Statistical learning and deep artificial neural networks: selected applications in proteomics

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Projects available!

Summary

- Part I: basics of artificial neural networks
  - Statistical learning basics
  - The artificial neuron
  - Multi-layer neural networks
  - Training, test, validation and pitfalls
- Part II: advanced ANN architectures
  - Convolutional NNs
  - Recurrent NNs
  - Autoencoders
  - Adversarial neural networks
  - Transformers

Summary

- Part III: applications
  - Pocket finding
  - Structure-based affinity ranking
  - Protein structure prediction
  - General-purpose sequence-based transformers
- Appendix
  - Merck's challenge
  - Datasets
  - Resources
  - Literature

Course objectives

1. Know what an artificial NN is
   - What problem does it solve?
   - Advantages and pitfalls
2. What DNN variations are there and what for?
3. How is the proteomics community using them

→ Grasp the essence of current research

(For the computationally-oriented: experiment in autonomy)

Part I

Basics of artificial neural networks

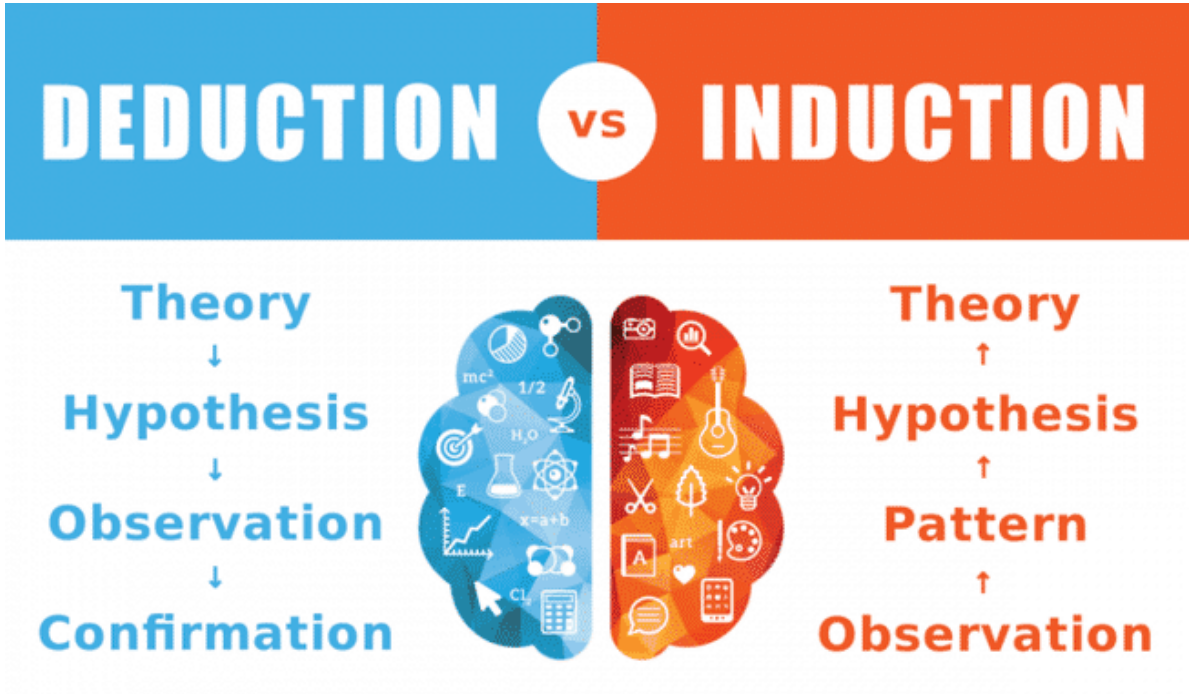
Inference = reasoning

Given the theory

"All humans are mortal.
Greeks are humans.
Therefore, Greeks are mortal."

Given the data

"I've never seen any donkey fly.
I've observed 10 donkeys.
Therefore, donkeys don't fly."



https://danielmiessler.com/blog/the-difference-between-deductive-and-inductive-reasoning/

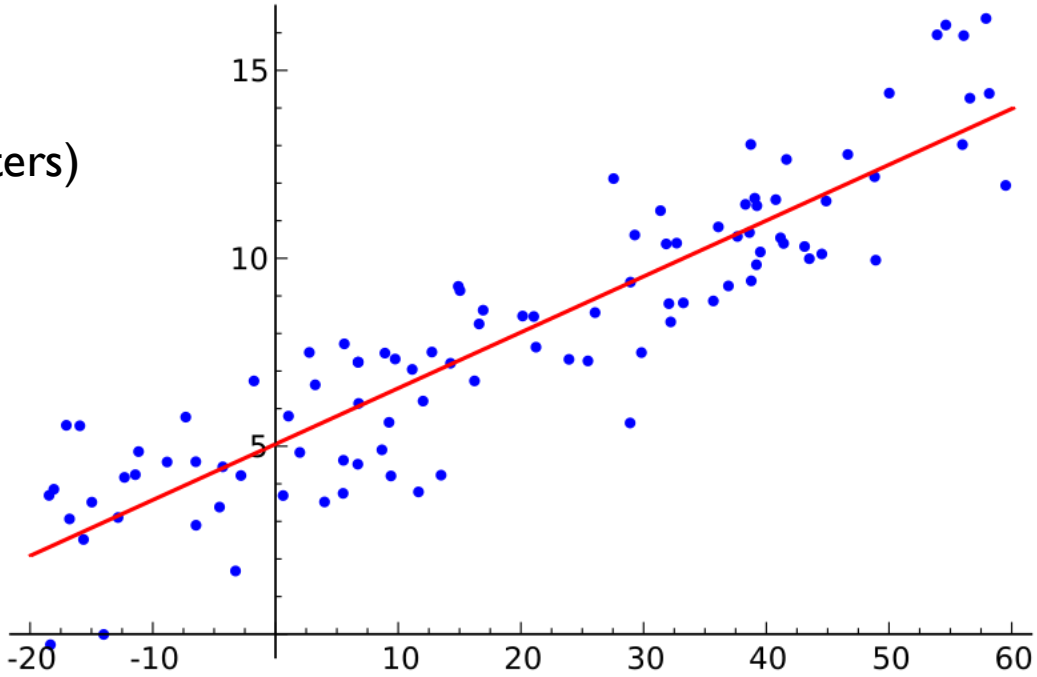
However

- For deductive reasoning:
  - Are the premises correct?
  - If so, the conclusion is **certain**
  - Upon observing a counter-example, we'd need to revise the premises/theory
- For inductive reasoning:
  - The induction is only **probabilistic**
  - In presence of noise: *statistical inference*

https://danielmiessler.com/blog/the-difference-between-deductive-and-inductive-reasoning/

Machine learning

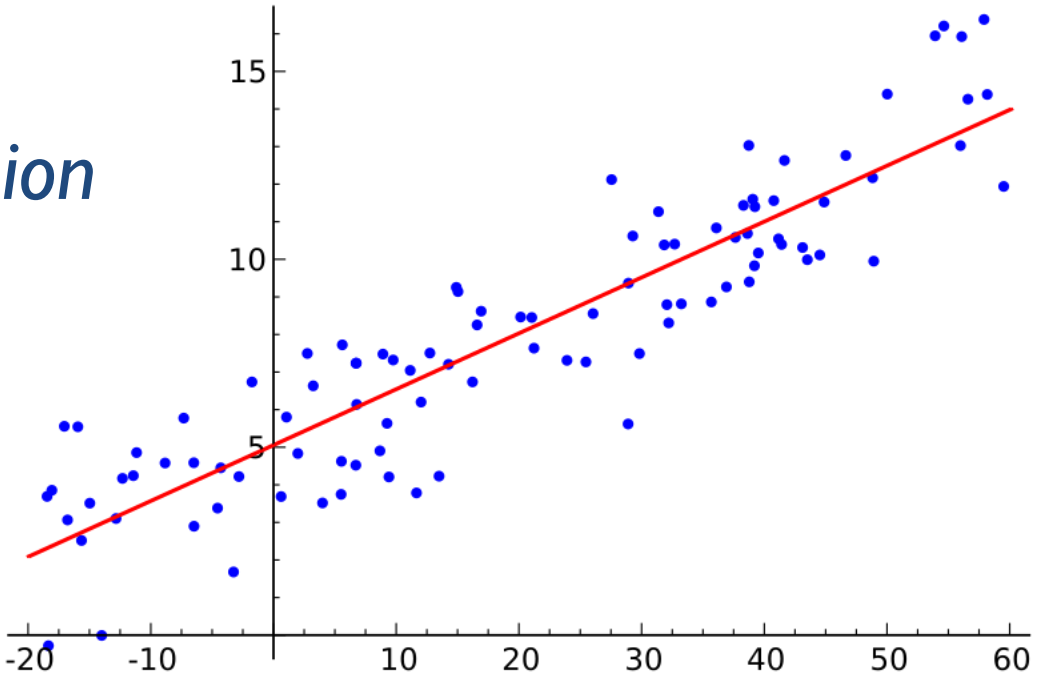
- Collect large amounts of data
- Let computers do the induction*
- Research focuses on algorithms to do so
- Example: regression
  - Note how (1) we are inferring a rule, i.e. the specific relationship (parameters) but we assumed a functional form → power
  - (2) Once rule obtained, we make **predictions**

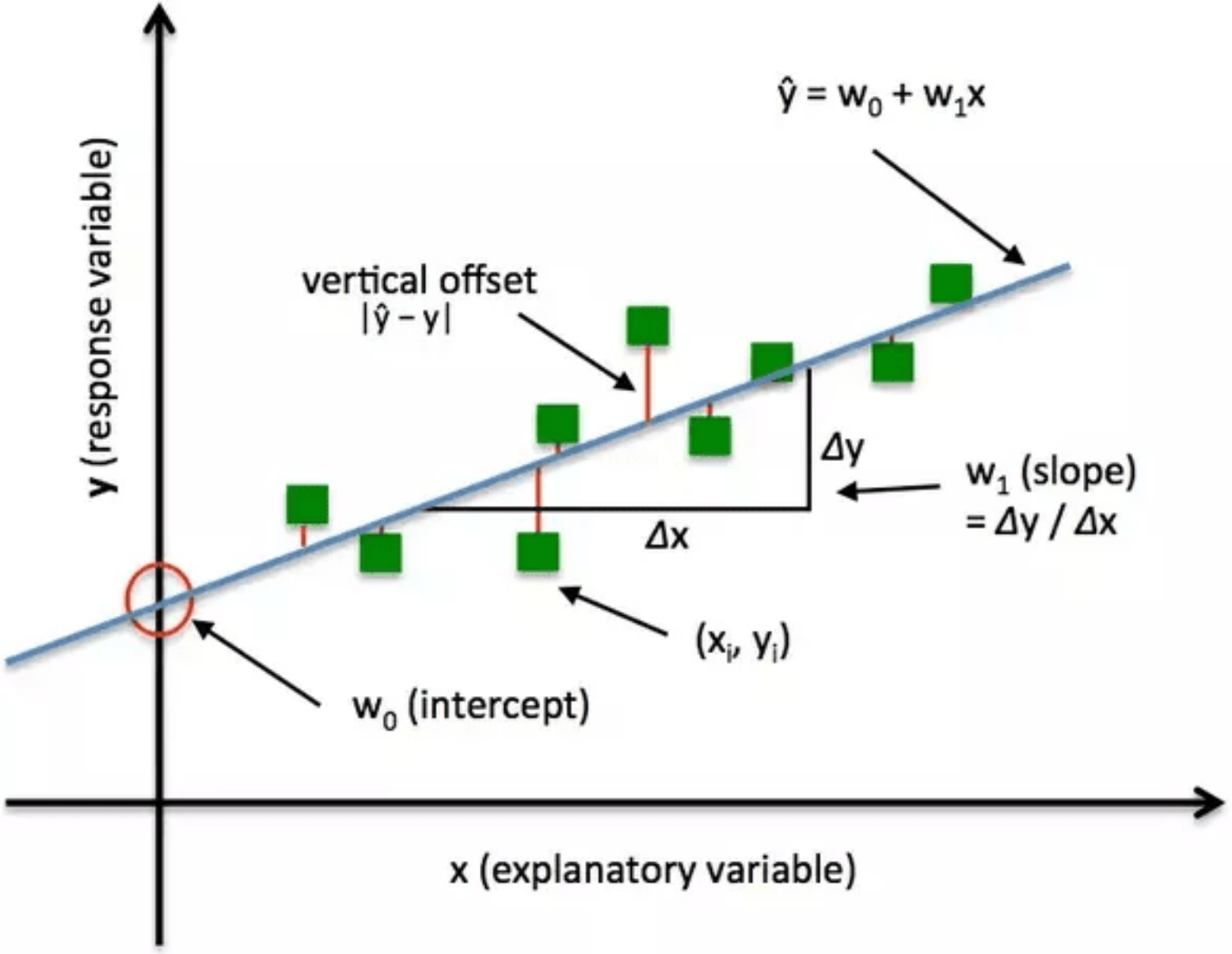


* dangerous!

Regression

- Regression (e.g. linear regression) is a form of learning.
- One assumes that data is generated (with noise) by a certain functional relation, and *induces* the missing parameters
- Real-valued: *regression*
- If discrete: called *classification*



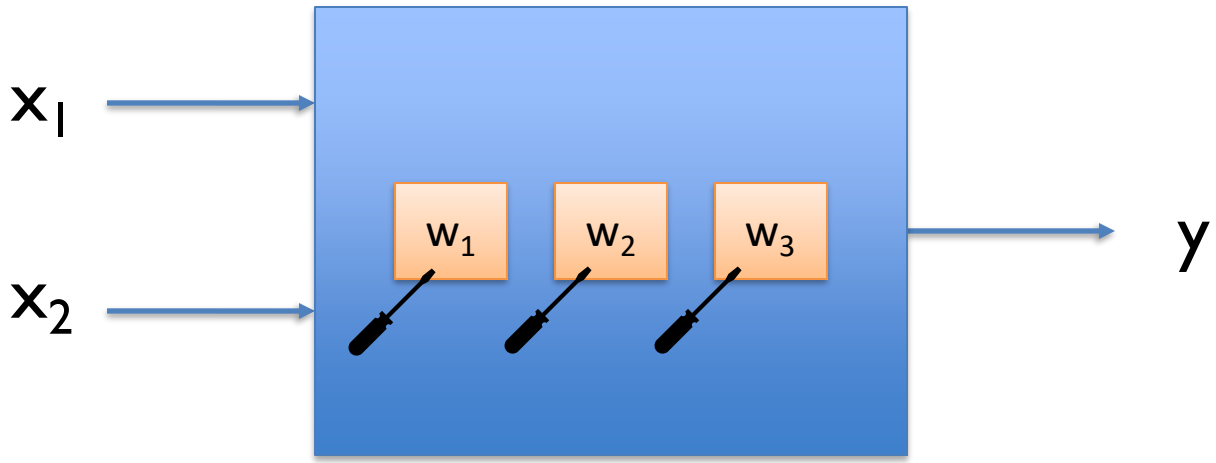

$\hat{y} = w_0 + w_1 x$
vertical offset
$|\hat{y} - y|$
y (response variable)
Δy
w_1 (slope)
$= \Delta y / \Delta x$
Δx
(x_i, y_i)
w_0 (intercept)
x (explanatory variable)

Interpretability

- Assumptions are dangerous as they tend to be hidden
  - Is linearity the "best" model? What if up/down?
- The rules found by induction may be precious *per se*!
  - Example: CV risk increases with age and smoking
  - How much *per year?*
- **Interpretability** is important
  - One may want to sacrifice accuracy for it

Regression as a box

$$y(x_1, x_2 | w_{1\ldots3}) = w_1 x_1 + w_2 x_2 + w_3$$

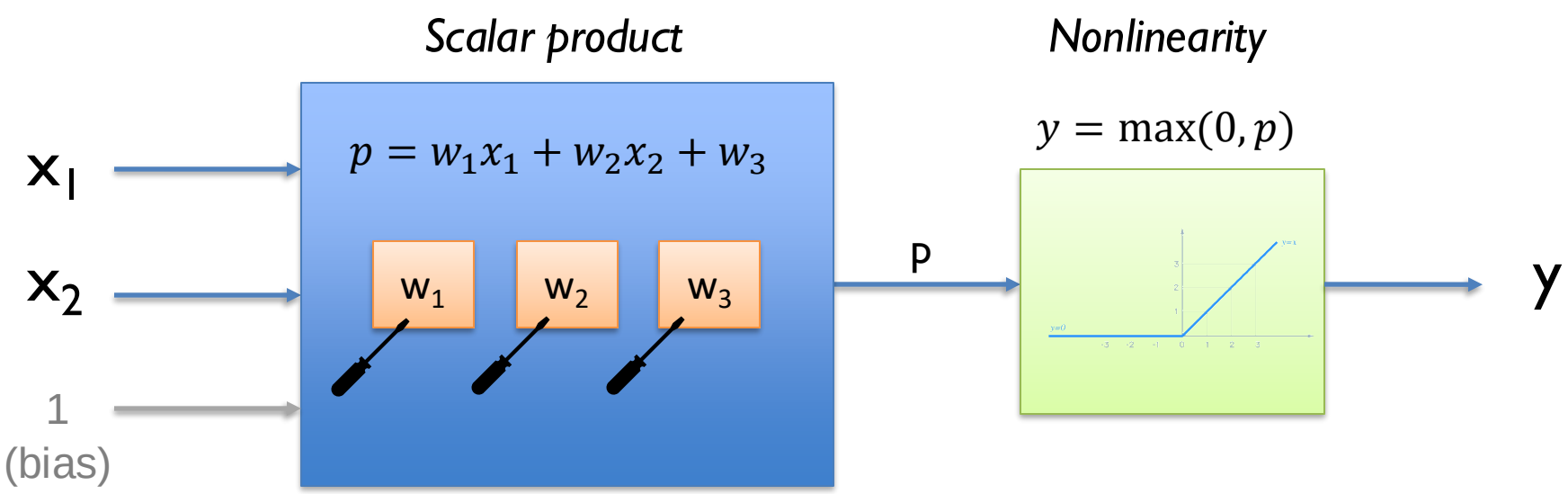


For now, *real numbers* in input and output

An artificial neuron

- Adding a *nonlinear activation function* gives an *artificial neuron*

- It is a *mathematical model!*
- It is **not** a biological model!



