Machine Learning for Molecules

Lessons and Challenges of Data-Centric Chemistry

Feb 5th, 2022

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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 @ ATR Kyoto
  2019- Hokkaido Univ
  (Inst. Chemical Reaction Design & Discovery)

RIKEN AIP Kyoto, Kyoto Univ CiRA, Nikon
jointly 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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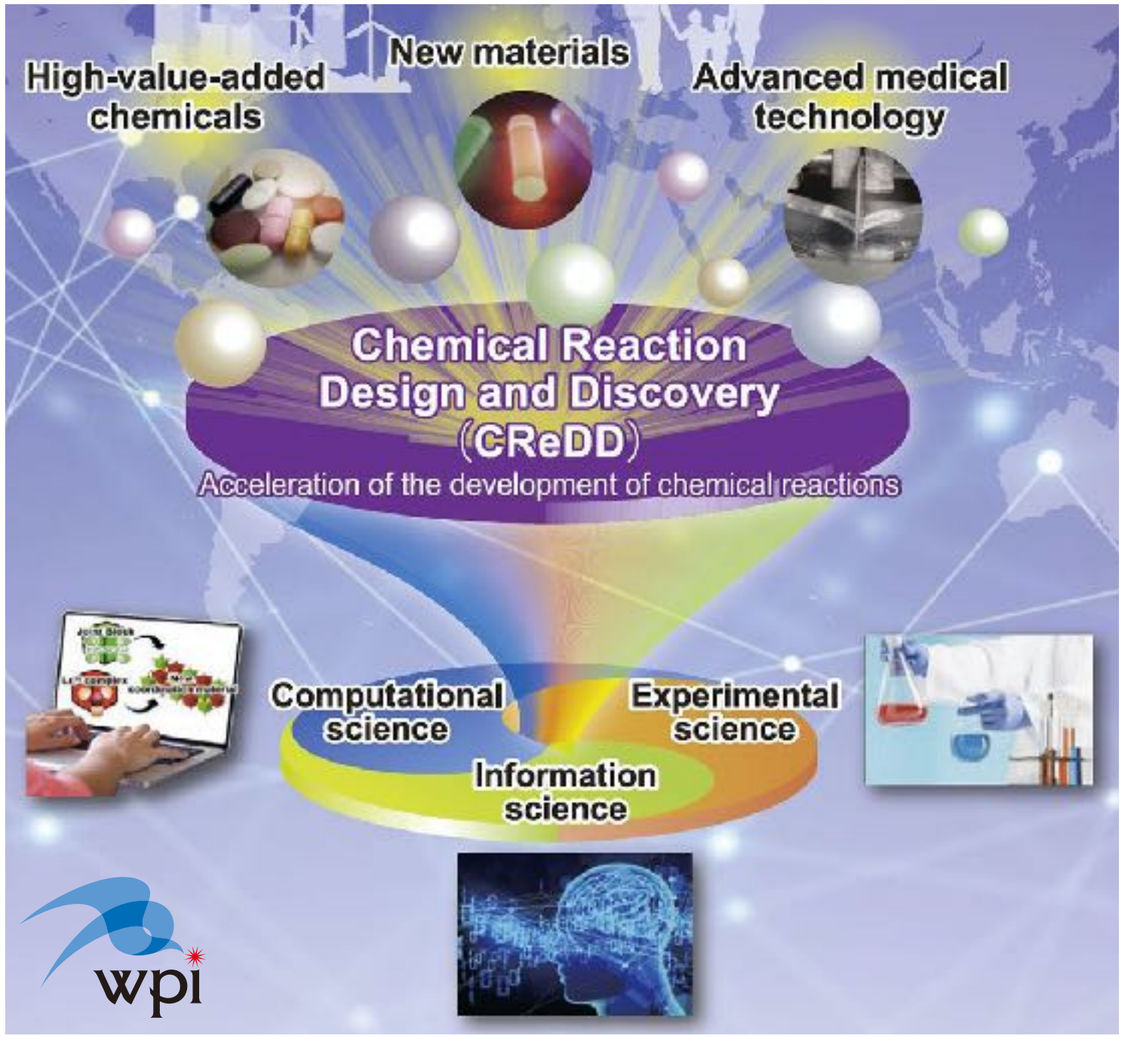
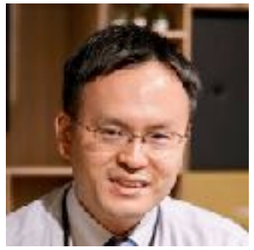
ICReDD
HOKKAIDO UNIVERSITY

Inst. Chemical Reaction Design and Discovery





We're working on real-world chemistry with great chemists!

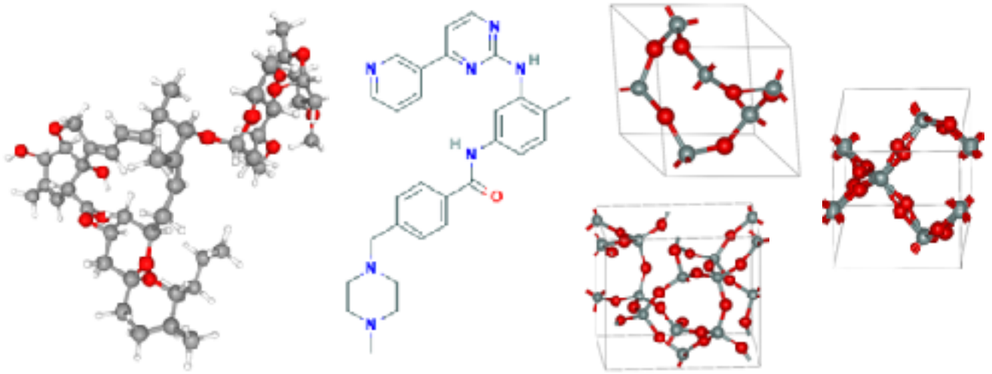
Prof. Ben List got 2021 Nobel Prize in Chemistry

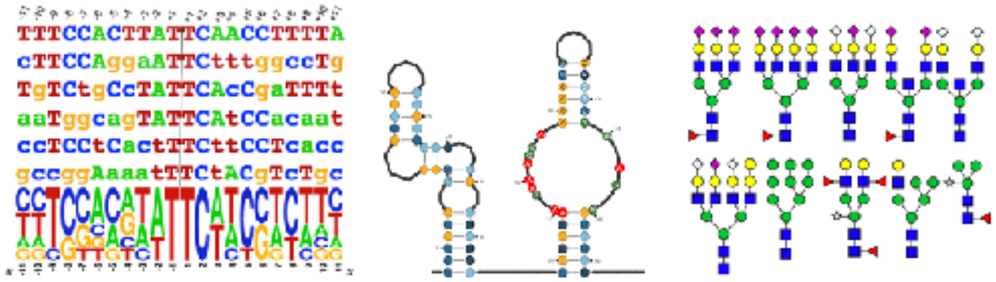
https://www.icredd.hokudai.ac.jp

My interest: Machine learning with discrete structures

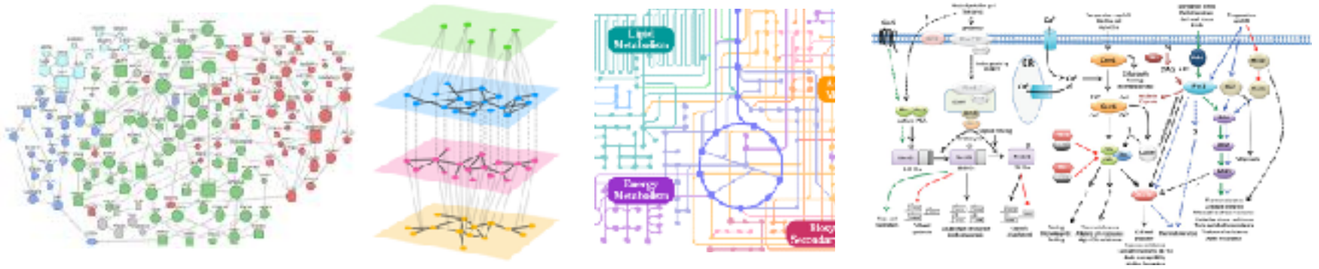
Discrete structures, i.e., combinatorial or algebraic structures
such as sets, groups, permutations, combinations, sequences, trees, and graphs

Target objects

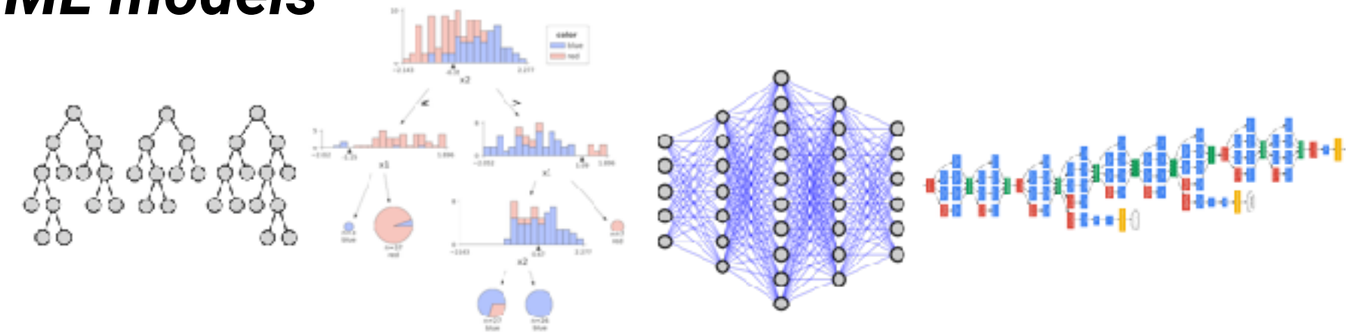




Relations between target objects



ML models



Molecules clearly have a combinatorial aspect

c&en

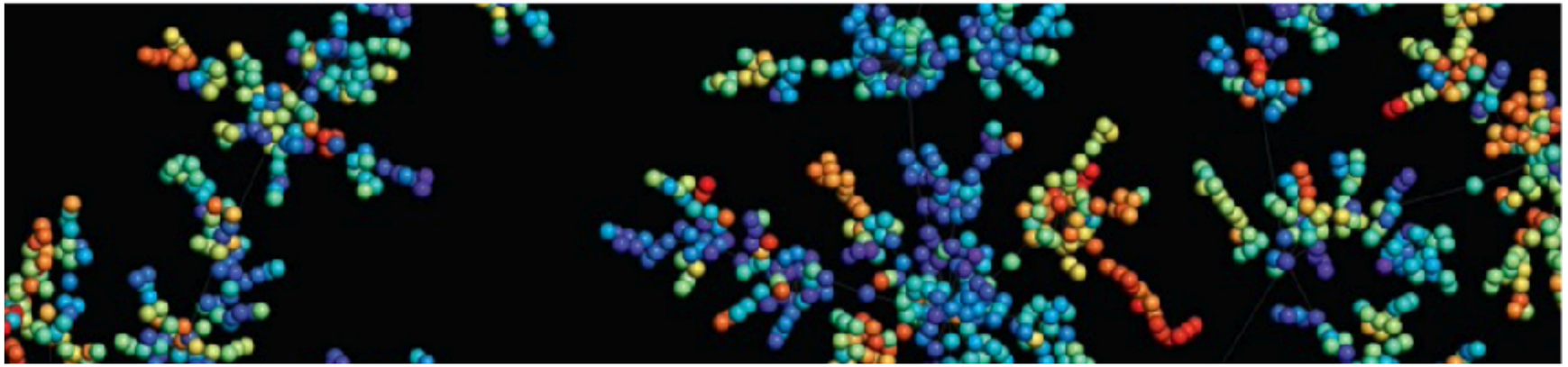
COMPUTATIONAL CHEMISTRY

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

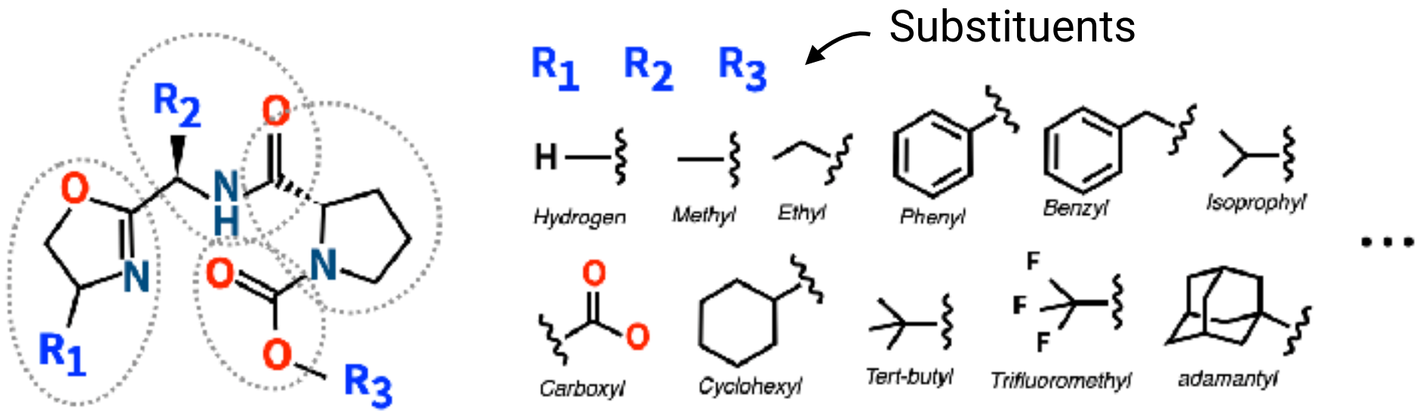
10^{8}

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

How can ML leverage these combinatorial nature?

- A molecule is a set of atoms and bonds

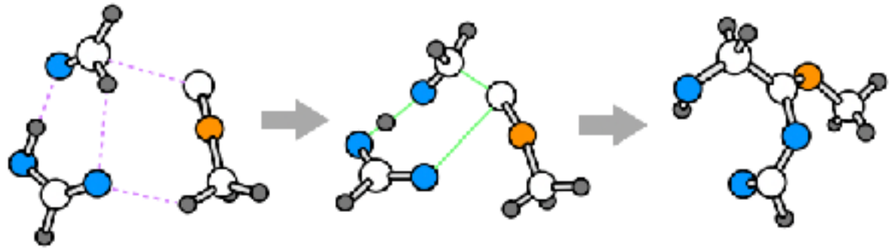


Compositionality and hiearchy

Similar to natural language?

We combine words to make any complicated sentences.

- A chemical reaction is a recombination pattern of bonds



The underlying rules are (largely) governed by many-body quantum chemistry of electrons

This talk

This slide is available at
https://itakigawa.github.io/news.html

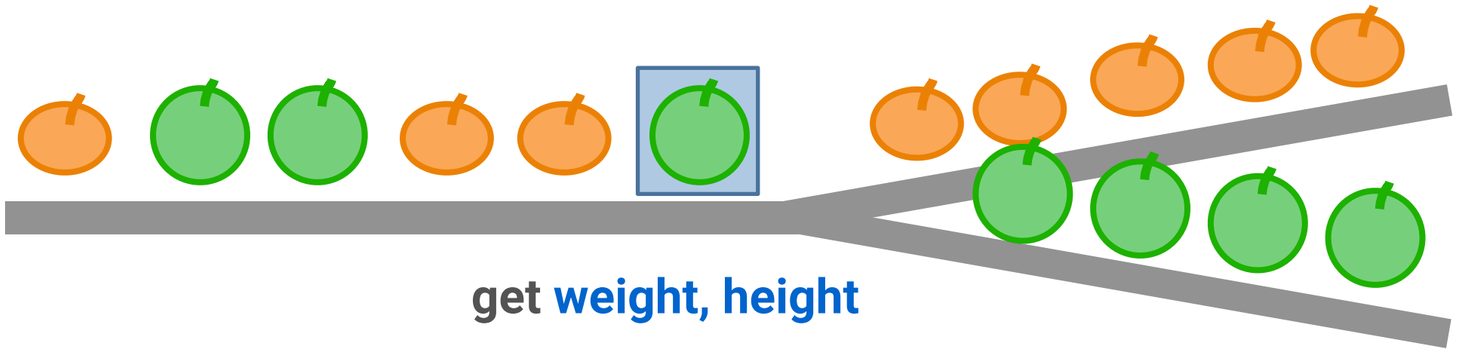
A quick review on the dark side and light side of ML
from both viewpoints as an ML algorithm researcher and an ML practitioner/user

1. What actually ML is?
2. The dark side: Modern aspects of ML
3. The light side: Deep learning for molecules

May the ML Force be with you…

> Science is built up of facts, as a house is built of stones;
> but an accumulation of facts is no more a science than
> a heap of stones is a house.
>
> *Henri Poincaré "Science and hypothesis"*

ML converts data into "prediction"



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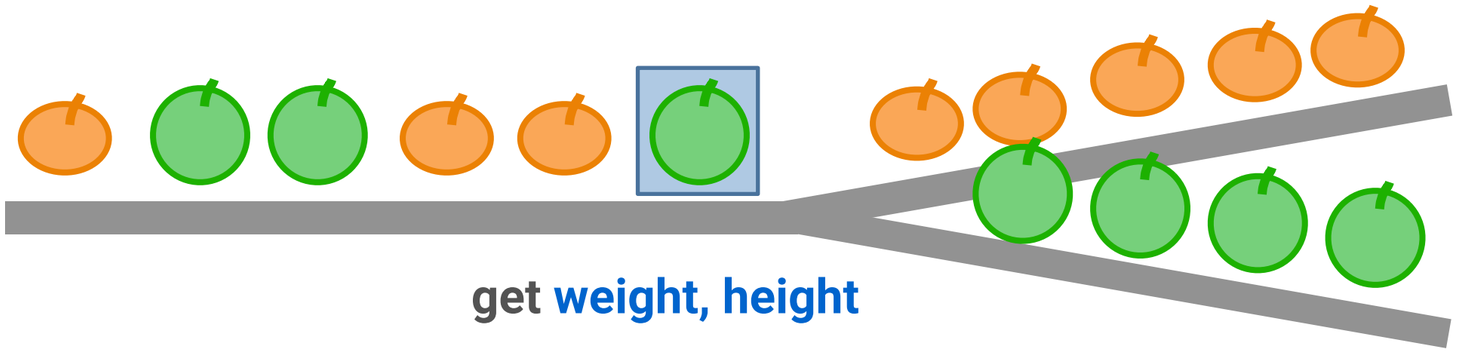

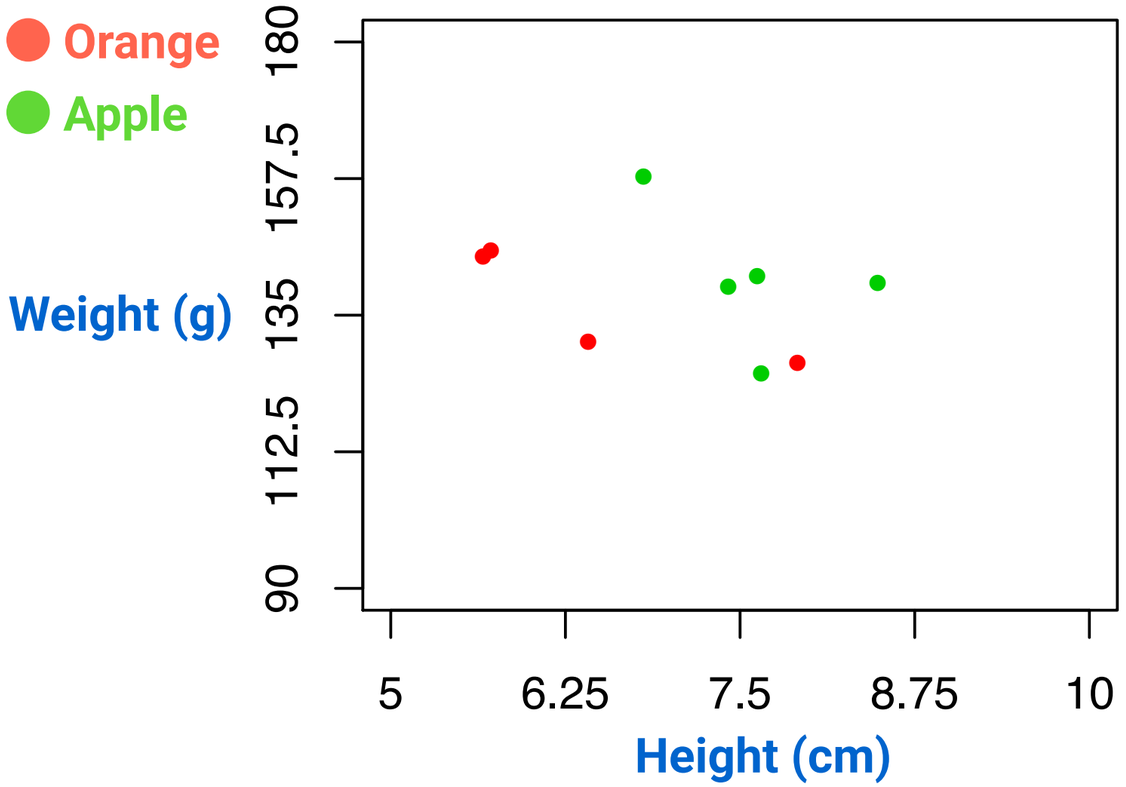

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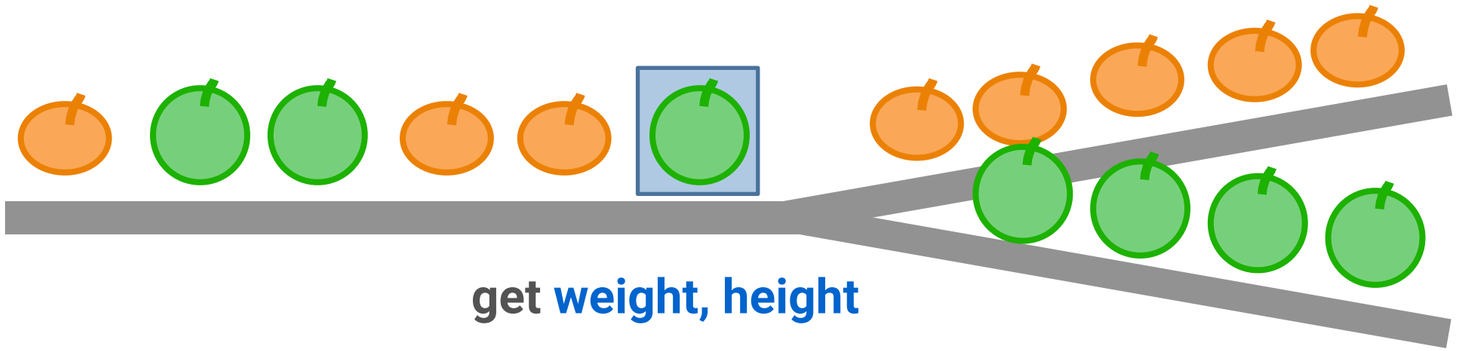

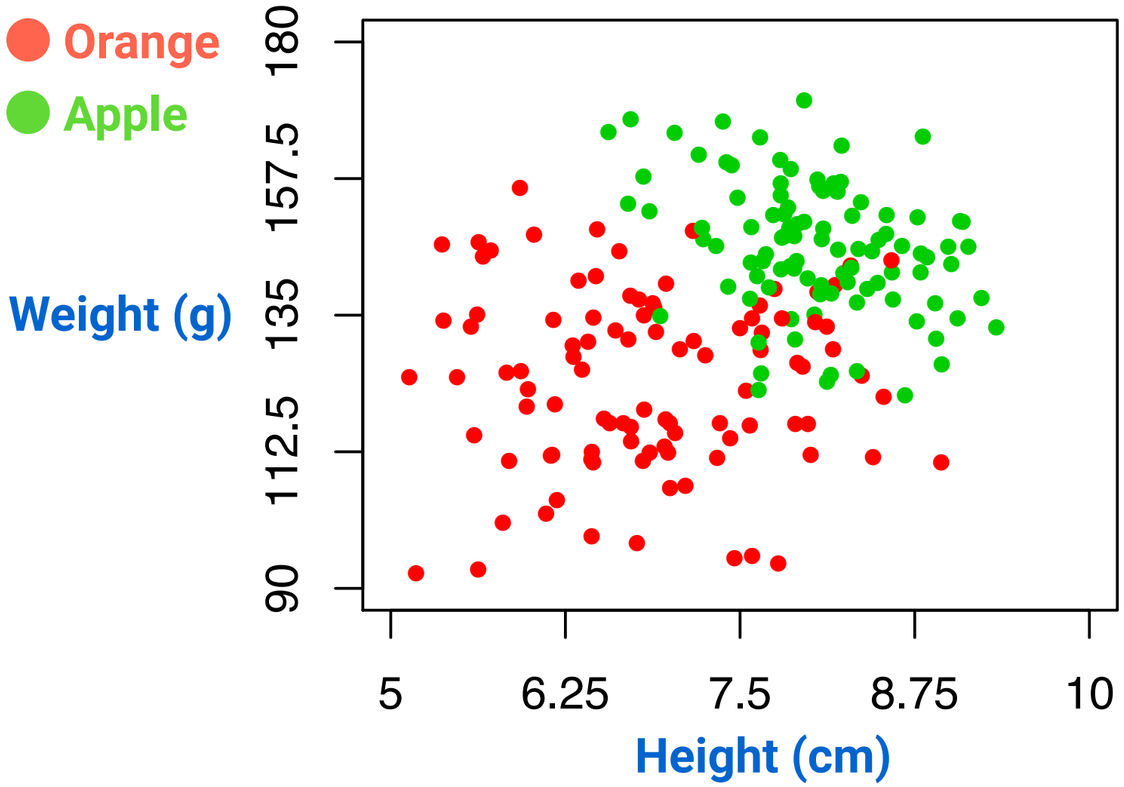

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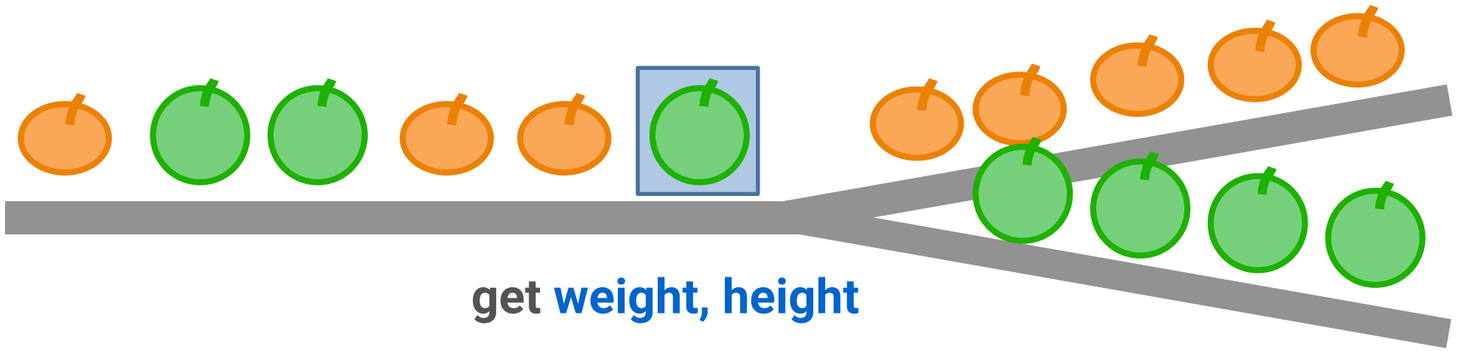

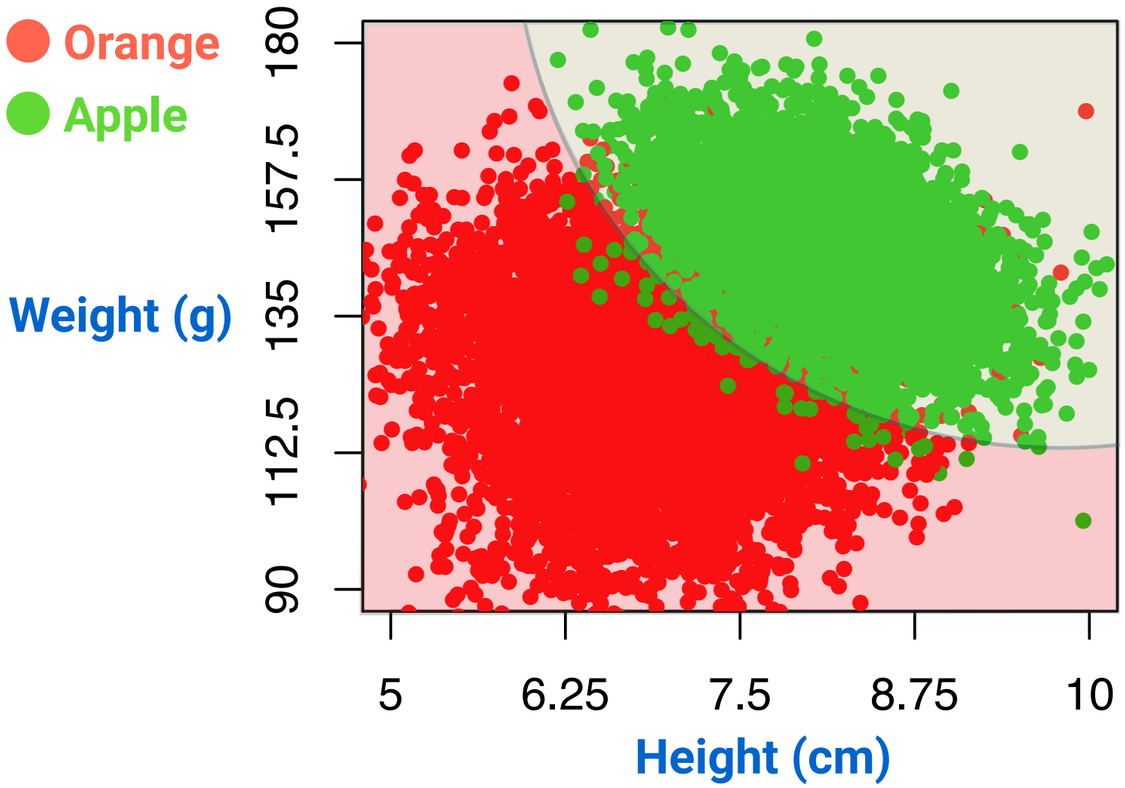

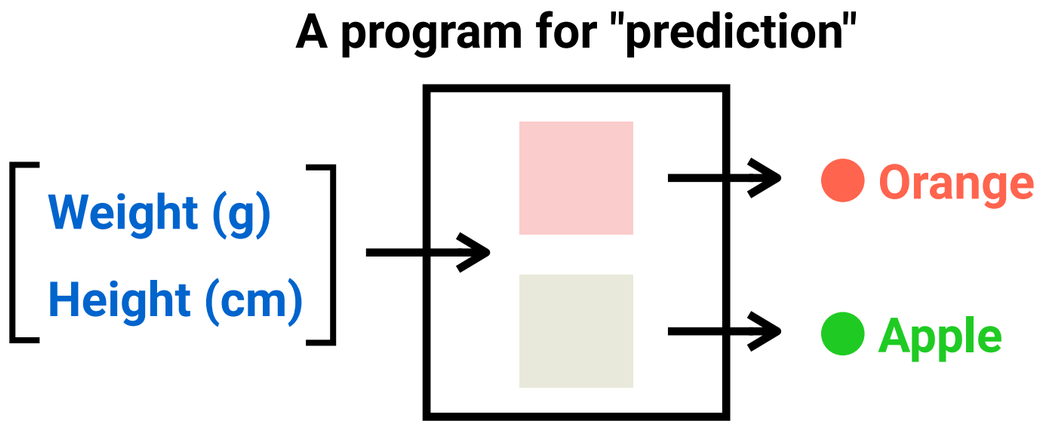

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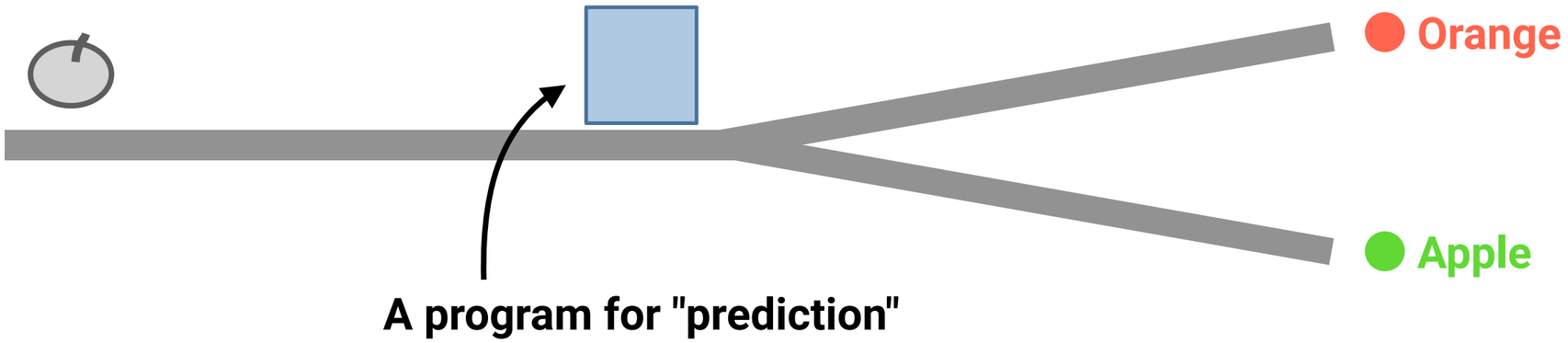

