Interval censored data: a note on the nonparametric maximum likelihood estimator of the distribution function

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Overview

1. The Problem
2. Uniqueness and a Characterization of the MLE of the Distribution Function
3. Algorithmic Construction
4. A Biometric Application

Ref.: Böhning, Schlattmann, Dietz (1996, *Biometrika)*
Gentleman and Geyer (1994, *Biometrika*)

1. The Problem

T Time until a certain event occurs

Pr ($T \leq t$) = F(t) distribution function

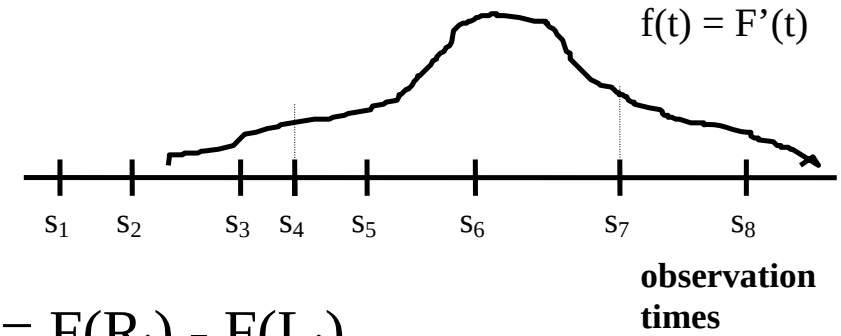
T is *intervalcensored*, e.g.

$T \in (L, R]$

Example: Repeated testing for occult events (in tumorgenesis)

contribution of i-th interval $(L_i, R_i]$ to the likelihood:

$$\Pr\{T_i \in (L_i, R_i]\} = \Pr\{L_i < T_i \leq R_i\}$$



$$= F(R_i) - F(L_i)$$

Example: $F(R_i) - F(L_i) = F(s_7)-F(s_4)$
$= F(s_7) - F(s_6)$
$+ F(s_6) - F(s_5)$
$+ F(s_5) - F(s_4)$

$$F(R_i) - F(L_i)$$

$$= \sum_{j=1}^{m} \alpha_{ij} [F(s_j) - F(s_{j-1})], \text{ with } F(s_0)=0$$

where $\alpha_{ij}= 1$, if $(s_{j-1},s_j] \subseteq (L_i\backslash,R_i]$ and 0 otherwise

full likelihood

$$\prod_{i=1}^{n} F(R_i)-F(L_i)$$

$$= \prod_{i=1}^{n} \sum_{j=1}^{m} \alpha_{ij} [F(s_j)-F(s_{j-1})]$$

$$= \prod_{i=1}^{n} \sum_{j=1}^{m} \alpha_{ij} p_j$$

Log-Likelihood

$$l(p) = \sum_{i=1}^{n} \log\left(\sum_{j=1}^{m} \alpha_{ij}\, p_j \right)$$

NPMLE $\hat{\mathbf{p}}$

$$\text{maximizes } l(p) = \sum_{i=1}^{n} \log\left(\sum_{j=1}^{m} \alpha_{ij}\, p_j \right)$$

under the restrictions

$p_j \geq 0$ f.a. $j=1,...,m$ and $p_1+p_2+...+p_m=1$

analogy to the mixture problem

$$\text{maximize } \sum_{i=1}^{n} \log\left(\sum_{j=1}^{m} f_j(x_i)\quad p_j \right)$$

under the restrictions

$p_j \geq 0$ f.a. $j=1,...,m$ and $p_1+p_2+...+p_m=1$

2. Uniqueness and a Characterization of the MLE of the Distributionfunction

a) Uniqueness

Score

$$d_j = \frac{\partial l}{\partial p_j} = \sum_{i=1}^{n} \frac{\partial}{\partial p_j} \log(\eta_i), \quad \eta_i = \sum_{j=1}^{m} \alpha_{ij} p_j$$

$$= \sum_{i=1}^{n} \alpha_{ik}/\eta_i$$

Hessian

$$\frac{\partial^2 l}{\partial p_k \partial p_j} = -\sum_{i=1}^{n} \alpha_{ij}\alpha_{ik}/\eta_i^2$$

$$-\nabla^2 l(p) = \sum_{i=1}^{n} \alpha_i \alpha_i^T/\eta_i^2 = A^T W A$$

symmetric and nonnegative definite

Result

A full rank $\Rightarrow$ $A^T W A$ positive definite

$\Rightarrow$ $-l$ strictly convex or l strictly concave

$\Rightarrow$ $\hat{p}$ unique

b) Characterisation

$$\Phi(p,q) = \lim_{\alpha\to 0} \frac{1}{\alpha} l\{((1-\alpha)p+\alpha q) - l(p)\}$$

$$= \mathbf{d^T(q - p)}$$

$$= \sum_{i=1}^{n} \sum_{j=1}^{m} \alpha_{ij} q_j / \eta_i - n$$

$$\Phi(p,e_k) = \sum_{i=1}^{n} \alpha_{ik} / \eta_i - n, \quad e_k = (0,..,0,1,0,..,0)^T$$