In other words…

Linear regression, 1 D → $y = wx + b$

Linear regression, *n* D → $y = \mathbf{w} \cdot \mathbf{x} + b$

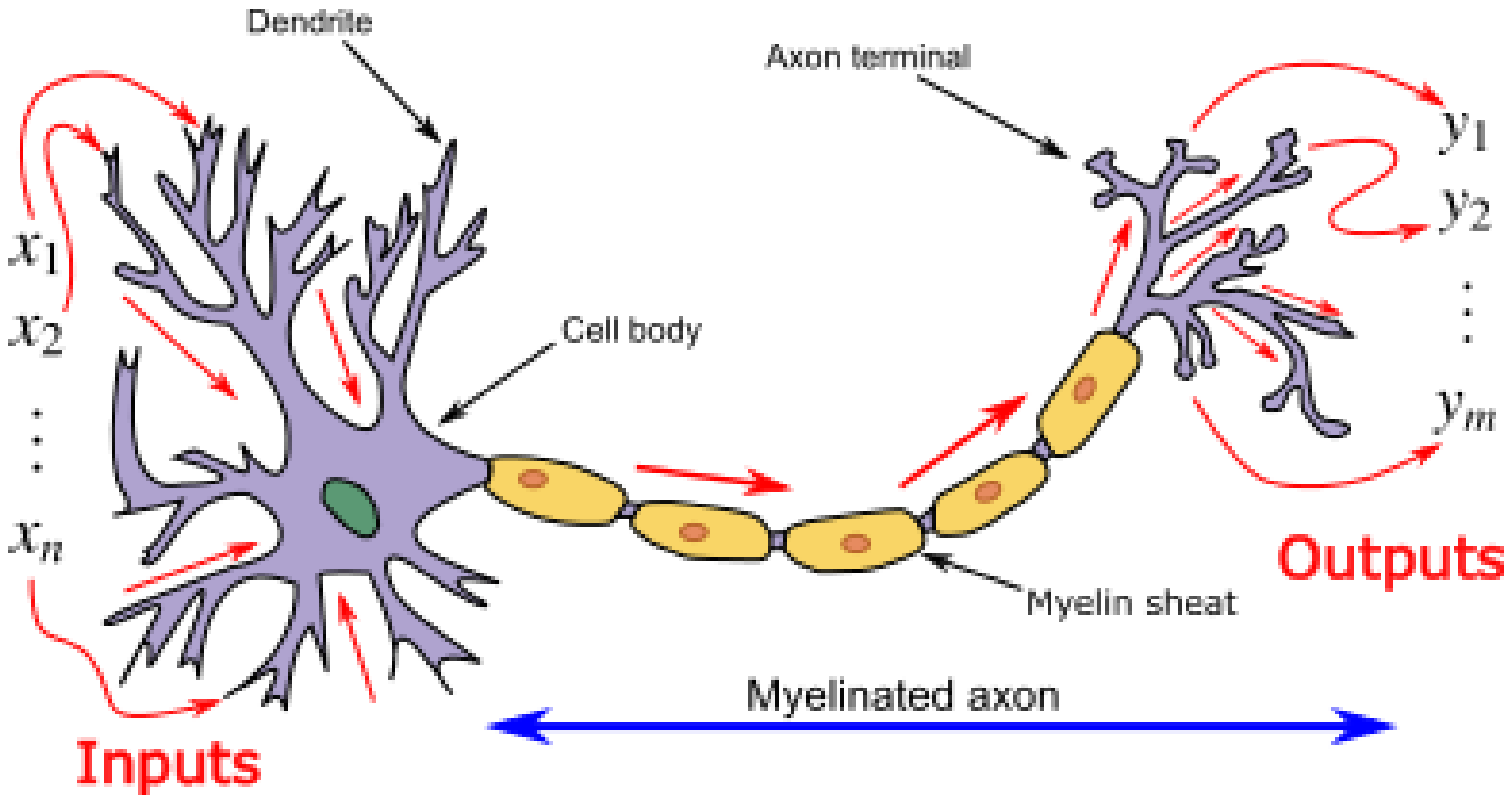
One artificial neuron → $y = f\left(\mathbf{w} \cdot \mathbf{x} + b\right)$

Activation function

Repeat: it is a **mathematical model.**

Not a model of biological significance.

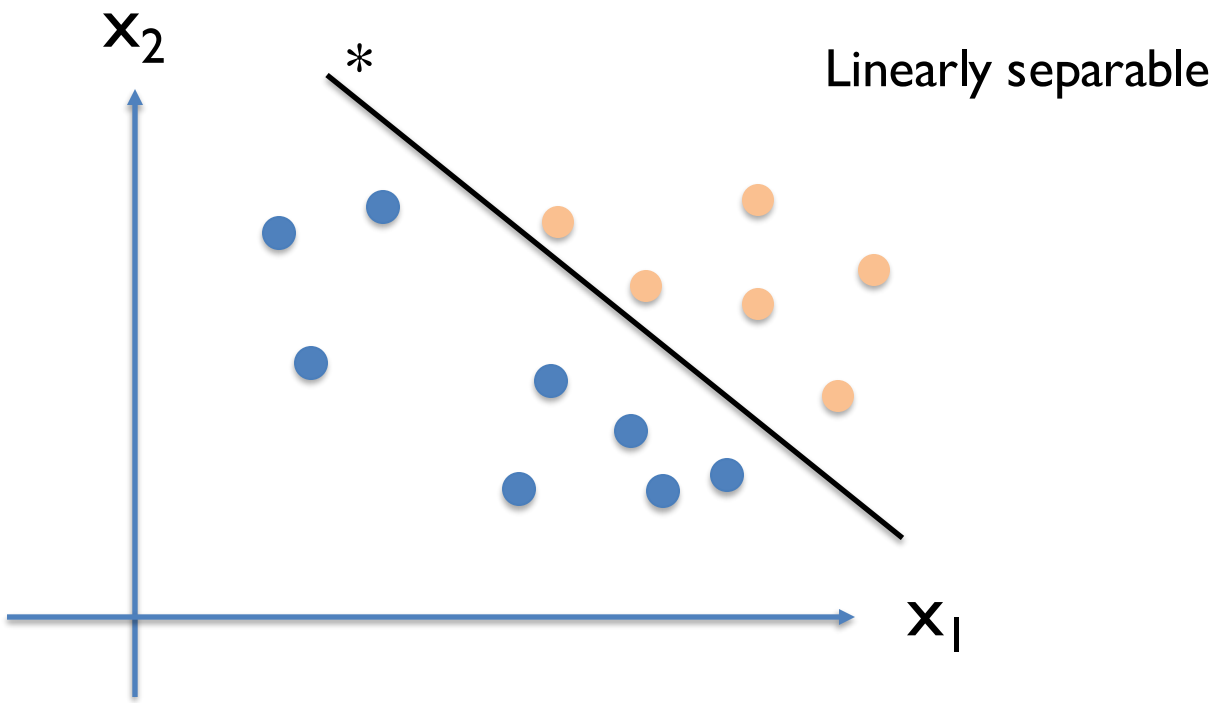
(This parallel with actual neurons is a curiosity.)



https://en.wikipedia.org/wiki/Artificial_neural_network

Linear separability

A **single-neuron** model would only solve *linearly separable* problems.



* defined by $w_{1,2,3}$

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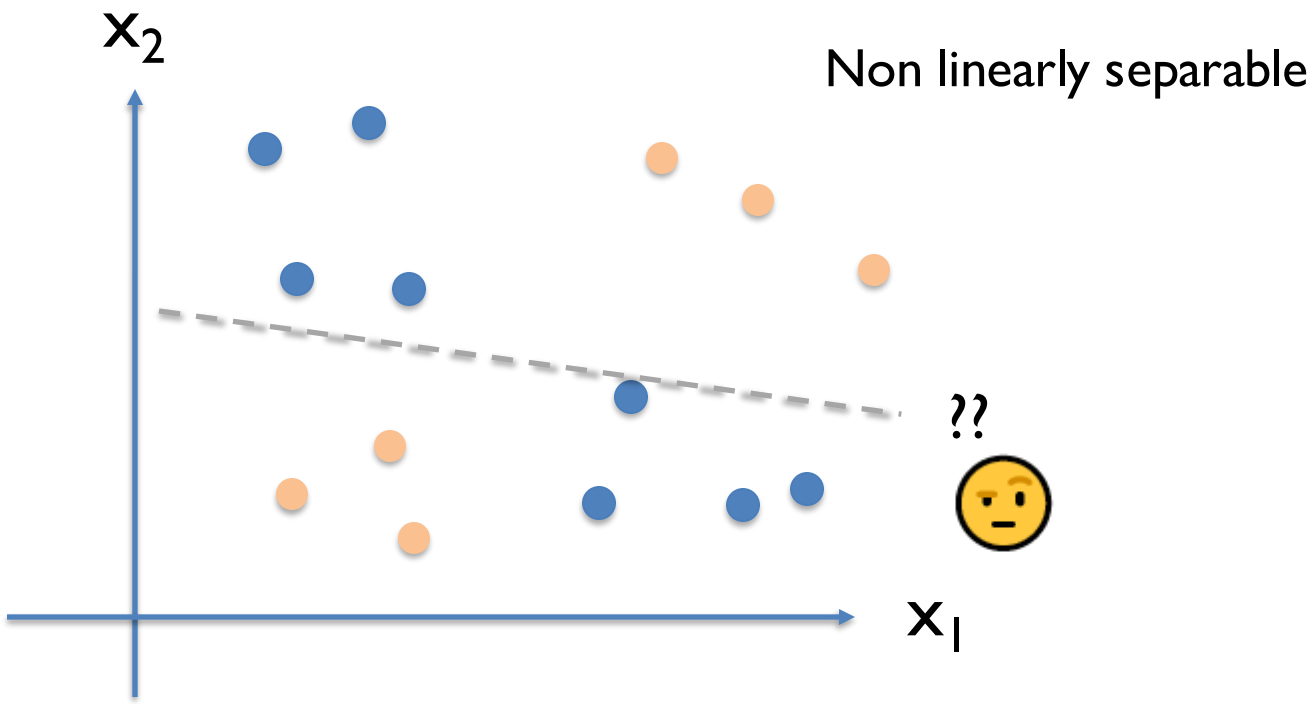
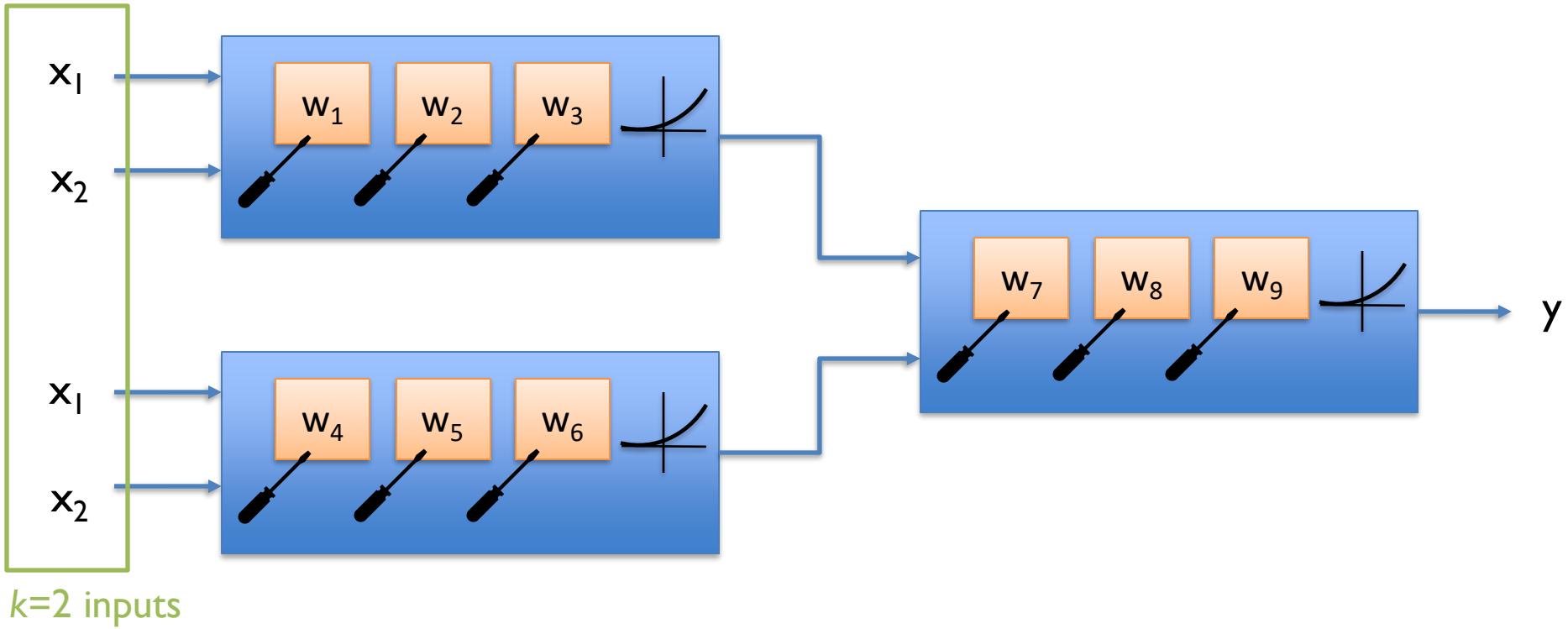


Artificial neural networks (ANNs)

- The power of this model comes from its modularity.
- A **repeated arrangement** of neurons as a network can solve much more complex problems.
- Addition of more neurons will require tuning many more parameters → 
  computing cost, data hunger, overfitting

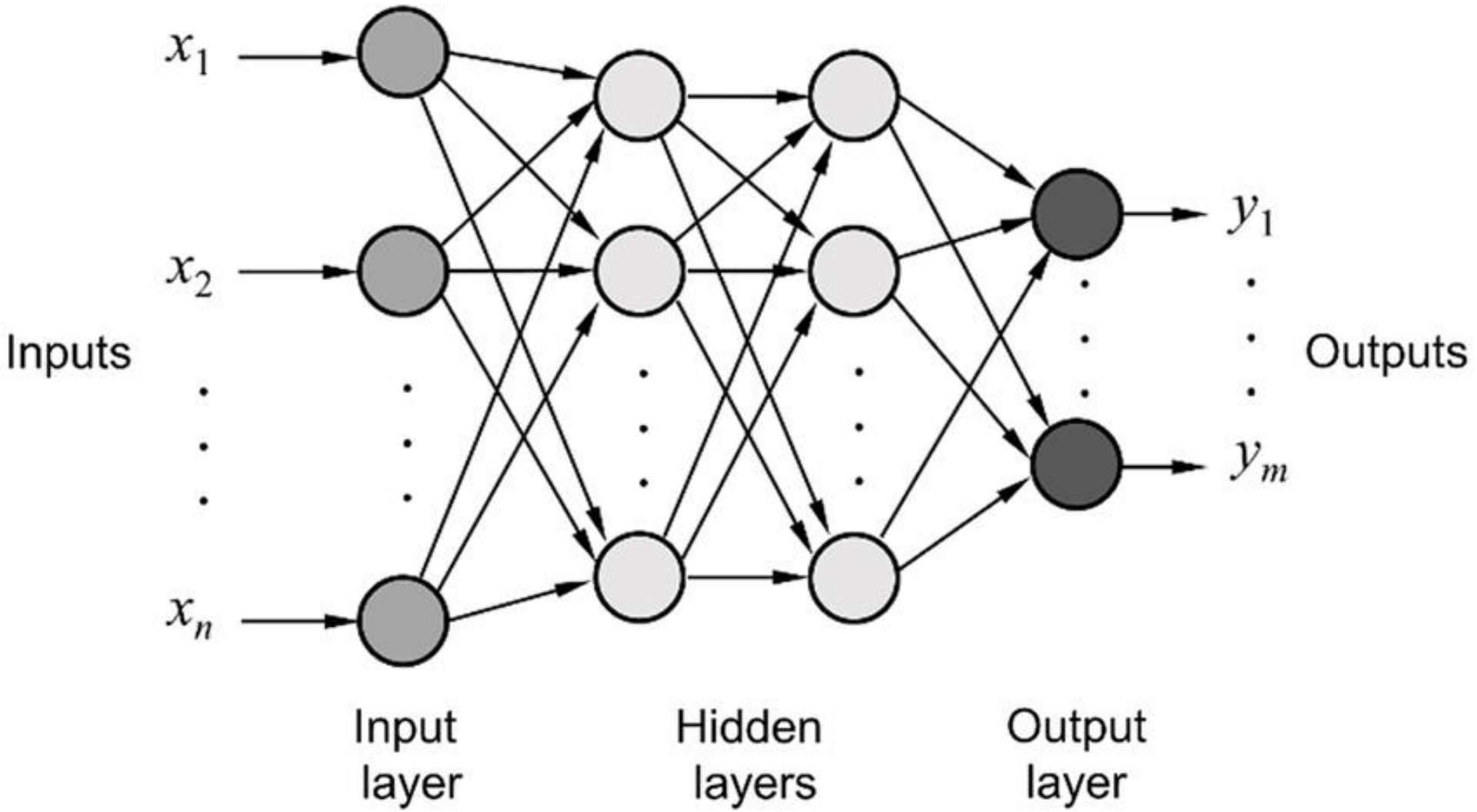
An artificial neural **network**



N=3 neurons *k*=2 inputs *u*=1 output

$n_w = N(k+1) = 9$ weights (in this case)

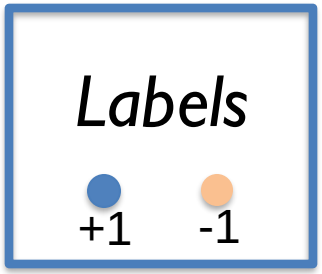
- An artificial neural network with sufficient complexity *and the correct weights* may approximate arbitrary functions
- The interest lies in the fact that one can find the "correct" weights with an automatic procedure…
- …*given enough data*
- Engineering problem → data collection problem (at least in principle!)



(Note: here showing *fully connected* layers. They needn't be.)

