Machine Learning – now and in the future

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Rise of the (chemical) machines

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The same team ran away with the competition in **CASP 14** in 2020, leading CASP co-founder John Moult to conclude "In some sense the problem is solved"

Rise of the (chemical) machines

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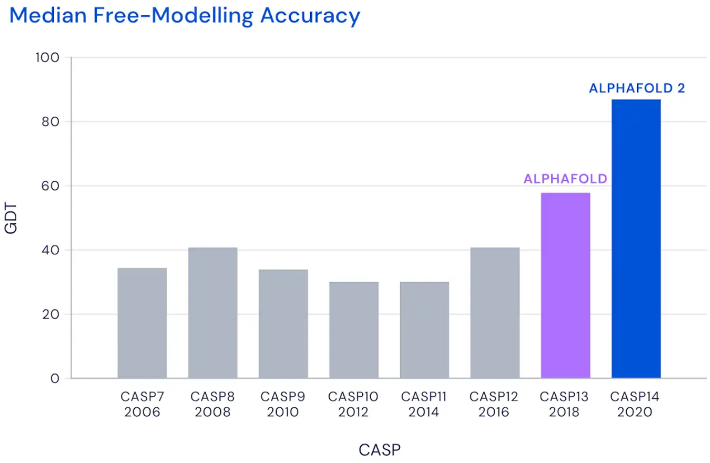

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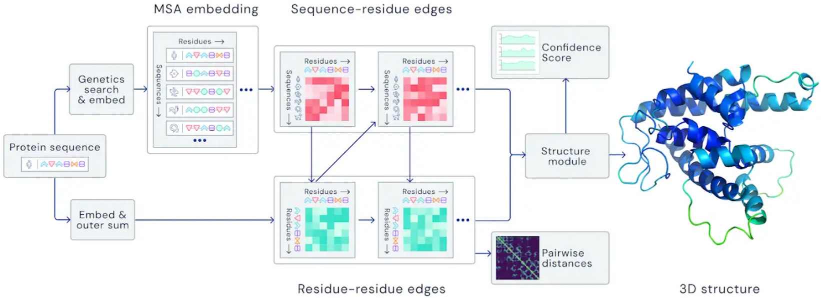

Senior, A.W., *et al.*, *Nature*, 577: 706–710, 2020.

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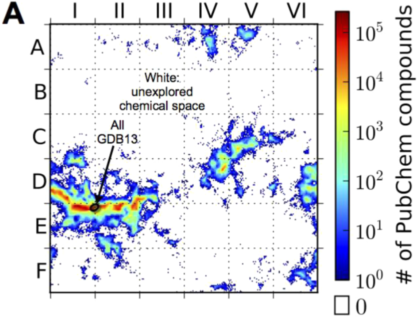
This is probably a bit strong, but all scientists generate data as a product. ML provides new, powerful ways to exploit this information.

Motivation: chemical discovery

Why is ML transforming chemisty?

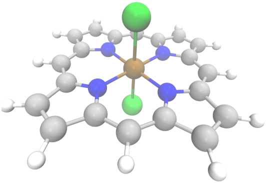
The space of possible chemistries is incredibly vast, with $\mathcal{O}(10^{60})$ small organic molecules.

All potentially undiscovered medicines, catalysts and materials are somewhere, out in this huge space.



Virshup *et al.*, *J. Am. Chem. Soc.*, 135(19): 7296–7303, 2013.

Why ML in chemical sciences?



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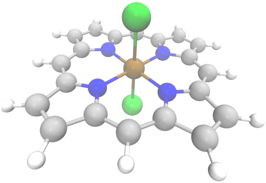

property

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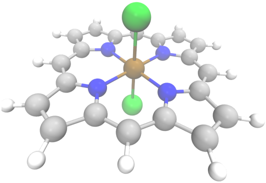

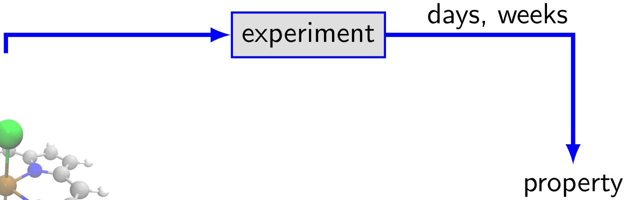

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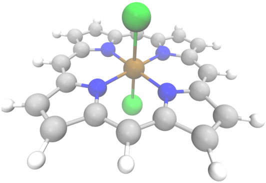

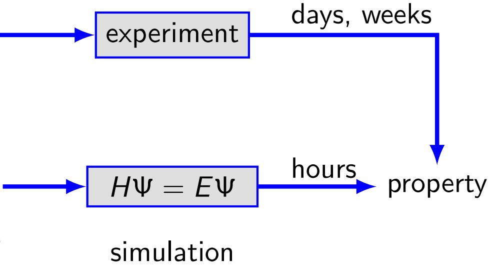

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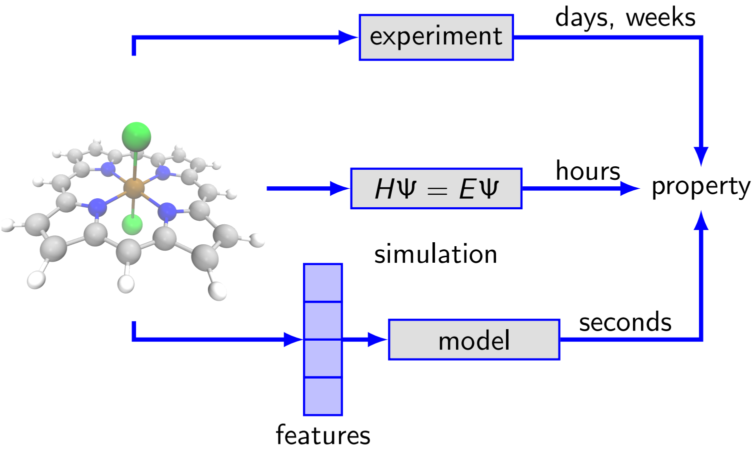

Why does ML seem to be taking over?

machine learning methods

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computer vision

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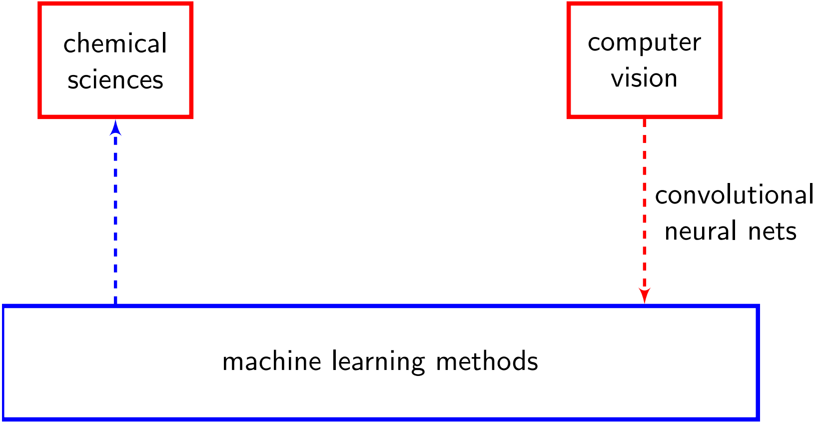

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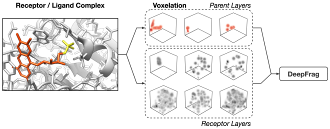

convolutional neural nets

Green, H., *et al.*, bioRxiv 2021.01.07.425790, 2021.

machine learning methods

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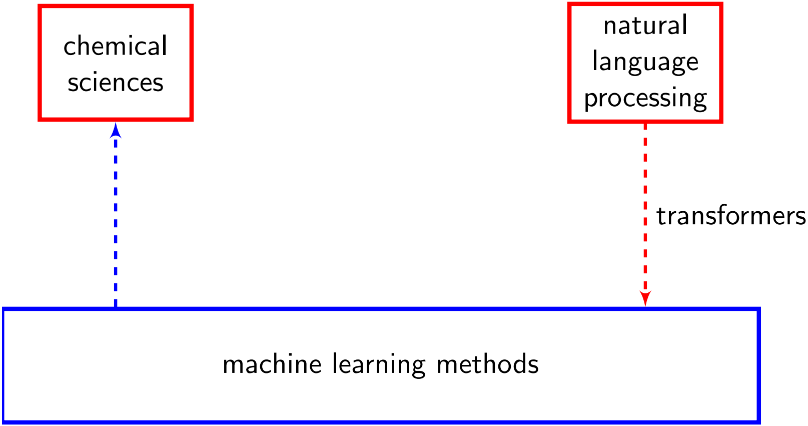

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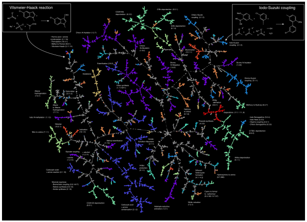

Schwaller, P., *et al.*, *Nat. Mach. Intell.*, 3: 144–152, 2021.

natural language processing

transformers

machine learning methods

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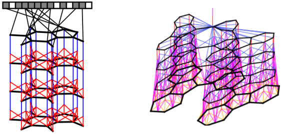

Duvenaud, D., *et al.*, *NeurIPS 28*, 2015.

graph convolutions

machine learning methods

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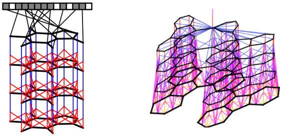
diverse applications from traffic networks to medicine



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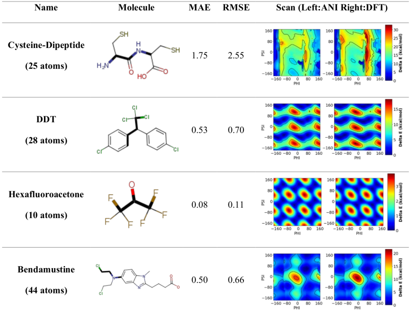
- Neural network potentials - quantum accuracy, force field cost. Reactive dynamics on your laptop!



Name	Molecule	MAE	RMSE	Scan (Left:ANI Right:DFT)
Cysteine-Dipeptide (25 atoms)		1.75	2.55	
DDT (28 atoms)		0.53	0.70	
Hexafluoroacetone (10 atoms)		0.08	0.11	
Bendamustine (44 atoms)		0.50	0.66	

Devereux, C., *et al.*, *J. Chem. Theory Comput.*, 16(7):4192–4202, 2020

Future directions for ML in chemistry

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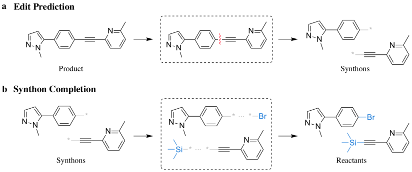
- Synthesis planning and optimization. Fully automated chemistry!



Somnath, V.R., *et al.*, arXiv:2006.07038v1, 2020

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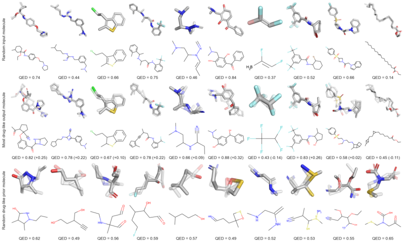
- Synthesis planning and optimization. Fully automated chemistry!
- Generative models. Designing new drugs directly into the pocket, *de novo*!



Ragoza, M., *et al.*, arXiv:2010.08687v3, 2020

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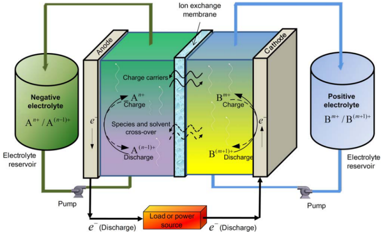

Perry, M.L. and Adam, Z., *J. Electrochem. Soc.*, 163(1):A5064–A5067, 2018.

