High dimensional statistics for genomic data

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Summary of the previous class

- Overfitting, bias/variance tradeoff, structural risk minimization.
  Two antagonistic sources of error. Needs to be dealt with carefuly.
- Penalized risk minimization.
- Ridge penalty: properties, ridge regression, SVM.
- Fundamentals of constrained optimization.

You now know one regression algorithm, one classification algorithm and why they make sense.

Outline

1. Relationship to ML estimation.
2. Validation.
3. Unsupervised learning.

Relationship to maximum likelihood estimation

Relationship to maximum likelihood estimation

- Until now we discussed risk minimization without involving probabilistic **models** for the data.
- This discussion and the related penalized methods are however related to methods based on the **likelihood** of data under some model.
- Given a model $p(D|\theta)$ of data D, for example

$$y = \bar{\theta}^\top x + \varepsilon,$$

where ε is endowed with some distribution, it is common to estimate θ by the value which maximizes the likelihood of the data under the model:

$$\hat{\theta} = \arg\max_\theta p(D|\theta).$$

(popularized by R. A. Fisher at the beginning of the 20th century).

Relationship to maximum likelihood estimation

- The maximum likelihood estimator has a few desirable asymptotic properties under some regularity conditions:
  - Consistency : $\hat{\theta}_{MLE} \to \bar{\theta}$ as n increases,
  - Asymptotic normality,
  - Efficiency (asymptotic minimal variance).
- Can be biased though.
- Can behave poorly when p/n is not small enough.

Relationship to maximum likelihood estimation

- In practice, it is often easier to minimize the **negative log likelihood**:

$$\hat{\theta} = \arg\min_{\theta} -\log p(D|\theta).$$

We recover an empirical risk minimization problem, where the loss function is defined by $L(D, \theta) \stackrel{\Delta}{=} -\log p(D|\theta)$.

- **Exercise :** which loss function $-\log p(D|\theta)$ corresponds to the negative log likelihood of the model:

$$y = \hat{\theta}^\top x + \varepsilon,\ \varepsilon \sim \mathcal{N}(0, \sigma^2)?$$

Why use the log?

Relationship to maximum likelihood estimation

- In Bayesian statistics, we define a **prior** distribution $p(\theta)$ over the parameter θ.
- By the Bayes rule, we can then define a **posterior** distribution $p(\theta|D)$ of θ :

$$p(\theta|D) = \frac{p(D|\theta)p(\theta)}{p(D)} \propto p(D|\theta)p(\theta),$$

- We can then estimate θ by maximizing its **posterior** likelihood (MAP):

$$\hat{\theta}_{MAP} = \arg\max_{\theta} p(\theta|D)$$

Relationship to maximum likelihood estimation

- Maximizing the posterior likelihood yields

$$\begin{aligned}\hat{\theta}_{MAP} = \arg\max_{\theta} p(\theta|D) &= \arg\min_{\theta} -\log p(\theta|D) \\ &= \arg\min_{\theta} -\log\left(p(D|\theta)p(\theta)\right) \\ &= \arg\min_{\theta} -\log p(D|\theta) - \log p(\theta).\end{aligned}$$

- We recover a penalized empirical risk minimization problem, where $\Omega(\theta) = -\log p(\theta)$.
- **Exercise :** what penalty do we get using the prior

$$\theta \sim \mathcal{N}(0, \sigma^2),$$

and which prior would lead to the ℓ_1 penalty?

Bayesian statistics

- In a purely Bayesian statistical framework, we would not look for the single value maximizing the posterior likelihood but rather consider distributions (over θ, over $\theta^\top x$...).
- This paradigm requires to know how to sample from the posterior distribution.

Relationship to maximum likelihood estimation

- Minimization of the penalized empirical risk can therefore be derived in the framework of likelihood maximization.
- Not necessary. Some loss functions (SVM) do not correspond to a negative log likelihood.
- Giving ourselves a model allows some type of theoretical analysis of our estimators: bias, variance, consistency...
- These analyses allow to understand the behavior of the estimators and to compare them, at the expense of some generality.
- This is useful, but it is important to keep in mind the sensitivity of the analysis to the assumptions made by the model, and the fact that in reality, the data was not generated by a model.

