Topics in Two-Sample Testing

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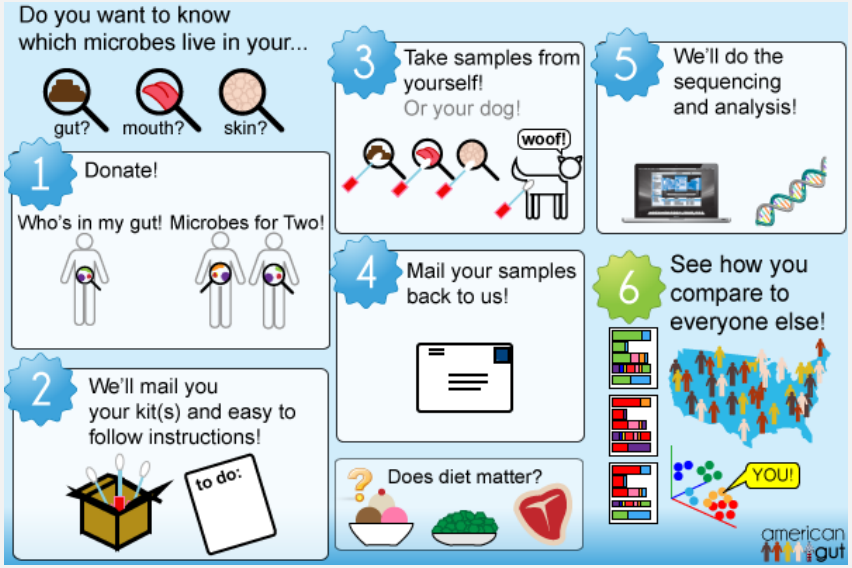
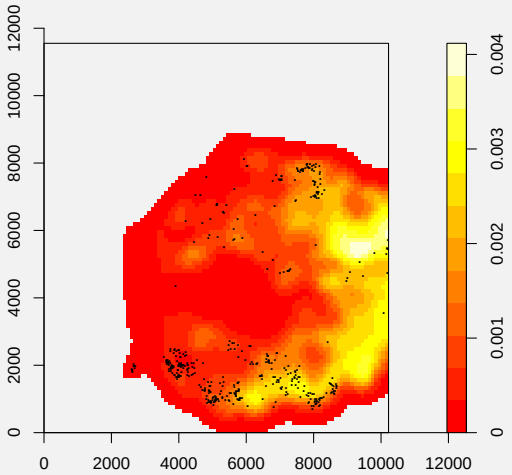
Motivation

American Gut Study: `www.indiegogo.com/americangut`



Breast Cancer Data: Spatial



Breast Cancer Data: Survival

Pathology no.	Initial Diagnosis Date	Relapse or Disease Free	RDF (R=relapsed; F=DF)	Recurrence Date	Last s
98_17969D	1997-08-25	Disease Free	F	Disease Free	
97_24046C8	1997-08-25	Disease Free	F	Disease Free	
98_8501C1	1998-04-03	Disease Free	F	Disease Free	
98_8501A1	1998-04-03	Disease Free	F	Disease Free	
98_9134D4	1998-04-09	Left in-situ BrCa in 1999 (2nd primary cancer, not a metastasis from the right BrCa in 1997)	F	Disease Free	
98_9134B	1998-04-09	Left in-situ BrCa in 1999 (2nd primary cancer, not a metastasis from the right BrCa in 1997)	F	Disease Free	
98_14783B1	1998-06-10	bone, brain, lymph nodes, pericardium, liver metastasis	R	2004-07-30	
98_14783A	1998-06-10	bone, brain, lymph nodes, pericardium, liver metastasis	R	2004-07-30	
98_16169C2	1998-06-24	Disease Free	F	Disease Free	
98_16169A	1998-06-24	Disease Free	F	Disease Free	
98_16169B	1998-06-24	Disease Free	F	Disease Free	
98_16253C1	1998-06-25	Disease Free	F	Disease Free	
60C1	1998-07-10	Disease Free	F	Disease Free	

Breast Cancer Data: Medical

Pathology no.	Age at time of diagnosis	Gender	SLN tumor status	Diagnosis	ER status	PR status	Her-2 overexpression
98_17969D	68	F	+	Invasive ductal carcinoma (IDC)	-	-	-
97_24046C8	68	F	+	Invasive ductal carcinoma (IDC)	-	-	-
98_8501C1	51	F	+	IDC & DCIS	+	+	?
98_8501A1	51	F	+	IDC & DCIS	+	+	?
98_9134D4	70	F	+	IDC	+	+	n/a
98_9134B	70	F	+	IDC	+	+	n/a
98_14783B1	67	F	+	IDC & DCIS	+	+	+
98_14783A	67	F	+	IDC & DCIS	+	+	+
98_16169C2	79	F	+mic	IDC	+	+	+
98_16169A	79	F	+mic	IDC	+	+	+
98_16169B	79	F	+mic	IDC	+	+	+
98_16253C1	70	F	+mic	IDC & DCIS	+	-	-
60C1	51	F	- (rare keratin+ cells)	IDC & DCIS	+	+	+
98_17969B1	61	F	+	intraductal papilloma	+	-	+

Luminal B	+	IIB	

Outline

- Motivation: heterogeneous data are ubiquitous.
- Friedman's two-sample test: leverage regression and classification techniques.
- Kernel methods for non-vectorial and heterogeneous data.
- Generalizes permutation t-test!
- Stein's method of exchangeable pairs for Berry–Esseen-type bound.

