

# Challenges of Machine Learning for Transcriptomics

## AI for genomics Bootcamp

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# Outline

## 1 Introduction

### 2 From real world to input data

- Dataset biases
- Acquisition biases
- Preprocessing

### 3 The supervised learning pipeline

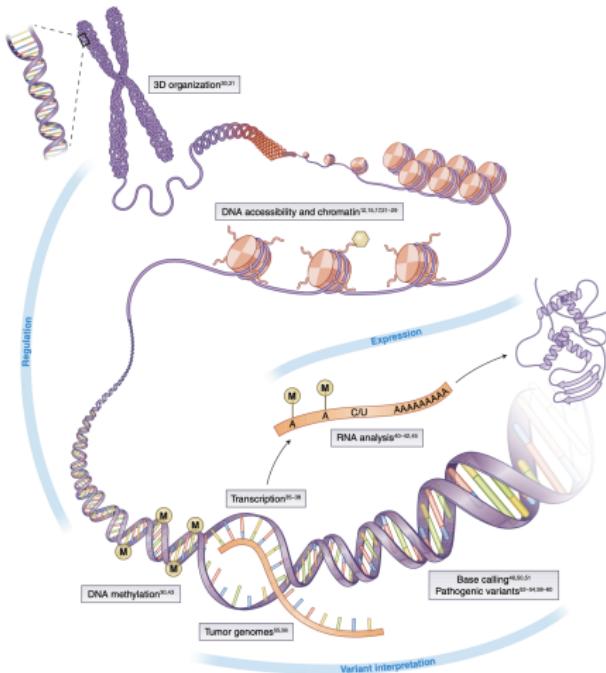
- The curse of dimensionality
- Making the right assumptions: inspiration from Comp. Vis.
- Which assumptions for transcriptomics?
- Gene interaction graphs?
- Parameter sharing among genes?
- Similar response to perturbation in latent space?

### 4 Model interpretability

- Feature importance for deep models
- Simpson's paradox

### 5 Conclusion

# Applications of deep learning in genomics.



- ▶ Lots of applications of deep learning in genomics
- ▶ Today focus on applications to **transcriptomics** and its challenges

Figure taken from *A primer on deep learning in genomics*

# What are transcriptomics?

- ▶ The study of an organism's transcriptome, the sum of all of its RNA transcripts
- ▶ We will focus on RNA-seq and single cell RNA-seq

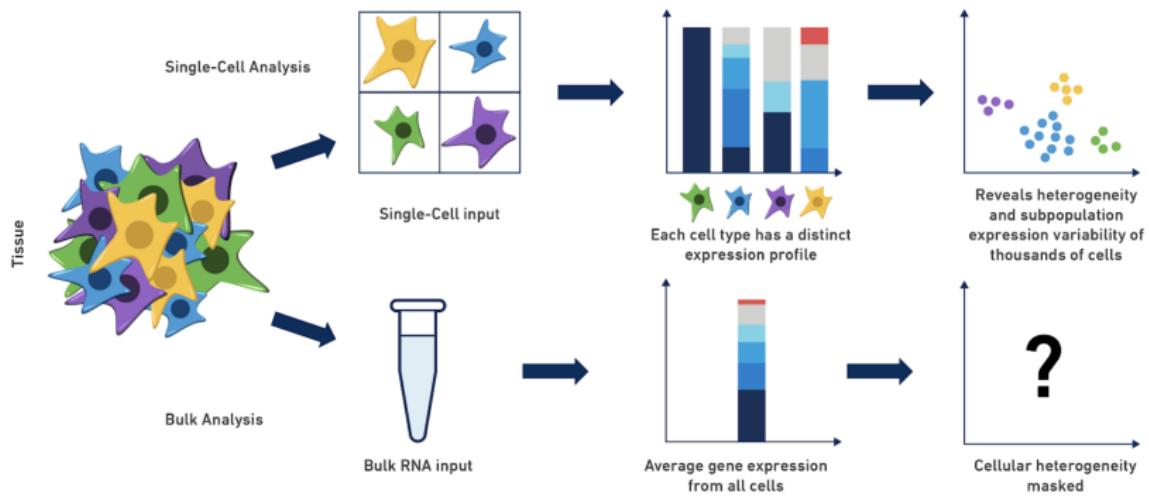


Figure taken from  
<https://www.biocompare.com/Bench-Tips/345311-Single-Cell-Set-Up-Sample-Preparation-Tips/>

# Lots of different cell types



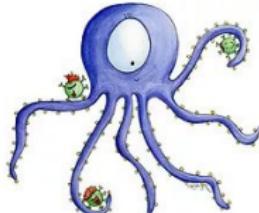
NK Cell



Cytotoxic T Cell



Helper T Cell



Follicular Dendritic Cell



Macrophage



Treg



B Cell



Plasma Cell



Mast Cell



Basophil

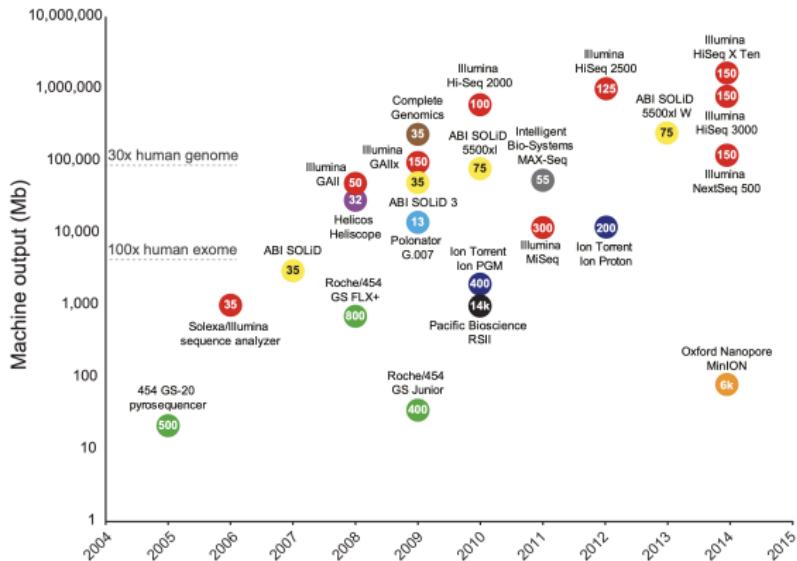


Neutrophil



Eosinophil

# More and more data



**Figure:** Plot of commercial release dates versus machine outputs per run are shown. Numbers inside data points denote current read lengths. Sequencing platforms are color coded.

Figure taken from *High-Throughput Sequencing Technologies*

# Apply modern machine learning techniques?

## Long term goals:

- ▶ Individualized medicine
- ▶ Better understanding the biology

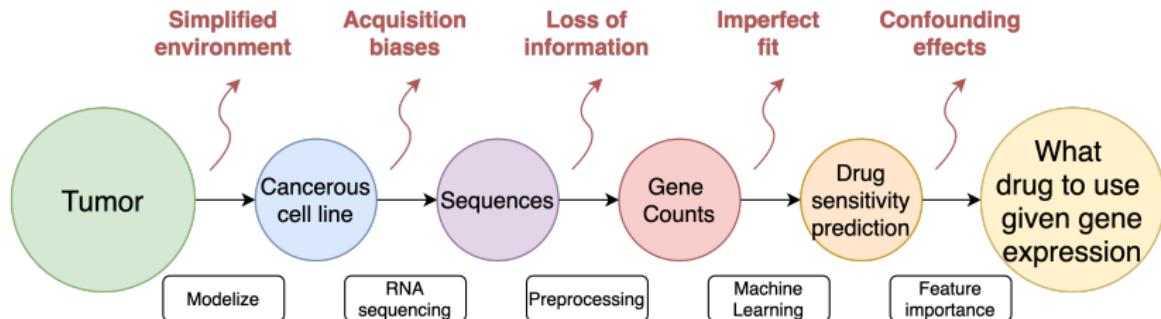
## Today's objective

Identify and understand the challenges facing machine learning (ML) and deep learning (DL) techniques when applied to transcriptomics

## Why should you care?

- ▶ Be aware of the limitations of usual ML
- ▶ Take those limitations into account when you use ML
- ▶ Discover fields of research in ML

# How can machine learning help?



- ▶ Example of a pipeline to find better cancer treatment using Machine Learning
- ▶ Let us study the limitations associated with each step

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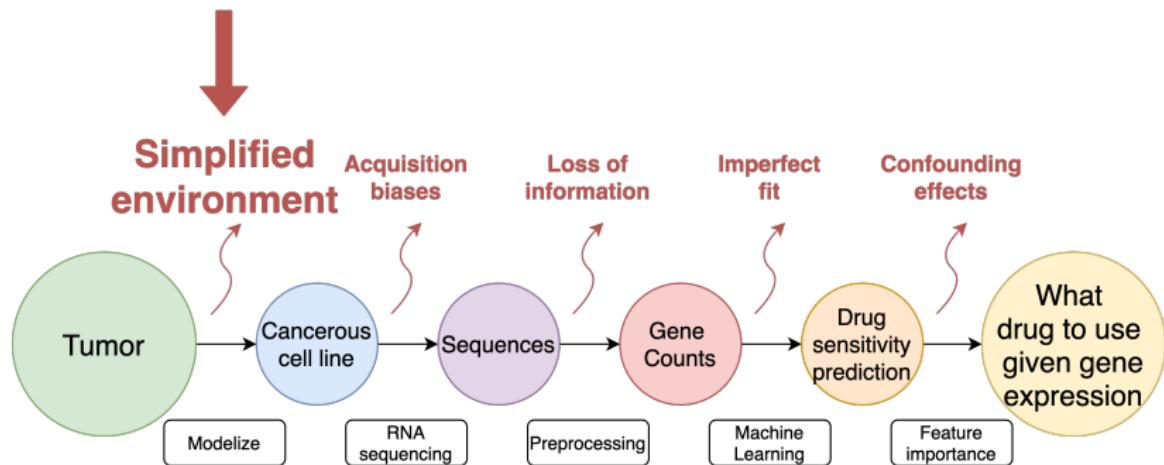
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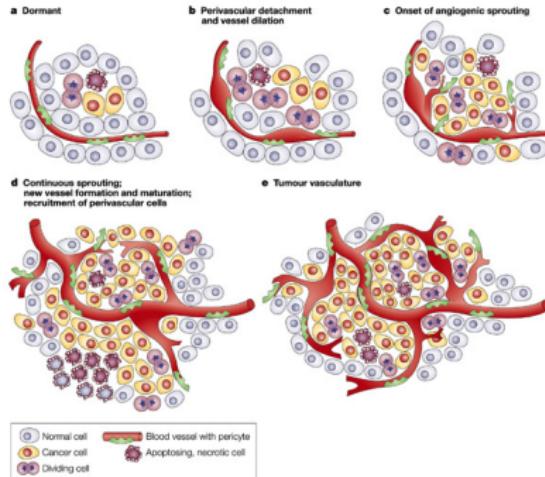
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# Cell lines, a model for tumors



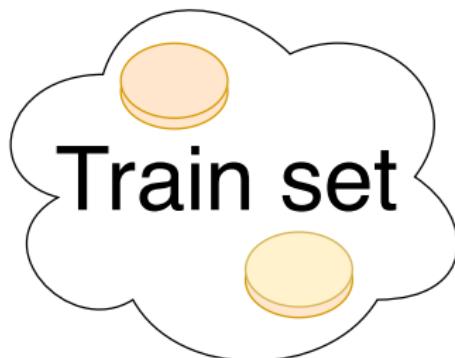
## Cell lines as a model

Cell lines are a simplified model of tumors

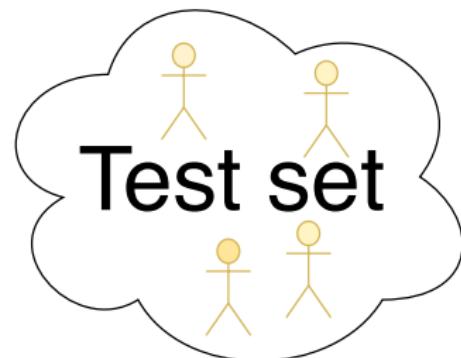
- ▶ Tumors are complex tissues
- ▶ Composed of different cell types
- ▶ Evolving in a living organism

Figure taken from *Biological Pathways Involved in Tumor Angiogenesis and Bevacizumab Based Anti-Angiogenic Therapy with Special References to Ovarian Cancer*

## Why is this an issue for ML?



Lab experiments



Patients

# A refresher on supervised learning

## Supervised learning

- ▶ Learn to predict target  $Y$  given input  $X$
- ▶ We model  $P_\theta(x|y)$  and learn the parameters  $\theta$  based on pairs of examples
- ▶ Questions: Are there any assumptions on the dataset?

# Let's have a quiz!



→

What can Supervised Learning do?

