# Supervised classification and outliers detection in gene expression data

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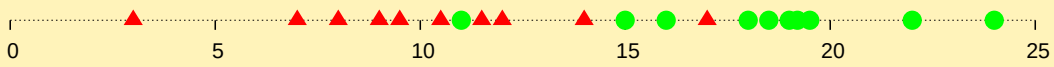
1. Gene expression data and classification
2. Outliers detection
3. Results

# Gene expression data

| | 1 | 2 | 3 | | p−1 | p |
|---|---|---|---|---|---|---|
| 1 | x11 | x12 | x13 | ··· | | |
| 2 | x21 | x22 | ··· | | | |
| 3 | x31 | ··· | | | | |
| 4 | ··· | | | | | |
| | | | | | | |
| n−1 | | | | | | |
| n | | | | | | |

- Huge number of genes;
- low number of samples;
- high level of noise;
- missing values;
- few discriminant genes.



# Applications

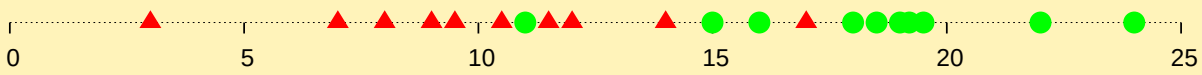
- Cancer diagnosis:
  - annotation (tumor vs. normal);
  - detection (early for better treatment);
  - distinction (cancers with same clinical symptoms);
  - prediction (prognostic).

- Biological interest :
  - what are the genes?
  - what are the classification rules?
  - etc.

# Gene selection

**Why ?**

- eliminate noise ;
- reduce computing time ;
- understand better.




Selection scheme:

1. Gene scoring. e.g., g-score : $s_g = \frac{|m_{g0} - m_{g1}|}{s_{g0} + s_{g1}}$.
2. Selection of the best $k$ genes.

# Learning a classifier - 1

- $G$ a set of selected genes.
- $\mathbf{x} = (x_1, \ldots, x_n)$ a new sample.

**Probabilist approach :**

$$c_{\text{MAP}} = \underset{c \in \{0,1\}}{\text{argmax}}\, P(c|\mathbf{x}_G) \;=\; \underset{c \in \{0,1\}}{\text{argmax}}\, \frac{P(\mathbf{x}_G|c)P(c)}{P(\mathbf{x}_G)} \;=\; \underset{c \in \{0,1\}}{\text{argmax}}\, P(\mathbf{x}_G|c)P(c)$$

- Estimating the $P(c)$ :

$$\widehat{P}(0) = \frac{\#\text{ ex. class 0}}{\#\text{ ex.}}$$

$$\widehat{P}(1) = \frac{\#\text{ ex. class 1}}{\#\text{ ex.}}$$

- The problem is more difficult for $P(\mathbf{x}_G|c)$.

# Learning a classifier - 2

**The naive Bayes approach :**
Gene expression levels are conditionally independent given the class:

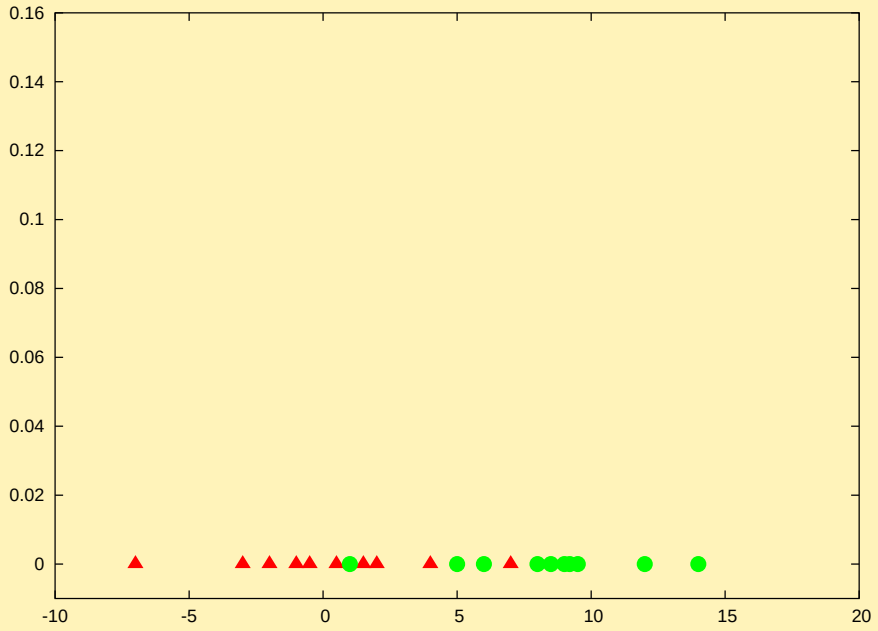
$$P(\mathbf{x}_G|c) = \prod_{g \in G} P(x_g|c).$$

