Luxembourg National Research Fund

DFG Deutsche Forschungsgemeinschaft

Machine Learning of Molecular Quantum Chemical Space

Opportunities and Challenges

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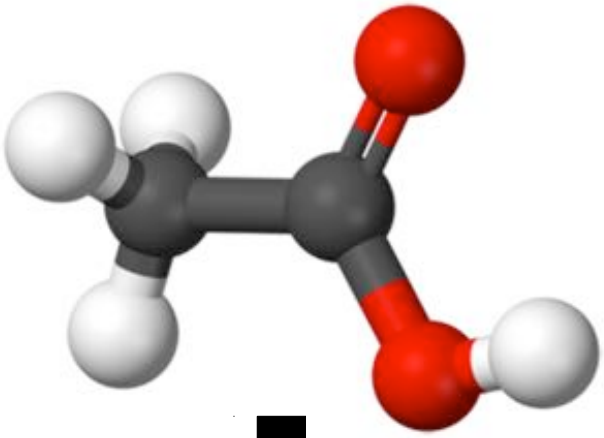
Quantum physics/chemistry today

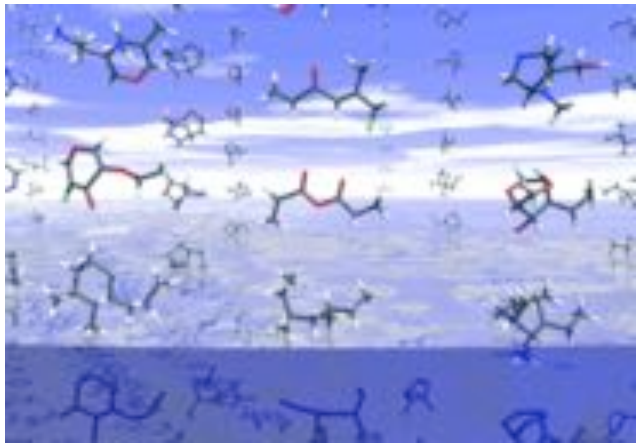


DFT
MP2
CCSD(T)
...

$$\hat{\mathcal{H}}(R_1, Z_1, ..., R_N, Z_N)\tilde{\Psi} = E\tilde{\Psi}$$

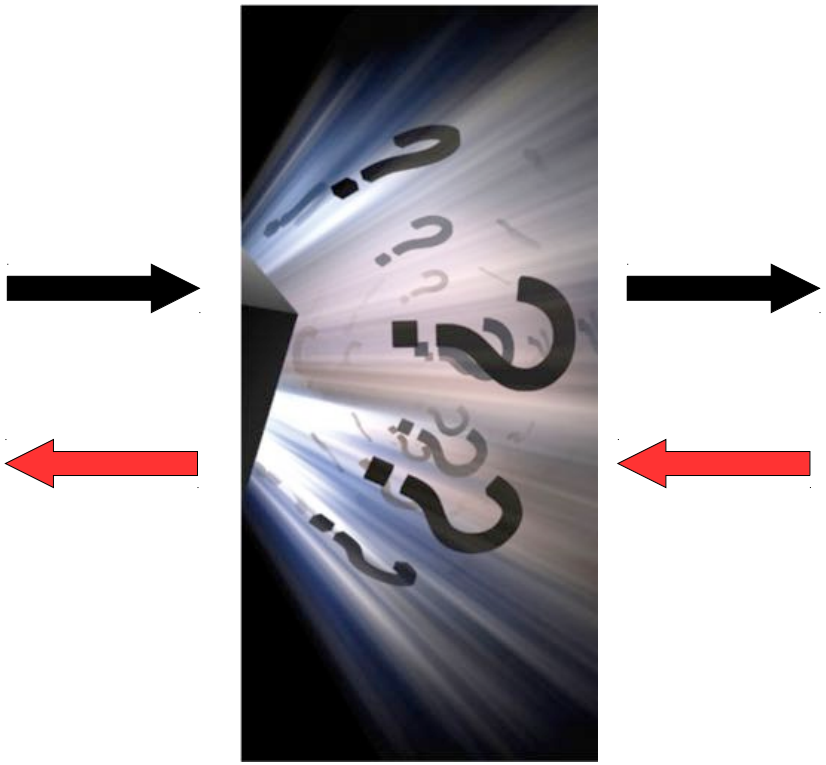
Properties: Energy, polarizability, HOMO, LUMO, …
Dynamics: Thermal properties, spectroscopy, ...

Quantum physics/chemistry tomorrow?



