Utiliser l'IA pour la recherche sur le cancer

Promesses et défis de l'apprentissage statistique pour la génomique

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institut Curie

Inserm

Machine learning

- Learn/build/define a **statistical model** using **data**
- **Model:** a function of input variables

$$f : \mathbb{R}^p \to \mathbb{R}$$
$$\vec{x} \mapsto \dots$$

```
def model(x):
    ...
    return ...
```

Supervised machine learning problems

- **Supervised** machine learning: learn a **predictive model**

Example: cancer detection from liquid biopsies

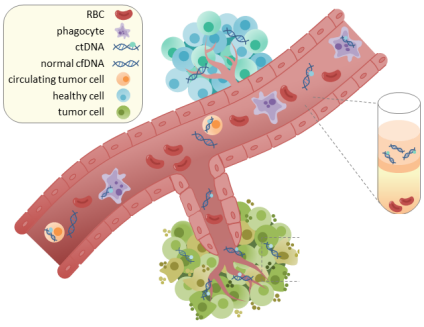
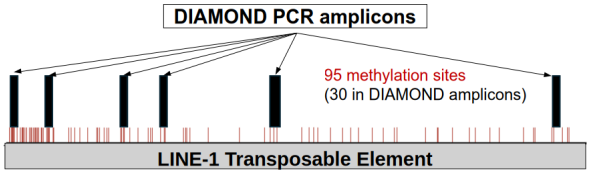


Image by Racheljunewong via Wikimedia Commons



ML task: predict **cancer vs healthy** status from the methylation levels of 30 LINE-1 CpG sites

M. Michel et al. **Noninvasive multicancer detection using DNA hypomethylation of LINE-1 retrotransposons** Clin Can Res 2024

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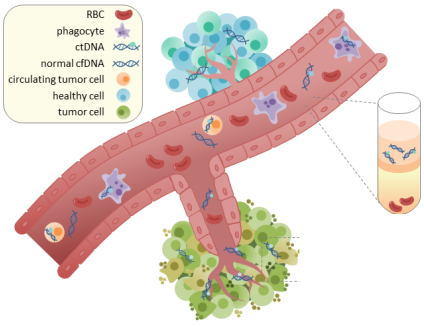

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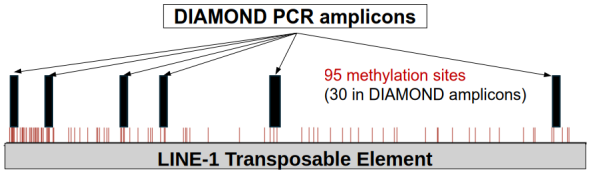

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Early ovarian	95% (n=18)	56% (n=45)
Metastatic colorectal	100% (n=75)	95%(n=17)
Sensitivity at 99% specificity		

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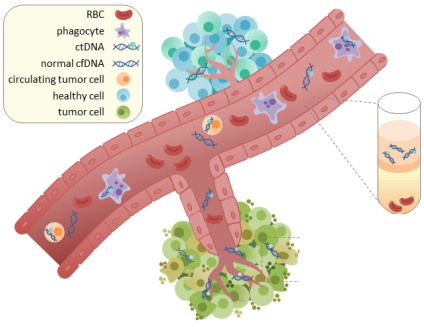

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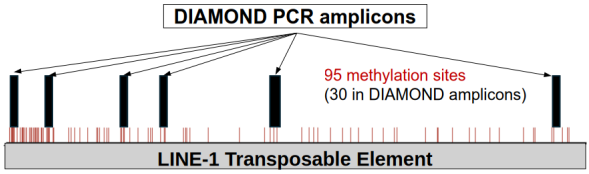

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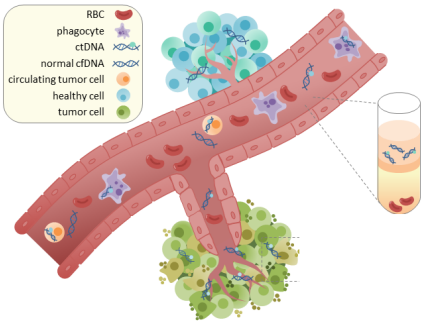

