Machine Learning for Molecules

Ichigaku Takigawa

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Hokkaido Univ ICReDD-Faculty of Medicine Joint Symposium

15 October 2021 @ Hokkaido University

A machine learning (ML) researcher working for

ML for Stem Cell Biology

RIKEN Center for AI Project
Medical-risk Avoidance based on iPS Cells Team
(A joint lab with Kyoto Univ CiRA)

ML for Chemistry

Inst. Chemical Reaction Design & Discovery
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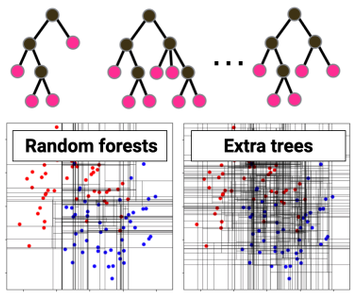

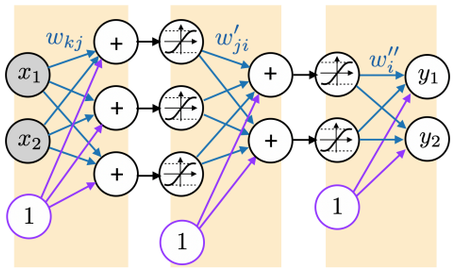

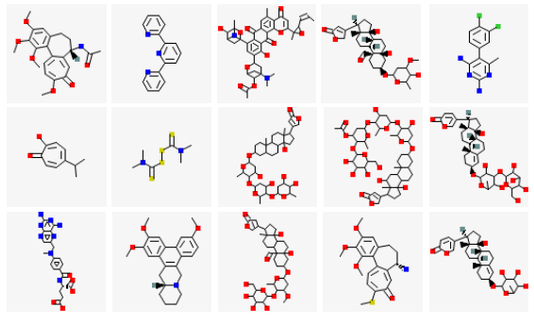

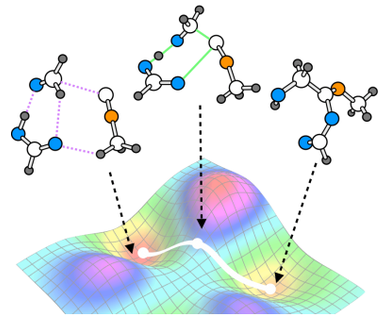

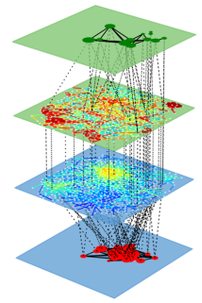

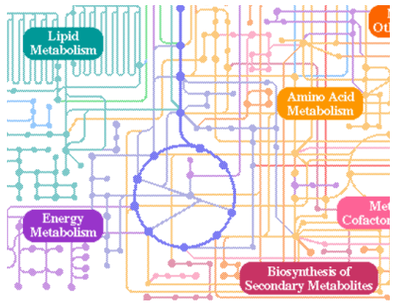

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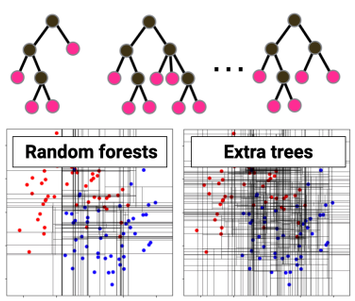
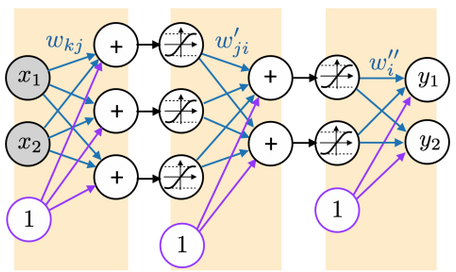
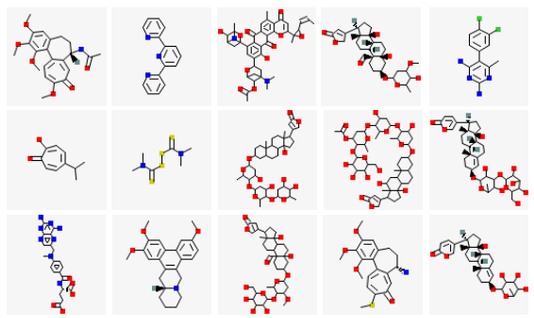
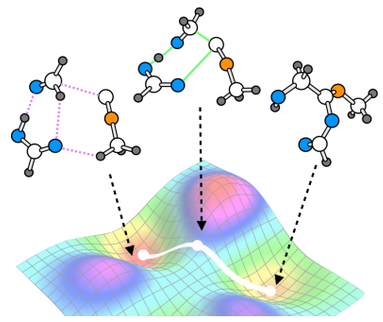
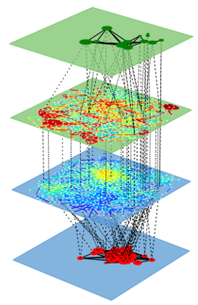
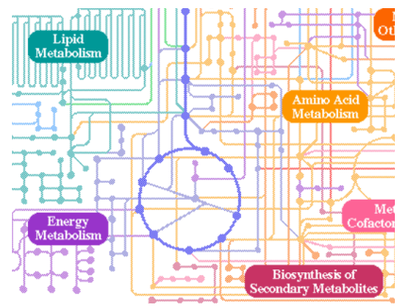












Joint project with HU Med Dept:

- Prof. Shinya Tanaka: Cancer diagnosis with fluorescent markers, Enzyme-catalyzed reaction design
- Prof. Shigetsugu Hatakeyama: Mediator complex of transcription regulations (*Nat Commun* 2020, 2015)
- Prof. Ichiro Yabe: Video-based predictions of motor symptom severity

- Prof. Yasuyuki Fujita: Cell competition (*Cell Reports* 2018; *Sci Rep* 2015)
- Prof. Hidenao Sasaki: Copy number variations for neurodegenerative diseases (*Mol Brain* 2017)

X-informatics: Bio- and Chemo-informatics

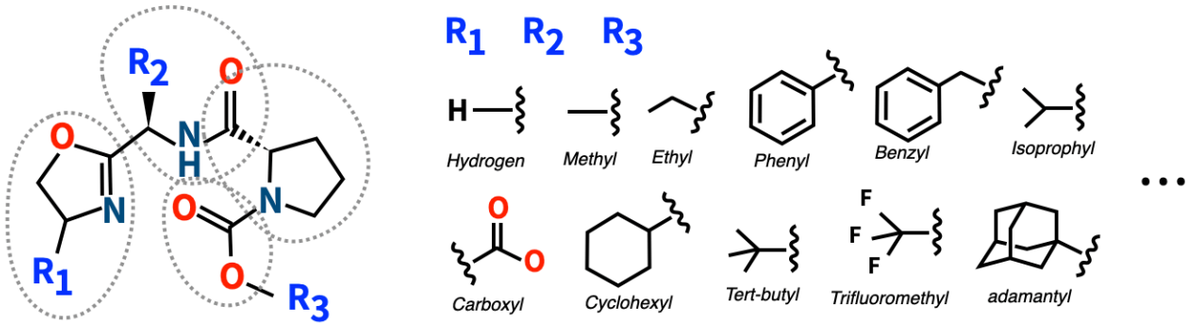
In addition to pure ML research, I've worked for bio/chemo-informatics

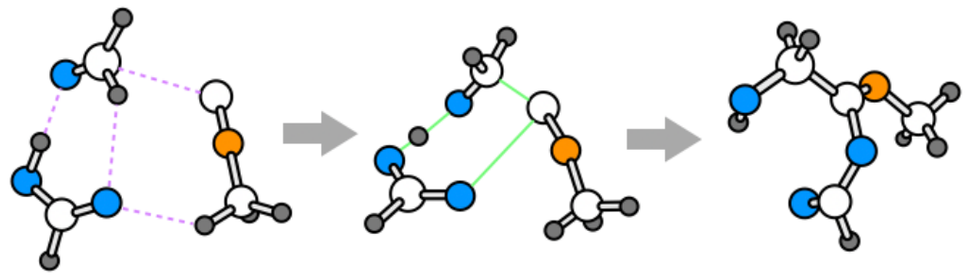
- **Biochemical reaction networks (Metabolic pathways)**
  Bioinformatics 2007, 2008a, 2008b, 2009, 2010
  Nucleic Acids Res 2011, PLoS One 2012, 2013, KDD'07
- **Drug-target interactions (Polypharmacology)**
  PLoS One 2011, Drug Discov Today 2013, Brief Bioinform 2014
- **Modulatory proteolysis**
  Mol Cell Proteom 2016, Genome Informatics 2009
  (We also developed a database http://calpain.org)
- **Genomic repeats**
  Discrete Appl Math 2013, 2016, AAAI 2020
- **Genetic variations in cancer cells**
  Brief Bioinform 2014
- **Mediator complex and transcription regulation**
  Nat Commun 2015, 2020 (w/ Prof. Hatakeyama)
- **Genomic copy number variations for neurodegenerative diseases**
  Mol Brain 2017 (w/ Prof. Sasaki)
- **Cell competitions and cancer cells**
  Cell Reports 2018, Sci Rep 2015 (w/ Prof. Fujita)

Pathway Commons

Access and discover data integrated from public pathway and interactions databases.

Molecules have a combinatorial aspect





c&en

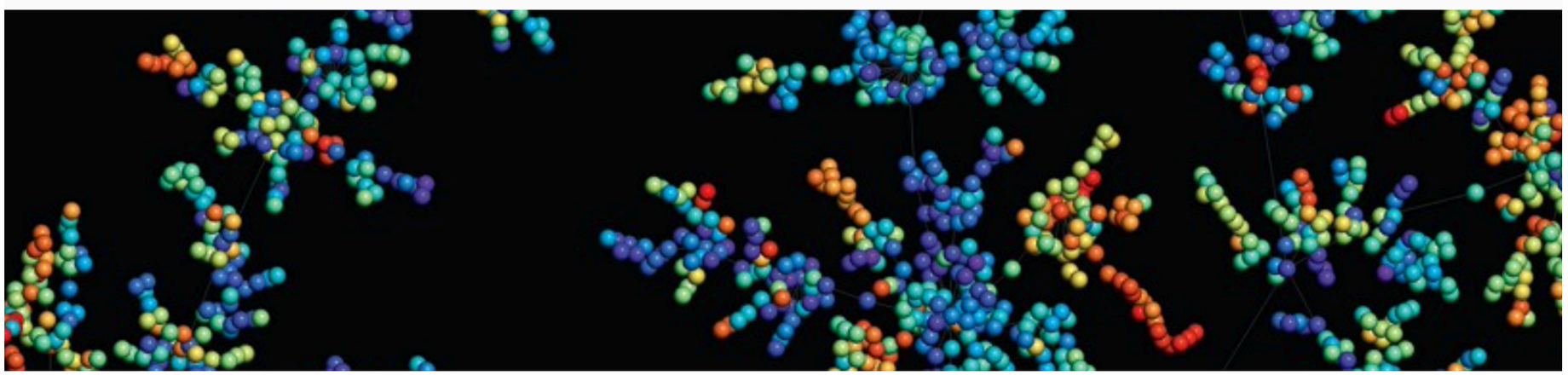
COMPUTATIONAL CHEMISTRY

Exploring chemical space: Can AI take us where no human has gone before?

Artificial intelligence is helping us find novel, useful molecules. For the field to really take off, though, these tools will need to be accessible to the wider chemistry community

by ***Sam Lemonick***

April 6, 2020 | A version of this story appeared in **Volume 98, Issue 13**



BY THE NUMBERS

10^{180}

An upper estimate of the number of possible molecules

10^{80}

Estimated number of atoms in the universe

10^{60}

An estimate of the number of possible small organic molecules

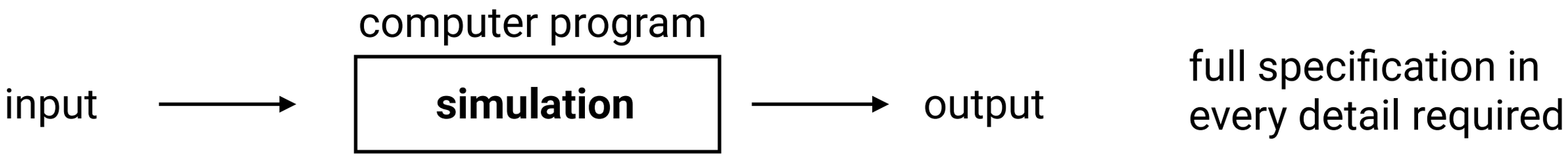
10^{8}

The number of organic and inorganic substances in the CAS database

https://cen.acs.org/physical-chemistry/computational-chemistry/Exploring-chemical-space-AI-take/98/i13

ML: A new way for (lazy) programming

deductive (rationalism)



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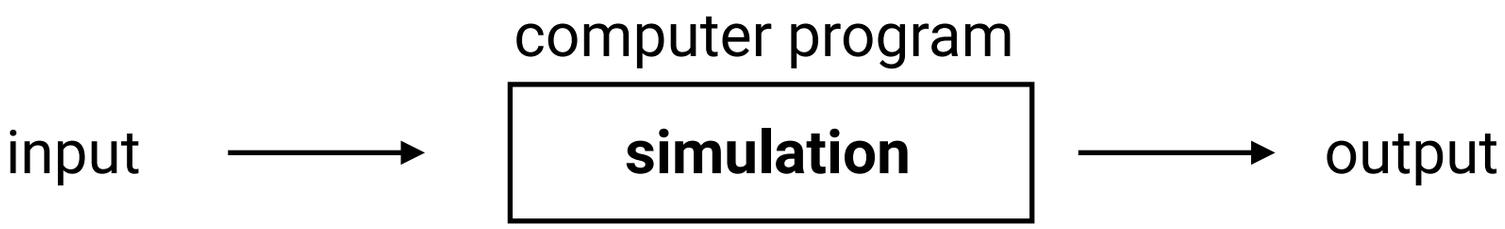

full specification in every detail required

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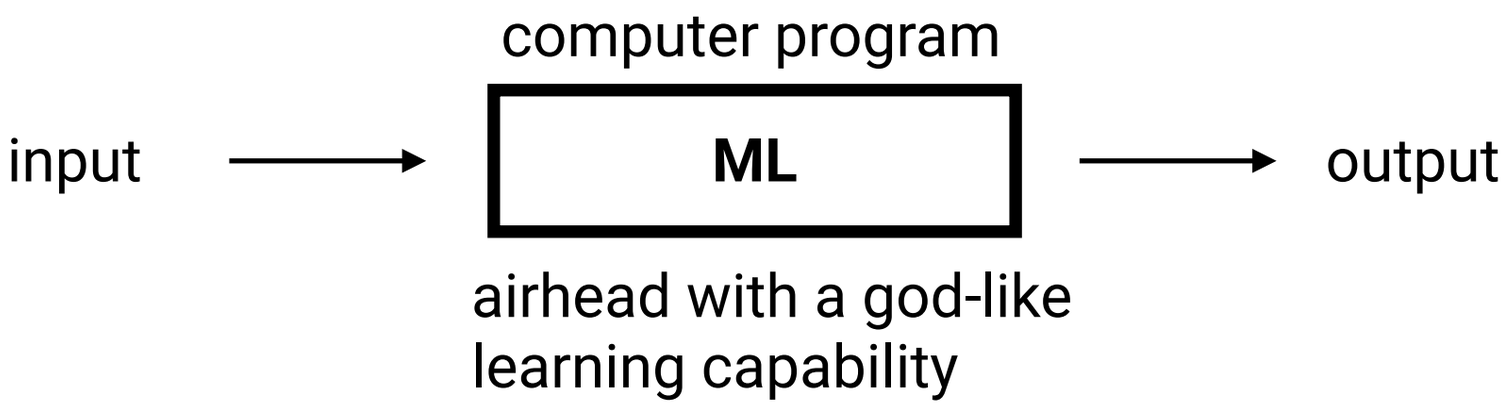
inductive (empiricism)

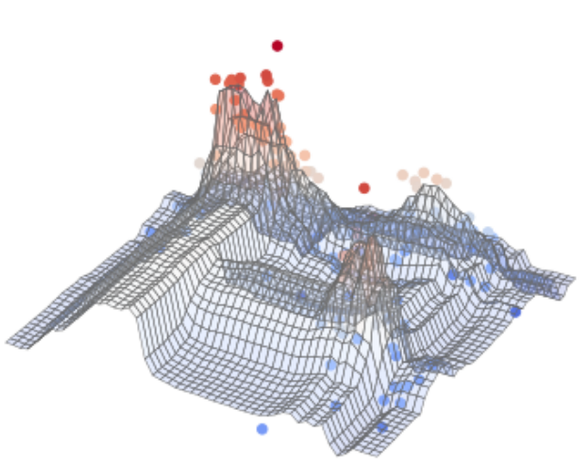


airhead with a god-like learning capability

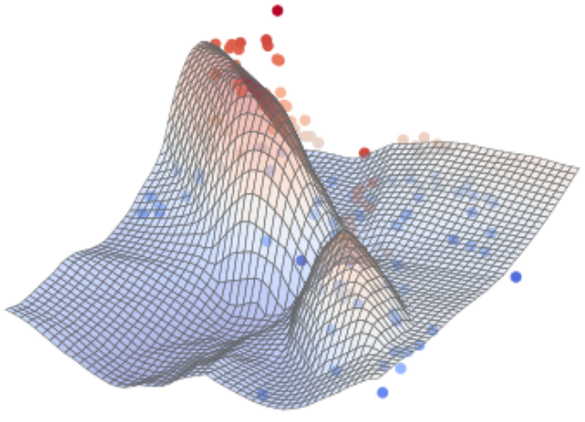
give up explicit model

instead, grab a tunable model, and show it many input-output instances

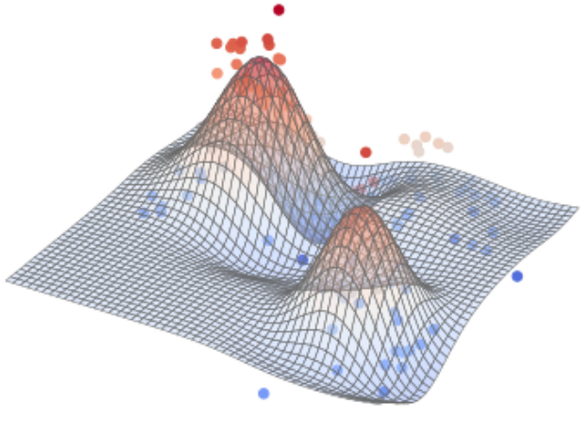
All about fitting a **very-flexible** function to **finite** points in **high-dimensional** space.



