Heuristics for General Efficient Estimation in Copula Models and an Example

Peter J. Bickel

Department of Statistics
University of California at Berkeley

(with assistance of Jorge Bañuelos)

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Joint work with Qunhua Li, James (Ben) Brown, Haiyan Huang
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Major issues and abridged references

Li et. al. 2011 algorithm: Practical success and theoretical problems

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The semiparametric copula model

\[ M \equiv \text{parametric “kernel” regular model} \]
\[ \equiv \{ f(\cdot, \theta) \text{ densities on intervals } J \subset \mathbb{R}, \theta \in \Theta \text{ open in } \mathbb{R}^d \}. \]

Semiparametric “copula” model:

\[ C_{SP}(M) = \{ P_\theta T \mid P_\theta \in M, T \in T \} \]

\[ T \equiv (T_1, \ldots, T_p), \ T_j : J \rightarrow J, \ J \text{ an interval, } T'_j > 0, \ j = 1, \ldots, p, \]
\[ T \equiv \text{ all such transformations} \]
Semiparametric copula (continued)

If $X = (X_1, \ldots, X_p)$:

$$X \sim P_\theta T \iff (T_1(X_1), \ldots, T_p(X_p)) \sim f(\cdot, \theta).$$

WLOG in future $p = 2$. 
Relation to copula generated by $\mathcal{M}$

\textbf{Copula} : $C(\mathcal{M}) = \{ P_\theta F^{-1}(\cdot, \theta) : \theta \in \Theta \}$

where $F(\cdot, \theta) = (F_1(\cdot, \theta), F_2(\cdot, \theta))$ marginal cdf.

So,

$X_j \sim U(0, 1), \ j = 1, 2$
Semiparametric copula (continued)

If $X^{(1)}, \ldots, X^{(n)}$ iid $C_{SP}(\mathcal{M})$, $\hat{R}^{(i)} = (R_{1i}, R_{i2})$, and $R_{ij} = \sum_{k=1}^{n} 1(X_{j}^{(k)} \leq X_{j}^{(i)})$ then for ($p = 2$), $\hat{R}^{(1)}, \ldots, \hat{R}^{(n)}$ are asymptotically sufficient, , LAN. See also Hoff (2007), and Bickel, Ritov (1997).
Basic Questions

Given an identifiable parametrization, \((\theta, T)\):

\[ P_{\theta_1, T_1} = P_{\theta_2, T_2} \iff \theta_1 = \theta_2, T_1 = T_2 \]

1. Construct a fitting algorithm which converges for fixed \(n\):

\[ (\hat{T}_m, \hat{\theta}_m) \to (\hat{T}, \hat{\theta}) \]

2. Have \((\hat{T}, \hat{\theta})\) which are semiparametrically efficient:

\[ (\sqrt{n}(\hat{\theta} - \theta_0), \sqrt{n}(\hat{T} - T_0)) \]

are asymptotically Gaussian, and achieving the information bound.

Treat problem for \(M\) and \(C\) as equivalent, assuming \(\theta \to F(\cdot, \theta)\) smooth.
Measuring reproducibility of high-throughput experiments
Qunhua Li, James B. Brown, Haiyan Huang, Peter J. Bickel
A Motivating Example: ChIP-seq experiment
Signal Identification

- Significance value represents relative strength of the signal. Commonly used: fold of enrichment, p-value, q-value
- Significance scores usually are not on well-calibrated probabilistic measures
  - The null distribution is difficult to approximate
  - Scale may vary across datasets

Arbitrary judgement often is involved in the selection of threshold
ENCODE’s request

Goal: *Uniformly* process data from *multiple sources*.

- Compare performance of different algorithms and select the best one to process data
- Select peaks using a uniform criterion across all datasets

However,
- No ground truth is available
Can replicates help?

Genuine signals should be reproducible across replicates

Can we use replicates to

- select reproducible signals?
- assess the reproducibility of algorithms?
Consistency between calls on two replicates

Suppose $X$ and $Y$ are the significance values on two replicates.

- Assume $X$ and $Y$ reasonably reflect relative strength of signals
- Their distributions are unknown and may be different.

