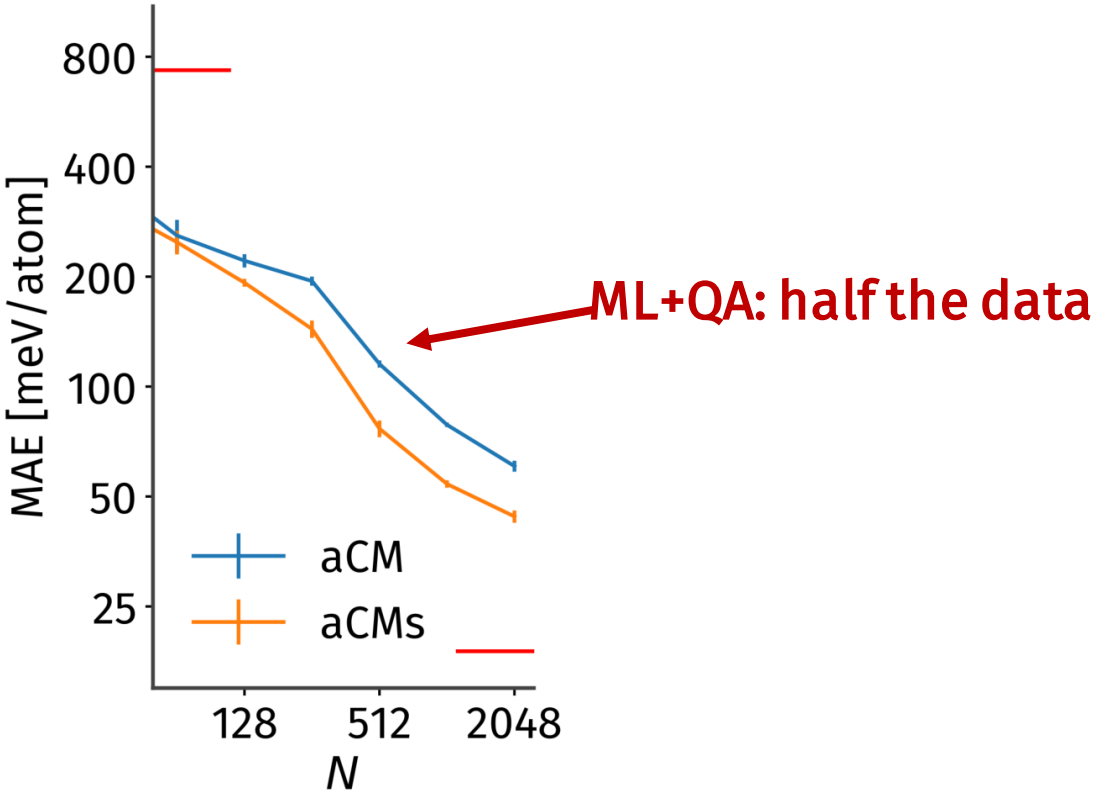
Alchemical enantiomers

Fundamentally new symmetry

Electronic energy only



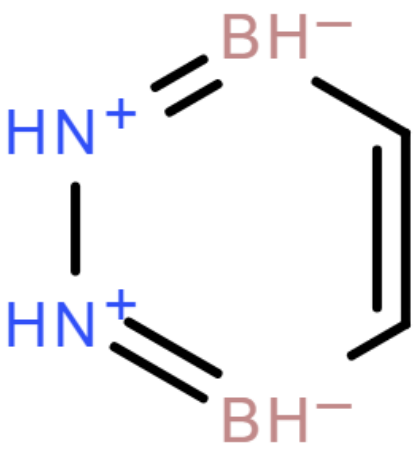
Speed up machine learning



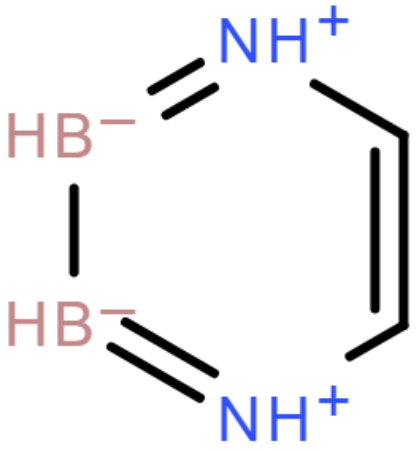
GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