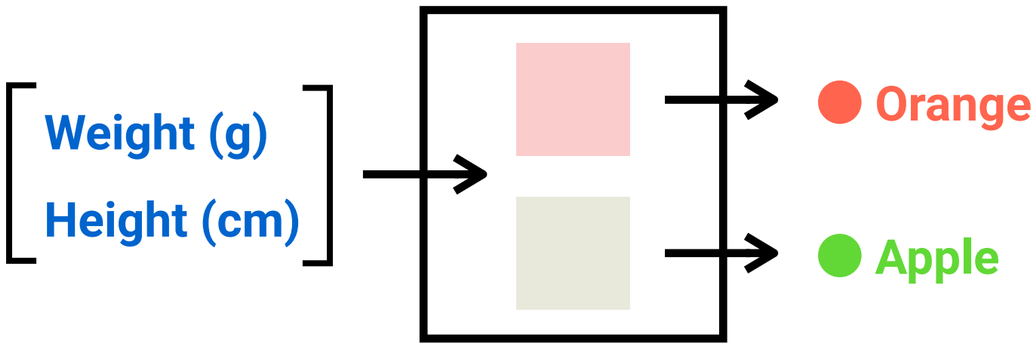

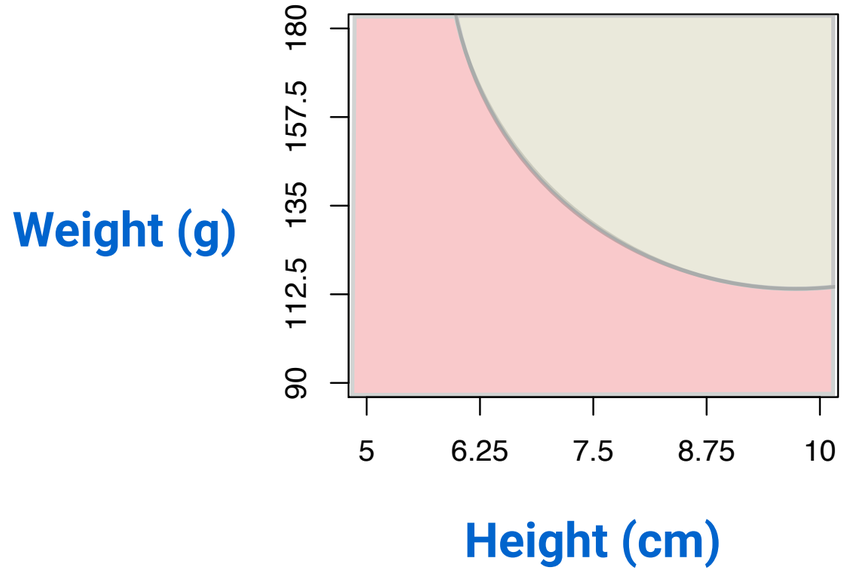

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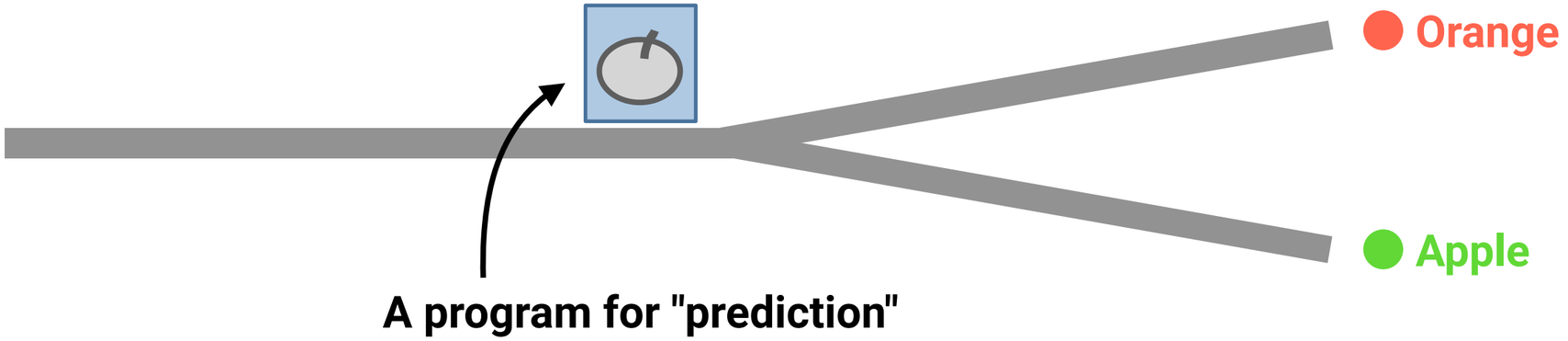
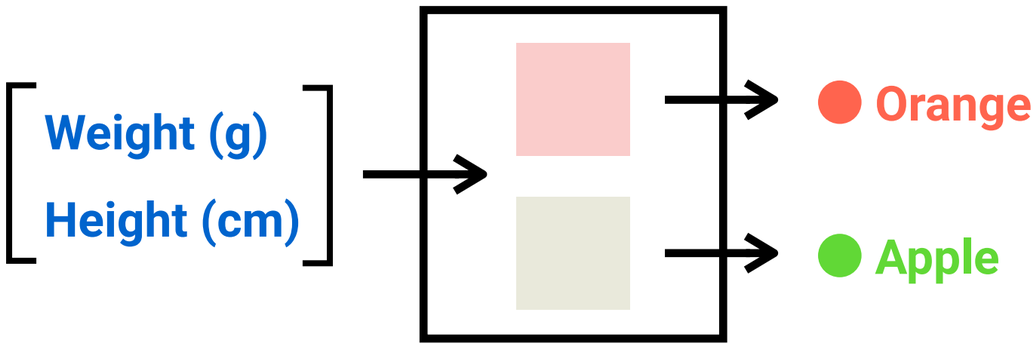
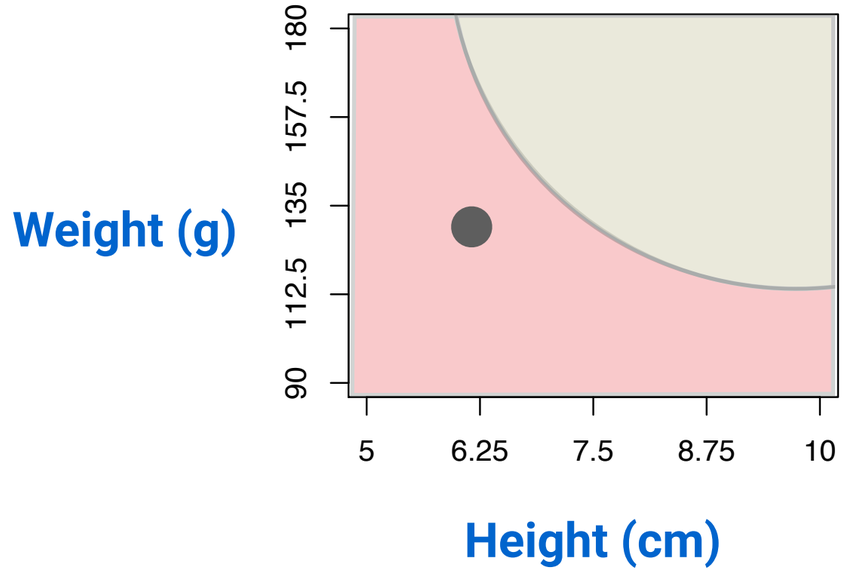


A program for "prediction"





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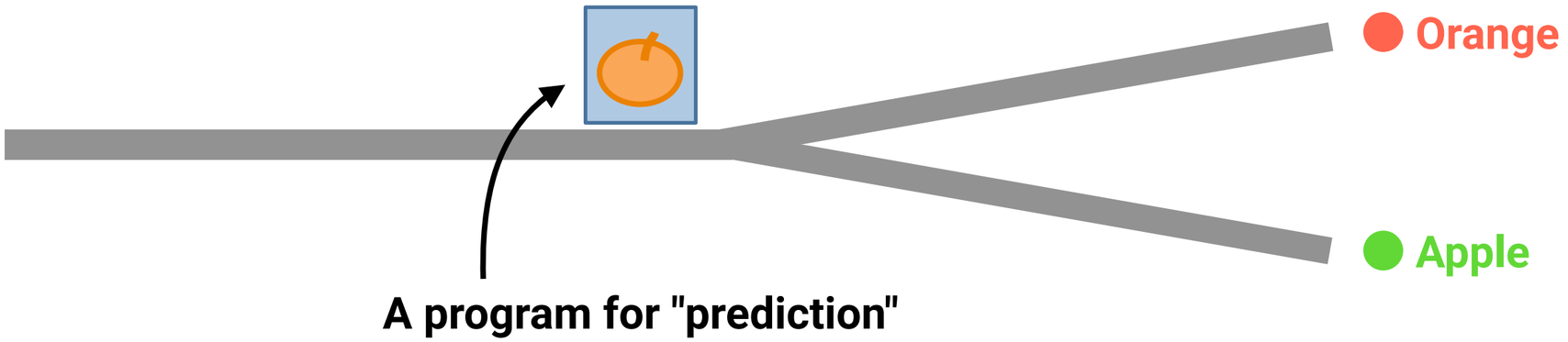

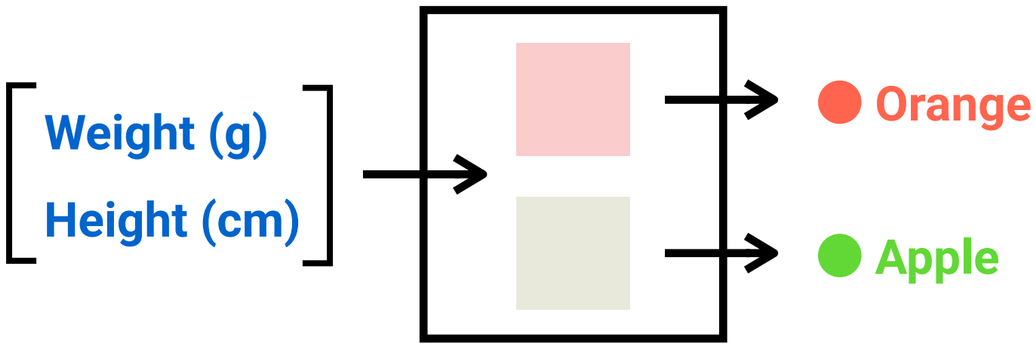

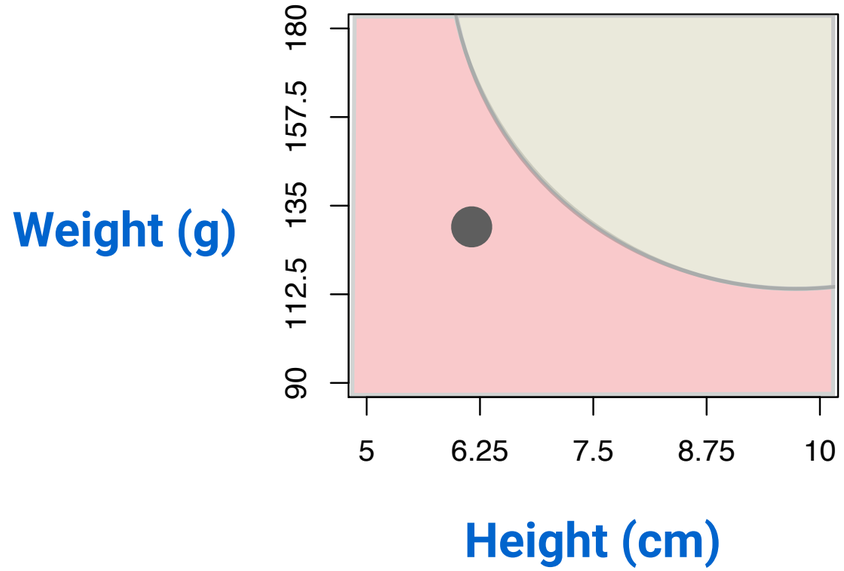

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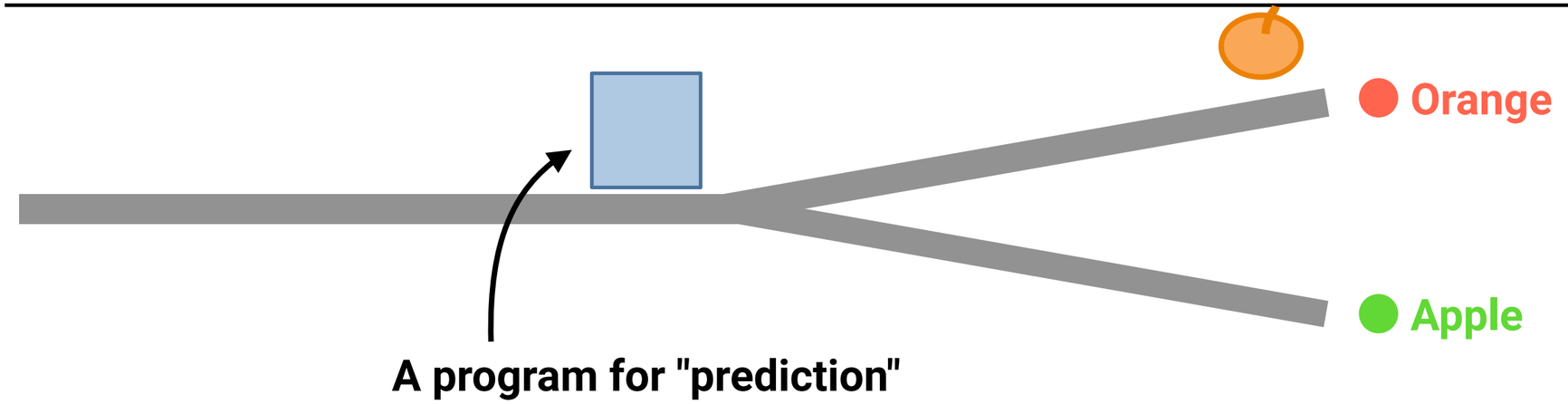

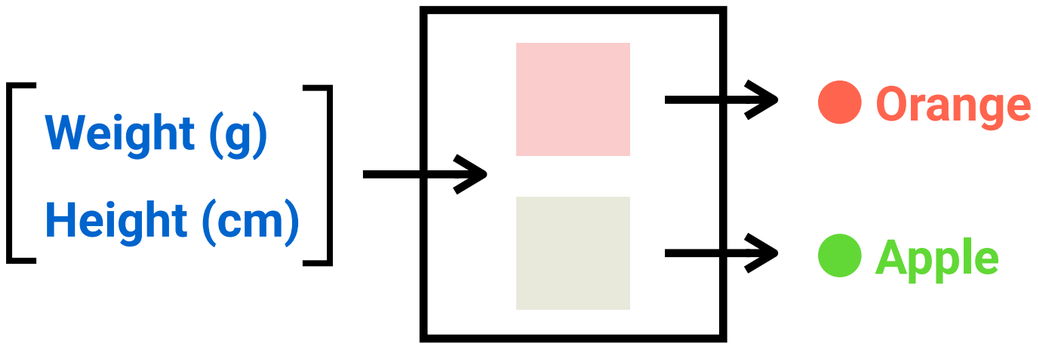

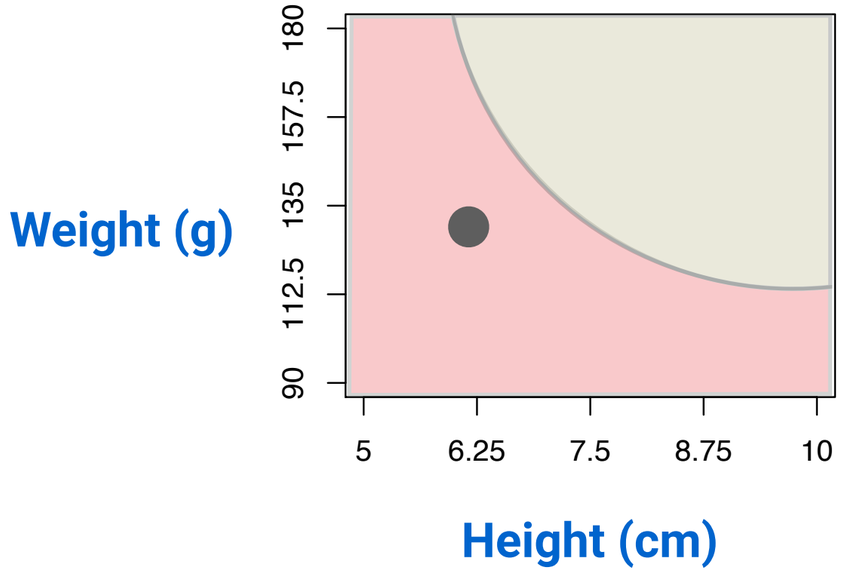

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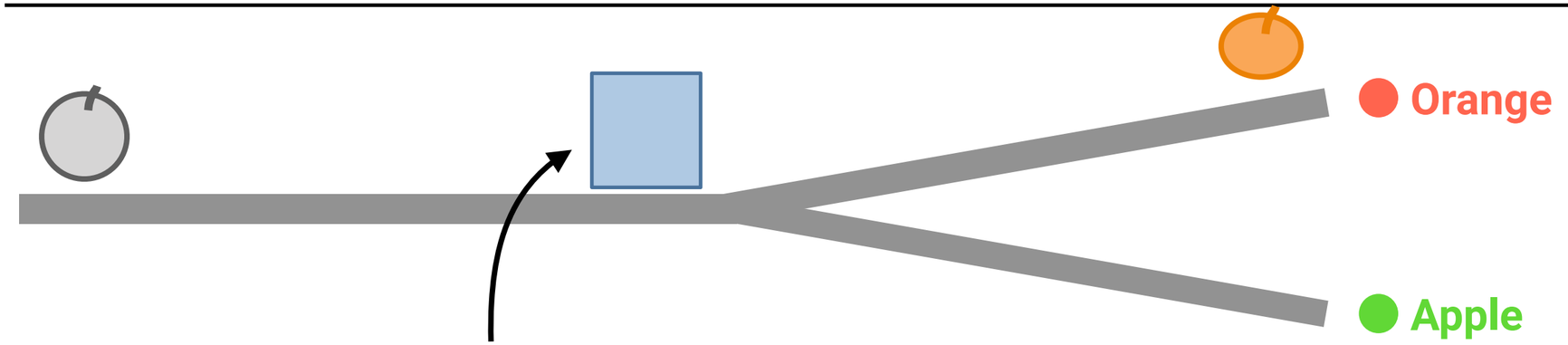
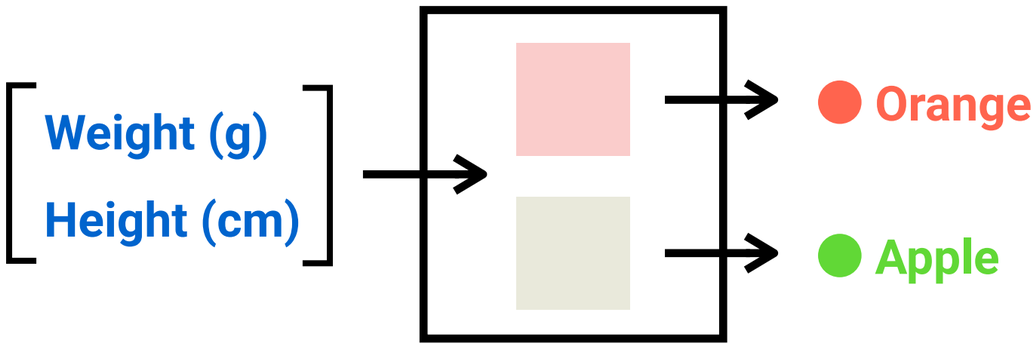
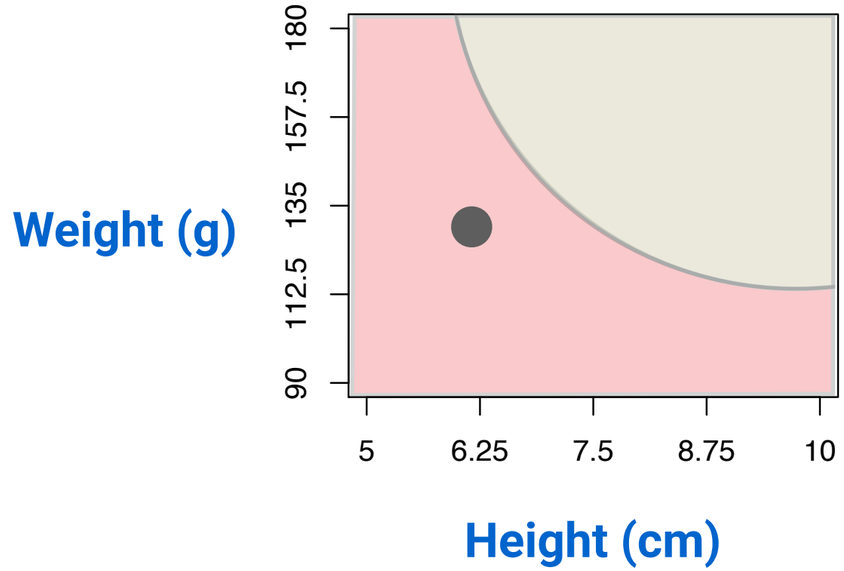


A program for "prediction"





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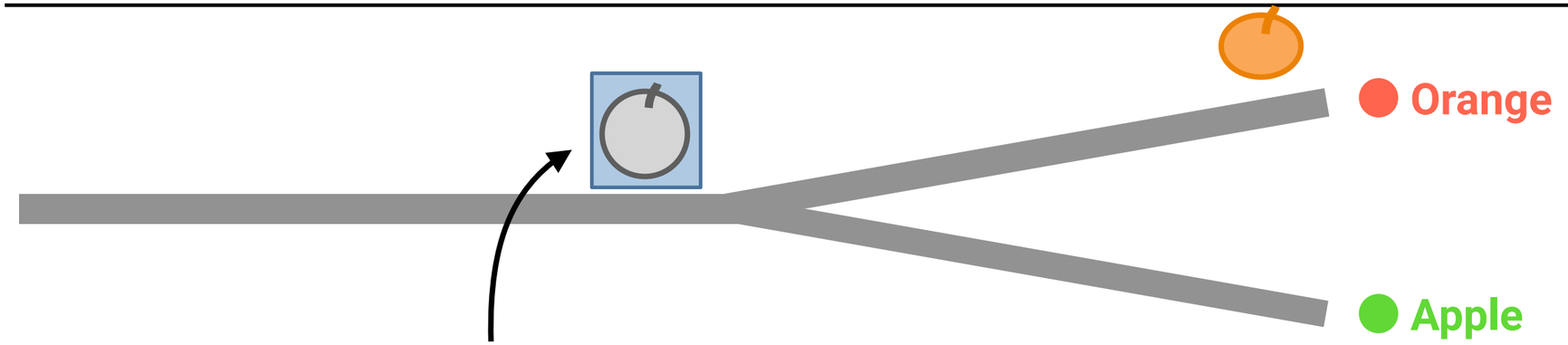

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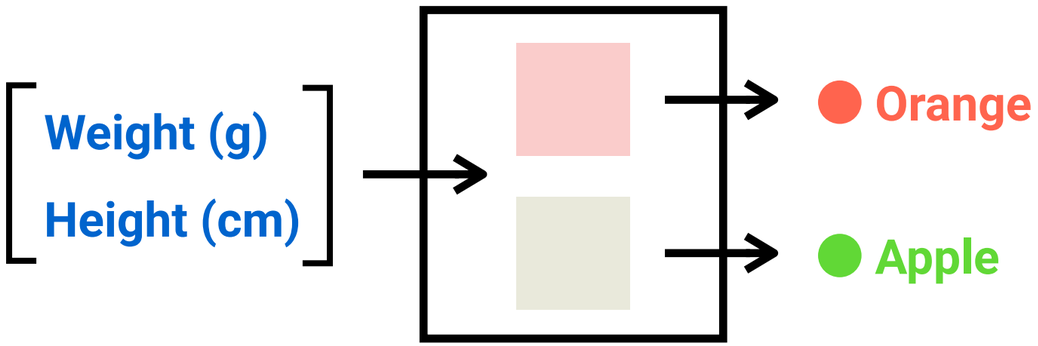

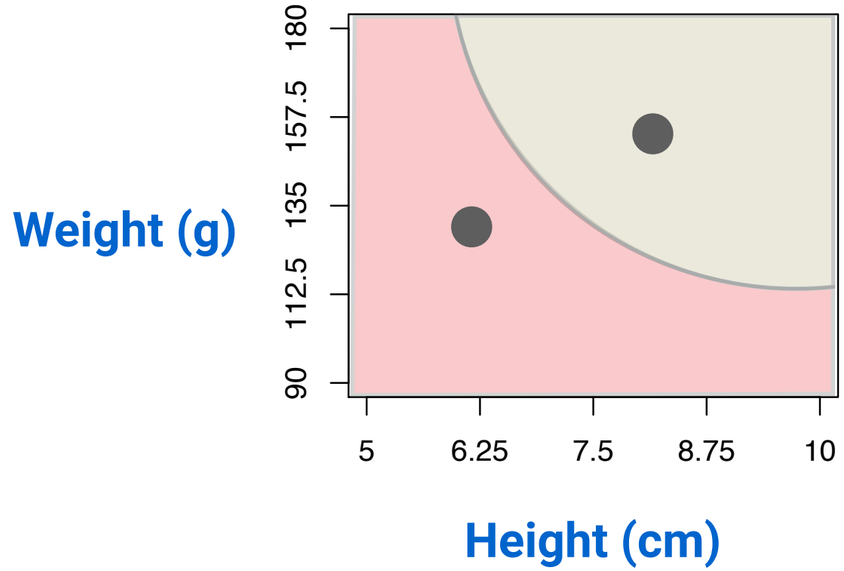

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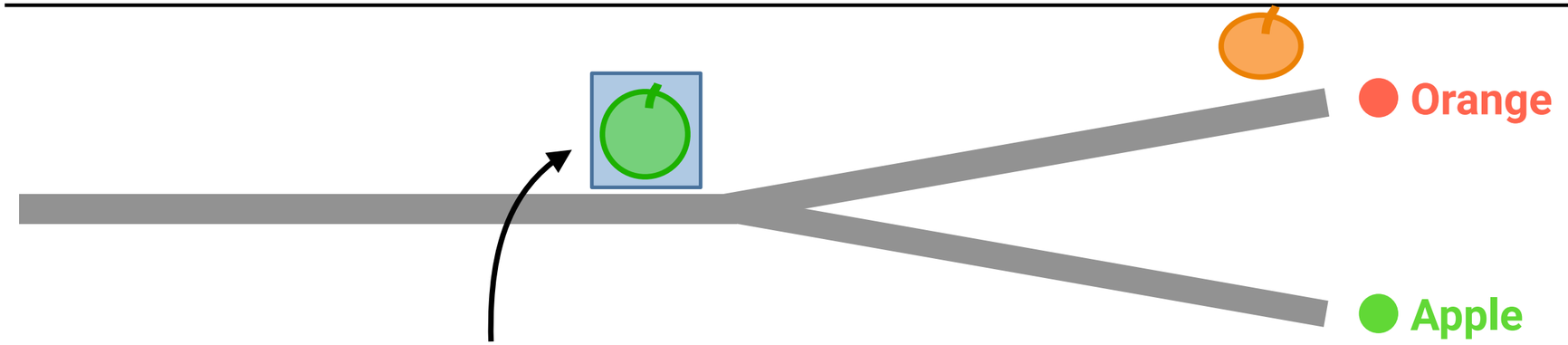

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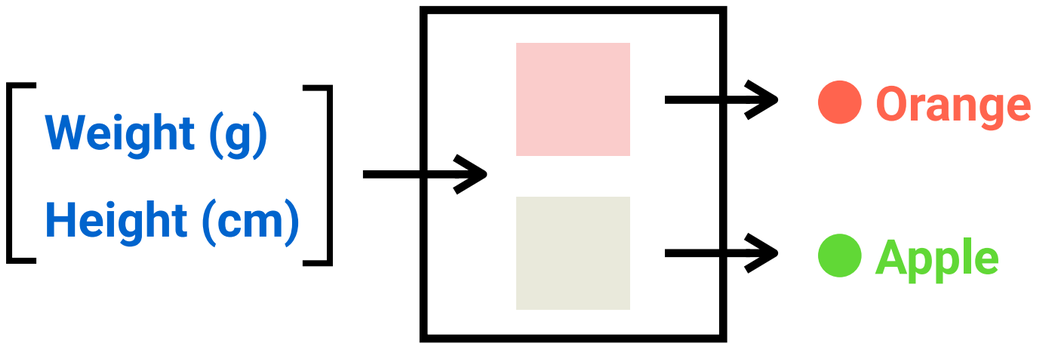

