GDB-9 & Small Molecule Universes

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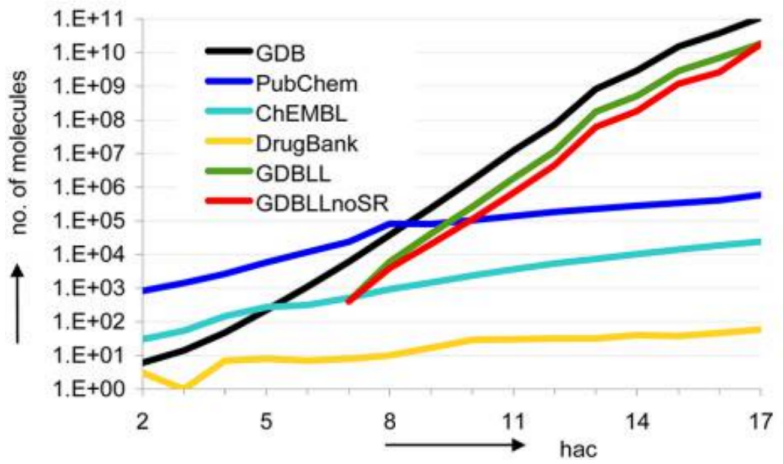
1. GDB-9 dataset
2. Small Ligand Universe
   - General
   - Reduction Rules
   - SLU Analysis
3. Assembly of complexes
   - General

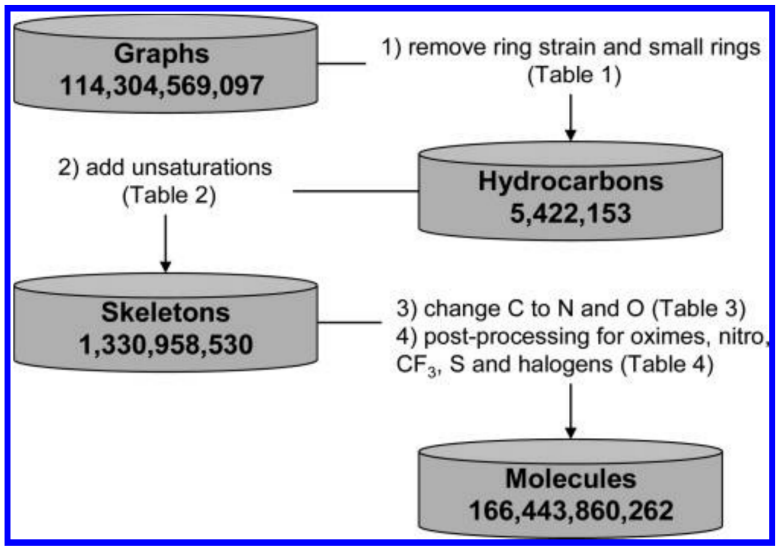
GDB-17

- Up to 17 atoms with CNOS and halogens
- Results in 166 billion molecules
- Contains more nonaromatic heterocycles, quarternary centers, stereoisomers than PubChem



GDB-17

- H4: C15 & C16 graphs are allowed max one 3- or 4-membered ring.
- S1: No allenes (C=C=C).
- F2: Maximum one N or O in small rings.
- P4: No aliphatic thiols or thioethers.



Examples of up to 4 atoms

1: C, N, O
2: C#C, C#N, C=O, CC, CO
3: CC#C, CC#N, CC=O, NC=O, CCC, CCO, COC
4: C1CC1, C1CO1, CC(=O)C, CC(=O)N, NC(=O)N, CC(C)C, CC(C)O, C(#C)C#C, C(#C)C#N, N#CC#N, O=CC#C, O=CC#N, O=CC=O, CC#CC, CCC#C, CCC#N, NCC#N, OCC#C, OCC#N, CCC=O, CNC=O, COC=O, OCC=O, CCCC, CCCO, CCOC, OCCO

GDB-9 and QM-9

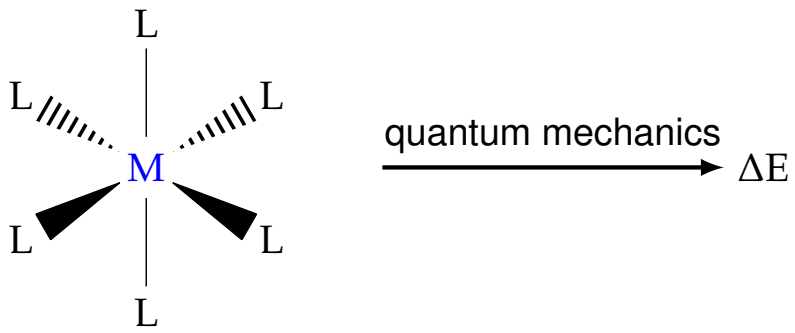
- 134,000 molecules up to 9 CHNOF atoms from GDB-17
- Minimum energies, harmonic frequencies, dipole moments, polarizabilities, enthalpies, free energies of atomization
- B3LYP/6-31G(2df,p)

Small Ligand Universe: Motivation

- GDB-9 analogon for inorganic chemistry (less restrictive)
- First and second shell complexes are representative
- Establish more informatics for inorganic chemistry

Scaling of different methods

Where do we find DLPNO?



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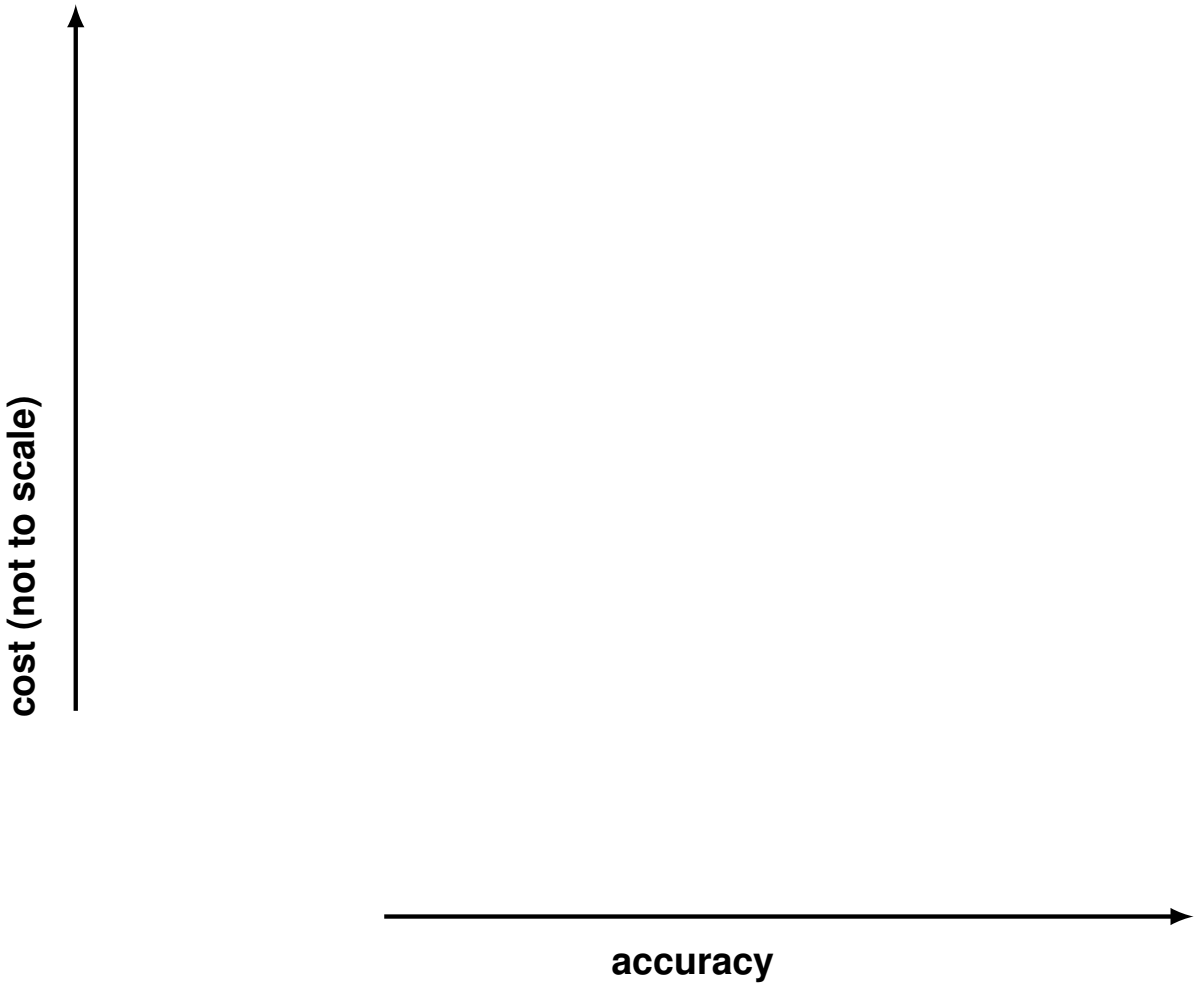

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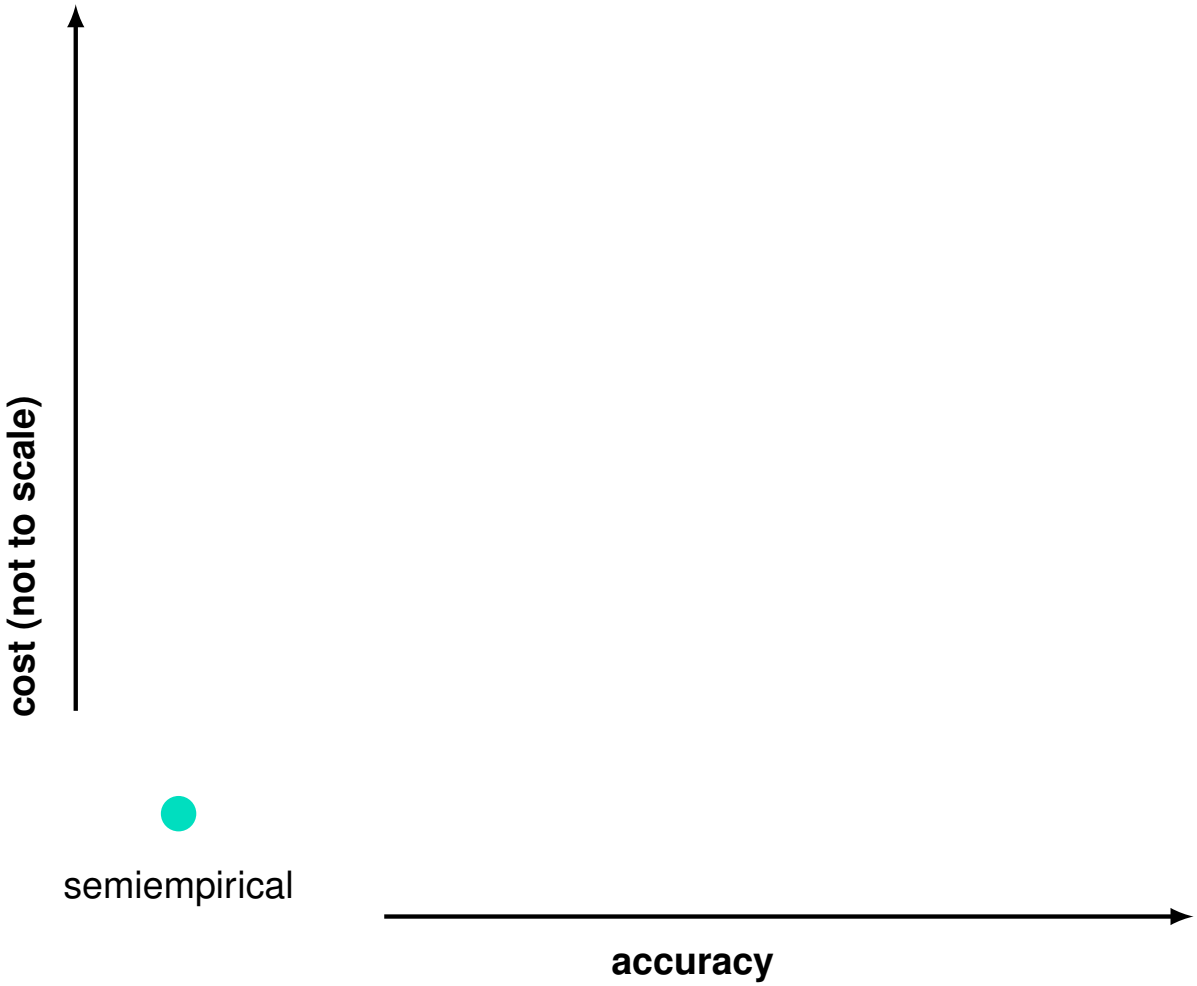

