Machine learning and chemistry

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the Kulik group at MIT, `hjkgrp.mit.edu/`

under the supervision of Professor Heather J. Kulik

for the most recent version and demos: `github.com/jpjanet/ML-chem-workshop`
this revision: `77912f6e6368dd7f92be8043f4d6ef5e2770295f` on branch `master`

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Rise of the (chemical) machines

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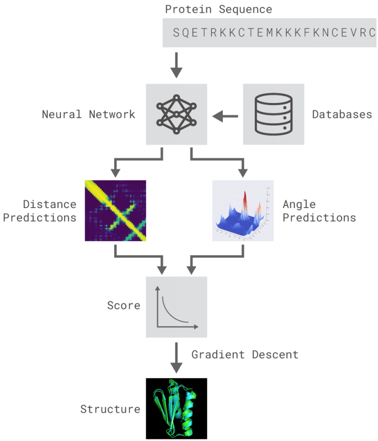

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This is probably a bit strong, but all scientists generate data as a product. ML provides new, powerful ways to exploit their that information.

Types of machine learning

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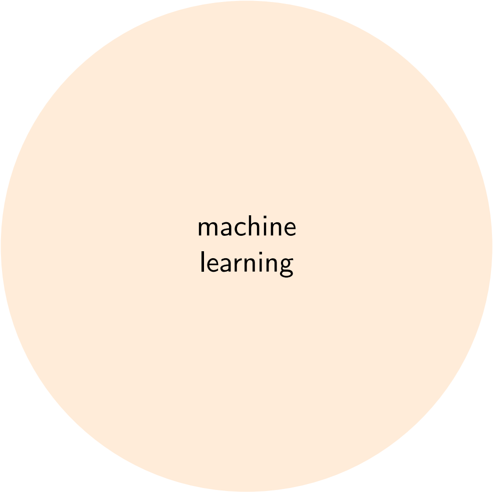

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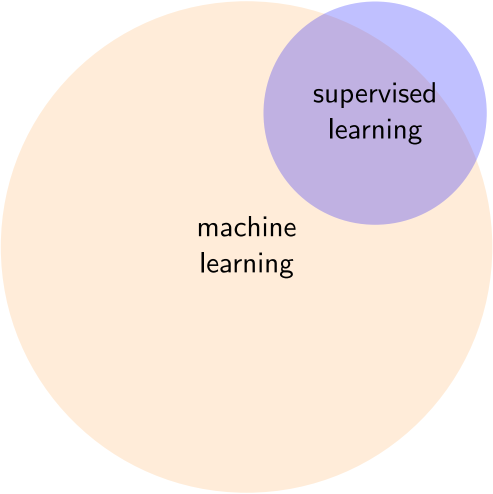

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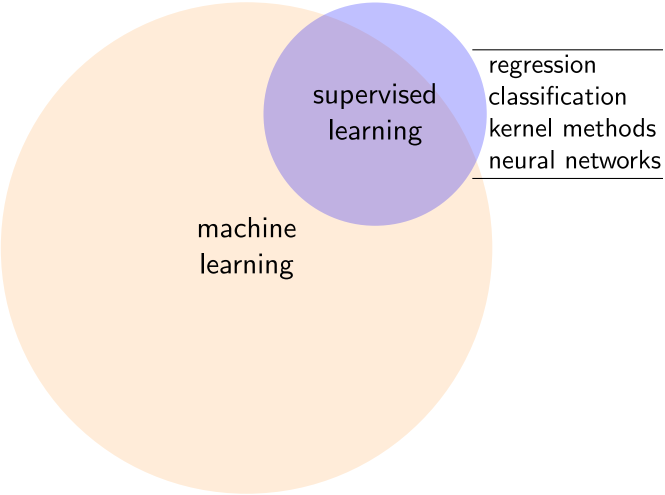

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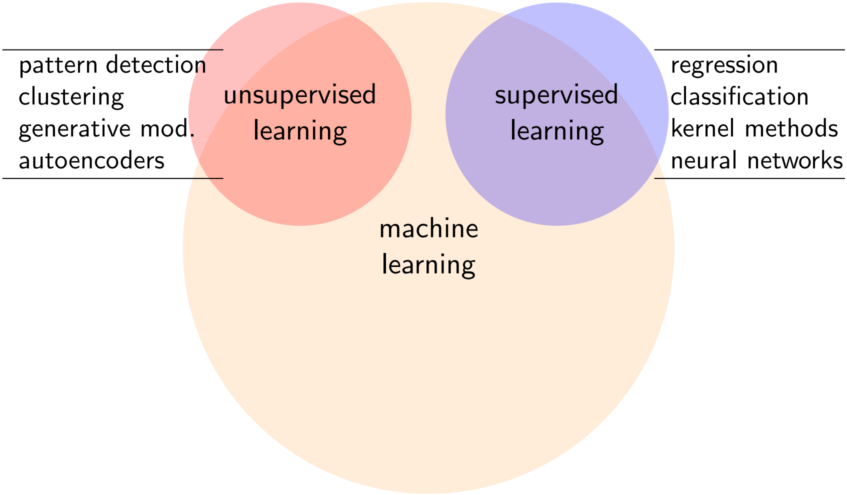

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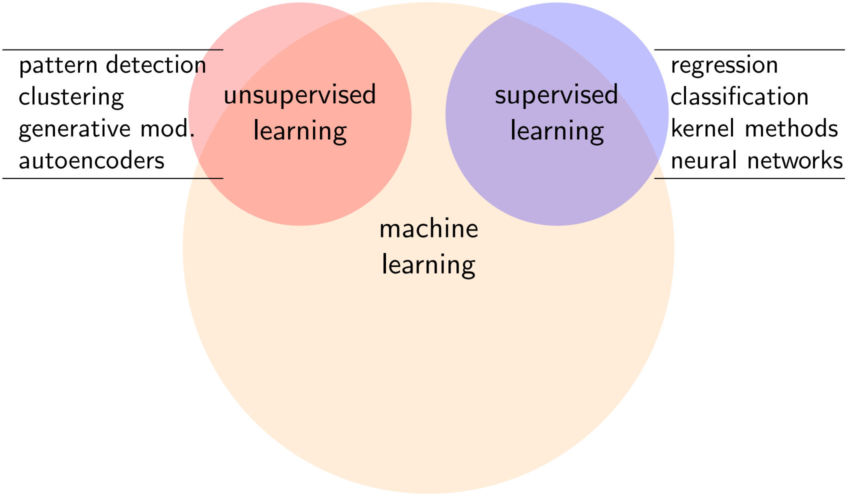

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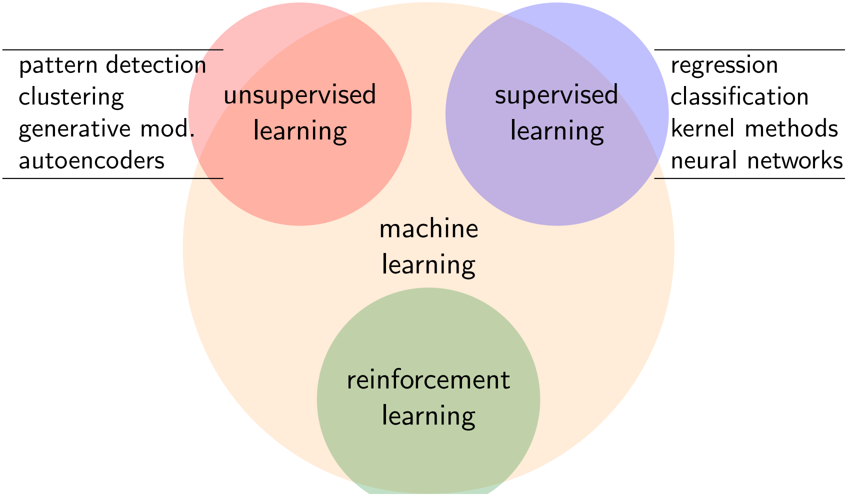

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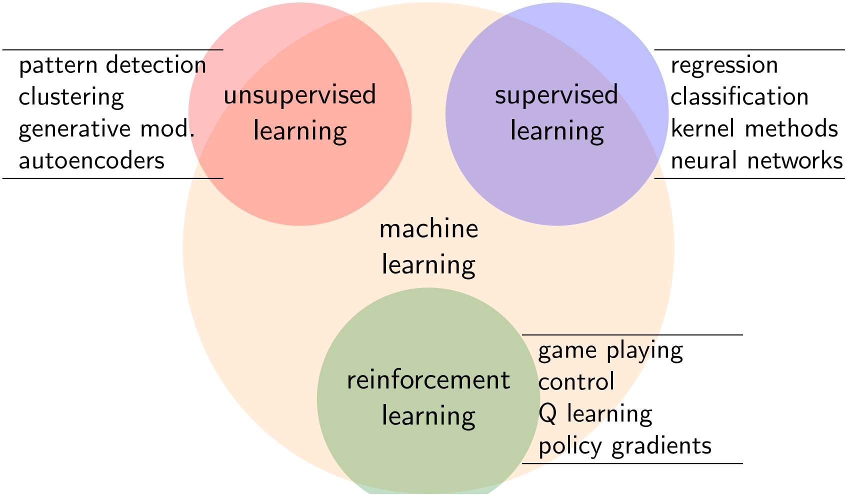

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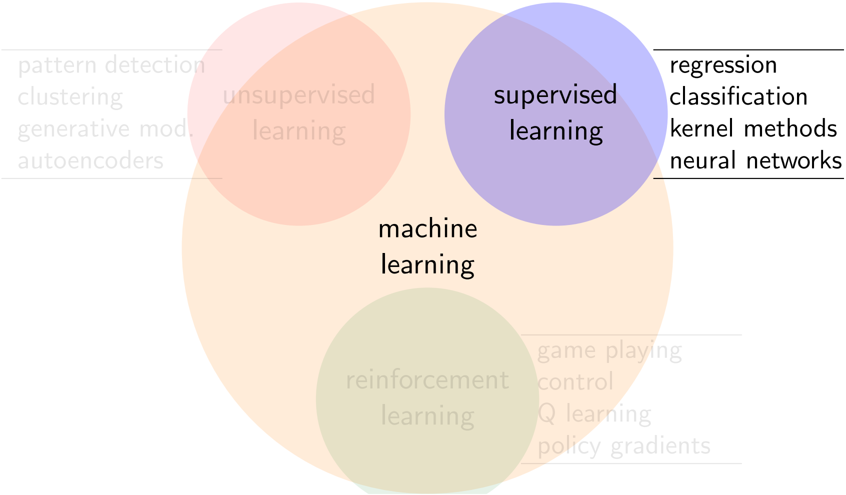
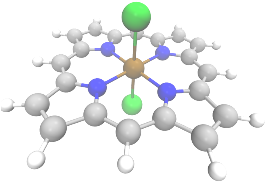


Why ML in chemistry?



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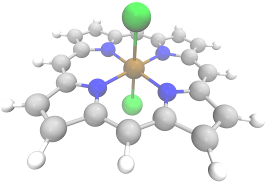

property

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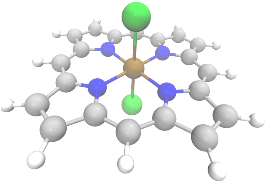

experiment

days, weeks

property

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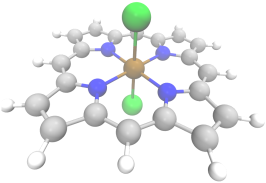


experiment

days, weeks

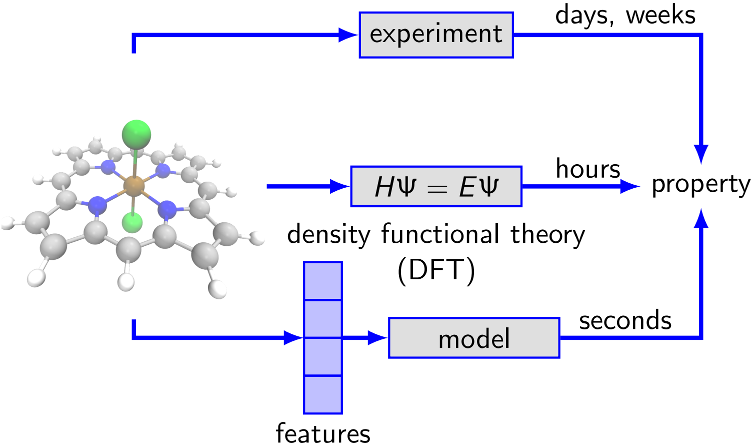
$H\Psi = E\Psi$

hours

property

density functional theory (DFT)

Why ML in chemistry?



Structure of this talk

We will cover the following topics:

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1. Statistical learning theory

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4. Feature Selection and Forests
5. Neural networks and representation learning

Please ask questions throughout!

Disclaimer

Warning: this talk contains some *light* mathematics.

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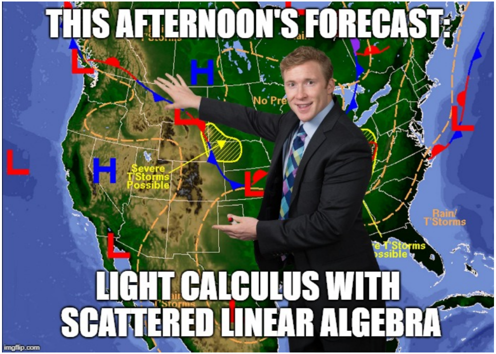

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Some useful notation:

X	training data, as rows
x^*	one new molecule/systems
$y, \hat{y}$	property(energy?), predicted value
$\mathcal{L} = \|y - \hat{y}\|_2^2$	loss function
W, w	model parameters
$\hat{y} = f(x, W)$	our model

The goal of statistical learning

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observation property

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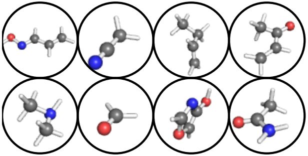
observation



property

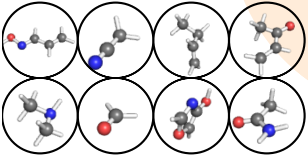
energy,
structre...

