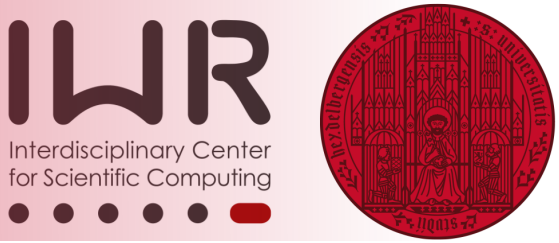

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Towards the design of molecular materials

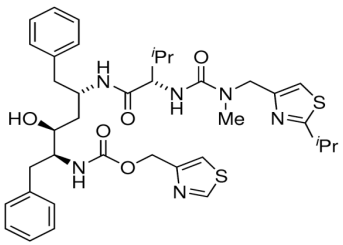
Gerit Brandenburg <j.g.brandenburg@gmx.de> | August 22, 2019

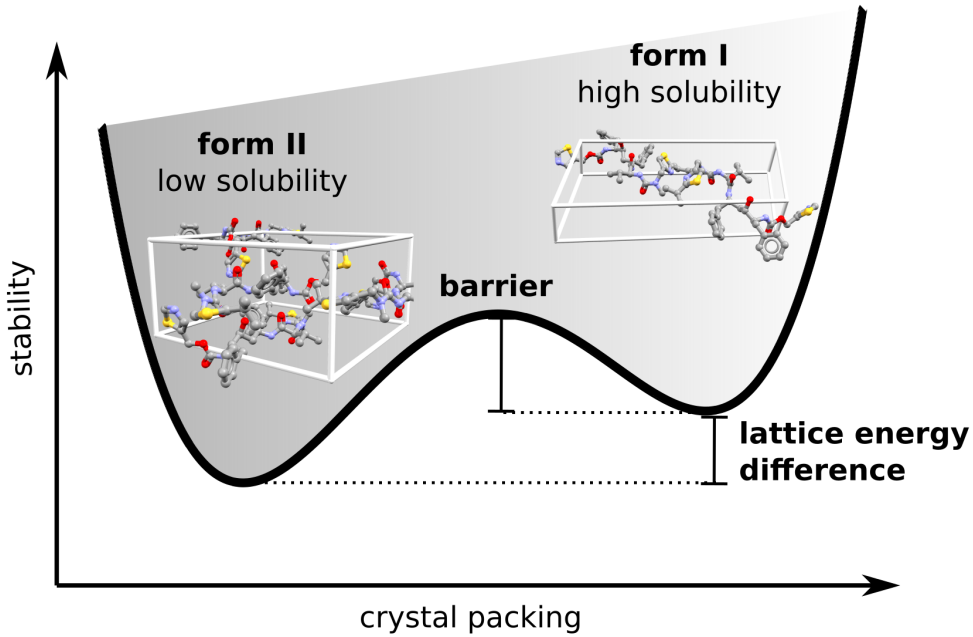
TALK AT 32ND EUROPEAN CRYSTALLOGRAPHIC MEETING, VIENNA, AUSTRIA

Interdisciplinary Center for Scientific Computing – Heidelberg University
Thomas Young Centre – University College London

Many properties depend on the polymorphic form of a crystal

API: ritonavir
- HIV antiviral drug
- industrially produced in form I
- form II found 2 years after market launch
- reformulation required [1]





- tools to predict possible polymorphs would be valuable[2]

  → Simulation methods aim at complementing experimental screening

[1] J. Bauer, et al., *J. Pharm. Res.* **18**, 859-866 (2001).

[2] S. L. Price, JGB, *Molecular Crystal Structure Prediction*; Elsevier Australia ISBN: 9780128098356 (2017).

Predict most stable crystal polymorphs based on the molecular diagram

The inability to predict something as simple as how a molecule would crystallize is one of the continuing scandals in the physical sciences.[3–5]

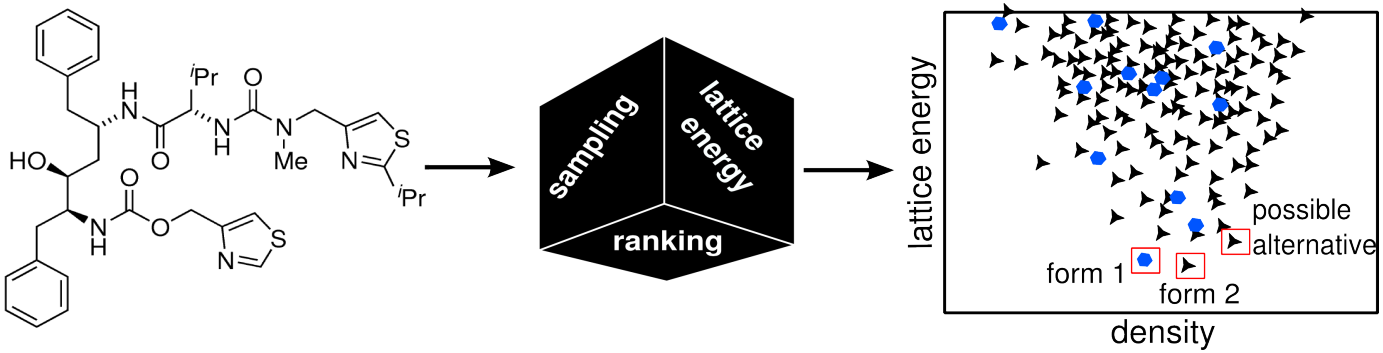
Task

- molecule is chosen due to its chemical/physical/biological properties
- based on the molecular diagram only, the most stable crystal structures should be predicted
- predict properties of interest for the most promising candidates

[3] A. Gavezzotti, *Acc. Chem. Res.* **27**, 309-314 (1994). [4] J. Maddox, *Nature* **335**, 201-201 (1988).

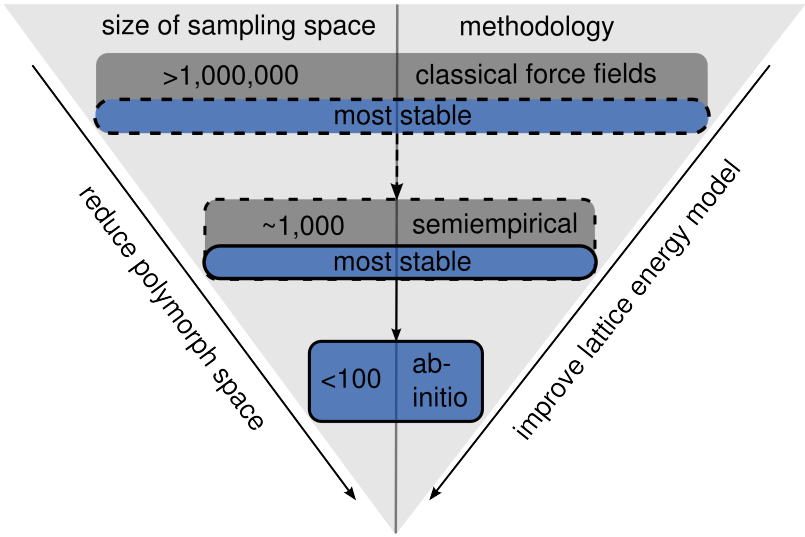
[5] K. N. Houk, F. Liu, *Acc. Chem. Res.* **50**, 539 (2017).