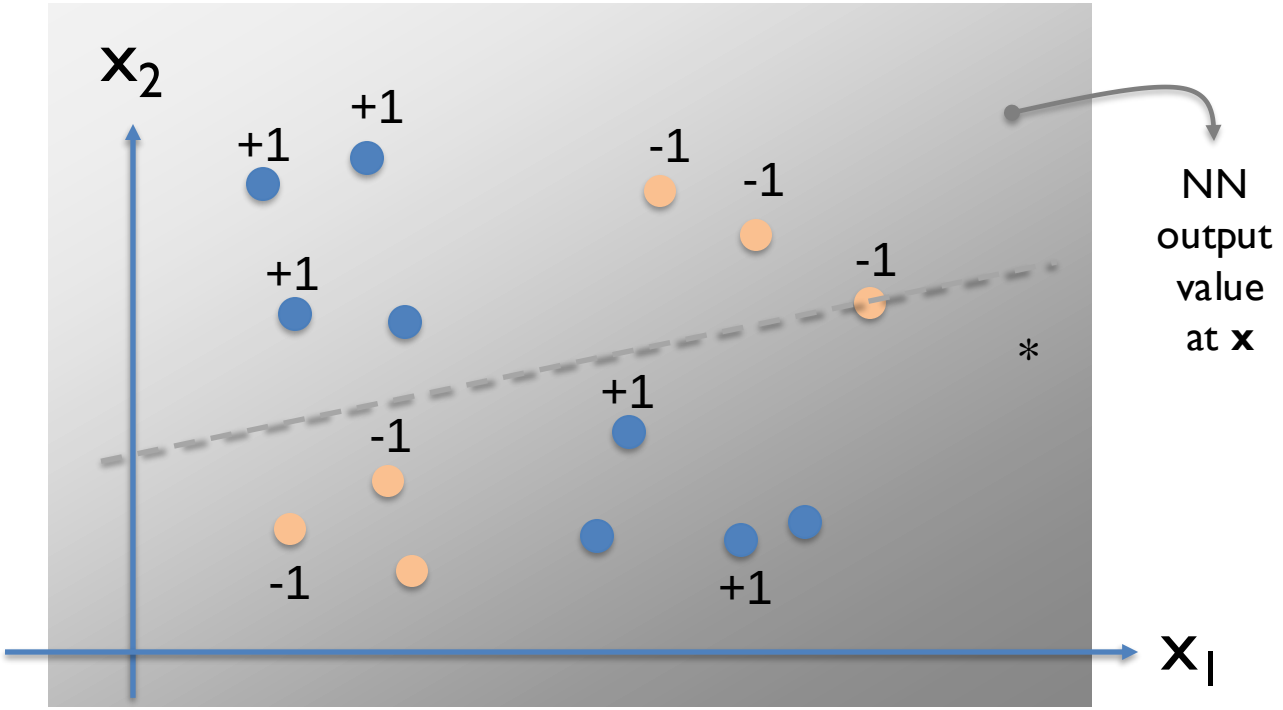
Pouliakis A, Karakitsou E, Margari N, et al. DOI: 10.4137/BECB.S31601

Training: loss function



1. An ANN is trained on a (large) set of *labeled* examples
2. They are used as inputs.
3. They are compared with expected outputs (labels)
4. The squared difference is the *loss*

* defined by $w_{1,2,\ldots,n}$



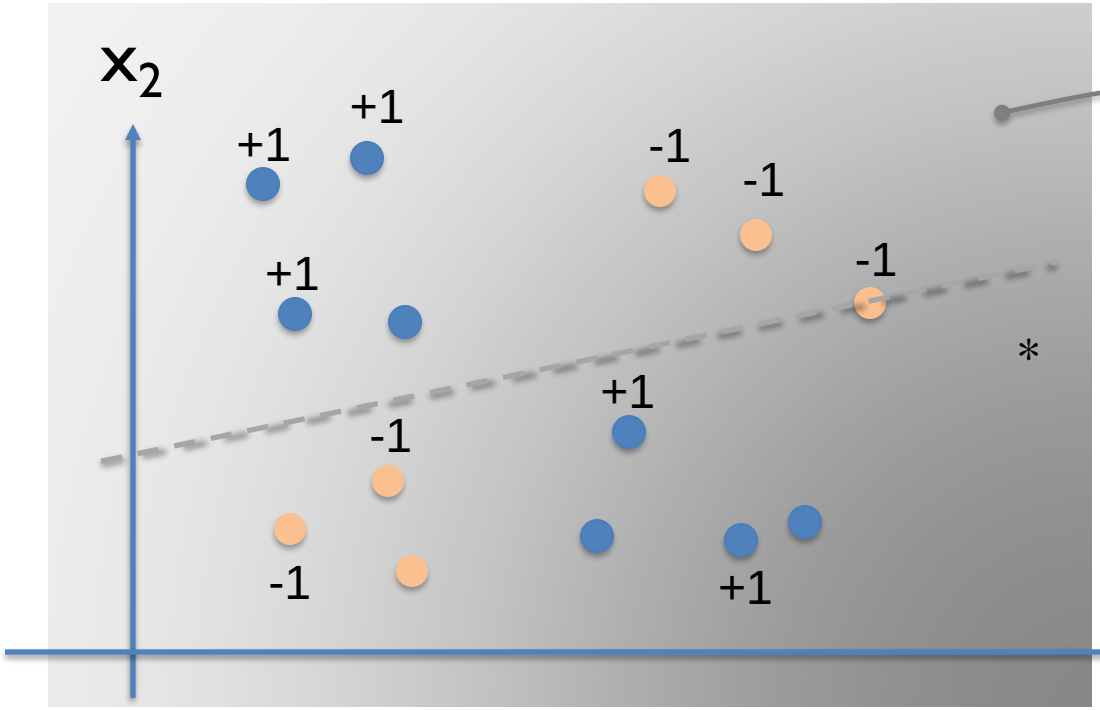
Training: loss function

ANN output

$$L(\mathbf{w}; \underbrace{\mathbf{x}_i, y_i}) = \sum_{i \in \text{ examples}} \left[f(\mathbf{x}_i, \mathbf{w}) - y_i \right]^2$$

Labeled examples

* defined by $\mathbf{w}_{1,2,\ldots,n}$

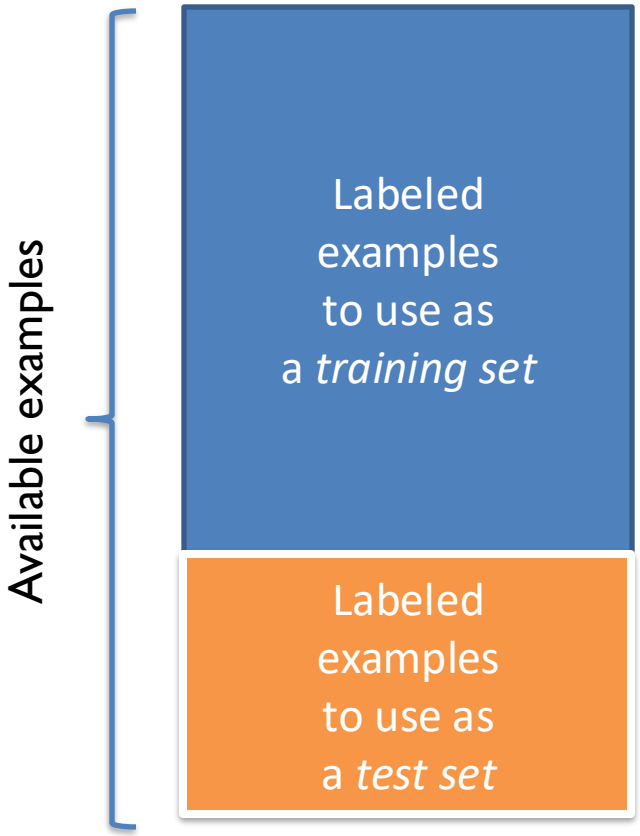


Shade = *f* = ANN output value at input **x**

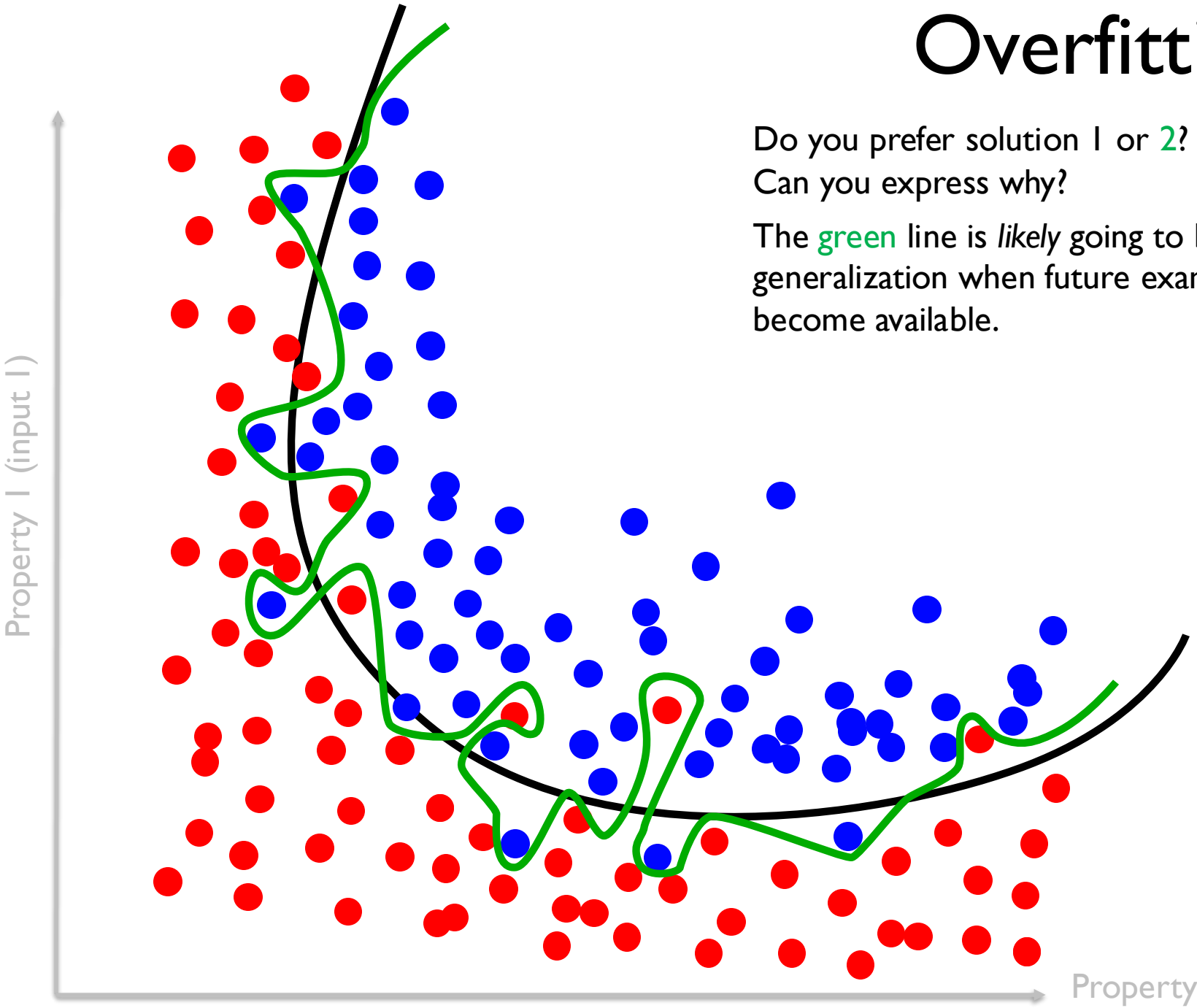
An optimization problem

$$\min_{\mathbf{w}} L(\mathbf{w}; \mathbf{x}_i, y_i)$$

- That is, vary the set of weights **w** until a "good enough" solution (=low loss) is found
- How *good*?



Overfitting

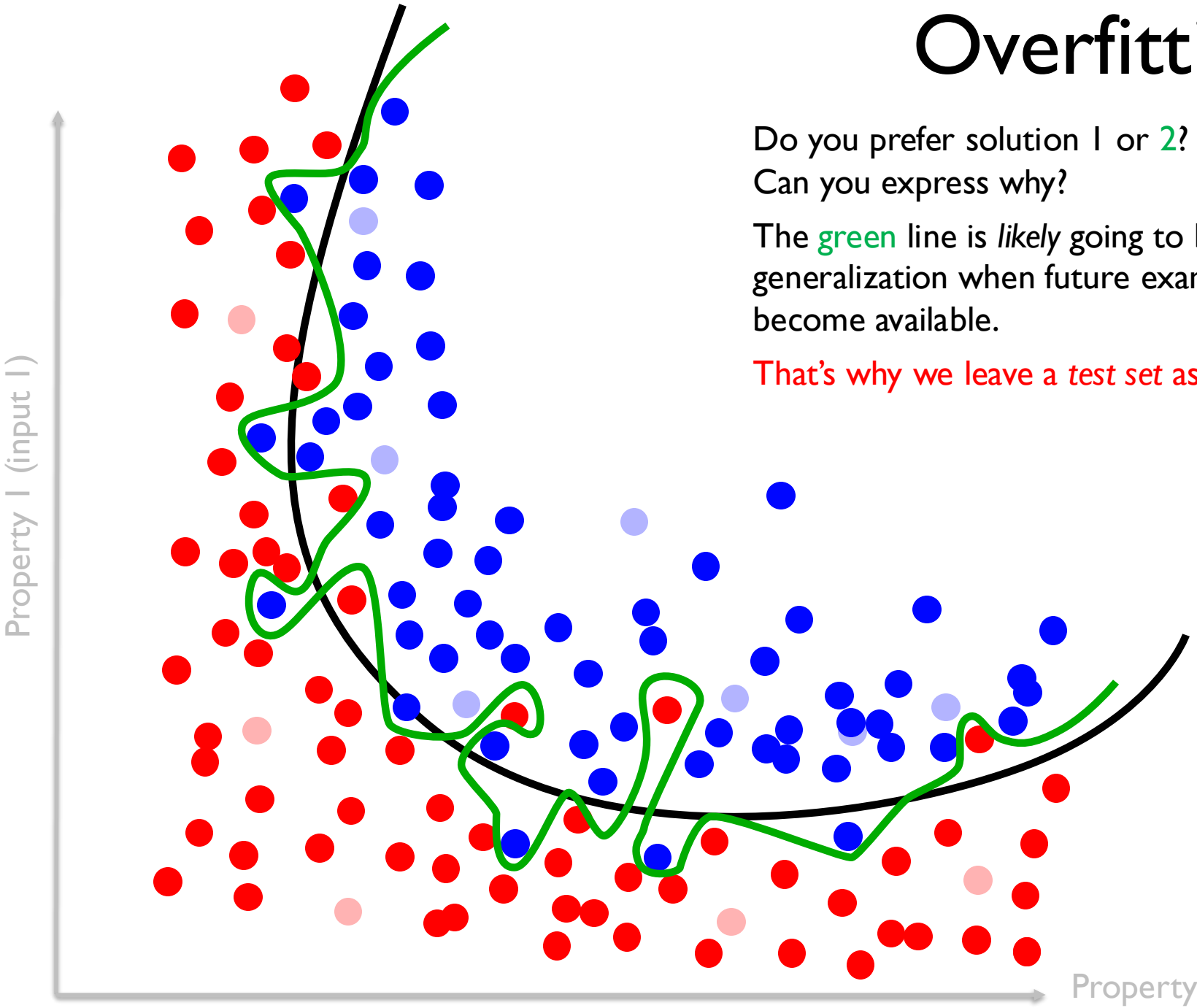


Do you prefer solution 1 or 2?
Can you express why?

The green line is *likely* going to be a bad generalization when future examples become available.

https://en.wikipedia.org/wiki/Overfitting

Overfitting



Do you prefer solution 1 or 2?
Can you express why?

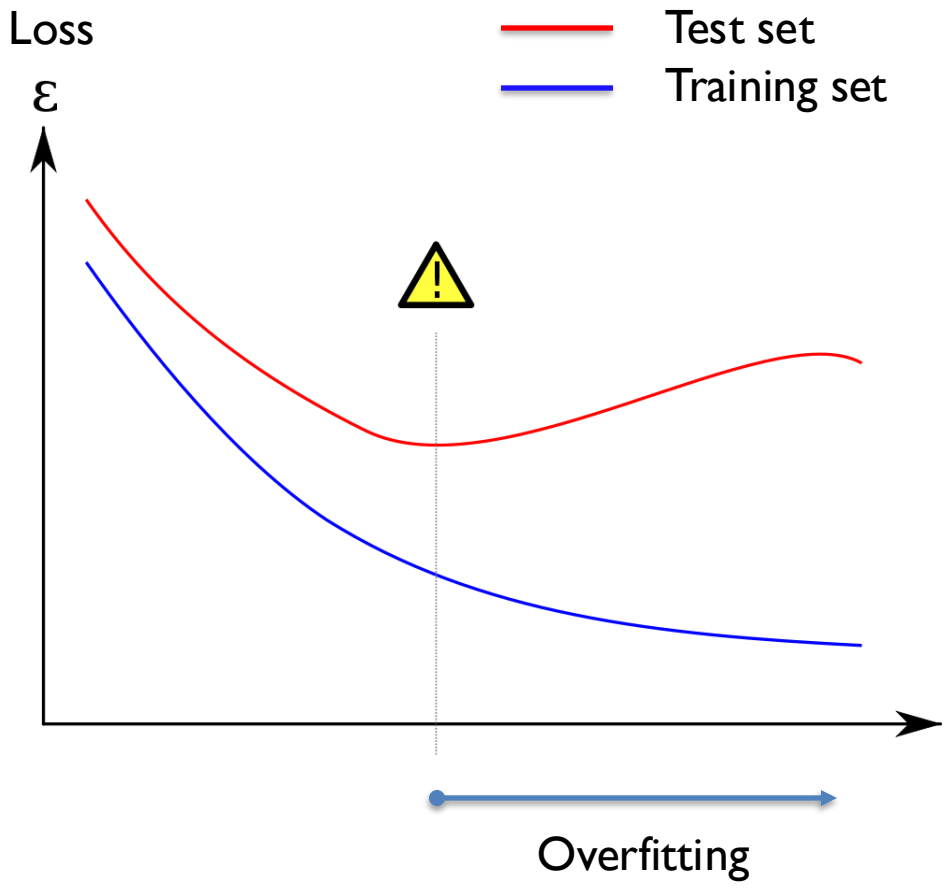
The green line is *likely* going to be a bad generalization when future examples become available.

That's why we leave a *test set* aside.

https://en.wikipedia.org/wiki/Overfitting

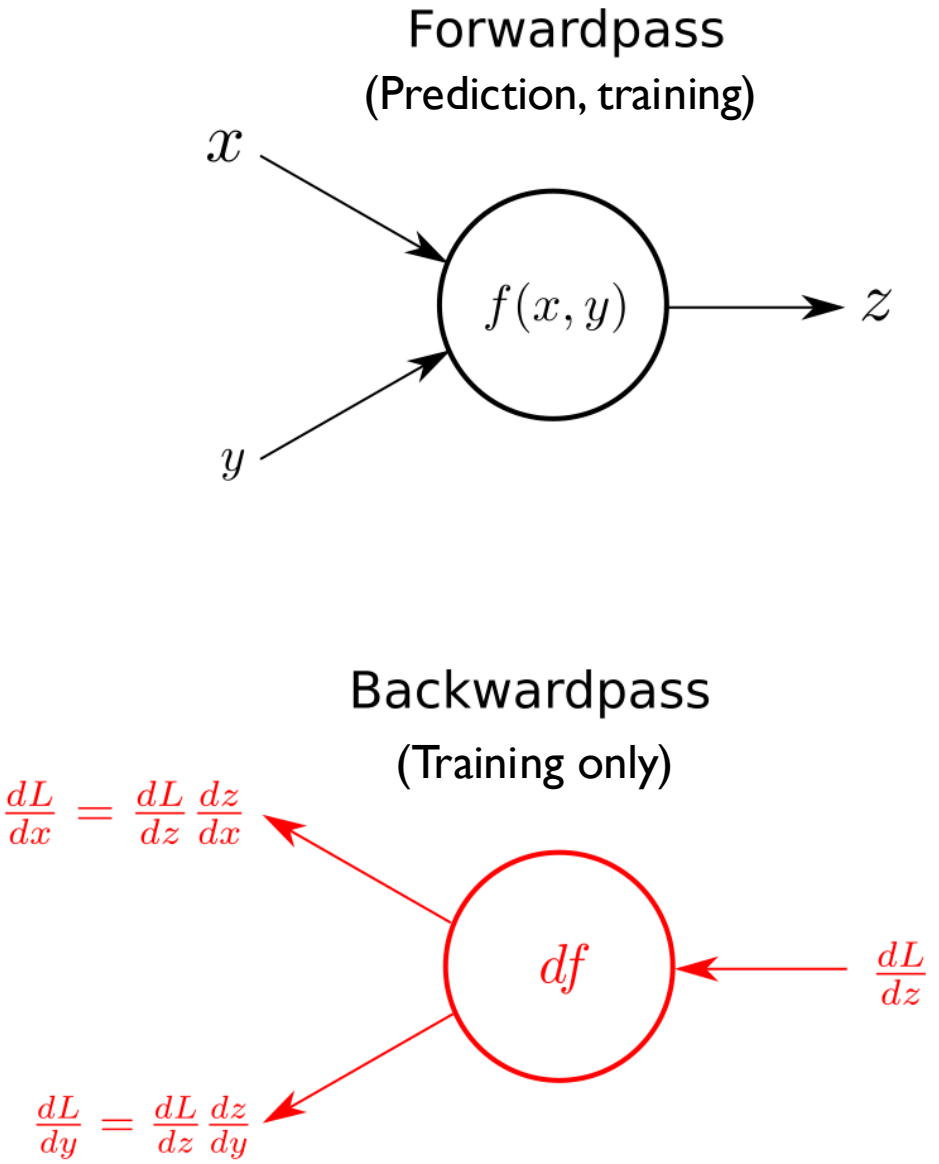
Training and stopping

- In practice, one computes the loss function on both the training set and the testing set, separately
- Uses the error on the training set to optimize parameters
- Training stops when loss on test set is minimized



Backpropagation

- The weights are adjusted in the direction that decreases the error on the test set
- BP is an algorithm determining how *each* training example would nudge the weights towards the most rapid decrease of the loss funtion
- Gradient/stochastic gradient descent (SGD) algorithms
- Illustration: www.3blue1brown.com/nn3-thanks

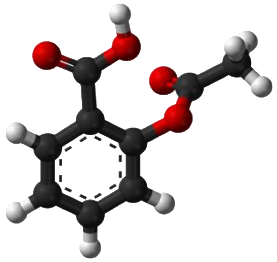


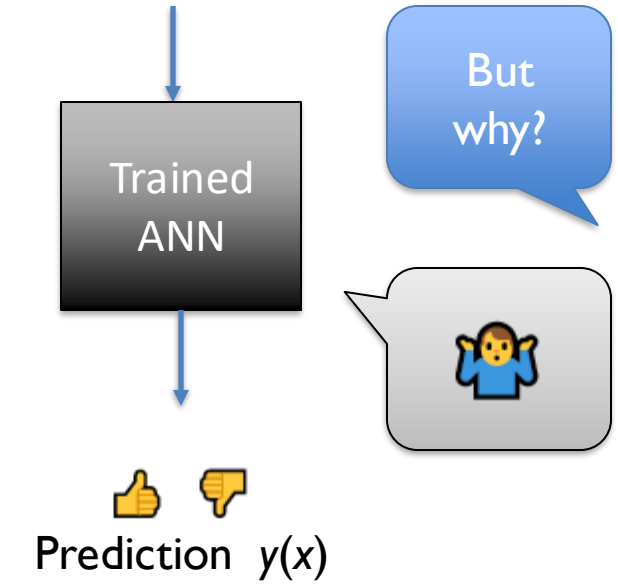
https://kratzert.github.io/2016/02/12/understanding-the-gradient-flow-through-the-batch-normalization-layer.html

Interpretability

I.e. try to recover the theory/logic behind the rules

- A simple *regression*, once trained, may hold useful information in its parameters
  - E.g.: predict toxicity from K_D's on various targets. What's ΔLD50 due to 1 ΔK_D of each target?
- ANNs (esp. if large) behave as "black boxes".
  - Will provide (hopefully) useful predictions, but you won't learn easily from them.
- Interpretability of ML models is problematic (with ethical implications too!).





