Machine Learning in Chemistry 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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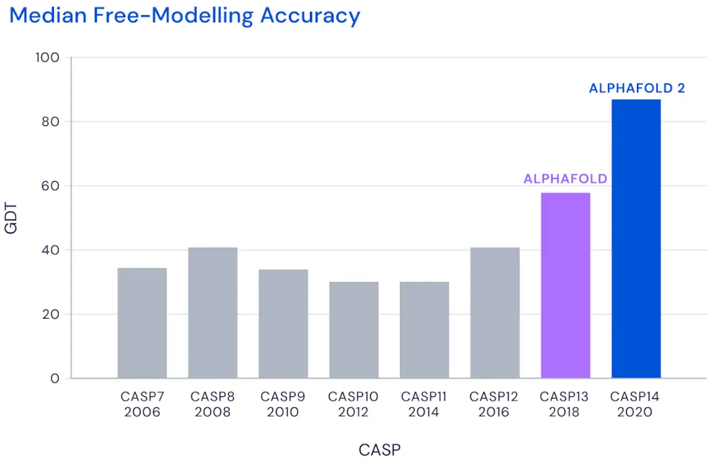

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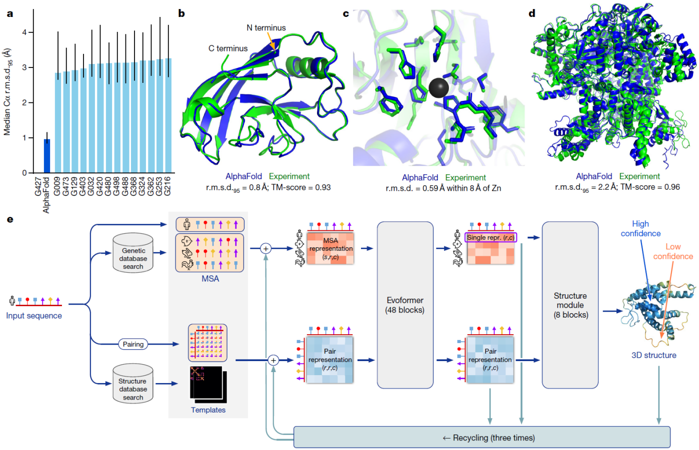

Senior, A.W., *et al.*, *Nature*, 577: 706–710, 2020. Jumper, J., *et al.*, *Nature*, 596: 583–589, 2021.

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"*It is not that machines are going to replace chemists. It's that the chemists who use machines will replace those that do not*"
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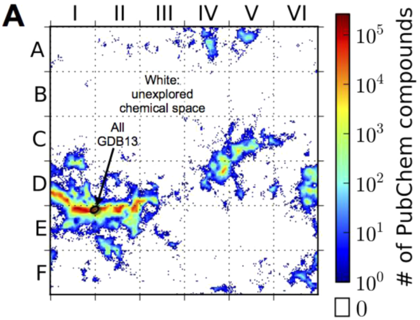
This is probably a bit strong, but all scientists generate data as a product. ML provides new, powerful ways to exploit this information.

Motivation: chemical discovery

Why is ML transforming chemisty?

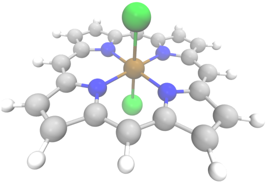
The space of possible chemistries is incredibly vast, with $\mathcal{O}(10^{60})$ small organic molecules.

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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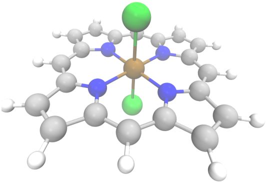

property

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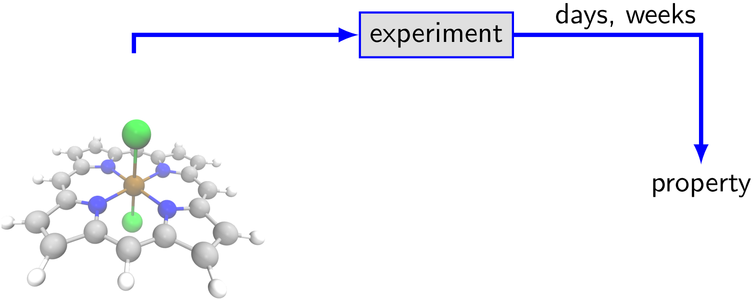

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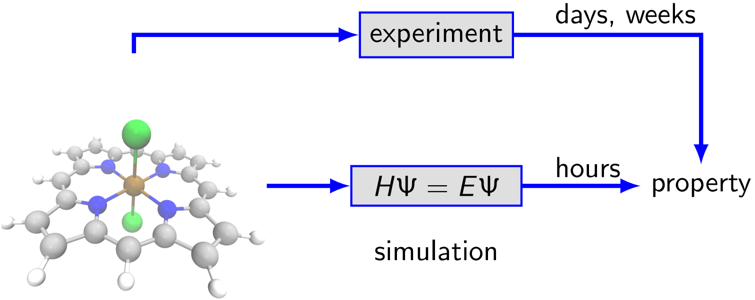

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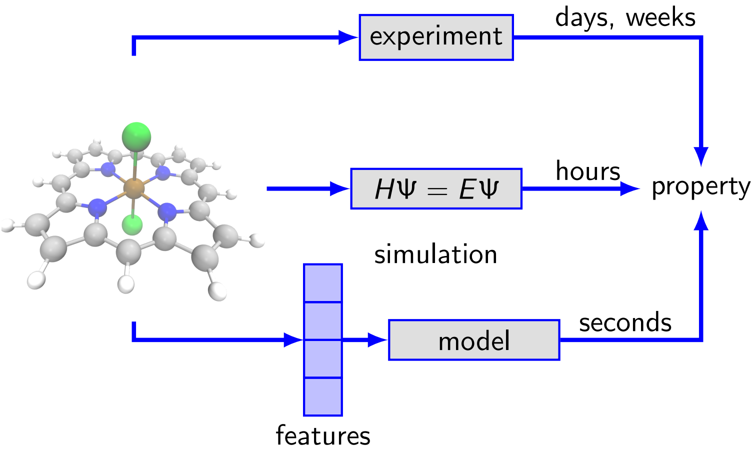

Why does ML work well in chemical sciences?

machine learning methods

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computer vision

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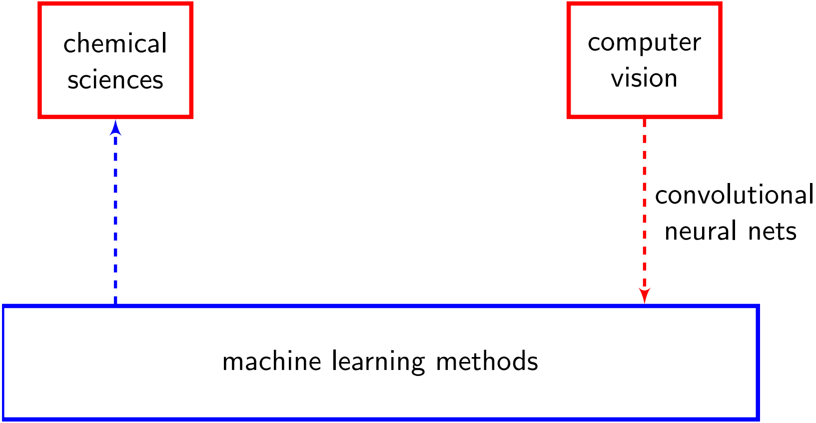

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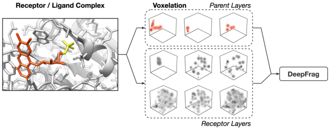

Green, H., *et al.*, bioRxiv 2021.01.07.425790, 2021.

convolutional neural nets

machine learning methods

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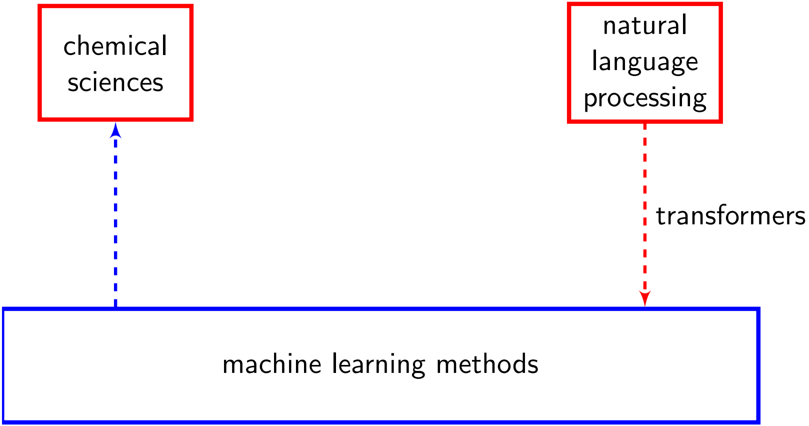

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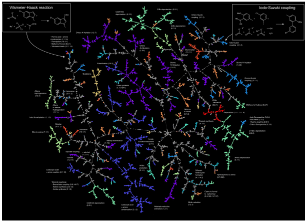

Schwaller, P., *et al.*, *Nat. Mach. Intell.*, 3: 144–152, 2021.

natural language processing

transformers

machine learning methods

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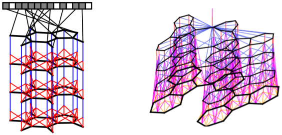

Duvenaud, D., *et al.*, *NeurIPS 28*, 2015.

graph convolutions

machine learning methods

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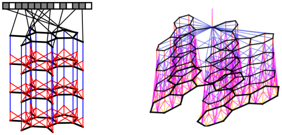
chemical sciences

diverse applications from traffic networks to medicine



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Future directions for ML in chemistry

Some areas of high current interest:

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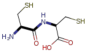
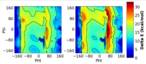
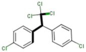
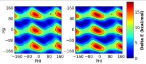
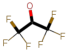
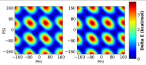
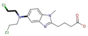
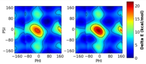
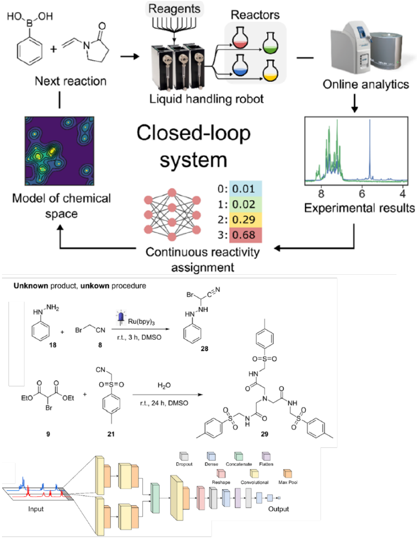
Name	Molecule	MAE	RMSE	Scan (Left:ANI Right:DFT)
Cysteine-Dipeptide (25 atoms)		1.75	2.55	
DDT (28 atoms)		0.53	0.70	
Hexafluoroacetone (10 atoms)		0.08	0.11	
Bendamustine (44 atoms)		0.50	0.66	

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

Future directions for ML in chemistry

Some areas of high current interest:

- Neural network potentials - quantum accuracy, force field cost. Reactive dynamics on your laptop!
- Synthesis planning and optimization. Fully automated chemistry!



Caramelli, D., *et al.*, *ACS Cent. Sci.*, just accepted, 2021

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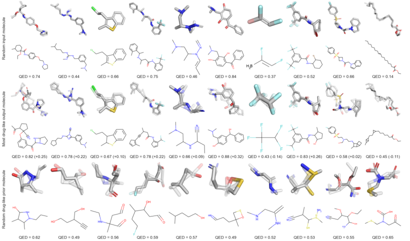
- Synthesis planning and optimization. Fully automated chemistry!
- Generative models. Designing new drugs directly into the pocket, *de novo*!



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

Guo, J., *et al.*, *J .Cheminform.*, 13(89), 2021

Arcidiacono, M. & Koes, D.R., *et al.*, https://arxiv.org/abs/2109.15308, 2021

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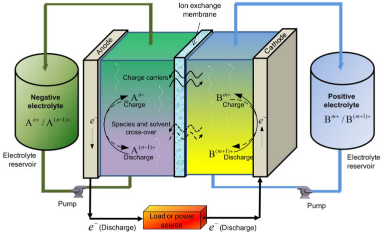

Perry, M.L. and Adam, Z., *J. Electrochem. Soc.*, 163(1):A5064–A5067, 2018.