**Normal assumption :**

$$P(x_g|c) \sim \mathcal{N}(x_g; \mu_{gc}, \sigma^2_{gc}).$$

and we have :

- $\widehat{\mu}_{gc} = m_{gc}$
- $\widehat{\sigma^2}_{gc} = s^2_{gc}$



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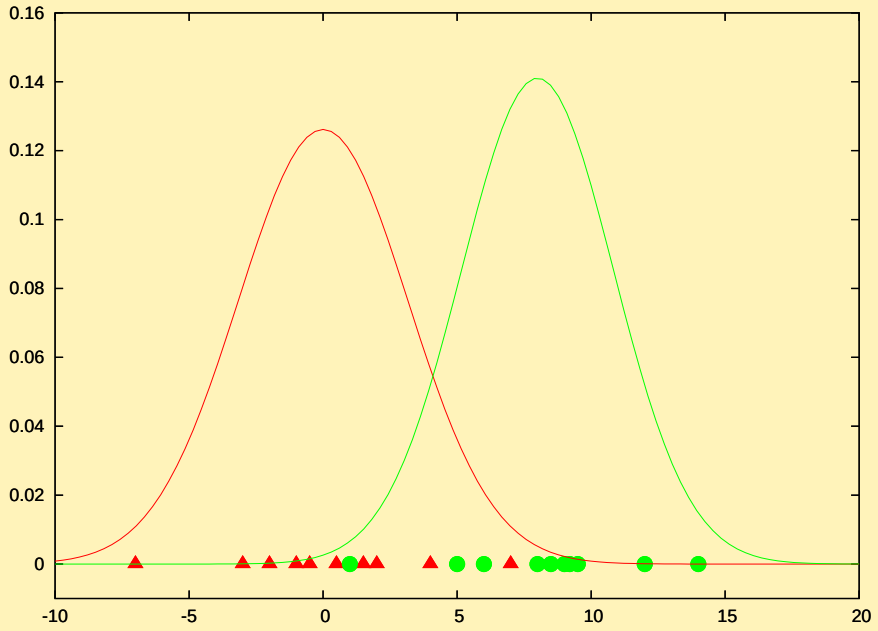

# Evaluating the classifier

Low number of samples $\rightarrow$ cross-validation.

**Leave-one-out procedure:**

**Data** : $X$, the complete set of samples.

**foreach** $x \in X$ **do**
  Learning using $X - x$;
  Classify $x$;

Return the fault coverage;