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- Correspondence is expected to decay when getting to noise
- The divergence point provides a guidance on how many calls cannot be trusted
Encode Data

- ChIP-seq experiments on transcription factor CTCF (Broad Institute)
- 2 biological replicates
- 9 algorithms
  - Enrichment: Erange, Fseq, QuEst, SPP, Cisgenome
  - p-value: HotSpot, MACS, SISSRS
  - q-value: Peakseq
- Peaks are normalized to a unified width
A copula mixture model

\[ p = 2 \]

- \( X_{ij} \): Intensity of Peak \( i \) on replicate \( j, j = 1, 2. \)
- Status of peaks

\[ S_i = \begin{cases} 1 & \text{if reproducible} \\ 0 & \text{if irreproducible} \end{cases} \]

- Assume the dependence in each component is induced from a Gaussian distribution (\( z_0 \) and \( z_1 \)) with different association parameters (\( \rho_0 = 0, \rho_1 > 0 \)).
- Assume \( z_1 \) is stochastically larger than \( z_0 \), i.e. \( \mu_1 > \mu_0, \mu_0 = 0 \).
Statistical Model

Let \((X_{i1}, X_{i2})_{i=1,...,n} = \text{Intensity of peak after 2 replicates}\)

Assume/Pretend:

1. These behave like a sample from a population.
2. On possibly different scales

\[ T_1, T_2 : \mathbb{R} \rightarrow \mathbb{R}, \uparrow \text{differentiable}, \]

a peak pair is distributed as a mixture of 2 bivariate Gaussian distribution

Copula Model

\((T_1(X_{11}), T_2(X_{12})) \sim (1 - \epsilon)N(\mu, \mu, \sigma^2, \sigma^2, \rho) + \epsilon N(0, 0, 1, 1, 0)\)

with \(\mu > 0, \theta = (\mu, \mu, \sigma^2, \sigma^2, \rho)\) unknown.

\[ N(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2, \rho) \equiv \text{bivariate Gaussian distribution} \]
Statistical Model

$I = “good peaks”, \quad \mathbb{I} = “noisy peaks”$

Scales $(T_1, T_2)$ are unknown so model is

\[
P(X_{11} < x, X_{12} < y) = (1 - \epsilon) \Phi \left( T_1^{-1}(x), T_2^{-1}(y); \theta \right) + \epsilon \Phi \left( T_1^{-1}(x) \right) \Phi \left( T_2^{-1}(y) \right)
\]

where $\theta = (\mu, \mu, \sigma^2, \sigma^2, \rho)$
Irreproducible discovery rate

In analogy to multiple testing,

- Two groups: *Reproducible* vs. *Irreproducible*
- Local irreproducible discovery rate

\[
\text{idr}(x_1, x_2) = \frac{\pi_0 f_0(x_1, x_2)}{f(x_1, x_2)}
\]

- Irreproducible discovery rate

\[
\text{IDR}(\gamma) \equiv P(\text{irreproducible} \mid I_{\gamma}) = \frac{\pi_0 \int_{I_{\gamma}} dF_0(x_1, x_2)}{\int_{I_{\gamma}} dF(x_1, x_2)}
\]

where \( I_{\gamma} = \{(x_1, x_2) : \text{idr}(x_1, x_2) < \gamma\} \).
For a desired control level $\alpha$, define
\[
\gamma_0 = \arg \max_{\gamma} \{\text{IDR}(\gamma) \leq \alpha\}.
\]
Selecting all pairs $\in l_{\gamma_0}$ gives an expected rate of irreproducible discoveries no greater than $\alpha$.