Sampling and energetic ranking for crystal structure prediction



Layers of complexity:

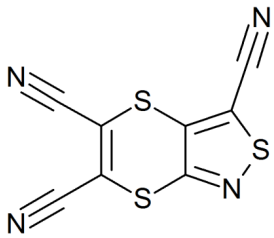
- molecular conformational space
- space groups (varying orientation, conformation, etc.)
- polymorph ranking according to free energy[6,7]



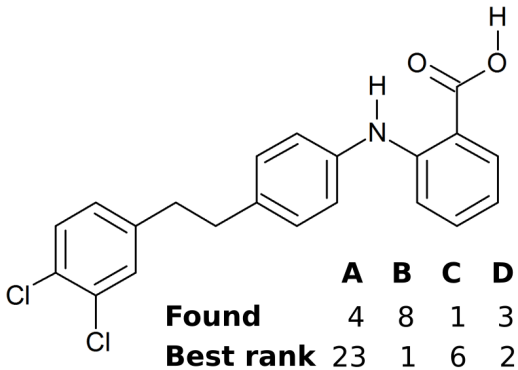
[6] S. Price, *Chem. Soc. Rev.* **43**, 2098 (2014)

[7] S. L. Price, JGB, *Molecular Crystal Structure Prediction*; Elsevier Australia, 336-363 (2017).

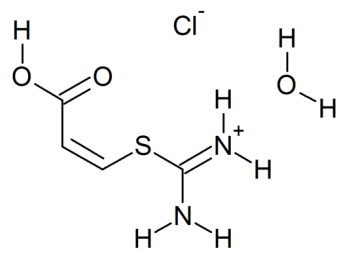
Results of the 6th blind test for organic crystal structure prediction



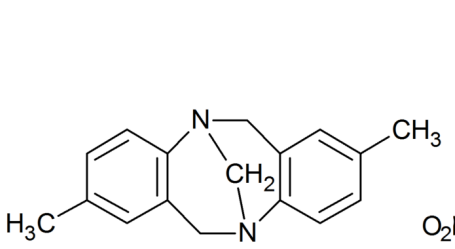
Found	12
Best rank	1



	A	B	C	D	E
Found	4	8	1	3	0
Best rank	23	1	6	2	

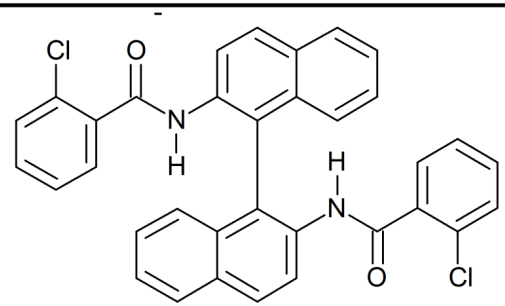


Found	1
Best rank	2



The Cambridge Crystallographic Data Centre

Found	5
Best rank	1



Found	3
Best rank	1

- No group had a perfect sampling and ranking of structures[8,9]

[8] A. Reilly, et al. *Acta Cryst. B*, **72**, 439 (2016). [9] J. G. Brandenburg, S. Grimme, *Acta Cryst. B*, **72**, 502 (2016).

CSP bind test highlights two remaining challenges

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1. Ranking stage

Crystal polymorphs are often separated by just a few kJ/mol, exceeding the accuracy of standard density functional approximations (DFAs).
$\Longrightarrow$ **Are many-body methods feasible?**

2. Sampling stage

Dealing with a vast search space, in particular for molecules with increased flexibility, one has to cover too many structures at DFT accuracy.
$\Longrightarrow$ **Can we improve modern DFAs & employ ML techniques?**

Outline of talk

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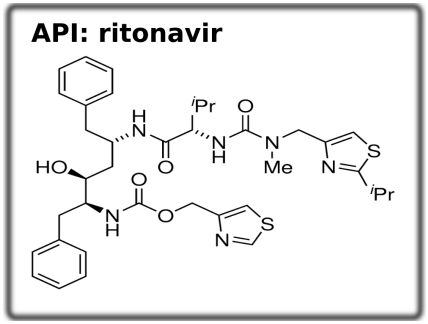
Challenge of treating the flexibility of large pharmaceutical-like molecules



- ritonavir is API with typical flexibility
- need of fast electronic structure method that can treat flexibility

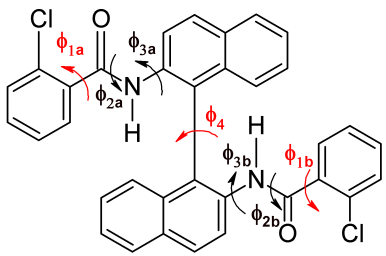
Density **F**unctional **T**ight **B**inding (DFTB3-D3):
3rd order, self consistent charges, 3OB atom-pair parameter, D3 dispersion

- huge speed-up compared to DFT ($\sim$ 4 orders of magnitudes)
- full treatment of all degrees of freedom
- good experience for proteins & energies of small molecular crystals

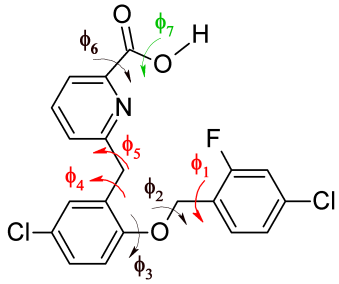
[10] A. S. Christensen, T. Kubař, Q. Cui, M. Elstner, *Chem. Rev.* **116**, 5301 (2016).

[11] JGB, S. Grimme, *J. Phys. Chem. Lett.* **5**, 1785 (2014).