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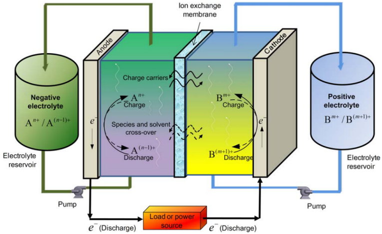

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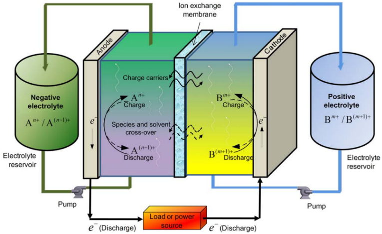

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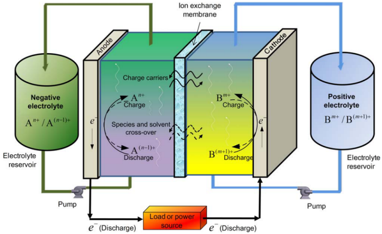

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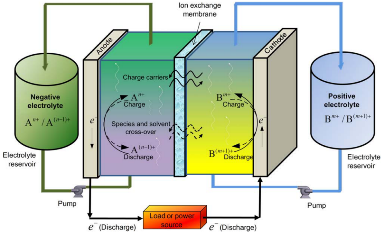

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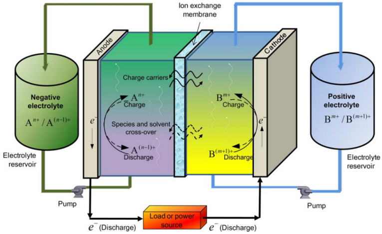

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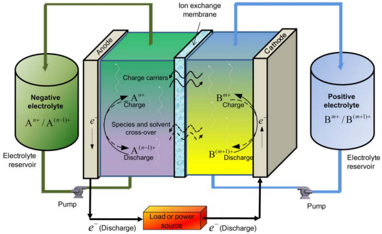

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We need complexes that have high redox potential **and** good solubility

A design space for RFBs

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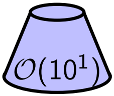

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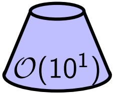

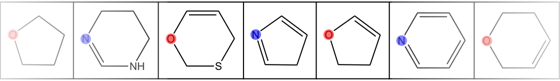

38 heterocycles

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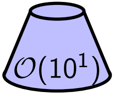

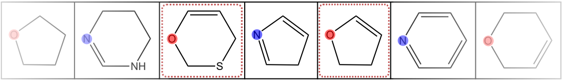

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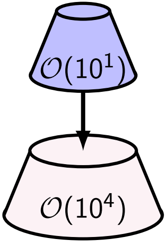

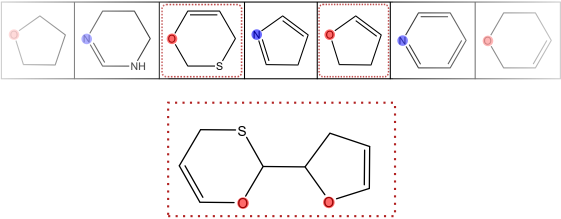

779 base ligands

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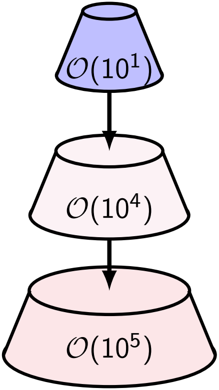

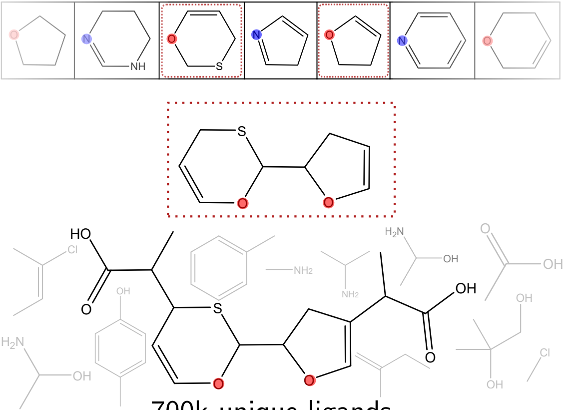

700k unique ligands

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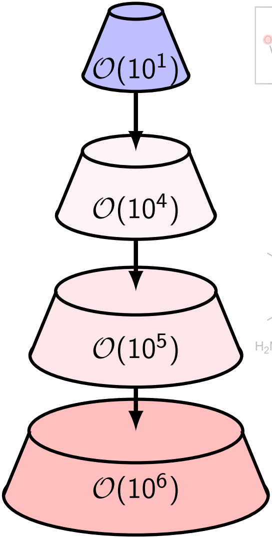
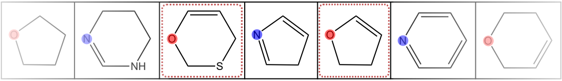
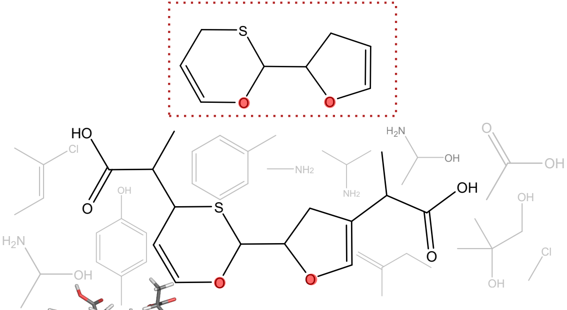
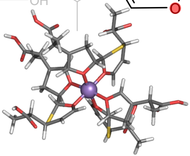




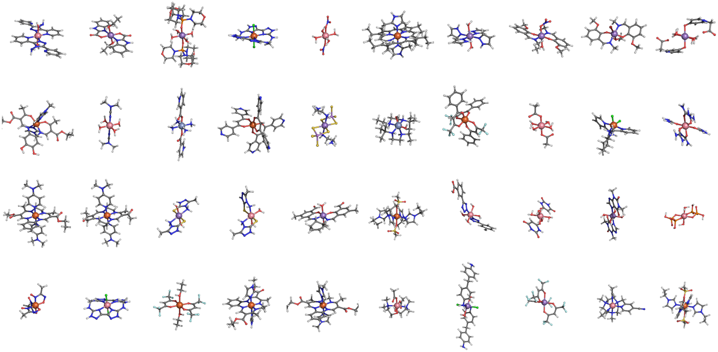




$\sim$ 3M complexes
with 4 metals

Computational approaches to chemical discovery

Computational methods can search for suitable complexes



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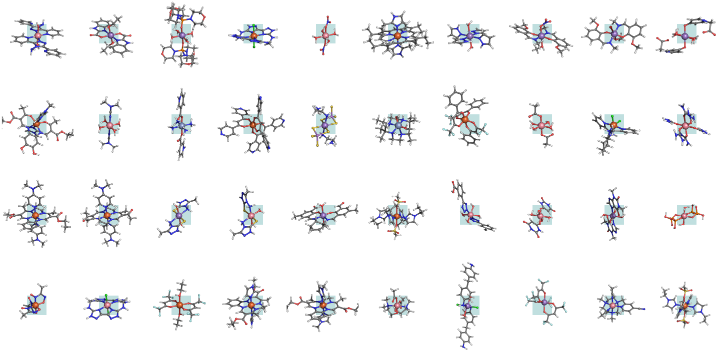

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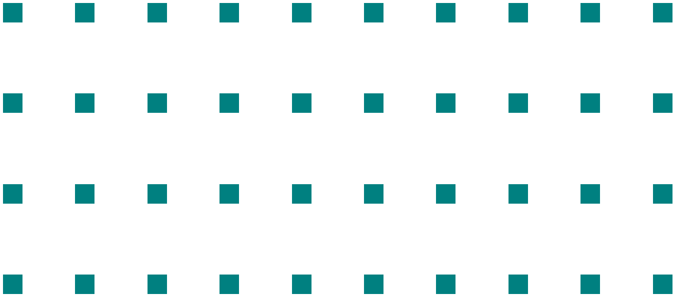

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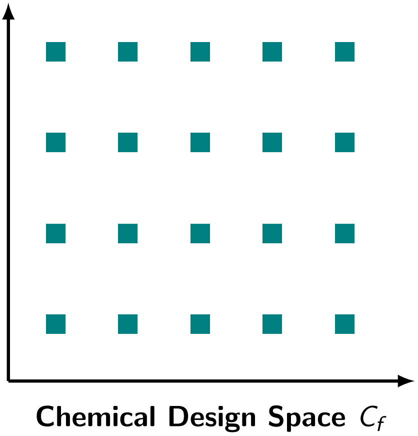

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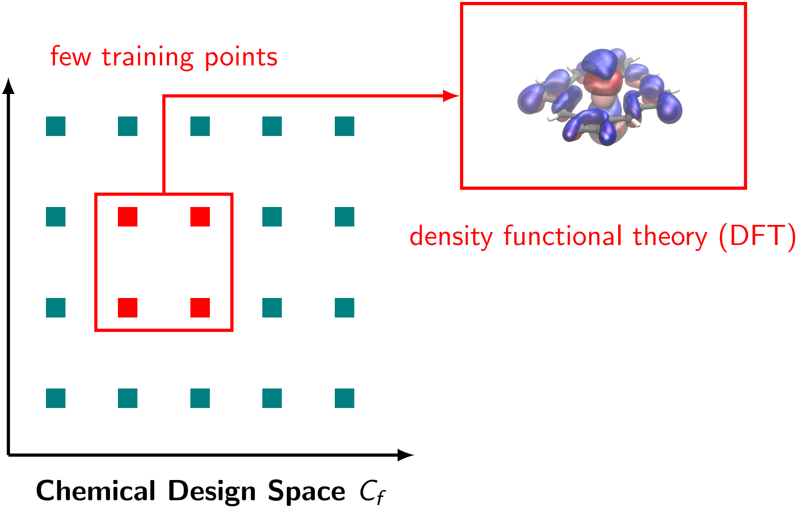

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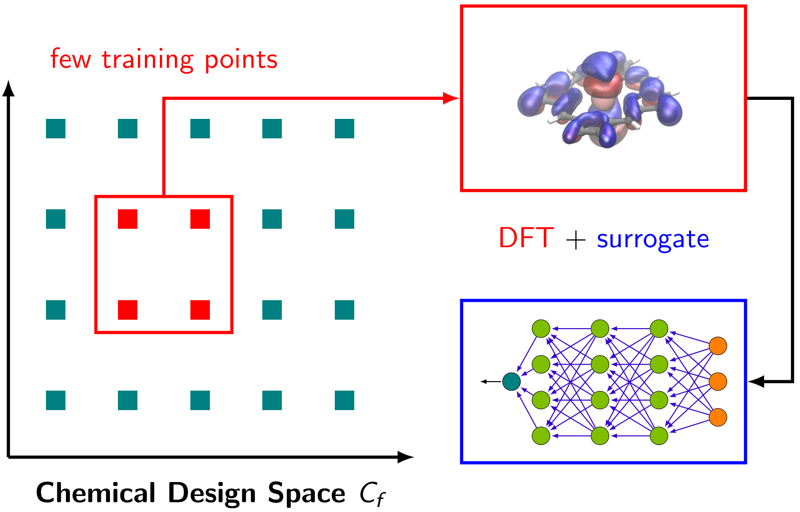

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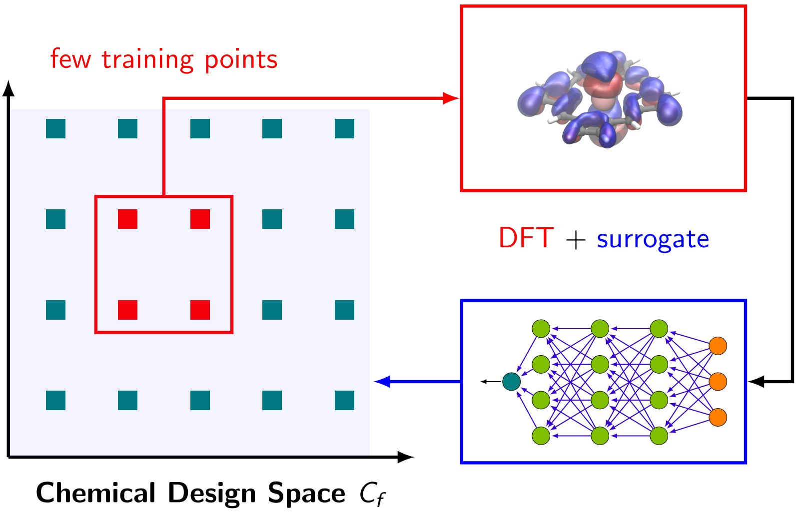