Penalized empirical risk minimization: summary

- Penalized empirical risk minimization allows us to **implement the idea of structural risk minimization**.
- **Lots** of penalties have been proposed, leading to various types of regularity for the estimators.
- Ideally, a good penalty corresponds to a prior for the estimator: we assume there exists a low risk function with this type of regularity.

Part IV

Validation

Reminder: structural risk minimization

1. Define nested function sets of increasing complexity.
2. Minimize the empirical risk over each family.
3. **Choose the solution giving the best generalization performances.**

- Best generalization means lowest (population) risk

$$R(f) = \int_{\mathcal{X}\times\mathcal{Y}} L(y, f(x)) d\mathbb{P} = \mathbf{E}[L(y, f(x))].$$

- But the very reason we need all this is that we don't have access to R!
- We need to estimate it as well.

Validation/Hold out procedure

- Split available data into training and test sets.

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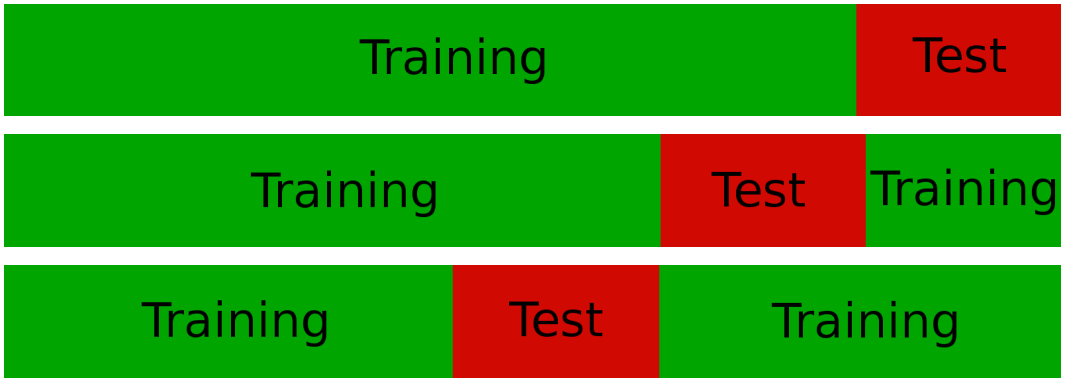
- Formally:

$$\hat{R}^{\mathrm{HO}}\left(\hat{f}; D_n; I^{(t)}\right) = \frac{1}{n_v} \sum_{i \in D_n^{(v)}} L\left(y_i, \hat{f}_{D_n^{(t)}}(x_i)\right).$$

- D_n: full set of n available data points. $I^{(t)}$: subset of indices used for training. $D_n^{(t)}$ (resp. $D_n^{(v)}$): set of data points restricted to training indices (resp. its complement).
- $\hat{f}$ denotes the learning algorithm whose risk we want to estimate. $\hat{f}_{D_n^{(t)}}$ is the function learnt by applying this algorithm to training data $D_n^{(t)}$.

Cross validation

- Idea: averaging several hold out estimators of the risk corresponding to different data splits:



...

- Formally:

$$\hat{R}^{\mathrm{CV}}\left(\hat{f}; D_n; \left(I_j^{(t)}\right)_{1\leq j\leq B}\right) = \frac{1}{B}\sum_{j=1}^{B} \hat{R}^{\mathrm{HO}}\left(\hat{f}; D_n; I_j^{(t)}\right),$$

where $I_1^{(t)}, \ldots, I_B^{(t)}$ are non-empty proper subsets of $\{1, \ldots, n\}$.

Cross validation procedures

- CV estimators differ in how they define $I_1^{(t)}, \ldots, I_B^{(t)}$.
- Most common: **V-fold CV**. Partition D_n into V sets of approximately equal cardinality $\frac{n}{V}$.
- **Leave-one-out** CV: V-fold with $V = n$.
- Monte-Carlo CV, leave-p-out CV...

