Enhancing Uncertainty Quantification in Chemical Modeling: A Comparative Study of Deep Evidential Regression and Ensembles with Post-Hoc Calibration

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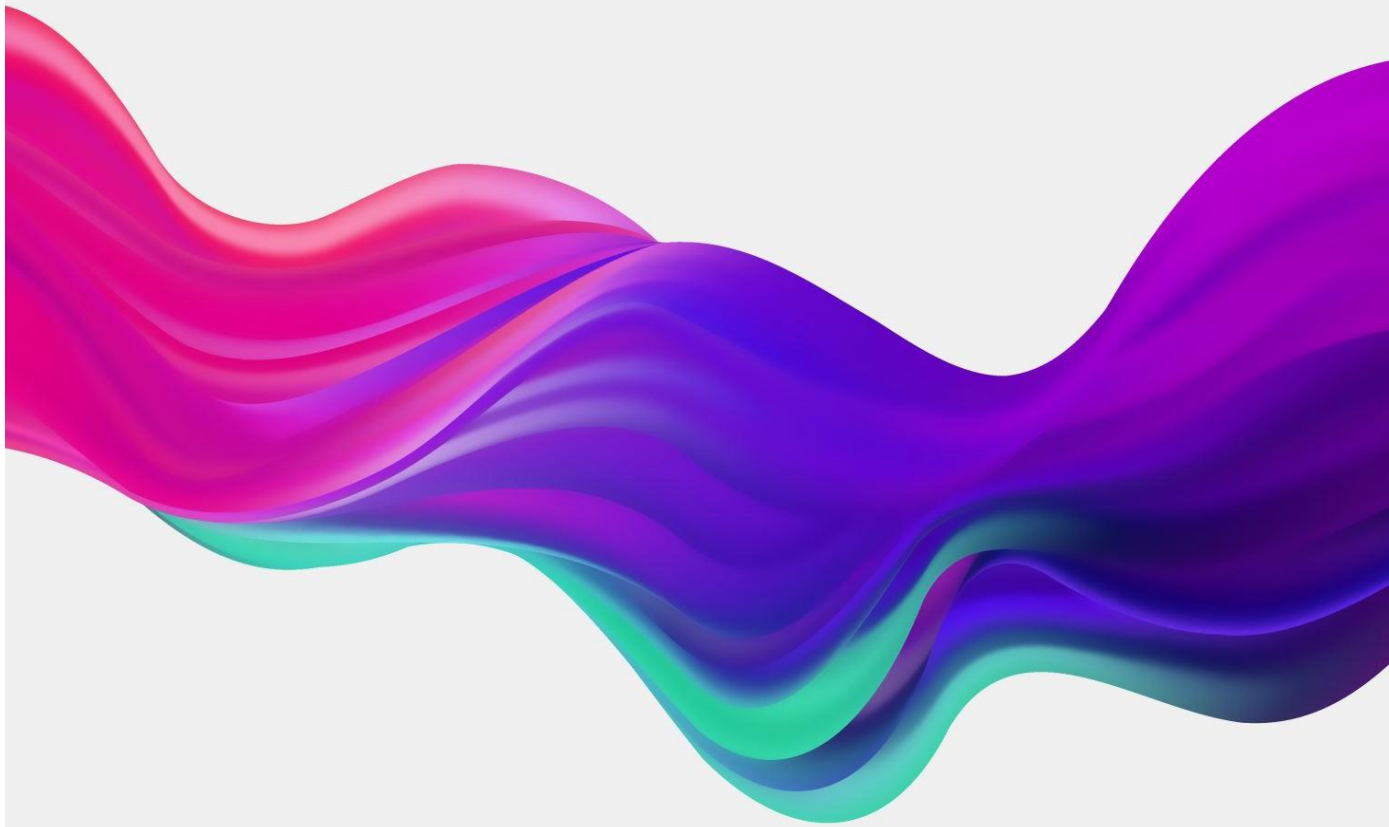
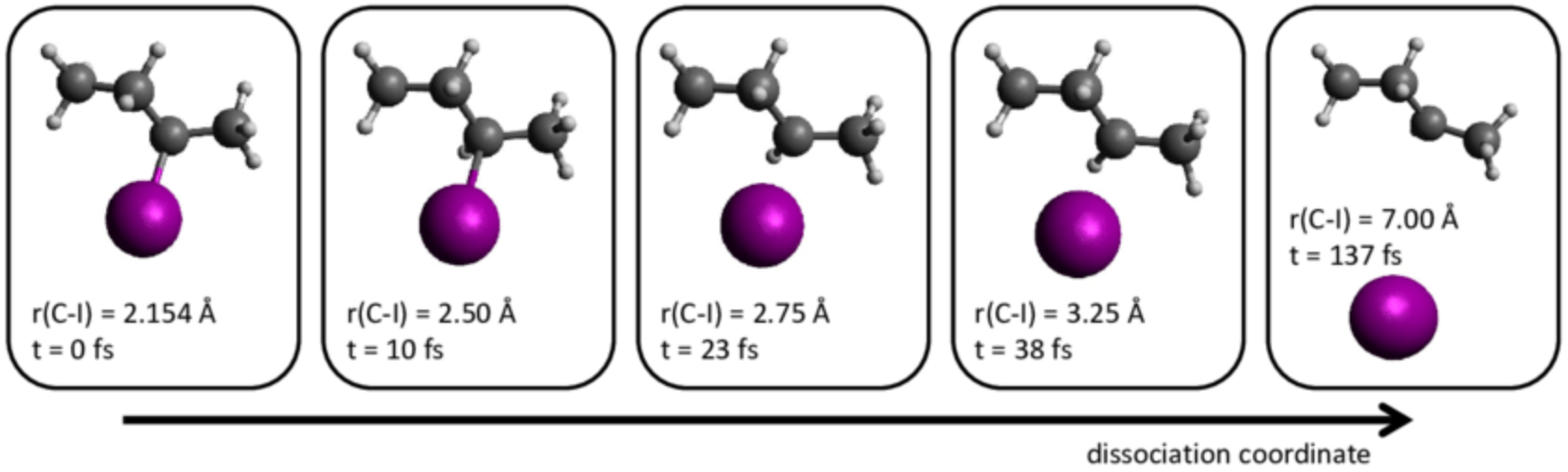


LIGHT AND MOLECULES
Mario Barbatti's Research Group

How light interacts with molecules and how this interaction changes the molecule's properties

Fluorescence

Photochemical reactions

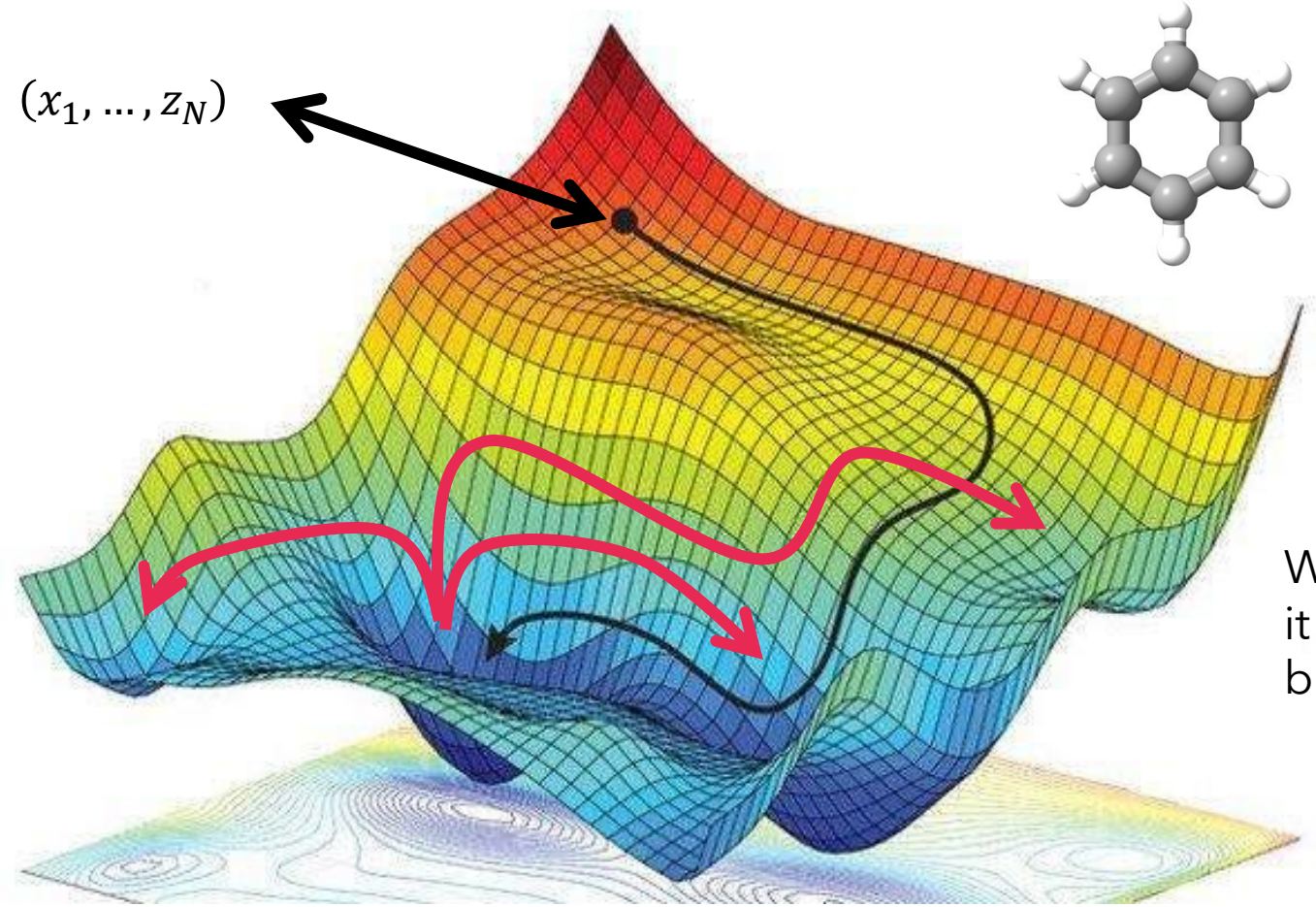


To understand these phenomena, we generally explore the potential energy surfaces (PES)

Potential Energy Surfaces (PES)

Optimization problem (gradient descent)

$(x_1, \ldots, z_N)$

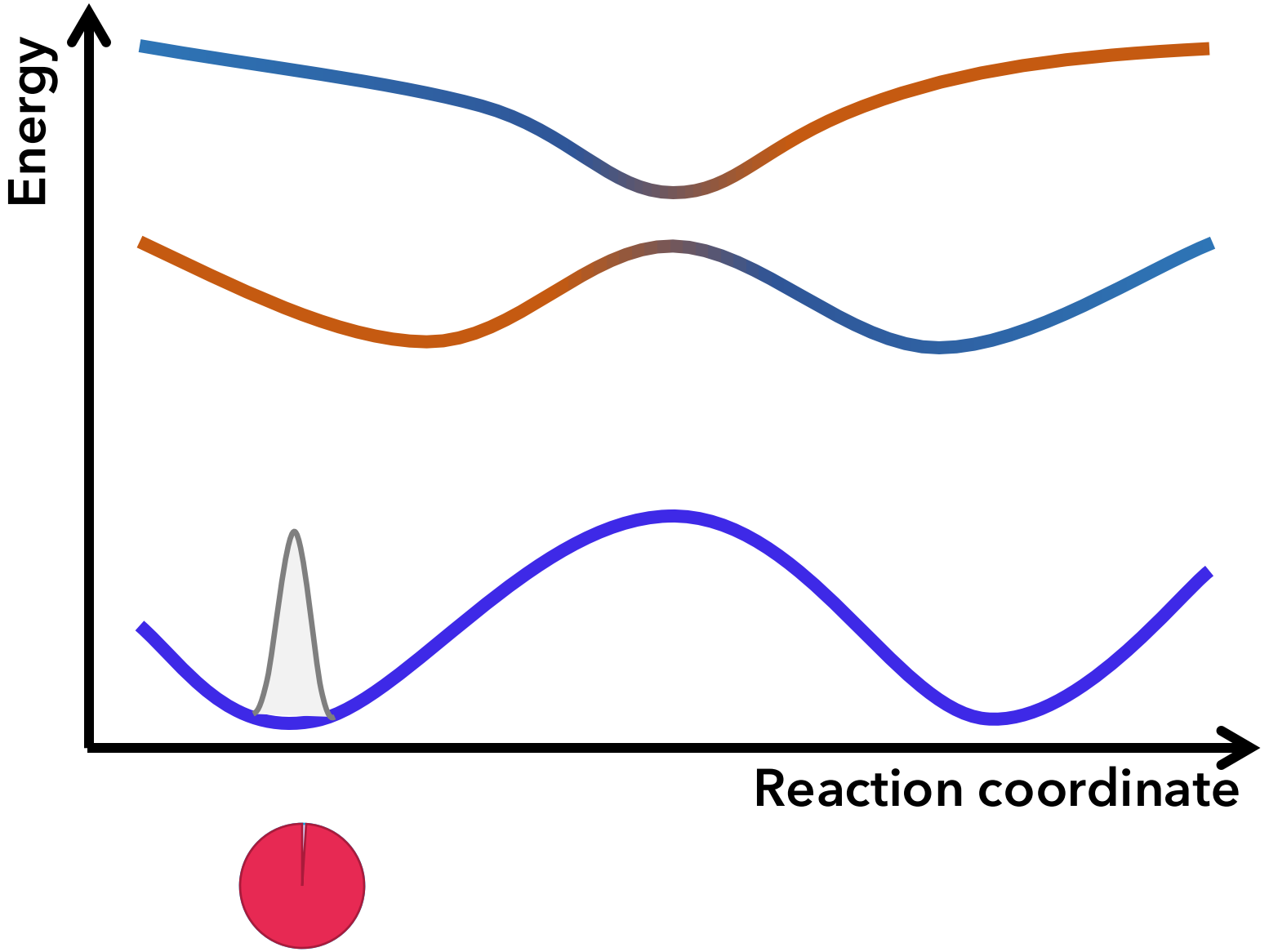


Energy $E = f(x_1, \ldots, z_N)$

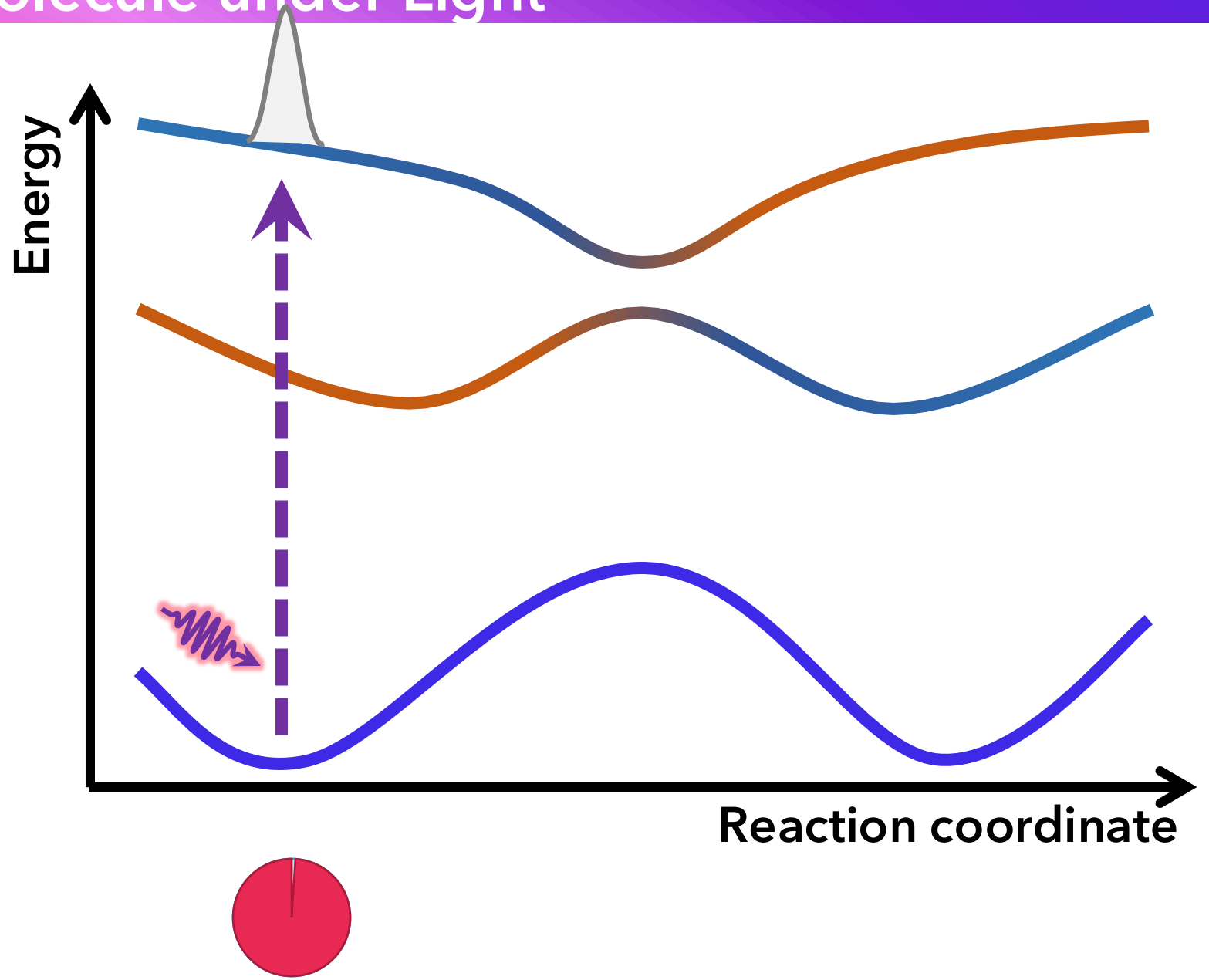
Forces $\frac{\partial E}{\partial x_1}, \ldots, \frac{\partial E}{\partial z_N}$

