Applications of Machine Learning in Cancer Research: a review

Cancer Biology: From Basic to Translational Research

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AI in the news

ars TECHNICA — SKIP TO MAIN CONTENT — BIZ & IT | TECH | SCIENCE | POLICY | CARS | GAMING & CULTURE

DID IT SAY "EEWWWWW"? —

Given enough training images, computers compete with medics on diagnosis

Not a fully accurate test, but still an impressive result.

An Algorithm Can Now Recognize Skin Cancer From Photos

BY SHAUNACY FERRO   JANUARY 25, 2017

Published: 25 January 2017

Dermatologist-level classification of skin cancer with deep neural networks

Andre Esteva, Brett Kuprel, Roberto A. Novoa, Justin Ko, Susan M. Swetter, Helen M. Blau & Sebastian Thrun

Nature **542**, 115–118(2017) | Cite this article

57k Accesses | **2502** Citations | **2870** Altmetric | Metrics

AI algorithm as good as dermatologists during spotting skin cancer   Health Medicine Network

From A&E to AI

Artificial intelligence will improve medical treatments

It will not imminently put medical experts out of work

The Economist

SAÚDE

Inteligência artificial pode ajudar operações a cancro no cérebro

Lusa · 7 de Janeiro de 2020, 21:25

Letter | Published: 06 January 2020

Near real-time intraoperative brain tumor diagnosis using stimulated Raman histology and deep neural networks

Todd C. Hollon, Balaji Pandian, [...] Daniel A. Orringer

Nature Medicine **26**, 52–58(2020) | Cite this article

Artificial intelligence-created medicine to be used on humans for first time

BBC NEWS

TECHNOLOGY FEATURE · 21 APRIL 2020   nature

Deep learning takes on tumours

Artificial-intelligence methods are moving into cancer research.

INTELIGÊNCIA ARTIFICIAL

Computador foi mais eficaz do que médicos a detectar cancros de pele

Num estudo, em média, os dermatologistas detectaram com precisão 86% dos cancros de pele, em comparação com os 95% da máquina.

PÚBLICO · 29 de Maio de 2018, 12:11

ESMO — GOOD SCIENCE BETTER MEDICINE BEST PRACTICE — ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

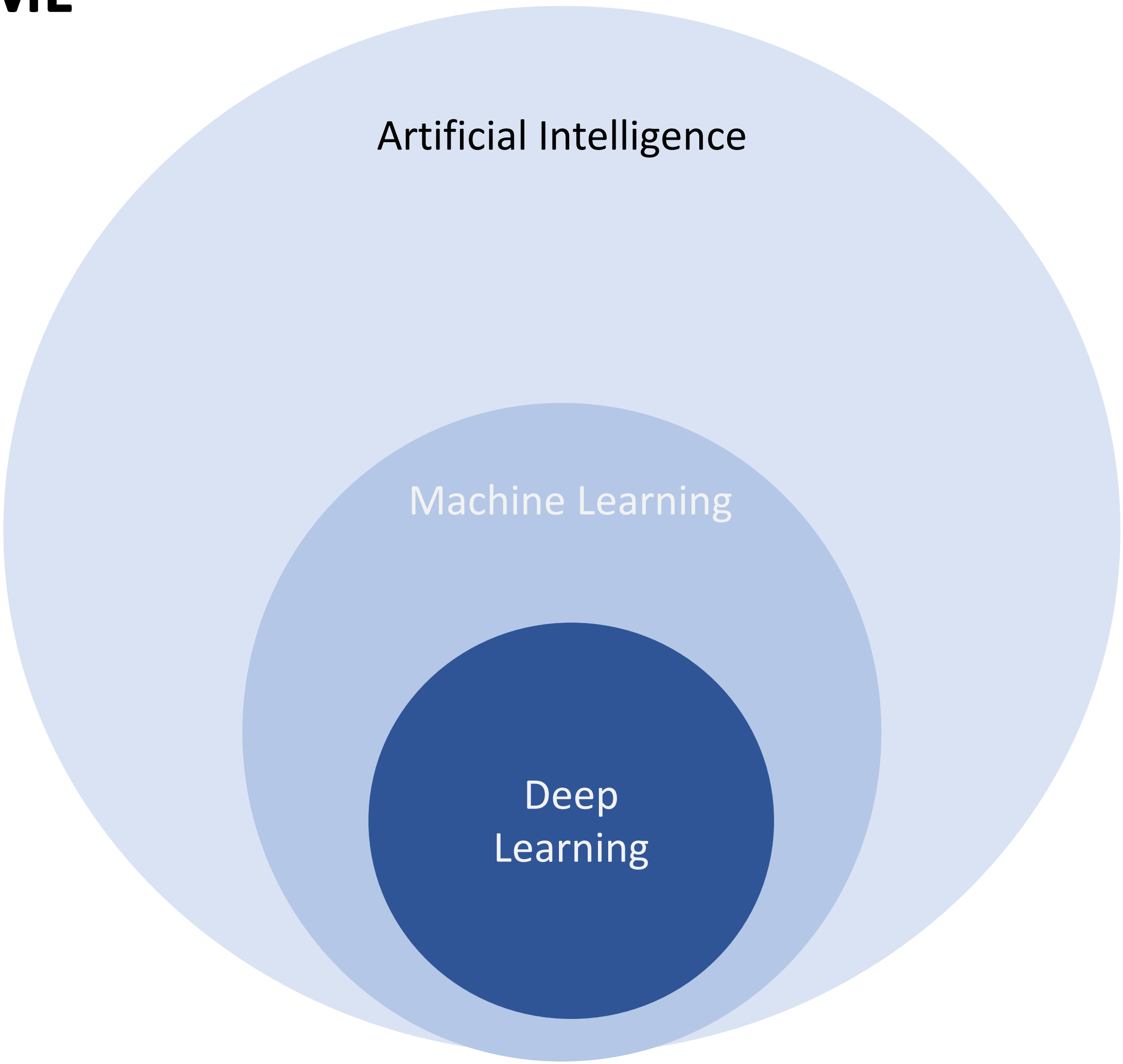
Man against machine reloaded: performance of a market-approved convolutional neural network in classifying a broad spectrum of skin lesions in comparison with 96 dermatologists working under less artificial conditions

H. A. Haenssle[1*], C. Fink[1], F. Toberer[1], J. Winkler[1], W. Stolz[2], T. Deinlein[3], R. Hofmann-Wellenhof[3], A. Lallas[4], S. Emmert[5], T. Buhl[6], M. Zutt[7], A. Blum[8], M. S. Abassi[9], L. Thomas[10], I. Tromme[11], P. Tschandl[12], A. Enk[1] & A. Rosenberger[13]; Reader Study Level I and Level II Groups

Observational Study > Ann Oncol. 2018 Aug 1;29(8):1836-1842. doi: 10.1093/annonc/mdy166.

Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists

AI and ML



- Computing power increased.
- Capacity to collect large amounts of (labelled) data from different sources and devices.
- Algorithmic advances.
- Breakthrough applications in many complex tasks: image detection, language translation, autonomous driving, game playing or natural language processing.

Machine Learning

“Machine learning, a field concerned with the development and application of computer algorithms that improve with experience.”

- Libbrecth and Noble, Nat. Review Genetics, Vol16, June 2015.

“Machine learning is the scientific discipline that focuses on how computers learn from data.”

- Rahul Deo, Circulation, 132(20), 2015.

The Learning Problem

X

y

Inputs: | Output

Attributes

Cases

(...)