The goal of statistical learning

model family

observation

property



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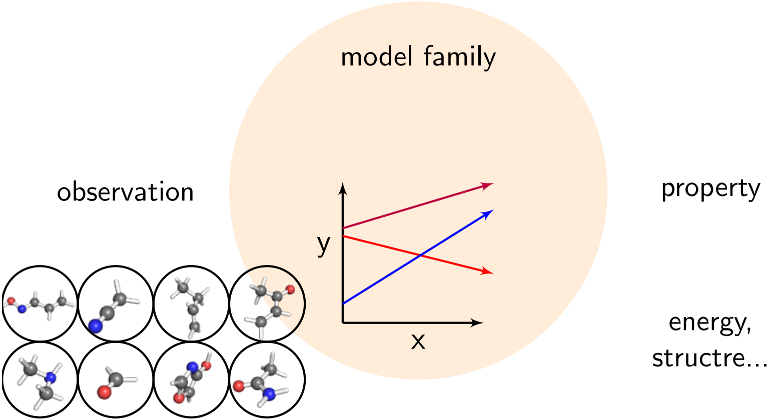

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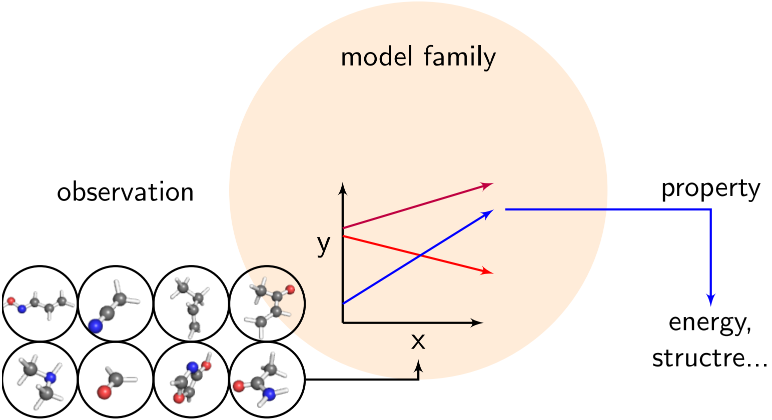

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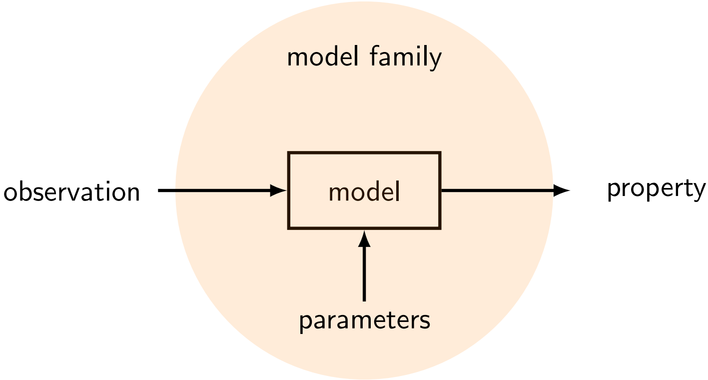

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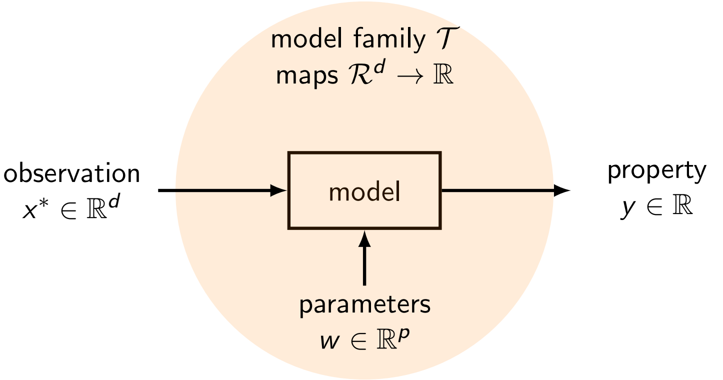
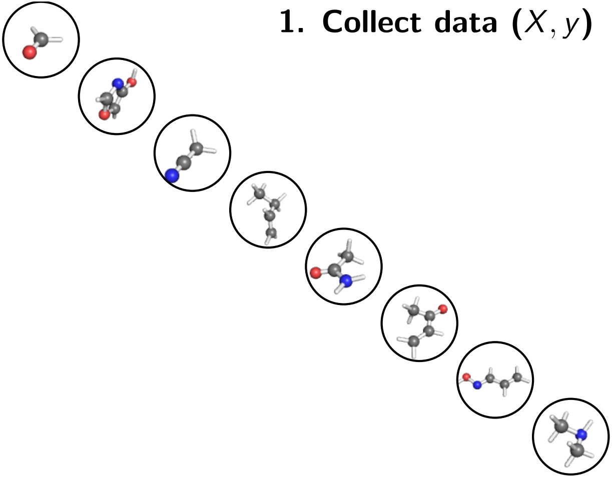


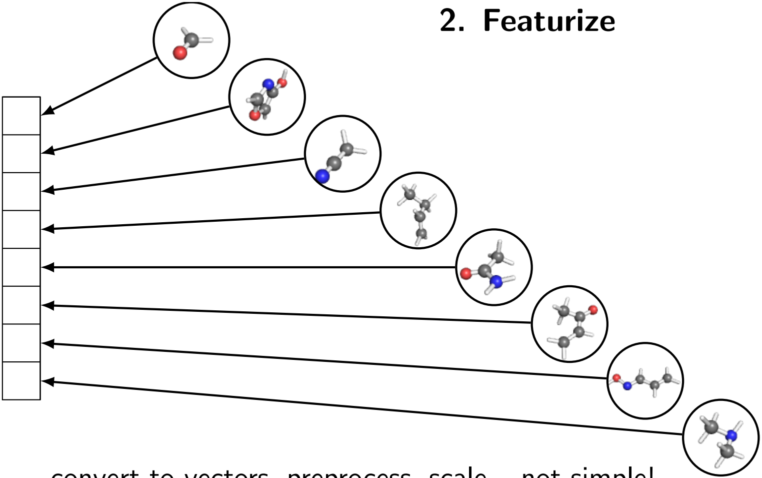
Overview of supervised learning



1. Collect data (X, y)

Overview of supervised learning

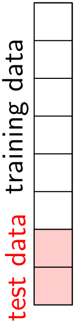
2. Featurize



convert to vectors, preprocess, scale – not simple!

Overview of supervised learning

3. Partition data



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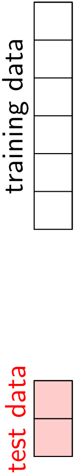

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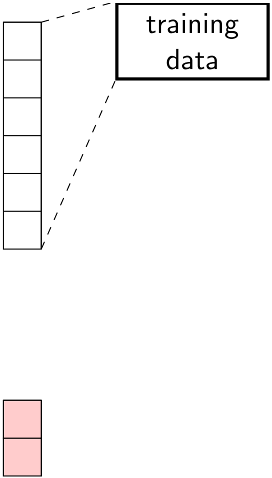
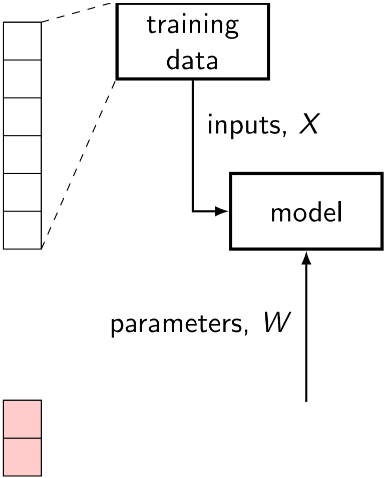


4. Learning phase

Overview of supervised learning



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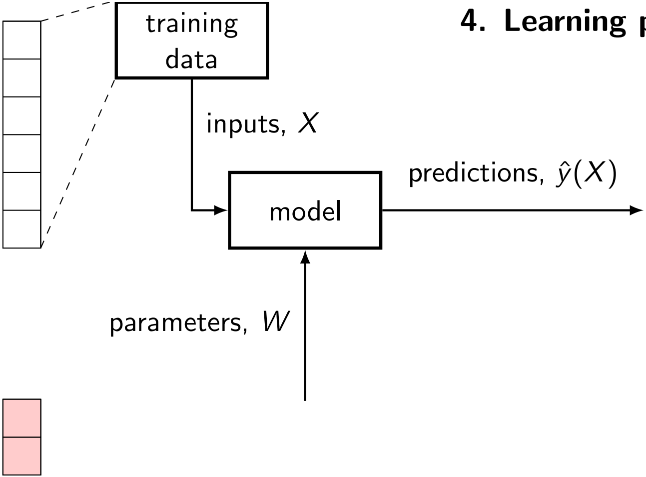

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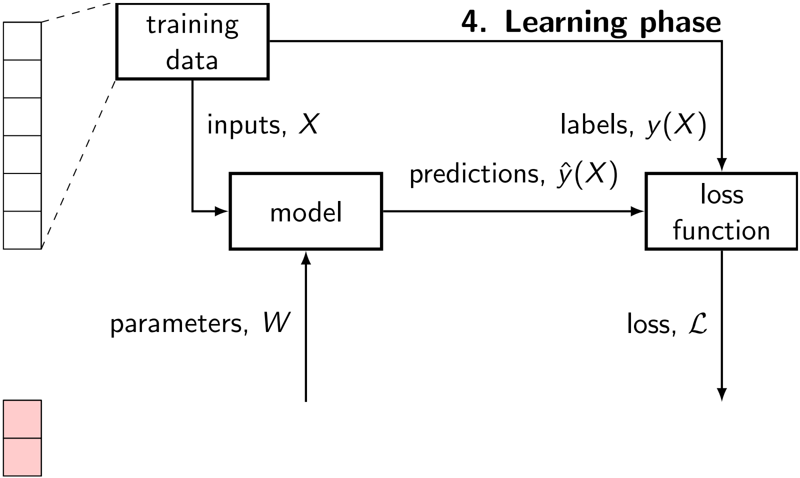

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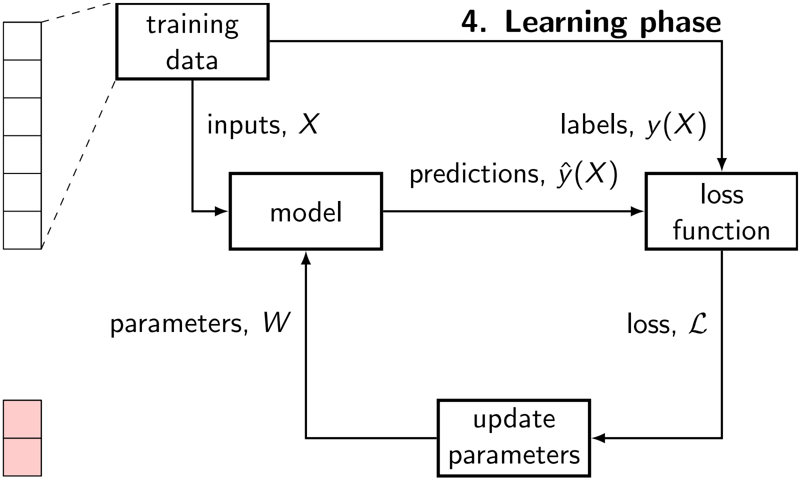

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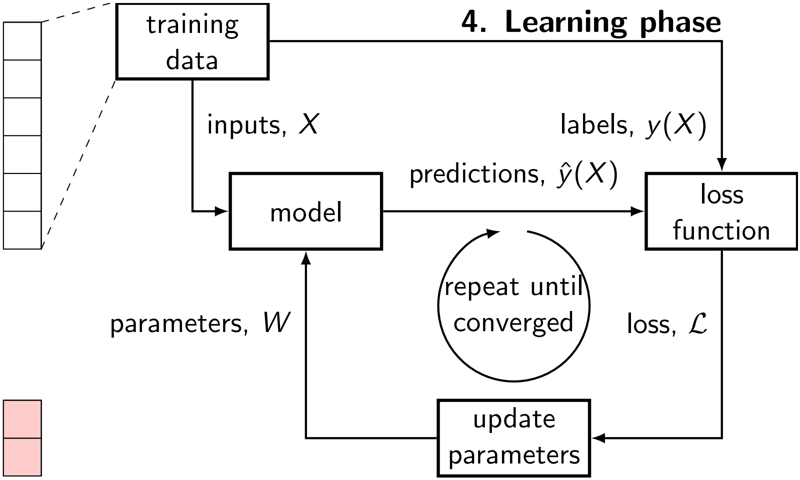

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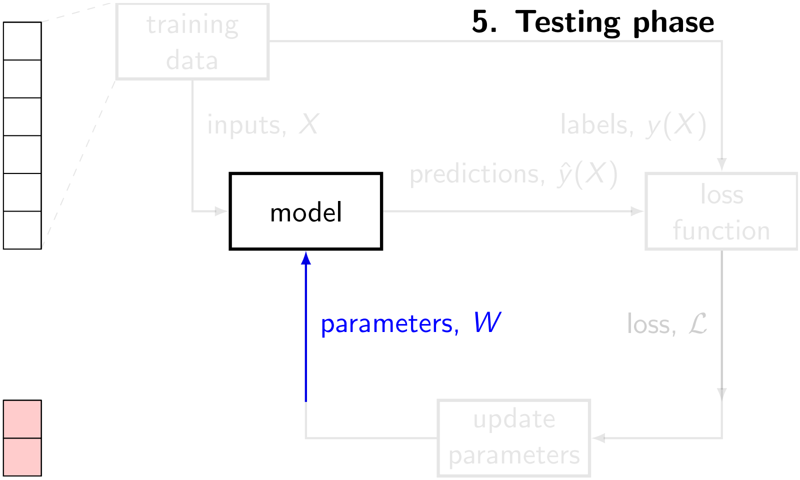

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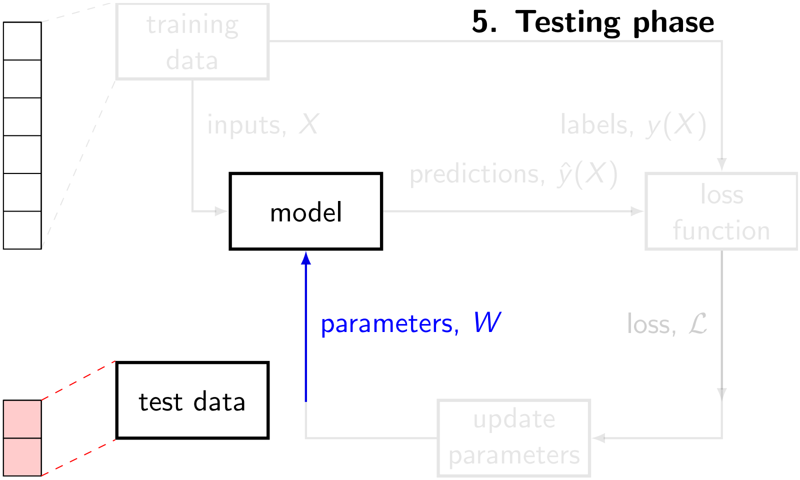

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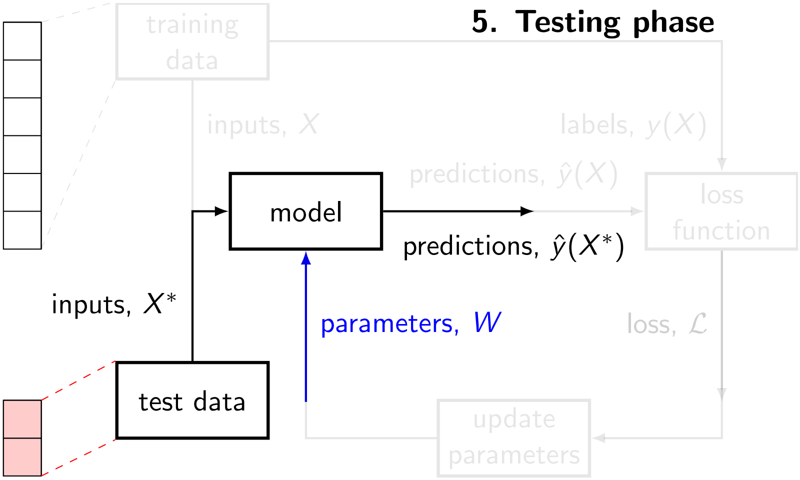

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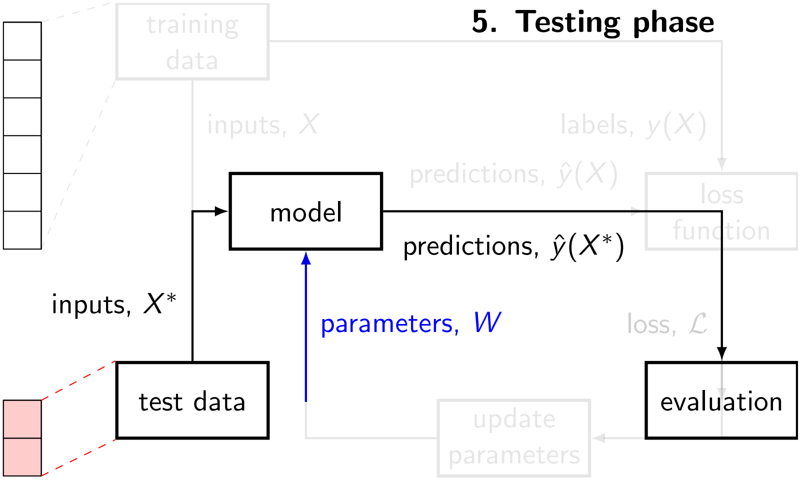

Risk and generalization - I

Our training data defines the *empirical risk*

$$\mathcal{E}_{emp}(f) = \frac{1}{n}\sum_{i=1}^{n}\mathcal{L}(y_i, f(x_i)) = \frac{1}{n}\sum_{i=1}^{n}(y_i - f(x_i))^2$$

we choose the model to minimize $\mathcal{E}_{emp}(f)$ over all the models in $\mathcal{T}$

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with minimum

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We cannot expect that f^* is in $\mathcal{T}$. The best we can do is $f^\dagger$:

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Two critical ideas that are worth noting. Under mild assumptions one can show that:

Risk and generalization - III

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We want $\mathcal{T}$ to be large/complicated enough to have low approximation error, **but no more complicated**.

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With limited data, we are often better off searching for a model in a simpler family models of that 'learn' more robustly and quickly as opposed to very complicated models with lots of parameters.