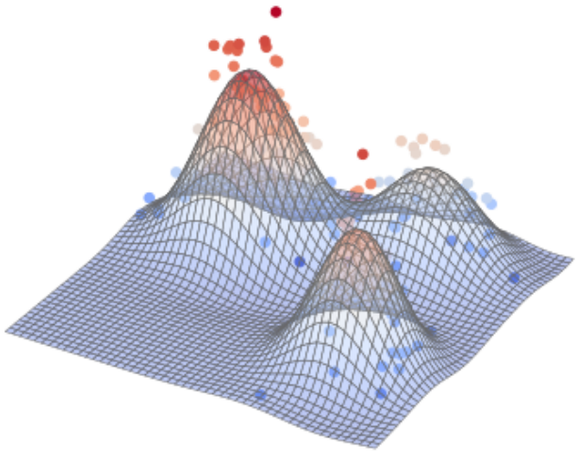
Random Forest



Neural Networks



SVR

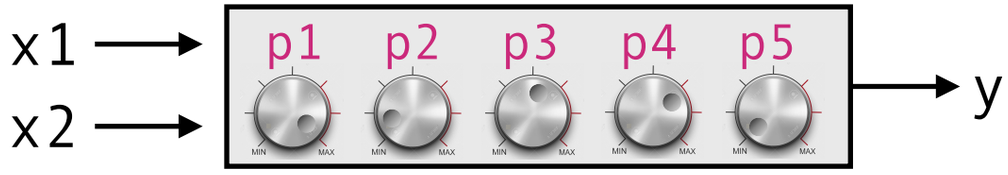


Kernel Ridge

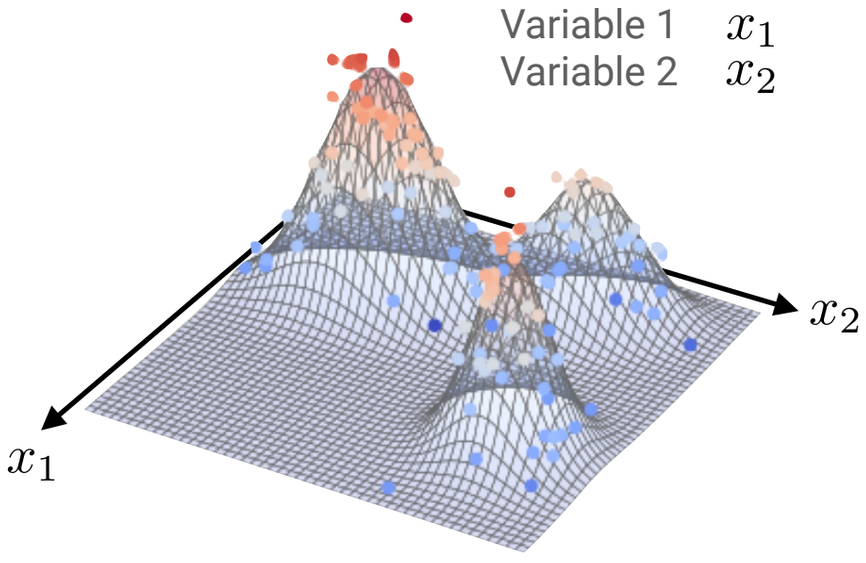
ML: A new way for (lazy) programming

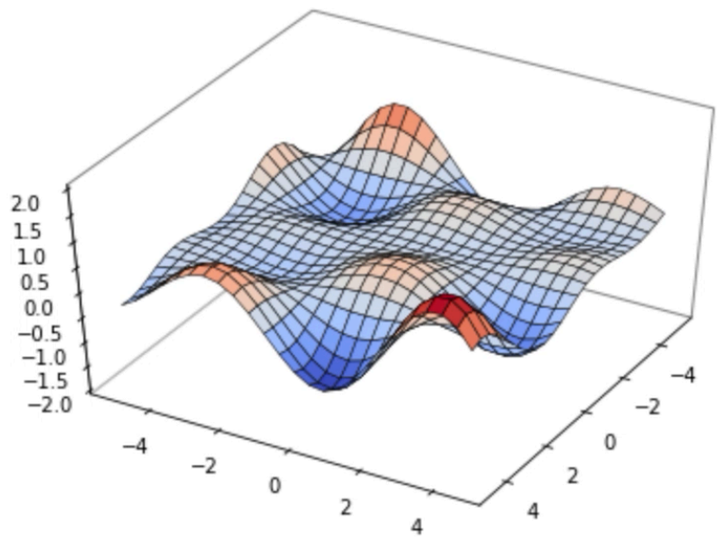
All about statistical and algorithmic techniques for
surface-model fitting to data points by adjusting model parameters.

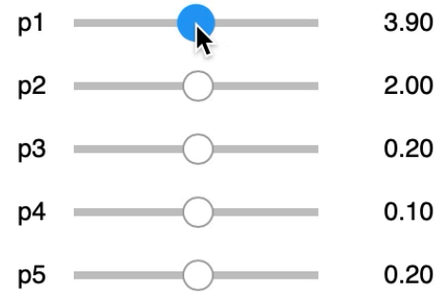
ML = Tweak these parameter values to
best fit a surface model to the given points.



5 params

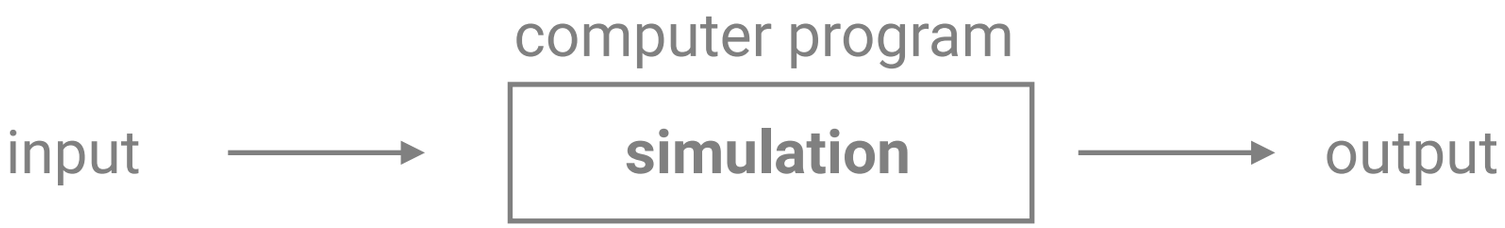






A modern aspect of ML

deductive (rationalism)



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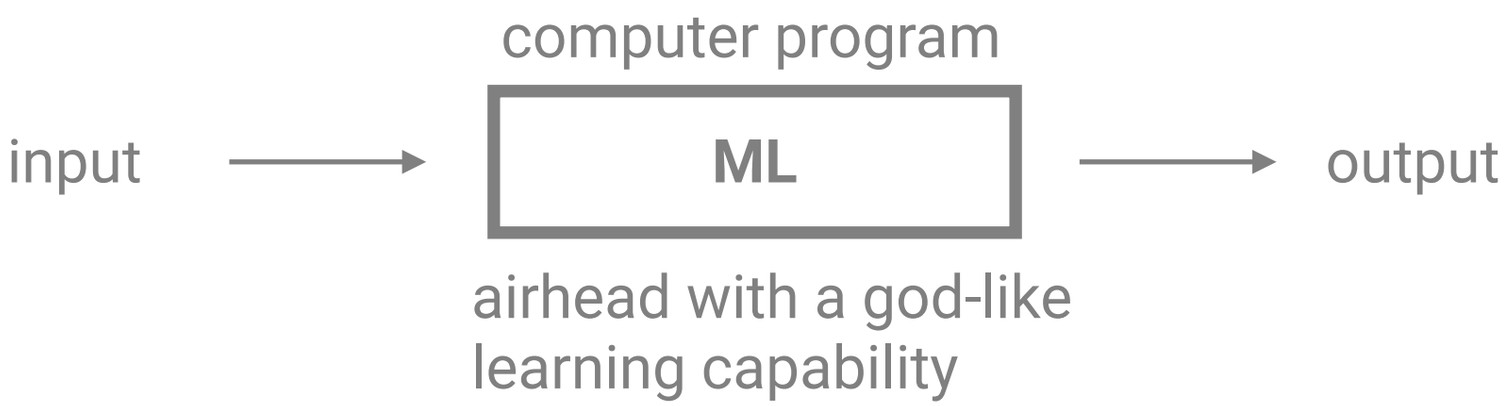


give up explicit model

instead, grab a tunable model, and show it many input-output instances

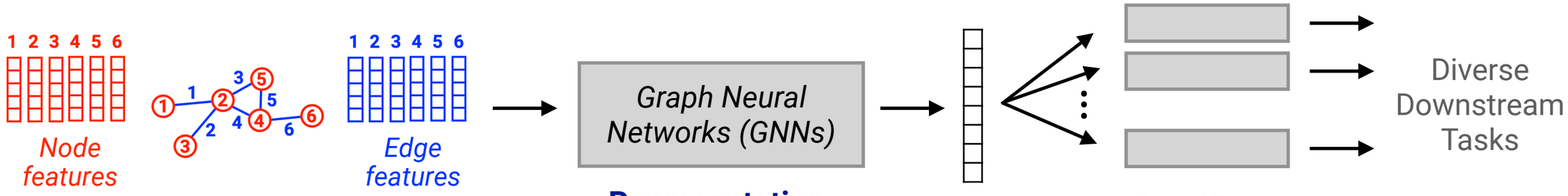
All about fitting a **very-flexible** function to **finite** points in **high-dimensional** space.

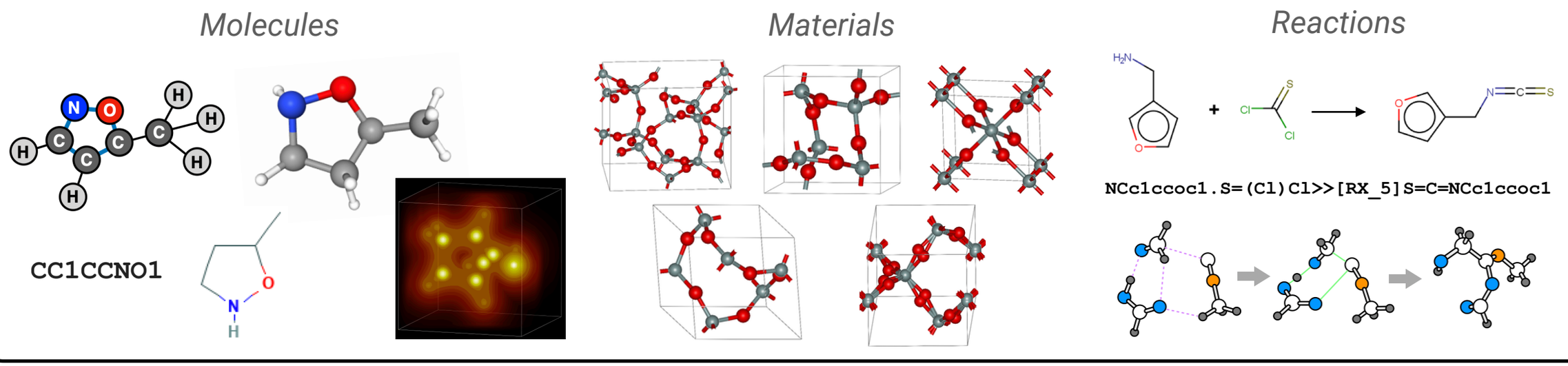
ResNet50: 26 million params
ResNet101: 45 million params
EfficientNet-B7: 66 million params
VGG19: 144 million params

12-layer, 12-heads BERT: 110 million params
24-layer, 16-heads BERT: 336 million params
GPT-2 XL: 1558 million params
GPT-3: 175 billion params

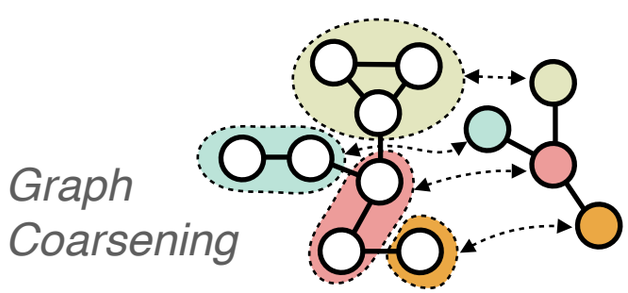
Modern ML: Can we imagine what would happen if we try to fit a function having **175 billion** parameters to **100 million** data points in **10 thousand** dimension??

This Talk: ML for Molecular Graphs

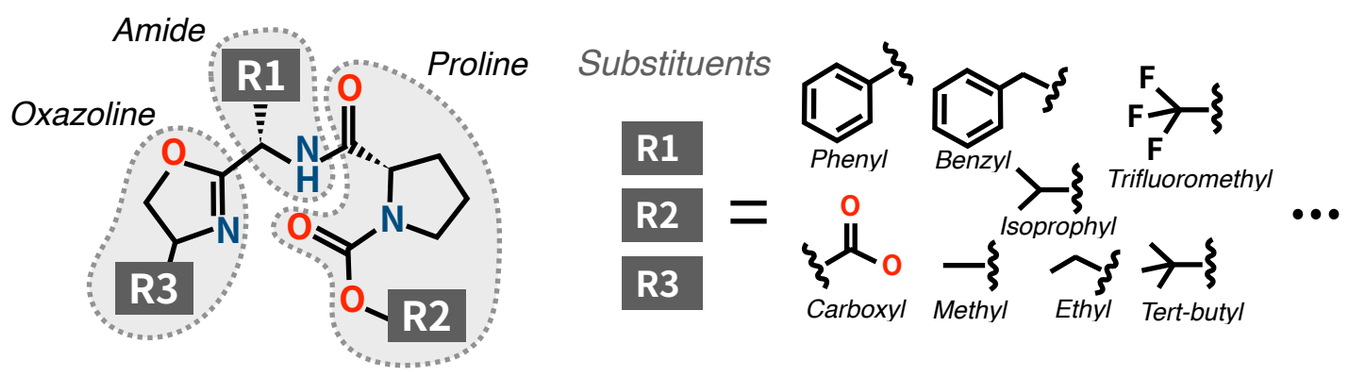




Combinatorial aspects



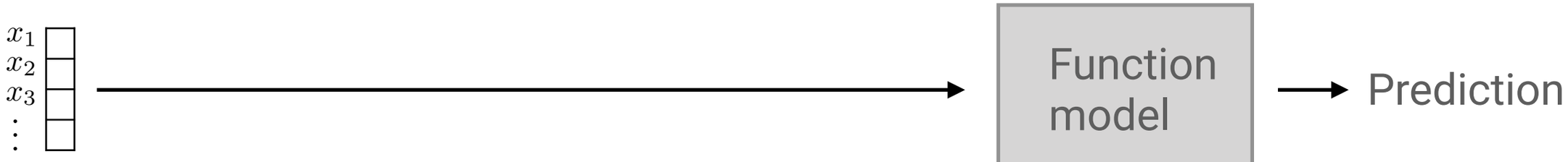
Modular Hierarchy

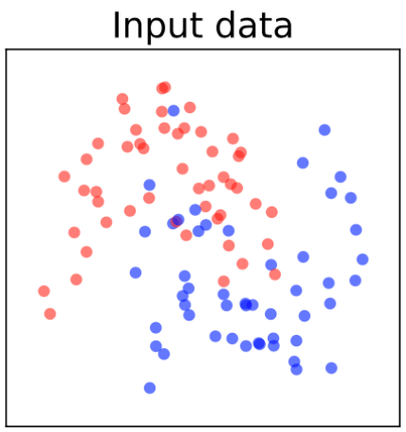


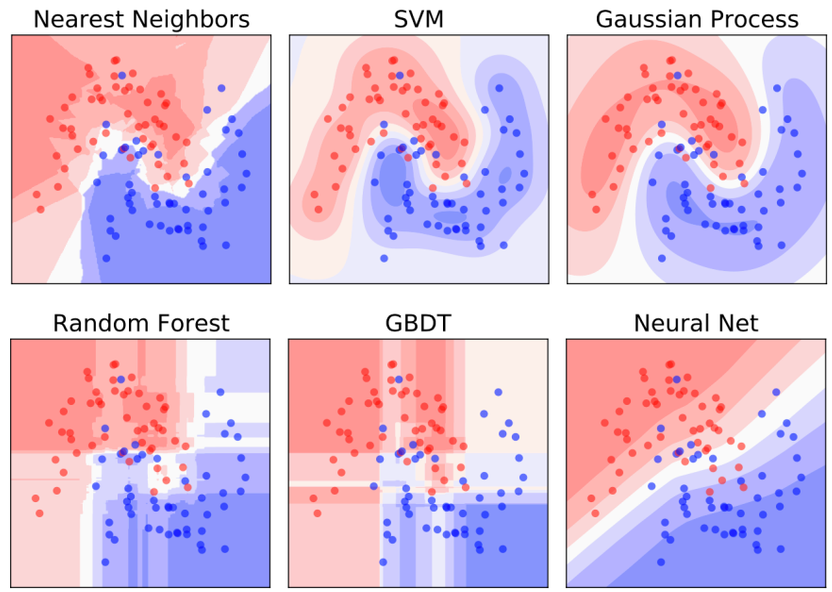
Compositionality

Representation Learning

Use **some inductive biases** to constrain/regularize the model space.







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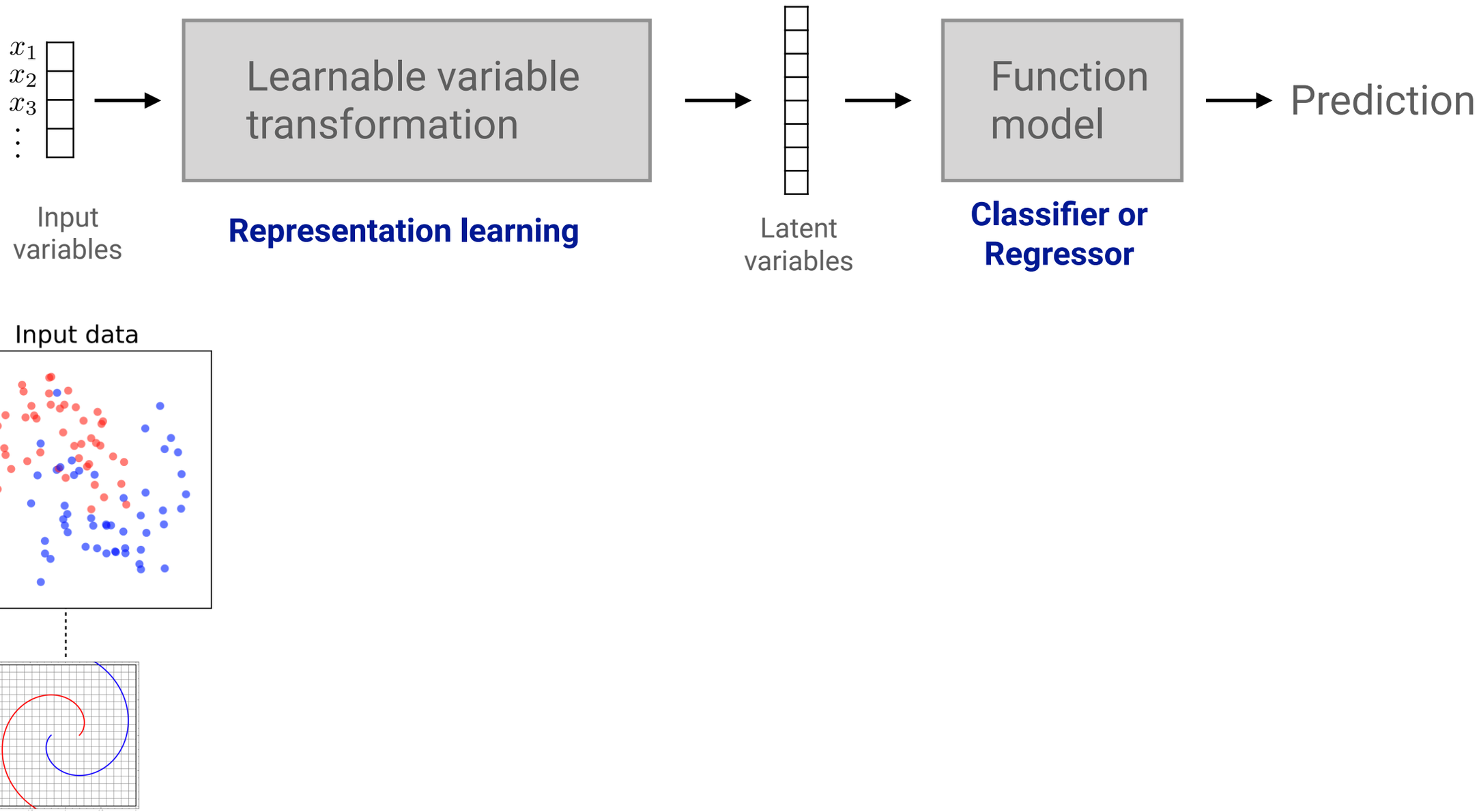

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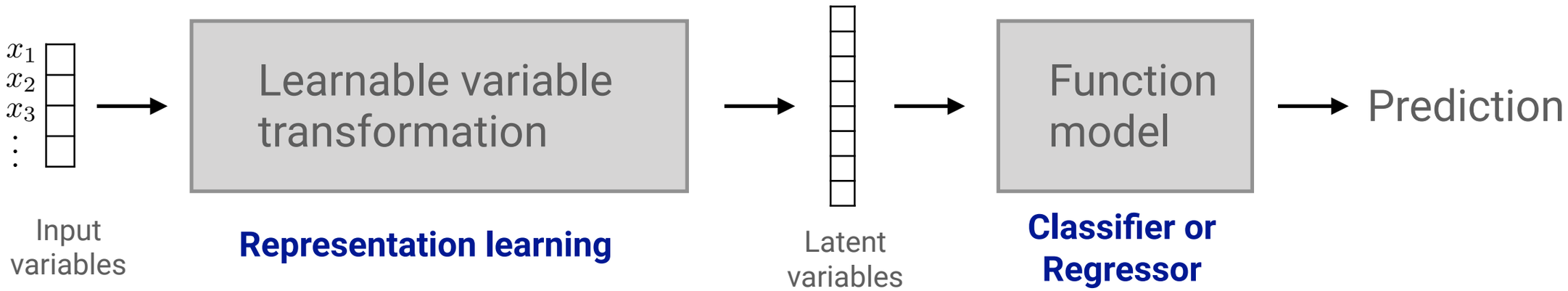

