Machine Learning

for Molecular Graph Representations and Geometries

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Hi, I am a machine-learning researcher

- 1995-2004 Hokkaido Univ (Grad School. Engineering)
  2004 PhD Computer Science
- 2005-2011 Kyoto Univ (Inst. Chemical Research)
  Bioinformatics Center, Assist. Prof.
  Grad School Pharmaceutical Sciences, Assit. Prof.
- 2012-2018 Hokkaido Univ (Grad School. Info Sci & Tech)
  Large-Scale Knowledge Processing Lab, Assoc. Prof.
  2015-2018 JST PRESTO for Materials Informatics
- 2019- RIKEN Center for AI Project
  2019- Hokkaido Univ
  (Inst. Chemical Reaction Design & Discovery)
  I belong to a joint research team based at Kyoto with RIKEN AIP and Kyoto Univ CiRA, working on stem cell biology.

Center for iPS Cell Research and Application, Kyoto University
CiRA

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But also, I am a machine-learning user

- 1995-2004 Hokkaido Univ (Grad School. Engineering)
  2004 PhD Computer Science
- 2005-2011 Kyoto Univ (Inst. Chemical Research)
  Bioinformatics Center, Assist. Prof.
  Grad School Pharmaceutical Sciences, Assit. Prof.
- 2012-2018 Hokkaido Univ (Grad School. Info Sci & Tech)
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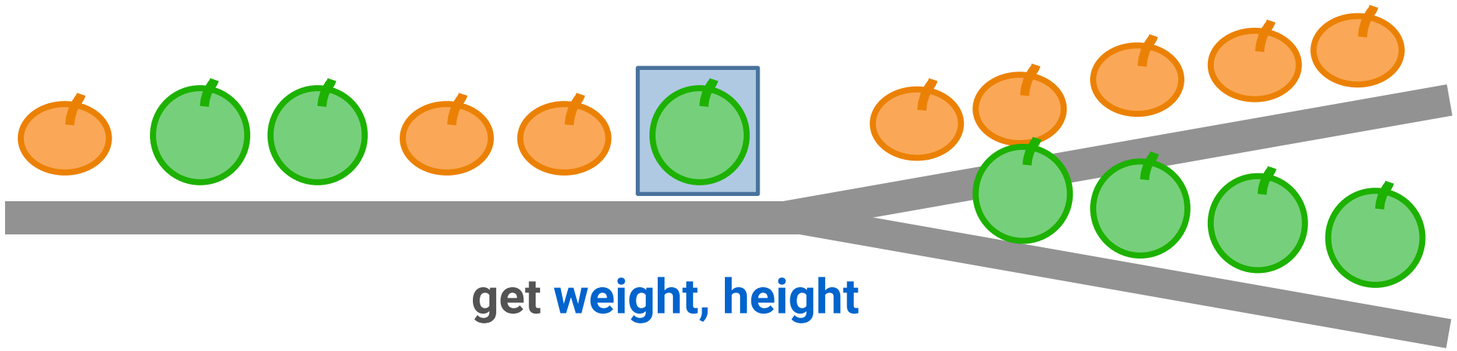
This talk

Machine Learning (ML) for Molecules

1. ML in a nutshell
2. The dark side: Modern aspects of ML
3. The light side: Deep learning for molecules
4. Challenges

May the ML Force be with you…

ML converts data into "prediction"



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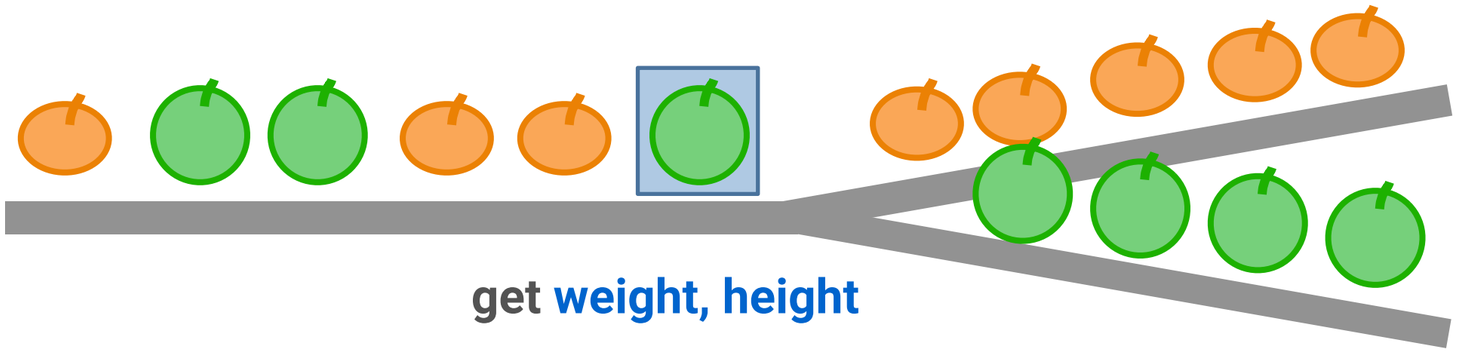

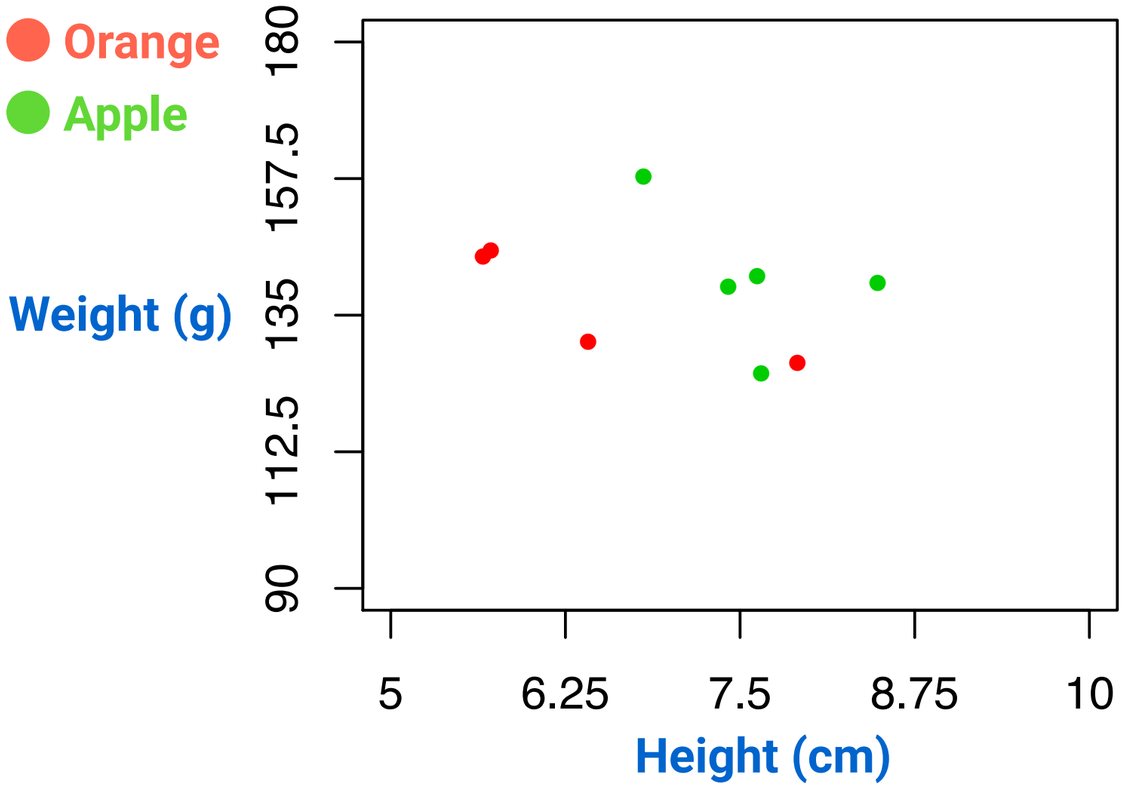

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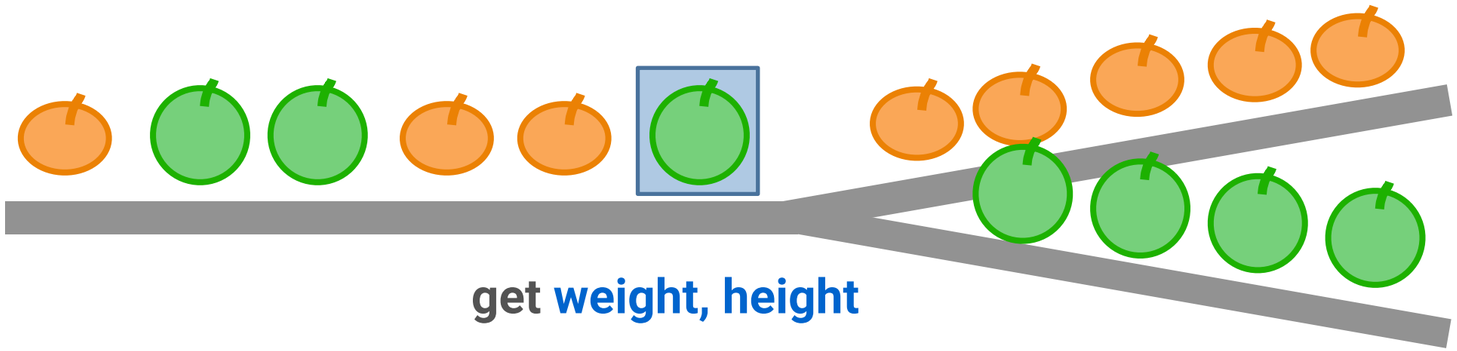

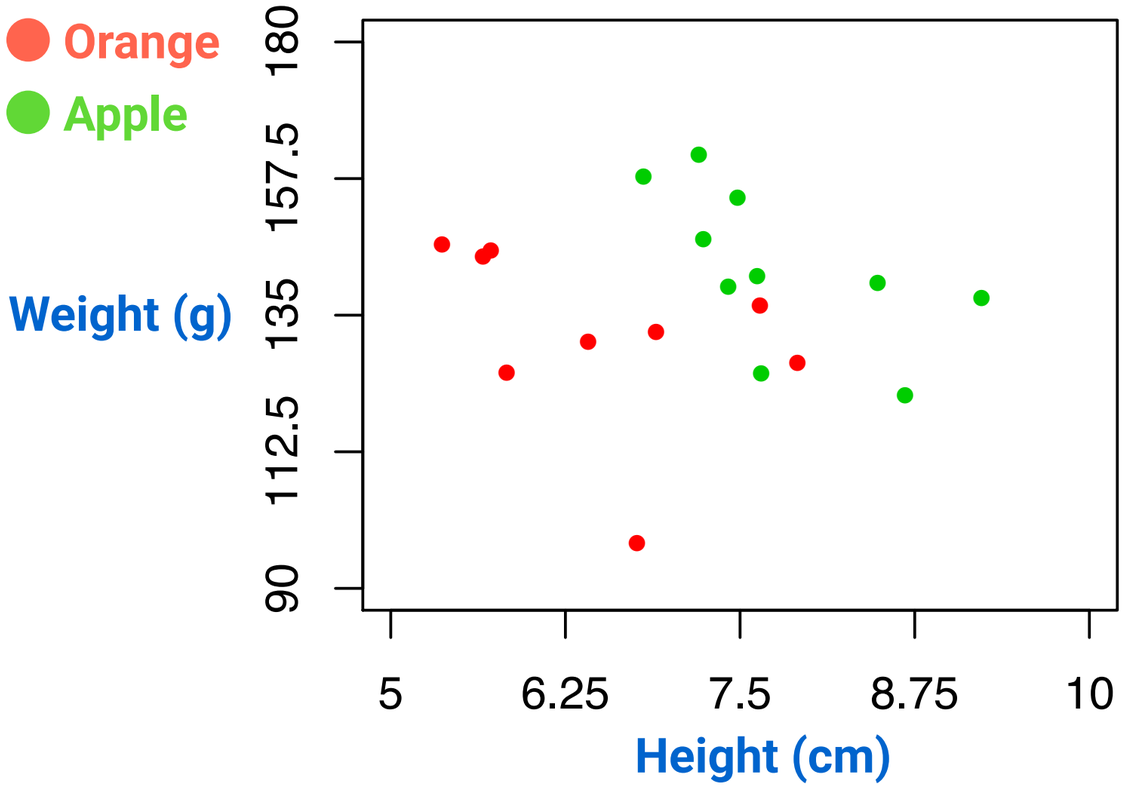

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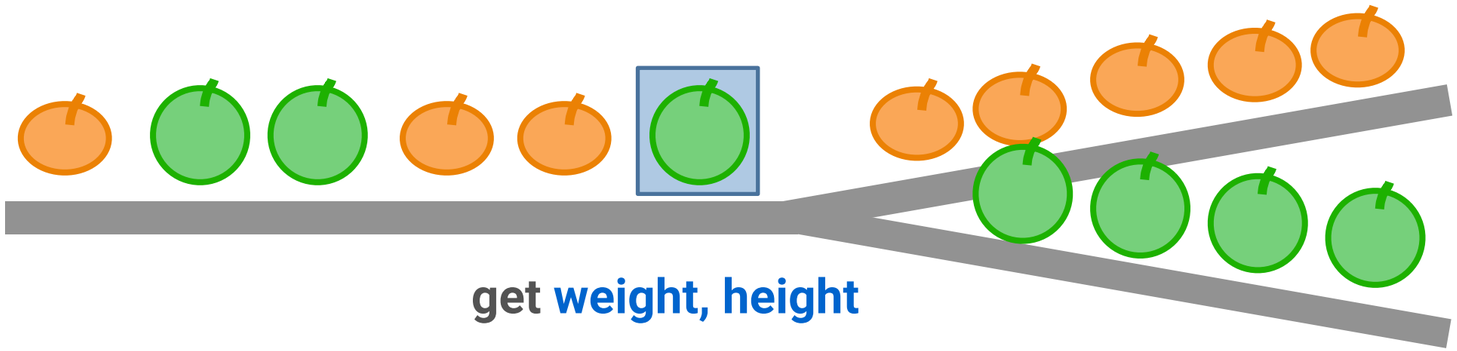

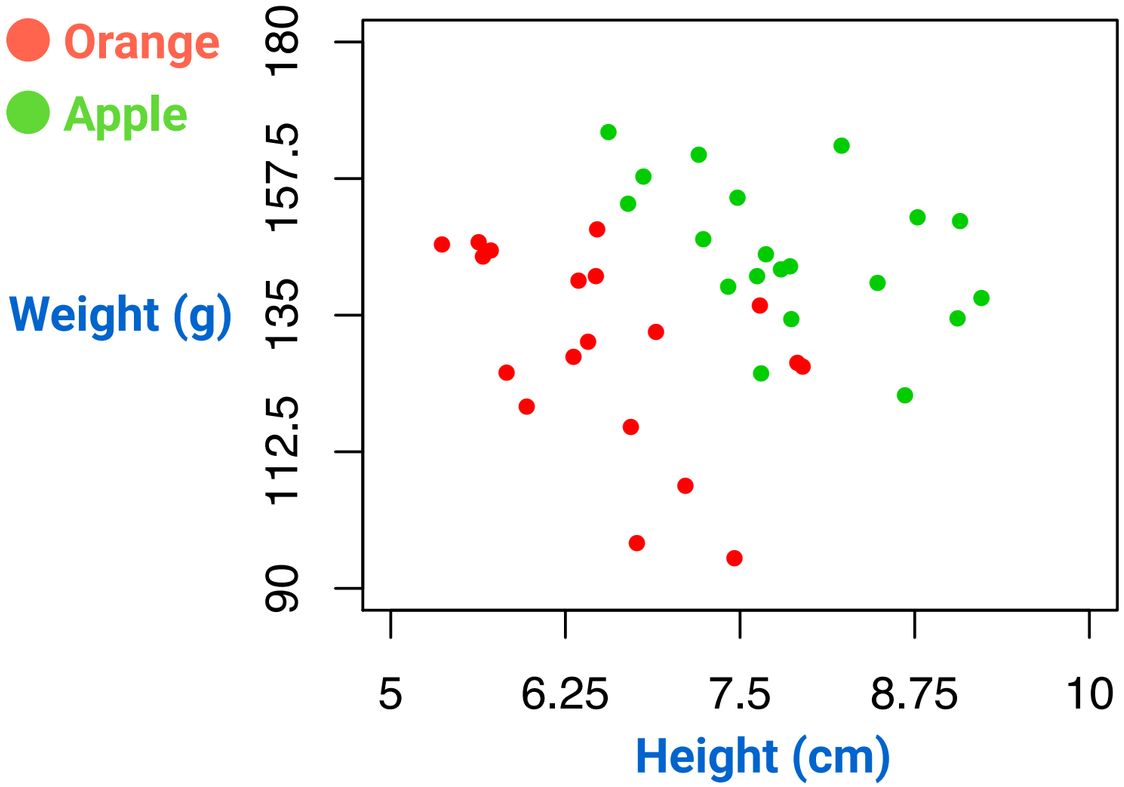

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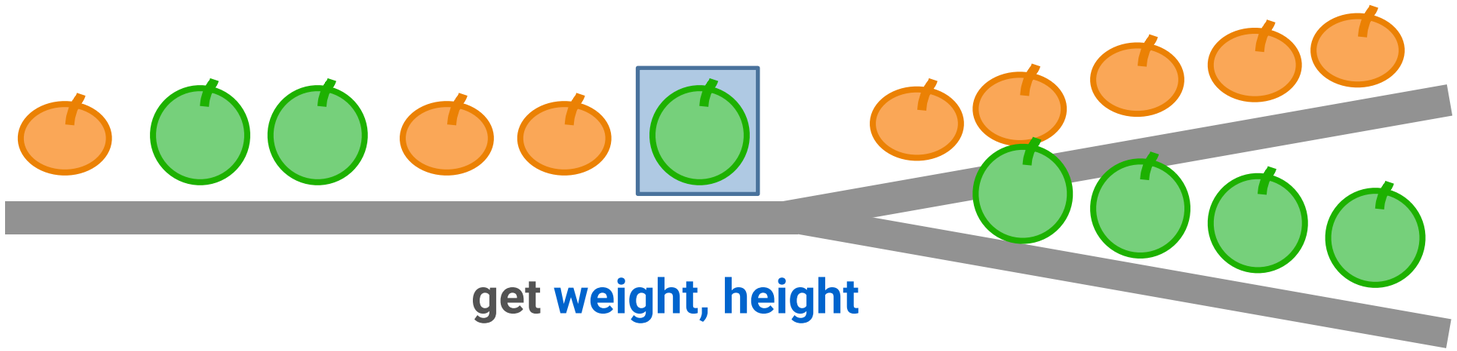

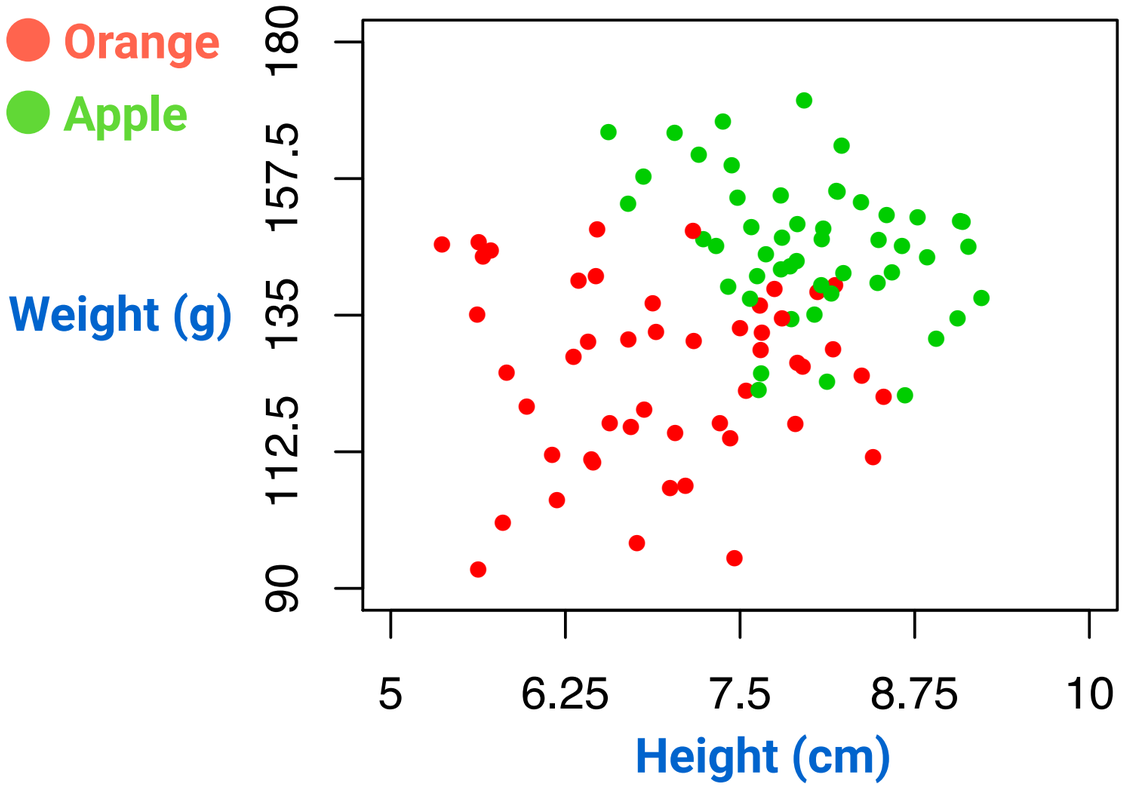

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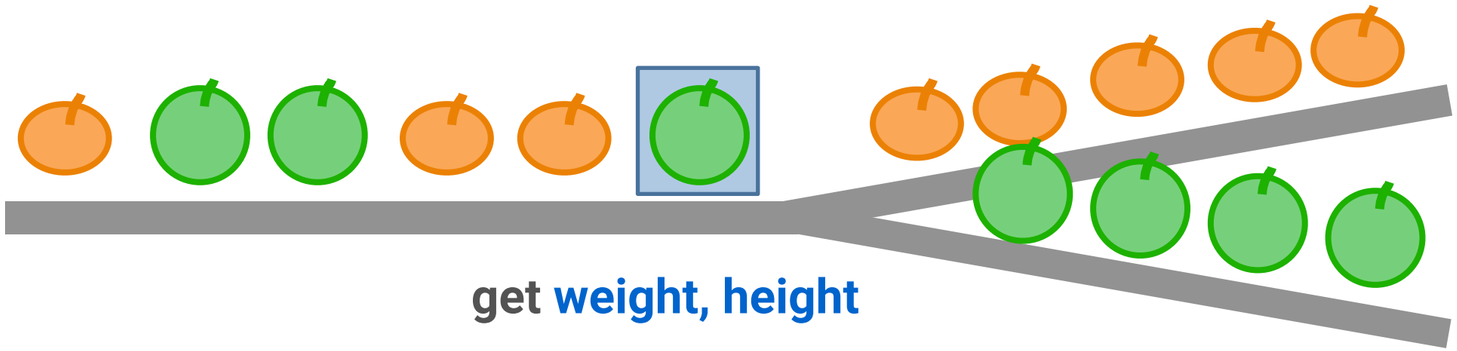

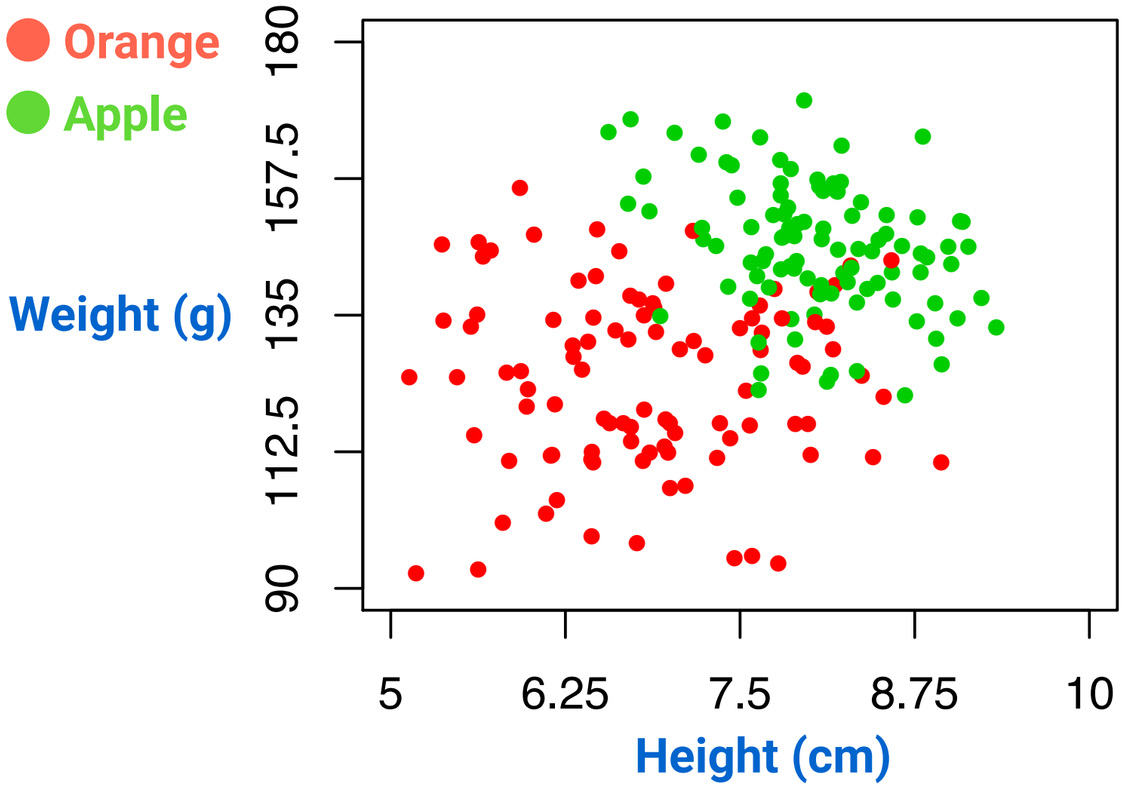

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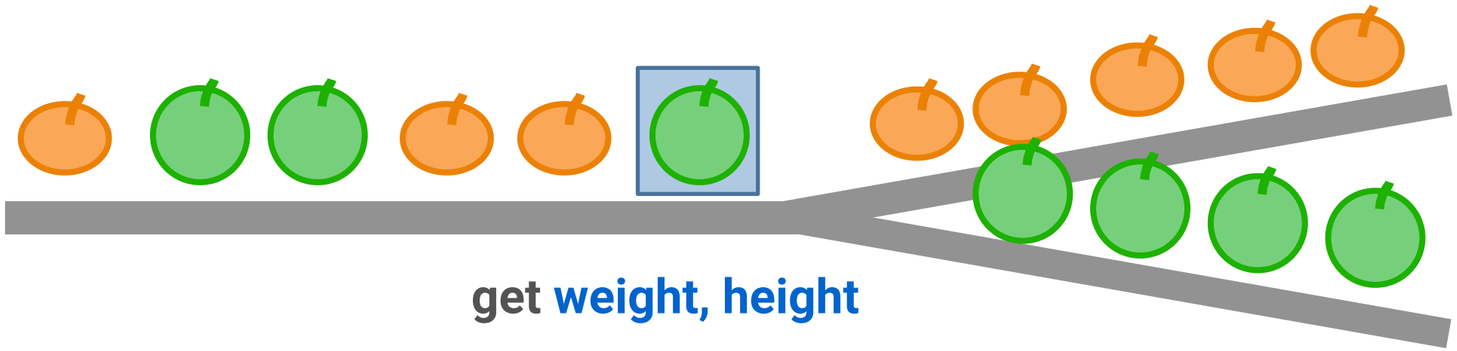