With thermal energy provided
it can explore the PES,
but what happens if you shine light

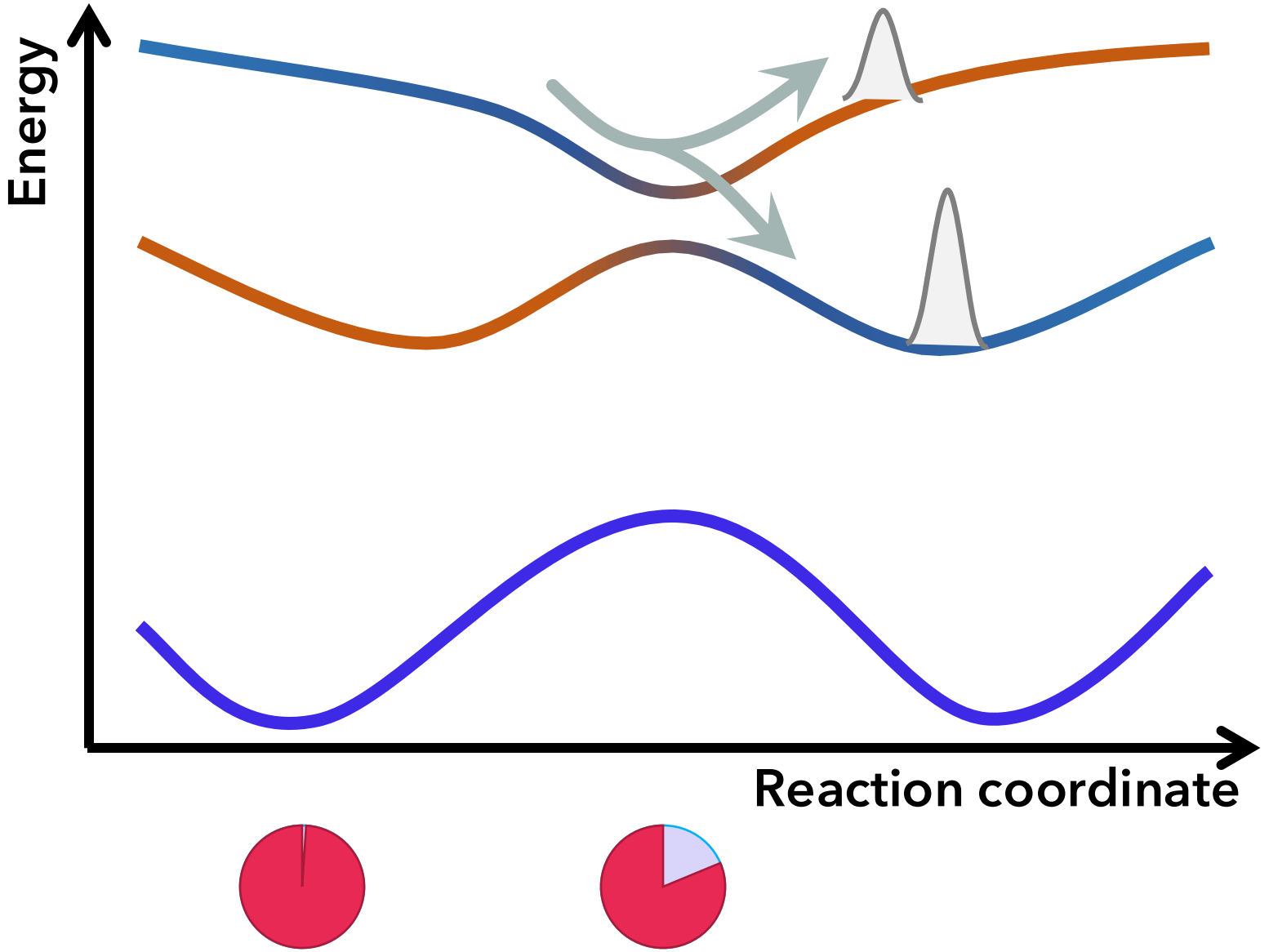
Molecule under Light



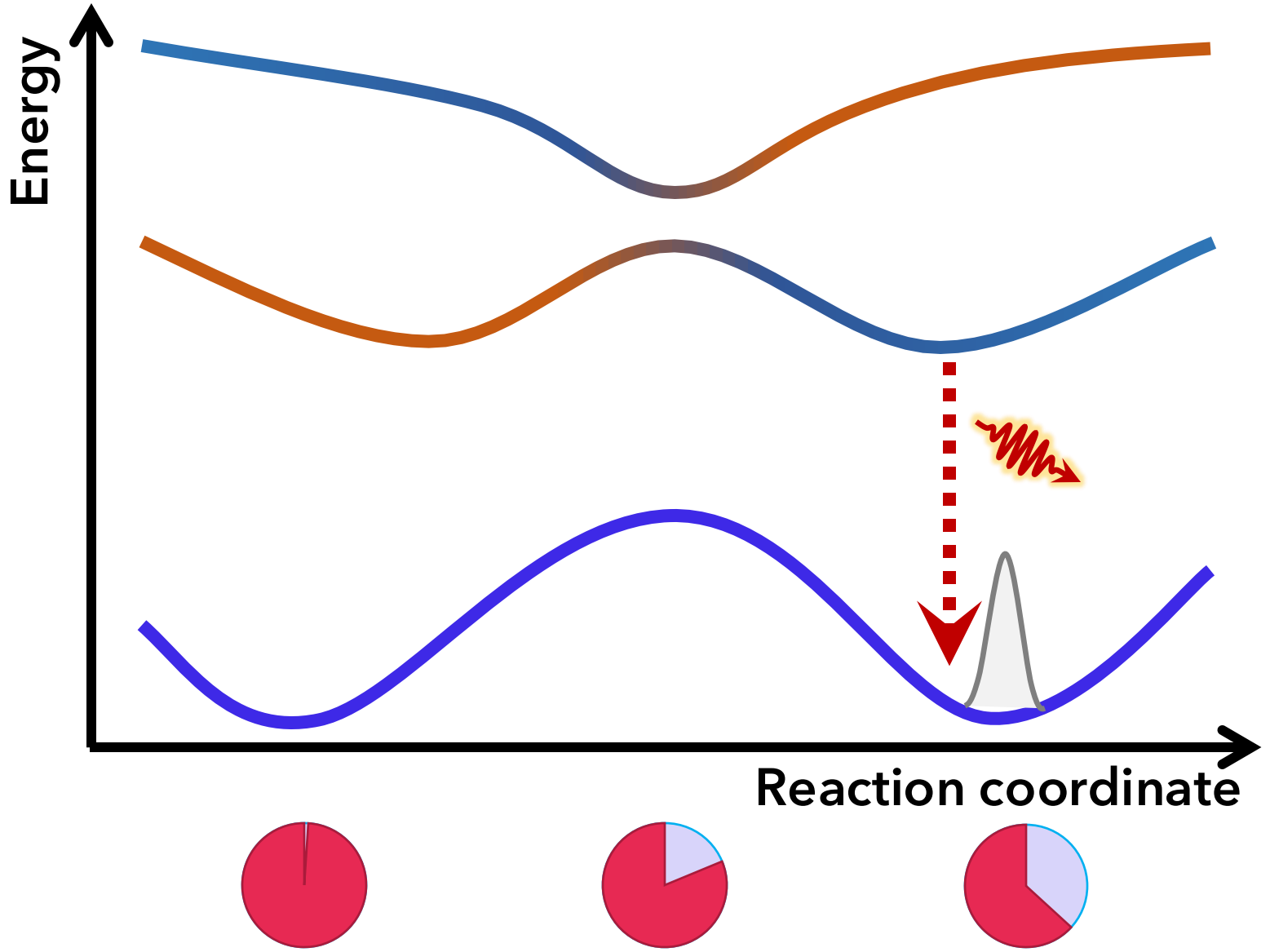
Molecule under Light



Molecule under Light

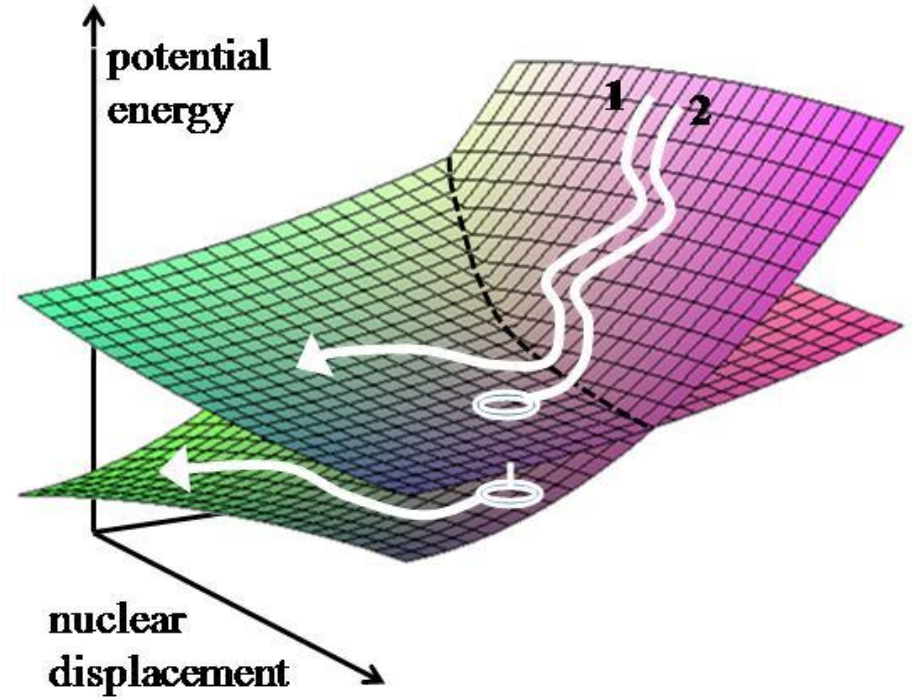


Molecule under Light



Nonadiabatic dynamics

Fewest Switches Surface Hopping



$$\frac{d^2\mathbf{R}_\alpha}{dt^2} = \frac{-\nabla_\alpha E_K(\mathbf{R})}{M_\alpha}$$

$$\left(\hat{T}_{elec} + V(\mathbf{r},\mathbf{R})\right)\varphi_{K,\mathbf{R}}(\mathbf{r}) = E_K(\mathbf{R})\varphi_{K,\mathbf{R}}(\mathbf{r})$$

$$\boldsymbol{v}.\boldsymbol{h}_{JL} = \frac{1}{2}\sqrt{\frac{1}{\Delta E_{JL}}\frac{d^2\Delta E_{JL}}{dt^2}}$$

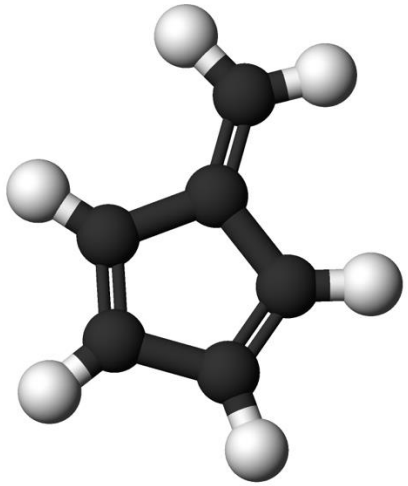
Computational Cost for 1 Trajectory:
Total time: 60 fs
Timestep: 0.5 fs
Total number of QM calculation: 120

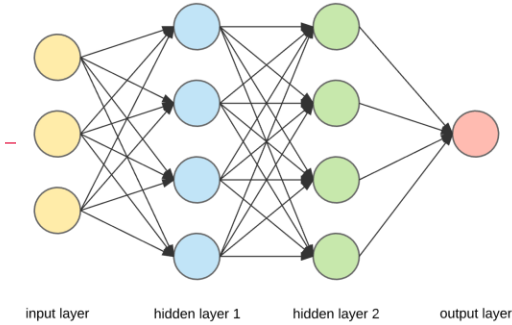
120000

Crespo-Otero; Barbatti. Chem. Rev. 2018, 118, 7026-7068.
Barbatti *et al*. JCTC 2022, 18, 6851-6865.
do Casal *et al*. *Open Res Europe* 2021, *1*, 49.

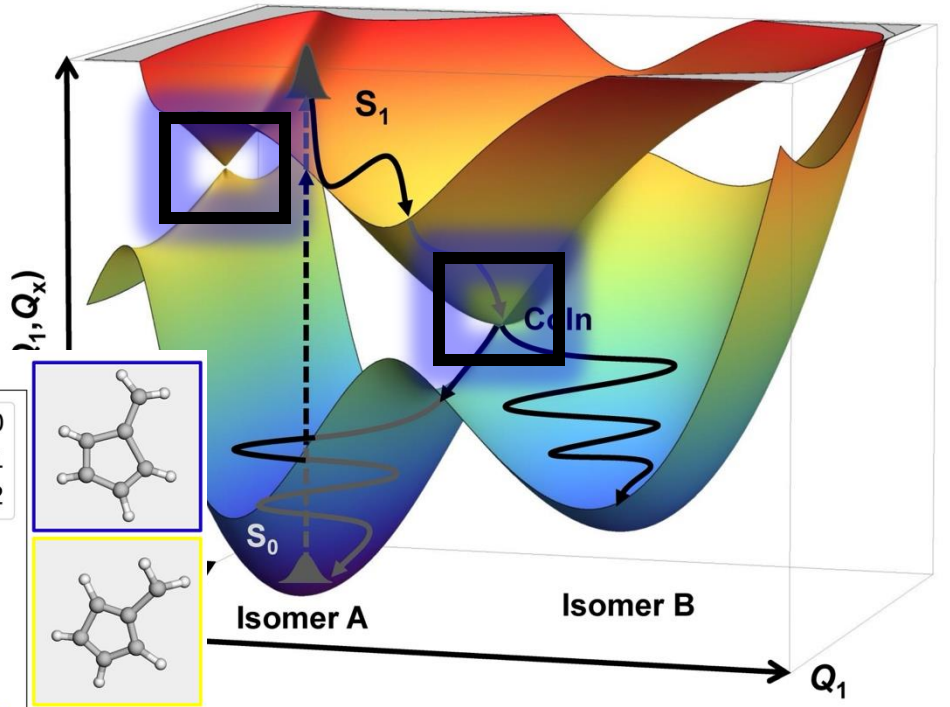
Importance of ML in NAMD:

Supervised Learning

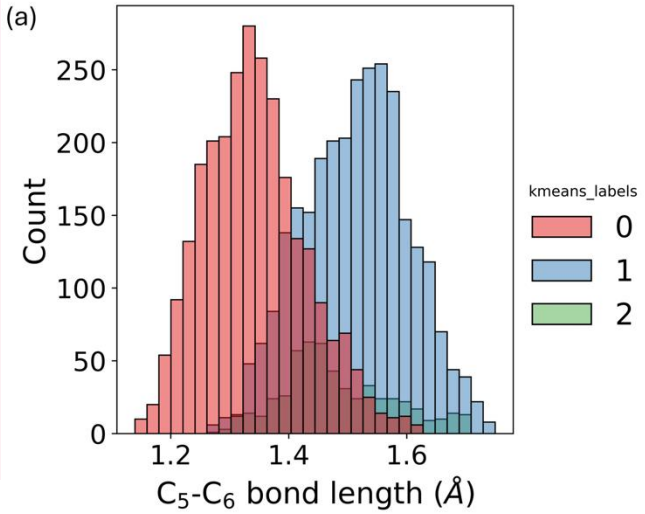


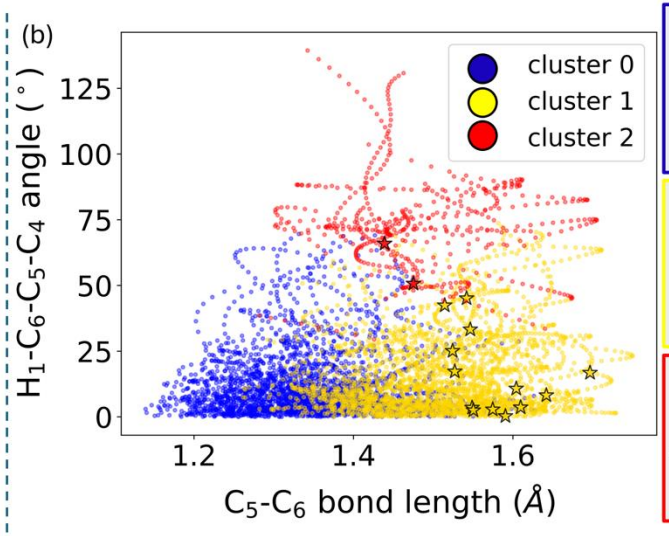


Energy Gradients



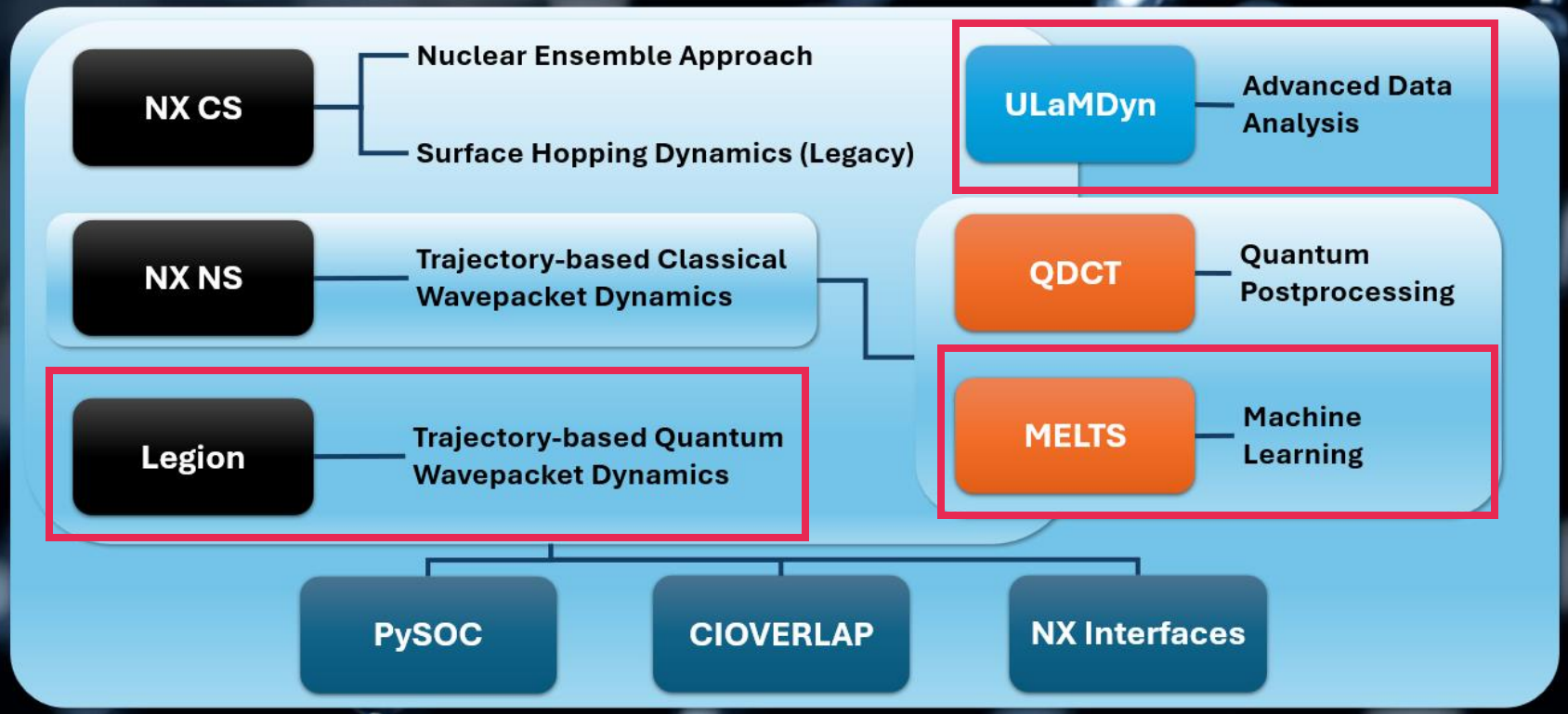
Unsupervised Learning





Pinheiro Jr. *et al*. ChemRxiv 2024. DOI: 10.26434/chemrxiv-2024-32h0p

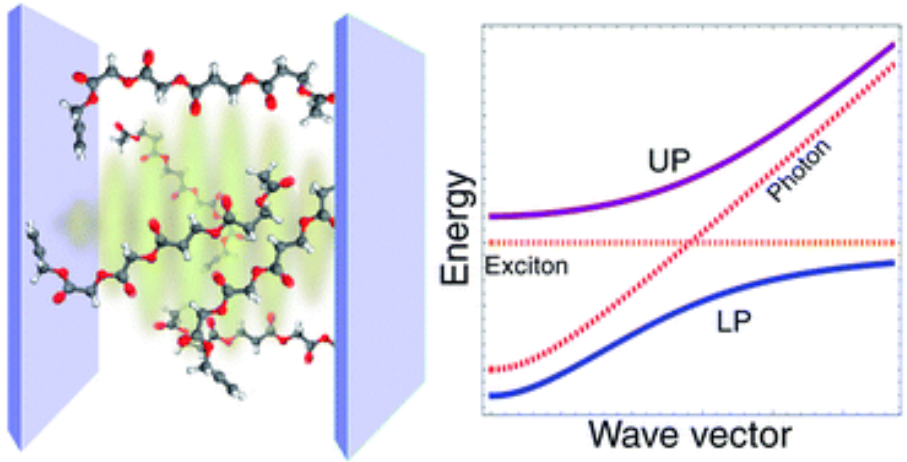
The Newton-X Platform



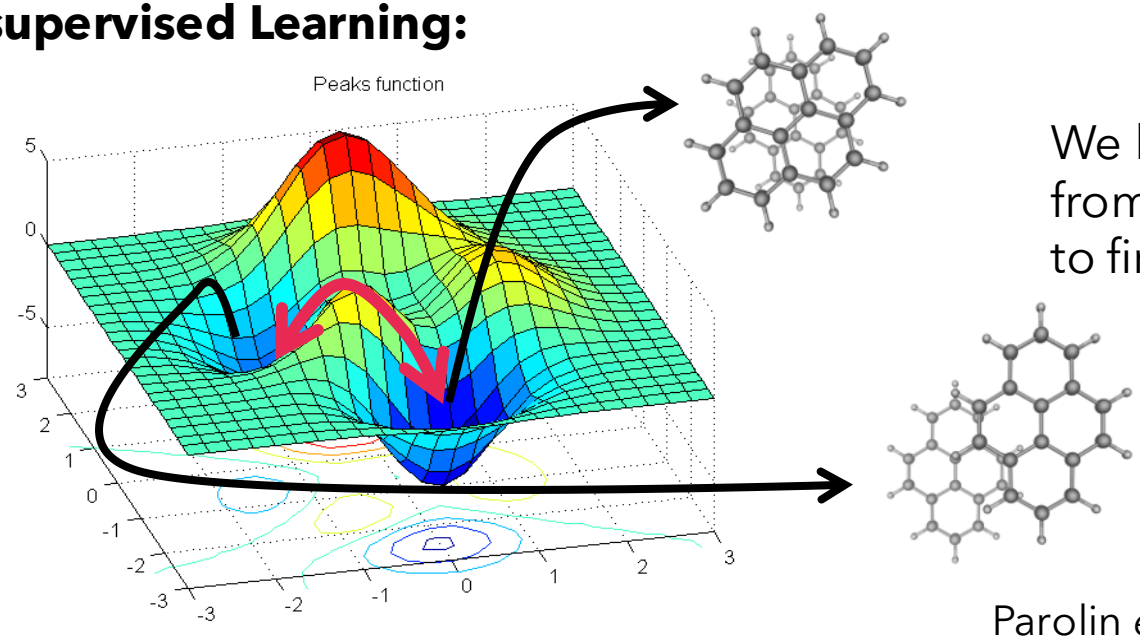
newtonx.org

amU Aix Marseille Université
Institut de Chimie Radicalaire
Theoretical Chemistry Team

Supervised Learning: Machine Learning assisted Polaritonic chemistry



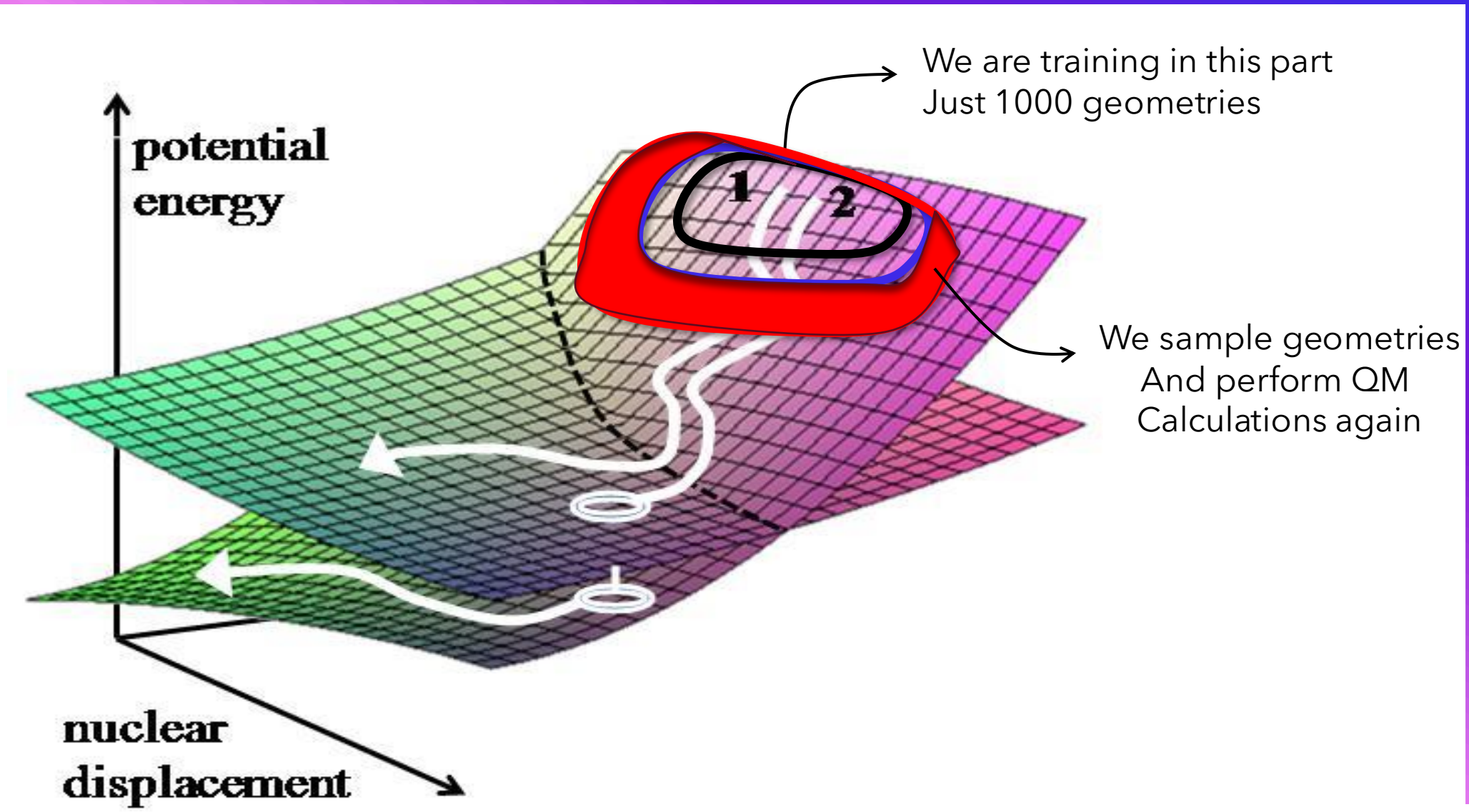
Unsupervised Learning:



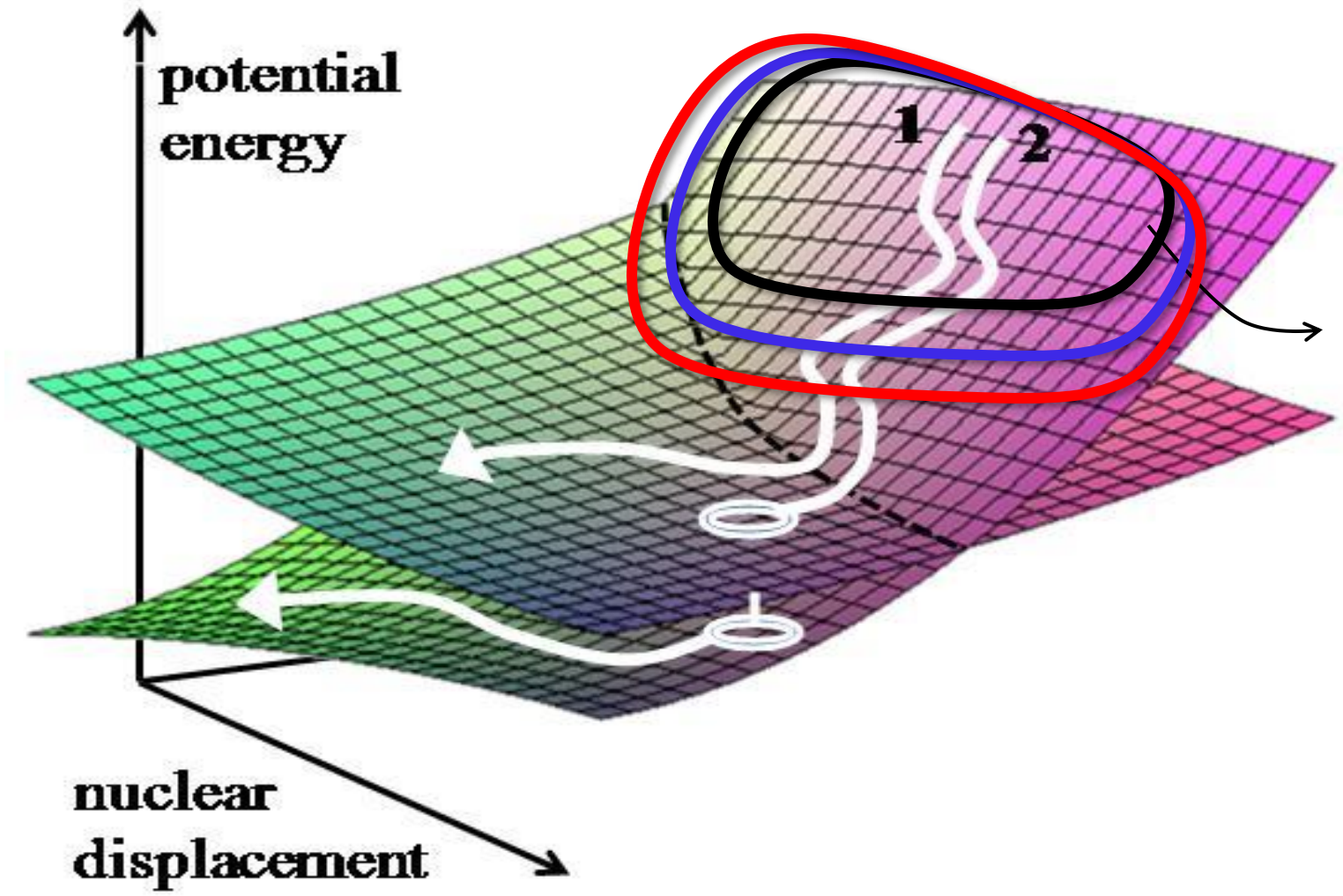
We have clustered the local minima from a pool of geometries, which helped to find out the reaction barriers

Parolin *et al*. ChemRxiv 2024. DOI: 10.26434/chemrxiv-2024-8hwr5

Motivation:


We are training in this part
Just 1000 geometries
potential
energy
1
2
We sample geometries
And perform QM
Calculations again
nuclear
displacement

