Desiging and combining kernels: some lessons learned from bioinformatics

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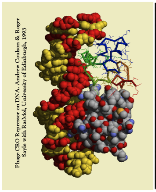
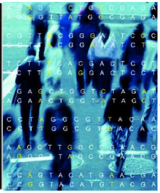
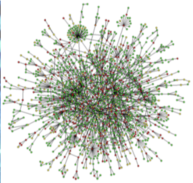
Kernels are very popular in bioinformatics

Why?

- Many problems can be approached by kernels methods (classification, regression, feature construction, ...)
- Many data with particular structures
  $\rightarrow$ Kernel design
- Need to integrate heterogeneous data
  $\rightarrow$ Kernel combination


Phage CRO Repressor on DNA. Andrew Coulson & Roger Sayle with RasMol, University of Edinburgh, 1993

Outline

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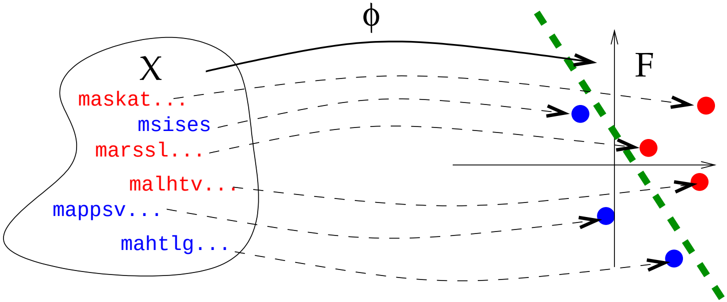
What is a GOOD kernel?

- Leads to good performances
- Mathematically valid
- Fast to compute
- Interpretable model (?)



How to MAKE a good kernel?

3 main ideas

1. Define good features

$$K(x,x') = \Phi(x)^\top \Phi(x')$$

2. Define a good metric

$$d(x,x') = \sqrt{K(x,x) + K(x',x') - 2K(x,x')}$$

3. Define a good functional penalty

$$\min_{f \in \mathcal{H}} \left\{ R(f) + \lambda \| f \|_{\mathcal{H}}^2 \right\}$$

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Idea 1: define good features

Motivation

- Estimate a function $f(x) = w^\top \Phi(x)$
- A good feature is more important than a good algorithm!

Examples

- Explicit feature computations
  - substring or subgraph indexation
  - Fisher kernel $\Phi(x) = \nabla_\theta \log P_\theta(x)$
- Implicit feature construction + kernel trick
  - Walk-based graph kernels
  - Mutual information kernels $K(x, x') = \int P_\theta(x) P_\theta(x') d\theta$

Caveats

- One good feature among too many irrelevant ones may not be enough with L_2 regularization

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Example: string kernel with substring indexation

Index the feature space by fixed-length strings, i.e.,

$$\Phi(\mathbf{x}) = (\Phi_u(\mathbf{x}))_{u \in \mathcal{A}^k}$$

where $\Phi_u(\mathbf{x})$ can be:

- the number of occurrences of u in $\mathbf{x}$ (without gaps) : spectrum kernel (Leslie et al., 2002)
- the number of occurrences of u in $\mathbf{x}$ up to m mismatches (without gaps) : mismatch kernel (Leslie et al., 2004)
- the number of occurrences of u in $\mathbf{x}$ allowing gaps, with a weight decaying exponentially with the number of gaps : substring kernel (Lohdi et al., 2002)

Idea 2: define a good metric

Motivation

- A kernel defines a Hilbert metric
  $d(x,x') = \sqrt{K(x,x) + K(x',x') - 2K(x,x')}$
- The functions we can learn are smooth w.r.t this metric

$$\left| f(x) - f(x') \right| \leq \| f \|_{\mathcal{H}} d(x,x')$$

Examples

- Edit distances for strings or graphs, local alignment of biological sequences, graph matching distances
- MAMMOTH distance between protein 3D structures

Caveats

- Most "good" distances are not Hilbertian

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Example: local alignment kernel

How to compare 2 protein sequences?

$$\mathbf{x}_1 = \texttt{CGGSLIAMMWFGV}$$
$$\mathbf{x}_2 = \texttt{CLIVMMNRLMWFGV}$$

Find a good alignment π:

```
CGGSLIAMM----WFGV
|...|||||....||||
C---LIVMMNRLMWFGV
```

Two non-Hilbertian metrics

$$SW(\mathbf{x},\mathbf{y}) := \max_{\pi \in \Pi(\mathbf{x},\mathbf{y})} s(\pi).$$

$$K_{LA}^{(\beta)}(\mathbf{x},\mathbf{y}) = \log \sum_{\pi \in \Pi(\mathbf{x},\mathbf{y})} \exp\left(\beta s\left(\mathbf{x},\mathbf{y},\pi\right)\right),$$

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Idea 3: define a good penalty function

Motivation

- The kernel constrains the set of functions over which we optimize (balls in RKHS).
- We may first define a penalty we like, then find the associated kernel.