Training data:
molecular properties

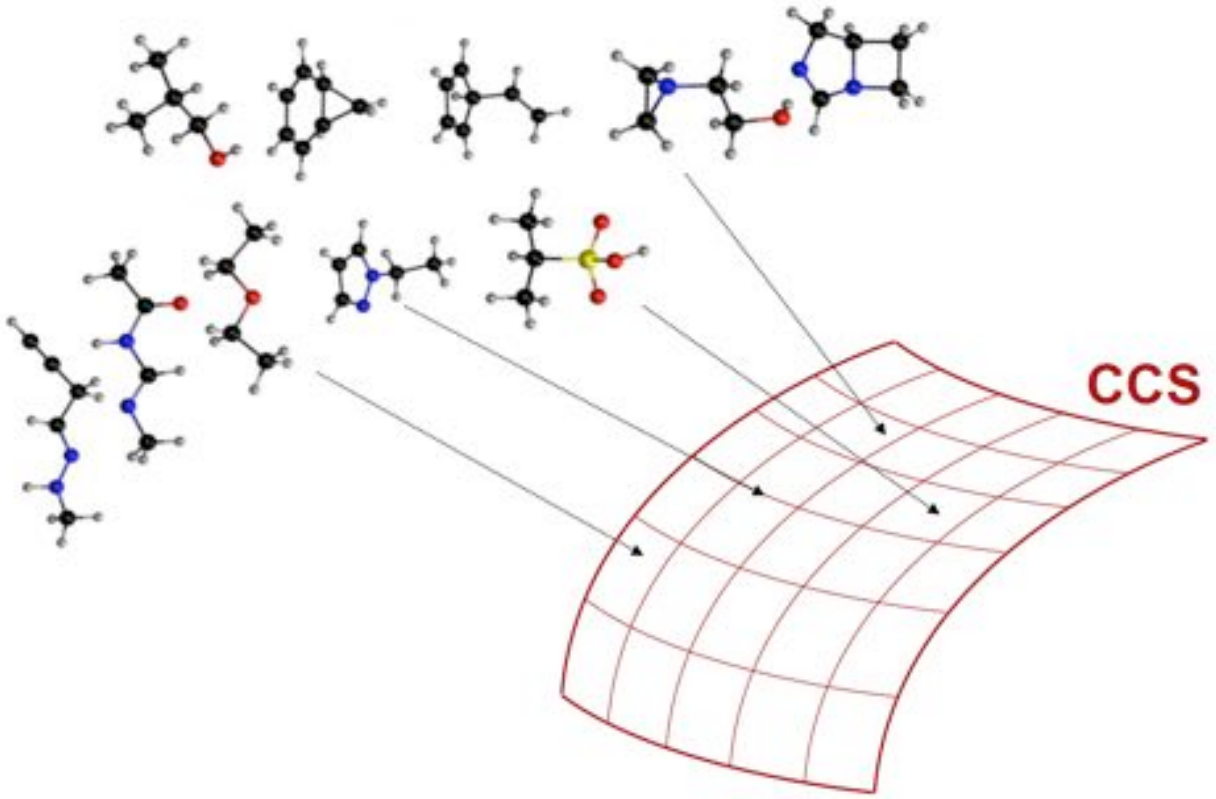
ML



Insights:

- Structure of chemical space
- Reactivity trends, aromaticity, “new” chemistry
- Molecular design through multi-property optimization
- ...

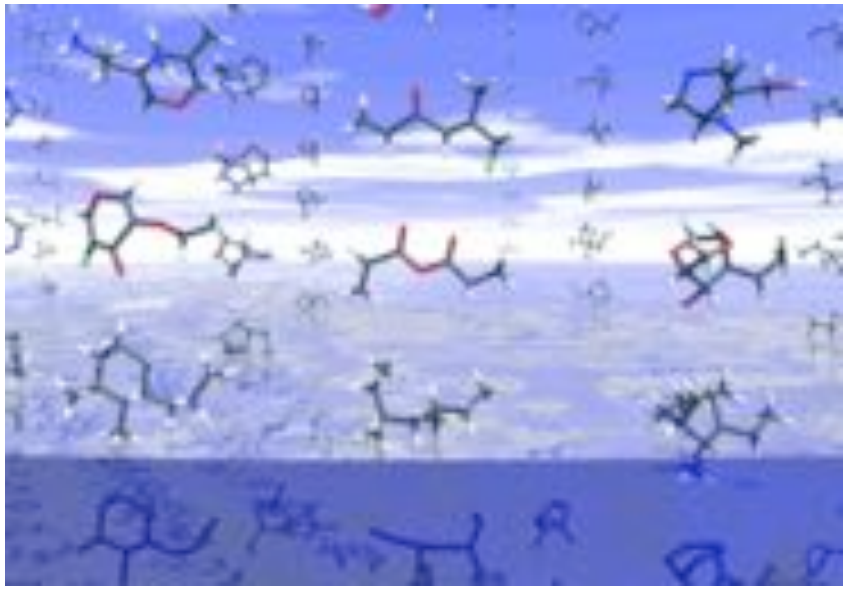
Molecular Quantum Chemical Space



- Graph theory: combinatorial explosion
- At least 10^{60} small drug candidate molecules
- Finding needles in a haystack

$\{\boldsymbol{R}_i, Z_i\}$ maps to $\{P_1, P_2, P_3, P_4, \ldots\}$

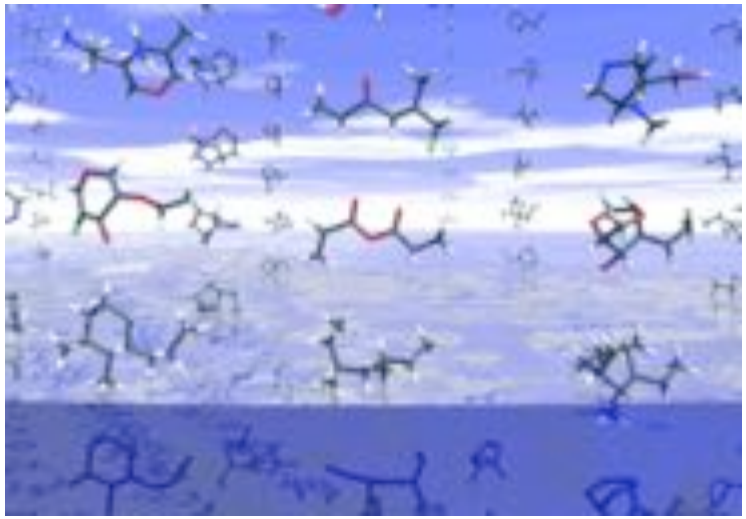
Machine learning for molecular big data

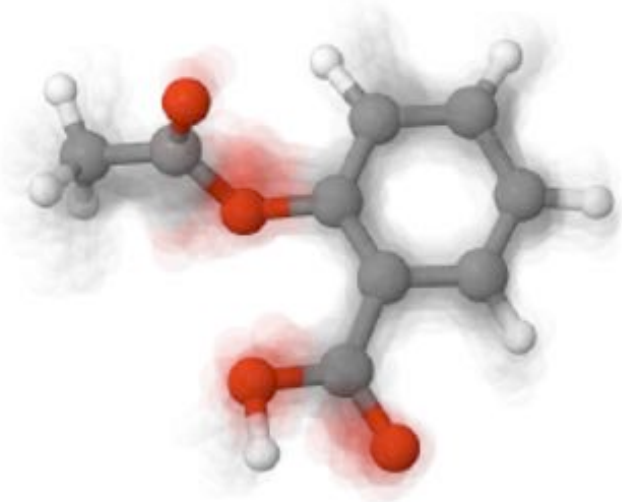


$\{\boldsymbol{R}_i, Z_i\}$ maps to $\{P_1, P_2, P_3, P_4, \ldots\}$

- Descriptor: what's a good representation of a molecule?
- Metric: how to define distance between two molecules?
- Data selection: Which molecules to use for training?
- Properties: which set of properties uniquely defines a molecule?
- Degrees of freedom: composition vs. conformation