Headache	Temperature	Age	Throath Inflam.	Flu?
None	36.6	35	No	**No**
None	38.3	40	Yes	**No**
Moderate	38.6	86	No	**Yes**
Strong	40.0	26	No	**Yes**
Strong	38.2	50	No	**Yes**
Strong	36.5	70	Yes	**No**
Moderate	39.1	65	Yes	**?**
None	38.3	15	No	**?**
(...)				

Attribute types: | **Categorical** | **Continuous** | **Continuous** | **Categorical** | **Categorical**

Learn
$Y = f(X) + e$

Predict y
from f

Supervised Learning

> *"… supervised statistical learning involves building a statistical model for predicting, or estimating, an output based on one or more inputs. "* - James, Witten, Hastie and Tibshirani. An Introduction to Statistical Learning

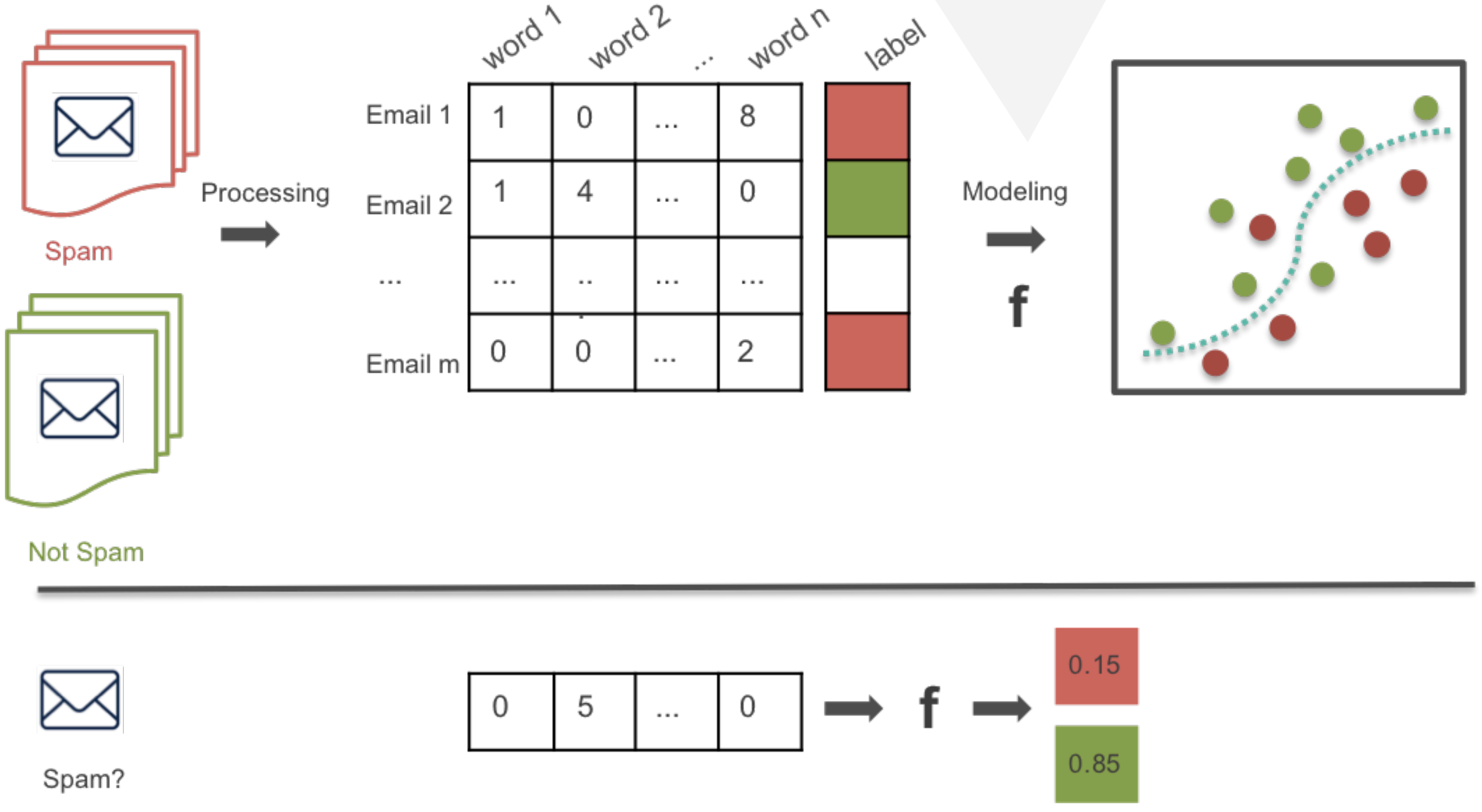
- Train: collection of (X, y) pairs
- Learn: **f**(X)-> y; predict y* with f given unseen X*

Models of f: Decision Trees, Random Forests, SVMs, Bayesian classifiers, Logistic Regression, Linear Regression, Neural Networks

GOOGLE SAYS ITS AI CATCHES 99.9 PERCENT OF GMAIL SPAM

Three years after it last released Gmail's spam stats, Google says that its spam rate is down to 0.1 percent, and its false positive rate has dipped to 0.05 percent. The company credits the significant drop in large part to the introduction of brain-like "neural networks" into its spam filters that can learn to recognize junk mail and phishing messages by analyzing scads off the stuff across an enormous collection of computers.

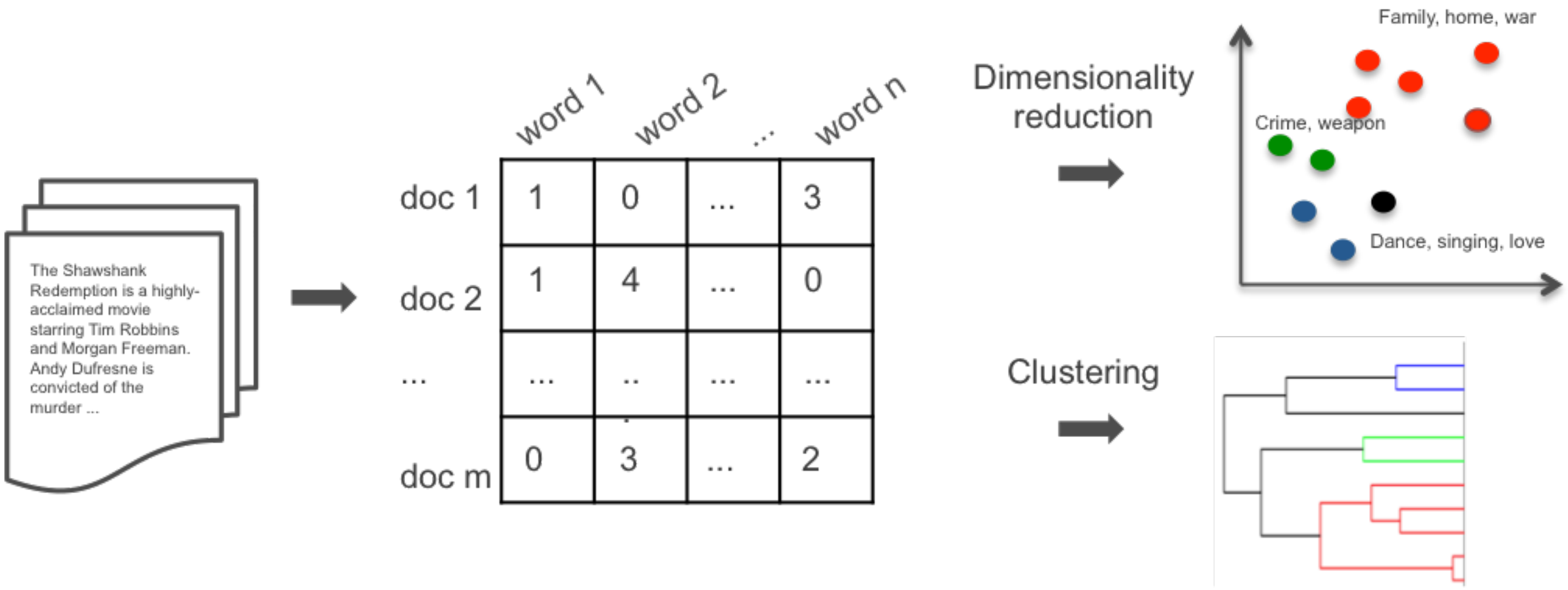
- Wired Magazine, July 2015



Unsupervised Learning

> *"With unsupervised statistical learning, there are inputs but no supervising output; nevertheless we can learn relationships and structure from such data."*
> - James, Witten, Hastie and Tibshirani. An Introduction to Statistical Learning