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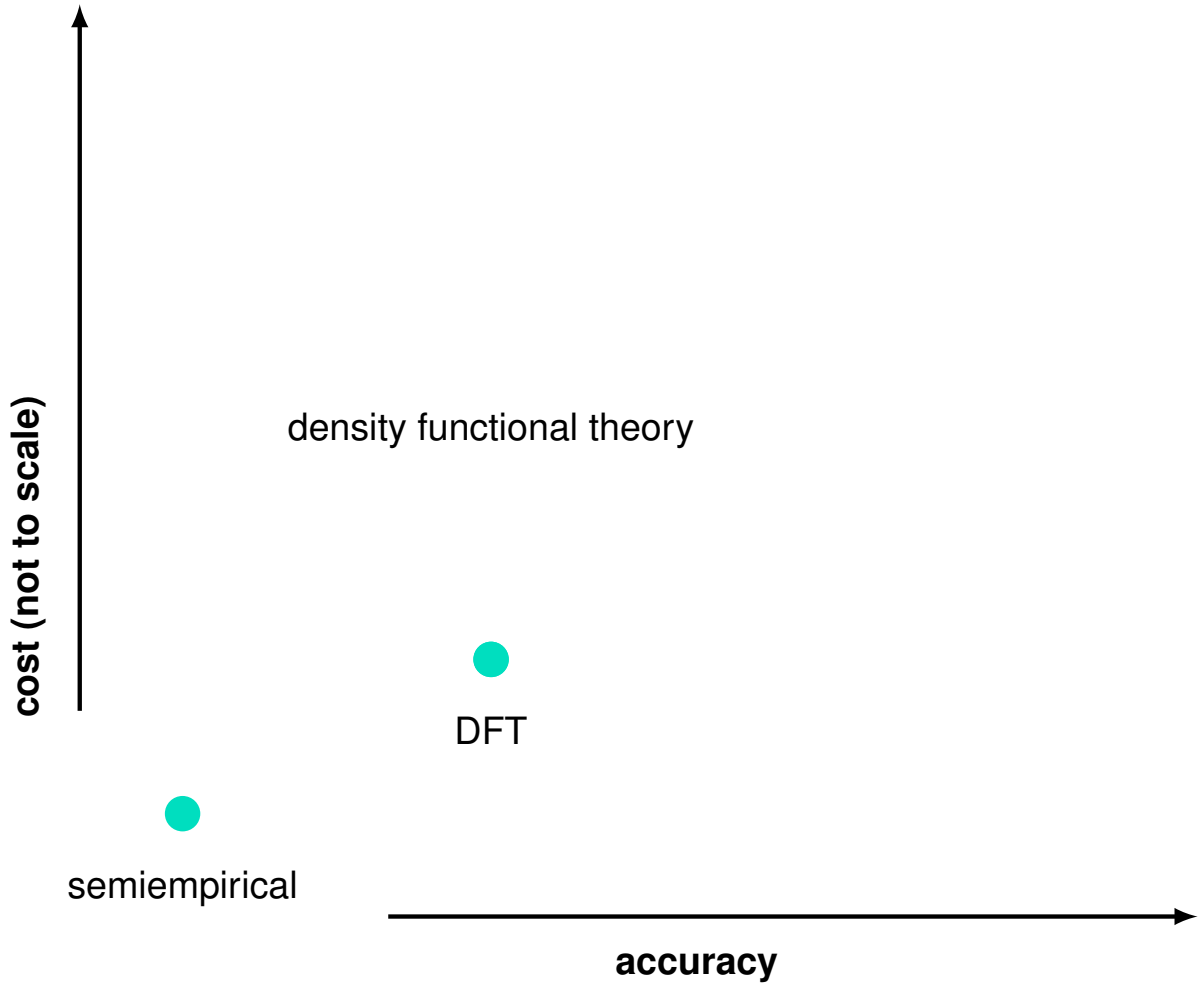

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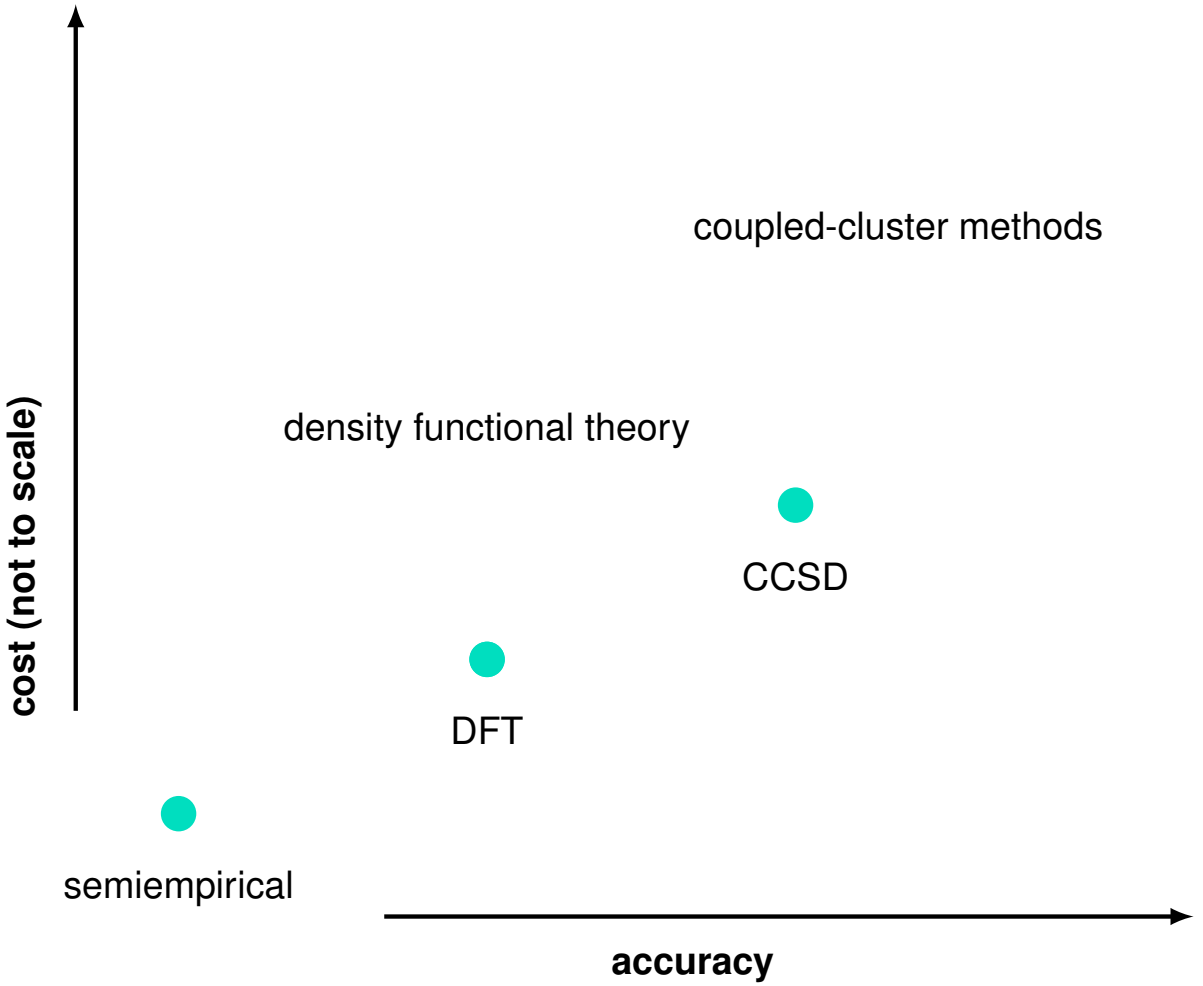

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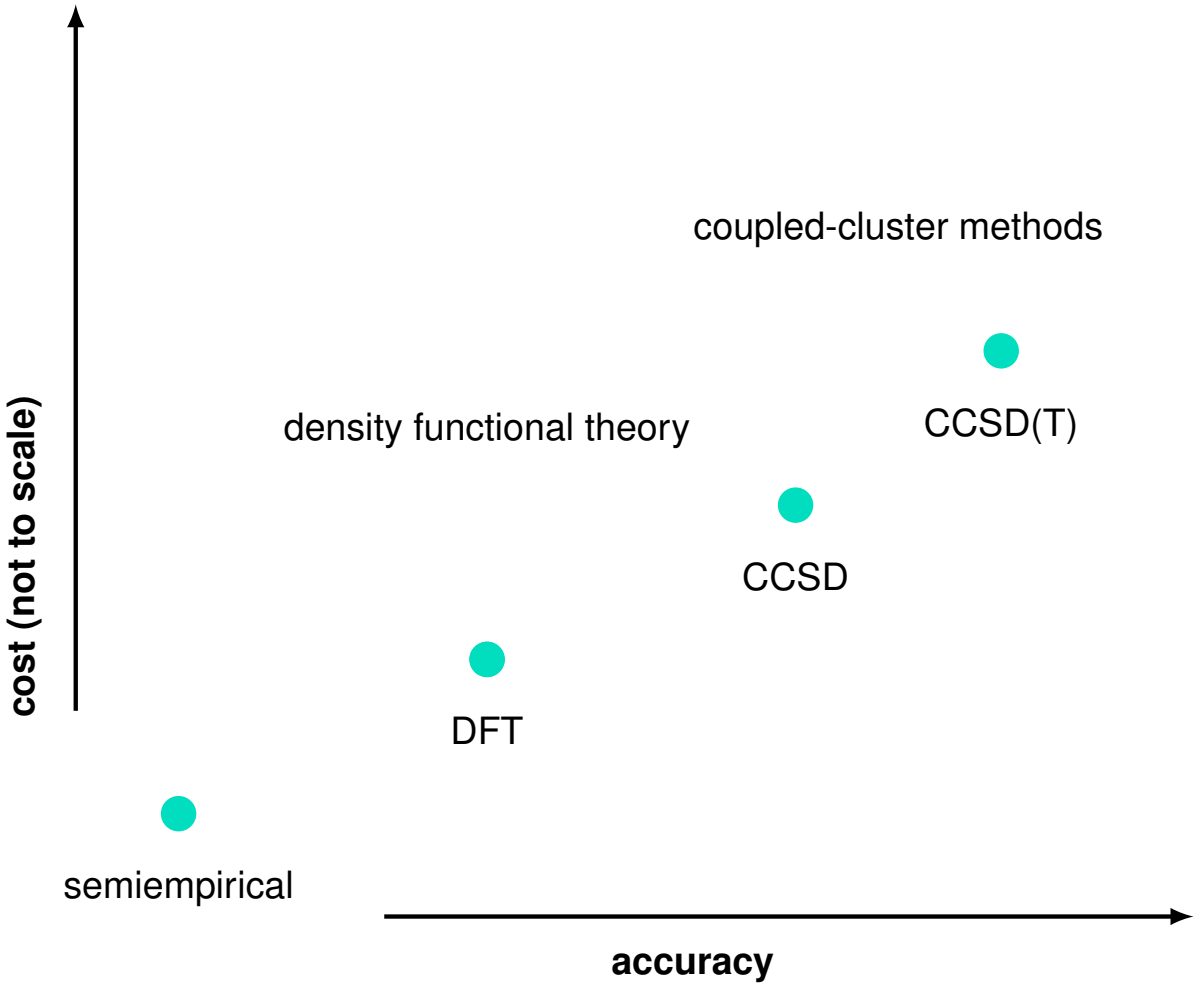

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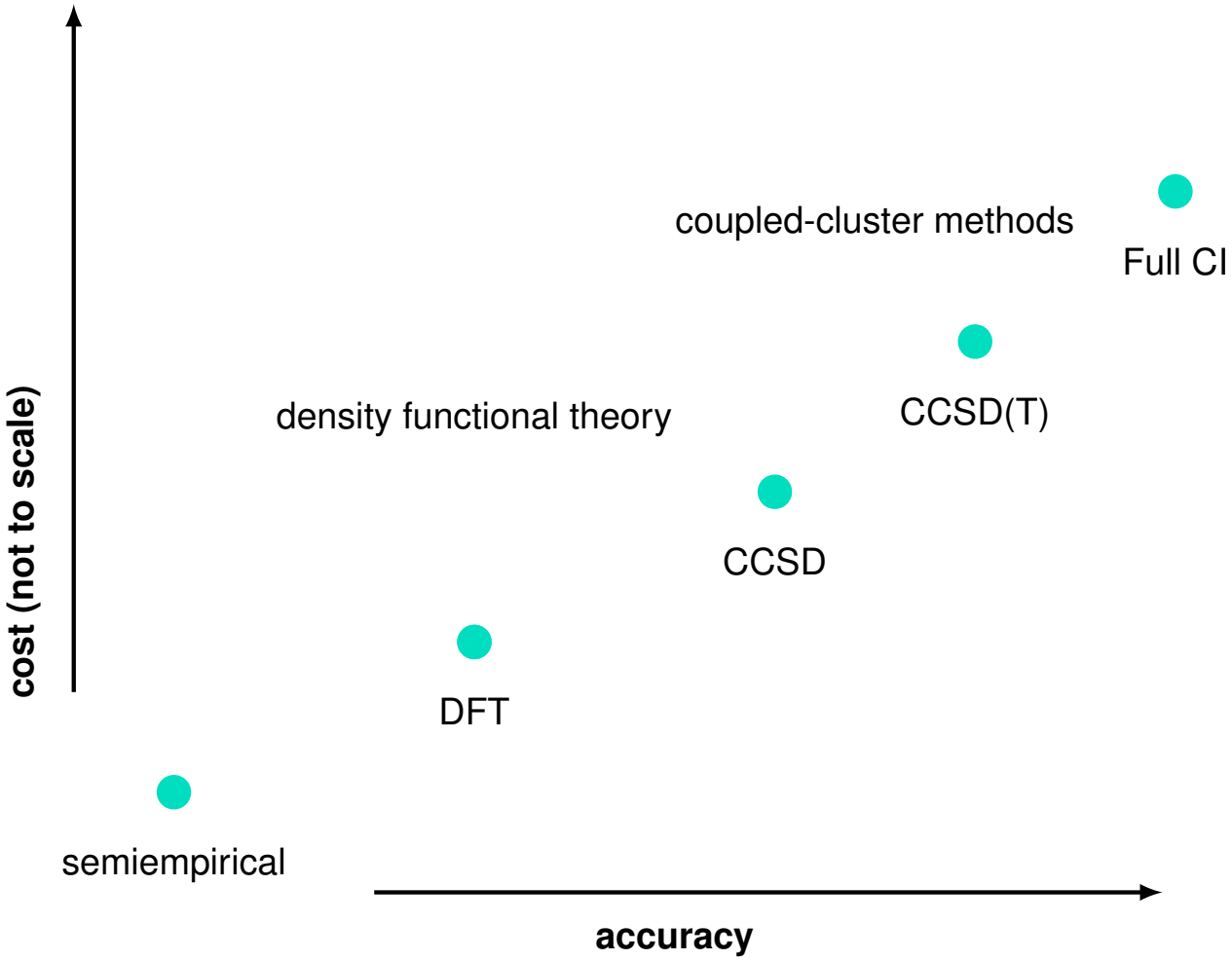