Examples

- graph Laplacian over gene networks
- cluster kernel for protein remote homology detection

Caveats

- Some penalties may not be RKHS norms (eg, total variation to estimate piecewise constant functions)

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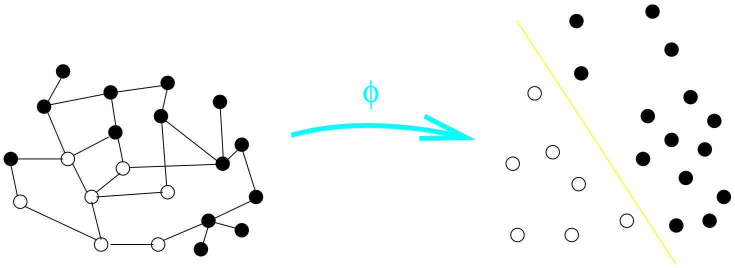
Example : Kernel on a graph



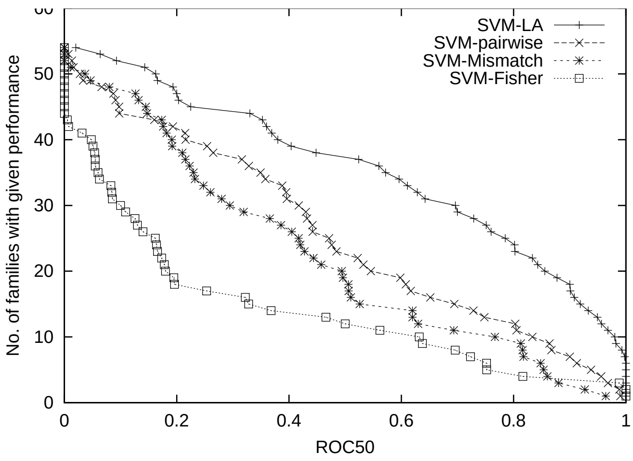
Laplacian-based kernel

The set $\mathcal{H} = \left\{ f \in \mathbb{R}^m : \sum_{i=1}^m f_i = 0 \right\}$ endowed with the norm:

$$\Omega(f) = \sum_{i \sim j} \left(f(\mathbf{x}_i) - f(\mathbf{x}_j) \right)^2$$

is a RKHS whose reproducing kernel is the pseudo-inverse of the graph Laplacian.

The choice of kernel makes a difference



Performance on the SCOP superfamily recognition benchmark.

Outline

Motivation

- We can imagine plenty of kernels for a given application
  - different kernels for the same data (e.g., different string kernels)
  - kernels for different types of data (e.g., integrating string and 3D structures for protein classification)
- Which one to use?
- Perhaps we can combine them to make better than each one individually?

Sum kernels

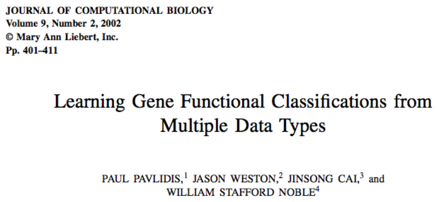
- Consider p kernels $K_1, \ldots, K_p$
- Form the sum (eg, Pavlidis et al., 2002):

$$K = \sum_{i=1}^{p} K_i \,.$$

- Equivalently, concatenate the features of the different kernels
- Equivalently, work in the RKHS $\mathcal{H} = \mathcal{H}_1 \oplus \ldots \oplus \mathcal{H}_p$ with

$$\| f \|_{\mathcal{H}}^2 = \inf_{f = f_1 + \ldots + f_p} \sum_{i=1}^{p} \| f_i \|_{\mathcal{H}_i}^2 \,.$$