- Train: collection of unlabelled data (X, ?)
- Learn: $\mathbf{g}(X_M)$-> X_N; M, N dimensions, where M >> N



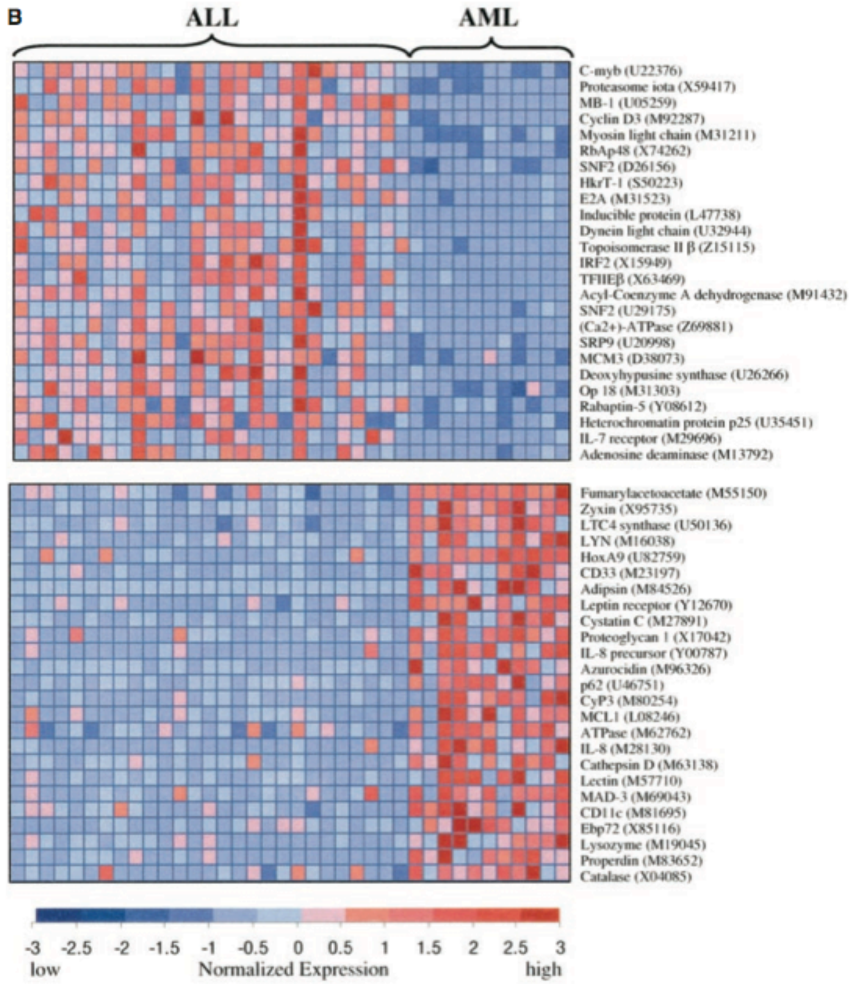
Paradigmatic applications of ML

Gene expression analysis in cancer research.

Supervised or unsupervised tools can be applied to learn from data.

- Unsupervised learning:
  - Principal Component Analysis: understand the variability patterns and visualize distance between samples.
  - Clustering: identify resembling samples.

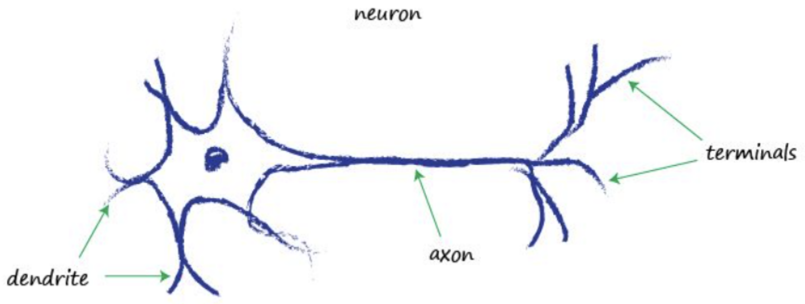
- Supervised learning:
  - Develop a classifier from gene expression profiles, that classifies a new sequenced sample as normal or tumor, including tumor sub-types.



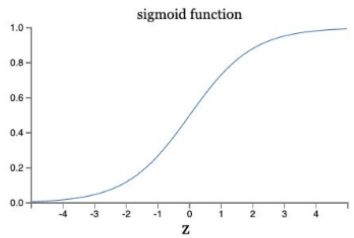
- Golub, *et al.* Science 1995.
- *Demonstrated the feasibility of cancer classification based solely on gene expression: Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL)*

Artificial Neurons

- Neural Networks were initially inspired by the neurons in the brain (McCulloch & Pitts 1943; Farley & Clark 1954; Rosenblatt 1958).



Adapted from:
Tariq Rashid. *A Gentle Introduction to Neural Networks.* 2016



Sum of the product of the inputs and the weights

Activation function

Inputs

x1 w1

x2 w2

x3 w3

z = x1.w1 + x2.w2 +x3.w3

f_act(z)

Output

Input neurons

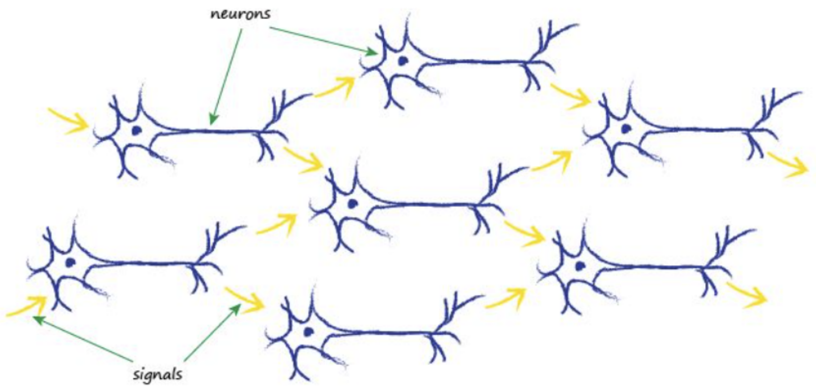
synapses / dendrites

Body of neuron
Signal integration and activation

Output neuron

Neuronal Networks

- Neural Networks consist of interconnected artificial neurons where each connection has a weight associated.