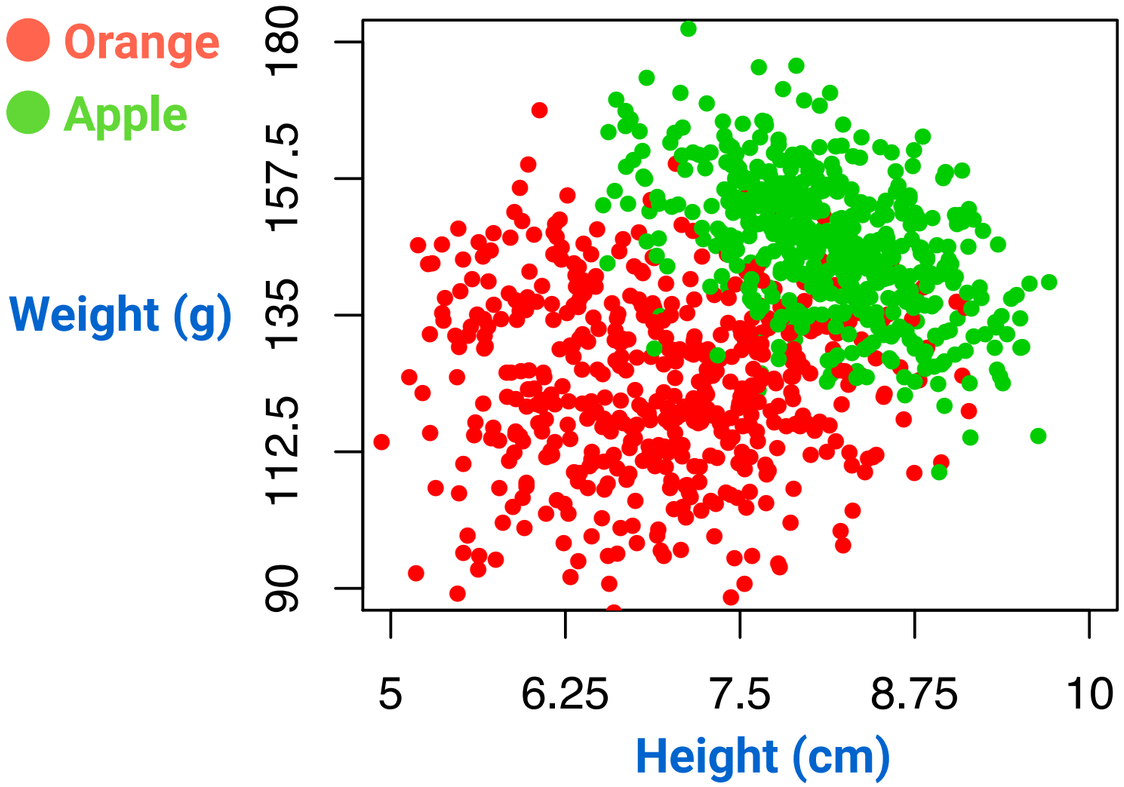

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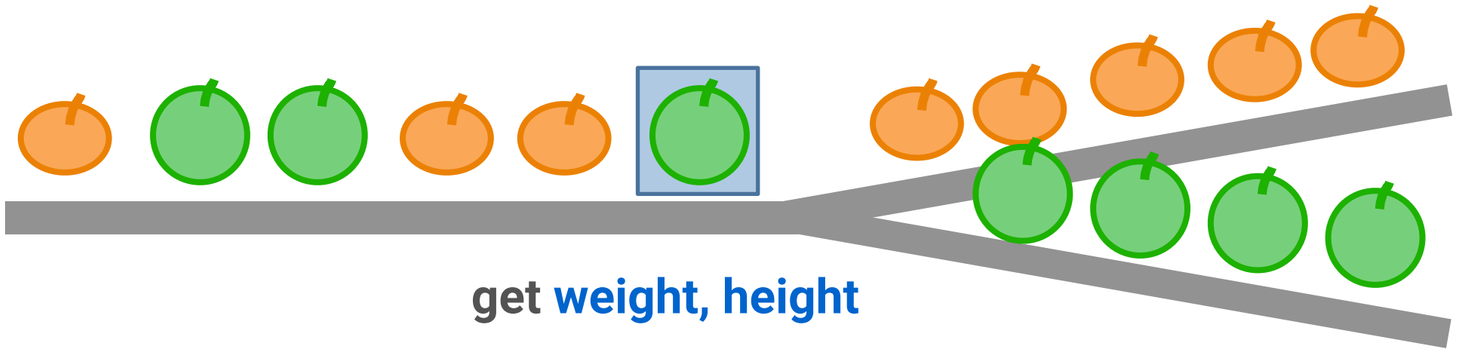

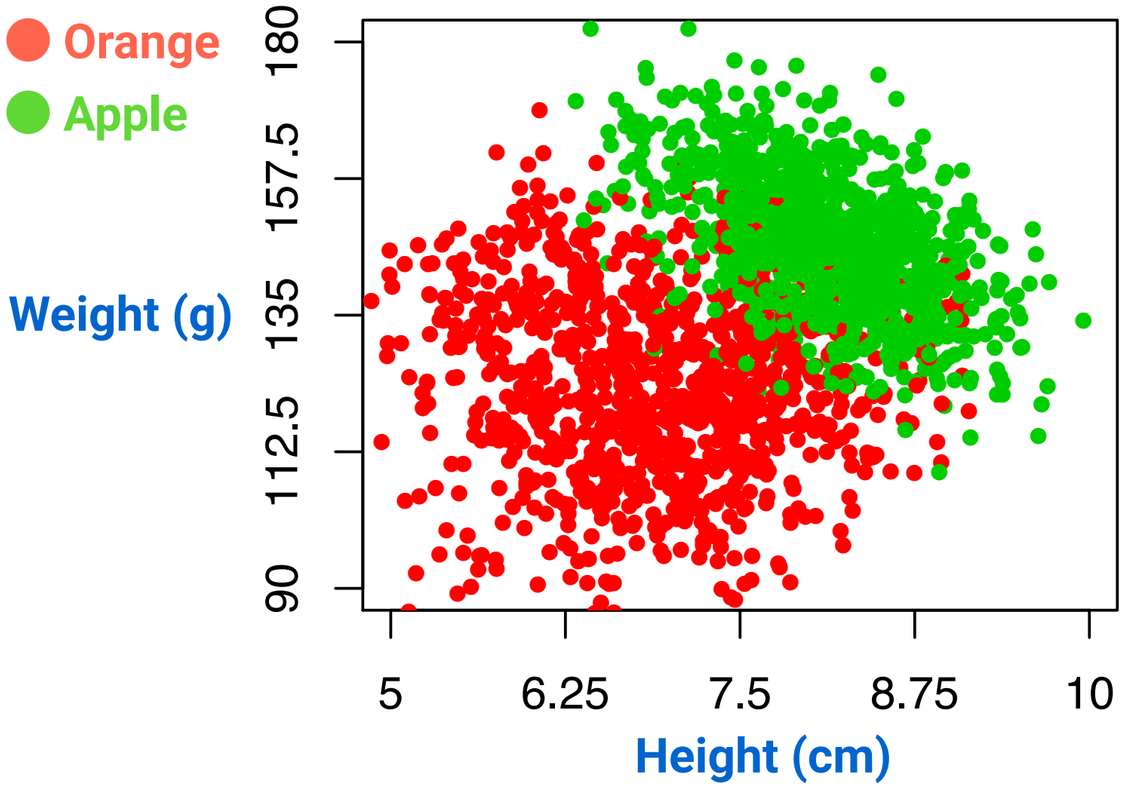

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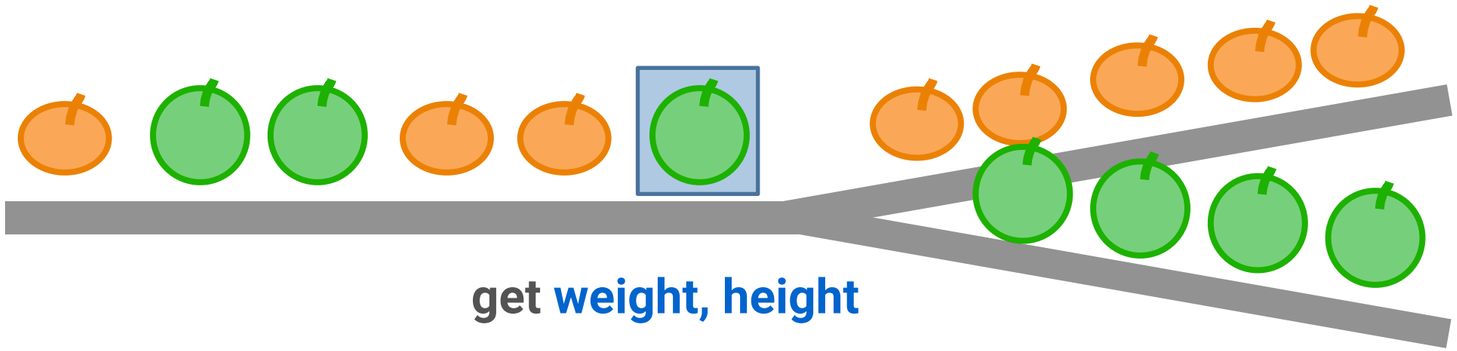

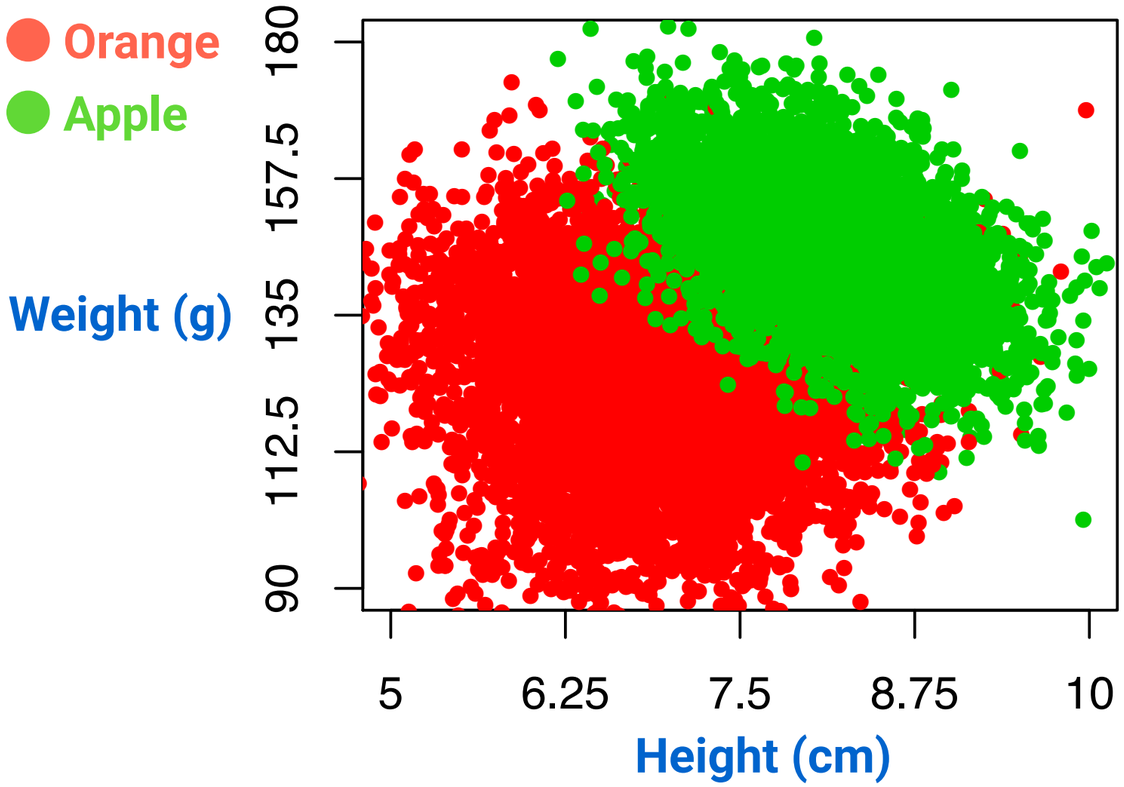

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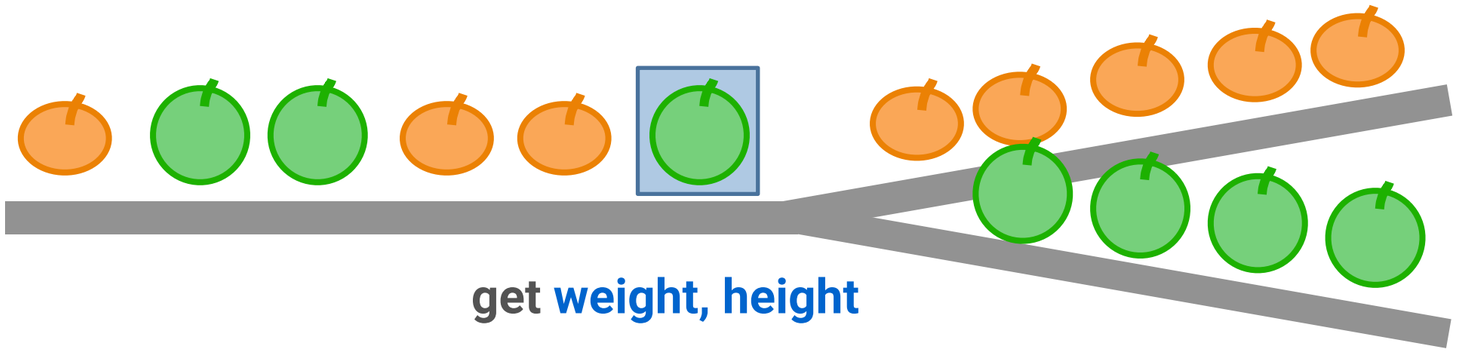

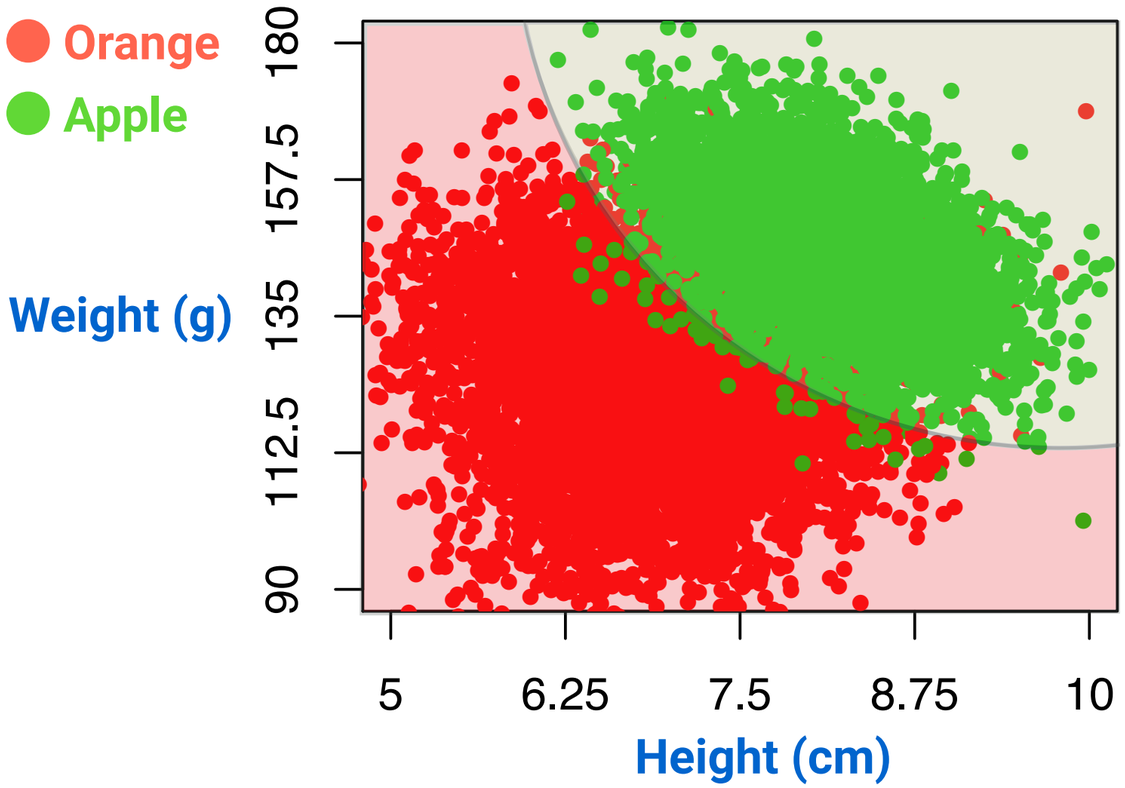

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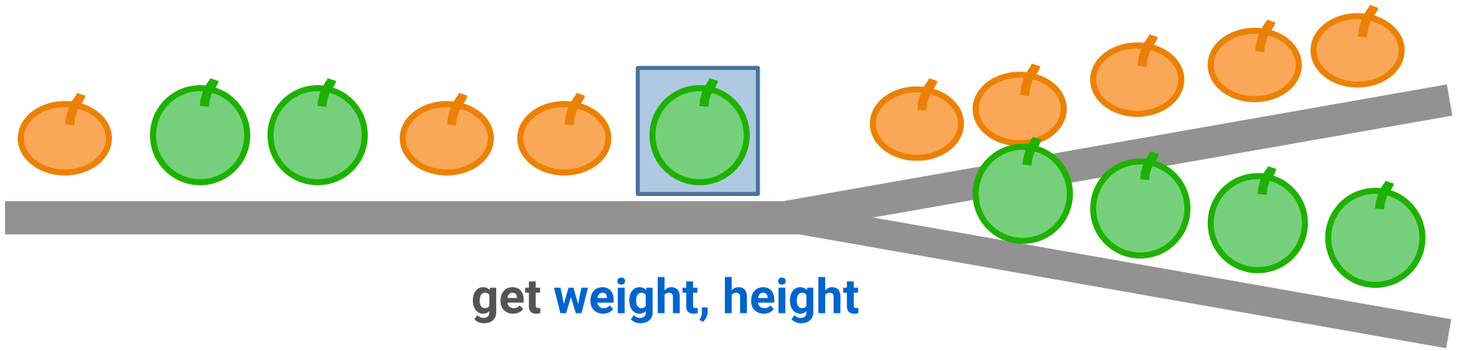

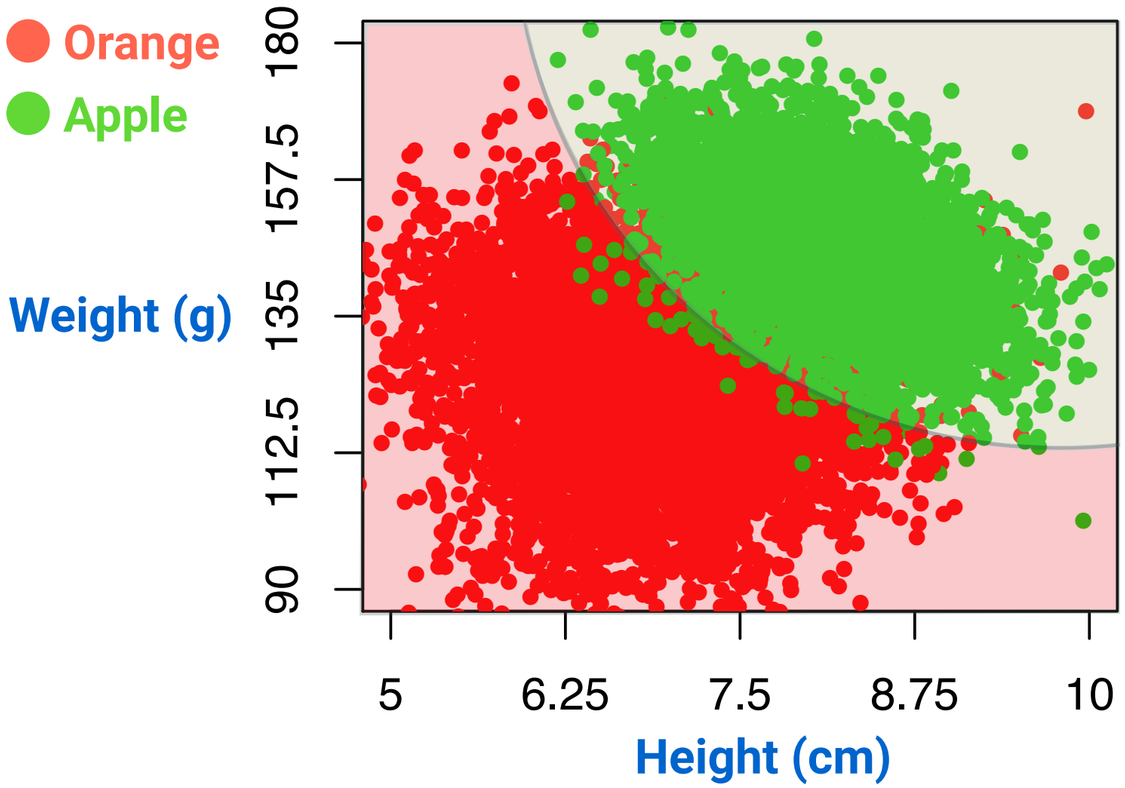

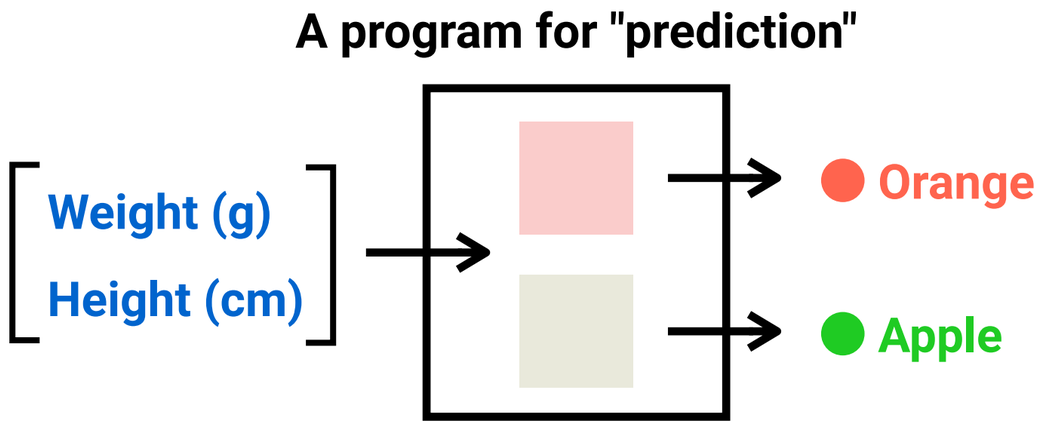

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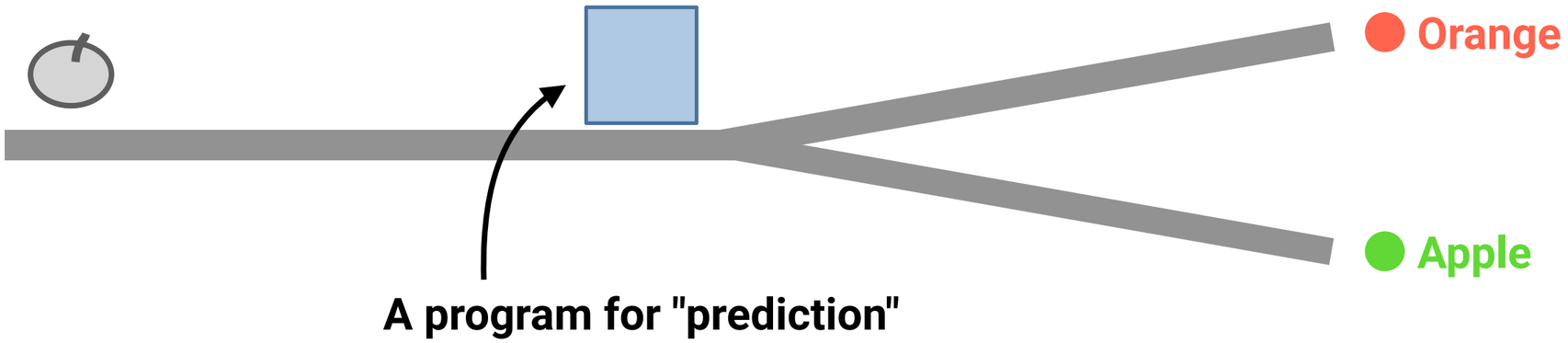

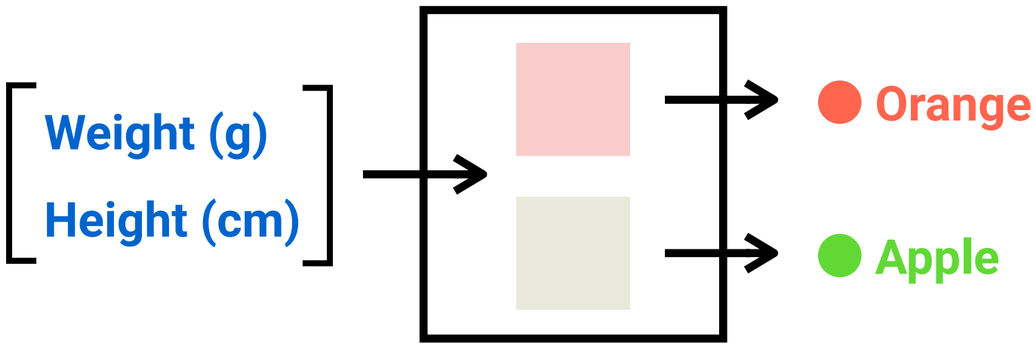

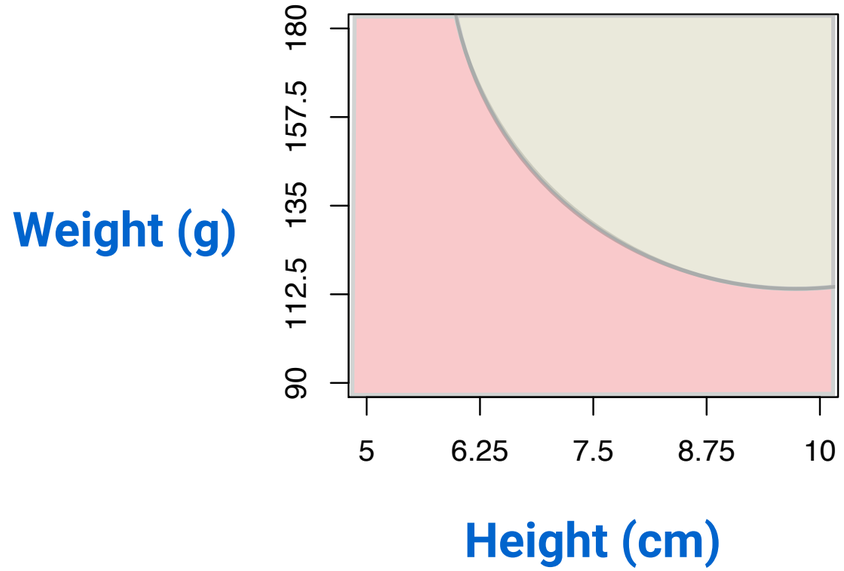

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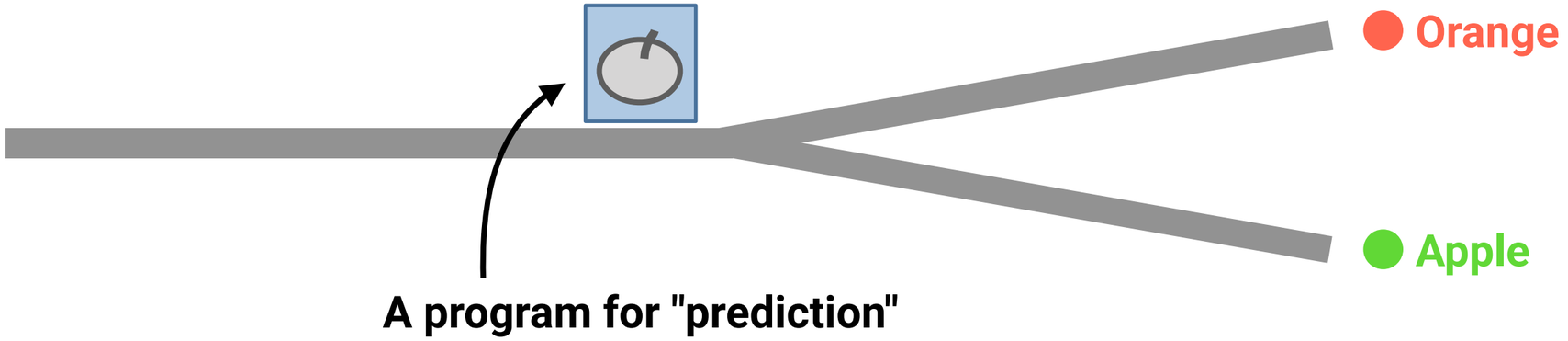

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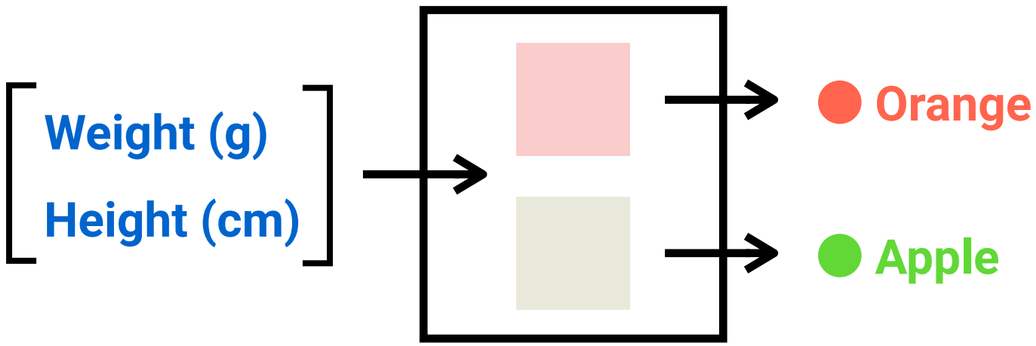