GFvR, O. A. von Lilienfeld, *in preparation.*

Alchemical enantiomers



CC
2BC
2BN
NN



CC
2NC
2BN
BB

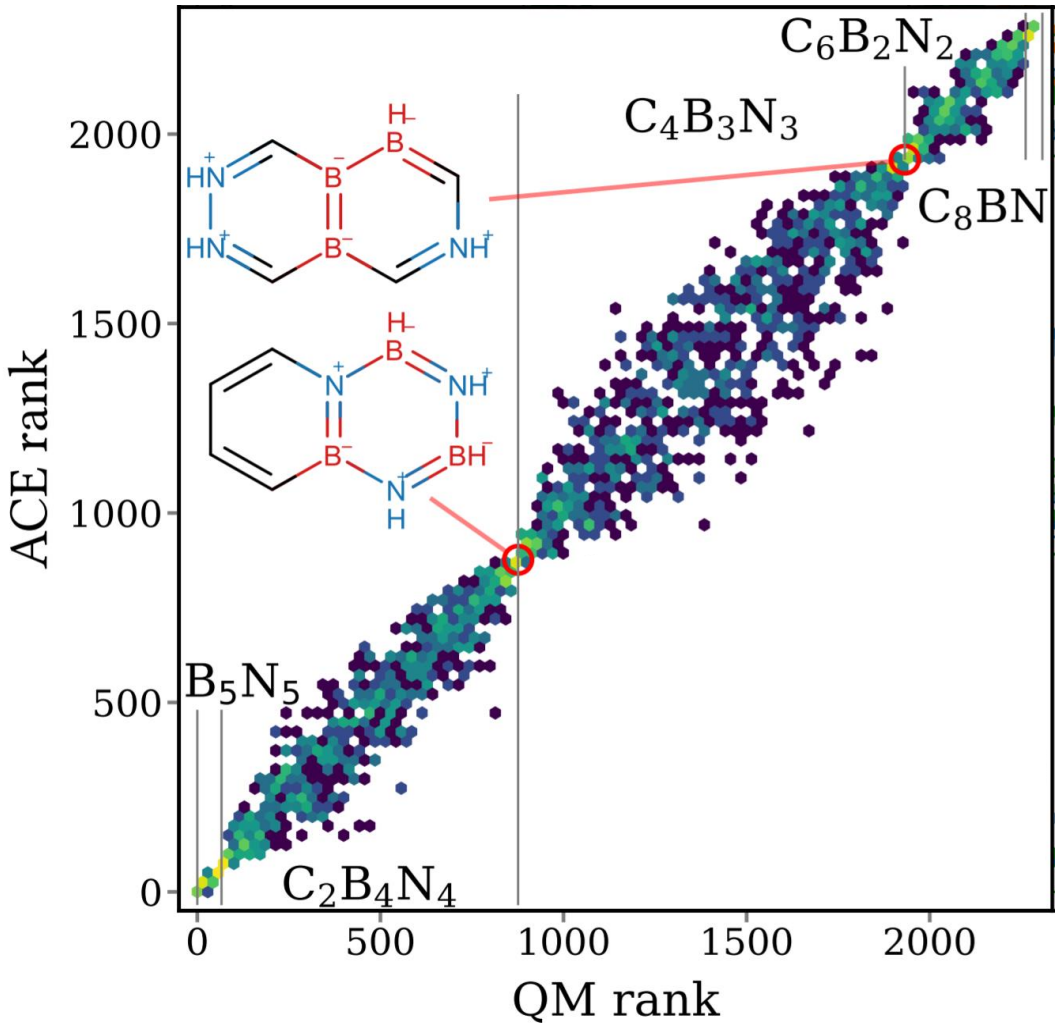
Consecutive Elements
Q R S
B C N

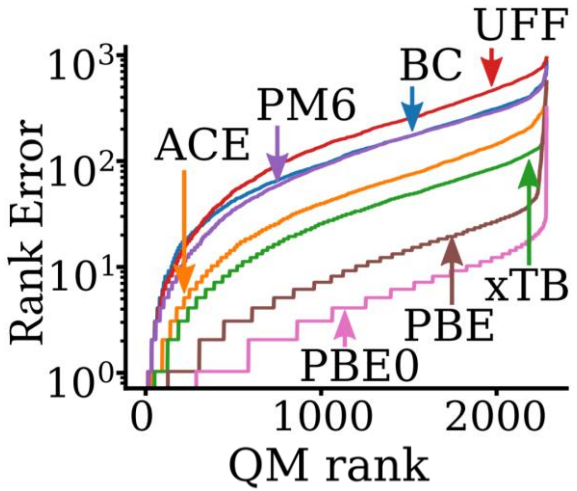
$$E_{\mathrm{QR}} \simeq E_{\mathrm{SR}} + 0.5(E_{\mathrm{QQ}} - E_{\mathrm{SS}})$$