Some early work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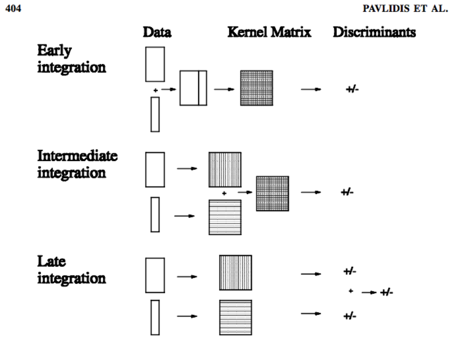
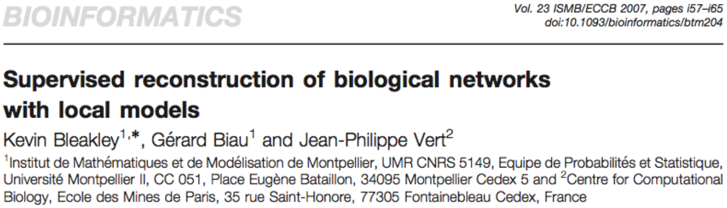
Learning Gene Functional Classifications from Multiple Data Types

PAUL PAVLIDIS,[1] JASON WESTON,[2] JINSONG CAI,[3] and WILLIAM STAFFORD NOBLE[4]


404 PAVLIDIS ET AL.

Huge improvements can be observed



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Supervised reconstruction of biological networks with local models

Kevin Bleakley[1,*], Gérard Biau[1] and Jean-Philippe Vert[2]

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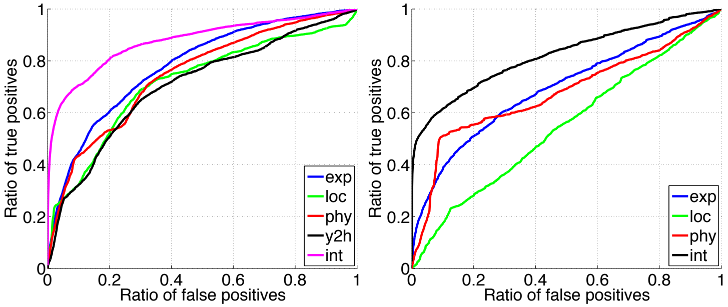


Multiple kernel learning (MKL)

- Form the convex combination:

$$K = \sum_{i=1}^{p} \eta_i K_i \,.$$

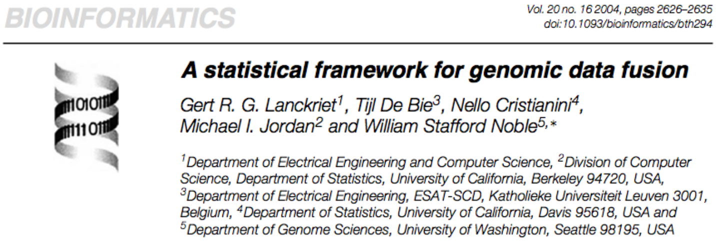
where the weights are chosen to minimize the following convex function under the constraint $tr(K) = 1$ (Lanckriet et al., 2003):

$$h(K) = \inf_{f \in \mathcal{H}_K} \left\{ R(f) + \lambda \| f \|_{\mathcal{H}_K} \right\}$$

- Equivalently, work in the space $\mathcal{H} = \mathcal{H}_1 + \ldots + \mathcal{H}_p$ with non-Hilbertian group L_1 norm (Bach et al., 2004):

$$\| f \|_{\mathcal{H}} = \inf_{f = f_1 + \ldots + f_p} \sum_{i=1}^{p} \| f_i \|_{\mathcal{H}_i} \,.$$

Example: Lanckriet et al. (2004)



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doi:10.1093/bioinformatics/bth294

A statistical framework for genomic data fusion

Gert R. G. Lanckriet[1], Tijl De Bie[3], Nello Cristianini[4], Michael I. Jordan[2] and William Stafford Noble[5,*]

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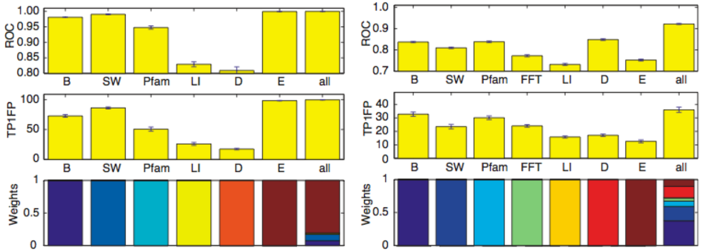
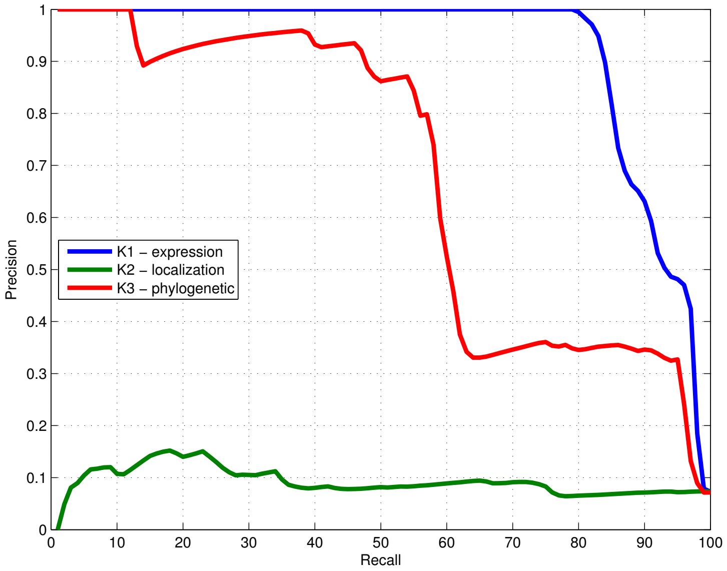