Friedman's Two-Sample Test

Friedman (2003)
$\{\mathbf{x}_i\}_{i=1}^{n}$ from $p(\mathbf{x})$ and $\{\mathbf{x}_i\}_{i=n+1}^{n+m}$ from $q(\mathbf{x})$ testing
$\mathcal{H}_A$: $p \neq q$ against $\mathcal{H}_0$: $p = q$

1. Label the first group $y_i = 1$ and the second group $y_i = -1$.
2. Score the observations $\{s_i := f(\mathbf{x}_i)\}_1^{n+m}$ with a learning machine f.
3. Calculate a univariate two-sample test statistic $T = T(\{s_i\}_1^n, \{s_i\}_{n+1}^{n+m})$.
4. Conduct statistical inference based on the permutation null distribution of the above statistic.

Twitter Example

Non-vectorial Data

"BarackObama: We need to reward education reforms that are driven not by Washington, but by principals and teachers and parents. http://OFA.BO/6p2EMy"

$\bar{x} = ?$
$\hat{\sigma}_x = ?$
Kernel methods allow us to lift ourselves up into an inner product space, where we can perform geometric calculations.

Kernel Methods

The Kernel Trick (Aizerman et al. 1964)

- Data x_i in a general set $\mathcal{X}$.
- Define a feature map $\phi : \mathcal{X} \to \mathcal{H}$, where $\mathcal{H}$ is a Hilbert space.
- $K(\mathbf{x_i}, \mathbf{x_j}) = \langle \phi(\mathbf{x_i}), \phi(\mathbf{x_j}) \rangle_{\mathcal{H}}$
- Use learning algorithms that only require inner products between vectors in $\mathcal{X}$.
- The inner products can be done implicitly, by a kernel function $K : \mathcal{X} \times \mathcal{X} \to \mathbb{R}$.

Twitter Data

Raw:

"BarackObama: We need to reward education reforms that are driven not by Washington, but by principals and teachers and parents. http://OFA.BO/6p2EMy"
"SarahPalinUSA: You betcha!! MT \"@AlaskaAces: Alaska Aces are 2011 Kelly Cup Champs w/ 5-3 win over Kalamazoo Wings! Aces win ECHL Championship series 4-1\""

After pre-processing:

"we need to reward education reforms that are driven not by washington but by principals and teachers and parents "
"you betcha mt alaskaaces alaska aces are kelly cup champs w win over kalamazoo wings aces win echl championship series "

The Spectrum Kernel

The Spectrum Kernel (Leslie 2002)
Compares two strings based on the their length k contiguous subsequences (k-mers).

- $\mathcal{X}$ = set of all finite-length sequences from an alphabet $\mathcal{A}$.
- $\phi_2(\mathbf{x}) = [\#_{\mathsf{aa}}(\mathbf{x}), \#_{\mathsf{ab}}(\mathbf{x}), \#_{\mathsf{ac}}(\mathbf{x}), \ldots]$
- $\mathcal{H} = \mathbb{R}^{|\mathcal{A}|^k}$
- $K_k(\mathbf{x_i}, \mathbf{x_j}) = \langle \phi_k(\mathbf{x_i}), \phi_k(\mathbf{x_j}) \rangle$

Support Vector Machines

ℓ_1-regularized (soft-margin) support vector classification problem (Vapnik and Cortes, 1995):

$$\begin{aligned} \underset{\mathbf{w}\in\mathcal{H}, b\in\mathbb{R}}{\text{minimize}} \quad & \frac{1}{2}\|\mathbf{w}\|^2 + C\sum_{i=1}^{n+m}\xi_i \\ \text{subject to} \quad & y_i(\mathbf{w}^t\mathbf{x}_i + b) \geq 1 - \xi_i \\ & \xi_i \geq 0 \qquad\qquad \text{for all } i = 1, \ldots, n+m. \end{aligned}$$

For the Friedman Test, our scoring function is the margin $f(\mathbf{x}) = \sum_{i=1}^{n+m} y_i\alpha_i K(\mathbf{x}, \mathbf{x}_i) + b$.

KMMD

Kernel Maximum Mean Discrepancy Test: (Gretton et al. 2006)
$\mathfrak{F}$ a class of functions (unit ball in RKHS), $f : \mathcal{X} \to \mathbb{R}$, p and q probability distributions, and $X \sim p$ and $Z \sim q$ random variables
MMD statistic:

$$\text{MMD}[\mathfrak{F}, p, q] := \sup_{f\in\mathfrak{F}}(\mathbb{E}_{\mathbf{x}\sim p}[f(\mathbf{x})] - \mathbb{E}_{\mathbf{z}\sim q}[f(\mathbf{z})])$$

Empirical Estimate:

$$\text{MMD}[\mathfrak{F}, X, Z] := \sup_{f\in\mathfrak{F}}\left(\frac{1}{N}\sum_{i=1}^{N} f(\mathbf{x}_i) - \frac{1}{M}\sum_{i=1}^{M} f(\mathbf{z}_i)\right)$$