Other skeletons and all substitution patterns
- More such rules
- No violations

GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

Alchemical enantiomers



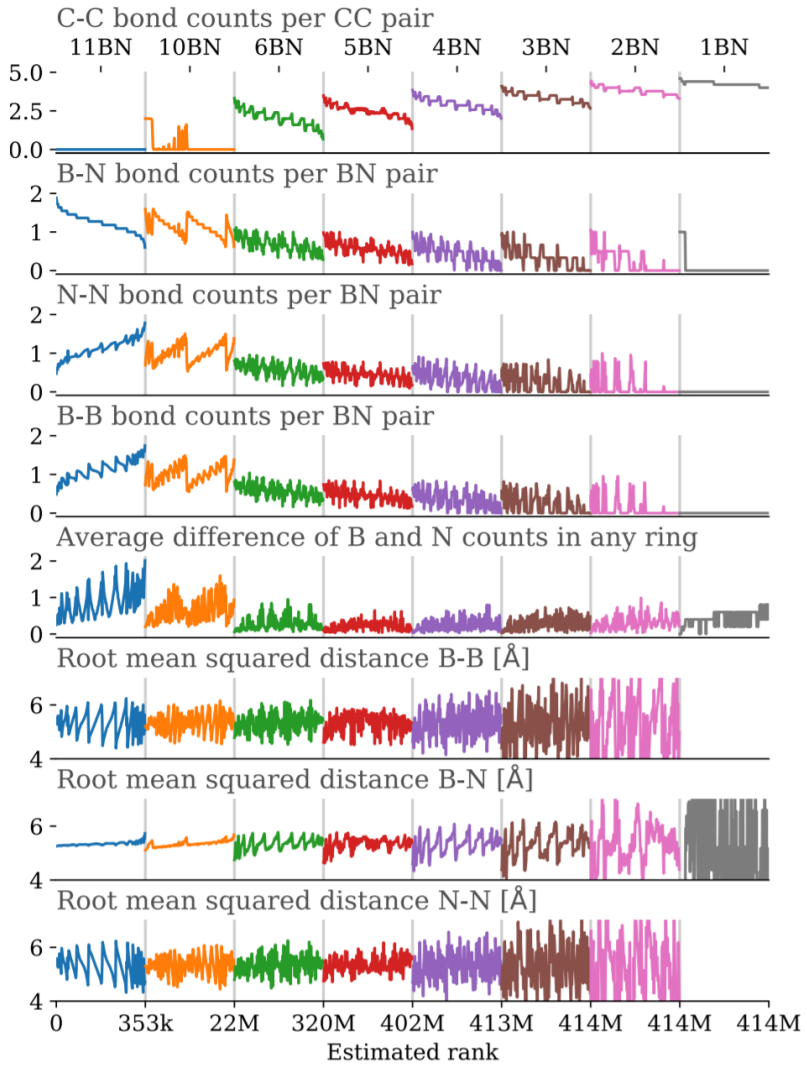


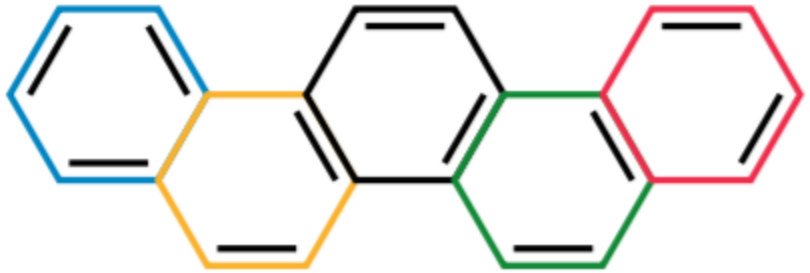
- **BN-doped naphthalene**
  CCSD/cc-pVDZ
  Molpro/MRCC/xTB-GFN2/mopac/OpenBabel

- **BN-doped naphthalene**
  CCSD/cc-pVDZ
  Molpro/MRCC

GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

Alchemical enantiomers





x 414 M

Design rules in order of decreasing strength

- Add BN pairs
- Maximize CC bonds
- Substitute sites shared between rings
- Maximize BN bonds
- Avoid N substitutions on rings sharing a larger amount of bonds with other rings
- Balance BN substitutions in each ring

QA: Millions at once!