Molecular Data in this Talk





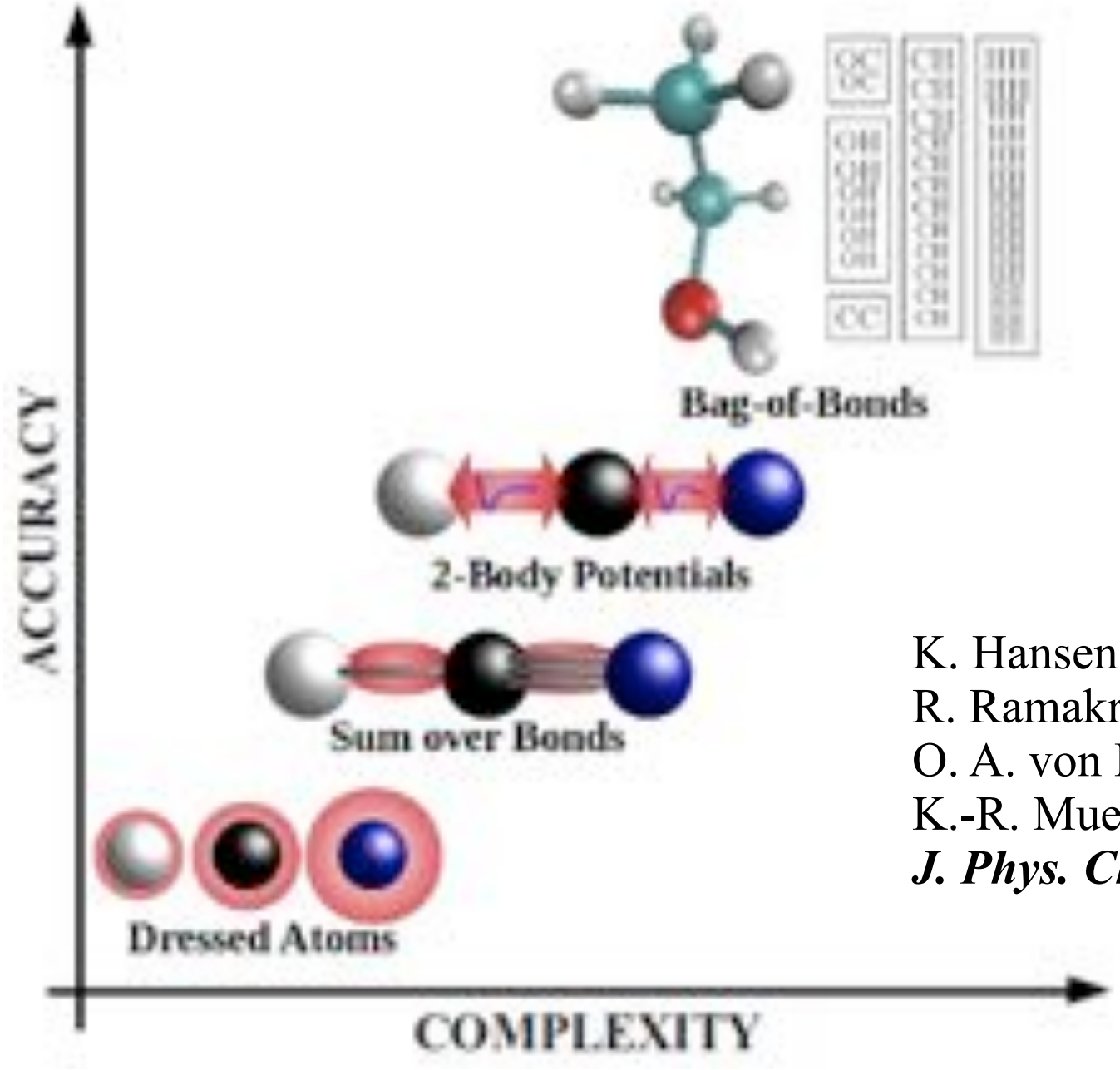
GDB mol graphs: J. L. Reymond (U. Bern)
http://gdb.unibe.ch/downloads/

QM7/QM9 datasets: Hybrid DFT calculations by von Lilienfeld's group (Sci. Data 2014) and my group (PRL 2012).

MD17/ISO17 datasets: Molecular dynamics trajectories from my group (DFT and CCSD(T) levels)

www.quantum-machine.org

Predicting Molecular Properties: The Importance of *Physical Baselines*



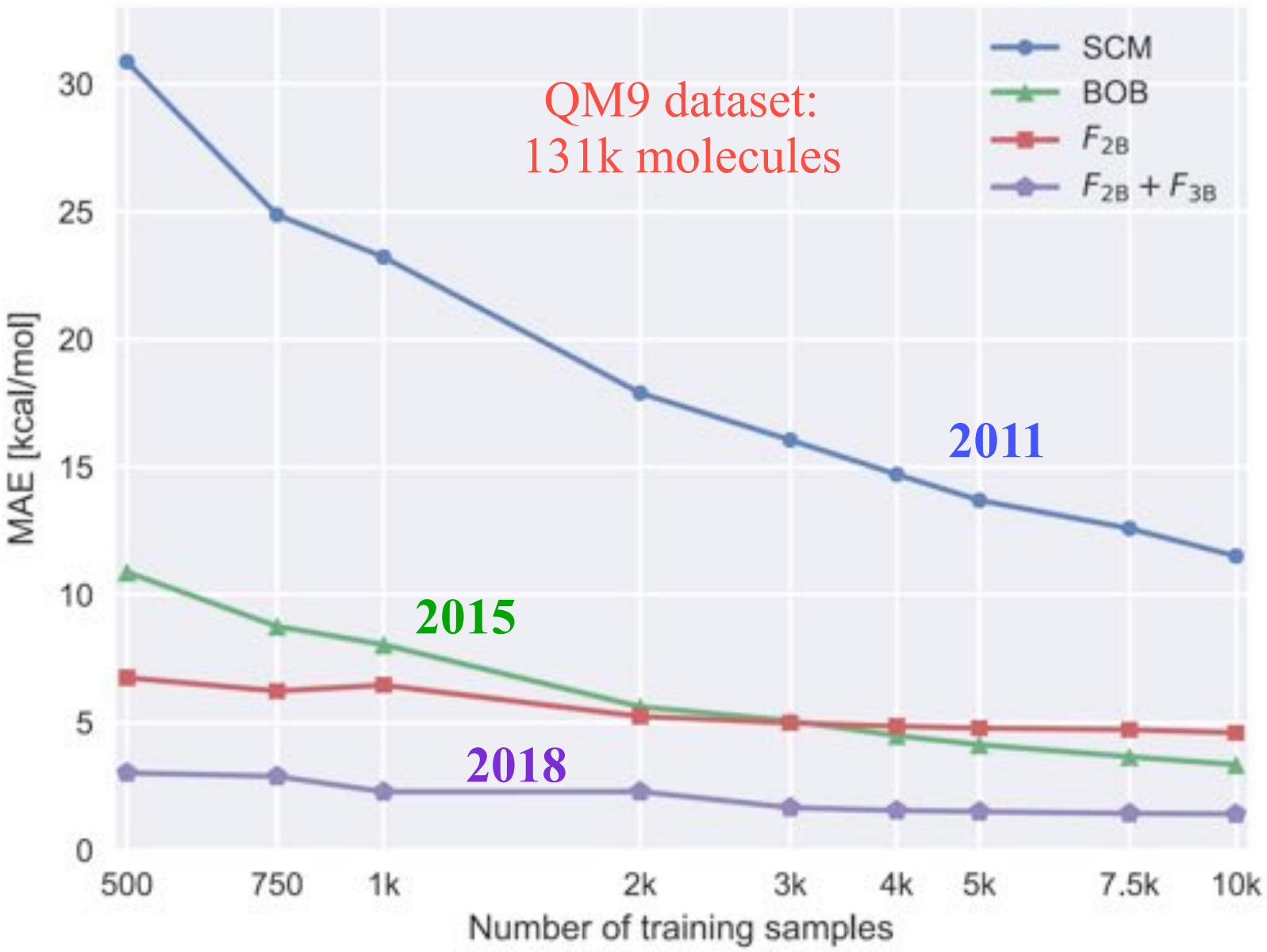
K. Hansen, F. Biegler,
R. Ramakrishnan, W. Pronobis,
O. A. von Lilienfeld,
K.-R. Mueller, and A. Tkatchenko,
J. Phys. Chem. Lett. 6, 2326 (2015).