Twitter Example

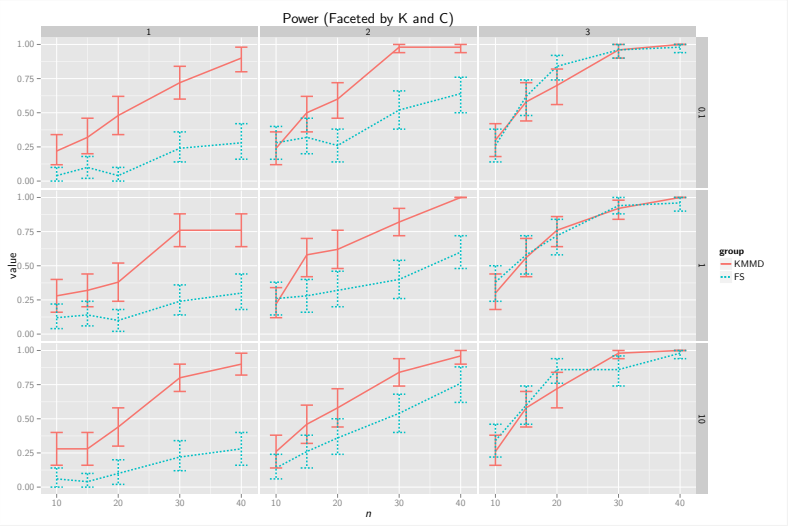
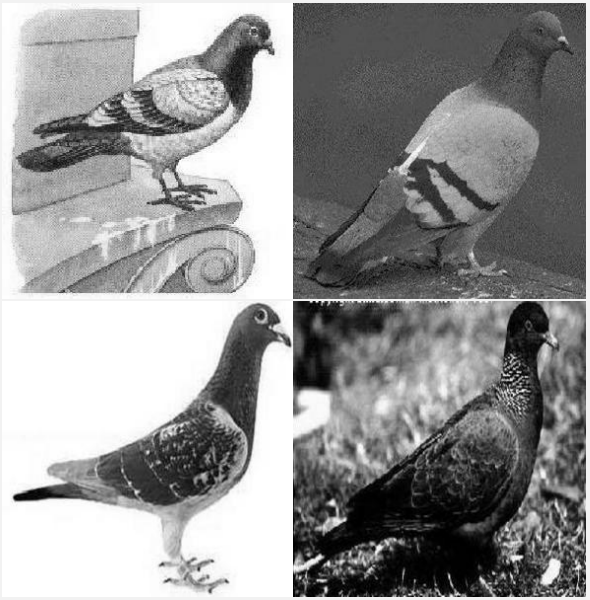


Image Data (Roosters)

Caltech 101 Object Categories (Li et al. 2007) (297×300 grayscale)

Image Data (Pigeons)

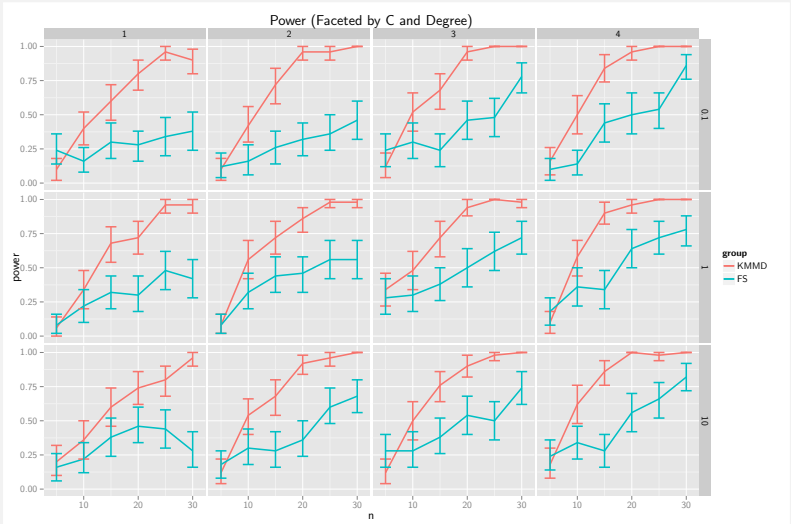


Polynomial Kernel

Compares 2 vectors (images) on products of elements (pixel intensities) up to a certain order.

- $\mathcal{X} = \mathbb{R}^p$
- $\phi_2([x_1, x_2]) = [x_1^2, 2x_1x_2, x_2^2, \sqrt{2c}x_1, \sqrt{2c}x_2, c]$
- $\langle \phi_2(\mathbf{x}), \phi_2(\mathbf{y}) \rangle$ is $\mathcal{O}(n^2)$
- $\mathcal{H} = \mathbb{R}^{p'}$, where $p' = \binom{n+d}{d}$
- $K_d(\mathbf{x}, \mathbf{y}) = (\mathbf{x}^T\mathbf{y} + c)^d$ is $\mathcal{O}(n)$

Rooster/Pigeon Example



Regression and MKL

Regularized regression

- Feature engineering/extraction: $\mathbf{x}_i$
- Feature normalization: $\mathbf{x}_i \leftarrow \frac{\mathbf{x}_i - \hat{\mu}_i}{\hat{\sigma}_i}$
- Regularization/feature selection:
  $\inf_{\boldsymbol{\beta}} \sum_{i=1}^{m+n} L(\beta_0 + \tilde{\mathbf{x}}_i^T\boldsymbol{\beta}, y_i)$ s.t. $||\boldsymbol{\beta}||_p \leq t$

