

Pairwise Dependence Diagnostics for Clustered Failure Time Data

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Motivation

- Interest: Familial aggregation of disease
- Outcome: age at onset
unaffected subjects censored
acknowledges importance of early onset
- Aggregation:
existence, strength, implications?

Multivariate Failure Time

- Example: Ages of appendectomy
Duffy, Australian Twin Study (1990)
- Data sampled in clusters (families)
 $i = 1, \dots, n$
- Clusters contain failures (T_1, \dots, T_K)
- How to describe, model dependence?

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Frailty Model

- ξ_i : latent 'frailty' for i th pair
- (T_{i1}, \dots, T_{iK}) independent given ξ_i
- Hazard for T_{ik} given ξ_i

$$\xi_i \alpha_{0k}(t)$$

- ξ belong to parametric family $g_\gamma(\cdot)$
 γ : *dependence parameter*
- Induces joint model for failures

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Joint Survival Function

- $p_\gamma(\cdot)$ and $q_\gamma(\cdot)$: Laplace & it's inverse of $g(\cdot)$
- Let $\mathcal{S}_k(\cdot)$ be marginal survivor function

$$\text{pr}(T_1 > t_1, \dots, T_K > t_K) = p_\gamma \left[\sum_{k=1}^K q_\gamma \{ \mathcal{S}_k(t_k) \} \right]$$

- Joint survival: function of $\mathcal{S}_k(\cdot)$ and γ
- Form of the function depends on $g(\cdot)$

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Why use a frailty model?

- Easy to specify joint model
marginal specification and frailty distribution
- Parsimonious model
flexible margins, parametric dependence
- Interpretable summaries of dependence
- Facilitates estimation of joint quantities
e.g., conditional risk of failure

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Australian Twin Study

- 1218 Female monozygotic twins
age at appendectomy recorded
- One twin has appendectomy at age 3
- What is risk of co-twin?
 $\text{pr}(T_2 \leq t_2 | T_1 = 3, T_2 > 3), t_2 > 3$
- Data too sparse to answer non-parametrically
- Do different frailties give similar answers?

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Conditional Risk of Appendectomy



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Bivariate Association

- Frailty unobserved
- Choice of $g(\cdot)$ reflected by cross-ratio (CR) function.

$$\theta(t_1, t_2) := \frac{\lambda_1(t_1|T_2 = t_2)}{\lambda_1(t_1|T_2 \geq t_2)} := \frac{\lambda_2(t_2|T_1 = t_1)}{\lambda_2(t_2|T_1 \geq t_1)}$$

- Relative hazard at t_1
given failure history of T_2 at t_2
- $\theta(\cdot, \cdot) \iff g(\cdot)$
Oakes (1989)

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A Local Association Measure

	$\text{pr}(T_1 = t_1)$	$\text{pr}(T_1 > t_1)$	
$\text{pr}(T_2 = t_2)$	a	b	$a + b$
$\text{pr}(T_2 > t_2)$	c	d	
	$a + c$		n

$$S(t_1, t_2) = \text{pr}(T_1 > t_1, T_2 > t_2)$$

$$\theta(t_1, t_2) = \frac{S(dt_1, dt_2)S(t_1^-, t_2^-)}{S(t_1^-, dt_2)S(dt_1, t_2^-)}$$

$$\theta(t_1, t_2) = \frac{a/(a+b)}{(a+c)/n}$$

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Selecting a Frailty Model

- Gamma: Constant CR function
- Positive Stable: CR markedly decreasing in time
converges to 1
- Inverse Gaussian: CR decreasing in time
converges to some limit
- Choice of model can lead to different inference

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Model Checking

- Most methods focused on gamma frailty
Shih & Louis; Shih; Glidden
key computations easy for gamma frailty
- These methods can test for lack-of-fit
- Graphics lack strong interpretation
- Methods don't lead to selection of better fit
- Fan et. (2000) estimated CR nonparametrically

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Checking Methods

A useful method would....

- Be able to check any model
- Unify graphical/inferential methods
- Closely tied to cross-ratio functions

I'll describe such an approach.