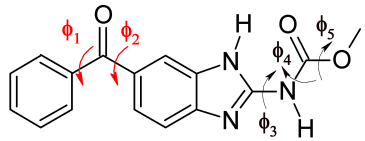
Focus on flexible molecules with previous CSP studies



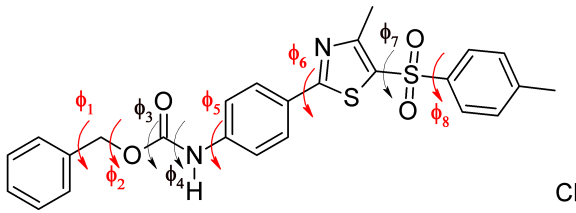
Molecule XXVI



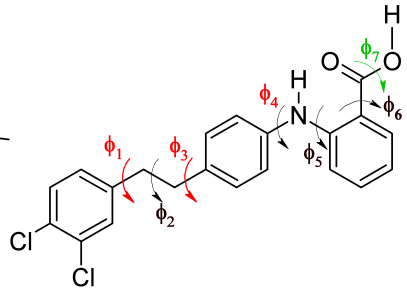
GSK269984B



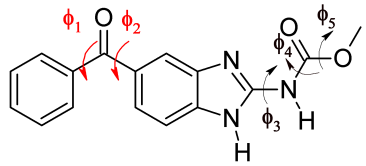
A-Mebendazole



Molecule XX



Molecule XXIII



C-Mebendazole

Possible advantages of DFTB3-D3 as an (intermediate) CSP step

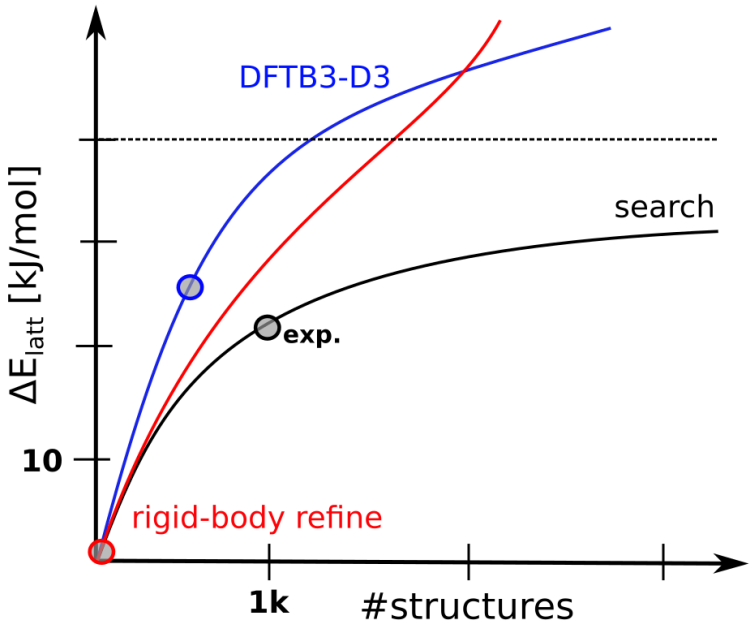
(1) improving geometries

(2) improving energy ranking

(3) reducing # minima

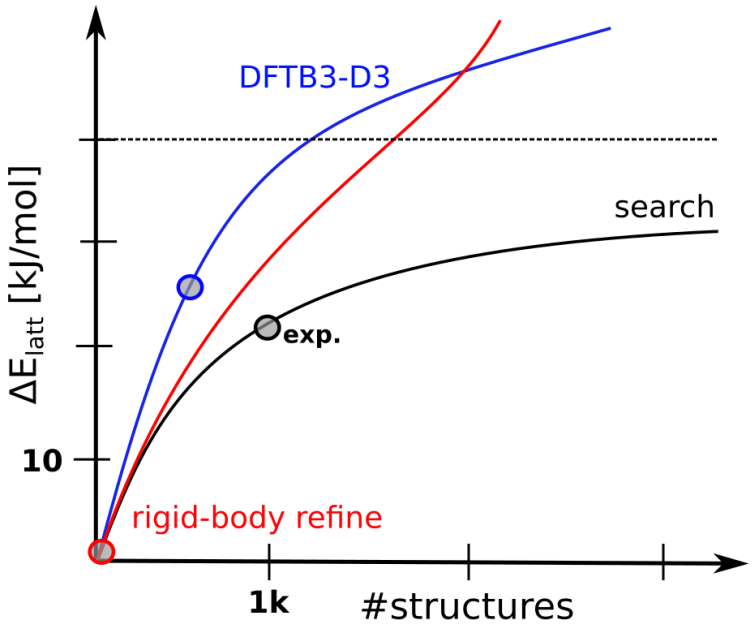
(4) free energy contributions

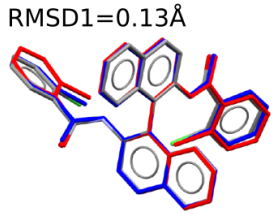
Though poor energetic ranking geometries improved



- 2.2 Mio structures generated for XXVI, 9 000 processed to reranking
- experimental polymorph is rather high in energy by DFTB3-D3
- successful reranking using rigid DFTB3-D3 structure

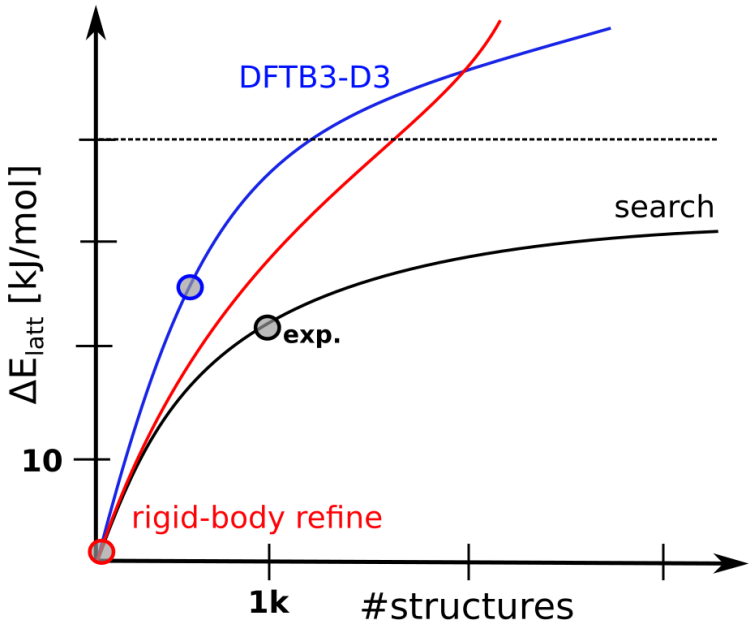
Though poor energetic ranking geometries improved