Not a single QM calculation required!

GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**

Alchemical Integral Transform

Derivatives without electronic perturbations

$$E_\mathrm{t} = E_\mathrm{r} + \Delta E^\mathrm{NN} + \int_\Omega d\mathbf{r} \sum_{n=0}^{\infty} \frac{1}{(n+1)!} \Delta v \frac{\partial^n \rho_\lambda(\mathbf{r})}{\partial \lambda^n}\bigg|_{\lambda=0}$$

$\mathbf{r} \rightarrow \mathbf{r}(\lambda)$ + chain rule + partial integration e.g. for second order in 1D

$$\Delta E^{(2)} = \frac{1}{2} \int_\Omega dr \Delta v(r(\lambda)) \frac{\partial \rho(r(\lambda))}{\partial r} \frac{\partial r}{\partial \lambda}\bigg|_{\lambda=0}$$

$$= -\frac{1}{2} \int_\Omega dr \rho(r(\lambda)) \frac{\partial \Delta v(r(\lambda))}{\partial r} \frac{\partial r}{\partial \lambda}\bigg|_{\lambda=0}$$

SL Krug, **GFvR**, O. A. von Lilienfeld, *arXiv, 2203.13794,* **2022.**

Alchemical Integral Transform

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3D, arbitrary order $2n+1 \rightarrow 0$

$$\Delta E = \int_\Omega d\mathbf{r} K(\mathbf{r}, v_i, v_f) \rho(v_i)$$

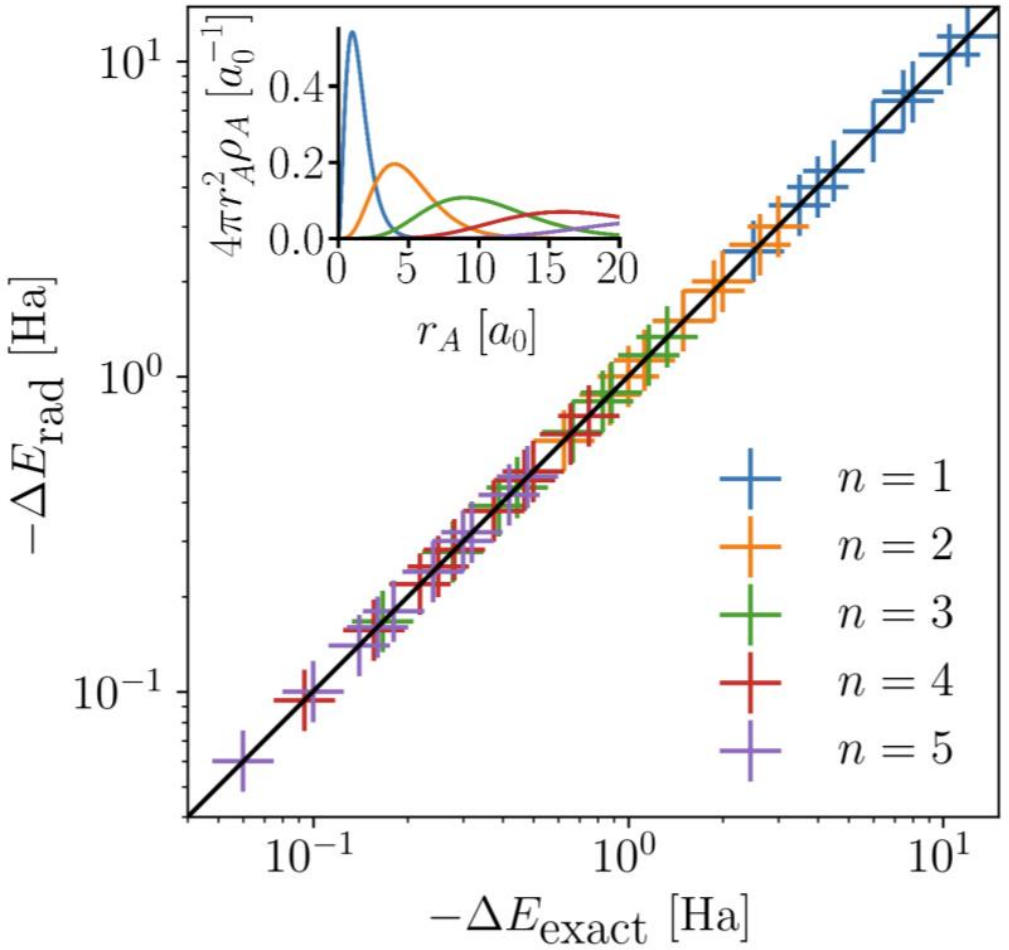
Ugly, but analytical

Only one!