Bias of the hold out estimator

- Hold out estimator: because training and validation samples are independent,

$$\begin{aligned}
\mathbf{E}_{D_n \sim \mathcal{P}}\left[\hat{R}^{\mathrm{HO}}\left(\hat{f}; D_n; I^{(t)}\right)\right] &= \frac{1}{n_v} \sum_{i \in D_n^{(v)}} \mathbf{E}_{(x_i,y_i) \cup D_n^{(t)} \sim \mathcal{P}}\left[L\left(y_i, \hat{f}_{D_n^{(t)}}(x_i)\right)\right] \\
&= \mathbf{E}_{(x,y) \cup D_n^{(t)} \sim \mathcal{P}}\left[L\left(y, \hat{f}_{D_n^{(t)}}(x)\right)\right] \\
&= \mathbf{E}_{D_n^{(t)} \sim \mathcal{P}}\left[\mathbf{E}_{(x,y) \sim \mathcal{P}}\left[L\left(y, \hat{f}_{D_n^{(t)}}(x)\right)\right]\right] \\
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\end{aligned}$$

- Does not depend on $D_n^{(v)}$.
- Only makes sense because $L\left(y_i, \hat{f}_{D_n^{(t)}}(x_i)\right)$ are i.i.d objects when (x_i, y_i) are independent of $\hat{f}_{D_n^{(t)}}$.

Bias of cross validation estimators

- For any cross validation estimator such that $\left|I_j^{(t)}\right| = n_t$,

$$\mathbf{E}_{D_n \sim \mathcal{P}}\left[\hat{R}^{\mathrm{CV}}\left(\hat{f}; D_n; I^{(t)}\right)\right] = \mathbf{E}_{D_n^{(t)} \sim \mathcal{P}}\left[R\left(\hat{f}_{D_n^{(t)}}\right)\right].$$

- The bias of such a CV estimator is therefore the difference between the risk expected using n and n_t training samples:

$$\mathrm{Bias}\left(\hat{R}^{\mathrm{CV}}\right) = \mathbf{E}_{D_n^{(t)} \sim \mathcal{P}}\left[R\left(\hat{f}_{D_n^{(t)}}\right)\right] - \mathbf{E}_{D_n \sim \mathcal{P}}\left[R\left(\hat{f}_{D_n}\right)\right].$$

- Usually non-negative (if $\hat{f}$ is a *smart rule*, *i.e.*, if its risk is a decreasing function of the size of the training set).
- More precise results for specific $\hat{f}$ and cross-validation estimators.

Bias of cross validation estimators

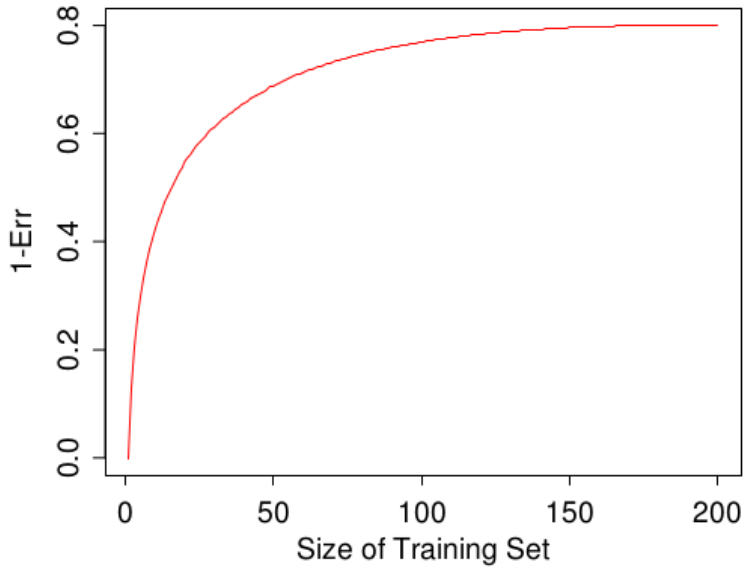

FIGURE 7.8. *Hypothetical learning curve for a classifier on a given task: a plot of* $1 - \text{Err}$ *versus the size of the training set* N*. With a dataset of* 200 *observations,* 5*-fold cross-validation would use training sets of size* 160*, which would behave much like the full set. However, with a dataset of* 50 *observations fivefold cross-validation would use training sets of size* 40*, and this would result in a considerable overestimate of prediction error.*