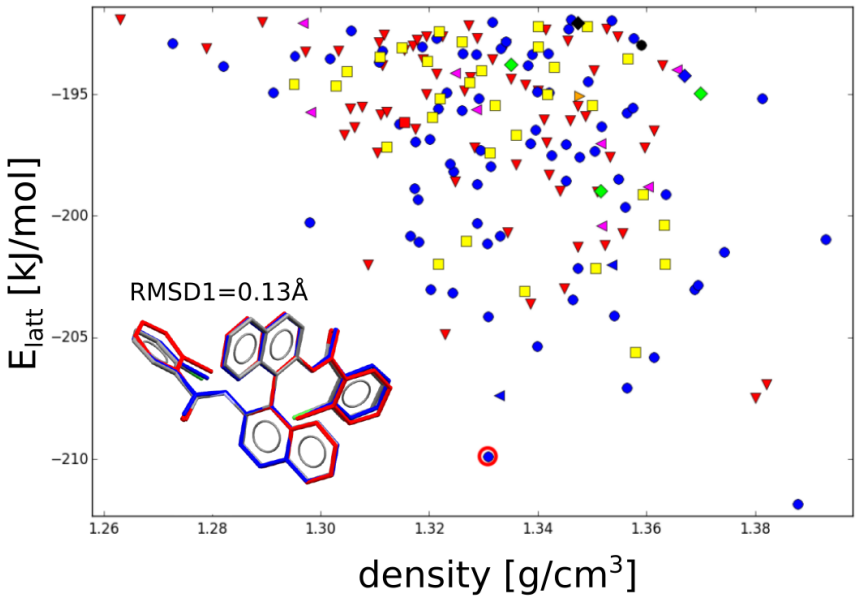




- 2.2 Mio structures generated for XXVI, 9 000 processed to reranking
- experimental polymorph is rather high in energy by DFTB3-D3
- successful reranking using rigid DFTB3-D3 structure

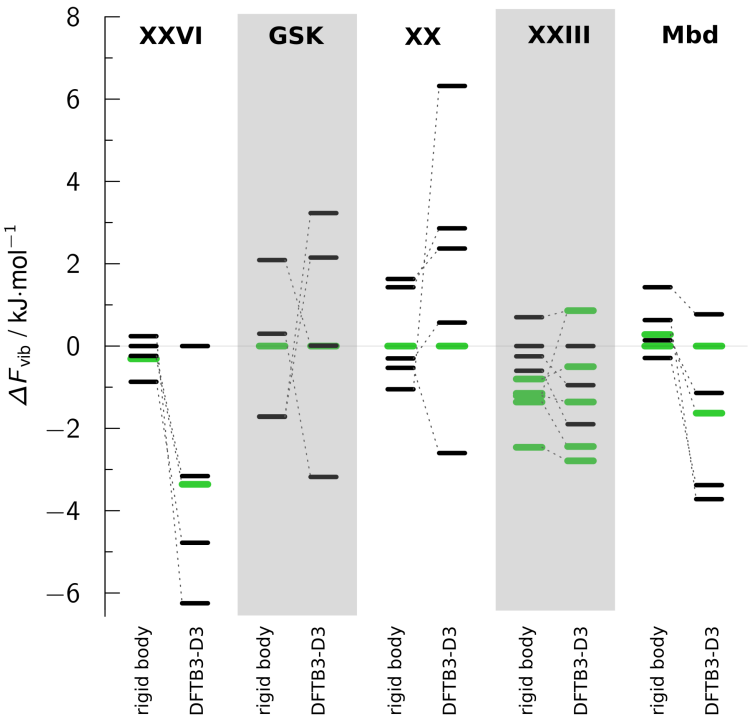
Though poor energetic ranking geometries improved





- 2.2 Mio structures generated for XXVI, 9 000 processed to reranking
- experimental polymorph is rather high in energy by DFTB3-D3
- successful reranking using rigid DFTB3-D3 structure
- final energy landscape: no important structure is lost

Impact of harmonic free energy contributions to relative stability

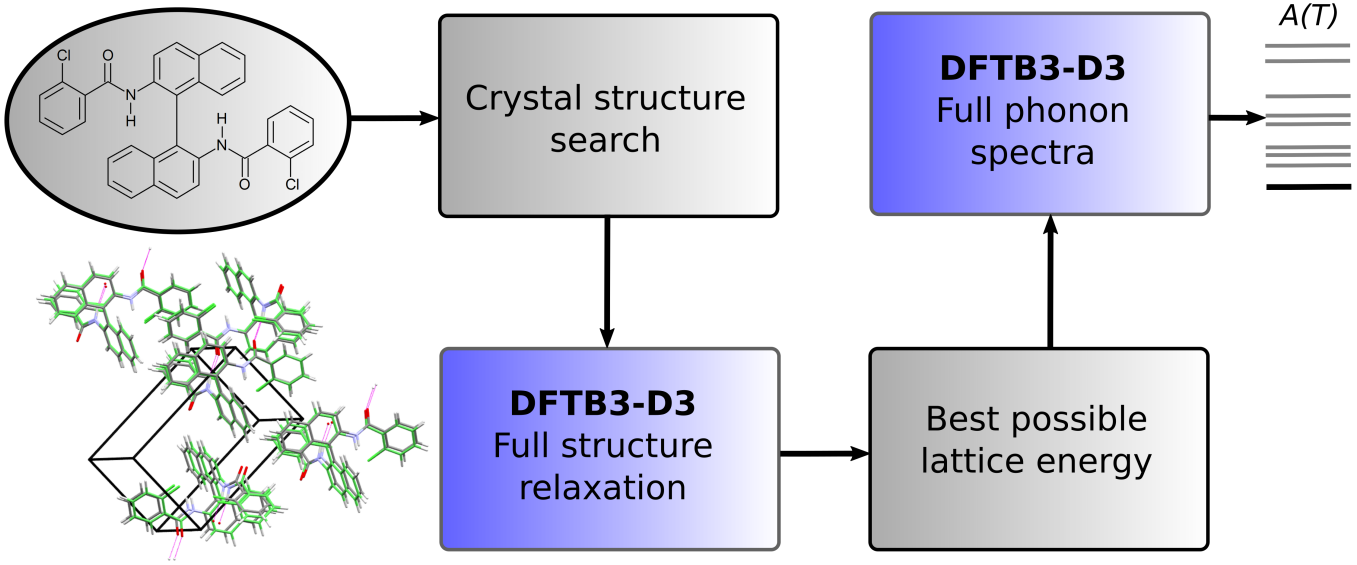


- significant impact of ZPE and thermal contribution on relative stability
- modified ranking of several putative polymorphs
- treating molecules as rigid underestimates the free energy
- rigid-body estimate: 9% of polymorph change stability upon including thermal contributions

[12] A.J. Cruz-Cabeza, J. Bernstein, *Chem. Rev.* **114** 2170 (2014).

[13] J. Nyman, G. M. Day, *CrystEngComm* **17**, 5154 (2015).

DFTB3-D3 intermediate optimization would be scaleable for larger molecules



Possible merits of DFTB3-D3

(1) improving geometries **yes**

(2) improving energy ranking **no**

(3) reducing # minima **partially**

(4) free energy contributions **yes**

[14] L. Iuzzolino, P. McCabe, S. L. Price, JGB, *Faraday Discuss.* **211**, 275 (2018).