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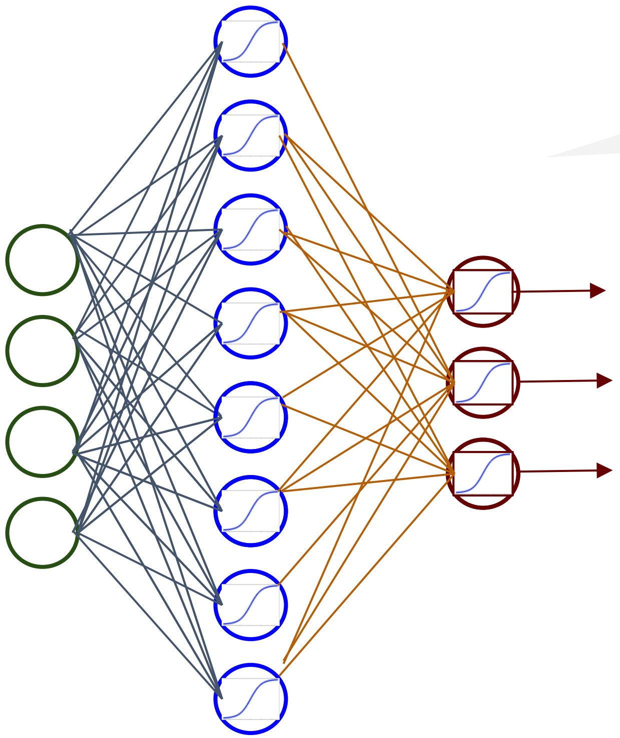


Neural Network with:
- 4 input nodes
- 8 intermediate nodes
- 3 output nodes

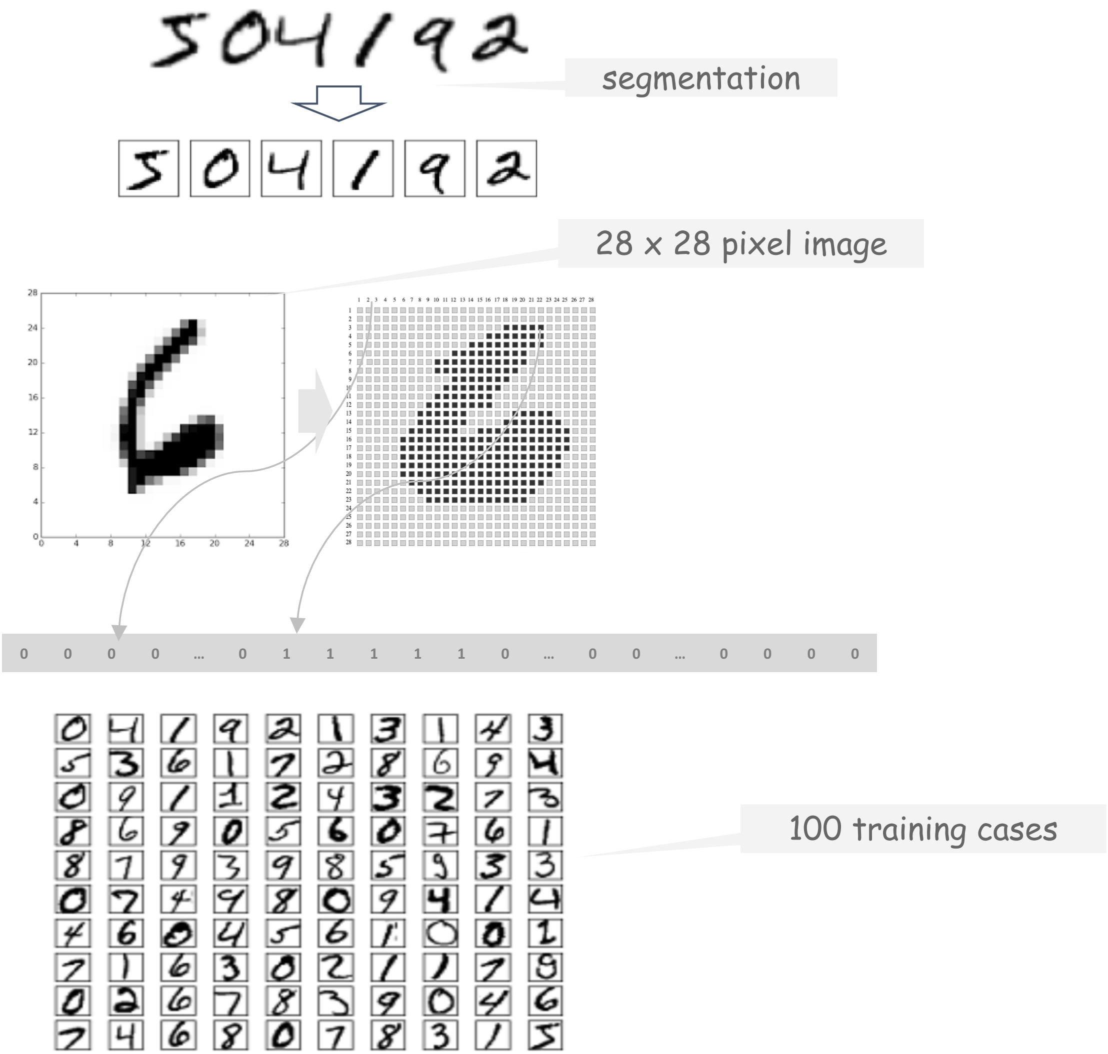
Input layer

Hidden layer

Output layer

Neuronal Networks for image classification

Goal: apply ML to create a program that predicts the digits in a sequence of hand-written numbers