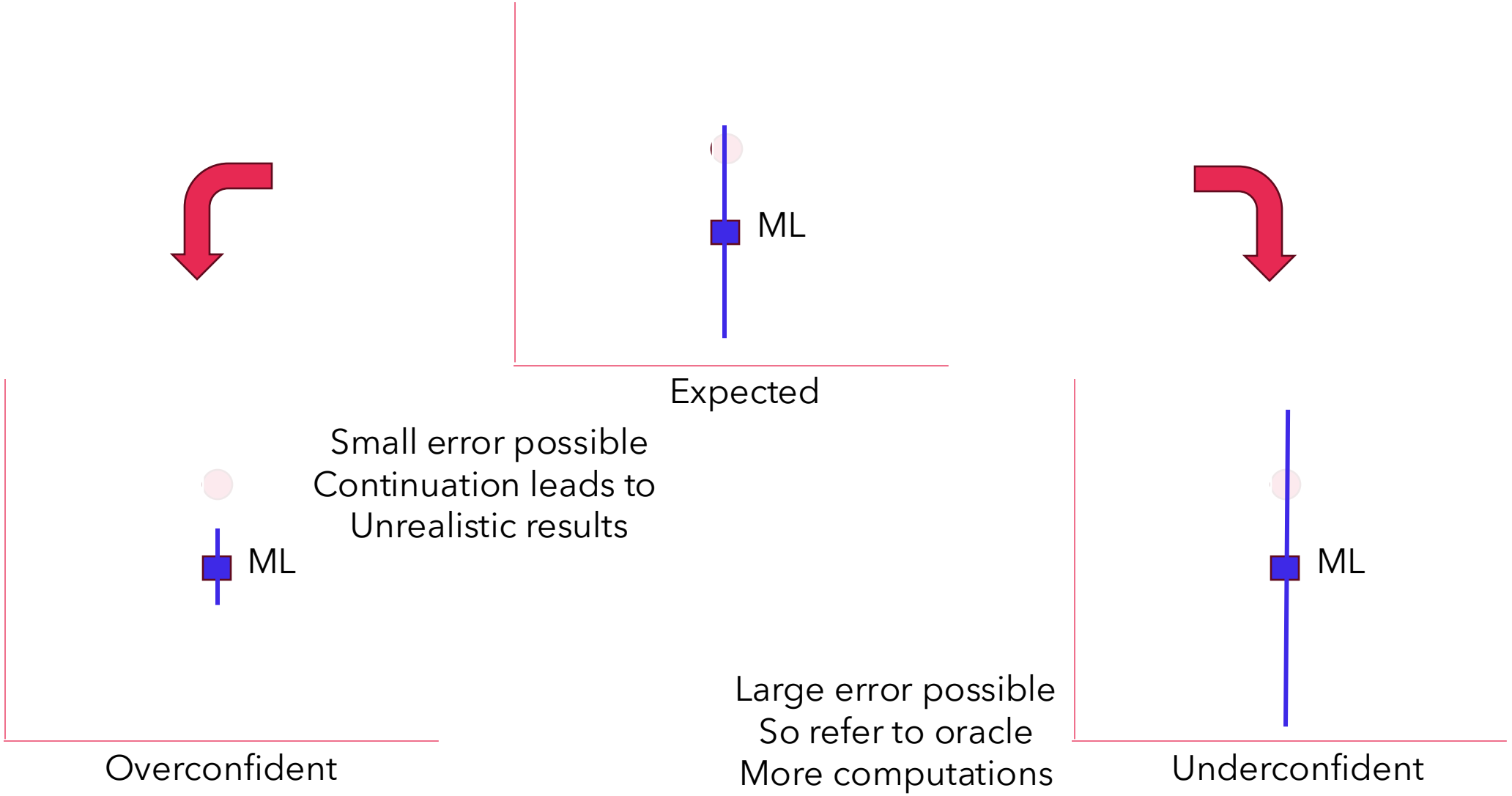
Active Learning:



This is our area of confidence

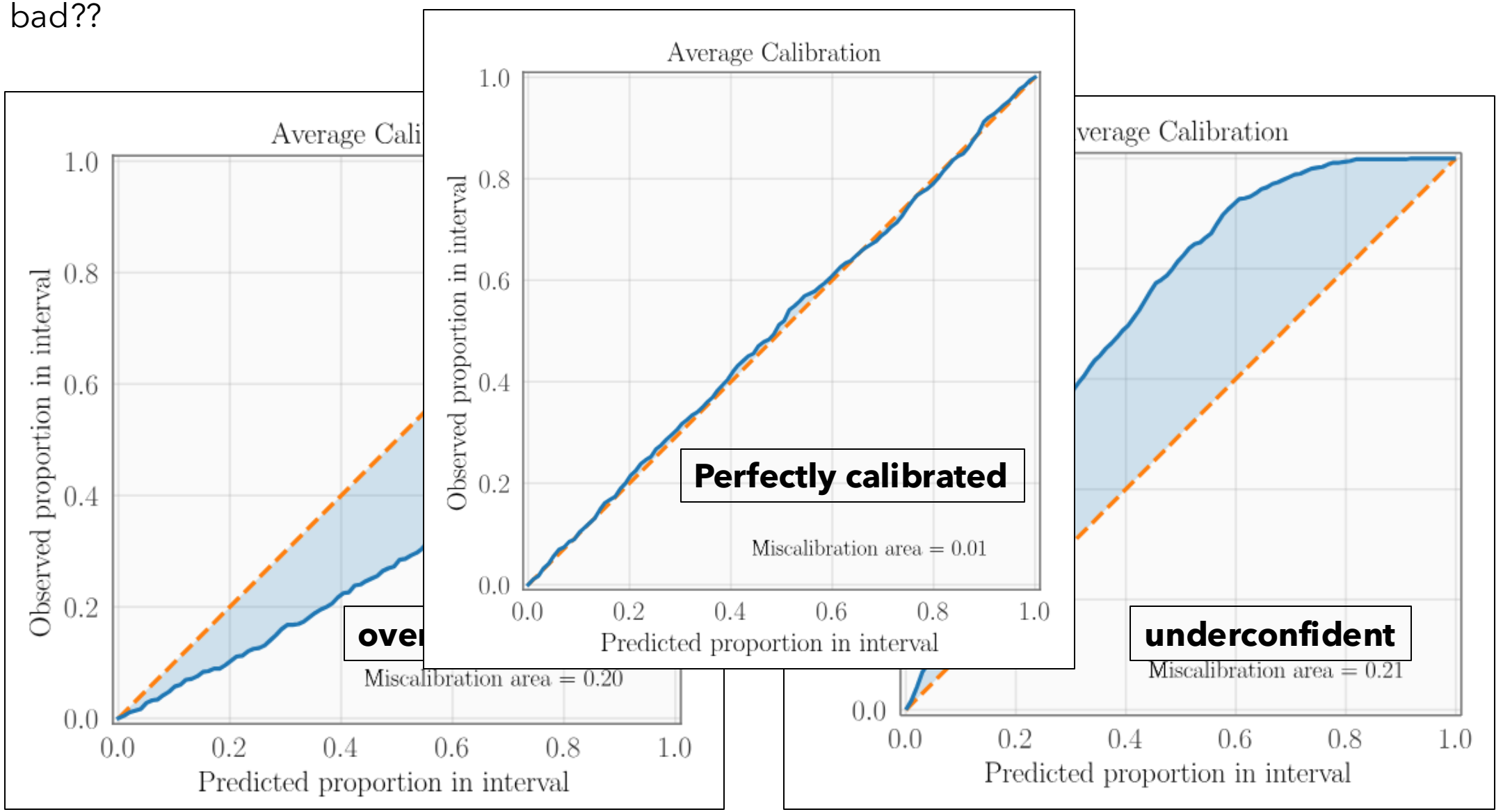
Introduction

What is the output for Out of Distribution (OOD) data



Introduction

How to measure the predicted uncertainty good/ bad??

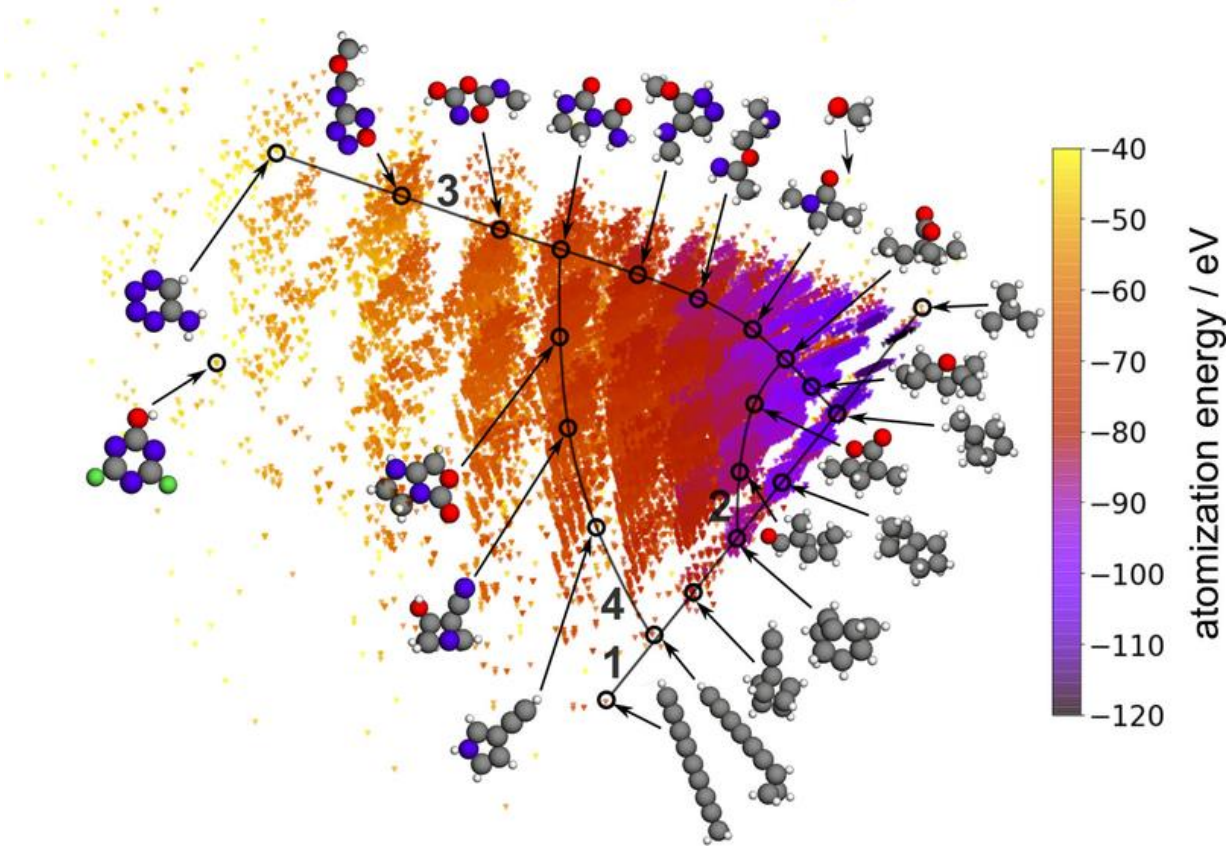


CASE - I
PREDICTION OF SCALAR PROPERTIES

Results and Discussion

Dataset: QM9

Contains ~138K small organic molecules with maximum of 9 heavy atoms
with 19 regression targets



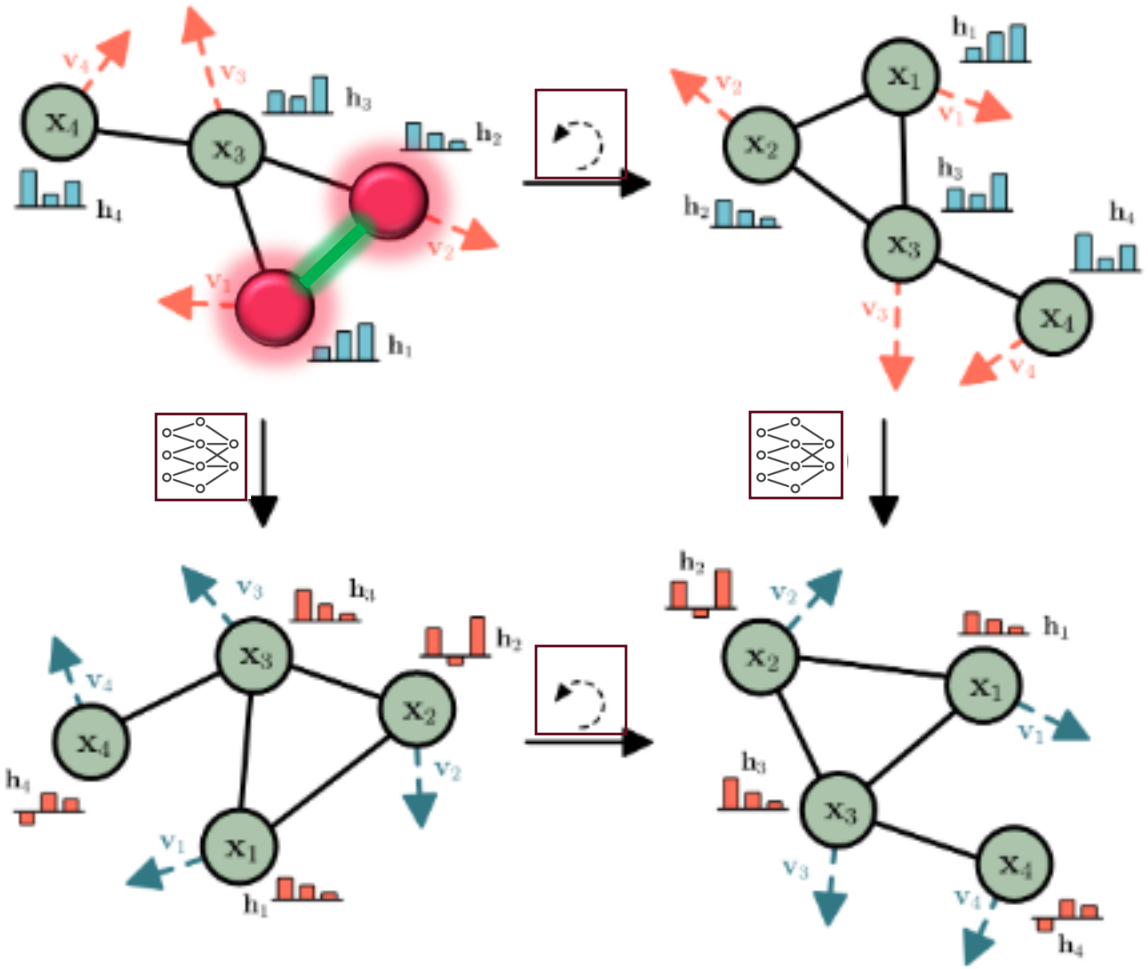
We used electronic spatial extent as target

Train ~ 80%
Validation ~ 10%
Test ~ 10%

Margraf. Angew. Chem. Int. Ed. 2023, 62, e202219170.
Ramakrishnan *et al*. Sci. Data 2014, 1, 1-7.

Results and Discussion

Model: Simple Equivariant Graph Neural Network (EGNN)



= Node/ Atom

= Edge/ Bond

$$h_i^0 = \psi_0(Z_i)$$

$$d_{ij} = ||X_i - X_j||^2$$

$$m_{ij}^l = \phi_l(h_i^l, h_j^l, d_{ij}) \qquad \text{for } l = 0, \ldots, L-1$$

$$h_i^{l+1} = \psi_l(h_i^l, \sum_{j \neq i} m_{ij}^l) \qquad \text{for } l = 0, \ldots, L-1$$

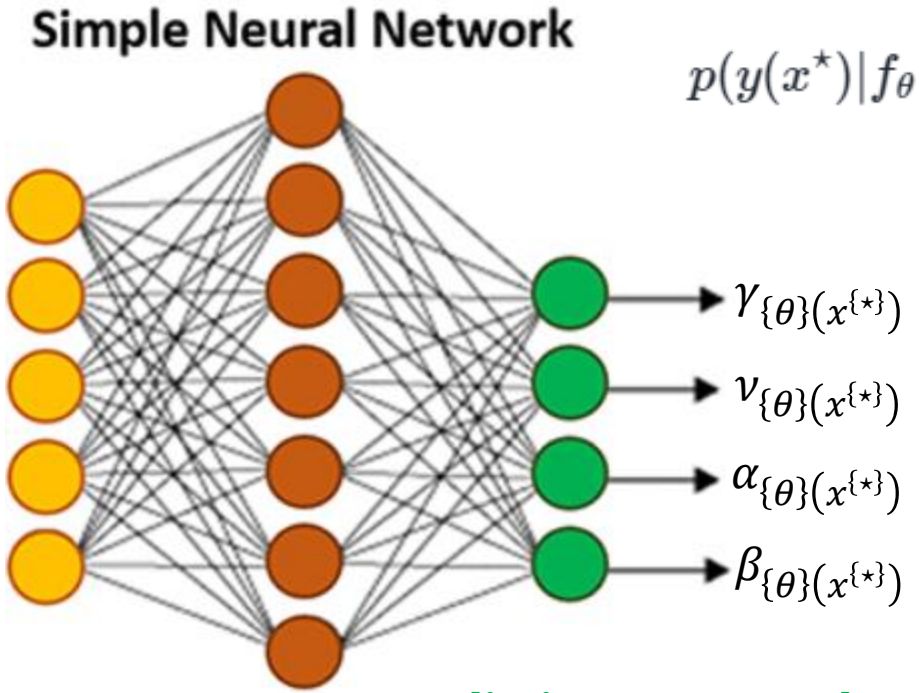
In the final layer, we aggregate the hidden Messages and apply a Deep Evidential Layer

Satorras; Hoogeboom; Welling. ICML 2021. PMLR.