Outline of talk

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Methods with 'benchmark quality' for noncovalent interactions

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CCSD(T)

+ 'gold standard' of quantum chemistry
+ linear scaling variants
- pair-screening thresholds
- slow basis set convergence
- non-trivial to parallelize (shared memory: 100 GB/core)

DMC

+ exact projection to ground state
+ N^3 scaling, [-] huge prefactor
+ fast basis set convergence
+ scaleable to HPCs
- stochastic error
- uncertainties from FN and non-local pseudopotentials

No benchmark quality: MP2, RPA, CCSD, CCSD(T)/cc-pVTZ, VMC

Quantum Monte-Carlo in a nutshell: A scalable high-level method

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Fixed-node diffusion Monte-Carlo

1) Enforce nodal surface of Fermions

$$\Gamma = \{\mathbf{R}; |\Psi_T\rangle = 0\}$$

2) Walkers in configuration space

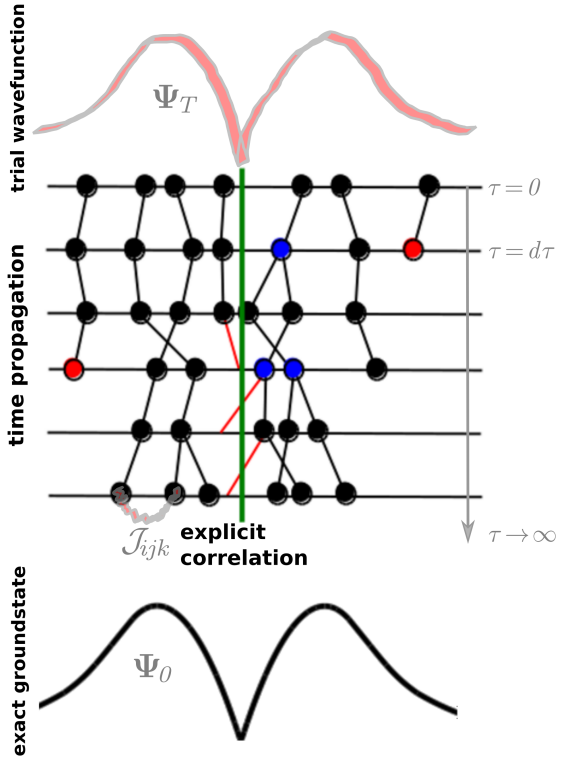
$$|\Psi_T(\mathbf{R},\tau)\rangle = \text{hist}\left[\sum \delta(\mathbf{R} - \mathbf{R_i}(\tau))\right]$$

3) Diffusion in imaginary time

$$\partial_\tau |\Psi_T(\mathbf{R},\tau)\rangle = \left[\frac{1}{2}\nabla^2_{\mathbf{R}} - (V - E_T)\right] |\Psi_T(\mathbf{R},\tau)\rangle$$

4) Projection to exact ground state

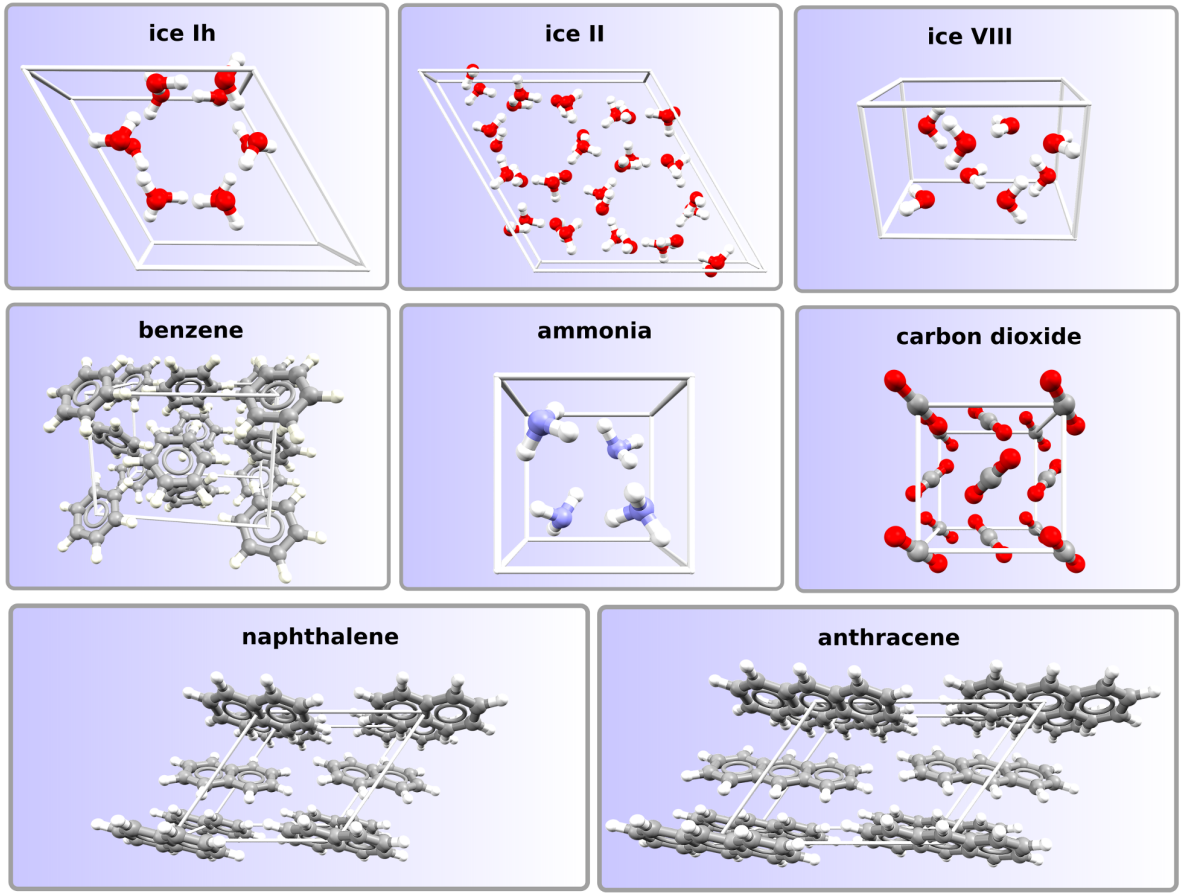
$$|\Psi_0(\mathbf{R})\rangle = \lim_{\tau\to\infty} \exp\left[-\tau(\hat{H} - E_T)\right] |\Psi_T(\mathbf{R},\tau)\rangle$$



- exact within Γ and $d\tau \to 0$ and $\tau \to \infty$[15]
- new DMC algorithms lead to substantial speed up[16]