Consider pairs then extend

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Three Hazard Functions

- $\Lambda_{11}(\cdot, \cdot), \Lambda_{10}(\cdot, \cdot), \Lambda_{01}(\cdot, \cdot)$: bivariate hazards
- Hazards of double and single failures
- Together they specify joint survival function
- Estimates have Aalen-like structure
- Theory for hazards estimates developed
Gill, van der Laan, Wellner (1995)
consistency, weak convergence, bootstrap

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Bivariate Hazard Functions

By definition of these functions

$$\theta(t_1, t_2) = \frac{\Lambda_{11}(dt_1, dt_2)}{\Lambda_{10}(dt_1, t_2^-)\Lambda_{01}(t_1^-, dt_2)}$$

thus

$$\Lambda_{11}(dt_1, dt_2) - \theta(t_1, t_2)\Lambda_{10}(dt_1, t_2^-)\Lambda_{01}(t_1^-, dt_2) = 0 \quad (1)$$

when $\theta(t_1, t_2)$ correctly specified

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The Approach

- Fit desired frailty model to the data
lots of ways to do this
- Based on model, estimate $\hat{\theta}(\cdot, \cdot)$
shape determined by model
- Estimate $(\hat{\Lambda}_{11}, \hat{\Lambda}_{10}, \hat{\Lambda}_{01})$
fully non-parametric
Nelson-Aalen type form
- Then calculate residuals based on formula (1)

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A Checking Process

- Residuals at observed failure times
- Residual at (t_1, t_2) :
$$\hat{\Lambda}_{11}(dt_1, dt_2) - \hat{\theta}(t_1, t_2) \hat{\Lambda}_{10}(dt_1, t_2^-) \hat{\Lambda}_{01}(t_1^-, dt_2)$$
- Magnitude of residual related to CR function
positive: CR locally underestimated
negative: CR locally overestimated

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The Residuals: Heuristically

$\{t_{1(1)}, \dots, t_{1(D_1)}\}$: D_1 failures of T_1

$\{t_{2(1)}, \dots, t_{2(D_2)}\}$: D_2 failures of T_2

At failure times, form the 2-by-2 table

	$T_1 = t_{1(i)}$	$T_1 > t_{1(i)}$	
$T_2 = t_{2(j)}$	Ψ_{ij}		d_{2ij}
$T_2 > t_{2(j)}$			
	d_{1ij}		R_{ij}

Ψ_{ij} : # of pairs: $T_1 = t_{1(i)}$ and $T_2 = t_{2(j)}$

Residual: $\Psi_{ij} - \hat{\theta} [t_{1(i)}, t_{2(j)}] \frac{d_{1ij}d_{2ij}}{R_{ij}}$

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Similar Methods

- Hsu & Prentice: test of independence
same residuals with $\theta(t_1, t_2) = 1$
- Fan, Prentice, Hsu (2000)
used similar expression for non-parametric estimate of CR function
- Clayton (1978) used Ψ for estimation in gamma frailty model

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The Checking Process

- The model-checking process:

$$\hat{F}(t_1, t_2) = \sqrt{n} \int_0^{t_2} \int_0^{t_1} W(s_1, s_2) \{ \hat{\Lambda}_{11}(ds_1, ds_2) - \hat{\theta}(s_1, s_2) \hat{\Lambda}_{10}(ds_1, s_2^-) \hat{\Lambda}_{01}(s_1^-, ds_2) \}$$

- Process: cumulative sum of residuals
- Residuals proportional to the 2 by 2 table residuals
- $W(\cdot, \cdot)$: arbitrary weight function
e.g., size of risk set, estimated surv fn.