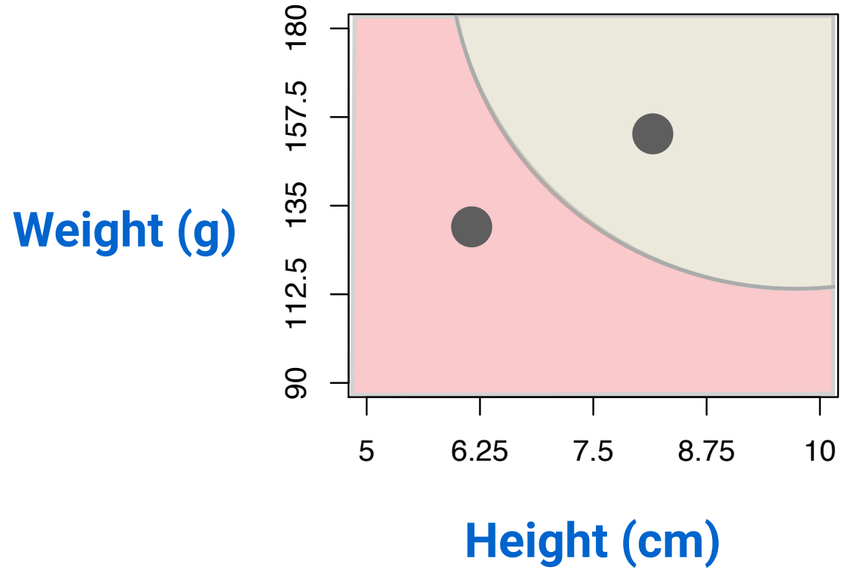

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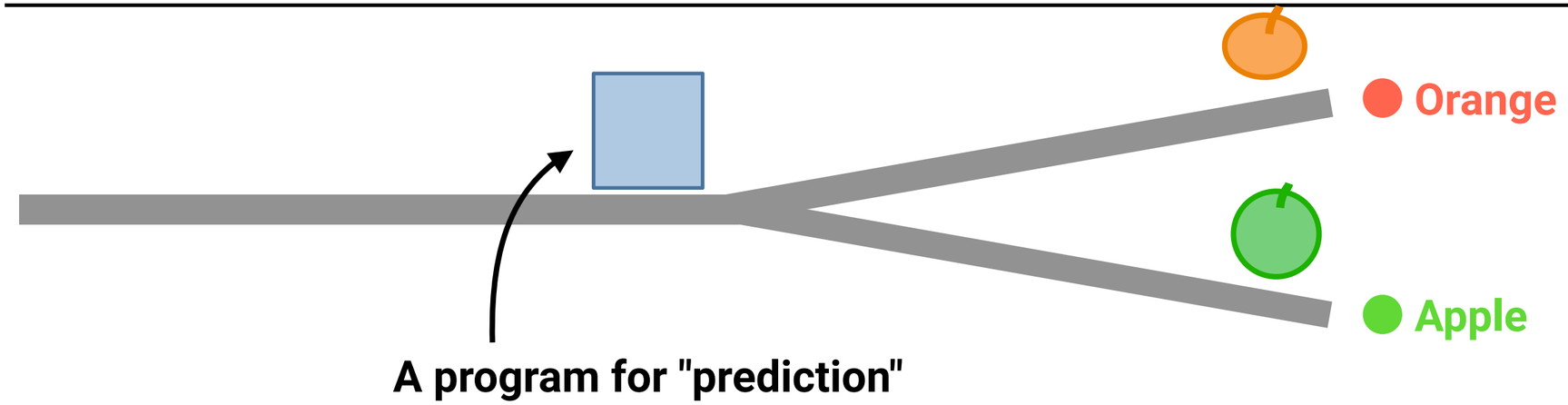

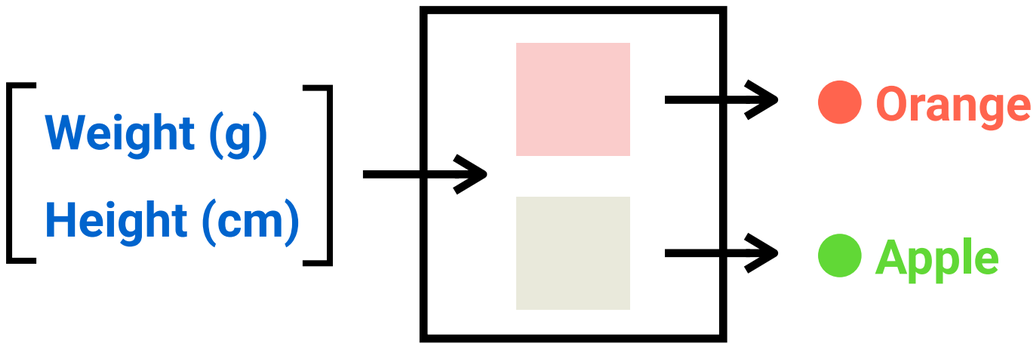

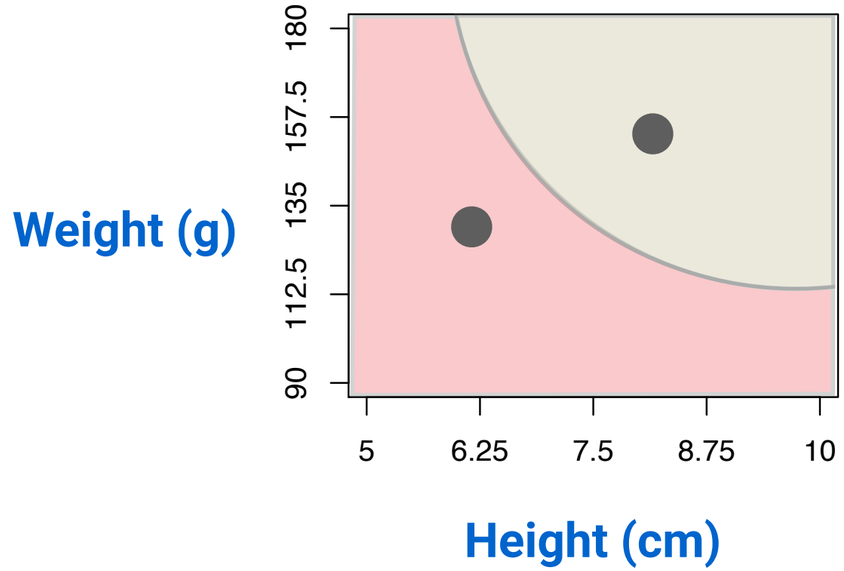

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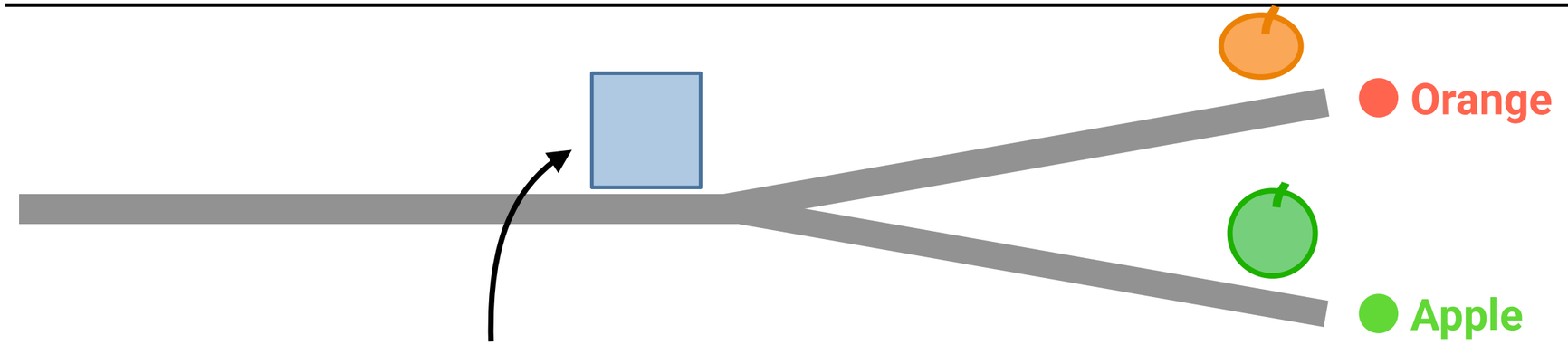
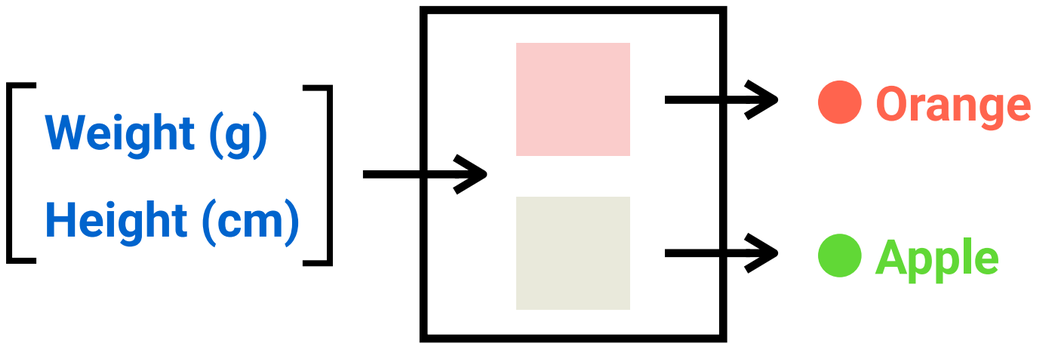
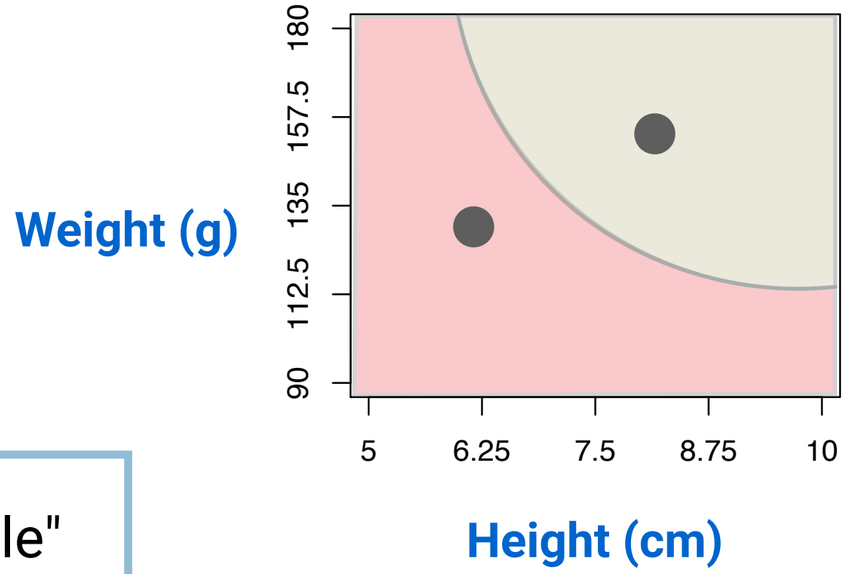


A program for "prediction"

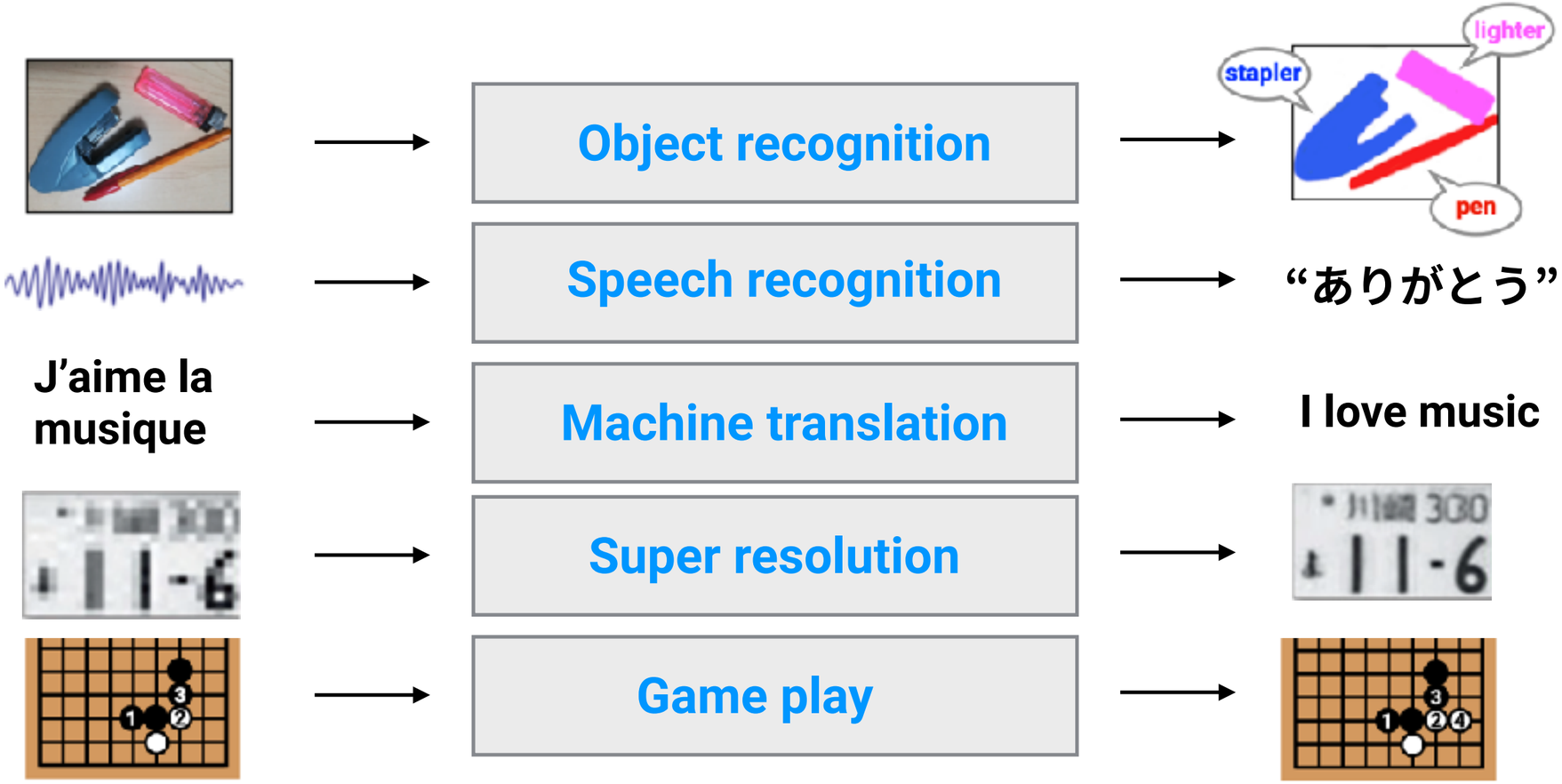




Now we got a computer program to predict "orange or apple" for any unseen ones **directly from collected data**

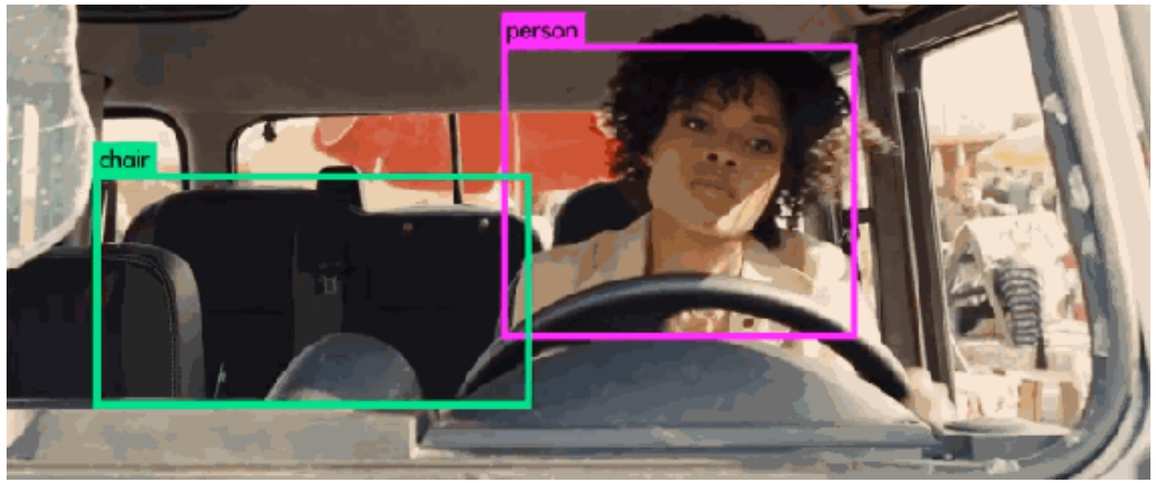
ML is a new (lazy) way of programming

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.



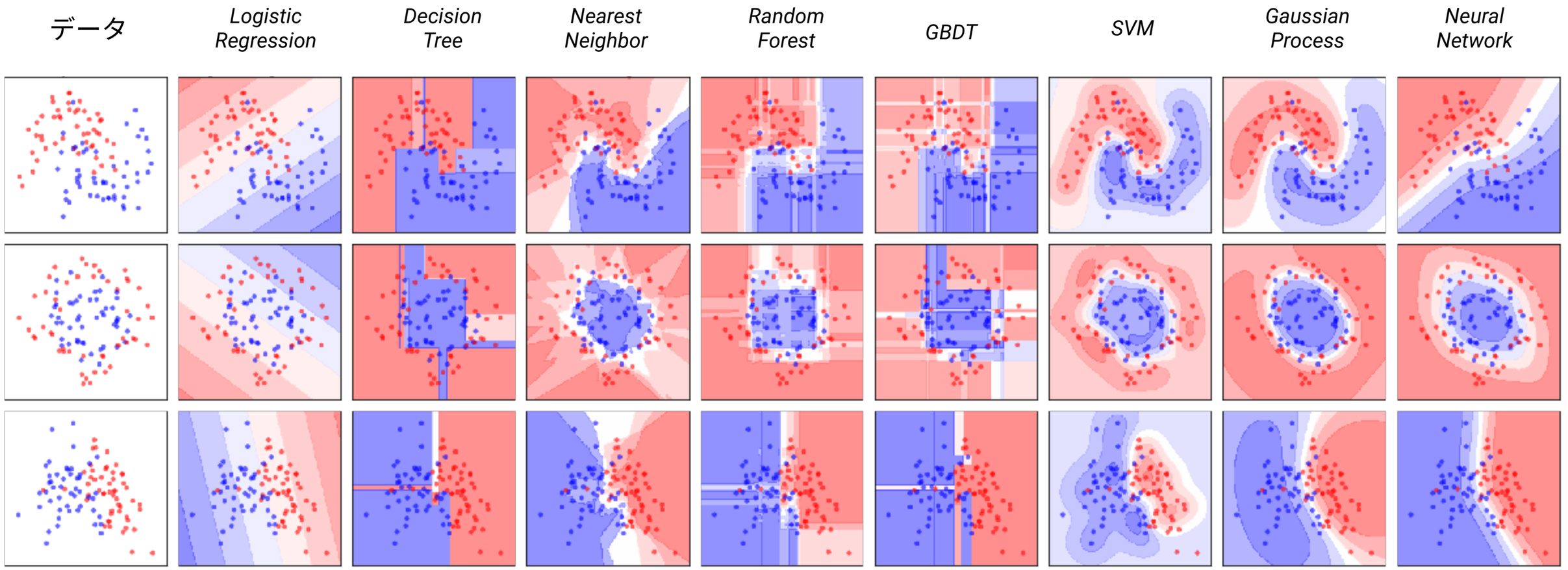
This simple idea is more powerful than you may think

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



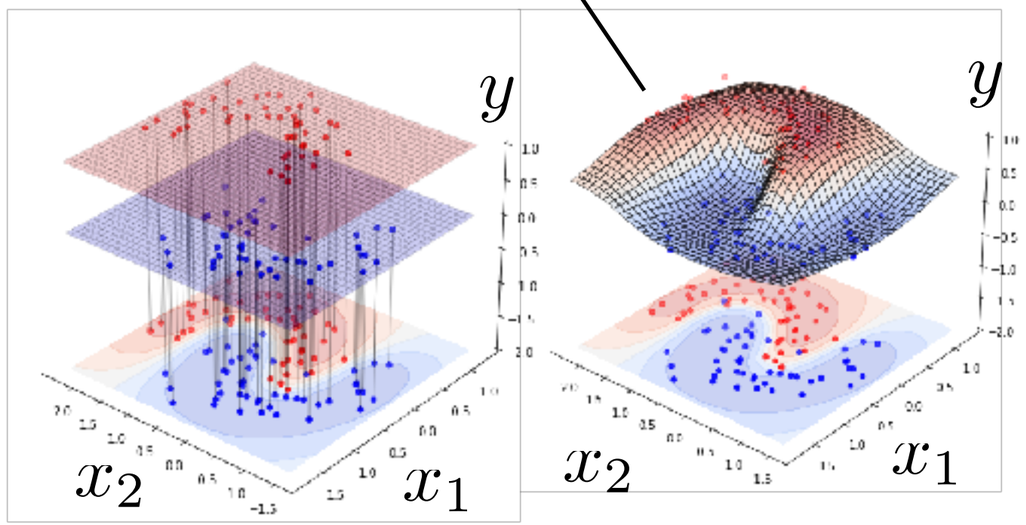
Many ways to mathematically represent the boundary

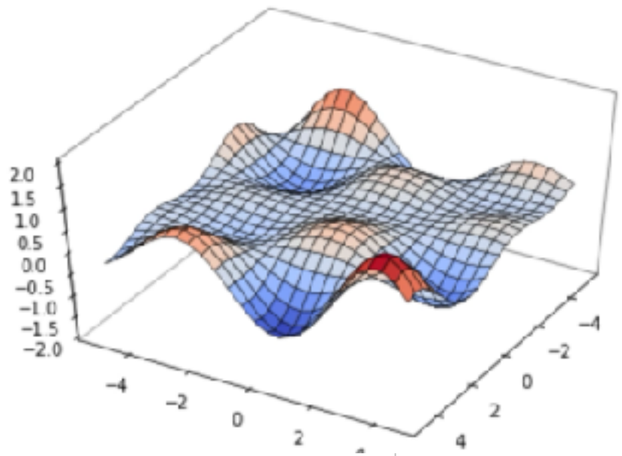
This is why you see too many algorithms when you start to learn ML…

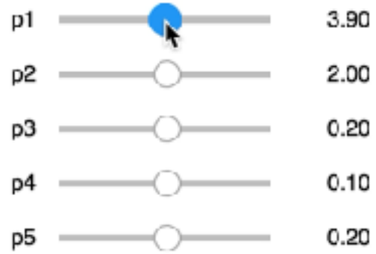


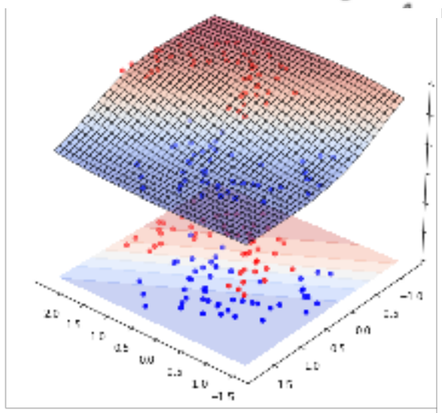
But anyway, we're just tweaking parameters for a good fit

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

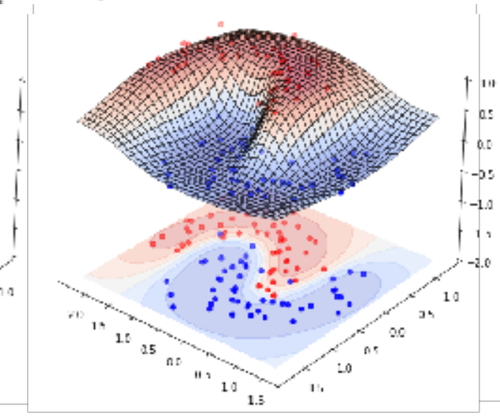




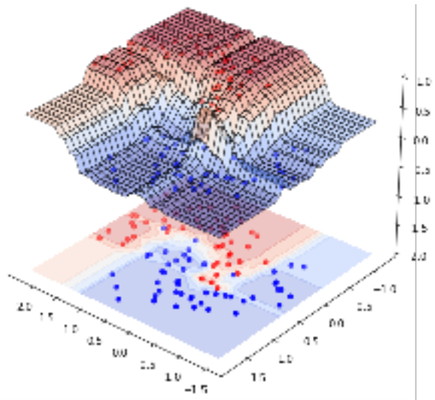




Logistic Regression

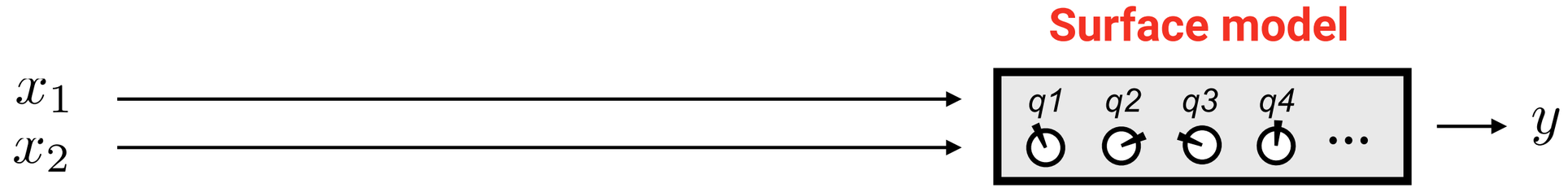


Gaussian Process

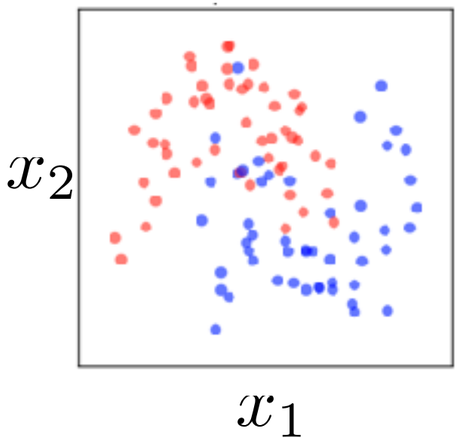


Random Forest

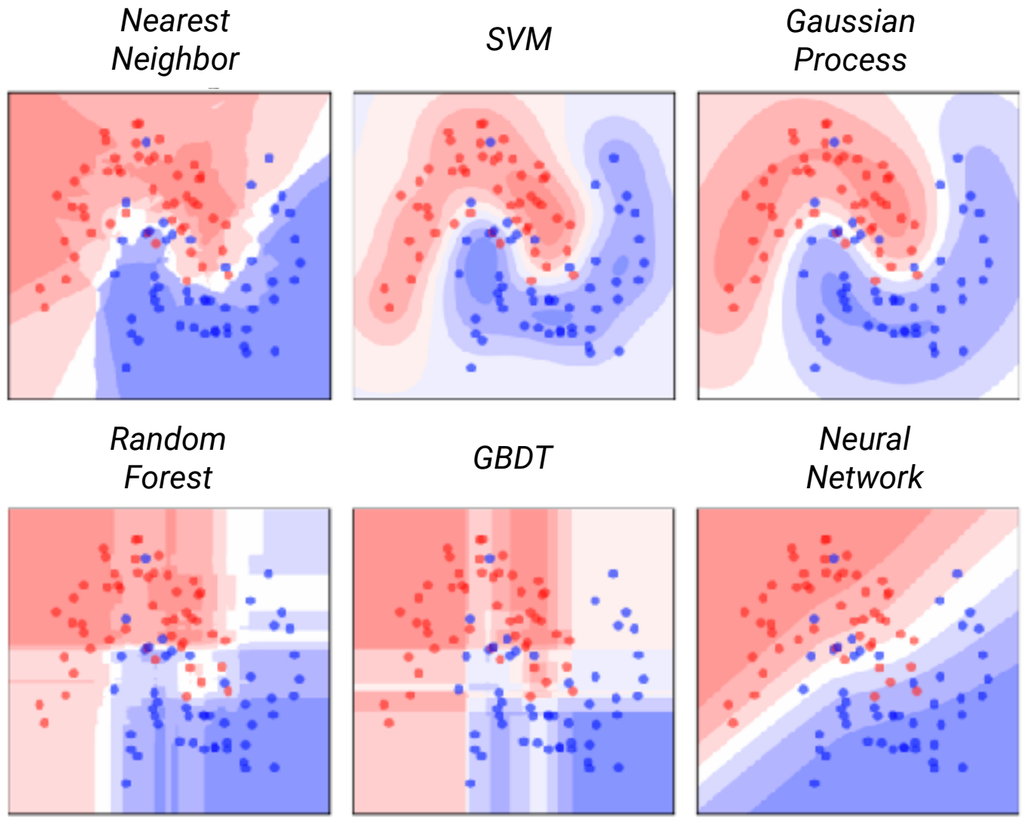
Deep Learning (Representation Learning)



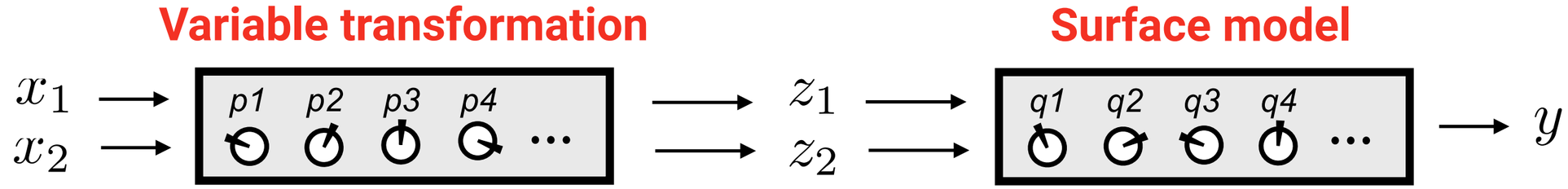
Input variables

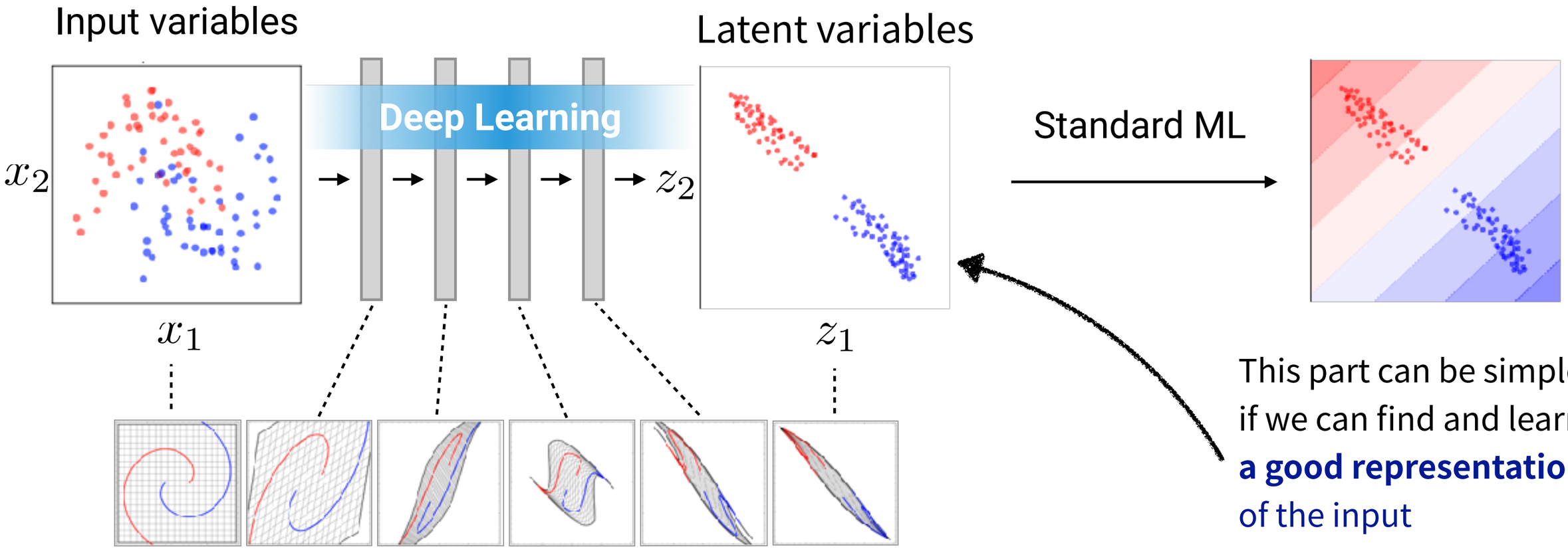


Standard ML



Deep Learning (Representation Learning)

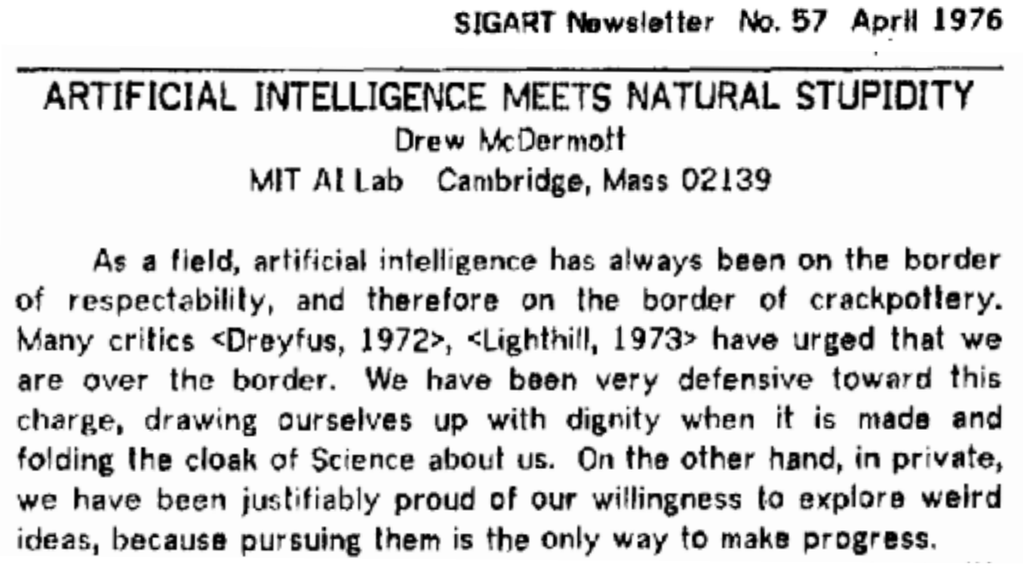




Pitfall: The lure of wishful wordings

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.