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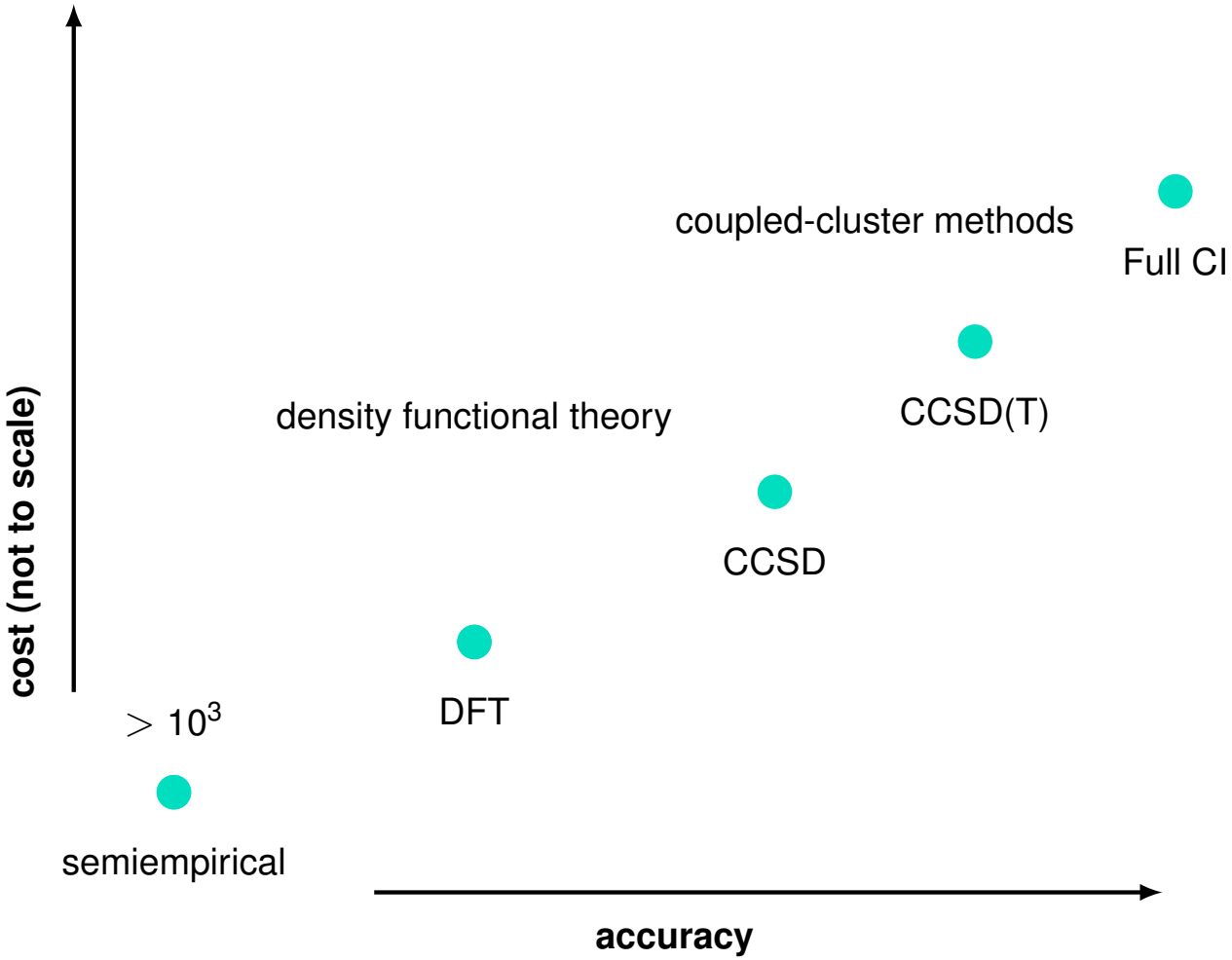

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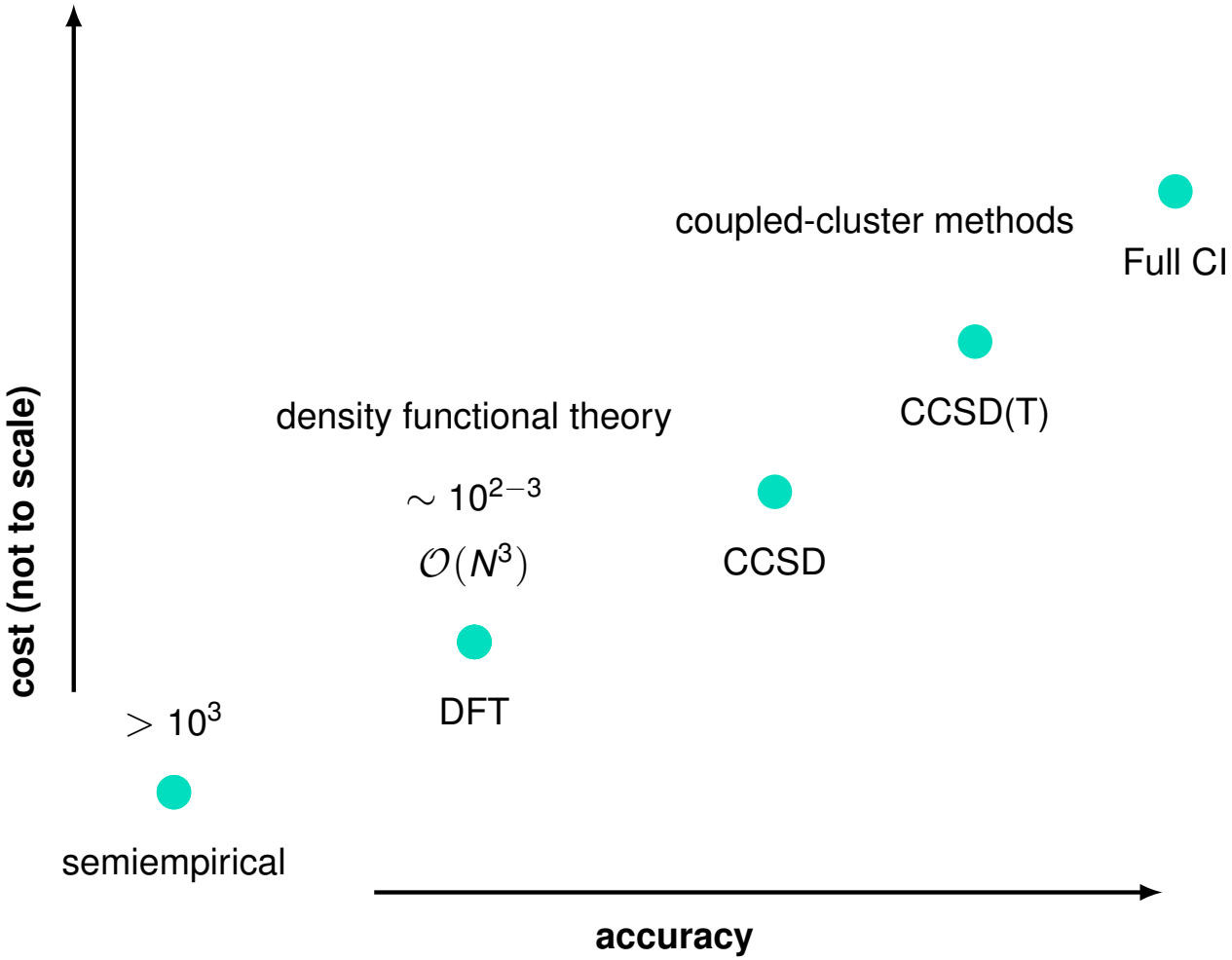

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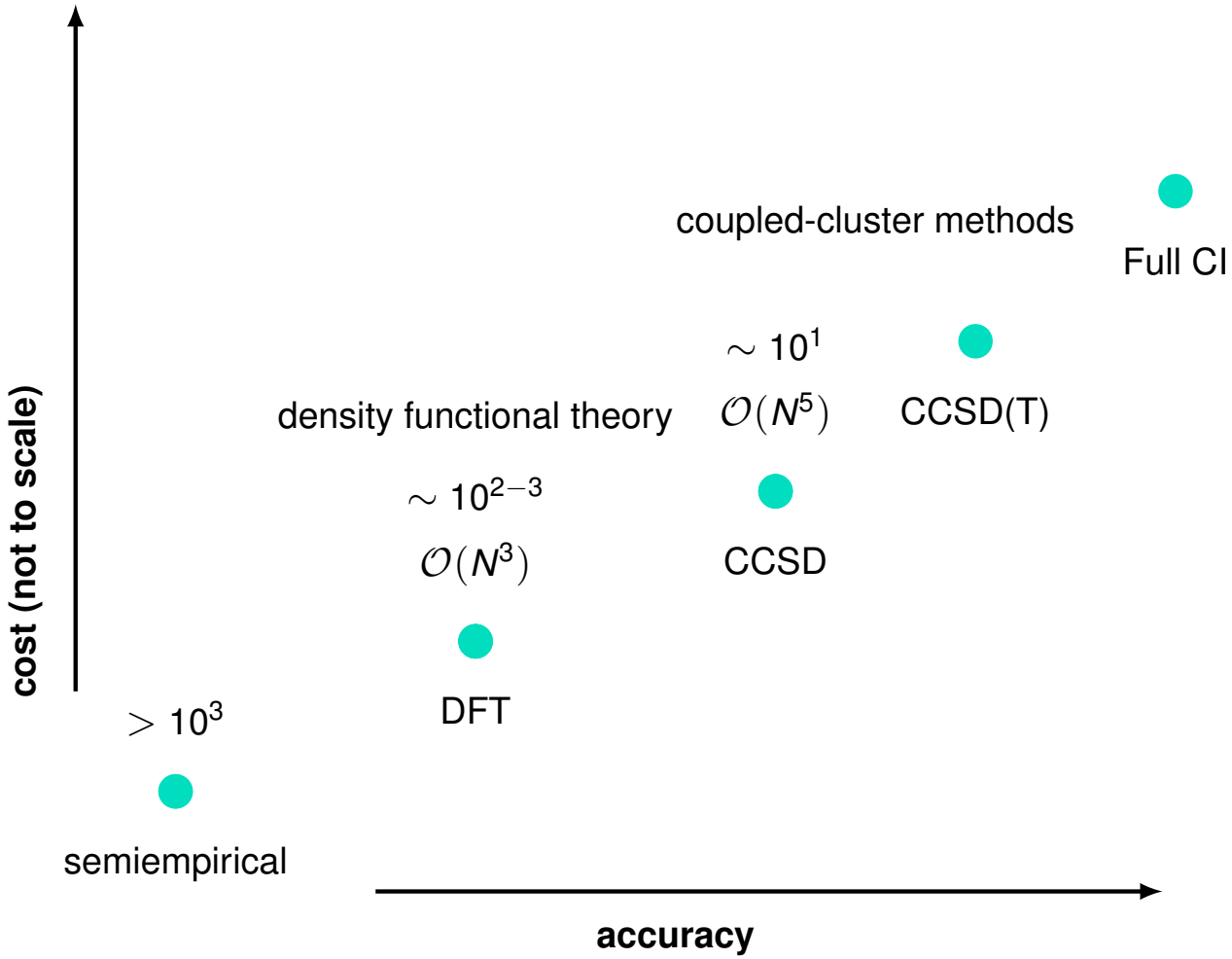

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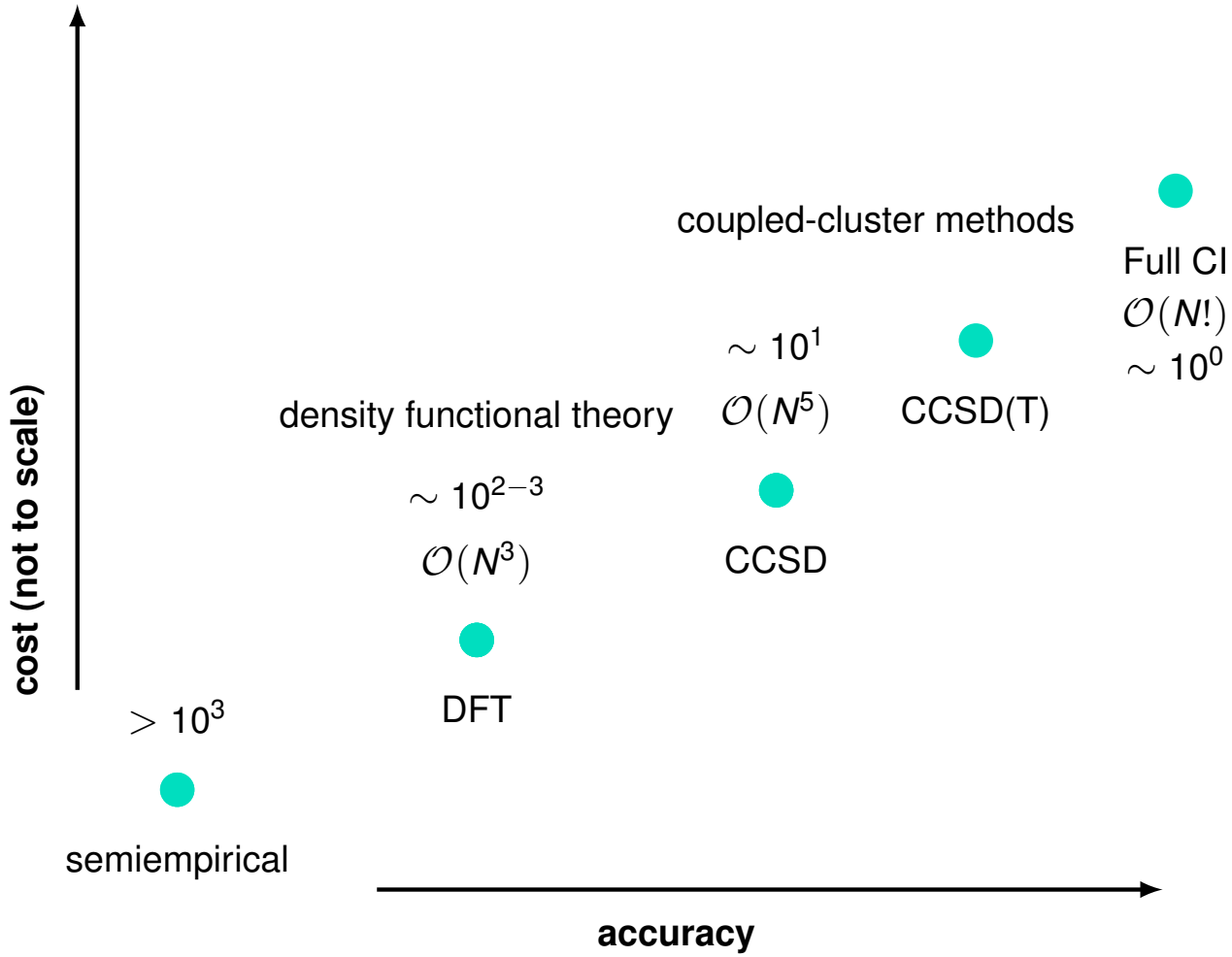
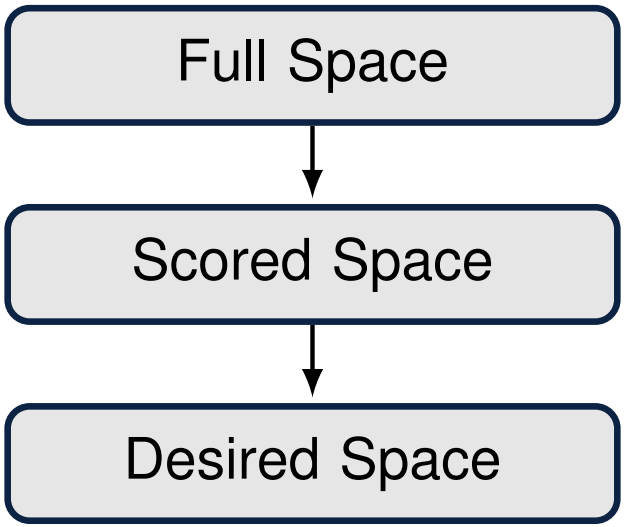