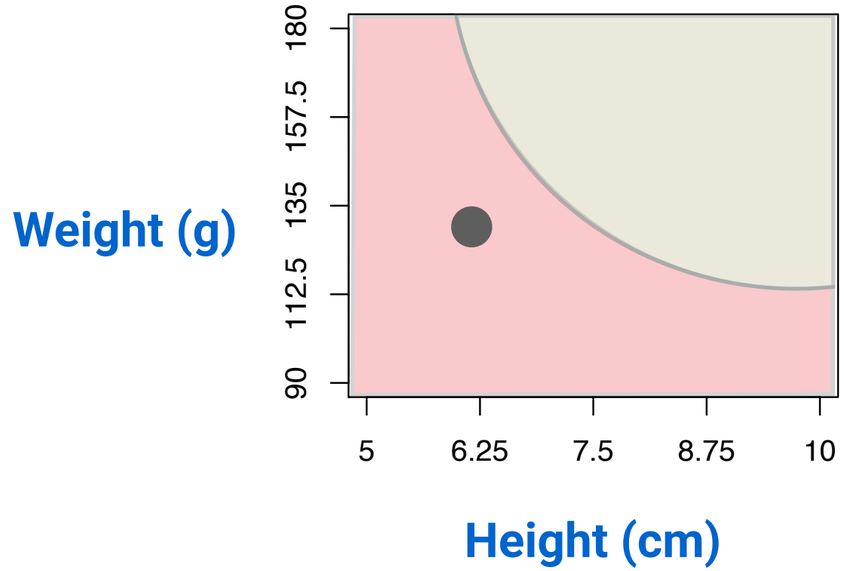

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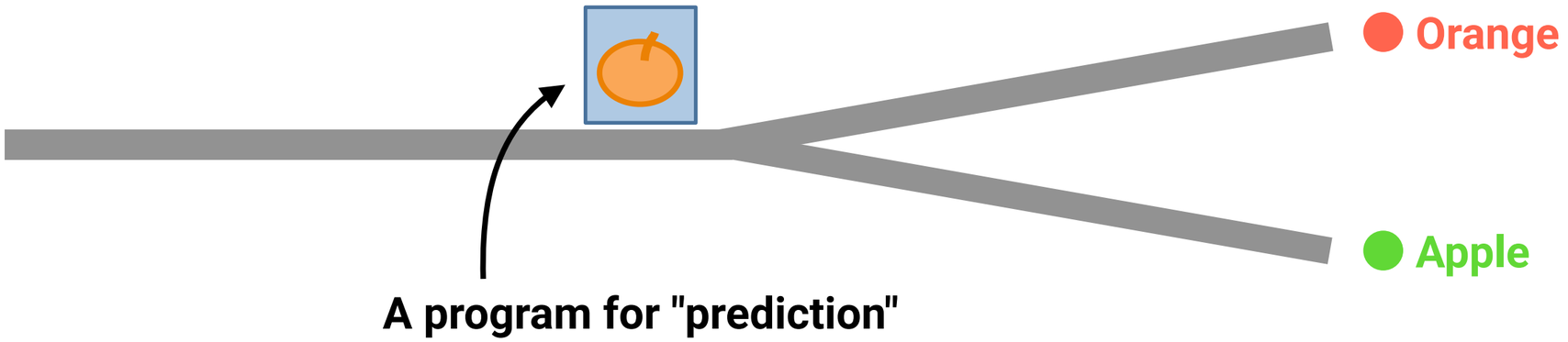

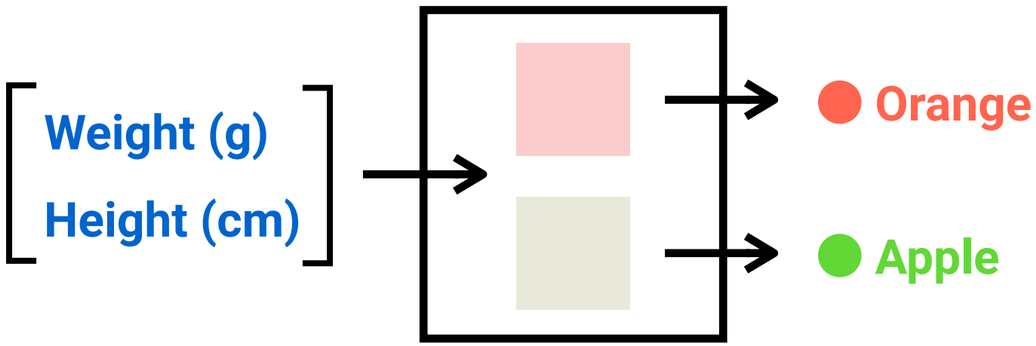

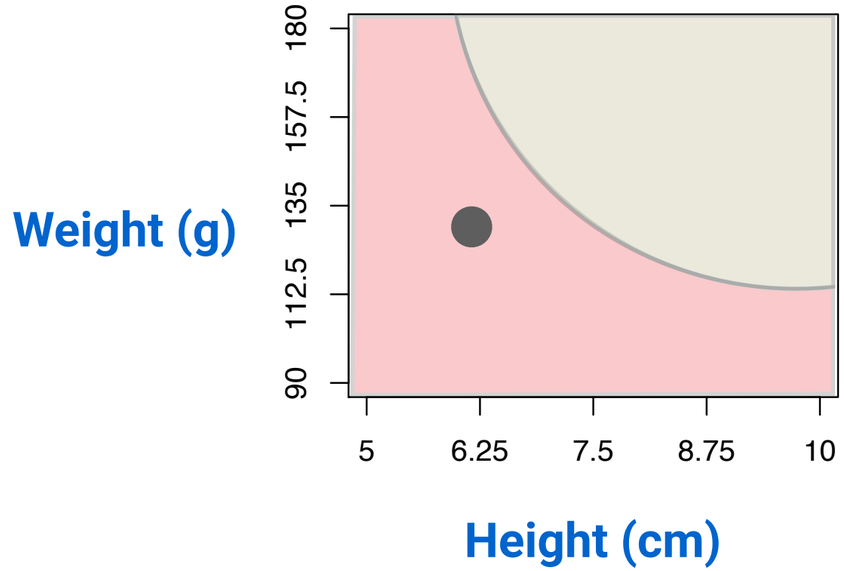

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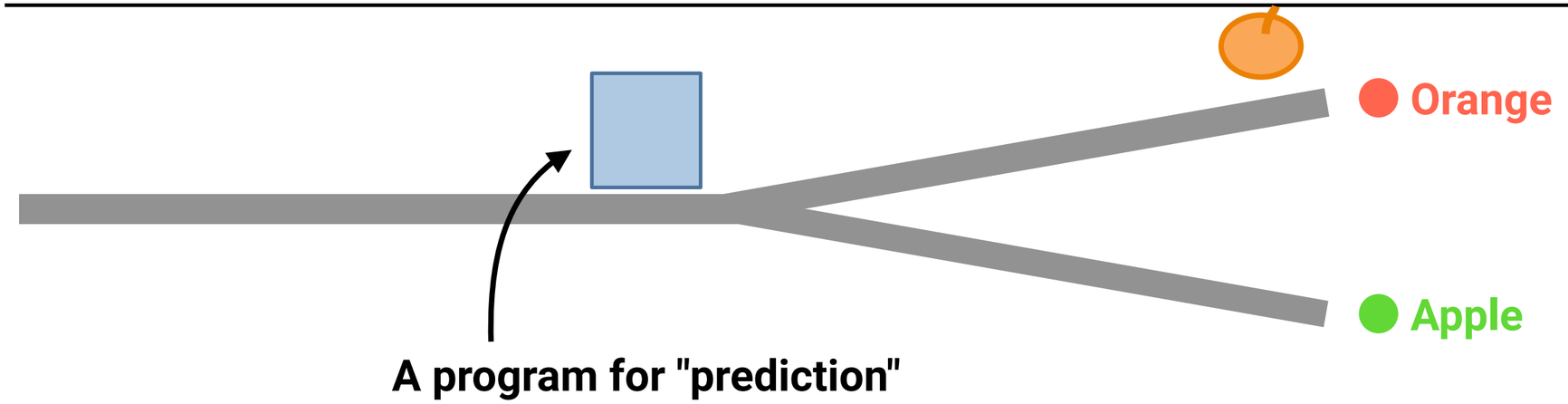

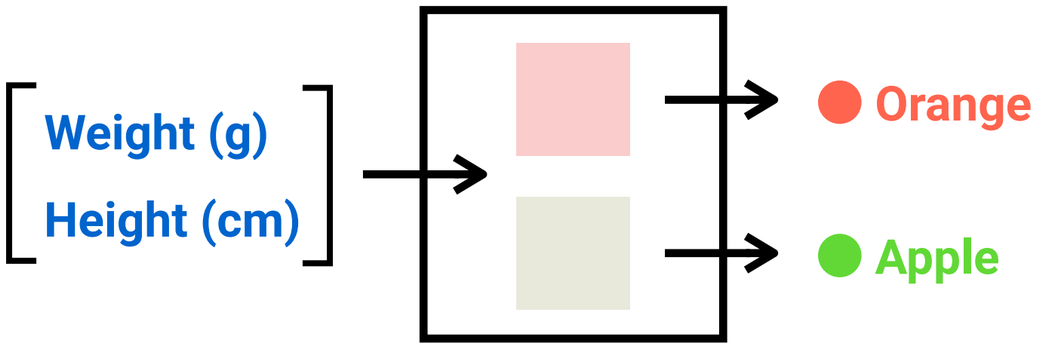

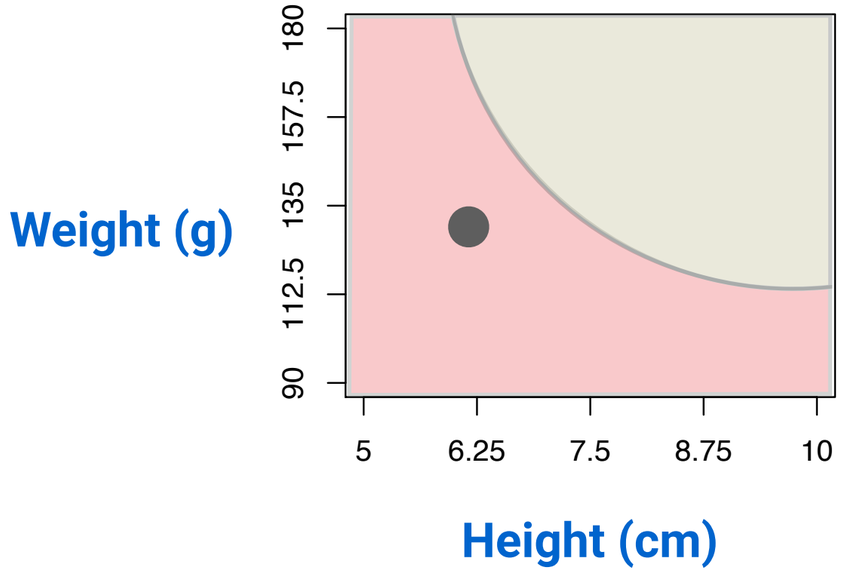

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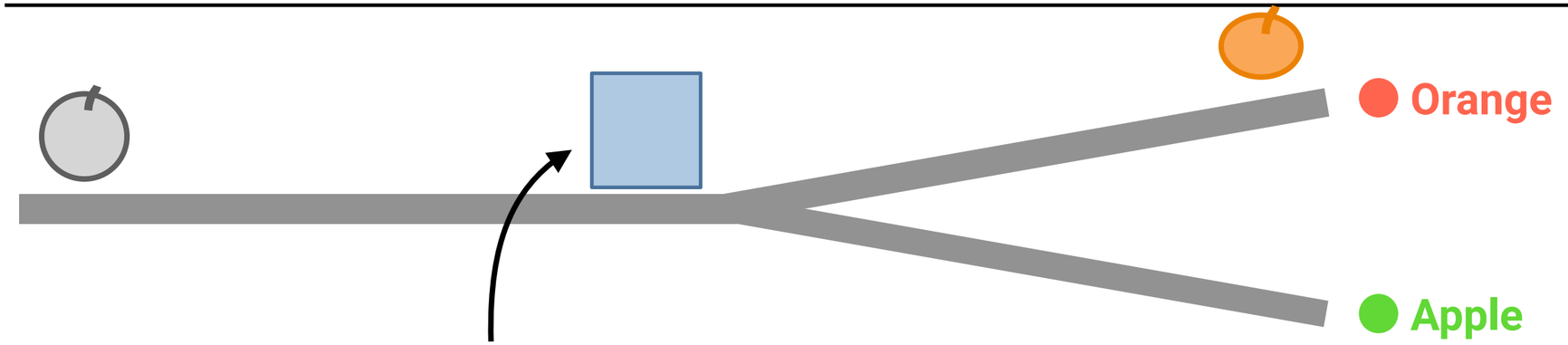

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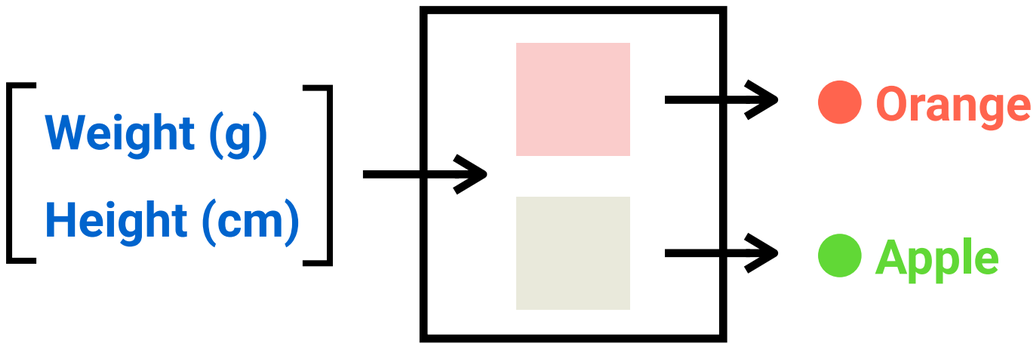

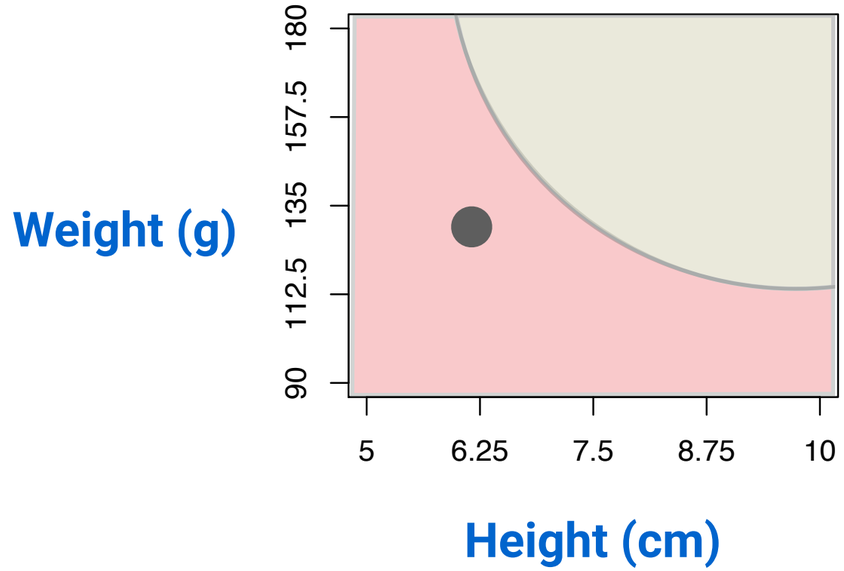

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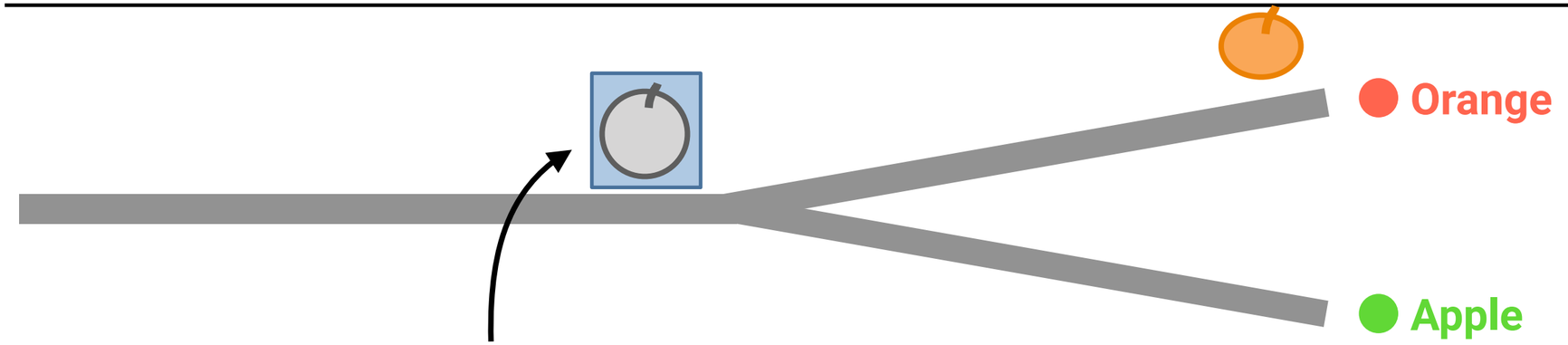

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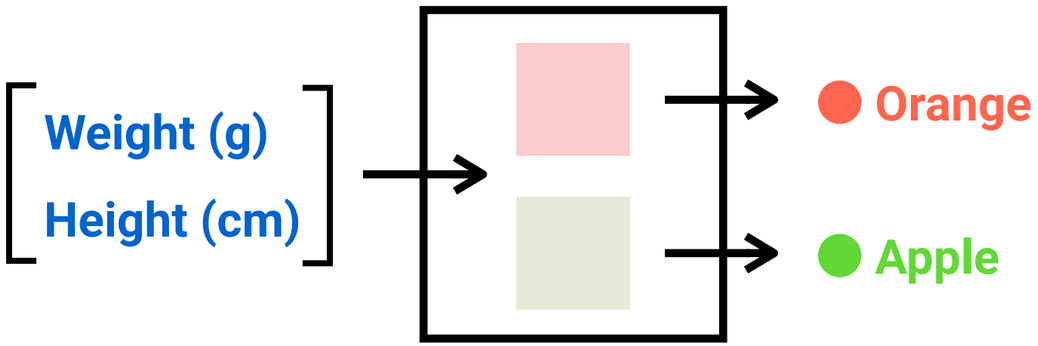

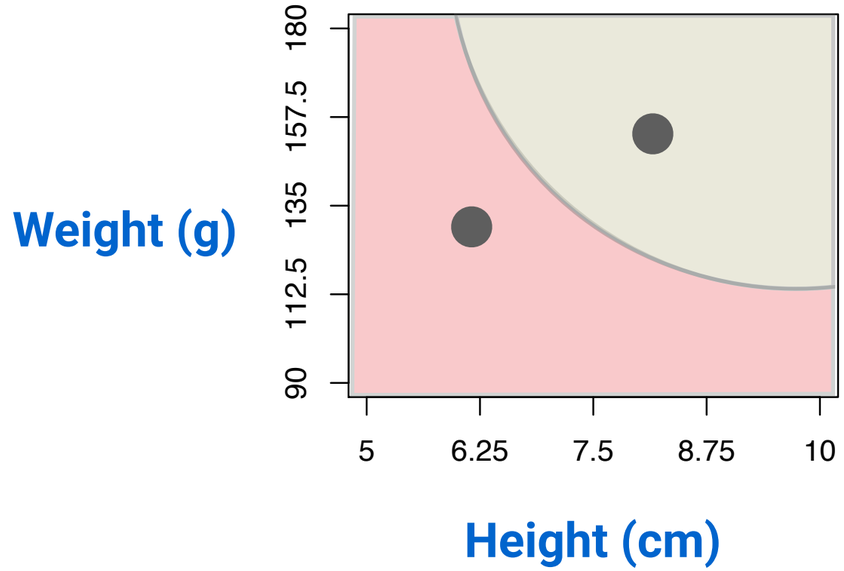

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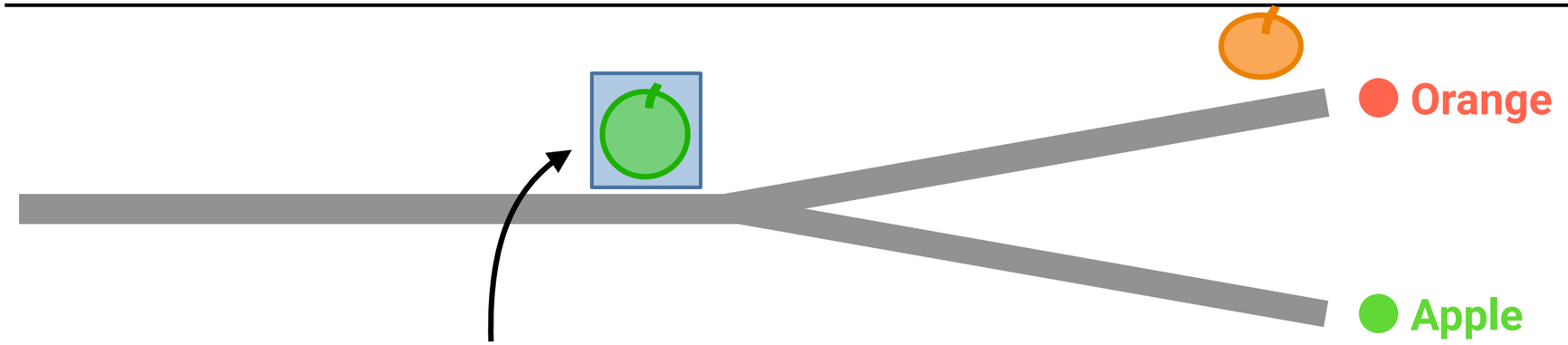

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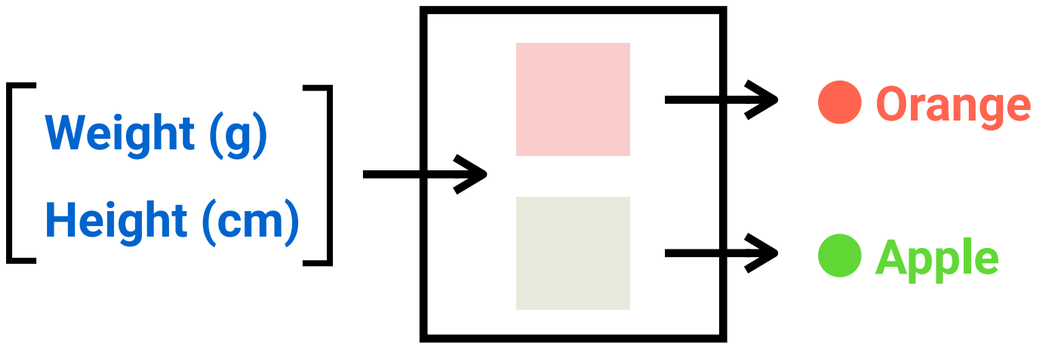

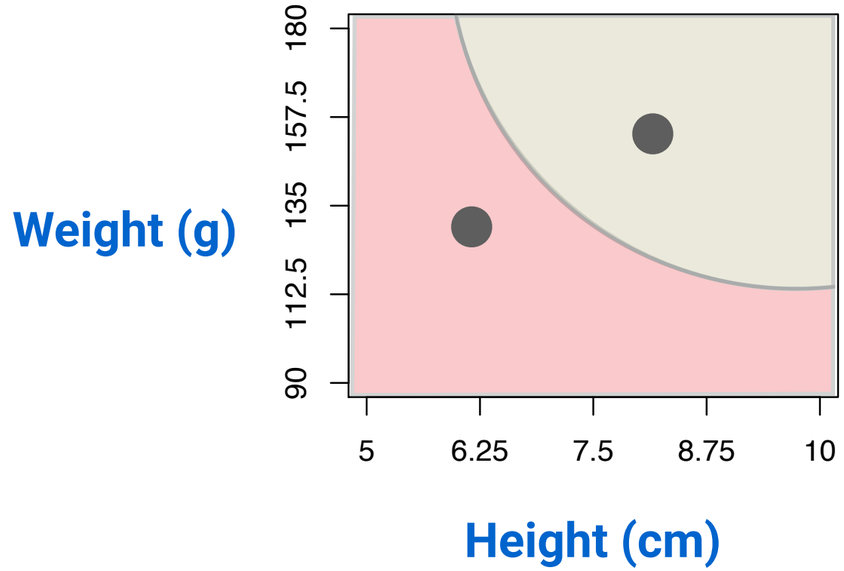

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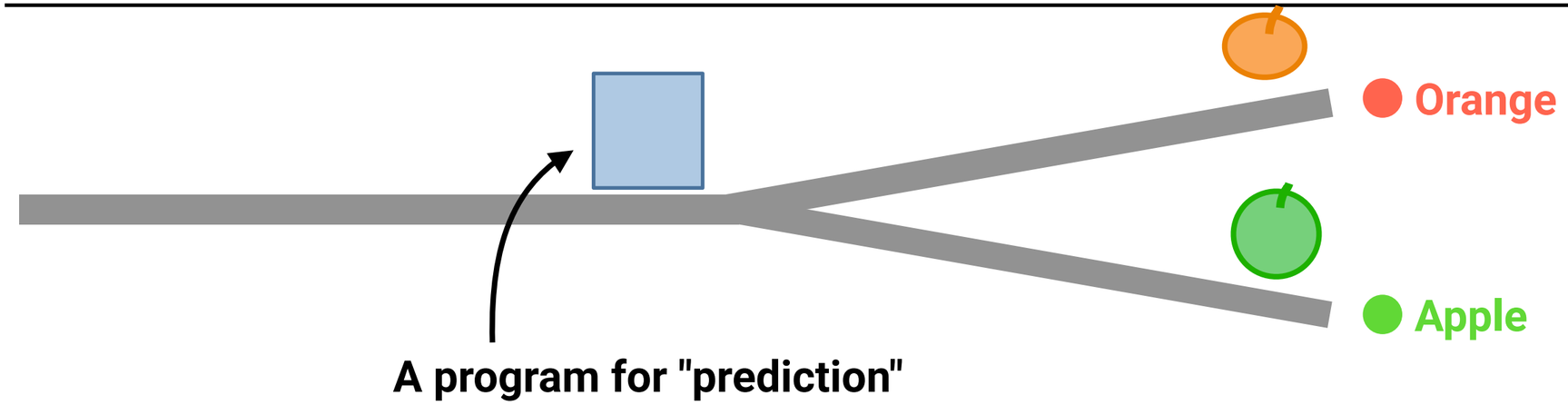

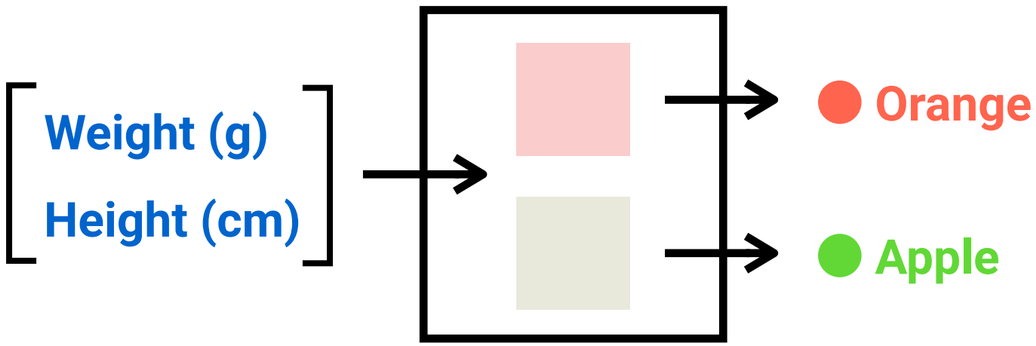

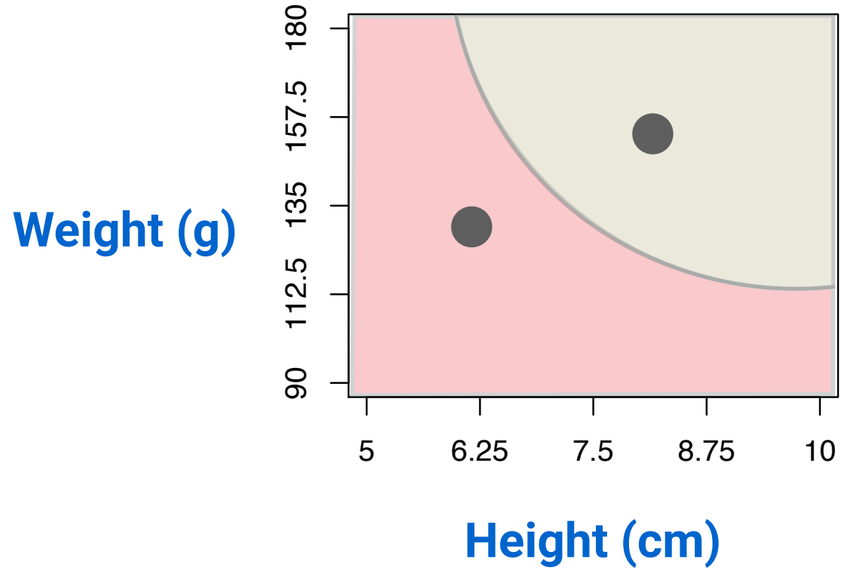

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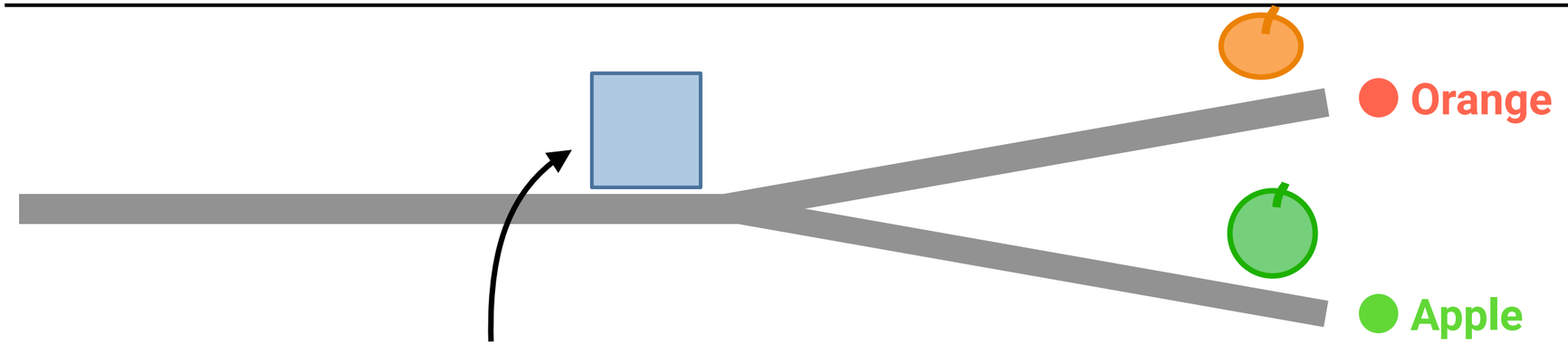