(from The Elements of Statistical Learning)

Variance of cross validation estimators

- All CV estimators with training sets of the same size n_t have the same bias. Difference of behavior explained by variances.
- For the hold out estimator,

$$\mathrm{Var}_{D_n}\left[\hat{R}^{\mathrm{HO}}\left(\hat{f}; D_n; I^{(t)}\right)\right] = \frac{1}{n_v}\mathbf{E}_{D_n^{(t)}}\left[\mathrm{Var}_{(x,y)}\left(L(y, \hat{f}_{D_n^{(t)}}(x))\right)\right] + \mathrm{Var}_{D_n^{(t)}}\left[R\left(\hat{f}_{D_n^{(t)}}\right)\right].$$

- First term: sensitivity of the error to a change of the validation sample. Also decreases in n_v (for fixed n_t).
- Second term: sensitivity of the risk to a change of the training set. Depends on stability of $\hat{f}$.

Variance of cross validation estimators

- No general result for CV.
- Less variable CV depends on framework (classification, regression, density estimation, model selection...).
- Factors of variability: n_v, n_t, B and stability of the algorithm.
- **What should I do**: no general answer, but it is standard to do 5 or 10 fold CV. Sometimes leave-one-out, but it is more expensive and known to often have large variance.
- More detailed answers in *A survey of cross-validation procedures for model selection* by S. Arlot and A. Celisse (from which this section is largely inspired).

Conditional vs expected prediction error

- There are actually two related quantities we could want to estimate:

$$R_{D_n} \triangleq \mathbf{E}_{(x,y)\sim\mathcal{P}}\left[L(y, \hat{f}_{D_n}(x))|D_n\right]$$
$$R \triangleq \mathbf{E}_{D_n,(x,y)\sim\mathcal{P}}\left[L(y, \hat{f}_{D_n}(x))\right] = \mathbf{E}_{D_n\sim\mathcal{P}}\left[R_{D_n}\right].$$

- Both can be useful depending on the context:
  1. are you always going to use this particular D_n
  2. or are you more interested in assessing the average performance of $\hat{f}$?
- CV empirically known to do a better job at estimating R than R_{D_n}. Actually hard to estimate R_{D_n} without using additional data. Keep that in mind if your objective is 1!

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- We also need a tool for **model selection**: choose best method or best class of hypothesis for a particular problem.
- Cross validation is commonly used for model selection as well. However, some **care** is necessary when doing both (which is often the case).

An example: selection bias in gene extraction

- 2002 paper by C. Ambroise and G. McLachlan: *Selection bias in gene extraction on the basis of microarray gene-expression data*.
- At the time, several paper using microarrays for cancer diagnosis claimed 0% generalization error estimated by cross validation:
  - Xiong et al.(2001), Mol Genet Metab, *Feature (Gene) Selection in Gene Expression-Based Tumor Classification*.
  - Zhang et al. (2001), Proc Natl Acad Sci USA, *Recursive partitioning for tumor classification with gene expression microarray data*.
  - Guyon et al. (2002), Mach Learn, *Gene Selection for Cancer Classification using Support Vector Machines*.

An example: selection bias in gene extraction

- General procedure was:
  1. Select a few genes which are good predictors over all samples.
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- The predictive genes are optimal for the samples used to estimate the generalization error, which leads to an over-optimistic assessment regarding what will happen for actually new samples.
- Picking a gene set is **model selection**, computing the generalization error of the estimator built over these genes is **model assessment**.

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- Same thing goes for selecting a regularization parameter or a method: cross-validation error over D_n gives you an estimate of your best option (**model selection**), but it doesn't tell you how your best option will perform on new data (**model assessment**).

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  - Train/Validation/Test split.
  - Double cross-validation.

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- Other frequent source of mistakes in CV: duplicate/non i.i.d. samples.