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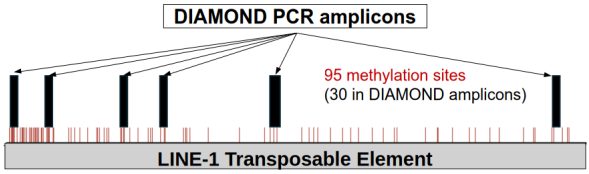

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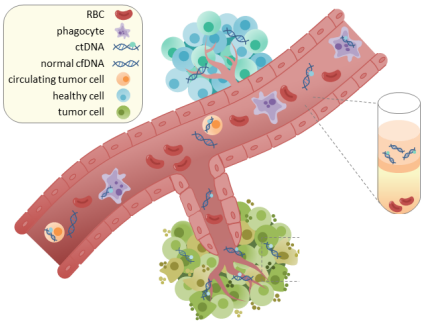

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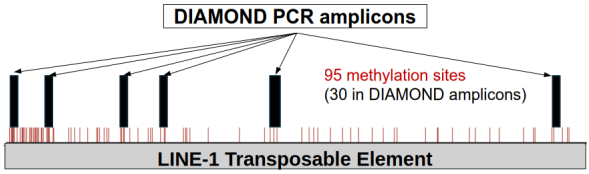

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Early ovarian (AUC)	1.00 (n=18)	0.96 (n=45)

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- when the data is **really big**
  - ImageNet: 14 million images
  - Llama4 training set: 30 trillion tokens

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Genomics does not fit this picture very well!

Talk outline

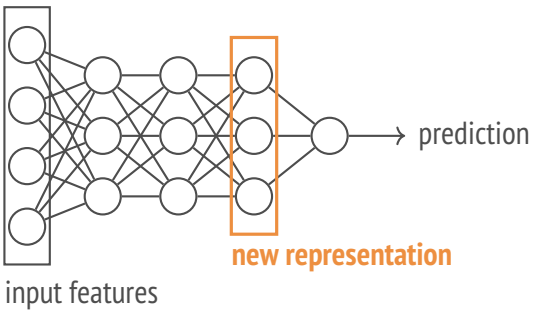
I. Good representations of genomic data

II. Identifying relevant genomic features

I. Good representations of genomic data

Representation learning

- **Good representations** = features from which learning is "easy"
- If we cannot **handcraft** good features using domain knowledge, can we **learn** them?



Foundation models

- **LOTS** of **broad** data
  - LAION-5B: 5.85 billion image-text pairs
  - GPT-3 was trained on 570 GB of text
- **self-supervision:**
  - Masked language modeling, next sentence prediction
  - Reconstructing a blurred, partially erased or scrambled image
- **Fine-tuning:** learned representations can then be used for any downstream task

Foundation models in genomics

- Pre-training = masked language modeling

- **NucleotideTransformer** [DT+24]
  - trained on 4k genomes (300B 6bp tokens)
  - 50M to 2.5B parameters
  - 12 kbp context length
  - trained on 16 $\times$8 A100 GPUs ($\sim$ 20 000 €)
  - Try it out: https://hclimente.eu/blog/hf-transformers/

- **Evo2** [Bri+25]
  - trained on up 8.8 Tbp (1 token = 1bp)
  - 7 to 40 B parameters
  - 1 million bp context length
  - training took 2.25 $\times 10^{24}$ FLOPS (on par with Llama 3.1)

Variant pathogenicity prediction

- **Evo2** predicts BRAC1 variant pathogenicity
  - without training!
  - “unnatural” sequence = pathogenic