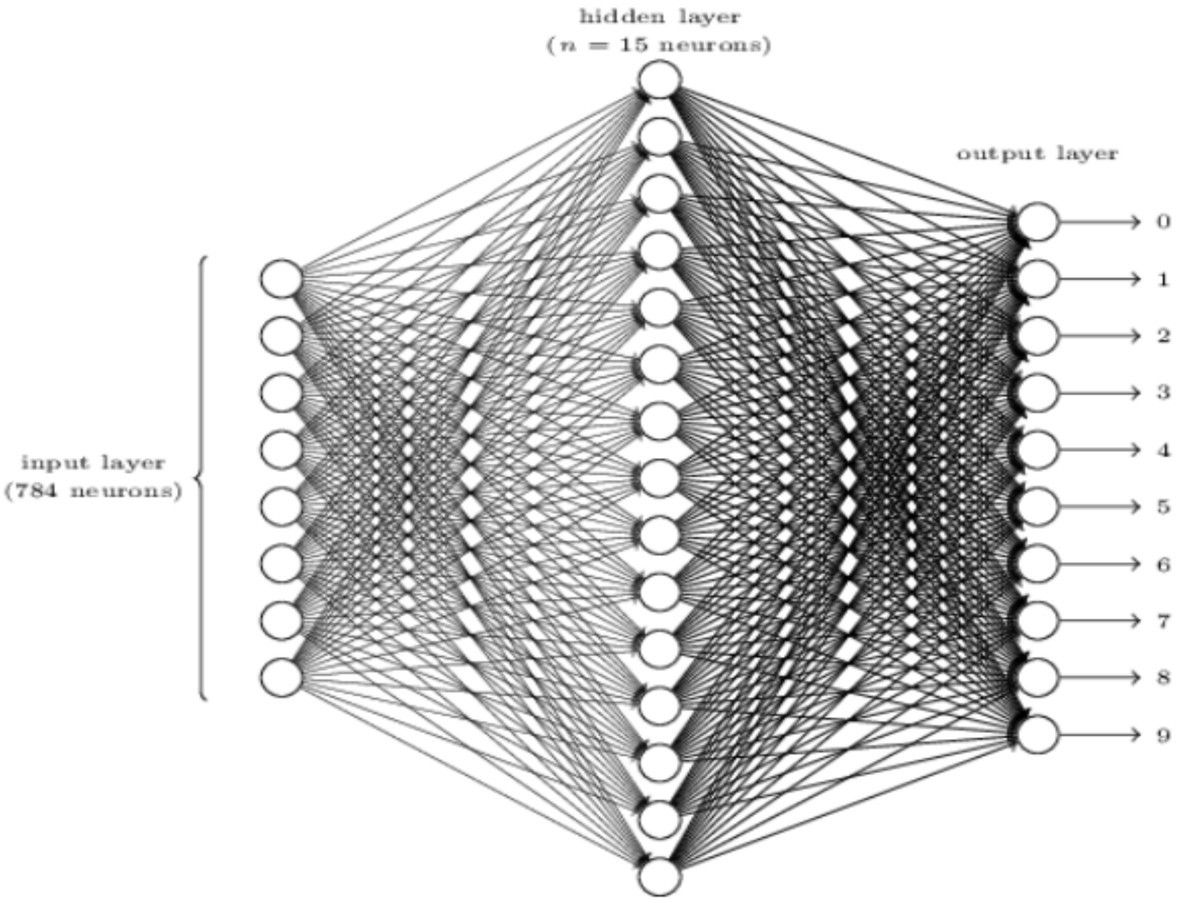


Image from:
Michael Nielsen. *Neural Networks and Deep Learning*. 2019

Deep Learning

- Uses NNs with many layers (representation levels) and complex architectures.
- Scales to very large datasets.
- Requires very little feature engineering by hand/expert.
- ML and recently DL have achieved human-level performance on several tasks that involve: human perception (image and speech recognition) and human action (game playing and NLP). Wide range of application areas.

Deep Learning Architectures

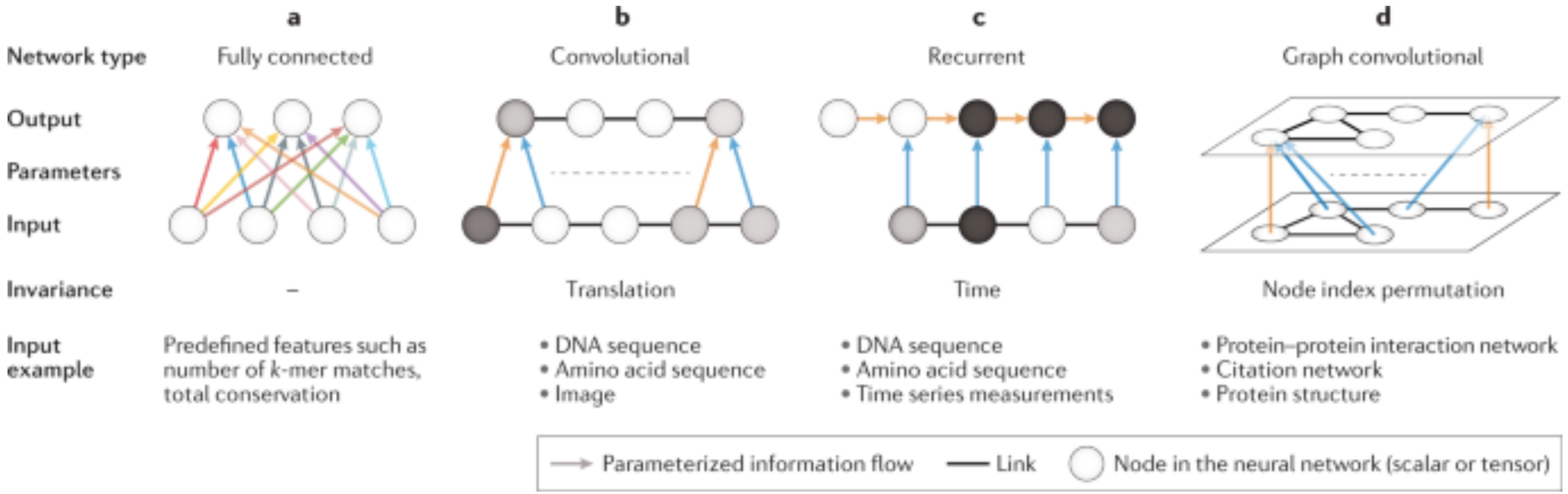
Type of data		Architecture
structured data (matrix format)	→	Fully connected and FeedForward (FNN)
image data	→	Convolutional (CNN)
text & sequence data	→	Recurrent (RNN)

for general prediction problems with no particular relation between input features.

input features show inter-dependence and spatial invariant patterns are expected

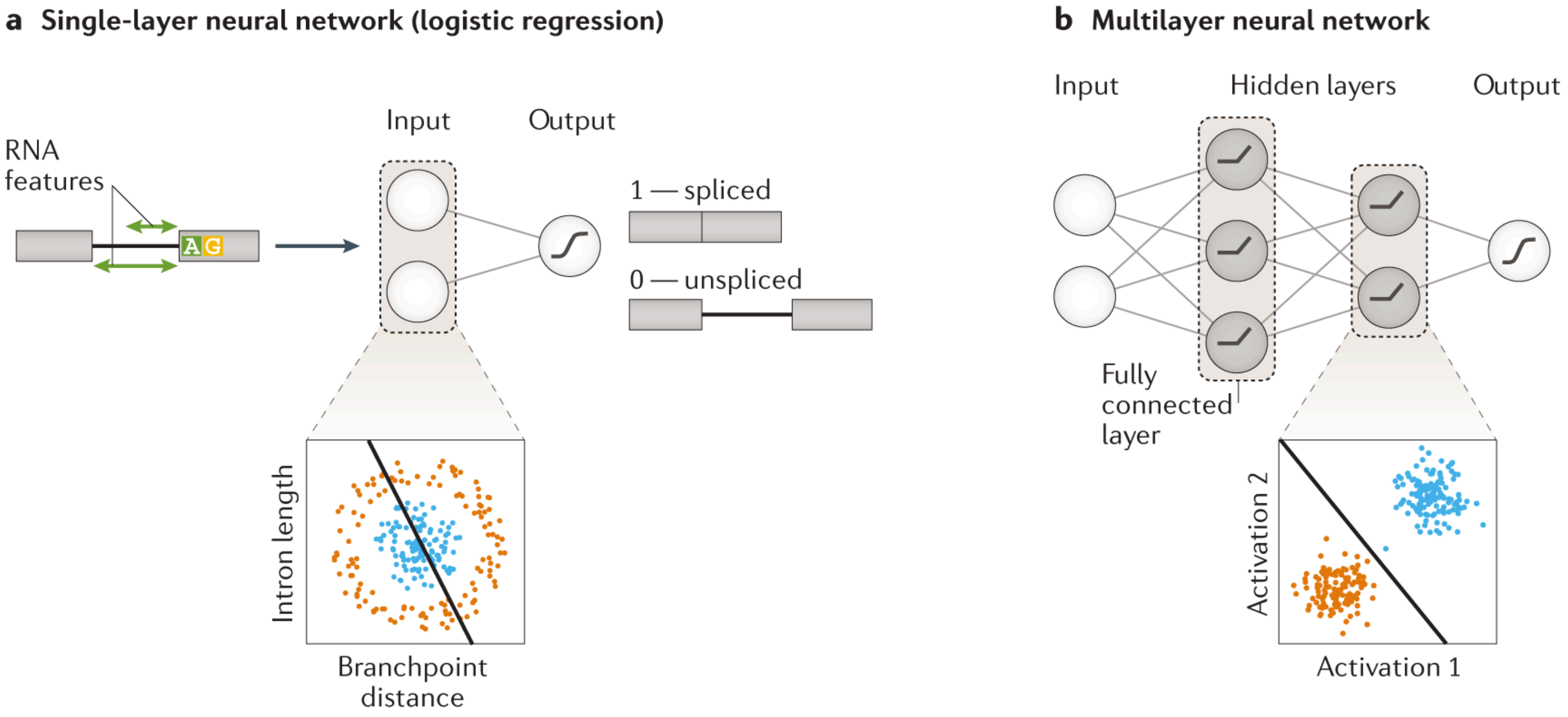
designed for sequence or temporal series