Methodology

Deep Evidential Regression:

$$f_{\{\theta\}(x^{\{\star\}})} = \left(\gamma_{\{\theta\}(x^{\{\star\}})}, \nu_{\{\theta\}(x^{\{\star\}})}, \alpha_{\{\theta\}(x^{\{\star\}})}, \beta_{\{\theta\}(x^{\{\star\}})}\right),$$



$$p(y(x^\star)|f_\theta(x^\star)) = \mathrm{St}_{2\alpha_\theta(x^\star)}\left(y^\star \middle| \gamma_\theta(x^\star), \frac{\beta_\theta(x^\star)(1+\nu_\theta(x^\star))}{\nu_\theta(x^\star)\alpha_\theta(x^\star)}\right).$$

The loss function

$$\mathcal{L}_i(\boldsymbol{w}) = \mathcal{L}_i^{\mathrm{NLL}}(\boldsymbol{w}) + \lambda \mathcal{L}_i^{\mathrm{R}}(\boldsymbol{w}).$$

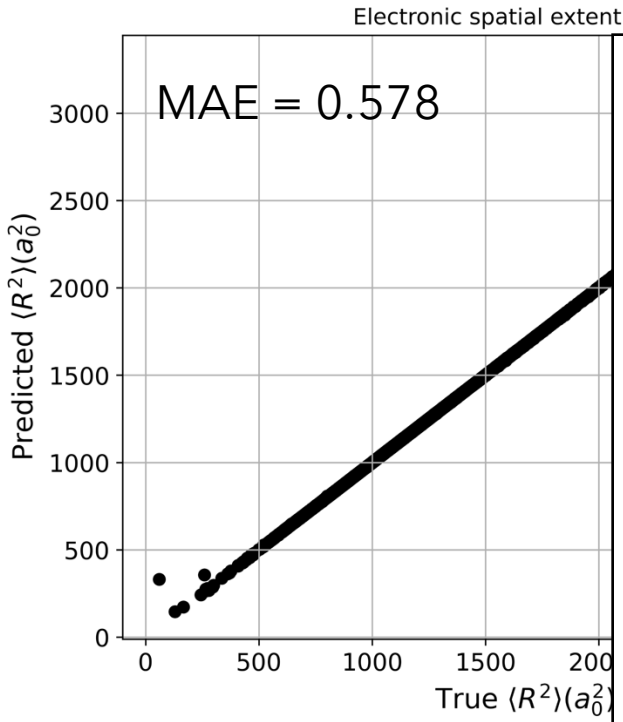
$$\mathcal{L}_i^{\mathrm{R}}(\boldsymbol{w}) = |y_i - \mathbb{E}[\mu_i]| \cdot \Phi = |y_i - \gamma| \cdot (2\upsilon + \alpha).$$

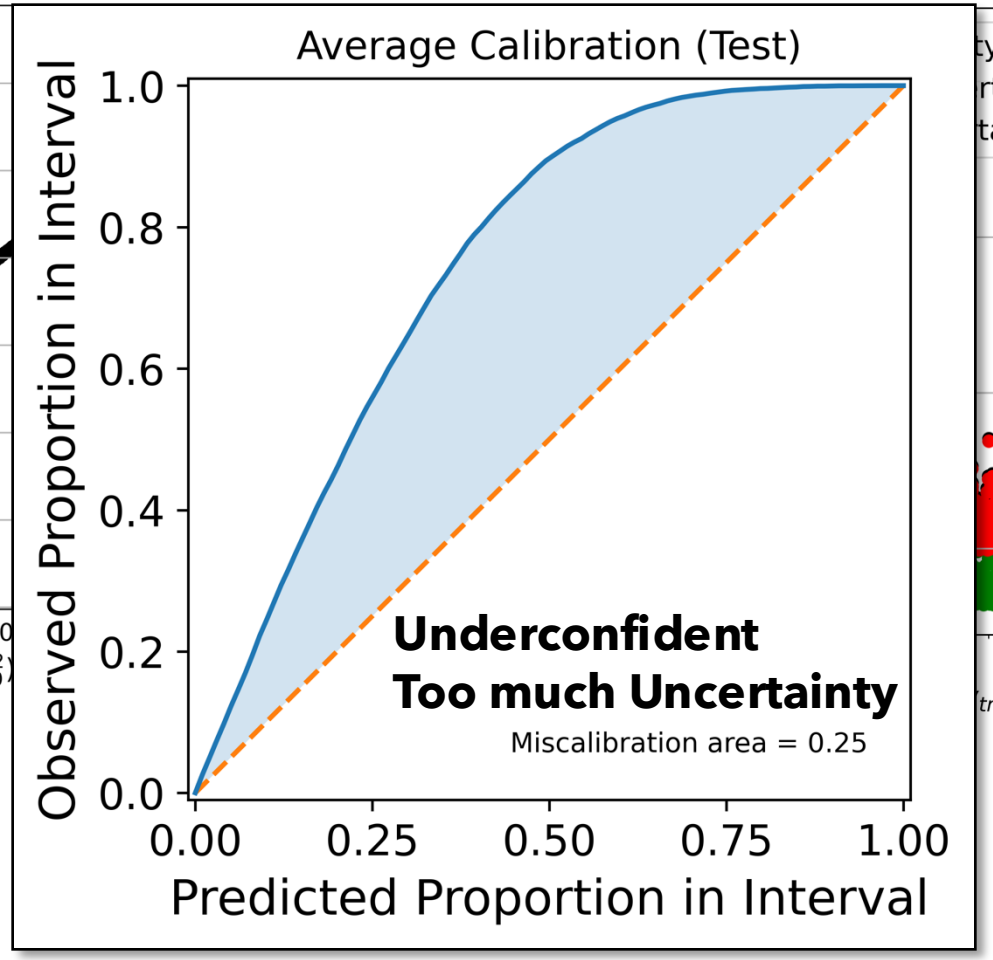
Predictive Mean and Uncertainty (Aleatoric and Epistemic)

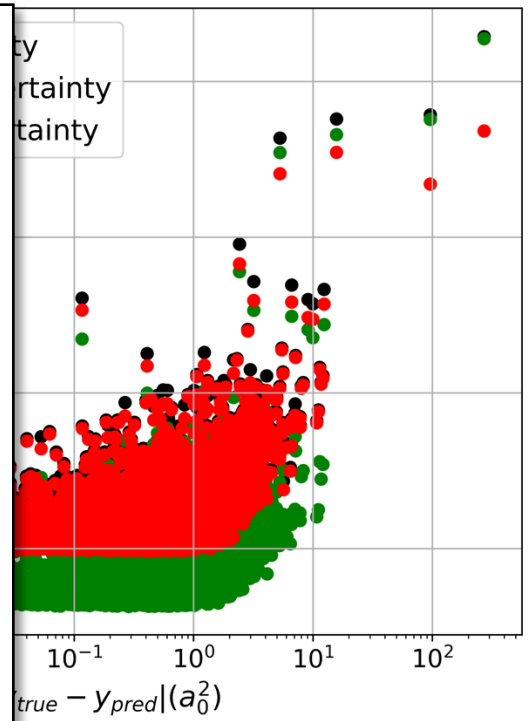
$$\underbrace{\mathbb{E}[\mu] = \gamma}_{\text{prediction}}, \quad \underbrace{\mathbb{E}[\sigma^2] = \frac{\beta}{\alpha-1}}_{\text{aleatoric}}, \quad \underbrace{\mathrm{Var}[\mu] = \frac{\beta}{\upsilon(\alpha-1)}}_{\text{epistemic}}.$$

Amini *et al*. NeurIPS 2020, 33, 14927-14937.

Results and Discussion



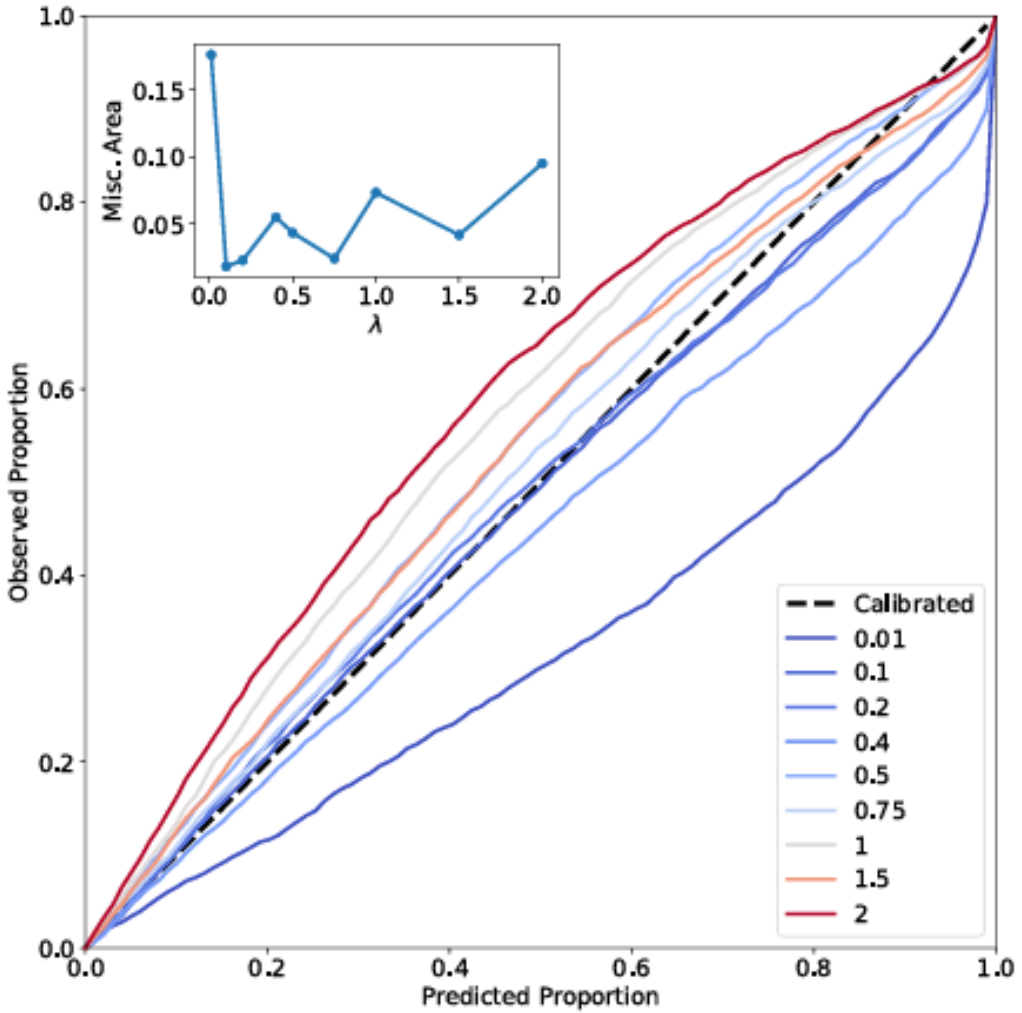




Miscalibration Area	Mean Miscalibration	RMSE Miscalibration	Sharpness	NLL
0.25	0.247	0.278	19.046	1.407

Results and Discussion

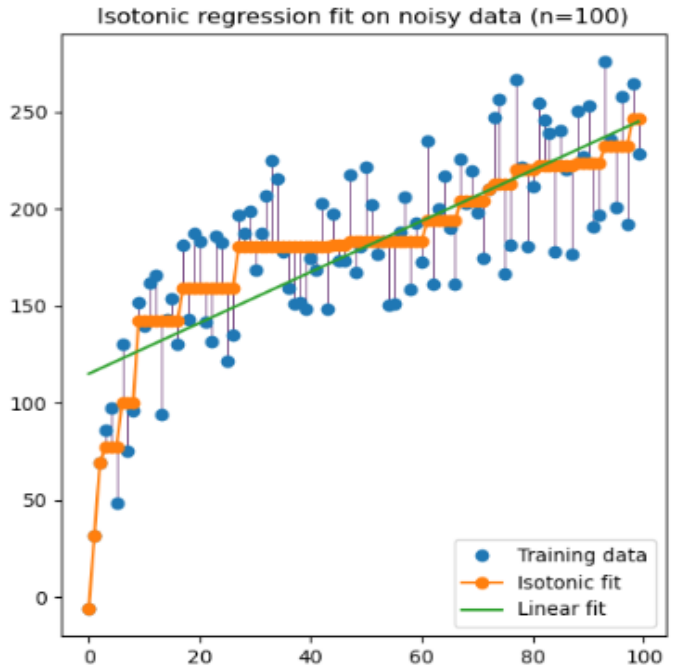
Recalibration for improved uncertainty



Requires training based on the reg. parameter

Post-hoc calibration Methods
Non-Parametric

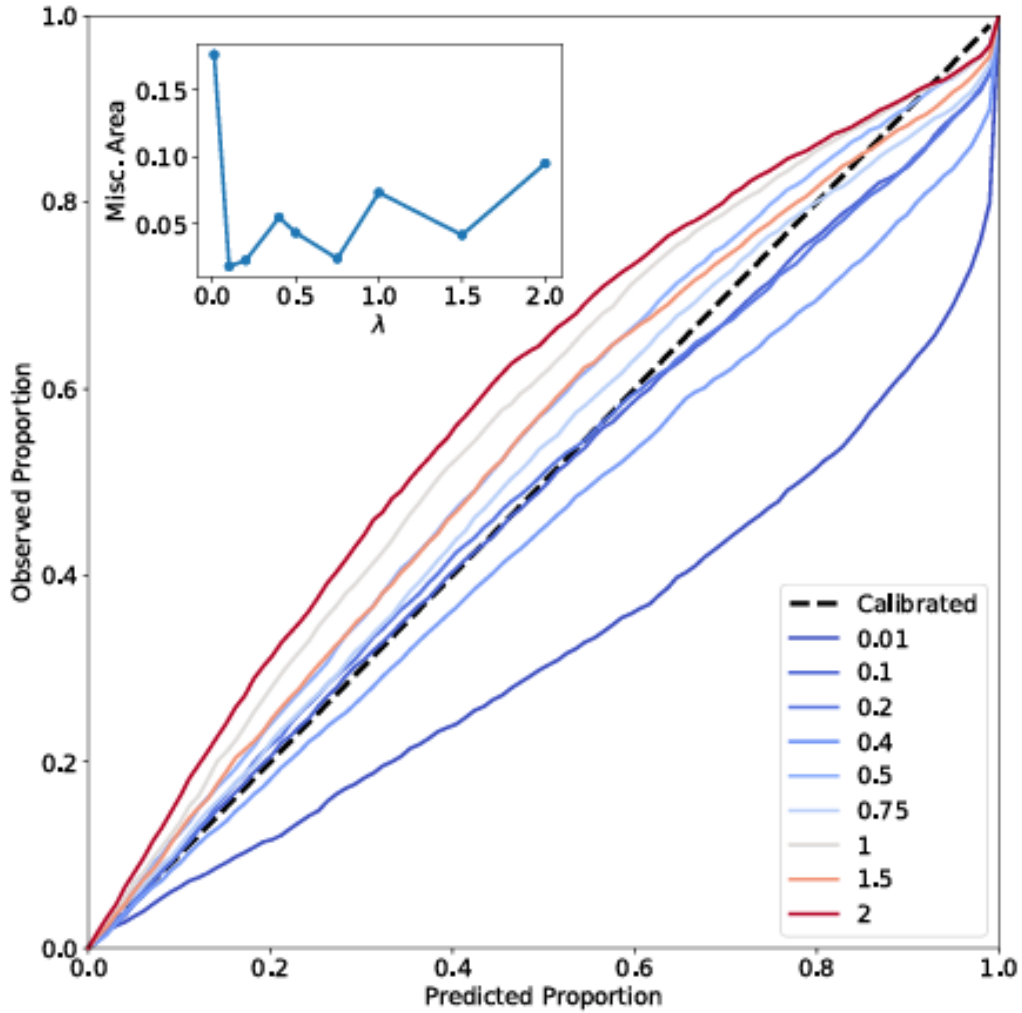
1) Isotonic Regression



Vazquez-Salazar; Boittier; Meuwly. Chem. Sci. 2022, 13, 13068-13084.