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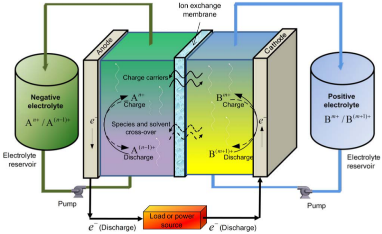

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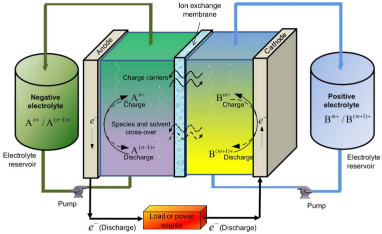

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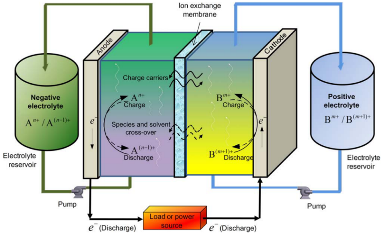

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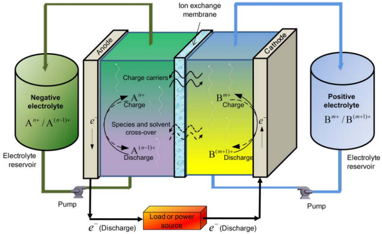

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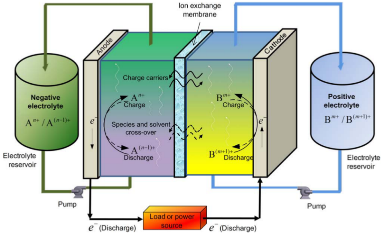

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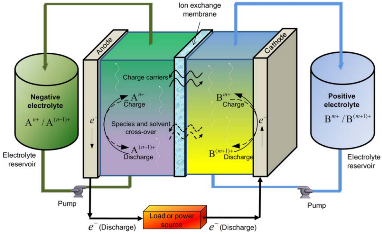

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We need complexes that have high redox potential **and** good solubility

A design space for RFBs

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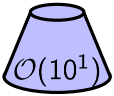

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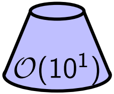

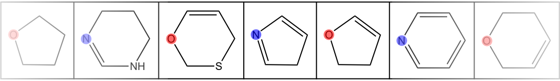

38 heterocycles

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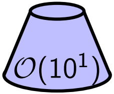

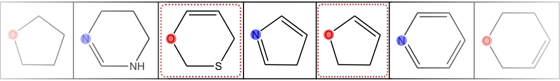

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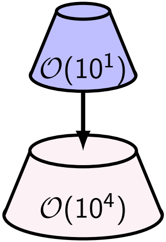

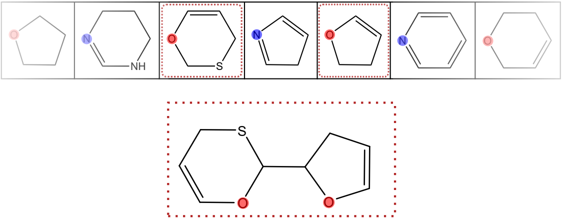

779 base ligands

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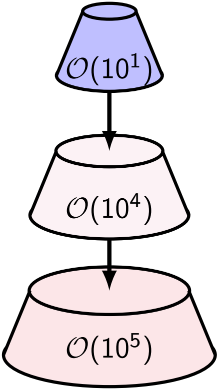

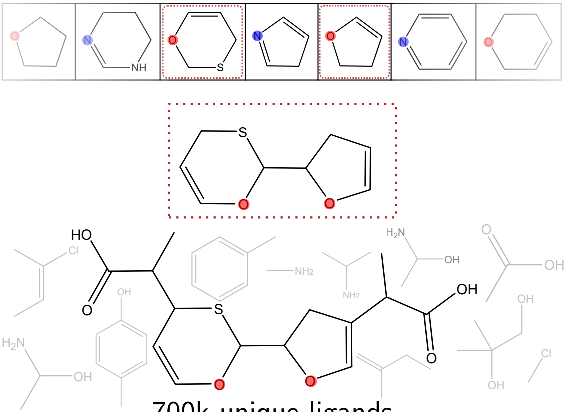

700k unique ligands

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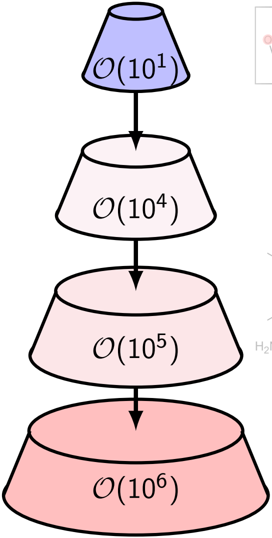
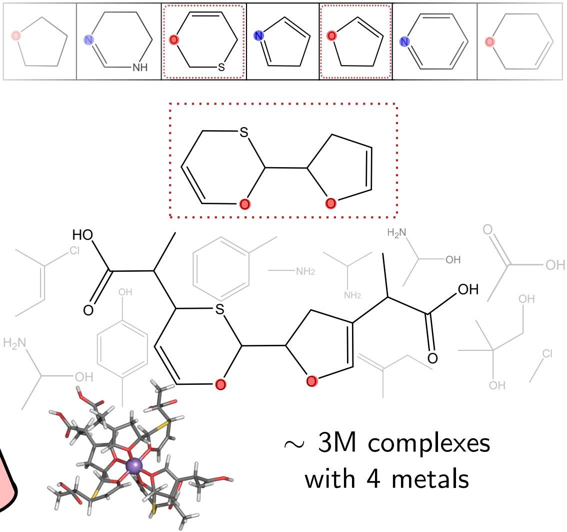
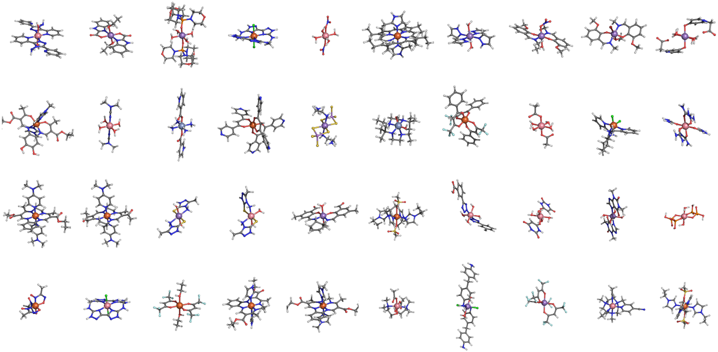




$\sim$ 3M complexes
with 4 metals

Computational approaches to chemical discovery

Computational methods can search for suitable complexes



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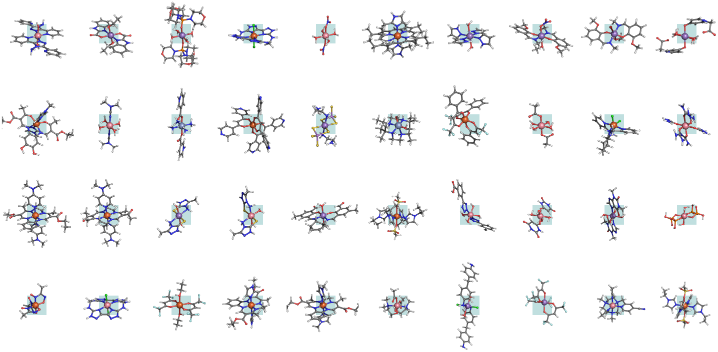

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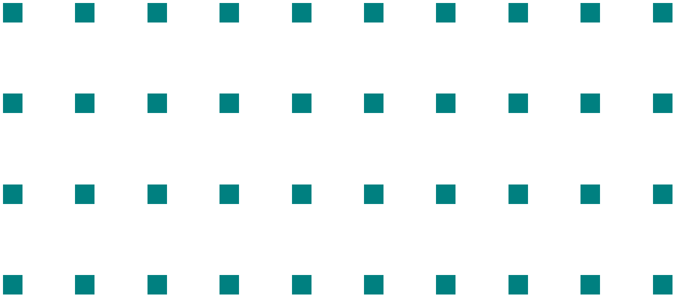

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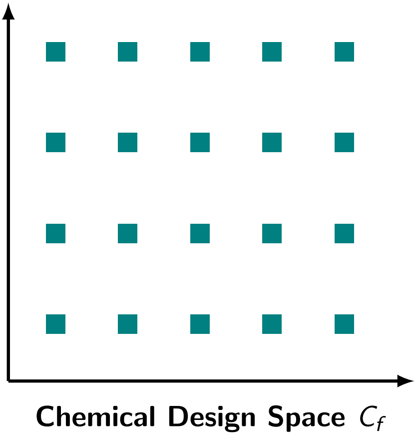

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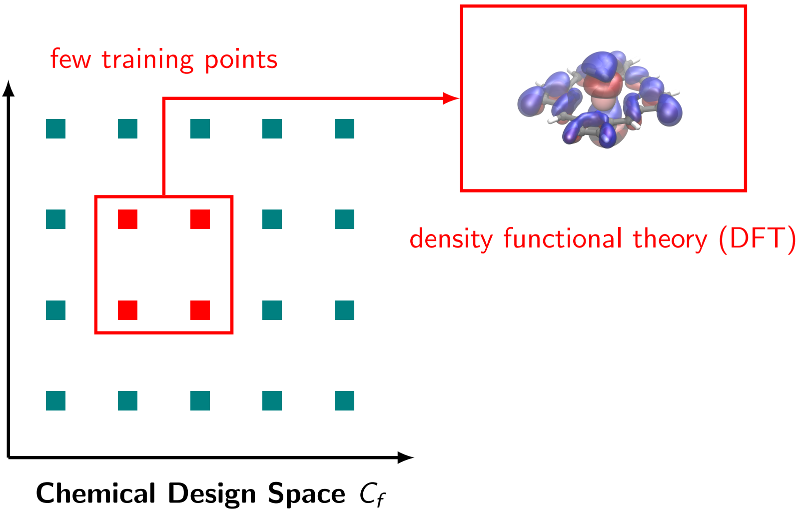

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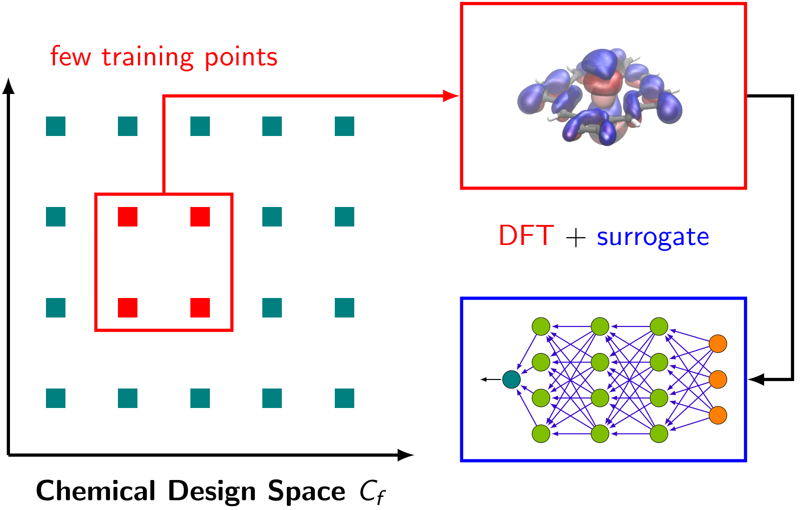

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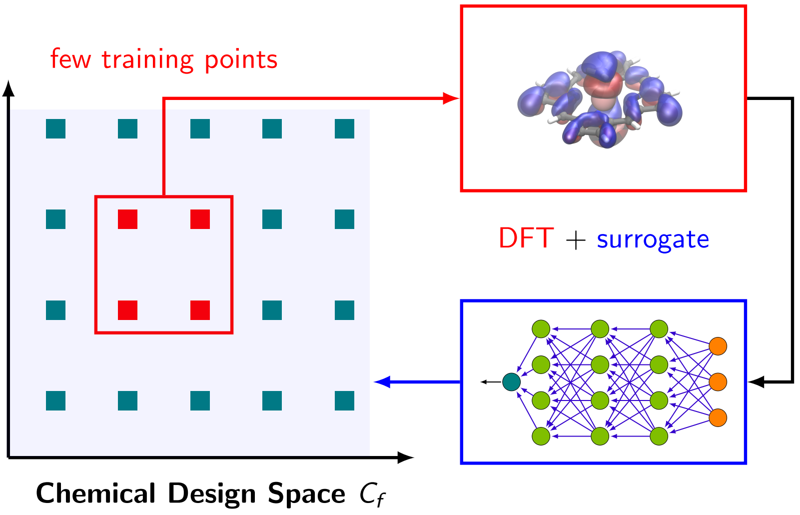