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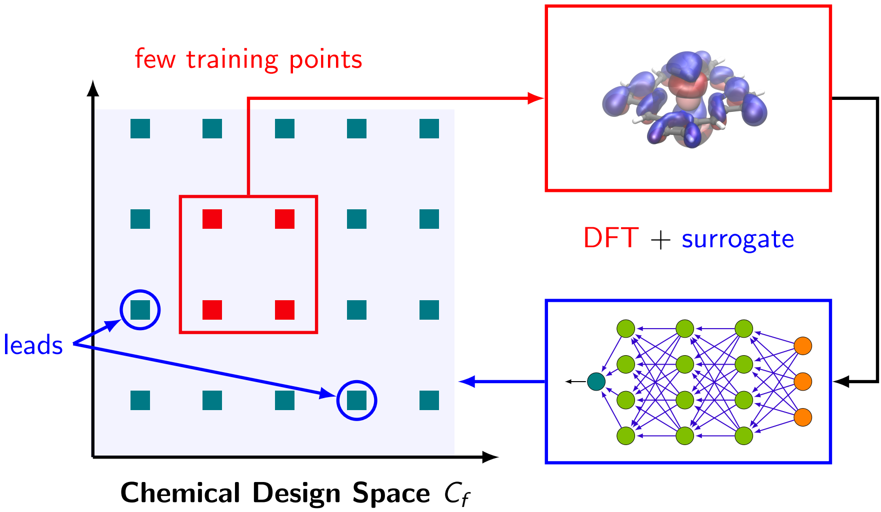

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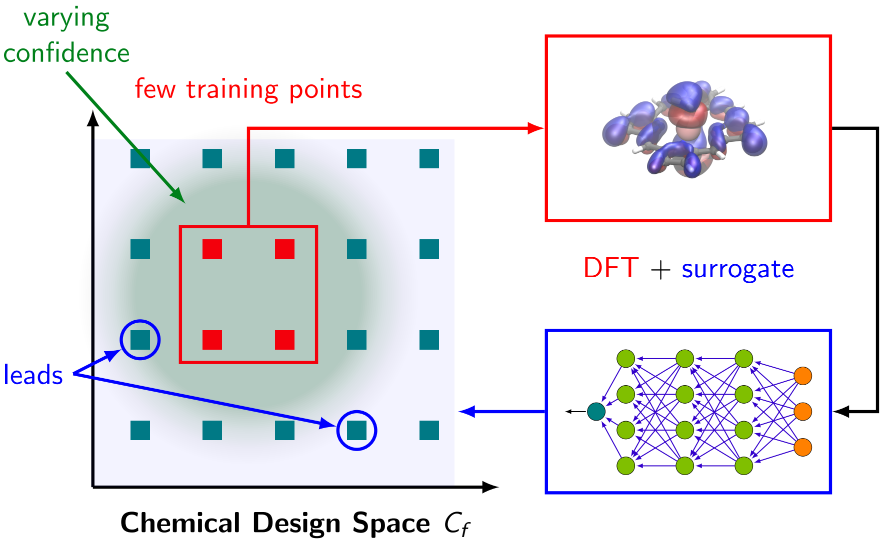

Multiobjective optimization

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

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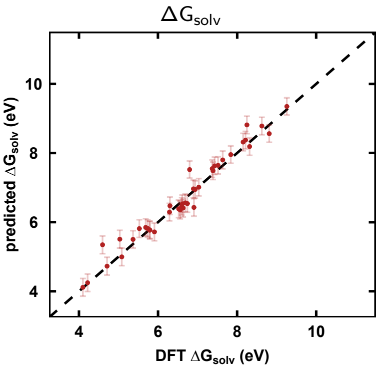

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3 × 100 tanh nodes, multitask, fully connected

Multiobjective optimization

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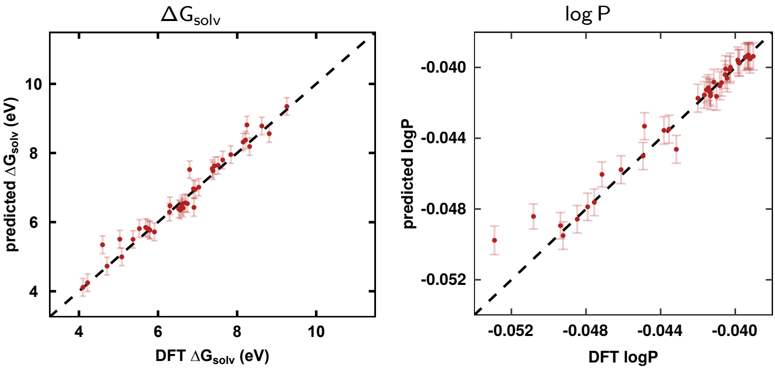

Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

3 × 100 tanh nodes, multitask, fully connected

Multiobjective optimization

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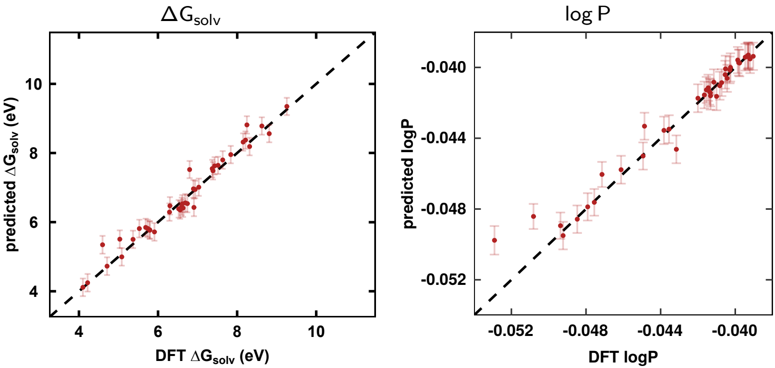

Screen $3M$ complexes in < 4 **minutes** on a regular workstation, c.f. 50 **GPU-years** with DFT

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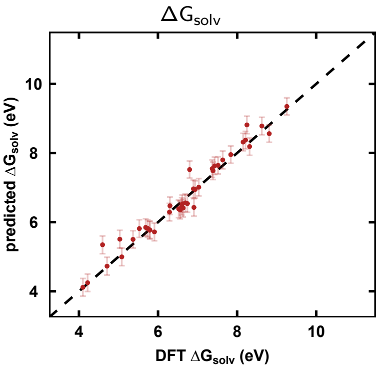

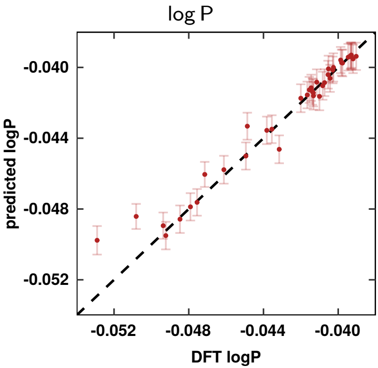

$$\begin{matrix}\Delta G_{solv} \\ \log P\end{matrix} = \begin{bmatrix}\hat{y}_1 \\ \hat{y}_2\end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix}\hat{\mu}_1 \\ \hat{\mu}_2\end{bmatrix}, \begin{bmatrix}\hat{\sigma}_1^2 & 0 \\ 0 & \hat{\sigma}_2^2\end{bmatrix}\right)$$

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

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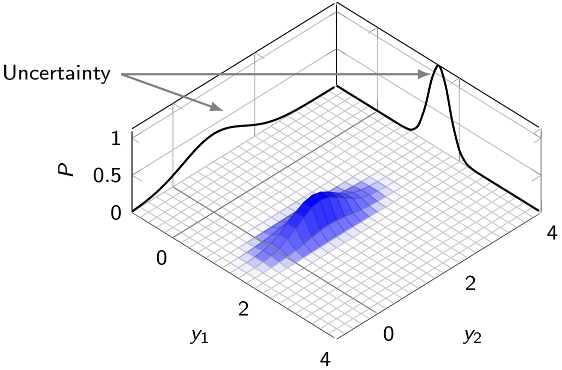


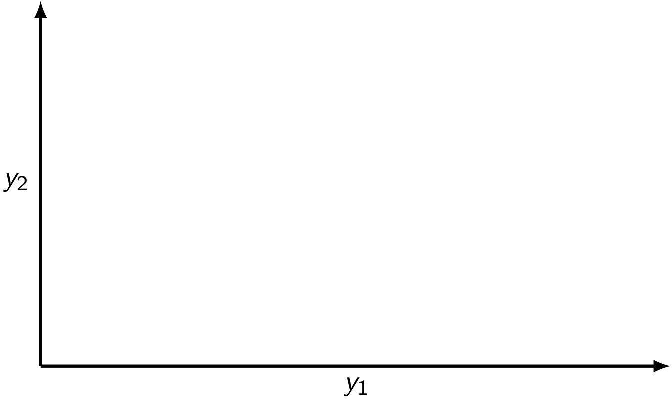
$$\begin{matrix}\Delta G_{\text{solv}} \\ \log P\end{matrix} = \begin{bmatrix}\hat{y}_1 \\ \hat{y}_2\end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix}\hat{\mu}_1 \\ \hat{\mu}_2\end{bmatrix}, \begin{bmatrix}\hat{\sigma}_1^2 & 0 \\ 0 & \hat{\sigma}_2^2\end{bmatrix}\right)$$

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

3×100 tanh nodes, multitask, fully connected

2D EGO Illustration

We will use a multiobjective expected improvement framework:



Keane, A. J., *AIAA Journal*, 44(4):879–891, 2006.

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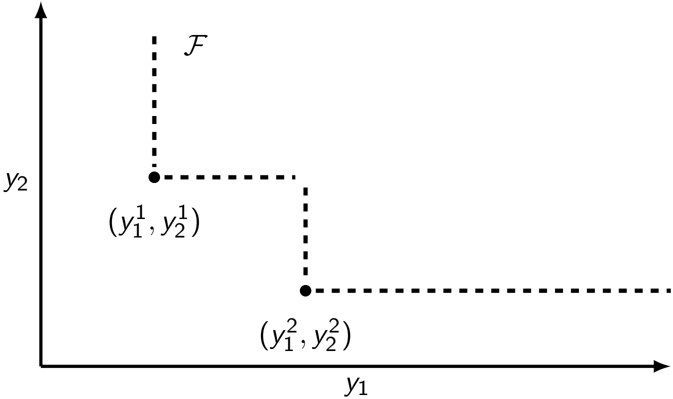

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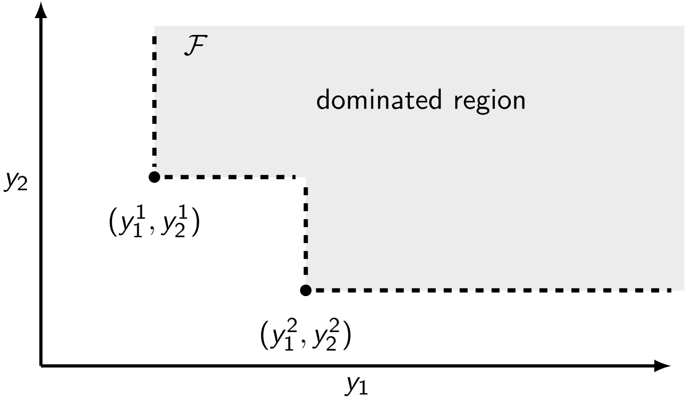

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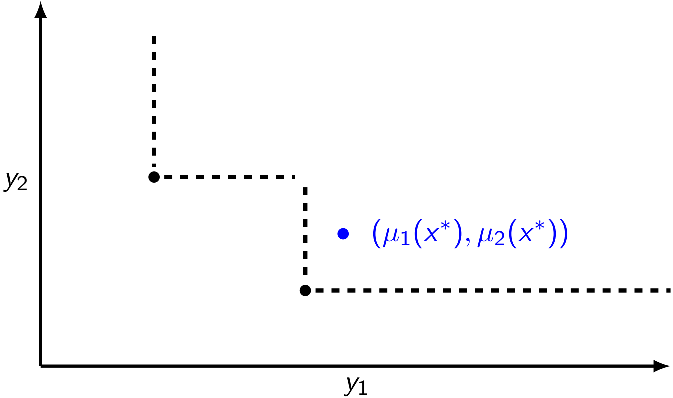

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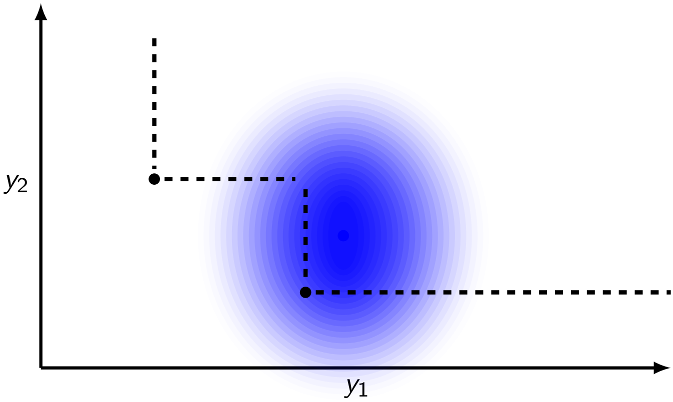