Featurization

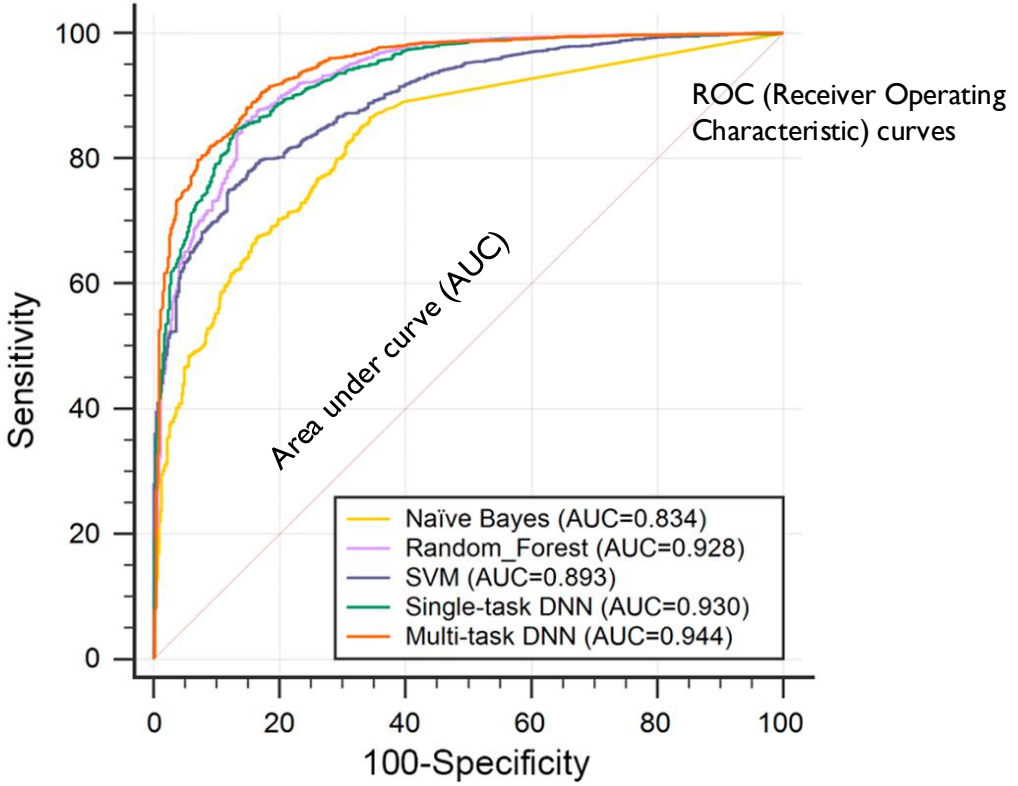
- What if the inputs are not a set of real numbers?
- We need to devise a *featurization* to convert arbitrary objects to (fixed length) vectors
  - Chemical topologies
  - Structures
  - Protein surfaces
  - Images…

Commonly-used features in proteomics / chemoinformatics:

- Sequences
- Grids (voxels)
- Molecular descriptors, fingerprints (binary or not)
- SMILES strings
- Graph-based models

Evaluation of (binary) classifiers

Prediction \ Reality	P	N
P	TP	FP
N	FN	TN



$$SE = \frac{TP}{TP + FN}$$ *Sensitivity*: fraction (%) real P's I caught

$$SP = \frac{TN}{TN + FP}$$ *Specificity*: fraction real N's I caught

$$Q+ = \frac{TP}{TP + FP}$$ *Pos. pred. accuracy*: fraction of my P's were correct

$$Q- = \frac{TN}{TN + FN}$$ *Neg. pred. accuracy*: fraction of my N's were correct

$$Q = \frac{TP + TN}{TP + FN + FP + TN}$$ *Overall pred. acc.*: fraction of my preds. were correct

Software

- The concepts are relatively easy…
- …implementation (e.g. gradients) is not
- Many software packages
  - PyTorch
  - Keras
  - TensorFlow
  - …

- Essentially you
  - describe the network topology (in code!)
  - Supply the examples
  - Run training
- Serious training requires GPUs

Part II

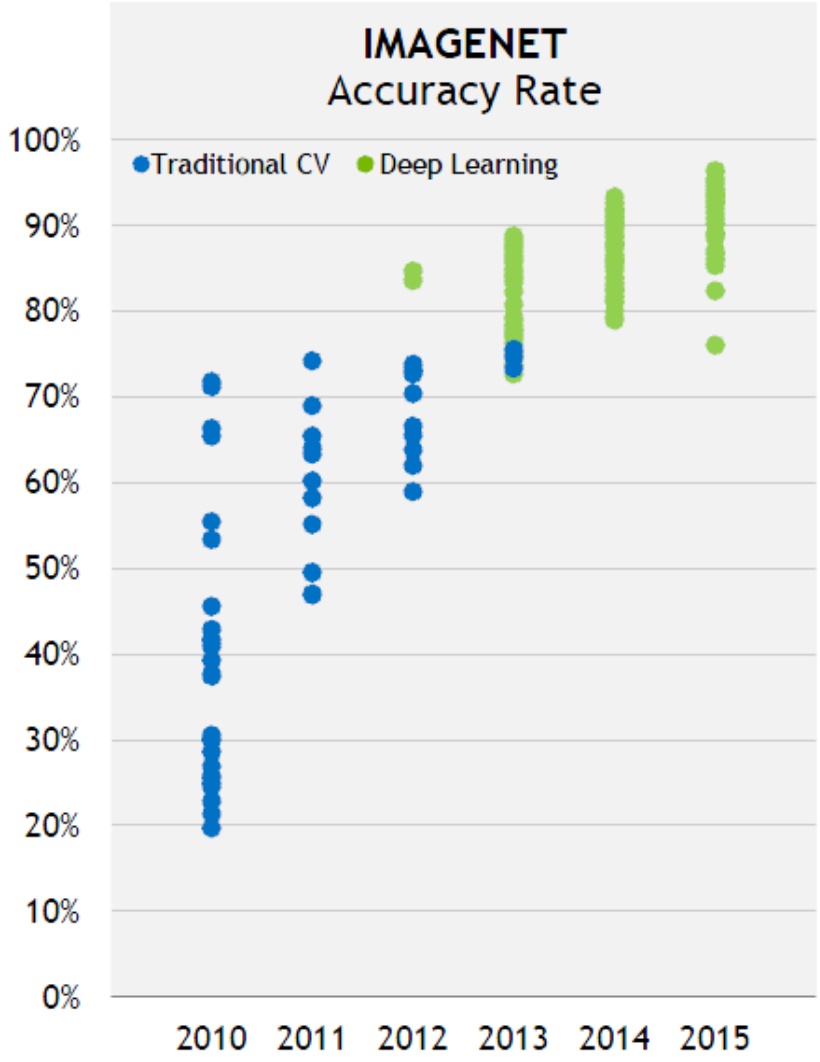
Advanced ANN architectures

Modularity and training

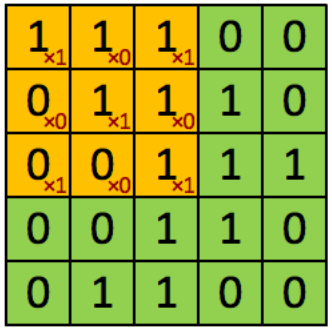
- ANNs with > 2-3 hidden layers are called *deep*.
  - In principle they may learn more "abstract" concepts
  - However, lots of data and computing power is needed.
- Architectures have become very varied…
- …but all of them rely on the concept of *finding the weights that minimize the loss function*
- Let's review some recent "famous" topologies (because they were successful).

Convolutional NNs (CNNs)

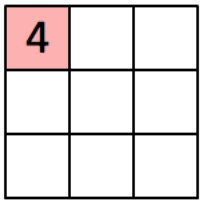
- Featurization is a problem. How to be sure to have the "best" features?
- → *Learn them*
- CNNs work "naturally" with spatially-correlated and translation-invariant problems, e.g. *images*.



Convolution operation



Image



Convolved Feature

Result for filter F1, for the given channel.

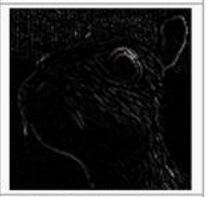
Will be processed with further convolutions!

1	0	1
0	1	0
1	0	1

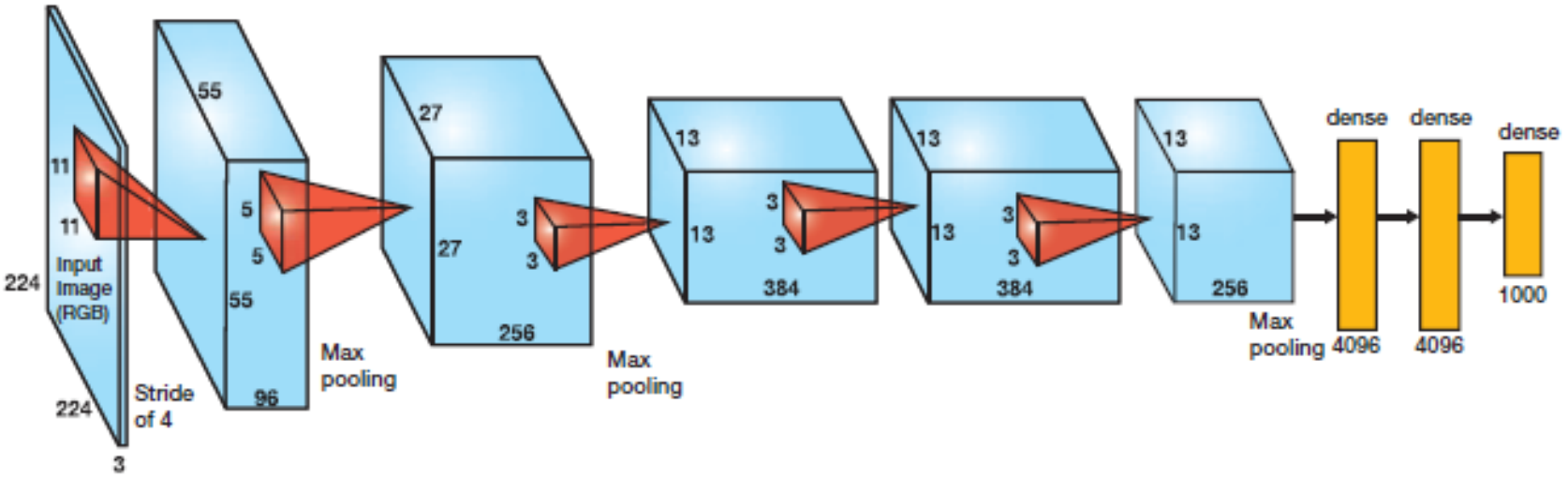
Convolution filter weights (will be trained)

Another illustration: https://youtu.be/Oqm9vsf_hvU?t=263

- Convolution weights are learned during the training process
- The most "useful" preprocessings for the given task (see aside) will emerge from the training
- Automatic feature selection

Operation	Filter	Convolved Image
Identity	$\begin{bmatrix} 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{bmatrix}$	
Edge detection	$\begin{bmatrix} 1 & 0 & -1 \\ 0 & 0 & 0 \\ -1 & 0 & 1 \end{bmatrix}$	
	$\begin{bmatrix} 0 & 1 & 0 \\ 1 & -4 & 1 \\ 0 & 1 & 0 \end{bmatrix}$	
	$\begin{bmatrix} -1 & -1 & -1 \\ -1 & 8 & -1 \\ -1 & -1 & -1 \end{bmatrix}$	
Sharpen	$\begin{bmatrix} 0 & -1 & 0 \\ -1 & 5 & -1 \\ 0 & -1 & 0 \end{bmatrix}$	
Box blur (normalized)	$\frac{1}{9}\begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix}$	
Gaussian blur (approximation)	$\frac{1}{16}\begin{bmatrix} 1 & 2 & 1 \\ 2 & 4 & 2 \\ 1 & 2 & 1 \end{bmatrix}$	

Example



AlexNet, 2012 ImageNet classification winner.

Hinton et al., NIPS 2012 paper #4824

[PDF] Imagenet classification with deep convolutional neural networks

A Krizhevsky, I Sutskever… - Advances in neural …, 2012 - proceedings.neurips.cc

We trained a large, deep convolutional neural network to classify the 1.2 million high-resolution images in the ImageNet LSVRC-2010 contest into the 1000 different classes. On the test data, we achieved top-1 and top-5 error rates of 37.5% and 17.0% which is …

☆ 99 Citato da 83853 Articoli correlati Importa in BibTeX »

LeNet, 1998

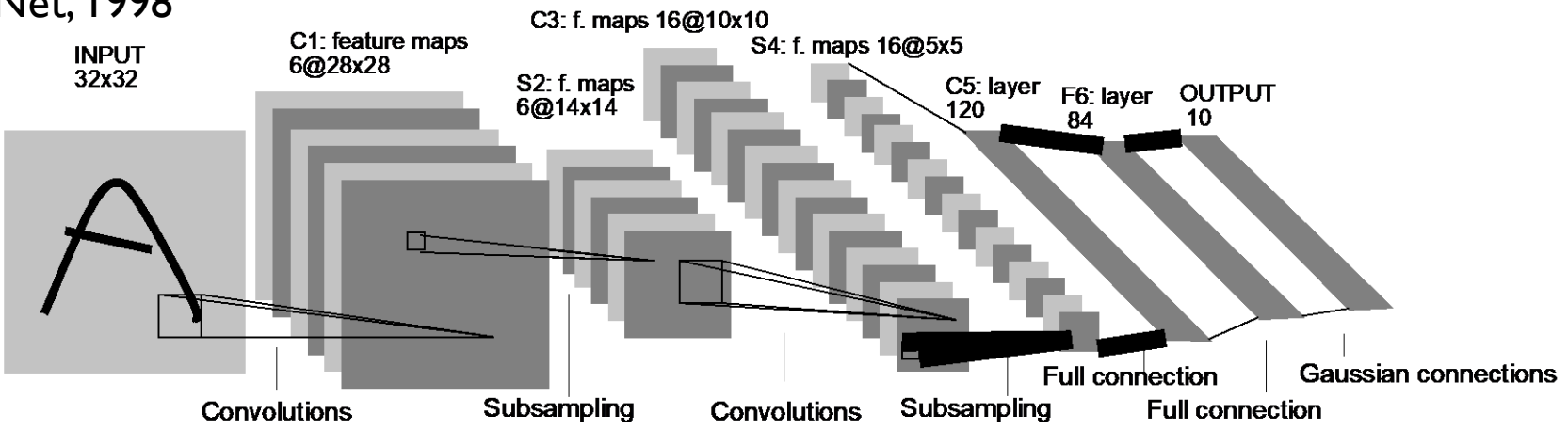
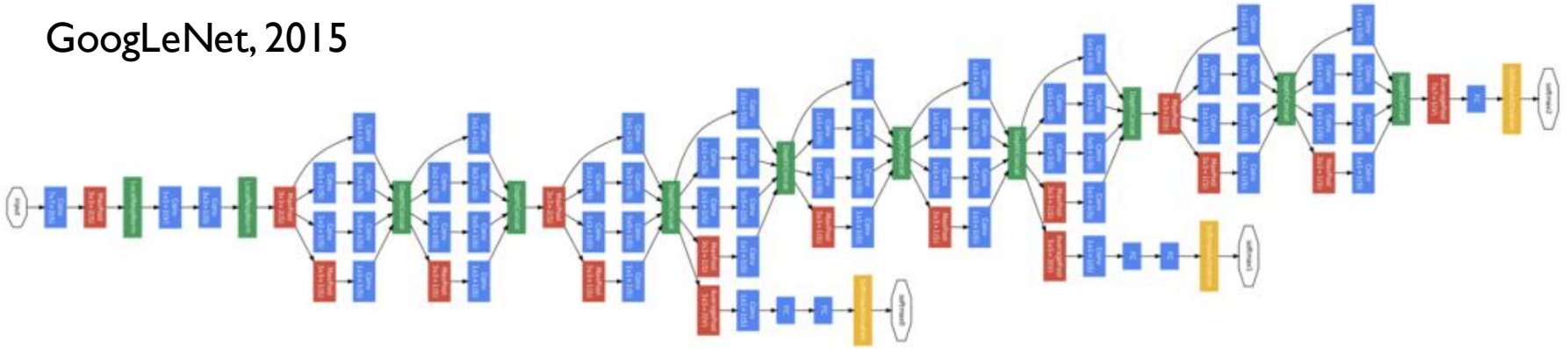


Fig. 2. Architecture of LeNet-5, a Convolutional Neural Network, here for digits recognition. Each plane is a feature map, i.e. a set of units whose weights are constrained to be identical.