Procedure

1. Generate small ligand universe (SLU)
2. Assemble complexes with different symmetries from truncated SLU
3. Analysis of symmetry classes

Reduction of the full space



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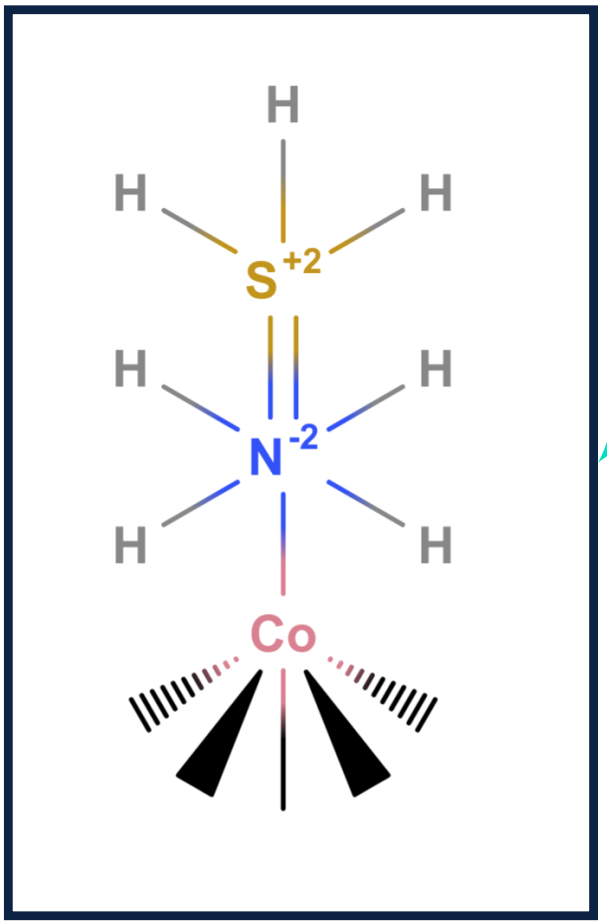

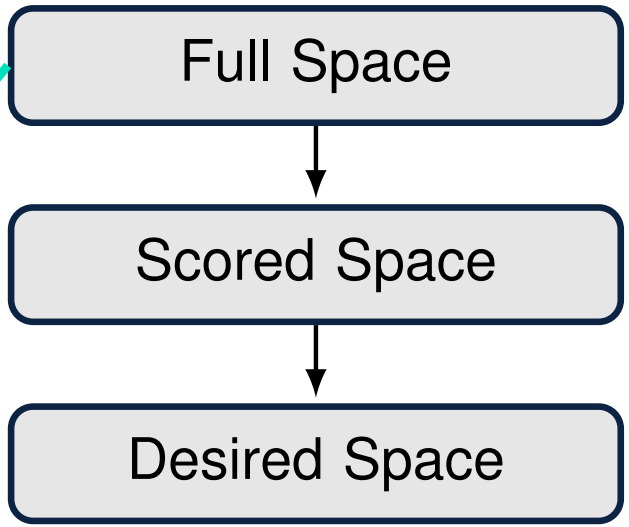

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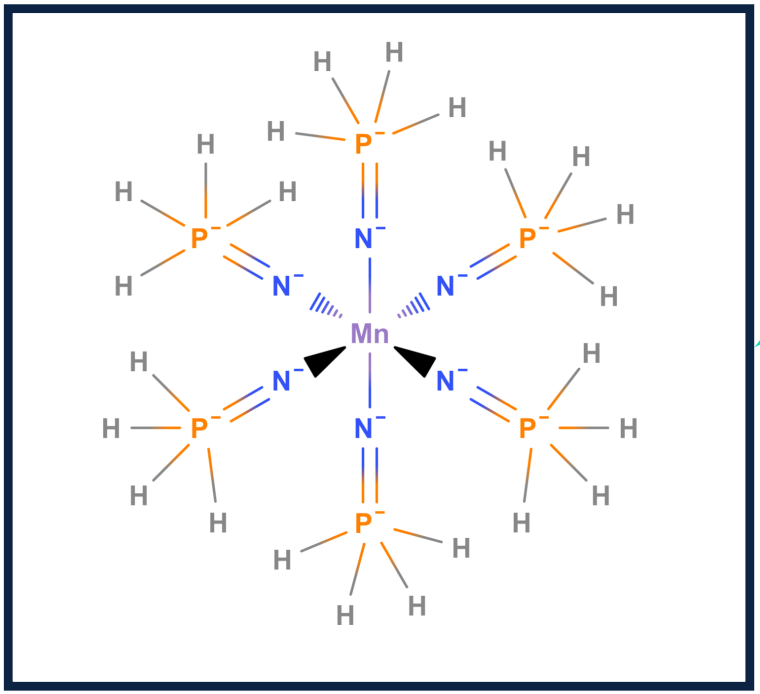

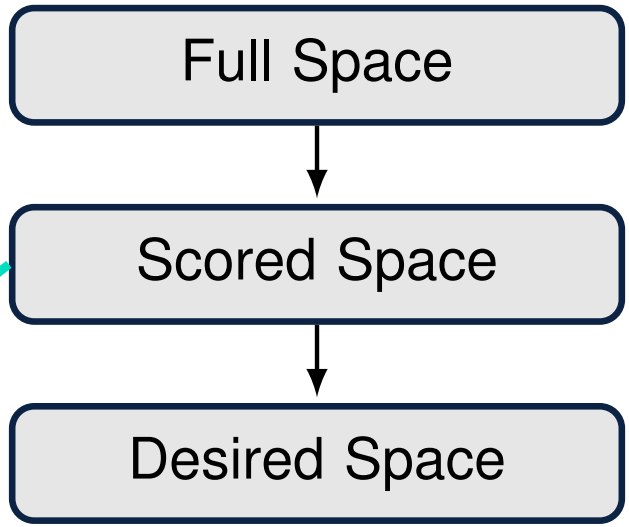

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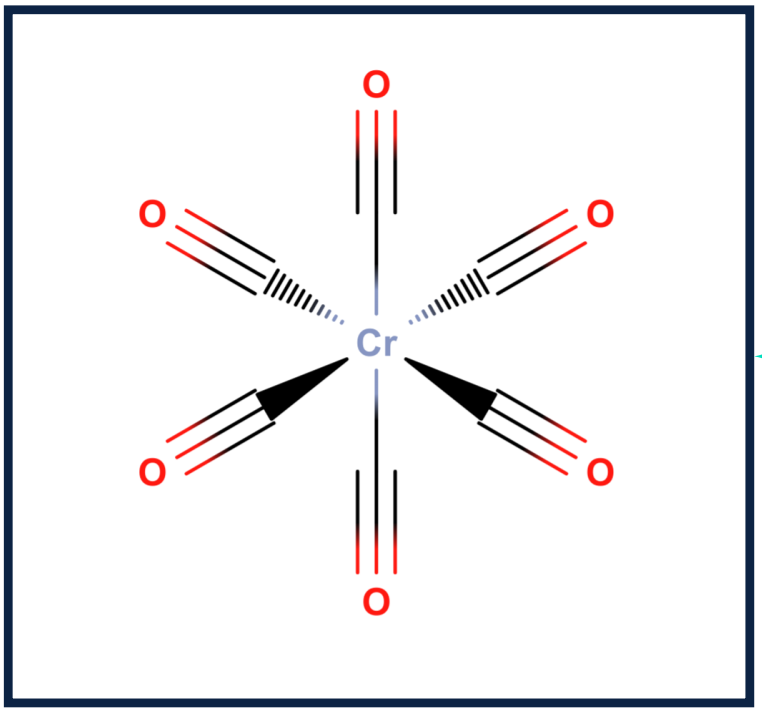


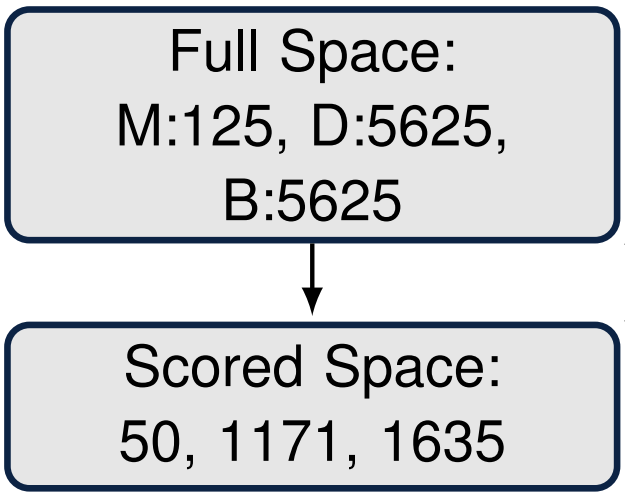
Full Space

Scored Space

Desired Space

Full Space $\rightarrow$ Scored Space

- charge $\in [-2, +2]$
- H atoms $\in [0, 4]$
- element $\in \{\mathrm{C}, \mathrm{N}, \mathrm{O}, \mathrm{P}, \mathrm{S}\}$



} charge, sterics, octet, shell, bond order

These rules are demonstrated in the following for the di-heavy-atoms.

Rules to reduce Full Space $\rightarrow$ Scored Space

Constraints:

- Charge $c = c_1 + c_2 \leq 1$
- Sterics: H atoms < 4 on connecting atoms
- Closed shell (even number of electrons)

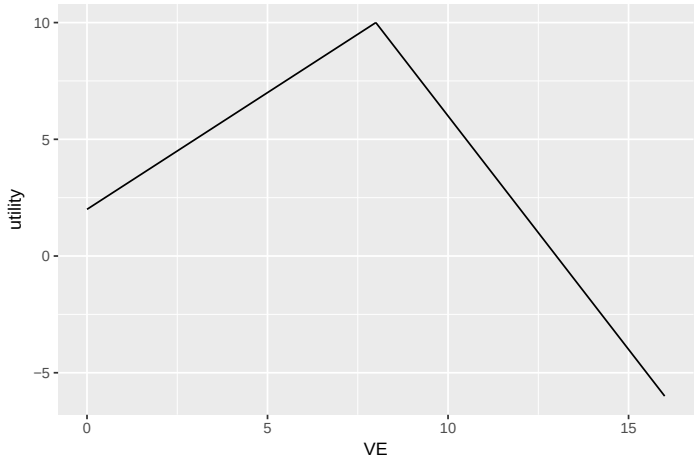
$\rightarrow$ Reduces 5625 ligands to 1171.

Octet Rule

Molecules that fulfill the octet rule are more stable.

$$u_{\text{octet,i}} = \begin{cases} 10 + 2 \cdot (8 - VE_i) & \text{if } 8 - VE_i < 0 \\ 10 - 1 \cdot (8 - VE_i) & \text{if } 8 - VE_i \geq 0 \end{cases} \tag{1}$$

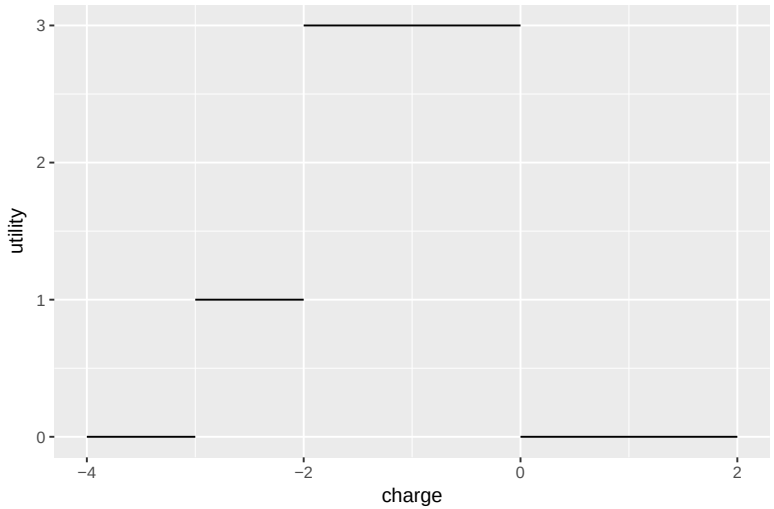
$$u_{\text{octet}} = \frac{1}{2} \sum_{i}^{2} u_{\text{octet,1}} + u_{\text{octet,2}} \tag{2}$$



Charge Constraints

We reward only mildly negatively charged compounds.

$$u_{\text{charge}} = \begin{cases} 0 & \text{if } c_1 + c_2 > 0 \\ 3 & \text{if } 0 \geq c_1 + c_2 \geq -2 \\ 1 & \text{if } c_1 + c_2 = -3 \\ 0 & \text{if } c_1 + c_2 = -4 \end{cases} \tag{3}$$