This talk

This slide is available at
https://itakigawa.github.io/news.html

A quick review on the dark side and light side of ML
from both viewpoints as an ML algorithm researcher and an ML practitioner/user

1. What actually ML is?
2. The dark side: Modern aspects of ML
3. The light side: Deep learning for molecules

May the ML Force be with you…

> Science is built up of facts, as a house is built of stones;
> but an accumulation of facts is no more a science than
> a heap of stones is a house.
>
> *Henri Poincaré "Science and hypothesis"*

The dark side: Modern aspect 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

The dark side: Modern aspect of ML

- **High dimensionality:** Too many input 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 aspect of ML

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

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

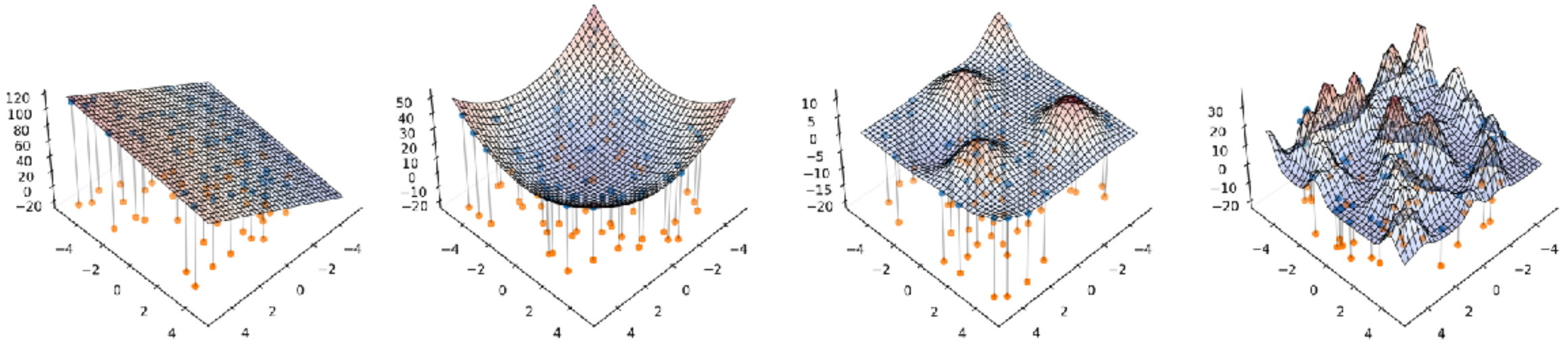
The dark side: Modern aspect of ML

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

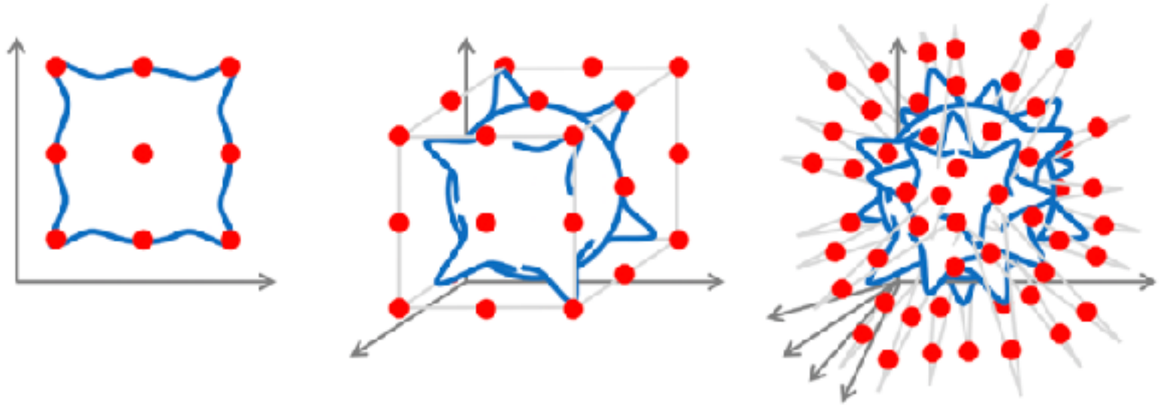
  As a result, it requires huge good data to make current ML models work.

  Think twice about how complex the input-output relationship you are trying to find by ML is.

  How many samples will be *statistically sufficient* to estimate *2-variable* functions like these? What if you're fitting a *100-variable* function, or *10-thousand-variable* function?



The curse of dimensionality



L-Lipschitz $f : \mathbb{R}^d \to \mathbb{R}$
gives similar outputs for similar inputs

$$|f(x) - f(x')| \leqslant L\|x - x'\|$$

for all $x, x' \in \mathbb{R}^d$

A classic result in function approximation: If we must approximate a function of d variables and we know only that it is Lipschitz, say, then we need order $(1/\varepsilon)^d$ observations on a grid in order to obtain an approximation scheme with uniform approximation error ε.

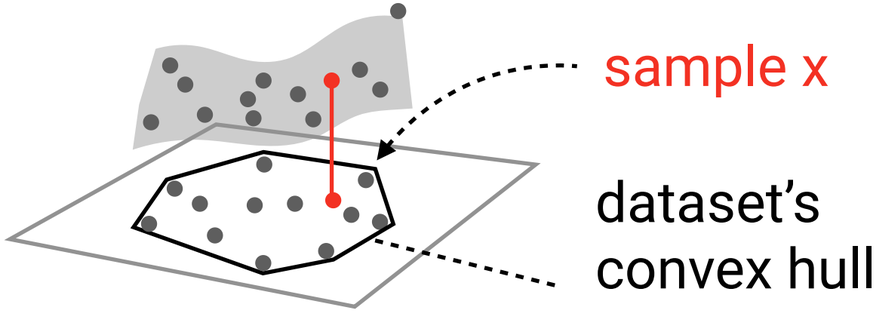
Donoho DL,
High-dimensional data analysis: The curses and blessings of dimensionality.
Plenary Lecture, AMS National Meeting on Mathematical Challenges of the 21st Century. 2000.

Bronstein MM, Bruna J, Cohen T, Veličković P.
Geometric Deep Learning: Grids, Groups, Graphs, Geodesics, and Gauges.
arXiv [cs.LG]. 2021. http://arxiv.org/abs/2104.13478

The interpolation vs extrapolation argument

Balestriero R, Pesenti J, LeCun Y.
Learning in High Dimension Always Amounts to Extrapolation.
arXiv [cs.LG]. 2021. http://arxiv.org/abs/2110.09485

- If we define 'interpolation' as
  Interpolation occurs for a sample x whenever this sample ***falls inside the given dataset's convex hull****.*
- Then, the paper empirically and theoretically demonstrates that **"on any high-dimensional (>100) dataset, interpolation almost surely never happens."**
- "Those results challenge the validity of our current interpolation/extrapolation definition as an indicator of generalization performances. "
- In high dimension, even just determining interpolation or extrapolation is already counter-intuitive…



Over 3 hours interview with authors @ MLStreetTalk

https://youtu.be/86ib0sfdFtw

Assessing ML predictions is intrinsically very hard!

It is quite **obvious** that ML correctly makes prediction for **the given training data**.

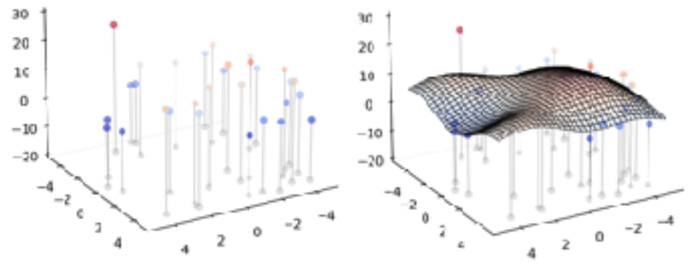
ML predictions **must** be evaluated by using some data **except** the given training data,
but they can mean **any data** we haven't seen yet.

✓ We have no other choice but to **use some finite data** for assessing any ML predictions.

✓ They are already in hand, and **unintended cheating (data leakage) is very likely to happen**

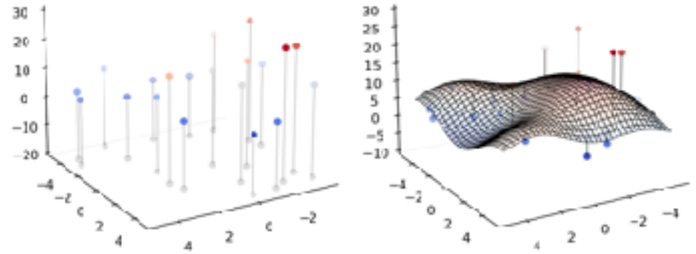
❶ ***Training***

Example/Practice Questions + Answers



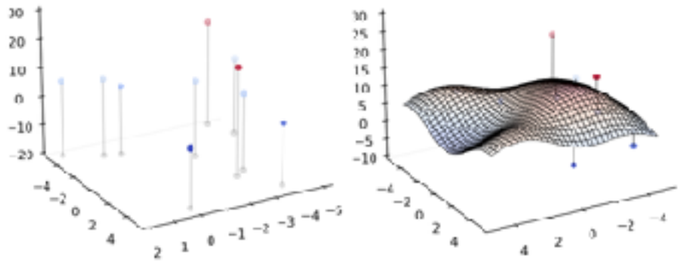
❷ ***Validation***

Practice Tests + Answers



❸ ***Test***

Real Test (+ Answers)



Big challenge: Rashomon effect and underspecification

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

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

Big challenge: Rashomon effect and underspecification

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

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

- Many explanations can exist for a single set of finite observations in general .
  (whether they are given by ML or by human experts.)

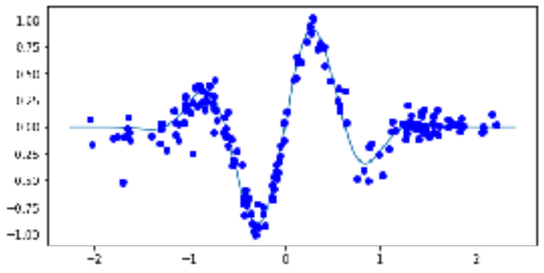
Big challenge: Rashomon effect and underspecification

Rashomon Effect: The multiplicity of good ML models

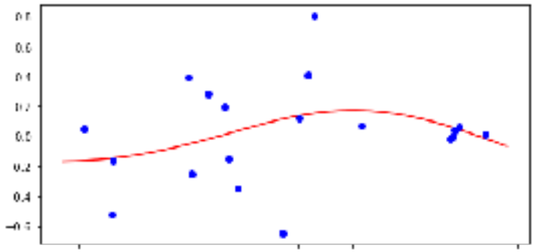
In general, we can have many equally good but very different ML models that give equally accurate predictions for the given data.

- 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.

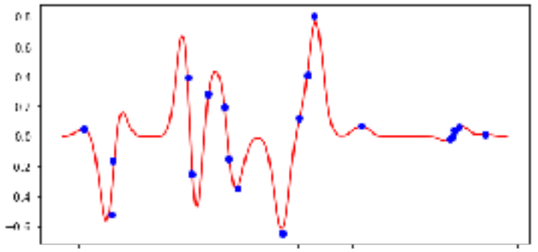
Any ML model will work



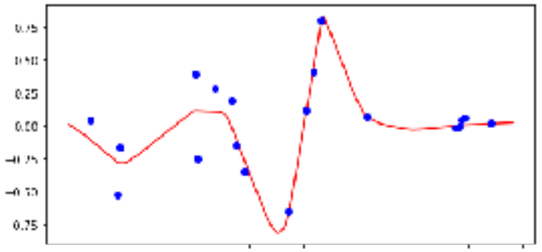
Different models can give very different predictions for out-of-sample cases



Neural Network (Tanh)



Kernel Ridge (RBF)



Neural Network (ReLU)

Underspecification appears in many practical ML systems?

- We often see **ML failures** in real-world domains even when we trained them on well-curated data that structurally matched with the application domain.
- "While ML models are validated on held-out data, this validation is often insufficient to guarantee that the models will have well-defined behavior when they are used **in a new setting.** "

https://ai.googleblog.com/2021/10/how-underspecification-presents.html

Google AI Blog

The latest from Google Research

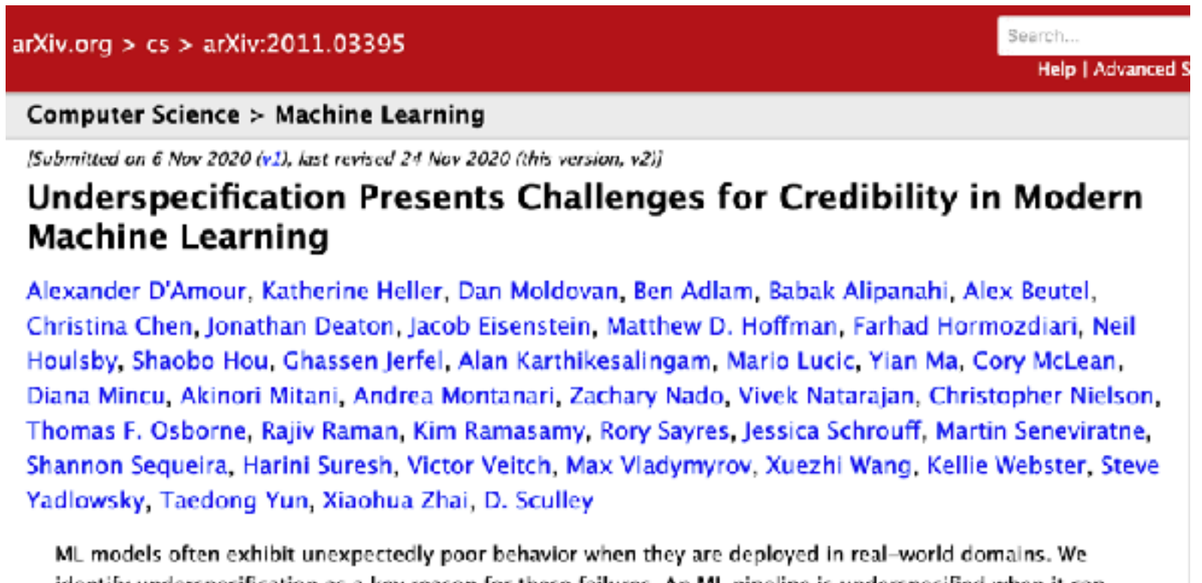
How Underspecification Presents Challenges for Machine Learning

Monday, October 18, 2021

Posted by Alex D'Amour and Katherine Heller, Research Scientists, Google Research

Machine learning (ML) models are being used more widely today than ever before and are becoming increasingly impactful. However, they often exhibit unexpected behavior when they are used in real-world domains. For example, computer vision models can exhibit surprising sensitivity to irrelevant features, while natural language processing models can depend unpredictably on

https://arxiv.org/abs/2011.03395



Many points in ML are still open problems!

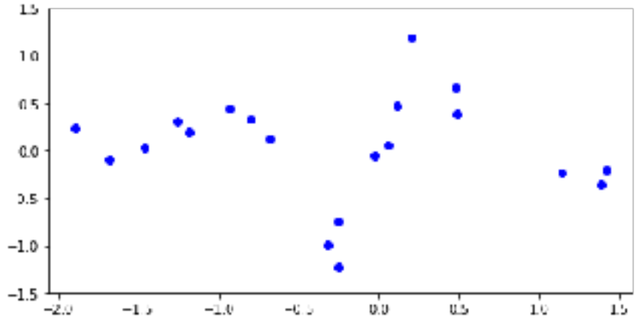
Definitely we still need to rethink our traditional understanding on concepts like generalization, overfitting, bias-variance tradeoff, interpolation/extrapolation, the curse of dimensionality, etc.

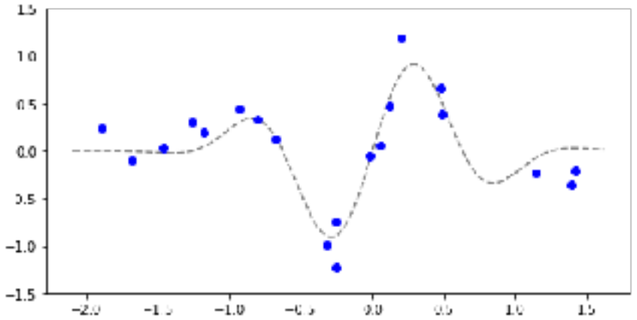
- **Too high expressive power**
  Zero training error on random labels. (DL can represent any function / memorize entire data)
- **Benign overfitting (when interpolating noisy training data)**
  Low test error even when we have zero training error on *noisy* training data.
- **Implicit regularization**
  Stochastic optimization like SGD prefers low-complexity solutions.

Berner J, Grohs P, Kutyniok G, Petersen P.
The Modern Mathematics of Deep Learning. arXiv [cs.LG]. 2021. http://arxiv.org/abs/2105.04026

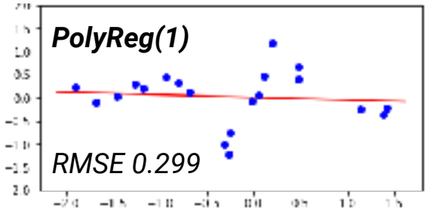
Zhang C, Bengio S, Hardt M, Recht B, Vinyals O.
Understanding deep learning (still) requires rethinking generalization. Commun ACM. 2021;64: 107–115.

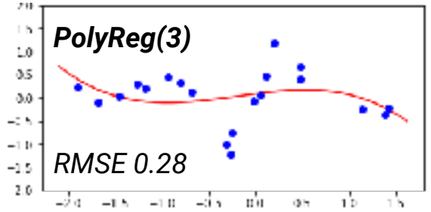
A toy case: 'Benign' zero training error on noisy data

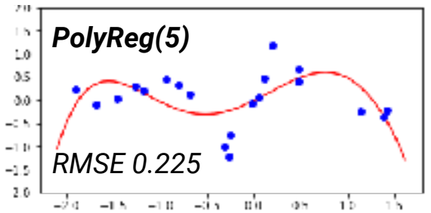


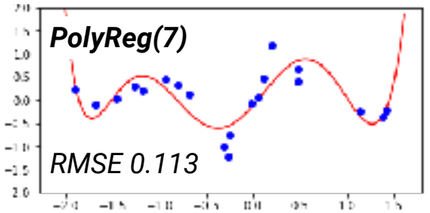


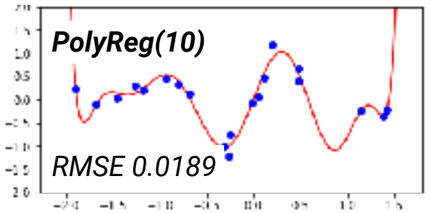
Problematic overfitting by polynomial regression of order k

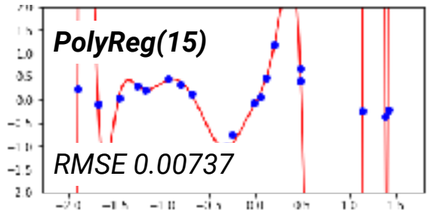


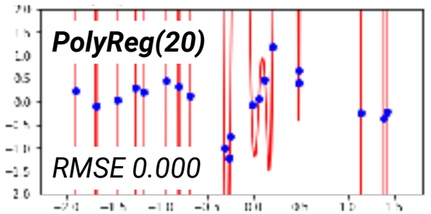


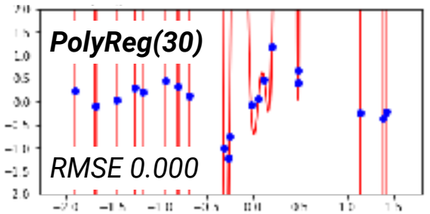




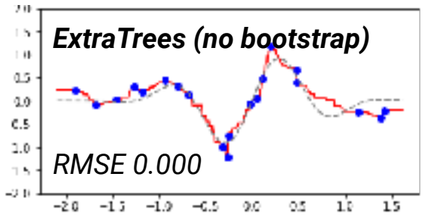


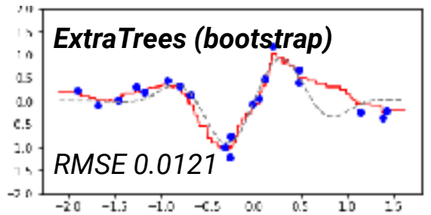


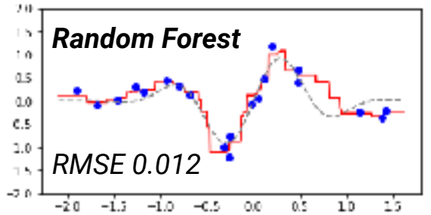


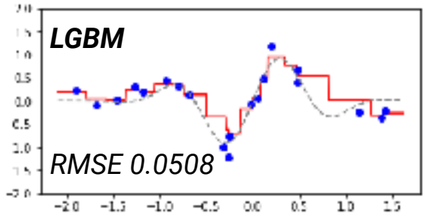


clearly overfitted but harmless (still informative)

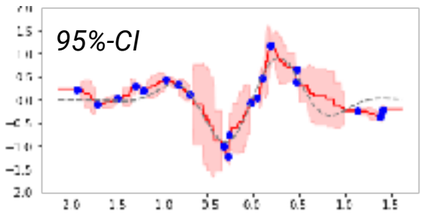


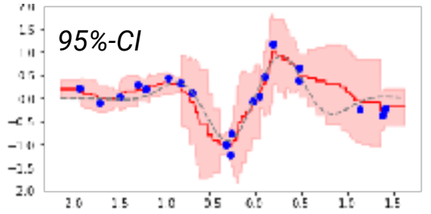


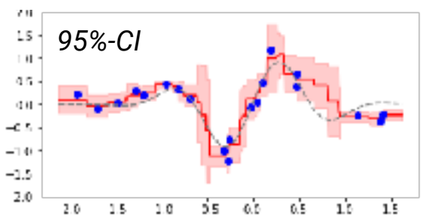


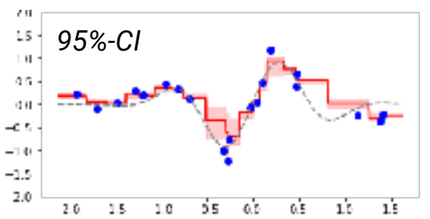


also we can assess the uncertainty









This talk

This slide is available at
https://itakigawa.github.io/news.html

A quick review on the dark side and light side of ML
from both viewpoints as an ML algorithm researcher and an ML practitioner/user

1. What actually ML is?
2. The dark side: Modern aspects of ML
3. The light side: Deep learning for molecules

May the ML Force be with you…

> Science is built up of facts, as a house is built of stones;
> but an accumulation of facts is no more a science than
> a heap of stones is a house.
>
> *Henri Poincaré "Science and hypothesis"*

ML's interests: How to tame the high dimensionality?

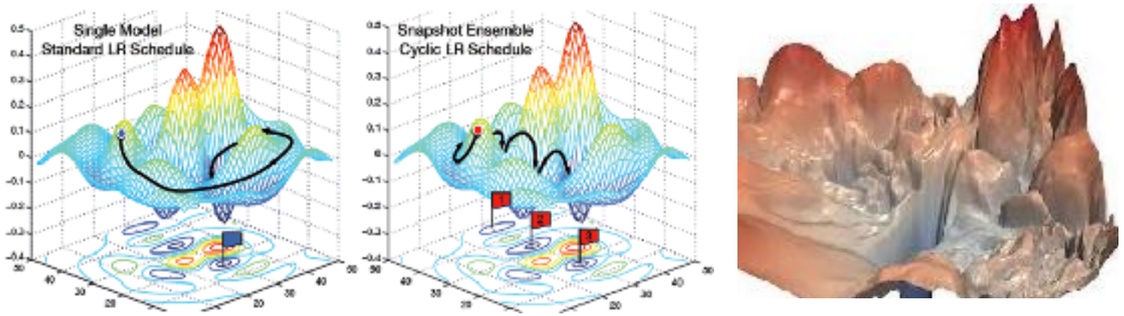
1. Regularization (inc. implicit regularization by SGD)

   Control, restrict, or stabilize the solution space or optimization

2. Good initial value (warm start) of general use

   Large-scale pretraining and its transfer

Trying to find the global minimum of very bumpy loss landscape…



ML's interests: How to tame the high dimensionality?

1. Regularization (inc. implicit regularization by SGD)

   Control, restrict, or stabilize the solution space or optimization

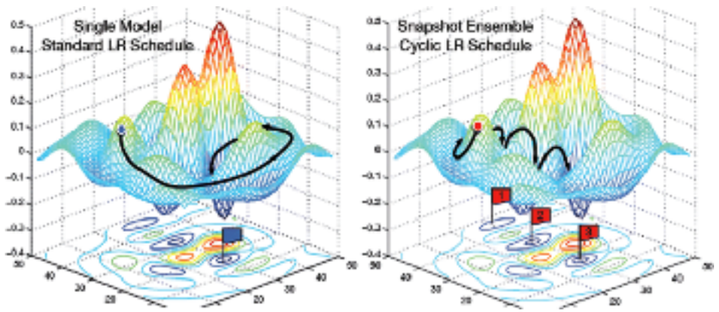
2. Good initial value (warm start) of general use

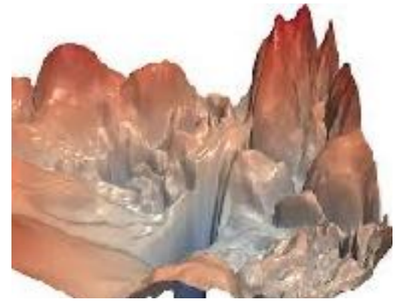
   Large-scale pretraining and its transfer

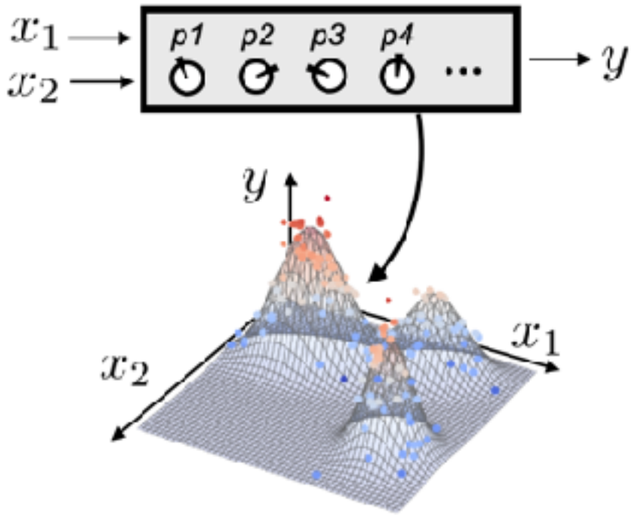
3. Relevant "inductive bias"

   ML models that can represent any function make worse the risk of Rashomon effect, underspecification, and spurious correlation.