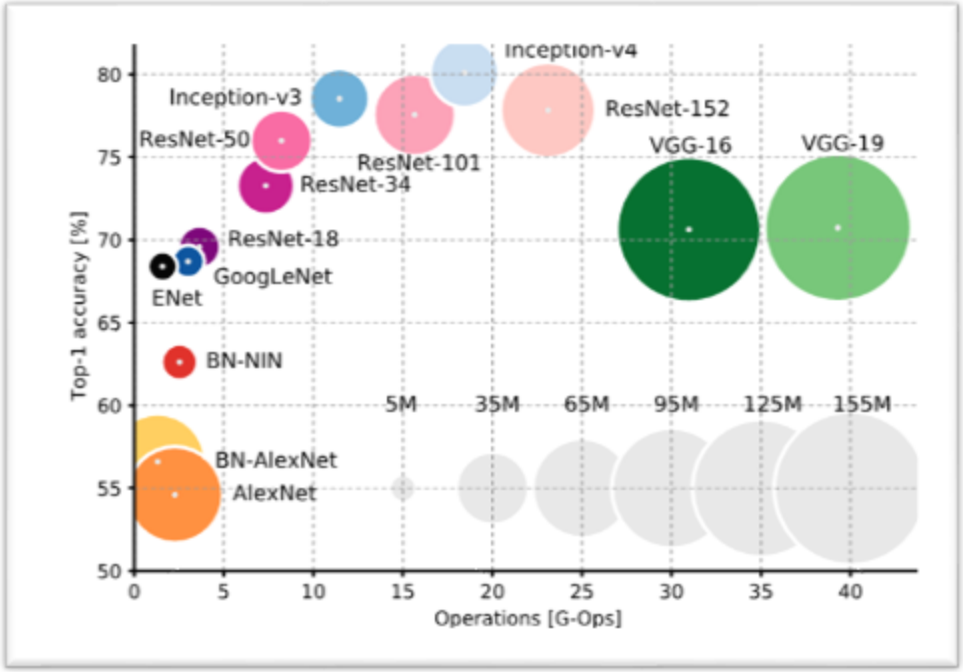
GoogLeNet, 2015



https://www.youtube.com/watch?v=Oqm9vsf_hvU

How complex can things become?

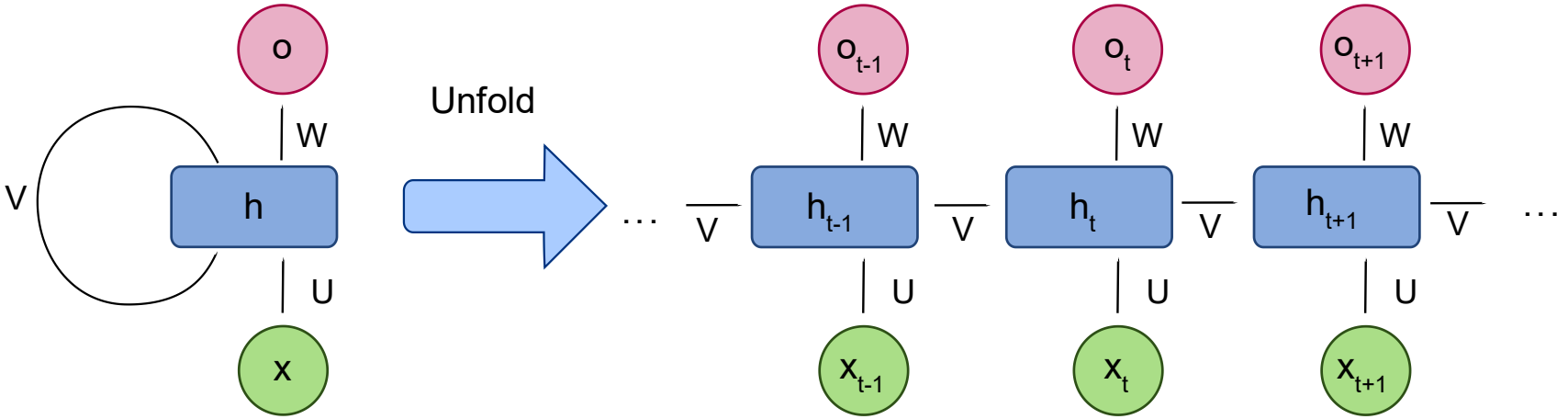
Year	CNN	Developed By	Error rates	No. of parameters
1998	LeNet	Yann LeCun et al		60 thousand
2012	AlexNet	Alex Krizhevsky, Geoffrey Hinton, Ilya Sutskever	15.3%	60 million
2013	ZFNet	Matthew Zeiler, Rob Fergus	14.8%	
2014	GoogLeNet	Google	6.67%	4 million
2014	VGGNet	Simonyan, Zisserman	7.3%	138 million
2015	ResNet	Kaiming He	3.6%	



Canziani et al., arXiv:1605.07678

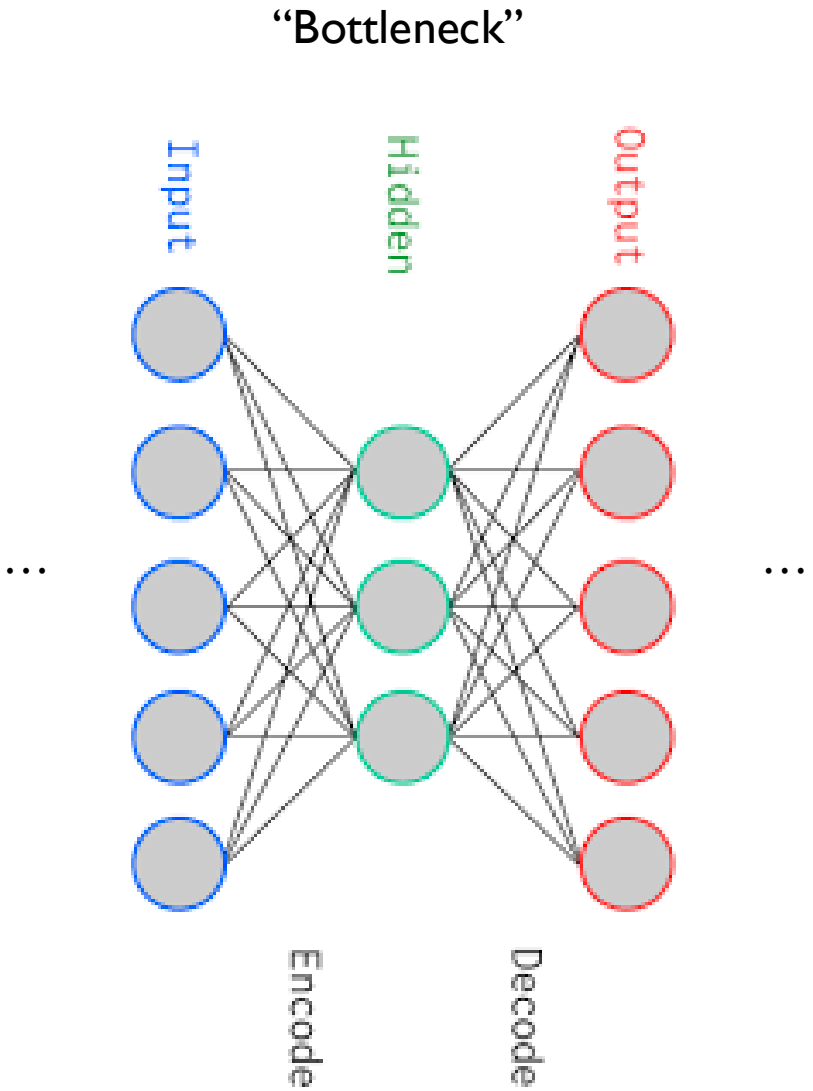
Recurrent NNs

- To address *time-varying* data, or sequences, we may feed the output of a neuron to itself in the next step.
- Inputs and outputs are sequences.
- Good for translation-like tasks.



Autoencoders

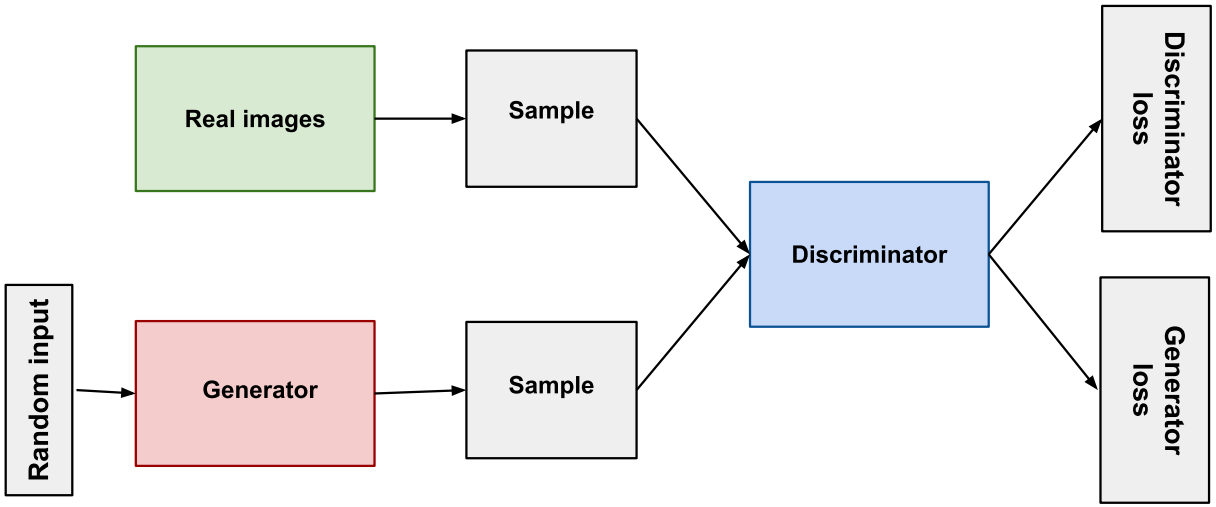
- "Force" the network to cut down information by creating a "funnel"
- Input is the same as output (loss is reproduction error)
- A dimensionality reduction technique



Generative Adversarial Networks

Goodfellow et al., 2014 16,000 citations

- Train *two* networks
  - the *generator* produces "fake" cases *from noise*
  - the *discriminator* must learn to tell fakes from actual examples
- Train simultaneously until convergence
- Used for "inventing" realistic molecules with given properties



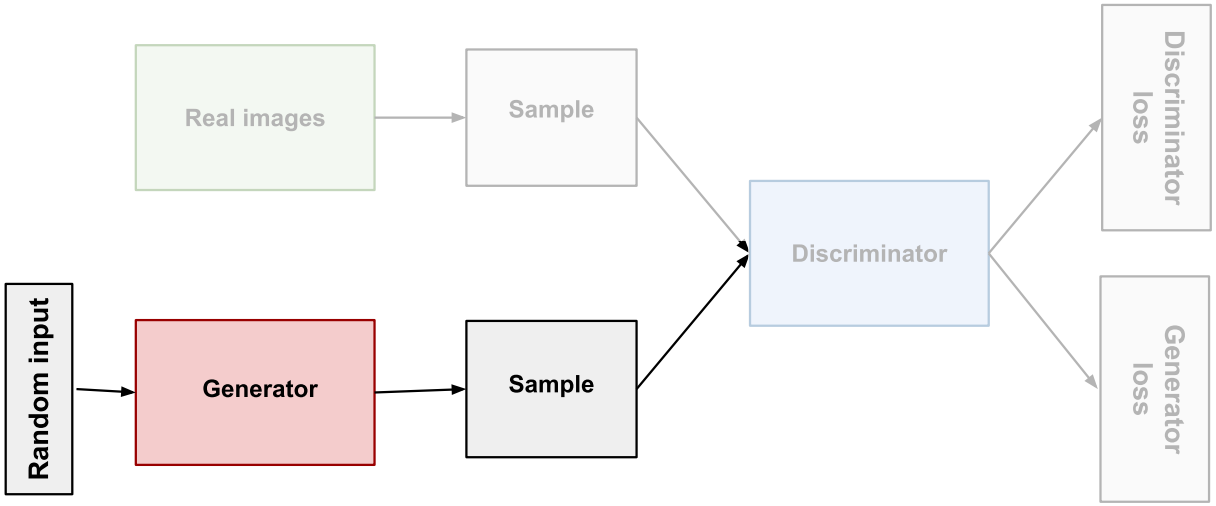
Generative Adversarial Networks

- Example: StyleGAN2
  - www.thispersondoesnotexist.com
  - www.whichfaceisreal.com

… ∞

Sampled from generator.

Idea (one of the many possible):
realistic faces → *molecules with given properties*

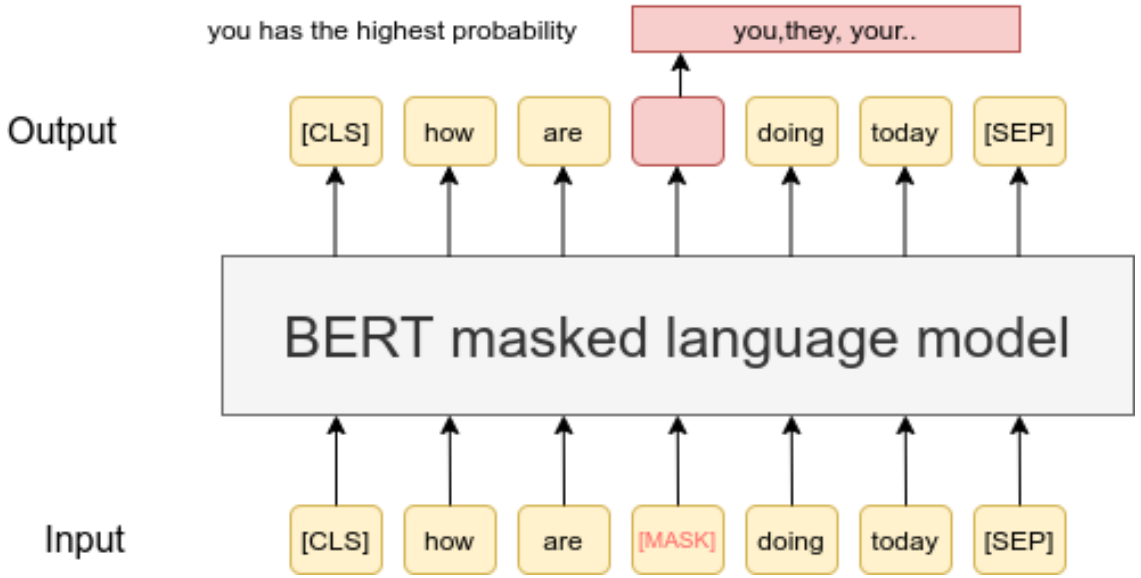


https://arxiv.org/abs/1912.04958

Transformers and self-attention

Bidirectional Encoder Representations from Transformers (BERT)

- In 2018 broke records in *many* natural-language tasks
  - Generation, understanding, summarization, translation…
  - Try @ huggingface.co/bert-base-multilingual-cased



- Google's - see https://arxiv.org/abs/1810.04805v2
- https://jalammar.github.io/illustrated-bert/

Attention heads

- Given *enough examples*, the network learns sequence and position-dependent features
- E.g. will learn to associate pronouns with the referenced object (~ language structure)
- "Attention mechanism"

The defining characteristic of the Transformer is its **attention** mechanism, which we'll illustrate with an example from natural language. Suppose we train a Transformer to predict the next word in a sentence – a task known as **language modeling**:

> *The girl kicked the ball into the woods. It* _____

For the model to guess a reasonable next word, e.g. "*rolled*", it must understand that "*it*" refers to "*ball*" (a relationship known as **coreference**). The Transformer does this by looking back at, or *attending to*, the earlier mention of "*ball*" when processing "*it*":

https://blog.einstein.ai/provis/

Transformer-based models for protein sequences

(a)

PRIMARY

MKLPIYTRF
GVNCSWQA
AIPLMN...

amino acids

ABCDEFGHIJKLMNO
PQRSTUVWXYZ

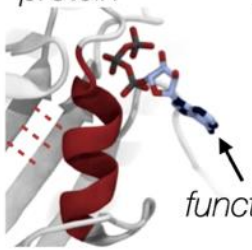
alphabet

SECONDARY

Jane
bicycle
ride

TERTIARY

protein



function

Jane rides her bicycle

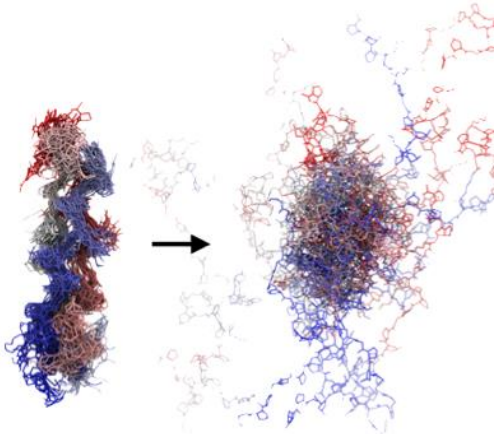
meaning

QUATERNARY

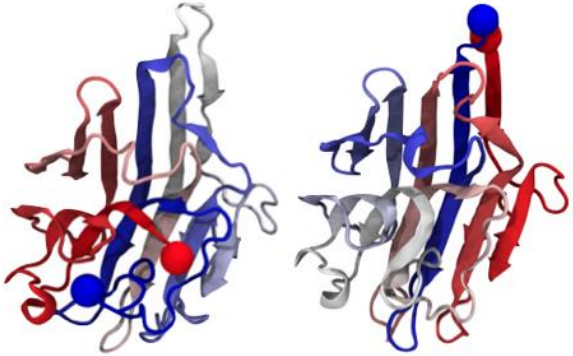
Jane rides her bicycle to school. But always with a big bright light and a helmet …

(b)

Your manuscript is now~~t~~ publishable



I am happy when it rains. When it rains, I am happy.