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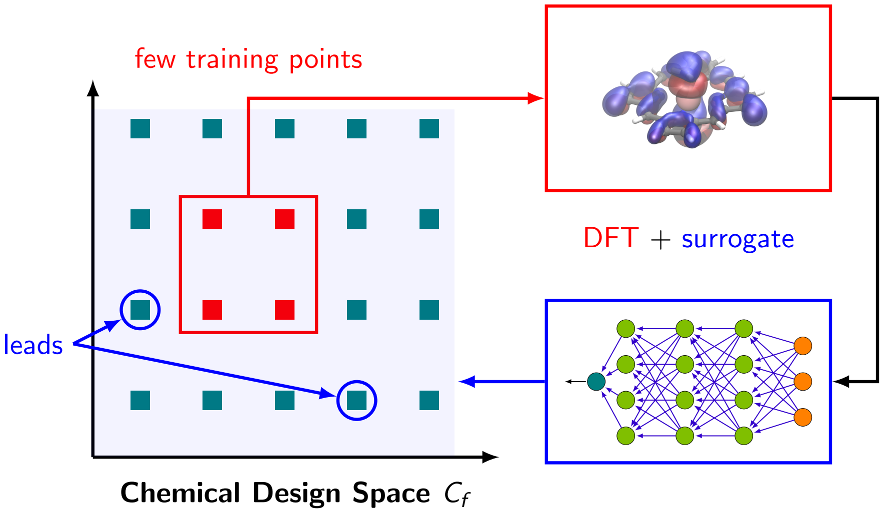

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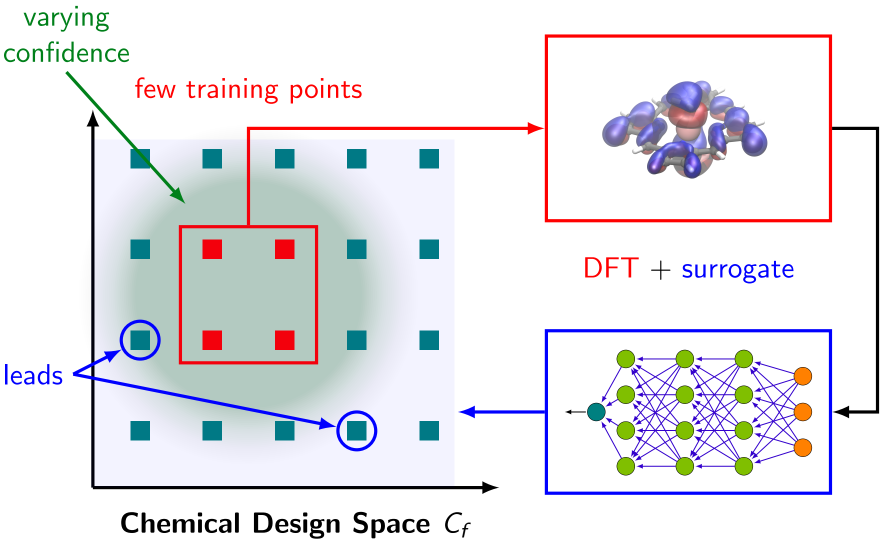

Multiobjective optimization

We can predict quantites of interest for our RFBs with ANNs

Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

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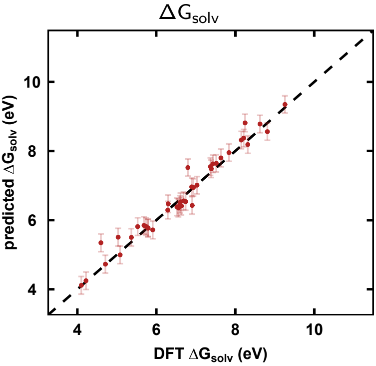

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3 × 100 tanh nodes, multitask, fully connected

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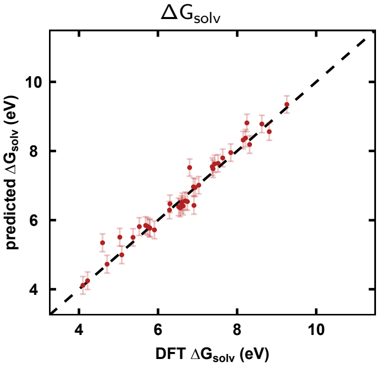

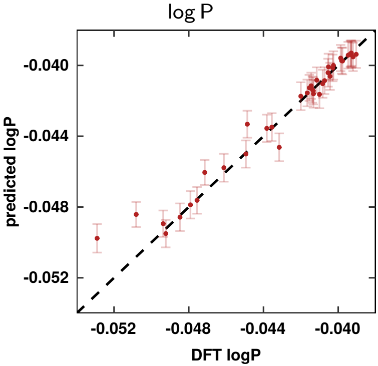

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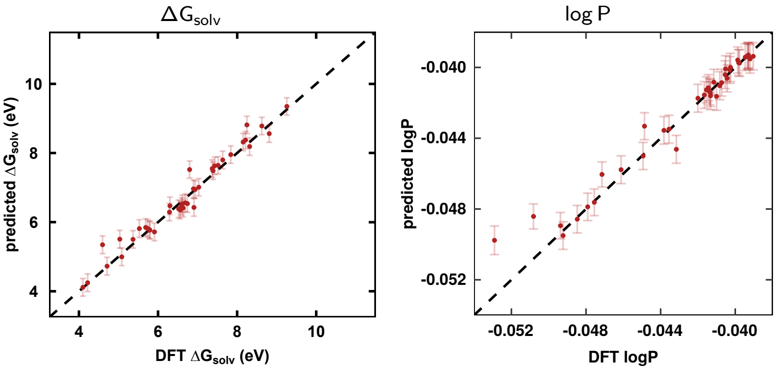

Screen $3M$ complexes in < 4 **minutes** on a regular workstation, c.f. 50 **GPU-years** with DFT

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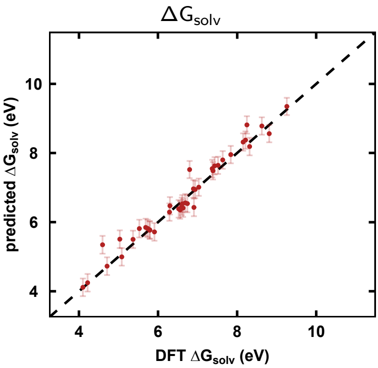
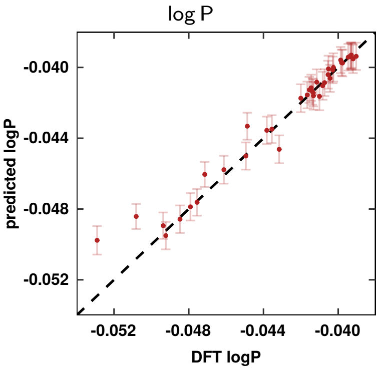




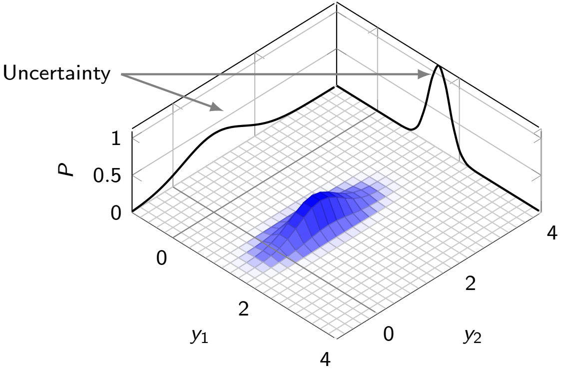
$$\begin{matrix}\Delta G_{solv} \\ \log P\end{matrix} = \begin{bmatrix}\hat{y}_1 \\ \hat{y}_2\end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix}\hat{\mu}_1 \\ \hat{\mu}_2\end{bmatrix}, \begin{bmatrix}\hat{\sigma}_1^2 & 0 \\ 0 & \hat{\sigma}_2^2\end{bmatrix}\right)$$

Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

3×100 tanh nodes, multitask, fully connected

Multiobjective optimization

We can predict quantites of interest for our RFBs with ANNs



$$\begin{matrix}\Delta \mathrm{G_{solv}} \\ \log \mathrm{P}\end{matrix} = \begin{bmatrix}\hat{y}_1 \\ \hat{y}_2\end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix}\hat{\mu}_1 \\ \hat{\mu}_2\end{bmatrix}, \begin{bmatrix}\hat{\sigma}_1^2 & 0 \\ 0 & \hat{\sigma}_2^2\end{bmatrix}\right)$$

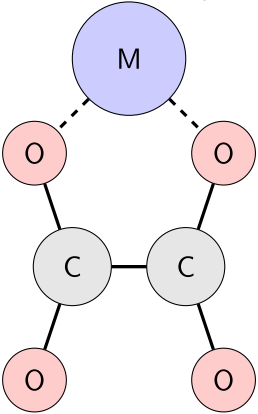
Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

3×100 tanh nodes, multitask, fully connected

Machine learning methods

Featurization:

Graph-based features (RACs) designed for TM complexes:



Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

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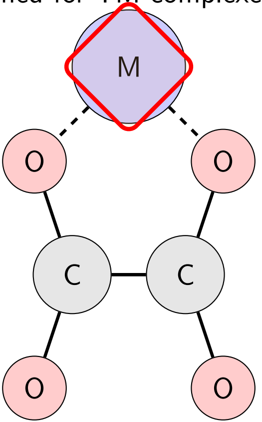

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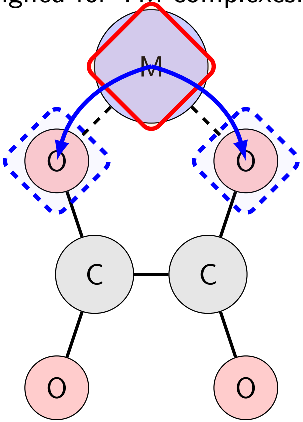

$$d_1 : \sum_{M,O} Z_M Z_O$$

Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

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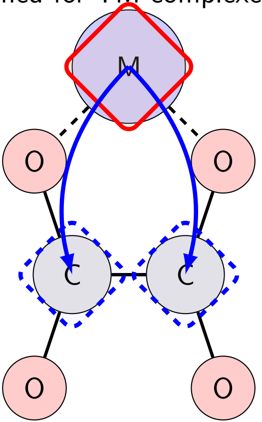

$$d_1 : \sum_{M,O} Z_M Z_O$$

$$d_2 : \sum_{M,C} Z_M Z_C$$

Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

Machine learning methods

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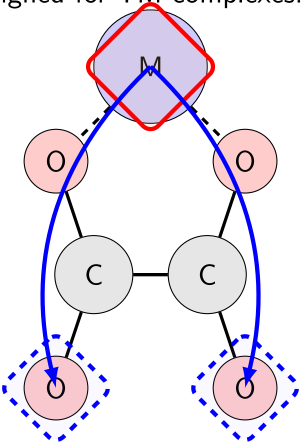

$$d_1 : \sum_{M,O} Z_M Z_O$$

$$d_2 : \sum_{M,C} Z_M Z_C$$

$$d_3 : \sum_{M,O} Z_M Z_O$$

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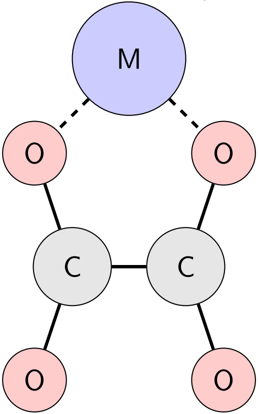


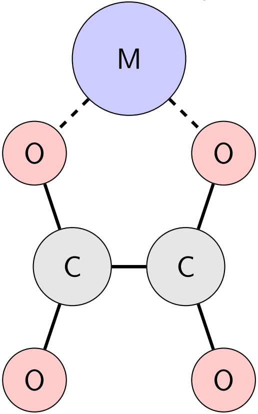
Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

Regression:

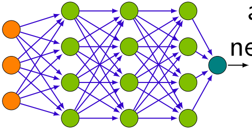
Machine learning methods

Featurization:

Graph-based features (RACs) designed for TM complexes:



Regression:



artifical neural networks (ANNs)

Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

Machine learning methods

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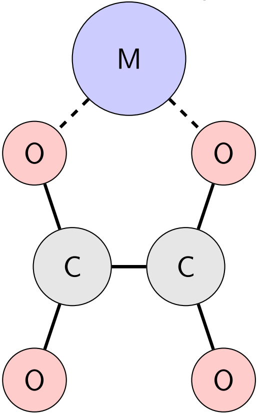
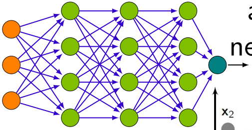
Graph-based features (RACs) designed for TM complexes:

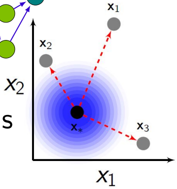


Regression:



artifical neural networks (ANNs)

Kernel methods (KRR)



Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

Machine learning methods

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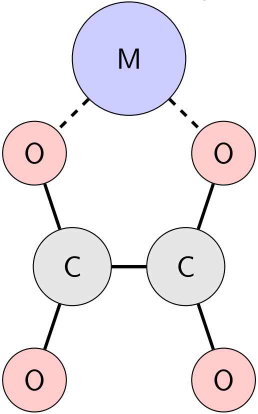
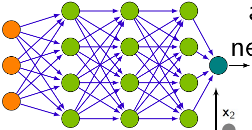
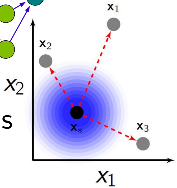


Regression:

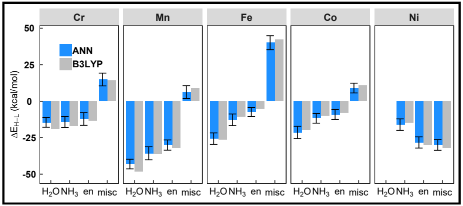


artifical neural networks (ANNs)



Kernel methods (KRR)

spin splitting energies



Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

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

Machine learning methods

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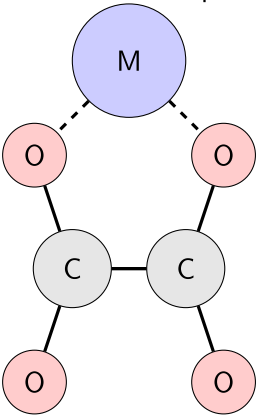
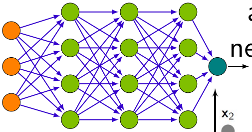
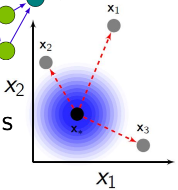


Regression:

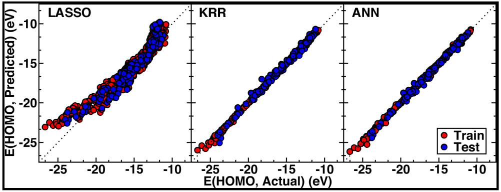


artifical neural networks (ANNs)

Kernel methods (KRR)



frontier orbital properties

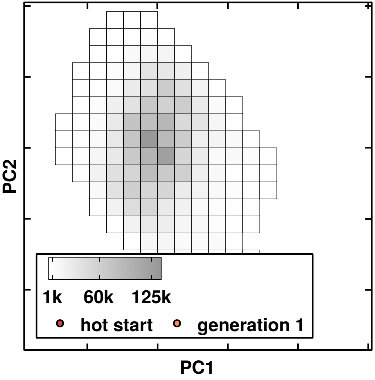


Janet, J.P., and Kulik, H.J., *J. Phys. Chem. A*, 121(46):8939–8954, 2017.

Nandy, A. *et al.*, *Ind. Eng. Chem. Res.*, 57(42):13973–13986, 2018.

Design space and clustering

Jump start the design with diversity-oriented cluster:



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

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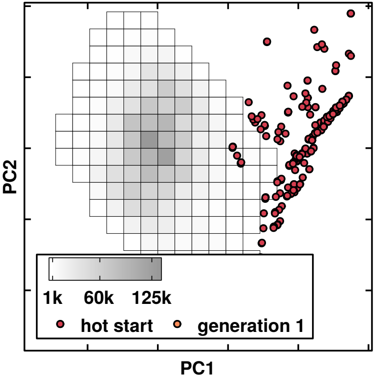

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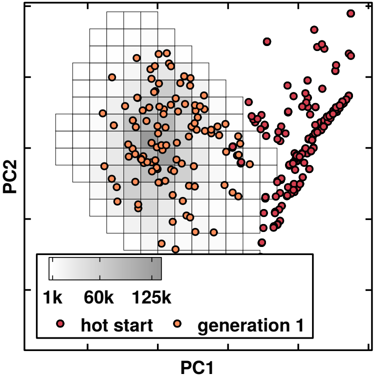

design space

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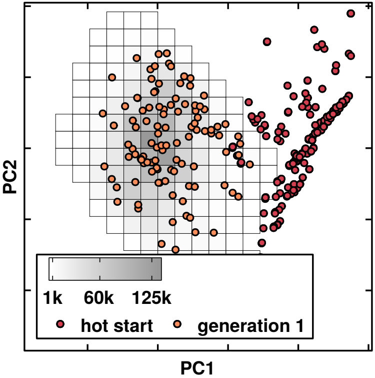

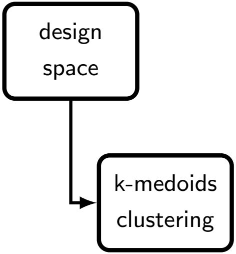

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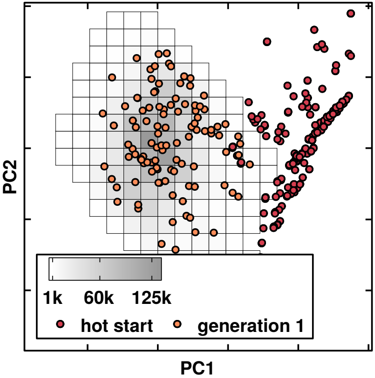

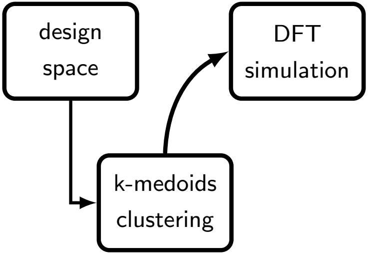

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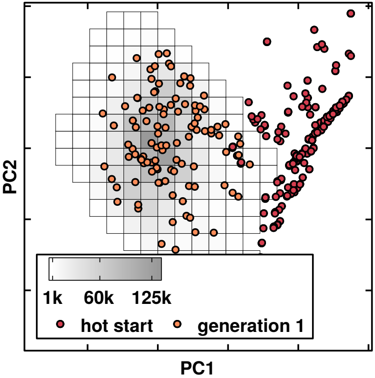

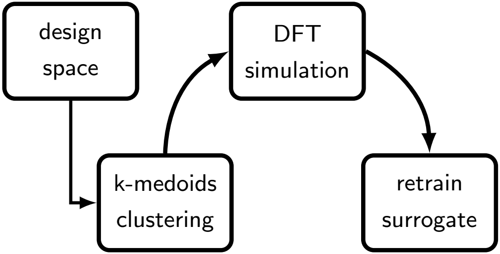

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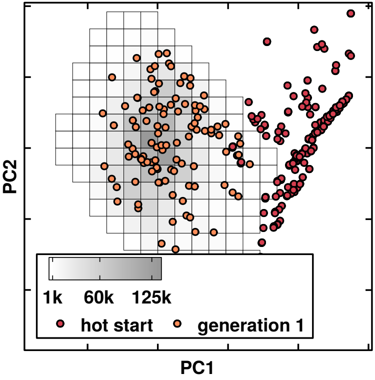

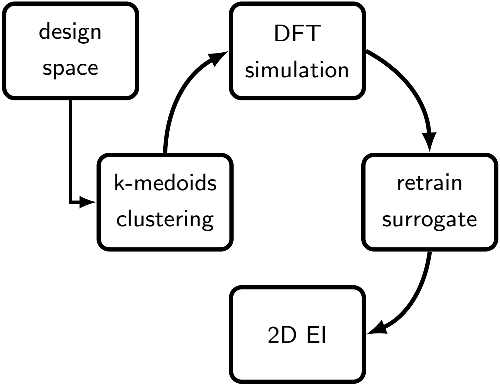

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multitask: 2 × 100 tanh nodes, fully connected

Design space and clustering

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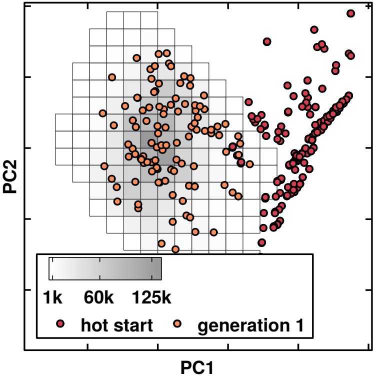

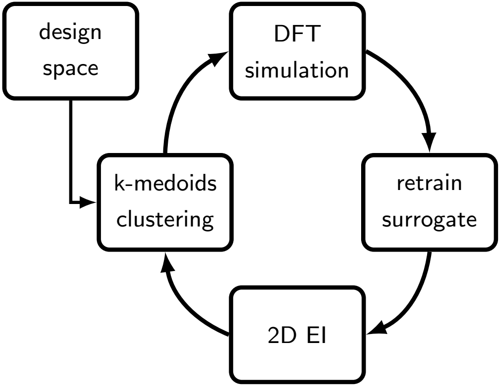

Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

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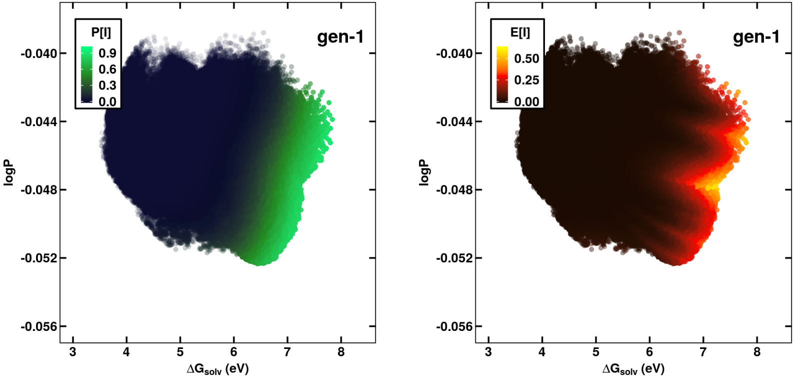
Evolution of PI and EI

probability of improvement expected improvement



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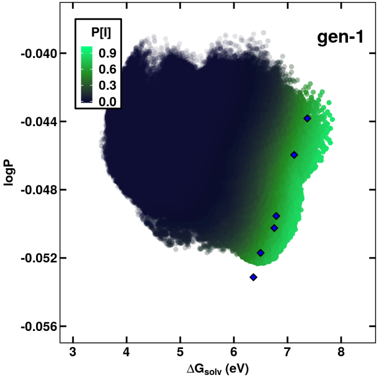
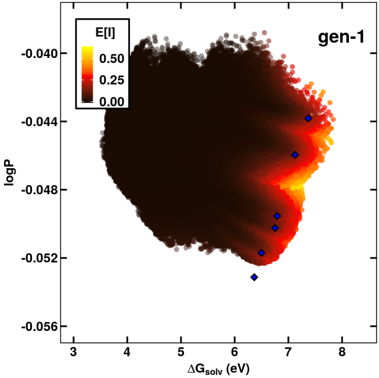


expected improvement



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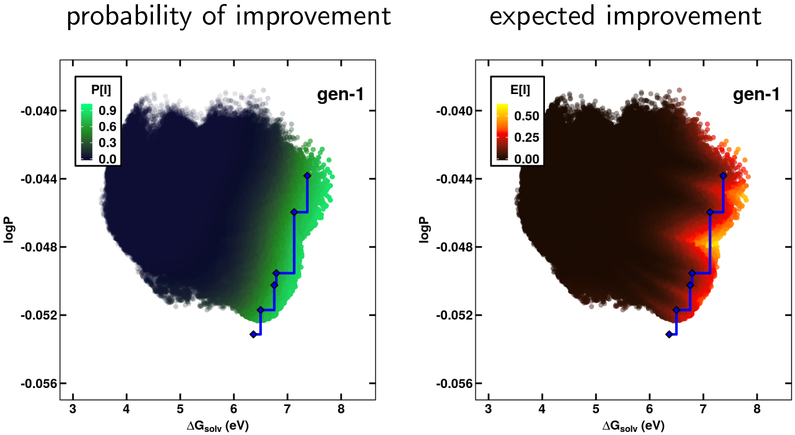

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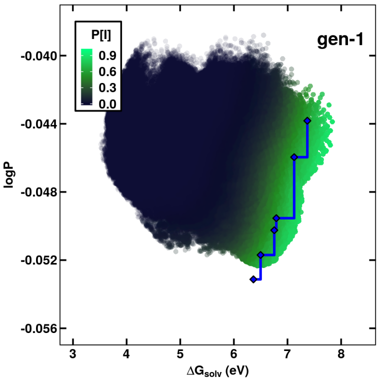