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Appealing Features

- Interpretable process
- $\hat{F}(t_1, t_2)$ increases, CR locally underestimated
- $\hat{F}(t_1, t_2)$ decreases, CR locally overestimated
- Any $\hat{\theta}(\cdot, \cdot)$ can be used
- Graphical and testing component
- Can use some existing theory!!
Gill et. al (1995)

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Covariates

- Marginal hazard for k th failure has structure
- $A_{ik}(dt) = \alpha_{0k}(t) \exp(\beta Z_{ik})$
- Z is a time-fixed covariate
- Under frailty model if margins known, then
- $[\exp\{-A_{i1}(T_{i1})\}, \exp\{-A_{i2}(T_{i2})\}]$
uniform margins
common CR function across clusters
- $\theta_\alpha(u_1, u_2)$ the common CR on unit square

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Approach

- Estimate model: $(\hat{\gamma}, \hat{A}_0, \hat{\beta})$
- Specifies $\hat{\theta}_\alpha(\cdot, \cdot)$
- Create $\hat{U}_{ik} = \hat{A}_{ik}(X_{ik})$
- Use $(\hat{U}_{ik}, \delta_{ik})$ to estimate the bivariate hazards
- Check based on

$$\hat{F}^\alpha = \sqrt{n} \int \int W(u_1, u_2) \{ \hat{\Lambda}_{11}^\alpha(du_1, du_2) - \hat{\theta}_\alpha(u_1, u_2) \hat{\Lambda}_{10}^\alpha(du_1, u_2^-) \hat{\Lambda}_{01}^\alpha(u_1^-, du_2) \}$$

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Arbitrary Cluster Sizes

- Failure vectors (T_1, \dots, T_K)
- Assume: $\text{pr}(T_j > t_1, T_k > t_2) = S(t_1, t_2)$
identical margins, exchangeable structure
- Margins not identical:
use prev. method to transform data
- Estimates of can be constructed of $(\hat{\Lambda}_{11}, \hat{\Lambda}_{10}, \hat{\Lambda}_{01})$
in a Nelson-Aalen spirit
- Define a model-checking process using formula for F

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Under Correct Frailty

- And regularity of $\sqrt{n}\{\hat{\theta}(t_1, t_2) - \theta_0(t_1, t_2)\}$
- $\hat{F}(t_1, t_2)$: approximately mean 0
- $\hat{F}(t_1, t_2) \implies \mathcal{F}(t_1, t_2)$
 $\mathcal{F}(t_1, t_2)$ mean 0, Gaussian process
- $\{F^\sharp(t_1, t_2) - \hat{F}(t_1, t_2)\} \implies \mathcal{F}(t_1, t_2)$
 *F^\sharp : bootstrapped process
bootstrap can approximate $\mathcal{F}(t_1, t_2)$*
- Results can be shown for covariates and $K > 2$

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How Proofs Work

- Repeated use of a delta method
- \hat{F} is a smooth function of empiricals
- Empirical dealt with by empirical process theory
done by Gill et al. (1995)
- Smooth: compactly differentiable
 - chain rule applies
 - transfers asymptotic theory
 - preserves the bootstrap
- Gill (1989) lays out the master plan

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Test for Fit

- Consider two simple summaries of $\hat{F}(\cdot, \cdot)$
- $Z_\tau = \hat{F}(\tau_1, \tau_2) / \hat{SE} \left\{ \hat{F}(\tau_1, \tau_2) \right\}$
compared to $N(0, 1)$
 τ_1, τ_2 some late time
bootstrap used to estimate SE
- $Q = \sup_t |\hat{F}(t_1, t_2)|$
compare to $Q^\# = \sup |\{F^\# - \hat{F}\}|$

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Gamma Frailty Simulations

- Generate gamma & positive stable frailty data
- Fit gamma frailty model
- 30% censoring
- $n = 50, 100, 200$ pairs
- Kendall's $\tau : 0.25, 0.50, 0.75$
- 2,000 datasets, 200 bootstrap samples
- Empirical size of Z_τ and Q statistics

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Size of Tests: Gamma Frailty

τ		$n = 50$	$n = 100$	$n = 200$
0.25	Z_τ	0.06	0.07	0.07
	Q	0.05	0.06	0.07
0.50	Z_τ	0.06	0.06	0.05
	Q	0.04	0.04	0.05
0.75	Z_τ	0.03	0.05	0.04
	Q	0.02	0.03	0.04