Results and Discussion

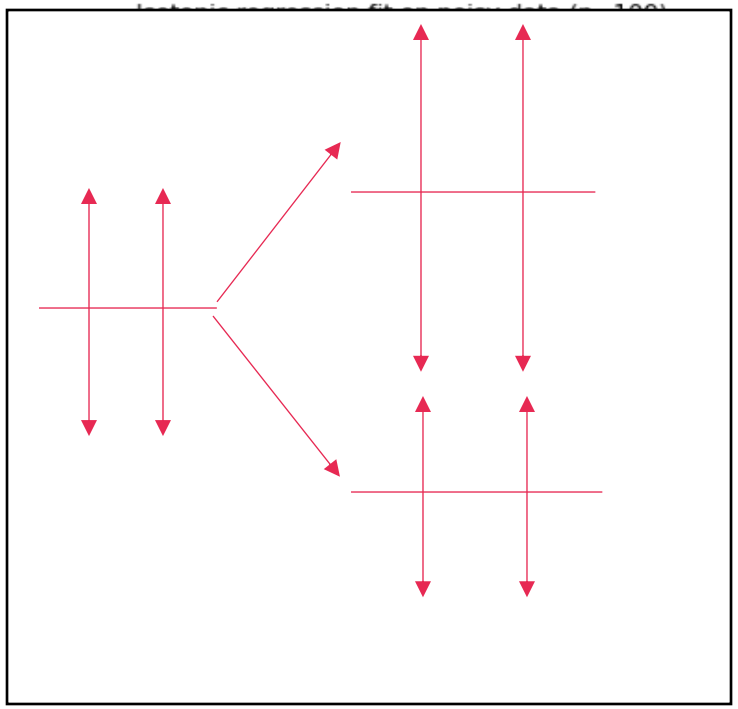
Recalibration for improved uncertainty



Requires training based on the reg. parameter

Post-hoc calibration Methods
Non-Parametric

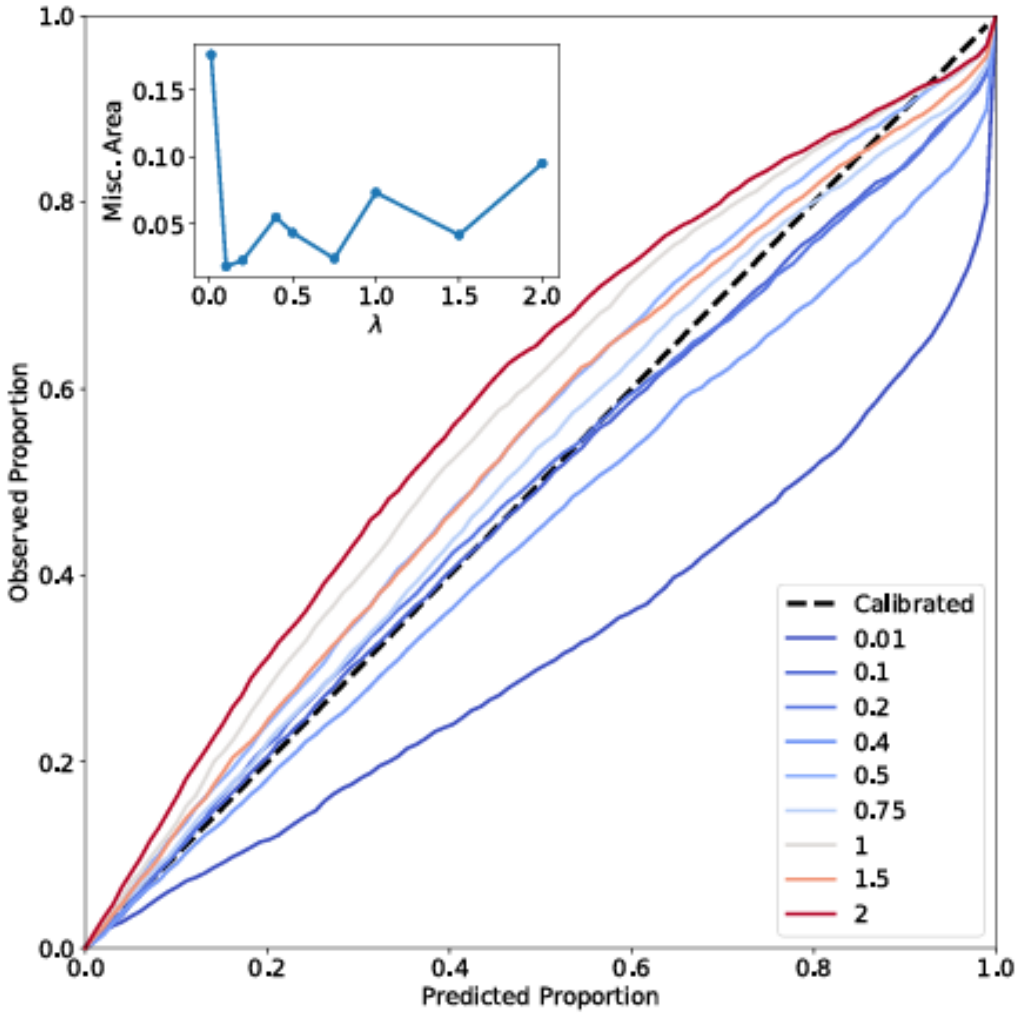
1) Standard Scaling



Vazquez-Salazar; Boittier; Meuwly. Chem. Sci. 2022, 13, 13068-13084.

Results and Discussion

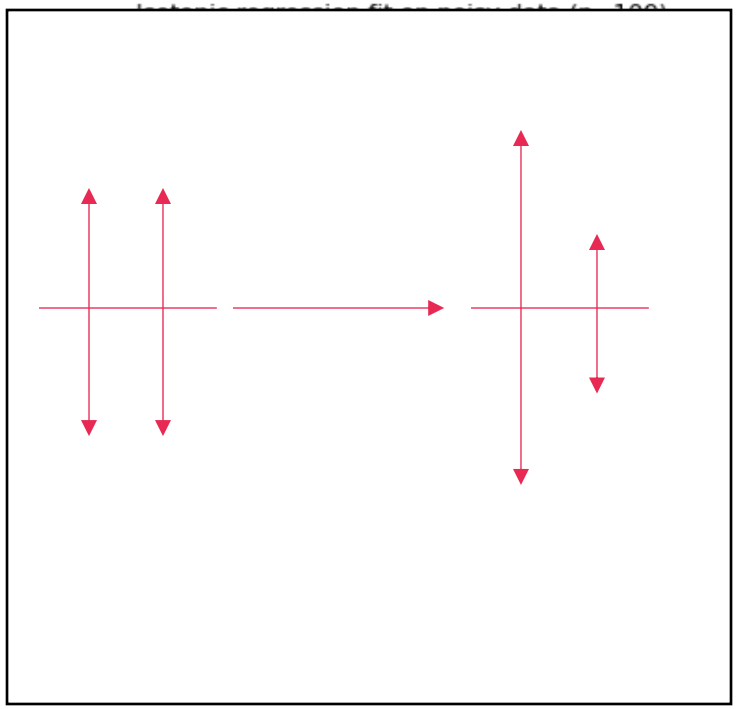
Recalibration for improved uncertainty



Requires training based on the reg. parameter

Post-hoc calibration Methods
Parametric

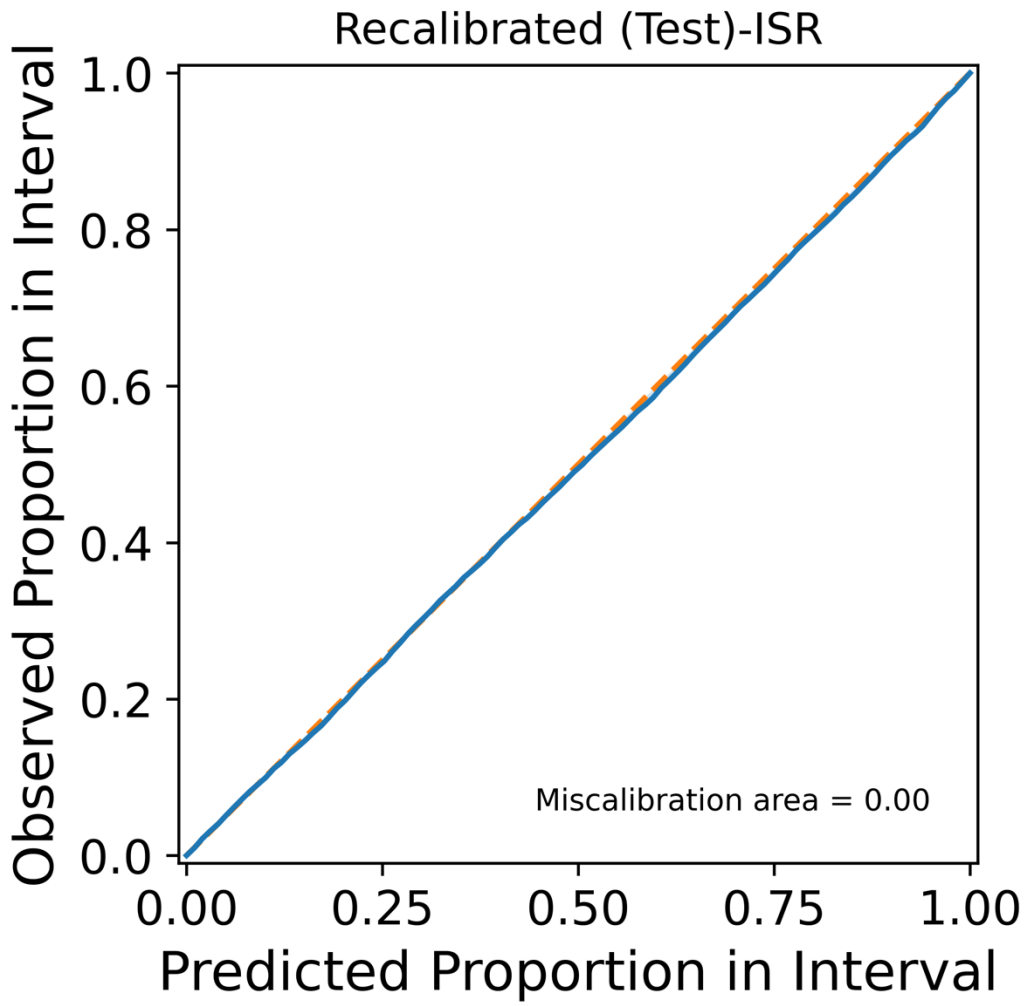
1) GPNormal



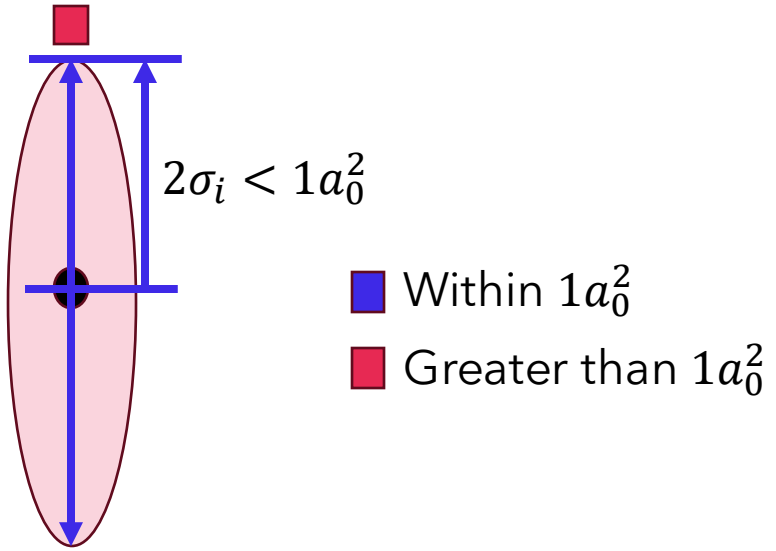
Vazquez-Salazar; Boittier; Meuwly. Chem. Sci. 2022, 13, 13068-13084.

Results and Discussion

Recalibration for improved uncertainty



Cost Effectiveness:



Calibrated Uncertainty

Method	Non query points	Misjudged
Uncalibrated	**0**	**0**
ISR	**4201**	**139**
Std. Scaling	**3766**	**115**
GPNormal	**3761**	**111**

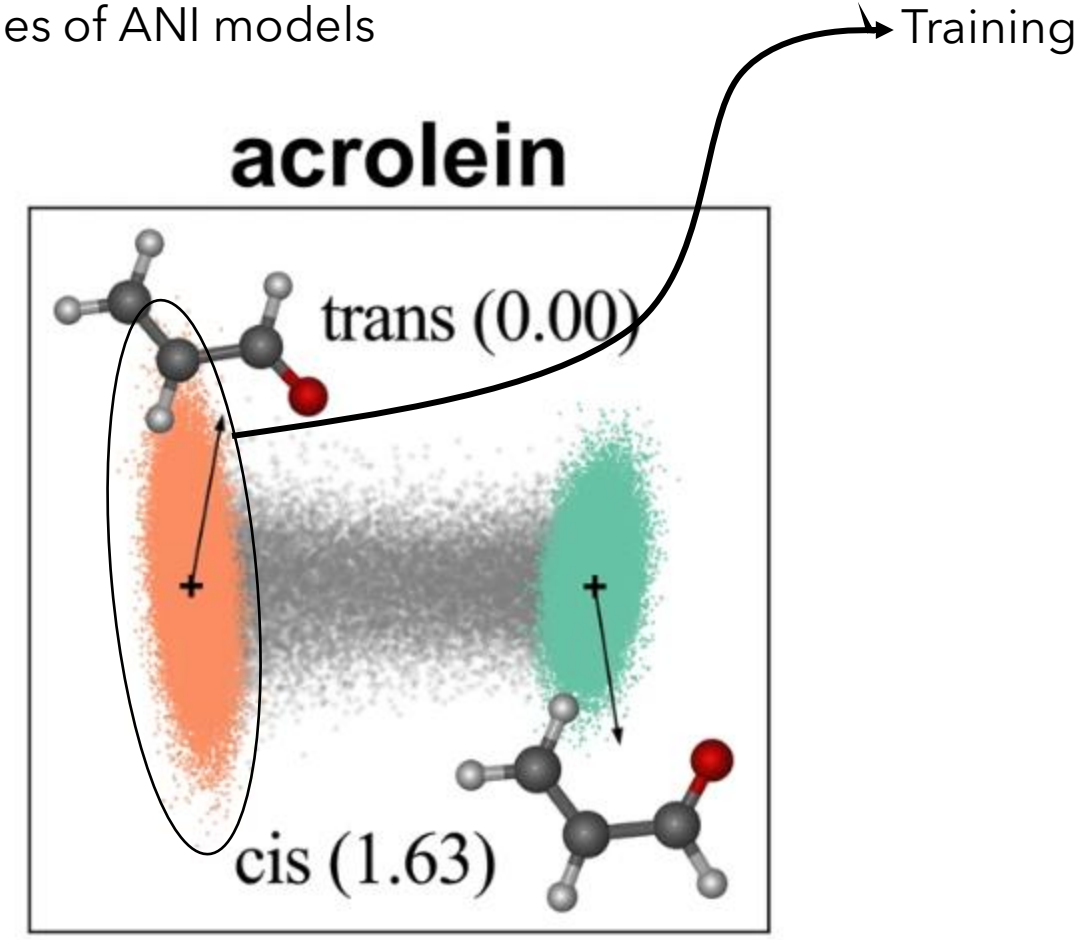
CASE - II
PREDICTION OF ML POTENTIALS

Results and Discussion

Uncertainty in case of distribution shift (OOD):

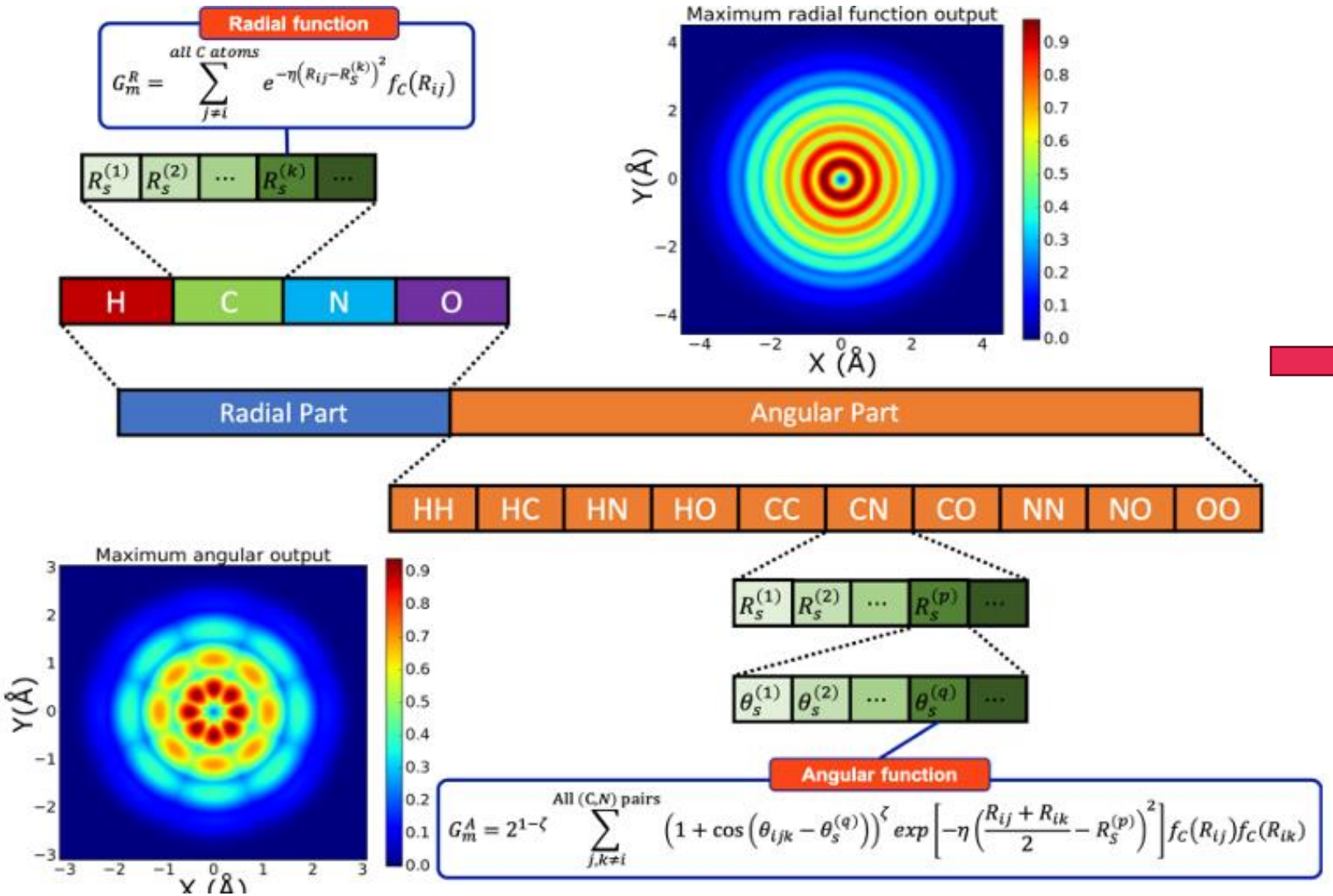
Dataset: WS22-Acrolein (120K) [50000 (trans) + 20000 (Reaction Coordinate) + 50000 (Cis)]