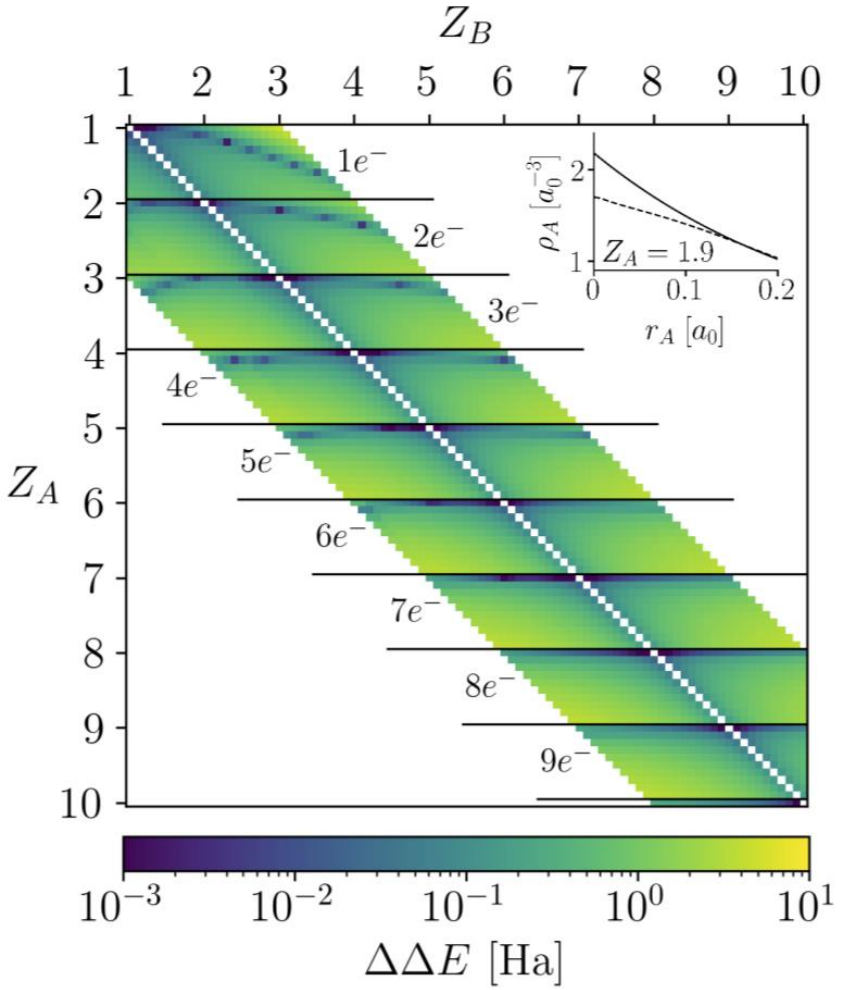
SL Krug, **GFvR**, O. A. von Lilienfeld, *arXiv, 2203.13794,* **2022.**

Alchemical Integral Transform

Hydrogen-like atom



Multi-electron atom



SL Krug, **GFvR**, O. A. von Lilienfeld, *arXiv, 2203.13794,* **2022.**

Limitations

Both energy and density derivatives are hard

- Finite differences — expensive, numerical instabilities
- Hellmann-Feynman — finite order, basis set inaccurate
- Coupled-perturbed — finite order, tedious
- Conceptual DFT — memory hungry, no post-HF
- Automatic differentiation — niche: DiffiQult, quax, dqc, …

ferchault/APDFT ferchault/APHF

aspuru-guzik-group/DiffiQult

CCQC/Quax

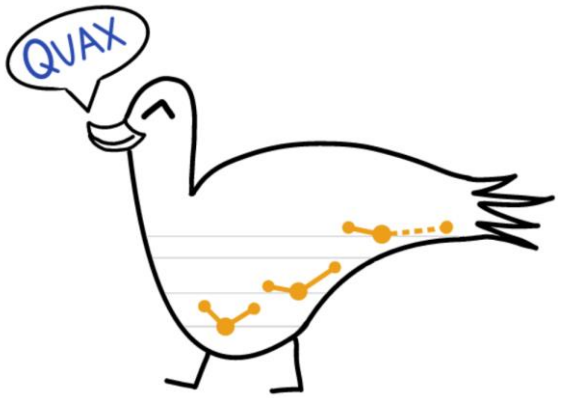
diffqc/dqc Alchemy!