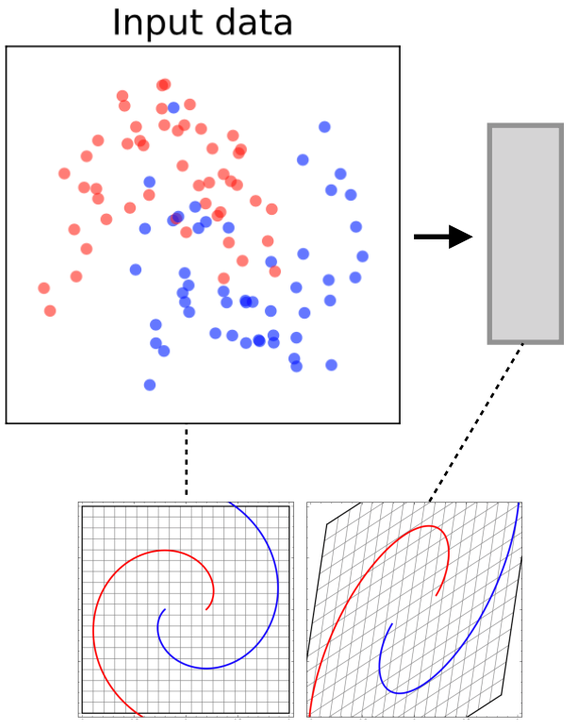

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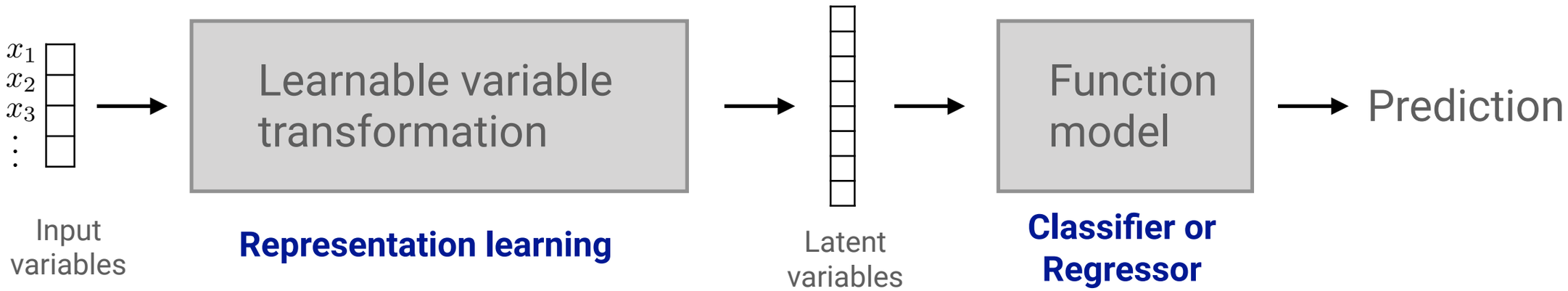

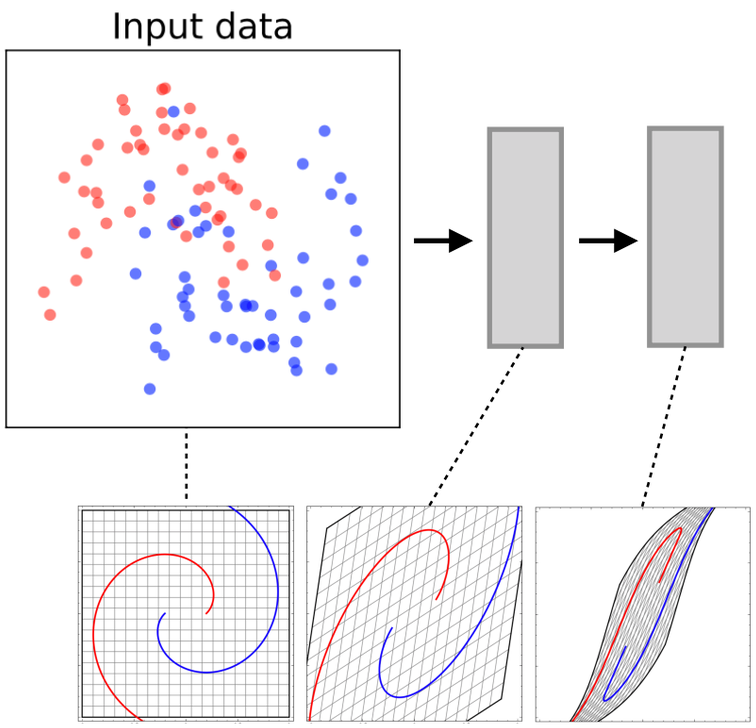

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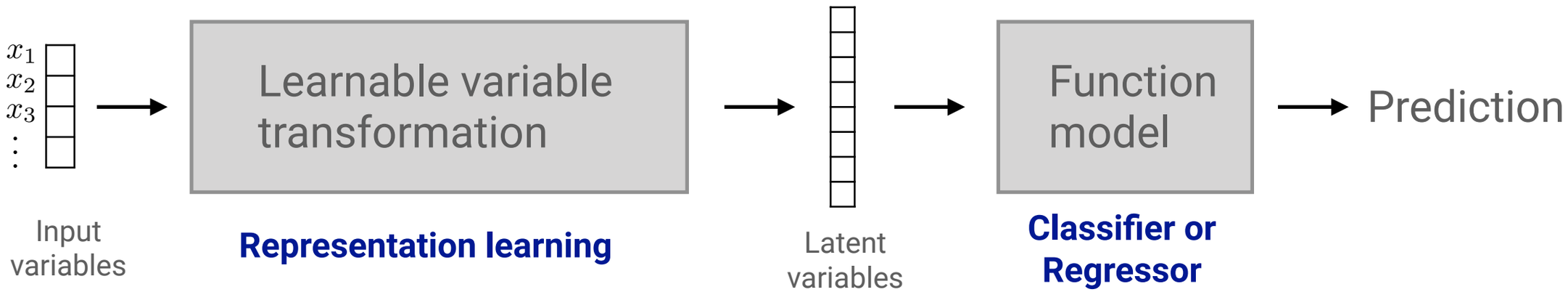

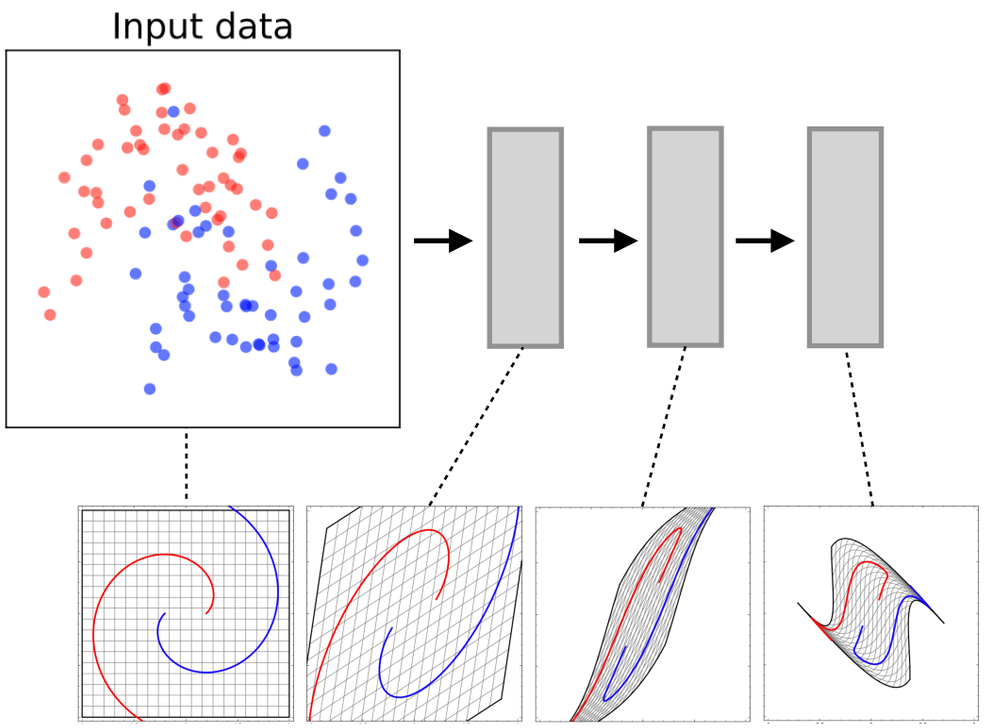

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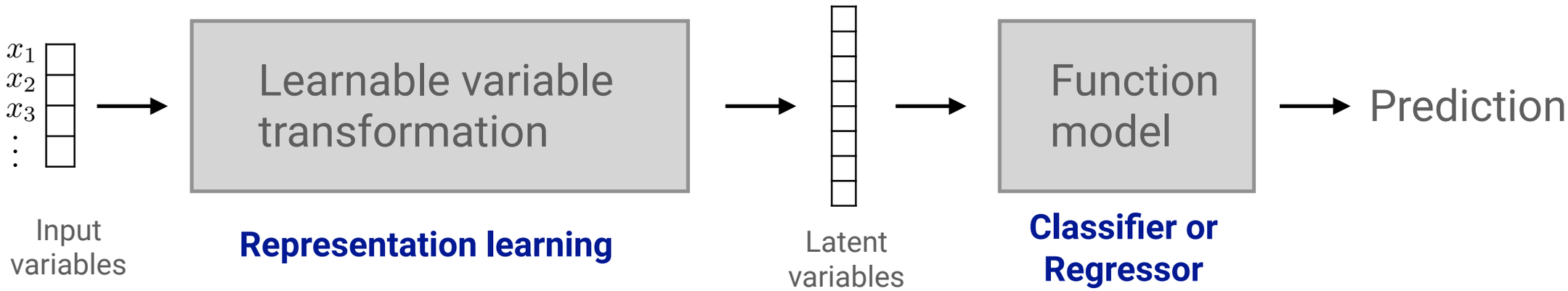
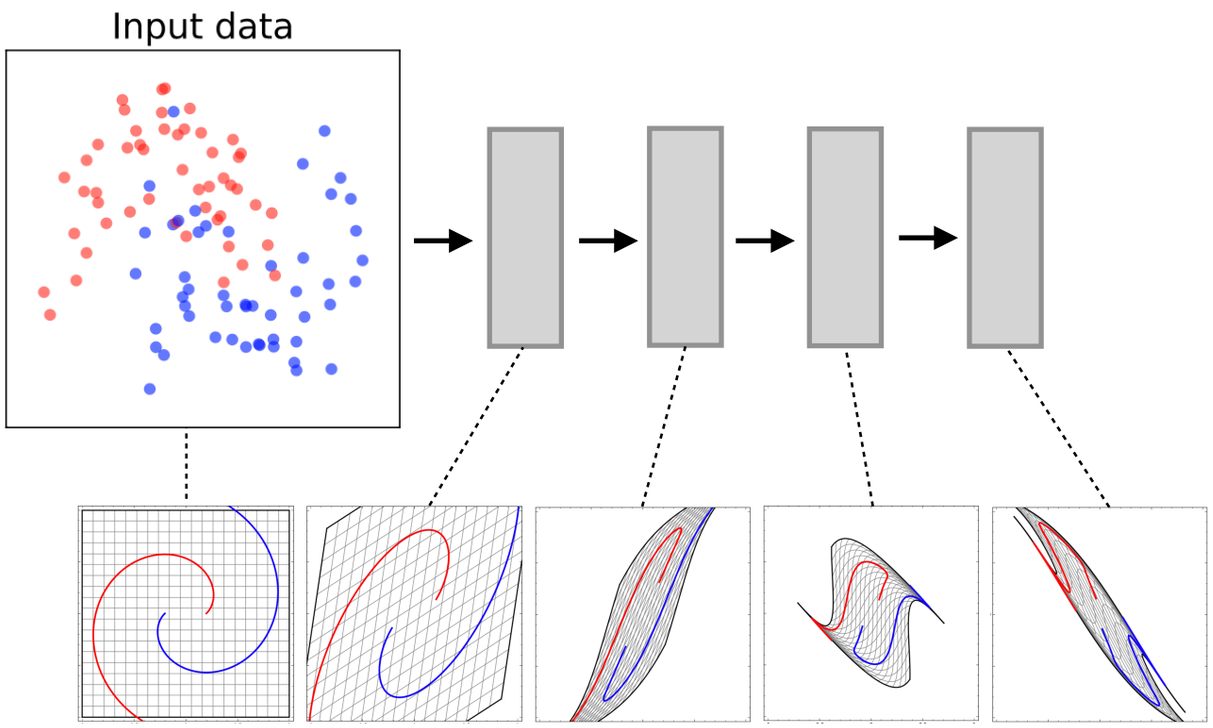
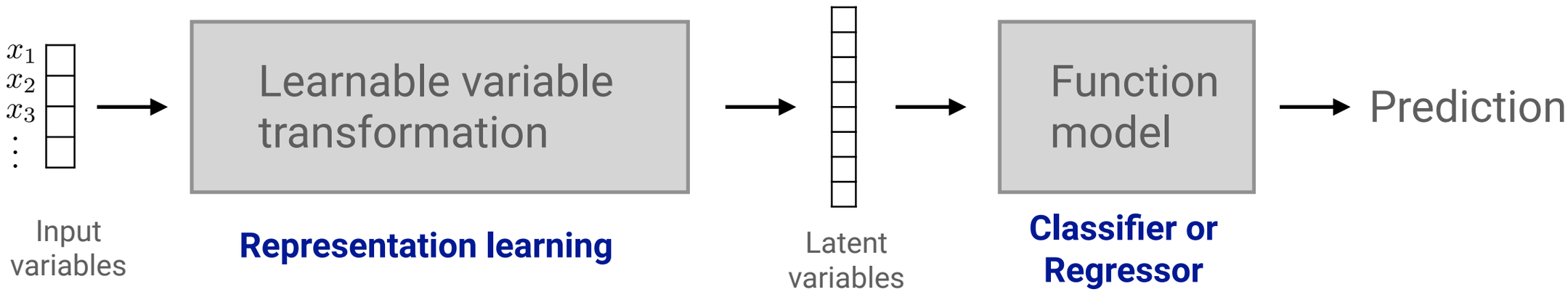
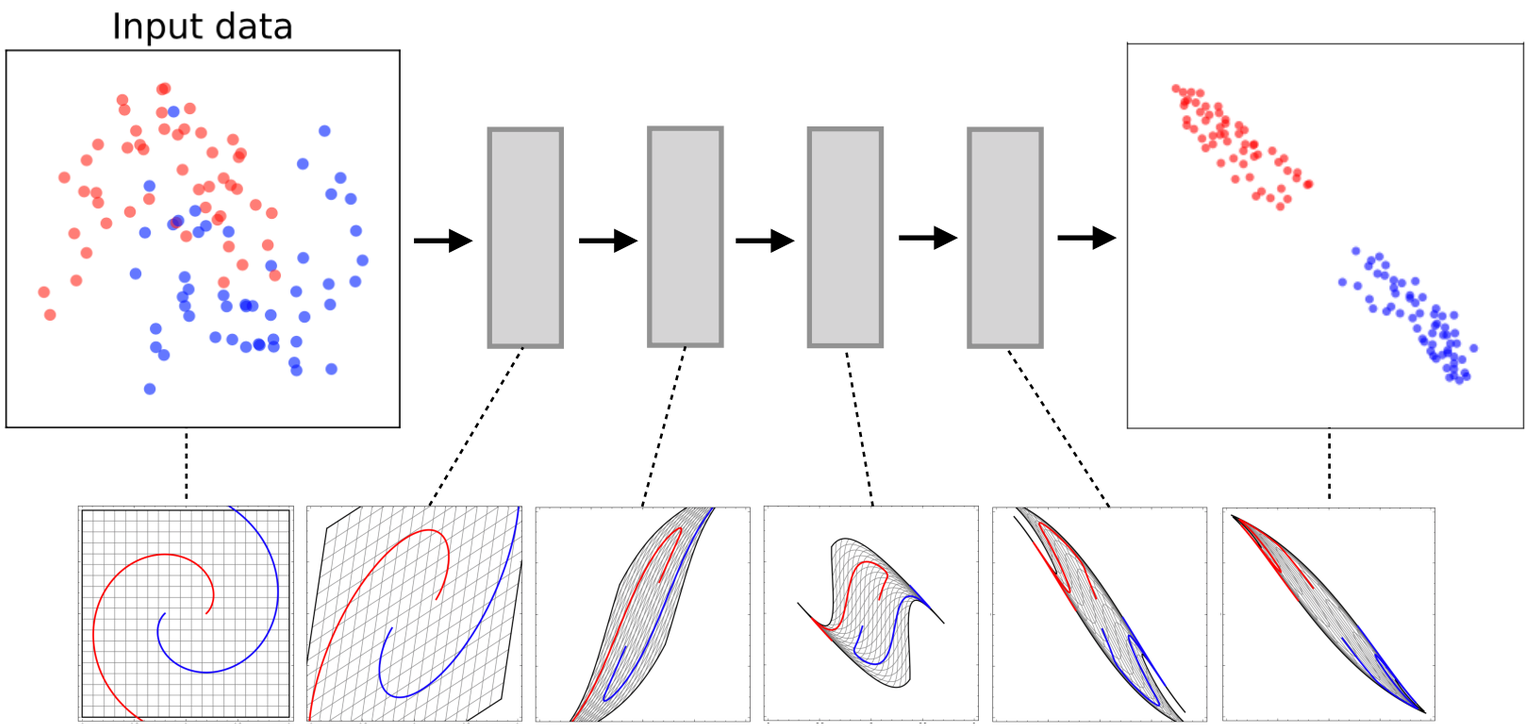




Representation Learning

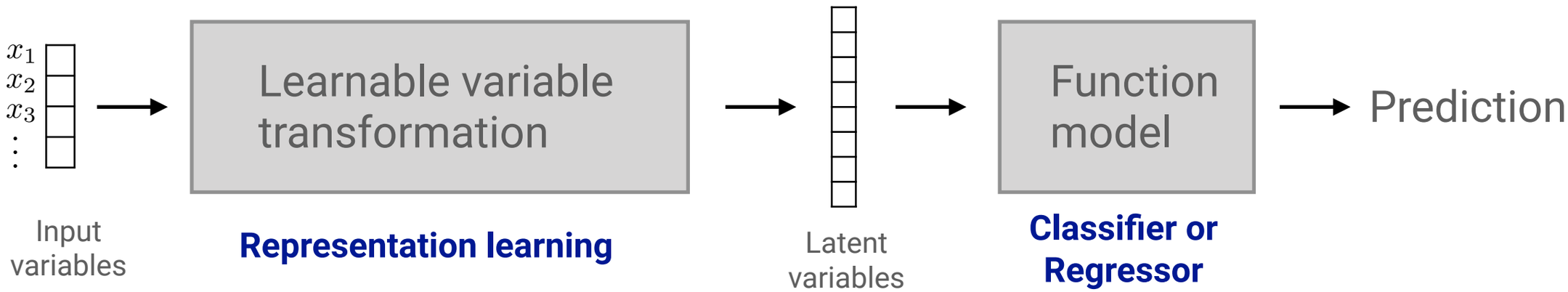
Use **some inductive biases** to constrain/regularize the model space.

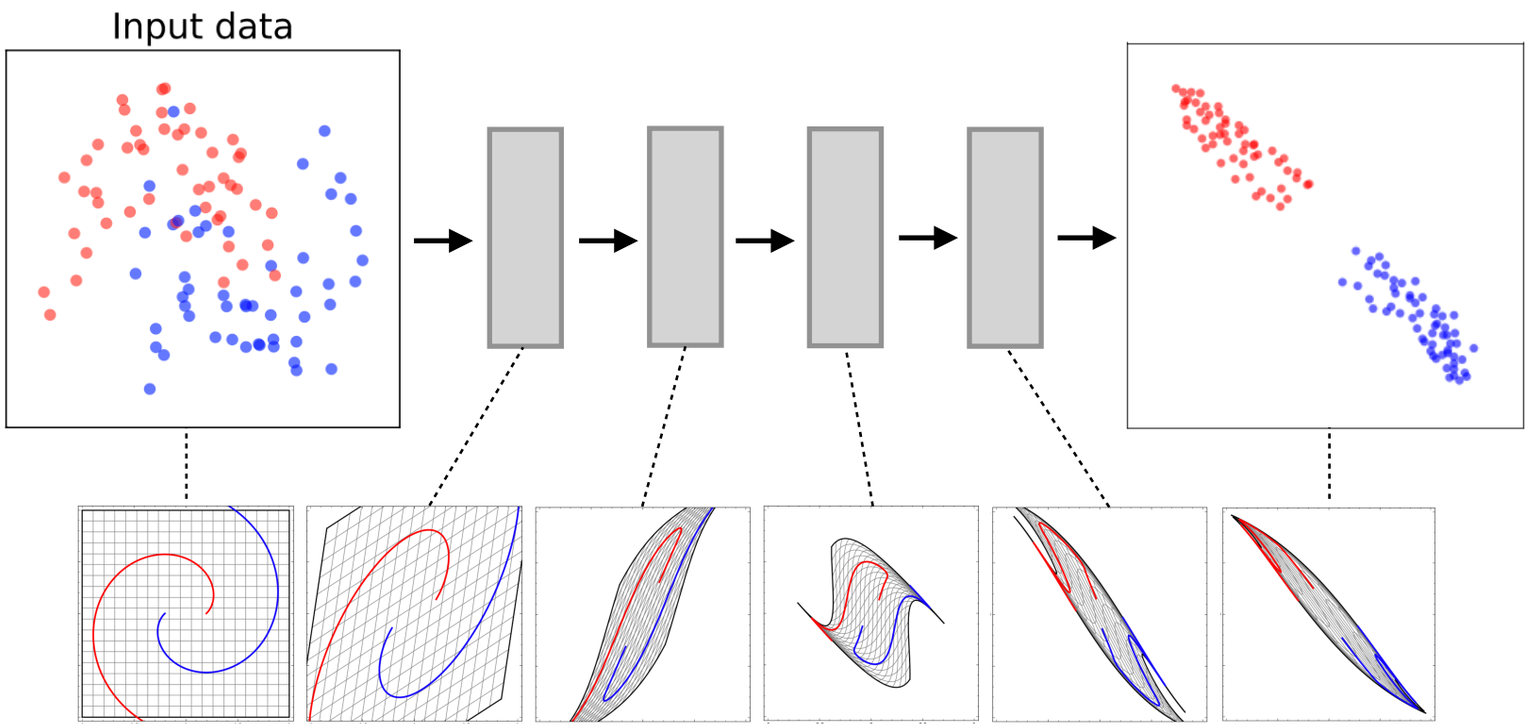


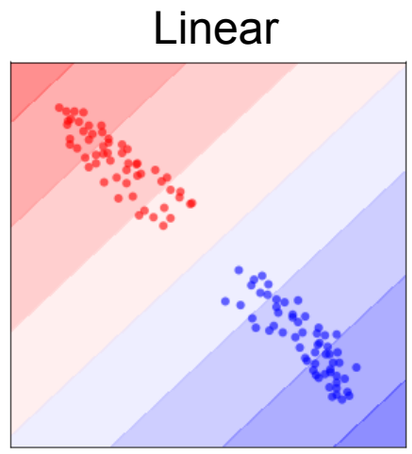


Representation Learning

Use **some inductive biases** to constrain/regularize the model space.