(A) Ribosomal proteins (B) Membrane proteins

MKL or sum kernel for protein network inference?



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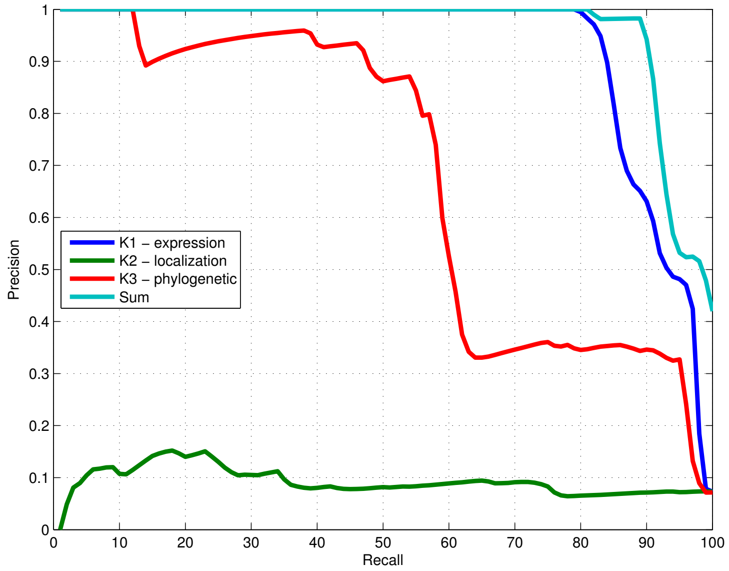

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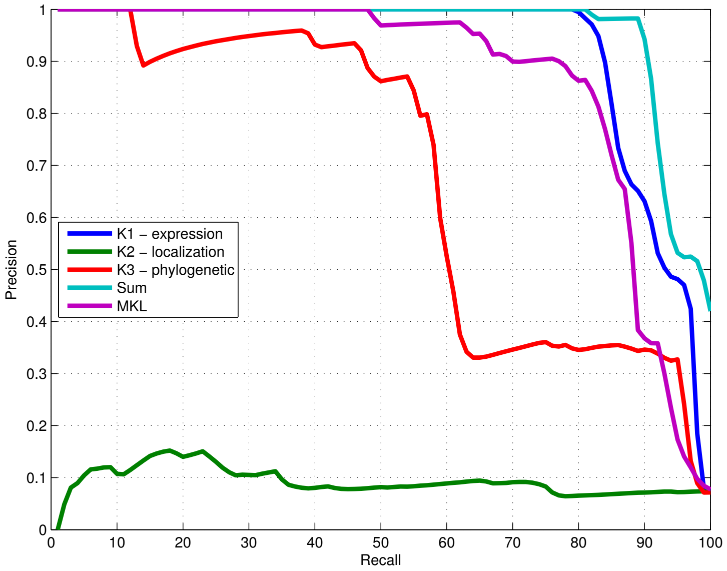

Why MKL does not estimate a good kernel combination

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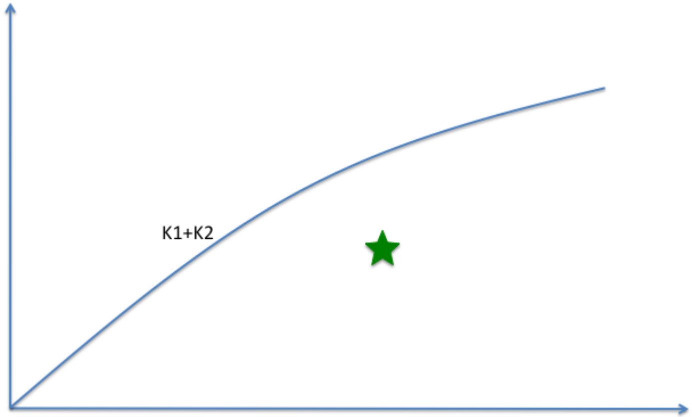