VSEPR Constraints

If two atoms have the same amount of bond ready electrons, they are more stable.

$$u_{\text{VSEPR}} = 5 - \underset{i}{\text{Diff}} \left(VE_i - 2 \cdot LP_i + c_i - 2 \cdot h_i \right) \tag{4}$$

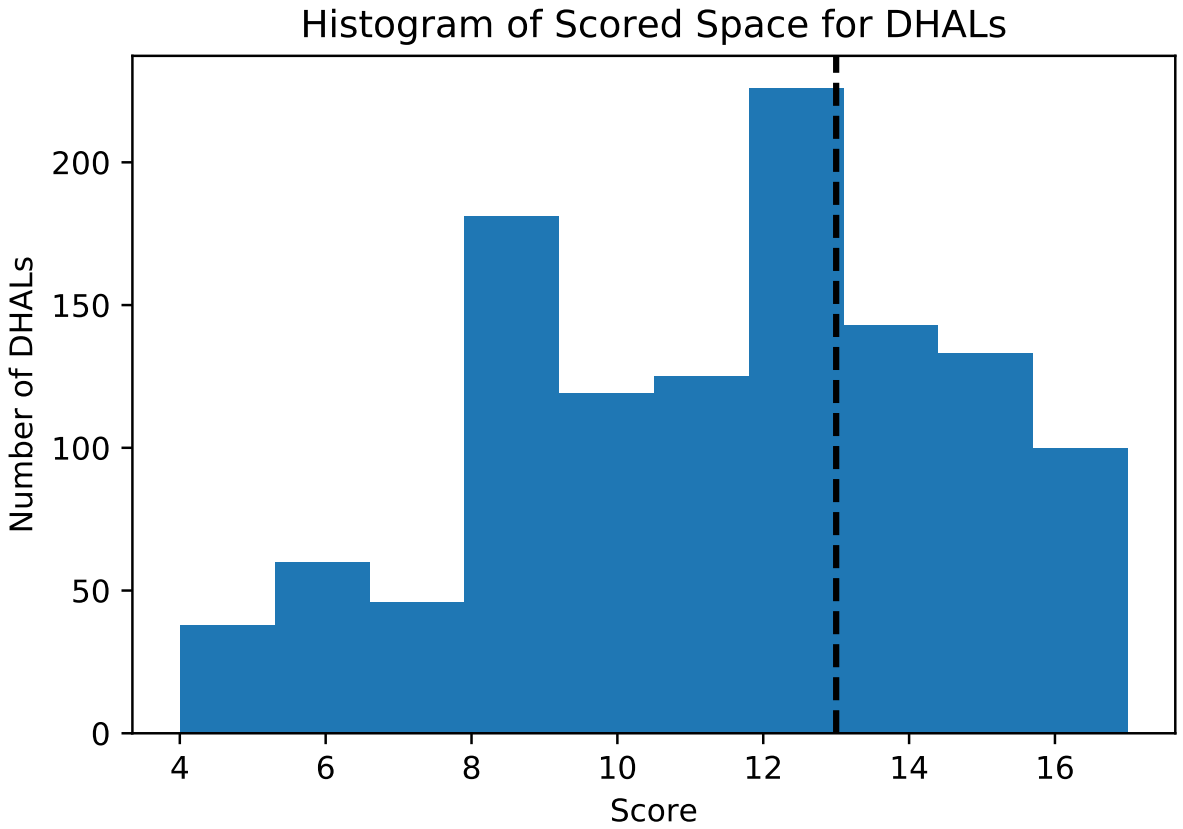
Sterics

All compounds with more than three H atoms on the connecting atom will be sterically hindered.

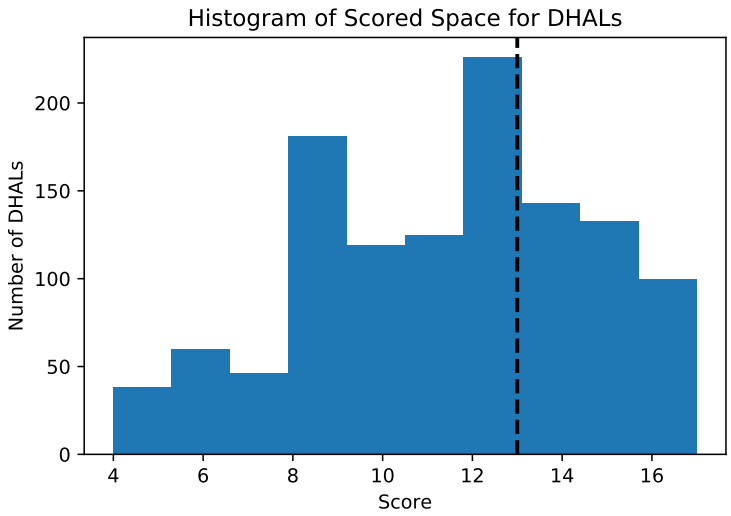
$$u_{\mathrm{CA}} = \begin{cases} 2 & \text{if } h_1 = 3 \\ 3 & \text{if } h_1 < 3 \end{cases} \tag{5}$$

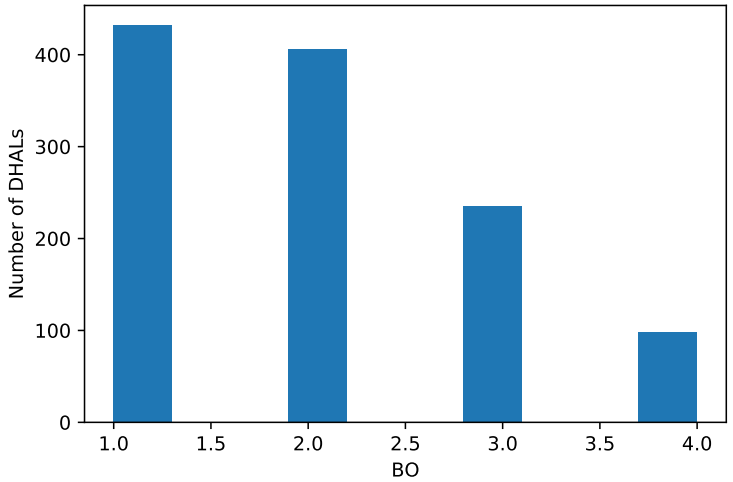
Global utility function

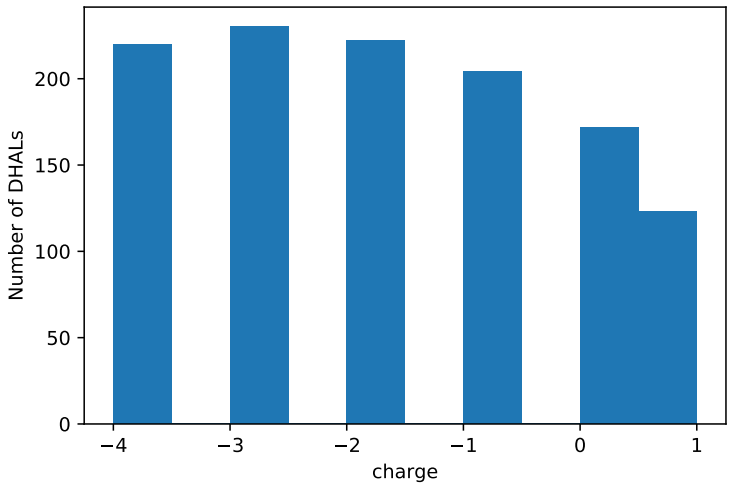
$$u_{\text{total}} = u_{\text{octet}} + u_{\text{charge}} + u_{\text{VSEPR}} + u_{\text{CA}} \tag{6}$$

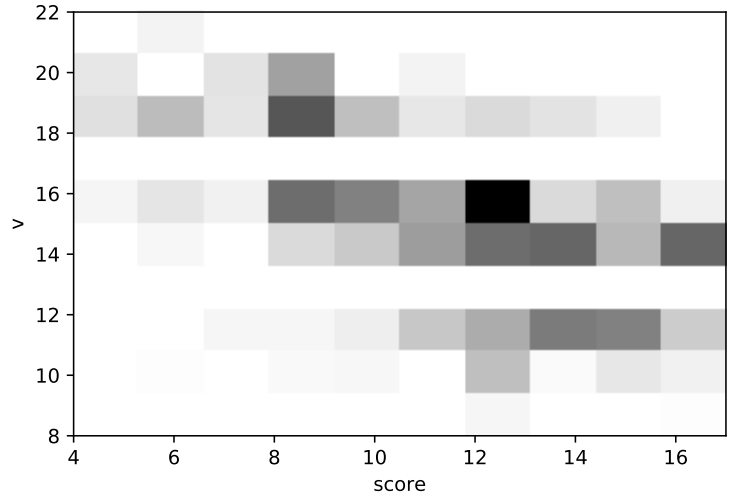


Analysis: Score, bond order, charge, valence electrons









Recover spectrochemical series

Spectrochemical series is recovered in the top scores.

Ligand	Score
[C]#[N-]	14
[C+]#[O-]	15
[N-]#[C]	15
[N+]=[O]	13
[O-]#[O-]	14
[S-]#[S-]	14

$s = 15$ also contains species like [CH2-]#[CH], [OH-]=[NH], [NH2--]#[P].

Desired space = top scoring ligands

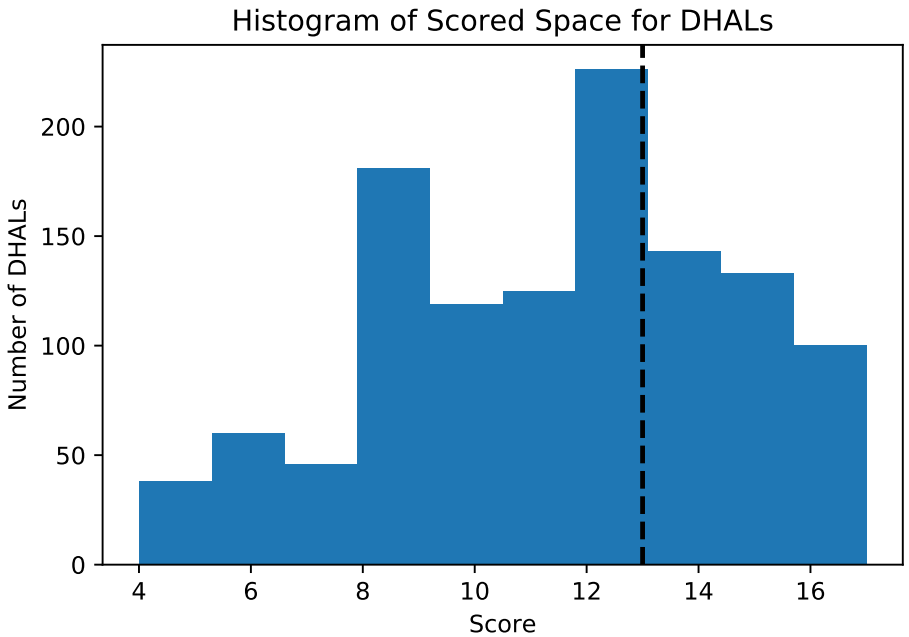
We include all ligands with a score at least as high as the lowest scoring spectrochemical series ligand ($s = 13$)

Scored Space:
50, 1171, 1635

↓

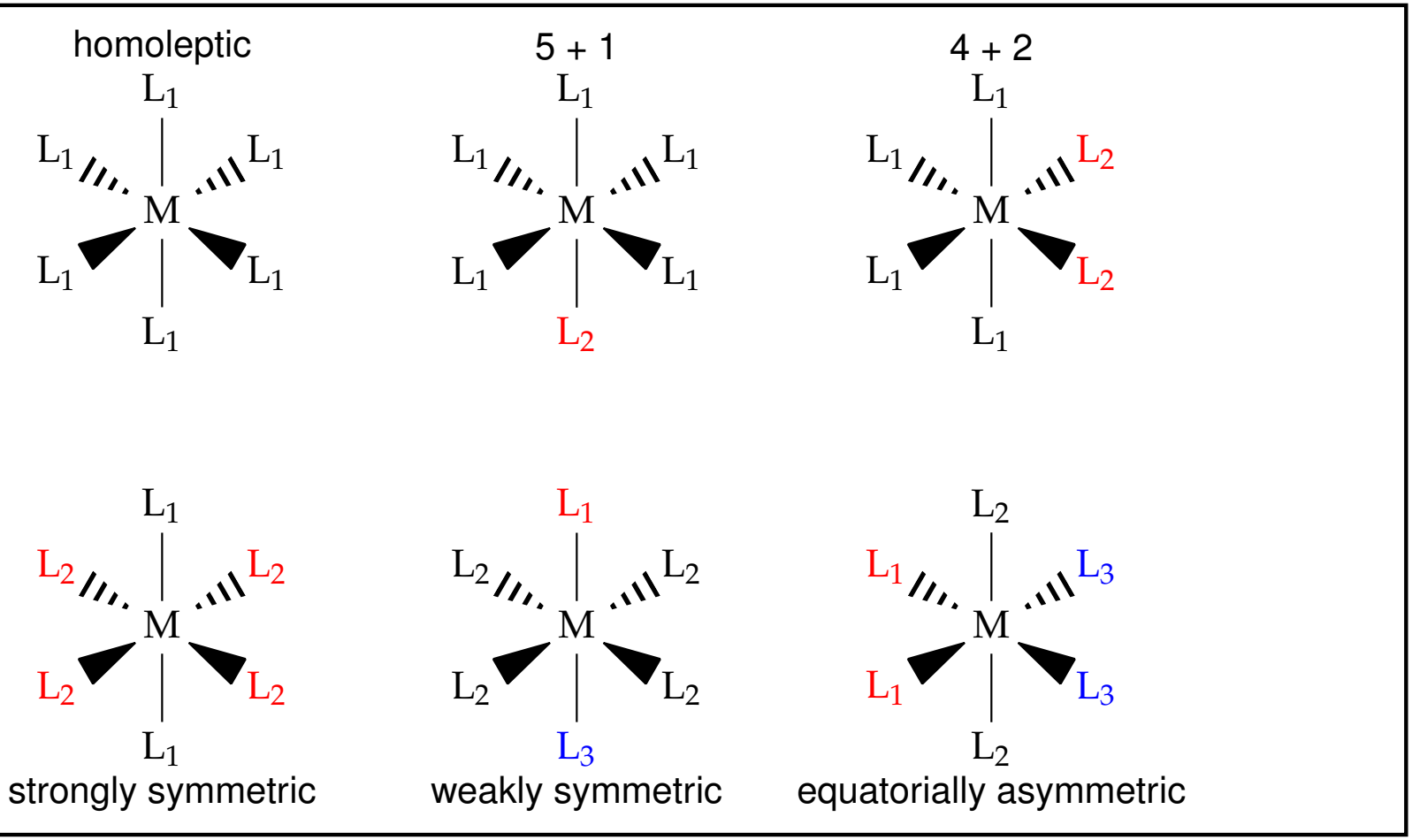
Desired Space:
29, 374, 148

} score $\geq s$



This gives us 553 ligands in total.