Variant pathogenicity prediction

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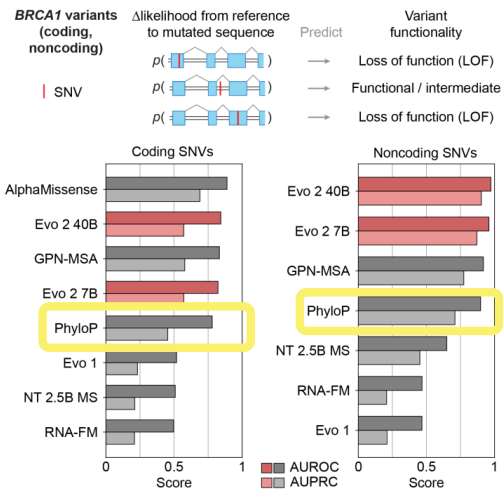
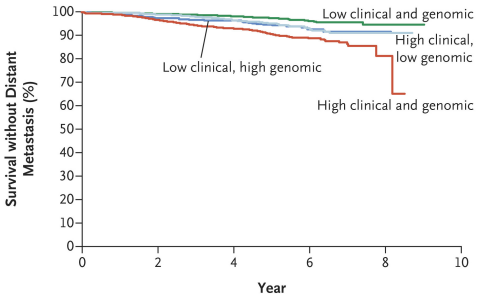
  - “unnatural” sequence = pathogenic
- So does **PhyloP** [Pol+09]
  - conservation score
  - number of parameters: 2
- much better than **NucleotideTransformer**



II. Identifying relevant genomic features

Selecting features in genomic data

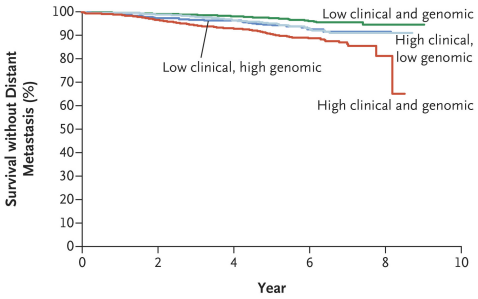
- **Goal:** Identify **genomic features** that can be used to predict a phentoype
  - **biomarker** or **signature** discovery



F. Cardoso et al., **70-gene signature as an aid to treatment decisions in early-stage breast cancer** NEJM 2016

Selecting features in genomic data

- **Goal:** Identify **genomic features** that can be used to predict a phentoype
  - **biomarker** or **signature** discovery
  - hypotheses on the underlying **biological mechanisms**



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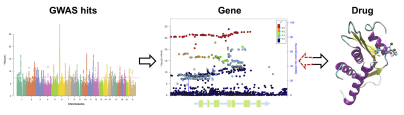

Trait	Gene with GWAS hits	Known or candidate drug
Type 2 Diabetes	*SLC30A8/KCNJ11*	ZnT-8 antagonists/Glyburide
Rheumatoid Arthritis	*PADI4/IL6R*	BB-CI-amidine/Tocilizumab
Ankylosing Spondylitis(AS)	*TNFR1/PTGER4/TYK2*	TNF-inhibitors/NSAIDs/fostamatinib
Psoriasis(Ps)	*IL23A*	Risankizumab
Osteoporosis	*RANKL/ESR1*	Denosumab/Raloxifene and HRT
Schizophrenia	*DRD2*	Anti-psychotics
LDL cholesterol	*HMGCR*	Pravastatin
AS, Ps, Psoriatic Arthritis	*IL12B*	Ustekinumab

P. Visscher et al., **10 years of GWAS discovery: biology, function and translation** AJHG 2017

Selecting features in genomic data

- **Challenges:**
  - Orders of magnitude **more features than samples** ($p \gg n$)
    - 20 000 **transcripts** or 500 000 **Single Nucleotide Poymorphisms** for a few hundreds/thousands samples

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- **Challenges:**
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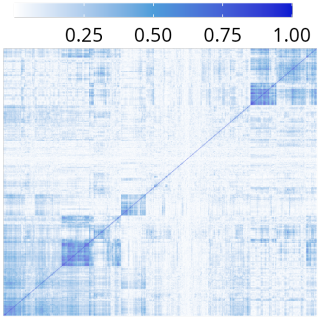
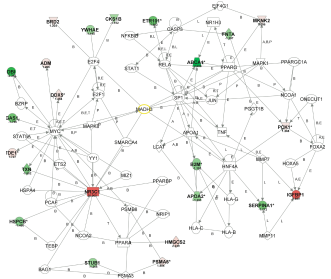
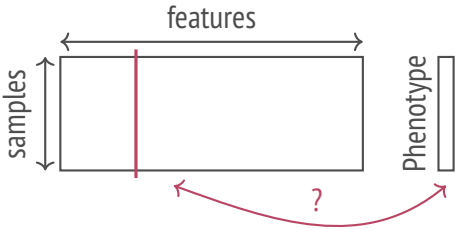
  - **Correlations** between features