Trying to find the global minimum of very bumpy loss landscape…

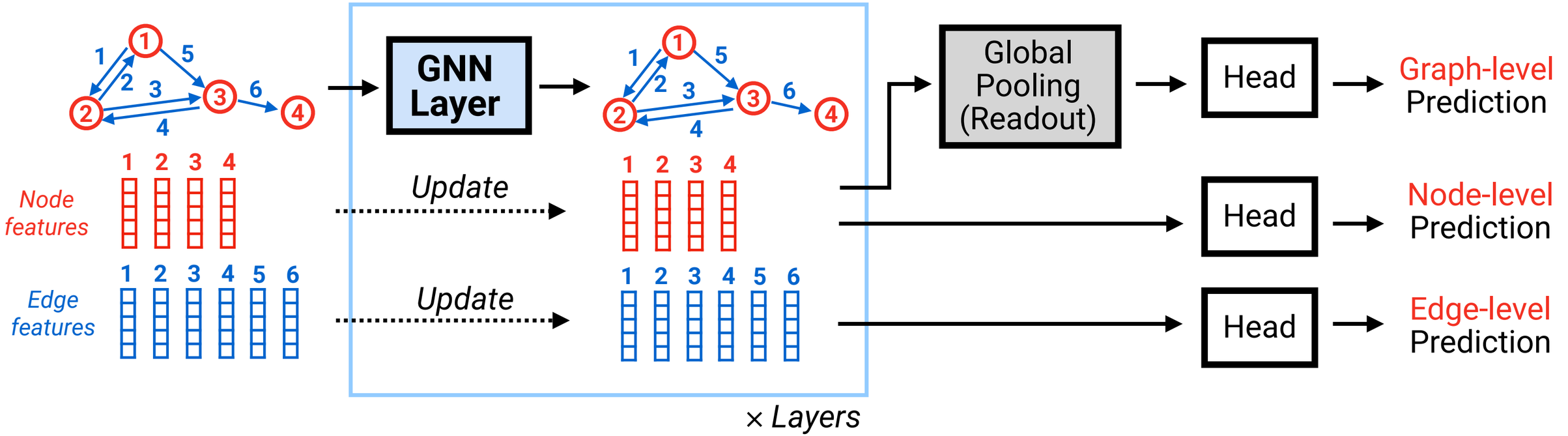






Design inductive biases (features, architectures, models, etc) by chemical knowledge, expert intuition, and theory
so that ML models don't unintentionally represent a function that lacks any chemical validity.

Graph Neural Networks (GNNs) in general



Travel Time Estimation (Google Maps, Baidu Maps)

Derrow-Pinion A, She J, Wong D, Lange O, Hester T, Perez L, et al. ETA Prediction with Graph Neural Networks in Google Maps.
CIKM 2021

Fang X, Huang J, Wang F, Zeng L, Liang H, Wang H. ConSTGAT: Contextual Spatial-Temporal Graph Attention Network for Travel Time Estimation at Baidu Maps.
KDD 2020

Siri Triggering (Apple)

Dighe P, Adya S, Li N, Vishnubhotla S, Naik D, Sagar A, et al. Lattice-Based Improvements for Voice Triggering Using Graph Neural Networks.
ICASSP 2020

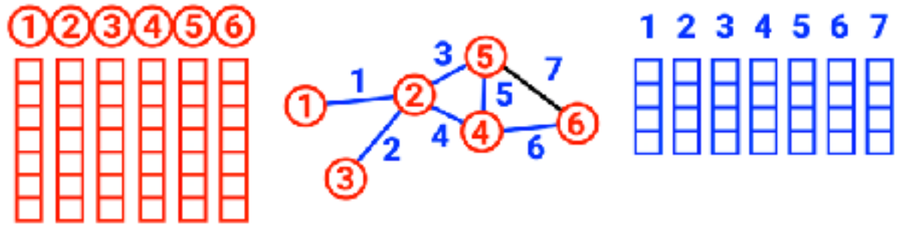
Knowledge Collection (Amazon)

Dong XL, He X, Kan A, Li X, Liang Y, Ma J, et al. AutoKnow: Self-Driving Knowledge Collection for Products of Thousands of Types.
KDD 2020

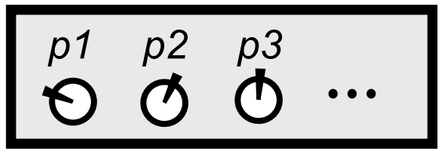
Graph neural networks for chemical problems

Other Info (Conditions, Environment, …)

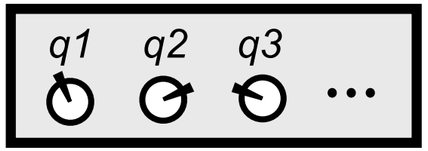
An input graph



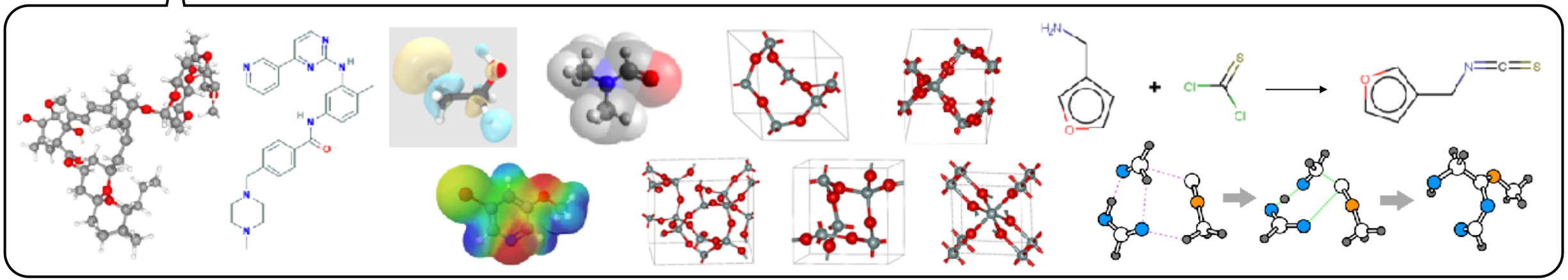
Representation Learning



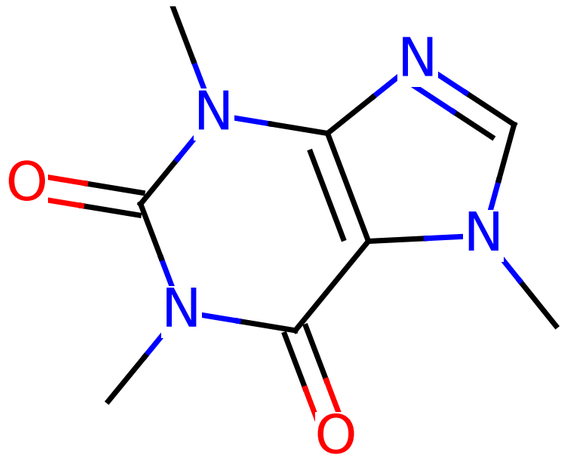
Classification / Regression Head

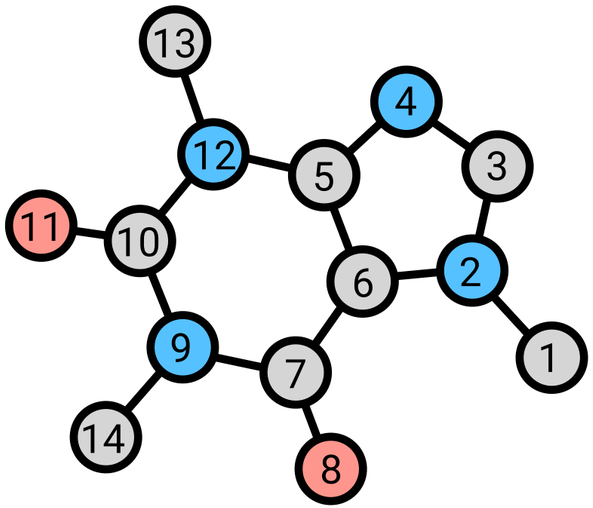


y



Molecular graphs





Node features

1. Atomic number
2. # of directly-bonded neighbors
3. # of hydrogens
4. Formal charge
5. Atomic mass
6. Is in a ring?

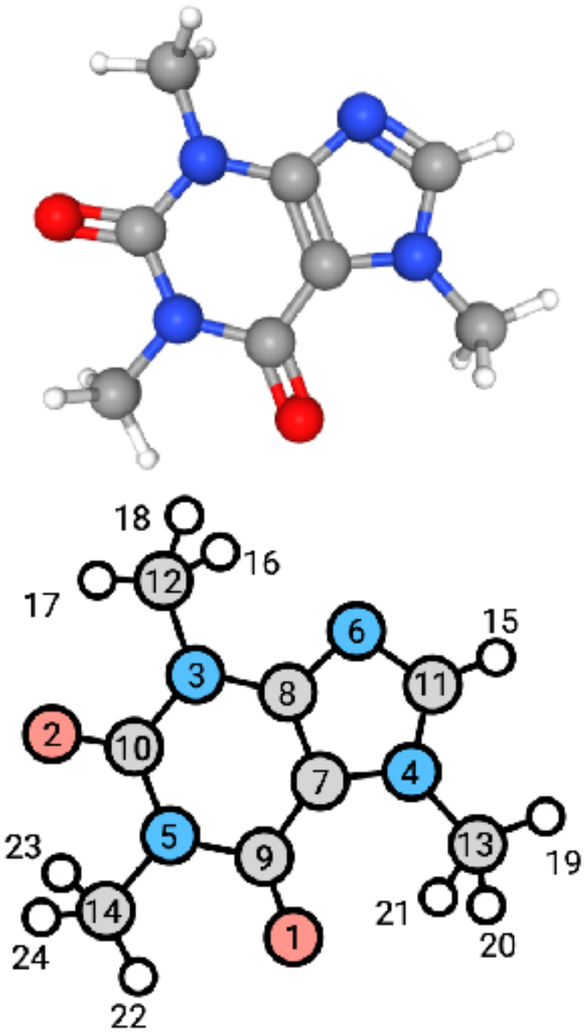
		1.	2.	3.	4.	5.	6.
1	C	6	4	3	0	12.011	0
2	N	7	3	0	0	14.007	1
3	C	6	3	1	0	12.011	1
4	N	7	2	0	0	14.007	1
5	C	6	3	0	0	12.011	1
6	C	6	3	0	0	12.011	1
7	C	6	3	0	0	12.011	1
8	O	8	1	0	0	15.999	0
9	N	7	3	0	0	14.007	1
10	C	6	3	0	0	12.011	1
11	O	8	1	0	0	15.999	0
12	N	7	3	0	0	14.007	1
13	C	6	4	3	0	12.011	0
14	C	6	4	3	0	12.011	0

Edge features

1. Bond type
2. Stereochemistry

		1.	2.
1	2	1	0
2	3	12	0
3	4	12	0
4	5	12	0
5	6	12	0
6	7	12	0
7	8	2	0
7	9	12	0
9	10	12	0
10	11	2	0
10	12	12	0
12	13	1	0
9	14	1	0
6	2	12	0
12	5	12	0

Geometric graphs



Nodes

		Z	x	y	z
1	O	8	0.470	2.569	0.001
2	O	8	-3.127	-0.444	-0.000
3	N	7	-0.969	-1.313	0.000
4	N	7	2.218	0.141	-0.000
5	N	7	-1.348	1.080	-0.000
6	N	7	1.412	-1.937	0.000
7	C	6	0.858	0.259	-0.001
8	C	6	0.390	-1.026	-0.000
9	C	6	0.031	1.422	-0.001
10	C	6	-1.906	-0.250	-0.000
11	C	6	2.503	-1.200	0.000
12	C	6	-1.428	-2.696	0.001
13	C	6	3.193	1.206	0.000
14	C	6	-2.297	2.188	0.001
15	H	1	3.516	-1.579	0.001
16	H	1	-1.045	-3.197	-0.894
17	H	1	-2.519	-2.760	0.001
18	H	1	-1.045	-3.196	0.896
19	H	1	4.199	0.780	0.000
20	H	1	3.047	1.809	-0.899
21	H	1	3.047	1.808	0.900
22	H	1	-1.809	3.165	-0.000
23	H	1	-2.932	2.103	0.888
24	H	1	-2.935	2.102	-0.885

Edges

		type	distance
1	9	2	1.228
2	10	2	1.236
3	8	1	1.388
3	10	1	1.417
3	12	1	1.458
4	7	1	1.365
4	11	1	1.371
4	13	1	1.443
5	9	1	1.420
5	10	1	1.442
5	14	1	1.459
6	8	1	1.369
6	11	2	1.317
7	8	2	1.368
7	9	1	1.427
11	15	1	1.082
12	16	1	1.094
12	17	1	1.093
12	18	1	1.094
13	19	1	1.093
13	20	1	1.093
13	21	1	1.093
14	22	1	1.092
14	23	1	1.095
14	24	1	1.095

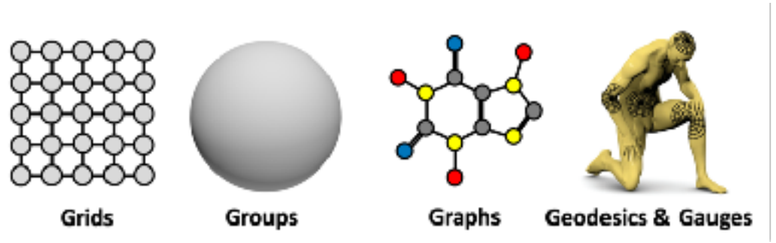
+ Can be added

Non-geometric node features

Non-geometric edge features

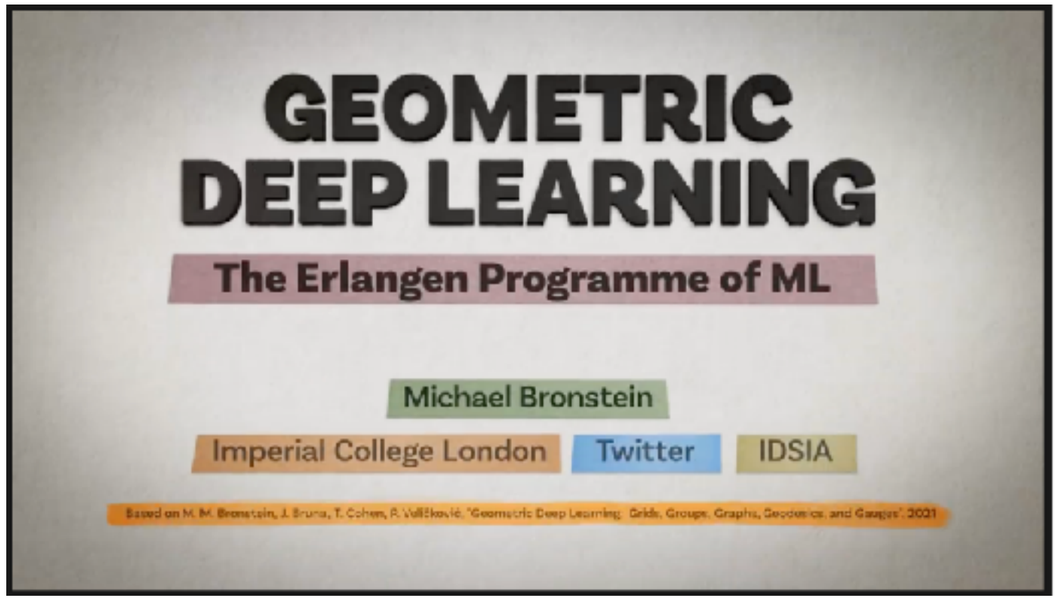
Geometric Deep Learning (GDL)

https://geometricdeeplearning.com



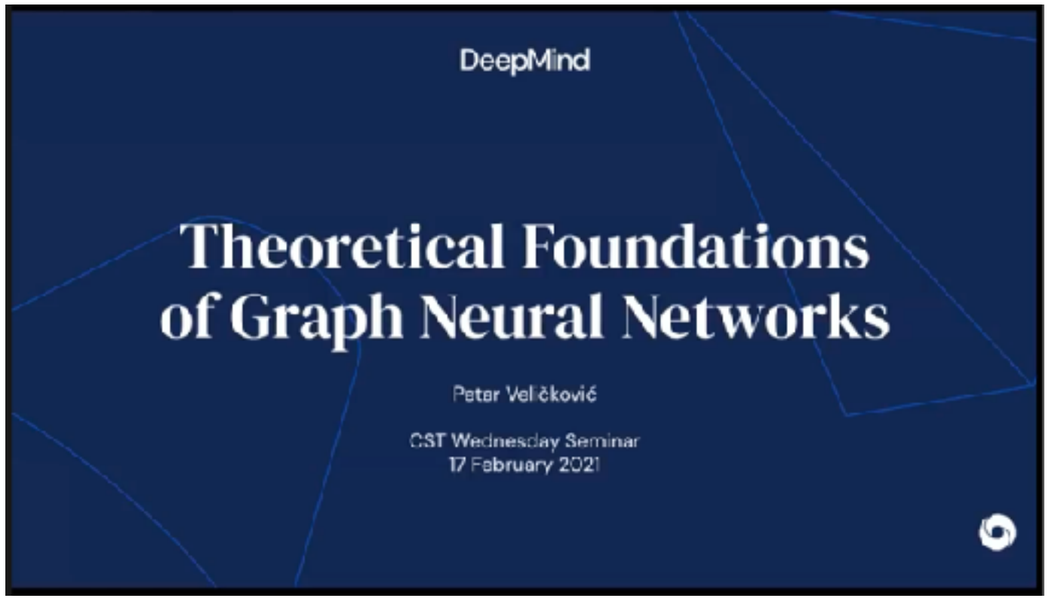
Bronstein MM, Bruna J, Cohen T, Veličković P.
Geometric Deep Learning: Grids, Groups, Graphs, Geodesics, and Gauges.
arXiv [cs.LG]. 2021. http://arxiv.org/abs/2104.13478

ICLR 2021 Keynote (Michael Bronstein)



https://youtu.be/w6Pw4MOzMuo

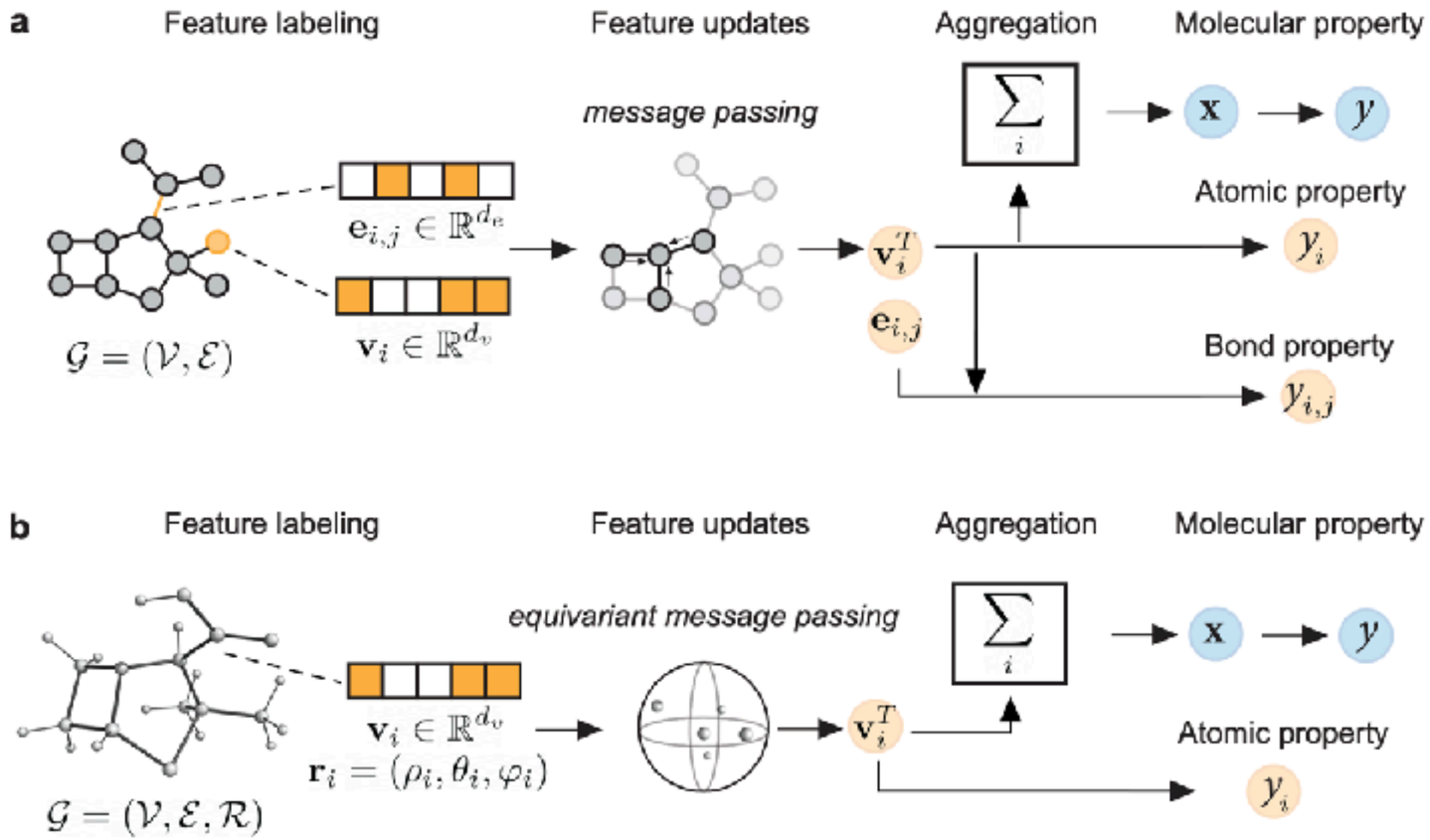
Seminar Talk (Petar Veličković)



https://youtu.be/uF53xsT7mjc

GDL for molecular representations

Atz K, Grisoni F, Schneider G.
Geometric deep learning on molecular representations.
Nature Machine Intelligence. 2021;3: 1023–1032. https://arxiv.org/abs/2107.12375

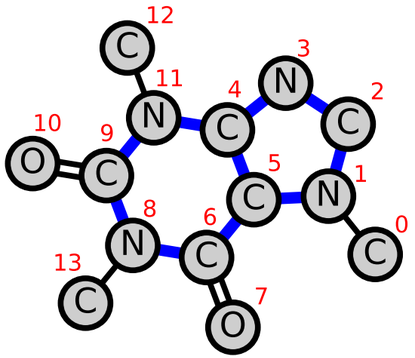


We need to consider equivariance under E(3) or SE(3) for some geometric features (coordinates, forces, vector field, etc)

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

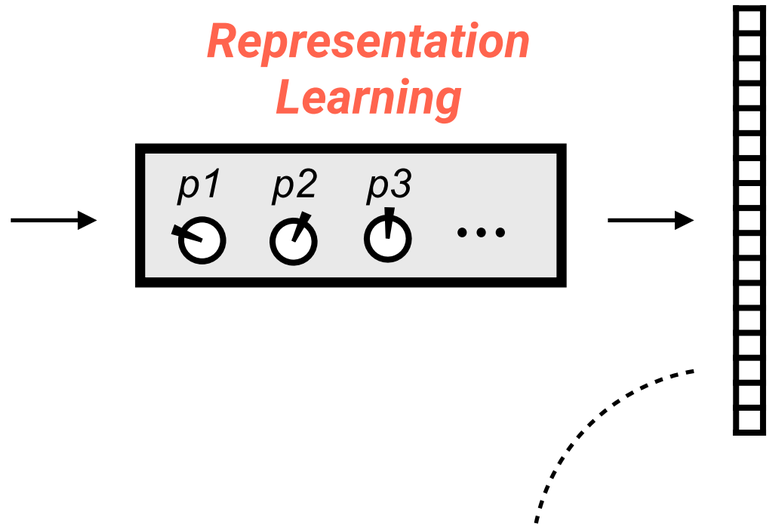


Node Features

	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

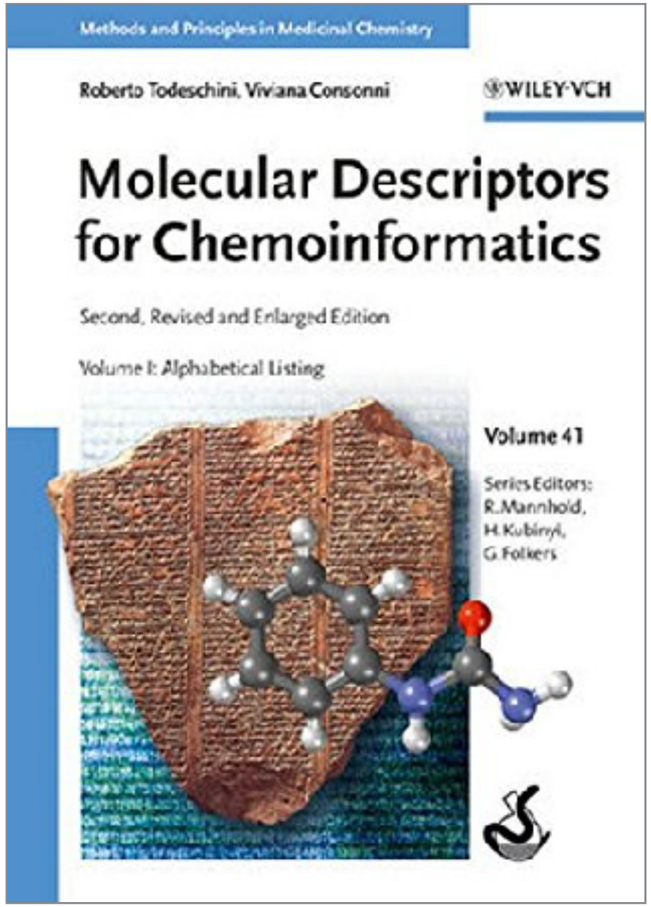


A relatively *low-dimensional* **good representation vector**

Beyond man-made descriptors

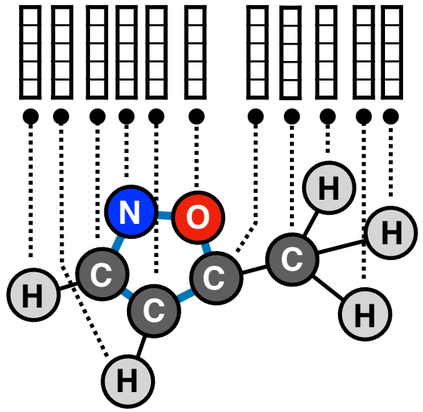
- **0-Dimensional Descriptors**
  - Constitutional descriptors
  - Count descriptors
- **1-Dimensional Descriptors**
  - List of structural fragments
  - Fingerprints
- **2-Dimensional Descriptors**
  - Graph invariants
- **3-Dimensional Descriptors**
  - 3D MoRSE, WHIM, GETAWAY, ...
  - Quantum-chemical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

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

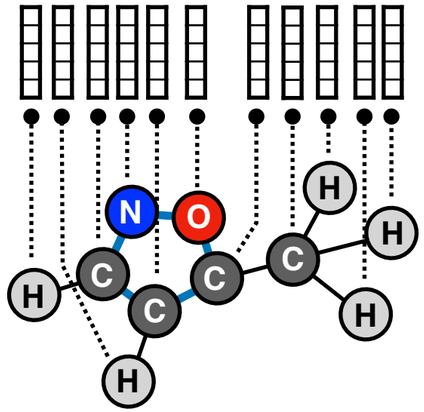


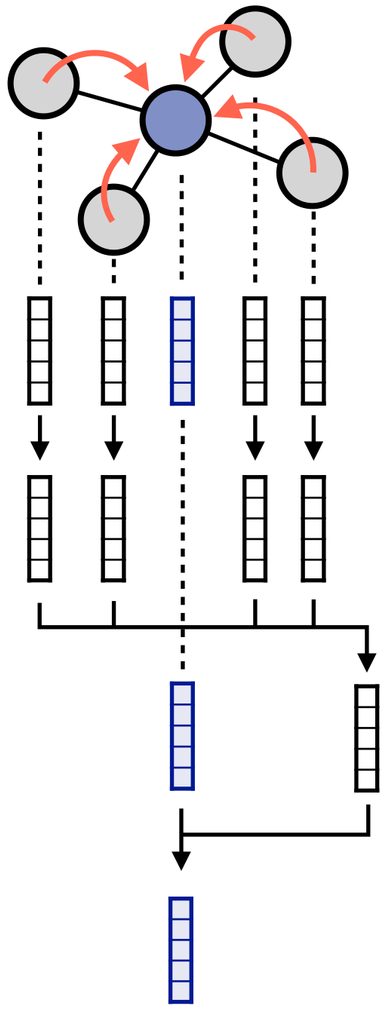
"Dragon calculates 5,270 molecular descriptors"

Message Passing: The inner workings of GNNs



GNN Layer





Message Passing

Update features by aggregating features around each node

❶ *Message*

Permutation equivariant operations

- NN such as MLPs
- Edge features usable

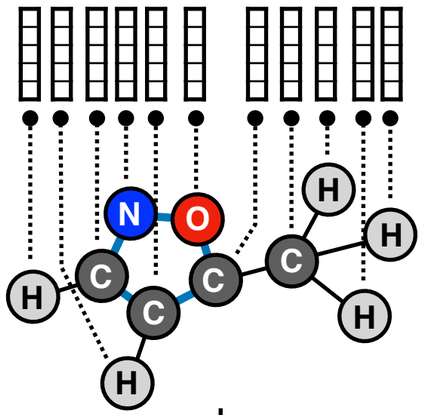
❷ *Aggregate*

Permutation invariant operations

- Sum, Mean or Max
- Attentive pooling

❸ *Update*

- NN such as MLPs

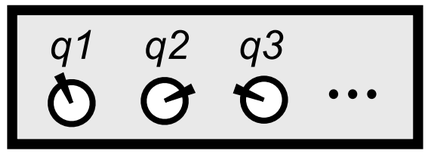


Readout

Permutation invariant operations

- Sum, Mean or Max
- Attentive pooling

Classification / Regression Head



y

Use Case 1: Virtual Screening (QSAR/QSPR)

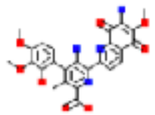
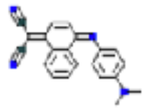
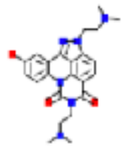
→ **ML** →

Very Noisy, Complex Relationship…

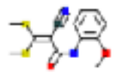
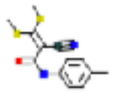
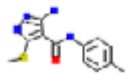
- ***Classification Task***
  Activity (Active or Inactive)
- ***Regression Task***
  LogGI50 value ---------- GI50: concentration required for 50% inhibition of growth

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

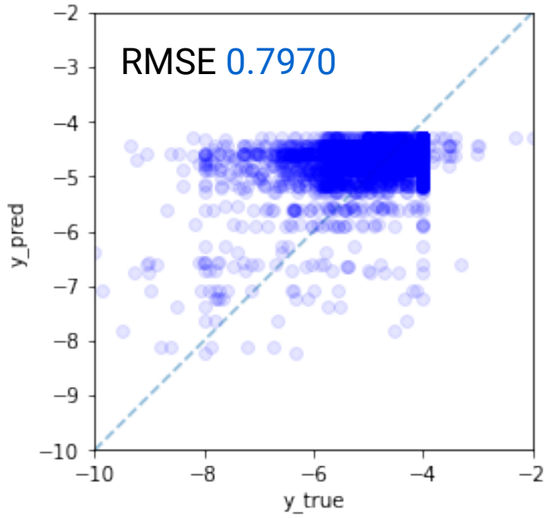
ChemProp
(Directed MPNN)