Selection is based on likelihood ratio, different from thresholding based on significance scores.
Abridged References


Our Method of Fitting

\[ \mathcal{M}: f(x, y, \theta) \]
\[ \mathcal{C}: \frac{f(F_1^{-1}(u, \theta), F_2^{-1}(v, \theta), \theta)}{f_1(F_1^{-1}(u, \theta))f_2(F_2^{-1}(v, \theta))} \]

Given: \((\hat{F}_1(x_i), \hat{F}_2(y_i)), i = 1, \ldots, n.\)

- Form \((x_i(\theta), y_i(\theta)), \) where
  \[ x_i(\theta) = F_1^{-1}(\hat{F}_1(x_i), \theta), y_i(\theta) = F_2^{-1}(\hat{F}_2(y_i), \theta) \]

- Maximize
  \[ \sum_{i=1}^{n} \log f(x_i(\theta), y_i(\theta), \theta) \]

**Advantage:** Can use EM for Mixture, NO Tuning Parameters
Method of Fitting

Our method (when scaled):

- Heuristics for $\sqrt{n}$-consistency
- Not efficient
- No algorithm convergence proven
Proposed Algorithm Revision

A revision sharing same features but heuristically efficient. Argument for \( p = 2 \) but simply generalizable. For simplicity write \( X_2 = Y \).

- An “NPMLE” for \( T_1, T_2, \theta_0 \) fixed.

\[
\mathcal{L} \equiv \int \left( \ell(T_1(x), T_2(y), \theta_0) + \log T'_1(x) + \log T'_2(y) \right) d\hat{F}(x, y)
\]

- \( \ell \equiv \) loglikelihood for \( n = 1 \), parametric model.

- \( \hat{F} \equiv \) Empirical distribution of \( (X_i, Y_i), i = 1, \ldots, n \) i.i.d. \( F_{\theta_0} \).

WLOG \( T_1^0, T_2^0 = \) Identity
Variational optimization (and formal trick)

1. Reparametrize $a_1(x) \equiv \log T'_1(x)$, $a_2(y) \equiv \log T'_2(y)$.
2. Replace $d\hat{F}(x, y)$ by $f(x, y) \, dx \, dy$, $f$ arbitrary

Then

$$T_1(x) = \int_0^x \exp\{a_1(u)\} \, du, \quad T_2(y) = \int_0^y \exp\{a_2(v)\} \, dv$$

Take $J = [0, 1]$. 

Variational optimization (and formal trick)

Let

\[ a_{1\epsilon}(u) = a_{10}(u) + \epsilon \Delta_1(u), \quad a_{2\epsilon}(v) = a_{20}(v) + \epsilon \Delta_2(v) \]

where \( a_{10}, a_{20} \) maximizers for \( \theta_0, f \) fixed.

For \( a_1 = a_{1\epsilon}, a_2 = a_{2\epsilon}, \)

\[ \mathcal{L}_\epsilon(T_{1\epsilon}, T_{2\epsilon}) \equiv \mathcal{L} \]
Variational argument (continued)

\[
\frac{\partial \mathcal{L}}{\partial \epsilon} (a_{10}, a_{20}) \mid_0 = \\
\int_0^1 \int_0^1 \left\{ \int_u^x [e^{a_{10}(u)} \Delta_1(u) \, du] \ell_1(T_{10}(x), T_{20}(y), \theta_0) \\
+ \int_v^y [e^{a_{20}(v)} \Delta_2(v) \, dv] \ell_2(T_{10}(x), T_{20}(y), \theta_0) \\
+ \Delta_1(x) + \Delta_2(y) \right\} f(x, y) \, dx \, dy
\]

for all \( \Delta_1, \Delta_2 \).
\( \ell_1, \ell_2 \equiv \) partials with respect to first and second coordinates
\((a_{10}, a_{20}), (T_{10}, T_{20})\) maximizers
Zeros of derivative of $\mathcal{L}_\epsilon$

$$T'_{10}(u) \int_0^1 \int_u^1 \ell_1(T_{10}(x), T_{20}(y), \theta_0)f(x, y) \, dx \, dy + f_{X_1}(u) = 0$$

and analogously for $T_{20}(v)$. 
Variational argument (continued)

“NPMLE”:
Integrate both sides and plug in $d\hat{F}$ for $f(x, y) \, dx \, dy$.