Predicting Molecular Properties: QM7 dataset

model	MAE [kcal/mol]
dressed atoms	15.1
sum-overbonds	9.9
Lennard-Jones potential	8.7
polynomial pot. ($n = 6$)	5.6
polynomial pot. ($n = 10$)	3.9
polynomial pot. ($n = 18$)	3.0
Bag of Bonds ($p = 2$, Gaussian)	4.5
Bag of Bonds ($p = 1$, Laplacian)	1.5
Coulomb matrix ($p = 2$, Gaussian)[17]	10.0
Coulomb matrix ($p = 1$, Laplacian)[16]	4.3
2+3body many-body expansion	**0.8**

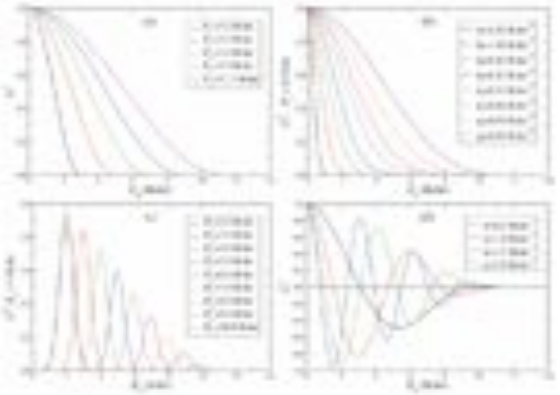
W. Pronobis, A. Tkatchenko, and K.-R. Mueller, ***J. Chem. Theory Comput.*** (2018).

QM9 dataset: Evolution from Coulomb Matrix to Many-Body Representation



W. Pronobis, A. Tkatchenko, and K.-R. Mueller, ***J. Chem. Theory Comput.*** (2018).

Zoo of Descriptors for Molecules and Solids



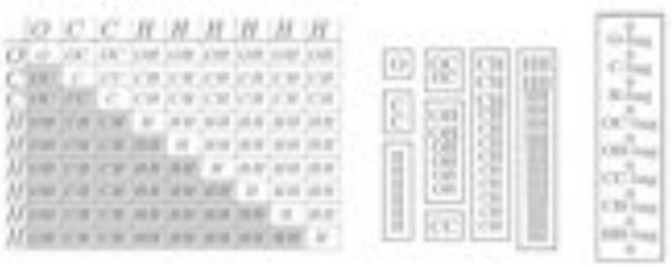
Atom-centered
symmetry functions
(Behler et al. 2007)

$$M_{ij} = \begin{cases} 0.5 Z_i^{2.4} & \text{for } i = j \\ \frac{Z_i Z_j}{d_{ij}} & \text{for } i \neq j \end{cases}$$

Coulomb matrix
(Rupp et al. 2012)

$$\{Z_i, \mathbf{R}_i\}$$

$$\{Z_i, d_{ij}\}$$



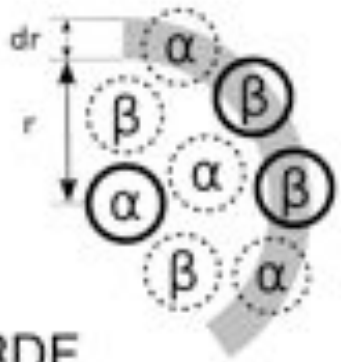
Bag of bonds
(Hansen et al. 2015)

$$k(\rho, \rho') = \int d\hat{R} \left| \rho(\mathbf{r}) \rho'(\hat{R}\mathbf{r}) \right|^n$$

SOAP
(Bartók et al. 2013)

$$x_{ij} = \begin{cases} 0.5 Z_i^{2.4} & \text{if } i = j \\ \frac{Z_i Z_j}{\phi(r_i, r_j)} & \text{if } i \neq j \end{cases}$$

Sine matrix
(Faber et al. 2015)

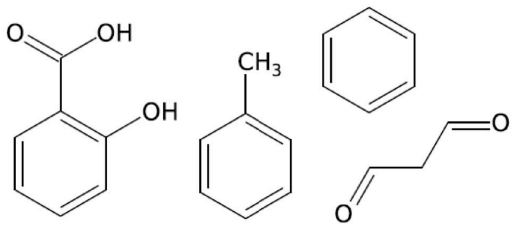


PRDF
(Schütt et al, 2014)