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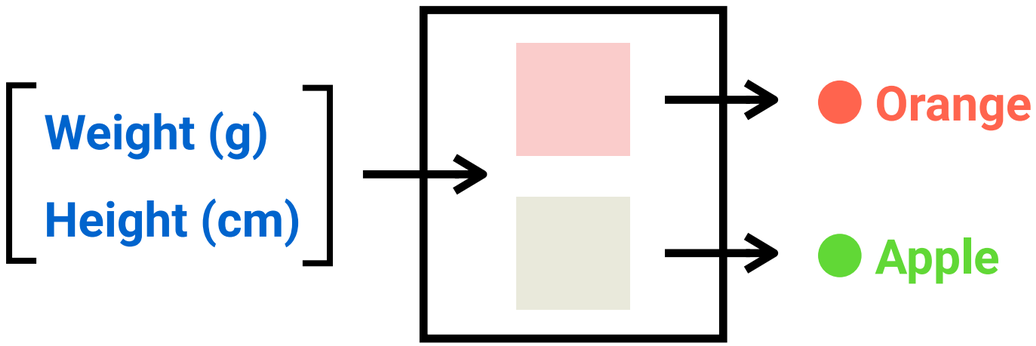
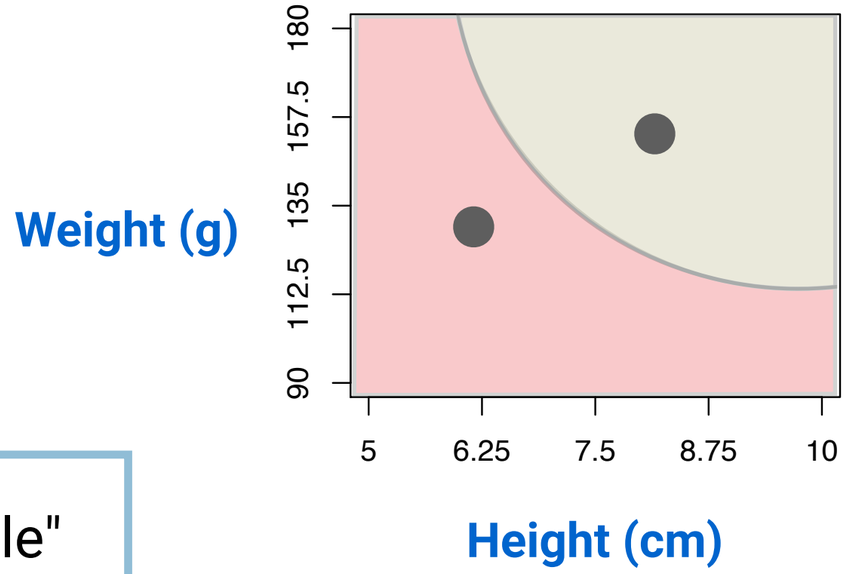
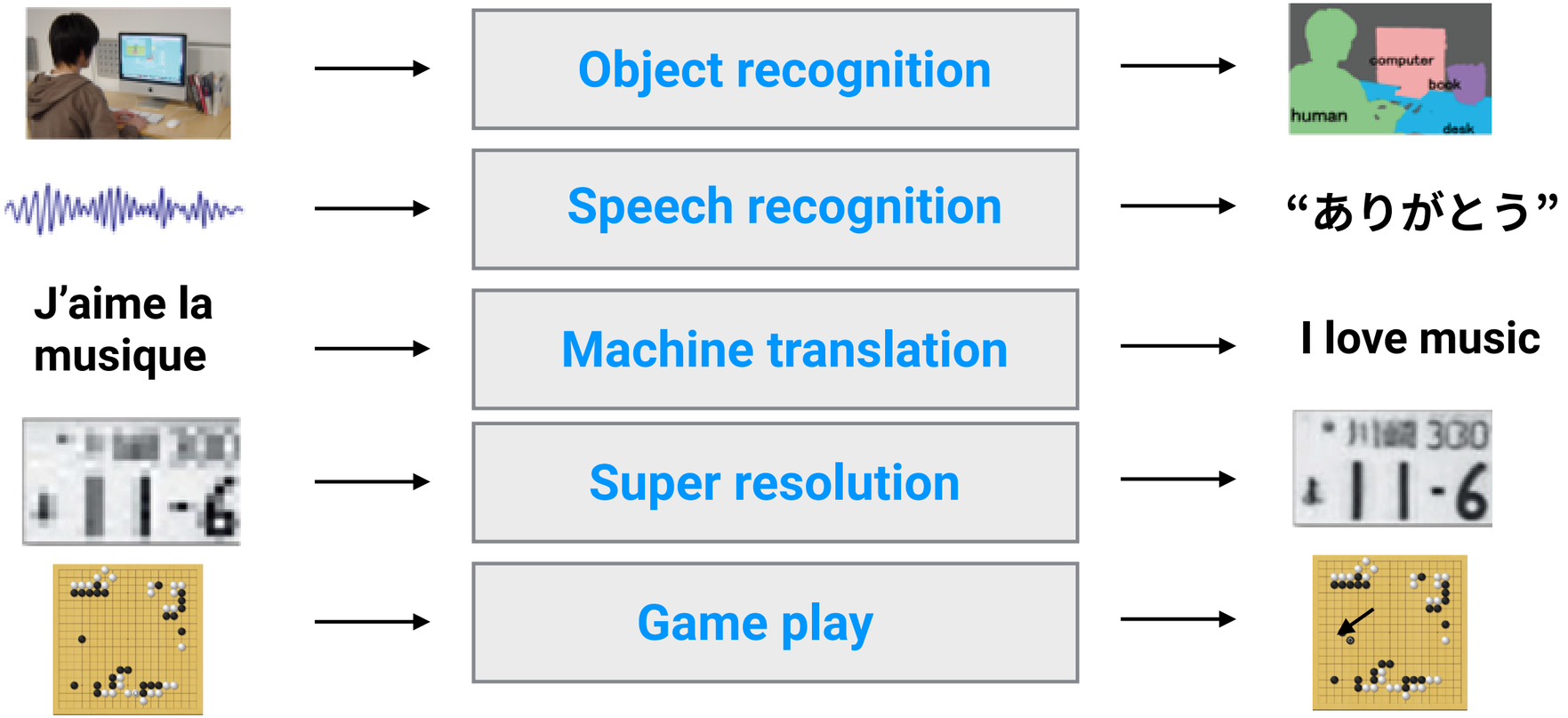




Now we got a computer program to predict "orange or apple" for any unseeen ones **directly from collected data**

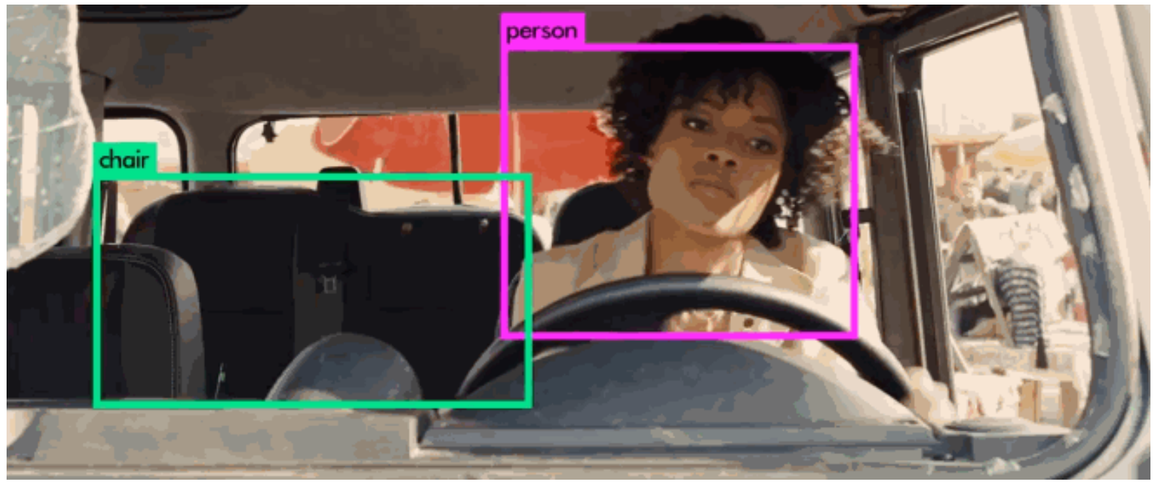
ML is a new (lazy) way of programming

ML generates a computer program just by giving many input-output examples
even when we **don't know** the underlying mechanism between inputs and outputs.



This simple idea is more powerful than you may think

Remarkably powerful when we have relevant input-output examples (it's useless if we don't)



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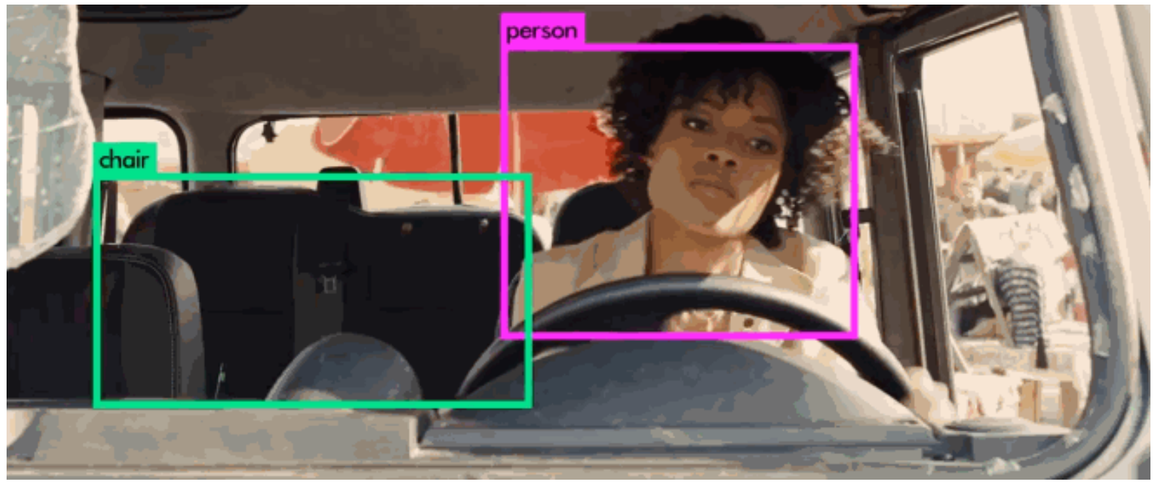
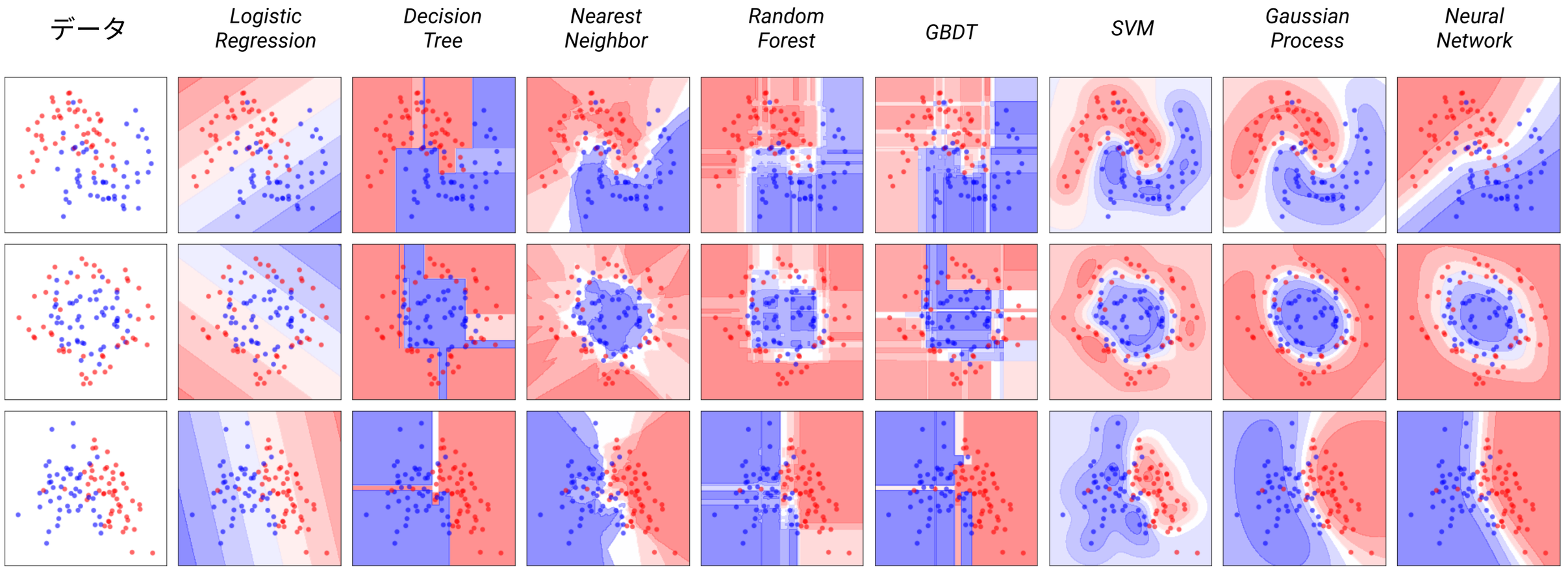


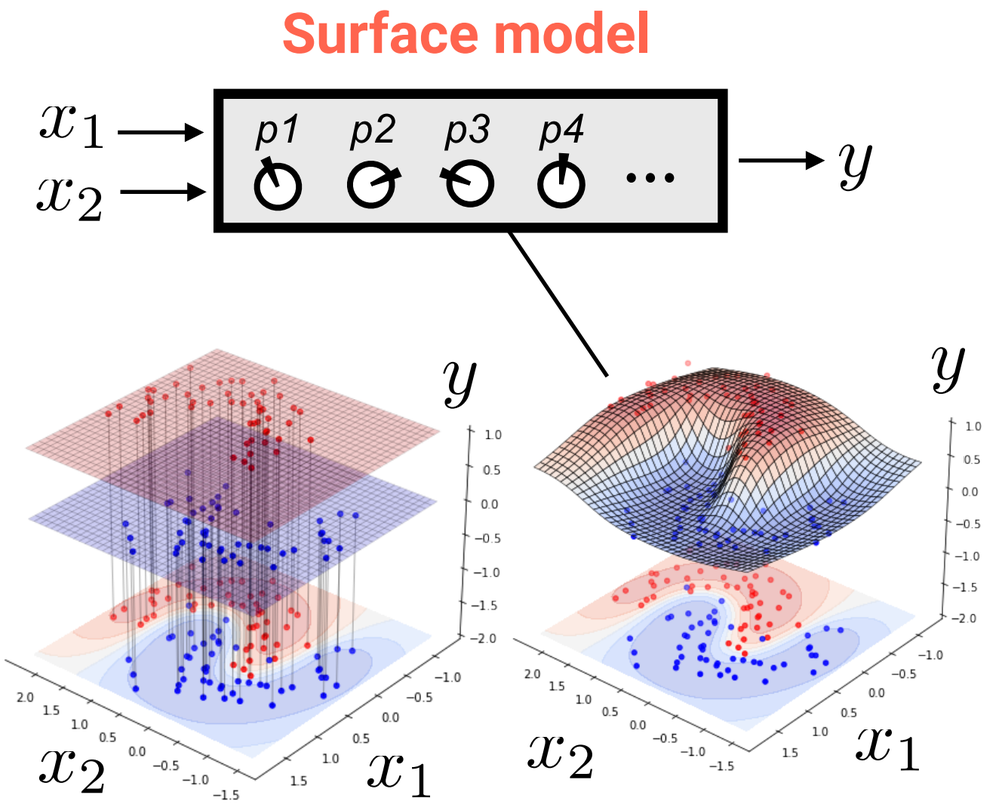
Many ways to mathematically represent the boundary

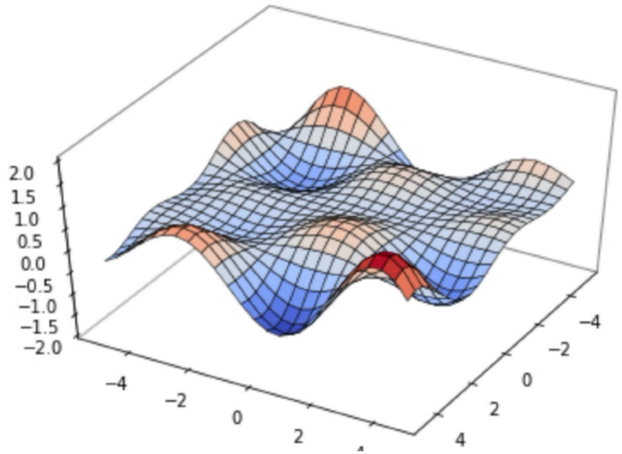
This is why you see too many algorithms when you start to learn ML…

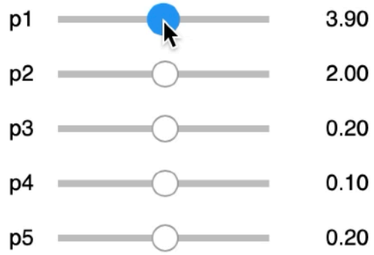


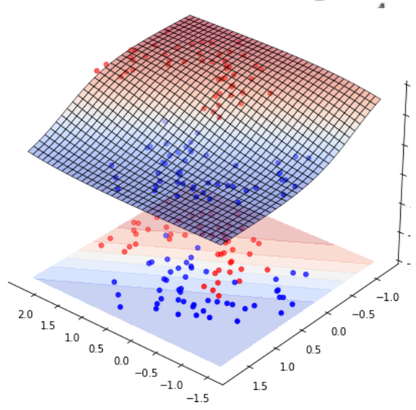
But anyway, we're just tweaking parameters for a good fit

Internally, we're just fitting a surface to given points by adjusting its parameter values.

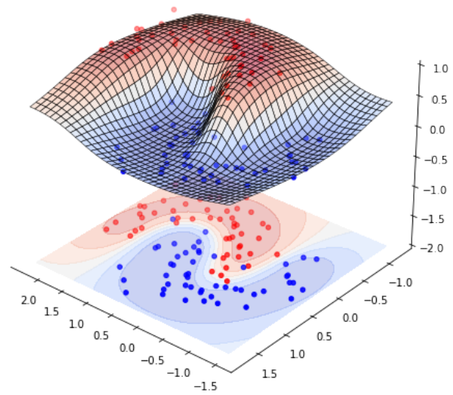




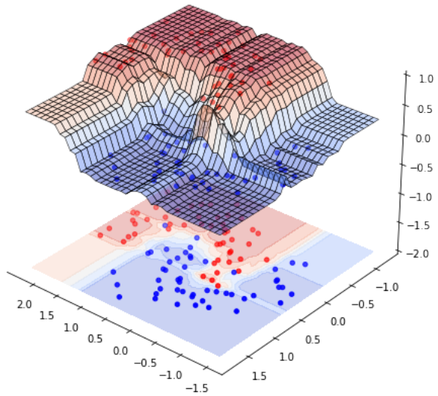




Logistic Regression



Gaussian Process



Random Forest

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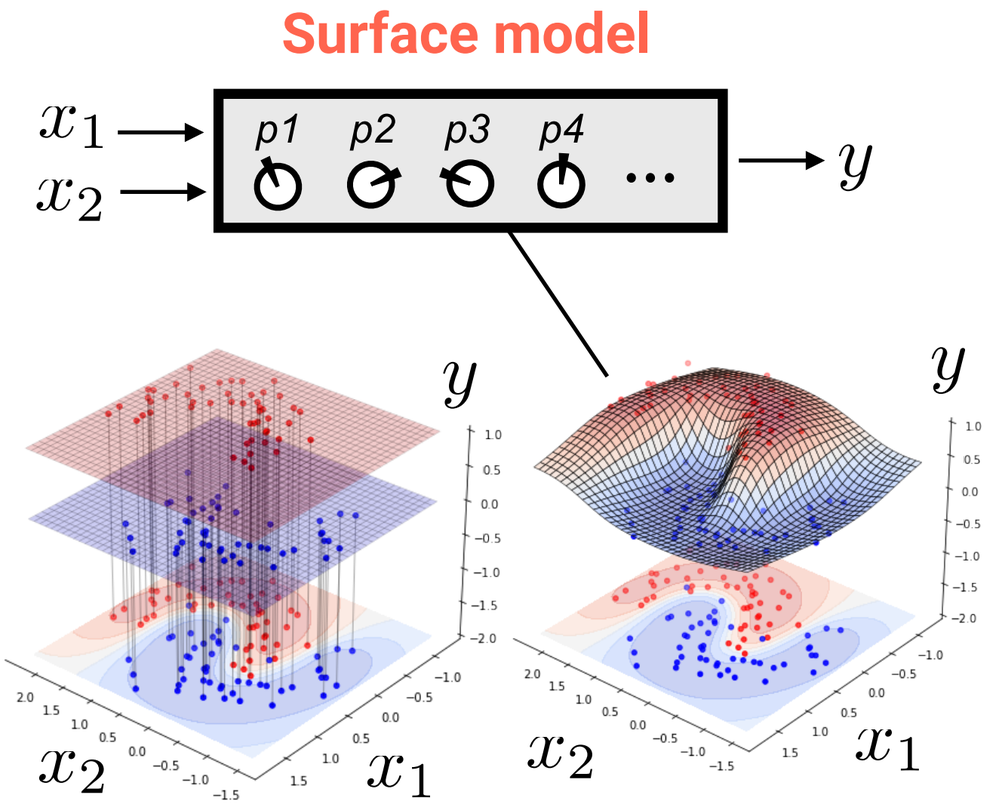

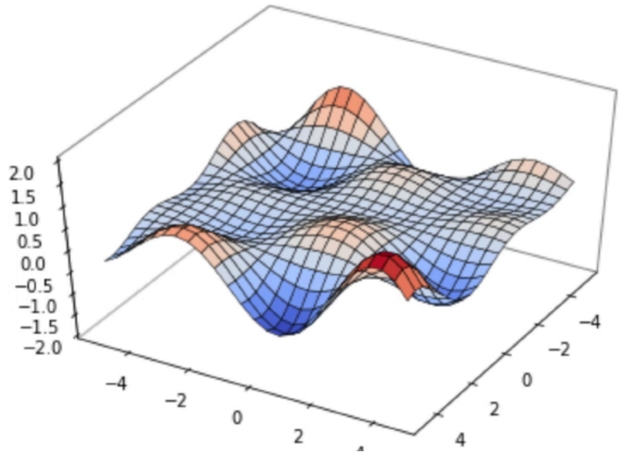

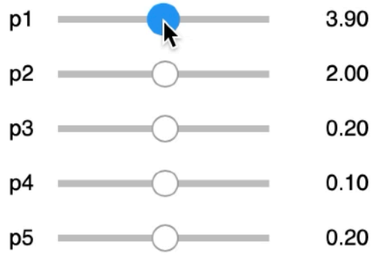

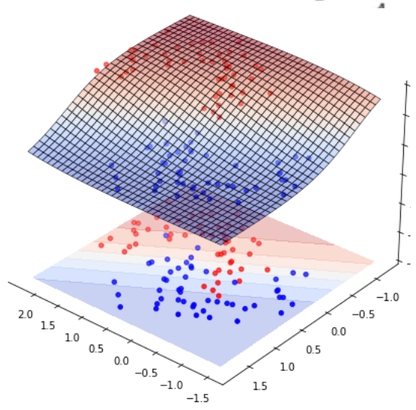

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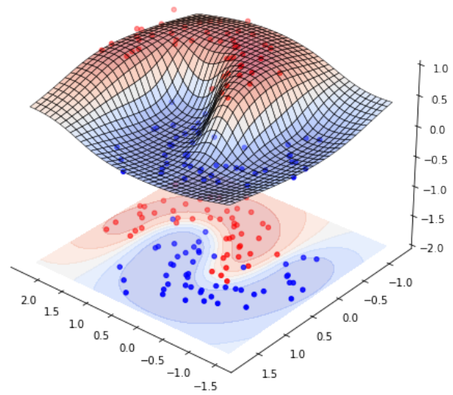

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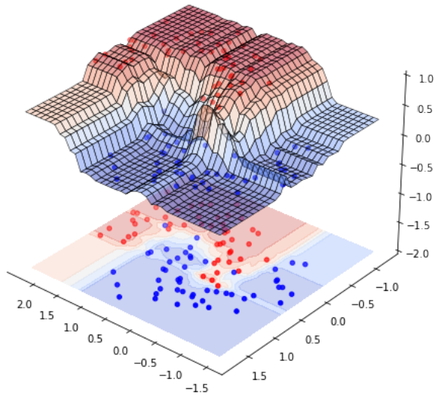
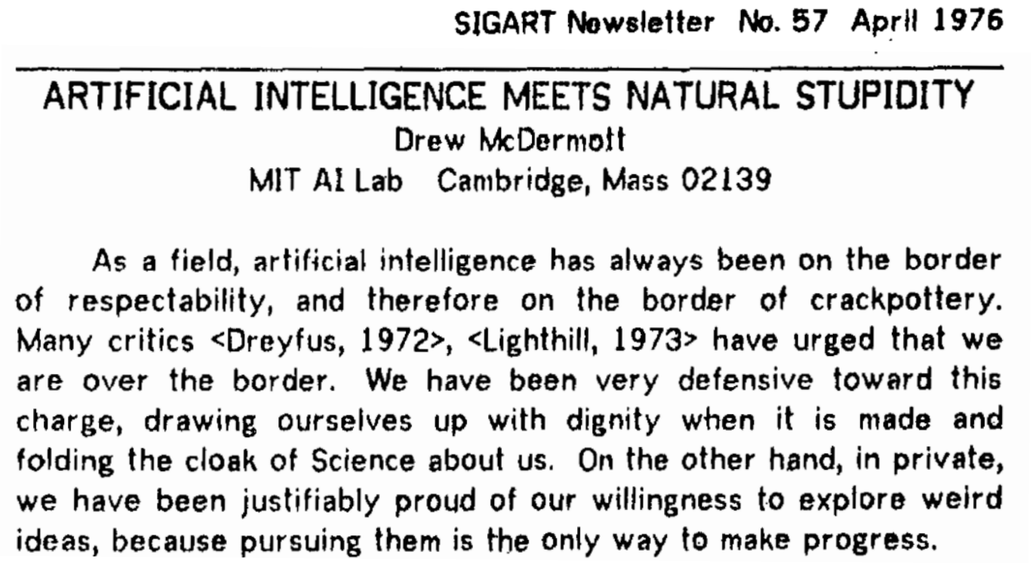


Random Forest

Pitfall: The lure of wishful wordings

The current ML is stunningly powerful but it's very different from our sci-fi image of "AI".
Be careful about these "wishful" wordings that needlessly distract and mislead us!

"Artificial intelligence" doesn't mean that we have something artificial also intelligent like us.
"Machine learning" doesn't mean that machines actually learn things like us.



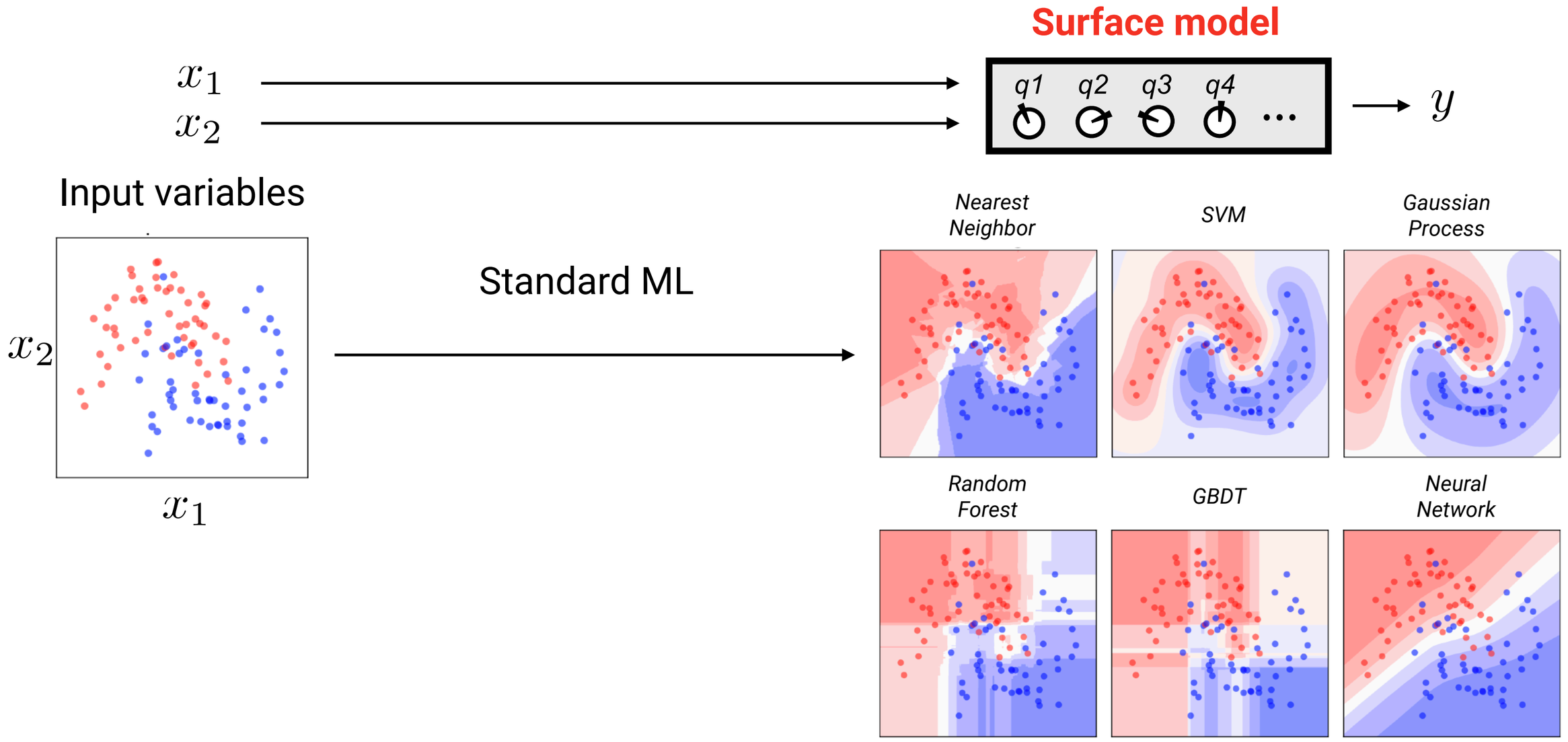
SIGART Newsletter No. 57 April 1976

ARTIFICIAL INTELLIGENCE MEETS NATURAL STUPIDITY

Drew McDermott
MIT AI Lab Cambridge, Mass 02139

As a field, artificial intelligence has always been on the border of respectability, and therefore on the border of crackpottery. Many critics <Dreyfus, 1972>, <Lighthill, 1973> have urged that we are over the border. We have been very defensive toward this charge, drawing ourselves up with dignity when it is made and folding the cloak of Science about us. On the other hand, in private, we have been justifiably proud of our willingness to explore weird ideas, because pursuing them is the only way to make progress.