Deep Learning Architectures



Deep learning: new computational modelling techniques for genomics, Eraslan et al 2020

Deep Learning Architectures



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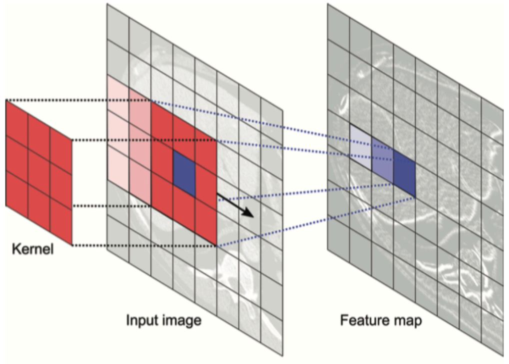
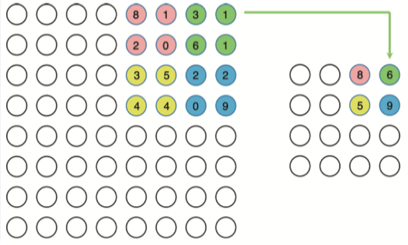
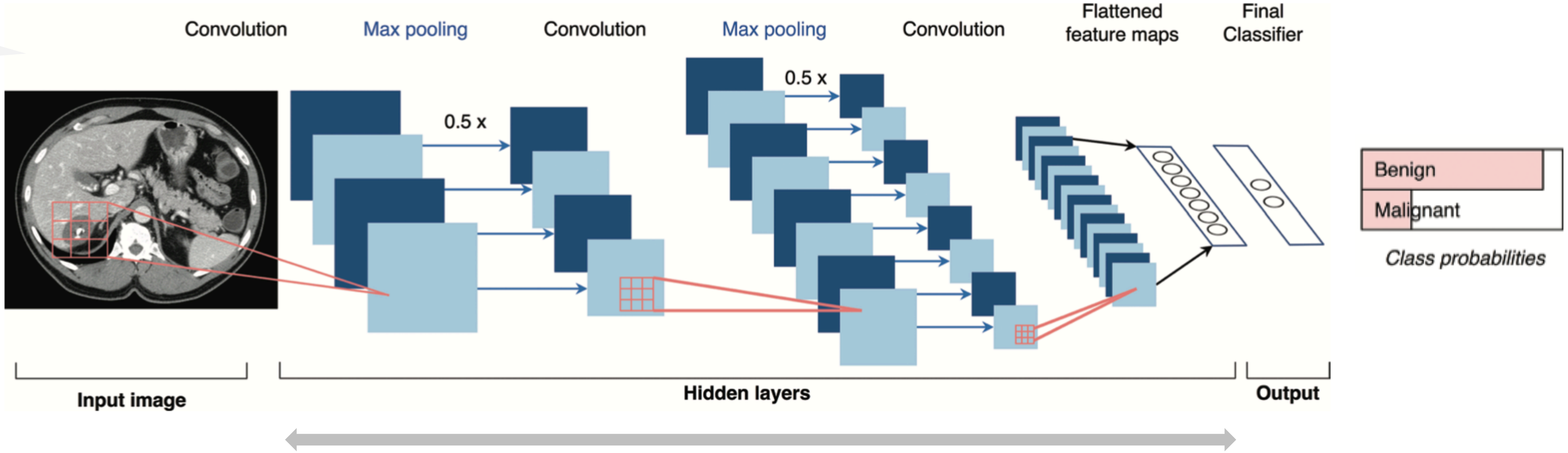
Convolutional Neural Networks (CNNs)





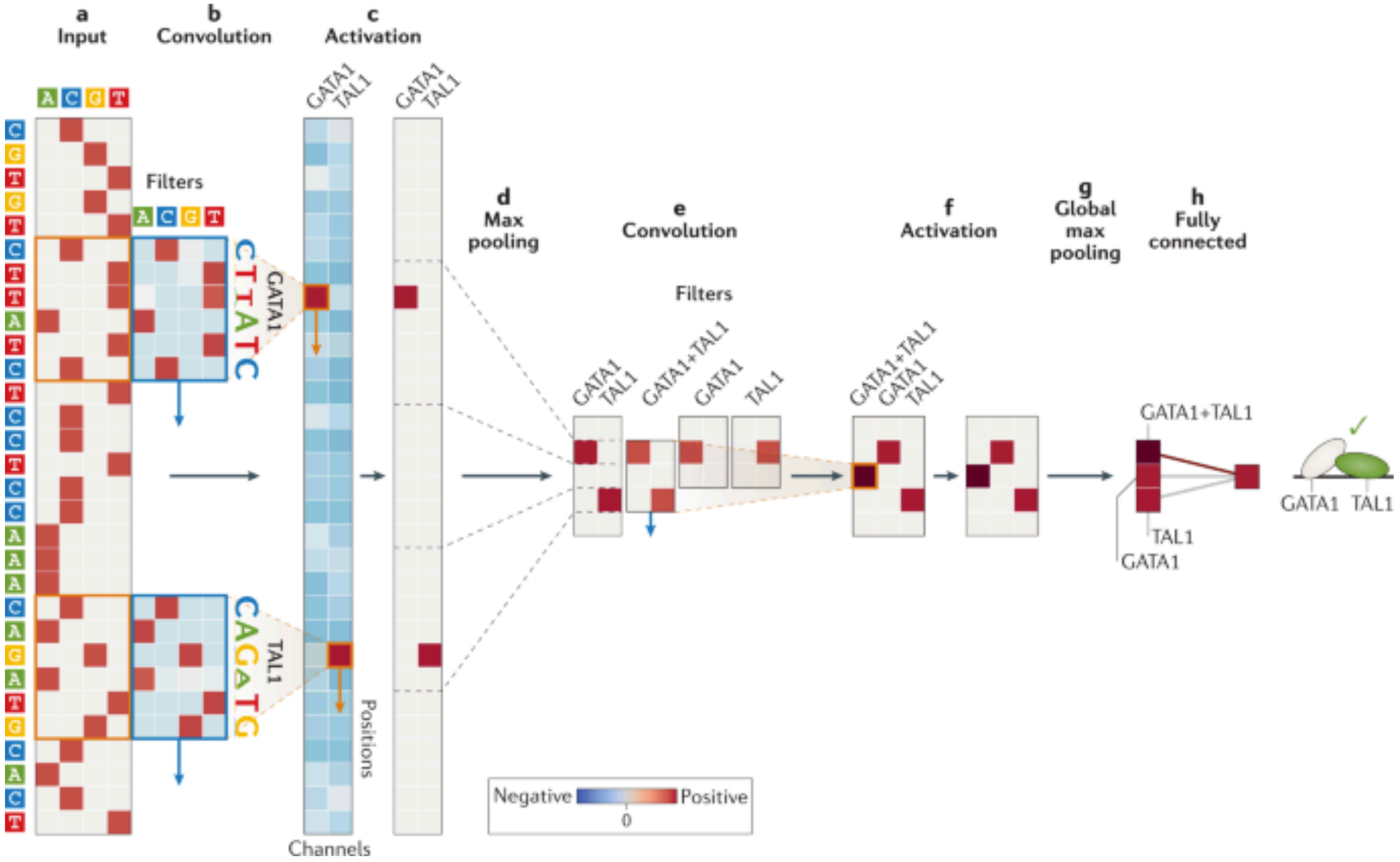
Adapted from:
Chartrand et al.
Radiographics, 37(7),
2017.