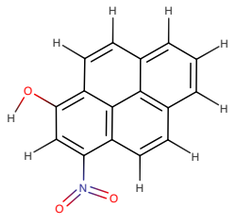




Simple model is enough when we have good features.

Use Case 1: Virtual Screening (QSAR/QSPR)

- **Mutagenic potency**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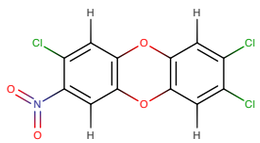
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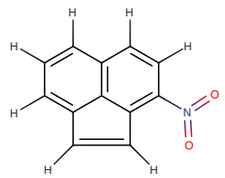
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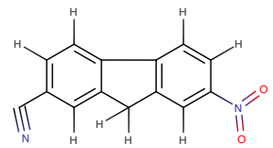
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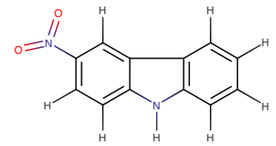
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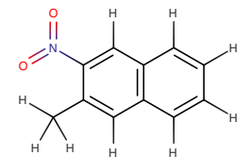
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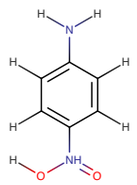
- **Carcinogenic potency**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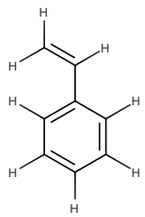
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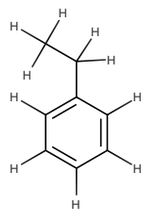
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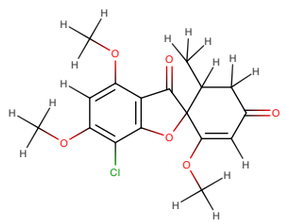
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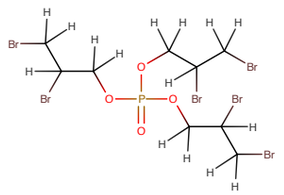
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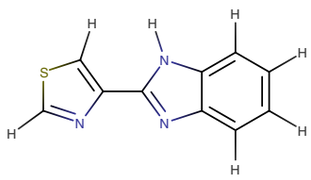
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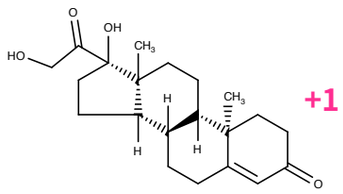
- **Endocrine disruption**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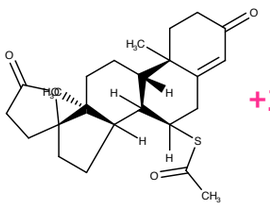
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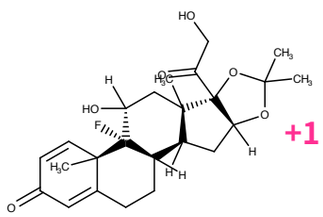
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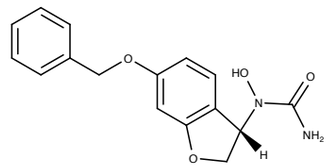
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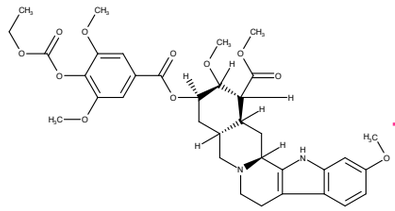
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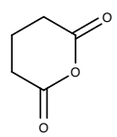
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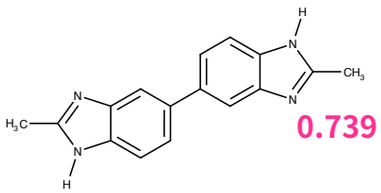
- **Growth inhibition**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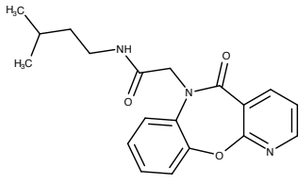
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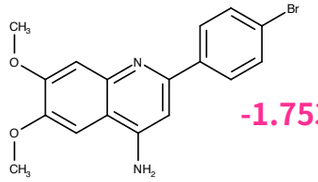
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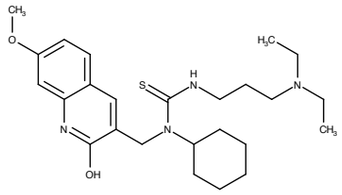
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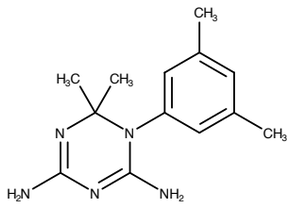
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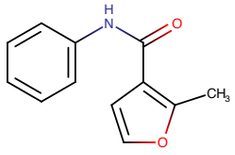
- **Aqueous solubility**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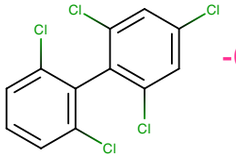
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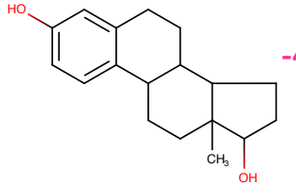
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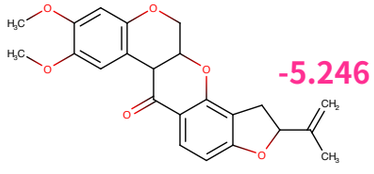
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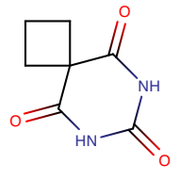
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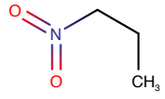
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Use Case 1: Virtual Screening (QSAR/QSPR)

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BIOASSAY RECORD

NCI human tumor cell line growth inhibition assay. Data for the NCI-H23 Non-Small Cell Lung cell line

Cite Download

PubChem AID	1
Source	DTP/NCI
External ID	NCI human tumor cell line growth inhibition assay. Data for the NCI-H23 Non-Small Cell Lung cell line
BioAssay Type	Confirmatory
Tested Substances	All (53,554) Active (3,025) Inactive (50,655) Data Table
Tested Compounds	All (51,583) Active (2,814) Inactive (48,922)
Version	2.1 Revision History
Status	Live
Dates	Modify 2021-07-12 Deposit 2004-08-15

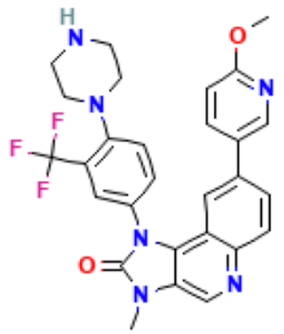
Please note that the bioassay record (AID 1) is presented as provided to PubChem by the source(depositor). When possible, links to additional information have been provided by PubChem.

CONTENTS

Title and Summary
1 Description
2 Comment
3 Result Definitions
4 Data Table
5 Entrez Crosslinks
6 Identity
7 BioAssay Annotations
8 Information Sources

Use Case 1: Virtual Screening (QSAR/QSPR)

input



CID 11978790

ML

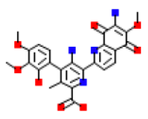
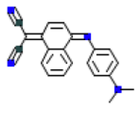
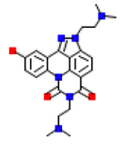
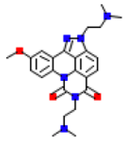
output

activity: “Active”
LogGI50: -7.8811

GI50: concentration required for 50% inhibition of growth

Tested Compounds All (51,583) Active (2,814) Inactive (48,922)

SORT BY Activity

Tested Substance							
Structure	CID	SID	Activity	Score	LogGI50_M	LogGI50_u	LogGI50_V
	5298	121832	Active	67	-8		
	363173	493713	Active	43	-6.5871		
	399631	530868	Active	51	-7.0678		
	399630	530867	Active	60	-7.617		

SORT BY Activity

Tested Substance							
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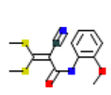
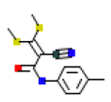
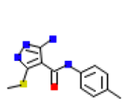
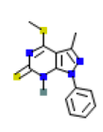
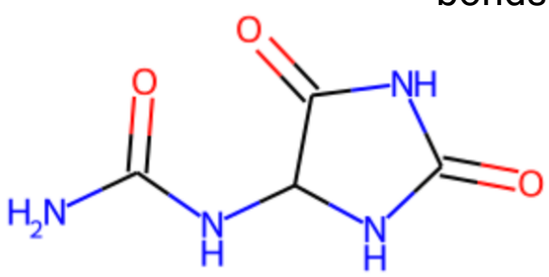
	390324	521601	Inactive	0	-4		
	390311	521588	Inactive	0	-4		
	390312	521589	Inactive	4	-4.214		
	135489876	521590	Inactive	13	-4.7552		

Use Case 1: Virtual Screening (QSAR/QSPR)

Input representation (molecular graph)

atoms → nodes
bonds → edges



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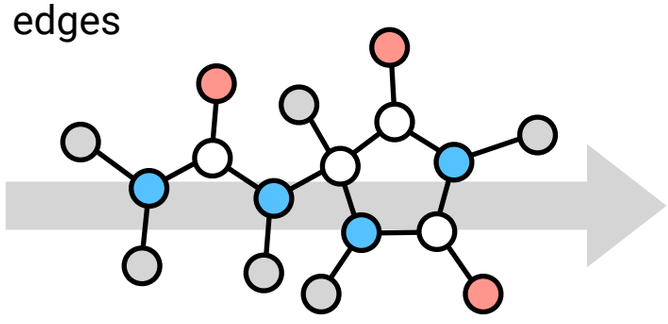
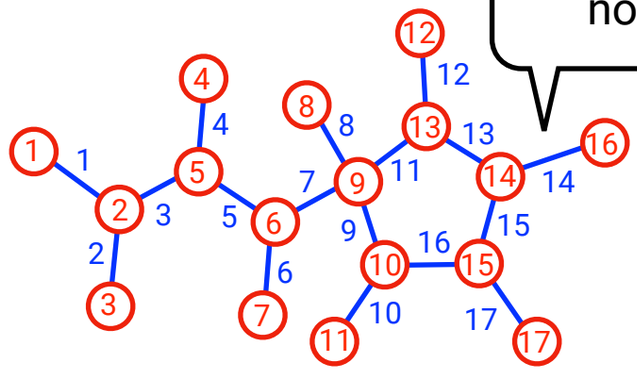


explicit Hs



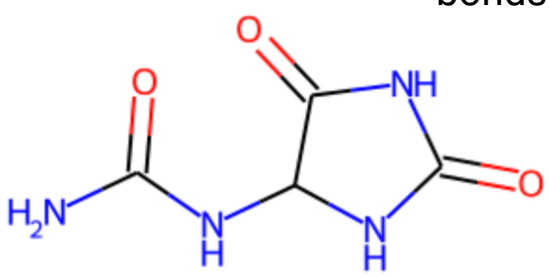
! Any permutation of this numbering should not change the results.

1. *permutation equivariance*
2. *permutation invariance*

Use Case 1: Virtual Screening (QSAR/QSPR)

Input representation (molecular graph)

atoms → nodes
bonds → edges



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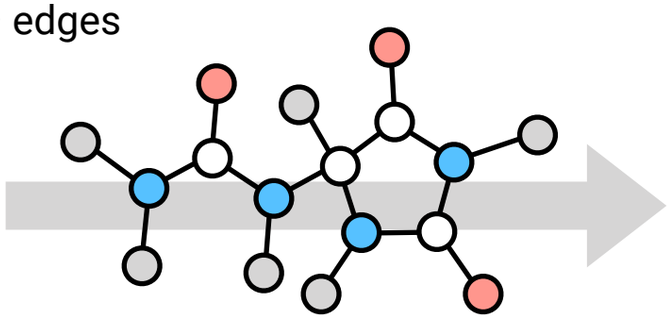
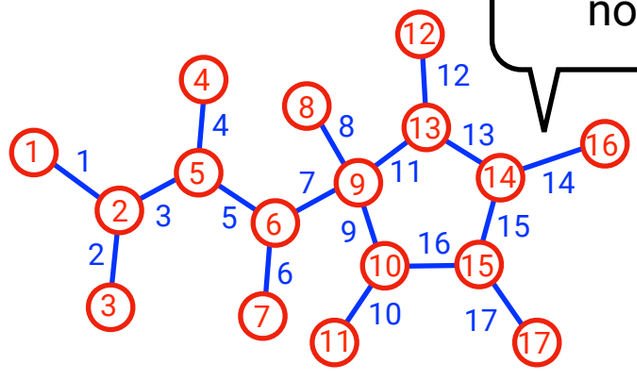


explicit Hs



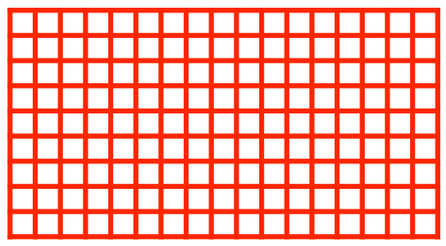
! Any permutation of this numbering should not change the results.

1. *permutation equivariance*
2. *permutation invariance*

e.g. Features for ChemProp (Yang et al, 2019)

node(atom) features

17



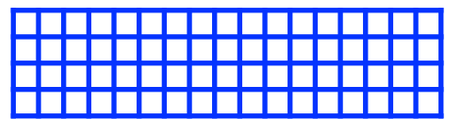
133

133 features

- atomic_num (one-hot, 101)
- total_degree (one-hot, 7)
- formal_charge (one-hot, 6)
- chiral_tag (one-hot, 5)
- num_Hs (one-hot, 6)
- hybridization (one-hot, 6)
- is_aromatic (binary, 1)
- atomic_mass (real, 1)

edge(bond) features

17



14

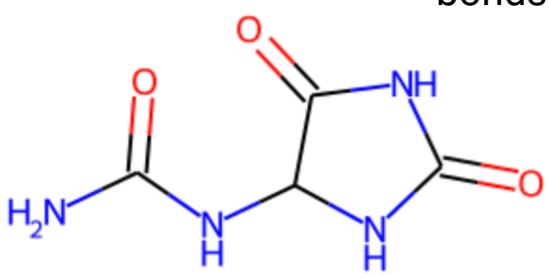
14 features

- no_bond (binary, 1)
- is_single (binary, 1)
- is_double (binary, 1)
- is_triple (binary, 1)
- is_aromatic (binary, 1)
- is_connjugated (binary, 1)
- is_in_ring (binary, 1)
- stereo (one-hot, 7)

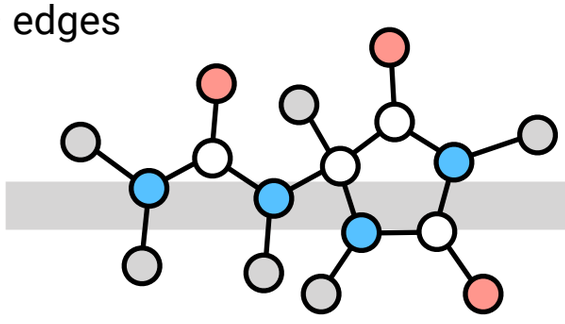
Use Case 1: Virtual Screening (QSAR/QSPR)

Input representation (molecular graph)

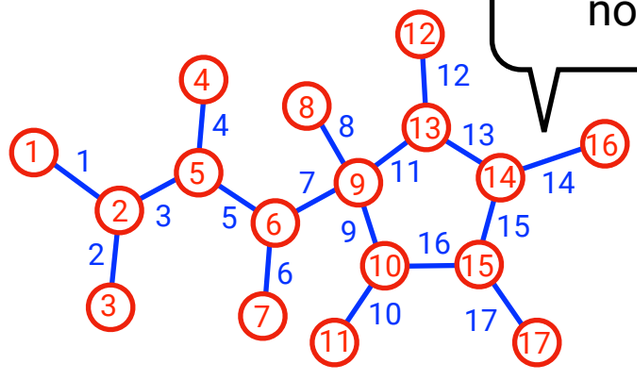
atoms → nodes
bonds → edges



CID 204



explicit Hs



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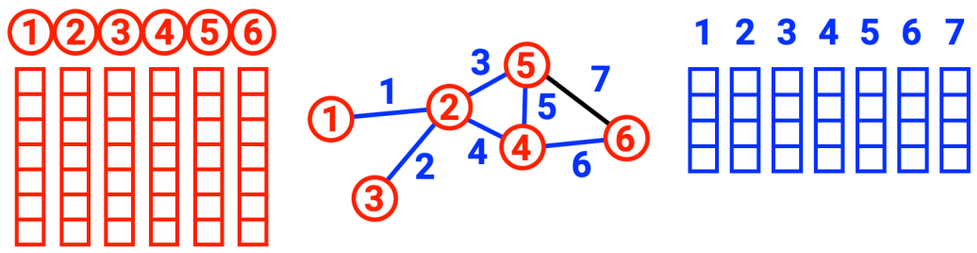
1. *permutation equivariance*
2. *permutation invariance*

e.g. Features for ChemProp (Yang et al, 2019)