(k-th position)

Result

$\hat{p}$ NPMLE $\Leftrightarrow \Phi(\hat{p}, e_k) \le 0$ for all k=1,..,m

$\Leftrightarrow d_k(\hat{p}) \le n$ for all k=1,..,m

$\Leftrightarrow \frac{1}{n} d_k(\hat{p}) \le 1$ for all k=1,..,m

Moreover, $\hat{p}_k > 0 \Rightarrow \frac{1}{n} d_k(\hat{p}) = 1$

Example

$l(p) = \log(p_1)+2\log(p_1+p_2)+2\log(p_2+p_3)+\log(p_3)$

$\hat{p} = \frac{1}{3}(1,1,1)^T$

$$d_1 = \frac{1}{p_1} + \frac{2}{p_1+p_2} = 3+3 = 6 = n$$

$$d_2 = \frac{1}{p_1+p_2} + \frac{2}{p_2+p_3} = 3+3 = 6 = n$$

$$d_3 = \frac{2}{p_2+p_3} + \frac{1}{p_3} = 3+3 = 6 = n$$

and

$$\hat{F}(t) = F(\hat{s}_{j-1})$$

$$= \begin{cases} 1; \text{ if } t \geq s_m \\ \sum_{s=1}^{j} p_s = (j-1)/3 \text{ für } s_{j-1} \leq t < s_j;\ j=1 \ldots m \\ 0; \text{ if } t < s_1 \end{cases}$$

3. Algorithmic Construction of the NPMLE

one possibility: EM iteration

$$p_j^{EM} = p_j \, d_j/n$$

attractive, because

$$l(\mathbf{p}^{EM}) \geq l(\mathbf{p})$$

and $\mathbf{p}^{EM} \rightarrow \hat{\mathbf{p}}$ (strict concavity)

disadvantage: converges slowly

alternative possibility (**V**ertex-**E**xchange **M**ethod)

$$\mathbf{p}^{VEM} = \mathbf{p} + \beta p_{min} (\mathbf{e}_{max} - \mathbf{e}_{min})$$

„min“ und „max“ indeces with:

$d_{min} = \min \{d_j | \; j=1,...,m\}$

$d_{max} = \max \{d_j | \; j=1,..,m\}$

and β is *monotone* step-length

available in package C.A.MAN (Böhning, Schlattmann, Lindsay, *Biometrics*, 1992)

4. A Biometric Application

Finkelstein und Wolfe (*Biometrics* 1985)
Breast Cancer Cosmetic Data

T = Time (in Month) until breast-retraction of 94 patients with breast cancer, after radiation therapy (46), and after radiation therapie and chemotherapy (48)

follow-up at clinical visits every 4-6 months

data:

$(L_i,R_i]$ $\downarrow$ $\qquad$ $(s_{j-1},s_j]$ $\rightarrow$

	(4,5]	(6,7]	(7,8]	(11,12]	(15,16]	(17,18]	(24,25]	....	(34,35]	(40,44]	(46,48]
(45,*]	0	0	0	0	0	0	0	....	0	0	1
(6,10]	0	1	1	0	0	0	0	....	0	0	0
(0,7]	1	1	0	0	0	0	0	....	0	0	0
						.....					

complete matrix $A = (\alpha_{ij})$:

0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	1	1	0	0	0	0	0	0	0	0	0	0	0
1	1	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	0	1	1	1	0	0	0	0	0	0	0	0	0
0	0	0	0	0	1	1	1	1	1	1	1	1	1
0	0	1	1	0	0	0	0	0	0	0	0	0	0

0 0 0 0 0 0 0 0 0 0 0 1 1 0
1 1 1 0 0 0 0 0 0 0 0 0 0 0
1 1 1 0 0 0 0 0 0 0 0 0 0 0
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0 0 0 0 0 0 0 0 0 0 1 1 1 1

Weights and Gradient at NPMLE ($\max_{1\le k\le m} \bar{d}_k \le 0.000001$)

$\bar{d}_k$	p_k	k
1.0000	0.0463	1
1.0000	0.0334	2
1.0000	0.0887	3
1.0000	0.0708	4
0.4722	**0.0000**	5
0.8337	**0.0000**	6
1.0000	0.0926	7
0.7965	**0.0000**	8
1.0000	0.0818	9
0.7713	**0.0000**	10
0.9377	**0.0000**	11
1.0000	0.1209	12
0.9394	**0.0000**	13
1.0000	0.4656	14

Summary

Problem of finding the NPMLE in case of interval censored event times is equivalent to the problem finding the MLE of a mixture distribution of indicator functions

Uniqueness and a characterisation of the NPMLE is possible in a simple way

Algorithmic construction of the NPMLE is readily done with the C.A.MAN software

A demonstration was given using well-known clinical data