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2. estimation error is inversely related to model complexity, i.e. more complicated spaces of models require more data to generalize.

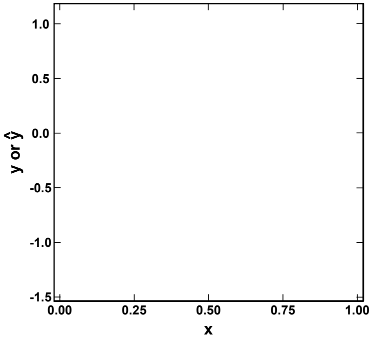
Conversely, a simple model will stop improving with more data past a certain point – where the approximation error dominates.

Risk and generalization - IV

Let us use **polynomials** to estimate:

$$y(x) = \sin(2\pi x)$$

Note that $f^* \notin \mathcal{T}$!



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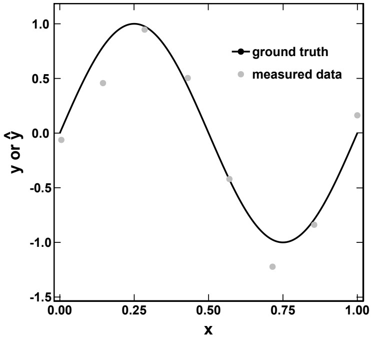
Assume 8 measurements with noise $\mathcal{N}(0, 0.2)$



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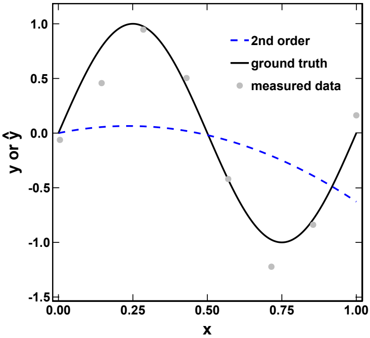
Start with degree 2...



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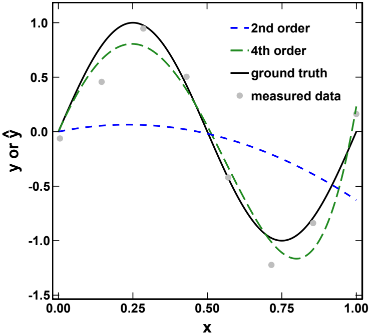
Start with degree 2...What happens when we increase the order?



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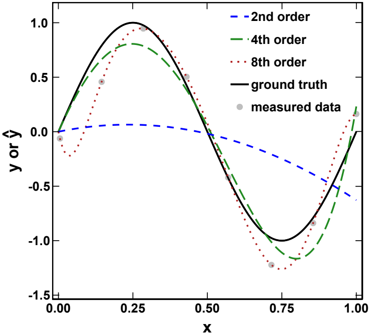

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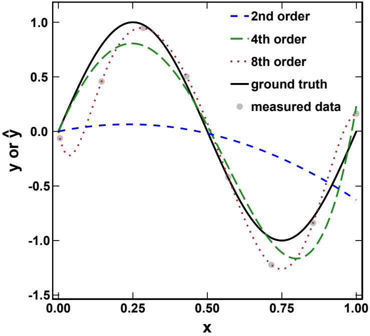
What do the risk terms look like?



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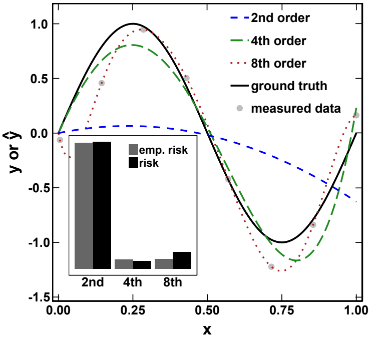
Note that $f^* \notin \mathcal{T}$!

What do the risk terms look like?



Risk and generalization - IV

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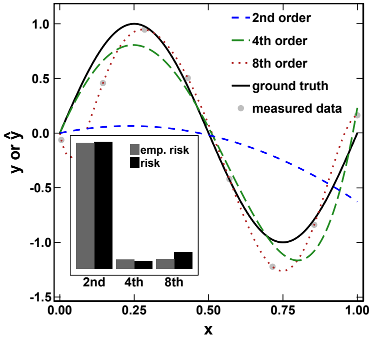
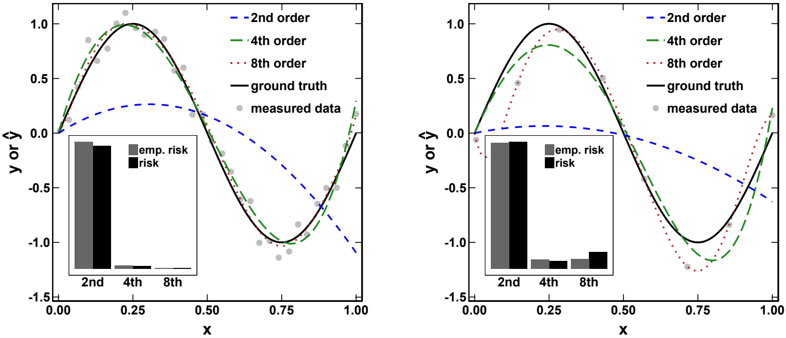


What happens if we add more data?

Risk and generalization - IV



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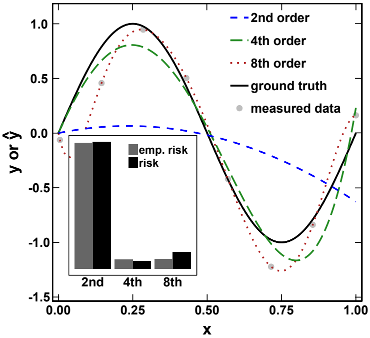
- This makes empirical errors worse.
- This *can* improve generalization/excess risk.

Controlling Complexity

Let's return to our previous example:



Remember: larger $\lambda =$ simpler, flatter model.

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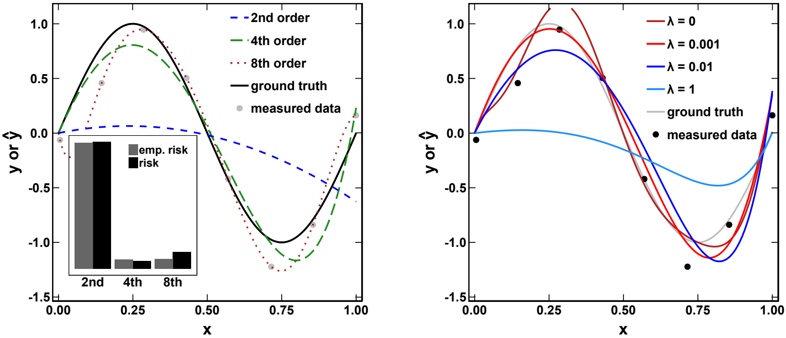

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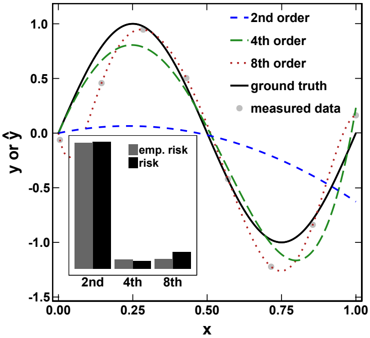

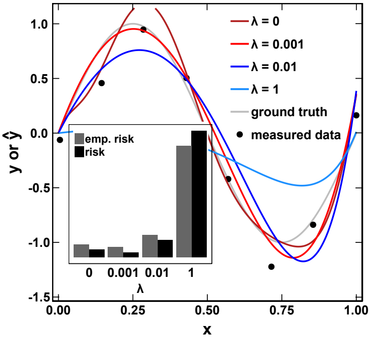

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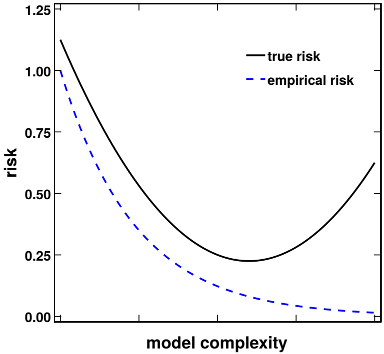

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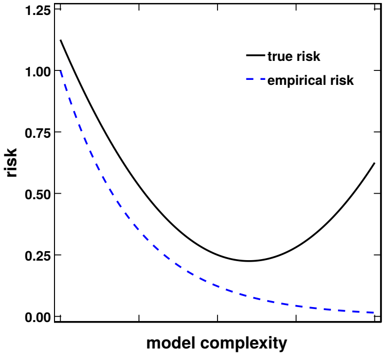

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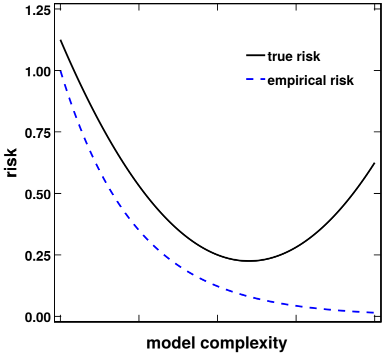
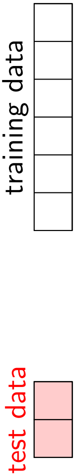


None of this helps us understand a how complicated our model should be. Unfortunately, **errors on our training data cannot tell us the answer**

(Cross)-validation



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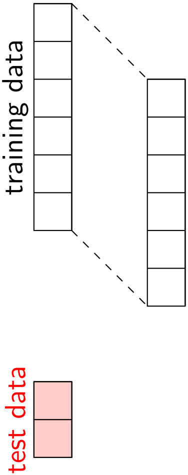

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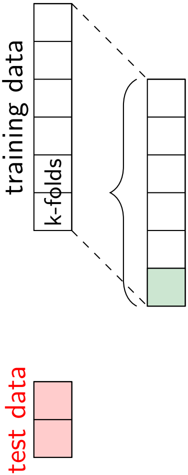

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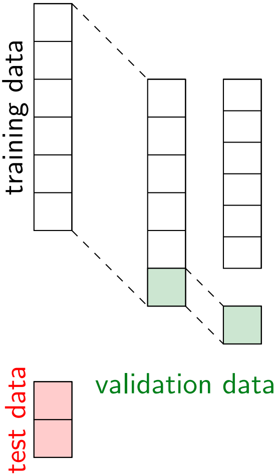

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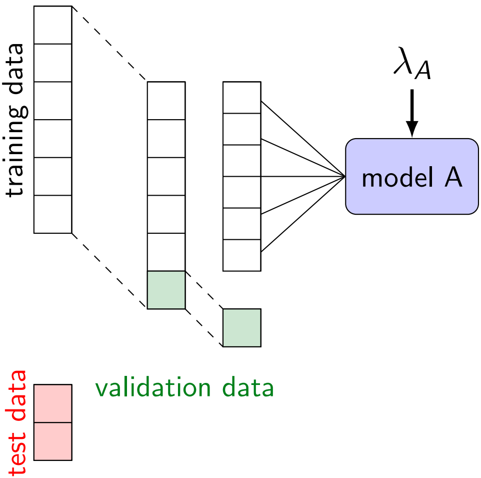

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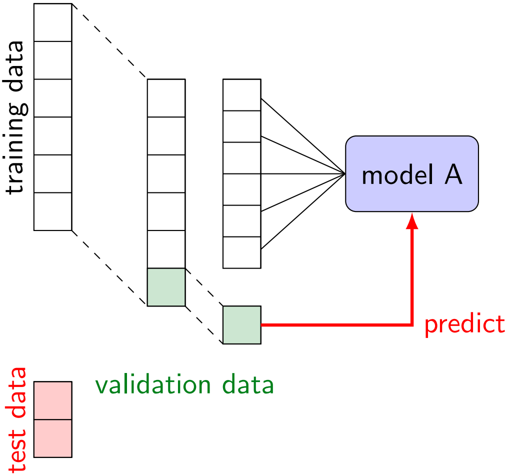

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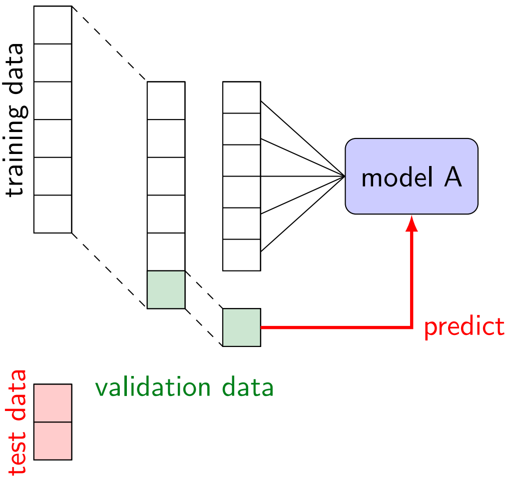

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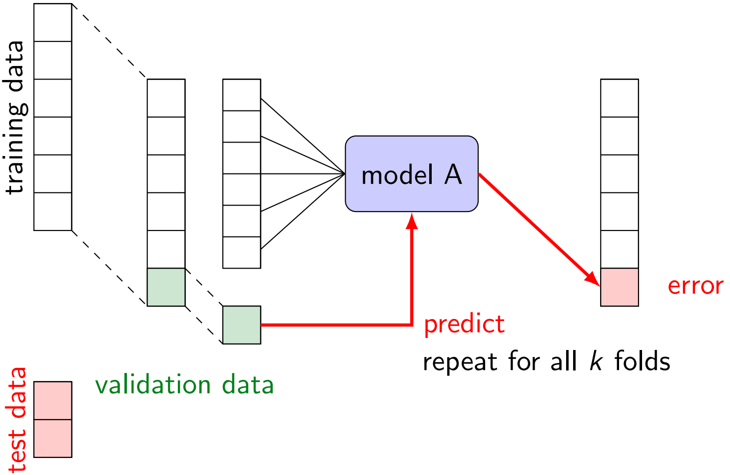

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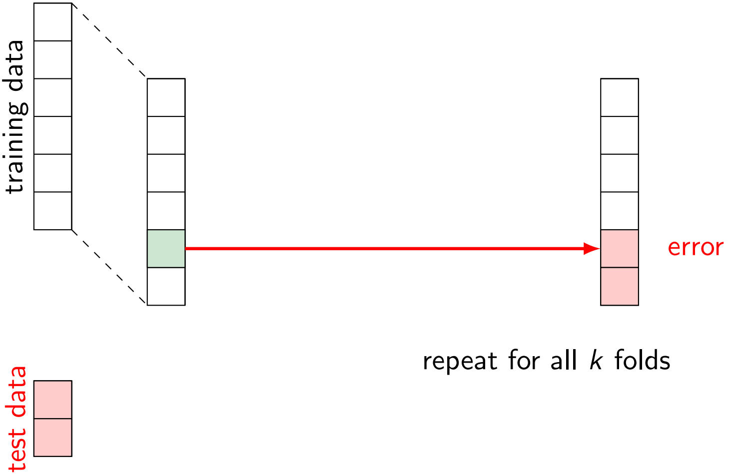

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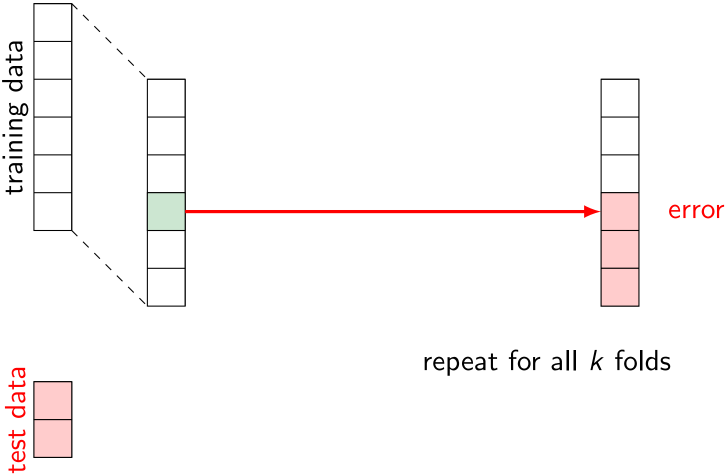

repeat for all k folds

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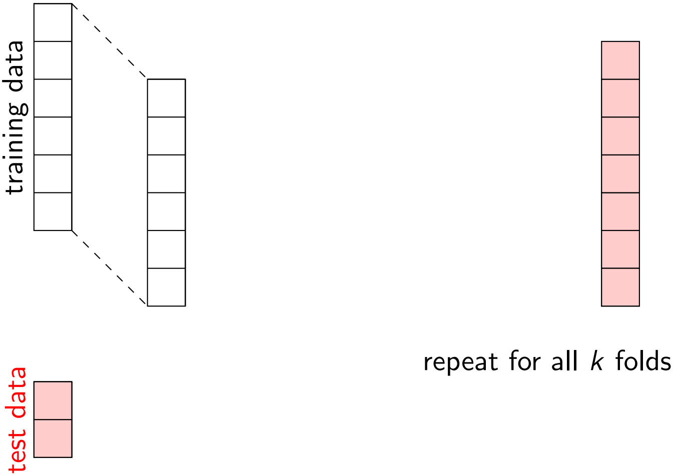