Colourless green ideas sleep furiously.

amyloid fibril

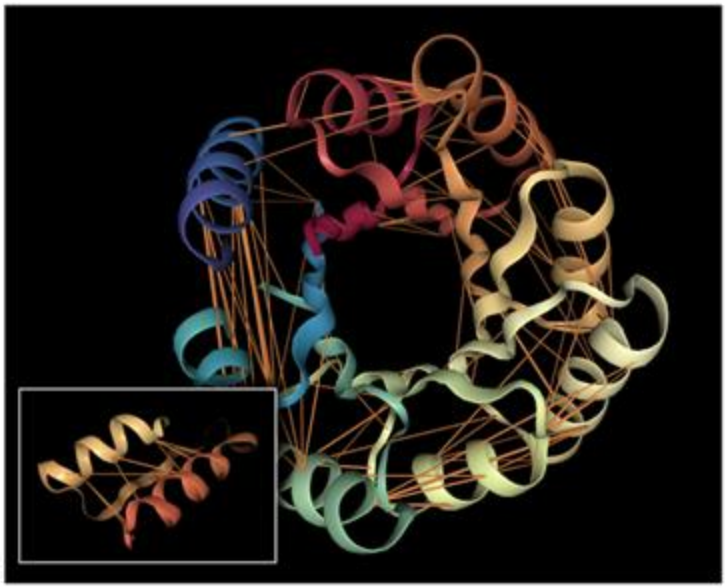
Ferruz et al., Nat Mach Int, 2022

Transformer-based sequence analysis

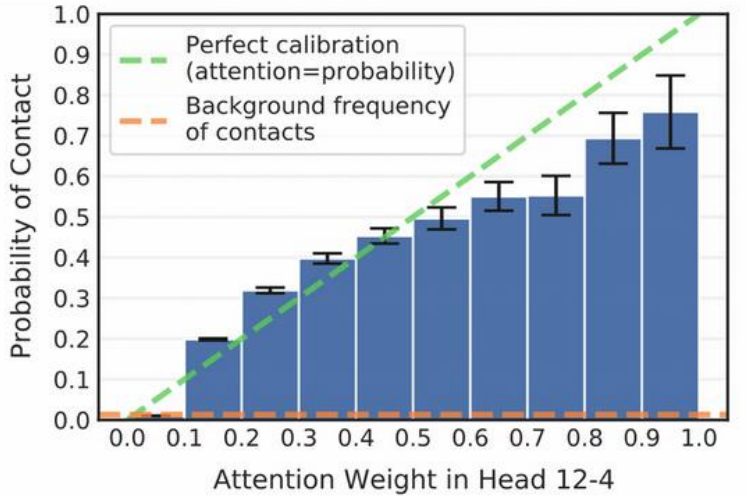
- **ProteinBERT**
- **BERTology** (Salesforce Research)
- UDSMProt
- ESM* (Facebook)
- UniRep
- TAPE
- ProtTrans (ProtBERT)

* Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences

BERTology



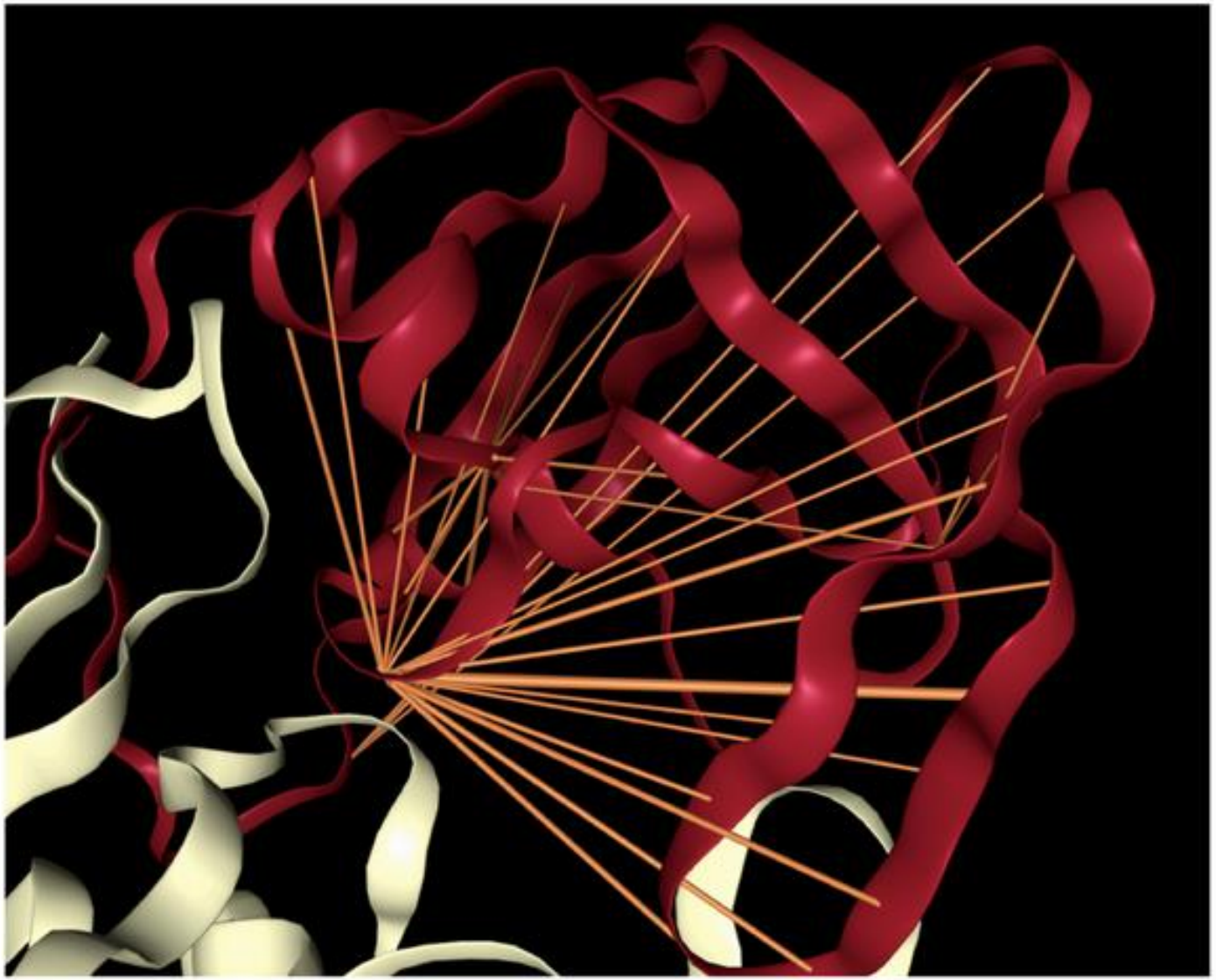
Head 12-4 has learned to focus attention (indicated by orange lines) between amino acids that are spatially close in the folded protein structure (see inset subsequence 117D-157I) but lie apart in the sequence, based solely on language model pre-training. The example is a *de novo* designed TIM-barrel. 76% of high-confidence (>0.9) attention from this head aligns with ground-truth contact maps on average over a dataset.



Probability that two amino acids are in contact [95% confidence intervals], as a function of attention between the amino acids in Head 12-4, showing attention approximates a perfectly-calibrated estimator

arXiv:2006.15222
github.com/salesforce/provis

https://blog.einstein.ai/provis/



Head 7-1 has learned to focus attention (indicated by orange lines) on binding sites, a key functional component of proteins. Example is HIV-1 protease (7HVP). The primary location receiving attention is 27G, a binding site for protease inhibitor small-molecule drugs. 44% of high-confidence (>0.9) attention from this head focuses on binding sites on average over a dataset.

ProteinBERT: A universal deep-learning model of protein sequence and function

doi:10.1101/2021.05.24.445464

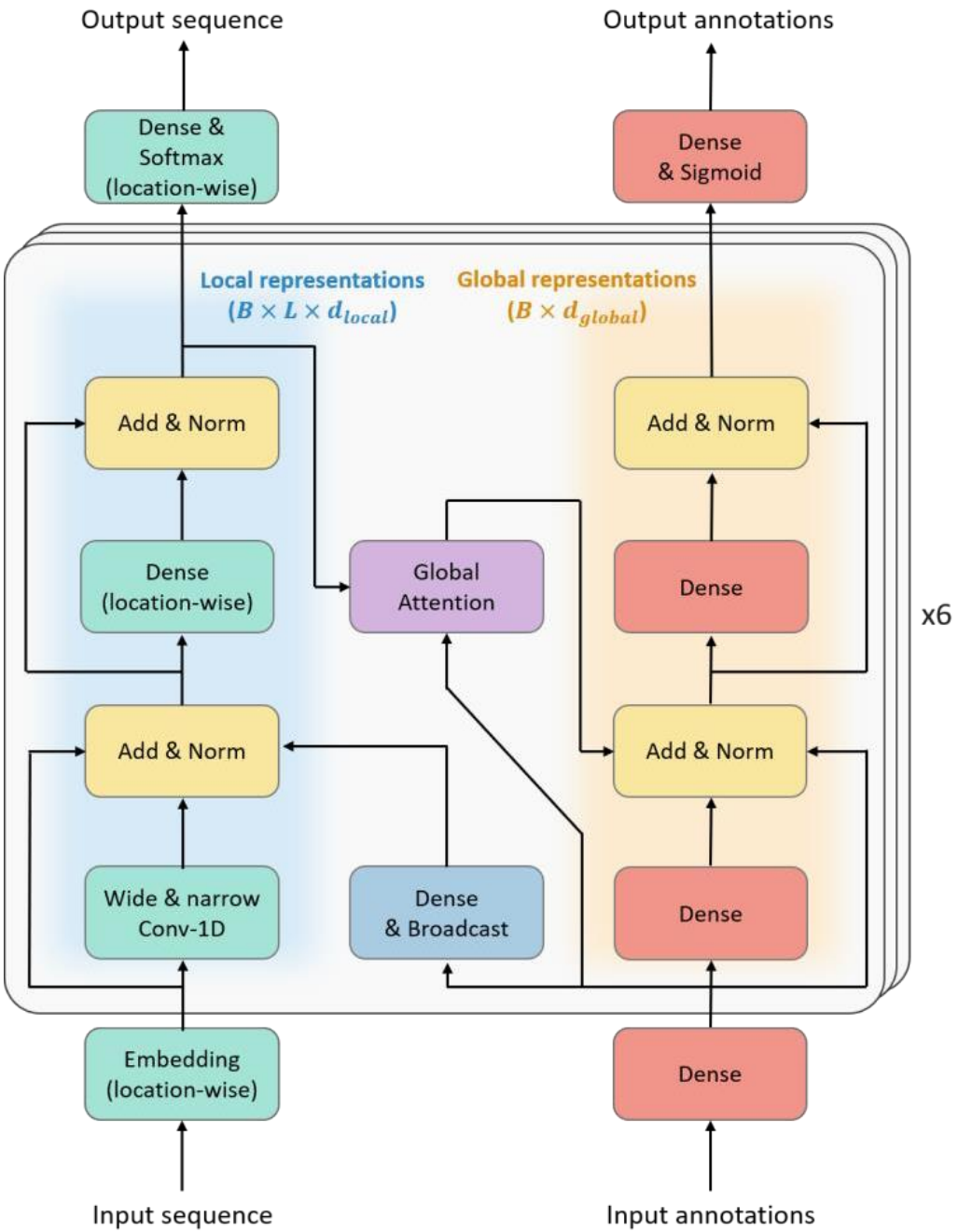
https://github.com/nadavbra/protein_bert

Self-supervised deep language modeling has shown unprecedented success across natural language tasks, and has recently been repurposed to biological sequences. However, existing models and pretraining methods are designed and optimized for text analysis. We introduce ProteinBERT, a deep language model specifically designed for proteins. Our pretraining scheme consists of masked language modeling combined with a novel task of Gene Ontology (GO) annotation prediction. We introduce novel architectural elements that make the model highly efficient and flexible to very large sequence lengths. The architecture of ProteinBERT consists of both local and global representations, allowing end-to-end processing of these types of inputs and outputs. ProteinBERT obtains state-of-the-art performance on multiple benchmarks covering diverse protein properties (including protein structure, post translational modifications and biophysical attributes), despite using a far smaller model than competing deep-learning methods. Overall, ProteinBERT provides an efficient framework for rapidly training protein predictors, even with limited labeled data. Code and pretrained model weights are available at https://github.com/nadavbra/protein_bert.

"Exemplary" as it provides:

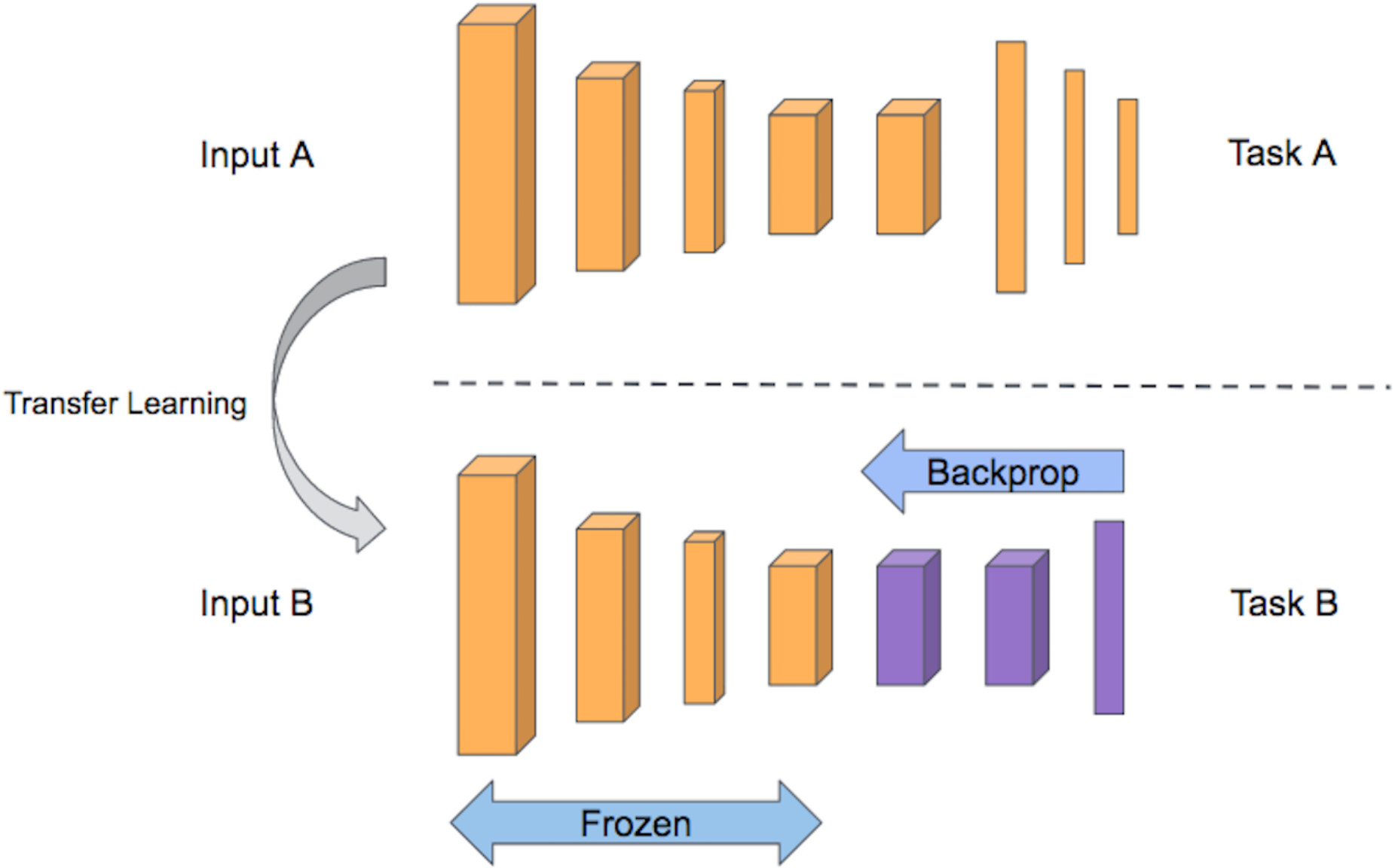
- Paper
- Code
- Model
- Weights
- Data!

Easy to *reproduce* and *repurpose*



doi:10.1101/2021.05.24.445464

Transfer learning



Topic	Benchmark	Target type[a]	Resolution	# Training sequences	Source
Protein structure	Secondary structure	Categorical (3)	Local	8,678	[21, 30]
	Disorder	Binary	Local	8,678	[30]
	Remote homology	Categorical (1,195)	Global	12,312	[21, 31, 32]
	Fold classes	Categorical (7)	Global	15,680	[31, 32]
Post-translational modifications	Signal peptide	Binary	Global	16,606	[33]
	Major PTMs	Binary	Local	43,356	[34]
	Neuropeptide cleavage	Binary	Local	2,727	[35–37]
Biophysical properties	Fluorescence	Continuous	Global	21,446	[21, 38]
	Stability	Continuous	Global	53,679	[21, 39]

[a]For categorical targets, the number of classes appears in parentheses.

Sequence examples

ftp://ftp.cs.huji.ac.il/users/nadavb/protein_bert/protein_benchmarks/*

- Global (signal peptide)

label,seq

0,MLGMIRNSLFGSVETWPWQVLSTGGKEDVSYEERACEGGKFATVEVTDKPVDEALREAMPKIMKYVGGTN

1,MQPAKNLLFSSLLFSSLLFSSAARAASEDGGRGPYVQADLAYAAERITHDYPKPTGTGKNKISTVSDYFR

0,MDKGEGLRLAATLRQWTRLYGGCHLLLGAVVCSLLAACSSSPPGGVKVVDRNGSAPAAARRTPVTSGQYI

...

- Local (secondary structure)

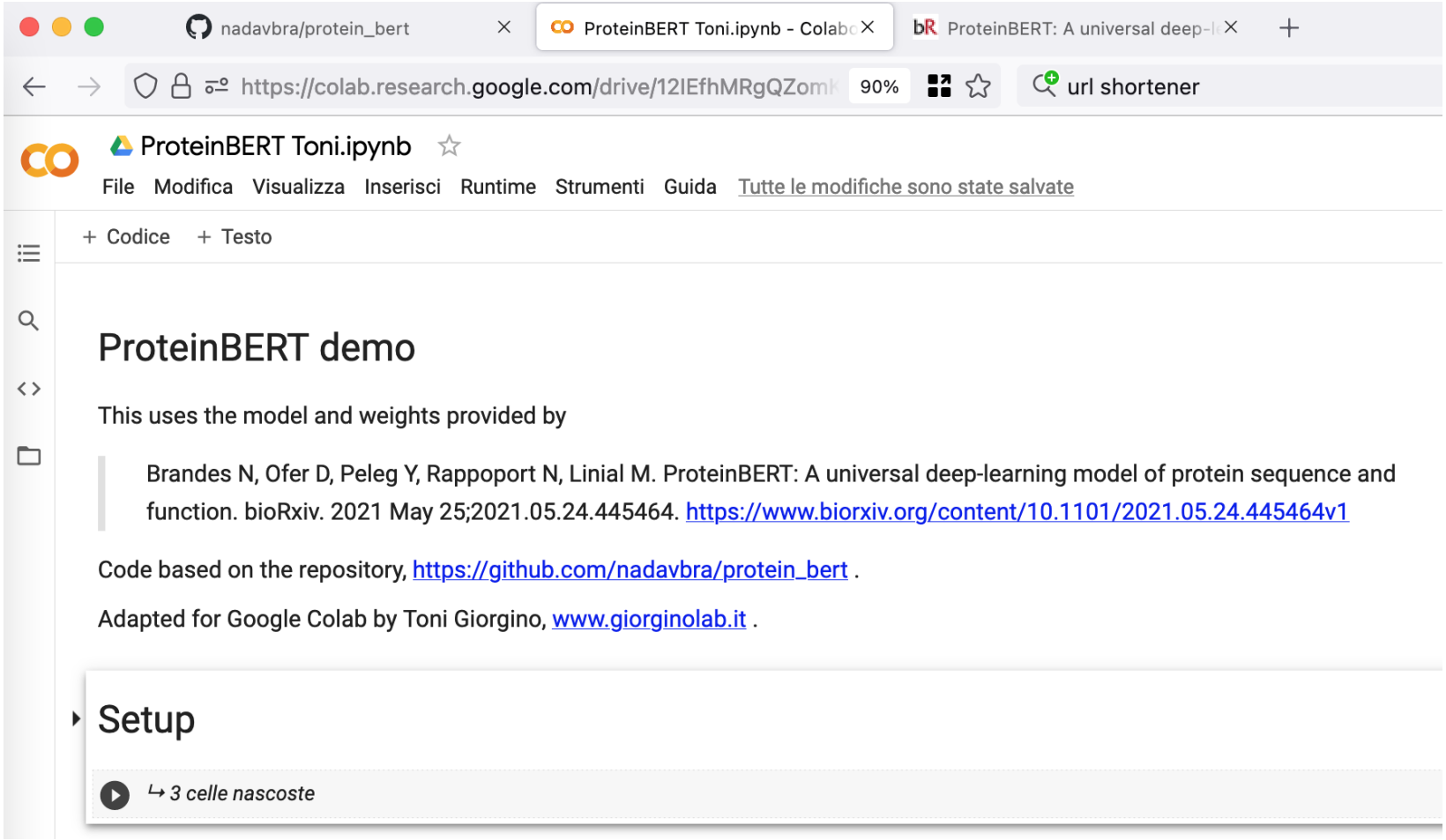
seq,label

MNDKRLQFNETLSKLILGGLRLRGISNSITDYQKLYKITFDAAEFTHRDELKRISMGSGEEVSFESLQETVETLLKLFTKSLEHHHHH
H,22222000000000000000022222222200000000000000002000000002222