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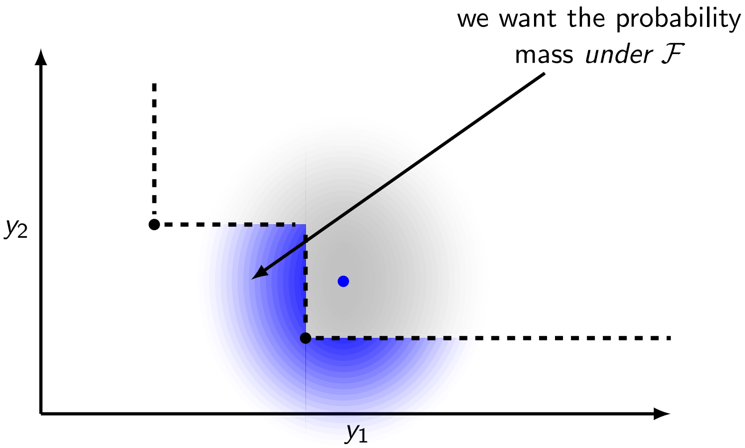

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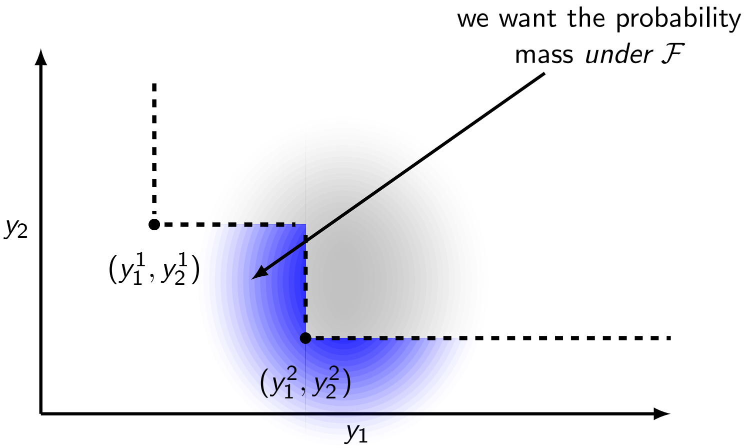

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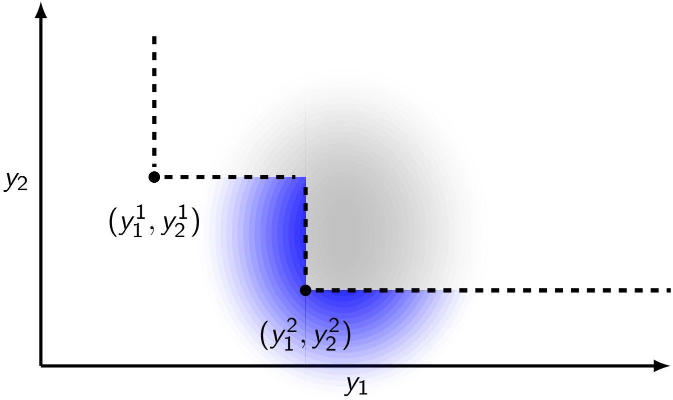
2D EGO Illustration

We will use a multiobjective expected improvement framework:

$$P(I) =$$

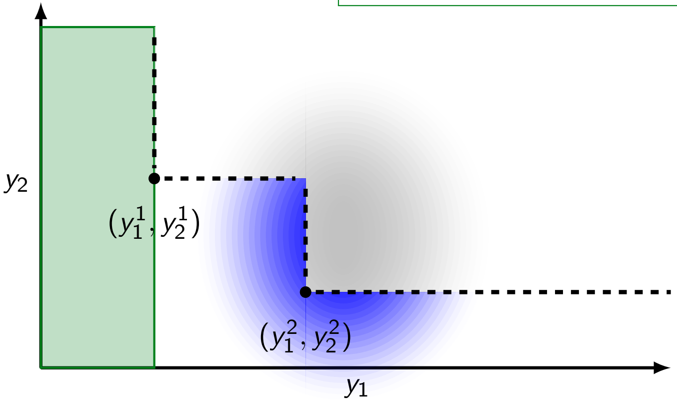


Keane, A. J., *AIAA Journal*, 44(4):879–891, 2006.

2D EGO Illustration

We will use a multiobjective expected improvement framework:

$$P(I) = \boxed{\int_{-\infty}^{y_1^1} \int_{-\infty}^{\infty} p(\hat{y}_1(x^*), \hat{y}_2(x^*)) dy_1 dy_2}$$



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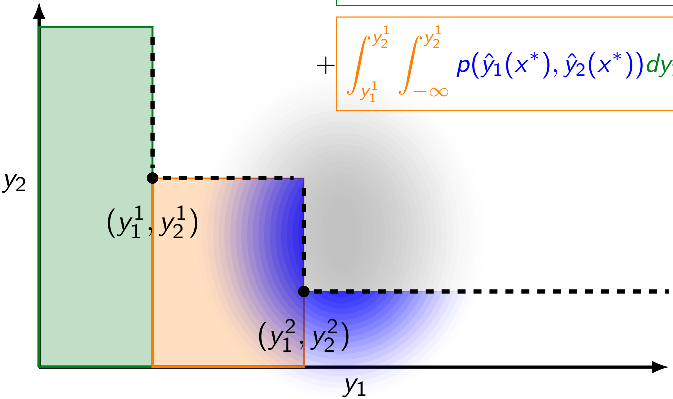
$$P(I) = \boxed{\int_{-\infty}^{y_1^1}\int_{-\infty}^{\infty} p(\hat{y}_1(x^*), \hat{y}_2(x^*))dy_1 dy_2}$$

$$+ \boxed{\int_{y_1^1}^{y_2^1}\int_{-\infty}^{y_2^1} p(\hat{y}_1(x^*), \hat{y}_2(x^*))dy_1 dy_2}$$



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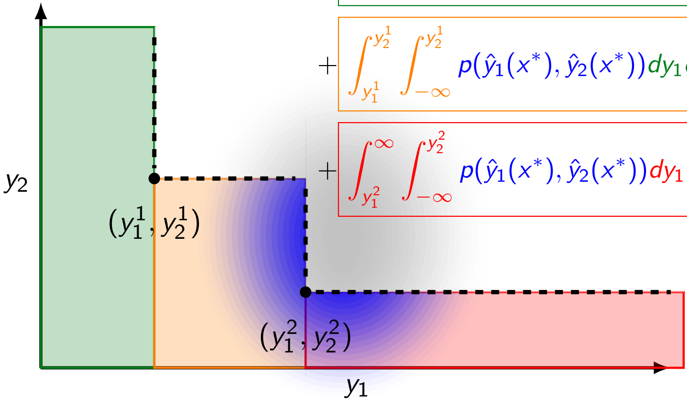

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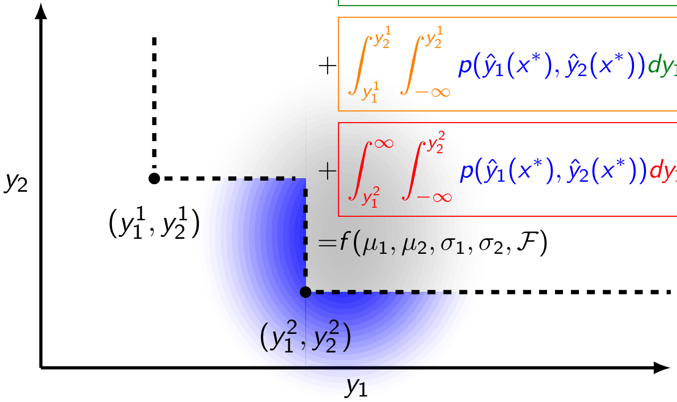
$$+ \boxed{\int_{y_1^2}^{\infty} \int_{-\infty}^{y_2^2} p(\hat{y}_1(x^*), \hat{y}_2(x^*))\, dy_1\, dy_2}$$

$$= f(\mu_1, \mu_2, \sigma_1, \sigma_2, \mathcal{F})$$



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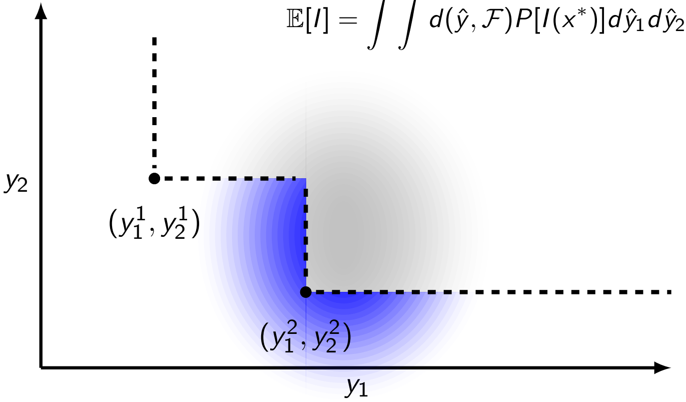
2D EGO Illustration

We will use a multiobjective expected improvement framework:

$$\mathbb{E}[I] = \int\int d(\hat{y}, \mathcal{F}) P[I(x^*)] d\hat{y}_1 d\hat{y}_2$$



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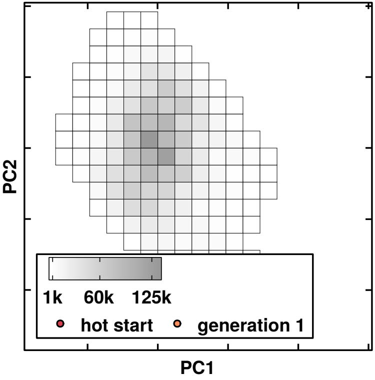
Design space and clustering

Jump start the design with diversity-oriented cluster:



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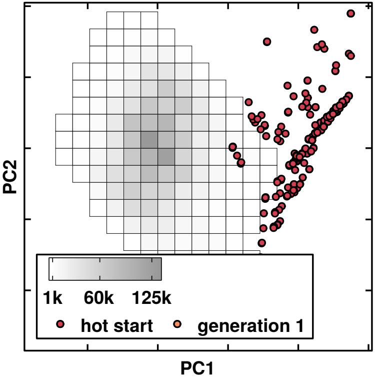

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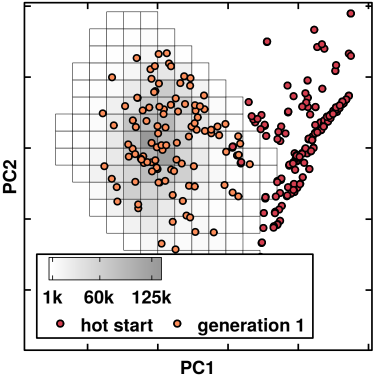

design space

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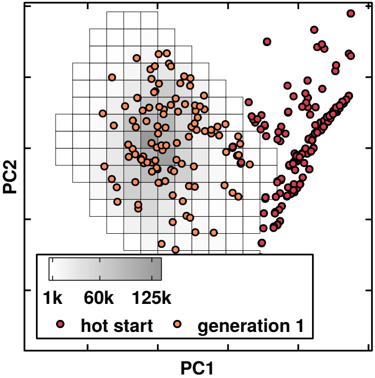

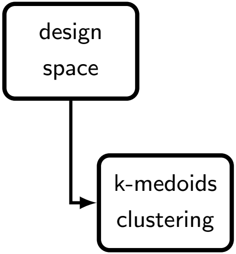

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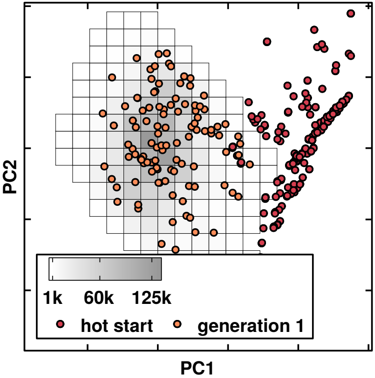

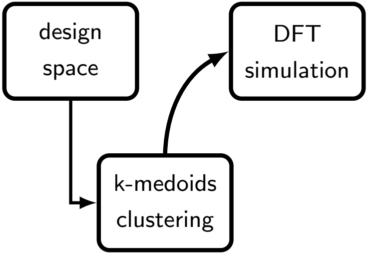

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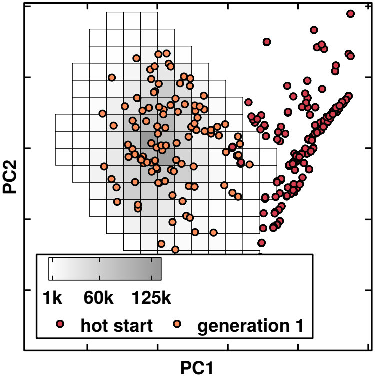