Deep Learning (Representation Learning)



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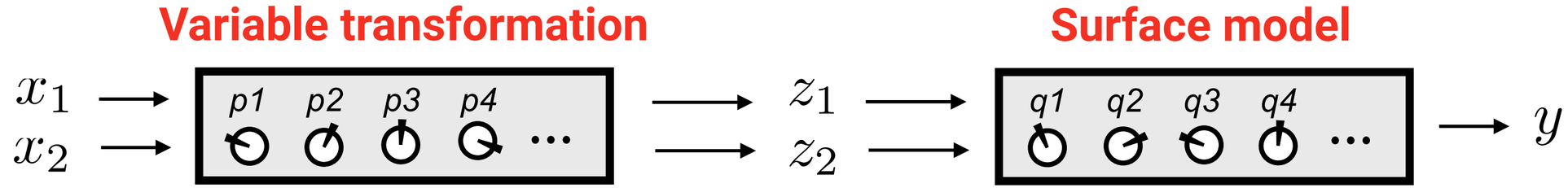
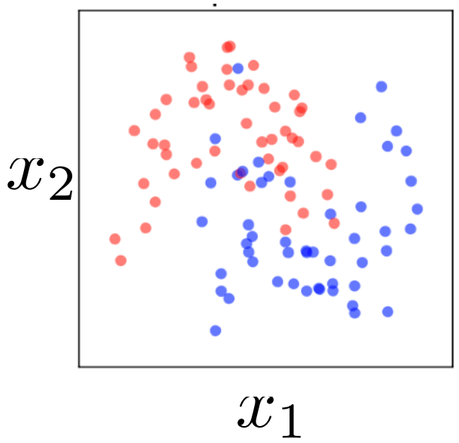


Input variables



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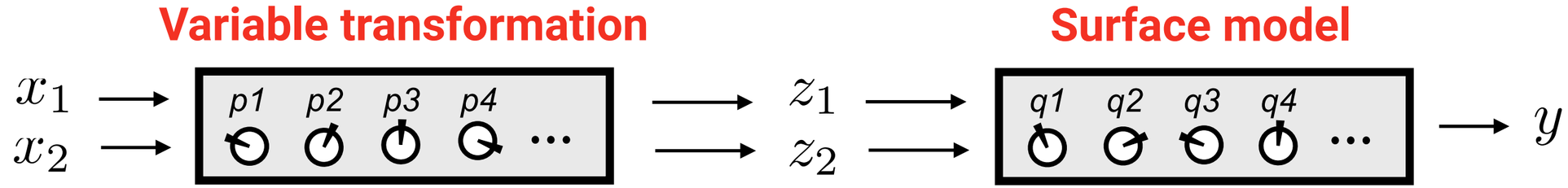

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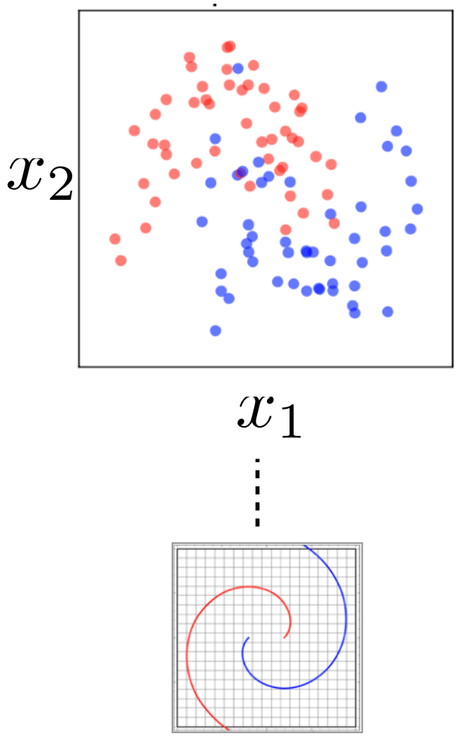

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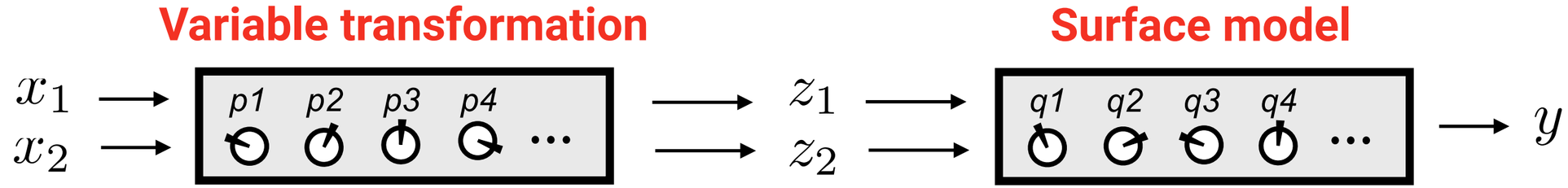

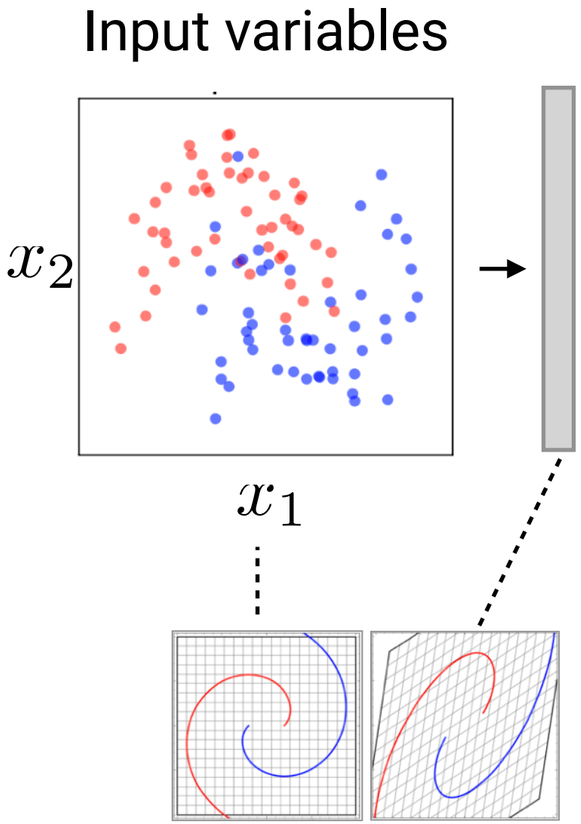

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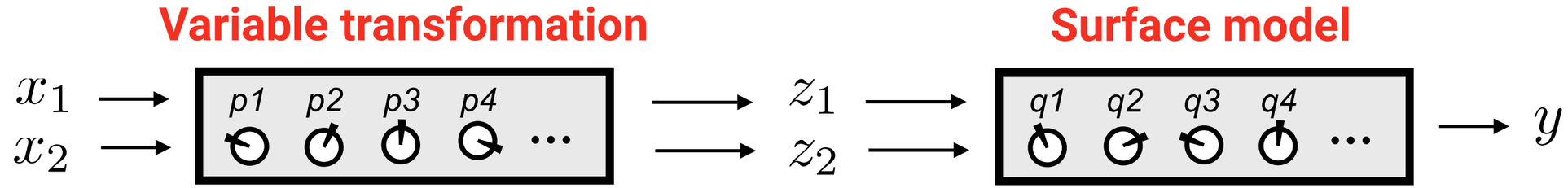

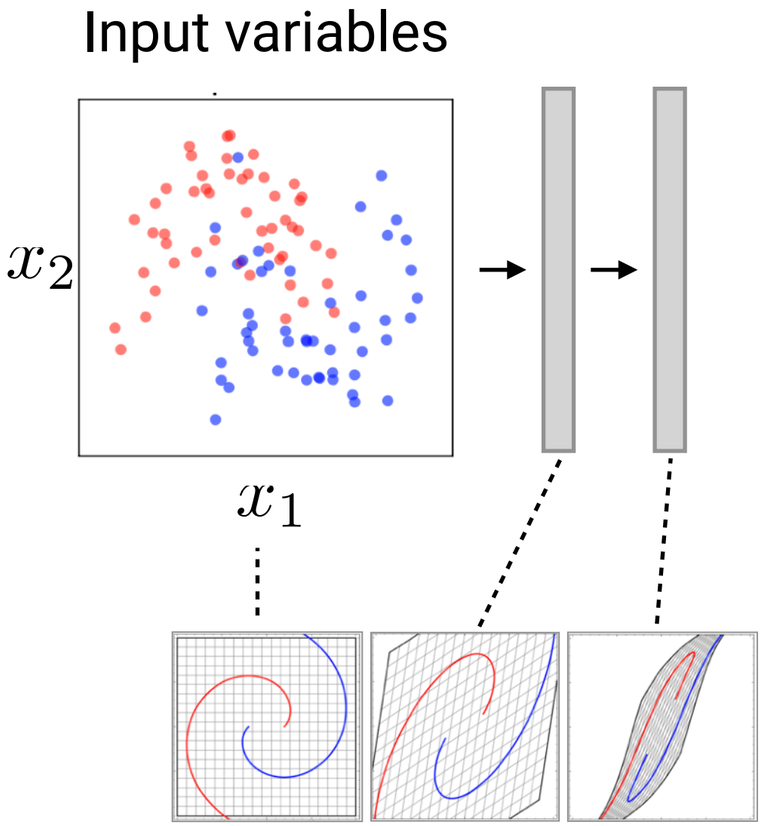

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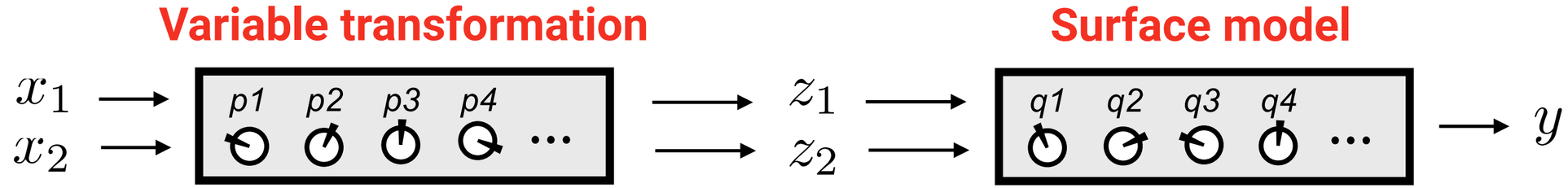

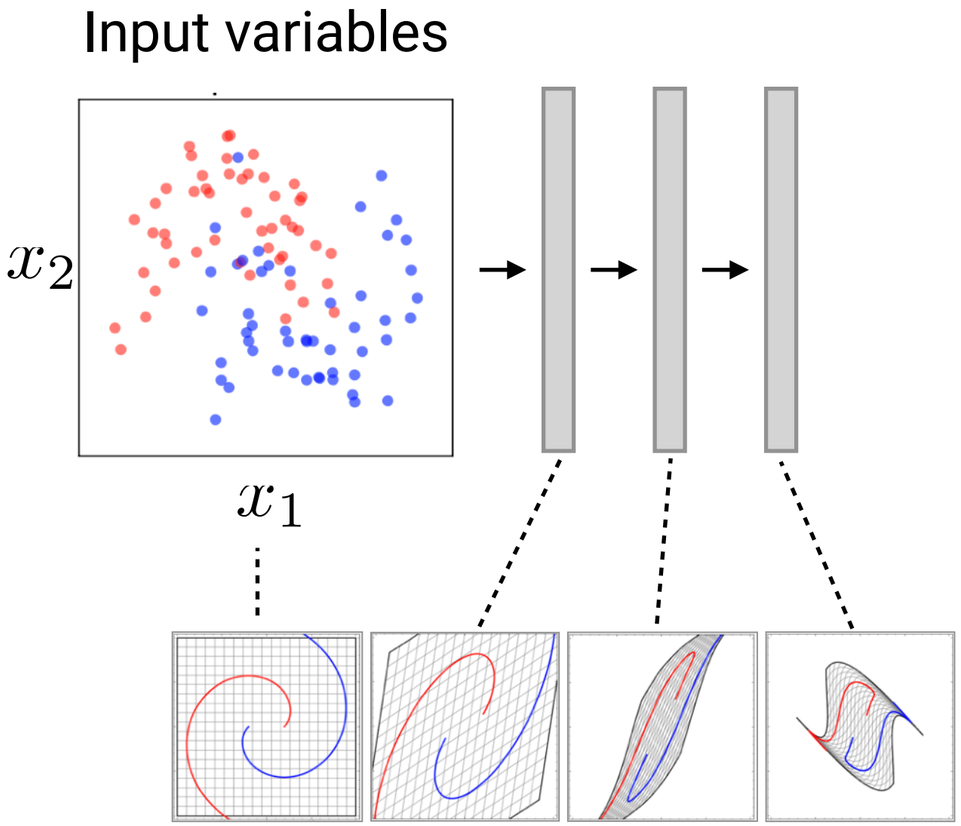

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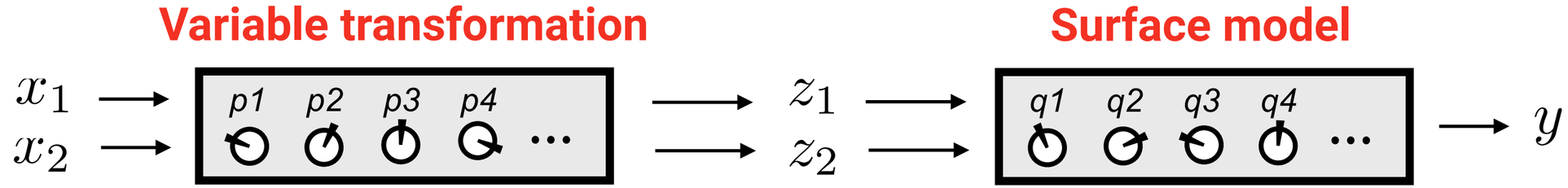

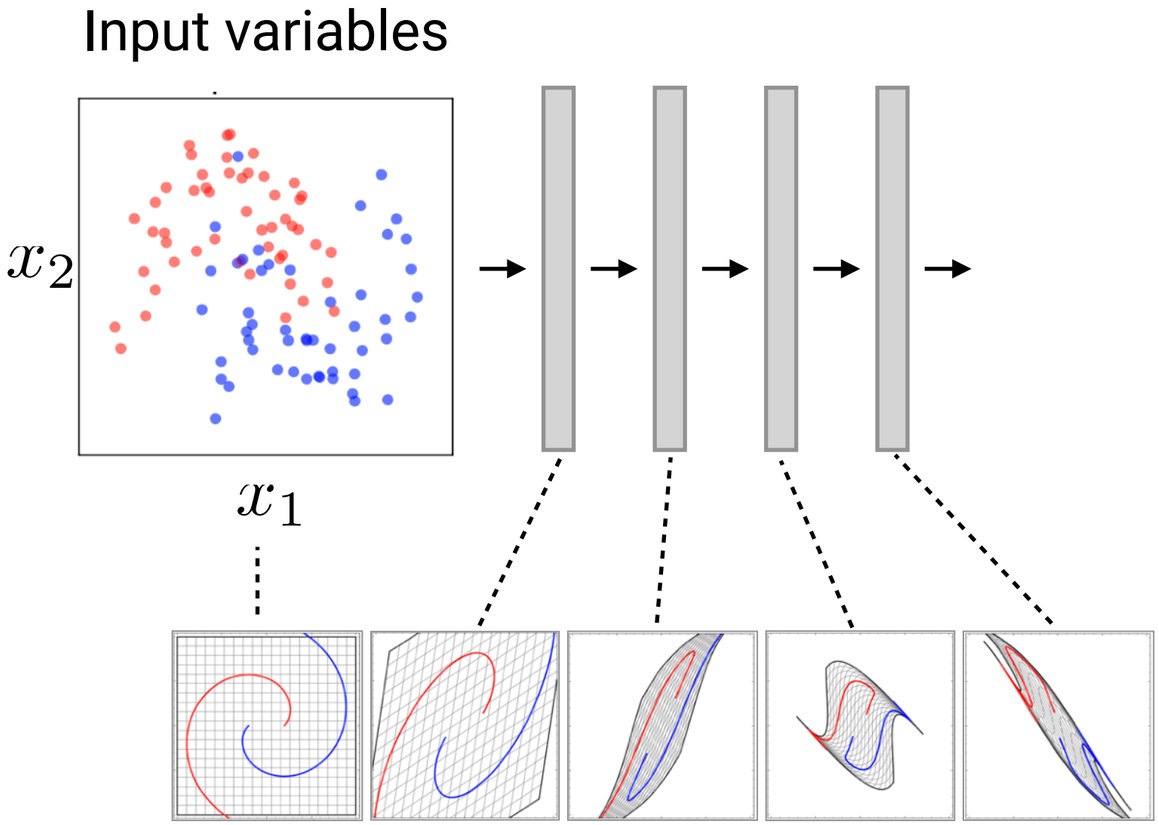

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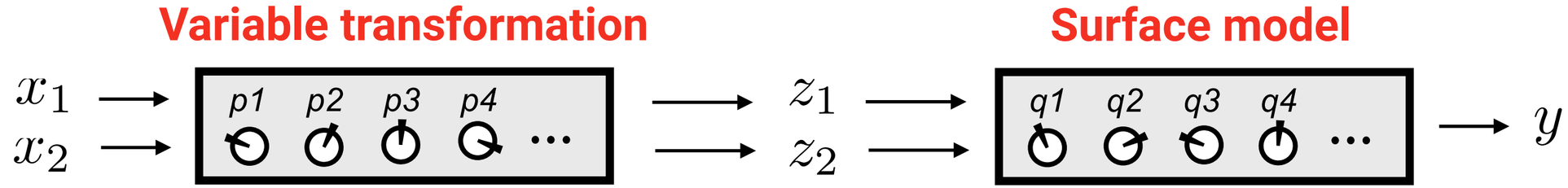

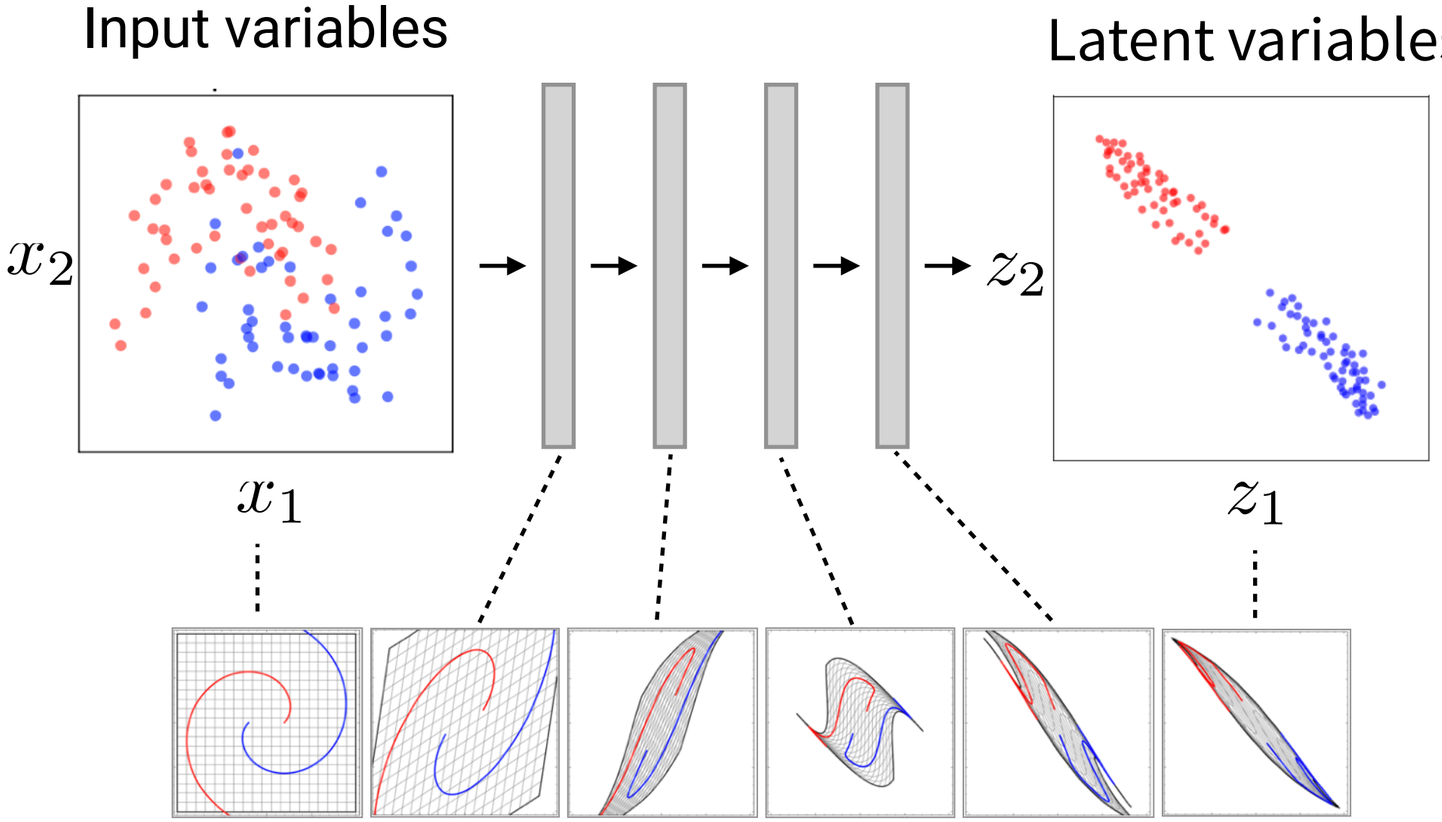

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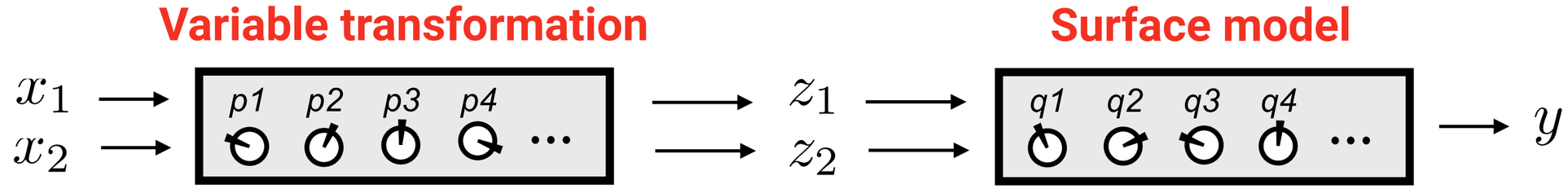

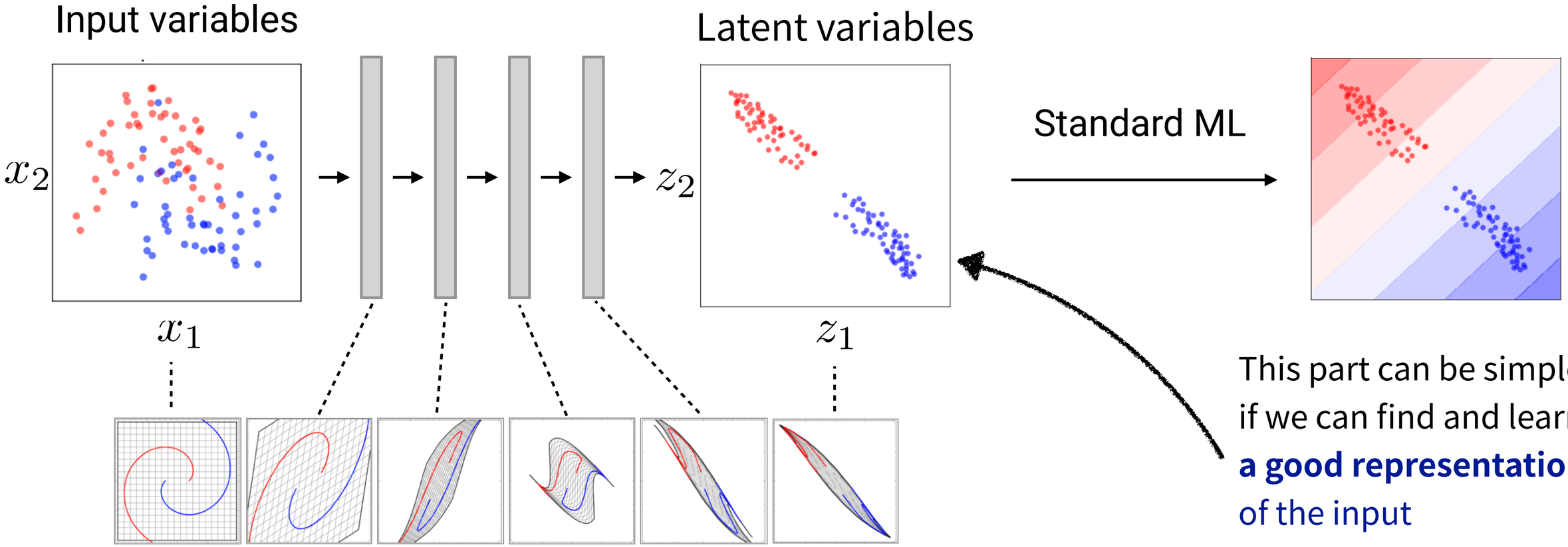

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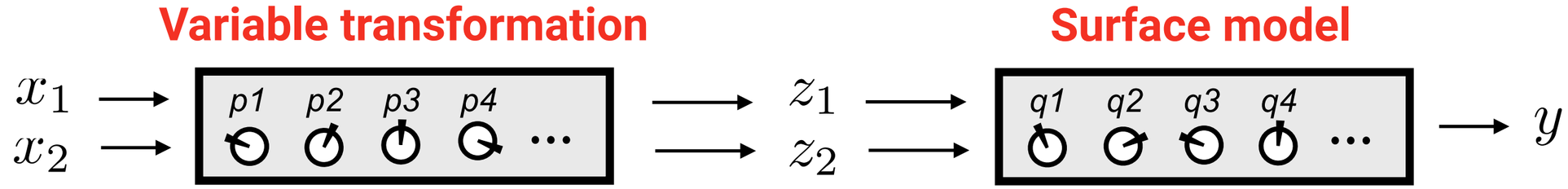

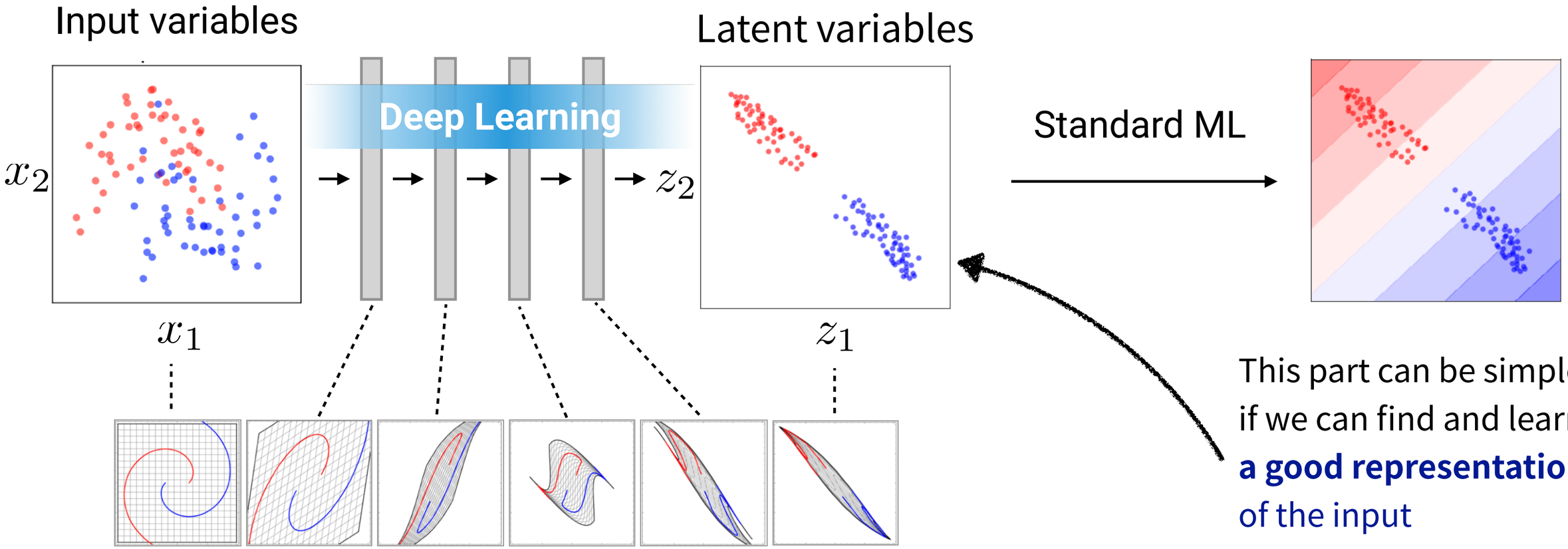

The Dark Side: Modern Aspects of ML

- **High dimensionality:** Too many input variables

  We tend to use many input variables because ML is completely unaware of any information **not** in the input variables. Missing relevant factors results in spurious correlation.

  e.g.) 100 x 100 RGB image = 30 thousand variables

  1000 x 1000 RGB image = 3 million variables

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  1000 x 1000 RGB image = 3 million variables

- **Overrepresentation:** Too many parameters

  Remember that we're fitting a surface with *hundreds million* parameters in a *several million* dimensional space!

  e.g.) 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

The Dark Side: Modern Aspects of ML

- **Data hungriness:** Big data is big for human, but can be too small for ML models…

  As a result, it requires huge data to make current ML models work.