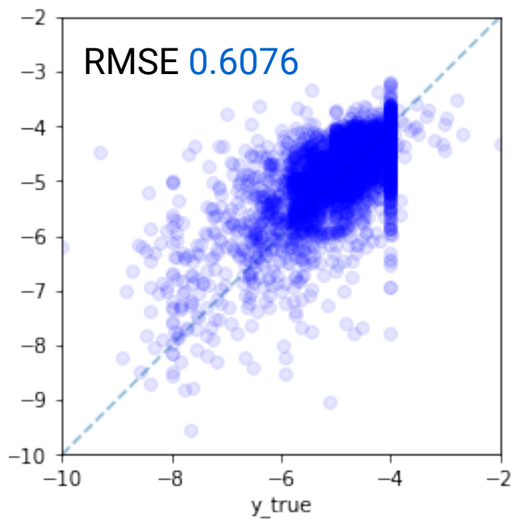
- ***Classification Task*** Activity (Active or Inactive)

95.079%

95.604%

- ***Regression Task*** LogGI50 value





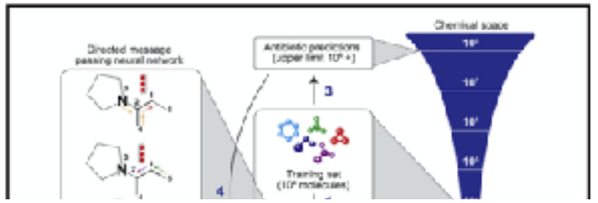
ChemProp (Yang et al, 2019)

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

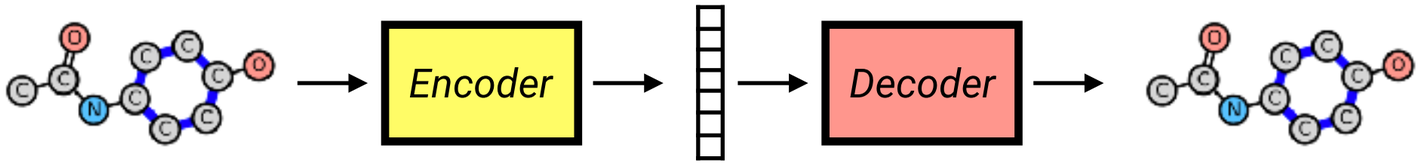
Powerful antibiotics discovered using AI

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

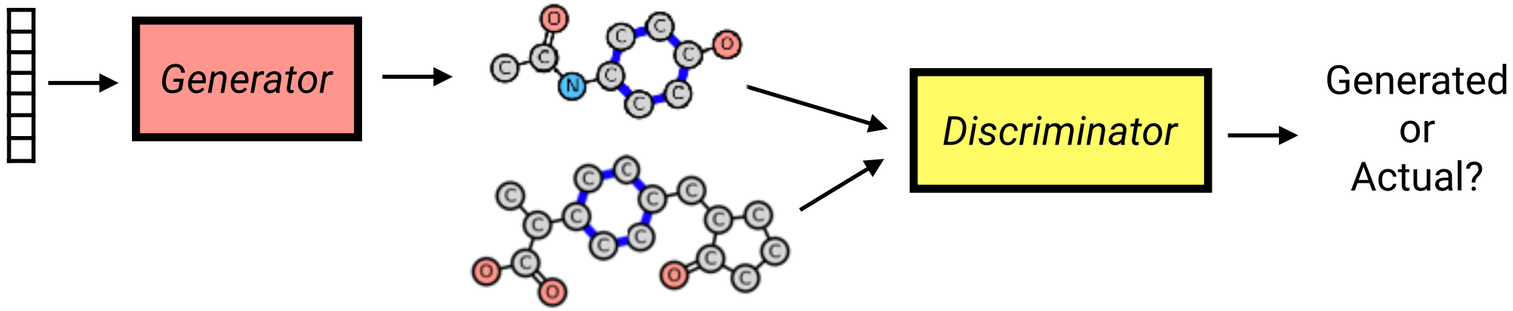
Jo Marchant

Use Case 2: Molecule Generation

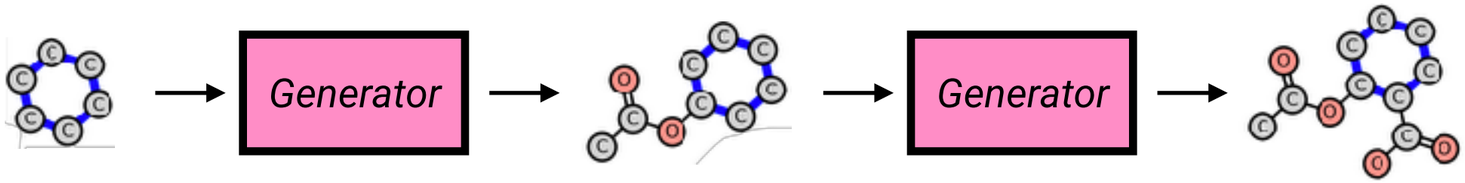
- Autoencoder-based / Flow-based



- Adversarial



- Autoregressive
- Reinforcement-learning-based



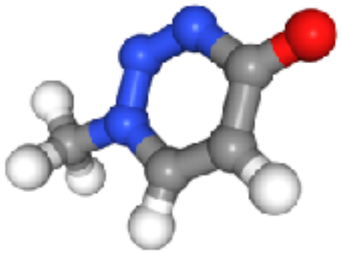
Faez F, Ommi Y, Baghshah MS, Rabiee HR. Deep Graph Generators: A Survey. *IEEE Access*. 2021;9: 106675–106702.

GNNs are an important building block to design generation modules.

The design patterns to generate images, sounds, texts, are quite useful!

Use Case 3: 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	5.152491	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	3.696857	-1.222422
H	6.372399	1.276980	-2.825015
H	5.428656	5.805758	-5.033531
H	1.116529	6.657080	-2.763050

100,000 times faster!

∼ 0.01 sec

ML

≀

∼ 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*

⋮

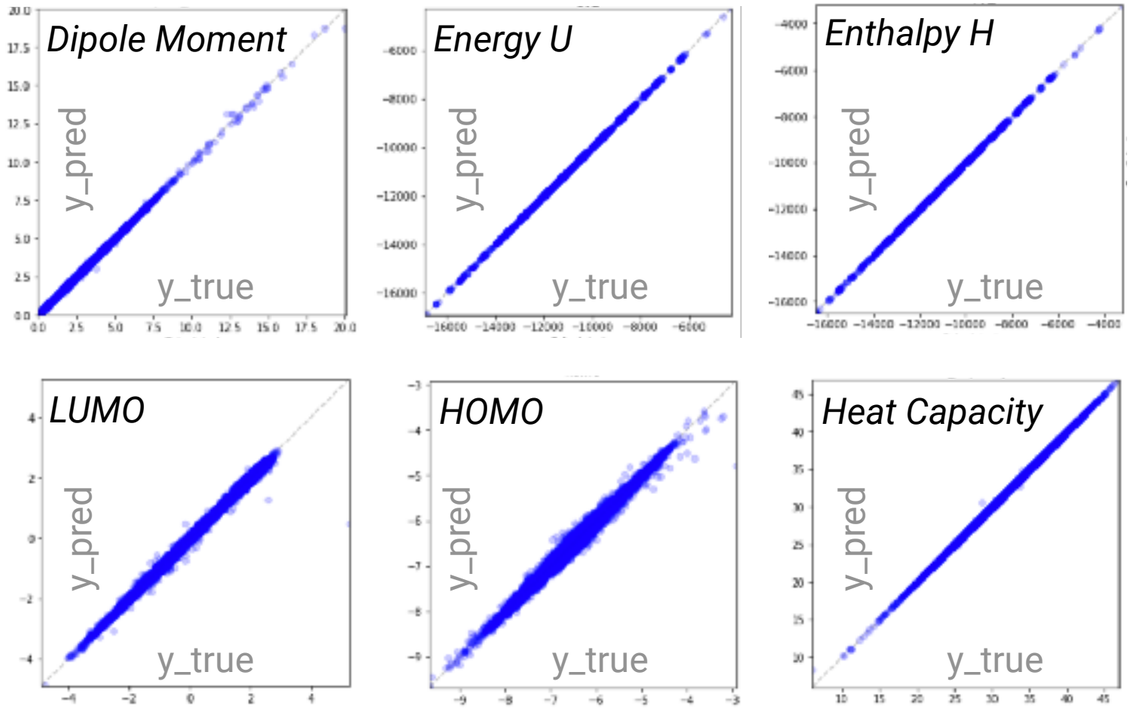
	property	value
0	dipole_moment	7.214000
1	isotropic_polarizability	65.360001
2	homo	-6.280388
3	lumo	-1.649010
4	gap	4.631378
5	electronic_spatial_extent	884.587524
6	zpve	2.610307
7	energy_U0	-10742.250000
8	energy_U	-10742.060547
9	enthalpy_H	-10742.035156
10	free_energy_G	-10743.111328
11	heat_capacity	21.756001
12	U_0_atom	-55.213203
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/

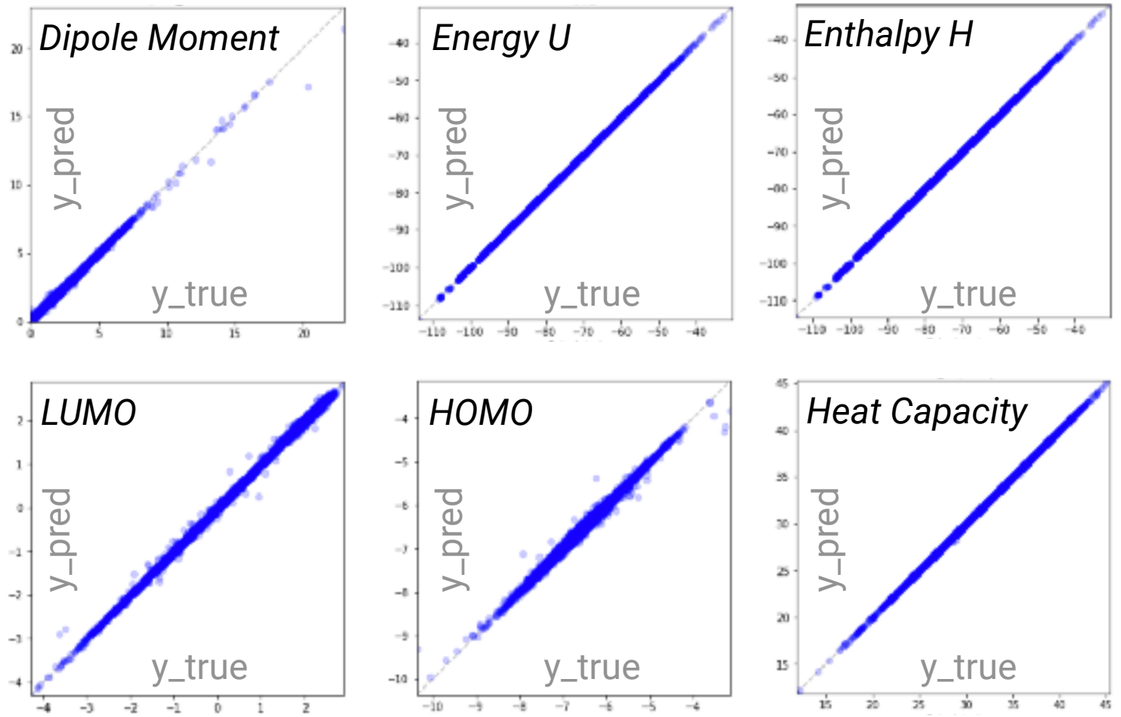
Use Case 3: Fast Approximation for QM Calculations

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!

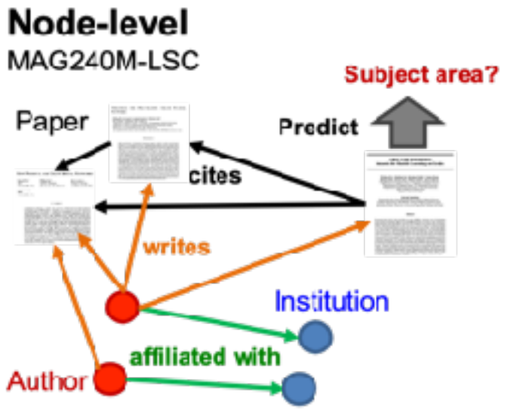
Predictions for Test Data by SchNet (Schütt et al, 2017)

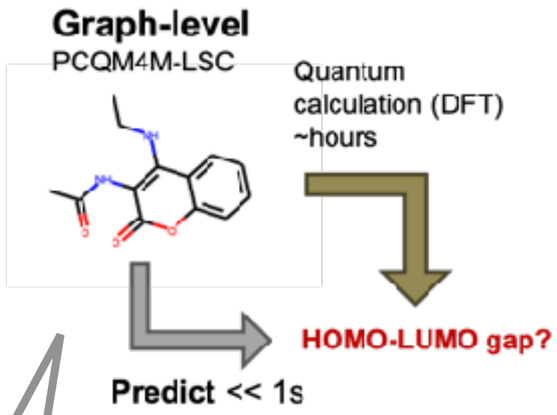


Predictions for Test Data by DimeNet (Klicpera et al, 2020)



OGB Large-Scale Challenge (KDDCup 2021)





Graph Regression: to predict the DFT-calculated HOMO-LUMO from 2D molecular graphs

Dataset: 3,803,453 graphs from PubChemQC (cf. QM9 = 133,885 graphs)

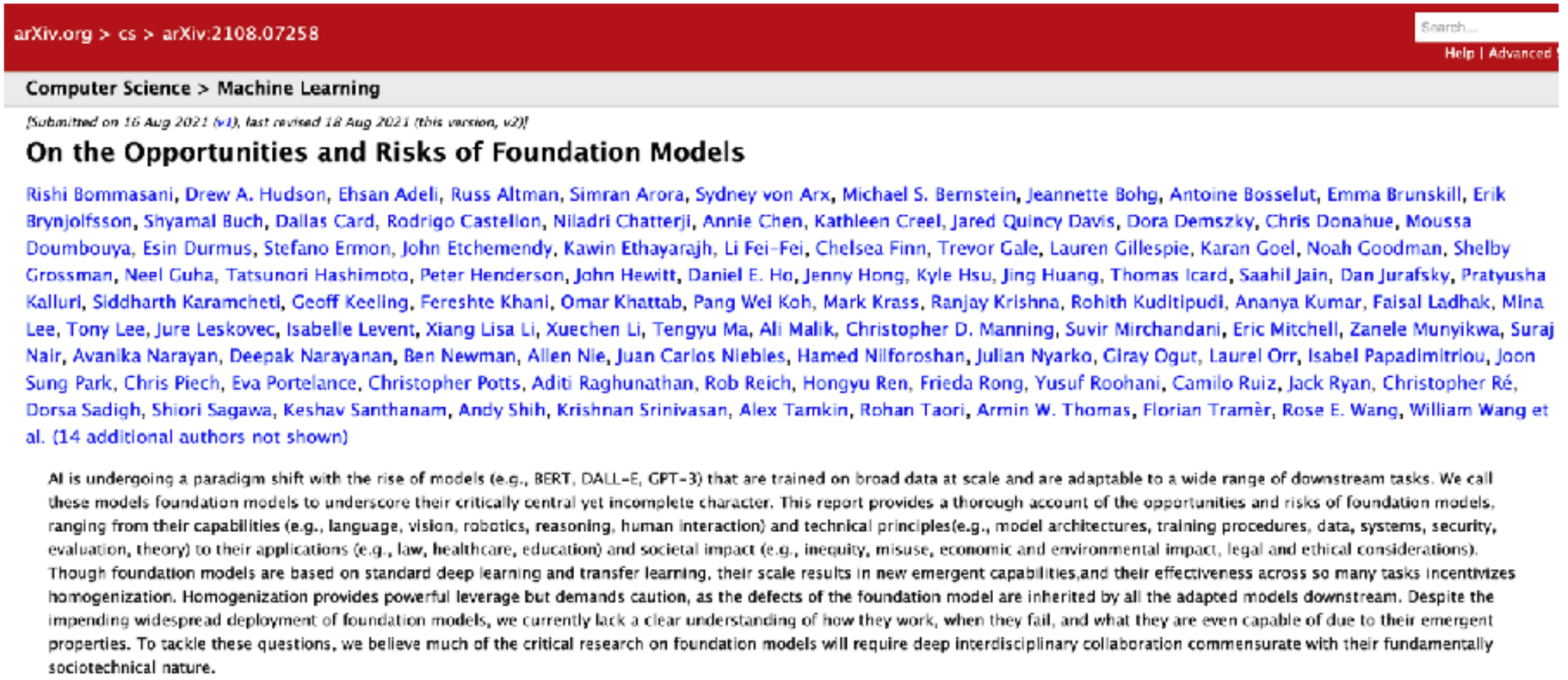
Rank	Test MAE	**Models**
1	0.1200 (eV)	**10 × GNNs** (12-layer Graphormer) **+ 8 × ExpC*s** (5-layer ExpandingConv)
2	0.1204 (eV)	**73 × GNNs** (11-layer LiteGEMConv + SSL pretraining)
3	0.1205 (eV)	**20 × GNNs** (32-layer GNN + Noisy Nodes)

https://ogb.stanford.edu/kddcup2021/results/

Pretrained models drive applied DL (ImageNet, BERT, ...)

Many practical applications lack large data, and the use of *pretrained models* are critical.

Especially, the models that are pre-trained on broad data at scale and are adaptable to a wide range of downstream tasks.



arXiv.org > cs > arXiv:2108.07258

Search...

Help | Advanced

Computer Science > Machine Learning

[Submitted on 16 Aug 2021 (v1), last revised 18 Aug 2021 (this version, v2)]

On the Opportunities and Risks of Foundation Models

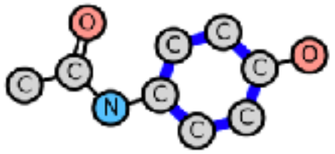
Rishi Bommasani, Drew A. Hudson, Ehsan Adeli, Russ Altman, Simran Arora, Sydney von Arx, Michael S. Bernstein, Jeannette Bohg, Antoine Bosselut, Emma Brunskill, Erik Brynjolfsson, Shyamal Buch, Dallas Card, Rodrigo Castellon, Niladri Chatterji, Annie Chen, Kathleen Creel, Jared Quincy Davis, Dora Demszky, Chris Donahue, Moussa Doumbouya, Esin Durmus, Stefano Ermon, John Etchemendy, Kawin Ethayarajh, Li Fei-Fei, Chelsea Finn, Trevor Gale, Lauren Gillespie, Karan Goel, Noah Goodman, Shelby Grossman, Neel Guha, Tatsunori Hashimoto, Peter Henderson, John Hewitt, Daniel E. Ho, Jenny Hong, Kyle Hsu, Jing Huang, Thomas Icard, Saahil Jain, Dan Jurafsky, Pratyusha Kalluri, Siddharth Karamcheti, Geoff Keeling, Fereshte Khani, Omar Khattab, Pang Wei Koh, Mark Krass, Ranjay Krishna, Rohith Kuditipudi, Ananya Kumar, Faisal Ladhak, Mina Lee, Tony Lee, Jure Leskovec, Isabelle Levent, Xiang Lisa Li, Xuechen Li, Tengyu Ma, Ali Malik, Christopher D. Manning, Suvir Mirchandani, Eric Mitchell, Zanele Munyikwa, Suraj Nair, Avanika Narayan, Deepak Narayanan, Ben Newman, Allen Nie, Juan Carlos Niebles, Hamed Nilforoshan, Julian Nyarko, Giray Ogut, Laurel Orr, Isabel Papadimitriou, Joon Sung Park, Chris Piech, Eva Portelance, Christopher Potts, Aditi Raghunathan, Rob Reich, Hongyu Ren, Frieda Rong, Yusuf Roohani, Camilo Ruiz, Jack Ryan, Christopher Ré, Dorsa Sadigh, Shiori Sagawa, Keshav Santhanam, Andy Shih, Krishnan Srinivasan, Alex Tamkin, Rohan Taori, Armin W. Thomas, Florian Tramèr, Rose E. Wang, William Wang et al. (14 additional authors not shown)

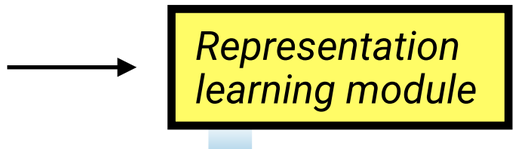
AI is undergoing a paradigm shift with the rise of models (e.g., BERT, DALL-E, GPT-3) that are trained on broad data at scale and are adaptable to a wide range of downstream tasks. We call these models foundation models to underscore their critically central yet incomplete character. This report provides a thorough account of the opportunities and risks of foundation models, ranging from their capabilities (e.g., language, vision, robotics, reasoning, human interaction) and technical principles(e.g., model architectures, training procedures, data, systems, security, evaluation, theory) to their applications (e.g., law, healthcare, education) and societal impact (e.g., inequity, misuse, economic and environmental impact, legal and ethical considerations). Though foundation models are based on standard deep learning and transfer learning, their scale results in new emergent capabilities,and their effectiveness across so many tasks incentivizes homogenization. Homogenization provides powerful leverage but demands caution, as the defects of the foundation model are inherited by all the adapted models downstream. Despite the impending widespread deployment of foundation models, we currently lack a clear understanding of how they work, when they fail, and what they are even capable of due to their emergent properties. To tackle these questions, we believe much of the critical research on foundation models will require deep interdisciplinary collaboration commensurate with their fundamentally sociotechnical nature.

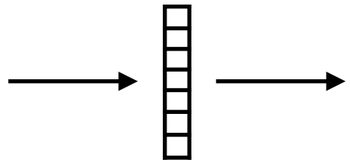
Call them "foundation models"?

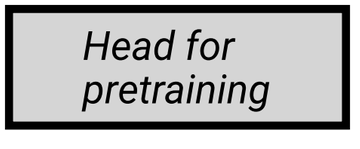
Large-scale pretraining by self-supervised learning tasks

Pretraining
Large-scale Pretext task
(often self-supervised)

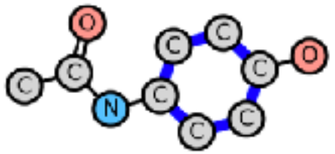


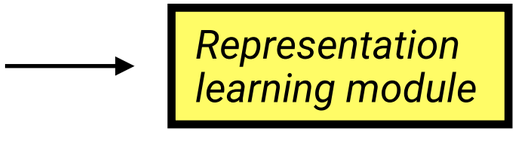


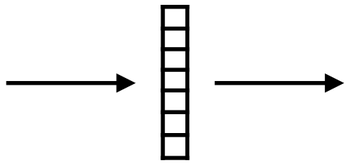


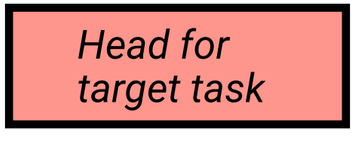


Target downstream task
(small-data problem)

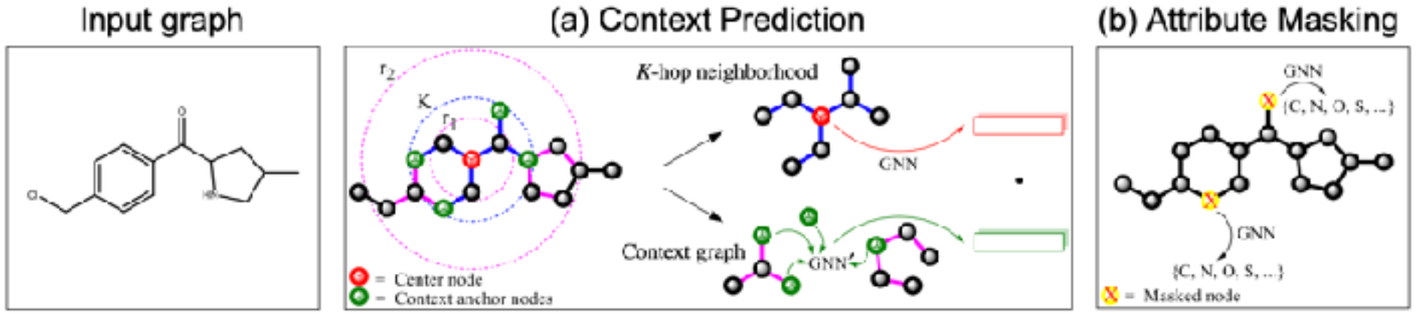


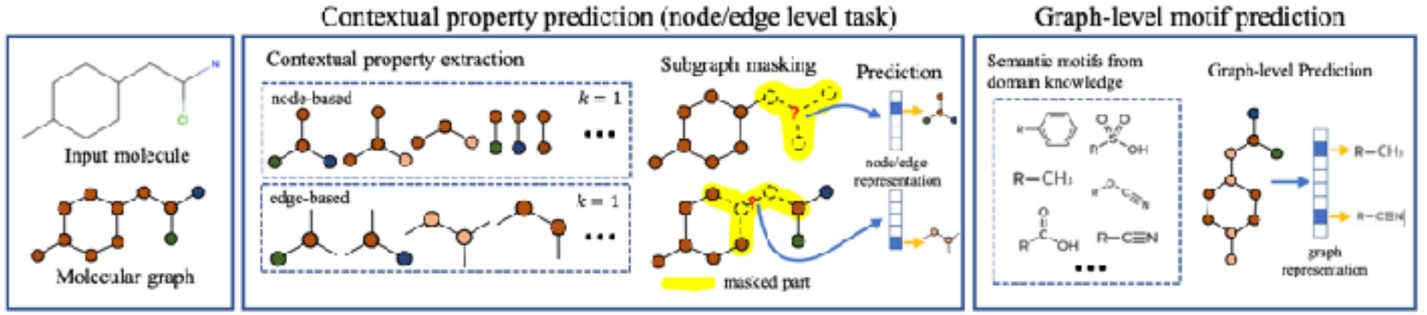






SSL tasks
for molecules





Strategies for Pre-training Graph Neural Networks
Hu, Liu, Gomes, Zitnik, Liang, Pande, Leskovec (ICLR 2020)
https://arxiv.org/abs/1905.12265

Self-Supervised Graph Transformer on Large-Scale Molecular Data
Rong, Bian, Xu, Xie, Wei, Huang, Huang (NeurIPS 2020)
https://arxiv.org/abs/2007.02835

Geometric symmetry: Invariance and equivariance

Fundamental Requirements for Geometric GNNs:

The xyz coordinates cannot be directly used as node features.
We need to consider the invariance and equivariance under the motion group

- Euclidean group E(3)： translations, rotations, reflections in 3D
- Special Euclidean group SE(3)： translations, rotations in 3D

E(3)-invariant
- Schütt et al, SchNet. (2017) https://arxiv.org/abs/1706.08566
- Unke et al, PhysNet. (2019) https://arxiv.org/abs/1902.08408
- Klicpera et al, DimeNet++. (2020) https://arxiv.org/abs/2011.14115

SE(3)-equivariant
- Anderson et al, Cormorant. (2019) https://arxiv.org/abs/1906.04015
- Fuchs et al, SE(3)-Transformers. (2021) https://arxiv.org/abs/2006.10503

E(3)-equivariant
- Thomas et al, Tensor Field Networks. (2018) https://arxiv.org/abs/1802.08219
- Köhler et al, Equivariant Flows (Radial Field). (2020) https://arxiv.org/abs/2006.02425
- Satorras et al, E(n) Equivariant Graph Neural Networks. (2021) https://arxiv.org/abs/2102.09844

Invariant

$$f(g \cdot x) = f(x)$$

Equivariant

$$f(g \cdot x) = g \cdot f(x)$$

Edge-aware Message Passing Neural Networks (MPNNs)

Table 2. Comparison of Previous Approaches (left) with MPNN baselines (middle) and our methods (right)

Target	BAML	BOB	CM	ECFP4	HDAD	GC	GG-NN	DTNN	enn-s2s	enn-s2s-ens5
mu	4.34	4.23	4.49	4.82	3.34	0.70	1.22	-	**0.30**	0.20
alpha	3.01	2.98	4.33	34.54	1.75	2.27	1.55	-	**0.92**	0.68
HOMO	2.20	2.20	3.09	2.89	1.54	1.18	1.17	-	**0.99**	0.74
LUMO	2.76	2.74	4.26	3.10	1.96	1.10	1.08	-	**0.87**	0.65
gap	3.28	3.41	5.32	3.86	2.49	1.78	1.70	-	**1.60**	1.23
R2	3.25	0.80	2.83	90.68	1.35	4.73	3.99	-	**0.15**	0.14
ZPVE	3.31	3.40	4.80	241.58	1.91	9.75	2.52	-	**1.27**	1.10
U0	1.21	1.43	2.98	85.01	0.58	3.02	0.83	-	**0.45**	0.33
U	1.22	1.44	2.99	85.59	0.59	3.16	0.86	-	**0.45**	0.34
H	1.22	1.44	2.99	86.21	0.59	3.19	0.81	-	**0.39**	0.30
G	1.20	1.42	2.97	78.36	0.59	2.95	0.78	.84[2]	**0.44**	0.34
Cv	1.64	1.83	2.36	30.29	0.88	1.45	1.19	-	**0.80**	0.62
Omega	0.27	0.35	1.32	1.47	0.34	0.32	0.53	-	**0.19**	0.15
Average	2.17	2.08	3.37	53.97	1.35	2.59	1.36	-	**0.68**	0.52

Atom features

Atom type	H, C, N, O, F (one-hot)
Atomic number	# of protonns (int)
Acceptor	0 or 1 (binary)
Donor	0 or 1 (binary)
Aromatic	0 or 1 (binary)
Hybridization	sp, sp2, sp3 (one-hot or null
# of hydrogens	(integer)

Bond features

Euclidean distace between atom pair	(real)
Bond types	single, double, triple, aromatic (one-hot)

→ E(3)-invariant

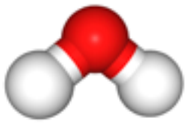
xyz are used only as distances

Gilmer J, Schoenholz SS, Riley PF, Vinyals O, Dahl GE.
Neural Message Passing for Quantum Chemistry.
ICML 2017

Faber FA, Hutchison L, Huang B, Gilmer J, Schoenholz SS, Dahl GE, et al.
Prediction Errors of Molecular Machine Learning Models Lower than Hybrid DFT Error.
J Chem Theory Comput. 2017;13: 5255–5264.