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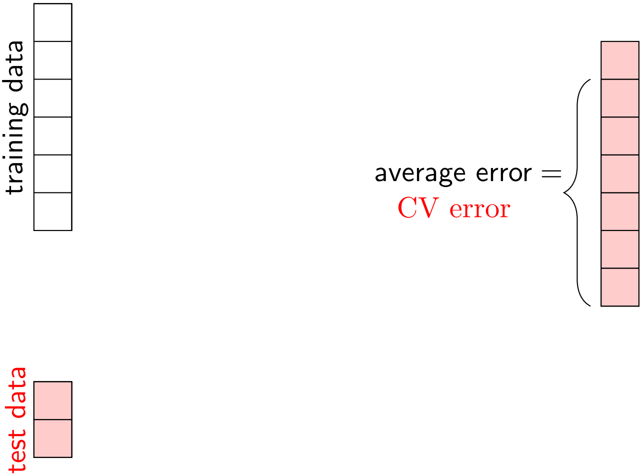

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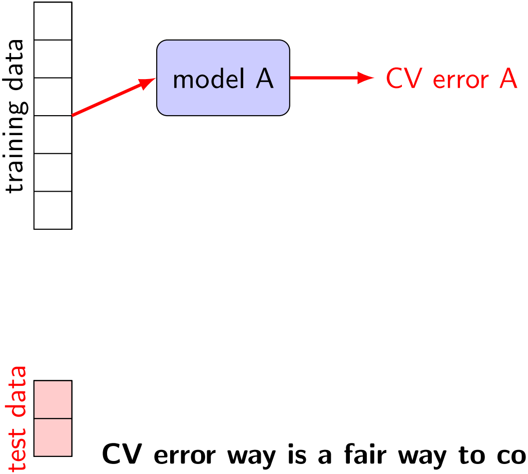

CV error way is a fair way to compare models

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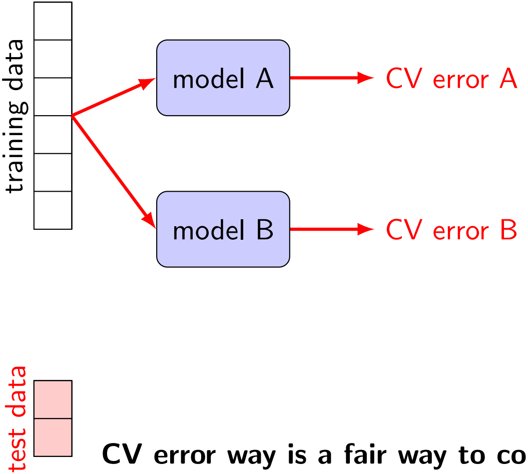

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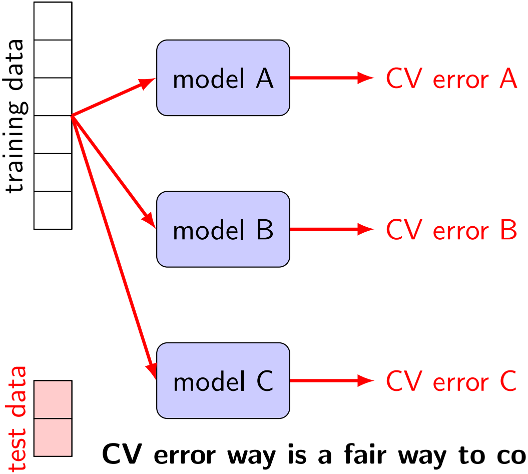

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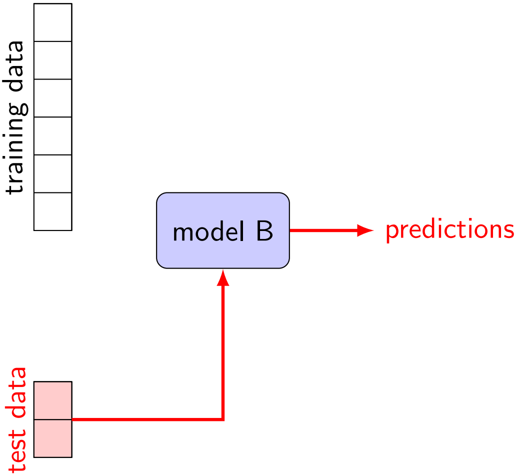

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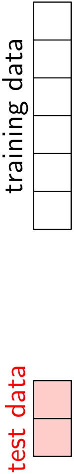

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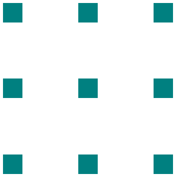
Deep neural networks (might) need better theories.

Purpose



Chemical Space C_f

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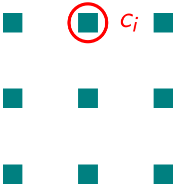

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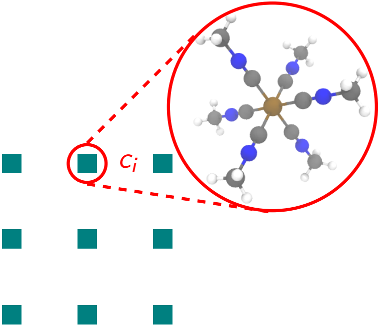

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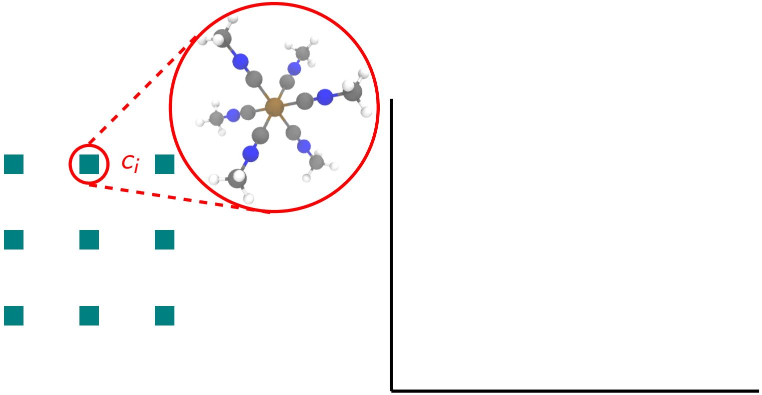

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Descriptor Space $\mathcal{X} \subset \mathbb{R}^d$

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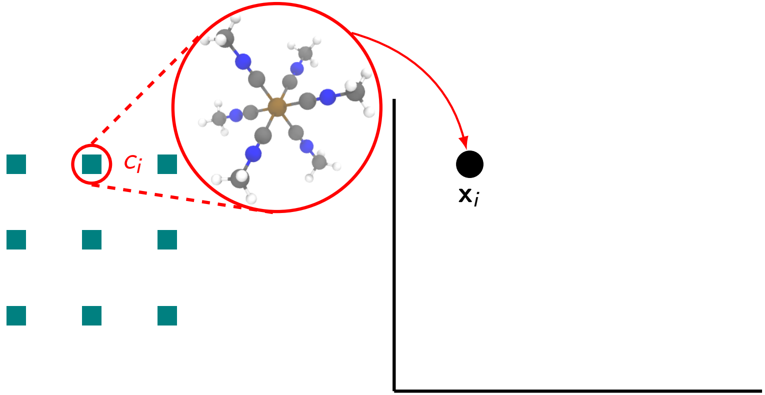

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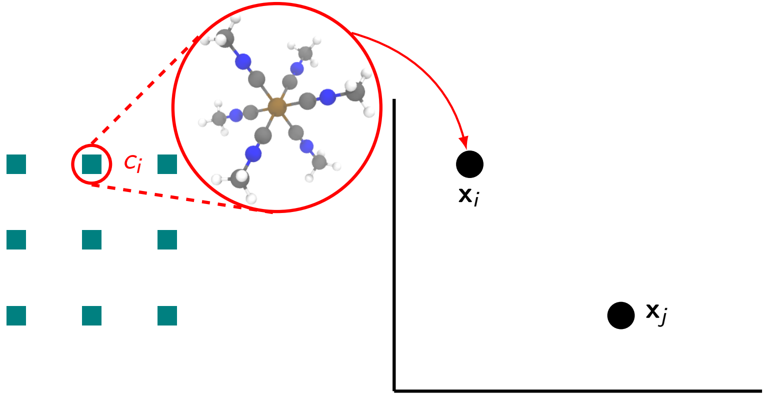

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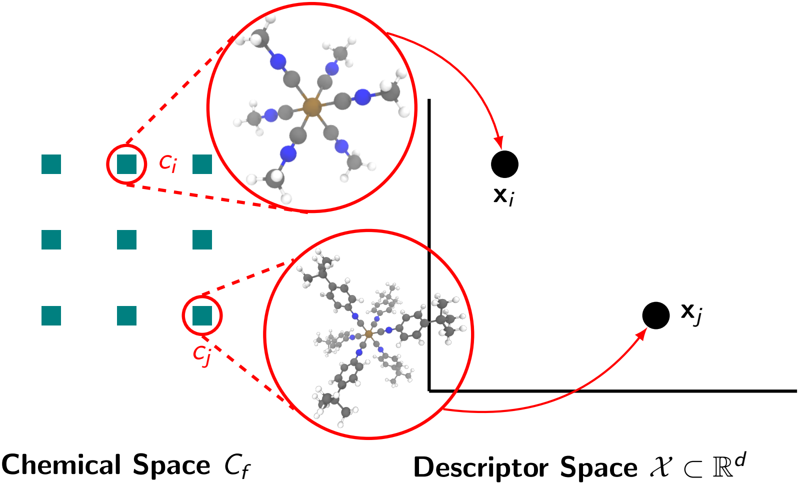
c_i
c_j
$\mathbf{x}_i$
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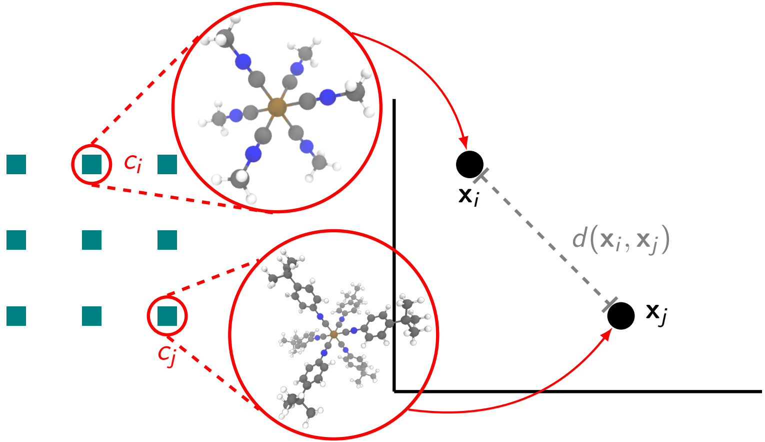

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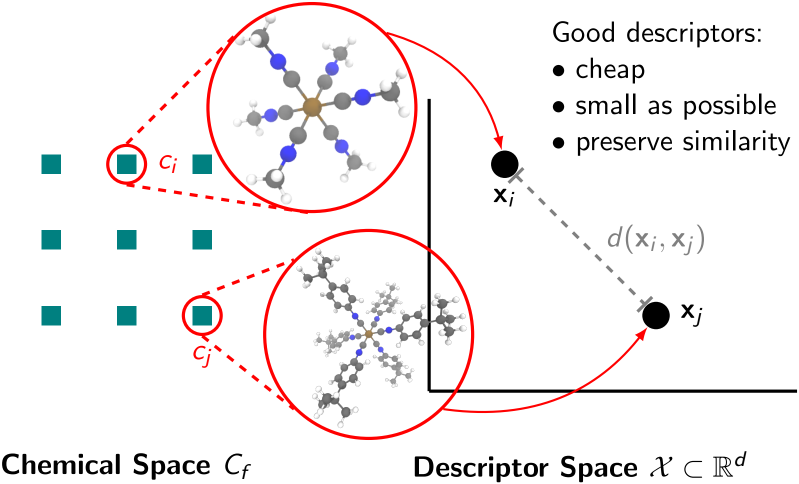

Good descriptors:

- cheap
- small as possible
- preserve similarity

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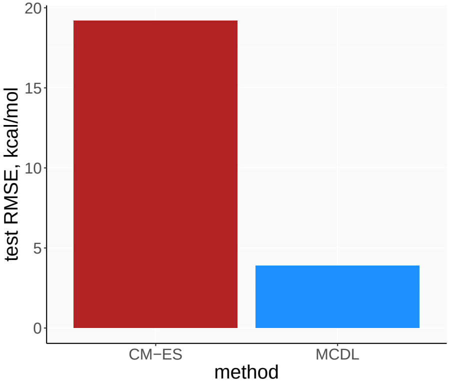

Janet, J.P., and Kulik, H.J. *Chem. Sci.*, 2017, 8, 5137-5152.

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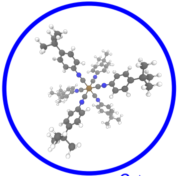

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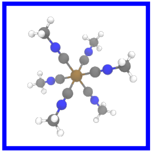

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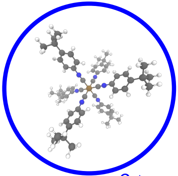

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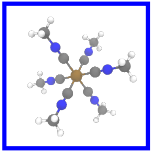
$\Delta E_{H\text{-}L} = 37.7$ kcal/mol



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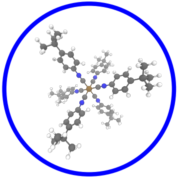

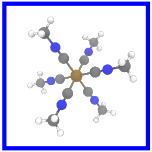

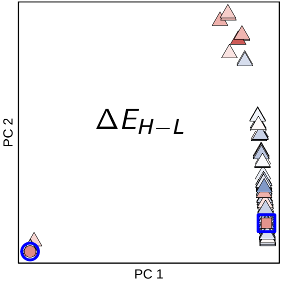

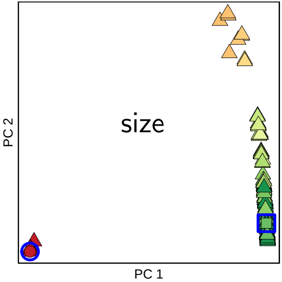

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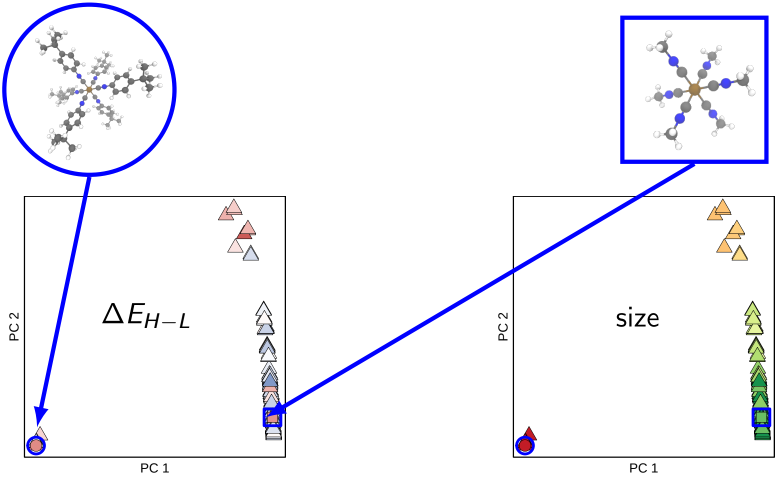