Molecular Graph

atom features — topology — bond features



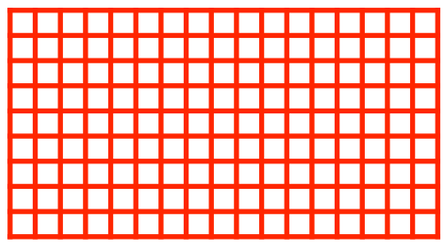
read out

graph-level output

- sum, mean or max
- attentive pooling

node(atom) features

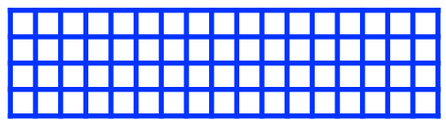
17



133

edge(bond) features

17



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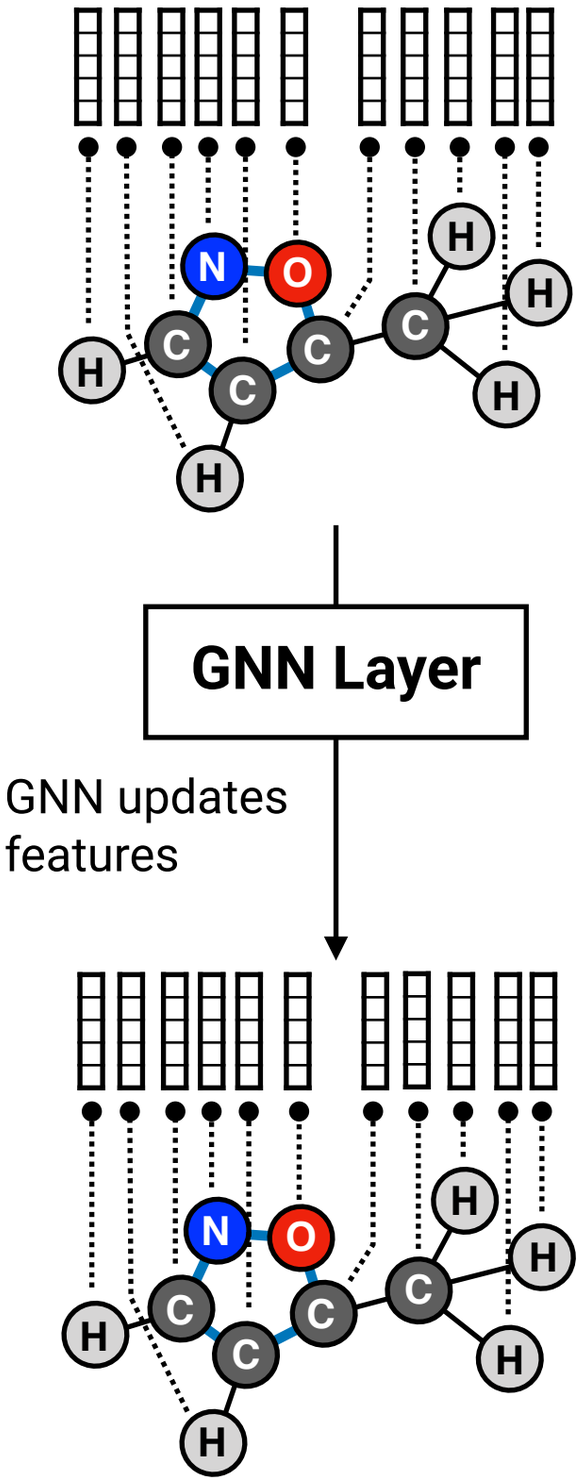
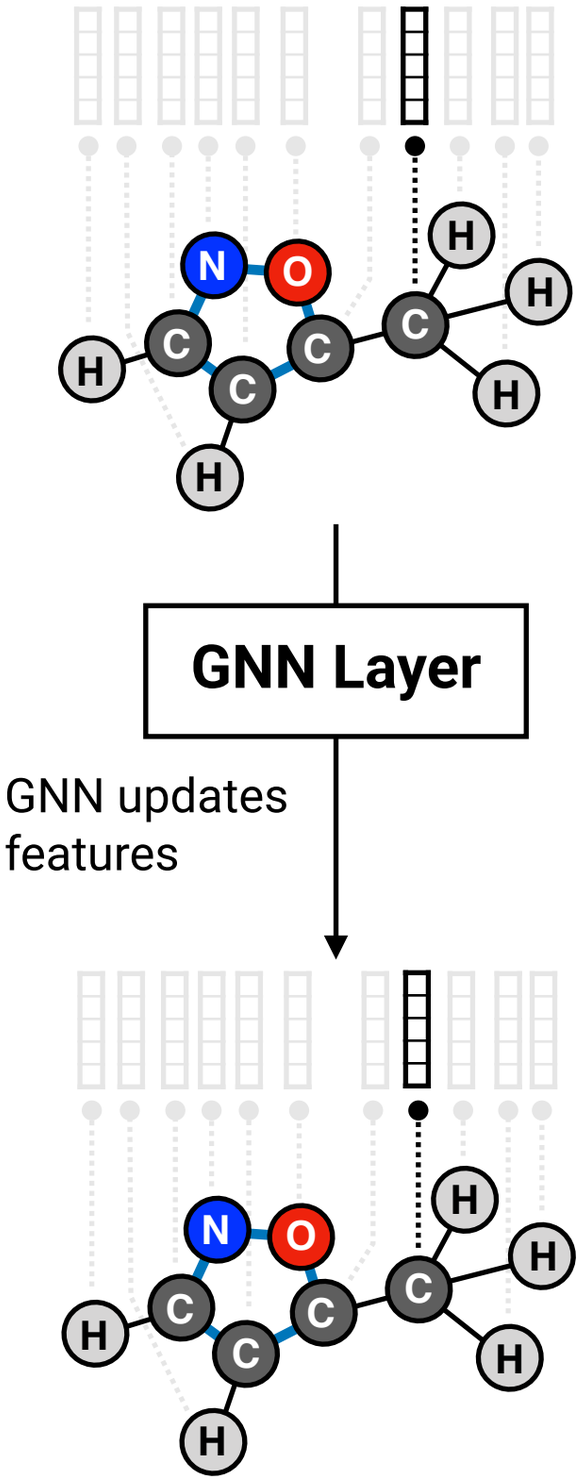
- is_in_ring (binary, 1)
- stereo (one-hot, 7)

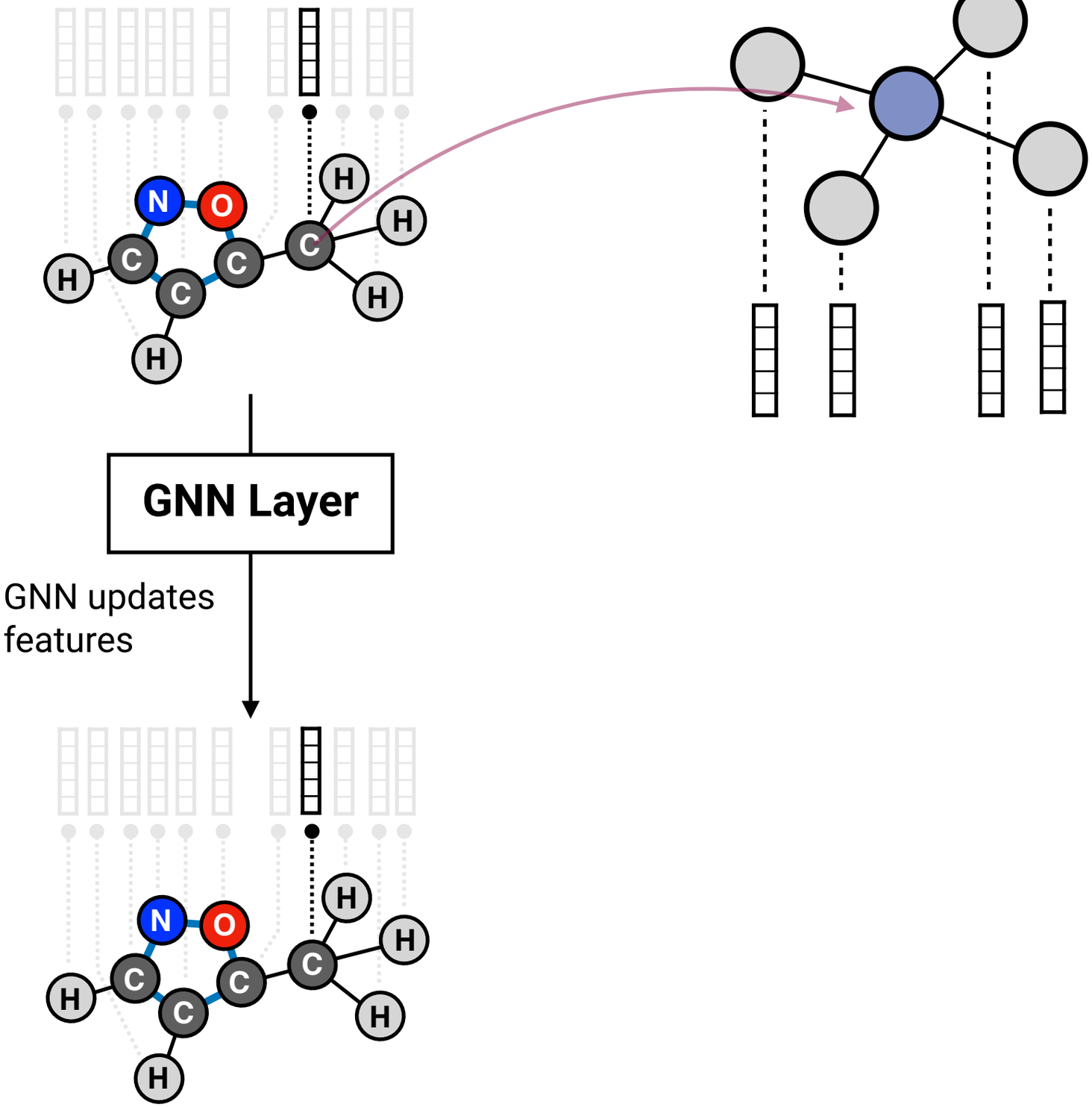
Graph Neural Networks (GNNs)



Graph Neural Networks (GNNs)



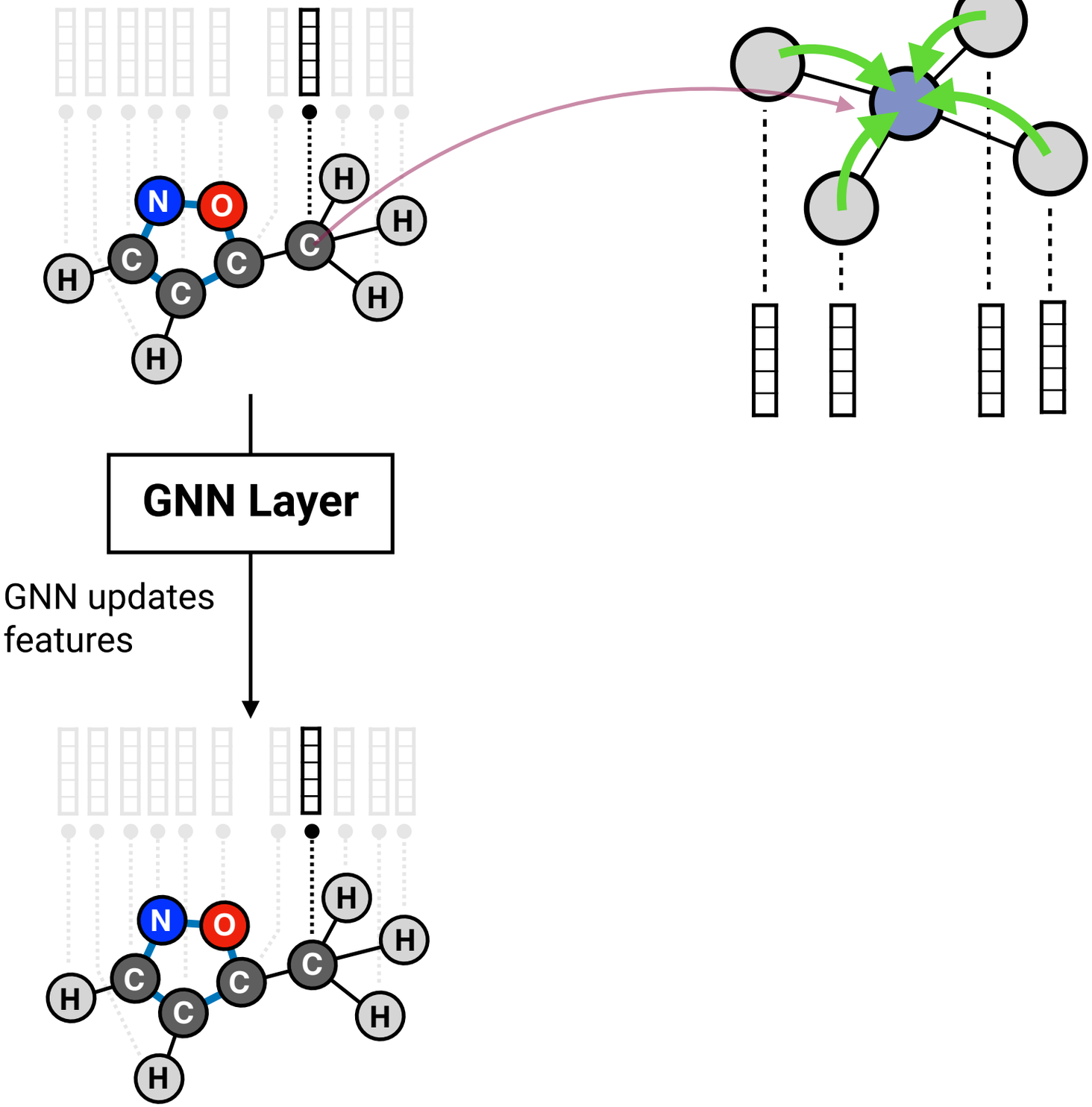
Graph Neural Networks (GNNs)



$\boldsymbol{h}_i$ atom features

$\boldsymbol{e}_{ij}$ bond features

Graph Neural Networks (GNNs)



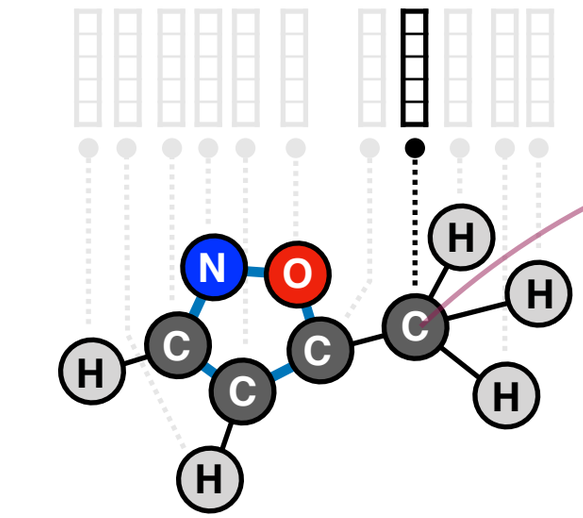
$\boldsymbol{h}_i$ atom features

$\boldsymbol{e}_{ij}$ bond features

Update by "Message Passing"

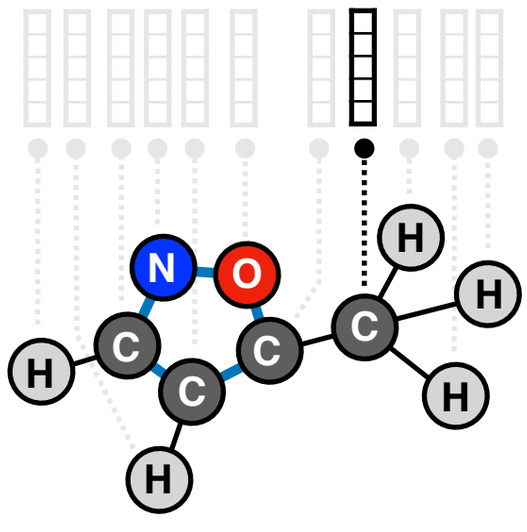
$$\boldsymbol{h}_i \leftarrow \psi\left(\boldsymbol{h}_i, \bigoplus_{j \in \mathcal{N}_i} \phi(\boldsymbol{h}_i, \boldsymbol{h}_j, \boldsymbol{e}_{ij})\right)$$

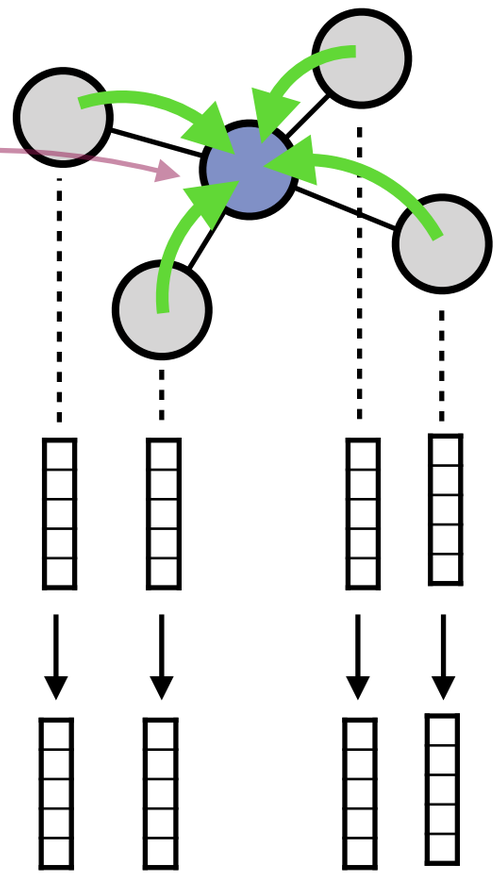
Graph Neural Networks (GNNs)



GNN Layer

GNN updates features





❶ *Message*

Permutation equivariant operations

- nn.Linear

$\boldsymbol{h}_i$ atom features

$\boldsymbol{e}_{ij}$ bond features

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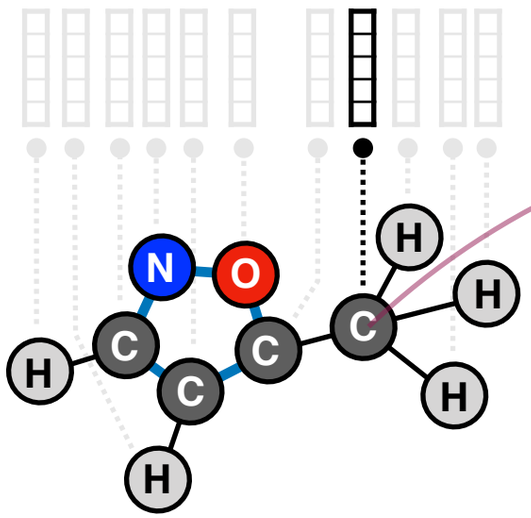
❶

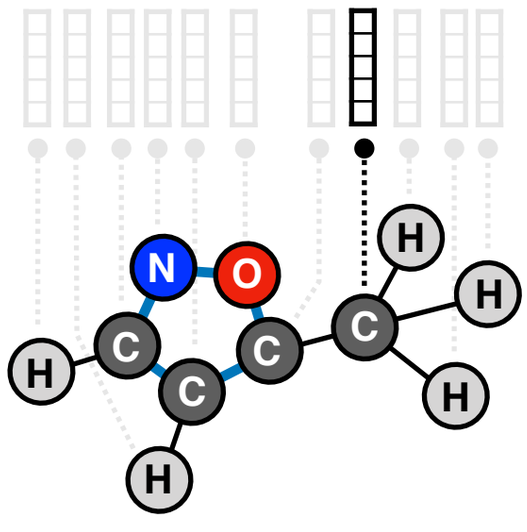
Bond features can be used (typically in ❶)

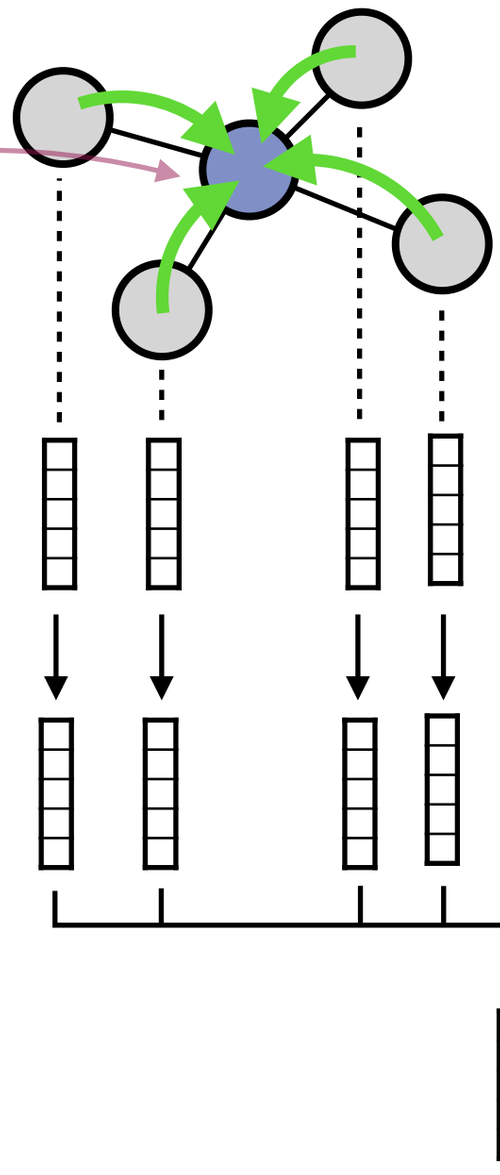
Graph Neural Networks (GNNs)



GNN Layer

GNN updates features





❶ ***Message***

Permutation equivariant operations

- nn.Linear

❷ ***Aggregate***

Permutation invariant operations

- sum, mean or max
- attentive pooling

$\boldsymbol{h}_i$ atom features

$\boldsymbol{e}_{ij}$ bond features

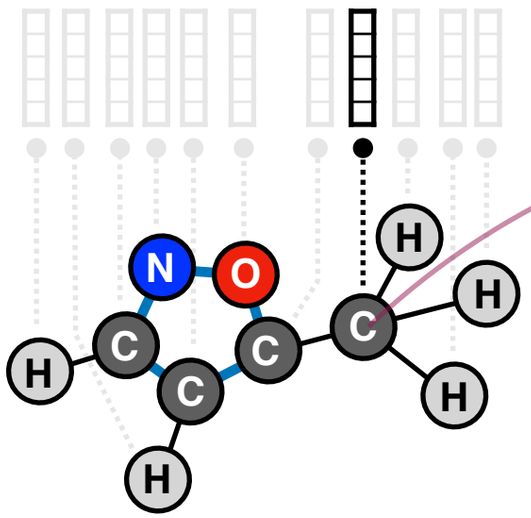
Update by "Message Passing"

$$\boldsymbol{h}_i \leftarrow \psi\left(\boldsymbol{h}_i, \bigoplus_{j \in \mathcal{N}_i} \phi(\boldsymbol{h}_i, \boldsymbol{h}_j, \boldsymbol{e}_{ij})\right)$$