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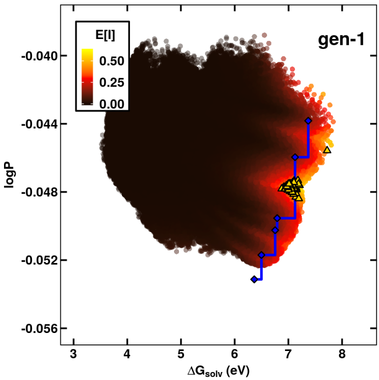

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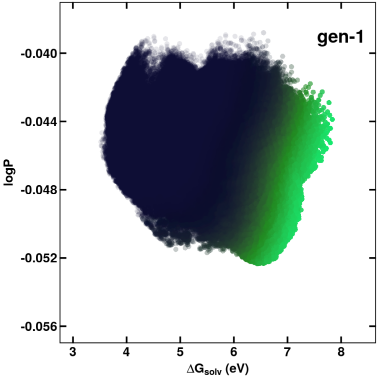

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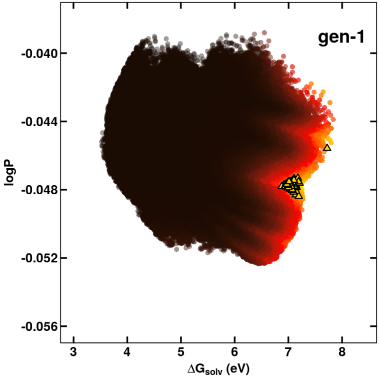
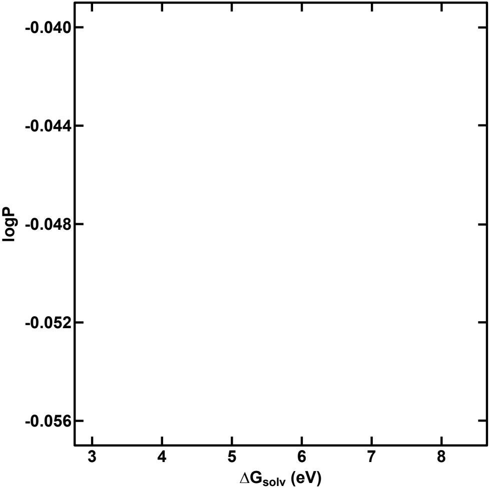


Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

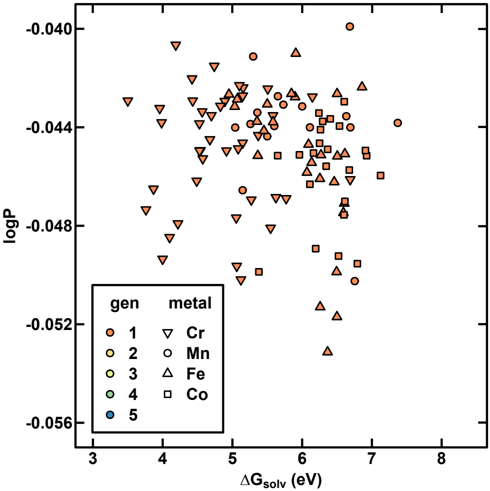
DFT Data



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

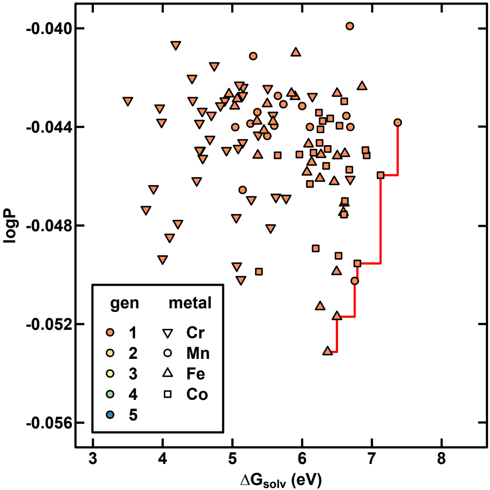
k-medoids points (generation 1)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

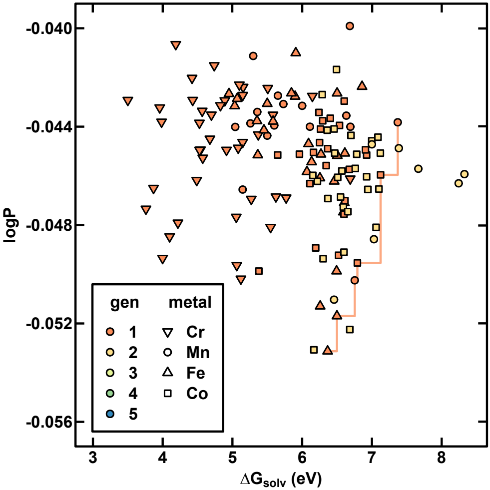
pareto front (generation 1)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

EI points (geneneration 2)



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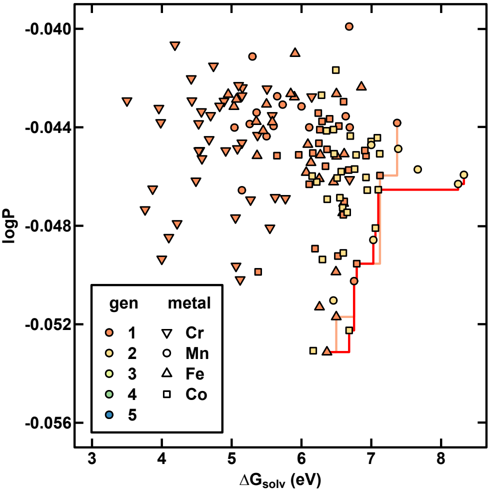
Simulation results

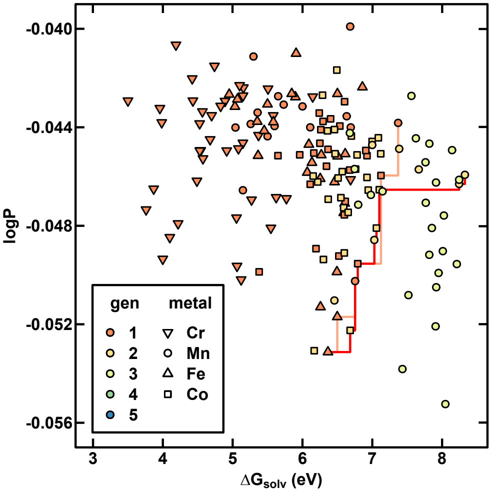
pareto front (generation 2)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

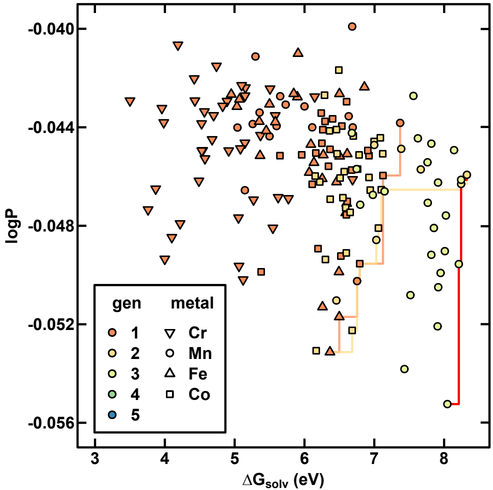
EI points (generation 3)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

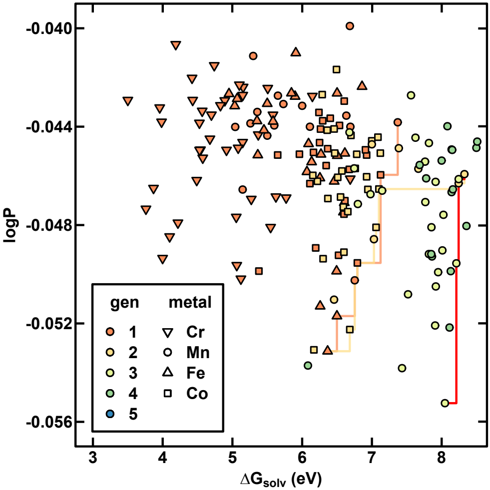
pareto front (generation 3)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

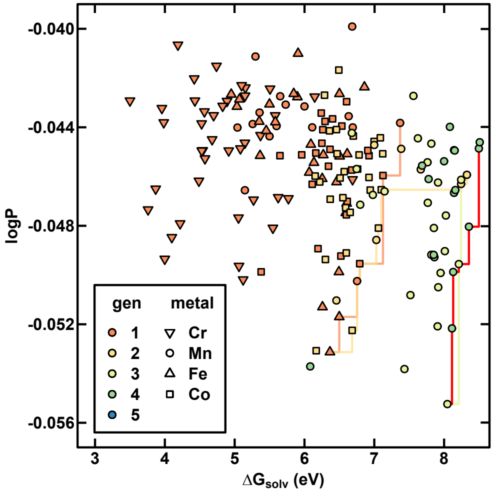
EI points (generation 4)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

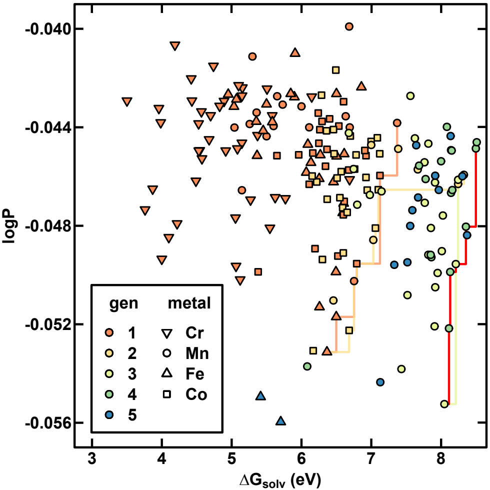
pareto front (generation 4)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results

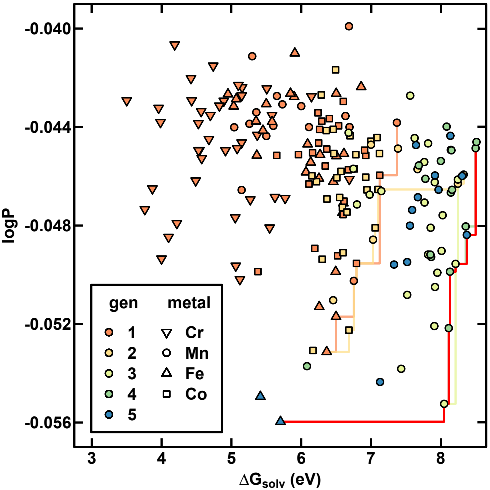
EI points (generation 5)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

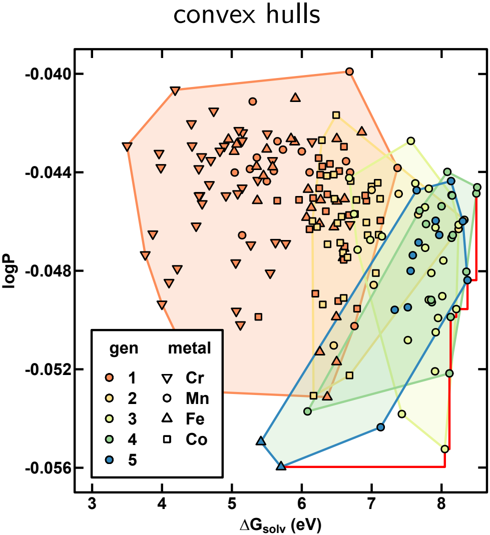
Simulation results

pareto front (generation 5)



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Simulation results



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Conclusions

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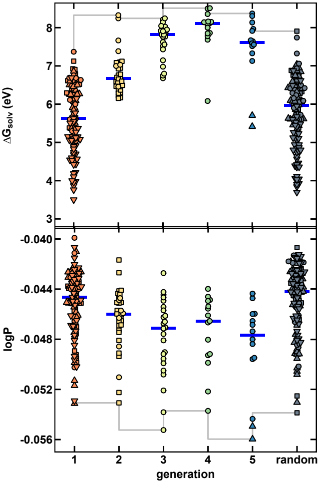
- EI framework provides high resolution in the region of interest (c.f. maximum uncertainty), converges quickly