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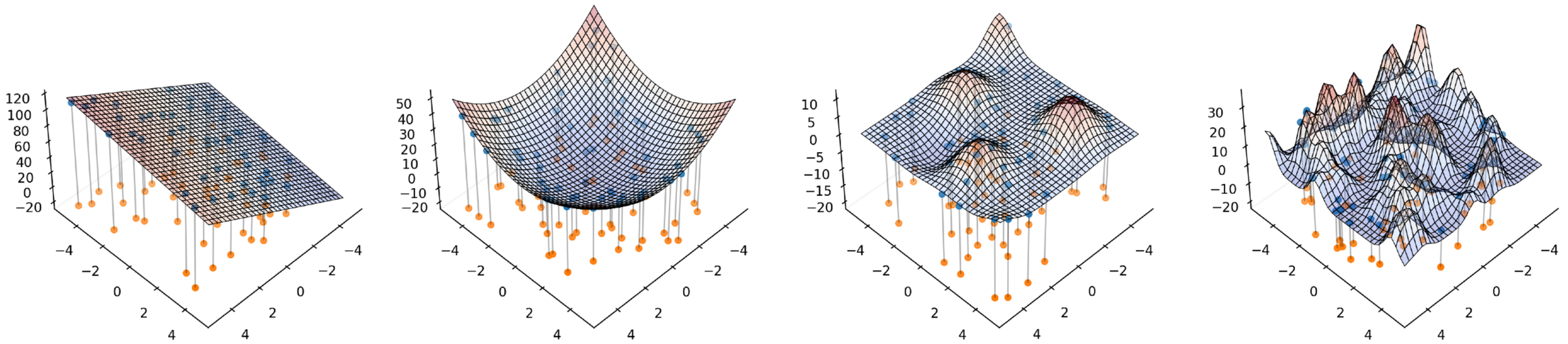
  Think twice about how complex the input-output relationship you are trying to find will be.

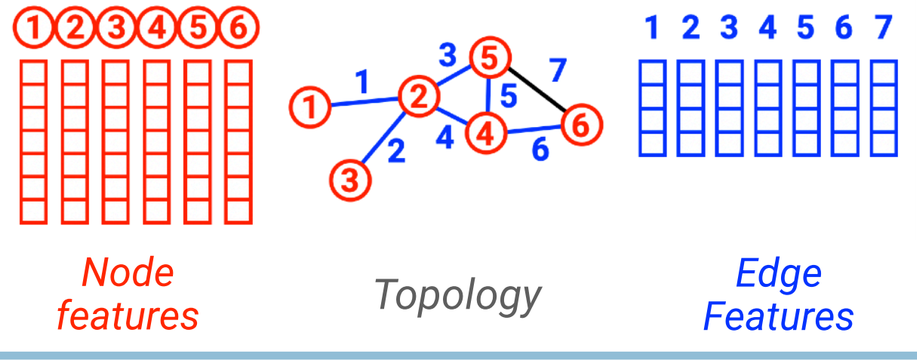
  How many samples will be *statistically sufficient* to estimate *2-variable* functions like these? What if you're fitting a *100-variable* function?



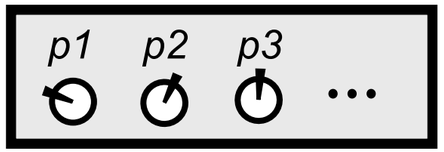
Graph Neural Networks (aka Geometric Deep Learning)

Other Info (Conditions, Environment, …)

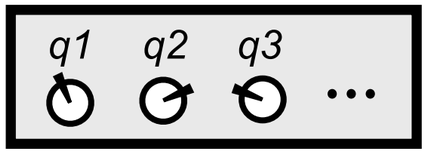
An input graph



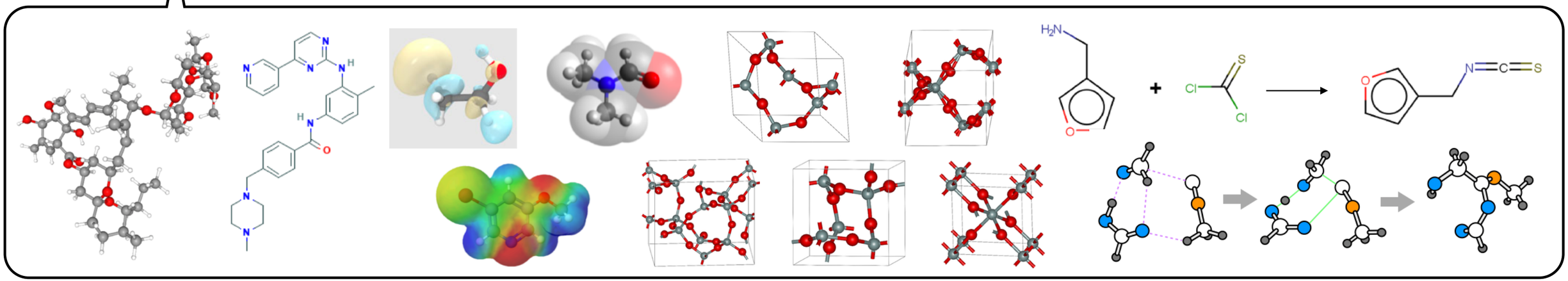
Representation Learning



Classification / Regression Head



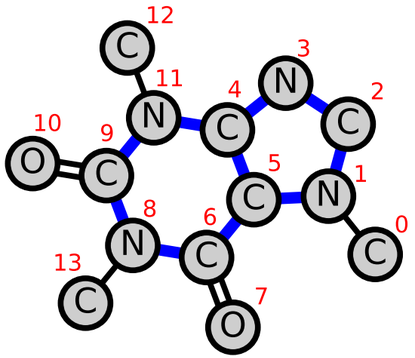
y



Graph Representation Learning

We can seek for a good representation vector that can be computed from a molecular graph, which is expected to be superior to any man-made descriptors!

Topology

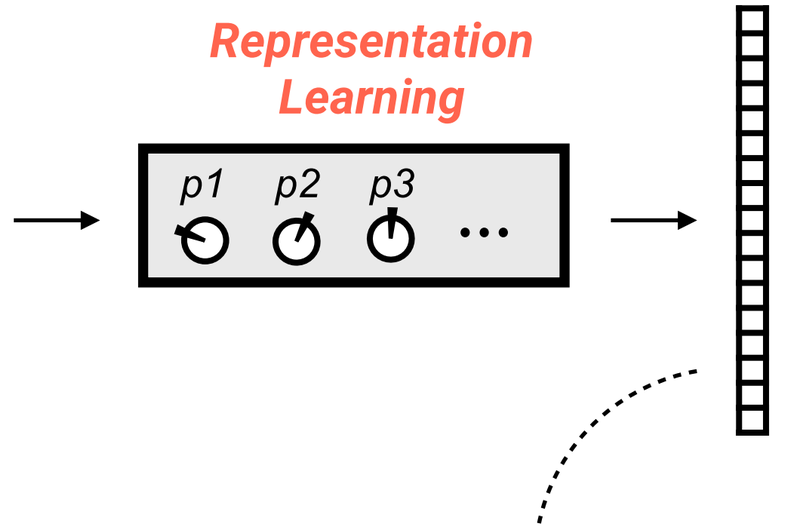


Node Features

	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Symbol	C	N	C	N	C	C	C	O	N	C	O	N	C	C
AtomicNum	6	7	6	7	6	6	6	8	7	6	8	7	6	6
TotalDegree	4	3	3	2	3	3	3	1	3	3	1	3	4	4
TotalNumHs	3	0	1	0	0	0	0	0	0	0	0	0	3	3
FormalCharge	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DeltaMass	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IsInRing	0	1	1	1	1	1	1	0	1	1	0	1	0	0

Edge Features

	0-1	1-2	2-3	3-4	4-5	5-6	6-7	6-8	8-9	9-10	9-11	11-12	8-13	5-1	11-4
BondType	1	12	12	12	12	12	2	12	12	2	12	1	1	12	12
Stereo	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

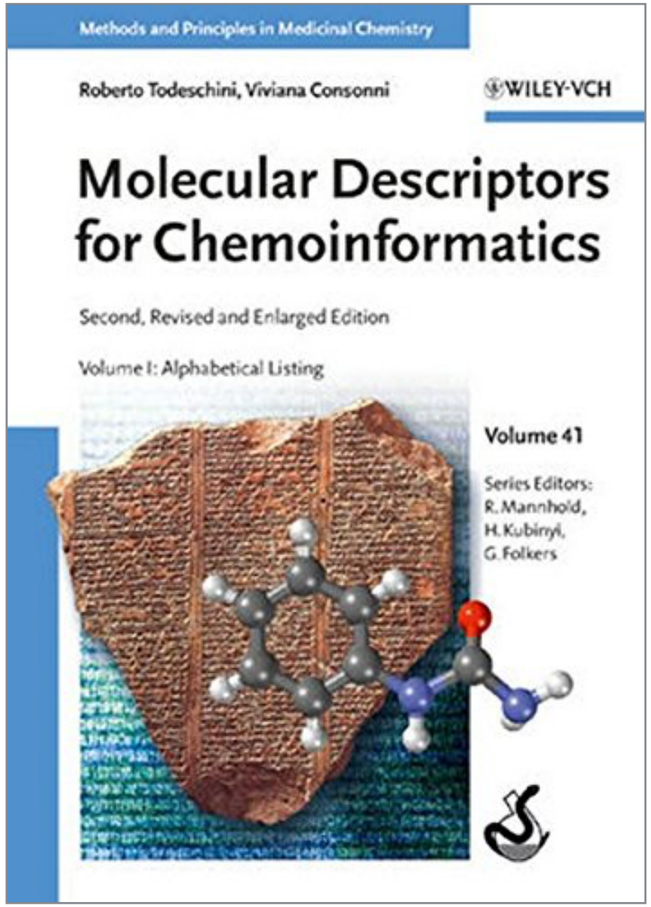


A relatively *low-dimensional* **good representation vector**

Beyond Man-Made Descriptors

- **0-Dimensional Descriptors**
  - Constitutional descriptors
  - Count descriptors
- **1-Dimensional Descriptors**
  - List of structural fragments
  - Fingerprints
- **2-Dimensional Descriptors**
  - Graph invariants
- **3-Dimensional Descriptors**
  - 3D MoRSE, WHIM, GETAWAY, ...
  - Quantum-chemical descriptors
  - Size, steric, surface, volume, ...
- **4-Dimensional Descriptors**
  - GRID, CoMFA, Volsurf, ...

"Vol 1 contains an alphabetical listing of more than 3,300 descriptors"



"Dragon calculates 5,270 molecular descriptors"

kode chemoinformatics

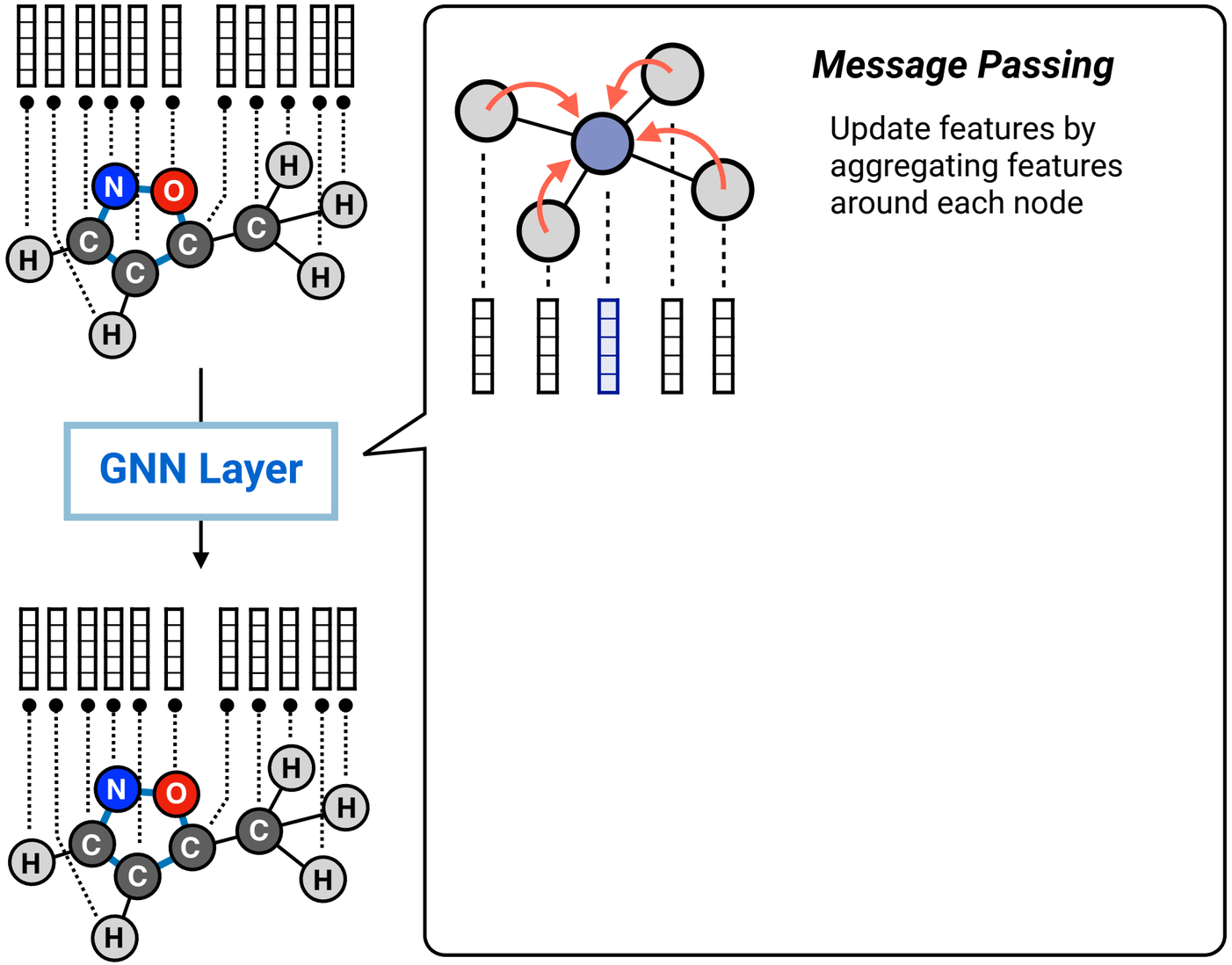
DRAGON 7.0

DESCRIPTORS | FINGERPRINTS | PROJECT AND SCIENTIFIC WORKS

Dragon 7.0 calculates **5,270** molecular descriptors, organized in different **logical blocks** as in the previous versions. Blocks are further divided into sub-blocks to make management, selection, and analysis of descriptors easier. Following, the summary of molecular descriptors blocks calculated by Dragon 7.0 is reported.

BLOCK NO	BLOCK NAME	DESCRIPTORS
1	Constitutional	47
2	Ring descriptors	32
3	Topological indices	75
4	Walk and path counts	46
5	Connectivity indices	37
6	Information indices	50
7	2D matrix-based descriptors	607
8	2D autocorrelations	213
9	Burden eigenvalues	96
10	P-VSA-like descriptors	55

Message Passing: The Inner Workings of GNNs



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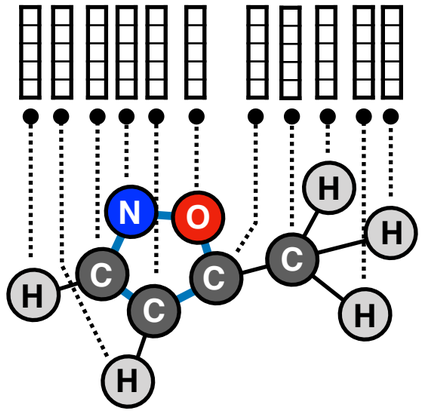
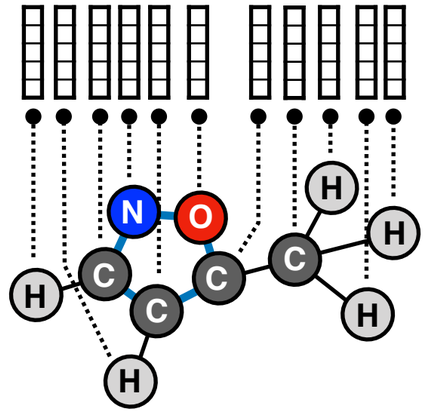
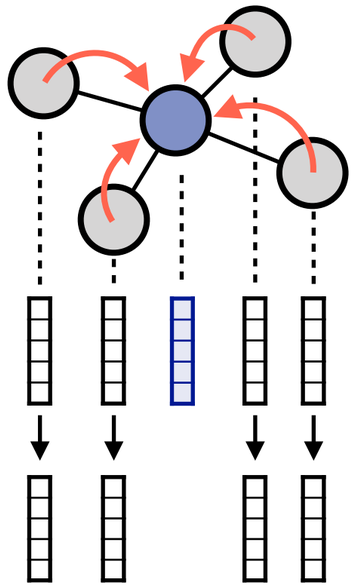


GNN Layer





Message Passing

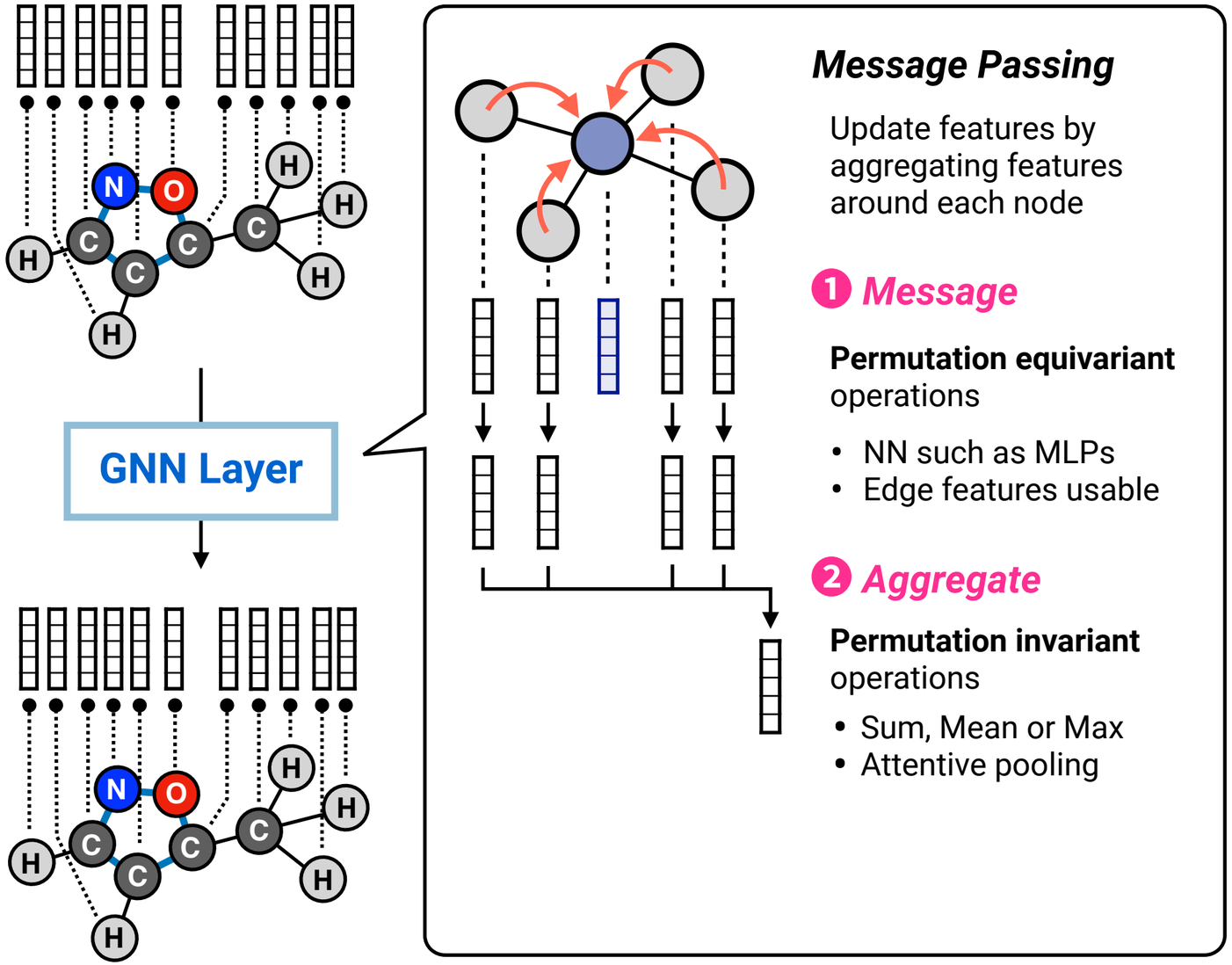
Update features by aggregating features around each node

❶ ***Message***

Permutation equivariant operations

- NN such as MLPs
- Edge features usable

Message Passing: The Inner Workings of GNNs



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❷ *Aggregate*

Permutation invariant operations

- Sum, Mean or Max
- Attentive pooling

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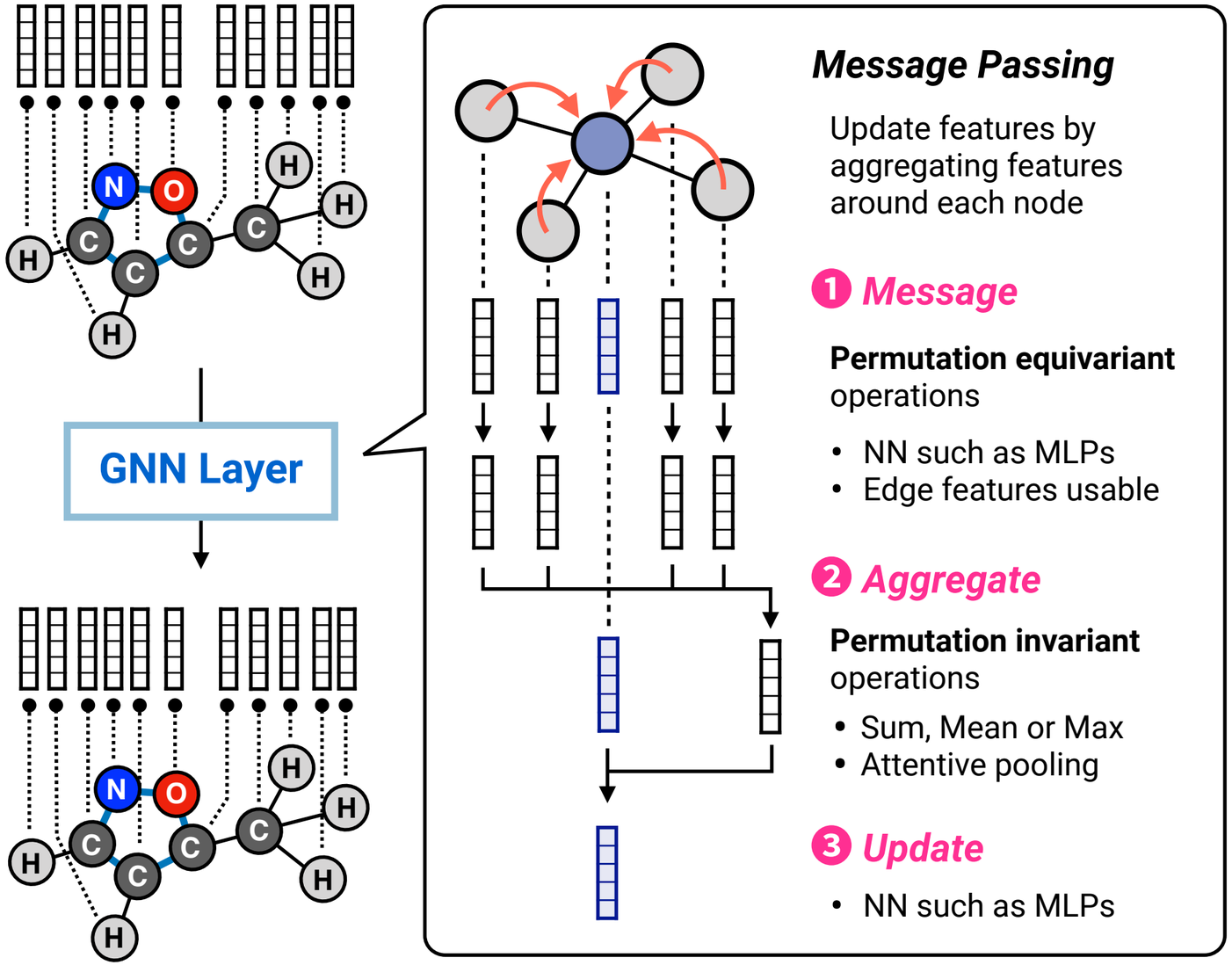

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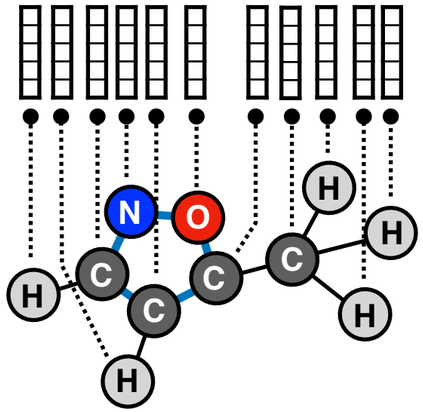
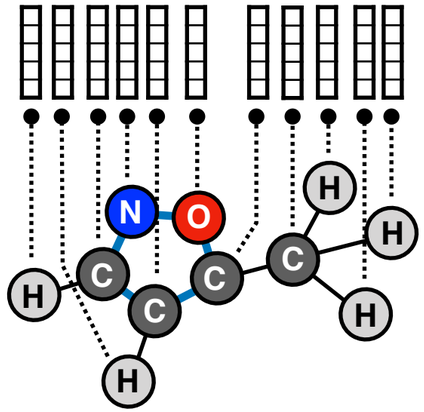
❸ *Update*

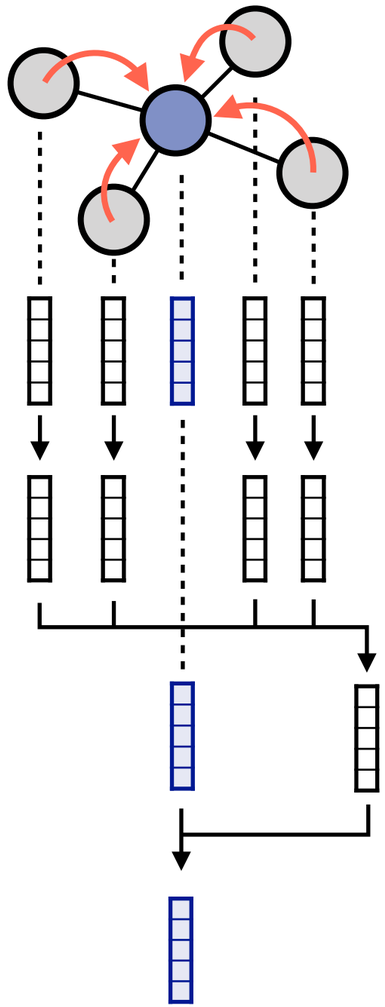
- NN such as MLPs

Message Passing: The Inner Workings of GNNs



GNN Layer





Message Passing

Update features by aggregating features around each node

1 ***Message***

Permutation equivariant operations

- NN such as MLPs
- Edge features usable

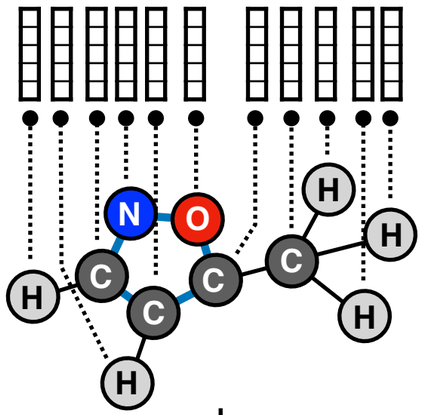
2 ***Aggregate***

Permutation invariant operations

- Sum, Mean or Max
- Attentive pooling

3 ***Update***

- NN such as MLPs

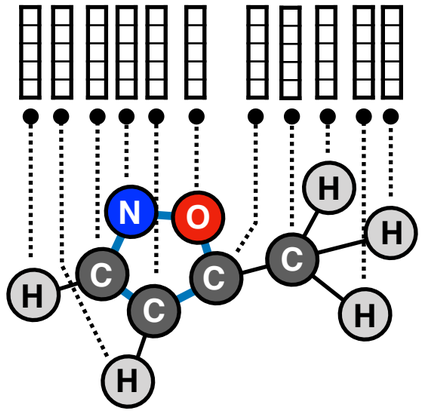


Readout

Permutation invariant operations

- Sum, Mean or Max
- Attentive pooling

Message Passing: The Inner Workings of GNNs



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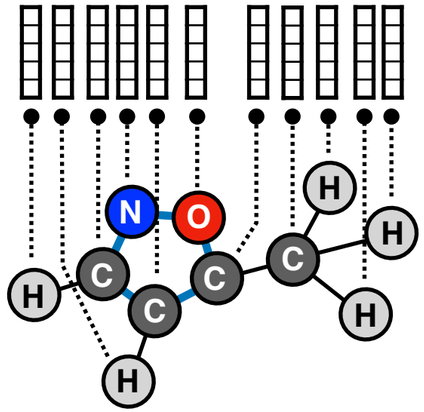