❷ ❶

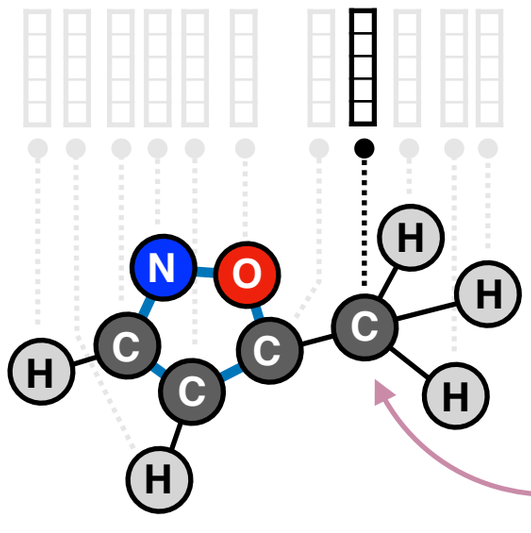
Bond features can be used (typically in ❶)

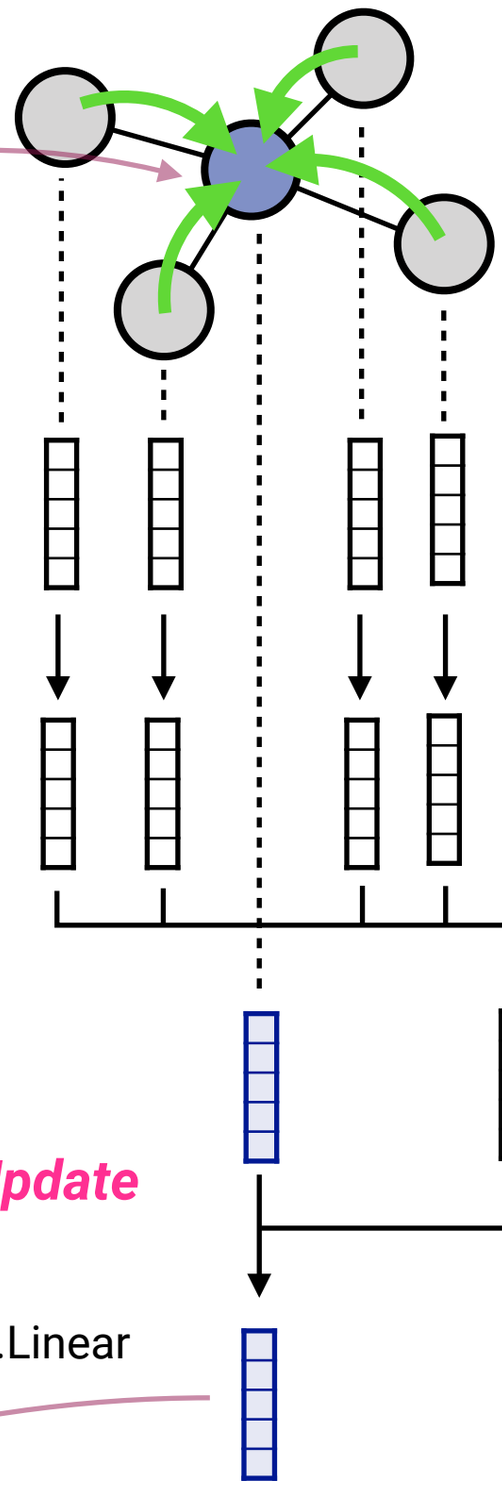
Graph Neural Networks (GNNs)



GNN Layer

GNN updates features





❶ *Message*

Permutation equivariant operations

- nn.Linear

❸ *Update*

Any

- nn.Linear

❷ *Aggregate*

Permutation invariant operations

- sum, mean or max
- attentive pooling

$\boldsymbol{h}_i$ atom features

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Update by "Message Passing"

$$\boldsymbol{h}_i \leftarrow \psi\left(\boldsymbol{h}_i, \bigoplus_{j \in \mathcal{N}_i} \phi(\boldsymbol{h}_i, \boldsymbol{h}_j, \boldsymbol{e}_{ij})\right)$$

❸ ❷ ❶

Bond features can be used (typically in ❶)

Use Case 1: Virtual Screening (QSAR/QSPR)

Performance for unseen (test) data:

Activie/Inactive (Classification), LogGI50 (Regression)

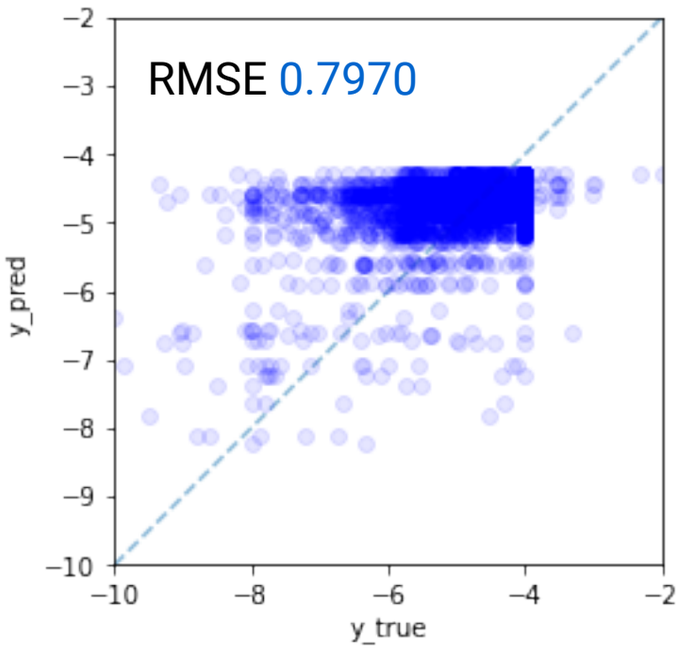
Standard ML

ExtraTrees
w/ ECFP6(1024)

- Classification accuracy

  95.079% (Active/Inactive)

- Regression for LogGI50



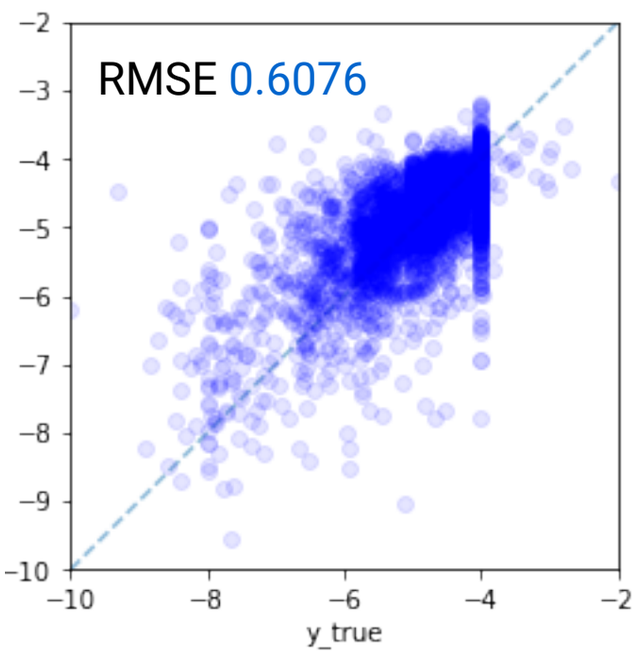
GNN

ChemProp
(Directed MPNN)

- Classification accuracy

  95.604% (Active/Inactive)

- Regression for LogGI50



Disclaimer: This is just for a toy demo. This should be taken as classification for `ACTIVITY_OUTCOME` (Active or Inactive)

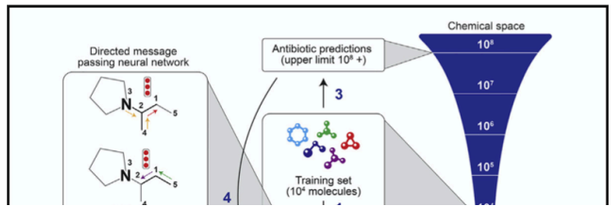
ChemProp (Yang et al, 2019)

from MIT MLPDS (Machine Learning for Pharmaceutical Discovery and Synthesis) Consortium

Cell

A Deep Learning Approach to Antibiotic Discovery

Graphical Abstract



Authors

Jonathan M. Stokes, Kevin Yang, Kyle Swanson, ..., Tommi S. Jaakkola, Regina Barzilay, James J. Collins

Correspondence

regina@csail.mit.edu (R.B.), jimjc@mit.edu (J.J.C.)

Stokes et al, *Cell* (2020) https://doi.org/10.1016/j.cell.2020.01.021

nature

NEWS | 20 February 2020

Powerful antibiotics discovered using AI

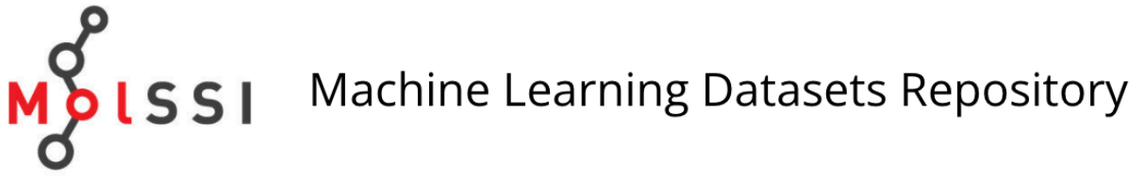
Machine learning spots molecules that work even against 'untreatable' strains of bacteria.

Jo Marchant

Marchant, *Nature* (2020) https://doi.org/10.1038/d41586-020-00018-3

Use Case 2: Quantum chemistry

https://qcarchive.molssi.org/apps/ml_datasets/



	Name	Quality	Data Points	Elements	Sampling	Download
+	ANI-1	DFT	22,057,374	C H N O	NMS	HDF5 TEXT
+	ANI-1x	DFT	4,956,005	C H N O	MD,NMS,DS,TS	HDF5
−	QM9	DFT	133,885	C H F N O	Minima	HDF5 TEXT

Description

Small organic molecules with up to 9 heavy atoms sampled from GDB-17, optimized at the B3LYP/6-31G(2df,p) level of theory. Ground state, orbital, and thermodynamic properties are available (at the B3LYP/6-31G(2df,p) level). All molecules are neutral singlets. This dataset was sourced from quantum-machine.org and qmml.org.

Elements: C H F N O

Labels

energy homo lumo polarizability dipole freqency zpve enthalpy free energy heat capacity rotational constant

Tags

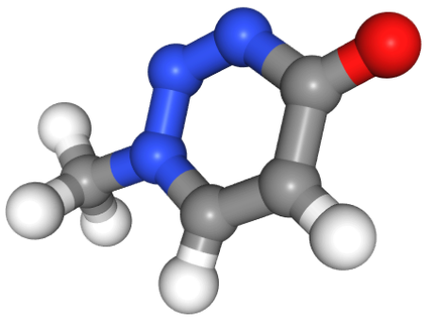
organic thermodynamics GDB

Citations

- Blum, L. C. & Reymond, J.-L. 970 million druglike small molecules for virtual screening in the chemical universe database GDB-13.

Use Case 2: Quantum chemistry

input



gdb_21014

	x	y	z
O	0.314096	-0.129589	-0.389150
C	0.111219	2.102676	-0.051749
C	2.331344	3.941075	0.212303
O	4.667017	2.677399	0.437948
C	6.152491	3.062553	-1.780599
C	4.732264	5.009654	-3.282819
C	2.562527	5.549427	-2.143825
H	-1.771427	3.048695	0.071772
H	1.977918	5.086871	1.919865
H	8.050245	3.696867	-1.222422
H	6.372399	1.276980	-2.825015
H	5.428656	5.805758	-5.033531
H	1.118529	6.857080	-2.763050

∼ 1000 sec

Q*uantum chemical calculations*

by solving a one-electron Schrödinger equation (Kohn–Sham equation)

Density Functional Theory (DFT)
B3LYP/6-31G(2df, p)

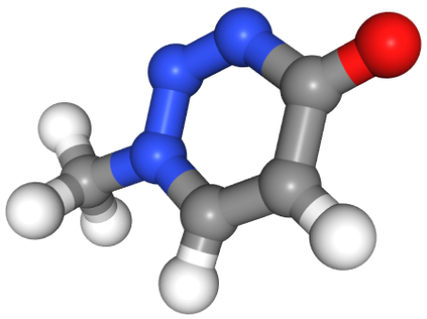
$$\hat{H}\Psi = E\Psi$$

output

	property	value
0	dipole_moment	7.214000
1	isotropic_polarizability	65.360001
2	homo	-6.280388
3	lumo	-1.649010
4	gap	4.631378
5	electronic_spatial_extent	884.587524
6	zpve	2.610307
7	energy_U0	-10742.250000
8	energy_U	-10742.060547
9	enthalpy_H	-10742.035156
10	free_energy_G	-10743.111328
11	heat_capacity	24.756001
12	U_0_atom	-56.213203
13	U_atomization	-56.525291
14	H_atomization	-56.833679
15	G_atomization	-52.407772
16	rotational_a	5.712810
17	rotational_b	1.644960
18	rotational_c	1.287640

Use Case 2: Quantum chemistry

input



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H	5.428656	5.805758	-5.033531
H	1.118529	6.857080	-2.763050

100,000 times faster!

~ 0.01 sec

ML

≀

~ 1000 sec

Q*uantum chemical calculations*

by solving a one-electron Schrödinger equation (Kohn–Sham equation)

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B3LYP/6-31G(2df, p)

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

output

	property	value
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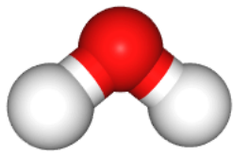
3	lumo	-1.649010
4	gap	4.631378
5	electronic_spatial_extent	884.587524
6	zpve	2.610307
7	energy_U0	-10742.250000
8	energy_U	-10742.060547
9	enthalpy_H	-10742.035156
10	free_energy_G	-10743.111328
11	heat_capacity	24.756001
12	U_0_atom	-56.213203
13	U_atomization	-56.525291
14	H_atomization	-56.833679
15	G_atomization	-52.407772
16	rotational_a	5.712810
17	rotational_b	1.644960
18	rotational_c	1.287640

Use Case 2: Quantum chemistry

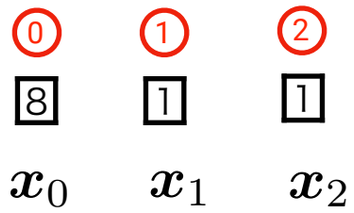
input molecule H_2O



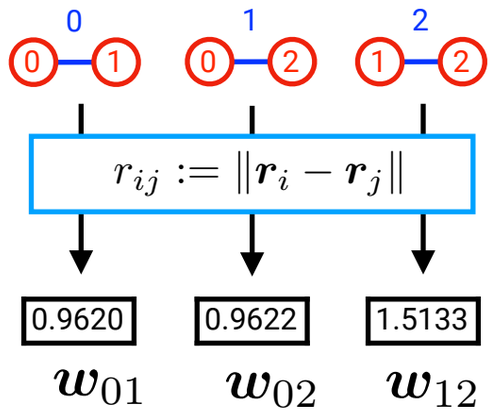
gdb_3

	x	y	z	AN
O	-0.0344	0.9775	0.0076	8
H	0.0648	0.0206	0.0015	1
H	0.8718	1.3008	0.0007	1

atom features



bond features

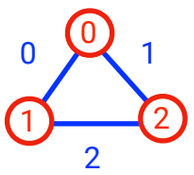


SchNet (Schütt et al, 2017)

Message Passing with residual connections

$$\boldsymbol{x}_i \leftarrow \boldsymbol{x}_i + \psi\left(\sum_{j \in \mathcal{N}_i} \phi(\boldsymbol{x}_j) \odot \boldsymbol{\omega}_{ij}\right)$$

graph (SchNet)



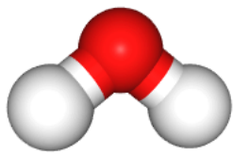
edge_index

edges w/ cutoff (10Å)

$$\boldsymbol{r}_0 = [-0.0344, 0.9775, 0.0076] \qquad Z_0 = 8$$
$$\boldsymbol{r}_1 = [0.0648, 0.0206, 0.0015] \qquad Z_1 = 1$$
$$\boldsymbol{r}_2 = [0.8718, 1.3008, 0.0007] \qquad Z_2 = 1$$

Use Case 2: Quantum chemistry

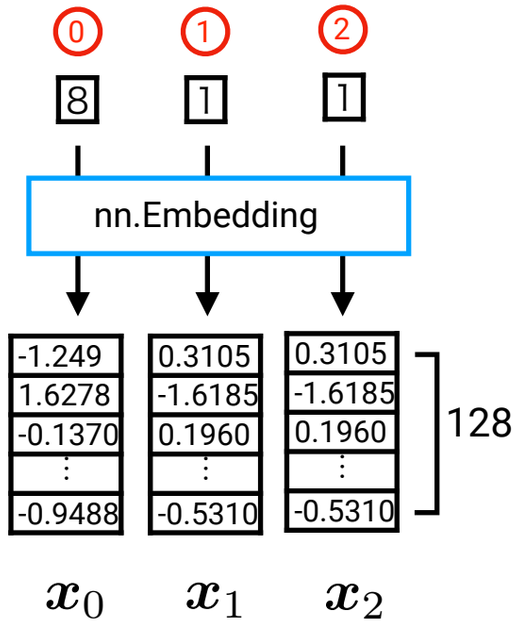
input molecule H_2O



gdb_3

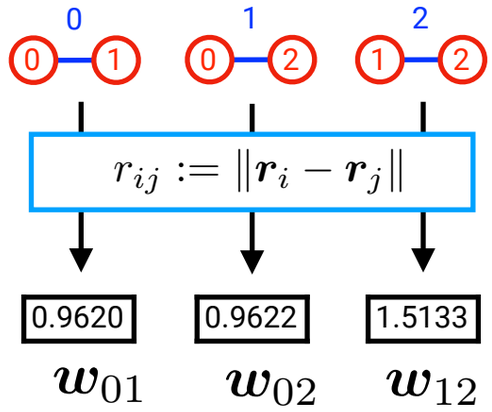
	x	y	z	AN
O	-0.0344	0.9775	0.0076	8
H	0.0648	0.0206	0.0015	1
H	0.8718	1.3008	0.0007	1

atom features



$\boldsymbol{x}_0 \quad \boldsymbol{x}_1 \quad \boldsymbol{x}_2$

bond features



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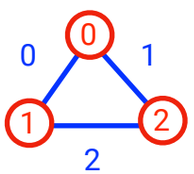

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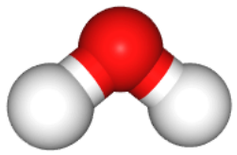

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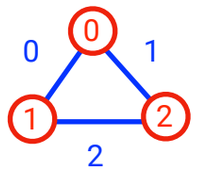

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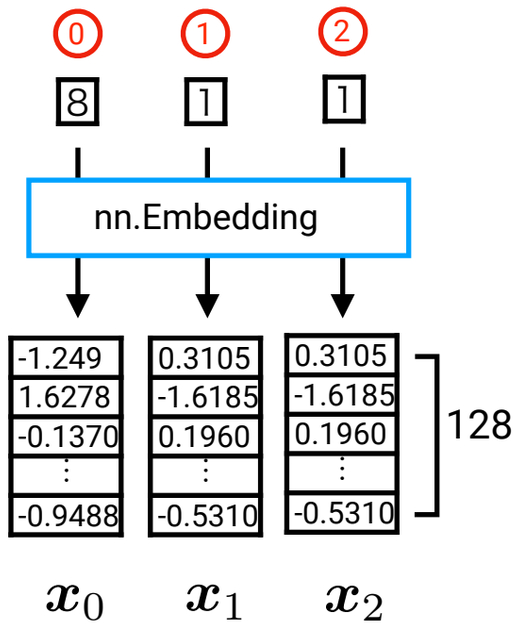