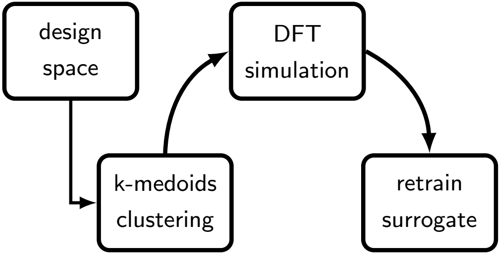

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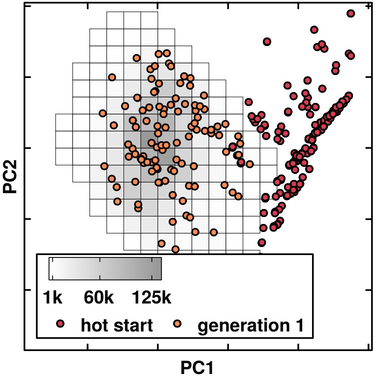

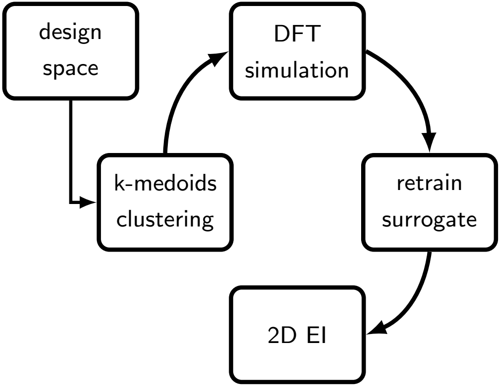

Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

multitask: 2 × 100 tanh nodes, fully connected

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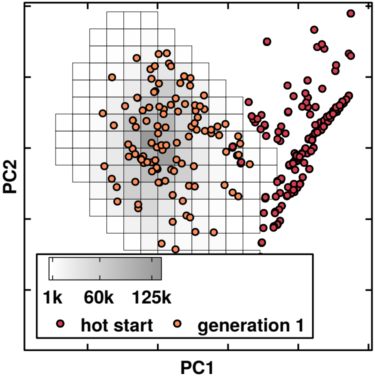

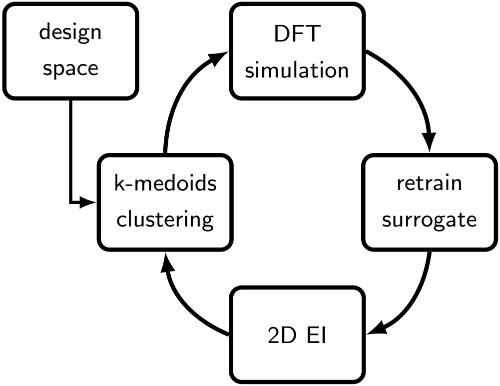

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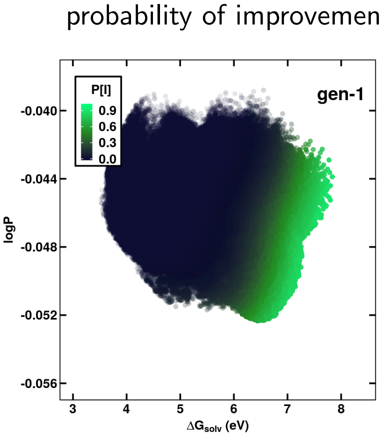
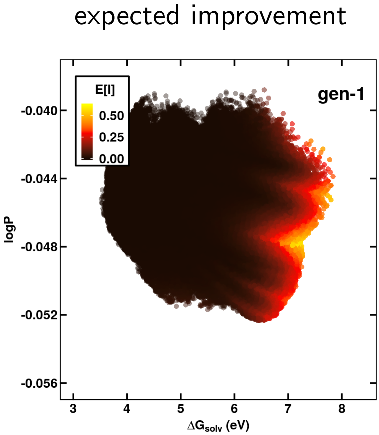
Evolution of PI and EI





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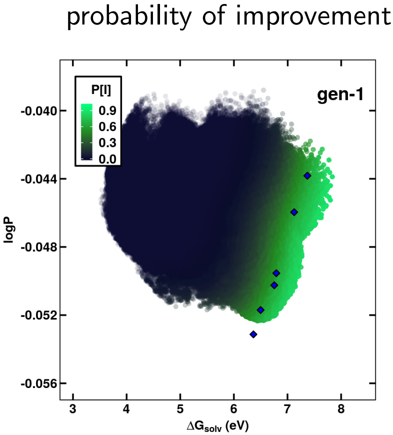

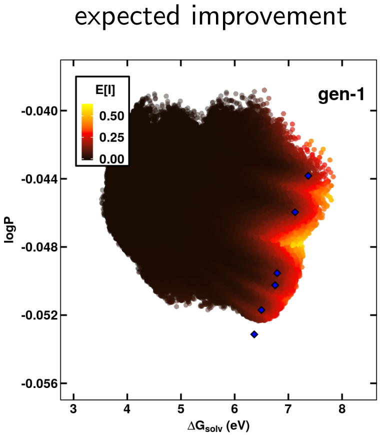

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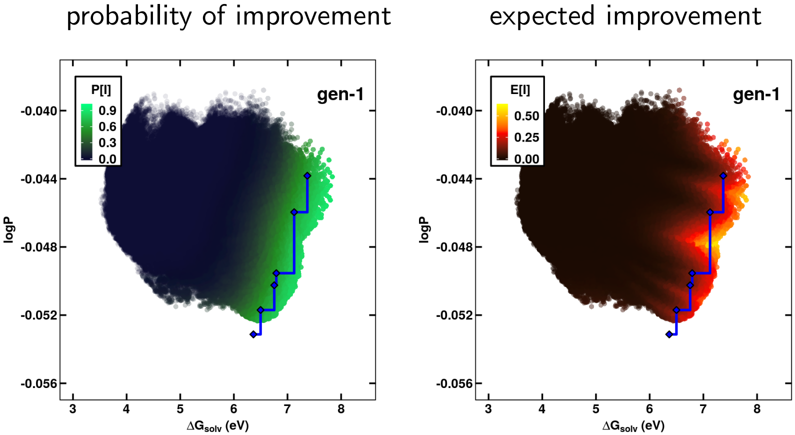

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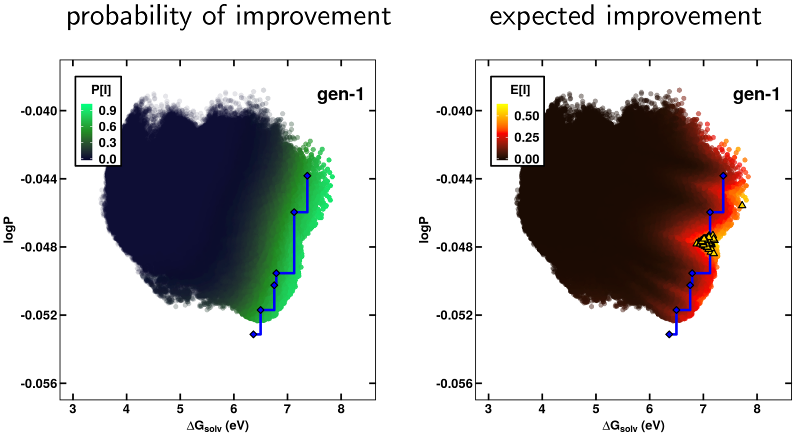

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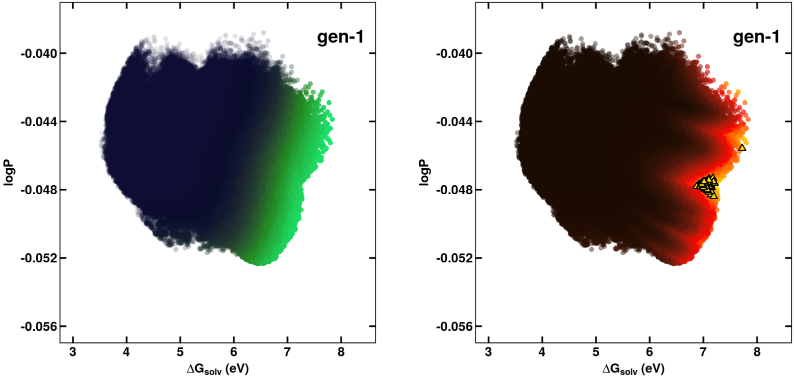
Evolution of PI and EI

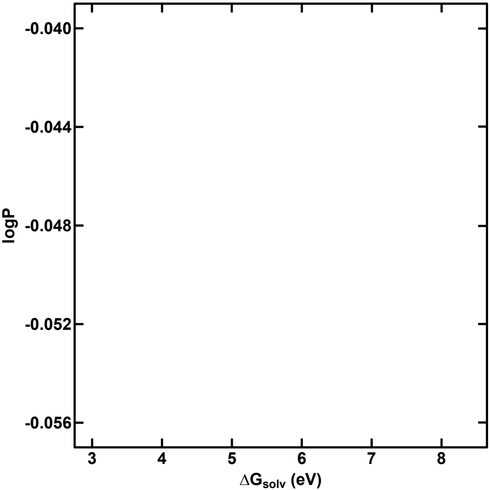
probability of improvement expected improvement



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

Simulation results

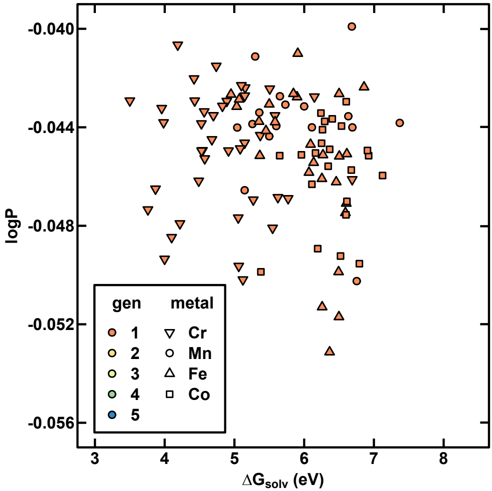
DFT Data



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

Simulation results

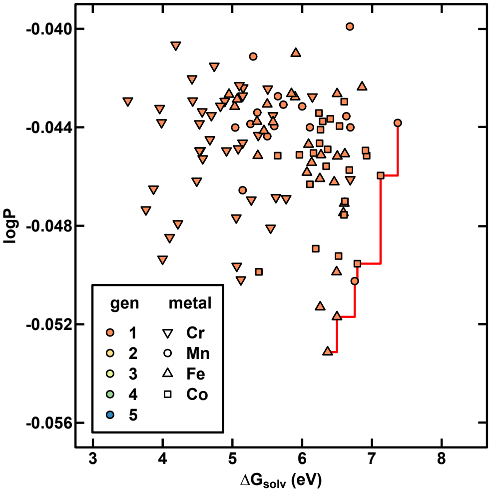
k-medoids points (generation 1)



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

Simulation results

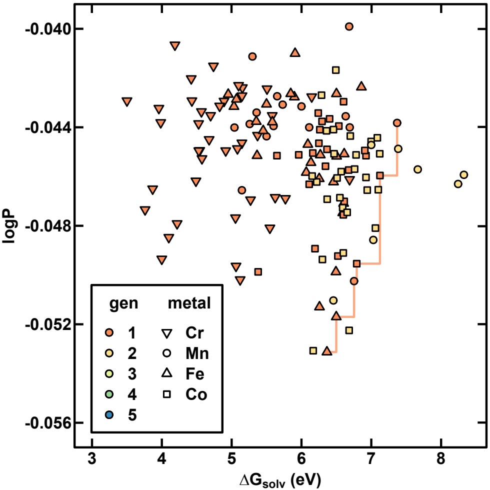
pareto front (generation 1)



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

Simulation results

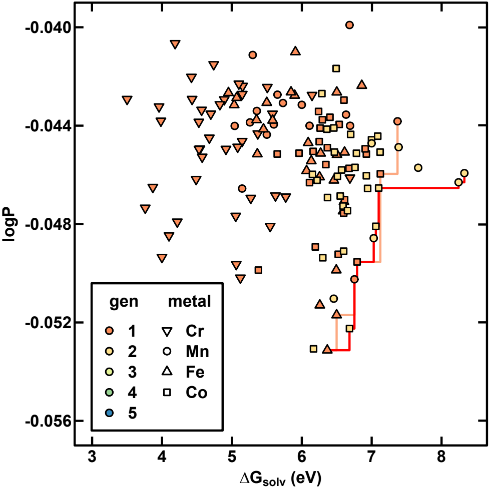
EI points (geneneration 2)