- A: Replace any domain knowledge
- B: Provide explanations for observed patterns
- C: Estimate functions from IID samples
- D: Reliably generalize to other domains

# Machine Learning cannot do everything!

The slide features a 'Who Wants to Be a Millionaire' logo at the top. Below it is a question: "What can Supervised Learning do?". Four options are listed below, each in a colored box:

- A: Replace any domain knowledge
- B: Provide explanations for observed patterns
- C: Estimate functions from IID samples
- D: Reliably generalize to other domains

# The main assumption of Supervised Learning

- ▶ **Intuition:** Pick balls at random from the same *bag* (and put the ball back before picking another one)

## Independent Identically Distributed

All samples are independently drawn from a fixed probability distribution

- ▶ This assumption can be violated in several ways

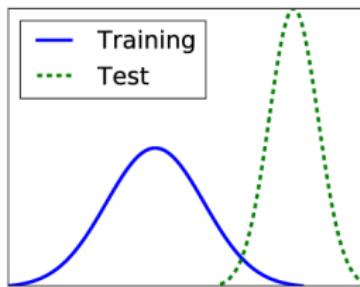


Figure: Counterexample where train and test inputs have different distributions

## Covariate shift

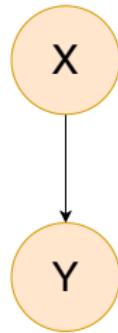
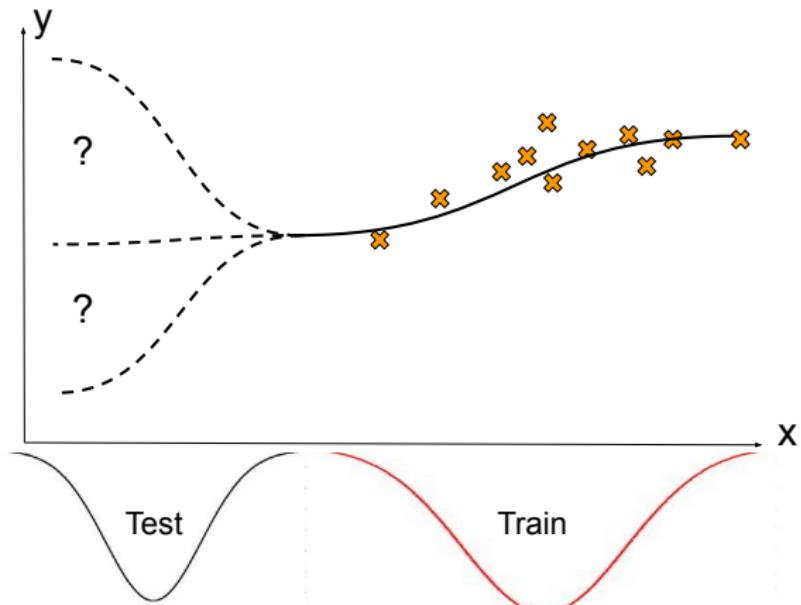


Figure: X causes Y

- ▶ Happens in X causes Y problems
- ▶ **Covariate shift:**  $P(x)$  changes between train and test but  $P(y|x)$  does not change
- ▶ At test time, the model will be confronted with parts of the input space that it has not seen during training

# Covariate Shift



## Prior probability shift

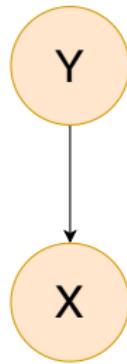


Figure: Y causes X

- ▶ Happens in Y causes X problems
- ▶ **Prior probability shift:**  $P(y)$  changes between train and test but  $P(x|y)$  does not change
- ▶ Difficult because both the input distribution  $P(x)$  and what we model ( $P(y|x)$ ) change

## Concept shift

- ▶ **Concept shift** in X causes Y problems:  $P(x)$  does not change but  $P(y|x)$  changes
- ▶ **Concept shift** in Y causes X problems:  $P(y)$  does not change but  $P(x|y)$  changes

# Different shifts together?

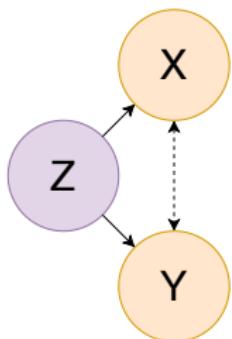


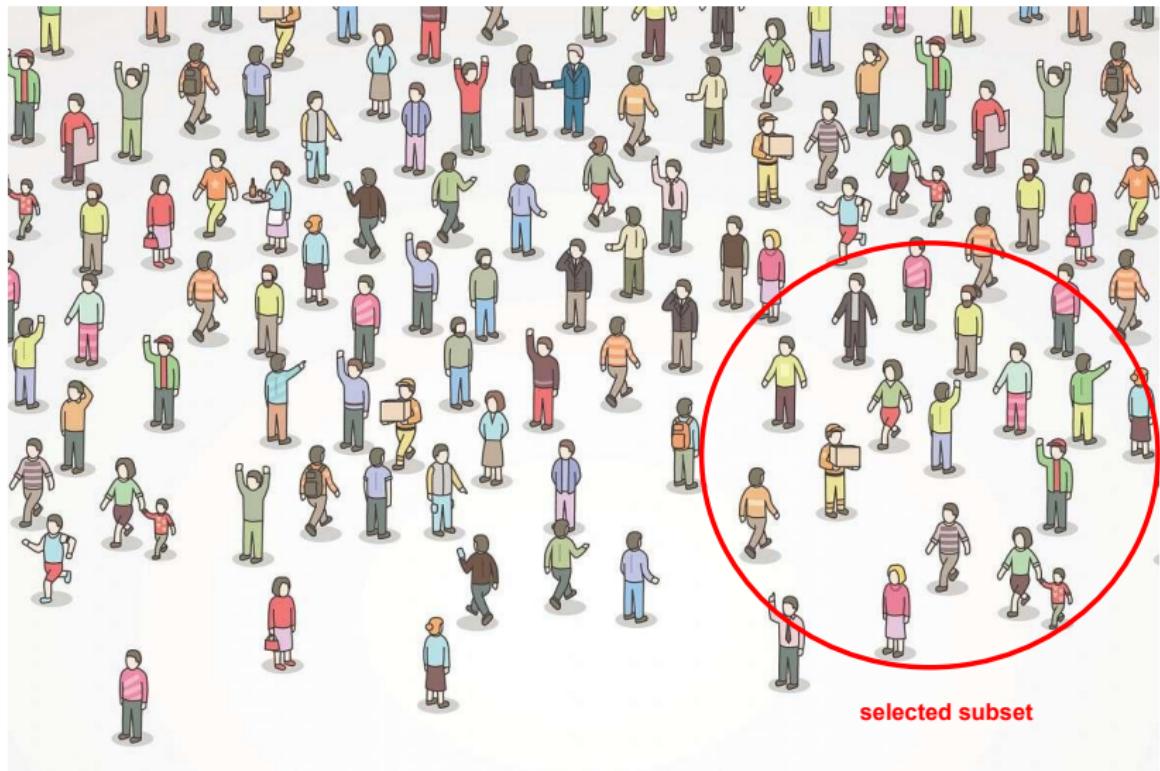
Figure: Z causes X and Y in addition to direct effects

## What happens in transcriptomics?

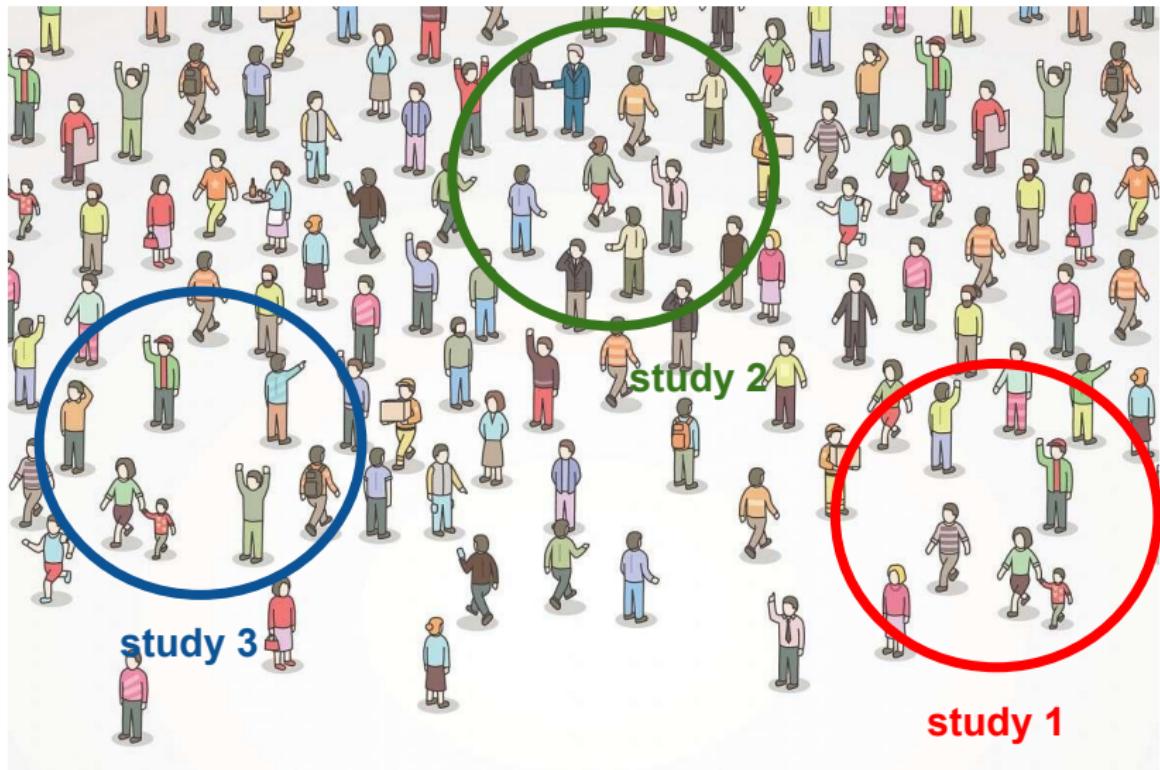
In biology, there are most certainly (very) complicated relationships between inputs and targets. Probably lots of things change together

- ▶ Examples: **covariate shift** from one individual to the other, **concept drift** from one cell type to the other.
- ▶ Quick (imperfect) fix: Normalize data
- ▶ Warning: Normalizing also means loosing information!

# Selection bias



# Multiple studies



# Towards multi-environment learning and meta-learning?

- ▶ Other learning procedures exist and can be adapted to transcriptomics
  - ▶ **Multi-environment training:** assume that data comes from different environments
  - ▶ **Meta-learning:** Learn to adapt fast to a new environment
- 

## The TCGA Meta-Dataset Clinical Benchmark

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Mandana Samiei<sup>1</sup> Tobias Würfl<sup>2</sup> Tristan Deleu<sup>3</sup> Martin Weiss<sup>3</sup>  
Francis Dutil<sup>5</sup> Thomas Fevens<sup>1</sup> Geneviève Boucher<sup>3,4</sup> Sébastien Lemieux<sup>3,4</sup>  
Joseph Paul Cohen<sup>3</sup>

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- **Acquisition biases**
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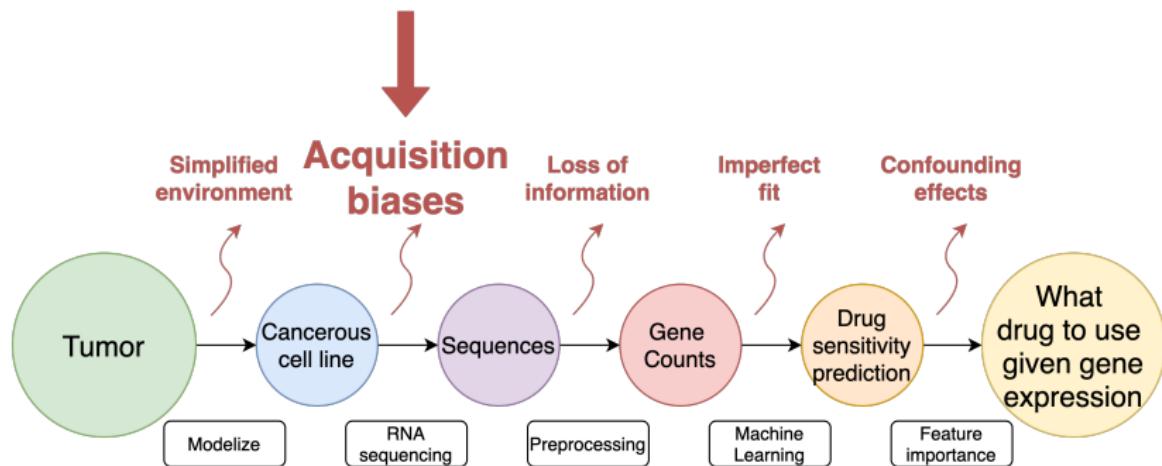
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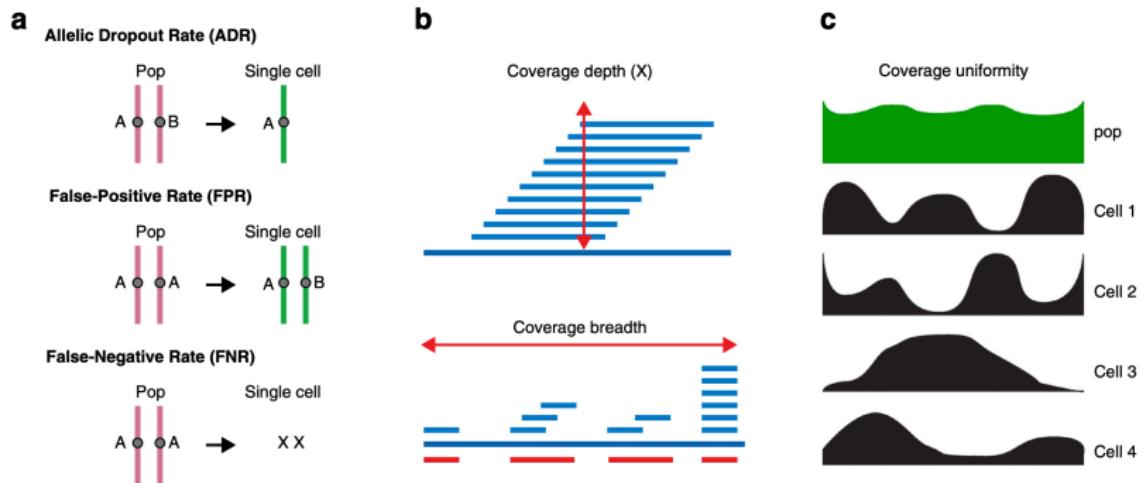
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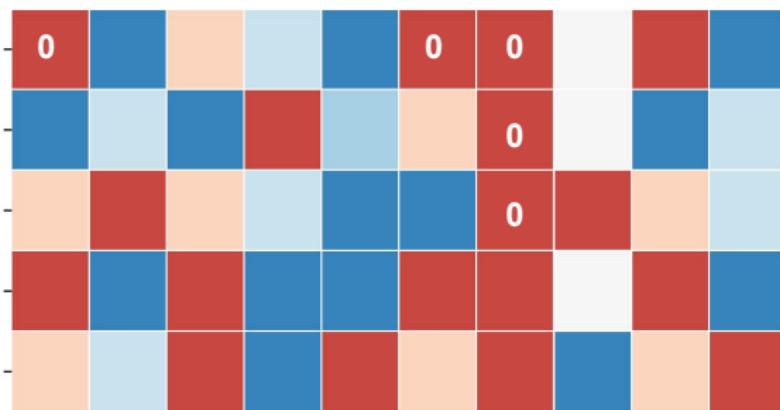
# The acquisition process