$$\hat{T}_1(x, \hat{F}) = -\int_0^x d\hat{F}_{X_1}(u) \Lambda_1^{-1}(\hat{T}_1, \hat{T}_2, \hat{F}, \theta_0)(u)$$ (1)

where

$$\Lambda_1(\hat{T}_1, \hat{T}_2, \hat{F}, \theta_0)(u) = \int_0^1 \int_0^1 \ell_1(\hat{T}_1(s), \hat{T}_2(t), \theta_0) \, d\hat{F}(s, t)$$

Compute analogously for $\hat{T}_2(y, \hat{F})$ and label the resulting equation by (7).
Proposed Algorithm

1. Initialize with $\hat{\theta}_0$.

2. Let $\hat{T}_1(\cdot, \hat{\theta}_1), \hat{T}_2(\cdot, \hat{\theta}_1)$ solve (6), (7)

3. At stage $m$ let

   $X_i(\hat{\theta}_{m-1}) = \hat{T}_1(X_i, \hat{\theta}_{m-1}), \ Y_i(\hat{\theta}_{m-1}) = \hat{T}_2(Y_i, \hat{\theta}_{m-1})$

4. Let $\hat{\theta}_m$ maximize

   $$\sum_{i=1}^{n} \ell \left[ \hat{T}_1(X_i(\hat{\theta}_{m-1})), \hat{T}_2(Y_i(\hat{\theta}_{m-1})), \theta \right]$$

5. Determine $\hat{T}_1(X_i(\hat{\theta}_m)), \hat{T}_2(Y_i(\hat{\theta}_m))$, by solving (6), (7)

6. Repeat until convergence

That is, follow Li et al. (2011) but $\hat{T}_1(X_i(\hat{\theta}_m))$ replaces $F_1^{-1}(\hat{F}_1(X_i), \hat{\theta}_{m-1})$ and similarly for $\hat{T}_2$.

Assume algorithm converges to $(\hat{\theta}, \hat{T})$ where $\hat{T}$ satisfies (6), (7) and $\hat{\theta}$ the likelihood equations.
Issues with Proposed Algorithm

1. No obvious way of solving (6), (7)
2. Solutions may not be monotone $\uparrow$. Certainly not $\uparrow$ strictly.
Heuristic Asymptotic Analysis of (6), (7)

The true \( (\theta_0, T_0) \) satisfies (6), (7).

\[
T_0(x, y, \theta_0) = (x, y) = \left( -\int_0^x \frac{dF_x(u, \theta_0)}{\Lambda_1(x, y, \theta_0)}, -\int_0^y \frac{dF_y(v, \theta_0)}{\Lambda_2(x, y, \theta_0)} \right)
\]

Since

\[
\Lambda_1(x, y, \theta_0)(u) = \int_0^1 \int_u^1 \left[ \frac{\partial f}{\partial x}(s, t, \theta_0)f^{-1}(s, t, \theta_0) \right] \ldots \int_u^1 \left[ \frac{\partial f}{\partial x}(s, t, \theta_0)f^{-1}(s, t, \theta_0) \right] \ldots \int_u^1 \left[ \frac{\partial f}{\partial x}(s, t, \theta_0)f^{-1}(s, t, \theta_0) \right] ds dt
\]

\[
= -f_X(u, \theta_0).
\]

Similarly, \( \Lambda_2(x, y, \theta_0) = -f_Y(v, \theta_0) \).
Computation of Influence Function

**Simplify:** Assume that underlying distribution satisfies the copula assumption. If \( \theta \) is true that means just redefining

\[
X_i^{NEW}(\theta) = F_X(X_i, \theta), \quad Y_i^{NEW}(\theta) = F_Y(Y_i, \theta)
\]

Call the new transformations \( T_{1\theta} = F_X T_1(X) \), \( T_{2\theta} = F_Y T_2(Y) \).

So the truth is \((\theta_0, T_{\theta_0})\) and the estimates are \(\hat{\theta}, \hat{T}_{\hat{\theta}}\).

We compute formally the influence function of \((\hat{\theta}, T)\) by expanding around \((\theta_0, T_{\theta_0})\).
Heuristics for General Efficient Estimation in Copula Models and an Example

A general proposal with heuristic backing

Computation of Influence Function (cont.)