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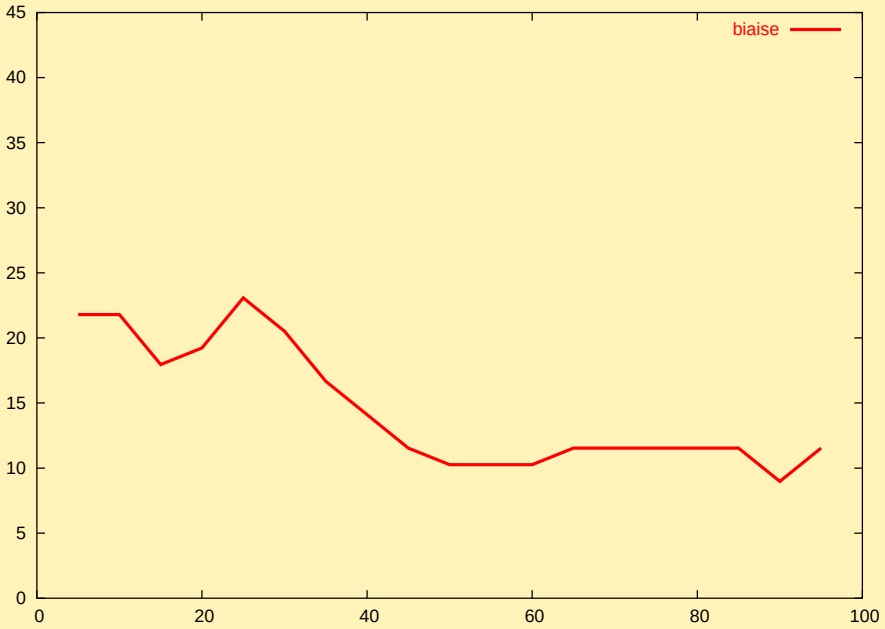
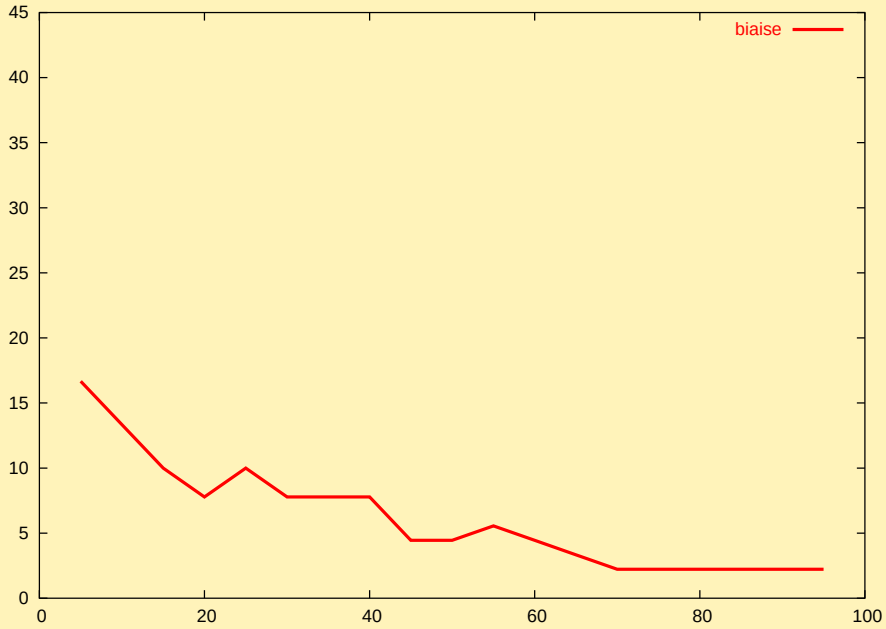



Breast cancer




SAGE data

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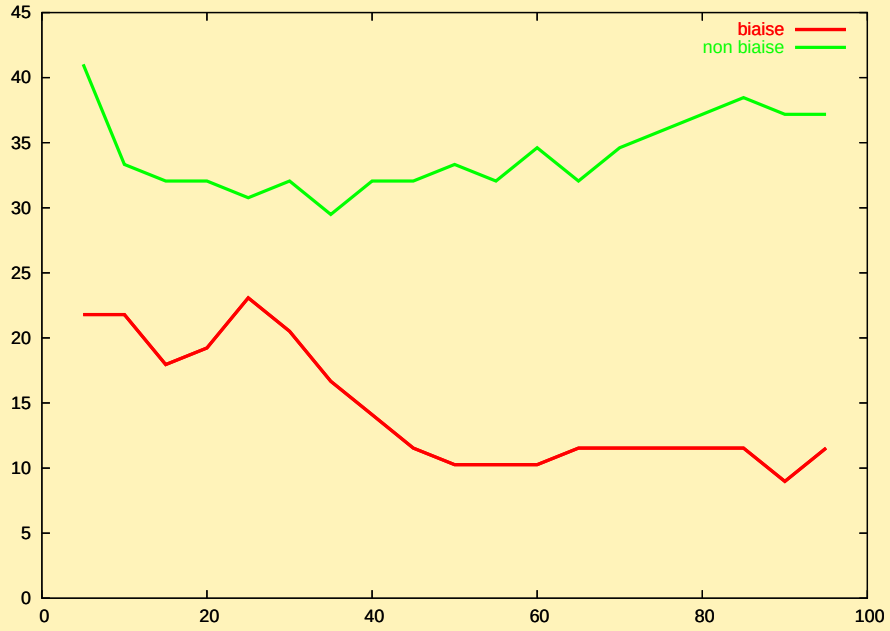