**Figure 3 Technical errors and coverage in single-cell sequencing data.** (a) Technical errors that occur in single-cell sequencing (SCS) data include: false-positive errors, allelic dropout events and false-negative errors due to insufficient coverage. 'Pop' indicates a population of cells. (b) Coverage metrics in SCS data include coverage depth and total physical coverage, or breadth. (c) Coverage uniformity, or 'evenness' in SCS data can vary from cell to cell, but is often more uniform in standard genomic DNA sequencing experiments using populations of cells.

## Dropout in single cell

Gene counts



# Denoising Autoencoder

- ▶ How to denoise the data?
- 

## Extracting and Composing Robust Features with Denoising Autoencoders

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Yoshua Bengio

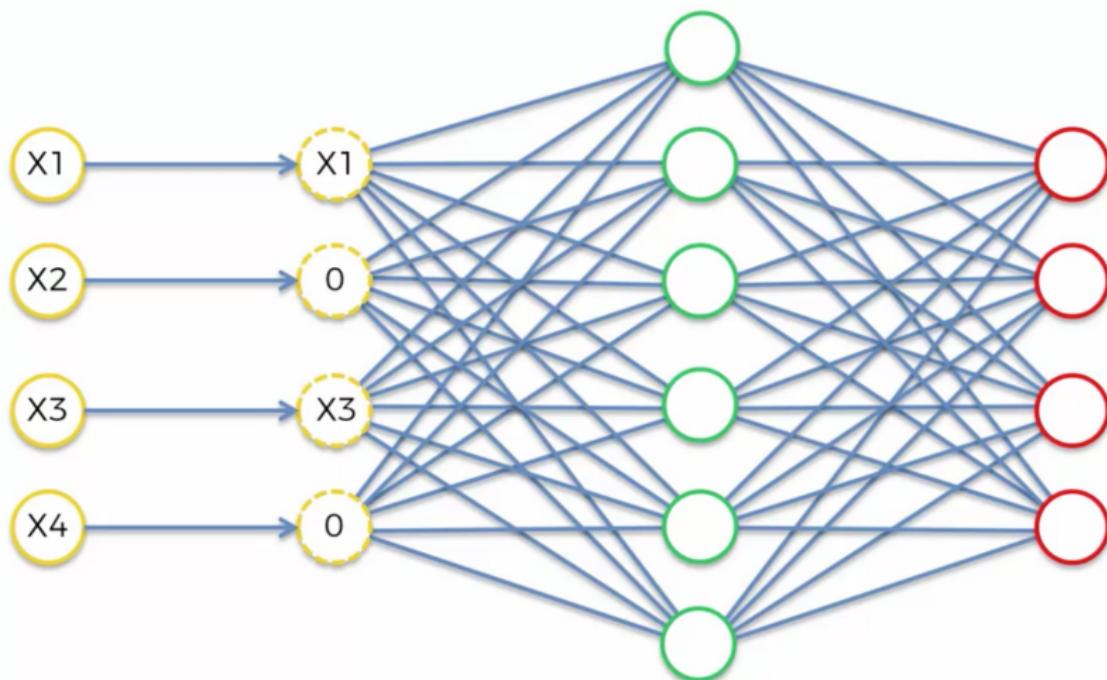
BENGOY@IRO.UMONTREAL.CA

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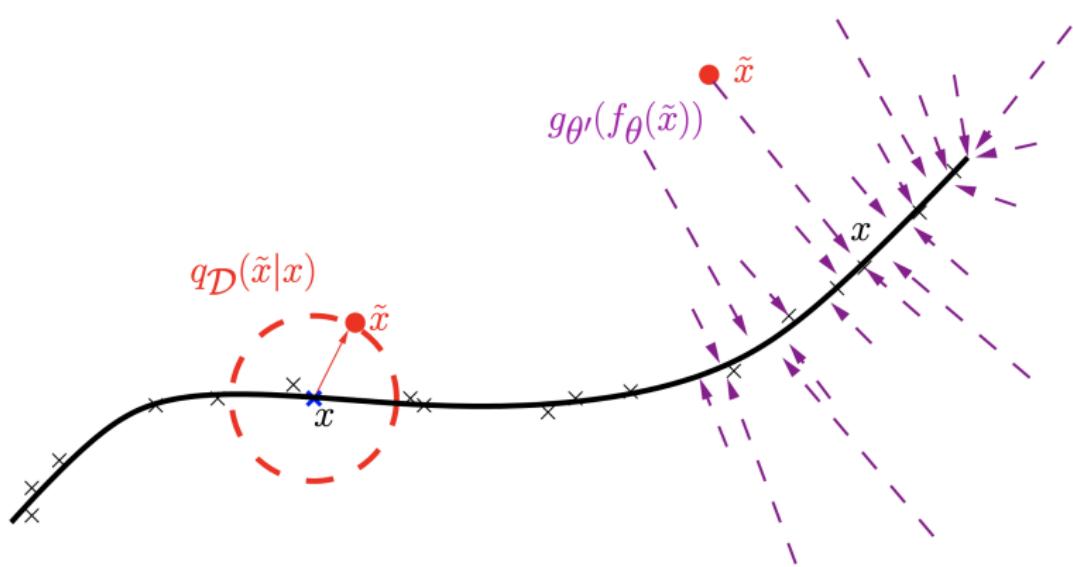
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## Denoising Autoencoder



# Denoising Autoencoder



Tan *et al.* BMC Bioinformatics (2017) 18:512  
DOI 10.1186/s12859-017-1905-4

BMC Bioinformatics

METHODOLOGY ARTICLE

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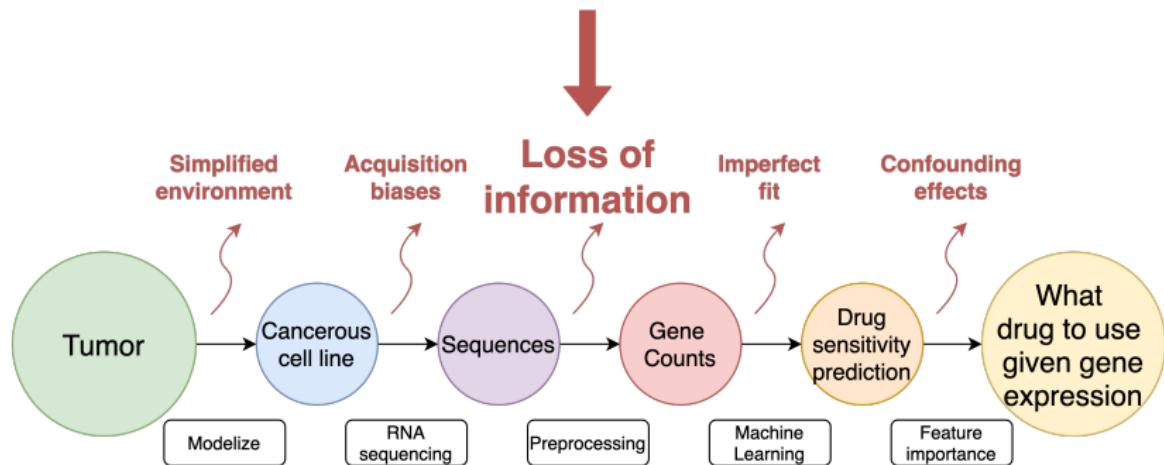
## ADAGE signature analysis: differential expression analysis with data-defined gene sets

Jie Tan<sup>1</sup>, Matthew Huyck<sup>2,3</sup>, Dongbo Hu<sup>2</sup>, René A. Zelaya<sup>2</sup>, Deborah A. Hogan<sup>3</sup> and Casey S. Greene<sup>2\*</sup> 

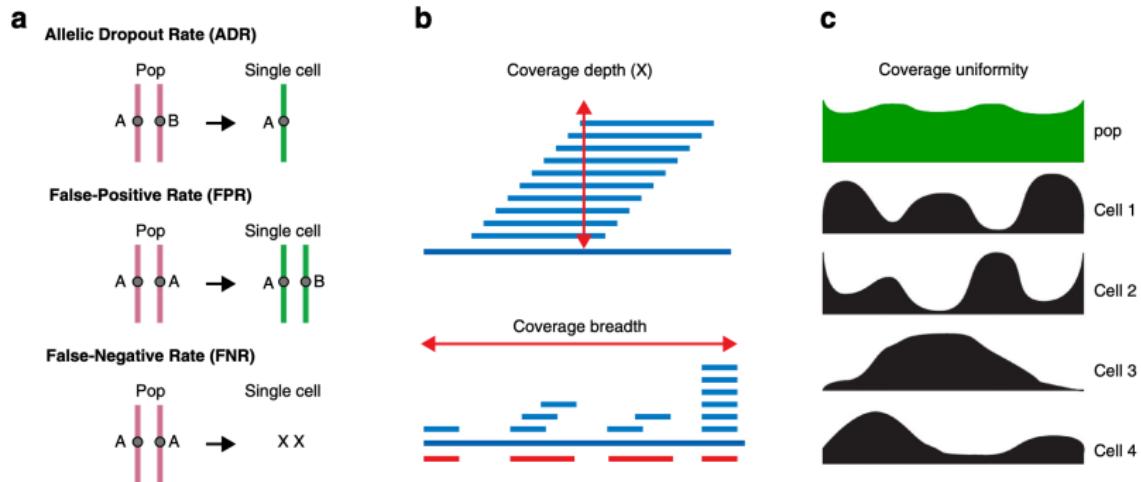
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# Different preprocessings

## A key step

Preprocessing is a key step that determines what data will be fed to our machine learning model. Each technique comes with limitation and drawbacks

- ▶ Need to account for different **total amounts of reads** in the different samples
- ▶ Need to account for the **lengths of the genes**
- ▶ Classic normalization methods: RPKM (Read Per Kilobase Million), FPKM (Fragment Per Kilobase Million), TPM (Transcripts Per Kilobase Million)
- ▶ **Alignment:** different reference genomes can be used from one dataset to the other!

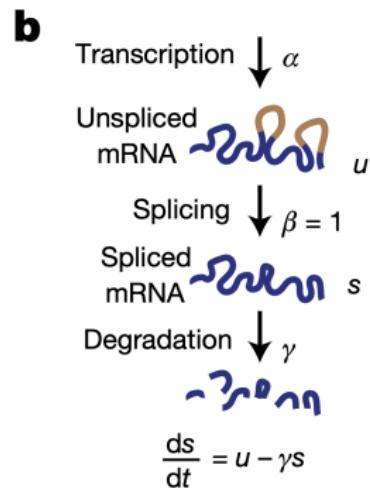
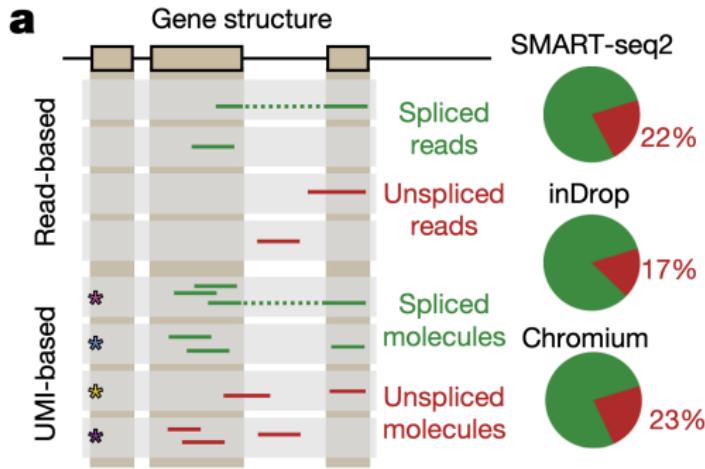
# Tremendous information loss!