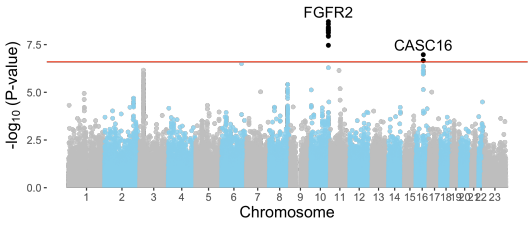


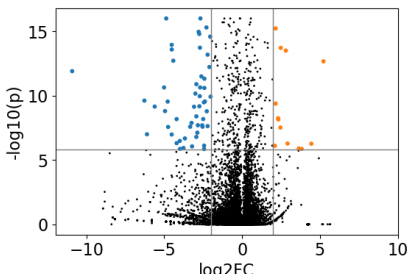


P. Lee et al., **Glucocorticoid Receptor-Dependent Gene Regulatory Networks** AJHG 2005

Classical statistical testing







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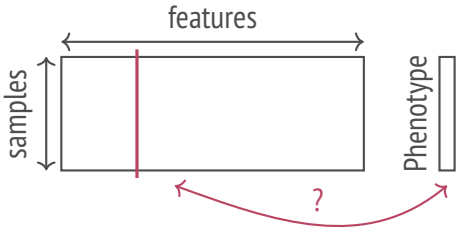
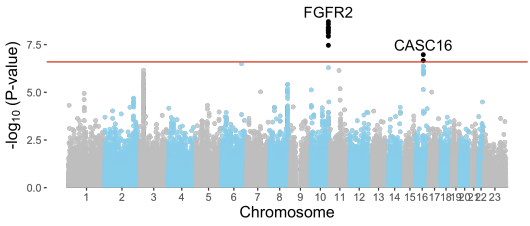
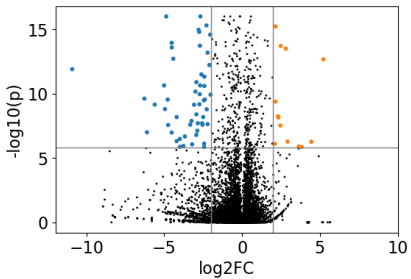




- ☹ Lack of **power**
- ☹ Does not account for **other features** (joint/conditional effects)
- ☹ Potentially high **false discovery rate** [Hej+24]



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- **XAI:** methods that help understand how ML algorithms arrived at a given result [ISO20; Mol25]
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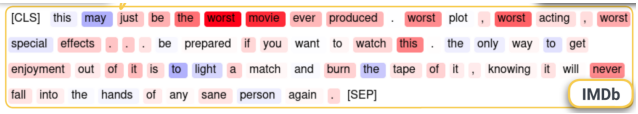
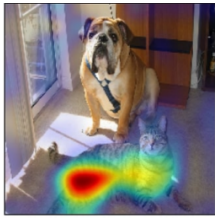


Integrated gradients



Grad-CAM

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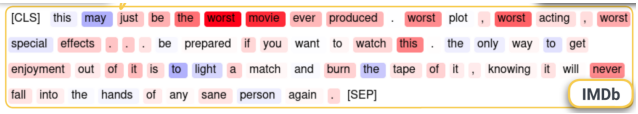

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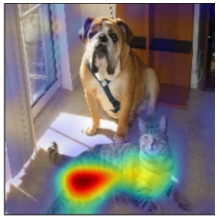