Overview of considered symmetry classes

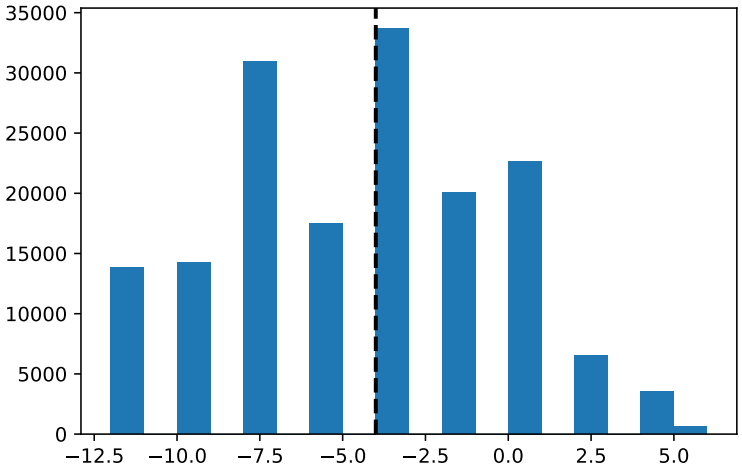


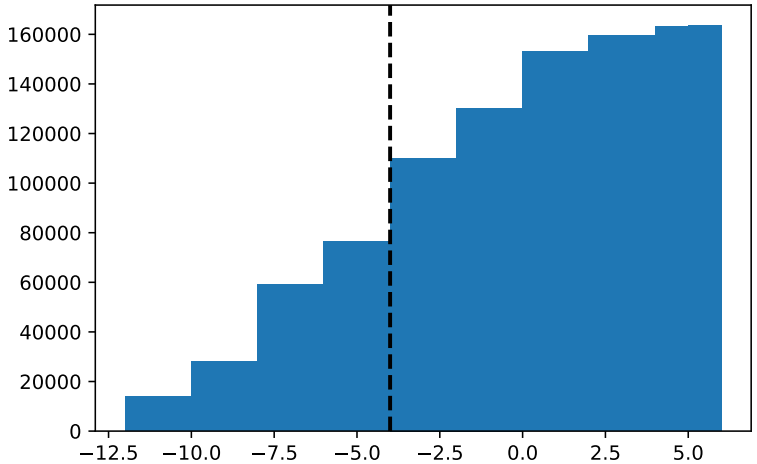
Subsets of octahedral space

Set	description	size
Homoleptics	eq = ax	553
”5+1” symmetric	eq = ax1 $\neq$ ax2	163,620
”4+2” symmetric	eq1 $\neq$ eq2 = ax	185,376
Strongly symmetric	eq $\neq$ ax	245,316
Equatorially asymmetric	eq1 $\neq$ eq2 $\neq$ ax	15,924,796
Weakly symmetric	eq $\neq$ ax1 $\neq$ ax2	45,077,310
Complete Heteroleptics	$L_i \neq L_j$	$\approx 5.9 \cdot 10^{12}$
Octahedral Space	all	$> 1.8 \cdot 10^{14}$

Properties of the sets

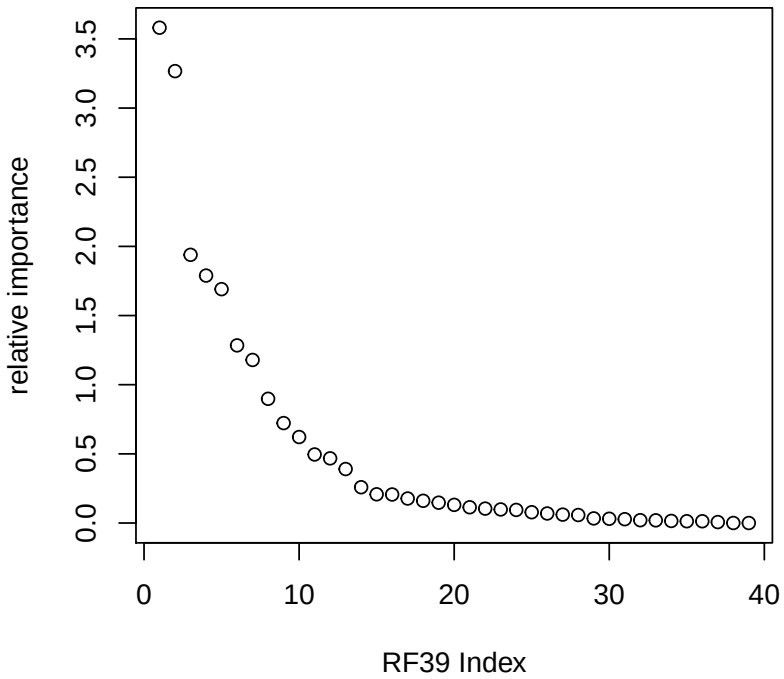
- Reduce space to facilitate sampling from non-homoleptics
- Example: strongly symmetric, monodentate ligand fields (163,620)
- Exclude all with charge smaller than -4, which results in 87,150 ligand fields (53 %).

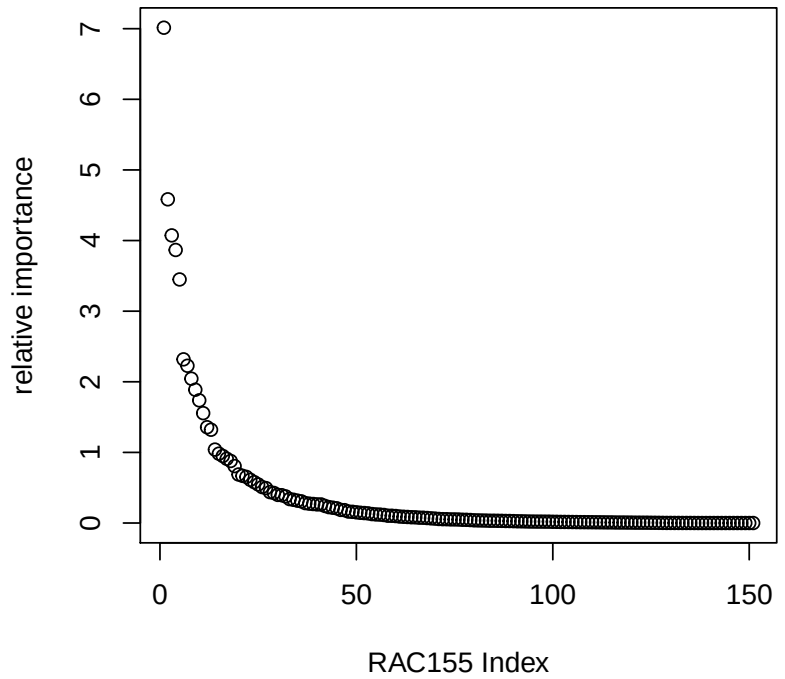




Principal Component Analysis

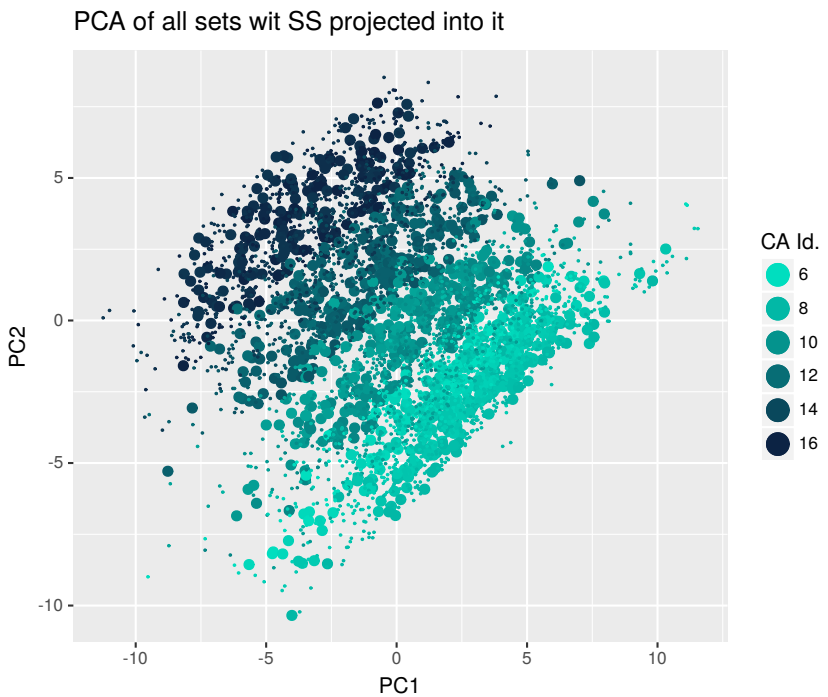
- Use RACs to characterize complexes (JP in JPCA 2017).
- PCA shows highest variance
- Compare eigendecay on RAC155 and RAC RF39.

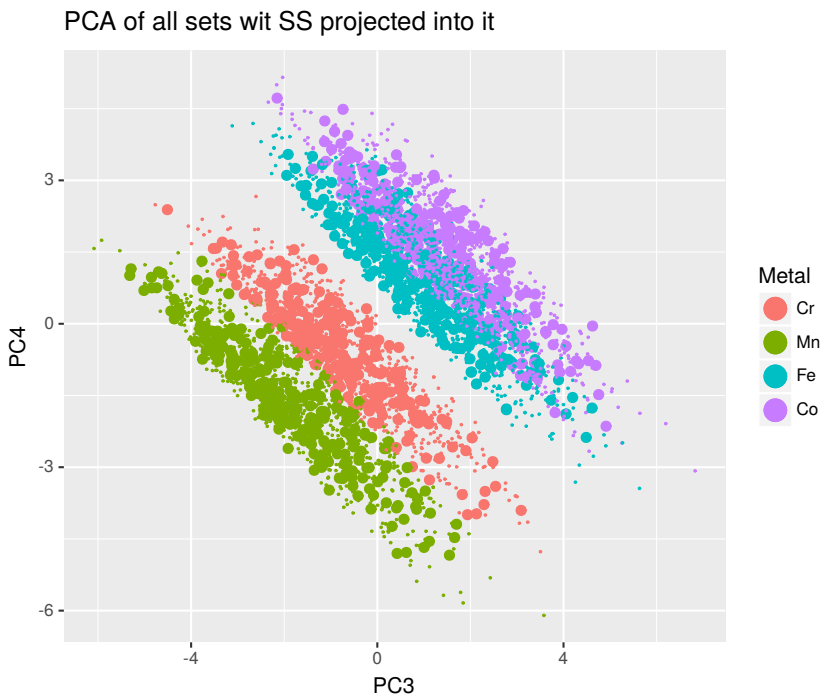




PCA: Strongly symmetric complexes

- Only RF39.
- Colored by connecting atom type (PC1 and PC2)
- Colored by metal type (PC3 and PC4)