Towards a more clever preprocessing?

A lot of **information is lost** during those preprocessing steps, **limiting what can be achieved downstream**. Moreover, the non standardized normalization and alignment limit our ability to transfer knowledge from one dataset to the other.

- ▶ Could we do better?
- ▶ Example: RNA velocity inference using splicing information.

# RNA velocity



you can visit <https://scvelo.org>

# RNA velocity

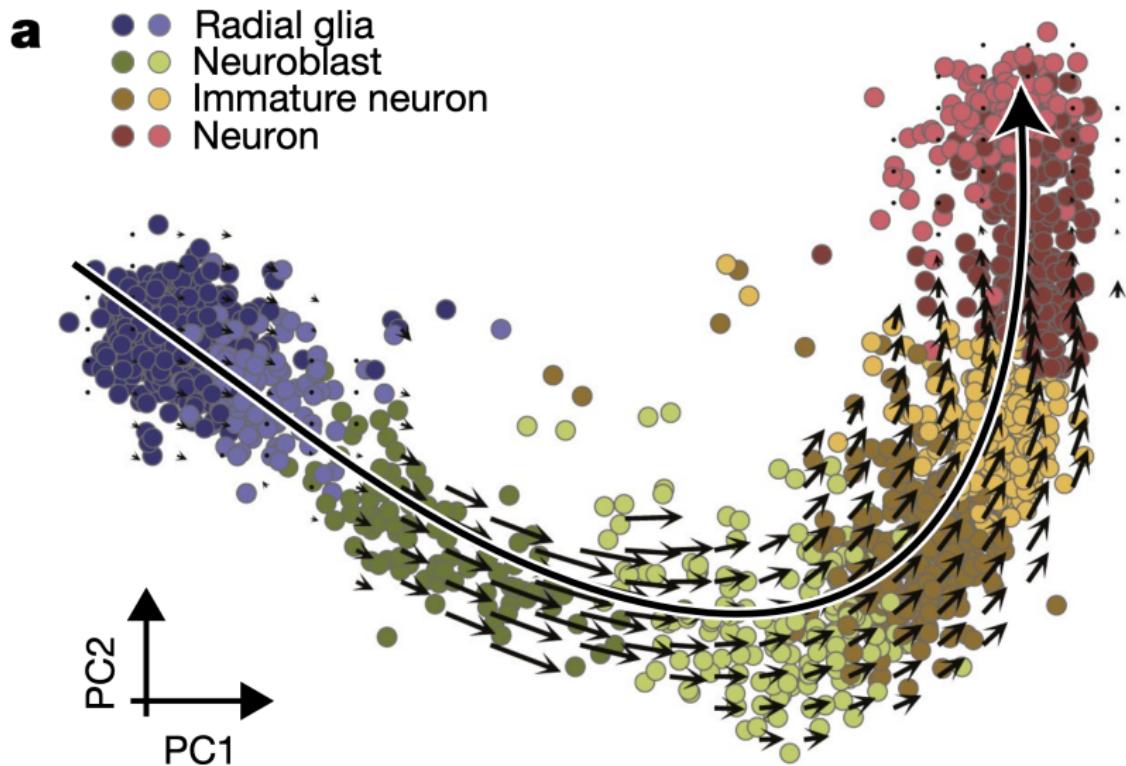


Figure taken from *RNA velocity of single cells*

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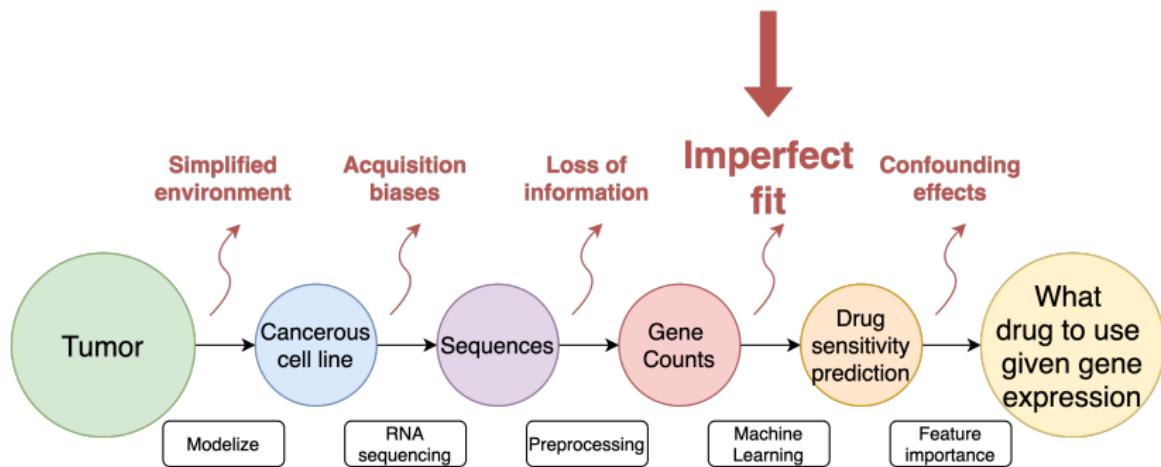
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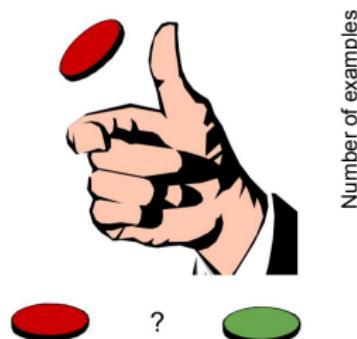
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## Fat data



Figure: When data has lots of feature but few examples, data is called fat

# Fat data: Beware of spurious correlations!

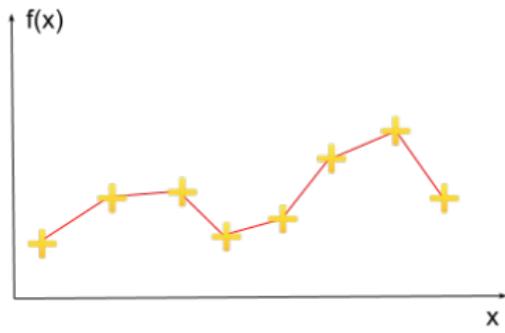


- ▶ **Spurious correlations:** with fat data, features can be highly correlated together out of chance!
- ▶ Example: binary, independent features and 2 samples. Some features will have a correlation of 1 out of chance!

## Conclusion

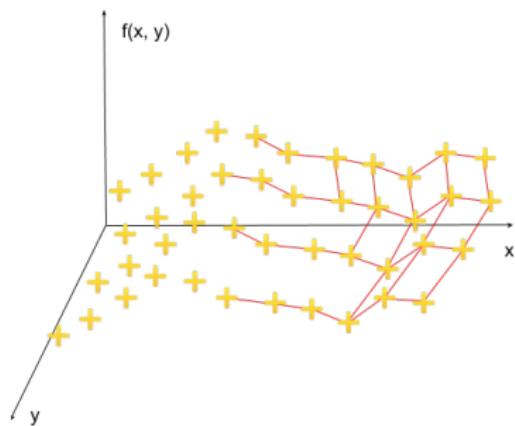
**In high dimension, you need lots of examples!**

## Estimate a function of 1 variable



- ▶ We want a *high* density of samples (distance between two sample points  $< \frac{1}{N}$ ) in order to estimate the function reliably
- ▶  $N$  samples to estimate the function on  $[0, 1]$

## Estimate a function of 2 variables



- ▶ To have the same density of sample in 2 dimensions we need  $N^2$  samples
- ▶ In dimension 3, we need  $N^3$  samples...

# And with 20,000 dimensions?

calculator

All Shopping Books News Images More Settings Tools

About 1,870,000,000 results (0.45 seconds)

⌚ 2<sup>20000</sup> =

**Infinity**

Rad	Deg	x!	(	)	%	AC
Inv	sin	ln	7	8	9	÷
π	cos	log	4	5	6	×
e	tan	√	1	2	3	-
Ans	EXP	x <sup>y</sup>	0	.	=	+

More info

# Volumes in high dimension

Cover the space in  $d$  dimensions

The volume of a hypercube  $[0, a] \times [0, a] \times \dots \times [0, a]$  of dimension  $d$  is :

$$a^d$$

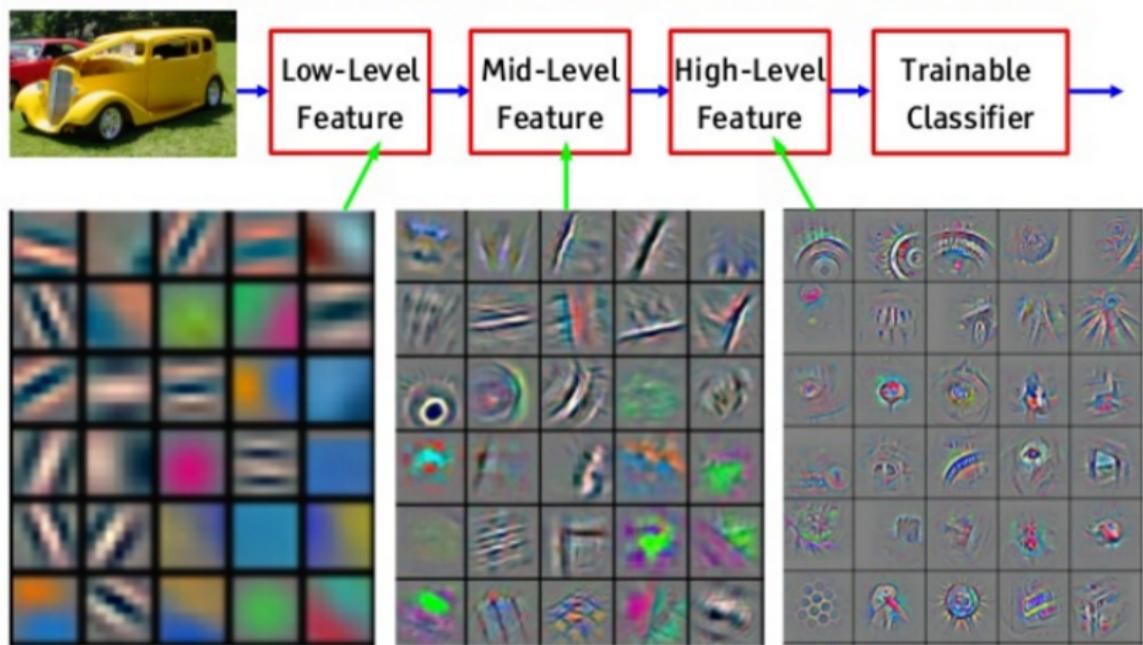
**In high dimension, volumes are very big!**

- ▶ This is why **kNN does not work in high dimension**
- ▶ How to estimate a function in dimension 20k?
- ▶ **Machine learning is about making the right assumptions**  
to overcome the need for many samples.