MKL

- Feature engineering/extraction: K_i
- Feature normalization: $K_i(\mathbf{x}, \mathbf{x}') \leftarrow \frac{K_i(\mathbf{x},\mathbf{x}')}{\sqrt{K_i(\mathbf{x},\mathbf{x})}\sqrt{K_i(\mathbf{x}',\mathbf{x}')}}$
- Regularization/feature selection (Kloft et al. 2011):
  $\inf_{\mathbf{w},b,\boldsymbol{\theta}:\boldsymbol{\theta}\succeq 0} C \sum_{i=1}^{m+n} L(\sum_{j=1}^{M} \sqrt{\theta_j}\langle \mathbf{w}_j, \phi_j(\mathbf{x_i})\rangle_{\mathcal{H}_j} + b, y_i)$
  $+\frac{1}{2}\sum_{j=1}^{M} ||\mathbf{w}_j||_{\mathcal{H}_j}^2$ s.t. $||\boldsymbol{\theta}||_p \leq 1$

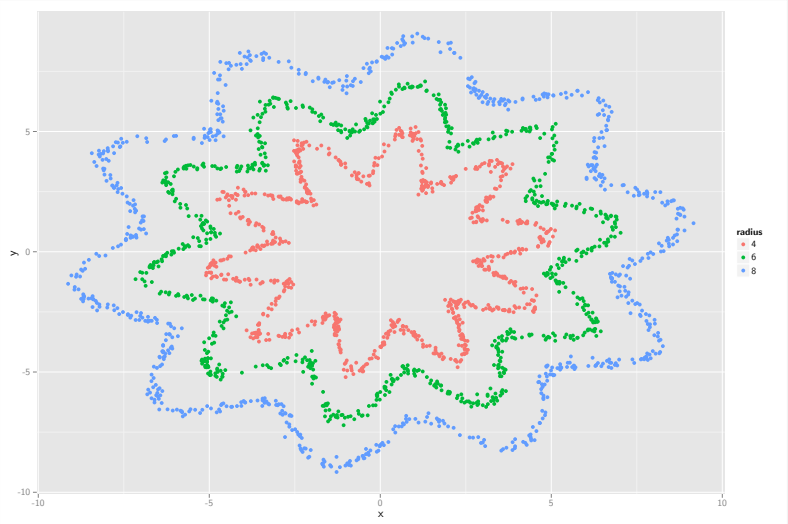
Simulated Data (DNA)

Generate independent DNA sequences of length $N \sim \text{Pois}(100)$ according to the transition matrix

$$M(p^\star) = \begin{array}{c} \\ A \\ C \\ T \\ G \end{array} \begin{array}{c} \begin{array}{cccc} A & C & T & G \end{array} \\ \begin{pmatrix} \frac{1-p^\star}{3} & p^\star & \frac{1-p^\star}{3} & \frac{1-p^\star}{3} \\ \frac{1-p^\star}{3} & \frac{1-p^\star}{3} & p^\star & \frac{1-p^\star}{3} \\ \frac{1-p^\star}{3} & \frac{1-p^\star}{3} & \frac{1-p^\star}{3} & p^\star \\ p^\star & \frac{1-p^\star}{3} & \frac{1-p^\star}{3} & \frac{1-p^\star}{3} \end{pmatrix} \end{array}$$

with stationary distribution $[.25, .25, .25, .25]$.
p takes $p^\star = .25$, and q takes $p^\star > .25$.
p and q generate similar numbers of 1-mers, but q can generate more AC, CT, TG, GA 2-mers.

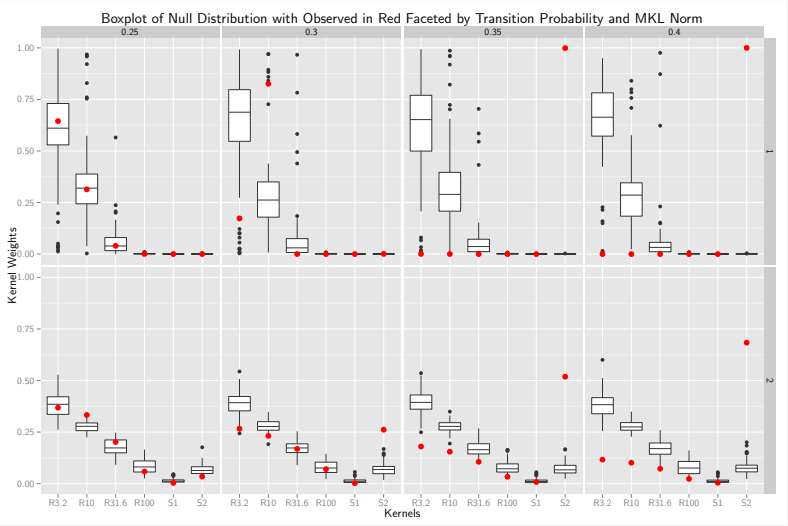
Simulated Data (Star)