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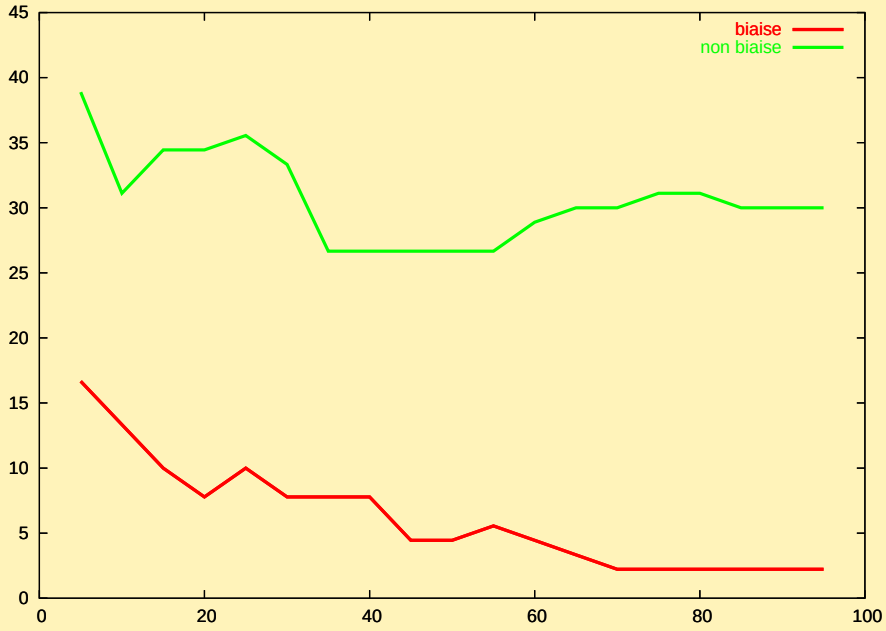
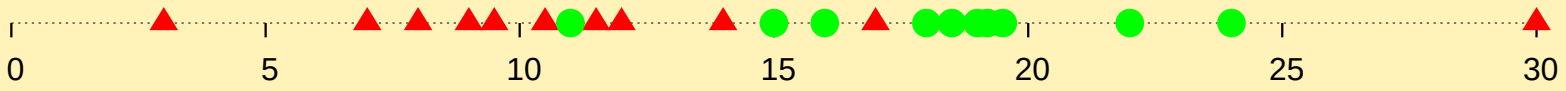



SAGE data

# Outliers

**Outlier :** A gene expression measurement which differs surprisingly from the other measurements obtained for the same gene on other samples of the same class.




**Outliers bias :**

- the estimates of the model parameters ($\mu_{cg}$ and $\sigma^2_{cg}$) ;
- the gene score.

Ex. g-score : $s_g = \frac{|m_{g0} - m_{g1}|}{s_{g0} + s_{g1}}$

# Origins

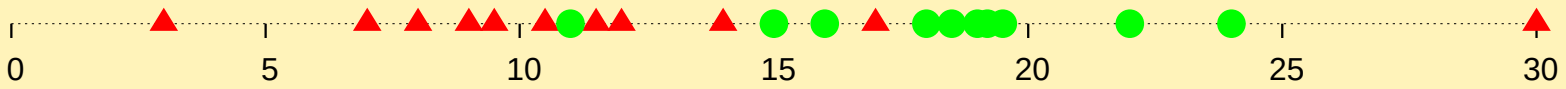
- **Intrinsic factors :** the surprising measurement is actually the true measure. It results from rare but non impossible biological phenomena.

- **Extrinsic factors :** Error measurement :
  - material reasons;
  - human reasons;
  - inherent limits of the measurement method;
  - ...