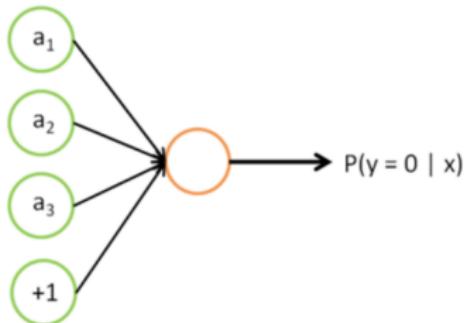
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## Automatic feature extraction

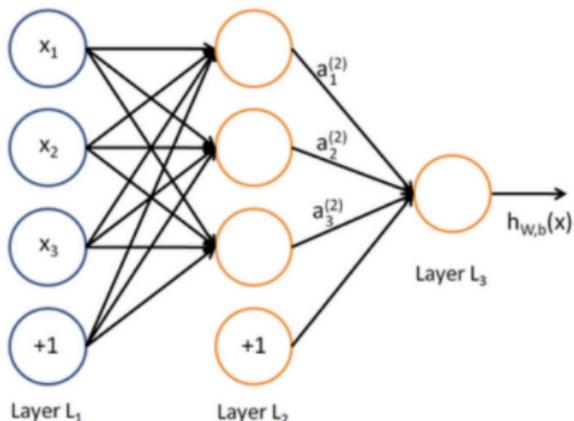


# Comparison with logistic regression



Input  
(features)      Logistic  
classifier

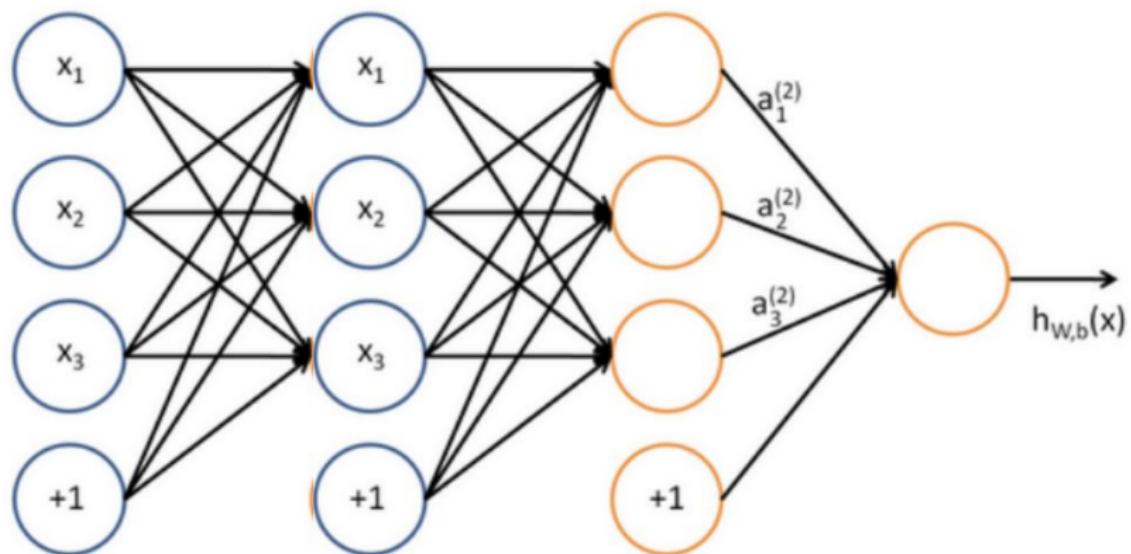
**Logistic Regression**



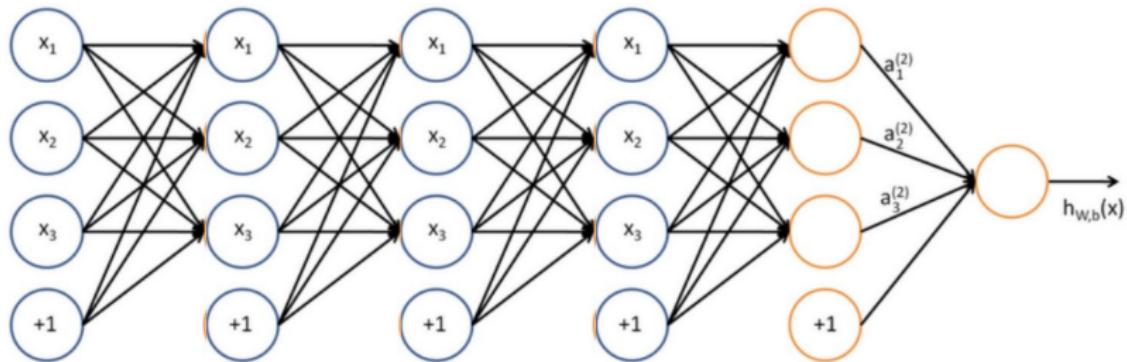
**Neural Network**

- ▶ 1 hidden layer NN: the features fed to the logistic regression are learnt

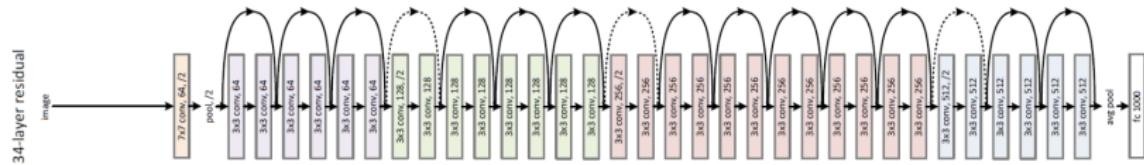
## Going deeper!



# Going deeper!

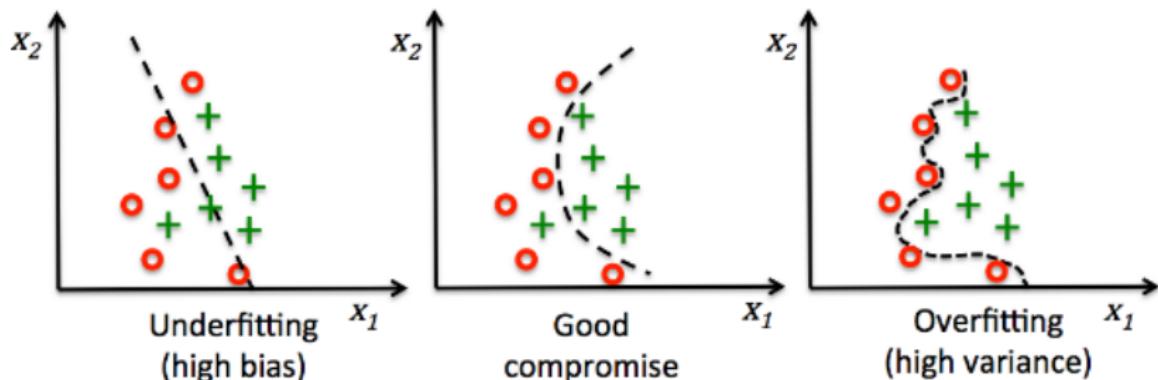


# Going deeper!



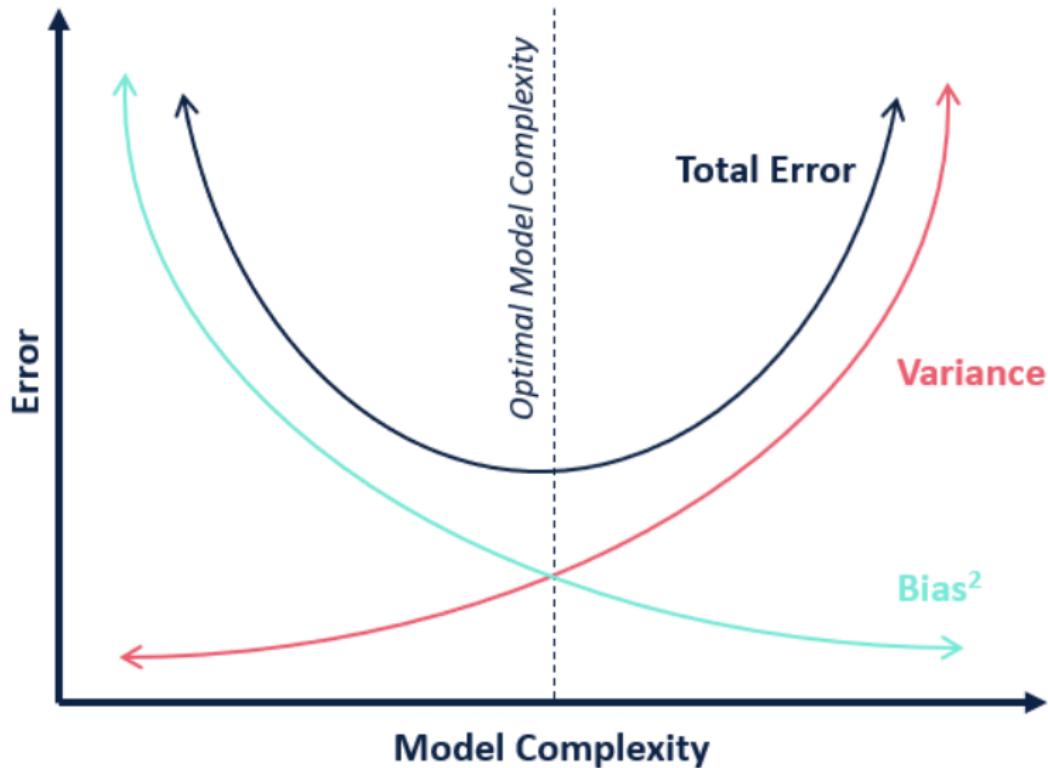
- ▶ Example: **Resnet**, a 34 layer network!
- ▶ Needs additional trick (residuals) for forward and backward signals to pass through

# The bias variance trade-off



- ▶ High model complexity: high variance low bias
- ▶ Low model complexity: low variance high bias
- ▶ **You have to choose the right model complexity!**  
(regularization, model depth,...)

## The bias variance trade-off



# Why does ML work so well in Computer Vision?

Why does ML work so well in Computer Vision?

People have made simplifying assumptions that hold well in Computer Vision

- ▶ Let us dive into the details of CNNs

## Fully connected

- ▶  $X_L$  and  $X_{L+1}$  activations vectors in layers  $L$  and  $L + 1$
- ▶  $X_{L+1} = \sigma(W_L X_L + B)$

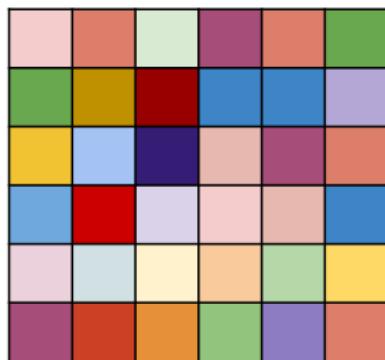
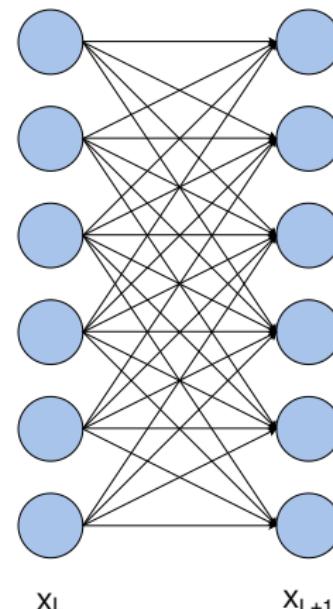


Figure: matrix  $W_L$



## Fully connected

$$x_{L+1} = \sigma(X_L \times W + B)$$

The diagram illustrates a fully connected layer. On the left, six blue circles represent the input vector  $x_L$ . In the center, a 6x6 grid represents the weight matrix  $W$ , showing various colored squares (pink, orange, green, yellow, red, purple) indicating different weights. To the right, another set of six blue circles represents the output vector  $x_{L+1}$ .

The equation  $x_{L+1} = \sigma(X_L \times W + B)$  describes the computation. The input  $x_L$  is multiplied by the weight matrix  $W$ , and the result is added to the bias vector  $B$ . The function  $\sigma$  (not explicitly shown in the diagram) applies element-wise to the result to produce the final output  $x_{L+1}$ .

## Convolutional layer

- ▶  $X_{L+1} = \sigma(W_L X_L + B)$
- ▶ parameter sharing :  
constraints on  $W_L$

0.2	-0.7					
1.4	0.2	-0.7				
	1.4	0.2	-0.7			
		1.4	0.2	-0.7		
			1.4	0.2	-0.7	
				1.4	0.2	

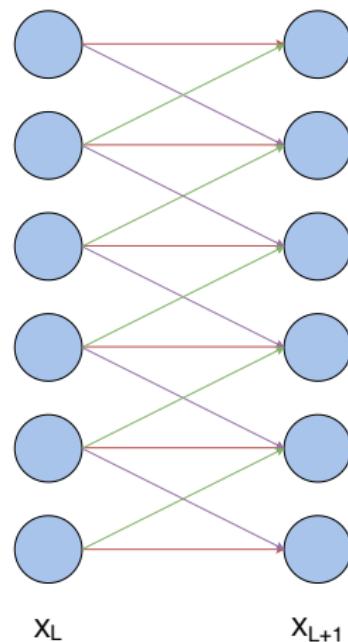


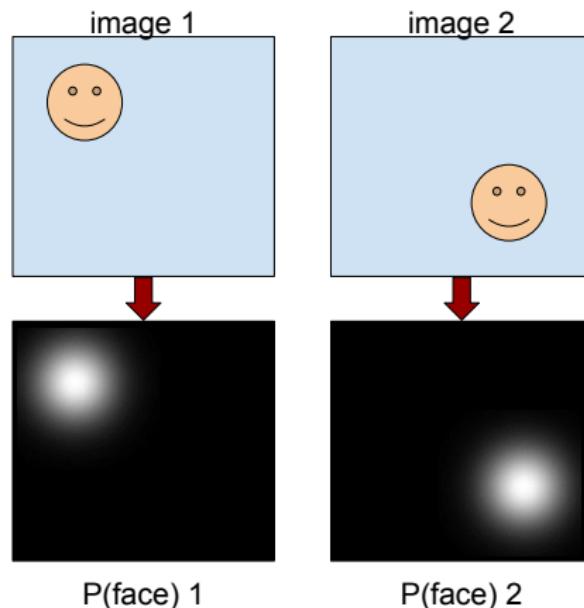
Figure: matrix  $W_L$  with constraints

## Convolutional layer

$$X_{L+1} = \sigma(X_L \times W + B)$$

The diagram illustrates a convolutional layer operation. On the left, a vertical stack of six blue circles represents the input features  $X_L$ . In the center, a 3x3 weight matrix  $W$  is shown, containing values 0.2, -0.7, 1.4, 0.2, -0.7, 1.4, 0.2, -0.7, and 1.4. To the right of the matrix, the expression  $\times W + B$  is shown, where  $X$  is represented by a vertical stack of six blue circles and  $B$  is represented by a vertical stack of six blue circles below it. The result of the multiplication is a vertical stack of six blue circles.