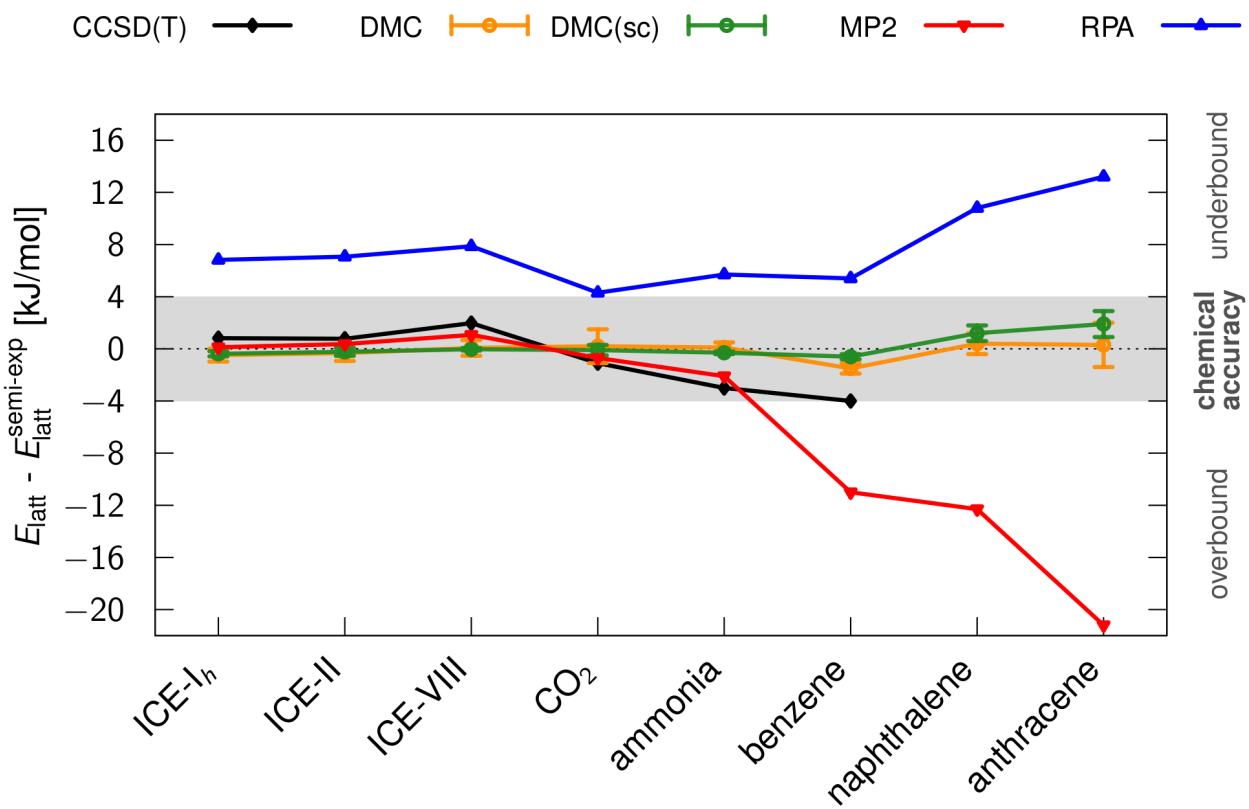
[15] *Chem. Rev.* **116**, 5188 (2016) [16] A. Zen, S. Sorella, M. J. Gillan, A. Michaelides, D. Alfé, *Phys. Rev. B* **93**, 241118(R) (2016).

Molecular crystals as challenging test



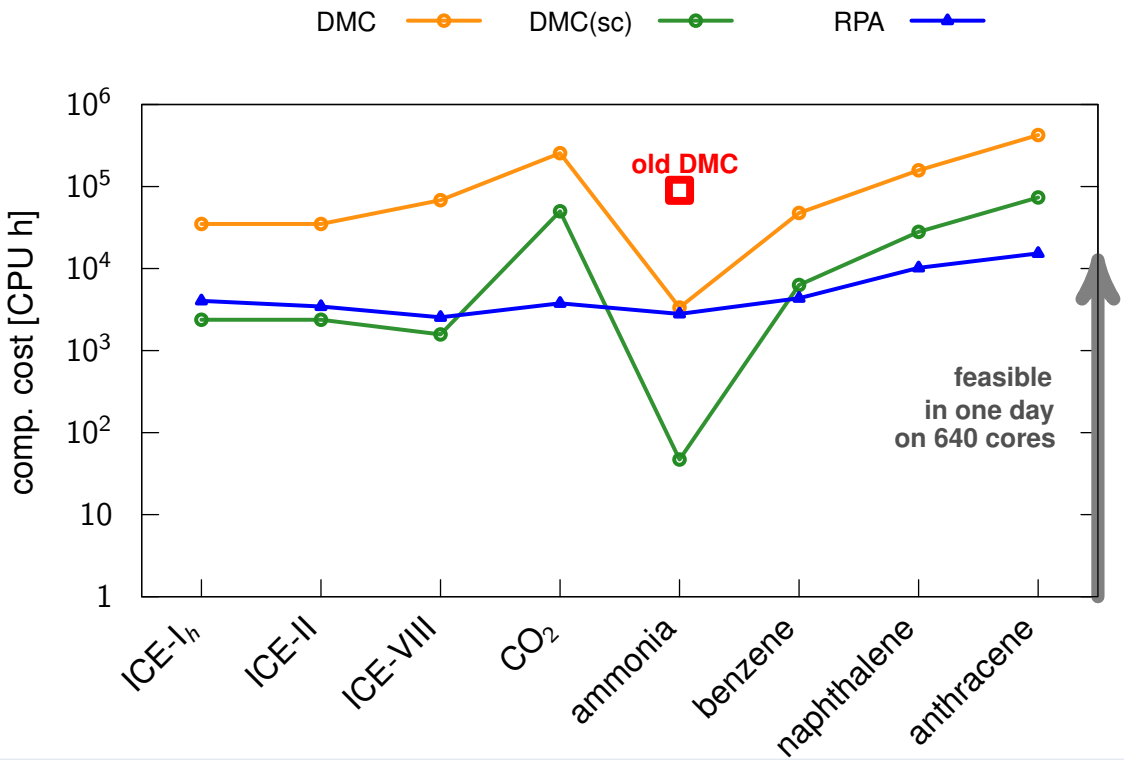
- strong H-bonds, vdW of saturated and unsaturated molecules
- problematic for all readily applicable methods (DFA-DISP, MP2)

QMC delivers (sub-) chemical accuracy for all tested systems



- excellent agreement with experiment and CCSD(T)
- uncertainty in H_{sub}^{exp} probably larger than DMC errors

QMC is feasible within one day on standard computer cluster



- up to three orders of magnitude speed-up compared to best DMC practice two years ago
- significance will extend to all classes of systems[17]

[17] A. Zen, JGB, J. Klimeš, A. Tkatchenko, D. Alfè, A. Michaelides, *Proc. Natl. Acad. Sci. U.S.A* , **115**, 1724 (2018).