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

Simulation results

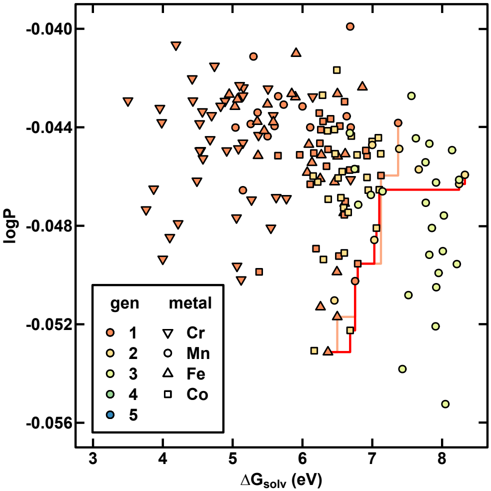
pareto front (generation 2)



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

Simulation results

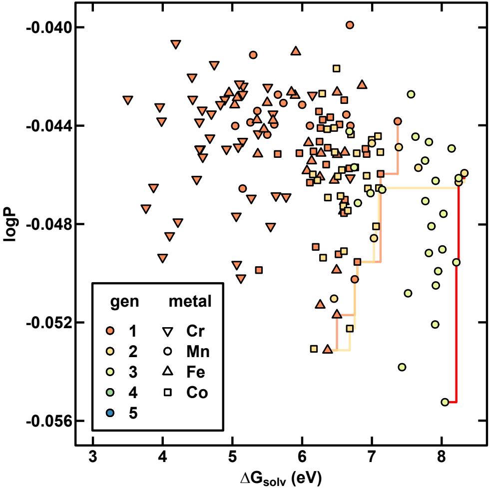
EI points (generation 3)



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

Simulation results

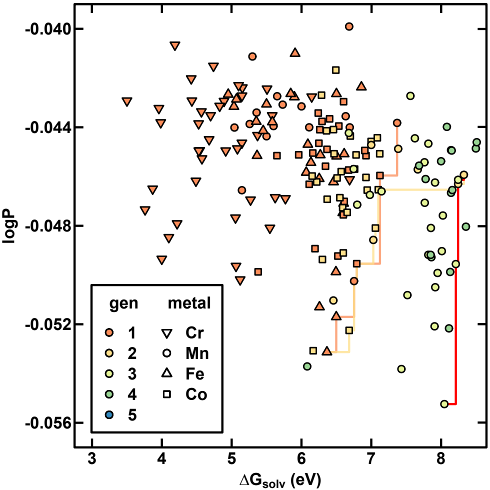
pareto front (generation 3)



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

Simulation results

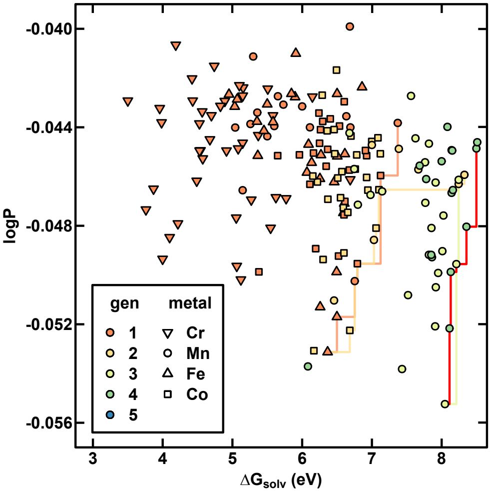
EI points (generation 4)



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

Simulation results

pareto front (generation 4)



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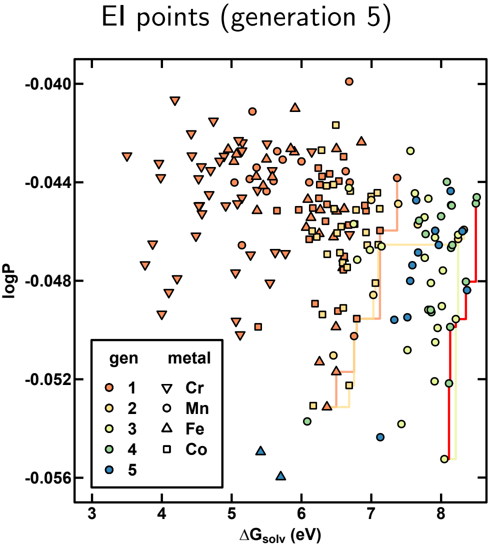
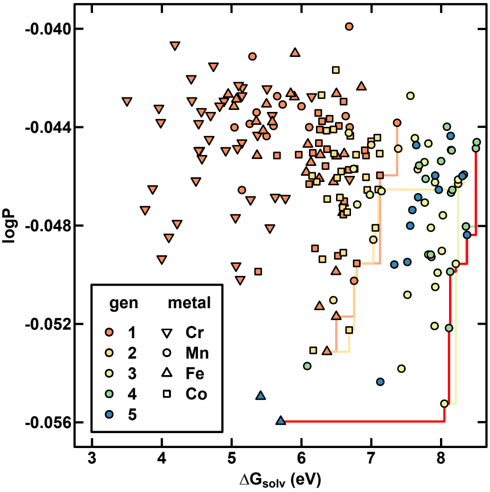
Simulation results



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

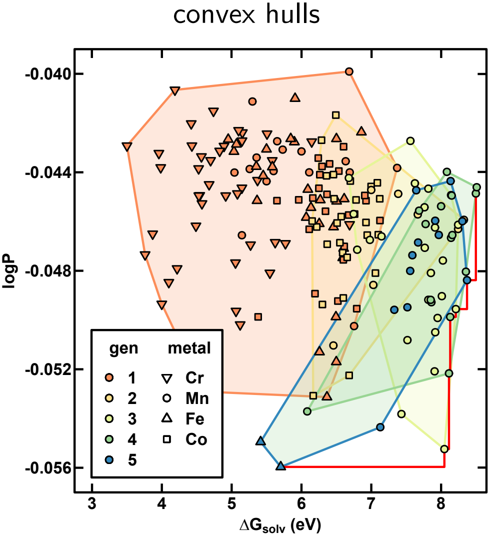
Simulation results

pareto front (generation 5)



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

Simulation results



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

Conclusions

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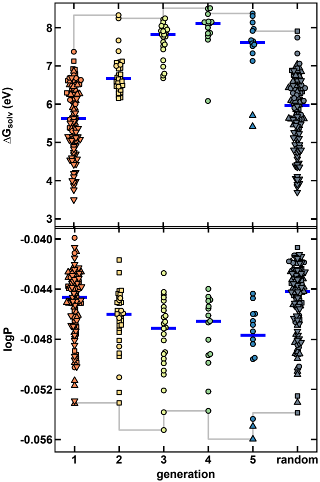
- EI framework provides high resolution in the region of interest (c.f. maximum uncertainty), converges quickly



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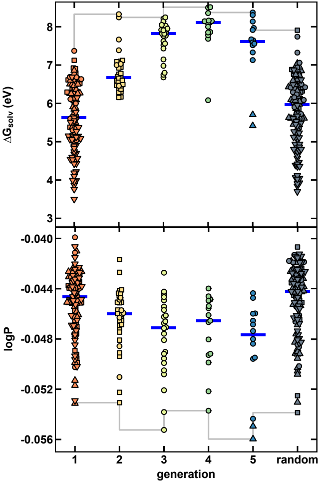

Janet, J.P., *et al.*, *ACS Cent. Sci.*, 6(4):513–524, 2020

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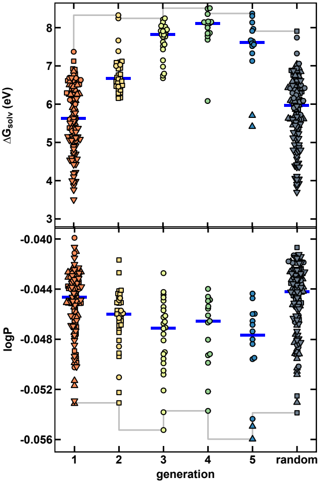

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Acknowledgments

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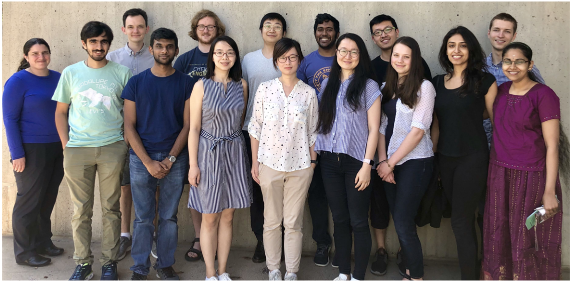

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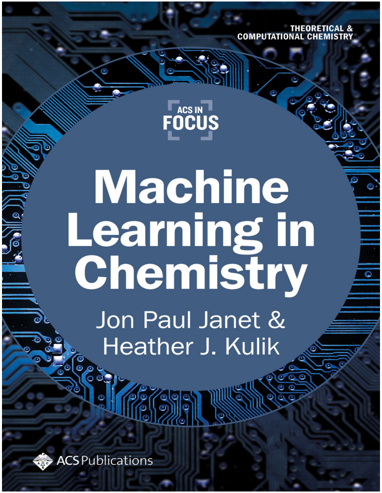

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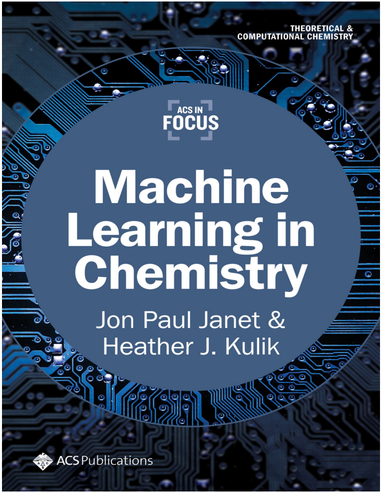

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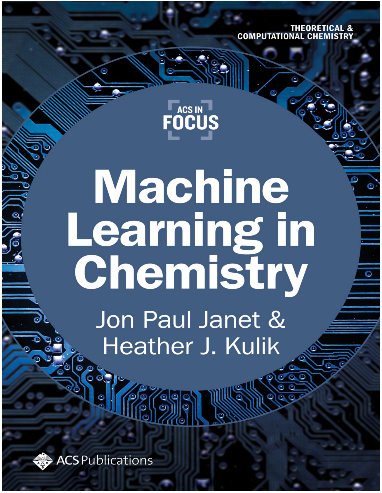

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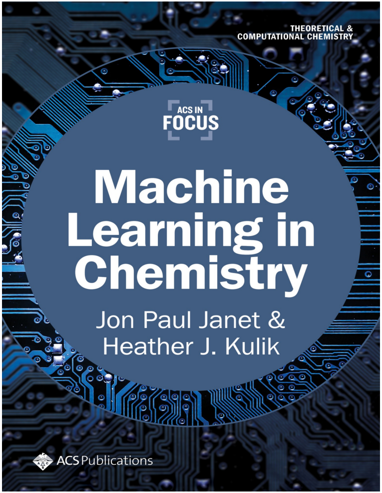

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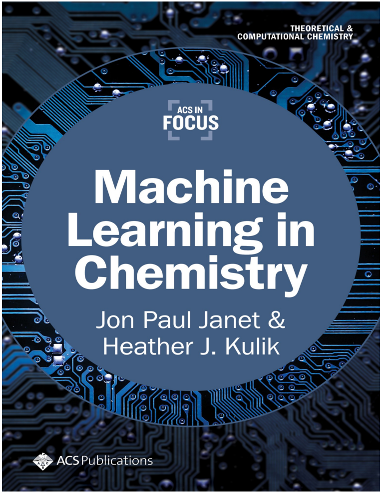

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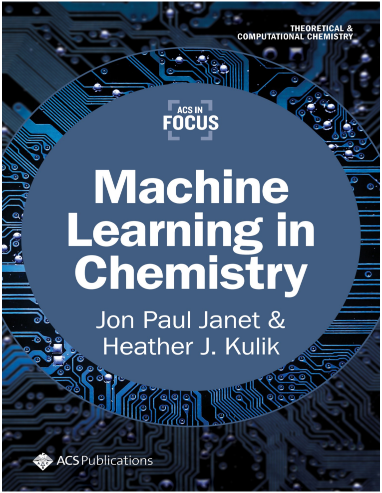

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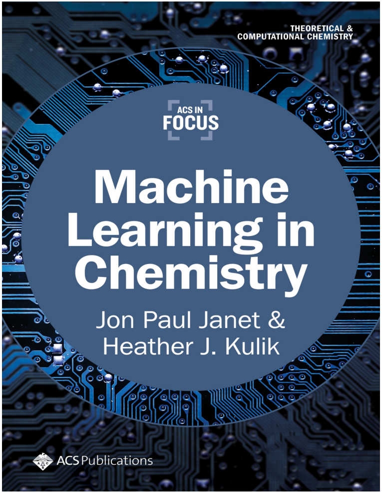