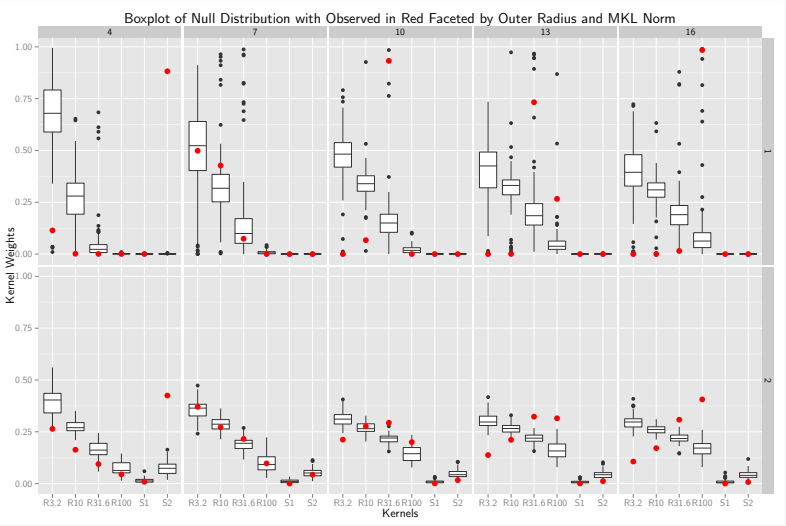
Two-Sample Tests

Two-sample tests typically provide 1 bit of information: accept or reject.
The MKL-based two-sample test generates the observed kernel weight vector $\boldsymbol{\theta}$ and its permuted values $\boldsymbol{\theta}^{(i)}$.

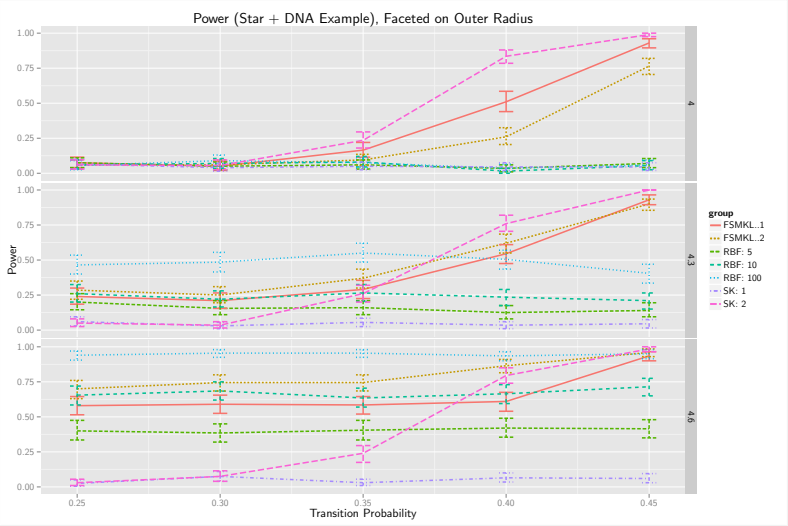
MKL Weights



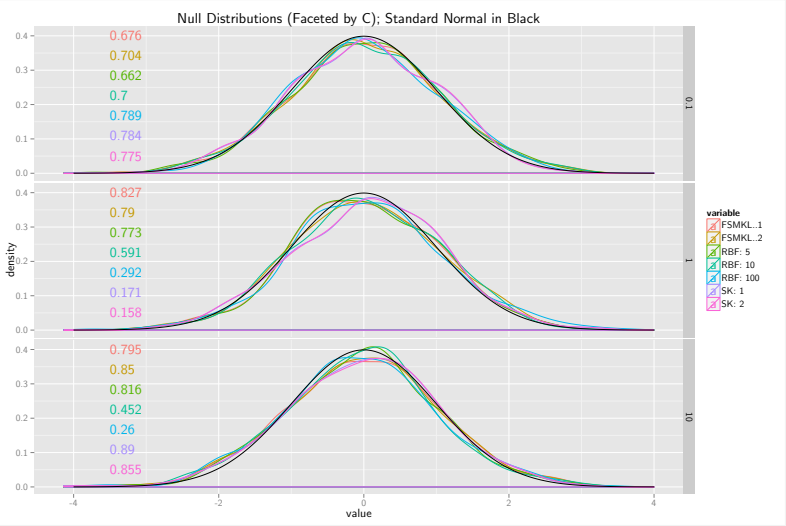
MKL Weights



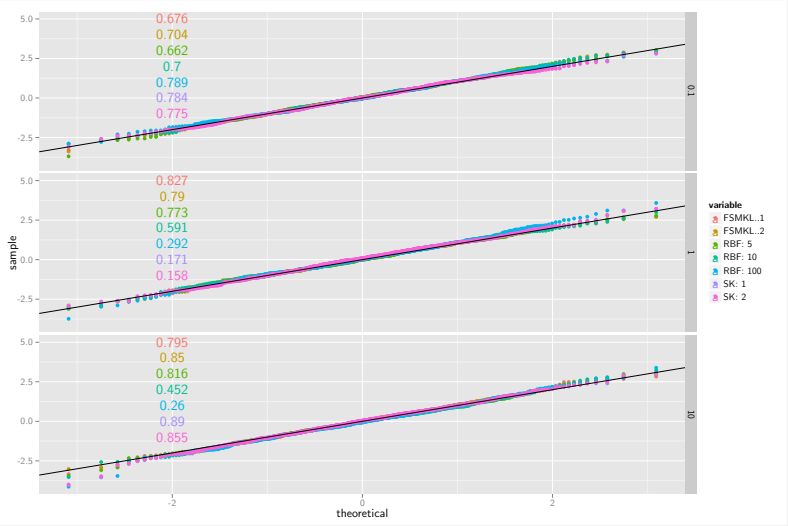
MKL Power



MKL Null Distribution



MKL Null Distribution



Permutation t-test Connection

Want to understand theoretically why the randomization null is normal-like.
And we wish to derive bounds on

$$\sup_{t\in\mathbb{R}} |P(T_\Pi \le t) - \Phi(t)|,$$

where

$$T_\Pi = T_\Pi\left(\{f(\mathbf{x}_{\Pi(i)})\}_{i=1}^{n}, \{f(\mathbf{x}_{\Pi(i)})\}_{i=n+1}^{2n}\right).$$

If $f(x)$ is affine, we recover the permutation t-test.
SVM with linear kernel: $f(x) = \sum_{i=1}^{2n} y_i \alpha_i x x_i + b$.