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Conclusions

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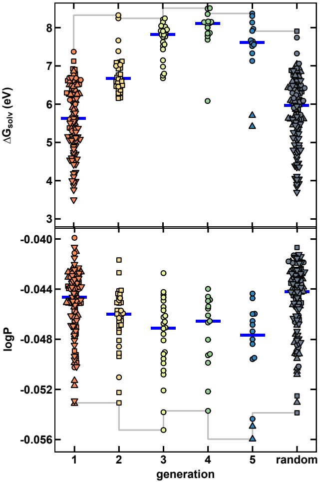
- We are able to identify fruitful regions from large chemical spaces based on few DFT evaluations



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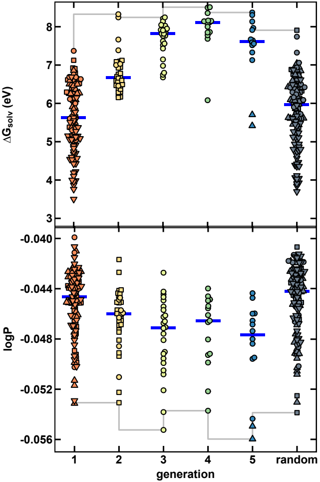
Conclusions

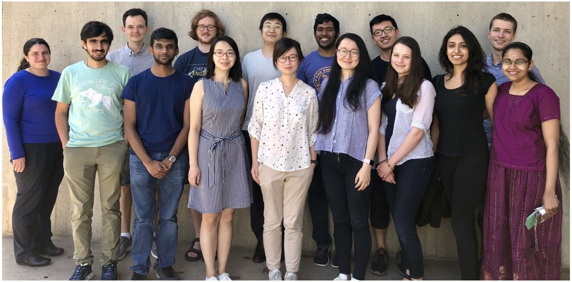
- EI framework provides high resolution in the region of interest (c.f. maximum uncertainty), converges quickly
- We are able to identify fruitful regions from large chemical spaces based on few DFT evaluations
- Multiobjective DFT optimization guided by data-driven method efficiency generates lead complexes



Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

Acknowledgments

This work is thanks to the Kulik group and funding partners:



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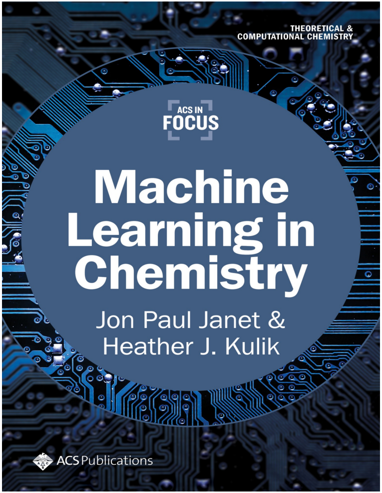

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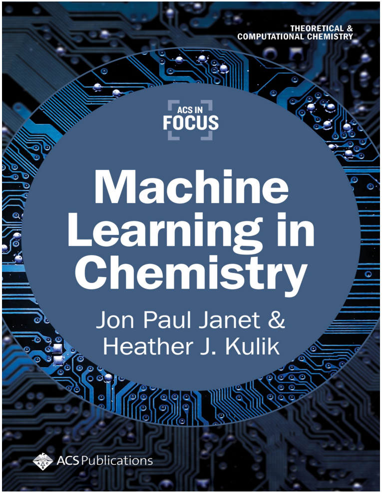

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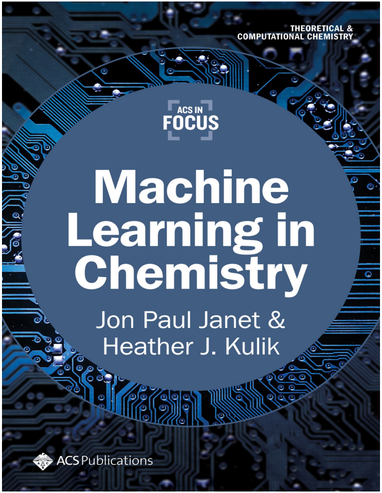

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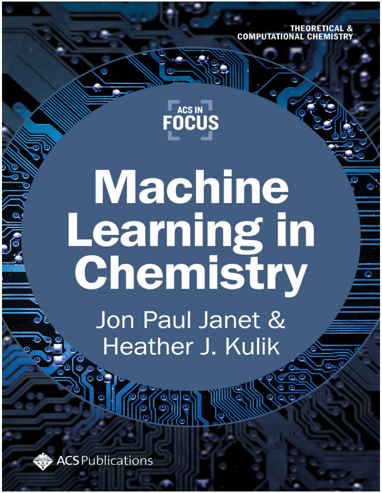

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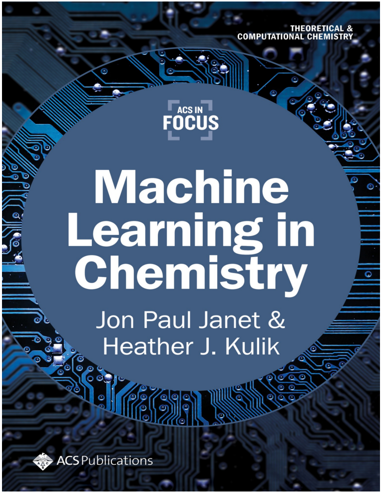

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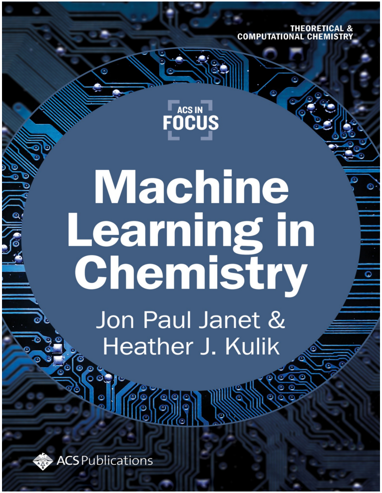

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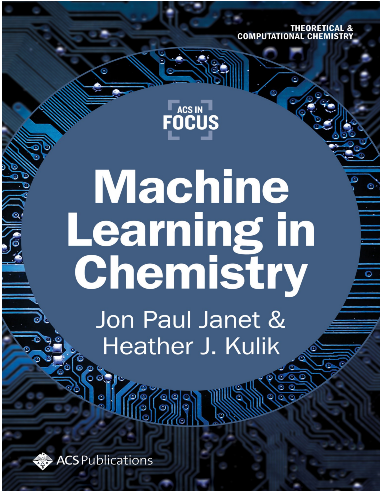

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Supervised learning methods attempt to connect patterns in data to known endpoints by learning model parameters that reproduce the observed relationship.

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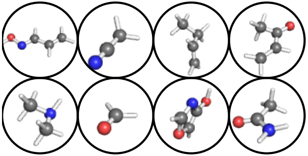

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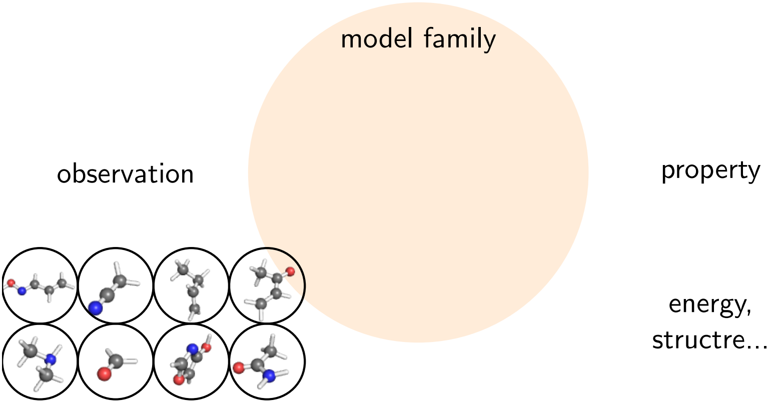

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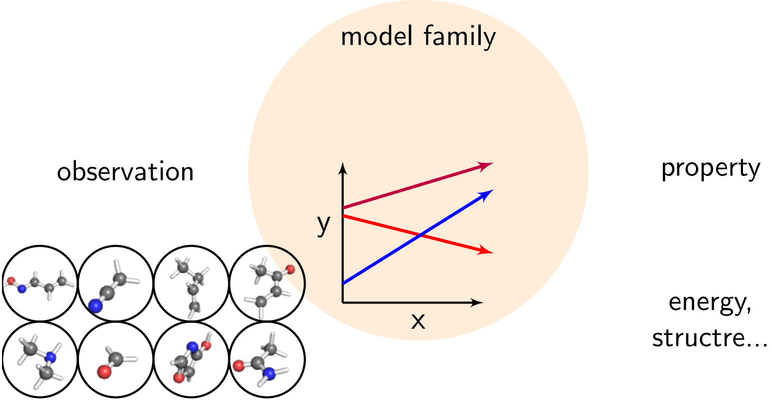

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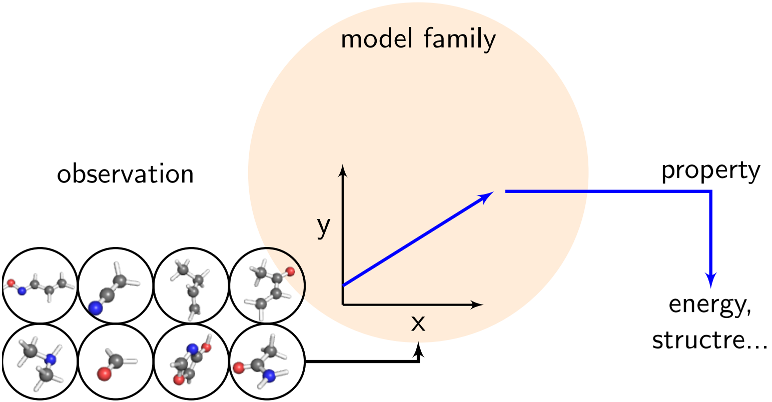

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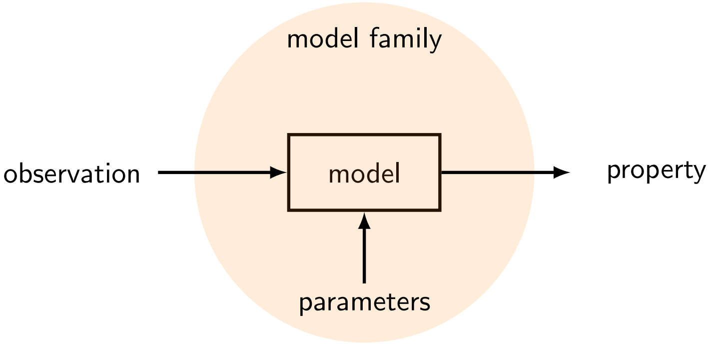

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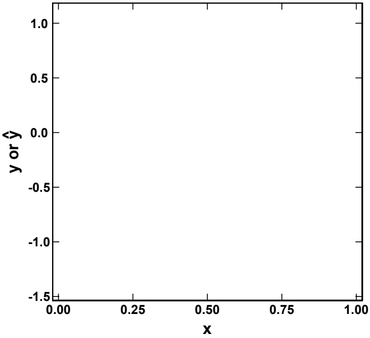

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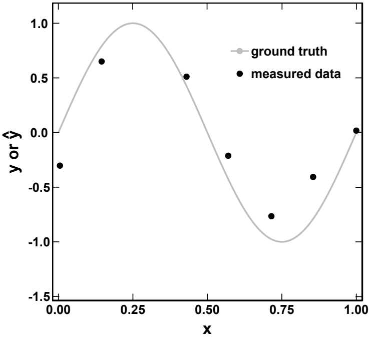
Assume 8 measurements with noise $\mathcal{N}(0, 0.2)$



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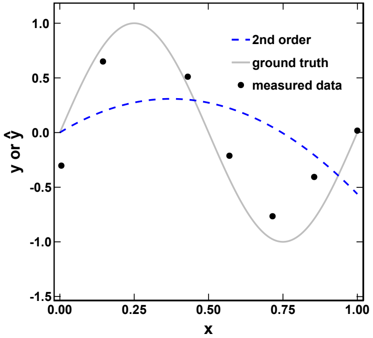

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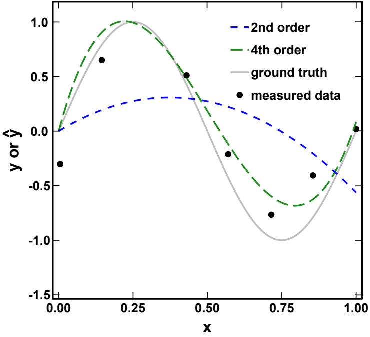

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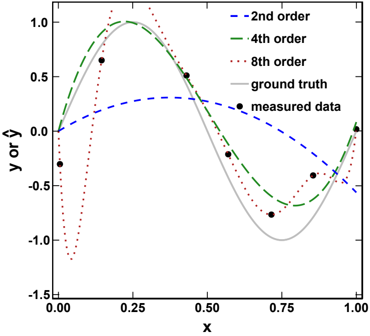

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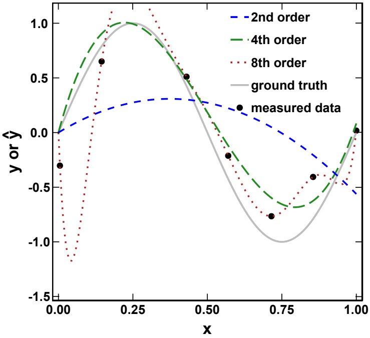

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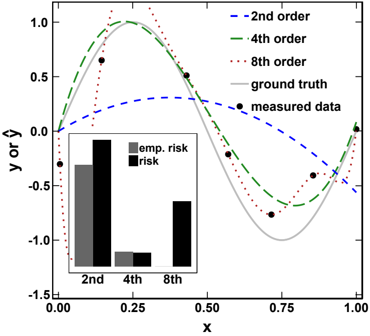

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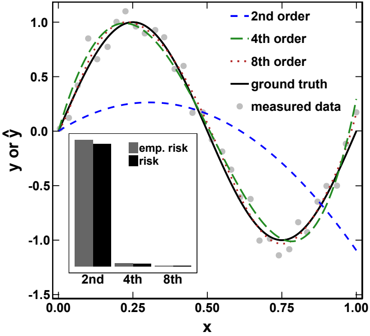
What happens if we add more data?