Slide from K. Schuett

Learning the Representation: Deep Tensor Neural Networks (DTNN)

Input: Atomic numbers and interatomic distances



$$Z = [\, Z_1 \quad Z_2 \quad \cdots \quad Z_n \,]$$

$$D = \begin{bmatrix} d_{11} & d_{12} & \cdots & d_{1n} \\ d_{21} & d_{12} & \cdots & d_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ d_{n1} & d_{n2} & \cdots & d_{nn} \end{bmatrix}$$

Embedding of based on atom types

$$\mathbf{x}_i^{(0)} = \mathbf{x}_{Z_i} \in \mathbb{R}^d$$

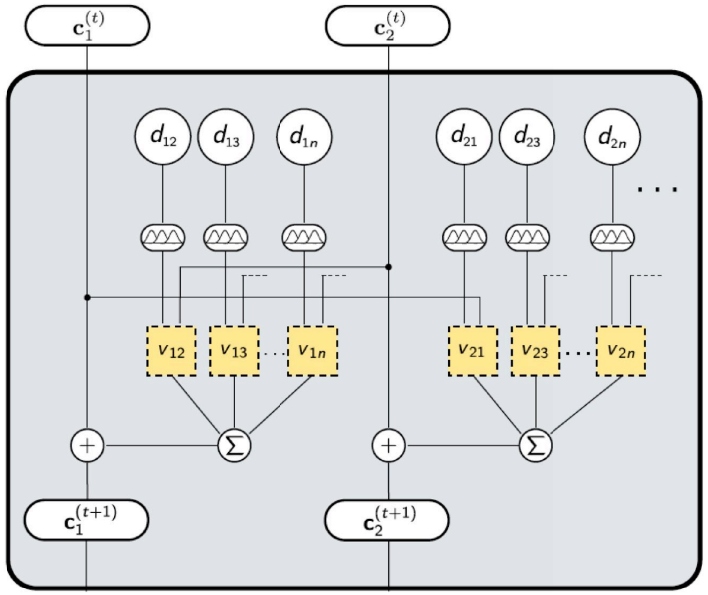
Add interaction with environment using $t = 1 \ldots T$ sequential refinements $\mathbf{v}_i^{(t)}$

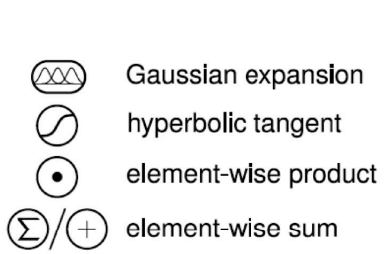
$$\mathbf{x}_i^{(t+1)} = \mathbf{x}_i^{(t)} + \mathbf{v}_i^{(t)} \left(\mathbf{x}_1^{(t)}, \ldots \mathbf{x}_{n_{\text{atoms}}}^{(t)}, d_{i1}, \ldots, d_{in_{\text{atoms}}} \right)$$

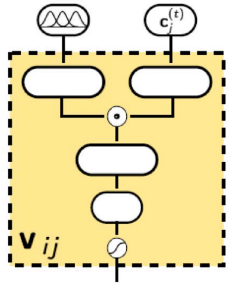
Prediction via atom-wise contributions:

$$\hat{E} = \sum_{i=1}^{n_{\text{atoms}}} f_{\text{out}}(\mathbf{x}_i^{(T)})$$

$$\hat{\mathcal{H}}\Psi = E\Psi$$





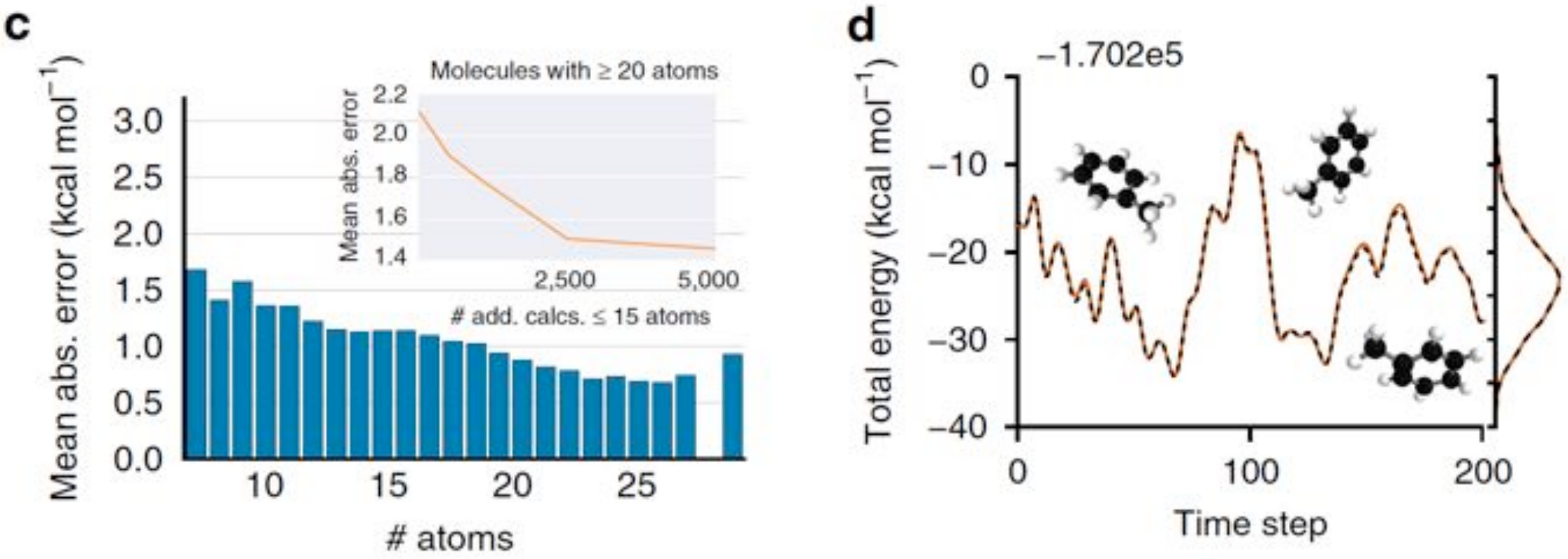


$$\tanh\left(W^{fc}((W^{cf}\mathbf{c}_j + \mathbf{b}^{f_1}) \circ (W^{df}\hat{\mathbf{d}}_{ij} + \mathbf{b}^{f_2}))\right)$$

Mean absolute error on QM9: **0.2 kcal/mol**

K. T. Schuett, F. Arbabzadah, S. Chmiela, K.-R. Mueller, and A. Tkatchenko, ***Nature Commun.*** 8, 13890 (2017).

Learning Full Chemical Space with DTNN?