Other Work

- Fisher (1935) proposed distribution-free randomization test.
- Lehmann proved a normal convergence result for the randomization distribution.
- Bentkus et al. (1996), Shao (2005) proved Berry–Esseen bounds for Student's t-statistic in independent case.

Other Results

Theorem (Berry–Esseen 1941, 1942)

Suppose $X_1, \ldots, X_n$ are i.i.d. random variables with $\mathbb{E}X_i = 0$, $\mathbb{E}X_i^2 = \sigma^2 > 0$, and $\mathbb{E}|X_i|^3 = \rho < \infty$. Let $F_n(x)$ denote the CDF of standardized sample mean of the X_i. Then

$$\sup_x |F_n(x) - \Phi(x)| \le \frac{0.33477(\rho + 0.429\sigma^3)}{\sigma^3\sqrt{n}} = \frac{C}{\sqrt{n}} f(\rho, \sigma).$$

Note that ρ and σ are fixed as $n \to \infty$.

Other Results

Theorem (Hoeffding 1951, Stein 1986)

Let $A = \{a_{ij}\}_{i,j\in\{1,\ldots,n\}}$ be a square array of numbers such that $\sum_j a_{ij} = 0$ for all i, $\sum_i a_{ij} = 0$ for all j, and $\sum_i \sum_j a_{ij}^2 = n - 1$. Then with $F_n(x) = P(\sum_i a_{i\Pi(i)} \le x)$,

$$\sup_x |F_n(x) - \Phi(x)| \le \frac{C}{\sqrt{n}} \left(\sqrt{\sum_{i,j} a_{ij}^4} + \sqrt{\sum_{i,j} |a_{ij}|^3} \right) = \frac{C}{\sqrt{n}} f(A).$$

Given a sampling scheme for A, $f(A)$ must be $\mathcal{O}(1)$ to have rate $\mathcal{O}(n^{-1/2})$.

Exchangeable Pair

Assume $m = n$. Fix data $\{u_1, \ldots, u_n, u_{n+1}, \ldots, u_{2n}\}$. Π is a uniformly random permutation, and let

$$T_\Pi = T_\Pi\left(\{u_{\Pi(i)}\}_{i=1}^n, \{u_{\Pi(i)}\}_{i=n+1}^{2n}\right).$$

Let $(I, J) = (i, j)$ w.p. $\frac{1}{n^2}$ for $1 \le i \le n$ and $n+1 \le j \le 2n$. Then

$$T' = T\left(\{u_{\Pi\circ(I,J)(i)}\}_{i=1}^n, \{u_{\Pi\circ(I,J)(i)}\}_{i=n+1}^{2n}\right).$$

T and T' form an exchangeable pair.

Main Theorem

Theorem

If T, T' are mean 0, exchangeable random variables with variance $\mathbb{E}[T^2]$ satisfying

$$\mathbb{E}[T' - T \,|\, T] = -\lambda(T - R)$$

for some $\lambda \in (0,1)$ and some random variable R, then $\sup_{t\in\mathbb{R}} |P(T \le t) - \Phi(t)|$ is bounded by

$$\underbrace{(2\pi)^{-1/4}\sqrt{\frac{\mathbb{E}|T'-T|^3}{\lambda}}}_{\le n^{-1/4} f_1(\mathbf{x})} + \underbrace{\frac{1}{2\lambda}\sqrt{\mathrm{var}(\mathbb{E}[(T'-T)^2|T])}}_{\le n^{-1} f_2(\mathbf{x})}$$

$$\underbrace{|\mathbb{E}T^2 - 1|}_{\le n^{-1} f_3(\mathbf{x})} + \underbrace{\mathbb{E}|TR|}_{\le n^{-1/2} f_4(\mathbf{x})} + \underbrace{\mathbb{E}|R|}_{\le n^{-1/2} f_5(\mathbf{x})} \le n^{-1/4} f_6(\mathbf{x})$$

Main Theorem (Improved Rate)

Theorem

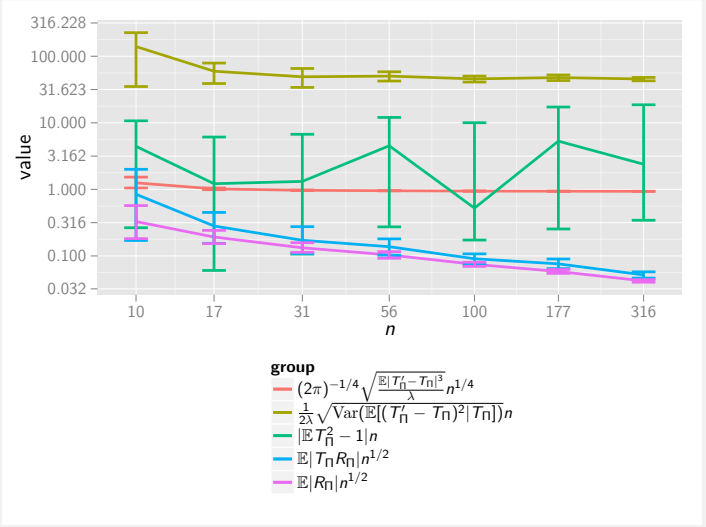
If in addition $|T' - T| \le \delta$, $\sup_{t\in\mathbb{R}} |P(T \le t) - \Phi(t)|$ is bounded by

$$\underbrace{\frac{.41\delta^3}{\lambda}}_{\le n^{-1/2} c_1''^*} + \underbrace{3\delta(\sqrt{\mathbb{E}T^2} + \mathbb{E}|R|)}_{\le n^{-1} f_1'(\mathbf{x})^*} + \underbrace{\frac{1}{2\lambda}\sqrt{\mathrm{var}(\mathbb{E}[(T'-T)^2|T])}}_{\le n^{-1} f_2(\mathbf{x})}$$