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

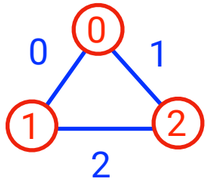
H_2O



gdb_3

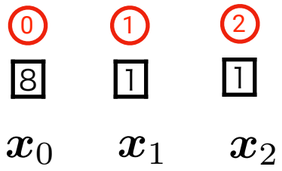
	x	y	z	AN
O	-0.0344	0.9775	0.0076	8
H	0.0648	0.0206	0.0015	1
H	0.8718	1.3008	0.0007	1

Graph

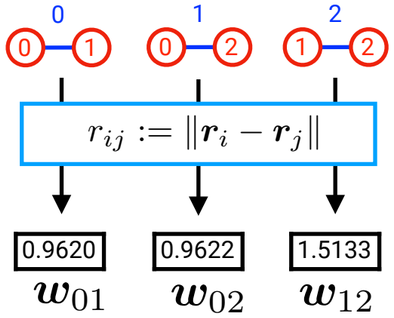


edges w/
cutoff (10Å)

atom features



bond features



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$\Delta\varepsilon$	meV	63	69	**58.0**
ZPVE	meV	1.7	**1.5**	**1.49**
μ	Debye	0.033	0.030	**0.029**
α	Bohr^3	0.235	0.092	**0.077**
$\langle R^2 \rangle$	Bohr^2	**0.073**	0.180	**0.072**
U_0	meV	14	19	**10.5**
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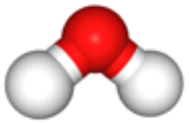

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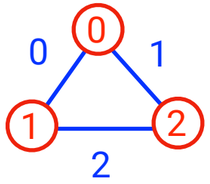

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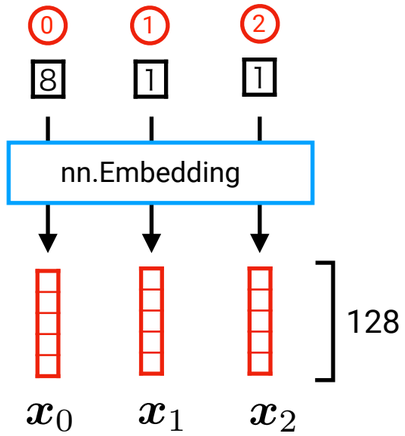

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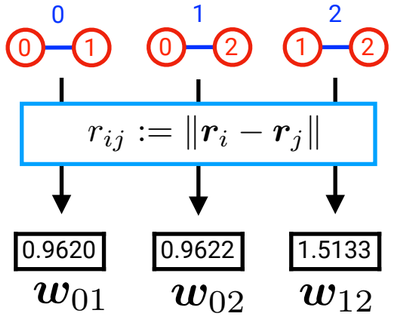

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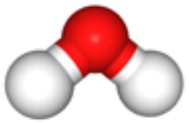

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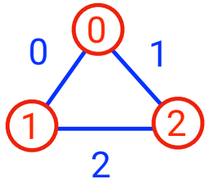

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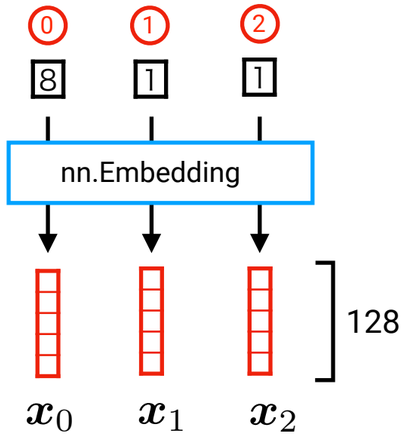

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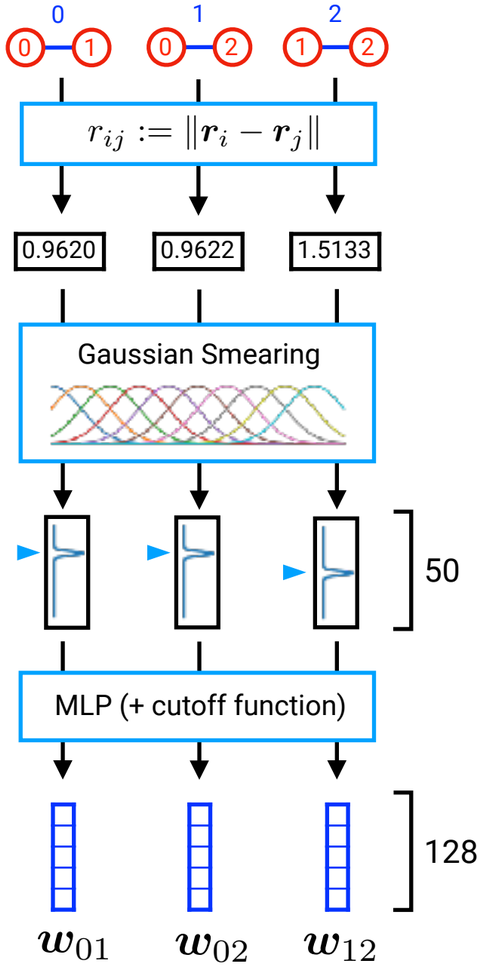

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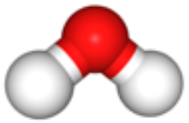

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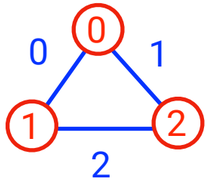

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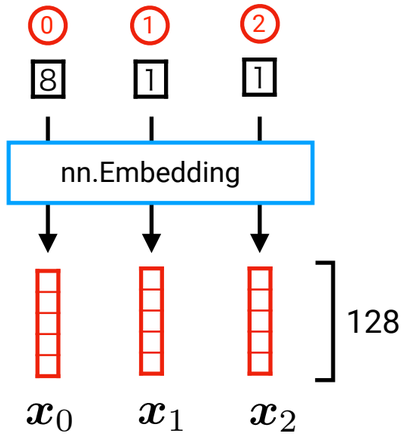
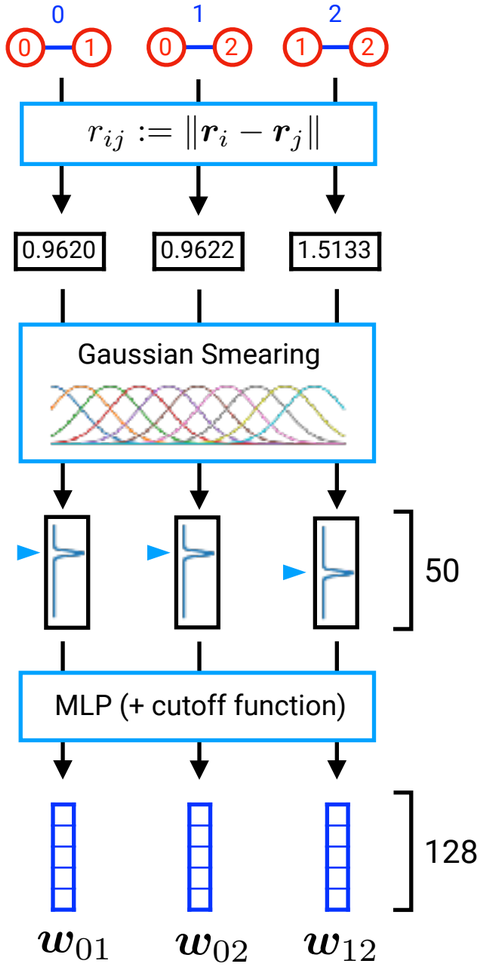
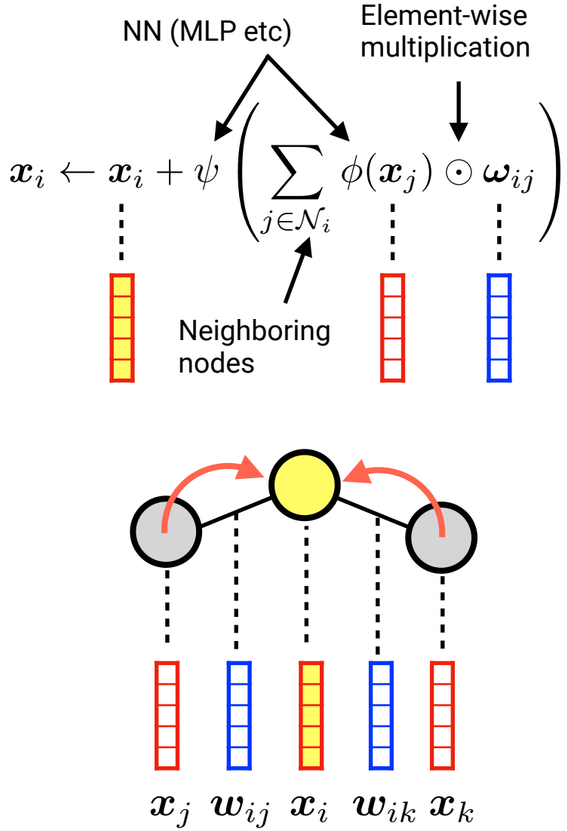


bond features



Message Passing with residual connections



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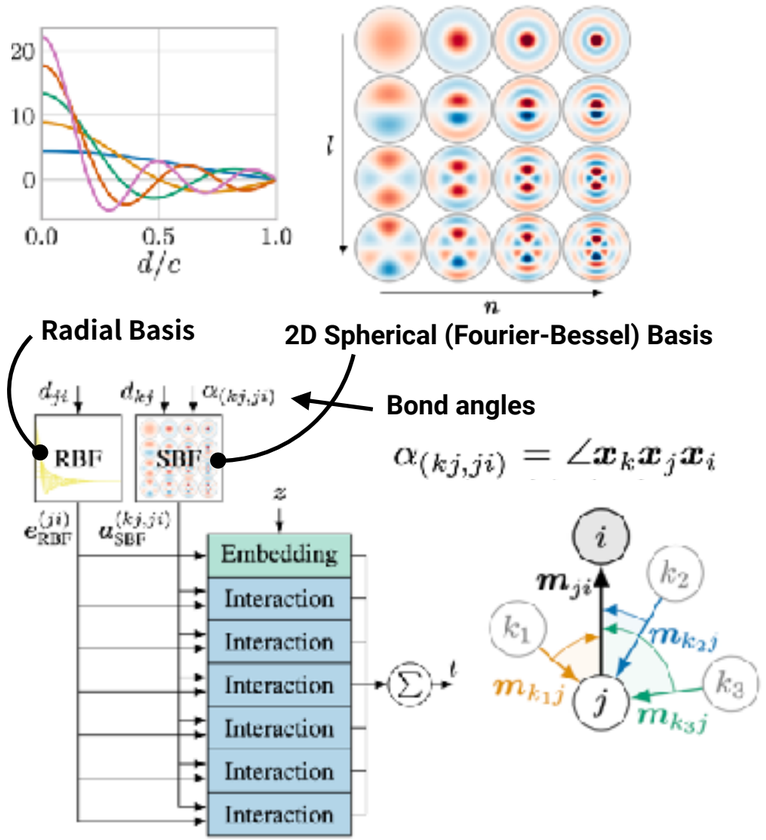
QSAR/QSPR, QM Approximation, Molecule Generations, …

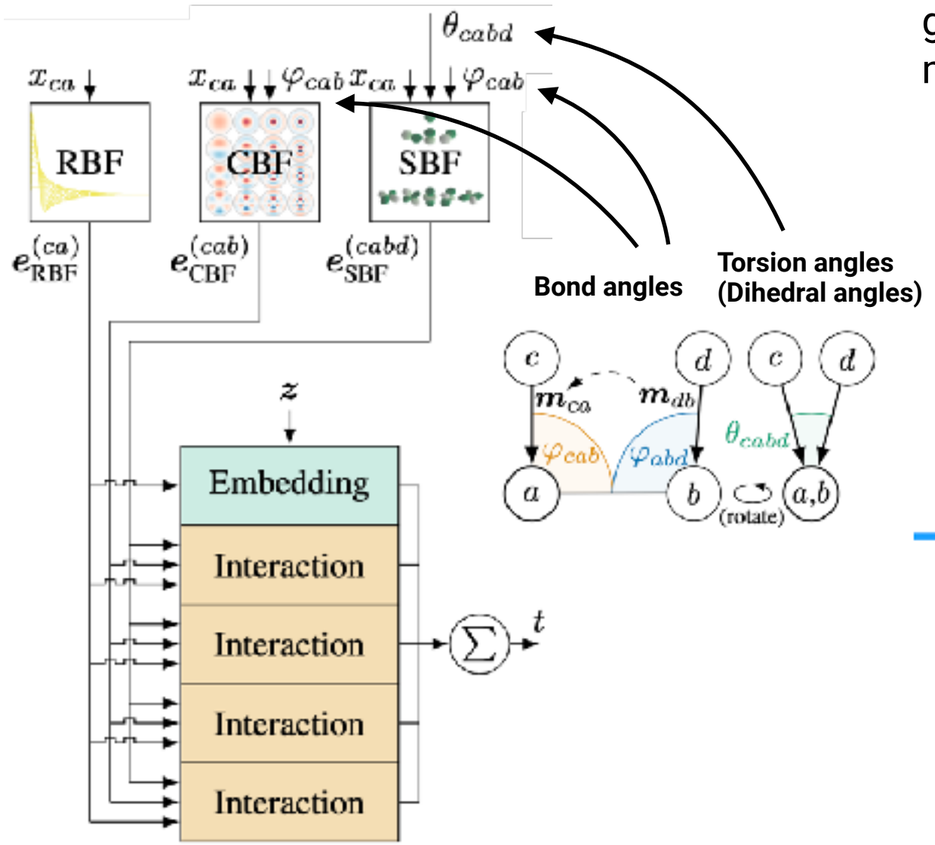
DimeNet++

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



GemNet

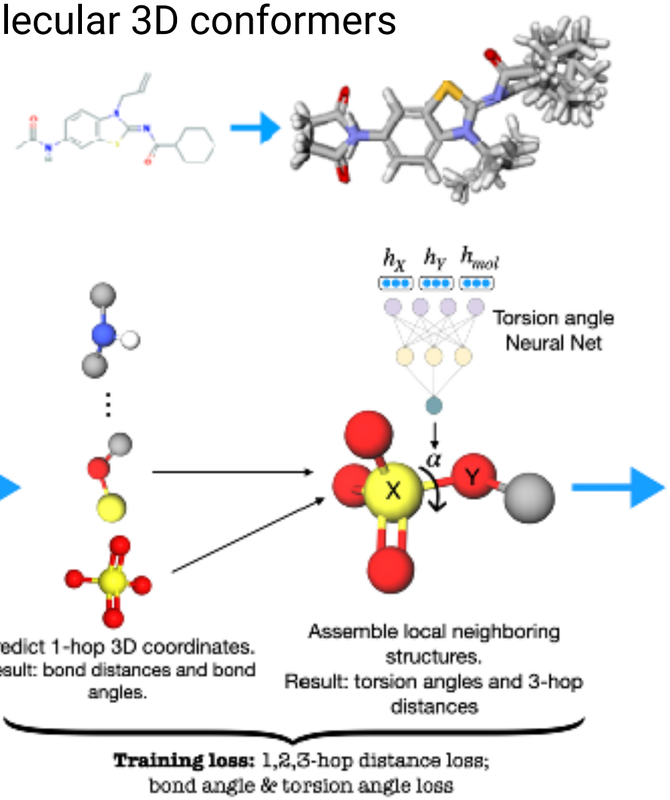
Klicpera et al (NeurIPS2021)
https://arxiv.org/abs/2106.08903



GeoMol

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

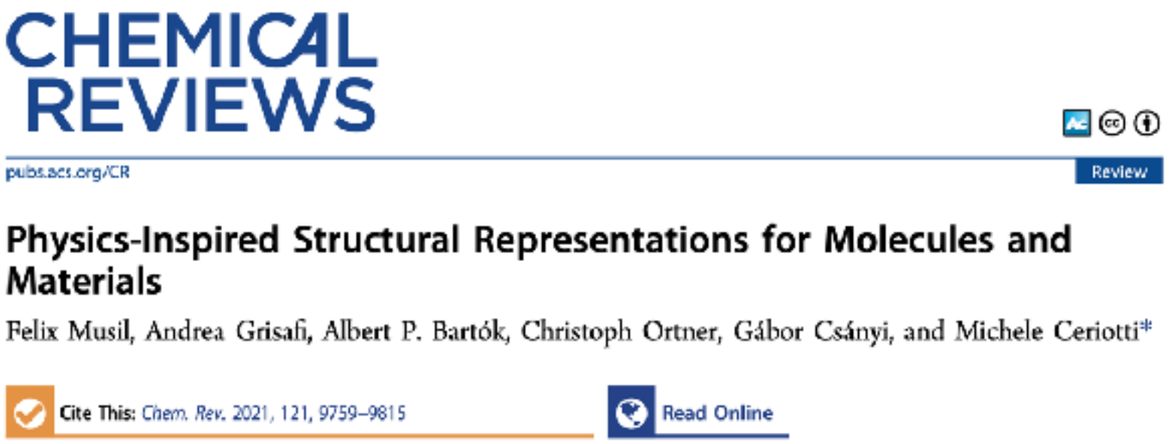
generates distributions of low-energy molecular 3D conformers

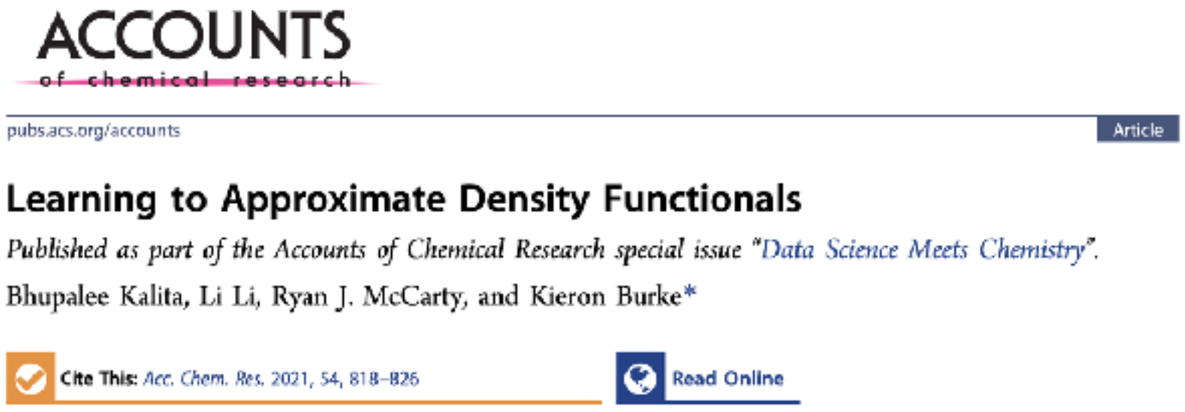


ML × QM: ML Potentials, Force fields, Density functionals

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





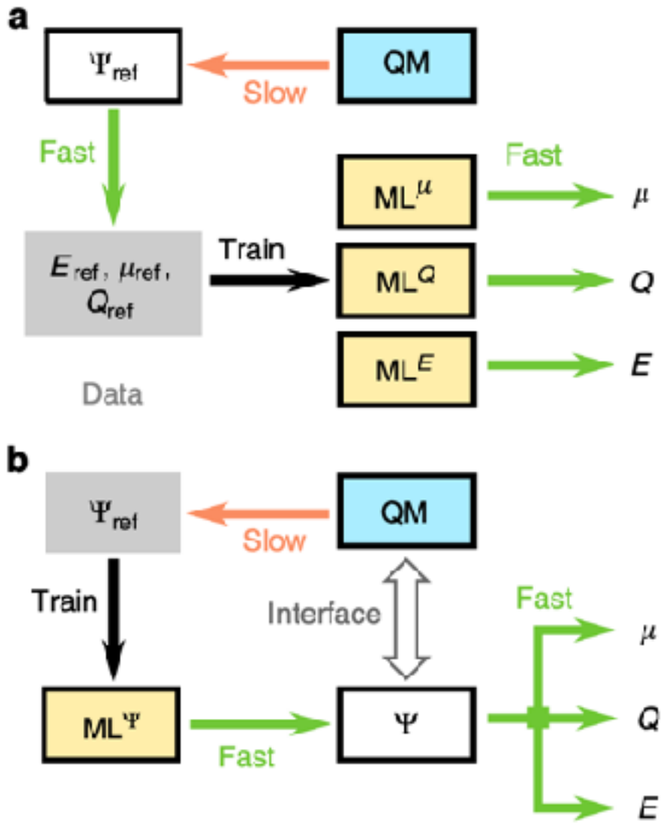
SchNOrb (Schütt et al, Nat Commn, 2019)

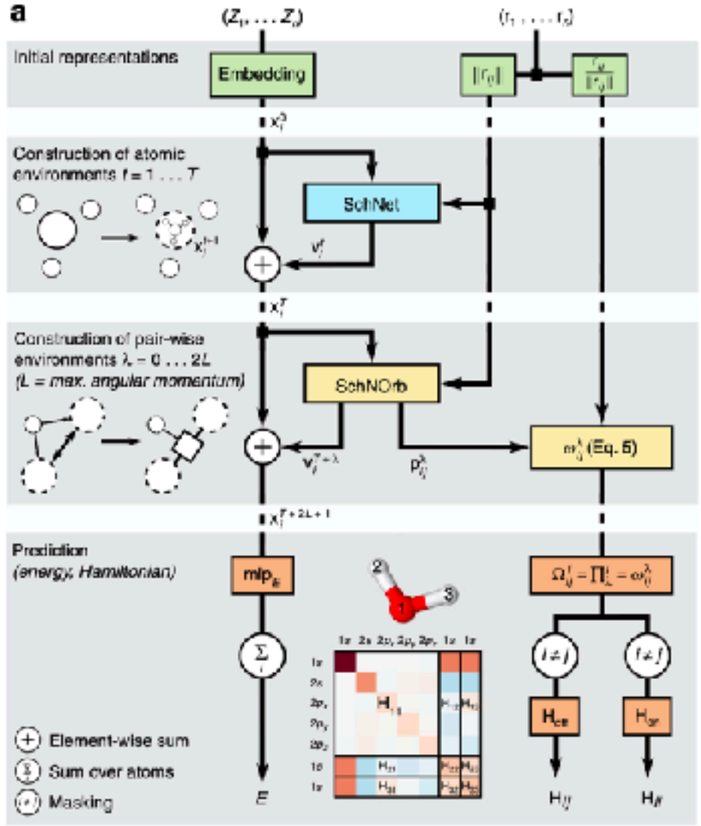
Unifying machine learning and quantum chemistry with a deep neural network for molecular wavefunctions

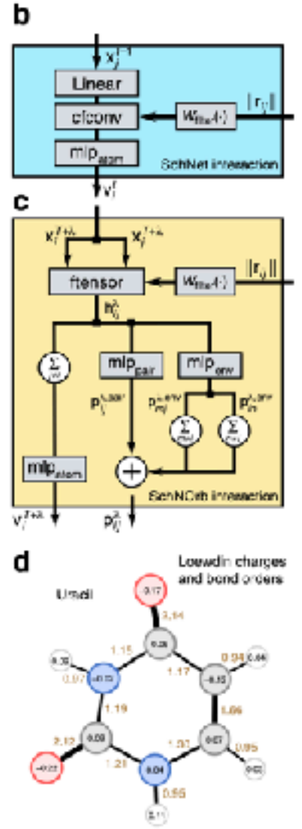
K. T. Schütt, M. Gastegger, A. Tkatchenko ✉, K.-R. Müller ✉ & R. J. Maurer ✉

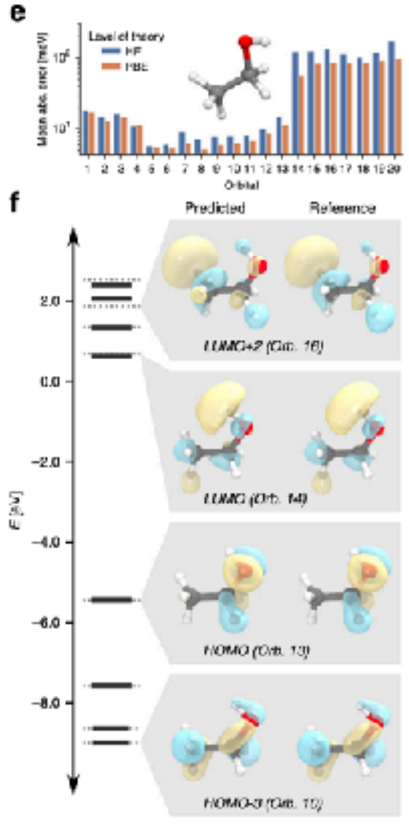
nature COMMUNICATIONS

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









DM21 Density functional (Kirkpatrick et al, Science, 2021)

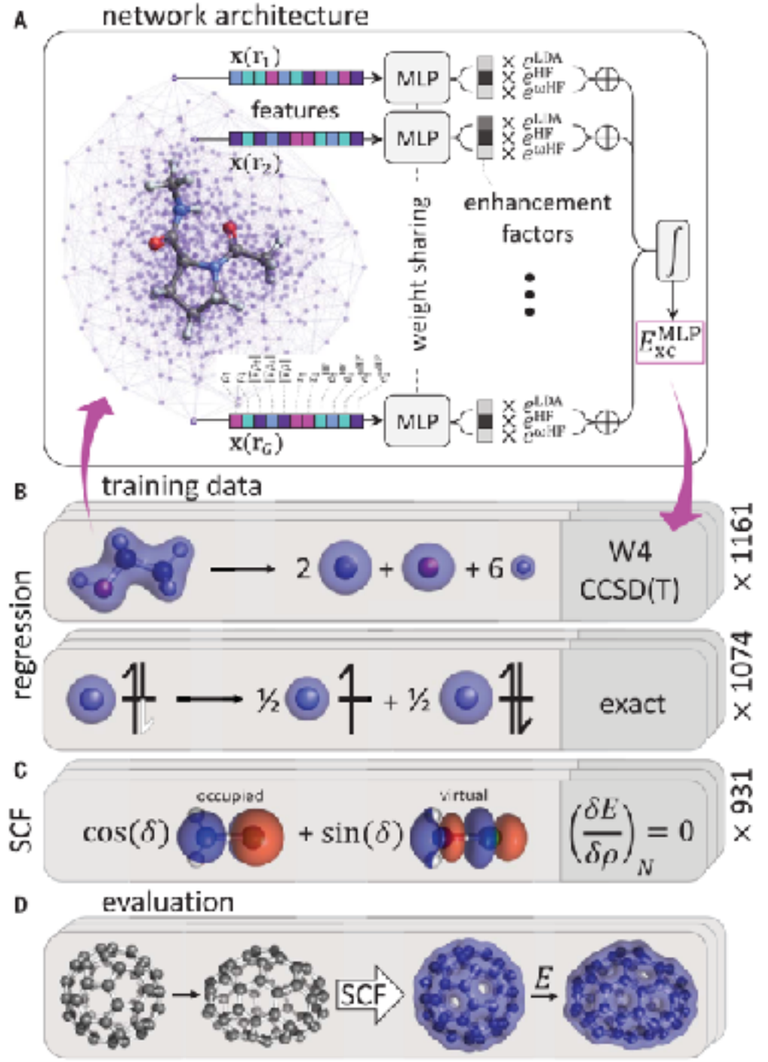
Kirkpatrick *et al.*, *Science* **374**, 1385–1389 (2021) 10 December 2021

QUANTUM CHEMISTRY

Pushing the frontiers of density functionals by solving the fractional electron problem

James Kirkpatrick[1*†], Brendan McMorrow[1†], David H. P. Turban[1†], Alexander L. Gaunt[1†], James S. Spencer[1], Alexander G. D. G. Matthews[1], Annette Obika[1], Louis Thiry[2], Meire Fortunato[1], David Pfau[1], Lara Román Castellanos[1], Stig Petersen[1], Alexander W. R. Nelson[1], Pushmeet Kohli[1], Paula Mori-Sánchez[3], Demis Hassabis[1], Aron J. Cohen[1,4*]

Density functional theory describes matter at the quantum level, but all popular approximations suffer from systematic errors that arise from the violation of mathematical properties of the exact functional. We overcame this fundamental limitation by training a neural network on molecular data and on fictitious systems with fractional charge and spin. The resulting functional, DM21 (DeepMind 21), correctly describes typical examples of artificial charge delocalization and strong correlation and performs better than traditional functionals on thorough benchmarks for main-group atoms and molecules. DM21 accurately models complex systems such as hydrogen chains, charged DNA base pairs, and diradical transition states. More crucially for the field, because our methodology relies on data and constraints, which are continually improving, it represents a viable pathway toward the exact universal functional.



"Learn to simulate"

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

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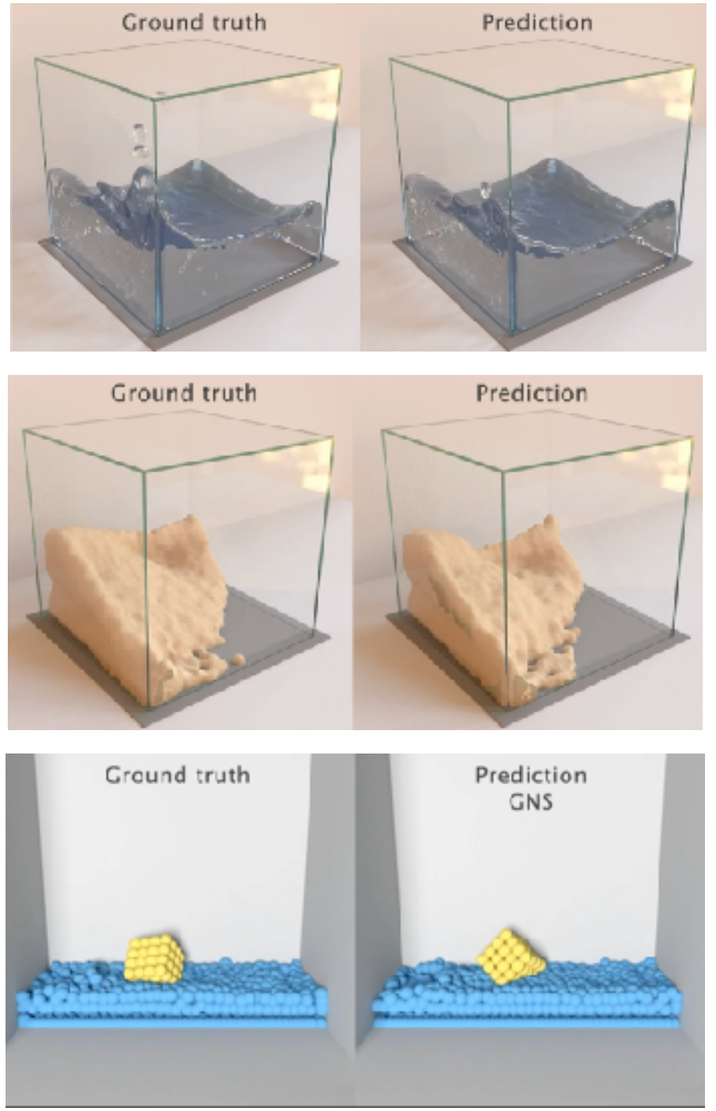
Learning to Simulate Complex Physics with Graph Networks

Abstract

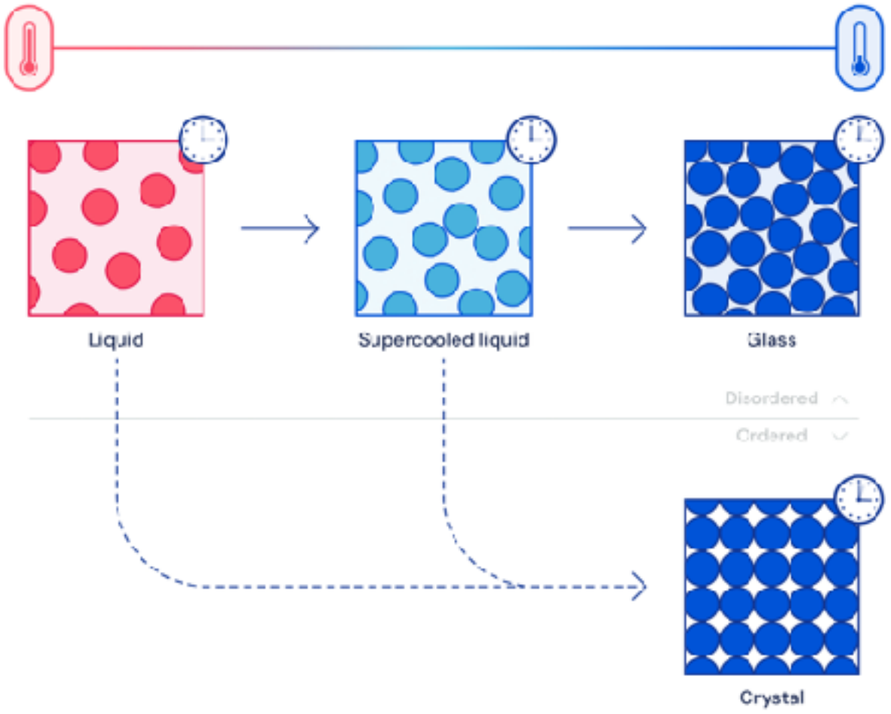
Here we present a machine learning framework and model implementation that can learn to simulate a wide variety of challenging physical domains, involving fluids, rigid solids, and deformable materials interacting with one another. Our framework—which we term "Graph Network-based Simulators" (GNS)—represents 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.