Outline of talk

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Employing ML to enhance CSP workflow

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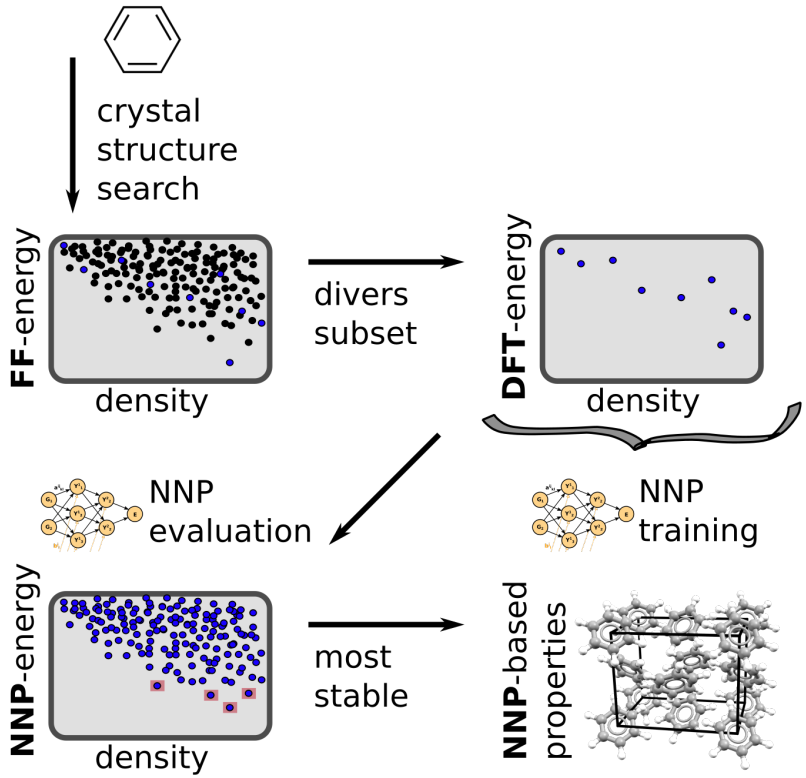
1. Generate putative structures with crude FF stability
2. Construct a divers subset of structures
3. Compute DFT stability on subset
4. Train a high-dimensional NNP on DFT references
5. Recompute stability of all structures employing the NNP



[18] V. L. Deringer, D. M. Proserpio, G. Csányi, and C. J. Pickard, *Faraday Discuss.* **211**, 45 (2018).

[19] E. V. Podryabinkin, E. V. Tikhonov, A. V. Shapeev, and A. R. Oganov, *Phys. Rev. B* **99**, 064114 (2019).

[20] JGB and J. Behler, *in preparation*.

High-dimensional neural network for benzene crystal landscape

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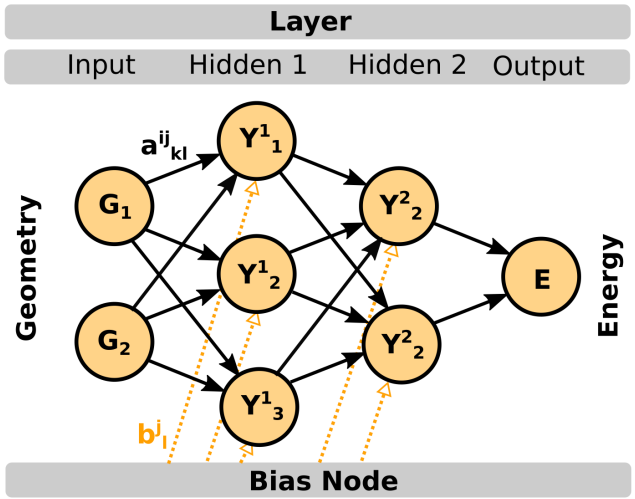
Energy decomposed to atomic contributions

$$E_{\text{tot}} = \sum_{i}^{\text{atoms}} E_i \left[Z_i, G(\{R_j\}) \right]$$

- symmetry functions as local geometry descriptors G[21–23]
- element specific feed-forward neural network (2 hidden layers, 25 nodes each)
- training based on electronic energies and nuclear forces



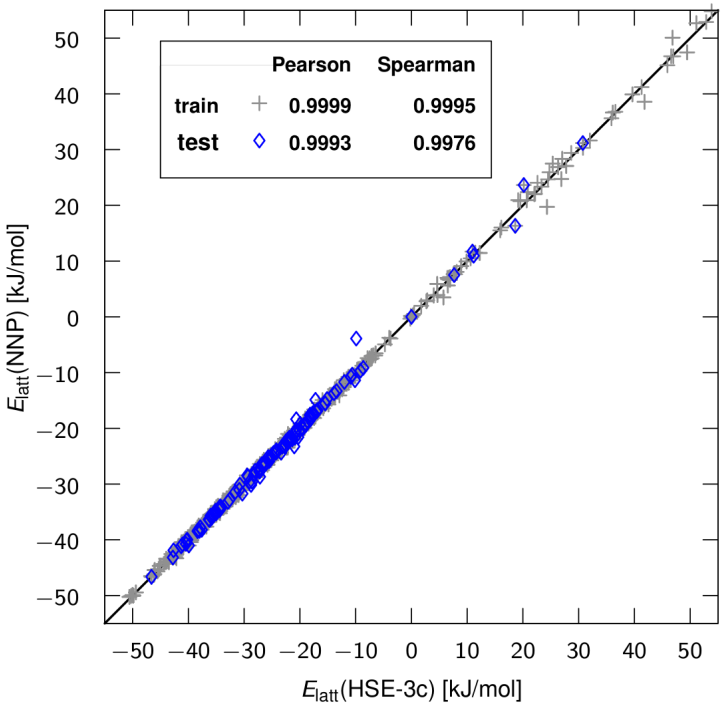
[21] J. Behler and M. Parrinello, *Phys. Rev. Lett.* **98**, 146401 (2007).

[22] J. Behler, *J. Chem. Phys.* **134**, 074106 (2011).

[23] J. Behler, *Angew. Chem. Int. Ed.* **56**, 12828 (2017).