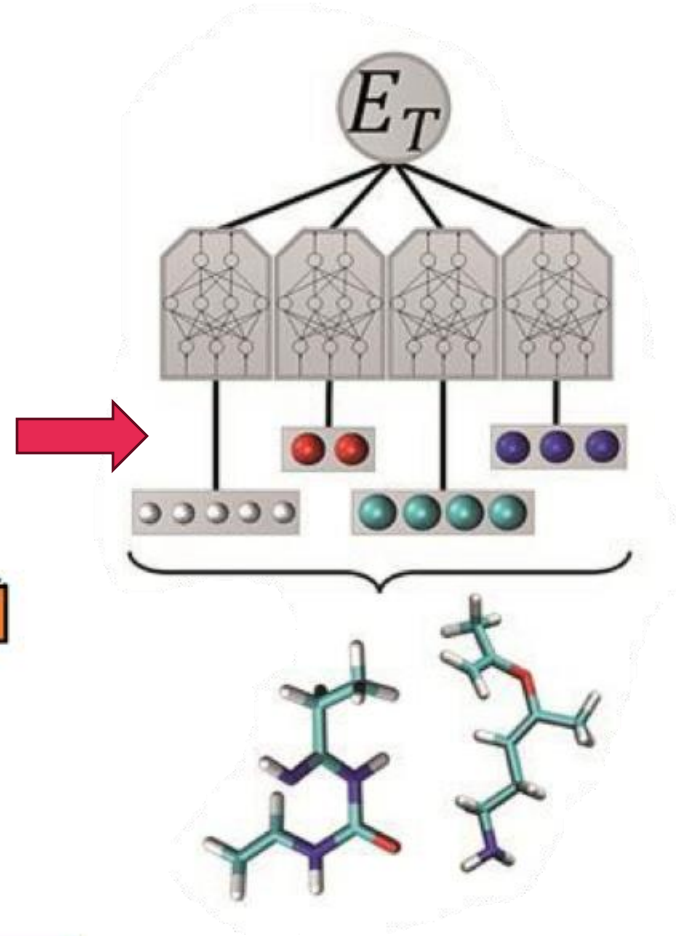
Model: Deep Ensembles of ANI models



Pinheiro Jr *et al*. Sci. Data 2023, 10, 95.

Featurization: Atomic Environment Vector (AEV)





Gao *et al*. J. Chem. Inf. Model. 2020, 60, 3408-3415.

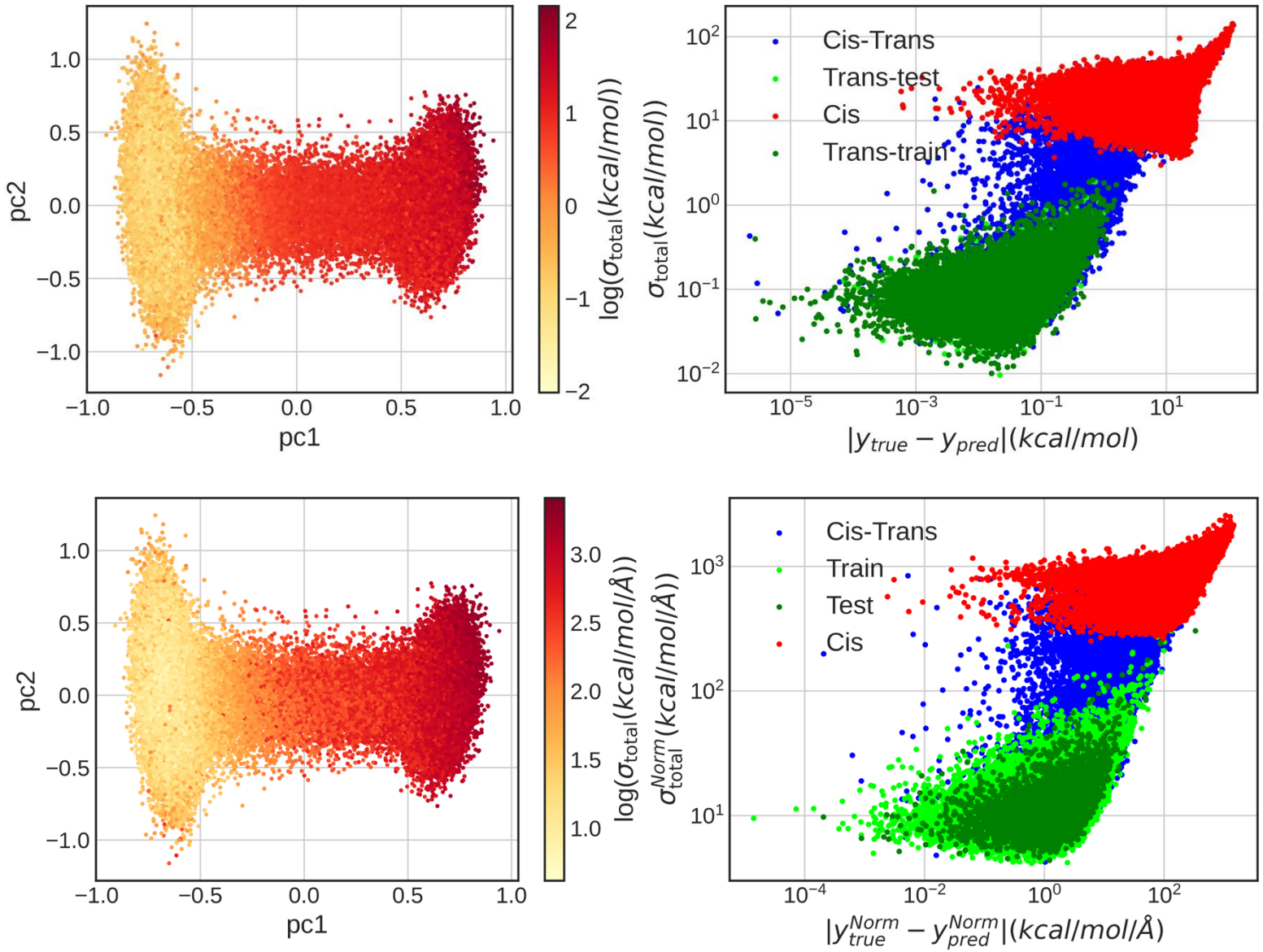
ANI Ensemble Results

1) Neuron: 32 / 64
2) Activation: CELU/ ReLU
3) Learning rate: 0.001/ 0.002

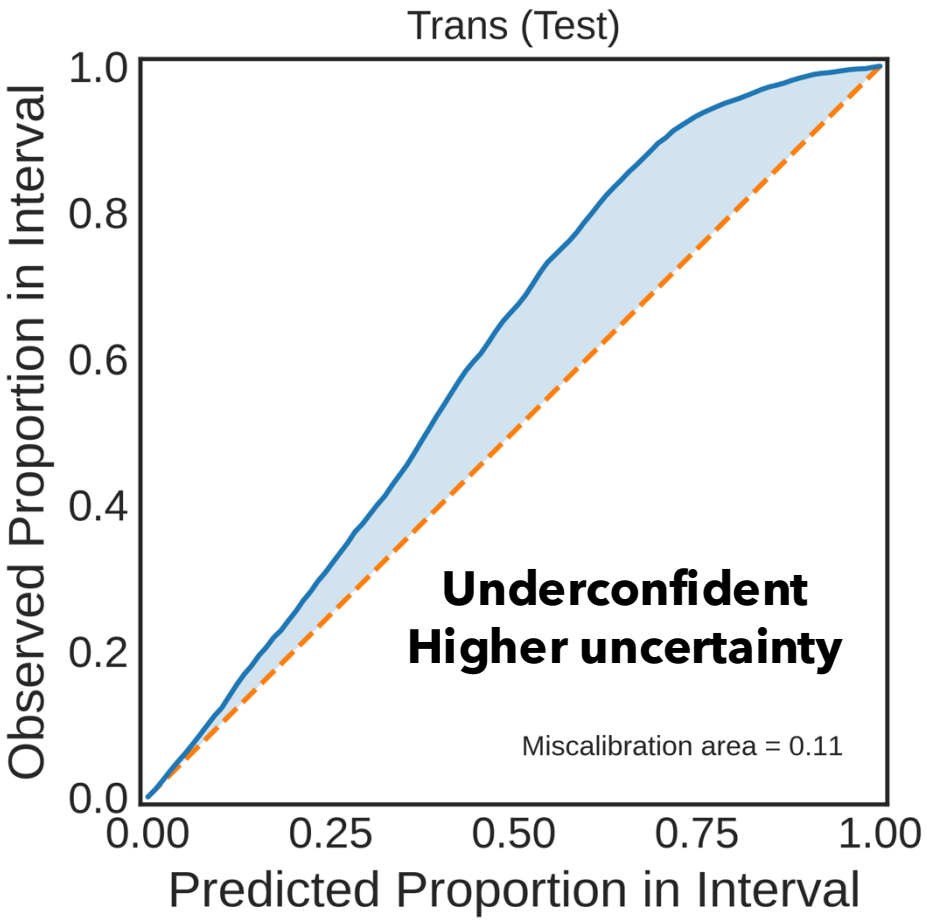
$2^3 = 8$ Neural Networks

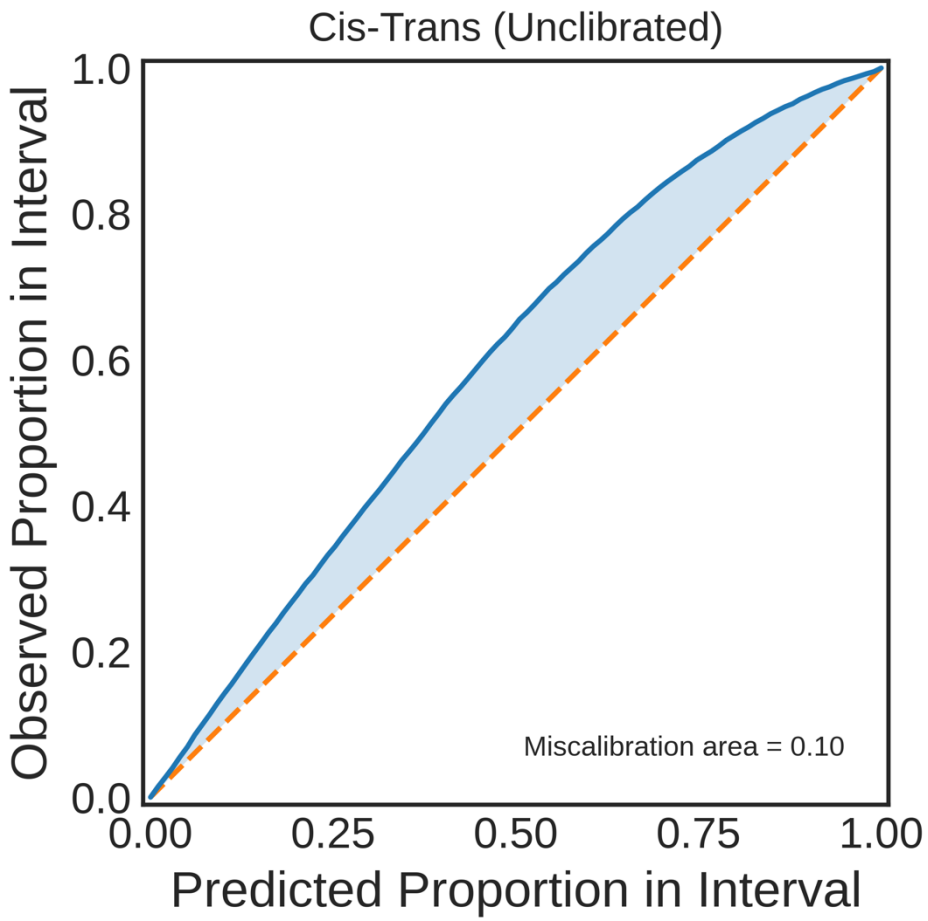
Model No.	Neuron x [72, 64, **x**, 16]	**Activation**	**Learning rate**	RMSE energy (kcal /mol)	RMSE Force (kcal / mol /Å)
1	32	ReLU	0.002	0.391	2.806
2	32	ReLU	0.001	0.161	2.093
3	32	CELU	0.001	0.069	0.851
4	32	CELU	0.002	0.069	0.782
5	64	CELU	0.002	0.046	0.598
6	64	CELU	0.001	0.069	0.759
7	64	ReLU	0.001	0.207	2.162
8	64	ReLU	0.002	0.414	3.059