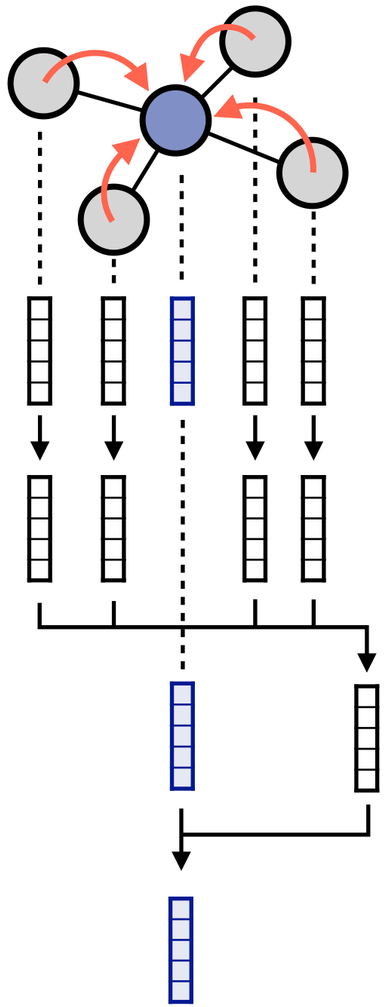

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Update features by aggregating features around each node

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Permutation invariant operations

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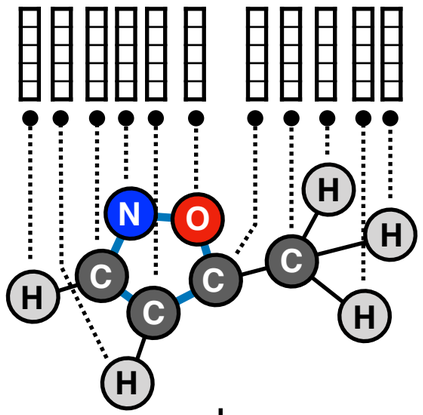
❸ *Update*

- NN such as MLPs

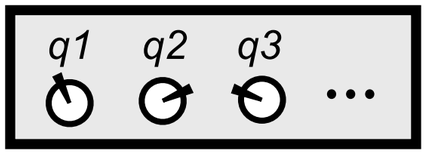


Readout

Permutation invariant operations

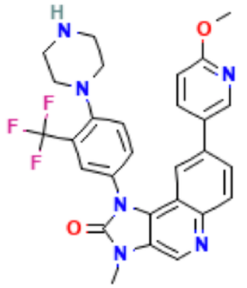
- Sum, Mean or Max
- Attentive pooling

Classification / Regression Head



y

Use Case 1: Virtual Screening (QSAR/QSPR)



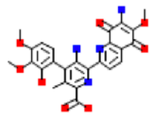
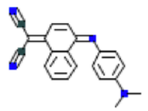
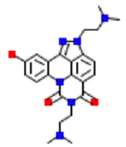
ML

Very Noisy, Complex Relationship…

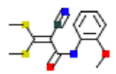
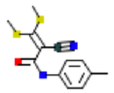
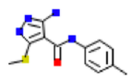
- ***Classification Task***
  Activity (Active or Inactive)
- ***Regression Task***
  LogGI50 value ---------- GI50: concentration required for 50% inhibition of growth

NCI Human Tumor Cell Line Growth Inhibition Assay *(PubChem AID 1)*

Active (2,814)

Structure	CID	SID	Activity	Score	LogGI50_M
	5298	121832	Active	67	-8
	363173	493713	Active	43	-6.5871
	399631	530868	Active	51	-7.0678

Inactive (48,922)

Structure	CID	SID	Activity	Score	LogGI50_M
	390324	521601	Inactive	0	-4
	390311	521588	Inactive	0	-4
	390312	521589	Inactive	4	-4.214

Use Case 1: Virtual Screening (QSAR/QSPR)

Standard ML

ExtraTrees
w/ ECFP6(1024)

GNN

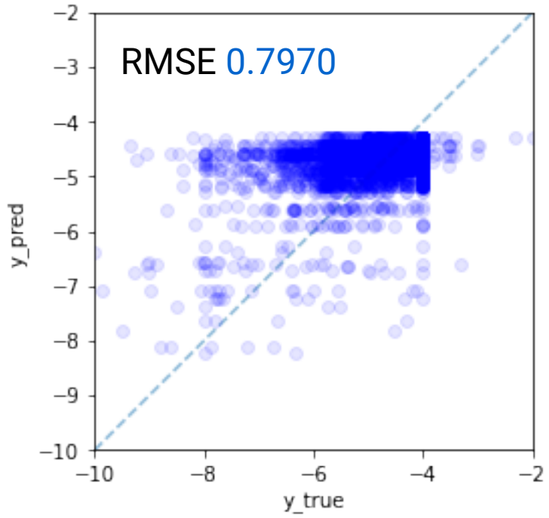
ChemProp
(Directed MPNN)

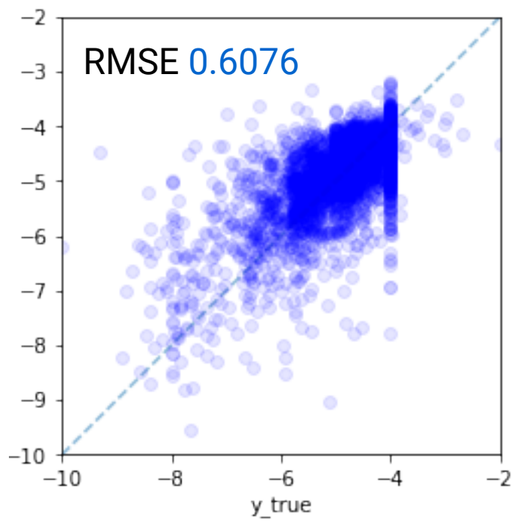
- ***Classification Task*** Activity (Active or Inactive)

95.079%

95.604%

- ***Regression Task*** LogGI50 value





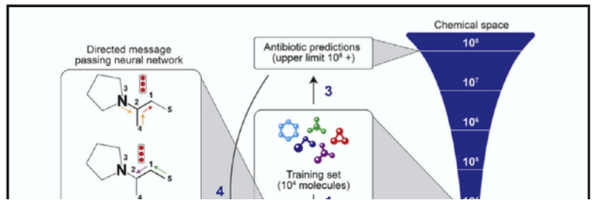
ChemProp (Yang et al, 2019)

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.)

nature

NEWS | 20 February 2020

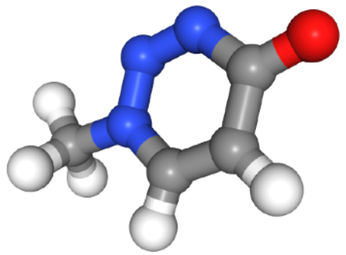
Powerful antibiotics discovered using AI

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

Jo Marchant

Use Case 2: Fast Approximation for QM Calculations

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

Quantum mechanical calculations

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

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

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

output

- *Internal energy*
- *Free energy*
- *Zero point vibrational energy*
- *Energy of HOMO*
- *Energy of LUMO*
- *Isotropic polarizabiliity*
- *Dipole moment*
- *Electronic spatial extent*
- *Enthalpy*
- *Heat capacity*

⋮

	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

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

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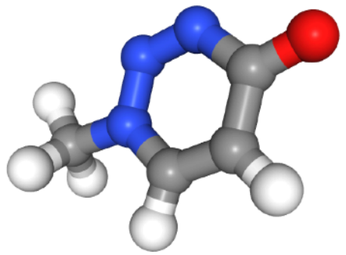

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100,000 times faster!

~ 0.01 sec

ML

≀

~ 1000 sec

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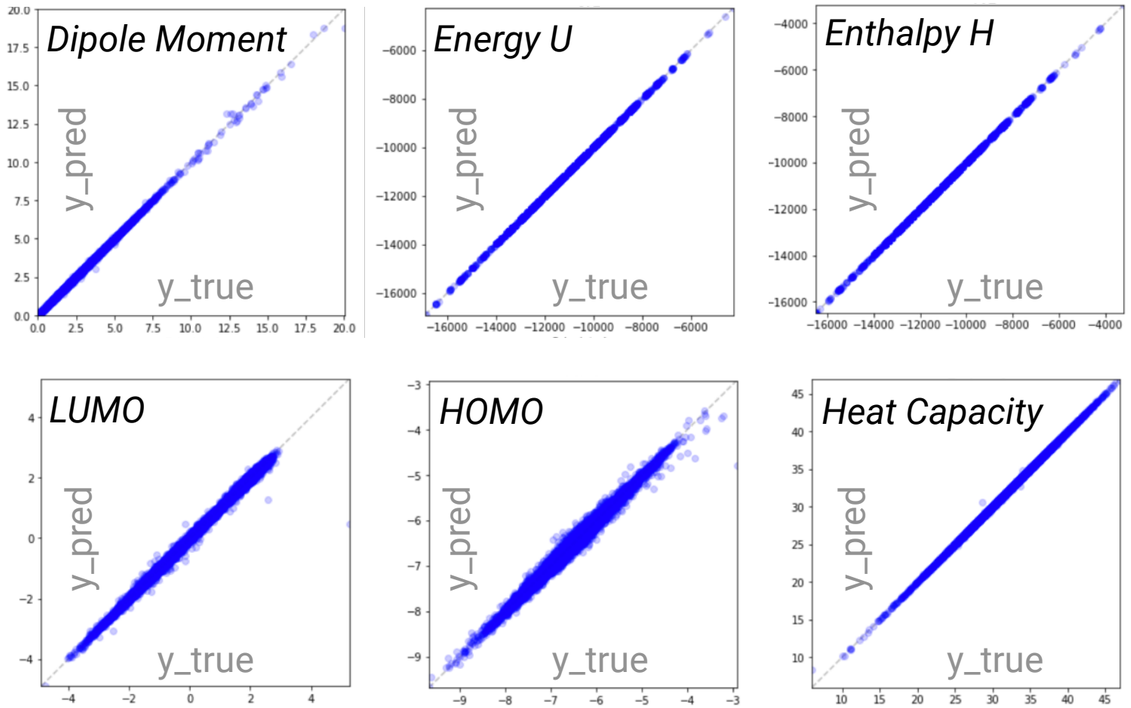
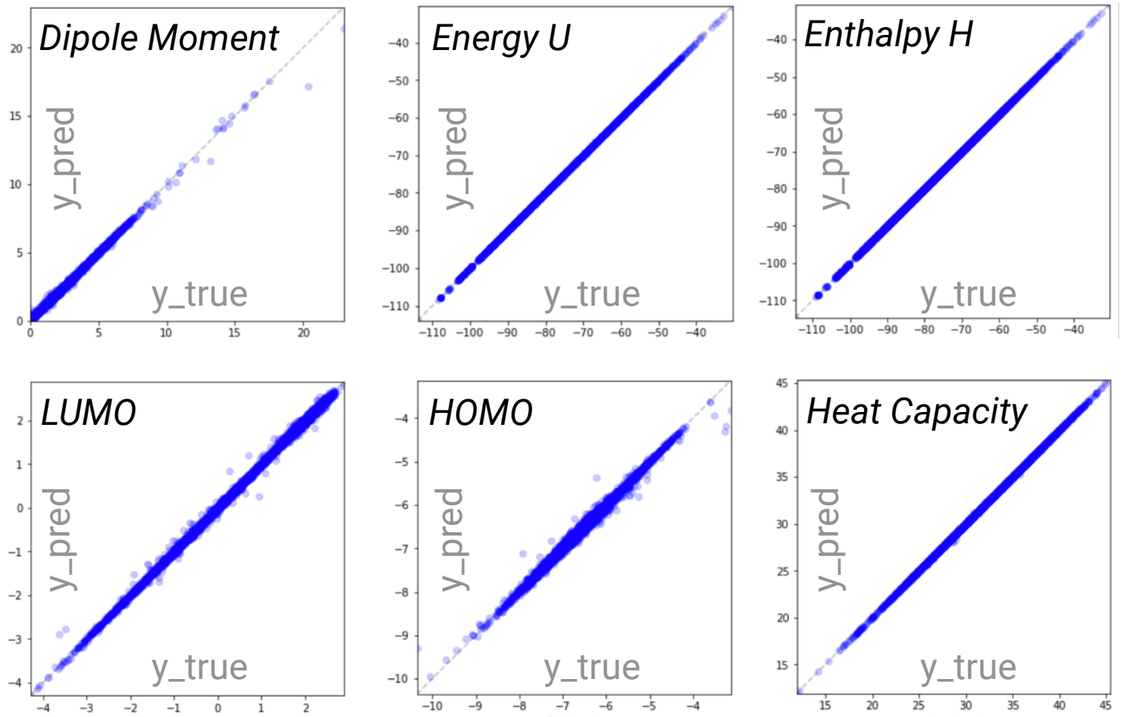
Use Case 2: Fast Approximation for QM Calculations

GNN predictions are strikingly accurate, in particular, for predicting enegies of a molecule of a conformation or forces at each atom to transition towards a more stable conformation!

Predictions for Test Data by SchNet (Schütt et al, 2017)



Predictions for Test Data by DimeNet (Klicpera et al, 2020)



Big Challenge: Rashomon Effect and Underspecification

Rashomon Effect: **The multiplicity of good ML models**

In general, we can have many good but very different ML models that give equally accurate predictions for the given data.

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Big Challenge: Rashomon Effect and Underspecification

Rashomon Effect: The multiplicity of good ML models

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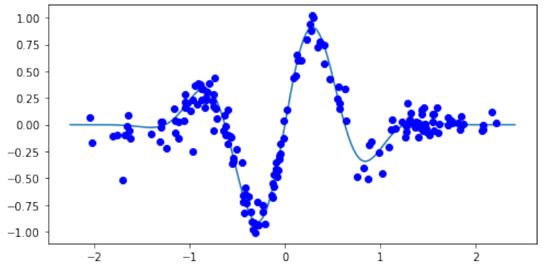
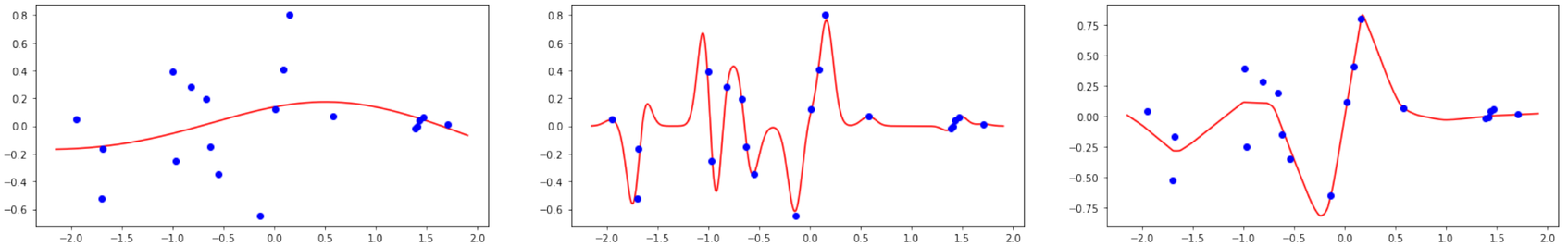
- Many explanations can exist for a single set of finite observations in general . (whether they are given by ML or by human experts.)
- They can largely disagree in a underspecified situation where data is statistically insufficient.

Any ML model will work



Different models can give very different predictions for out-of-sample cases



Designing Relevant Inductive Bias for Molecules

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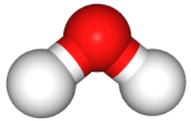
One remedy: Fusing rationalism (theory/simulation) and empiricism (ML/data-driven)

Encoding what we already know for ML ***not to needlessly explore chemically invalid forms***

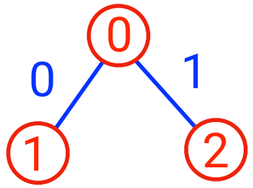
⟶ In other words, restrict ML models not to represent irrelevant input-output mappings.

Designing Relevant Inductive Bias for Molecules

Water molecule H_2O



A molecular graph (RDKit)

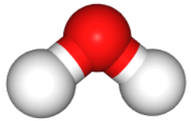


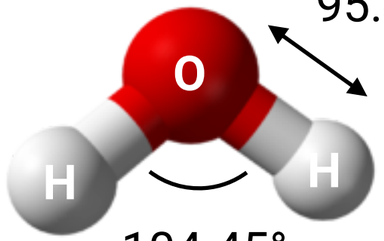
	⓪	①	②	
AtomicNum	8	1	1	*Atom Invariants*
TotalDegree	2	1	1	
TotalNumHs	0	0	0	
FormalCharge	0	0	0	
deltaMass	0	0	0	
IsInRing	0	0	0	

	0	1	
BondType	0	0	*Bond Invariants*
Stereo	0	0	

Designing Relevant Inductive Bias for Molecules

Water molecule H_2O





95.84 pm

atom-atom distance

104.45°

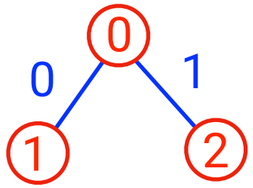
bond angle

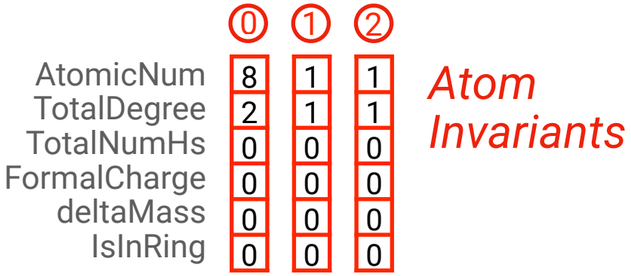
8 + 1 + 1 = 10 electrons

O $1s^2\ 2s^2\ 2p^4$

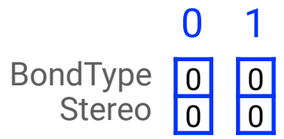
H $1s^1$ H $1s^1$

A molecular graph (RDKit)

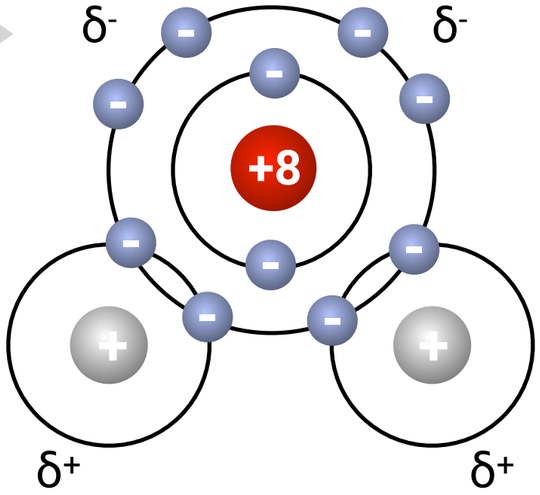




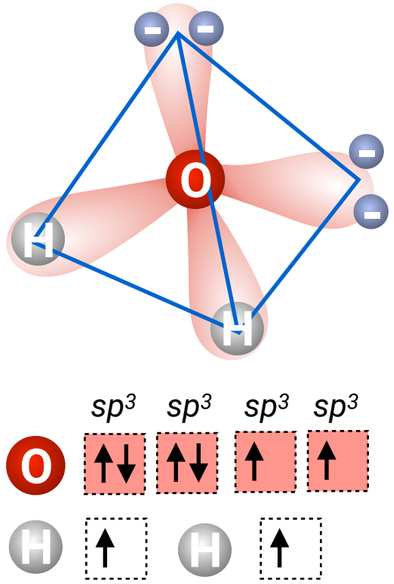
Atom Invariants



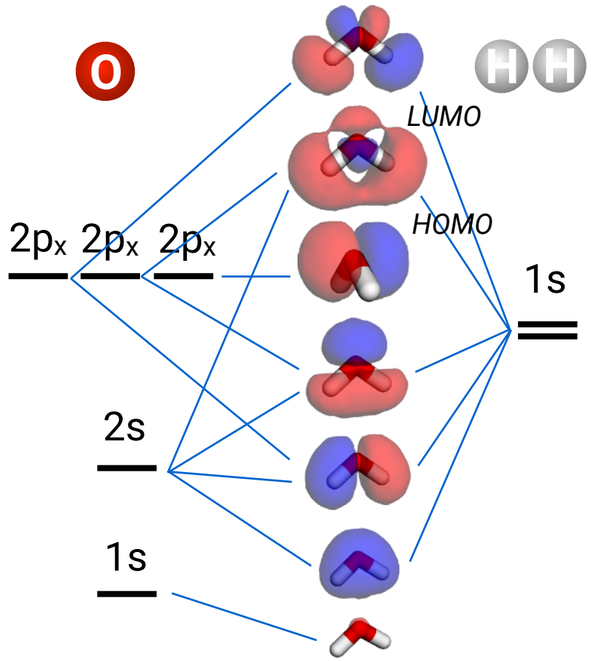
Bond Invariants



covalent bonds



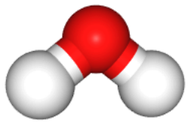
sp³ hybridization



molecular orbitals

SchNet (Schütt et al, 2017): Standard Geometric GNN

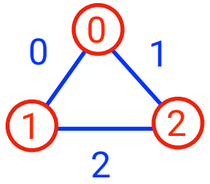
H_2O



gdb_3

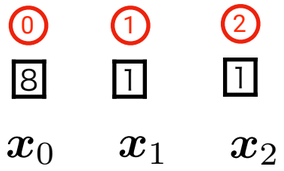
	x	y	z	AN
O	-0.0344	0.9775	0.0076	8
H	0.0648	0.0206	0.0015	1
H	0.8718	1.3008	0.0007	1

Graph

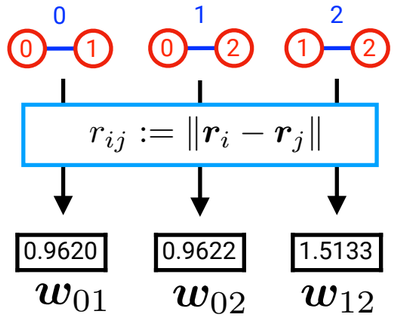


edges w/
cutoff (10Å)

atom features



bond features



SchNet (Schütt et al, 2017): Standard Geometric GNN

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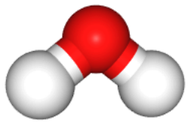

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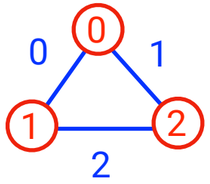

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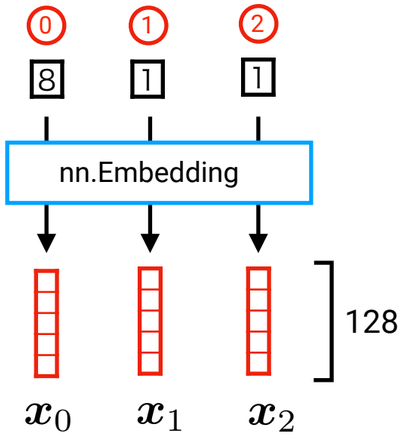
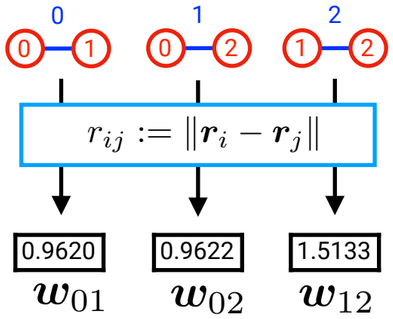


bond features



SchNet (Schütt et al, 2017): Standard Geometric GNN

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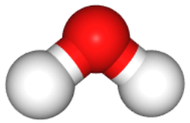

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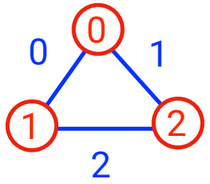

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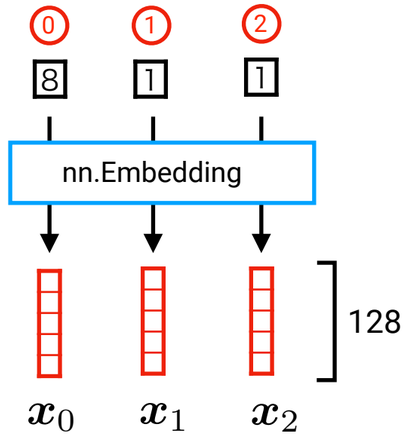

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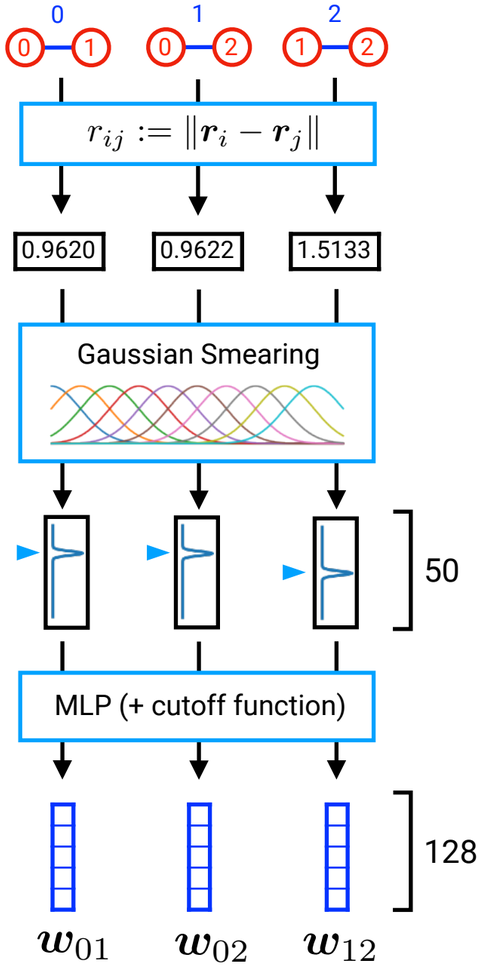

SchNet (Schütt et al, 2017): Standard Geometric GNN

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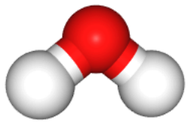

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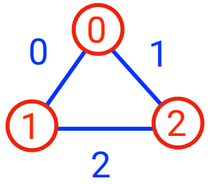

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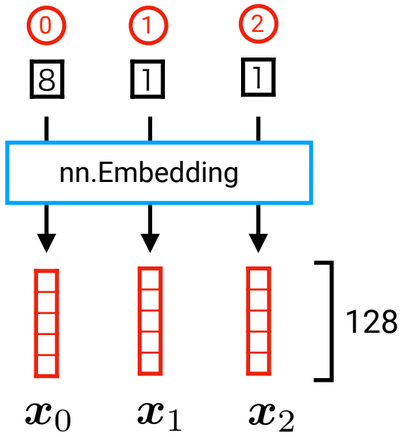

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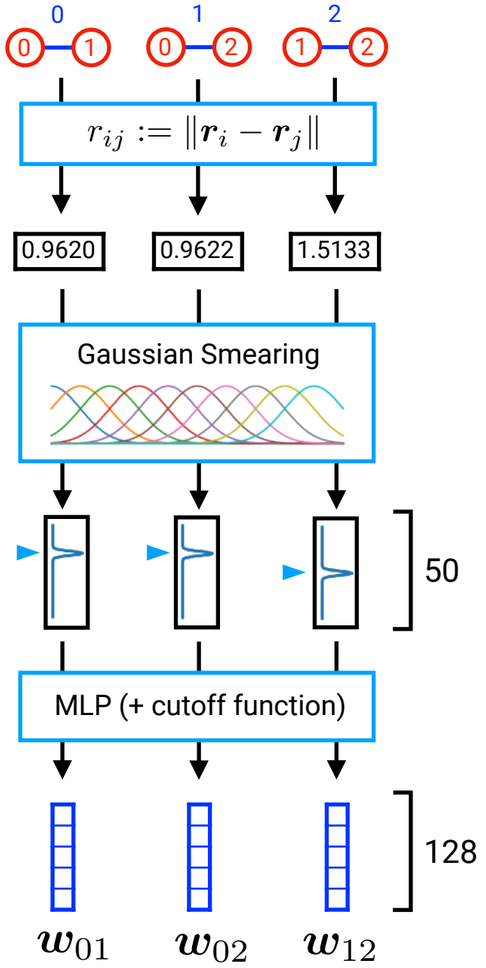
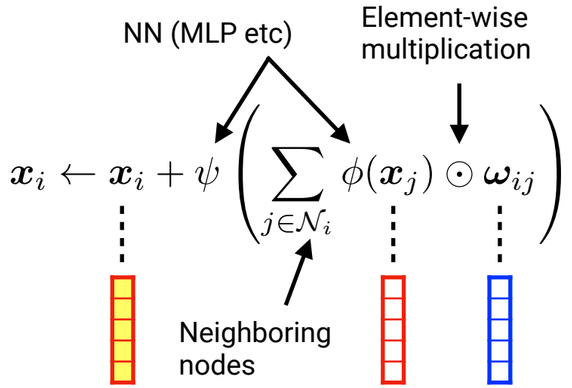
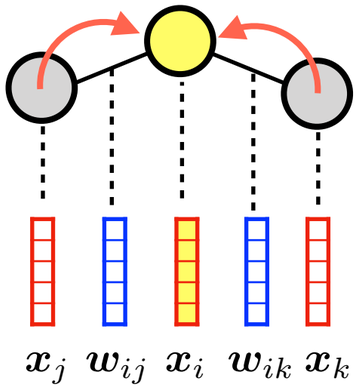