Stable training on 10% of generated putative polymorphs

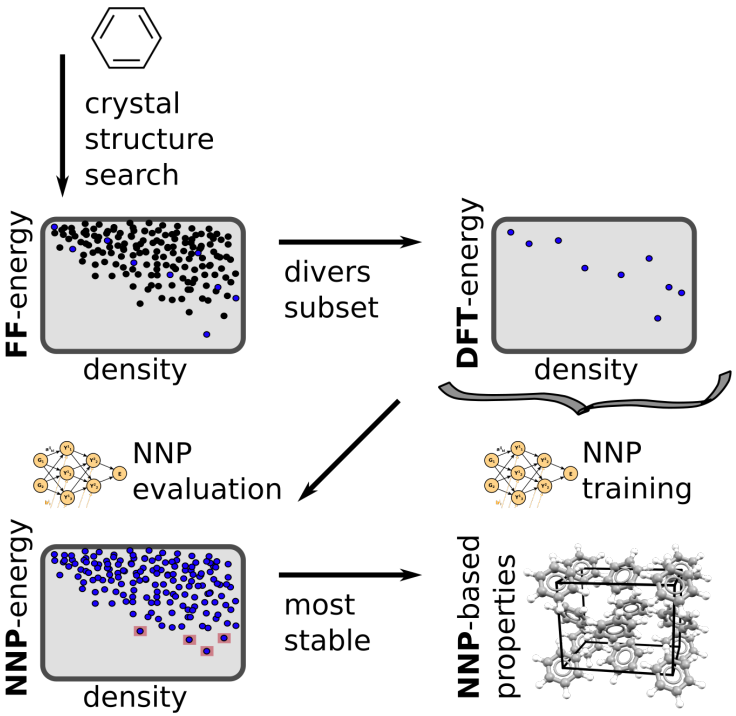
	training	testing
#structures	1 077	127
#data points	39 849	4 699
range E [kJ/mol]	[-50:147]	[-55:120]
range ρ [g/cm^3]	[0.1:1.1]	[0.1:1.1]
RMSD(E) [kJ/mol]	**0.53**	**0.93**
RMSD(F) [a.u.]	0.001	0.001

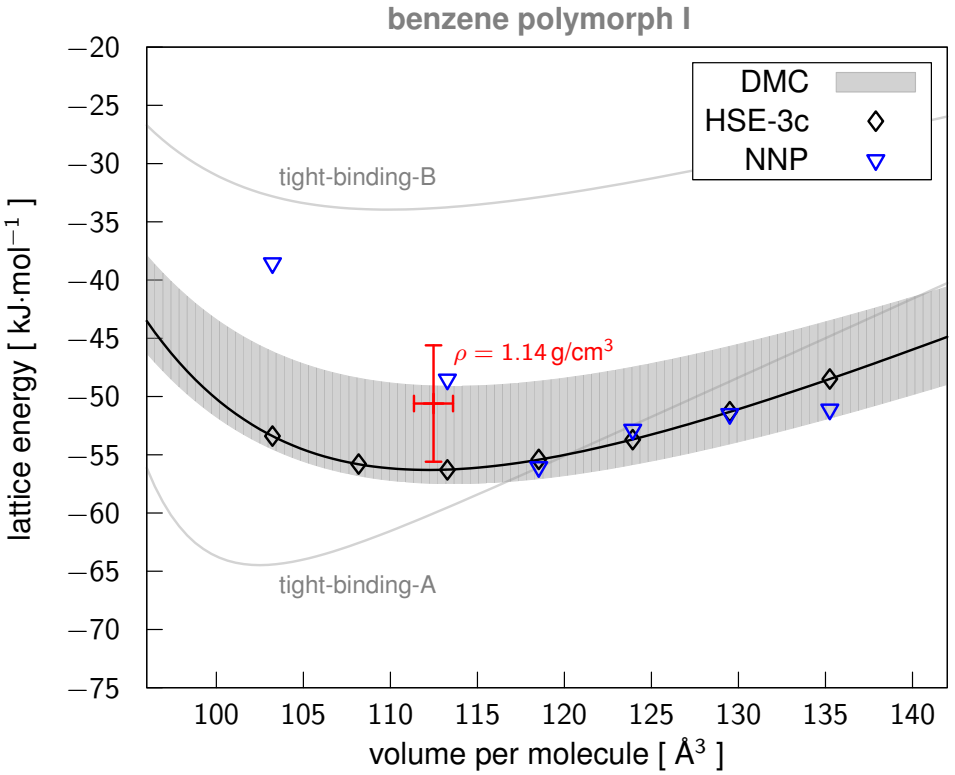


- neural network delivers sub-chemical accuracy
- CSP cost reduced by one order of magnitude [20]

[20] JGB and J. Behler, *in preparation*.

Employing ML to enhance CSP workflow





- EOS within 1 kJ/mol for ρ <1.1 g/cm^3, large errors for ρ >1.2 g/cm^3
- too few data points to generate globally smooth EOS

[20] JGB and J. Behler, *in preparation*.

Outline of talk

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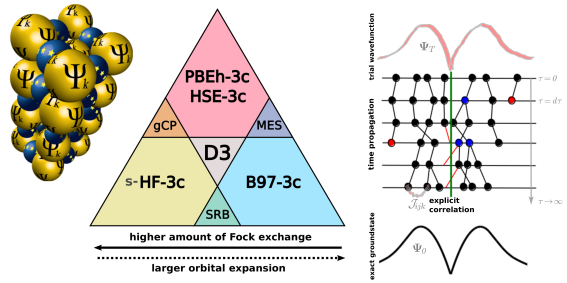
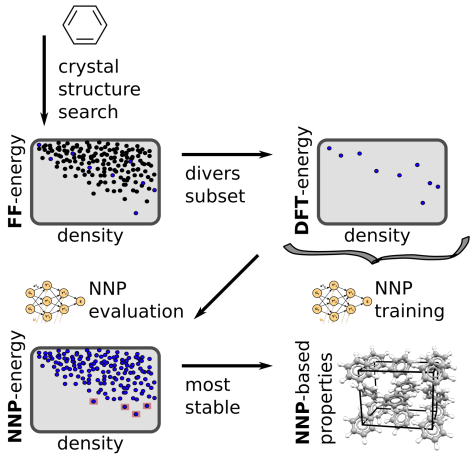
Remaining challenges in crystal structure prediction

- Thermodynamics of crystals, i.e. full PT phase diagram
- Kinetics of crystallization
- Reducing the human and CPU time for prediction

Summary

- Fast electronic structure methods to treat flexible molecules
- High-level solution of Schrödinger eq. for accurate energies
- Enhancing CSP by machine learning





Acknowledgements

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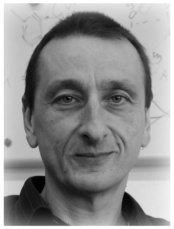
Alfè (UCL)

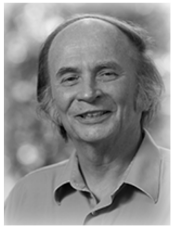

Tkatchenko (Luxembourg)


Klimes (Prague)


Benjamin Ramberger


Theodoros Tsatsoulis


Grimme (Bonn)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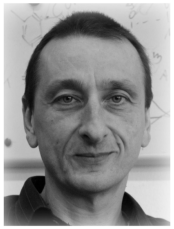
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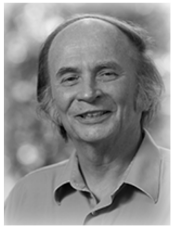
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