22220000000000000022222222222

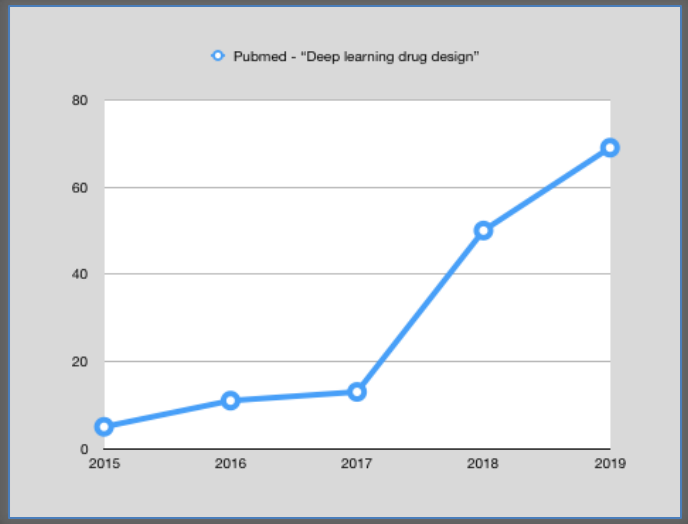
...

github.com/giorginolab/protein_bert
https://tinyurl.com/4xfswksu



Part III

Applications from the literature



Motivation for DNN in DD

- Can handle thousands of descriptors without selection
- Promise of increased classification accuracy
  - (Hope to reproduce the *exploit* achieved in image recognition)
- Will automatically trained features surpass "hand-crafted" ones?
- Tackle open problems such as precise K_D prediction

- Virtual screening
- Affinity prediction
- Affinity ranking
- Pose generation
- Pocket finding
- *De novo* generation
- Reaction plans

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

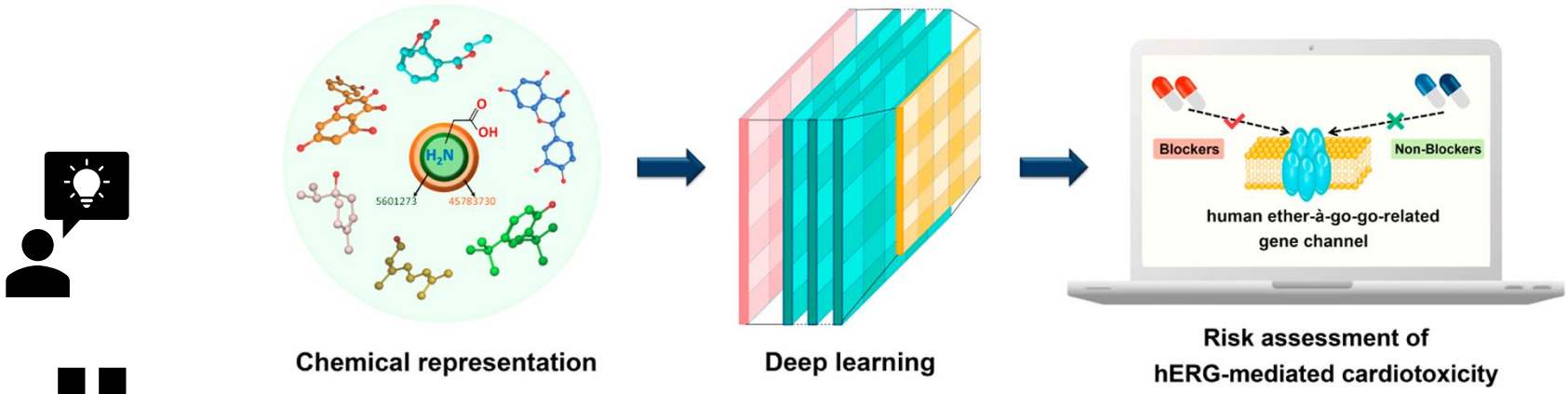
Cite This: J. Chem. Inf. Model. 2019, 59, 1073−1084

pubs.acs.org/jcim

deephERG

Deep Learning-Based Prediction of Drug-Induced Cardiotoxicity

Chuipu Cai,[†,‡] Pengfei Guo,[†] Yadi Zhou,[§] Jingwei Zhou,[†] Qi Wang,[†] Fengxue Zhang,[‡] Jiansong Fang,[*,†] and Feixiong Cheng[*,∥,⊥,#]



Data Preparation. The original compounds with experimental hERG blockage bioactivities were assembled from various well-defined experimental assays: (i) patch-clamp measurements from ChEMBL bioactivity database; (ii) radioligand binding measurements on mammalian and non-mammalian cell lines; (iii) hERG K^+ channel binding affinity, and (iv) literature-derived data (Supporting Information, **Table S1**).[25,28,29,34] We then implemented three criteria: (i) compounds without well-defined experimental hERG blocking bioactivities were eliminated; (ii) incompatible measuring units were converted to unified IC_{50} value (μM); (iii) only compounds with IC_{50} value $\leq$ 10 μM were considered as hERG blockers, while the rest were regarded as "decoy pool" for further screening according to different threshold settings. validating single 3D conformers. Finally, a comprehensive collection consisted of 7,889 compounds with well-defined experimental hERG blocking bioactivities was obtained, and 4,355 of the compounds whose experimental values were less than or equal to 10 μM were regarded as hERG blockers (Supporting Information, **Table S2 and Table S3**).

Subsequently, all compounds were split into three sets—training set, test set, and validation set—with ratios of 8:1:1 via chemical diversity analysis performed by Tanimoto Coefficient measure based on MACCS fingerprint in MOE 2010. Such a split would assign the chemical structures uniformly and avoid potential data bias. Following standard practice, the training

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Article
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deephERG

Deep Learning-Based Prediction of Drug-Induced Cardiotoxicity

Chuipu Cai,[†,‡] Pengfei Guo,[†] Yadi Zhou,[§] Jingwei Zhou,[†] Qi Wang,[†] Fengxue Zhang,[‡] Jiansong Fang,[*,†] and Feixiong Cheng[*,∥,⊥,#]

Descriptors:

- MOE (x 185)
- Mol2vec (x 100, "embeddings")

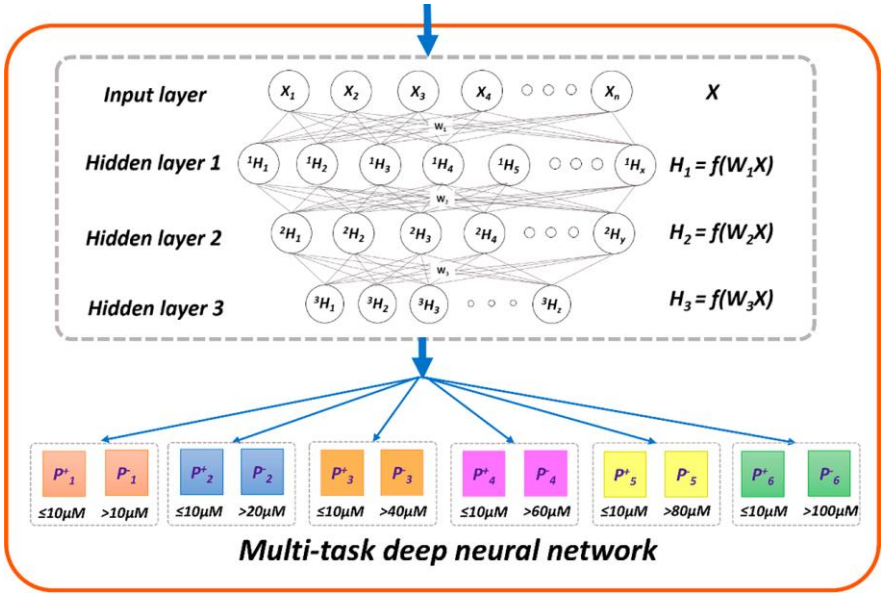


Table 1. Detailed Description of All Data Sets Used in This Stud

	training set			
threshold value of decoy (μM)	positive	negative	total	pc
10	3,485	2,826	6,311	
20	3,485	1,755	5,240	
40	3,485	863	4,348	
60	3,485	644	4,129	
80	3,485	469	3,954	
100	3,485	380	3,865	

Structural bioinformatics

DeepSite: protein-binding site predictor using 3D-convolutional neural networks

J. Jiménez[1], S. Doerr[1], G. Martínez-Rosell[1], A. S. Rose[2] and G. De Fabritiis[1,3,*]

[1]Computational Biophysics Laboratory (GRIB-IMIM), Universitat Pompeu Fabra, Barcelona Biomedical Research Park (PRBB), 08003 Barcelona, Spain, [2]San Diego Supercomputer Center, UC San Diego, MC 0505, 9500 Gilman Drive, La Jolla, CA 92093-0505. USA and [3]ICREA, 08010 Barcelona, Spain

*To whom correspondence should be addressed.

Associate Editor: Alfonso Valencia

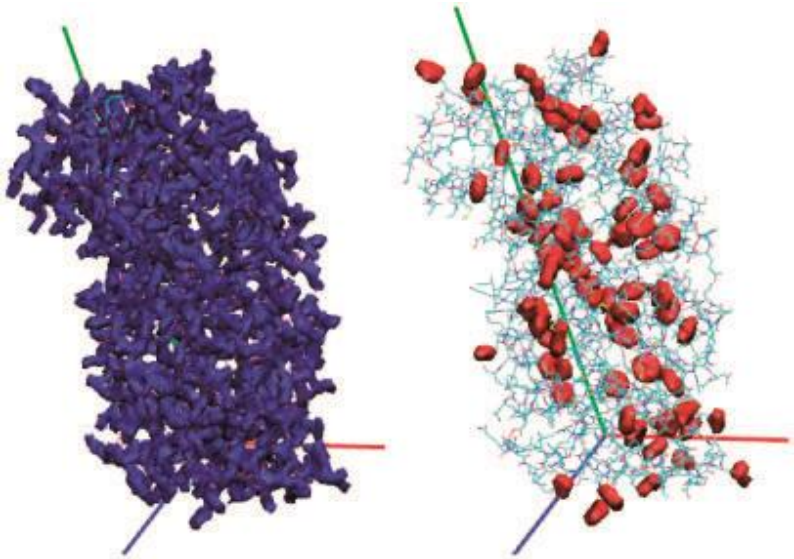
Received on January 10, 2017; revised on May 9, 2017; editorial decision on May 29, 2017; accepted on May 30, 2017

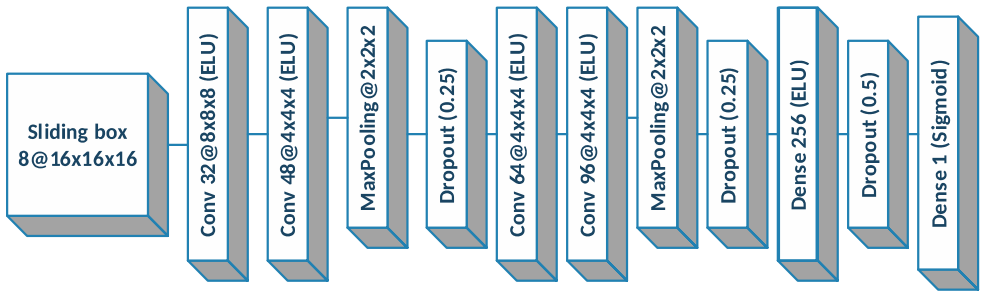
Bioinformatics, 33(19), 2017, 3036–3042
doi: 10.1093/bioinformatics/btx350
Advance Access Publication Date: 31 May 2017
Original Paper

OXFORD

Table 2. Property-atom type (AutoDock 4) correspondence used for Deepsite's 3D descriptor computation

Property	Rule
Hydrophobic	atom type C or A
Aromatic	atom type A
Hydrogen bond acceptor	atom type NA or NS or OA or OS or SA
Hydrogen bond donor	atom type HD or HS with O or N partner
Positive ionizable	atom with positive charge
Negative ionizable	atom with negative charge
Metal	atom type MG or ZN or MN or CA or FE
Excluded volume	all atom types





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www.playmolecule.org

Jimenez et al., Bioinformatics 2017

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

Cite This: J. Chem. Inf. Model. 2018, 58, 287−296

pubs.acs.org/jcim

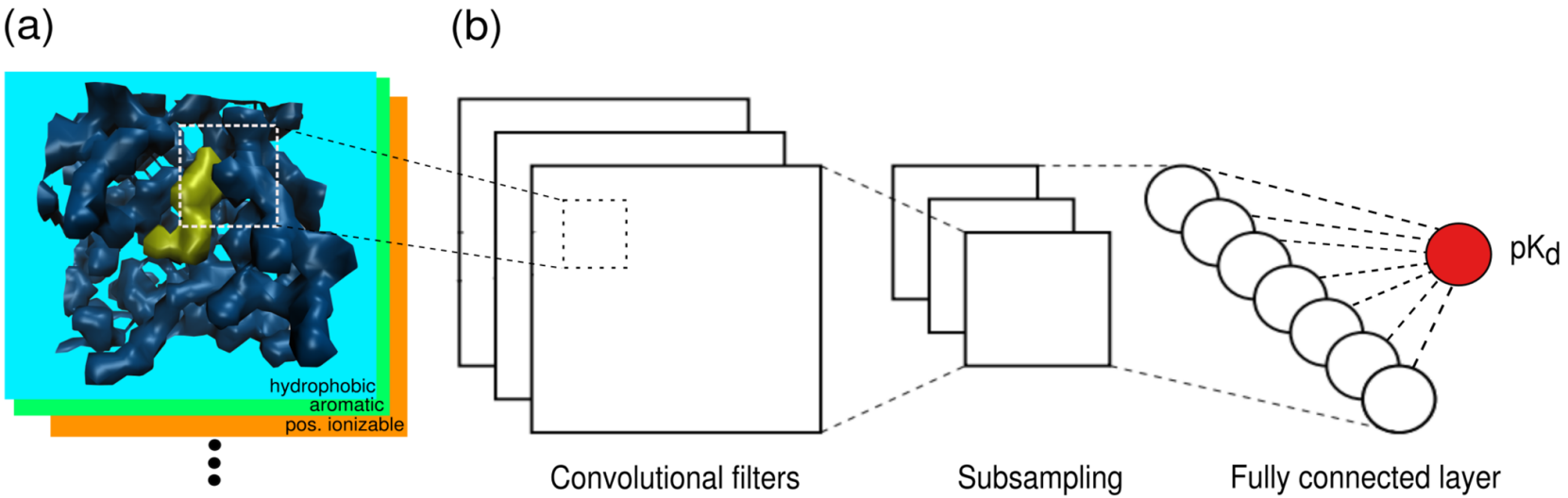
K_{DEEP}: Protein−Ligand Absolute Binding Affinity Prediction via 3D-Convolutional Neural Networks

José Jiménez,[†] Miha Škalič,[†] Gerard Martínez-Rosell,[†] and Gianni De Fabritiis*[,†,‡]

[†]Computational Biophysics Laboratory, Universitat Pompeu Fabra, Parc de Recerca Biomèdica de Barcelona, Carrer del Dr. Aiguader 88, Barcelona 08003, Spain

[‡]Institució Catalana de Recerca i Estudis Avançats (ICREA), Passeig Lluis Companys 23, 08010 Barcelona, Spain

Supporting Information



Cite this: *Chem. Sci.*, 2019, **10**, 10911

All publication charges for this article have been paid for by the Royal Society of Chemistry

DeltaDelta neural networks for lead optimization of small molecule potency†

José Jiménez-Luna, [a] Laura Pérez-Benito, [bc] Gerard Martínez-Rosell, [f] Simone Sciabola, [d] Rubben Torella, [e] Gary Tresadern [c] and Gianni De Fabritiis *[afg]

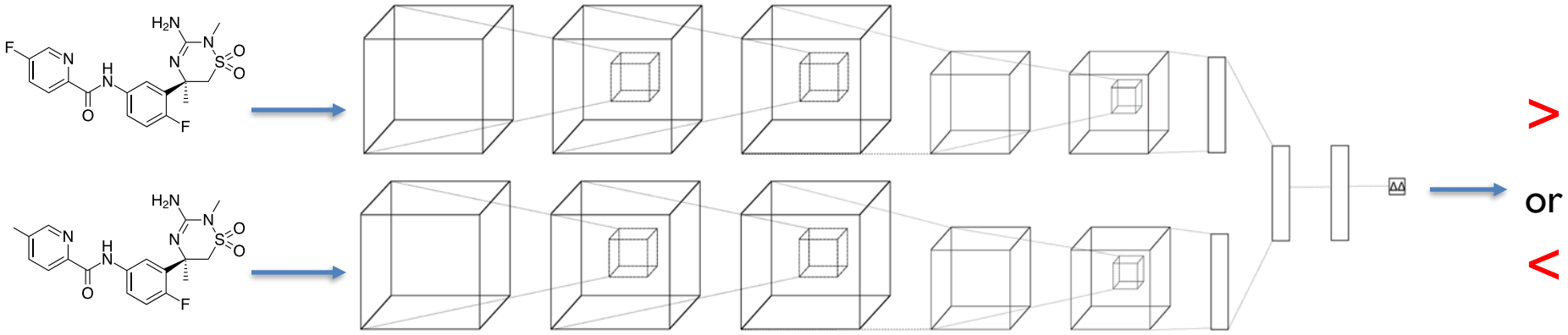


Fig. 1 Architecture of the proposed model. A two-legged neural network with tied weights was constructed, and a pair of protein–ligand voxelization is feed-forwarded through it to later perform a latent space difference.