PCA: Homoleptics span the space

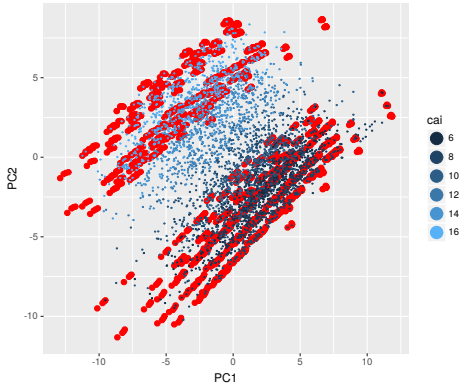


Figure : Homoleptics

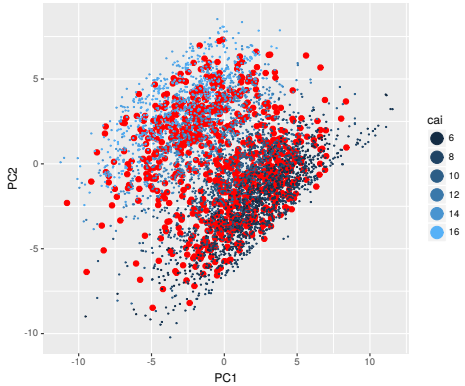


Figure : 5+1

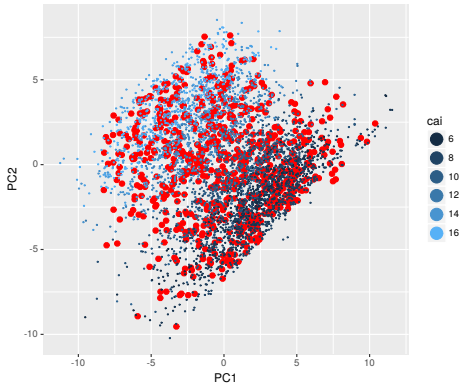


Figure : 4+2

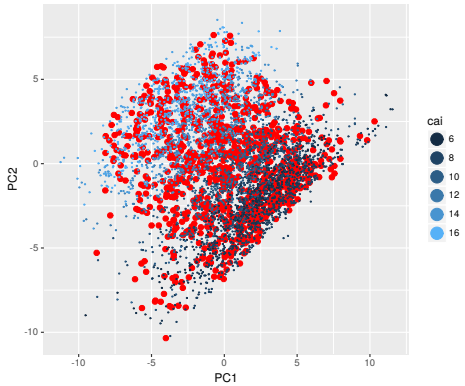


Figure : Strongly Symmetric

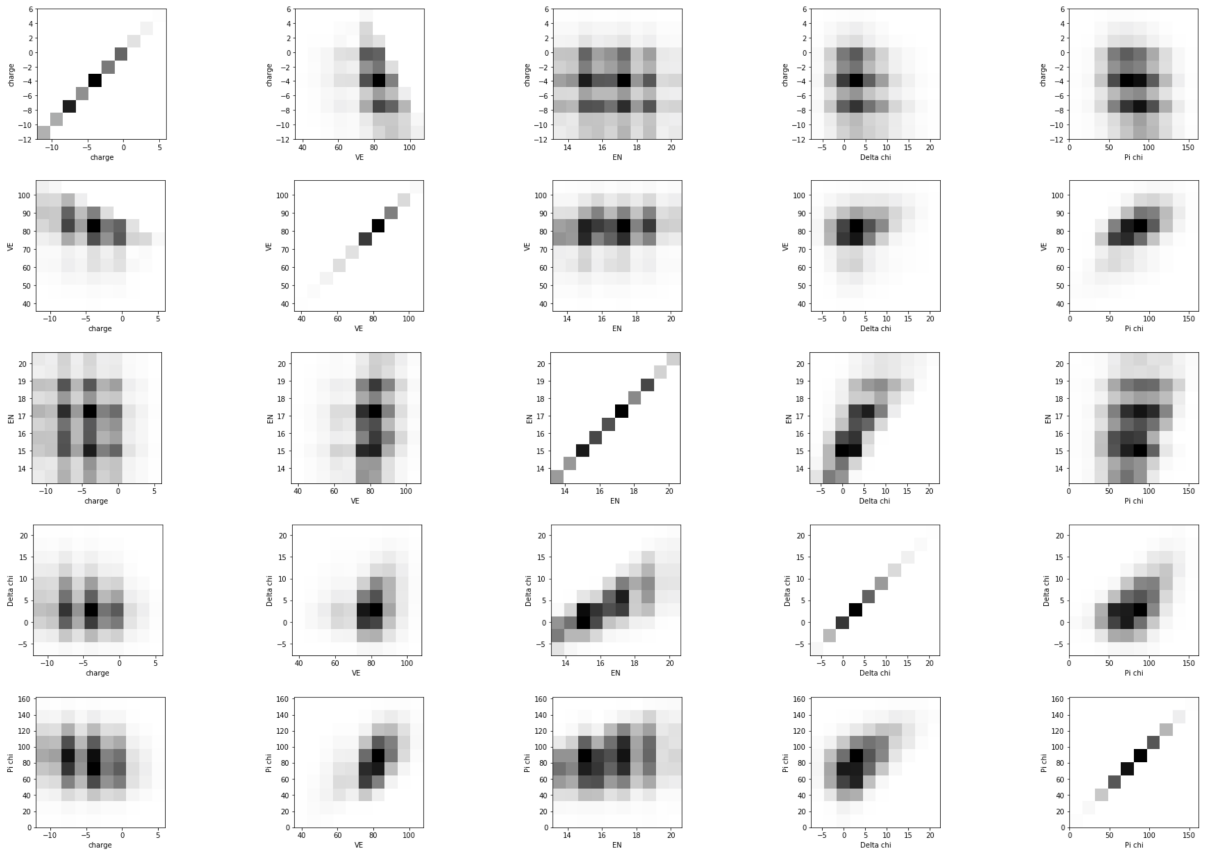
Footprint

We use five properties inspired by MCDL25 to characterize the ligand field and generate a five dimensional distribution:

- total charge
- total valence electrons
- electronegativity of the connecting atom
- ${}^{\mathrm{lc}}_{\mathrm{ax,eq}}\chi_1 = \sum EN_{\mathrm{CA}} \cdot EN_i$
- ${}^{\mathrm{lc}}_{\mathrm{ax,eq}}\chi'_1 = \sum EN_{\mathrm{CA}} - EN_i$

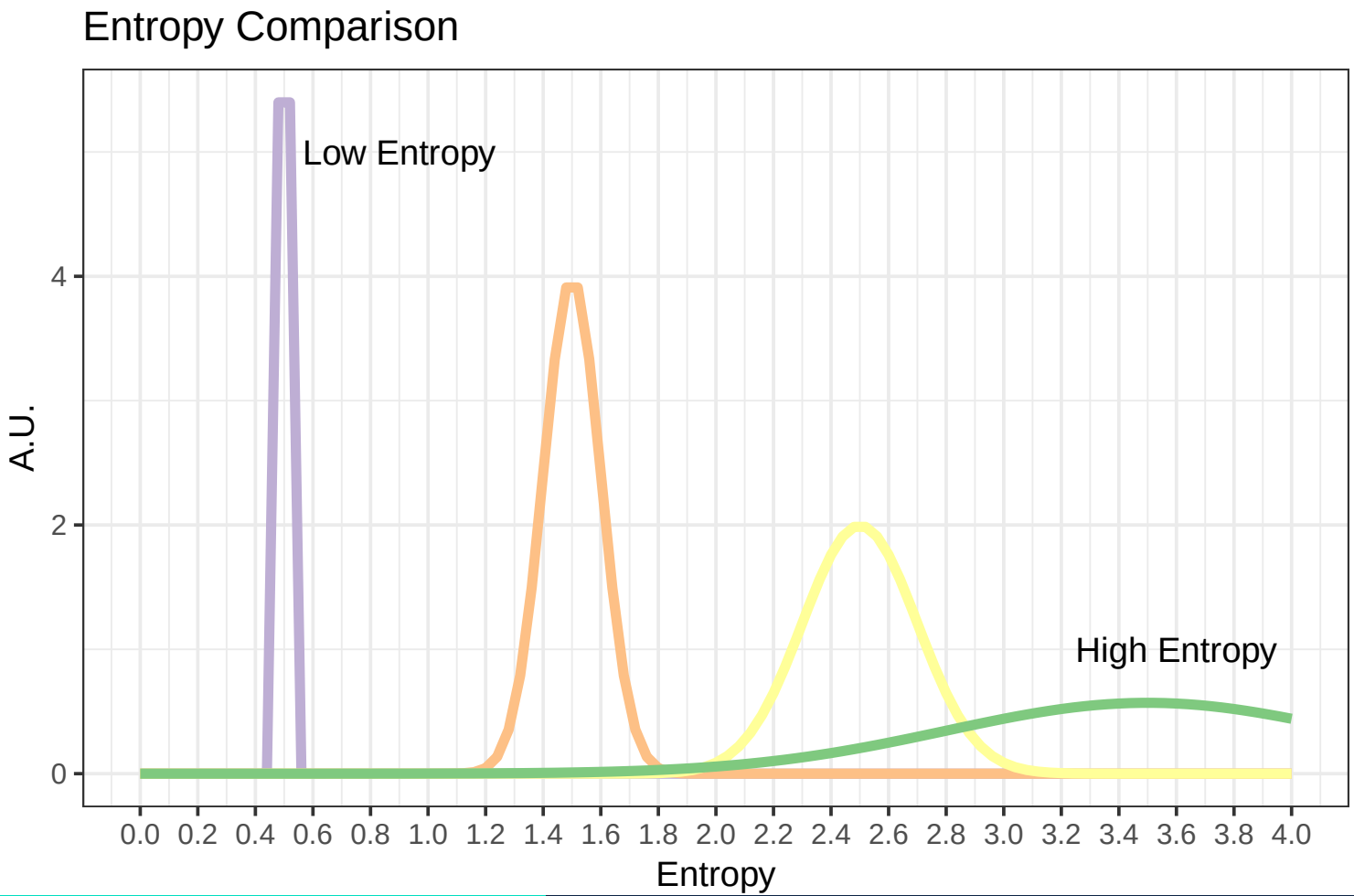
Correlations for strongly symmetric monodentates

The less peaky the better.



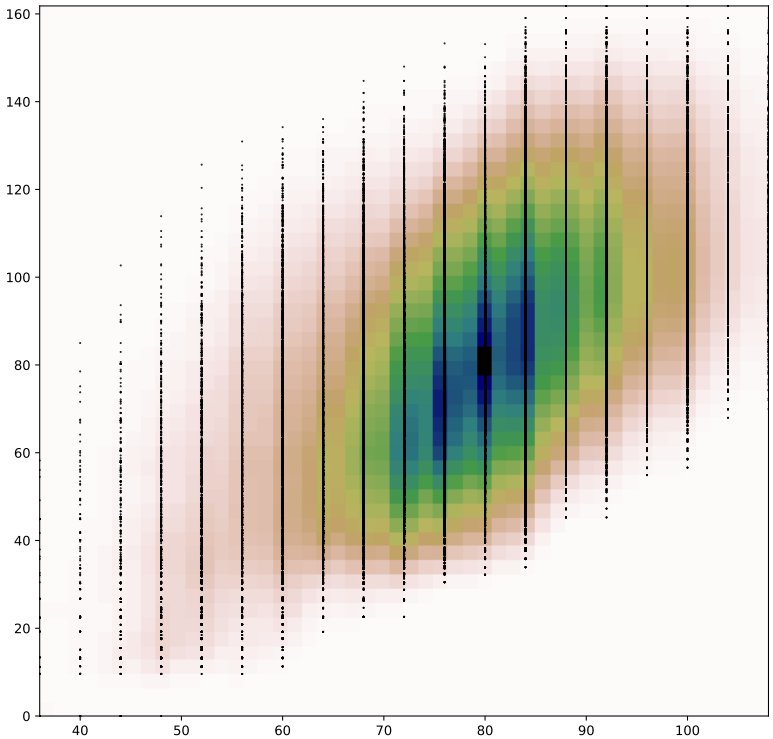
Entropy and KDE

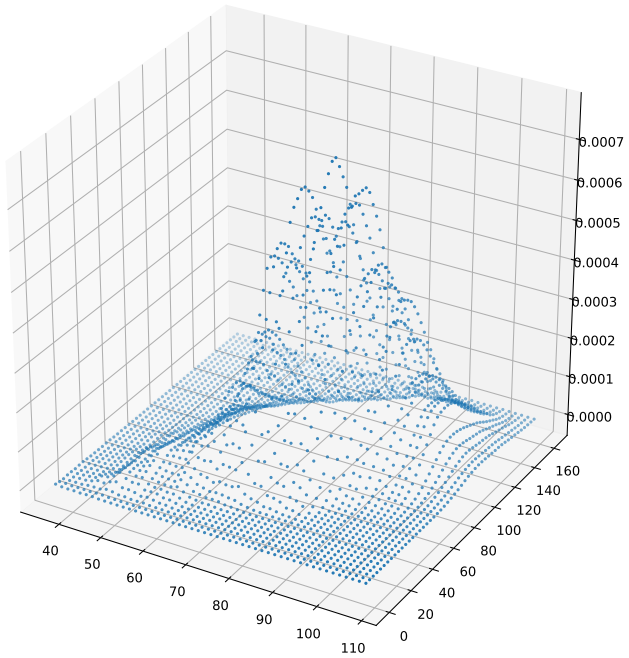
We then calculate the entropy, H_{KDE}, of the Kernel Density Estimated distrbution. We want it to be uniform (high entropy) not to oversample.



Example of KDE slice

Dimensions ${}^{\mathrm{lc}}_{\mathrm{ax,eq}}\chi_1$ vs. charge in H_{KDE} for strongly symmetric monodentates.



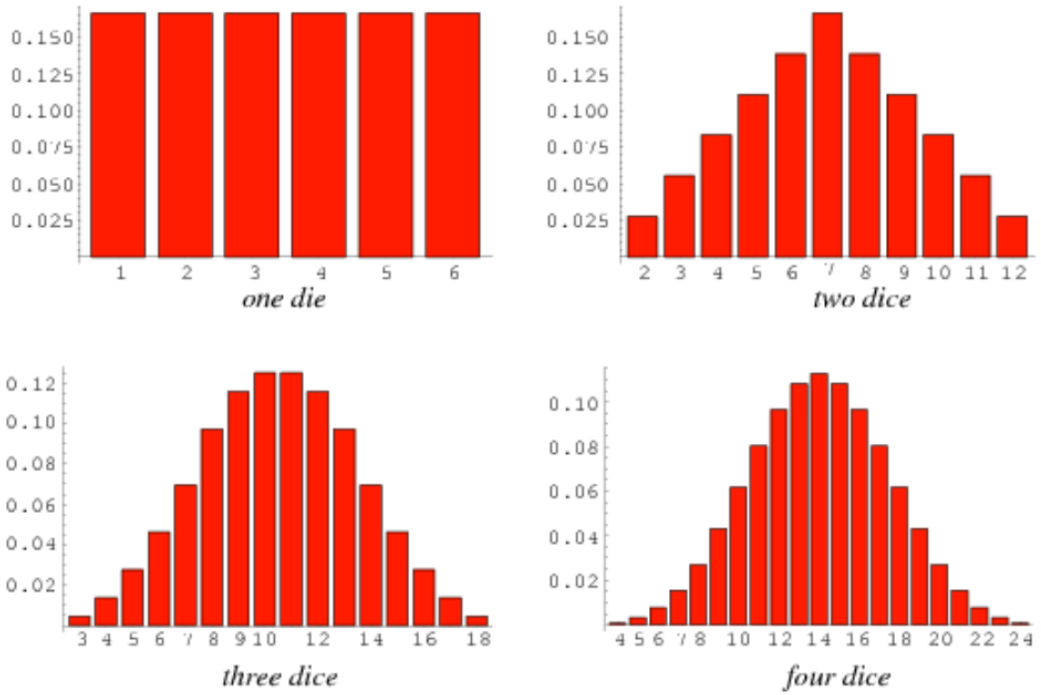


Entropies of various symmetry classes

Table : Entropic footprint

Set	H_{KDE}
Homoleptics	20.18
Strongly symmetric	14.04
”4+2” symmetric	13.68
”5+1” symmetric	13.65
Equatorially asymmetric	10.57
Weakly symmetric	8.86

Multinomial peaking



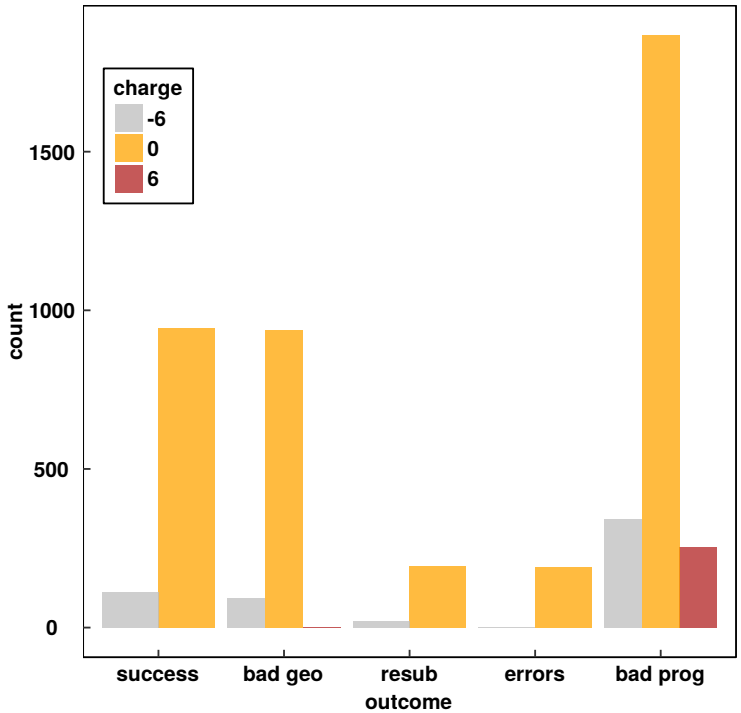
- The more dice, the more the distribution peaks which results in low entropy.
- Sample from low entropy uniformly and get similar molecules.