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Power to Reject Gamma Frailty

τ		$n = 50$	$n = 100$	$n = 200$
0.25	Z_τ	0.34	0.57	0.84
	Q	0.35	0.60	0.89
0.50	Z_τ	0.74	0.97	1.00
	Q	0.73	0.96	1.00
0.75	Z_τ	0.81	1.00	1.00
	Q	0.70	1.00	1.00

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Positive Stable Frailty Simulations

- Generate positive stable & gamma frailty data
- Fit positive stable frailty model
- 30% censoring
- $n = 50, 100, 200$ pairs
- Kendall's $\tau : 0.25, 0.50, 0.75$
- 2,000 datasets, 200 bootstrap samples
- Empirical size of Z_τ and Q statistics

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Size of Tests: Positive Stable Frailty

τ		$n = 50$	$n = 100$	$n = 200$
0.25	Z_τ	0.08	0.07	0.06
	Q	0.06	0.04	0.06
0.50	Z_τ	0.07	0.07	0.06
	Q	0.04	0.05	0.06
0.75	Z_τ	0.09	0.06	0.06
	Q	0.03	0.06	0.05

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Power: Positive Stable Frailty

τ		$n = 50$	$n = 100$	$n = 200$
0.25	Z_τ	0.38	0.66	0.92
	Q	0.20	0.49	0.83
0.50	Z_τ	0.88	1.00	1.00
	Q	0.66	0.97	1.00
0.75	Z_τ	0.97	1.00	1.00
	Q	0.85	1.00	1.00

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Australian Twin Study

- 1218 Australian female monozygotic twins
- Age at appendectomy recorded
censored at current age
- Duffy et al (1990) *Am J Hum Genet*
- Strong clustering
higher in MZ than DZ twins
- Gamma Frailty fit: $\hat{\theta}(t_1, t_2) = 2.83$
significant clustering

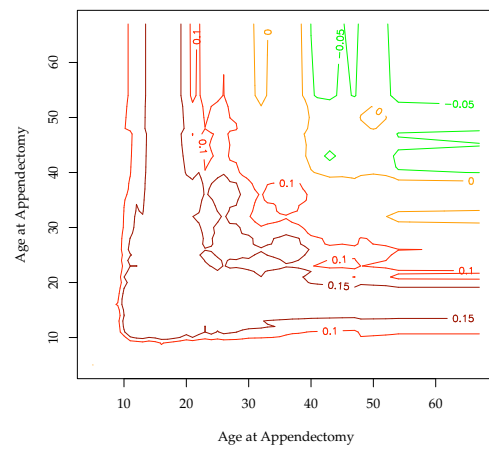
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Constant CR function?

- Non-constant CR function suggested
Fan et al, 2000; Kooperberg
- Glidden (1999): martingale residual method
non-significant, $p = 0.12$
- Calculated test: 10,000 bootstrap samples
 $Z_\tau: p=0.0004, Q: p=0.0026$
- Positive stable fits reasonably:
 $Q: p=0.38$

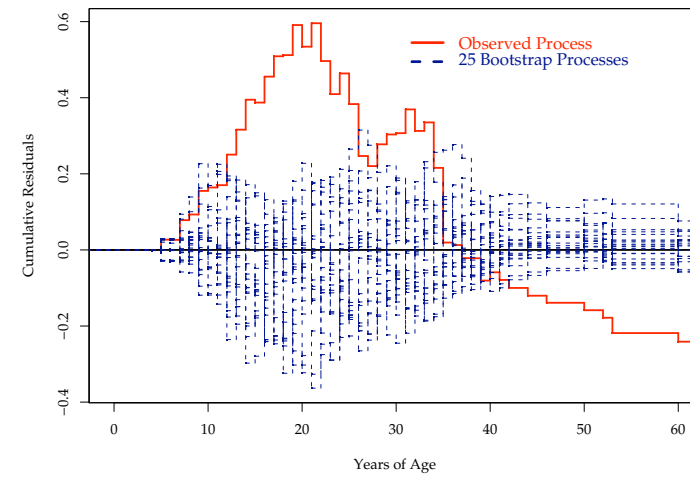
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The Process $\hat{F}(\cdot, \cdot)$