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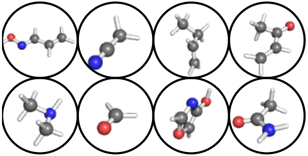

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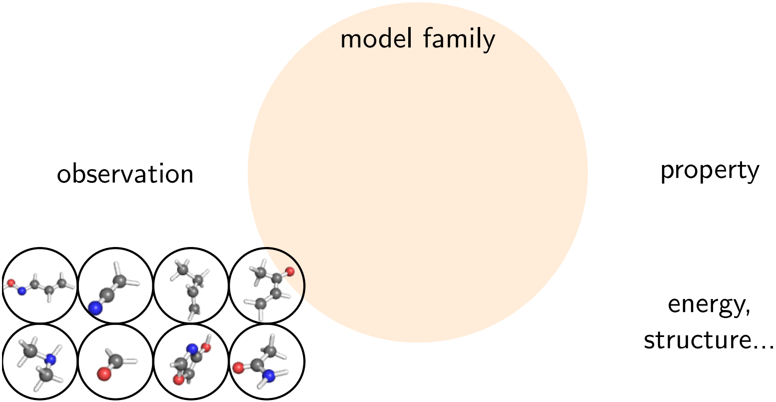

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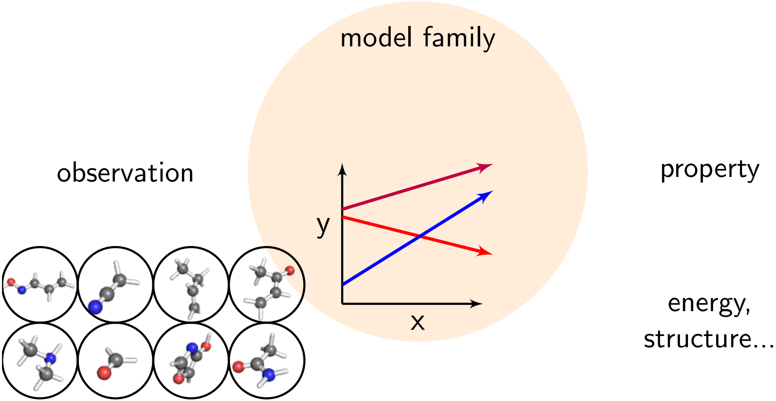

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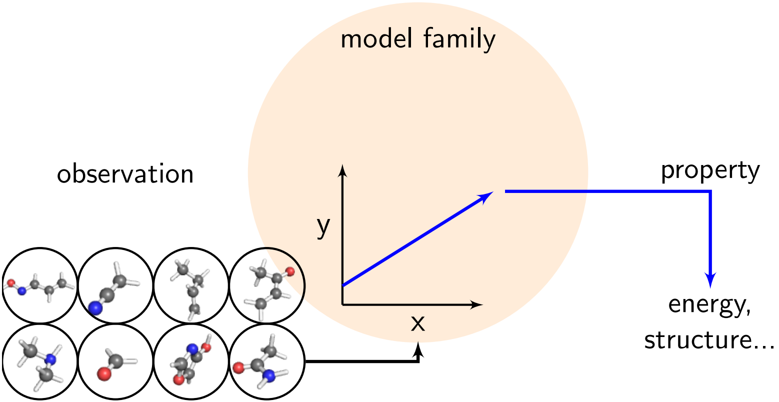

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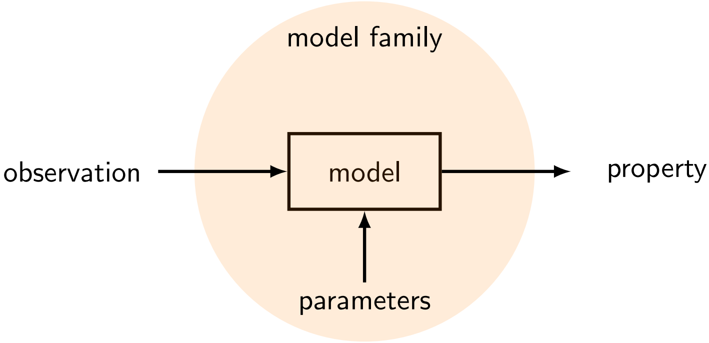

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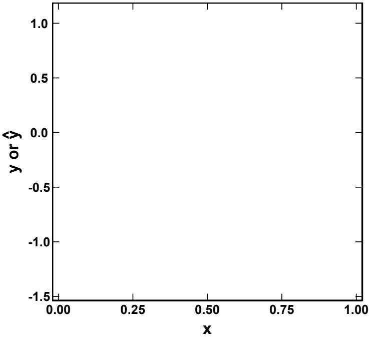

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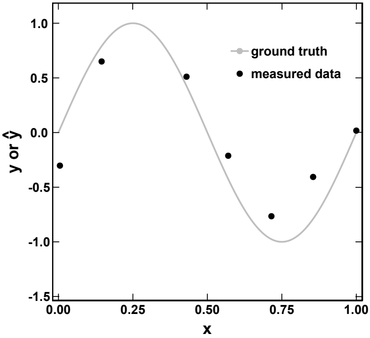
Assume 8 measurements with noise $\mathcal{N}(0, 0.2)$



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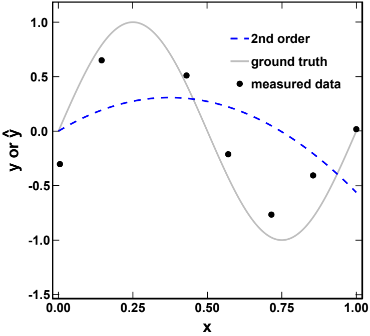

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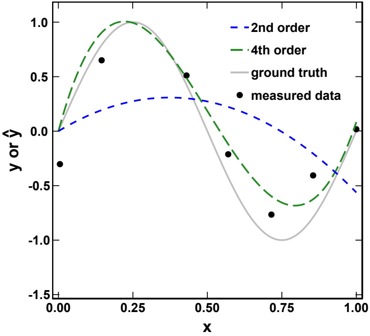

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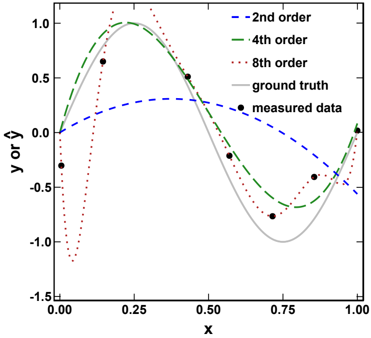

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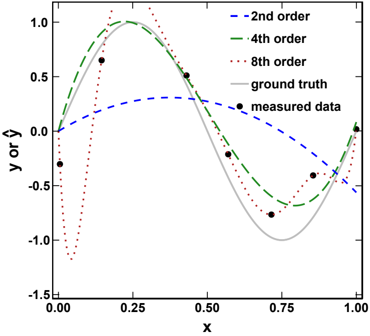

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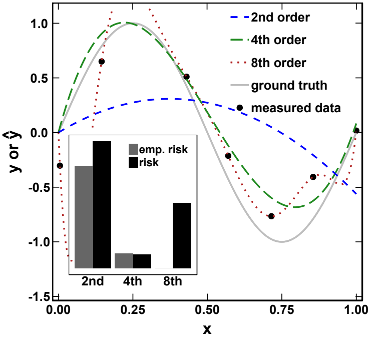

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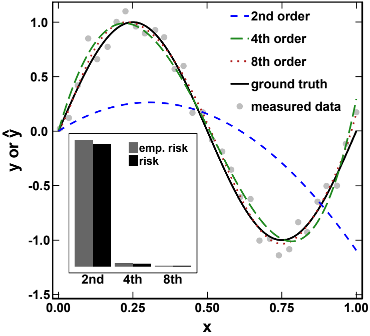
What happens if we add more data?



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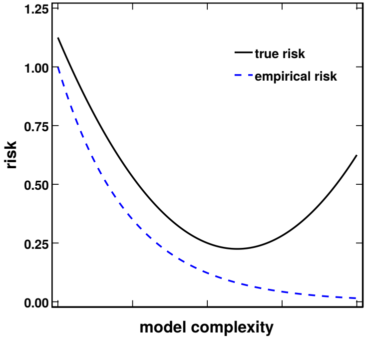
We cannot choose model complexity (hyperparameters, regularization) based on training data.

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



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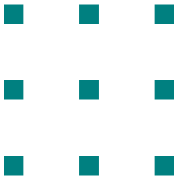

Chemical Space C_f

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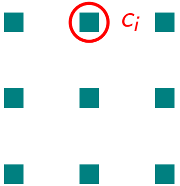

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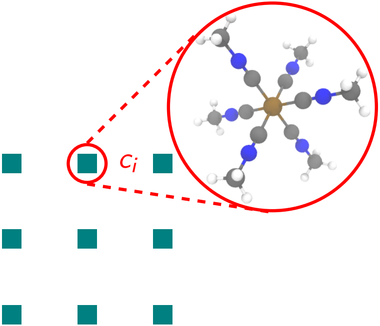

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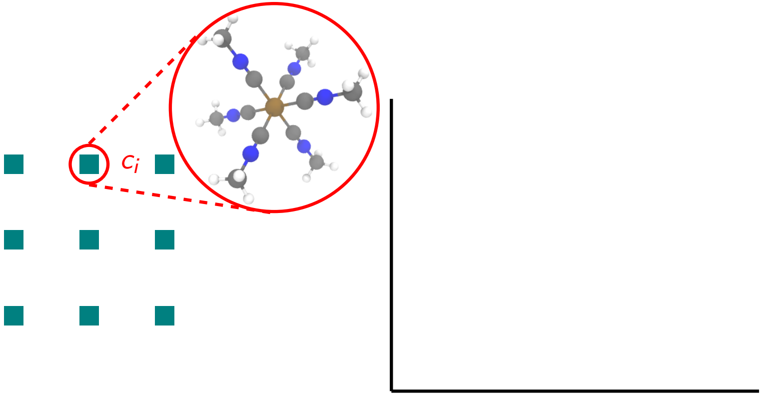

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Descriptor Space $\mathcal{X} \subset \mathbb{R}^d$

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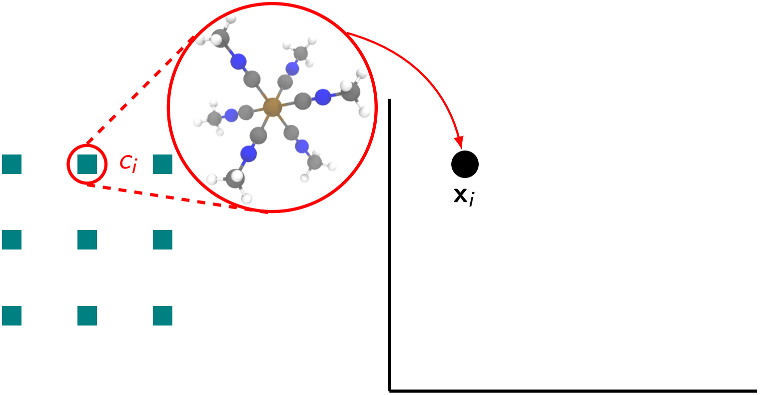

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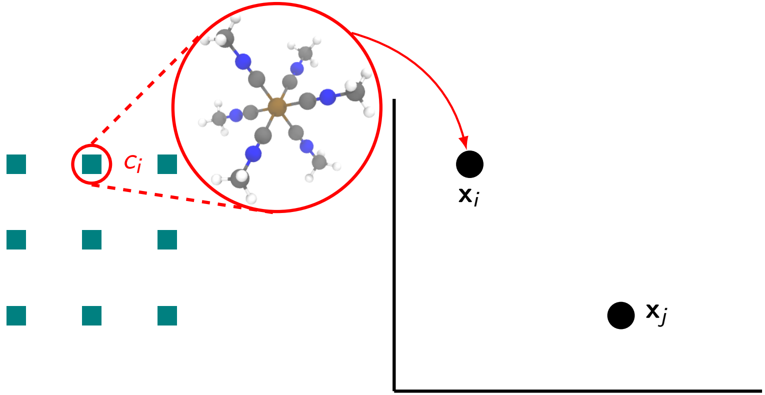