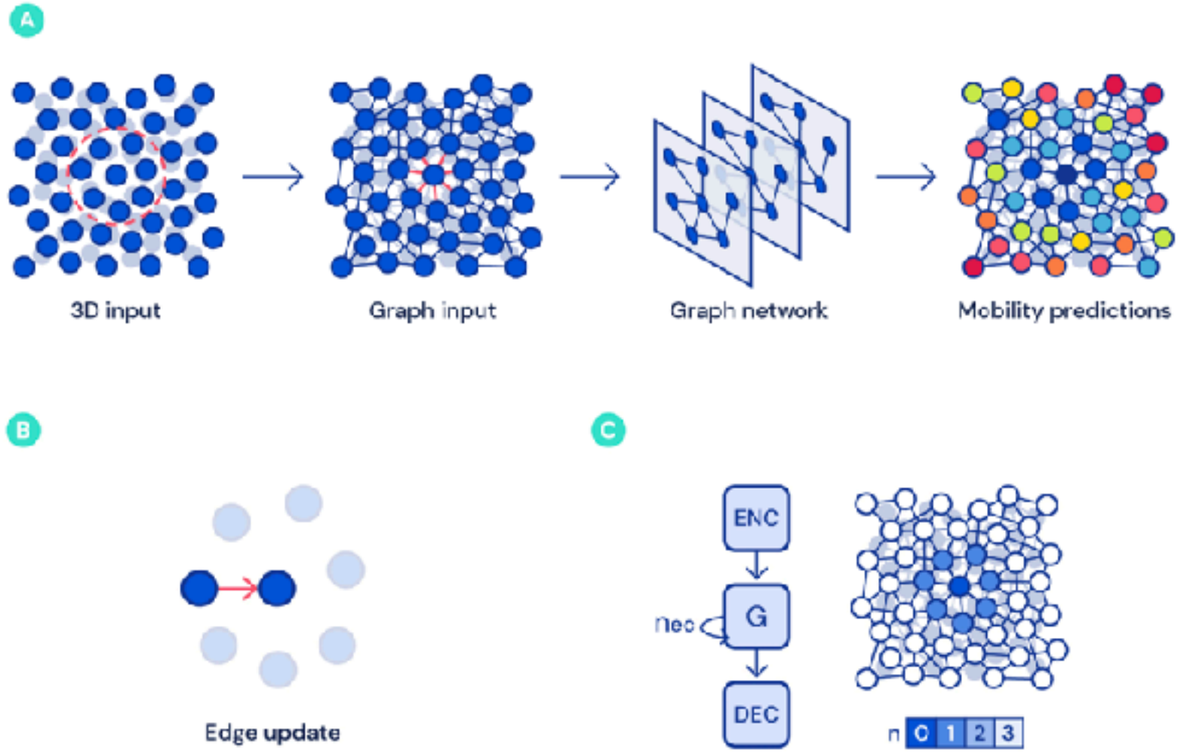
Datasets and example model and training code available.



Learn to simulate long-time evolution of a glassy sytem

Bapst V, Keck T, Grabska-Barwińska A, Donner C, Cubuk ED, Schoenholz SS, et al.
Unveiling the predictive power of static structure in glassy systems.
Nature Physics. 2020;16: 448–454.





https://deepmind.com/blog/article/Towards-understanding-glasses-with-graph-neural-networks

DL/GNNs × Simulations

How to fuse ML (empiricism) and simulations (rationalism) is one of the recent hot topics.

Annu. Rev. Phys. Chem. 71:361–90 (2020)

ANNUAL REVIEWS

Annual Review of Physical Chemistry

Machine Learning for Molecular Simulation

Frank Noé,[1,2,3] Alexandre Tkatchenko,[4] Klaus-Robert Müller,[5,6,7] and Cecilia Clementi[1,3,8]

Acc. Chem. Res. 54(7):1575–1585 (2021)

ACCOUNTS of chemical research

pubs.acs.org/accounts Article

Development of Multimodal Machine Learning Potentials: Toward a Physics-Aware Artificial Intelligence

Published as part of the Accounts of Chemical Research special issue "Data Science Meets Chemistry".

Tetiana Zubatiuk and Olexandr Isayev*

PNAS (2020)

The frontier of simulation-based inference

Kyle Cranmer[a,b,1], Johann Brehmer[a,b], and Gilles Louppe[c]

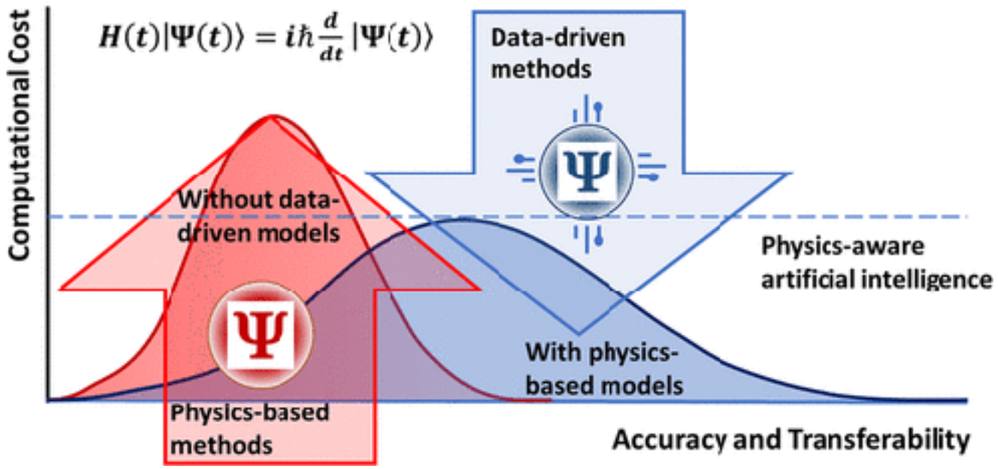
[a]Center for Cosmology and Particle Physics, New York University, New York, NY 10003; [b]Center for Data Science, New York University, New York, NY 10011; and [c]Montefiore Institute, University of Liège, B-4000 Liège, Belgium

Edited by Jitendra Malik, University of California, Berkeley, CA, and approved April 10, 2020 (received for review November 4, 2019)

Many domains of science have developed complex simulations to describe phenomena of interest. While these simulations provide high-fidelity models, they are poorly suited for inference and lead to challenging inverse problems. We review the rapidly developing field of simulation-based inference and identify the forces giving additional momentum to the field. Finally, we describe how the frontier is expanding so that a broad audience can appreciate the profound influence these developments may have on science.

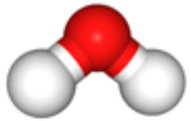
the simulator—is being recognized as a key idea to improve the sample efficiency of various inference methods. A third direction of research has stopped treating the simulator as a black box and focused on integrations that allow the inference engine to tap into the internal details of the simulator directly.

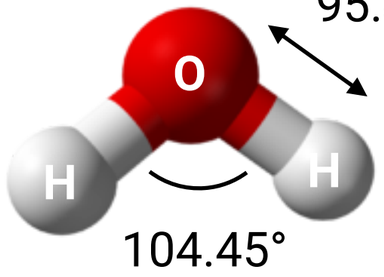
Amidst this ongoing revolution, the landscape of simulation-based inference is changing rapidly. In this review we aim to provide the reader with a high-level overview of the basic ideas



Toward more effective inductive bias?

Water molecule H_2O





95.84 pm

atom-atom distance

104.45°

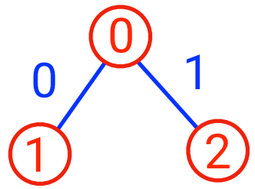
bond angle

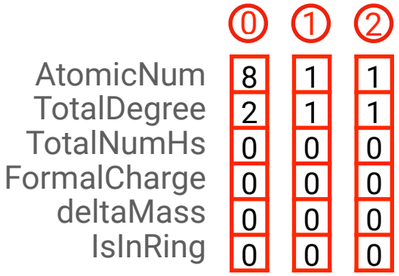
8 + 1 + 1 = 10 electrons

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

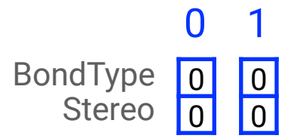
H $1s^1$ H $1s^1$

A molecular graph (RDKit)

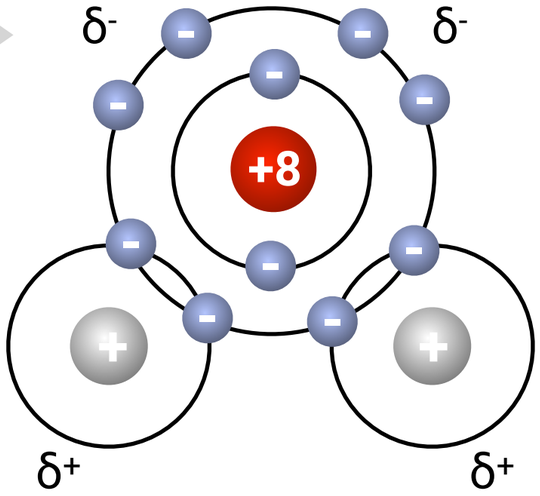




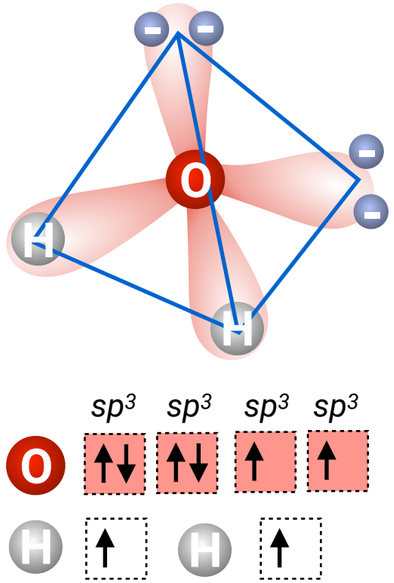
Atom Invariants



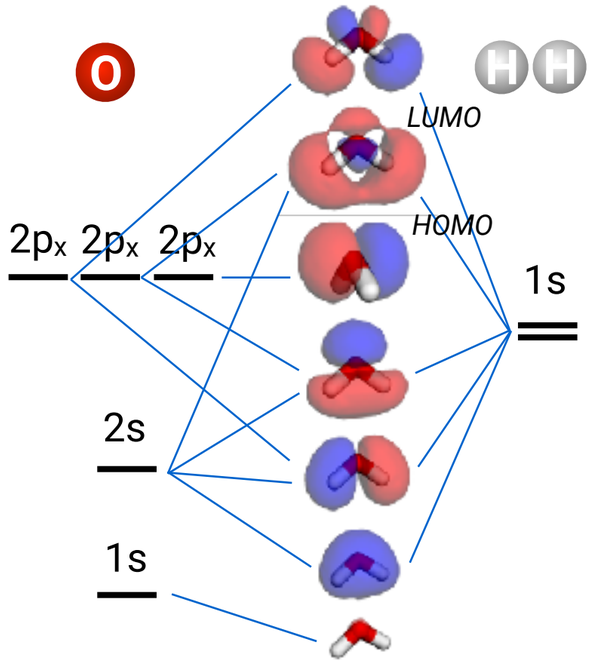
Bond Invariants



covalent bonds



sp^3 hybridization



molecular orbitals

Toward more effective inductive bias?

NATURE REVIEWS | PHYSICS
422 | JUNE 2021 | VOLUME 3

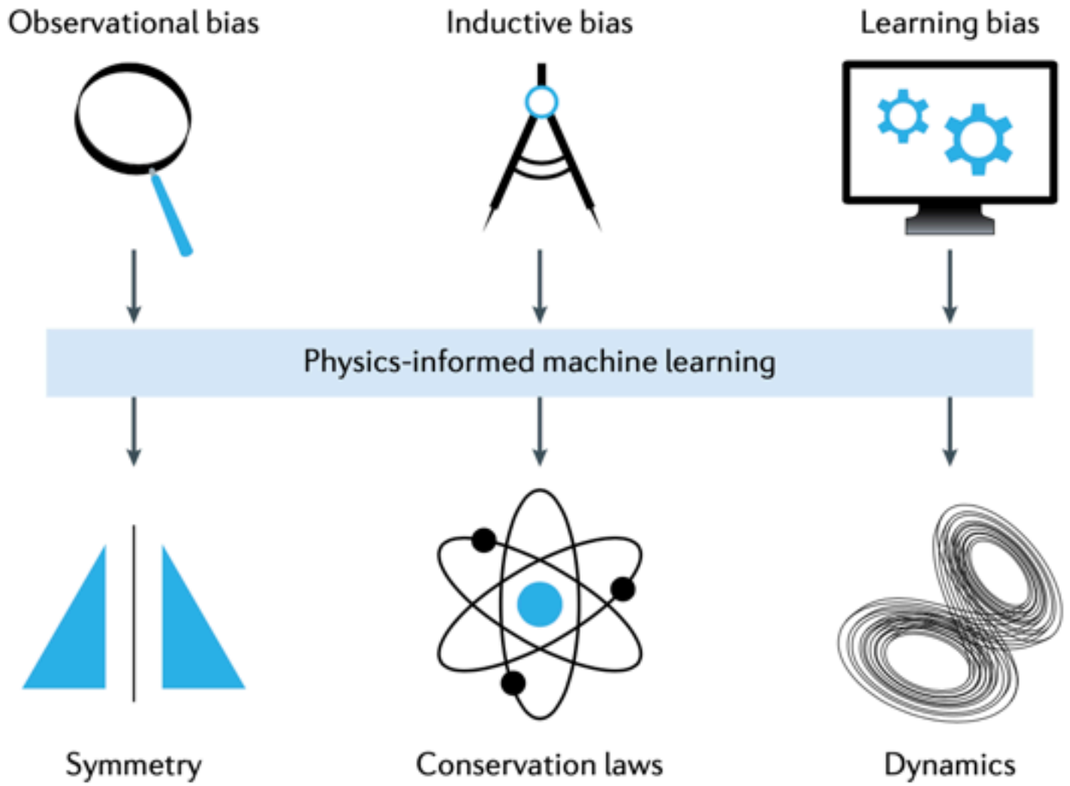
REVIEWS

https://doi.org/10.1038/ s42254-021-00314-5

Physics-informed machine learning

George Em Karniadakis[1,2]✉, *Ioannis G. Kevrekidis*[3,4], *Lu Lu*[5], *Paris Perdikaris*[6], *Sifan Wang*[7] *and Liu Yang*[1]

Abstract | Despite great progress in simulating multiphysics problems using the numerical discretization of partial differential equations (PDEs), one still cannot seamlessly incorporate noisy data into existing algorithms, mesh generation remains complex, and high-dimensional problems governed by parameterized PDEs cannot be tackled. Moreover, solving inverse problems with hidden physics is often prohibitively expensive and requires different formulations and elaborate computer codes. Machine learning has emerged as a promising alternative, but training deep neural networks requires big data, not always available for scientific problems. Instead, such networks can be trained from additional information obtained by enforcing the physical laws (for example, at random points in the continuous space-time domain). Such physics-informed learning integrates (noisy) data and mathematical models, and implements them through neural networks or other kernel-based regression networks. Moreover, it may be possible to design specialized network architectures that automatically satisfy some of the physical invariants for better accuracy, faster training and improved generalization. Here, we review some of the prevailing trends in embedding physics into machine learning, present some of the current capabilities and limitations and discuss diverse applications of physics-informed learning both for forward and inverse problems, including discovering hidden physics and tackling high-dimensional problems.



DL/GNNs × Symbolic Tasks, Logical Inference, Planning

Now we can use machine learning also for symbolic, logical, algorithmic tasks!

Neural Abstract Machines & Program Induction

https://uclnlp.github.io/nampi/

- **Differentiable Neural Computers / Neural Turing Machines** (Graves+ 2014)
- **Memory Networks** (Weston+ 2014)
- **Pointer Networks** (Vinyals+ 2015)
- **Neural Stacks** (Grefenstette+ 2015, Joulin+ 2015)
- **Hierarchical Attentive Memory** (Andrychowicz+ 2016)
- **Neural Program Interpreters** (Reed+ 2016)
- **Neural Programmer** (Neelakantan+ 2016)
- **DeepCoder** (Balog+ 2016)

:

Can we also use explicit chemical knowledges?

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CHEMATICA


Computer-Aided Synthetic Planning

International Edition: DOI: 10.1002/anie.201506101
German Edition: DOI: 10.1002/ange.201506101

Computer-Assisted Synthetic Planning: The End of the Beginning

*Sara Szymkuć, Ewa P. Gajewska, Tomasz Klucznik, Karol Molga, Piotr Dittwald, Michał Startek, Michał Bajczyk, and Bartosz A. Grzybowski**

Angew. Chem. Int. Ed. **2016**, *55*, 5904 – 5937


VIP AI-Assisted Synthesis Very Important Paper

International Edition: DOI: 10.1002/anie.201912083
German Edition: DOI: 10.1002/ange.201912083

Synergy Between Expert and Machine-Learning Approaches Allows for Improved Retrosynthetic Planning

*Tomasz Badowski, Ewa P. Gajewska, Karol Molga, and Bartosz A. Grzybowski**

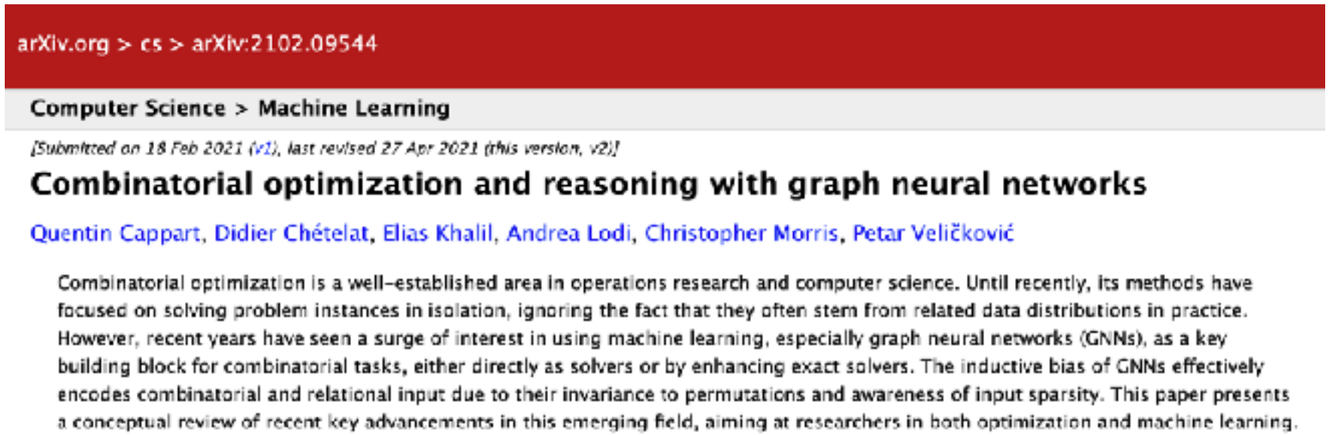
Angew. Chem. Int. Ed. **2019**, *58*, 1 – 7

DL/GNNs × Combinatorial Optimization and Reasoning

https://www.ipam.ucla.edu/dlc2021

https://youtu.be/QOBoZaDZYUI

https://arxiv.org/abs/2102.09544



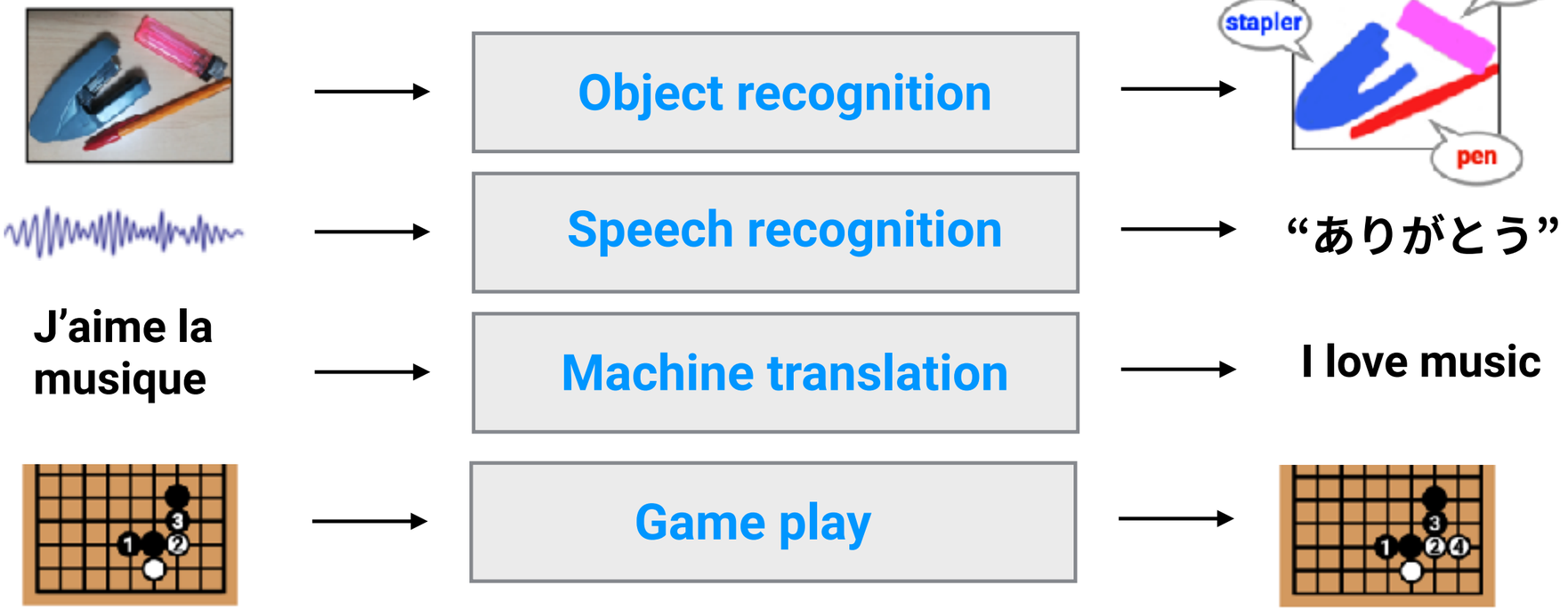
https://doi.org/10.1016/j.patter.2021.100273

One final remark on "the true dark side" ...

The huge gap between prediction and understanding

Prediction does not directly bring us Understanding nor Discovery.

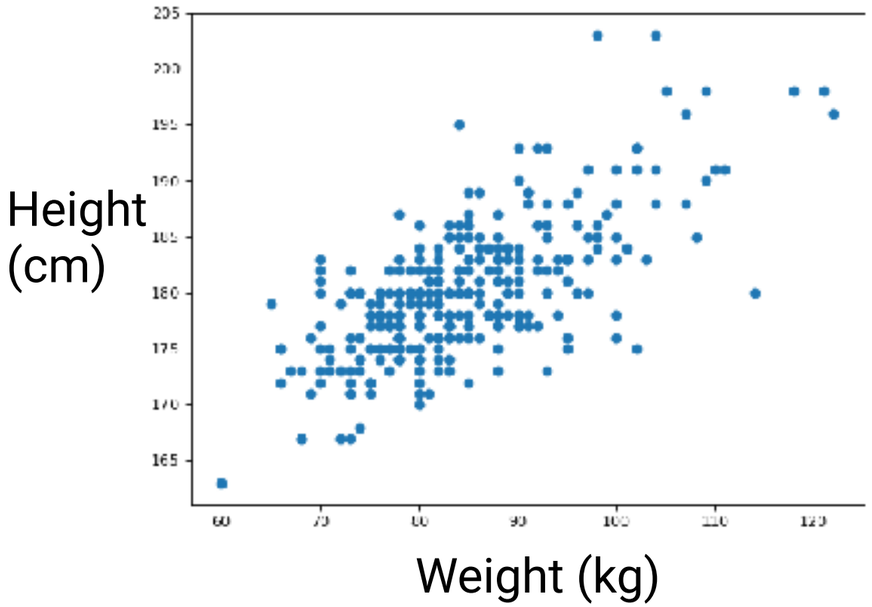
Current ML already provides practical applications below, but how we recognize objects and speech sounds, and how we aquire and use languages is still not well understood…



Observational vs experimental (interventional) studies

To find out what happens to a system when you interfere with it,
you have to interfere with it (not just passively observe it). George Box

Height and Weight of Pro baseball players (2016 NPB Website)



We see correlation, but these data never tell us "increase weight" does not imply "grow in height"

Applied Stats 101
Correlation does not imply causation

An Inconvenient Truth
All we can directly access is correlation

We need experiments! Passively observing data and applying ML to it is alway insufficient.

Toward causal representation learning

PROCEEDINGS OF THE IEEE | *Vol. 109, No. 5, May 2021* https://arxiv.org/abs/2102.11107

INVITED PAPER

Toward Causal Representation Learning

This article reviews fundamental concepts of causal inference and relates them to crucial open problems of machine learning, including transfer learning and generalization, thereby assaying how causality can contribute to modern machine learning research.

By BERNHARD SCHÖLKOPF, FRANCESCO LOCATELLO, STEFAN BAUER, NAN ROSEMARY KE, NAL KALCHBRENNER, ANIRUDH GOYAL, AND YOSHUA BENGIO

ABSTRACT | The two fields of machine learning and graphical causality arose and are developed separately. However, there is, now, cross-pollination and increasing interest in both fields to benefit from the advances of the other. In this article, we review fundamental concepts of causal inference and relate them to crucial open problems of machine learning, including transfer and generalization, thereby assaying how causality can contribute to modern machine learning research. This also applies in the opposite direction: we note that most work in causality starts from the premise that the causal variables are given. A central problem for AI and causality is, thus,

I. INTRODUCTION

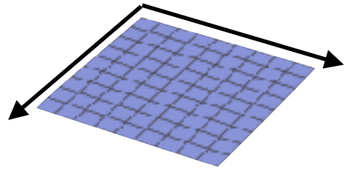
If we compare what machine learning can do to what animals accomplish, we observe that the former is rather limited at some crucial feats where natural intelligence excels. These include transfer to new problems and any form of generalization that is not from one data point to the next (sampled from the same distribution), but rather from one problem to the next—both have been termed *generalization*, but the latter is a much harder form thereof, sometimes referred to as *horizontal*, *strong*, or *out-of-distribution* generalization. This shortcoming is not too

From machine learning to machine discovery

The hard problems are happening at the interface between inside and outside of ML.

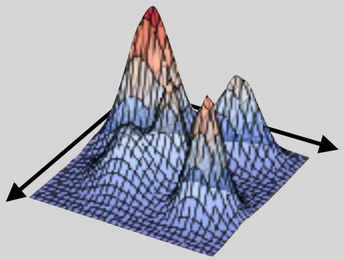
Representing

Input information of the outside



- Identify input variables
- Design ML tasks
- Prepare good training data
- Use existing data/knowledge

ML models

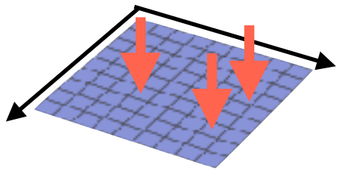


inside

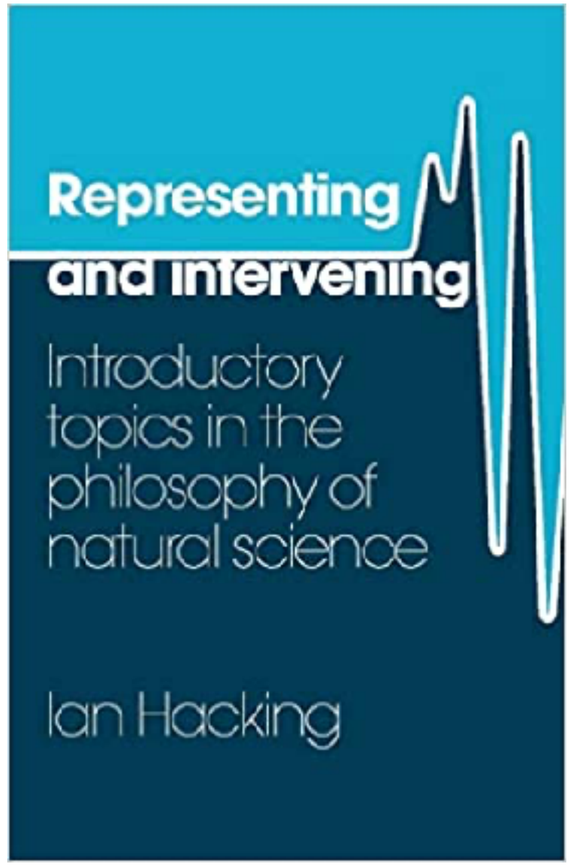
outside

Intervening

Get information back to the outside



- Design/plan and conduct experimens
- Evaluate observations
- **Work with experts**



The lesson: Science is a human activity, after all

We need to seriously take all "human factors" into consideration. All difficulty is our fault. We want "understanding" and "discovery", but neither machines nor nature do.

- **Interpretability**
  All information needs to be simple enough so that we feel like we understand it within our (poor) cognitive capability.
- **Partiality of information**
  We cannot observe everything, nor model everything. Any data is some finite, partial, and inevitably biased snapshot.
- **Finitude of time**
  Discovery needs to be done within the time limit of one's life (or the extinction of mankind)

Summary

This slide is available at
https://itakigawa.github.io/news.html

A quick review on the dark side and light side of ML
from both viewpoints as an ML algorithm researcher and an ML practitioner/user

1. What actually ML is?
2. The dark side: Modern aspects of ML
3. The light side: Deep learning for molecules

May the ML Force be with you…

Science is built up of facts, as a house is built of stones;
but an accumulation of facts is no more a science than
a heap of stones is a house.

Henri Poincaré "Science and hypothesis"