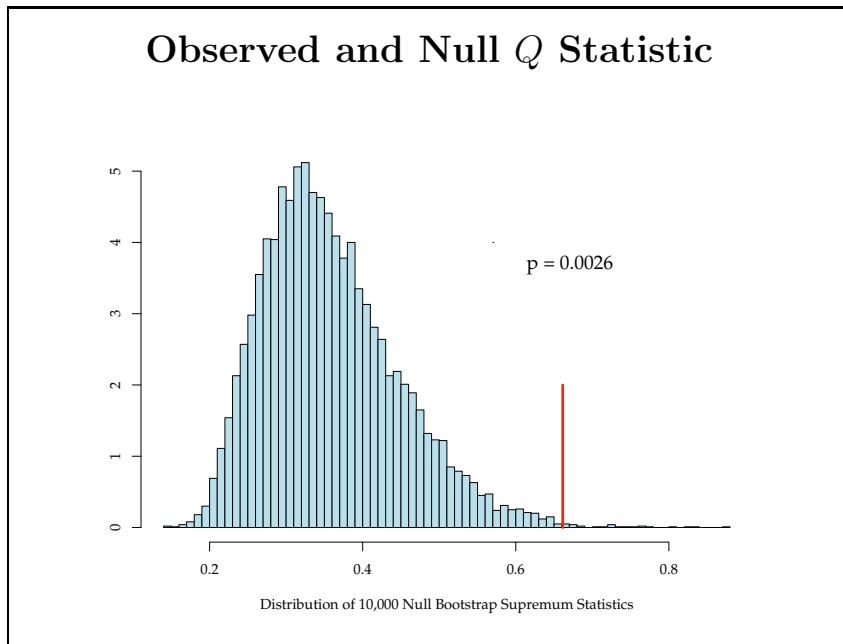


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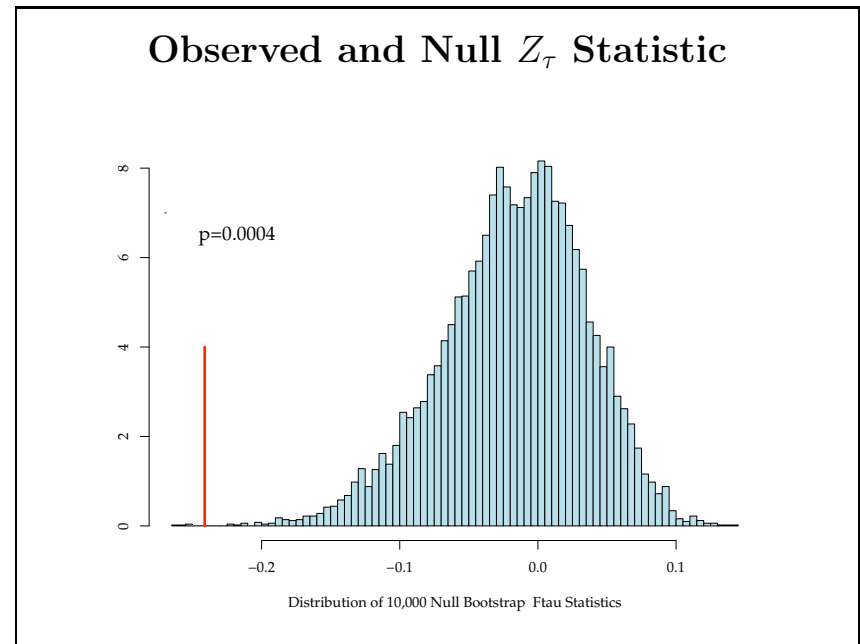
Observed and Null Processes



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Results

- Interpretable, general method
- Properties of F dependent on $\hat{\theta}(\cdot, \cdot)$
no completely general theory
- Bootstrap works well
well-attuned to approximate null distn
- 3-D plots perhaps overwhelming
2-D perhaps more manageable