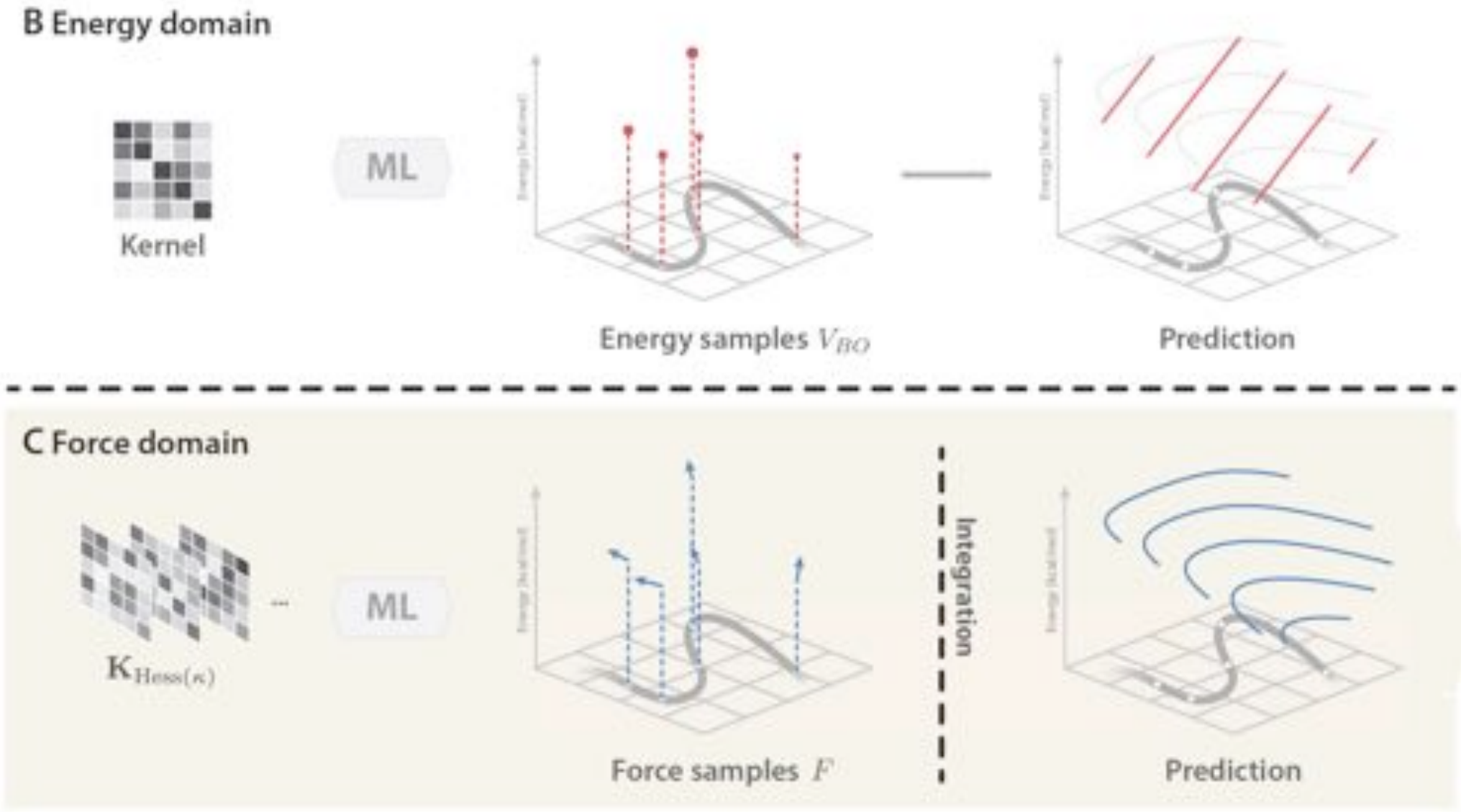


Accurately representing BOTH compositional and conformational degrees of freedom is difficult.

For C7O2H10 isomer and MD data, the error grows to > 1.0 kcal/mol

K. T. Schuett, F. Arbabzadah, S. Chmiela, K.-R. Mueller, and A. Tkatchenko, ***Nature Commun.*** 8, 13890 (2017).

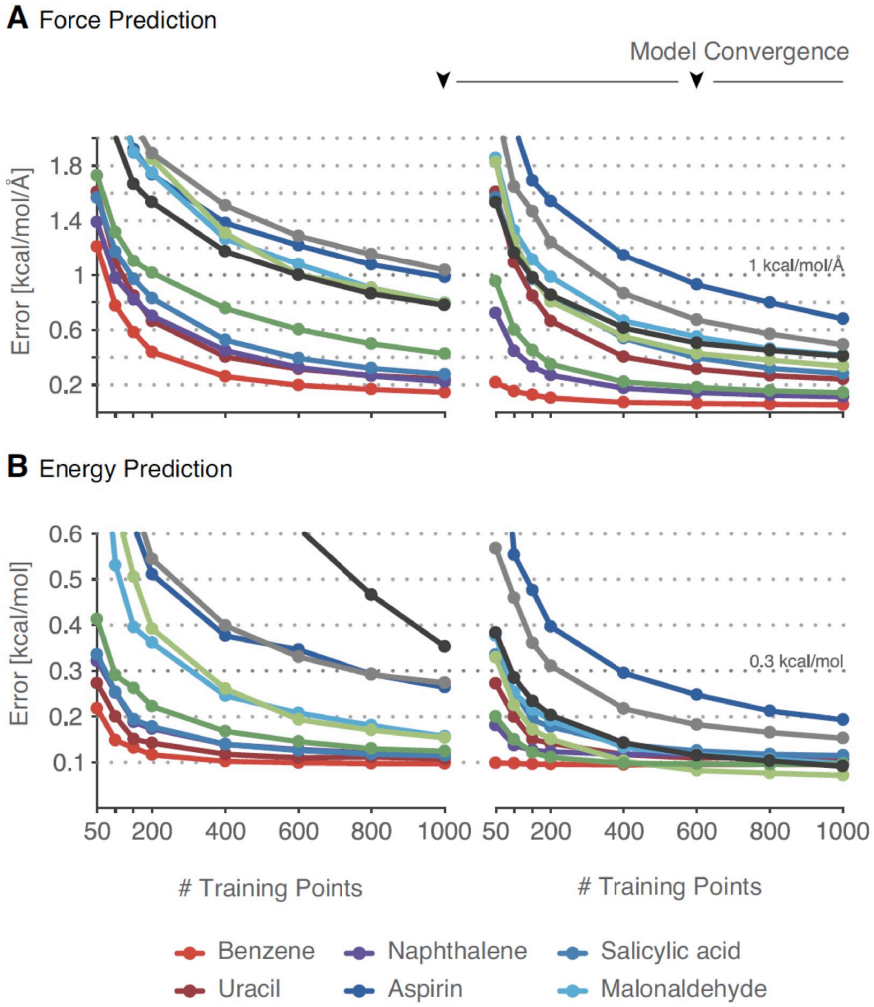
Beating the Hell out of Data:
Gradient-Domain Machine Learning (GDML)