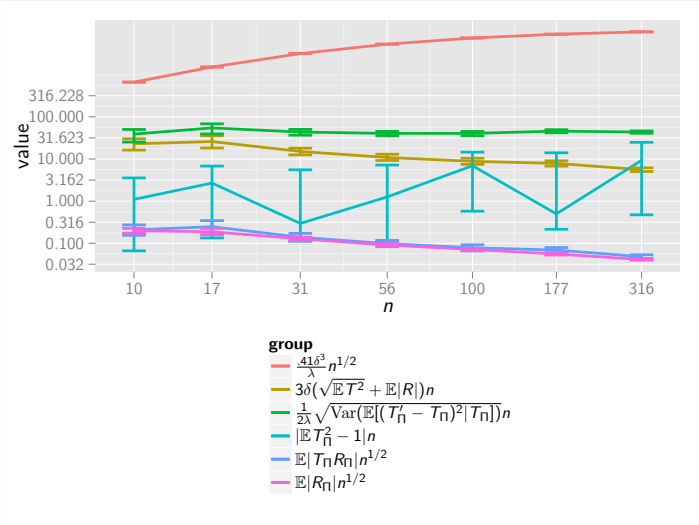
$$\underbrace{|\mathbb{E}T^2 - 1|}_{\le n^{-1} f_3(\mathbf{x})} + \underbrace{\mathbb{E}|TR|}_{\le n^{-1/2} f_4(\mathbf{x})} + \underbrace{\mathbb{E}|R|}_{\le n^{-1/2} f_5(\mathbf{x})} \le n^{-1/2} f_6'(\mathbf{x})^*$$

* if $\delta < c_1' n^{-1/2}$

Simulated Bounds

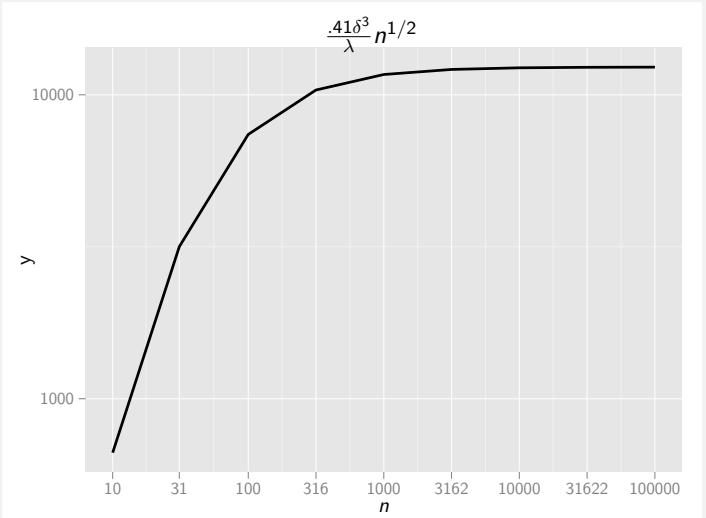


Simulated Bounds (Improved Rate)



When $\mathbf{u} = \{i\}_{i=1}^{i=2n}$, $\frac{.41\delta^3}{\lambda} n^{1/2} \to .205(16\sqrt{6})^3$