Message Passing with
residual connections

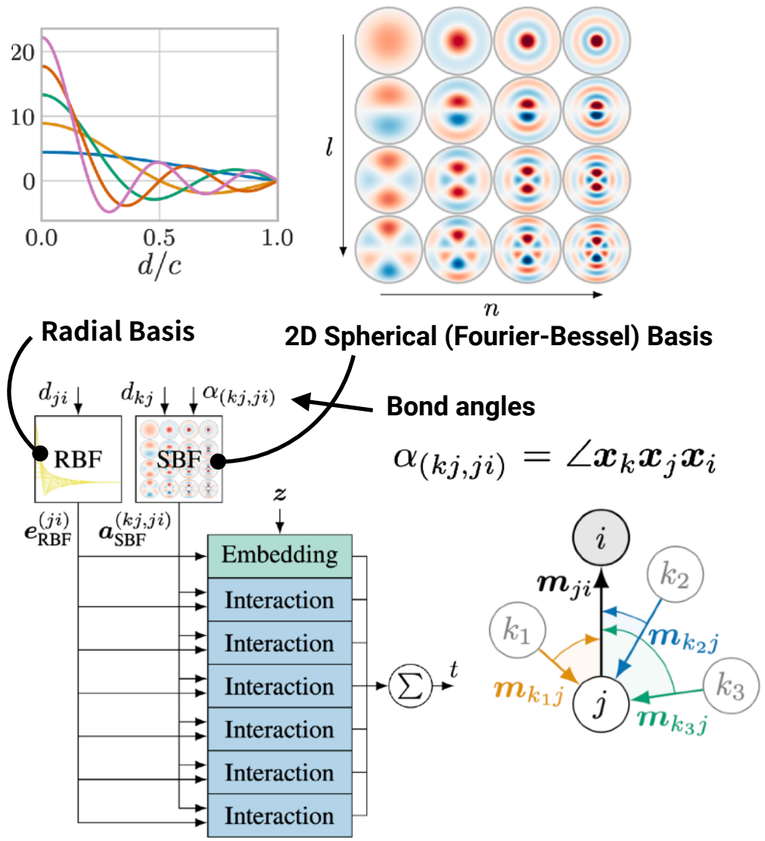




QSAR/QSPR, QM Approximation, Molecule Generations, …

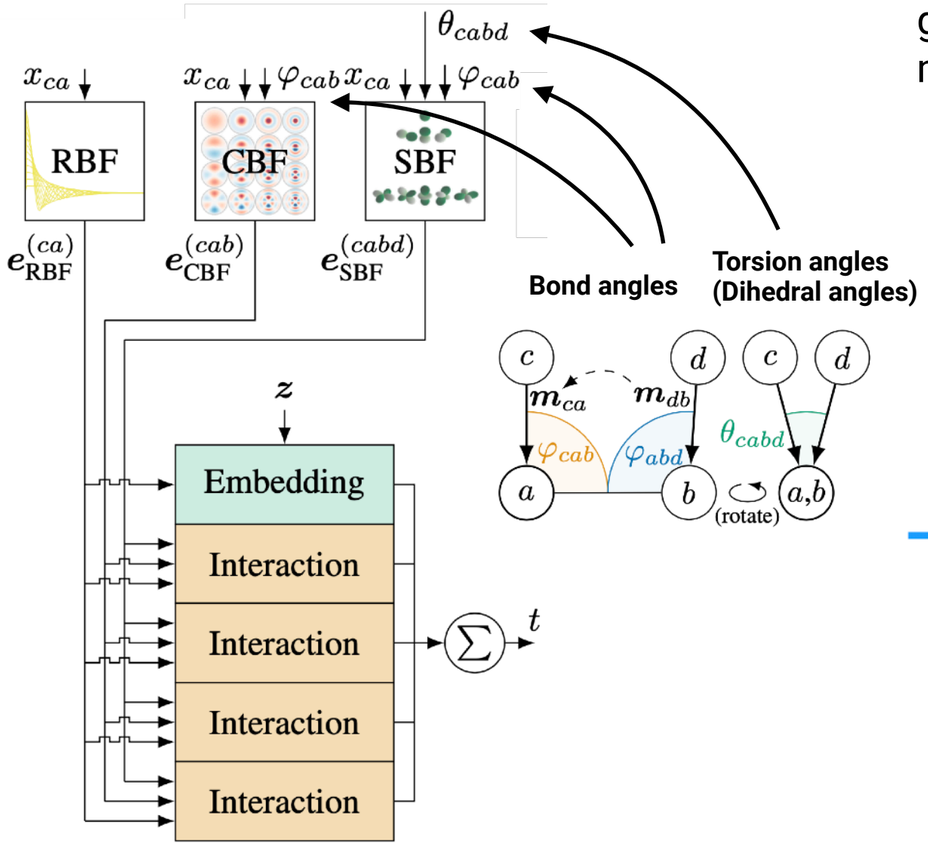
DimeNet++

Klicpera et al (NeurIPS WS2022)
https://arxiv.org/abs/2011.14115



GemNet

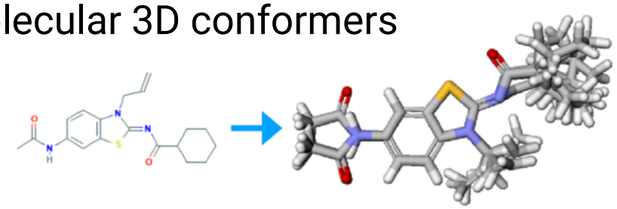
Klicpera et al (NeurIPS2021)
https://arxiv.org/abs/2106.08903

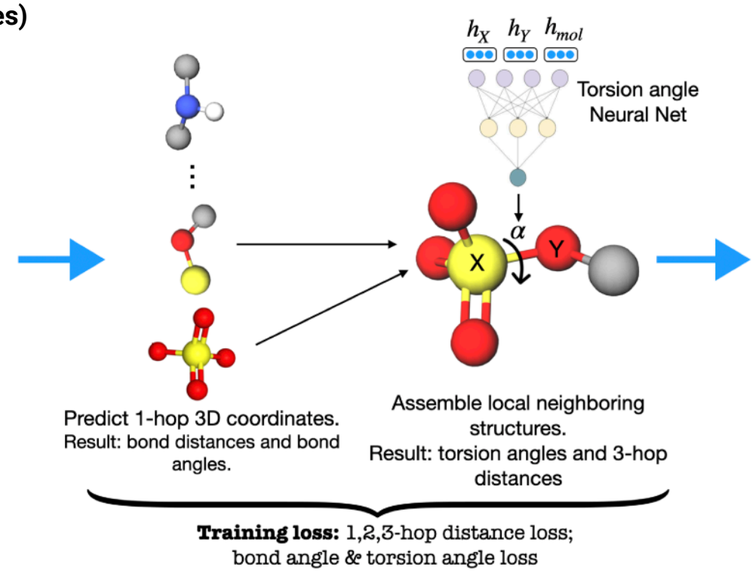


GeoMol

Ganea et al (NeurIPS2021)
https://arxiv.org/abs/2106.07802

generates distributions of low-energy molecular 3D conformers





"Learn to Simulate"

DeepMind > Research > Learning to Simulate Complex Physics with Graph Networks

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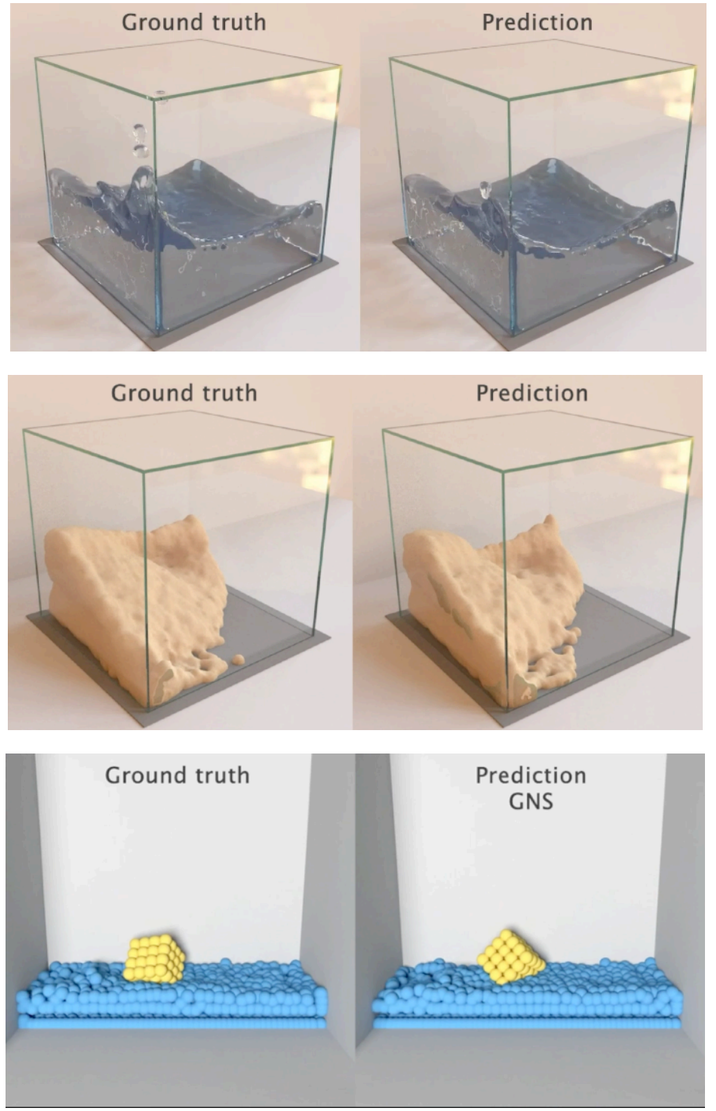
Learning to Simulate Complex Physics with Graph Networks

Abstract

Here we present a machine learning framework and model implementation that can learn to simulate a wide variety of challenging physical domains, involving fluids, rigid solids, and deformable materials interacting with one another. Our framework—which we term "Graph Network-based Simulators" (GNS)—represents the state of a physical system with particles, expressed as nodes in a graph, and computes dynamics via learned message-passing. Our results show that our model can generalize from single-timestep predictions with thousands of particles during training, to different initial conditions, thousands of timesteps, and at least an order of magnitude more particles at test time. Our model was robust to hyperparameter choices across various evaluation metrics: the main determinants of long-term performance were the number of message-passing steps, and mitigating the accumulation of error by corrupting the training data with noise. Our GNS framework advances the state-of-the-art in learned physical simulation, and holds promise for solving a wide range of complex forward and inverse problems.

Datasets and example model and training code available.



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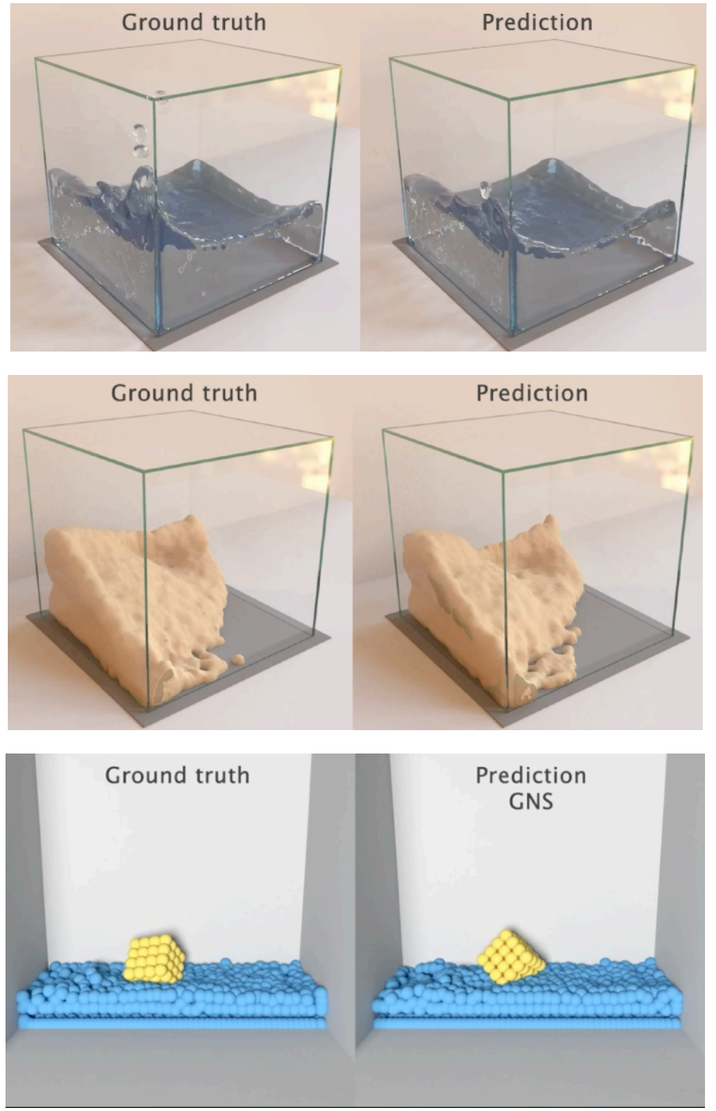
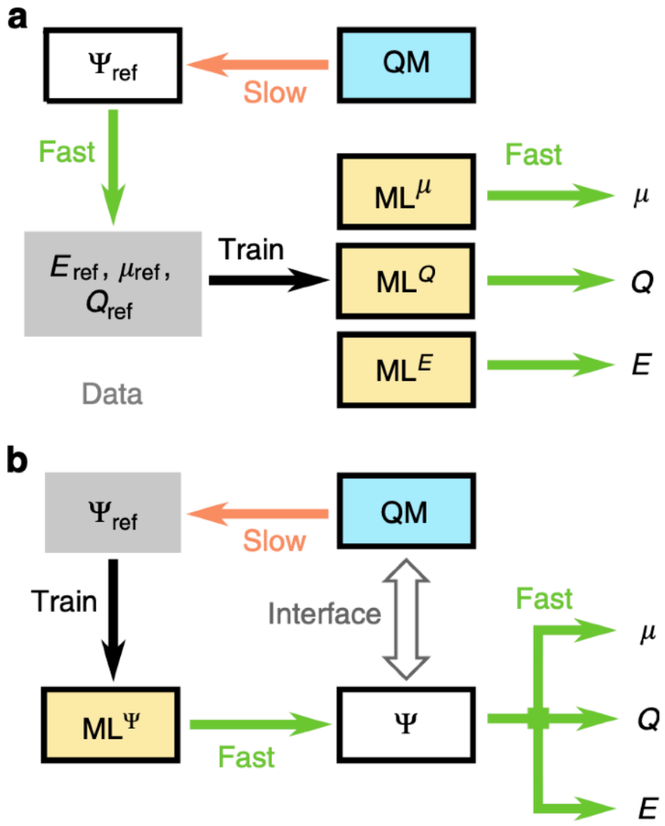


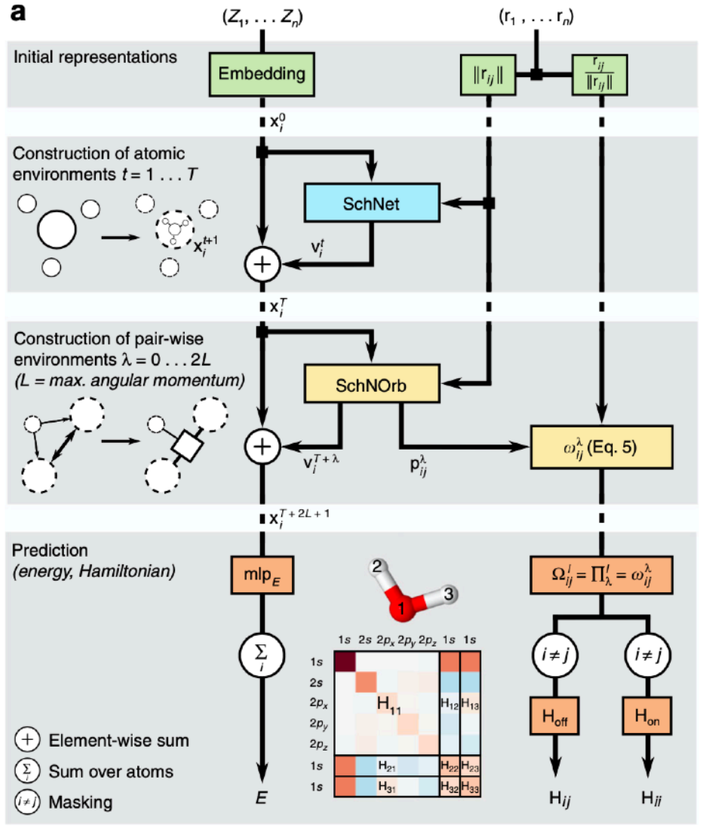
Fusing ML + Quantum Chemistry

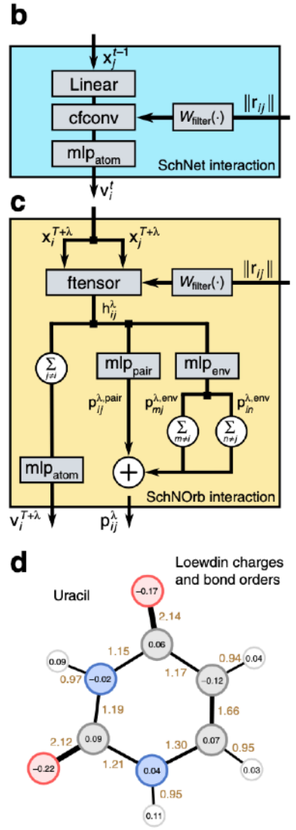
Unifying machine learning and quantum chemistry with a deep neural network for molecular wavefunctions

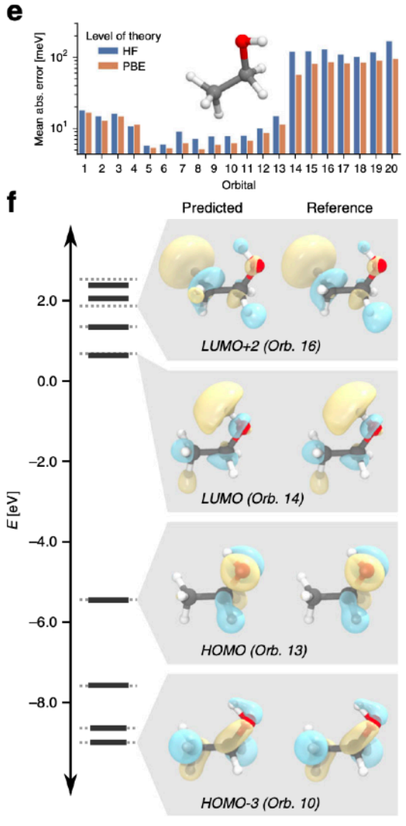
K. T. Schütt, M. Gastegger, A. Tkatchenko ✉, K.-R. Müller ✉ & R. J. Maurer ✉

Nature Communications **10**, Article number: 5024 (2019)



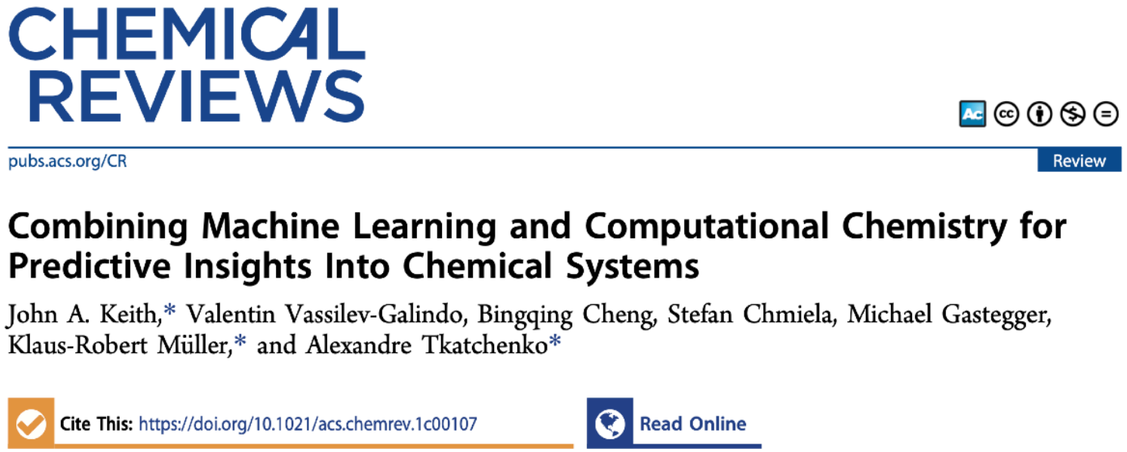




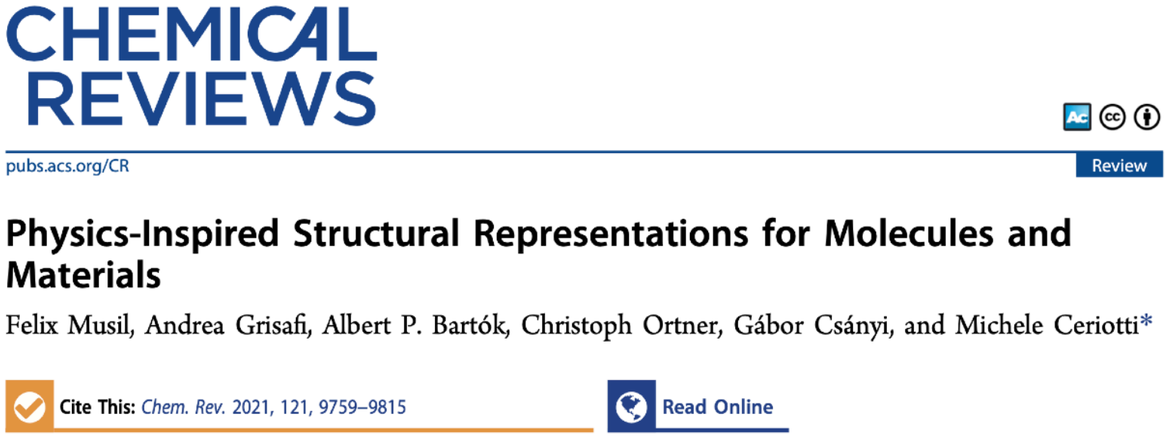


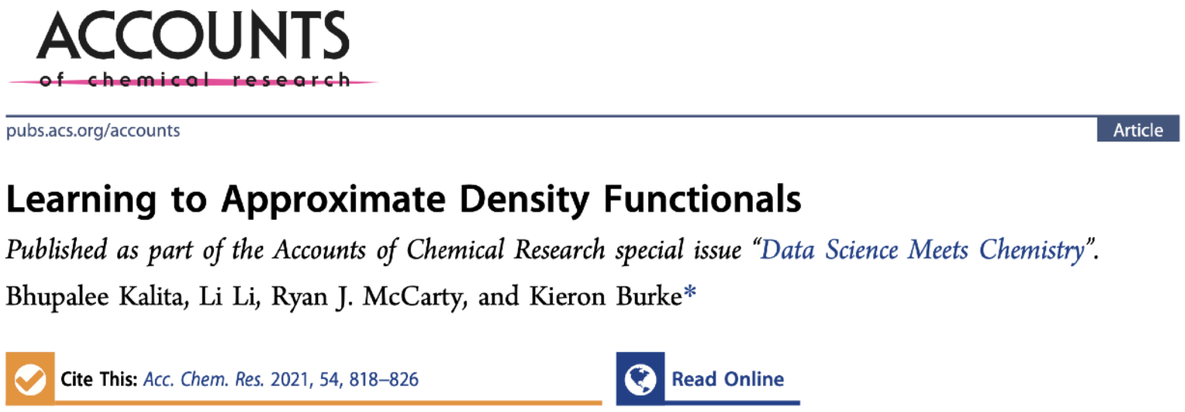
Fusing ML + Quantum Chemistry

Machine Learning at the Atomic Scale (Chem. Rev.)
https://pubs.acs.org/toc/chreay/121/16



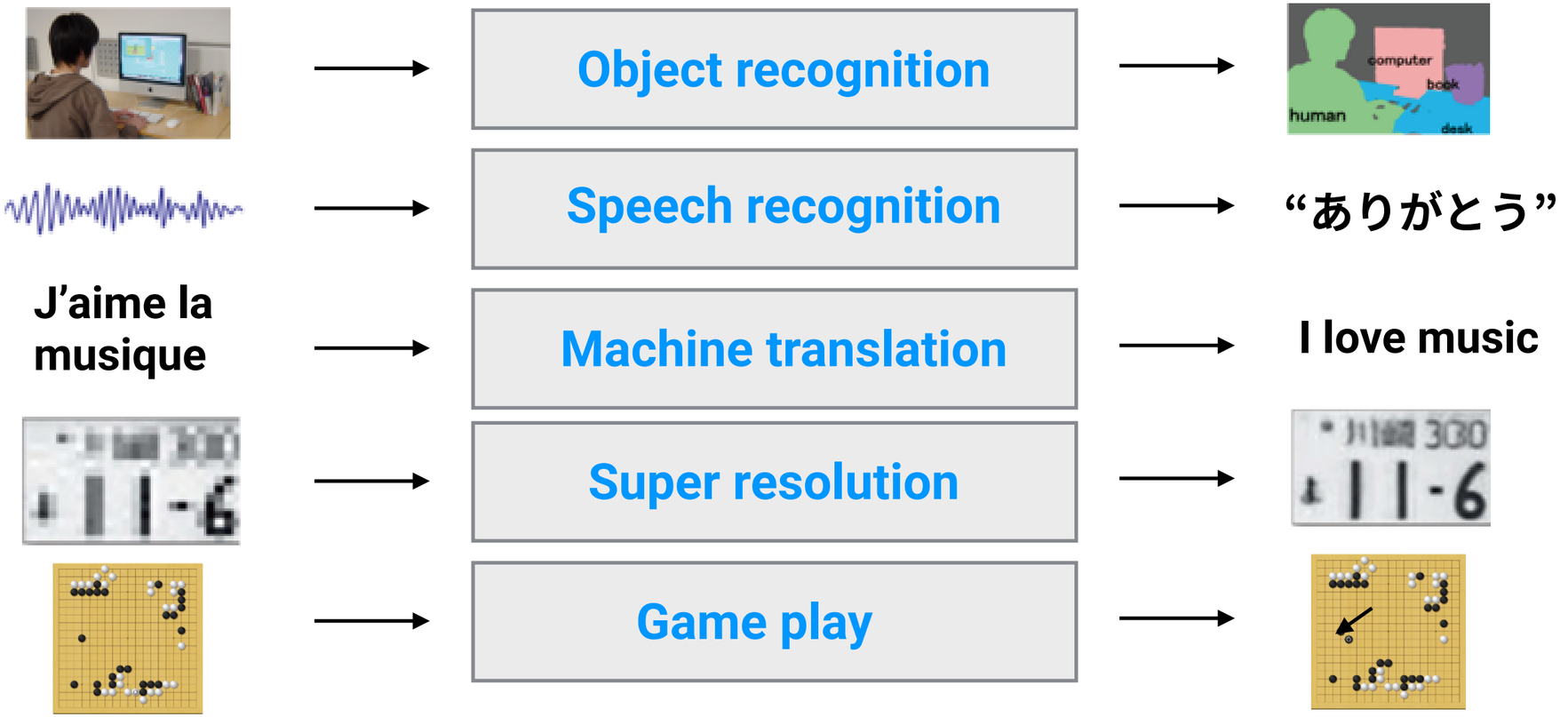
Data Science Meets Chemistry (Acc. Chem. Res.)
https://pubs.acs.org/page/achre4/data-science-meets-chemistry





One Final Remark: "The True Dark Side"

"We're able to predict smth." does not directly mean "We're able to understand it" nor "We're able to discover it". We still need further considerations to impact natural sciences…



Summary

This slide is available at

https://itakigawa.github.io/news.html

Machine Learning (ML) for Molecules

1. ML in a nutshell
   - *ML converts data into "prediction"*
   - *ML is a new (lazy) way of programming*
2. The dark side:
   Modern aspects of ML
   - *High dimensionality: Too many input variables*
   - *Overrepresentation: Too many parameters*
   - *Data hungriness: Big data is big for human, but can be too small for ML models…*
3. The light side :
   Deep learning for molecules
   - *Graph Neural Networks (GNNs)*
   - *Case 1: Virtual Screening (QSAR/QSPR)*
   - *Case 2: Fast Approximation for QM Calculations*
4. Challenges
   - *Rashomon Effect and Underspecification*
   - *Designing Relevant Inductive Bias for Chemistry*
   - *Prediction does not directly mean Understanding or Discovery*

May the ML Force be with you…