Since

$\Lambda_1(T_{\theta_0})(u) = -f_x(u, \theta_0) = 1 = \Lambda_2(T_{\theta_0})(v)$

Then

$\left[ \Lambda_1(\hat{T}_{\hat{\theta}}, \hat{F}) - \Lambda_1(T_{\theta_0}, F_{\theta_0}) \right](u) = \int_0^1 \int_0^1 \ell_x(x, y, \theta_0) dF_{\theta_0}(x, y)$

$+ \int_0^1 \int_0^1 \left[ \ell_{xx}(x, y, \theta_0)(\hat{T}_1 - T_{10})(x) + \ell_{xy}(x, y, \theta_0)(\hat{T}_2 - T_{20})(y) \right] dF_{\theta_0}(x, y)$

$+ \text{lower order terms}$

Where $\ell_x, \ell_{xx}, \ell_{xy}$ are partial second derivatives.

Similar expansion holds for $\Lambda_2(\hat{T}_{\hat{\theta}}, \hat{F}) - \Lambda_2(T_{\theta_0}, F_{\theta_0})$.
Computation of Influence Function (cont.)

Thus, if we view $T'$s as members of $\text{BV}(J) \times \text{BV}(J)$,

$$(I - M)(\hat{T}_\theta - T_{\theta_0})(x, y) = (A_1(x), A_2(y)) + \text{lower order terms}$$

$M \equiv$ linear operator and

$$A_1(x) = \int_0^1 1(x \geq u) d(\hat{F}_x(v, \theta_0) - v)$$

$$+ \int_0^1 \int_0^1 1(x \geq u) \ell_x(u, v, \theta_0) d(\hat{F}_x(u, v) - F_{\theta_0}(u, v))$$

$$A_2(y) = \int_0^1 1(y \geq v) d(\hat{F}_y(v, \theta_0) - v)$$

$$+ \int_0^1 \int_0^1 1(y \geq v) \ell_y(u, v, \theta_0) d(\hat{F}(u, v) - F_{\theta_0}(u, v))$$
Computation of Influence Function (cont.)

Since

\[ 1(x \geq u) + 1(x \geq u)\ell_x(u, v, \theta_0), 1(y \geq v) + 1(y \geq v)\ell_y(u, v, \theta_0) \in \dot{P}_{\theta_0}, \]

\[ \dot{P}_{\theta_0} \equiv \text{tangent space with } \theta_0 \text{ fixed,} \]

\[ I - M \text{ nonsingular} \Rightarrow \hat{T}_{\hat{\theta}} \text{ efficient} \]
Open questions

1. Consistency of $(\hat{\theta}, \hat{T})$
2. Invertibility of $I - M$
3. Validity of expansions
4. No guarantee that $\hat{T}$ is increasing.
5. It may be necessary for simplification to replace $d\hat{F}$ by $\hat{f}(x, y) \, dx \, dy$ i.e. smooth.
Possible Answers

1-3. If $\hat{\theta}_0$ is close enough to $\theta_0$ and $\hat{T}_{\hat{\theta}}$ to $T_{\theta_0}$ Cramér’s approach and Banach fixed point theorem should work.

4. Approximate each iteration by monotone function; Replace $\hat{T}_1(X_{(i)}) - \hat{T}_1(X_{(i-1)})$ by its positive part.

▶ Conjecture: If we can construct an estimate of $\theta$, $\hat{\theta}$, that is consistent and converges uniformly to $\theta_0$ then this construction using $\hat{\theta}$ and $(F_X^{-1}(\cdot, \hat{\theta})\hat{F}_X, F_Y^{-1}(\cdot, \hat{\theta})\hat{F}_Y)$ as a starting point should give efficiency. Constructions using pseudolikelihood should do it.
How broadly applicable should it be?

- Extension to $p > 2$ should work in principle although computation may be burdensome

Approach similar for smoothed proposal. BUT:

1. We distinguished between $\theta$ and $\hat{T}$ using fact that fitting $\theta$ for $\hat{T}$ fixed may have familiar algorithm.

2. Our argument suggests nothing special about splines over other smoothing.

3. If our original approach works no tuning parameters needed.