# Equivariance



# Equivariance

$$\begin{matrix} & \begin{matrix} 1.4 \\ 0.2 \\ -0.7 \\ \vdots \\ \vdots \end{matrix} \end{matrix} = \sigma \left( \begin{matrix} & \begin{matrix} 0.2 & -0.7 & \vdots & \vdots & \vdots & \vdots \end{matrix} \\ \begin{matrix} 1.4 \\ 0.2 \\ -0.7 \\ \vdots \\ \vdots \end{matrix} & \begin{matrix} 1.4 & 0.2 & -0.7 & \vdots & \vdots & \vdots \\ 0.2 & 1.4 & 0.2 & -0.7 & \vdots & \vdots \\ -0.7 & -0.7 & 1.4 & 0.2 & -0.7 & \vdots \\ \vdots & \vdots & \vdots & 1.4 & 0.2 & -0.7 \\ \vdots & \vdots & \vdots & 0.2 & 1.4 & 0.2 \\ \vdots & \vdots & \vdots & -0.7 & -0.7 & 1.4 \end{matrix} \end{matrix} \right) \times \begin{matrix} & \begin{matrix} 1 \\ \vdots \\ \vdots \end{matrix} \end{matrix} + \mathbf{B})$$

# Equivariance

$$\begin{matrix} & & \\ & & \\ & & \\ & & \\ \text{=} & \sigma( & \begin{matrix} & & & & & \\ 0.2 & -0.7 & & & & \\ & 1.4 & 0.2 & -0.7 & & \\ & & 1.4 & 0.2 & -0.7 & \\ & & & 1.4 & 0.2 & -0.7 \\ & & & & 1.4 & 0.2 \\ & & & & & 1.4 \end{matrix} & ) + B \end{matrix}$$

The diagram illustrates a linear transformation process. On the left, a vertical vector is shown as a stack of colored segments: white, green (labeled 1.4), pink (labeled 0.2), purple (labeled -0.7), and white. This is followed by an equals sign and the start of a function call,  $\sigma($ . Inside the function call, there is a 6x6 matrix with colored entries: the main diagonal consists of 1.4s, the second row has 0.2s in the first two columns and -0.7s in the next three, and the third column has -0.7s in the top four rows. To the right of the matrix is a plus sign and the end of the function call,  $) + B$ . To the right of the plus sign is another vertical vector, consisting of white, red (labeled 1), and white segments.

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  - The curse of dimensionality
  - Making the right assumptions: inspiration from Comp. Vis.
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  - Feature importance for deep models
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- 5 Conclusion

## What are the right assumptions for gene expression data?

- We would like to add **prior knowledge** and/or make **biologically grounded assumptions**

What are the right assumptions for gene expression data?

- Use gene interaction graphs?
- Assume similarity of processes between genes?
- Assume similar perturbation response between individuals/species?

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# Incorporate Graph Prior Knowledge?

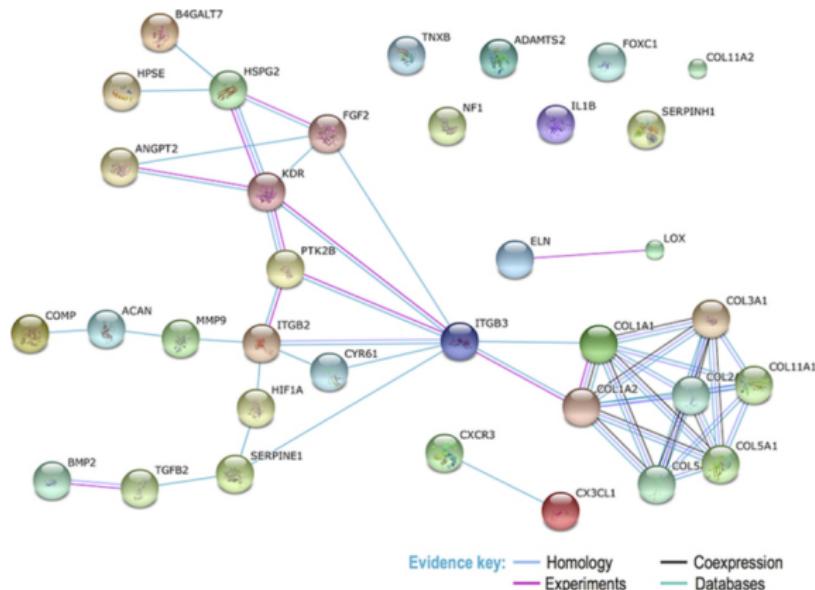
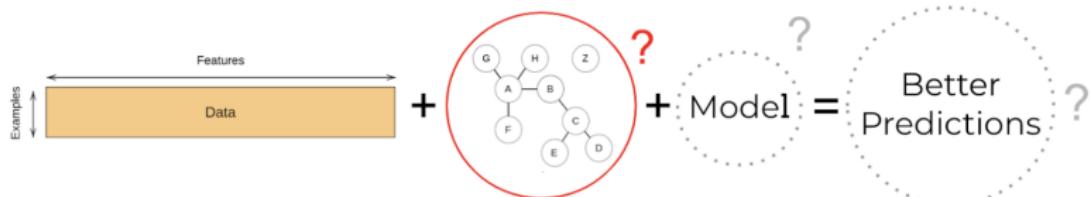


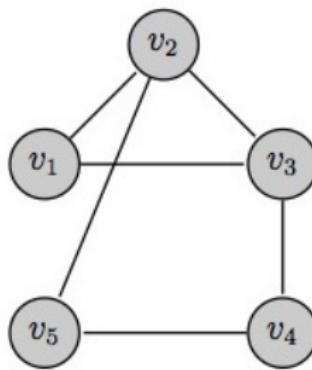
Figure: Example of a curated graph: StringDB

# Incorporate Graph Prior Knowledge?



- ▶ **Idea:** Use gene interaction graphs to **constrain a ML model**
- ▶ 2 questions:
  - ▶ How to use the graph in a machine Learning model?
  - ▶ Are curated graphs well suited for gene expression data?

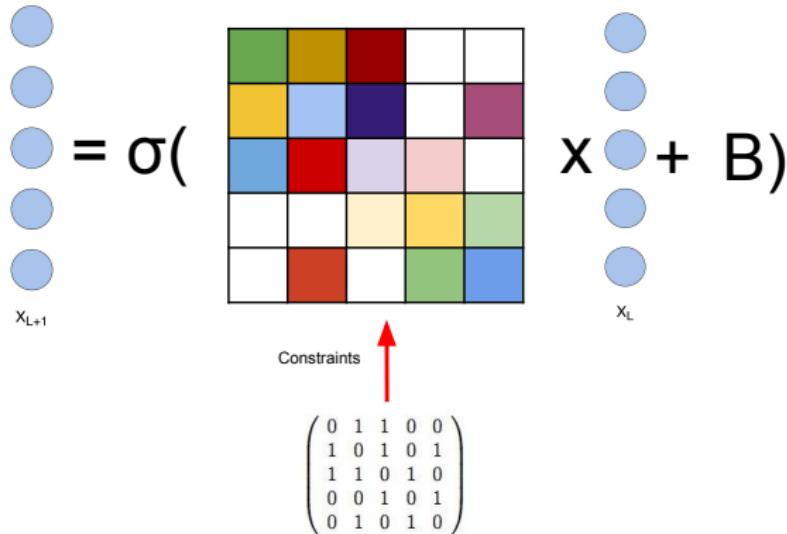
## Adjacency matrix of a graph



$$A_G = \begin{pmatrix} 0 & 1 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 \\ 1 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 \\ 0 & 1 & 0 & 1 & 0 \end{pmatrix}$$

- ▶ We can represent an undirected graph by its adjacency matrix
- ▶ **Adjacency matrix:** the value at coordinates  $(i, j)$  is 1 if nodes  $i$  and  $j$  are connected, 0 otherwise

## Constraining the model: a simple example



- ▶ This is one simple example
- ▶ Deep learning with graphs is a dynamic field of research!

# It does not seem to work!



- ▶ Curated graphs do not seem to be well suited for gene expression data when using all genes
- 

## Analysis of Gene Interaction Graphs as Prior Knowledge for Machine Learning Models

---

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**Martin Weiss**  
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**Vincent Frappier**  
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**Theodore J. Perkins**  
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**Geneviève Boucher**  
Institute for Research in Immunology and Cancer  
Université de Montréal  
Montréal, Canada

**Joseph Paul Cohen**  
Mila, Université de Montréal  
Montréal, Canada

## A current debate

Graph biased feature selection of genes is better than random for many genes

Jake Crawford \*† Casey S. Greene ‡‡

- ▶ A current debate: What if you choose the right genes?

### What's next?

Could there be an interplay between graph curation and ML model performance?

- ▶ Identify genes that hurt performance

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# Parameter sharing among genes?

## Low dimensional state of the cell

Gene expressions are far from being independent, the **data has a lot of structure.**

- ▶ Idea: Use **Representation Learning** with low dimensional latent spaces (e.g. dim  $\sim 500$ )
  - ▶ We can perform analysis in the lower dimensional latent space (e.g. fit a prediction model)
  - ▶ But we still need a matrix of shape (20k, 500): **lots of parameters!**
- ▶ Lots of things (regulatory processes, effects) might be similar among genes
- ▶ We can **share parameters among genes** → Diet Networks

Published as a conference paper at ICLR 2017

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## DIET NETWORKS: THIN PARAMETERS FOR FAT GENOMICS

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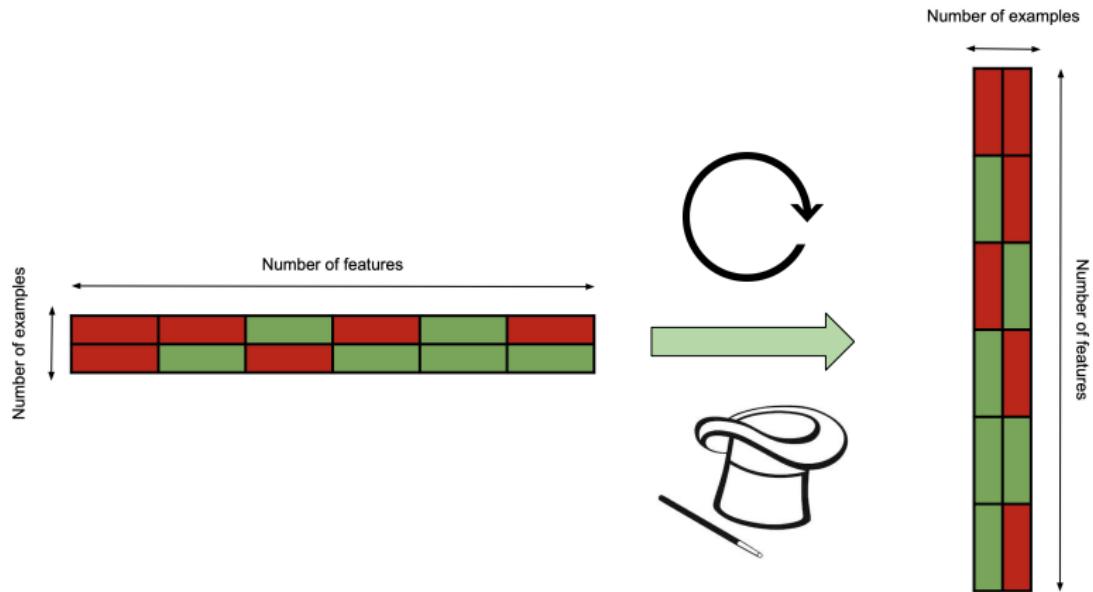
**Yoshua Bengio**