Behavior of δ

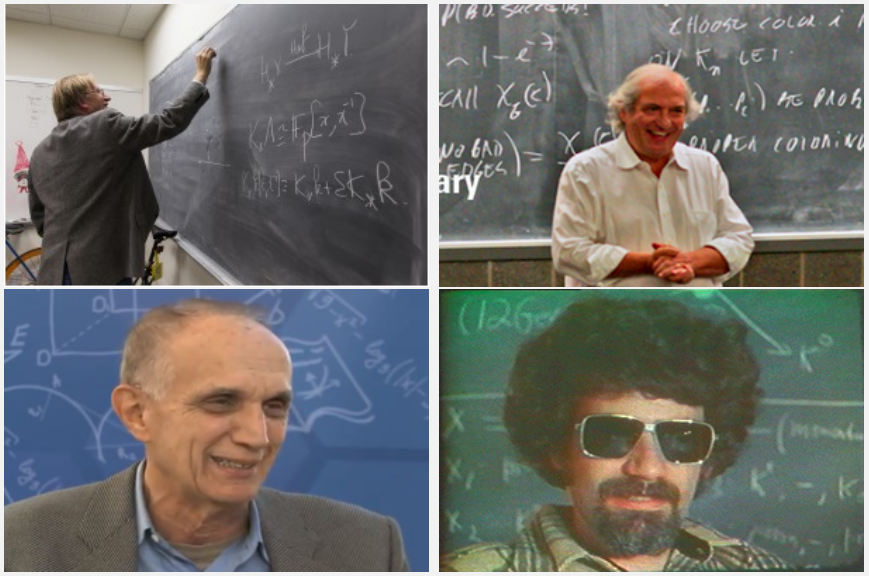


Conclusion

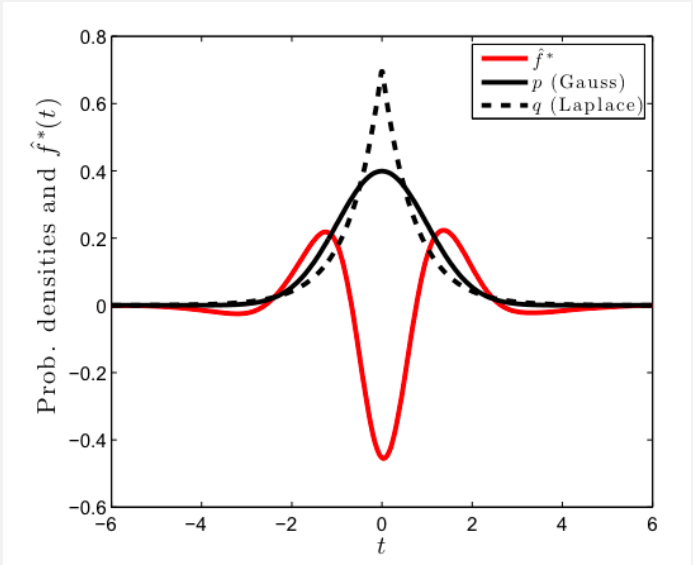
- Friedman's test for non-vectorial and heterogeneous data.
- MKL can learn structure of data.
- MKL power competitive with best-performing kernel and obviates multiple testing considerations.
- Normal-like null distributions.
- Berry–Esseen-type convergence result via Stein's method of exchangeable pairs.

Acknowledgements

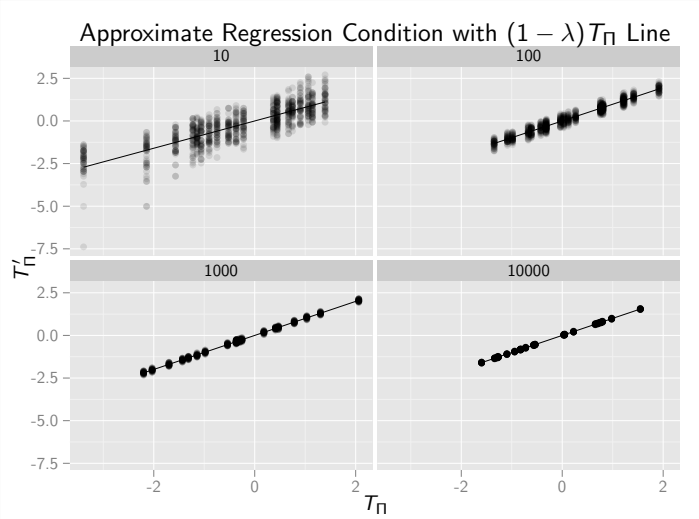
Acknowledgements



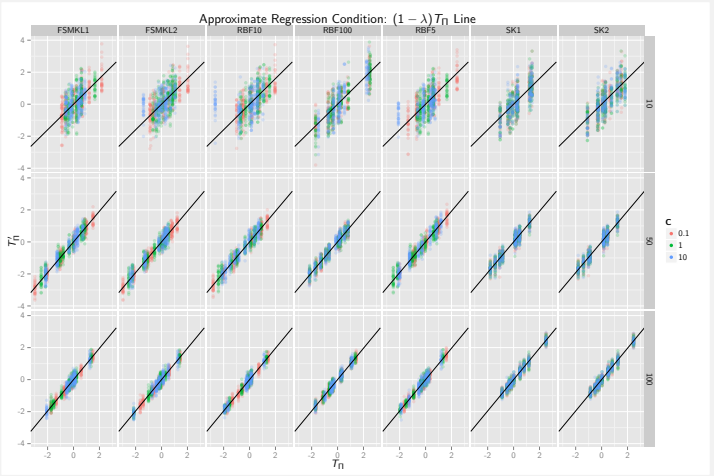
KMMD Function Example



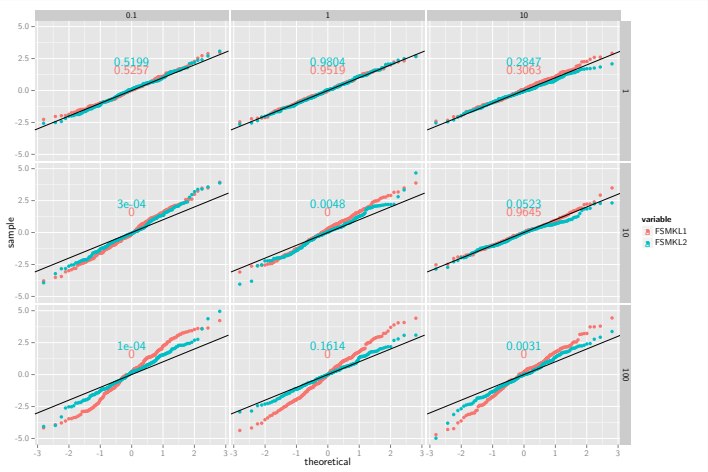
Approximate Regression Condition



ARC (MKL)



Overfitting on Kernels



ARC (MKL, Overfit)