S. Chmiela, A. Tkatchenko, H. Sauceda, I. Poltavsky, K. T. Schuett, K.-R. Mueller, ***Science Adv.*** 3, e1603015 (2017).

Symmetrized Gradient-Domain Machine Learning: Towards Exact Molecular Force Fields

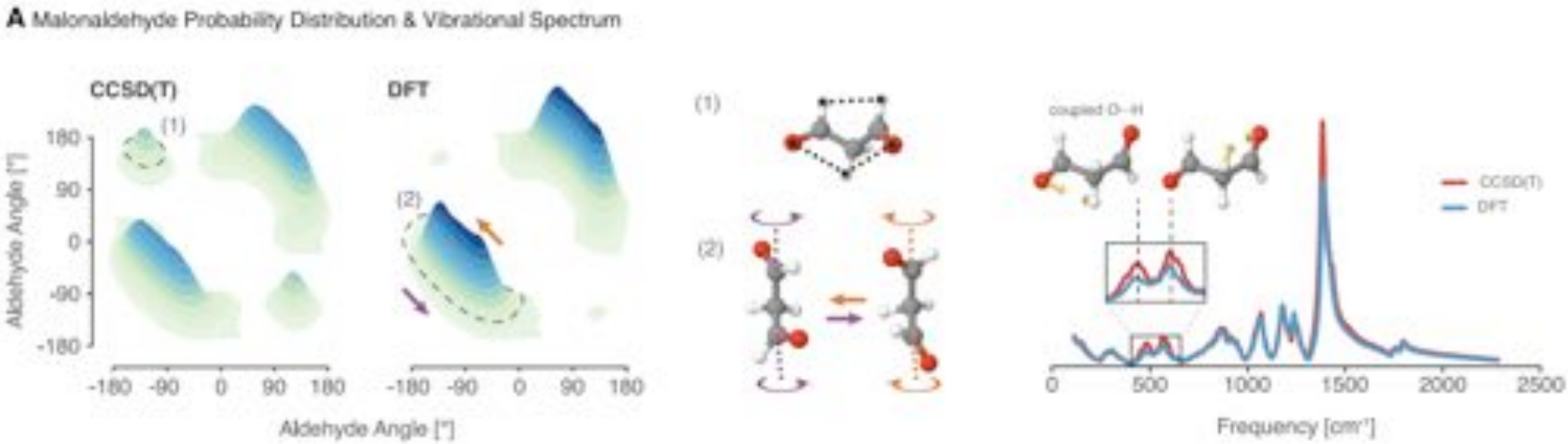
$$\hat{\mathbf{f}}_{\mathbf{F}}(\mathbf{x}) = \sum_{i}^{M} \sum_{l}^{3N} \sum_{q}^{S} (\mathbf{P}_q \alpha_i)_l \frac{\partial}{\partial x_l} \nabla \kappa\left(\mathbf{x}, \mathbf{P}_q \mathbf{x}_i\right)$$



Globally accurate force field from only 100s of conformations

S. Chmiela, H. Sauceda, K.-R. Mueller, and A. Tkatchenko, ***Nature Commun.*** 9, 3887 (2018).

Embarrassingly Quantum MD for Molecules: Quantized Electrons [CCSD(T)] and Nuclei [PIMD]



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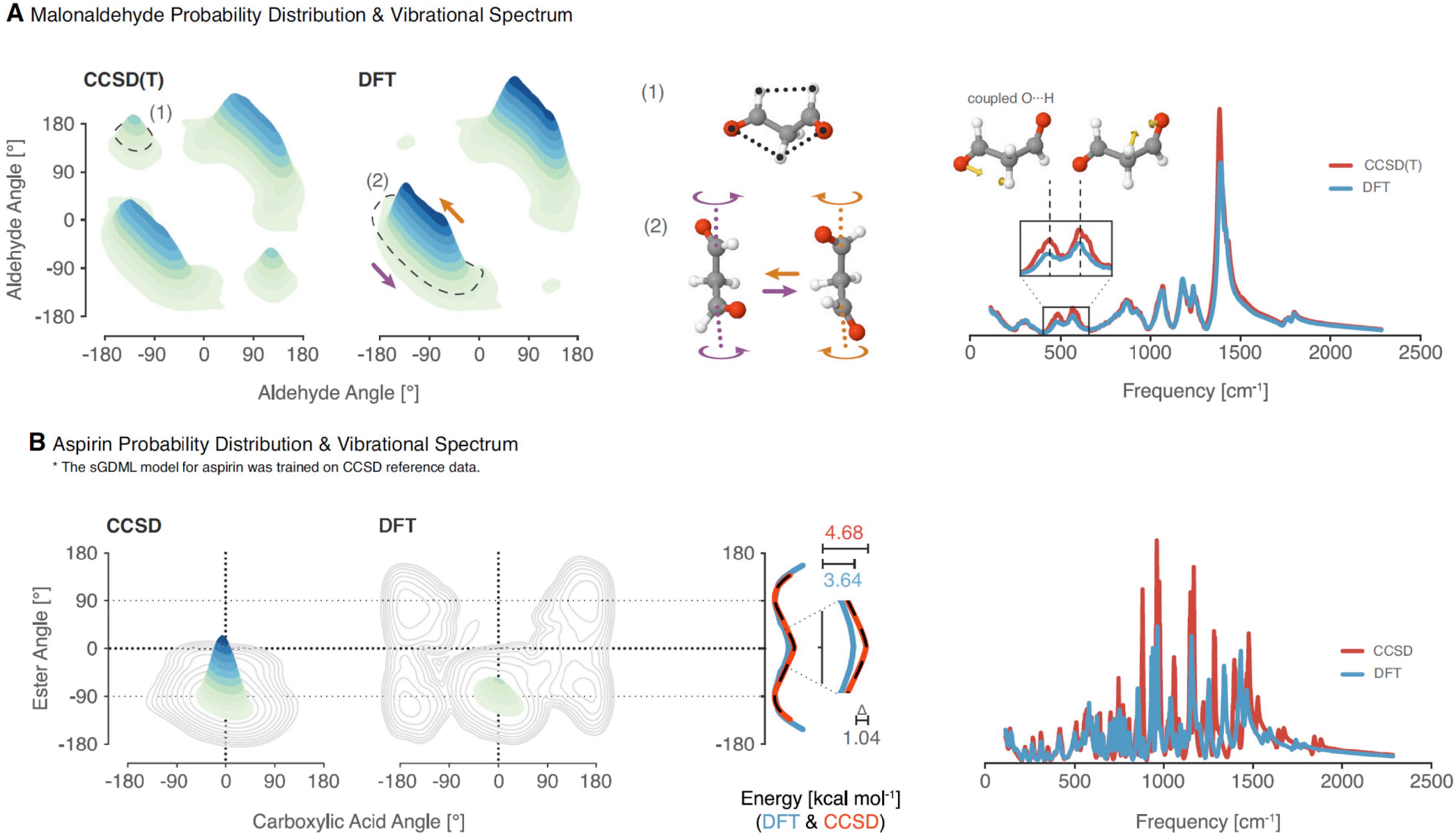