# Outlier detection - 1

**Principle :**

- assume that the data, with the possible exception of any outlier, form a sample of a given distribution —here the normal distribution;
- use a reasonable test statistical to decide whether or not the suspect measurement is an outlier.

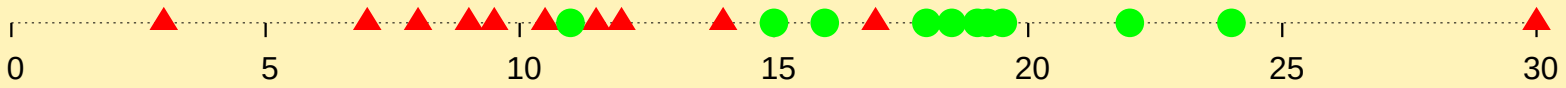



The Thompson statistic :

$$T_{gc} = \frac{|x^*_{gc} - m_{gc}|}{s_{gc}}$$

The greater $T_{gc}$ the more $x^*_{gc}$ is unlikely.

# Outlier detection - 2




**The rule :**

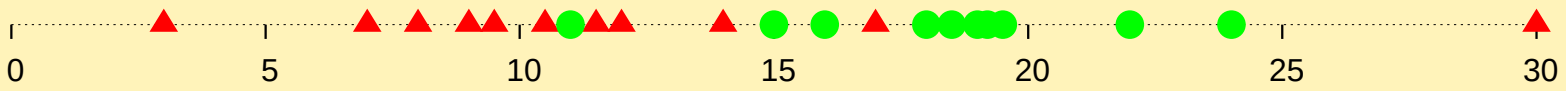
If $T_{gc} \geq \tau_{\alpha c}$ then $x^*_{gc}$ is an outlier.

**How can we set $\tau_{\alpha c}$ ?**

- Compare with what is expected in the null hypothesis $H_0$ that there is no spurious observation (i.e. all points belong to the same normal distribution).
- Find $\tau_{\alpha c}$ so that

$$P(T_{gc} > \tau_{\alpha c}|H_0) = \alpha. \text{ (e.g. } \alpha = 10^{-5}.)$$

# Leave-one-out & outliers

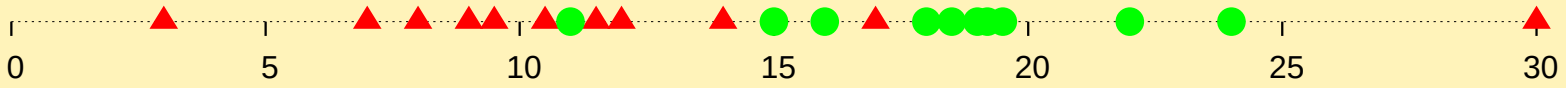



**Data** : $X$ and $\alpha$
**foreach** $x \in X$ **do**

Select a set of genes using $X - x$;
Estimate parameters using $X - x$;
Classify $x$;

Return the fault coverage;

# Leave-one-out & outliers




**Data** : $X$ and $\alpha$
**foreach** $x \in X$ **do**

Compute $\tau_{\alpha 0}$ and $\tau_{\alpha 1}$ from $\alpha$;

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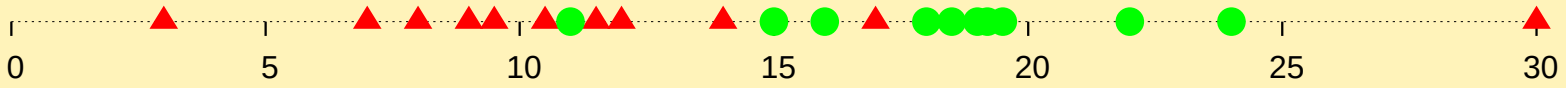
# Leave-one-out & outliers




**Data** : $X$ and $\alpha$
**foreach** $x \in X$ **do**
    Compute $\tau_{\alpha 0}$ and $\tau_{\alpha 1}$ from $\alpha$;
    **foreach** *gene* $g$ **do**
        Compute $T_{g0}$ and $T_{g1}$ using $X - x$;
    Select a set of genes using $X - x$;
    Estimate parameters using $X - x$;
    Classify $x$;
Return the fault coverage;