Simple features (edges and basic shapes)

High-level representations

Deep Learning Architectures



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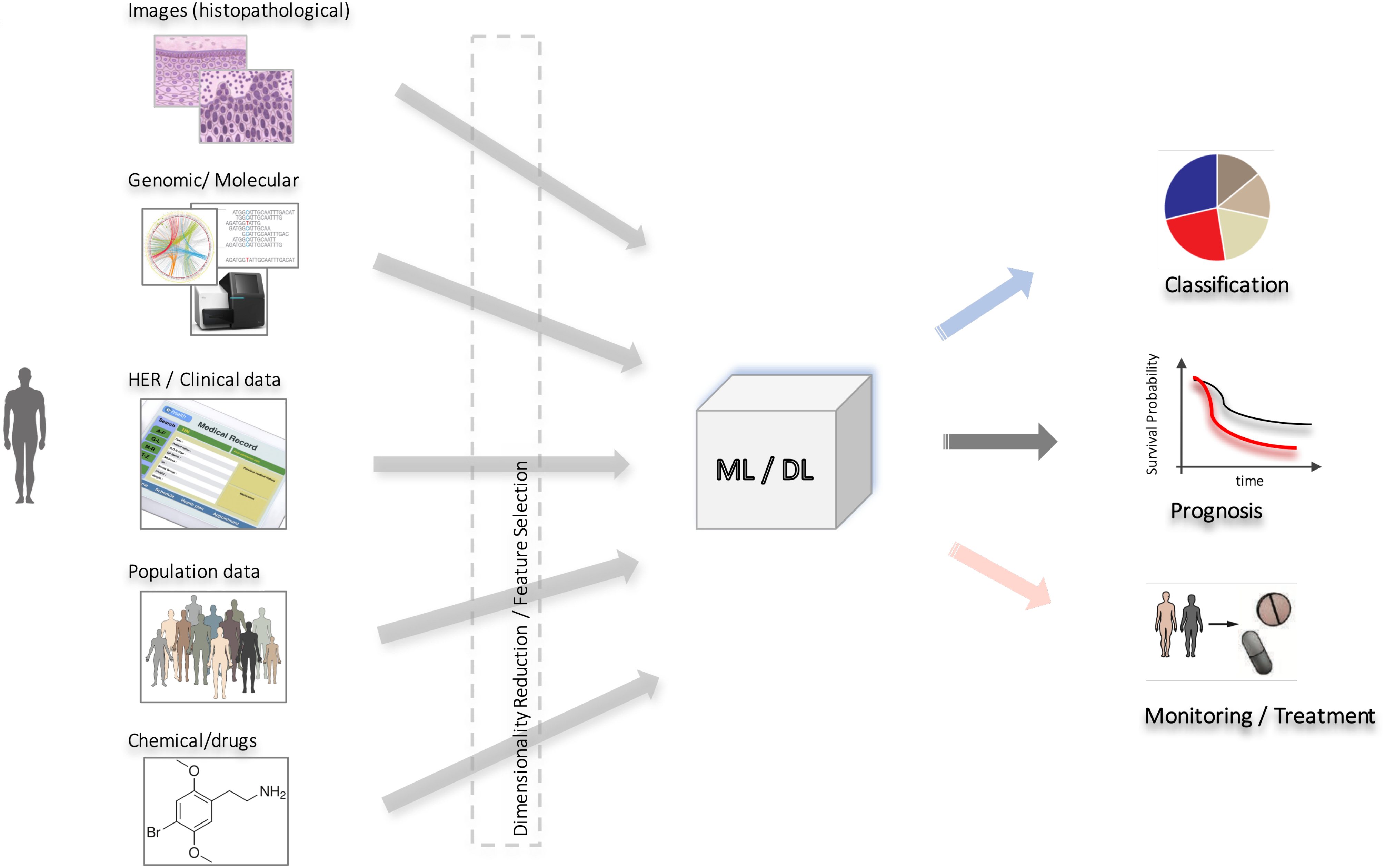
Applications



Cancer Diagnosis

Skin cancer image classification with DL - *Esteva et al, Nature 2017*

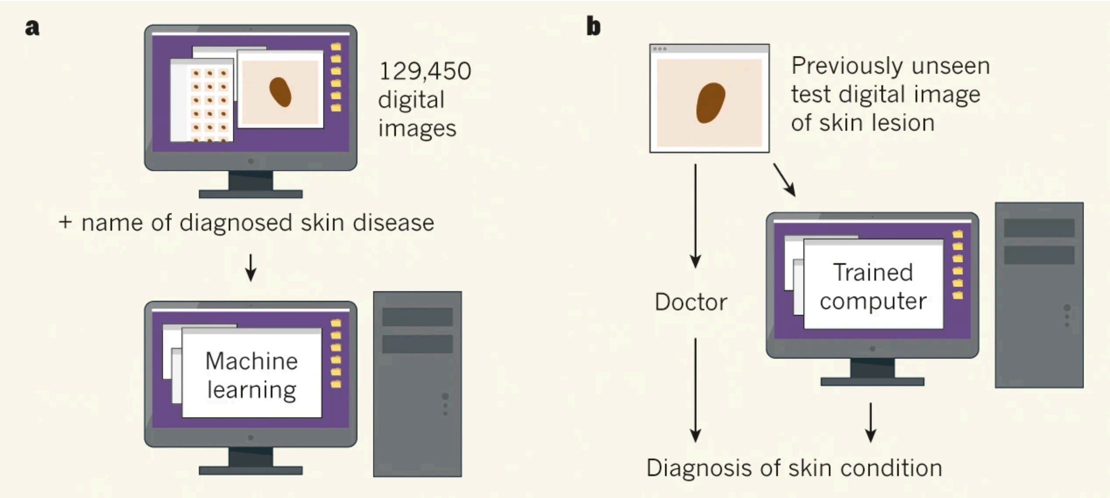


Image from:
Leachman & Merlino. *Nature 542, 2017.*

a. Used a pre-trained DL algorithm to train a computer (130k digital images from diagnosed samples) to recognize skin diseases.

b. presented a set of previously unseen images of skin to dermatologists to classify them as: benign; malignant lesion and non-neoplastic → diagnosis verified by biopsies testing.

- Deep CNN pre-trained (1.3M) for image recognition.
- Dermatologist-labelled images organized in a tree-structured taxonomy of 2,032 diseases.
- Trained on 130K images to properly identify each disorder.

Cancer Diagnosis

Skin cancer image classification with DL - *Esteva et al, Nature 2017*

Image from:
Esteva et al. *Nature 542, 2017.*

- Task 1: 1st levels (3) of taxonomy (accuracy: 72% CNN vs 66% of 2 dermatologists)
- Task2: 2nd levels (9) of taxonomy (accuracy: 55.4% CNN vs 55% of 2 dermatologists)
- Task3: biopsy-proven images on medically relevant cases; epidermal vs melanocytic malignant/benign classification (CNN outperforms all of the 21 board-certified dermatologists).