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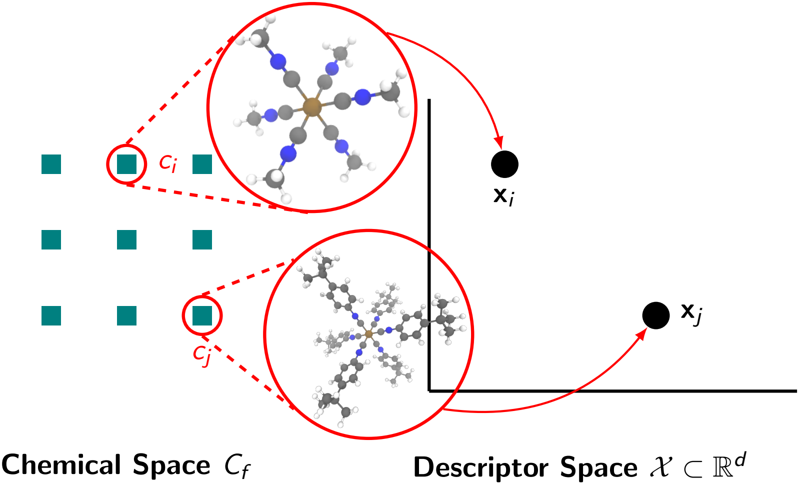

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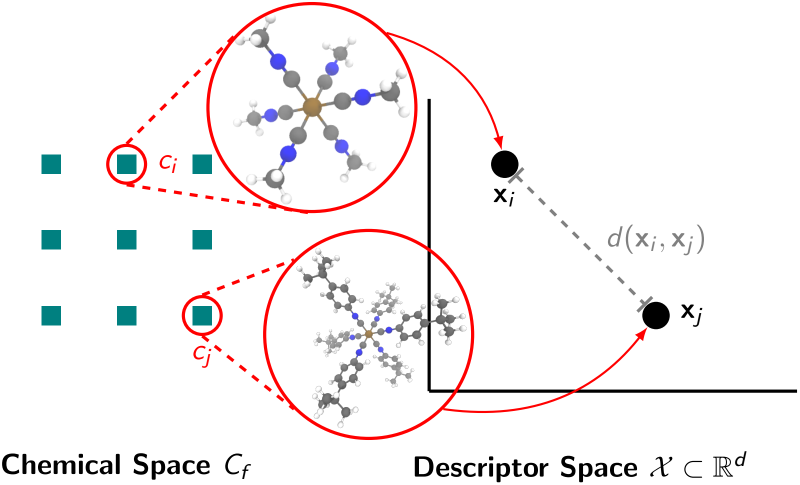

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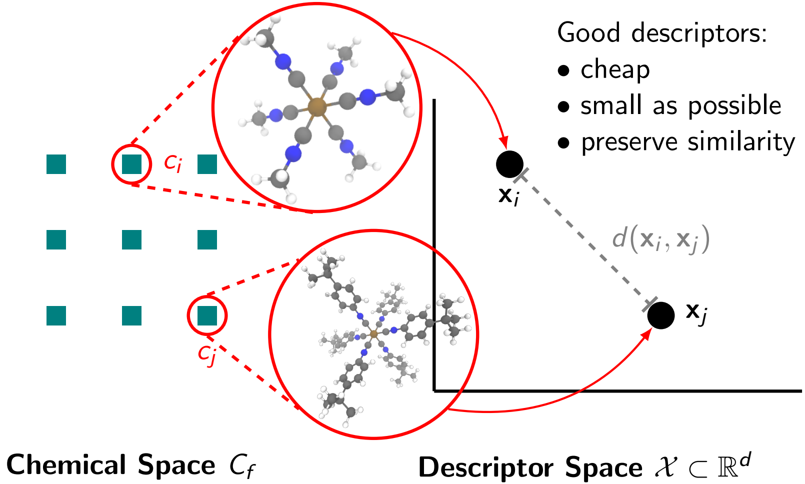

Good descriptors:

- cheap
- small as possible
- preserve similarity

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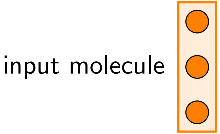

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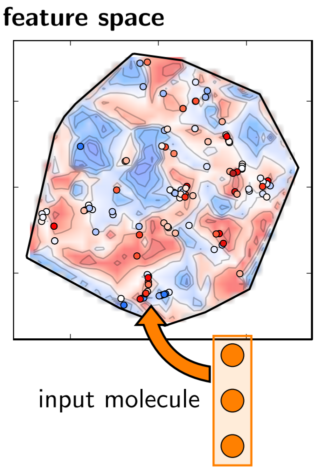

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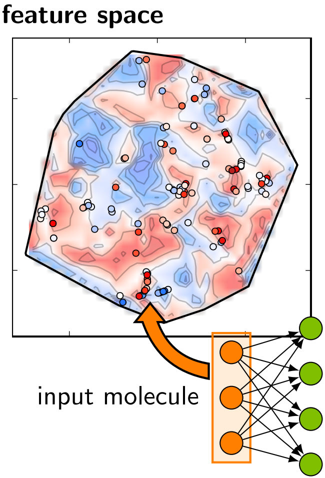

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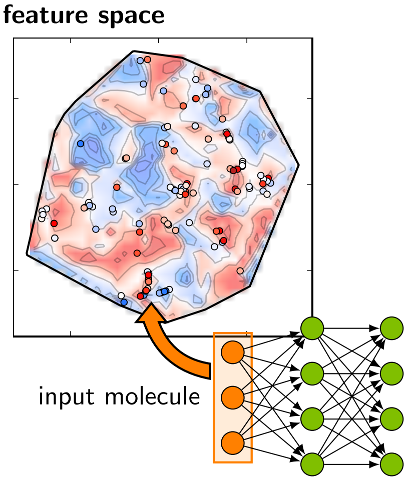

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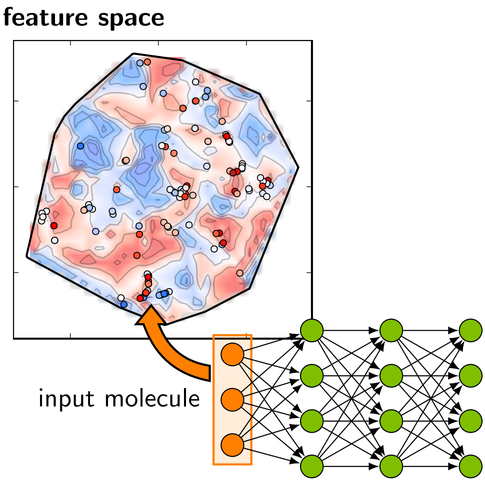

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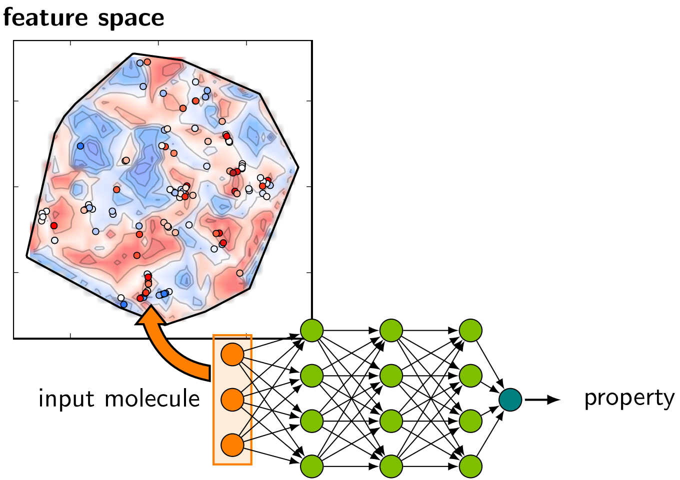

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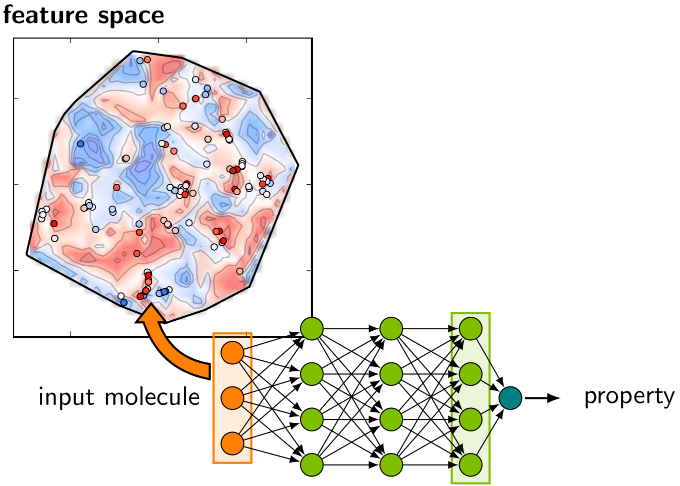

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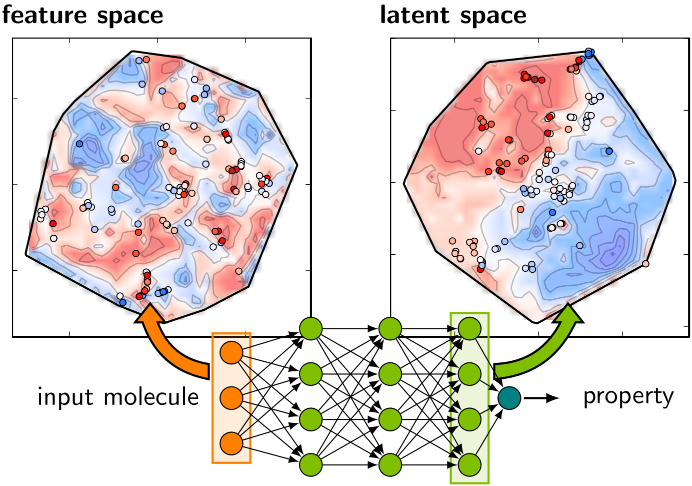

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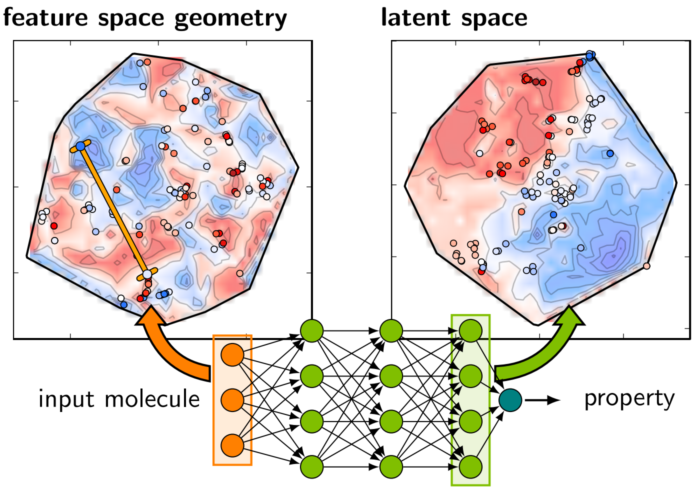

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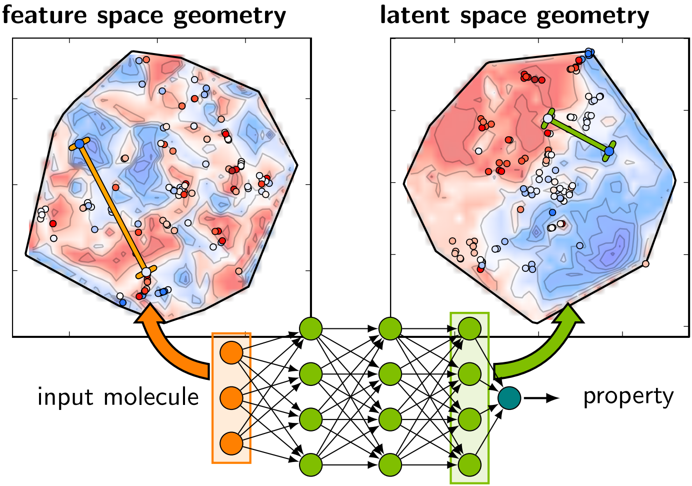

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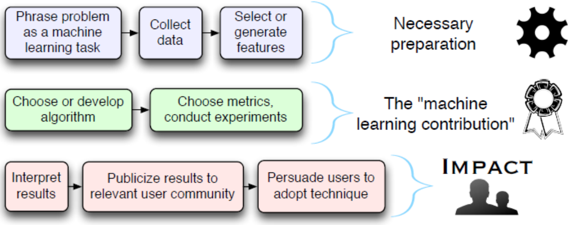

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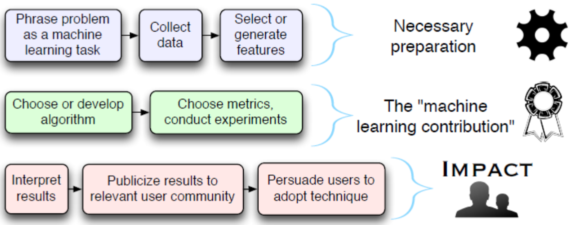

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Conversely, there is a growing need for domain experts to engage and derive impact from advances in ML, and you have a lot of value to contribute to interpreting and exploiting the results.