Montreal Institute for Learning Algorithms

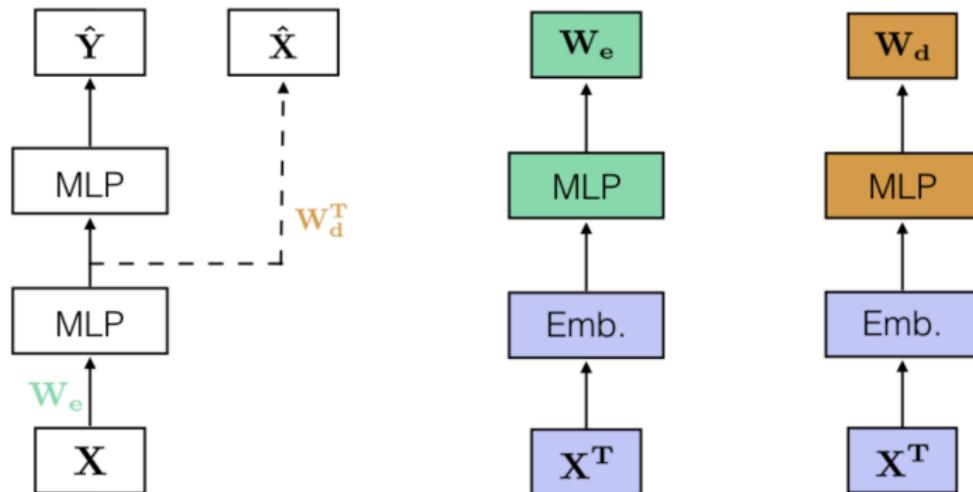
Montreal, Quebec, Canada

yoshua.umontreal@gmail.com

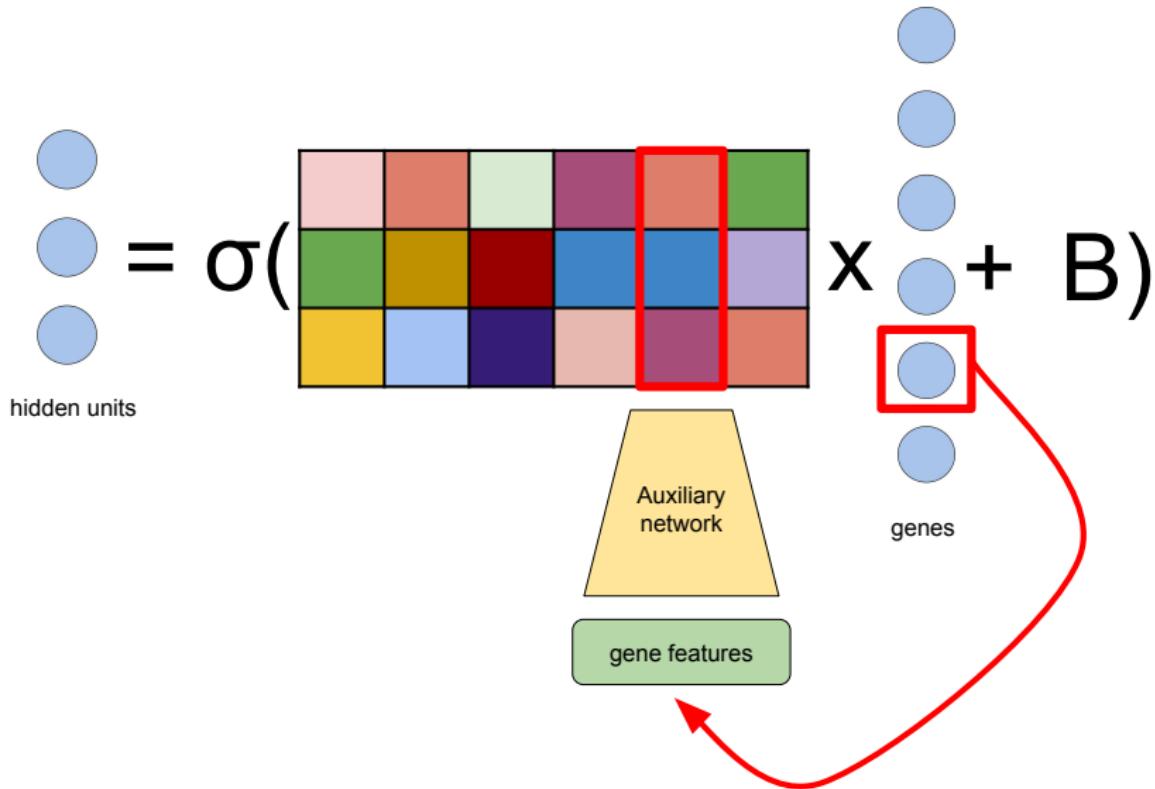
# Diet Networks: Magic trick!



# Diet Networks



## Diet Networks



# Diet Networks



- ▶ Not yet applied successfully to gene expression data!
- ▶ The features that are fed to the auxiliary networks have to contain **the relevant information about the task you want to solve!**

## Open question

What features to use for gene expression data?

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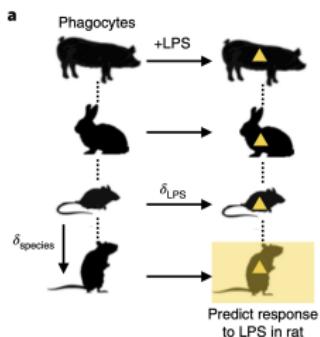
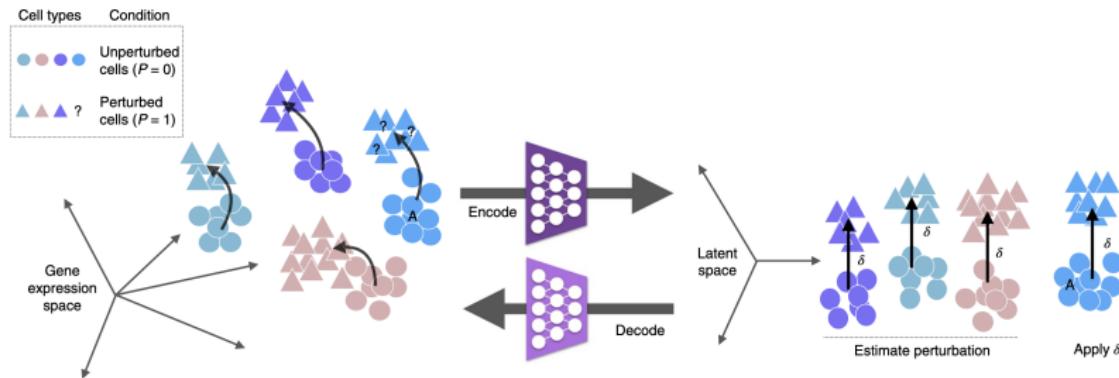
# Response to perturbation



## scGen predicts single-cell perturbation responses

Mohammad Lotfollahi <sup>1,2</sup>, F. Alexander Wolf <sup>1\*</sup> and Fabian J. Theis <sup>1,2,3\*</sup>

# Response to perturbation



- ▶ Observations: **arithmetic in latent space seem to make sense** (e.g. Word2Vec)
- ▶ Assumption: **response to perturbation is the same in latent space across species/cell types**

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- Preprocessing

## 3 The supervised learning pipeline

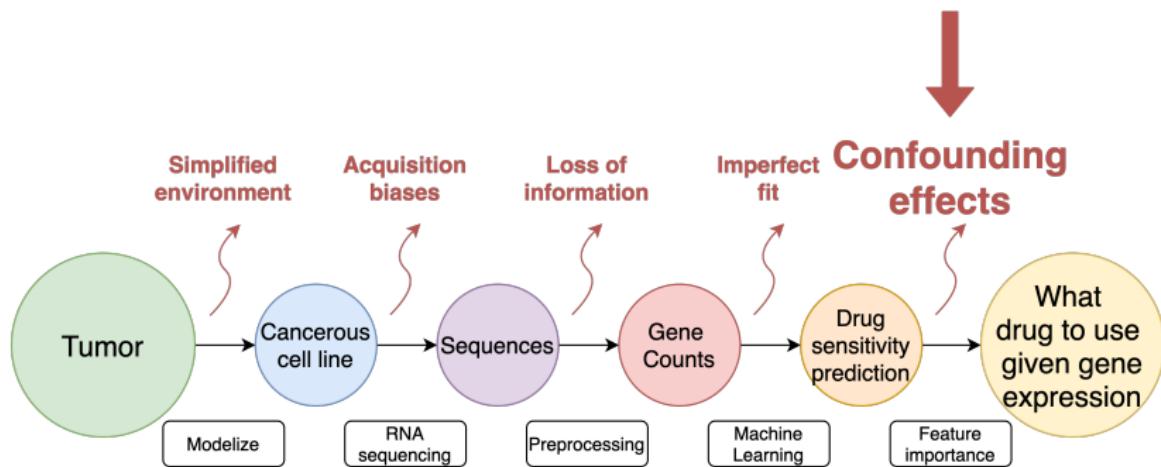
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# Overview



Want to get some explanations from the model?

How to better understand what is happening?

How to know what the model is *looking at*? Let us investigate feature importance techniques and their limitations

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## Deep Inside Convolutional Networks: Visualising Image Classification Models and Saliency Maps

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**Karen Simonyan**

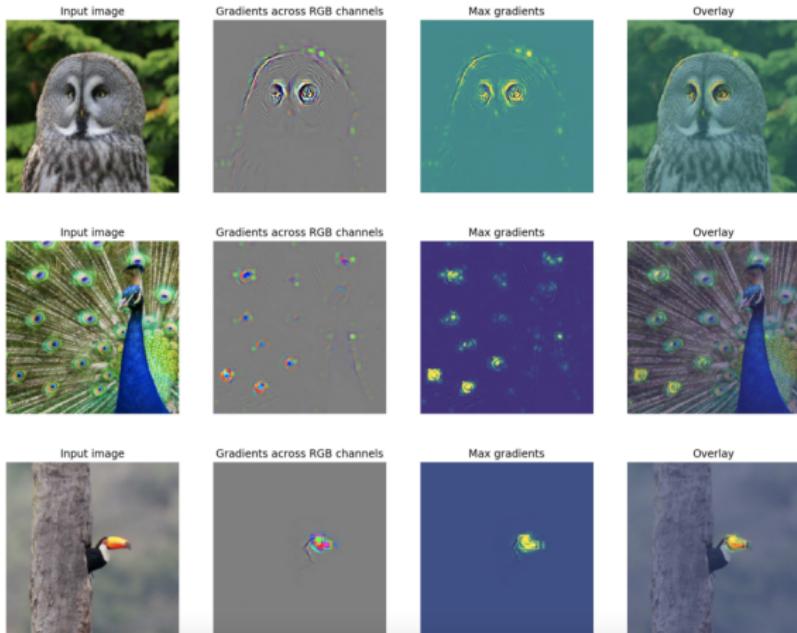
**Andrea Vedaldi**

**Andrew Zisserman**

Visual Geometry Group, University of Oxford

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# Saliency Maps

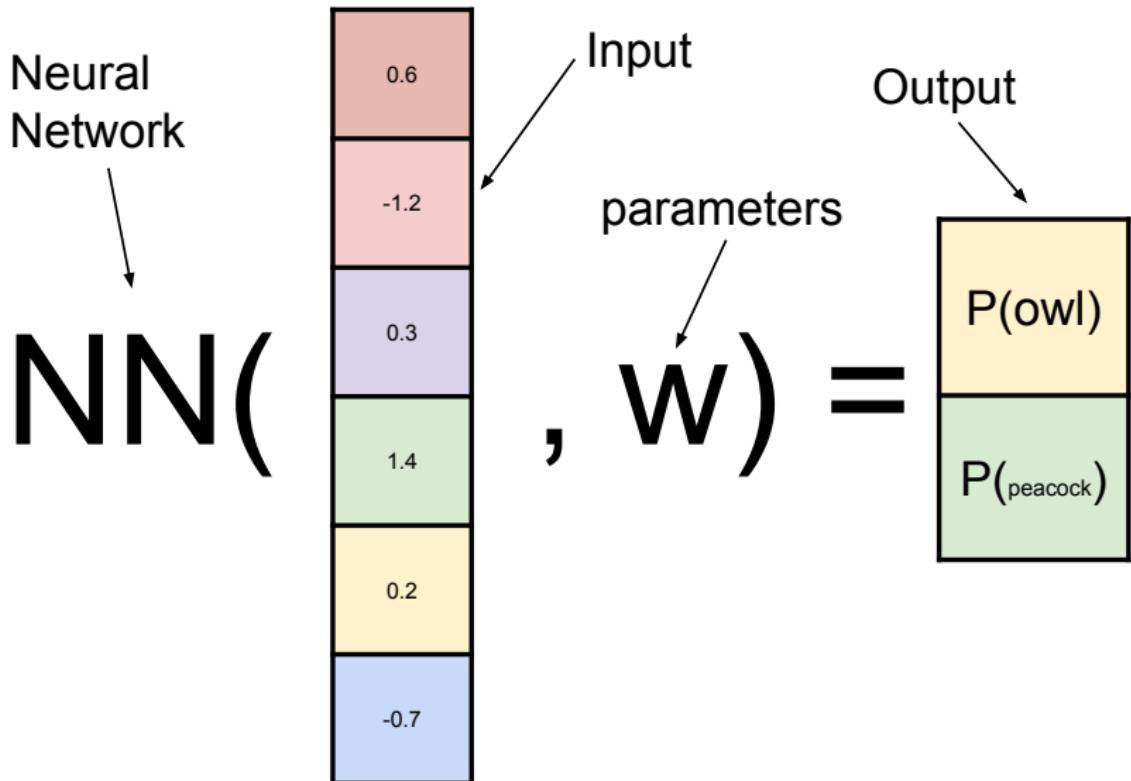


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Figure taken from

<https://mc.ai/feature-visualisation-in-pytorch%E2%80%8A-%E2%80%8Asaliency-maps/>

## Parametric models



# Usual training

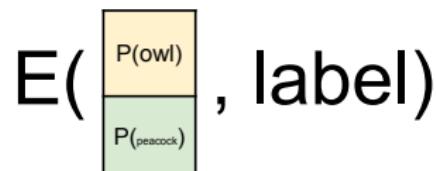
## How is a model usually trained?