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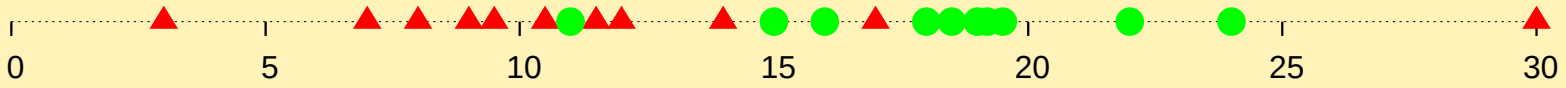


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        Compute $T_{g0}$ and $T_{g1}$ using $X - x$;
        **if** $T_{g0} > \tau_{\alpha 0}$ **then**
            remove $x^*_{g0}$;
    Select a set of genes using $X - x$;
    Estimate parameters using $X - x$;
    Classify $x$;
Return the fault coverage;

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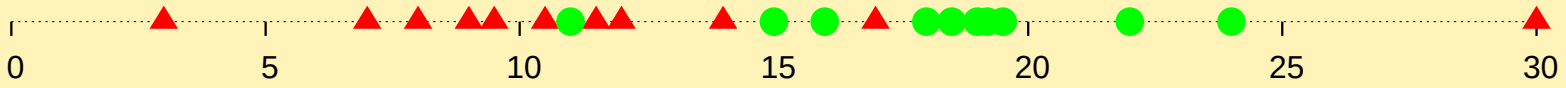


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# Gene selection & outliers

**Use the outlier detection in the gene selection procedure.**

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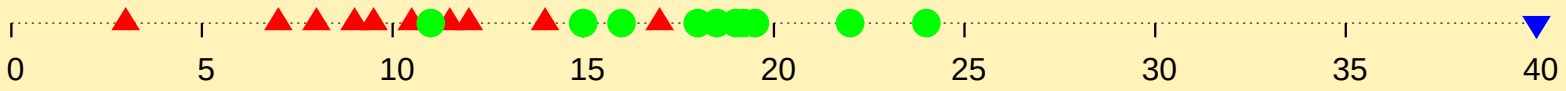

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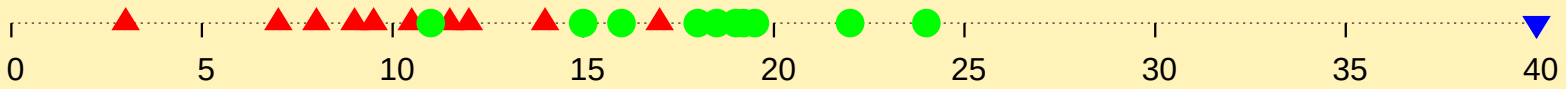
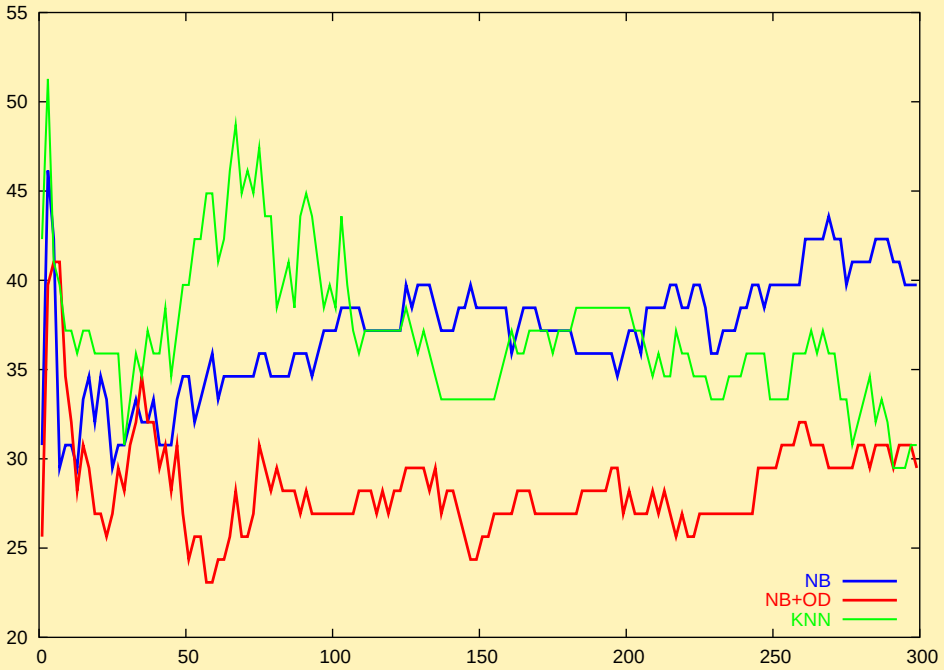