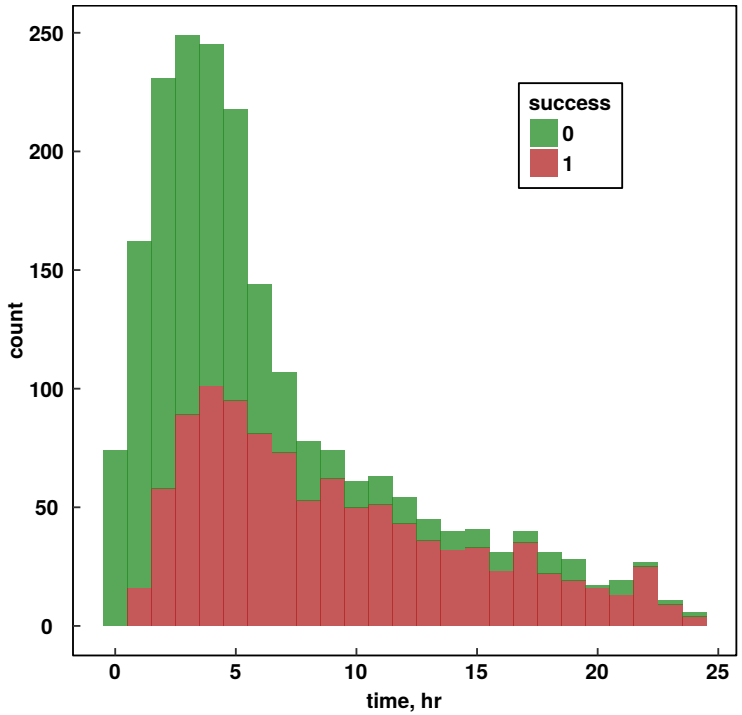
DFT calculations

We calculated the homoleptic sets (405 ligands).

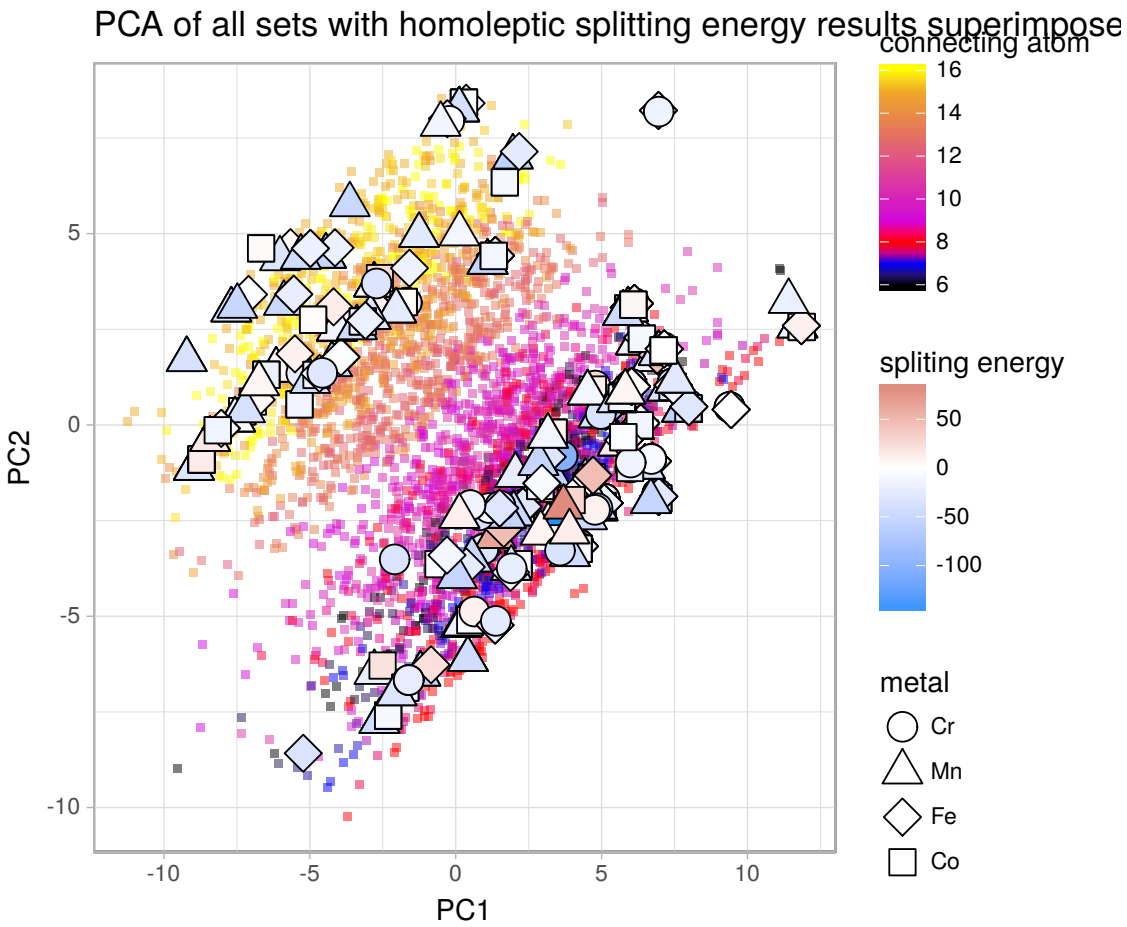
- Basis set: LACVPS (6-31G*)
- Effective core potential: LANL2DZ
- Functional: B3LYP

DFT calculations analysis





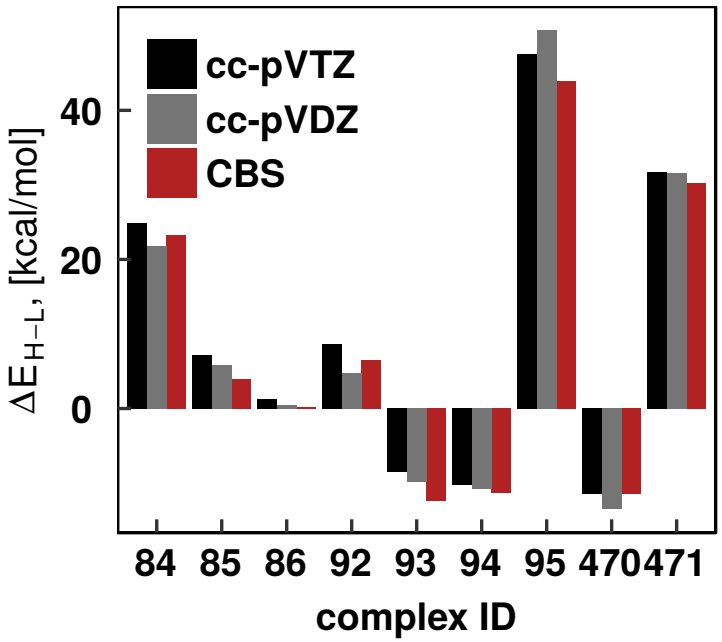
DFT calculations analysis

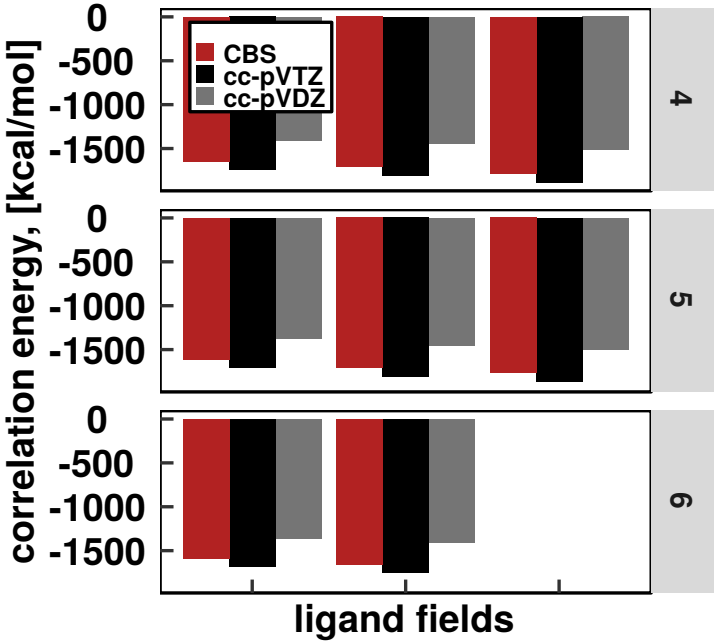


DLPNO-CCSD(T) calculations

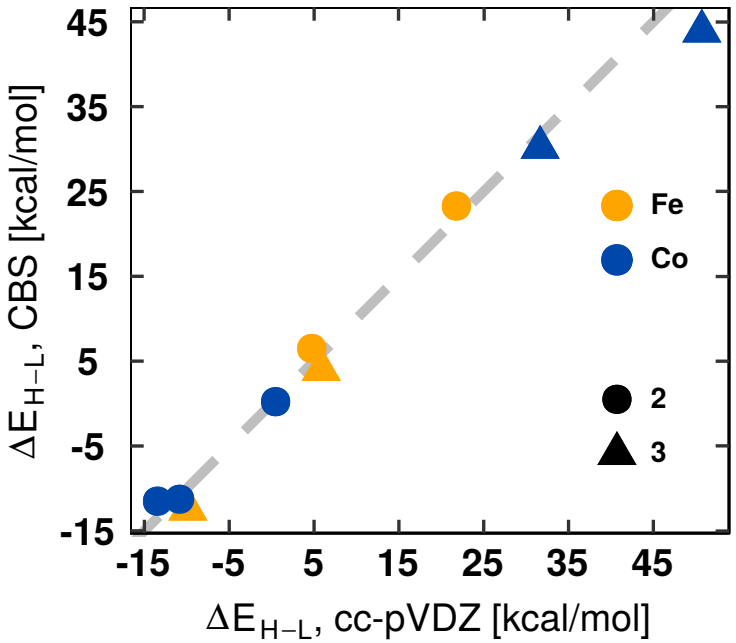
- Basis set: CC-pV(D/T)Z (also tried def2)
- Auxiliary Basis: AutoAux
- RIJCOSX approximation for speed-up
- Increased maximum iterations for SCF to 500
- NormalPNO vs. TightPNO

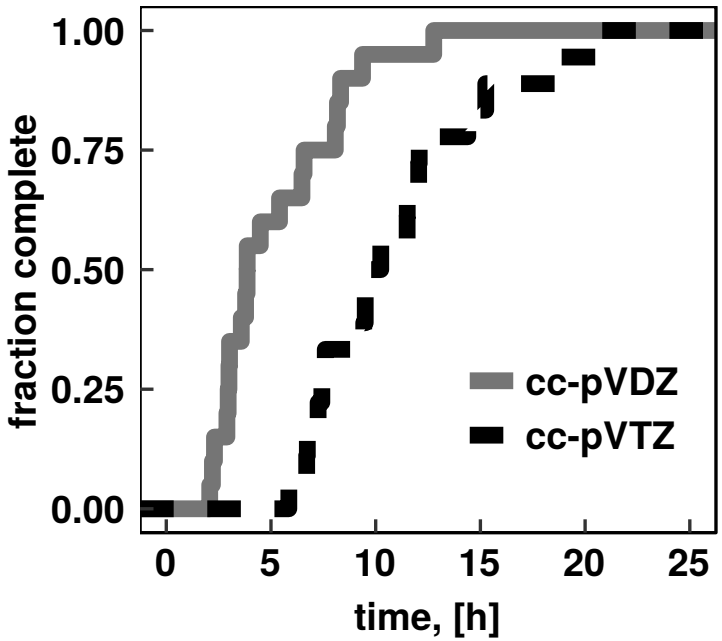
Basis set comparison



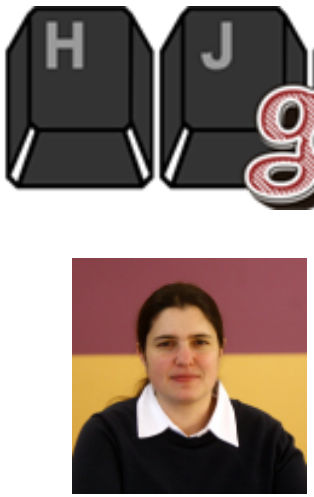


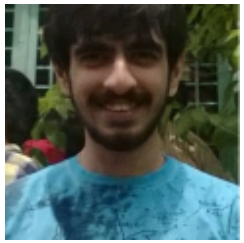
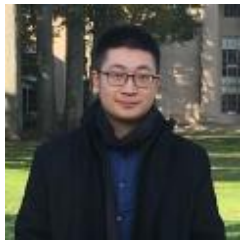
CBS comparison and time analysis





Thanks for the opportunity to work in this lab!





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