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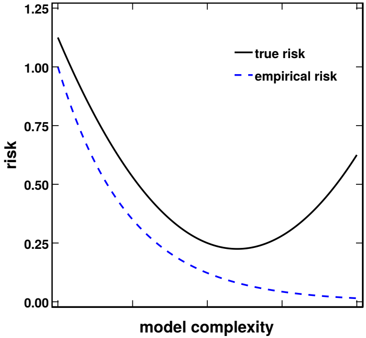
We cannot choose model complexity (hyperparameters, regularization) based on training data.

Cross-validation (and related techniques) must be used to compare models.



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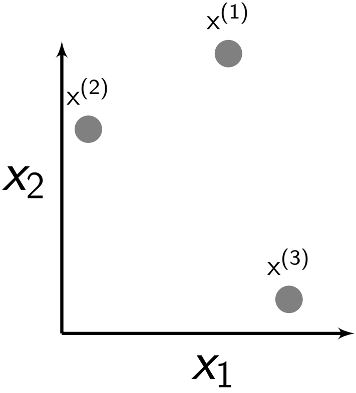
Linear models serve a tool to understand nonlinear models, regularization



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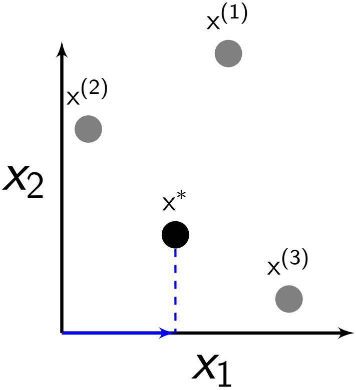

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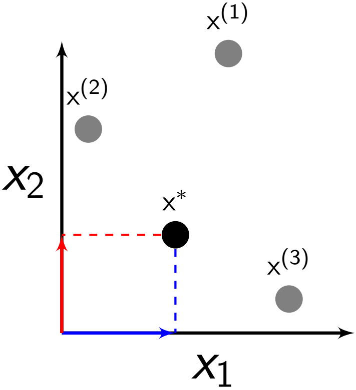

linear model

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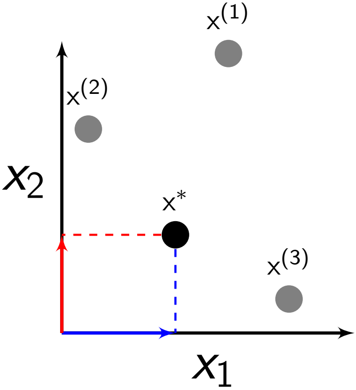
$$y(x^*) = w_1 x_1^* + w_2 x_2^*$$



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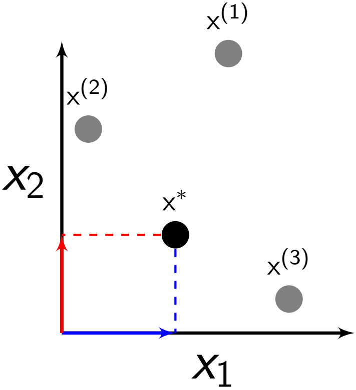

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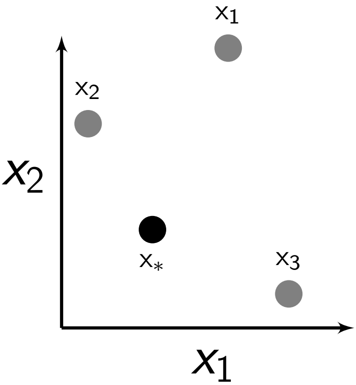

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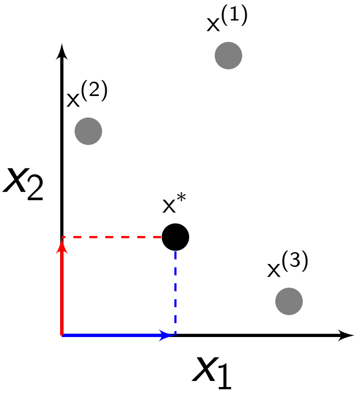
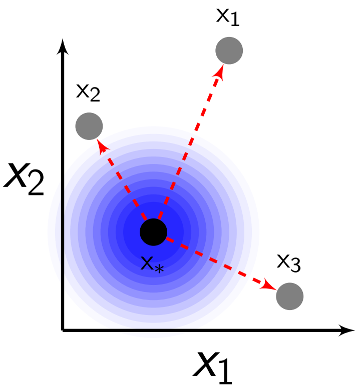


linear model

$$y(x^*) = \sum_{i=1}^{n} a_i k(x^*, x^{(i)})$$



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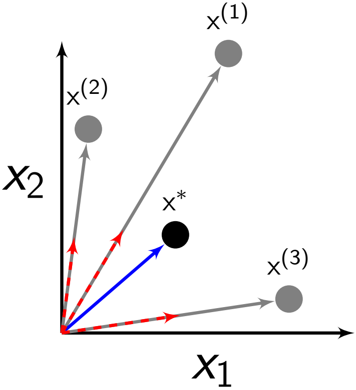

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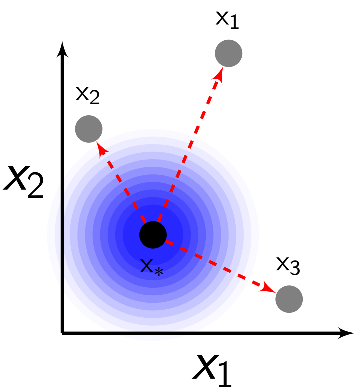

Gaussian kernel

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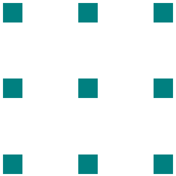

Chemical Space C_f

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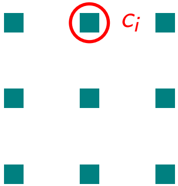

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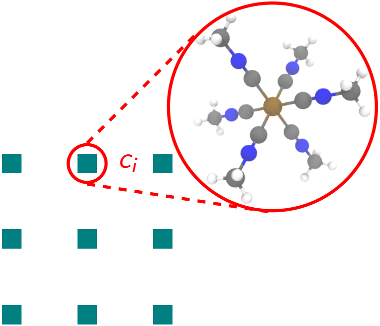

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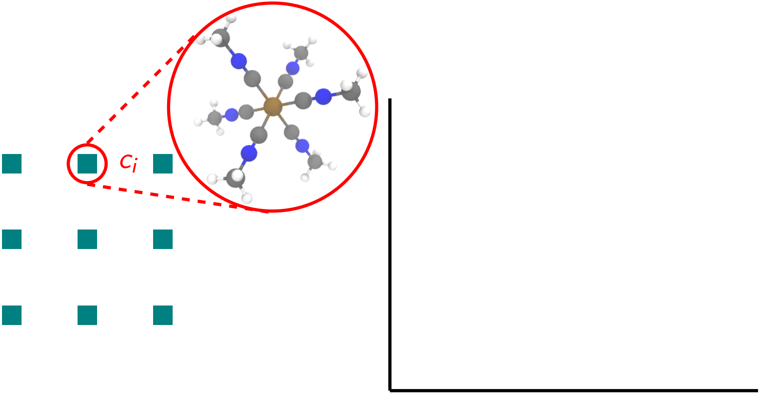

Chemical Space C_f

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

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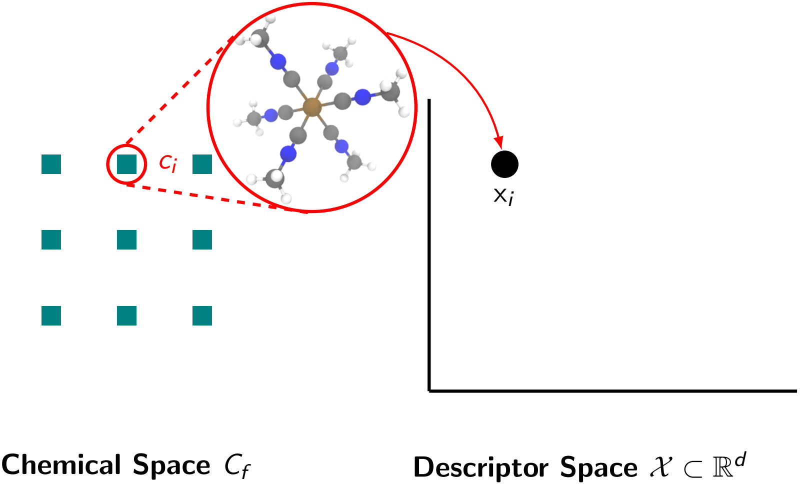

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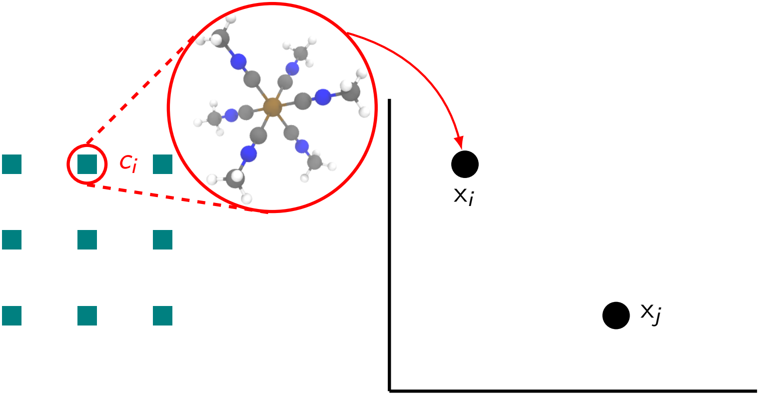

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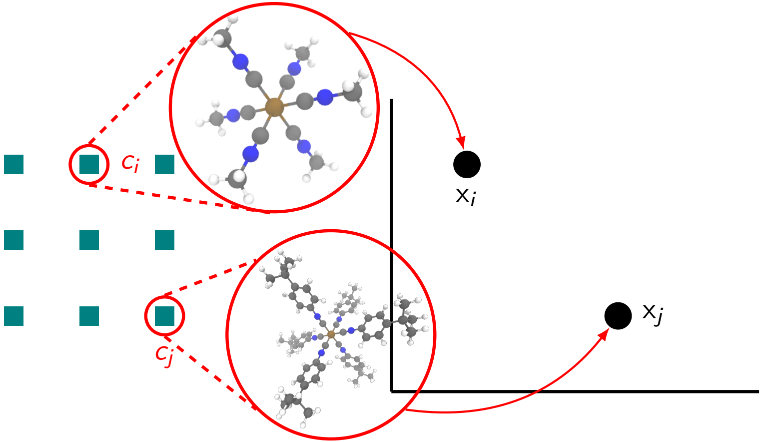