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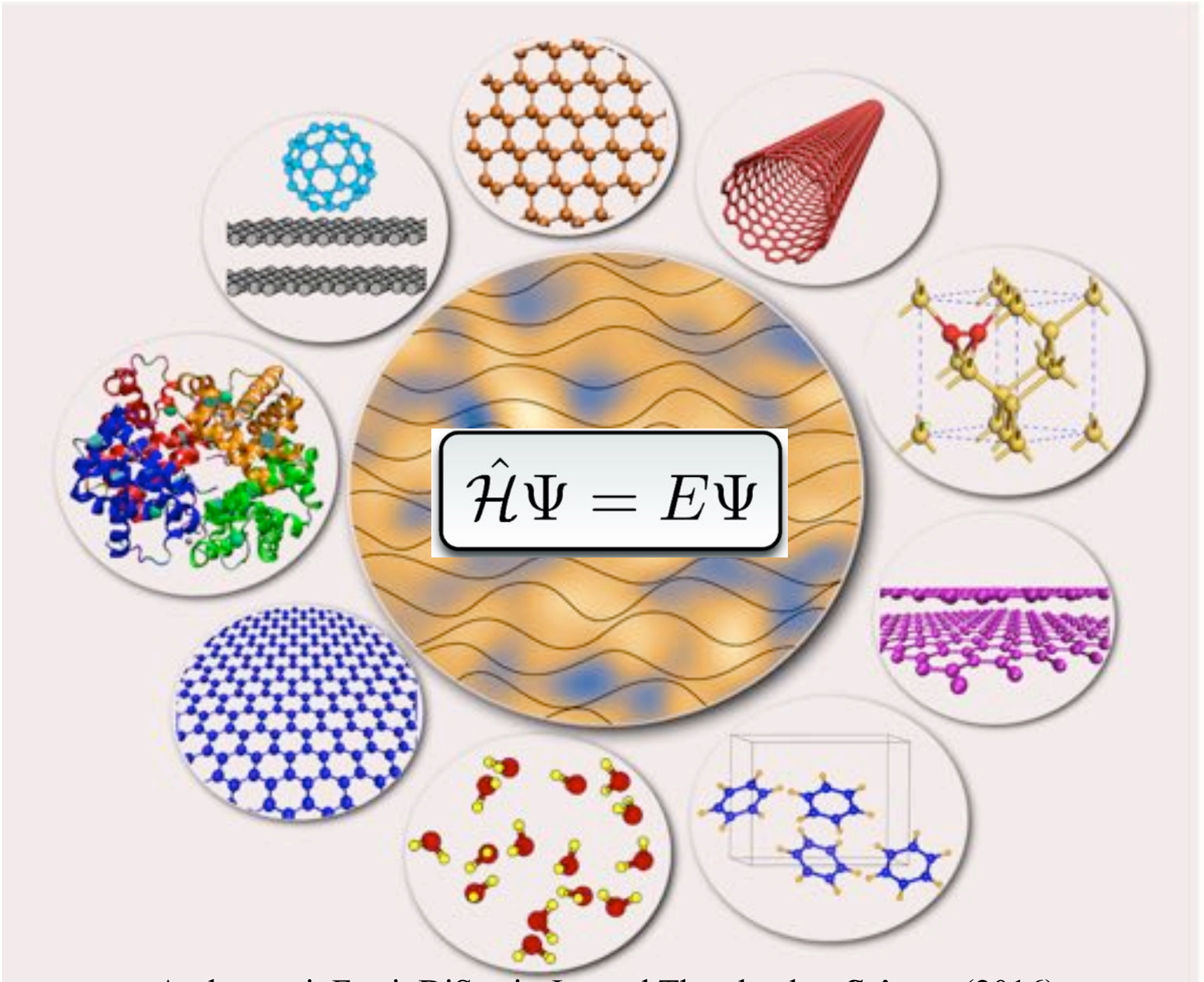

Ambrosetti, Ferri, DiStasio Jr., and Tkatchenko, ***Science*** (2016).

Grand Challenges for Machine Learning in Physics/Chemistry

- *What is chemical space*: descriptors of molecules and materials, metric?
- *How to learn intensive properties*: energy levels, excited states, spectra?
- How to combine ML with physical laws (symmetries) and interaction models?
- Can we learn (approximate) Hamiltonians?
- Can ML suggest better approximations for $\hat{\mathcal{H}}\Psi = E\Psi$?
- More and better (big) data

Towards rational design of molecules and materials in chemical space