Peptide generation via RNN

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

Cite This: *J. Chem. Inf. Model.* 2018, 58, 472–479

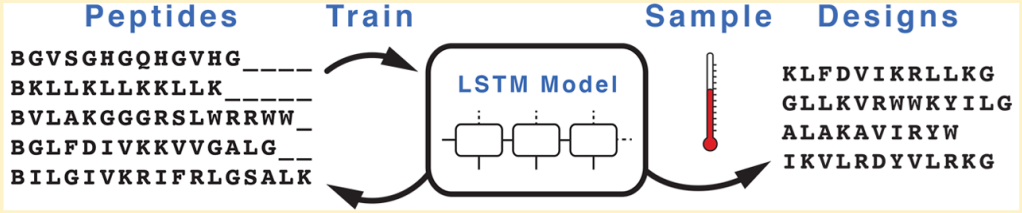
pubs.acs.org/jcim

Recurrent Neural Network Model for Constructive Peptide Design

Alex T. Müller, Jan A. Hiss, and Gisbert Schneider*

Swiss Federal Institute of Technology (ETH), Department of Chemistry and Applied Biosciences, Vladimir-Prelog-Weg 4, CH−8093 Zurich, Switzerland

Supporting Information

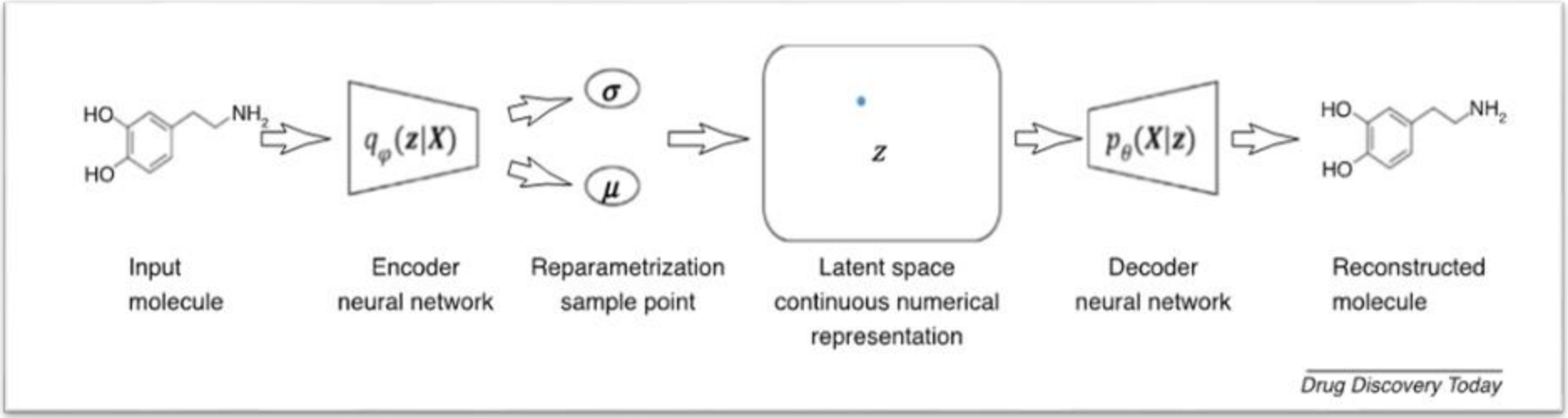


Training Data. We collected peptide sequences from the following three publicly accessible sources: "a database for antimicrobial peptides" (ADAM),[28] "antimicrobial peptide database" (APD),[29] and "database of Anuran defense peptides" (DADP).[30] The ADAM database contains sets of sequences for different secondary structures from which we extracted the helical AMPs (cluster ID: AC_003). From the APD, we retrieved all sequences annotated as "helical". We included the entire DADP peptide database. The majority of all of these

Also:
Grisoni et al., Chem Med Chem 2018

Structure generation via Variational Autoencoder (VAE)

1. Train an autoencoder
2. It will learn to project molecules in a continuous $\mathbb{R}^n$ (low n) space
3. Project a "lead" molecule
4. Perturb the projection
5. Decode



www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 7), pp: 10883-10890

Research Paper

The cornucopia of meaningful leads: Applying deep adversarial autoencoders for new molecule development in oncology

Artur Kadurin[1,2,3,4], Alexander Aliper[2], Andrey Kazennov[2,7], Polina Mamoshina[2,5], Quentin Vanhaelen[2], Kuzma Khrabrov[1], Alex Zhavoronkov[2,6,7]

Adversarial Autoencoder, AAE →

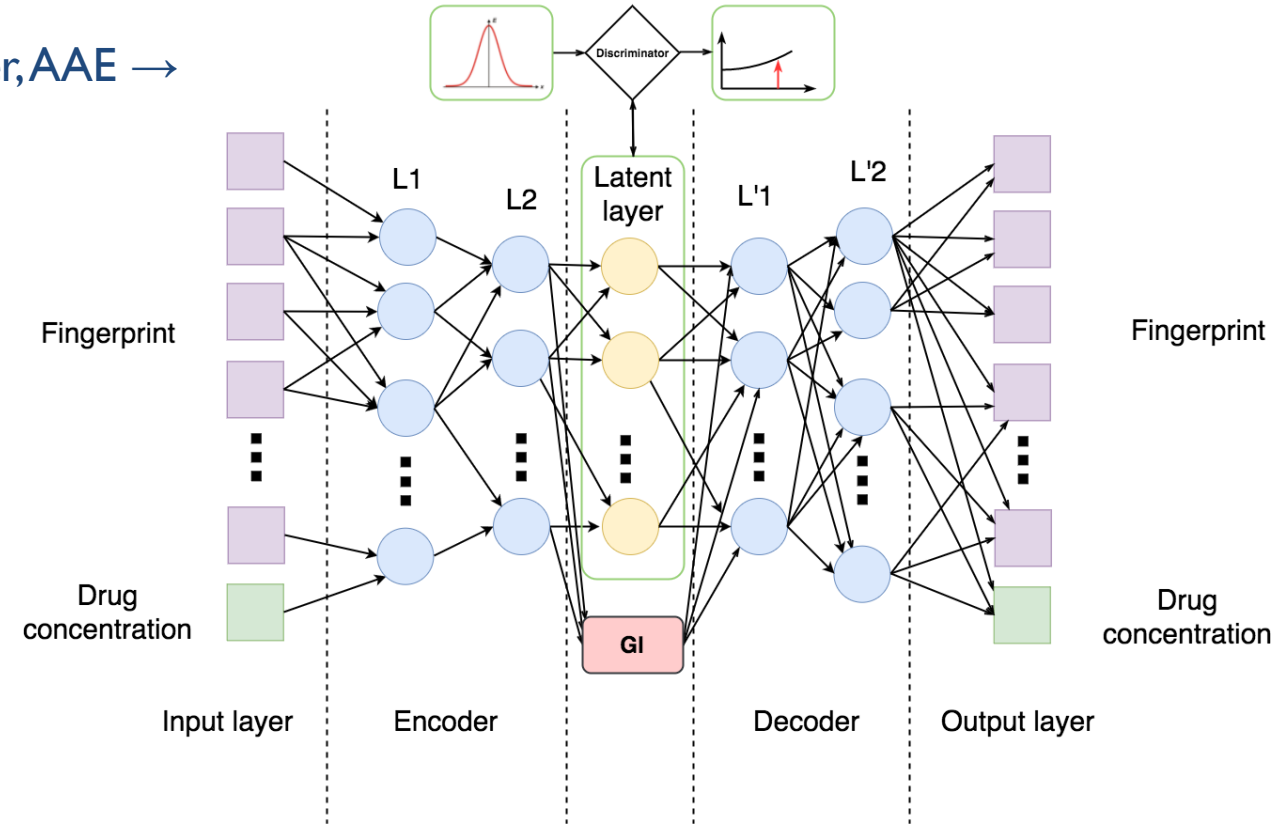
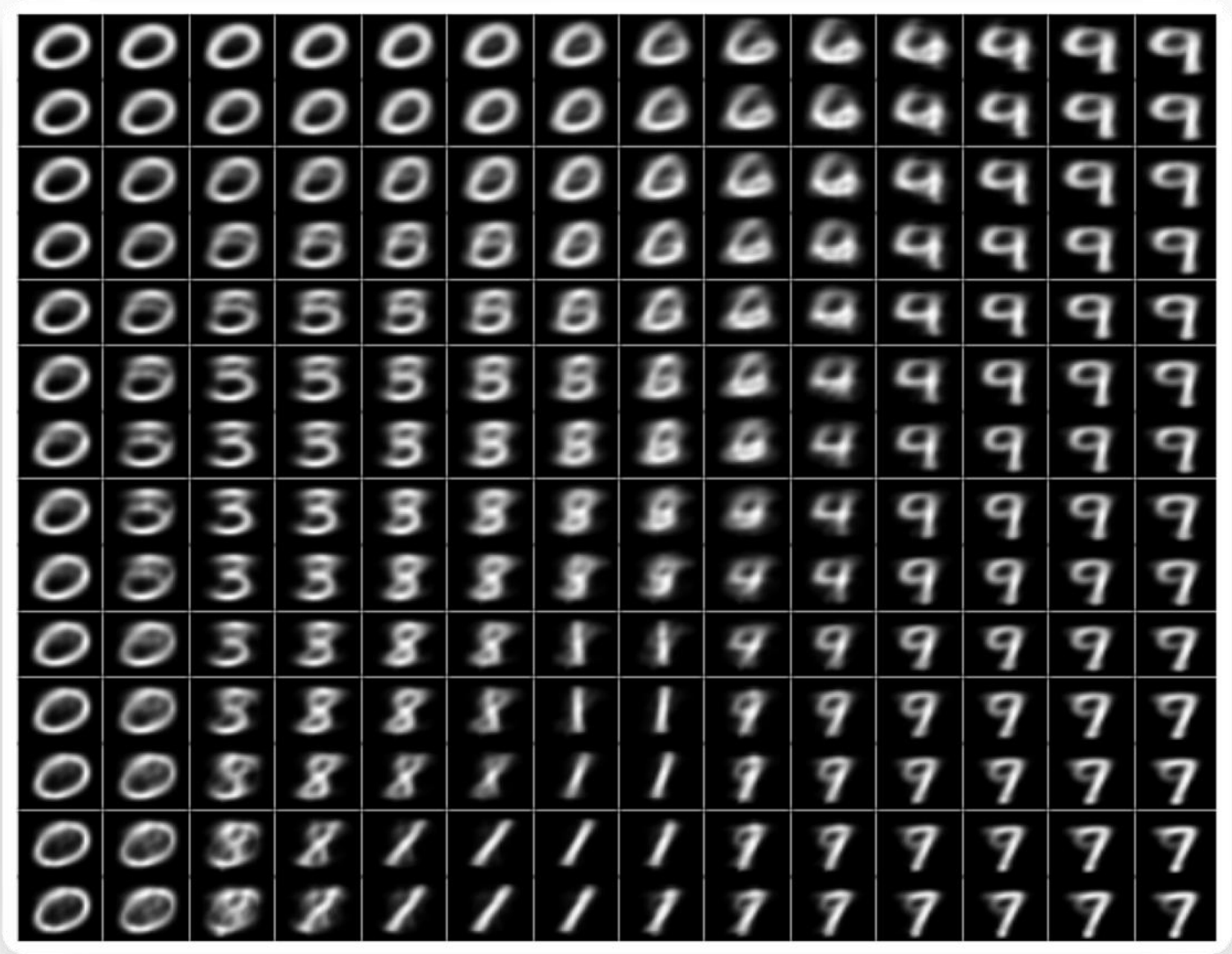


Figure 1: Architecture of Adversarial Autoencoder (AAE) used in this study. Encoder consists of two consequent layers L1 and L2 with 128 and 64 neurons, respectively. In turn, decoder consists of layers L'1 and L'2 comprising 64 and 128 neurons. Latent layer consists of 5 neurons one of which is Growth Inhibition percentage (GI) and the other 4 are discriminated with normal distribution.

Analogy:

molecular fingerprints	→ pixels
active candidates	→ handwritten digits
latent space	→ 2D plane



Latent axes may be made *meaningful* (Faceapp-like)*.

* See e.g. StyleGAN and "Face editing with GANs". Link. https://www.youtube.com/watch?v=dCKbRCUyop8

https://towardsdatascience.com/a-wizards-guide-to-adversarial-autoencoders-part-2-exploring-latent-space-with-adversarial-2d53a6f8a4f9

Role of simulation

- Time-consuming (compute intensive) methods may serve as inputs
- Examples:
  - QM to create classical FF
  - Classical all-atom FF to create coarse-grained potentials

SCIENTIFIC DATA

OPEN

Data Descriptor: ANI-1, A data set of 20 million calculated off-equilibrium conformations for organic molecules

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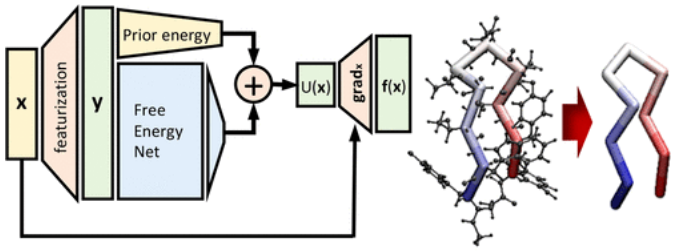
TorchMD: A Deep Learning Framework for Molecular Simulations

Stefan Doerr, Maciej Majewski, Adrià Pérez, Andreas Krämer, Cecilia Clementi, Frank Noe, Toni Giorgino, and Gianni De Fabritiis*



Real-world example: Merck's activity prediction competition

MERCK
Be well

Merck molecular activity challenge
on Kaggle

doi:10.1021/ci500747n

www.kaggle.com/c/MerckActivity

- The **Training** and **Test Sets** each consist of 15 biological activity data sets in comma separated value (CSV) format. Each row of data corresponds to a chemical structure represented by molecular descriptors.
- The **training files** are of the form
  - Column 1: Molecule ID
  - Column 2: Activity. Note that these are raw activity values and different data sets can have activity measured in different units.
  - Column 3-end: Molecular descriptors/features
- The **test files** are in the same format with *Column 2 removed*.
- Molecule IDs and descriptor names are global to all data sets. Thus some molecules will appear in multiple data sets, as will some descriptors.
- The challenge is to predict the activity value for each molecule/data set combination in the test set. To keep predictions for molecules unique to each data set, a data set identifier has been prepended to each molecule ID (e.g., "ACT1_" or "ACT8_").

- For each activity, the training/test set split is done by dates of testing. That is, the training set consists of compounds assayed by a certain date, and the test set consists of compounds tested after that date. Therefore it is expected that the distribution of descriptors will not necessarily be the same between the training and test sets.
- We find "time-split" validation is a much more realistic simulation of true prospective prediction in terms of R^2. We find construction of test sets by random sampling gives R^2's that are much too optimistic. That is what makes these data sets more of a challenge.

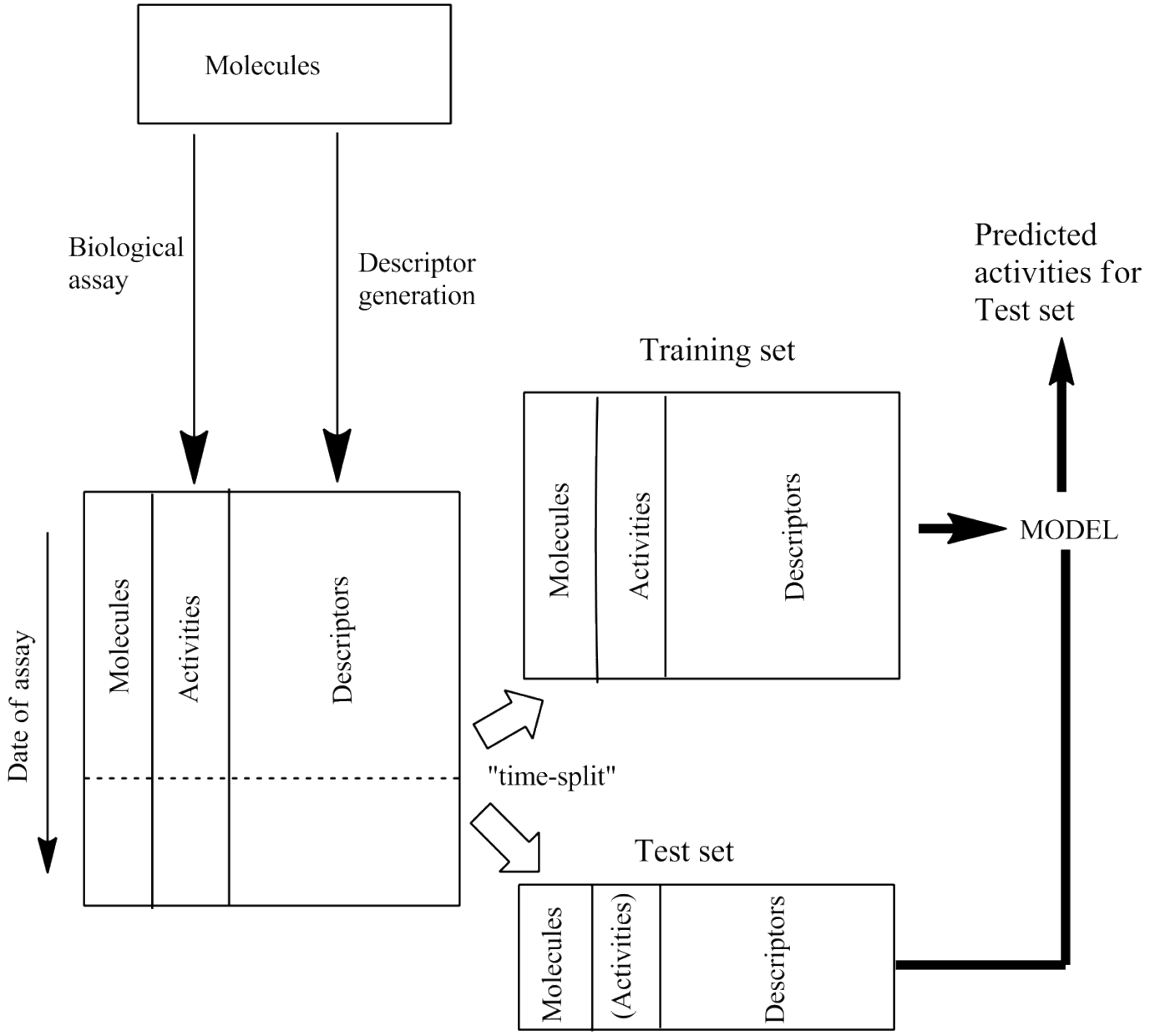
Example:

MERCK
Be well

Merck molecular activity challenge
on Kaggle

Approx 11k descriptors per molecule

2k-37k activities per target



Goodness of prediction is measured by R^2 between predicted activities and observed activities (withheld from the contestant) of the test set.

Final words

Take-home messages

- ANN are *mathematical models* that can be trained via examples to reproduce arbitrary functions
- Training is however not trivial: *many* examples are required, and independent test sets must be observed
- Failure to do so yields *overfitting*: models which predict only cases "already seen" in training. They don't generalize or predict.
- Deeper networks can be trained for a variety of tasks, including *de-novo* generation

Ethical issues

- Where do the data come from?
- Database errors contain biases. They reflect on results, yet they are hidden
- Cognitive biases
  - Hope in "magic boxes"
  - The machine told me and I don't want responsibility
- Optimization vs. understanding.
  - Black boxes do not empower discovery
  - Is this "epistemiologically" desirable for society?
- SOTA publishing selection
- Immense hype, AI winter.

Resources (self-study)

- Mathematics: 3Blue1Brown (YouTube)
- Prof. White's *Deep Learning for Molecules & Materials* - dmol.pub

- You should learn Python
- Compute power ("notebooks"): Google Colaboratory, Kaggle

Resources (datasets)

- Datasets, competitions: Kaggle (e.g. Merck's)
- Toxicology data: Tox21.gov (NIH)
- Many benchmark sets: moleculenet.ai →

- **BBBP**: Binary labels of blood-brain barrier penetration(permeability). Classification
- **Tox21**: Qualitative toxicity measurements on 12 biological targets, including nuclear receptors and stress response pathways. Classification
- **ToxCast**: Toxicology data for a large library of compounds based on *in vitro* high-throughput screening, including experiments on over 600 tasks. Classification
- **SIDER**: Database of marketed drugs and adverse drug reactions (ADR), grouped into 27 system organ classes. Classification
- **ClinTox**: Qualitative data of drugs approved by the FDA and those that have failed clinical trials for toxicity reasons. Classification

https://arxiv.org/abs/1703.00564

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End