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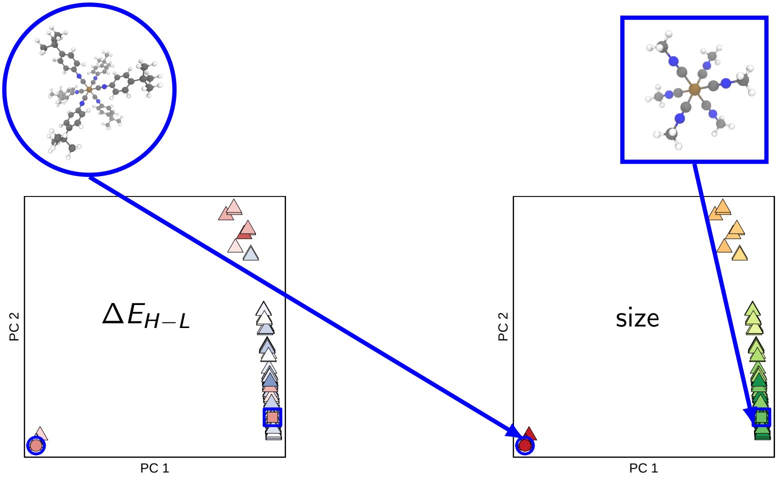

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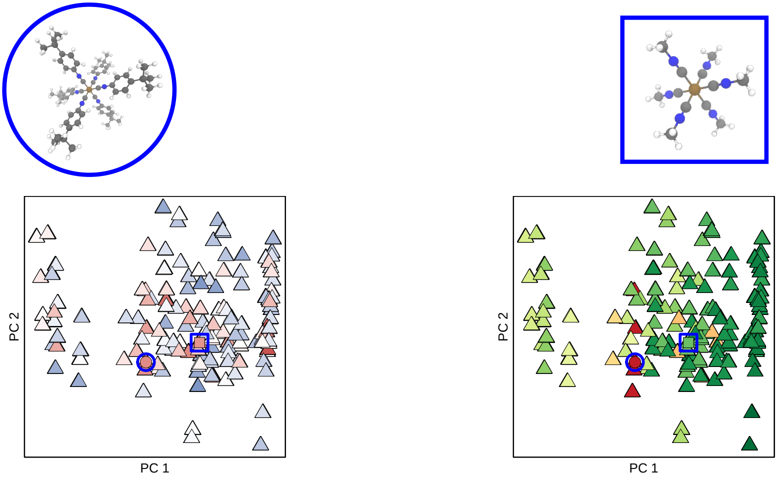

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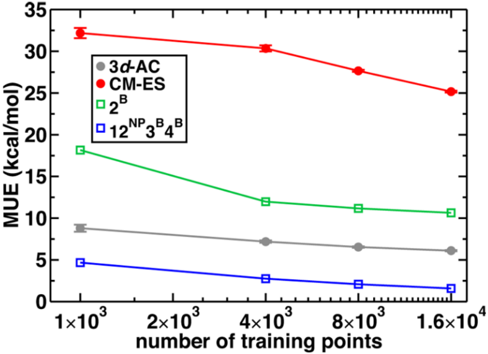

Types of representation

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– considerable use in drug design

– no information related to molecular topology

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3D structure

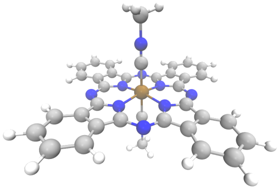
– fine-grained structural information in 3D

– mimic input to a quantum chemistry code

–expensive to compute, rich information

Ad-hoc properties

Sometimes, simple lists of atomic propties are sufficient, especially if informed by domain knowledge:



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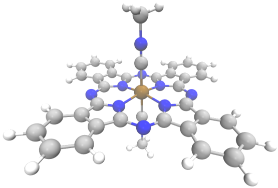
metal properties

identity

Fe(II)

oxidation state



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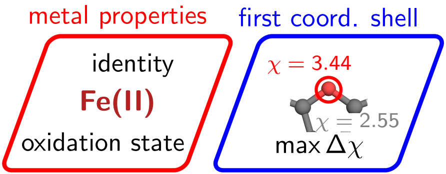

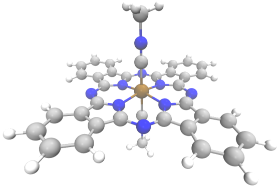

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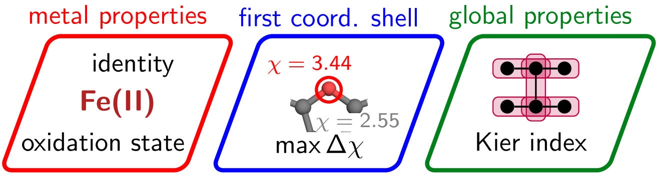

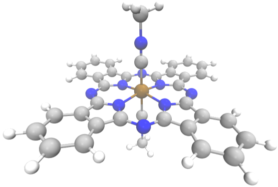

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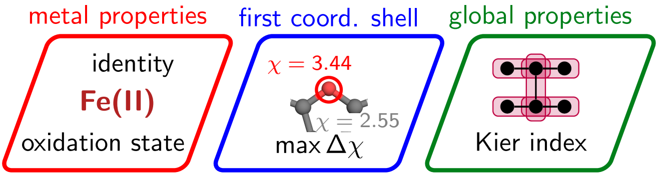

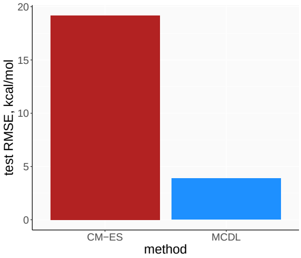

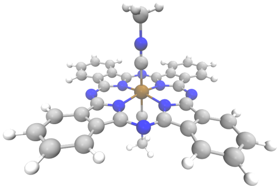

Janet, J.P., and Kulik, H.J. *Chem. Sci.*, 2017, 8, 5137-5152.

Fingerprints and the low-information limit

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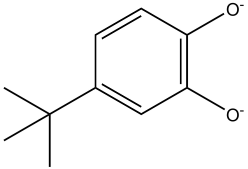

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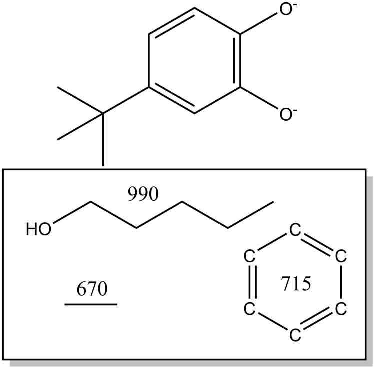

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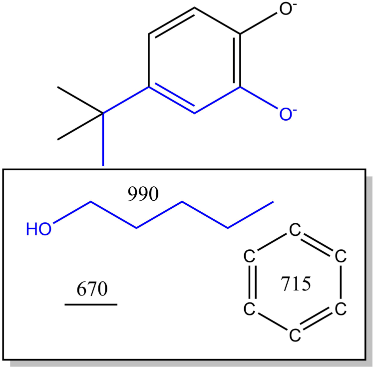
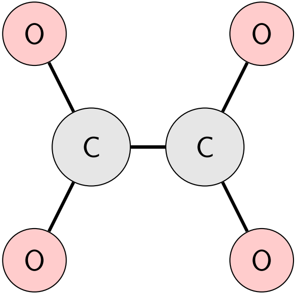


Molecular graphs

Based on autocorrelations[1]



[1] Broto, P., Moreau, G. and Vandycke, C. *Eur. J. Med. Chem.*, 19(1):71-78, 1984.

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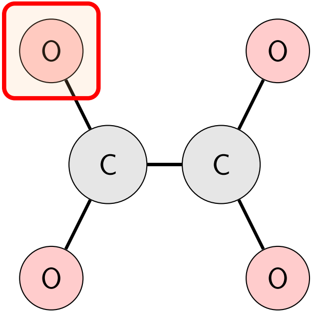

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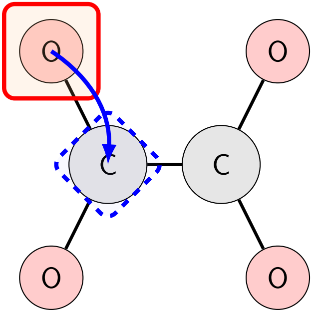

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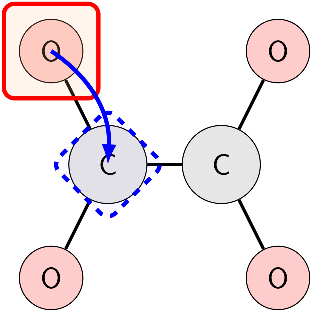

$$d_1 : \sum_{O,C} Z_O Z_C = 48$$

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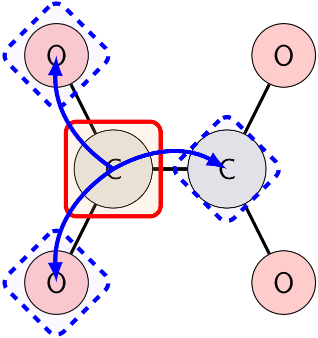

$$d_1 : 48 + \sum_{C,O} Z_O Z_C = 144 + 48$$

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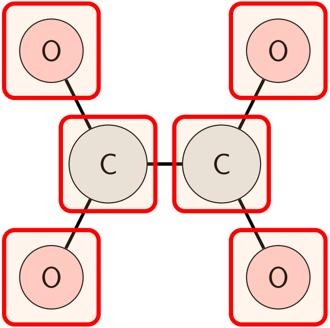

$$d_1 : \sum_i \sum_j Z_i Z_j \delta(d_{i,j}, 1)$$

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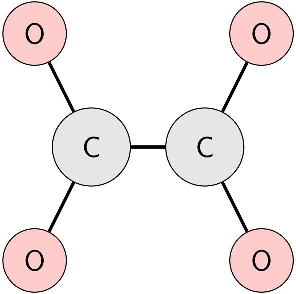
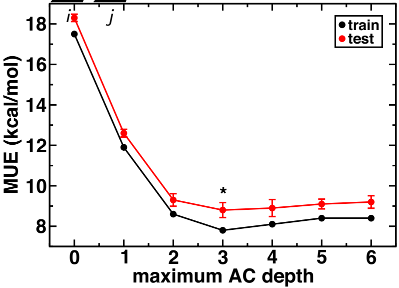


$$d_x : \sum_i \sum_j Z_i Z_j \delta(d_{ij}, x)$$



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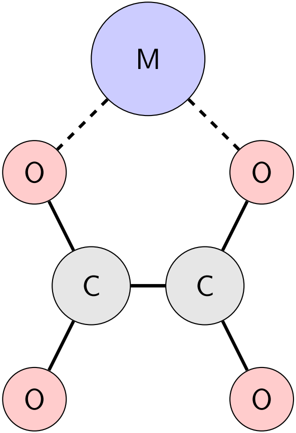

How to adapt to TM complexes?

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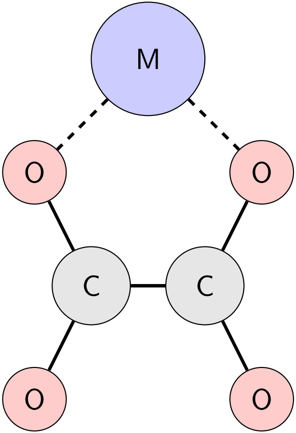

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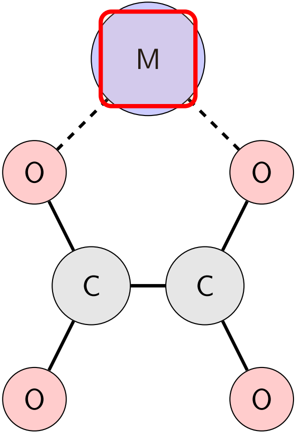

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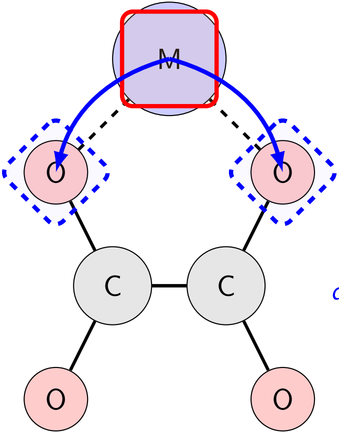

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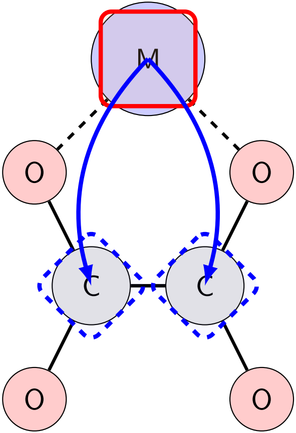

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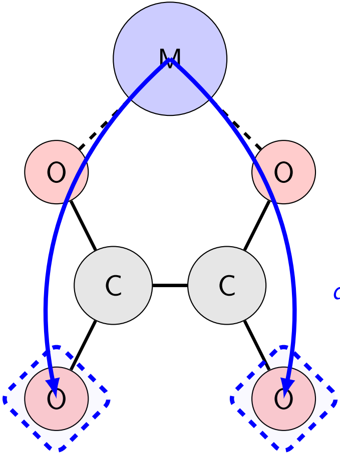

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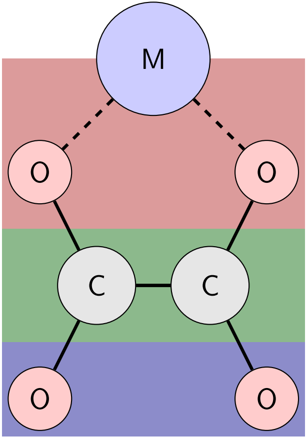

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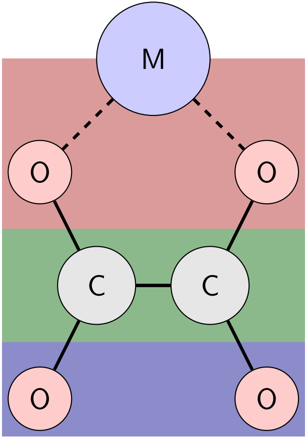

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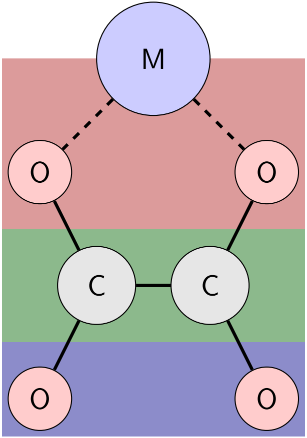

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properties: T, χ, Z, I, S

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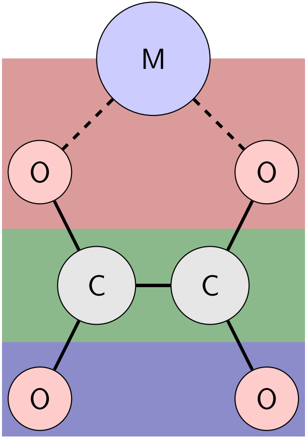

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$\boxed{\sim 160 \text{ features in total}}$

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Coulomb matrices

One family of 3D desciptors attempt to copy information used in quantum chemistry codes, e.g. Coulomb Matricies:

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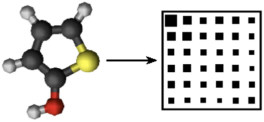

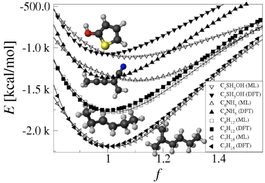

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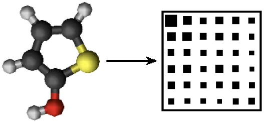
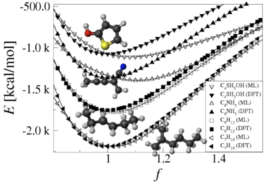


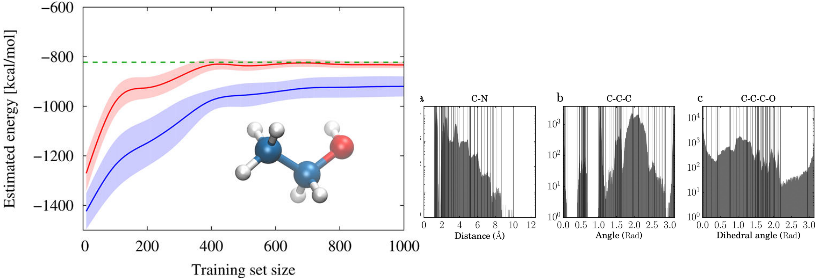


rotational and translational invariance

HDAD and beyond-CM

Subsequent work adds descriptors derived from geometric parameters, i.e. bonds, angles, and dihedral angles:

Faber, F. *et al.*. Prediction Errors of Molecular Machine Learning Models Lower than Hybrid DFT Error, *J. Chem. Theory Comput.* 2017, 13, 11, 5255-5264



System and atom level features

molecule-level

- one vector for each system of interest
- commonly used in QSAR/QSPR, related to how we think about molecules
- easy to compare whole molecules
- some properties are really 'global', like logP

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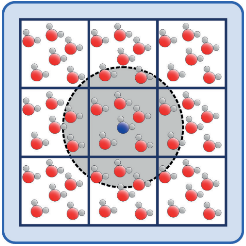

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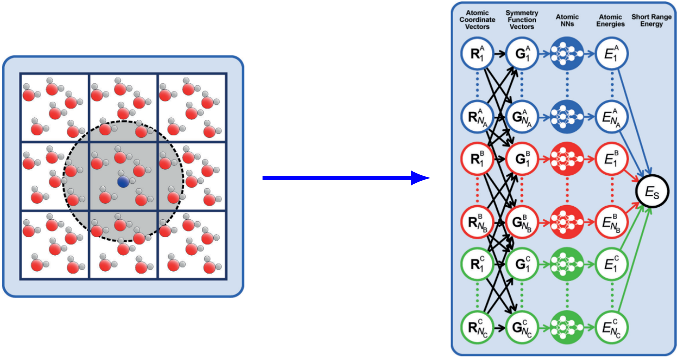

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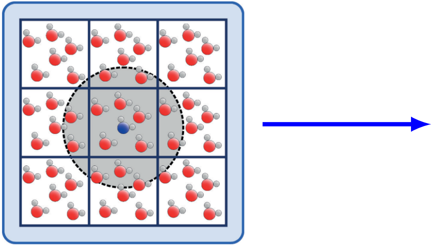
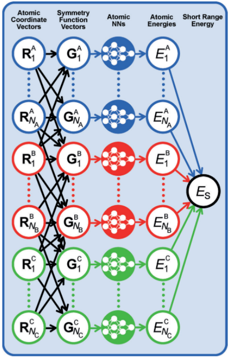


J. Behler and M. Parrinello. Generalized Neural-Network Representation of High-Dimensional Potential-Energy Surfaces, *Phys. Rev. Lett.*, 98, 146401, 2007



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We can directly learn what features to have using NNs – graph convolutions (more on this in NN section)
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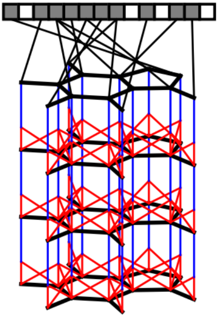

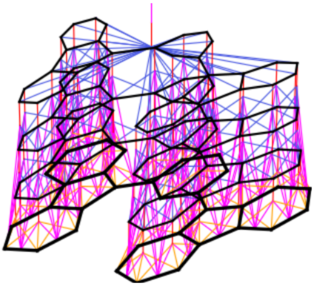

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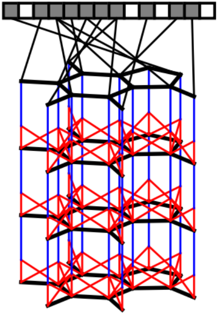

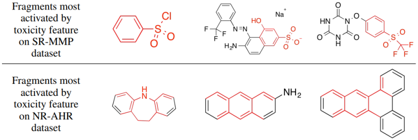

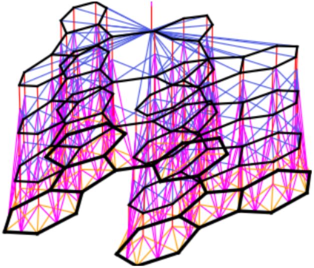

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5. atom-level featurization can be very effective for total energies

Multiple linear regression

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Linear models give $\hat{y}$ as linear function of the data matrix of X:

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We can write this in a matrix form as well:

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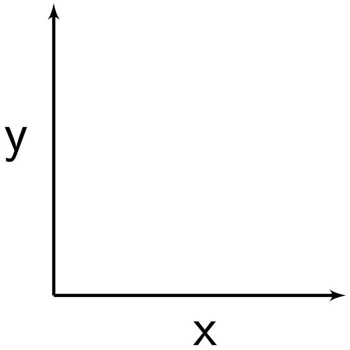
Notice how we handle the constant terms

Multiple linear regression II

Let's solve our regularized least-squares problem:

$$
\begin{aligned}
w &= \arg\min_{w \in \mathbb{R}^p} \frac{1}{n} \left\| y_{data} - Xw \right\|_2^2 + + \lambda \left\| w \right\|_2^2 \\
&= \frac{1}{n} \left(y_{data} - Xw \right)^T \left(y_{data} - Xw \right) + \lambda w^T w \\
\frac{\partial \mathcal{L}}{\partial w} &= -\frac{2}{n} X^T \left(y_{data} - Xw \right) + 2\lambda w = 0 \\
\implies (\lambda I + X^T X) w &= X^T y_{data} \\
w &= \left(\lambda I + X^T X \right)^{-1} X^T y_{data}
\end{aligned}
$$

Simple example in 1D



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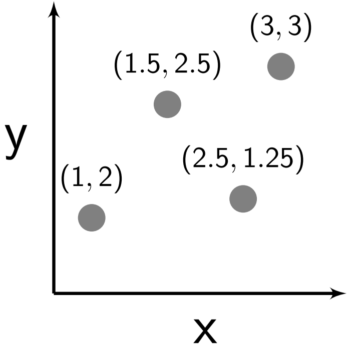

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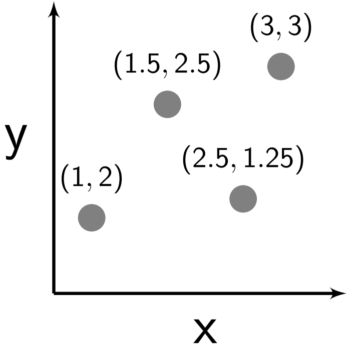

$$X = \begin{bmatrix} 1 & 1 \\ 1 & 1.5 \\ 1 & 2.5 \\ 1 & 3.0 \end{bmatrix}, \; y_{data} = \begin{bmatrix} 2 \\ 2.5 \\ 1.25 \\ 3 \end{bmatrix}$$

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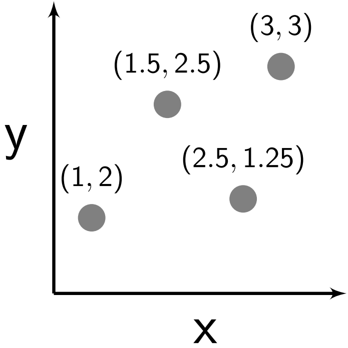

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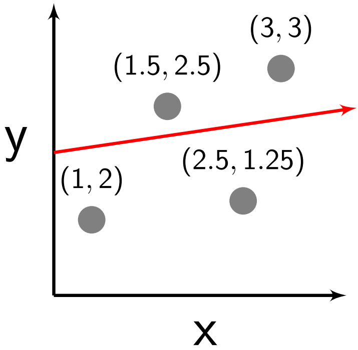

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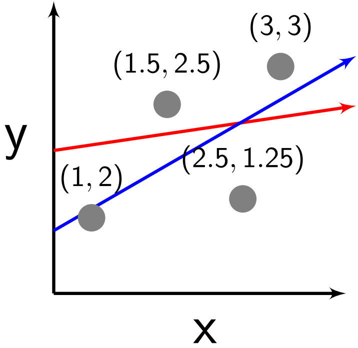

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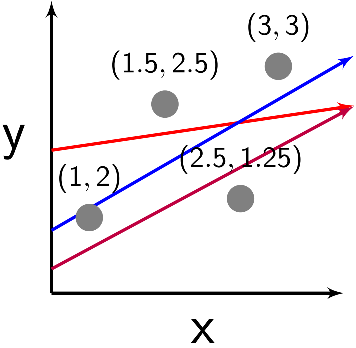

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$$= \begin{bmatrix} 0.32 \\ 0.54 \end{bmatrix} (\lambda = 10)$$

The linear kernel

We can rewrite our result to express $w = X^T a$ for $a \in \mathbb{R}^n$ (shift of basis).

$$\hat{y}_{MLR}(x^*) = x^* w = \sum_{j=1}^{d} x_j^* w_j$$

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The term $k\left(x^*, x_i\right) = x^* x_i^T = \langle x^*, x_i \rangle$is the **linear kernel**.

The linear kernel II

The matrix $K_{i,j} = \langle x_i, x_j \rangle$ is called the (linear) **kernel matrix**.
We can write the solution of the regression problem in this form – it is **exactly equivalent**:

$$\hat{y}(X) = Ka$$
$$a = (K + I_n\lambda)^{-1}y$$

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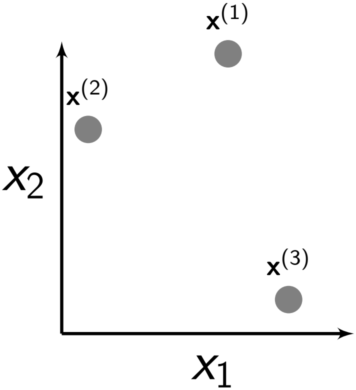
The prediction at any new point is proportional to the inner product of each training point and the new point:

$$\hat{y}_{MLR}(x^*) = \sum_{i=1}^{n} k\left(x^*, x_i\right) a_i = \sum_{i=1}^{n} k\left\langle x^*, x_i\right\rangle a_i$$

Linear kernel geometric picture

$$y(x^*) = w_1 x_1^* + w_2 x_2^*$$



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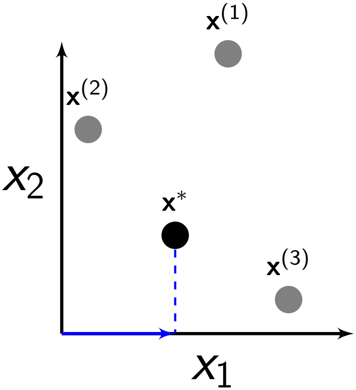

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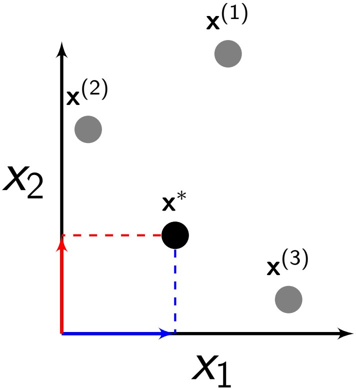

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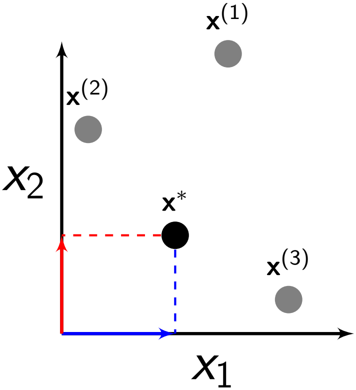

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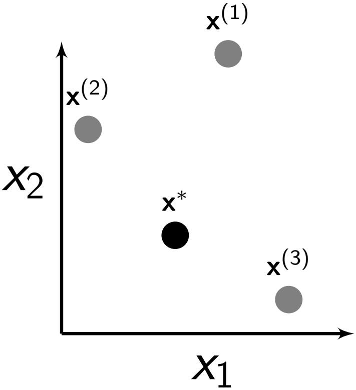

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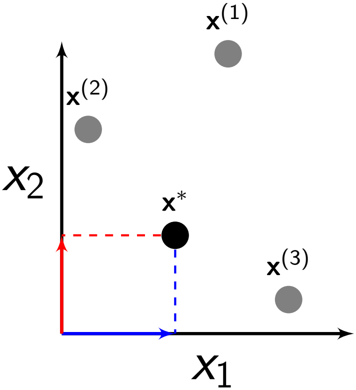

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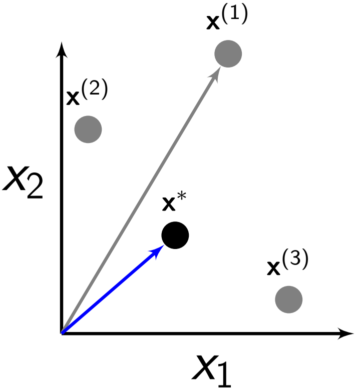

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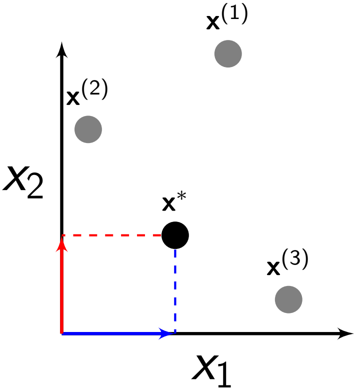

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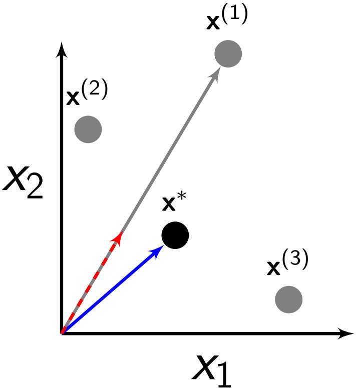

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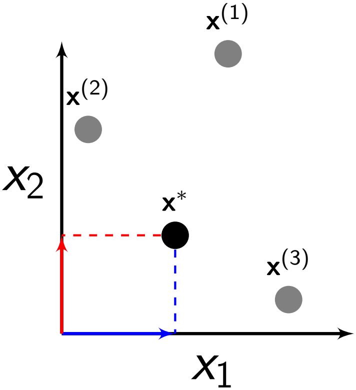

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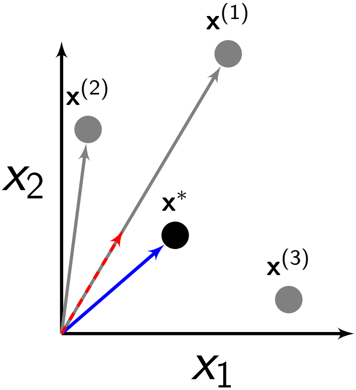

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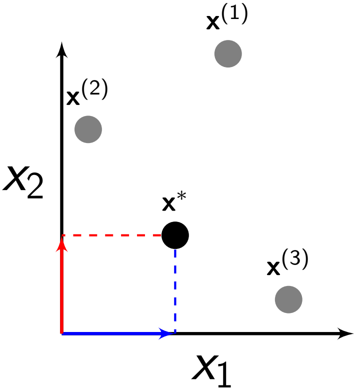

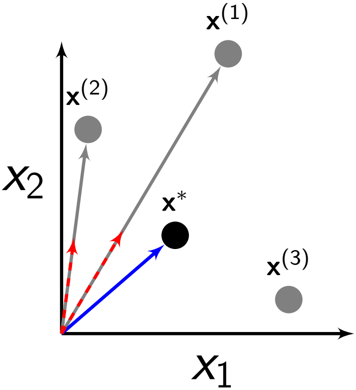

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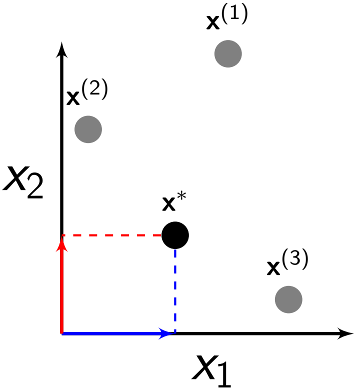

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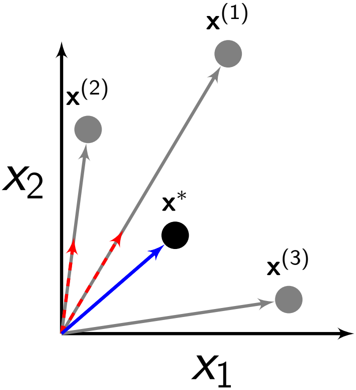

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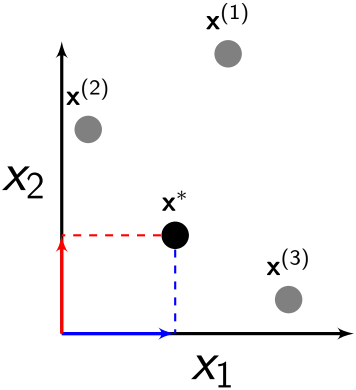

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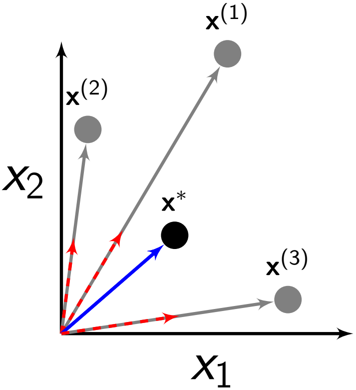

Nonlinear regression

What about non-linear regression?