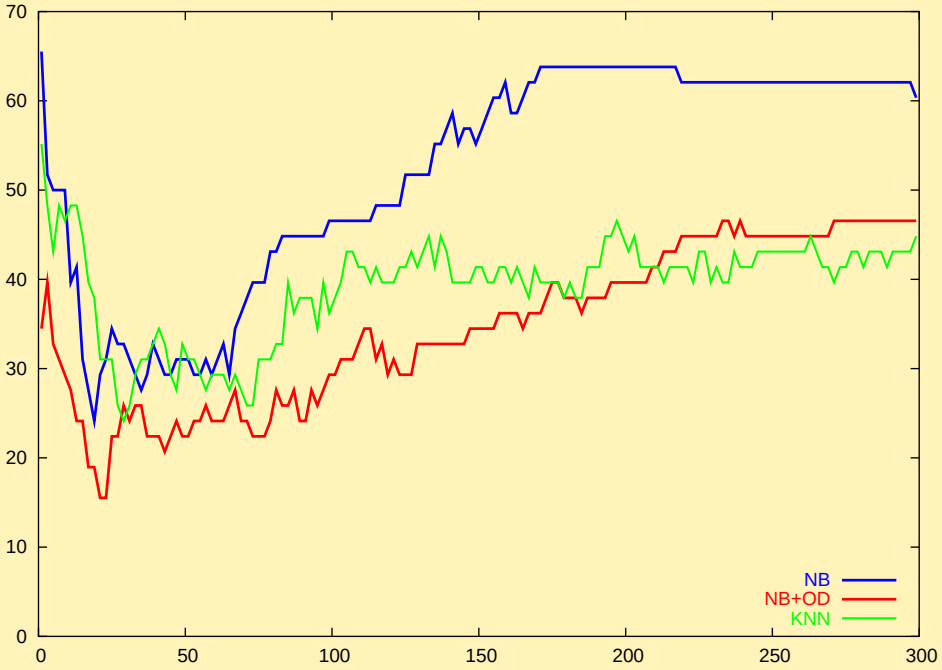

**Data** : $X$, $\alpha'$ and $x$

Compute the $\tau_{\alpha' 0}$ and $\tau_{\alpha' 1}$;
**foreach** *gene* $g$ **do**
    Compute $T'_{g0}$ **and** $T'_{g1}$;
    **if** $T'_{g0} > \tau_{\alpha' 0}$ *and* $T'_{g1} > \tau_{\alpha' 1}$ **then**
        Reject gene $g$;
    **else**
        Compute the score of $g$;
Return the best genes;

# Experiments

- $\alpha' = 10^{-2}$ ;
- $\alpha = 10^{-2},\ 10^{-5},\ 10^{-10},\ 10^{-15},\ 10^{-20}$.




**Breast cancer :**

- 78 samples : 44 vs. 34.
- $\sim$ 24000 genes.

**Lymphome :**

- 58 samples : 32 vs. 26.
- $\sim$ 7000 genes.

# Conclusions

- Outlier detection can improve the performance of the naive Bayes classifier.
- Naive Bayes classifier + outlier detection:
  - simple approach;
  - low computing time;
  - can achieve better results than more sophisticated methods.

Several questions:

- interest of outlier detection combined with other approaches: KNNs, SVMs, weighted voting approach, ...
- comparison with more robust estimates (e.g. median vs. mean);
- outlier origins: intrinsic or extrinsic factors?