Grad-CAM

- How **reliable** are those? No measure of **uncertainty!**

Stability

– **Stability:** Selecting the same features on subsets of the data

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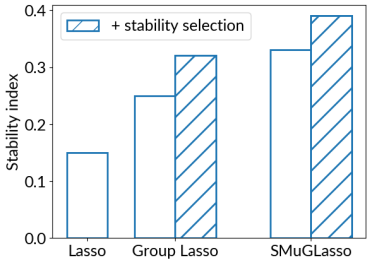
- **Structured sparsity** to incorporate **prior knowledge**

  E.g. Select features at the level of **predefined groups** or **connected in a given network** [Aze+13; Aze16; NA25]



A. Nouira & C.-A. Azencott. **Sparse multitask group lasso for genome-wide association studies**. PLoS Comp Bio 2025

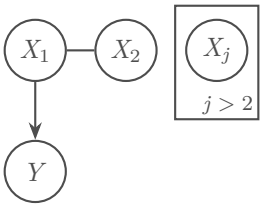
Post-selection inference

- How can one obtain **p-values** or **confidence intervals** on the parameters of models obtained from complex machine learning procedures?

- **Post-Selection Inference:** perform inference that **accounts for selection events** [Lee+16]
  - ☹ Model-specific
  - ☺ Possible for many **structured sparsity** approaches [Lee+16; Yan+16] and **kernel-based approaches** [Sli+19]
  - ☹ Computationally intensive

- **Conditional Feature Importance** [Str+08; RLNT26]
  - ☺ Model-agnostic
  - ☹ Does not currently scale to thousands of features

Correlation between features



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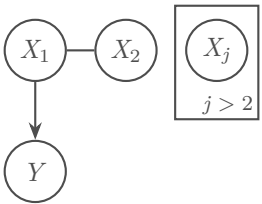

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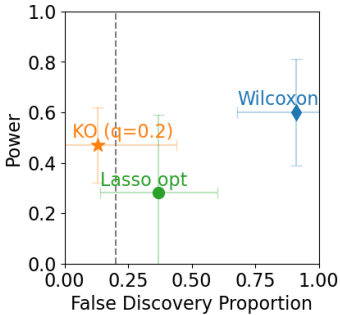
Statistical knockoffs [BC15; Can+18]

- Create **knockoffs** of the original features:
  same correlation structure, no relationship with the phenotype
- Compare importance of a feature with importance of its knockoff
- Threshold on the difference can be set to **control the false discovery rate**

Applying knockoffs to transcriptomics data

- **Simulation framework:** real transcriptomics data, simulated case/control outcomes
  - ☺ KO **control FDR well**, and better than Wilcoxon rank-summed test or the Lasso



J. Cartier et al. **Statistical knockoffs improve biomarker discovery from transcriptomic data** Briefings in Bioinformatics 2026

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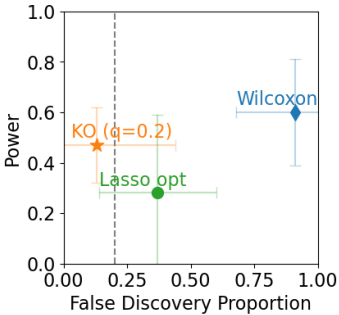

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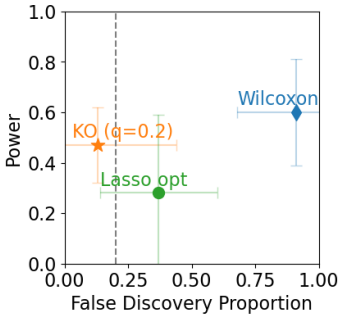

- On **real** outcomes:
  - ☹ The KO framework is **overly conservative**

cohort	CRUKPAP	AEGIS	BC HER2	BC ER	BC PgR
discoveries (q=0.5)	3	7	13	1	0

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Take-home messages

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  - a cost-benefit analysis
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  - the real use case
  - a cost-benefit analysis
  - comparison to state-of-the-art tools
- **Prediction** is easier than **explainability**
  - **XAI** usually comes with **no guarantees**
  - Incorporating **prior knowledge** can make XAI more **stable**
  - **post-selection inference** and **conditional feature importance** can give **p-values** or **confidence intervals** on model parameters
  - **statistical knockoffs** can help **control false discovery rate**

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