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Notice that this is *linear* in w for a 'lifted' feature space, $\varphi(X)$:

$$\begin{aligned} y_{QUAD}(x) &= \varphi(X)w \\ &= \begin{bmatrix} 1 & \sqrt{2}x_1^{(1)} & \sqrt{2}x_2^{(1)} & \sqrt{2}x_1^{(1)}x_2^{(1)} & (x_1^{(1)})^2 & (x_2^{(1)})^2 \\ \vdots & & \vdots & & & \\ 1 & \sqrt{2}x_1^{(n)} & \sqrt{2}x_2^{(n)} & \sqrt{2}x_1^{(1)}x_2^{(n)} & (x_1^{(n)})^2 & (x_2^{(n)})^2 \end{bmatrix} \begin{bmatrix} w_1 \\ \vdots \\ w_6 \end{bmatrix} \end{aligned}$$

except the dimension has increased from $\mathbb{R}^{n\times 2} \to \mathbb{R}^{n\times 6}$

Nonlinear regression II

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(c.f. the linear case) $w = (X^T X + I_d \lambda)^{-1} X^T y_{data}$

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by direct analogy to the previous slides, there is also a kernel form:

$$\hat{y}(x^*) = \sum_{i=1}^{n} k(x^*, x_i)\, a_i$$
$$k(x^*, x_i) = \langle\varphi(x_i), \varphi(x_j)\rangle$$
$$= \begin{bmatrix} 1 & \sqrt{2}x_1^{(i)} & \dots & (x_1^{(i)})^2 & (x_2^{(i)})^2 \end{bmatrix} \begin{bmatrix} 1 \\ \sqrt{2}x_1^{(j)} \\ \vdots \\ (x_1^{(j)})^2 \\ (x_2^{(j)})^2 \end{bmatrix}$$

The "kernel trick"

Notice that all that is required is vector products, i.e.

$$K_{i,j} = \langle \varphi(x_i), \varphi(x_j) \rangle$$

It turns out that these can often be computed *much* more efficiently, without ever forming the big, nonlinear feature space directly.

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$$K_{i,j} = \left((x^{(i)})^T x^{(j)} + 1 \right)^2 = (x_1^{(i)})^2 (x_1^{(j)})^2 + 2 x_1^{(i)} x_1^{(j)} x_2^{(i)} x_2^{(j)} + \ldots$$

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which can be computed entirely using vectors in $\mathbb{R}^2$, so we never have to allocate the (factorially large) feature space.

Detailed example of nonlinear regression

jupyter notebook: `github.com/jpjanet/ML-chem-workshop/blob/master/notebooks/workshop_compare_models.ipynb`

General kernels

Both kernel methods are the same except:

	linear	quadratic
K_{ij}	$(x^{(i)})^T x^{(j)}$	$\left((x^{(i)})^T x^{(j)} + 1\right)^2$

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we use the same machinery as the linear kernel, but the definition of similarity, defined by the kernel, has changed.

From the perspective of similarity, we can imagine arbitrary functions to be our kernel, without ever needing to know what the underlying feature map φ is.

The Gaussian kernel and KRR

The most widely used kernel is the Gaussian kernel:o

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Actually a Hilbert space (infinite dimensions...)
Depends on σ to control non-locality.

Similarity and Gaussian KRR

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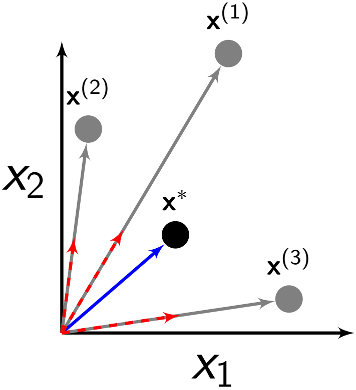

linear kernel

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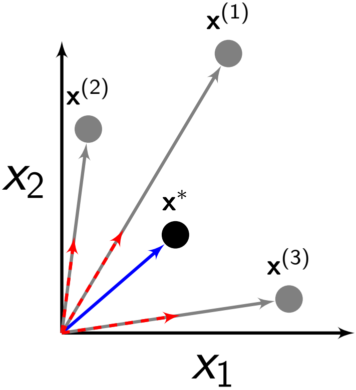
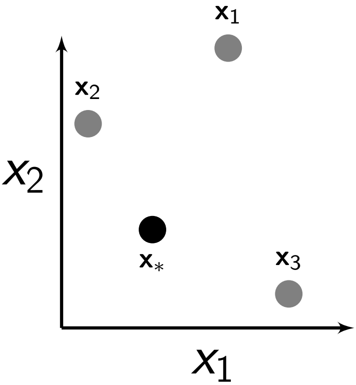


linear kernel



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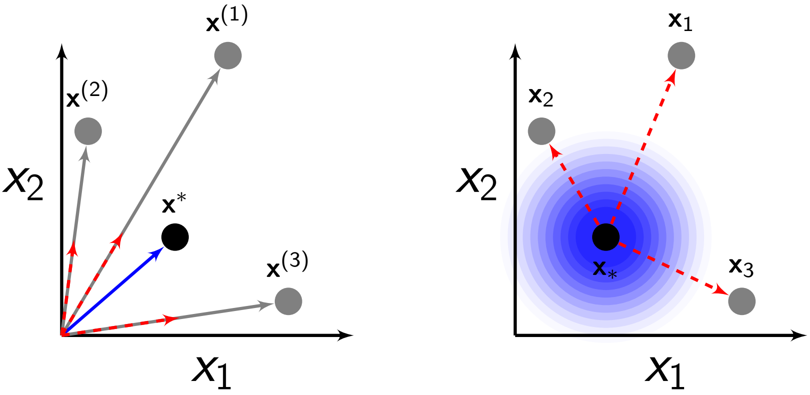

linear kernel **Gaussian kernel**

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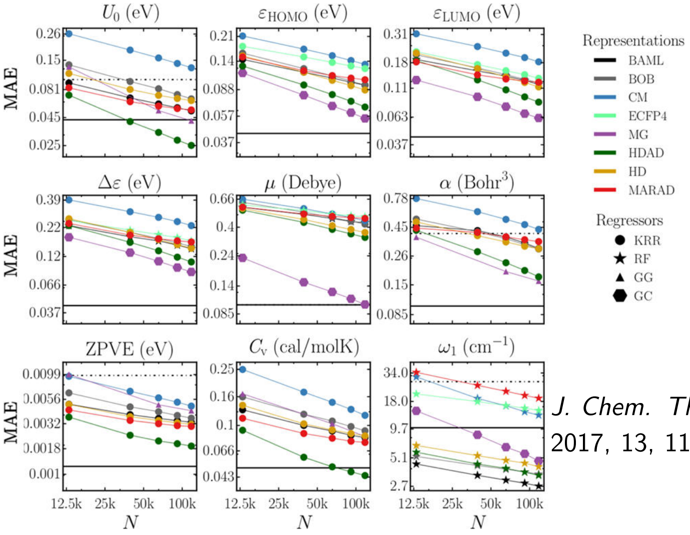
KRR is widely used in chemistry



J. Chem. Theory Comput. 2017, 13, 11, 5255–5264

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KRR example

jupyter notebook: `github.com/jpjanet/ML-chem-workshop/blob/master/notebooks/KRR.ipynb`

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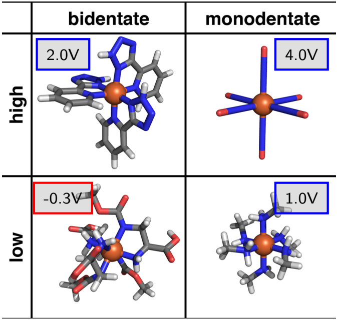

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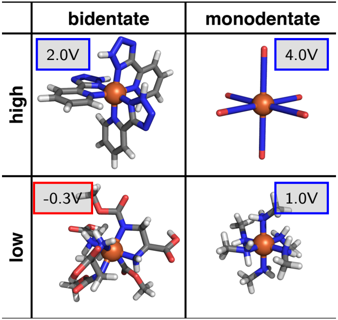

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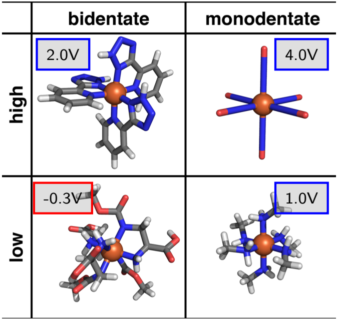

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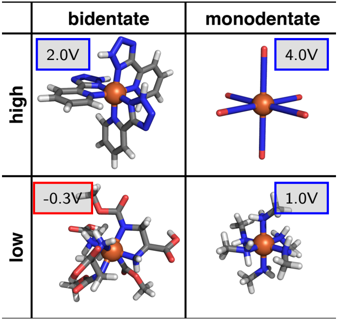

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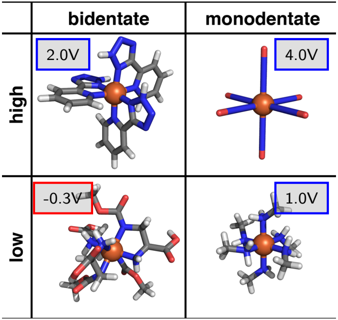

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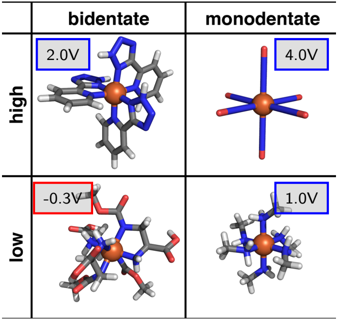

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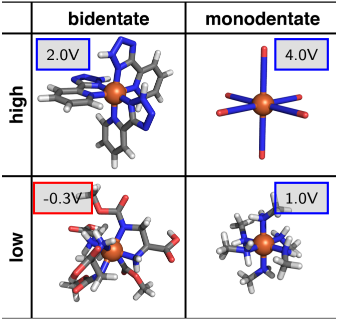

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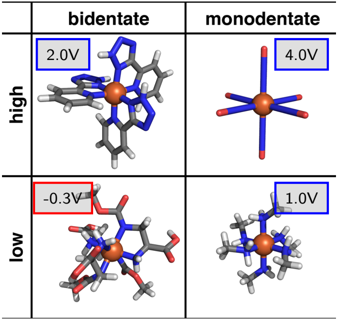

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$$\eta_{i,0} = p_i p_i$$

$$\eta_{i,k} = \sum_{i \neq j} p_i p_j \delta(d_{i,j} - d_k), \quad k \neq 0$$

$$\mathrm{AC}_k = \sum_i \eta_{i,k}$$

4 properties, $k \in [0, 5]$ $\implies$ 28 variables.

How to choose?

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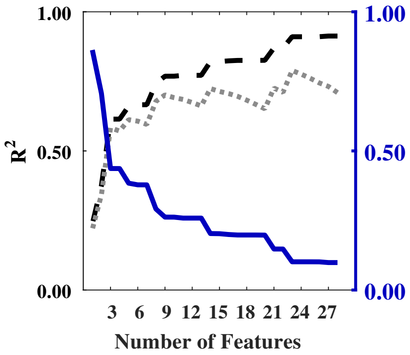

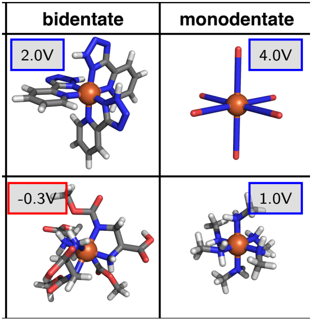

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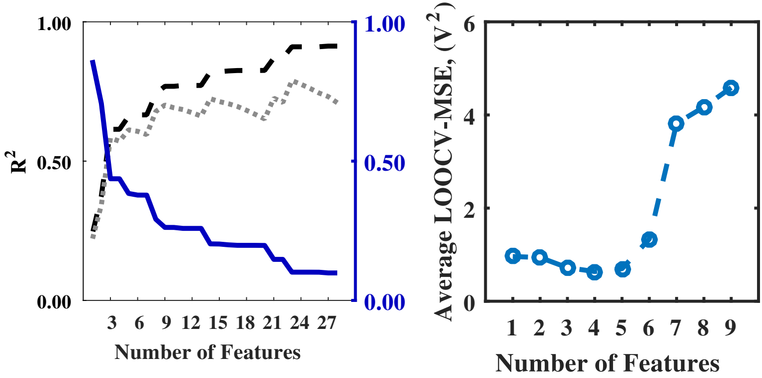

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How to pick important features?

Using unnecessary features can degrade model performance, so we want to able to pick the subset of variables that is best correlated with our objective, formally:

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We don't know the optimal number upfront, and this is a combinatorial problem – possible for ≤ 30 dimensions or so, but rapidly becomes unfeasible.

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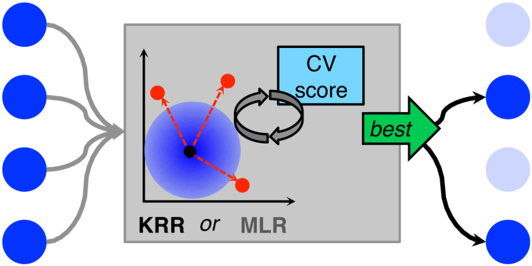

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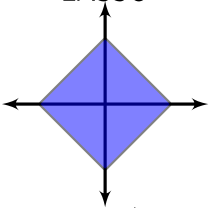

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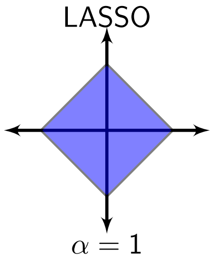

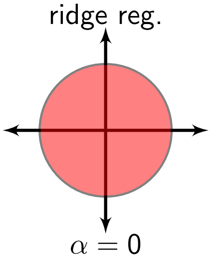

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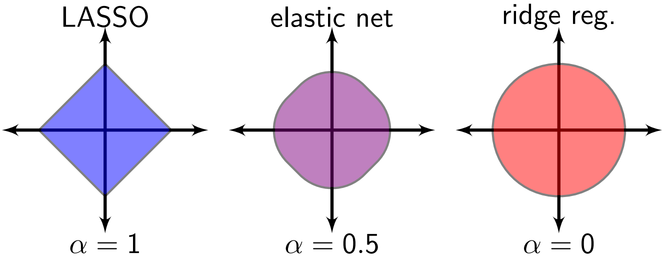

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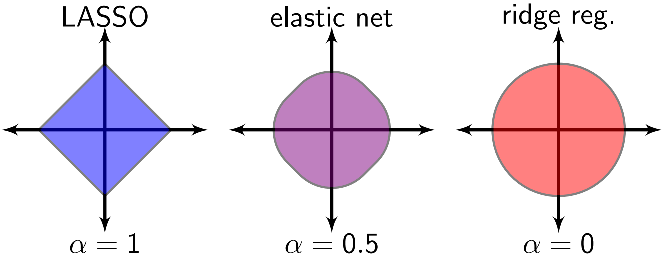

Using even a small $\alpha > 0$ ensures the minimization is stable.

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Why not use even lower norms such as $\|w\|_{0.5}^{0.5}$? Convexity!