Gaussian basis sets not overly cooperative

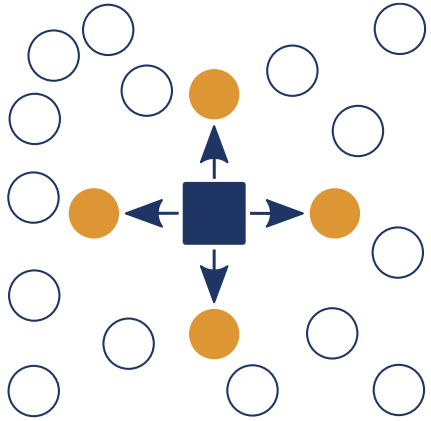
- Elements are discrete, derivatives are not
- Density converges more slowly with basis set quality than energy: Problem for APDFT and AIT
- Unless complete basis set limit: Pulay terms

Convergence

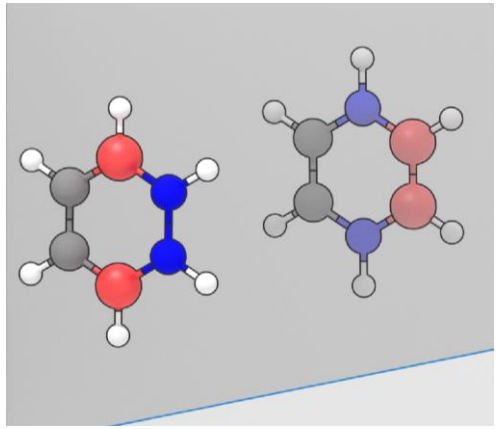
- Finite radius
- Not all systems are made equally



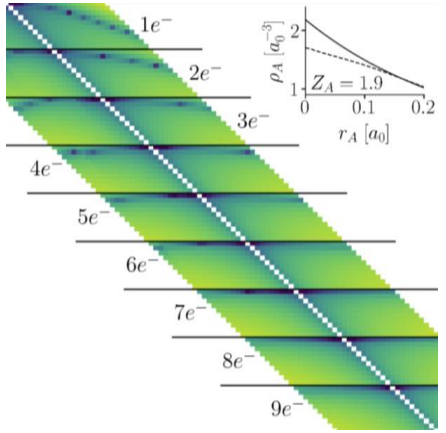
Summary



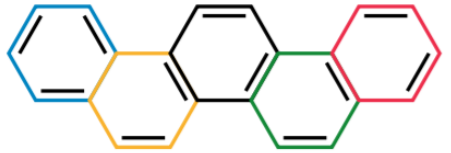
Quantum Alchemy yields systematically improvable results.



Closed expressions reveal structure of chemical space.



Efficient ways to obtain derivatives in progress.



x 414 M

Combinatorial scaling with size of system.

Quantum Alchemy | Phys. Rev. Res. 2020, 2, 023220.
Convergence | J. Chem. Phys. 2021, 155(22), 224103.
Alchemical Chirality | Sci. Adv. 2021, 7, eabf1173.
Integral Transform | arXiv 2022, 2203.13794.

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Theory

$$\Delta E_{ij}^{\mathrm{ele}} = E_0 - E_0 + \int_\Omega d\mathbf{r} \sum_{n=0}^{\infty} \frac{\Delta v_i}{(n+1)!} \left[\frac{\partial^n \rho}{\partial \lambda_i^n} + \frac{\partial^n \rho}{\partial \lambda_j^n} \right]$$

$$\Delta E_{(0)}^{\mathrm{ele}} = E_0 - E_0 = 0$$

$$\Delta E_{(1)}^{\mathrm{ele}} = 2 \int_\Omega \Delta v \rho = \int_\Omega e \cdot o = 0$$

$$\Delta E_{(2)}^{\mathrm{ele}} = \int_\Omega \Delta v \left[\frac{\partial \rho}{\partial \lambda_i} + \frac{\partial \rho}{\partial \lambda_j} \right]$$

$$= \int_\Omega \Delta v \left[\sum_I \frac{\partial \rho}{\partial Z_I} \frac{\partial Z_I}{\partial \lambda_i} + \frac{\partial \rho}{\partial Z_I} \frac{\partial Z_I}{\partial \lambda_j} \right] = 0$$

GFvR, O. A. von Lilienfeld, *Science Adv.* **2021.**