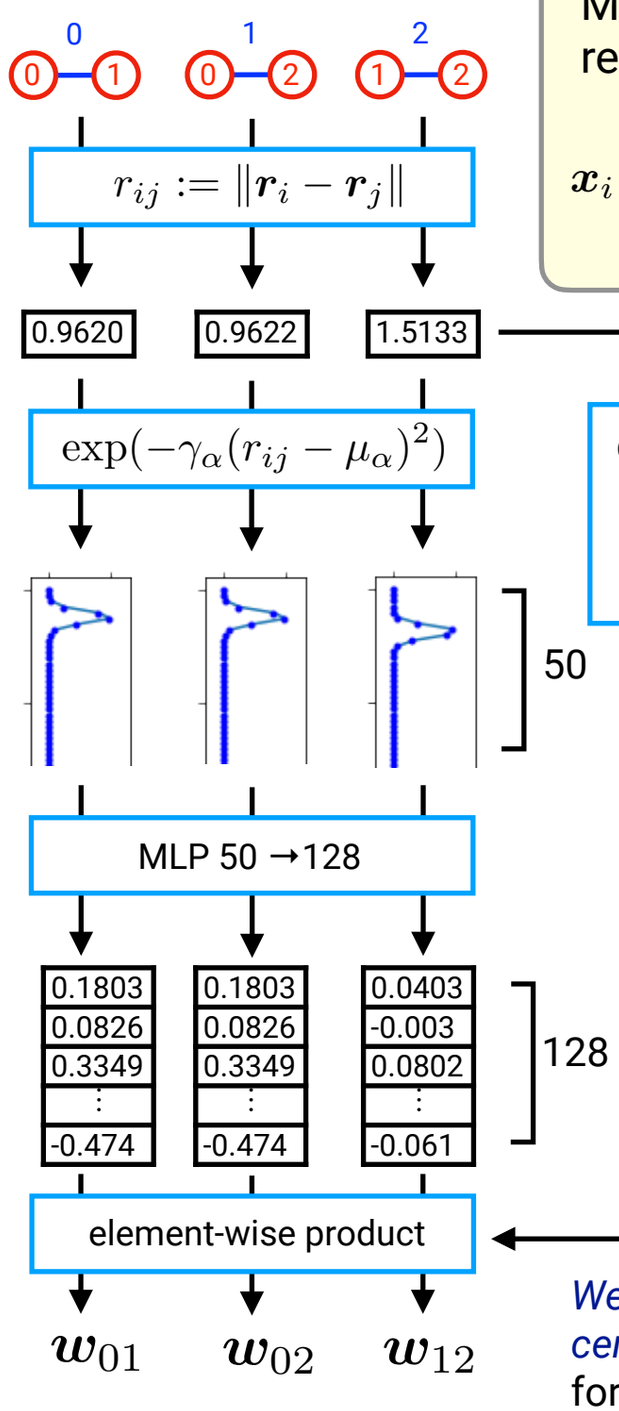

SchNet (Schütt et al, 2017)

Message Passing with residual connections

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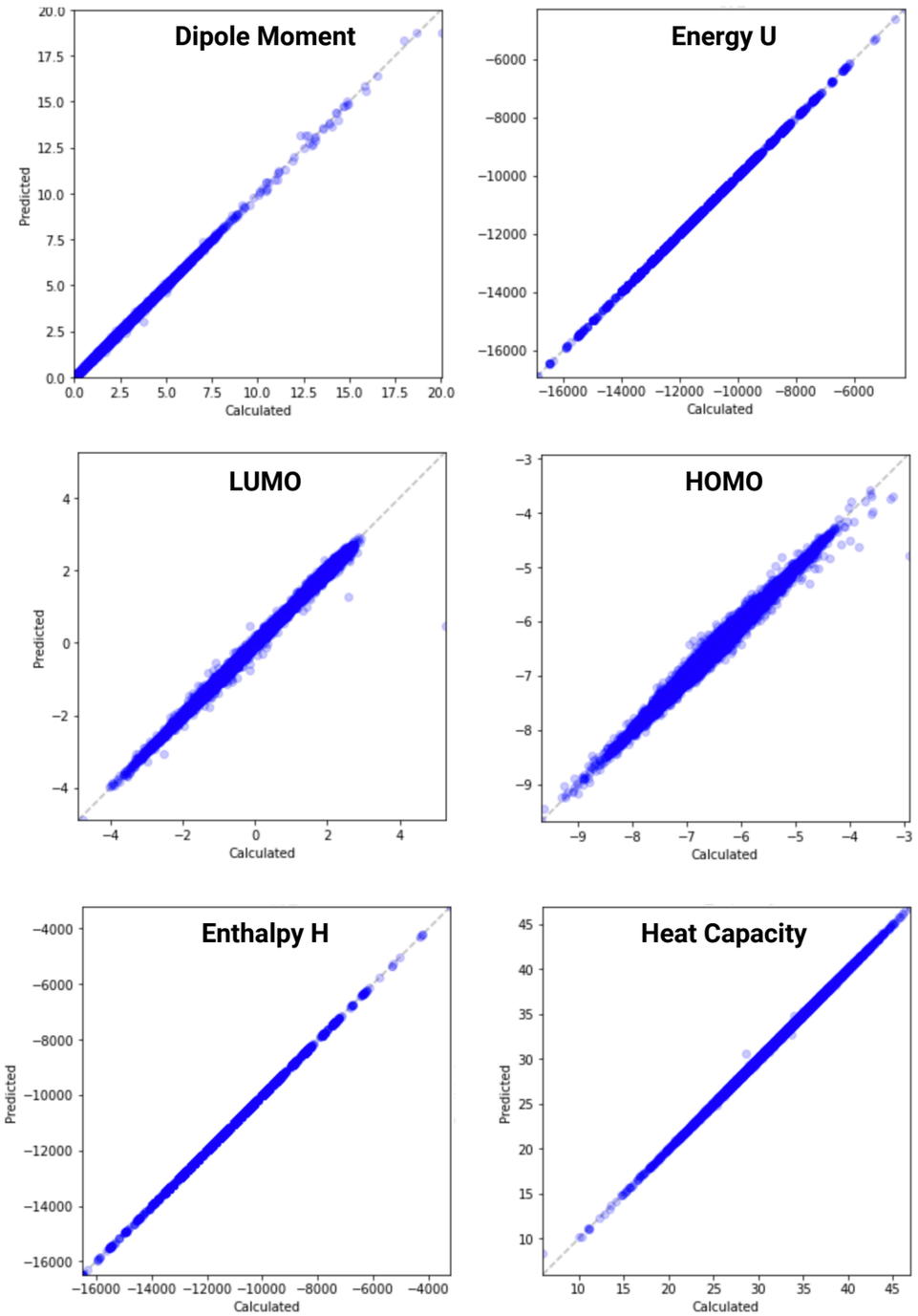
cutoff function

$$\frac{1}{2}\left(\cos\left(\frac{\pi r_{ij}}{r_c}\right) + 1\right)$$

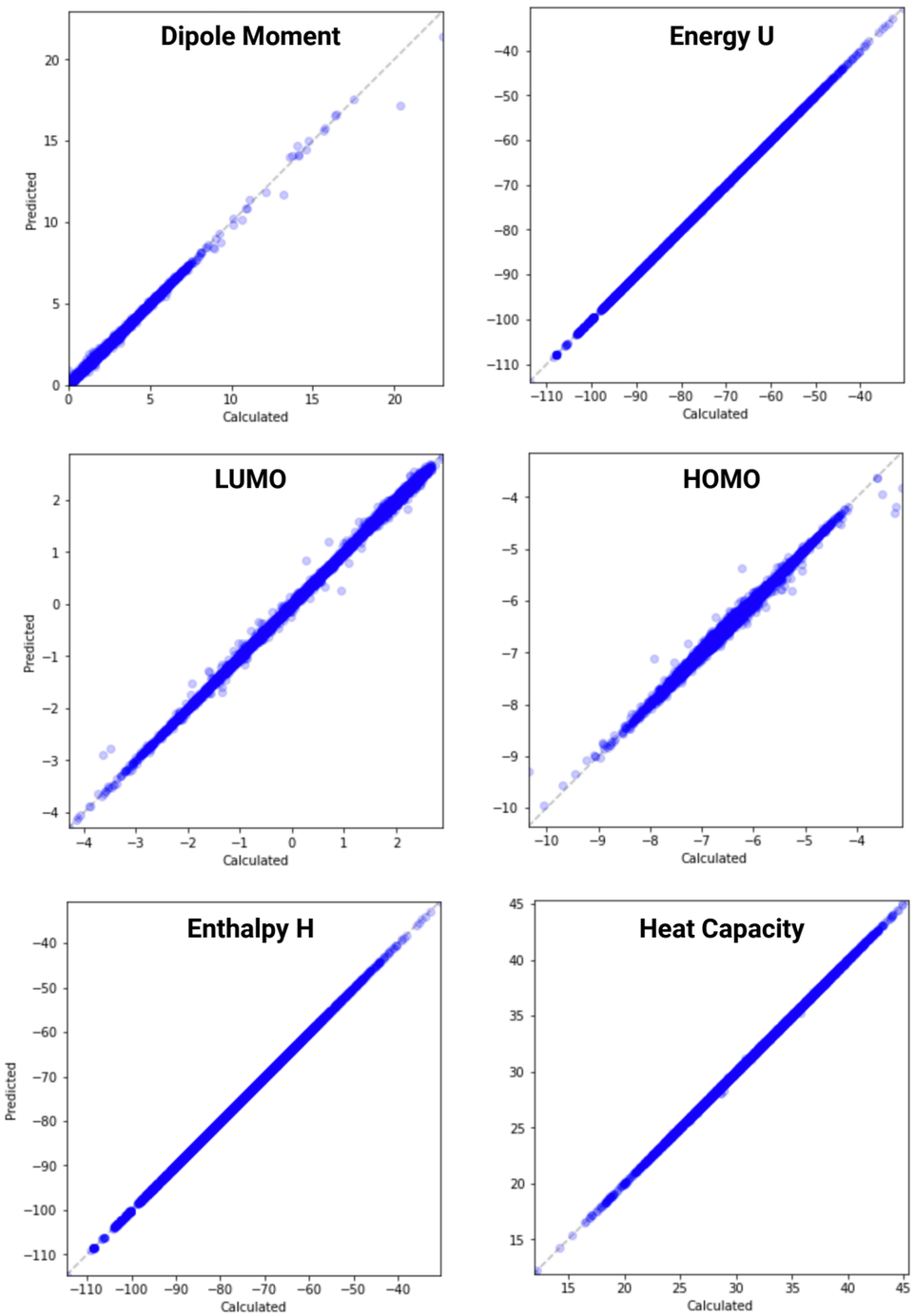
Weighted ACSFs (ACSFs = atom-centered symmetry functions) for Behler-Parrinello potentials

Use Case 2: Quantum chemistry

pred vs true for **SchNet** (Schütt et al, 2017)

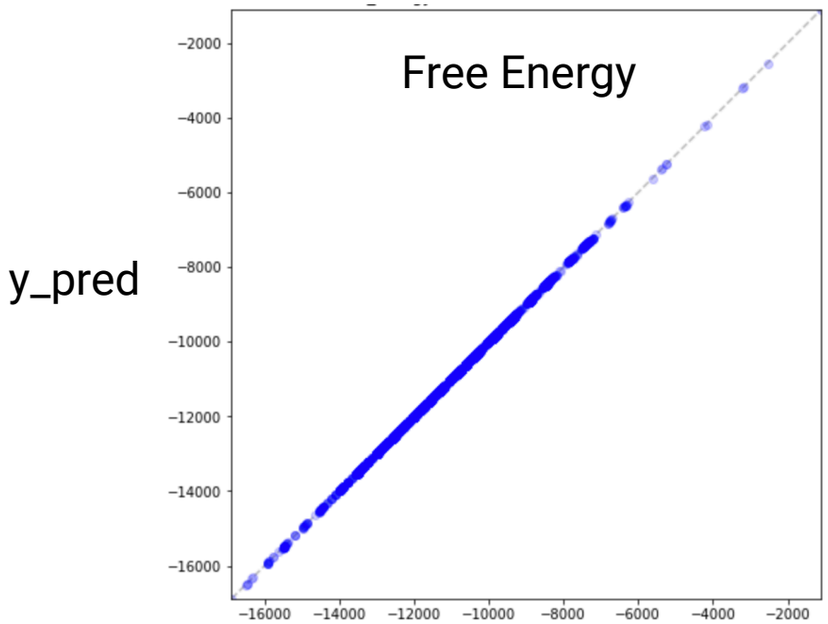


pred vs true for **DimeNet** (Klicpera et al, 2020)

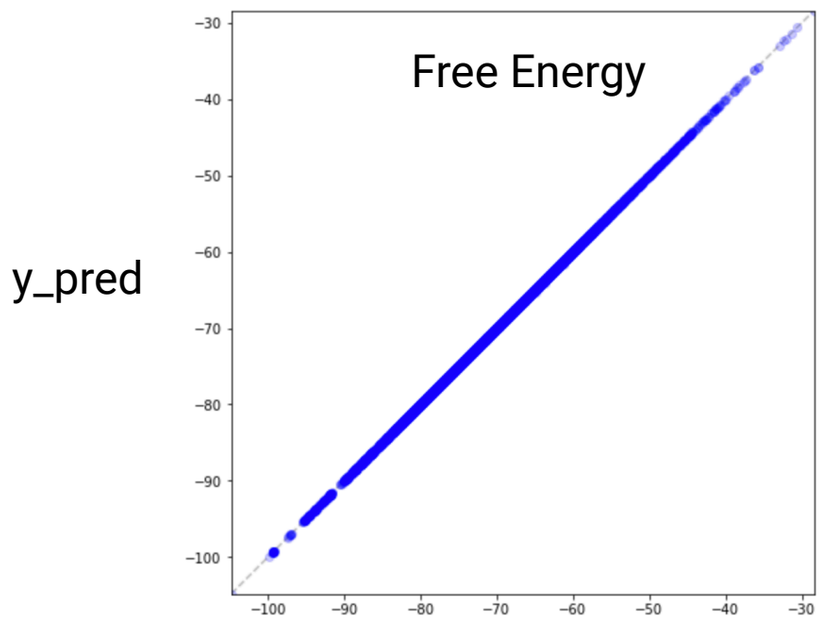


Use Case 2: Quantum chemistry

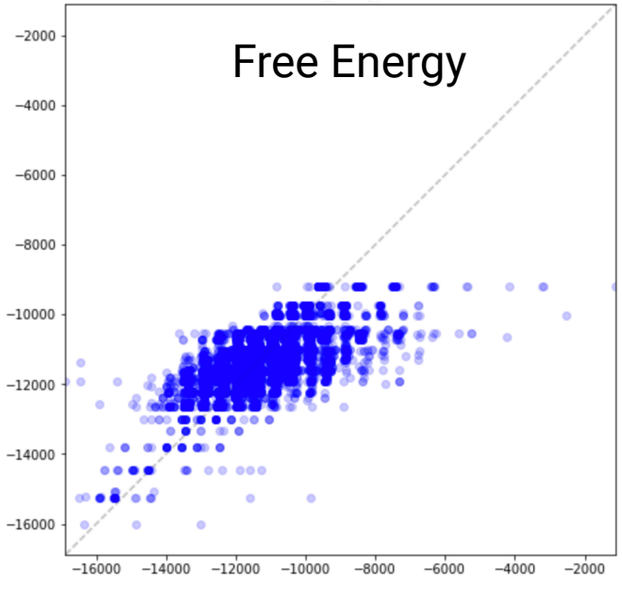
SchNet (Schütt et al, 2017)



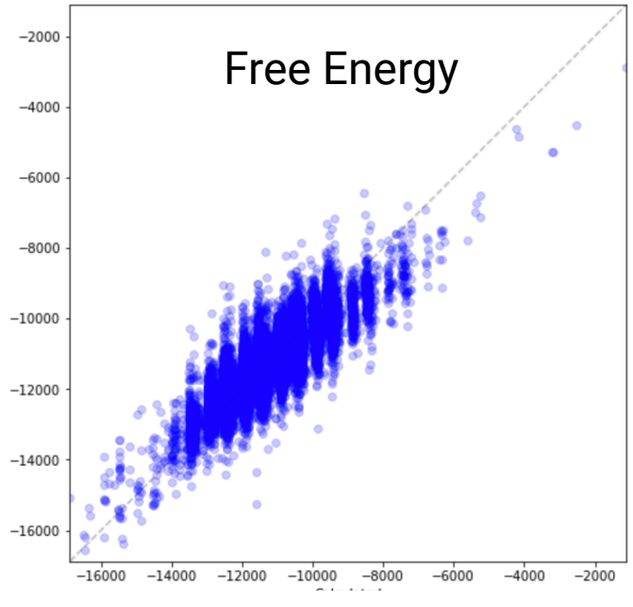
DimeNet (Klicpera et al, 2020)



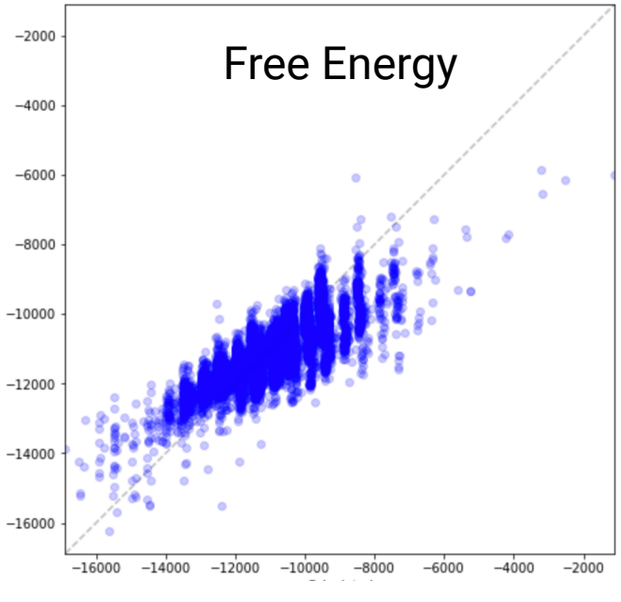
ExtraTrees w/ ECFP6
(without 3D geometry)



LightGBM w/ ECFP6
(without 3D geometry)



3-Layer MLP w/ ECFP6
(without 3D geometry)

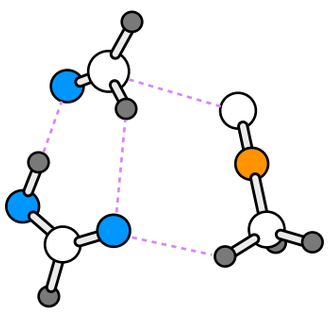


Chemical Reaction Design and Discovery

ICReDD

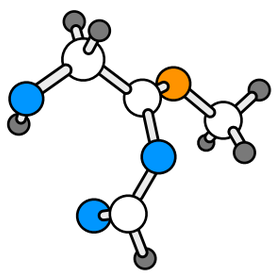
Chemical Reaction

EQ1



How we can have this?