- ▶ Iterate:
  - ▶ Compute the error for a given input
  - ▶ Compute the gradient of the error w.r.t each parameter  $\frac{\partial E}{\partial w_i}$  using backpropagation
  - ▶ Update the parameters in order to lower the error:

$$w_i^{t+1} = w_i^t - \lambda \frac{\partial E}{\partial w_i}$$

### Note

This is called **Stochastic Gradient Descent**



- ▶  $\lambda$  is called the learning rate
- ▶ In practice we use several inputs at once (in a **batch**)
- ▶ Other *gradient descent* algorithms exist (e.g. *Adam*)

# Back to the computation graph

$$\frac{1}{1 + e^{-(w_0x_0 + w_1x_1 + w_2)}}$$

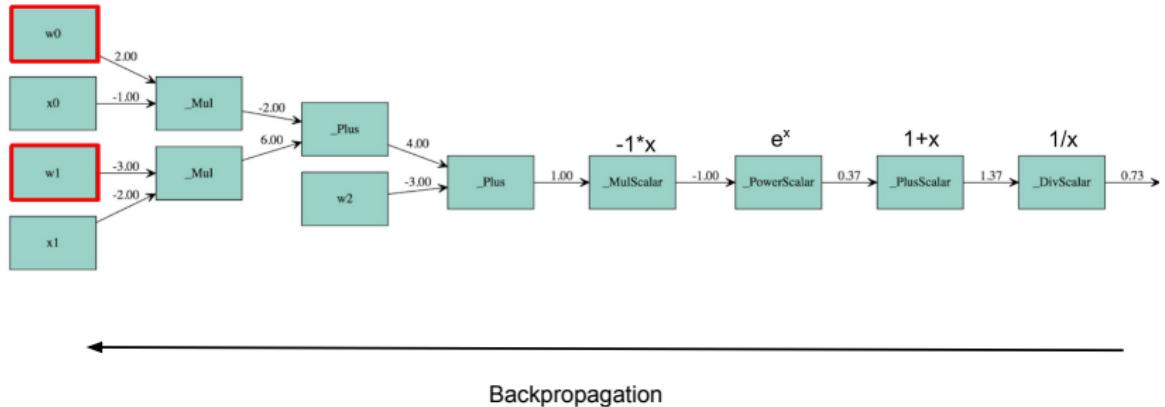


Figure by J. P. Cohen

# Back to the computation graph

$$\frac{1}{1 + e^{-(w_0x_0 + w_1x_1 + w_2)}}$$

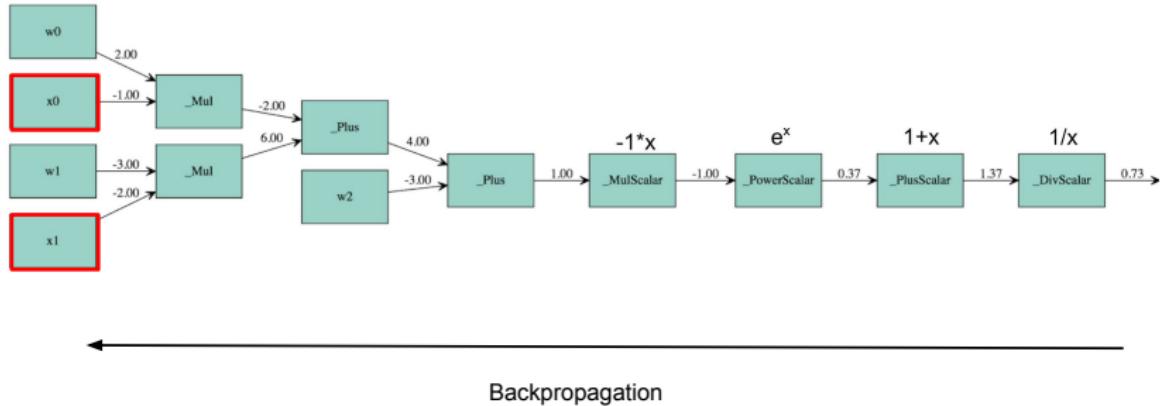


Figure by J. P. Cohen

# Saliency Maps

$\frac{\partial P(owl)}{\partial X_1}$
$\frac{\partial P(owl)}{\partial X_2}$
$\frac{\partial P(owl)}{\partial X_3}$
$\frac{\partial P(owl)}{\partial X_4}$
$\frac{\partial P(owl)}{\partial X_5}$
$\frac{\partial P(owl)}{\partial X_6}$

- ▶ For a given class probability, e.g.  $P(owl)$ , compute the **gradient with respect to the input**  $\frac{\partial P(owl)}{\partial x_i}$
- ▶ We get a real number for each input feature

## Interpretation

$\frac{\partial P(owl)}{\partial x_i}$ : how much the class probability  $P(owl)$  depends on feature  $x_i$

## Inceptionism: Going Deeper into Neural Networks

Wednesday, June 17, 2015

Posted by Alexander Mordvintsev, Software Engineer, Christopher Olah, Software Engineering Intern and Mike Tyka, Software Engineer

### Intuition

**Make the model dream** the input that would maximize a given class probability

- ▶ Gradient ascent in the input space to maximize a given class probability

# Deep Dream: Gradient Ascent in the input space

- ▶ Update the input by iterating:

$$\begin{matrix} X'_1 \\ X'_2 \\ X'_3 \\ X'_4 \\ X'_5 \\ X'_6 \end{matrix} = \begin{matrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ X_5 \\ X_6 \end{matrix} + \mathcal{E}$$

The diagram illustrates the iterative update of input features. It shows two vertical vectors of size 6. The first vector, labeled  $X'$ , has colored blocks corresponding to each feature: pink for  $X'_1$  and  $X'_2$ , purple for  $X'_3$ , green for  $X'_4$ , yellow for  $X'_5$ , and blue for  $X'_6$ . The second vector, labeled  $X$ , is entirely pink. An equals sign separates the two vectors, followed by a plus sign and a calligraphic letter  $\mathcal{E}$ . To the right of the equation is a vertical column of six matrices, each representing the gradient of the owl probability with respect to a specific input feature. The matrices are stacked vertically, with horizontal lines separating them. The first matrix is  $\frac{\partial P(\text{owl})}{\partial X_1}$ , the second is  $\frac{\partial P(\text{owl})}{\partial X_2}$ , the third is  $\frac{\partial P(\text{owl})}{\partial X_3}$ , the fourth is  $\frac{\partial P(\text{owl})}{\partial X_4}$ , the fifth is  $\frac{\partial P(\text{owl})}{\partial X_5}$ , and the sixth is  $\frac{\partial P(\text{owl})}{\partial X_6}$ .

# Deep Dream



- ▶ The input image has been updated in order to maximize the probability of the *dog* class

## At the end of the lecture

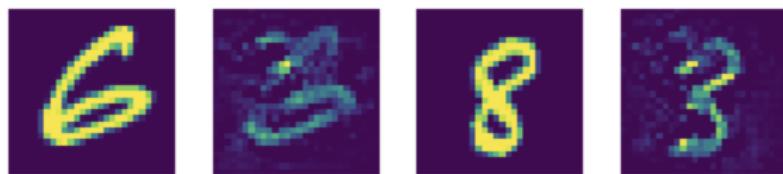


Figure: You will learn how to dream 3s from other numbers!

Visit the following notebook: **Google colab**

## Limitations of feature importance methods

### Limitations of feature importance methods

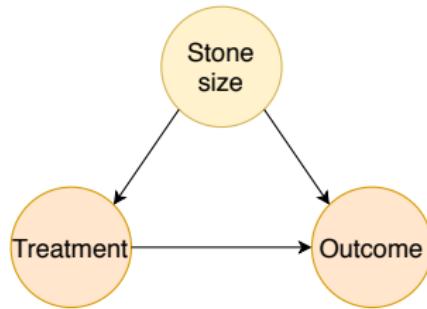
- ▶ Feature importance methods can be very noisy and difficult to interpret for gene expression data.
- ▶ **Feature importance does not provide a causal explanation as the prediction can be confounded.**

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# Simpson's paradox

	Treatment A	Treatment B
Small Stones	Group 1 93% (81/87)	Group 2 87% (234/270)
Large Stones	Group 3 73% (192/263)	Group 4 69% (55/80)
Both	78% (273/350)	83% (289/350)



- ▶ Two treatments for kidney stones
- ▶ **Which one is better?**

Figure: The size of kidney stones has an effect on both treatment assignment and outcome

## Simpson's paradox: an example from regression

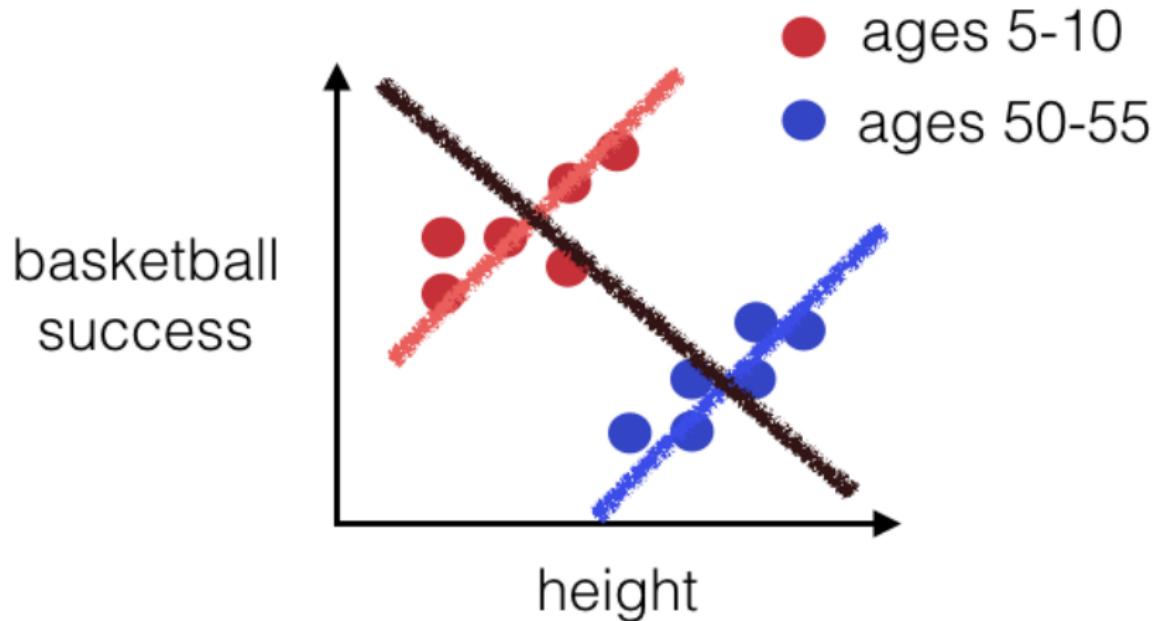
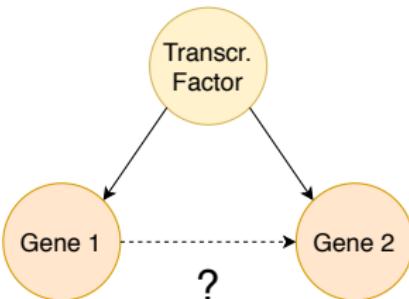
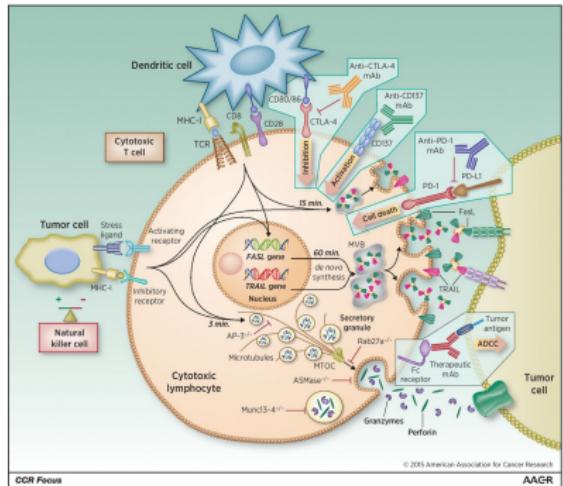


Figure: If we do not take age into account, we may conclude that height has a negative influence on basketball performance!

# How to understand the mechanisms of the cell?



- ▶ Would you like to identify the effect of a gene on another gene?
- ▶ Lots of confounders
- ▶ Current area of research (module networks...)

Figure taken from <https://clincancerres.aacrjournals.org/content/21/22/5047>

## Simpson's paradox: Take-away

### Take-away

If you are provided with data that contains several partitions<sup>1</sup>, you may want to **fit a model on a whole data** as well as **separate models for each partition**.

- ▶ You can analyse the *story* told by feature importance techniques applied to the different models.
- ▶ If all models agree, you have an interpretation that is robust across partitions (but no guarantee that the story is true...)
- ▶ If not, you may want to investigate further (lab experiments?)

**In transcriptomics, there are lot of unobserved confounders!**  
(e.g. non coding parts of the genome)

---

<sup>1</sup>e.g. cell lines, cell types, expression level of important Transcr. Factors

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# Conclusion

## Conclusion

- ▶ We investigated several challenges of Machine Learning when it is applied to transcriptomic data.
- ▶ **We need to design models making the right assumptions for gene expression data!**



# Practice time!

Visit the following notebook: [Google colab](#)