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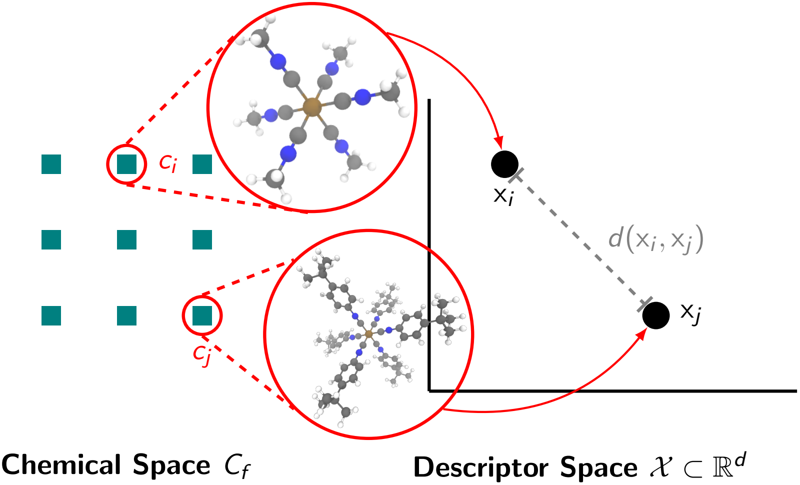

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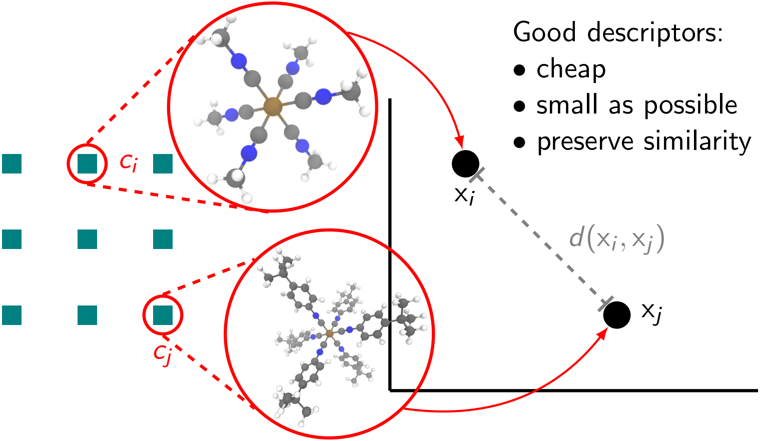

Good descriptors:

- cheap
- small as possible
- preserve similarity

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

C4: Types of representation

complexity

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Fingerprints

– considerable use in drug design

– no information related to molecular topology

– cheap to compute

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Graph-theoretic

– *topological* and *topochemical* representations

– includes all connectivity but no 3D information

– relatively easy to compute

3D structure

– fine-grained structural information in 3D

– mimic input to a quantum chemistry code

–expensive to compute, rich information

C5: How neural networks work

Simple neural networks can be understood as learned, continuous maps from the input space to a latent space, followed by linear regression

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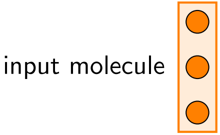
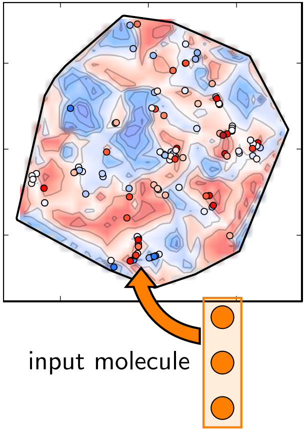


C5: How neural networks work

feature space



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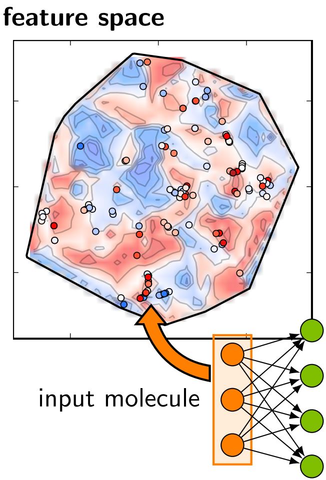

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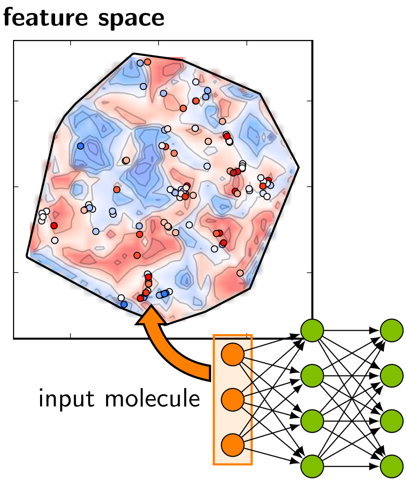

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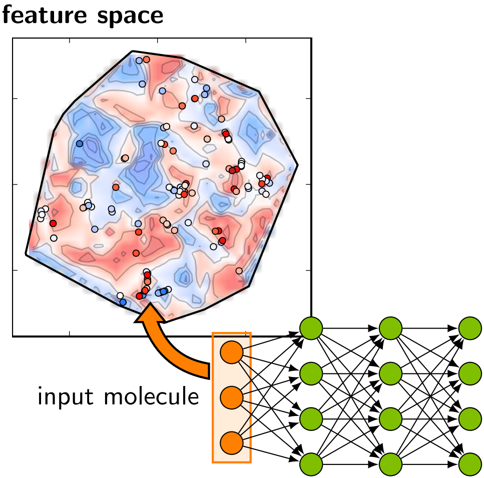

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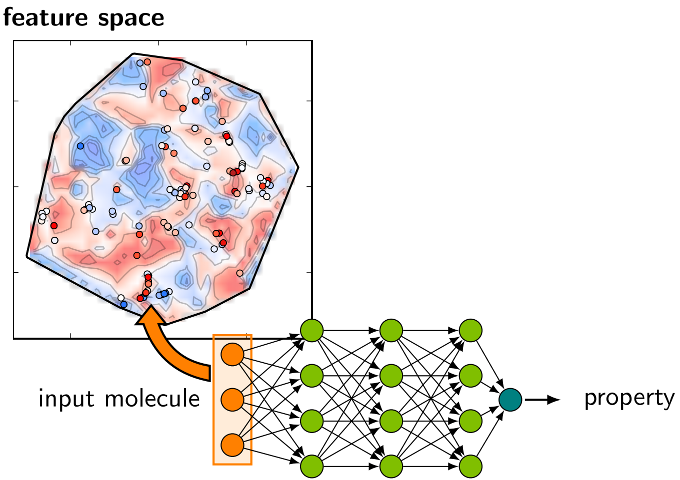

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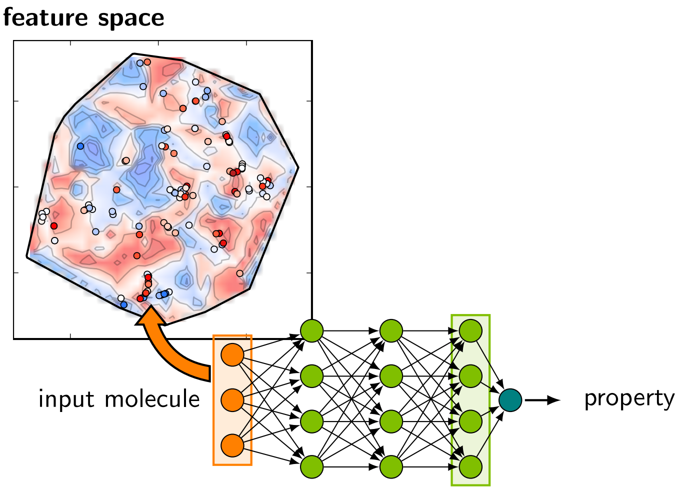

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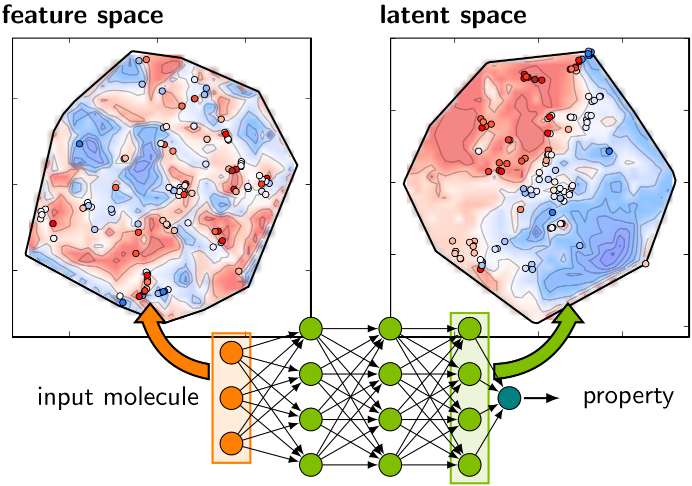

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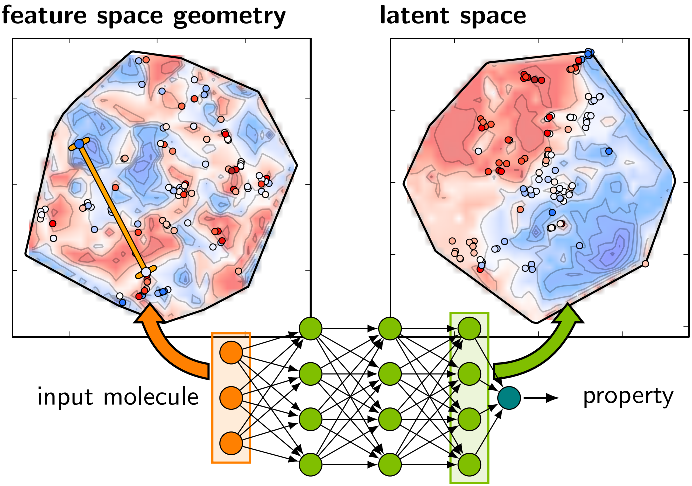

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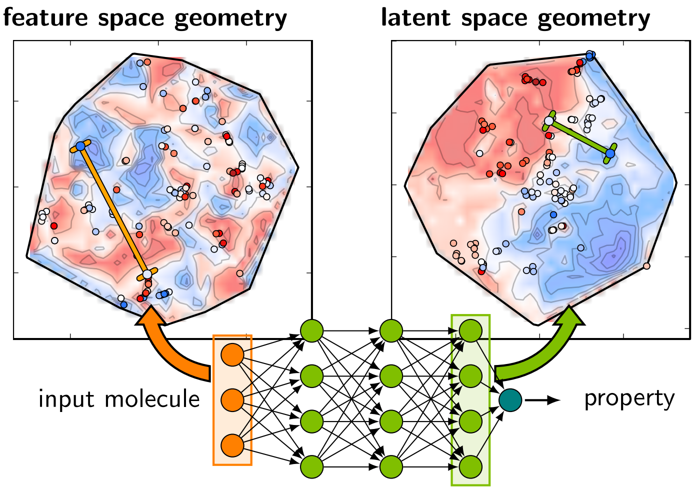

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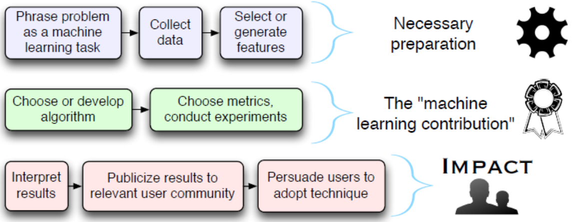
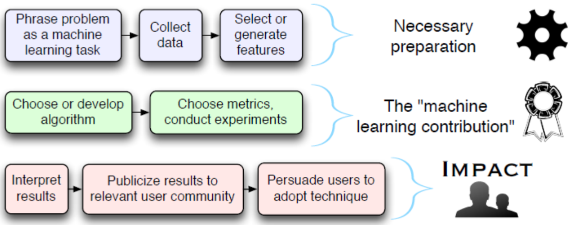


Wagstaff, K., "Machine Learning that Matters", ICML 29, 16(7):529–536, 2012

Final thoughts

It is increasingly important to be literate about ML concepts. Even if/when the hype lessens, ML tools will continue to have a large impact on our science.



Wagstaff, K., "Machine Learning that Matters", ICML 29, 16(7):529–536, 2012

Conversely, there is a growing need for domain experts to engage and derive impact from advances in ML, and you have a lot of value to contribute to interpreting and exploiting the results.