ANI Ensemble Results

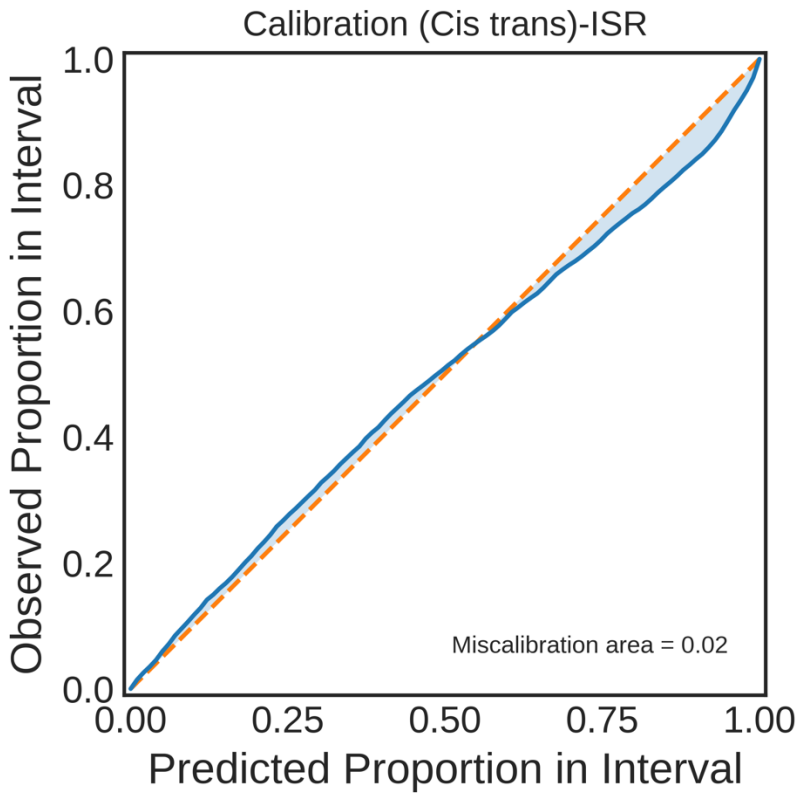


Quality of the Predicted Uncertainty for energy estimates





Post-hoc recalibrated Uncertainty on energy estimates

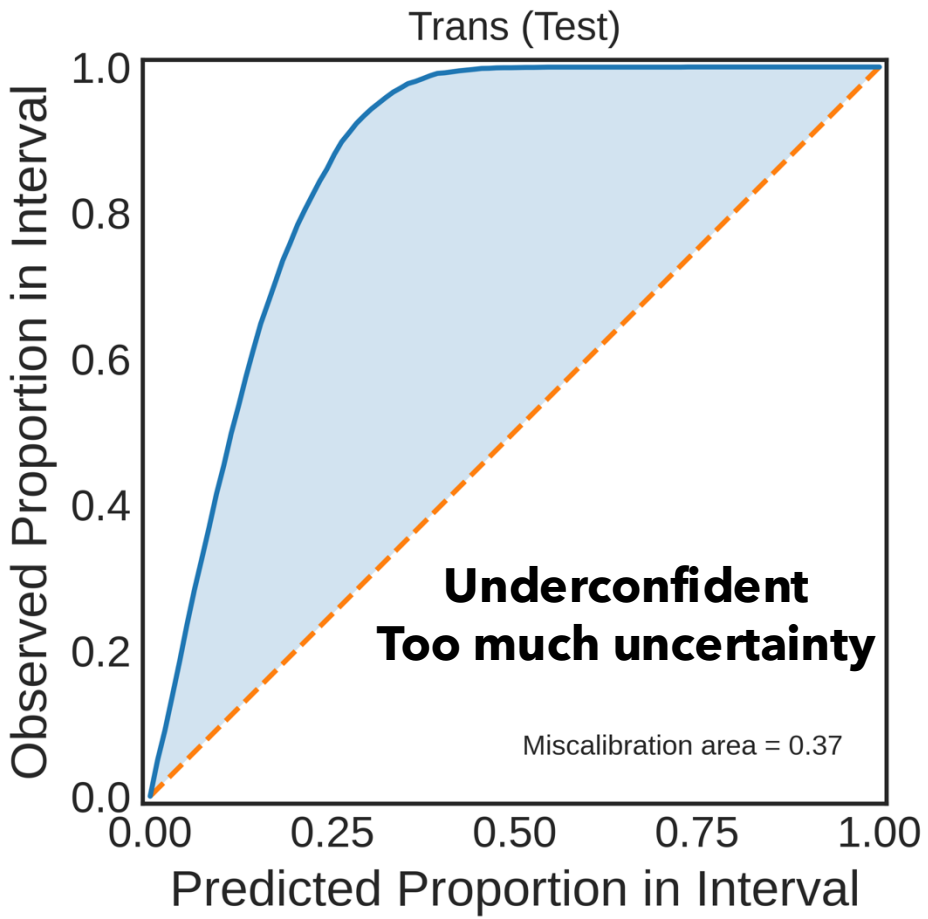


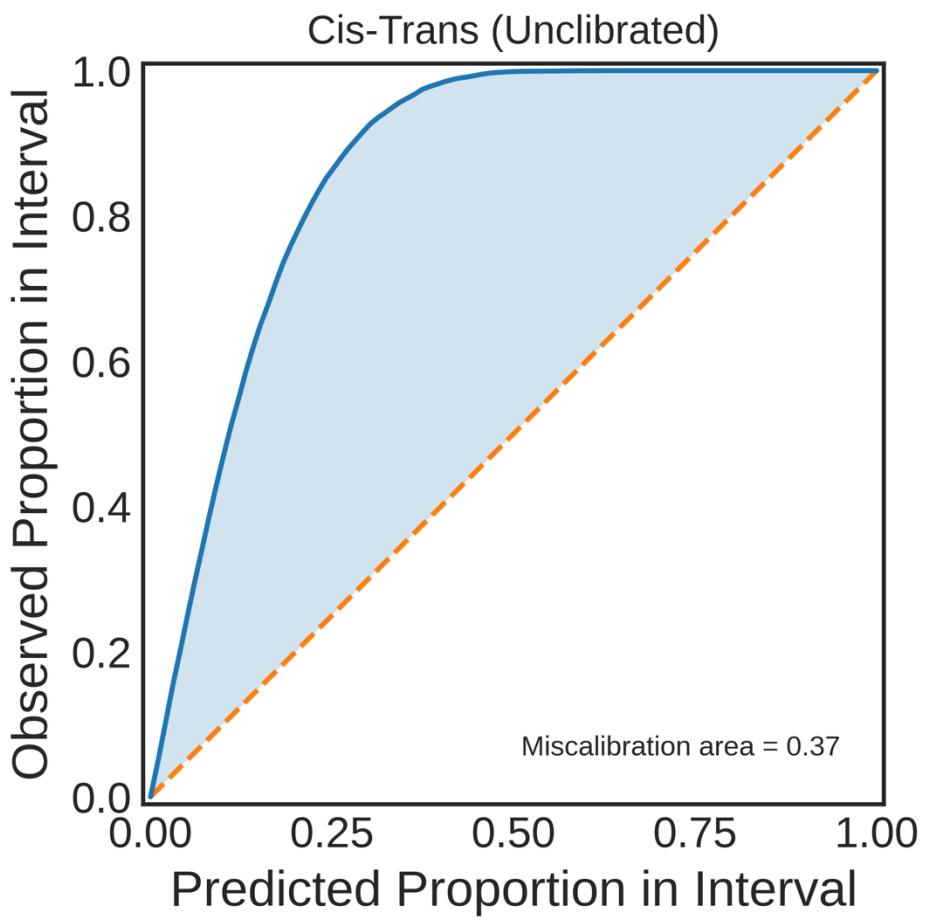
Threshold < 1kcal/mol

Calibrated Uncertainty

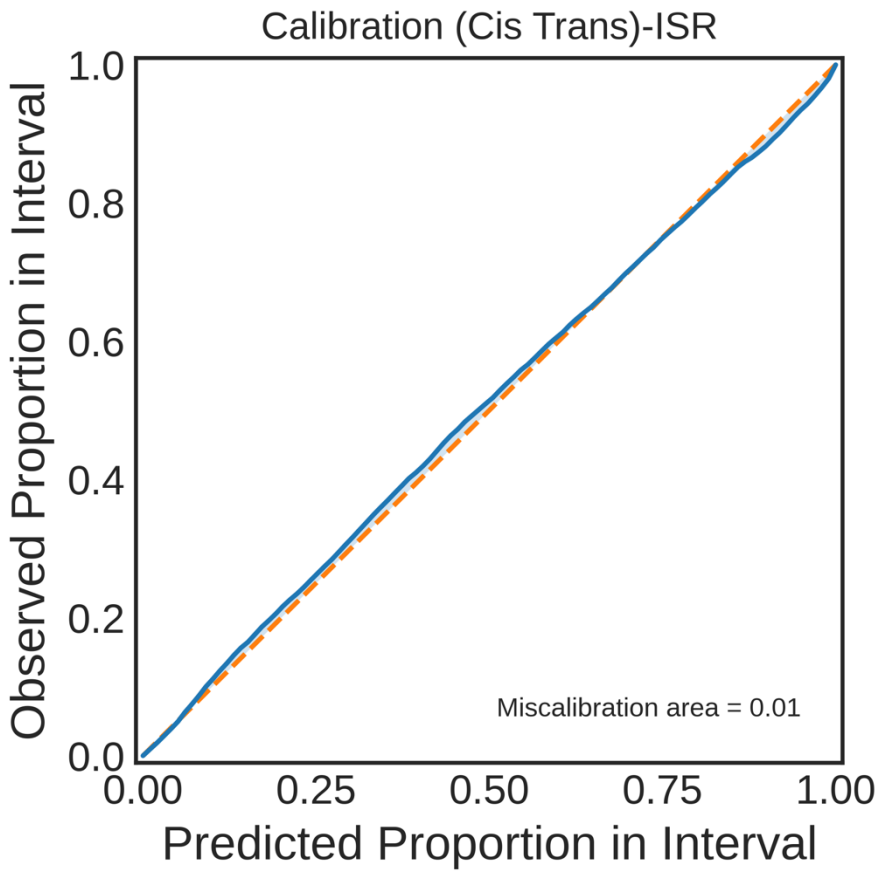
Method	Non query points	Misjudged
Uncalibrated	**5226**	**11**
ISR	**5946**	**48**
Std. Scaling	**5875**	**44**
GPNormal	**5948**	**47**

Quality of the Predicted Uncertainty for force estimates





Post-hoc recalibrated Uncertainty for force estimates



Energy

Calibrated Uncertainty

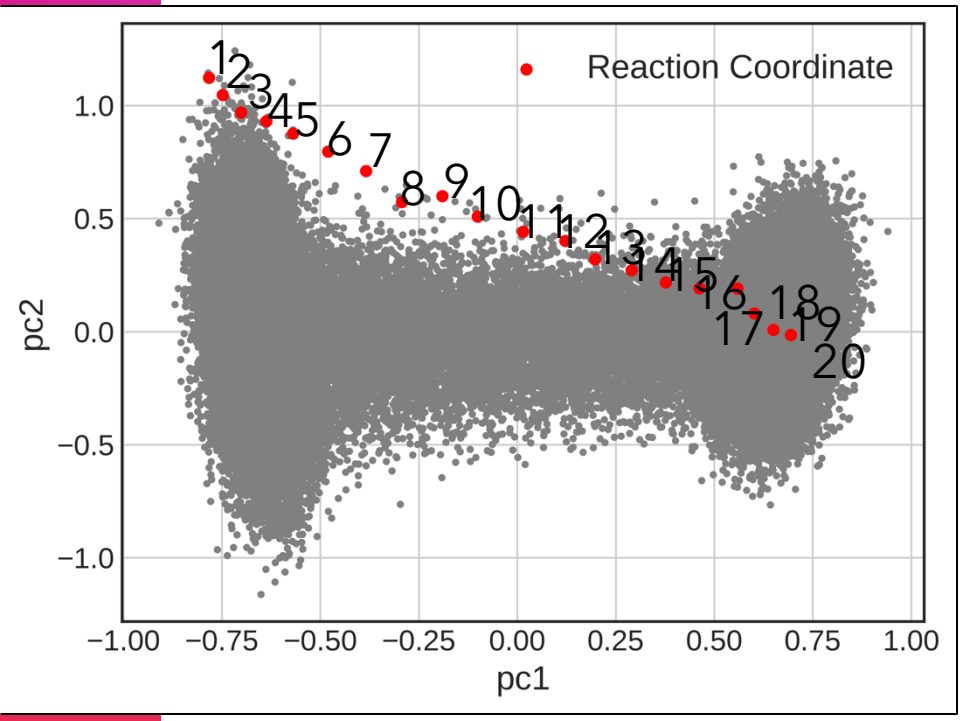
Method	Non query points	Misjudged
Uncalibrated	**5226**	**11**
ISR	**5946**	**48**
Std. Scaling	**5875**	**44**
GPNormal	**5948**	**47**

Force

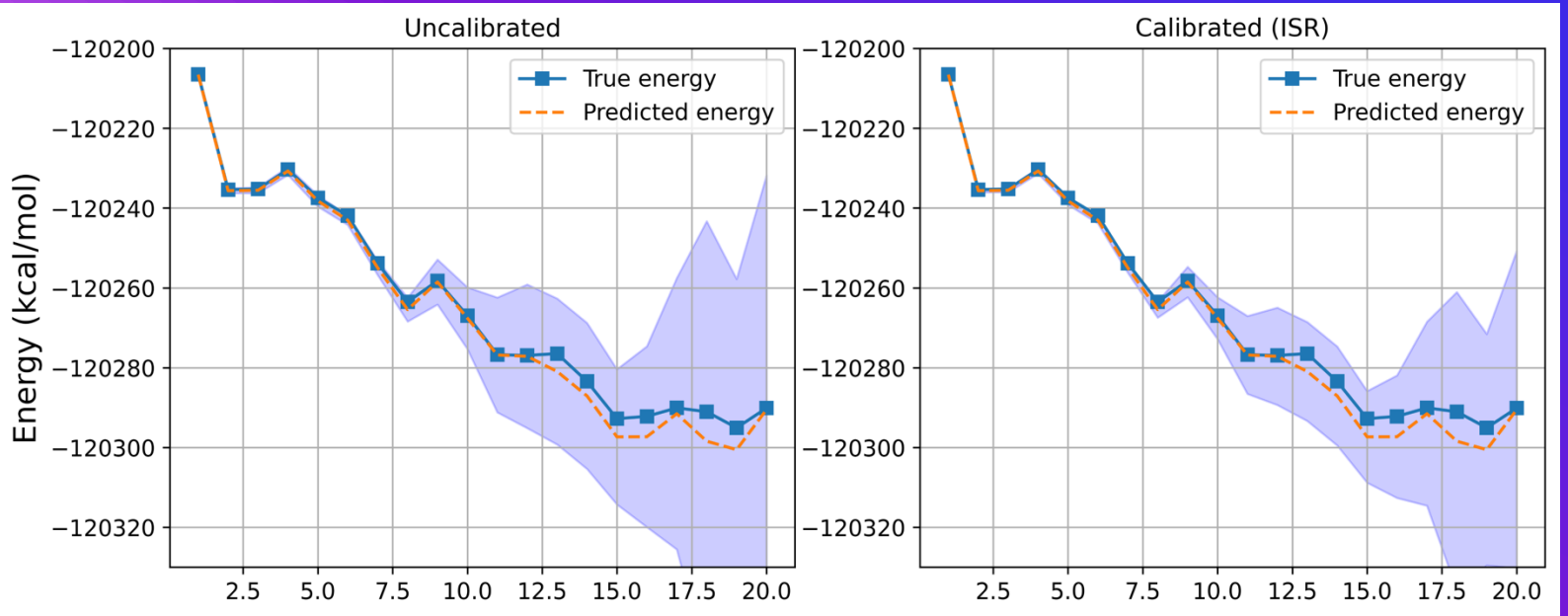
Calibrated Uncertainty

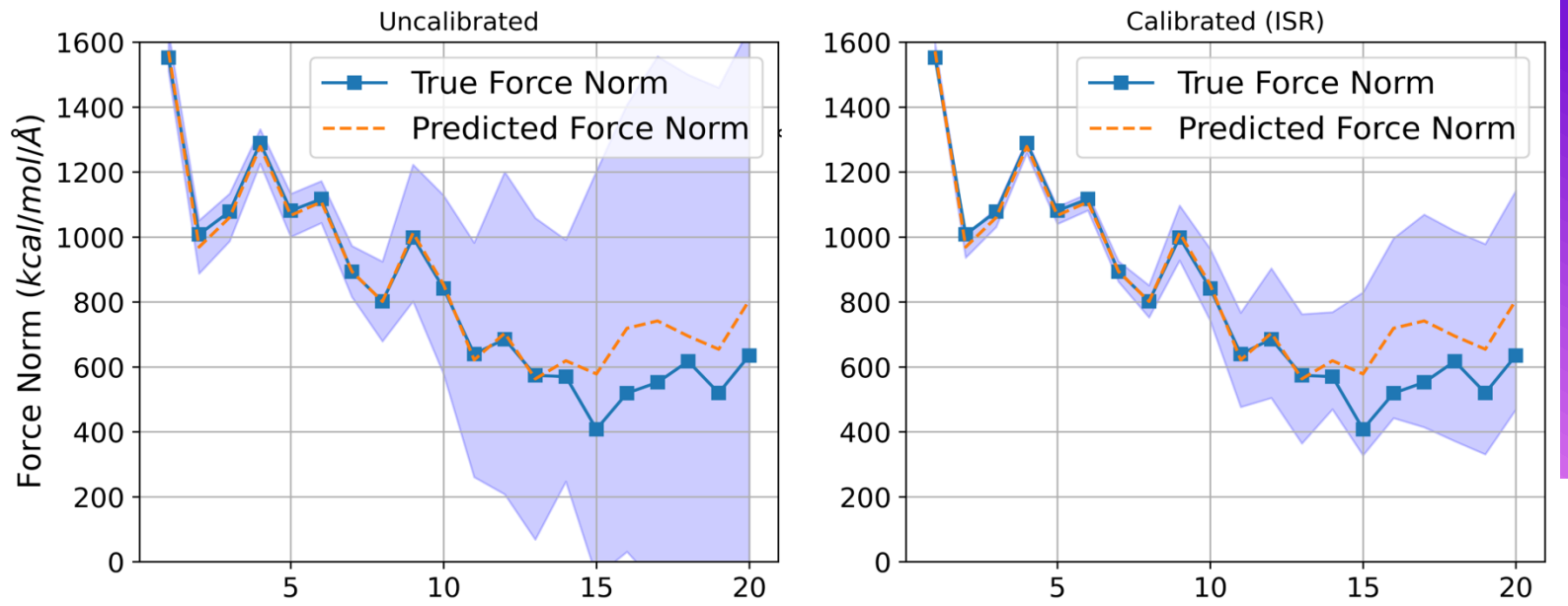
Method	Non query points	Misjudged
Uncalibrated	**3**	**0**
ISR	**4586**	**67**
Std. Scaling	**4487**	**58**
GPNormal	**4498**	**60**

Effect of calibration on uncertainty on energy and forces for a pathway



95 percentile confidence interval [**within 2σ**]





Conclusions

- Predicted uncertainties are mostly uncalibrated, which is not good for the deployment in real active learning scenario
- While both **parametric and non-parametric post hoc calibration** method **makes the uncertainties quantitative**
- Post-Hoc calibration methods can be easily be employed with any models. In an underconfident case, it can save redundant computations in a real active learning scenario

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QUESTIONS?
COMMENTS

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