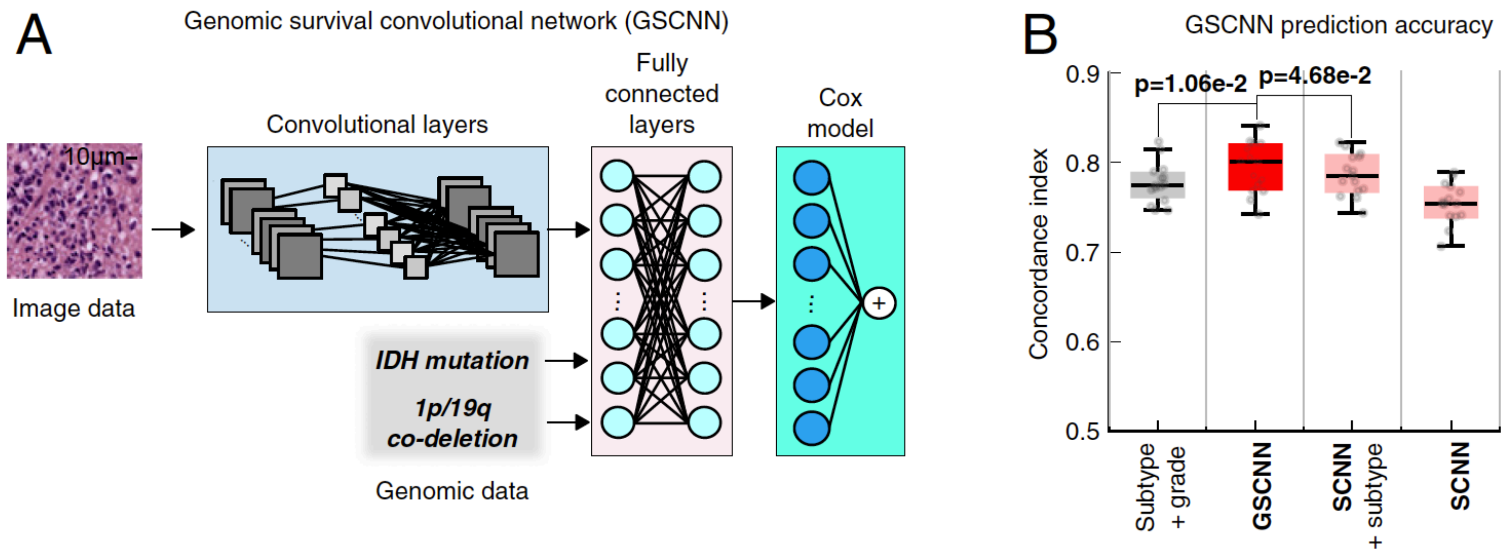
- System performed consistently slightly better than average performance of doctors.
- Both had bad performance to classify images from random skin disease.

Cancer Prognosis

Glioma prognosis with DL – *Mobadersany et al, PNAS 2018*

Image from:
Mobadersany et al. *PNAS, 2018.*

Gliomas



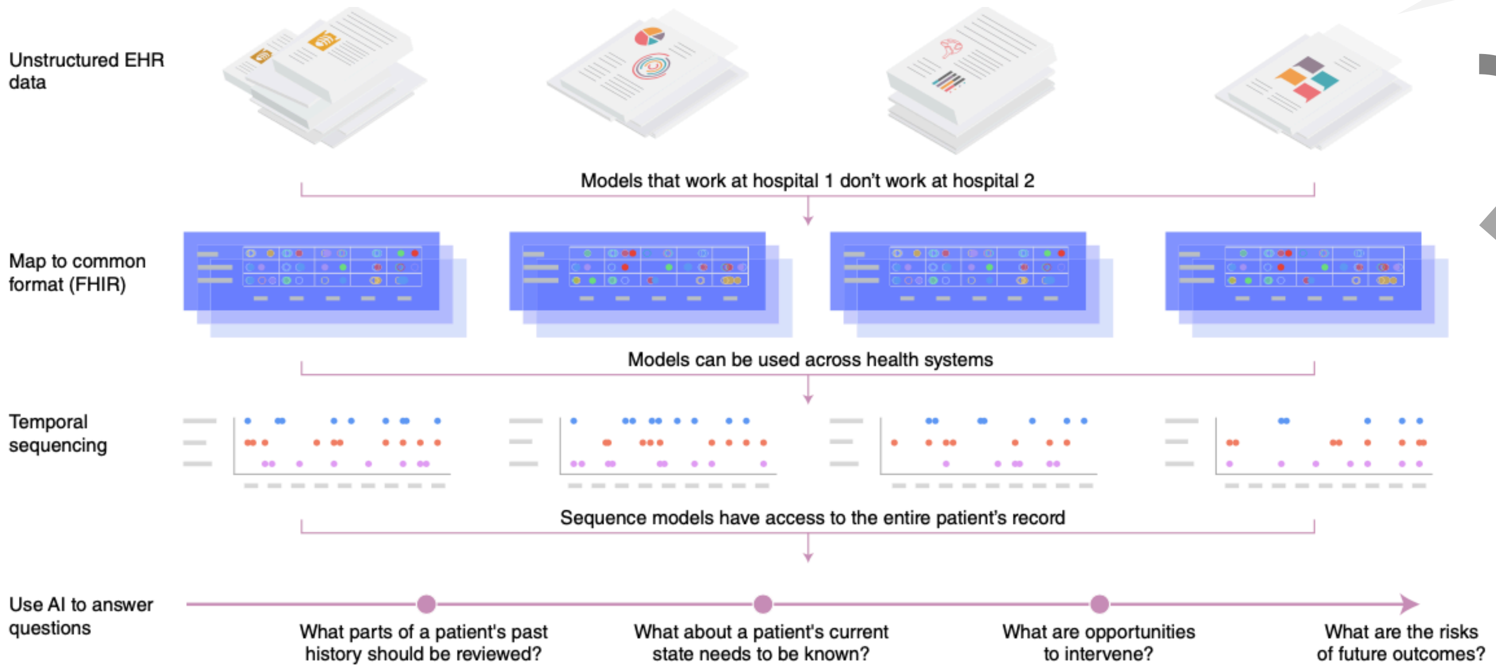
- Survival CNNs (SCNN): prediction of time-to-event outcomes from histology images.
- Techniques: Image sampling (tumour heterogeneity) and risk filtering (increase labelled train data).
- SCNNs have predictive accuracy equivalent to manual grading by neuropathologists.
- Genomic + SCNN (GSCNN): histology images + genomic biomarkers.
- GSCNN outperforms SCNN model and WHO subtype grade model based on genomic subtypes and histologic grading.

Cancer Monitoring and Treatment

Electronic Health Records (EHR): understand and estimate risk of cancer onset and recurrence

Image from:
Esteva et al. *Nat Genetics 2019.*

Massive Longitudinal Datasets



Standardization

ML/DL
RNN

- DeepPatient: Prediction performance for severe diabetes, schizophrenia, and various cancers were among the top performing.
- These studies indicate that ML/DL applied to EHRs can improve clinical predictions and provide more-intelligent personalized recommendations.

Miotto, R. et al. Deep patient: an unsupervised representation to predict the future of patients from the electronic health records. Sci. Rep. 6, 26094 (2016).
Rajkomar, A. et al. Scalable and accurate deep learning with electronic health records. NPJ Digit. Med. 1, 18 (2018).

ML/DL Strong points

- Enables unbiased discovery from experimental data.
- Human-level performance in several tasks: effectively learn from very large, complex and even heterogeneous datasets.
- Keep improving when more data is available.
- Integrative and systems-level view of cancer; complement to hypothesis driven approaches.
- Used under human guidance can reduce subjective evaluation and improve precise prognostication.

ML/DL Limitations

- Methods are “*data hungry*”.
- Labelled data is expensive. An algorithm is only accurate as its reference data.
- Datasets are often biased and imbalanced.
- Lack of external validation datasets.
- ML workflow still difficult to integrate in clinical practice.
- Lack of interpretability.

Perspectives

- In clinical practice high diagnostic sensitivity tends to be preferred!

- ML models could be used as a complement to laboratory and clinical practice:
    - Shorten the time of diagnosis.
    - Reduces the search space of hypothesis.
- Leverages the possibility of an intelligent precision medicine.