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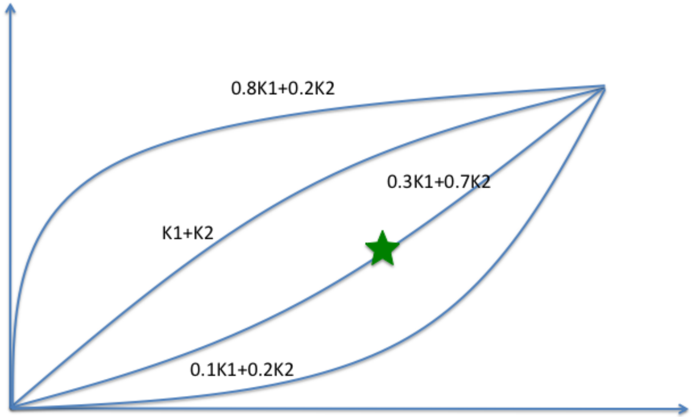

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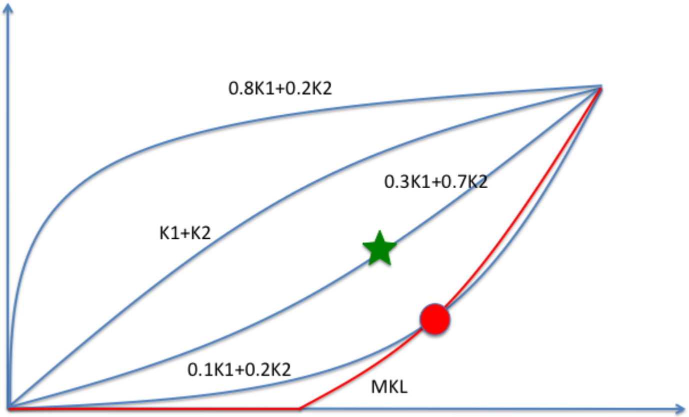
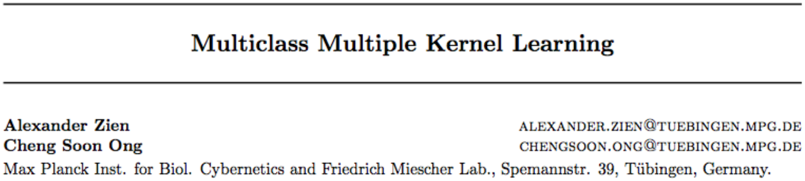


Sometimes MKL works

Subcellular protein classficiation from 69 kernels



Multiclass Multiple Kernel Learning

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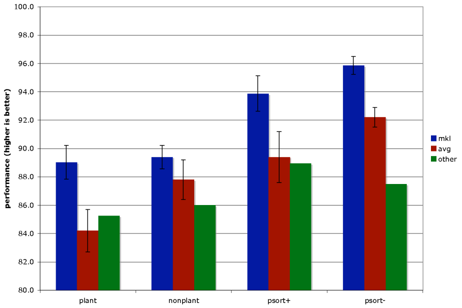
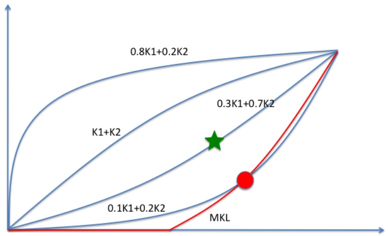


MKL or sum kernel?

- Sum is simpler and works better to combine well-engineered kernels (eg, for data integration).
- In spite of its misleading name, MKL is better suited for kernel selection than for weight optimization (ℓ_2 vs ℓ_1). Useful to select among large sets of kernels.
- We would love to be able to select the "optimal" linear combination of a few kernels



Outline

Conclusion

- Are kernels popular and useful in bioinformatics?
  $\rightarrow$ YES
- Is kernel design useful?
  $\rightarrow$ YES, and we have many tricks for that
- Is kernels combination useful for performance?
  $\rightarrow$ YES, and the sum kernel does a good job
- Is MKL useful?
  $\rightarrow$ Hardly yet, but it offers the promising possibility to work with MANY kernels and emphasize INTERPRETABILITY
- Do we want to learn good linear combinations?
  $\rightarrow$ YES