EQ2



Chemical Reaction Design and Discovery

ICReDD

Chemical Reaction

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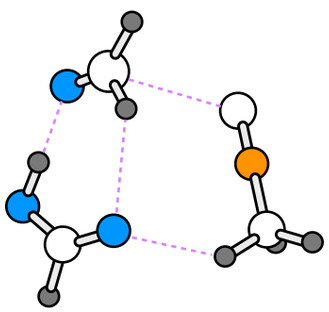
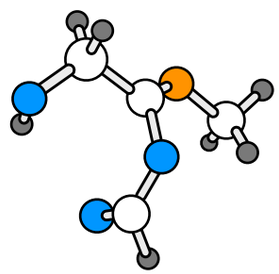


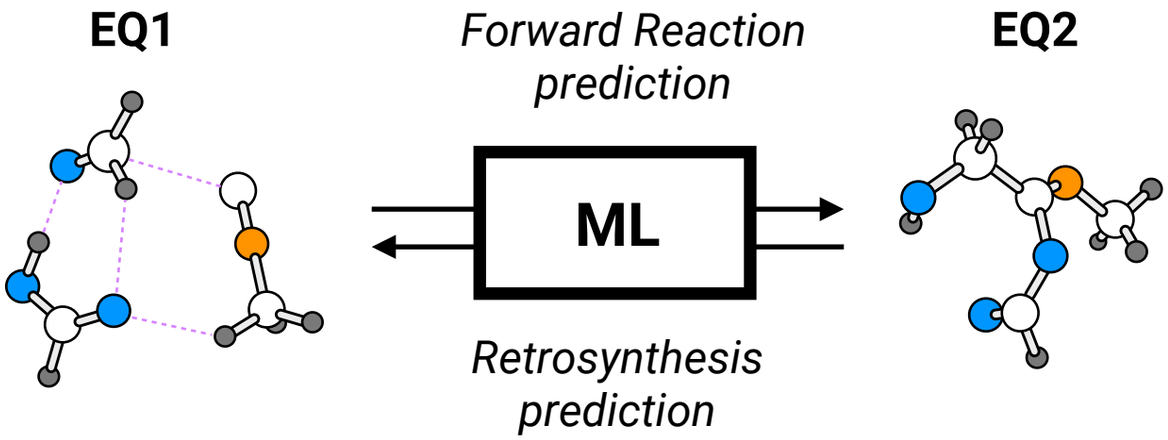
EQ2



Chemical Reaction Design and Discovery

ICReDD

Chemical Reaction



Chemical Reaction Design and Discovery

ICReDD

Chemical Reaction

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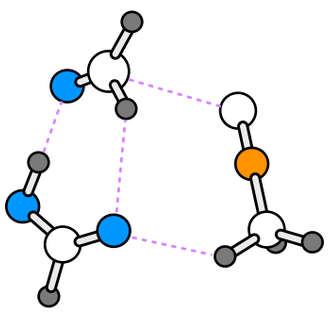
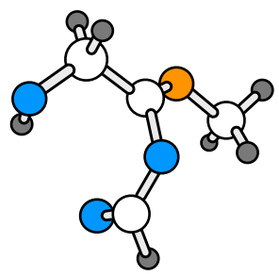


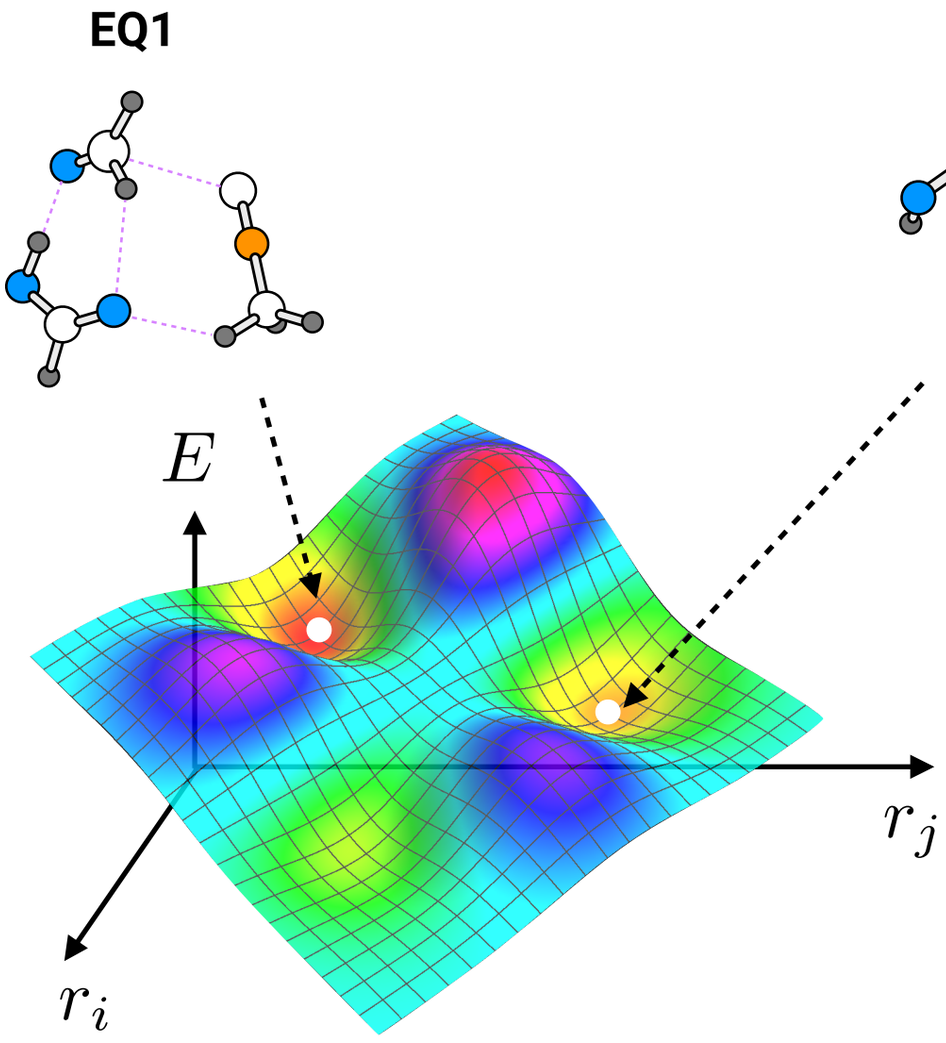
EQ2



Chemical Reaction Design and Discovery

ICReDD

Chemical Reaction

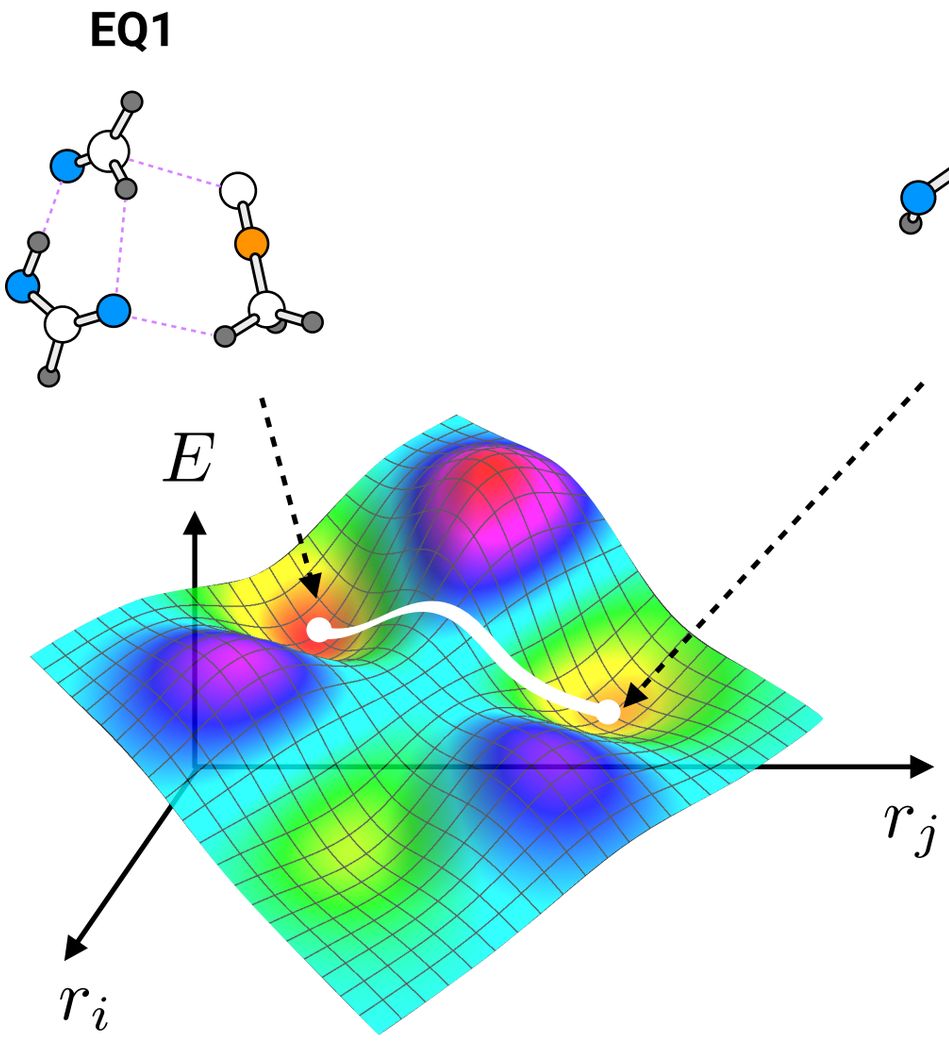


Potential Energy Surface

Chemical Reaction Design and Discovery

ICReDD

Chemical Reaction

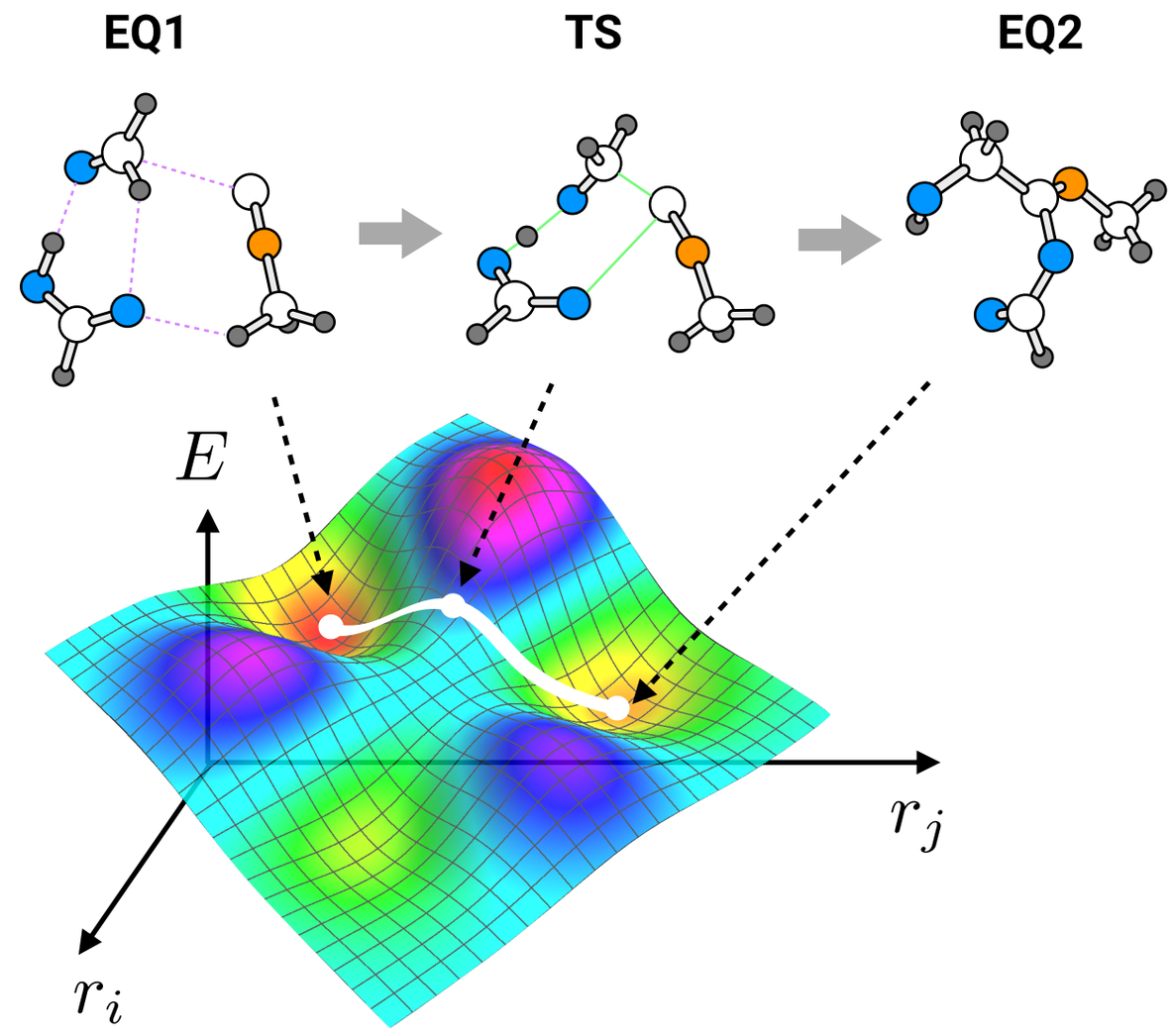


Potential Energy Surface

Chemical Reaction Design and Discovery

ICReDD

Chemical Reaction

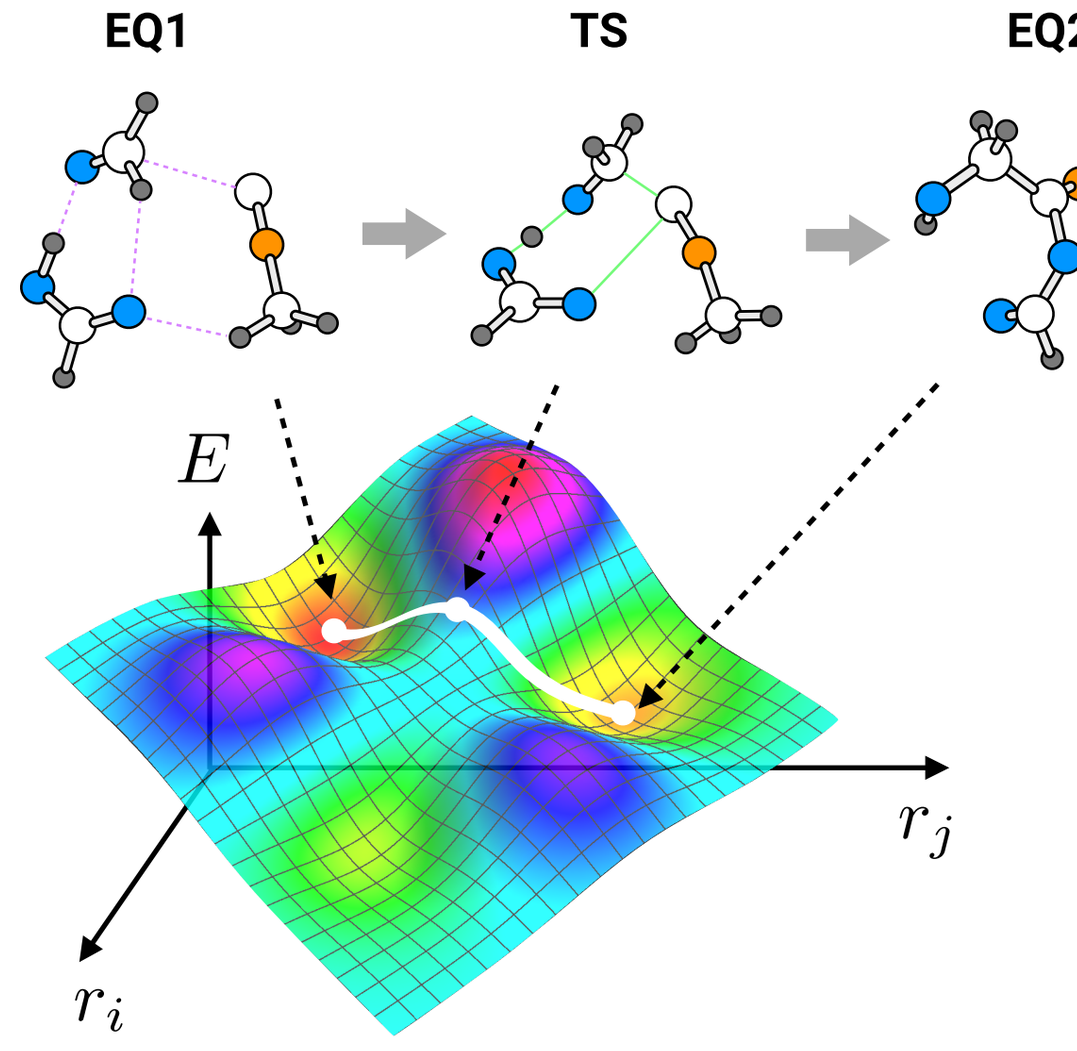


Potential Energy Surface

Chemical Reaction Design and Discovery

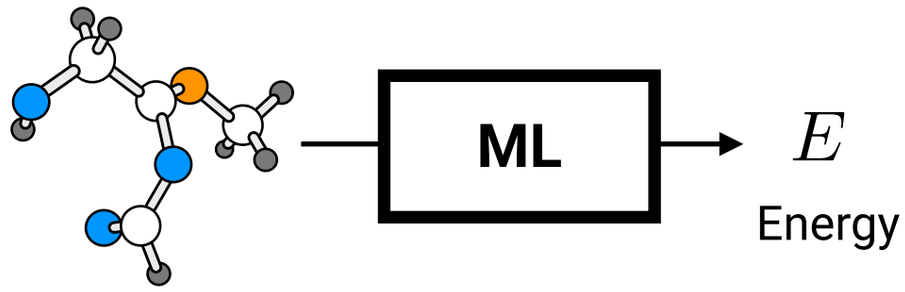
ICReDD

Chemical Reaction

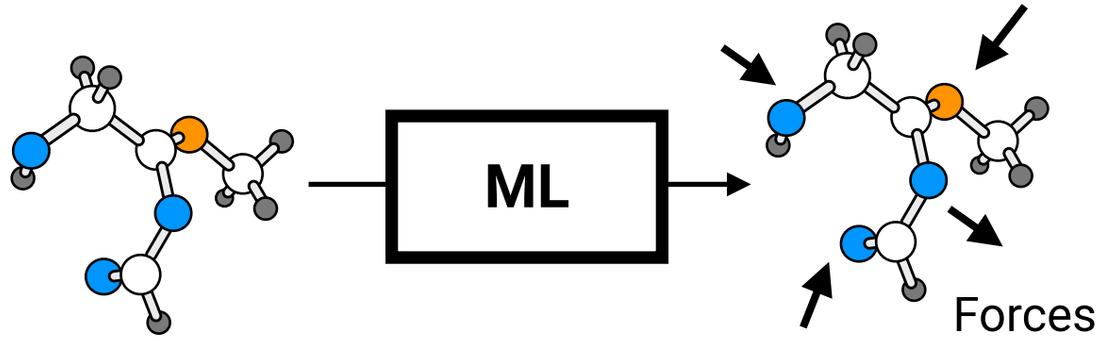


Potential Energy Surface

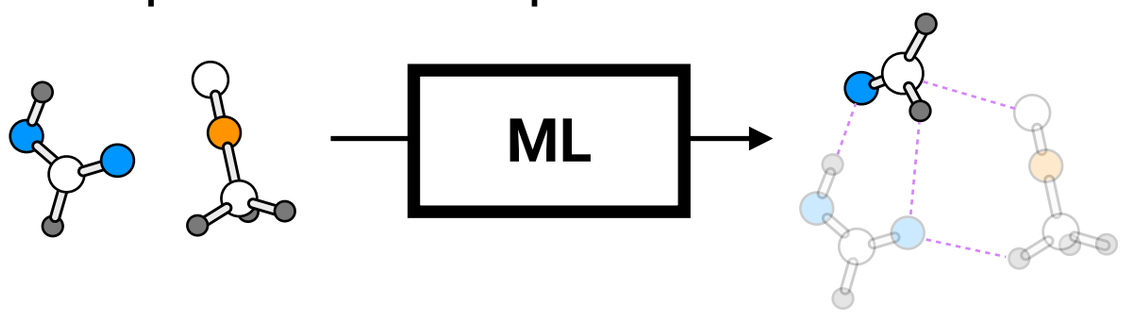
- Fill any gap between theory and experiments (reality) by data?
- Acceleration by ML potential?



- Artificial force learning?



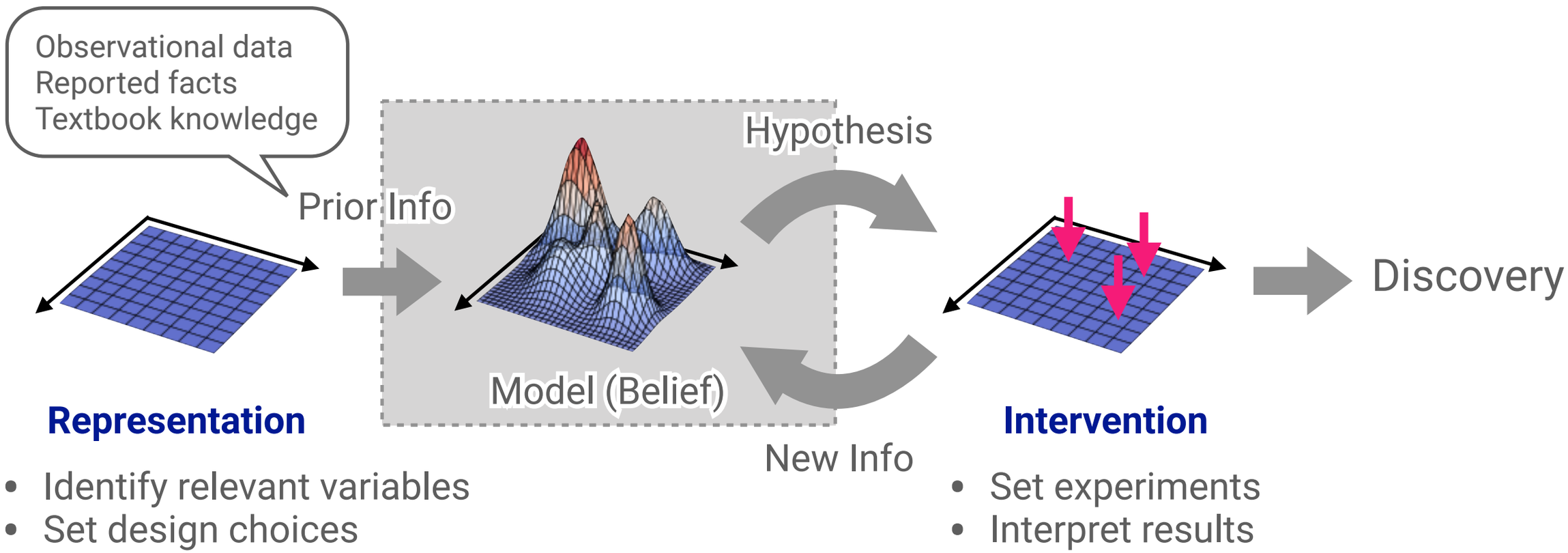
- Scope/network expansion?



Machine Learning and Machine Discovery

ICReDD An exciting “real-world” test bench for ML researchers!

- ***Machine Learning:*** many fascinating technical topics of my long-standing interests on “ML with combinatorial structures” (such as GNNs)
- ***Machine Discovery:*** many long-standing important open problems towards “AI for automating discovery”



This Slide https://itakigawa.github.io/data/icred_med_202110.pdf