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1. Feature selection techniques can help identify important features, for modeling and for interpretation
2. Iterative subset selection can be expensive since the model needs to be re-trained, including hyperparameters each time
3. LASSO/elastic net provide simple ways of extracting most important linear features

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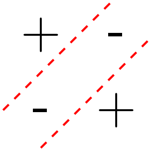

Decision boundary

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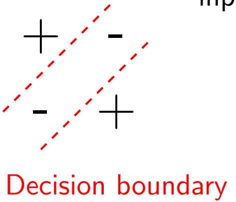

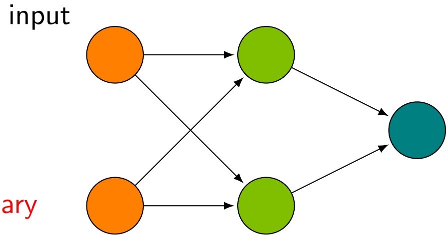

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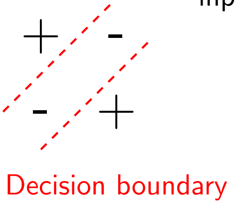
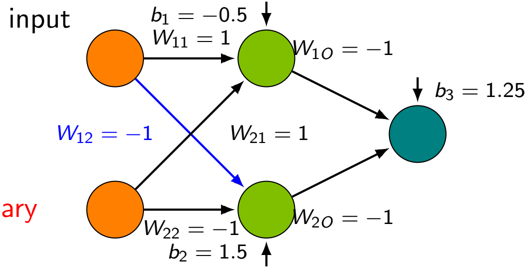
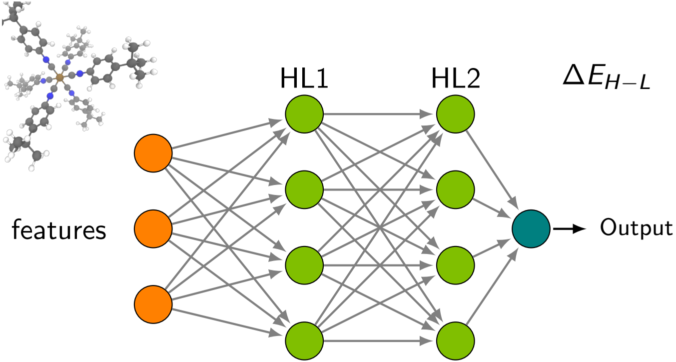




What do they look like?



Backpropagation (chain rule!)

Back-propagation updates neural network weights $\rightarrow$ example

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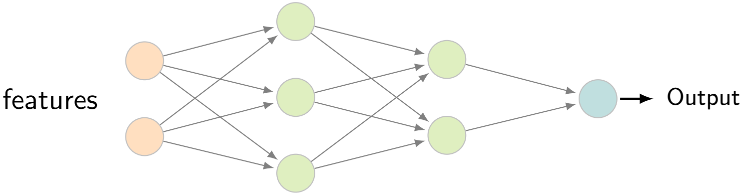

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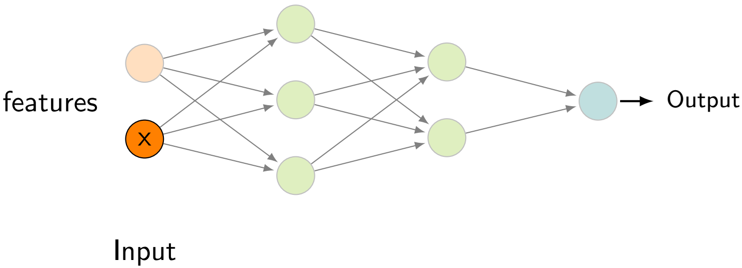

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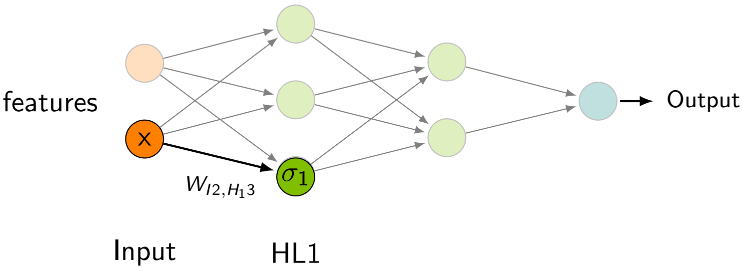

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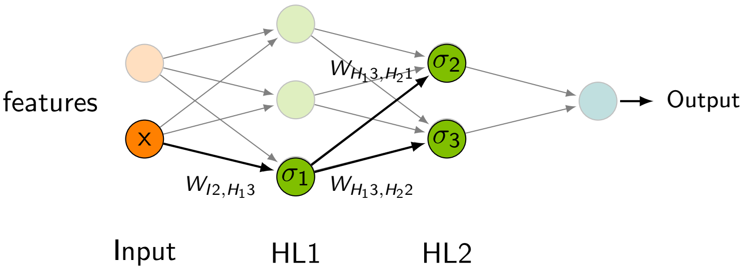

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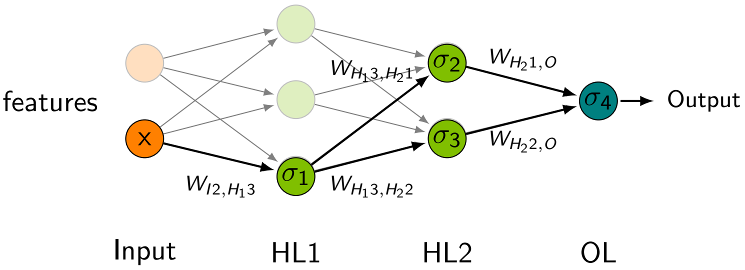

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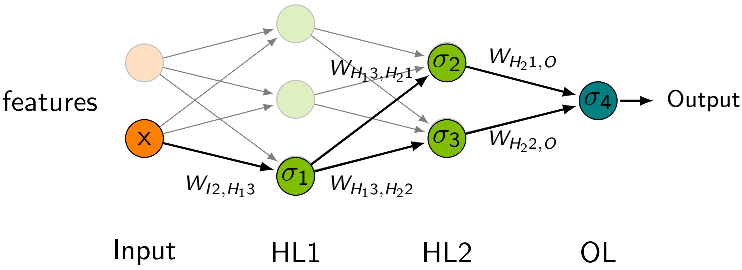
$$\text{Loss} \rightarrow \mathcal{L}(W) = \sum_{i=1}^{N}((y_i - y_{pred})^2)$$



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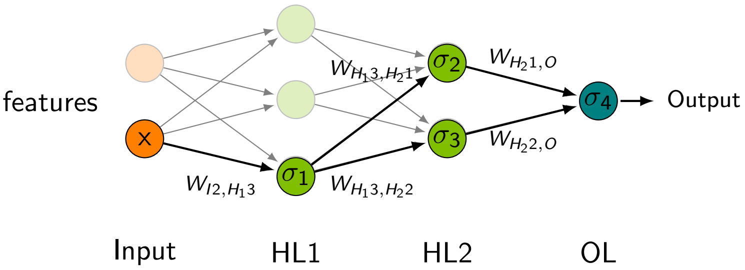
$$\text{Loss} \rightarrow \mathcal{L}(W) = \sum_{i=1}^{N}((y_i - y_{pred})^2) + \lambda(\sum_{l=1}^{L}||W_l||^2)$$



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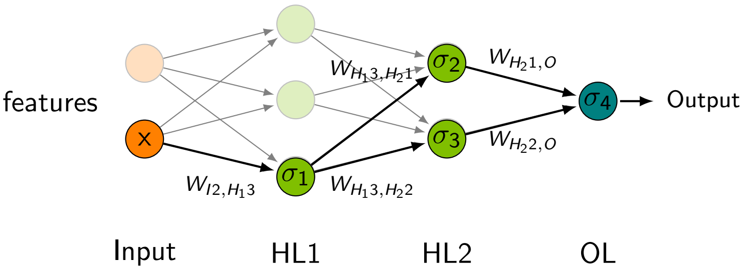
$$\left(\frac{\partial \mathcal{L}}{\partial W_{I2,H_13}}\right)$$



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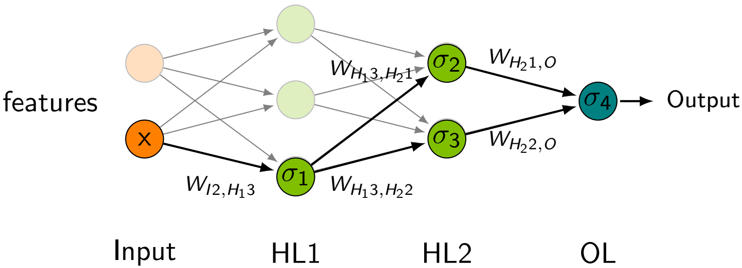
$$\left(\frac{\partial \mathcal{L}}{\partial W_{I2,H_13}}\right) = \left(\frac{\partial \mathcal{L}}{\partial \sigma_4}\right)$$



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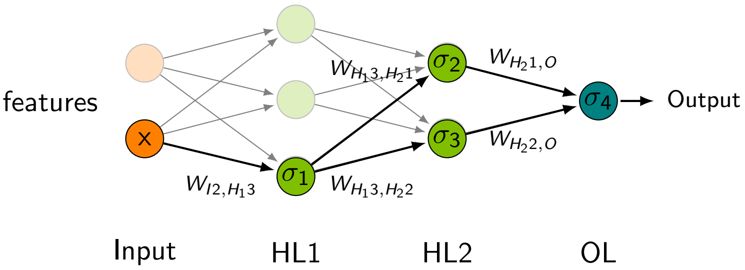
$$\left(\frac{\partial \mathcal{L}}{\partial W_{I2,H_13}}\right) = \left(\frac{\partial \mathcal{L}}{\partial \sigma_4}\right)\left(\frac{\partial \sigma_4}{\partial z_4}\right)$$



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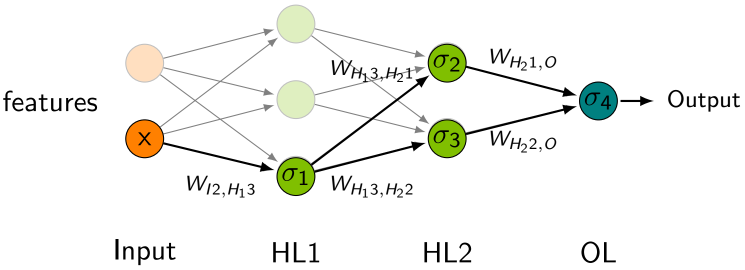
$$\left(\frac{\partial \mathcal{L}}{\partial W_{I2,H_13}}\right) = \left(\frac{\partial \mathcal{L}}{\partial \sigma_4}\right)\left(\frac{\partial \sigma_4}{\partial z_4}\right)\left[\left(\frac{\partial z_4}{\partial W_{H_21,O}}\right)\ldots + \left(\frac{\partial z_4}{\partial W_{H_22,O}}\right)\ldots\right]$$



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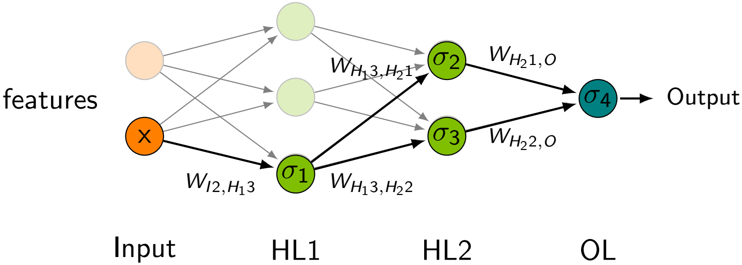
$$\left.\left(\frac{\partial \sigma_1}{\partial z_1}\right)\left(\frac{\partial z_1}{\partial W_{I2,H_13}}\right) + \left(\frac{\partial z_4}{\partial W_{H_22,O}}\right)\left(\frac{\partial W_{H_22,O}}{\partial \sigma_3}\right)\left(\frac{\partial \sigma_3}{\partial z_3}\right)\left(\frac{\partial z_3}{\partial W_{H_13,H_22}}\right)\left(\frac{\partial W_{H_13,H_22}}{\partial \sigma_1}\right)\left(\frac{\partial \sigma_1}{\partial z_1}\right)\left(\frac{\partial z_1}{\partial W_{I2,H_13}}\right)\right]$$



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Recurrent→ Layers that "store" information about previous times, thus commonly used in speech or handwriting recognition

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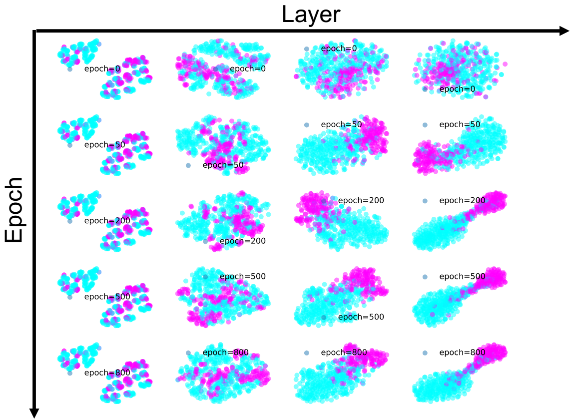

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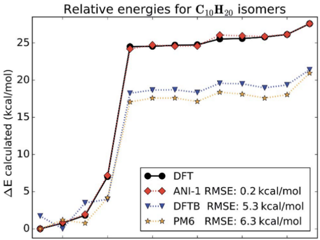
1. Neural network models provide model complexity ‘on tap’
2. Backpropagation allows easy access to derivatives
3. We can understand neural networks as automatic feature selection/transformation, followed by linear regression

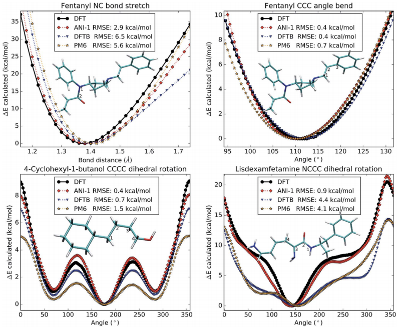
ANN example

jupyter notebook: `github.com/jpjanet/ML-chem-workshop/blob/master/notebooks/ANN.ipynb`

Neural network potentials

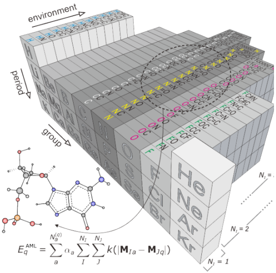
Smith, J. S., Isayev, O., and Roitberg, A. E. ANI-1: an extensible neural network potential with DFT accuracy at force field computational cost. *Chem. Sci.*, **2017**, *8*, 3192-3203.

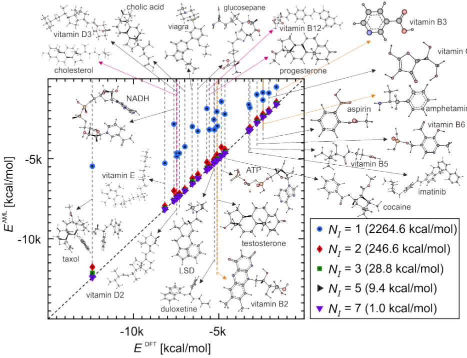




Property predictions

Huang, B. & von Lilienfeld, O.A. *arXiv* 1707.04146, "The 'DNA'of chemistry: Scalable quantum machine learning with amons", 2017.





Accelerating quantum chemistry

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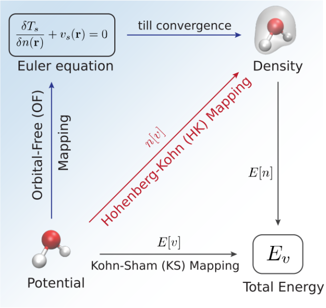

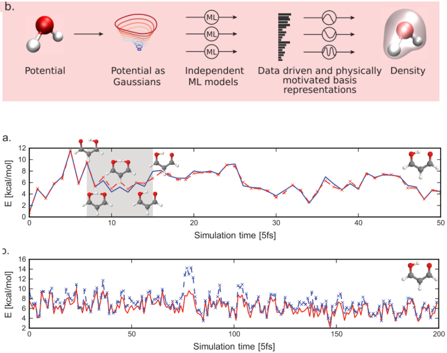

Controlling calculations on the fly

Chenru Duan *et. al.* *ChemRxiv* .7616009, “Learning from Failure: Predicting Electronic Structure Calculation Outcomes with Machine Learning Models”, 2019.