# CURRENT STATISTICAL METHODS FOR MORTALITY (FAILURE TIME) DATA

TEACHING SESSION

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The following pages contain copies of the overhead transparencies used in Dr. Kalbfleisch's presentations. An audio tape of the presentation can be obtained at nominal cost from the conference organizers, Harry H. Panjer and Frank G. Reynolds, University of Waterloo.

# Current Statistical Methods for Mortality (Failure Time) Data.

**Data**: r.v. $T \geq 0$ $T$ = time to an event.

**Explanatory Variables.**

$\underset{\sim}{z} = (z_1, \ldots, z_s)$ measured covariates.

e.g. age, weight, Blood pressure, ...

**Purpose:**

1. Estimate form or dist'n of $T$ given $\underset{\sim}{z}$
2. Explore Relationship between $T$ and $\underset{\sim}{z}$.

**References:**


Kalbfleisch & Prentice (1980) The Statistical Analysis of Failure Time Data, Wiley

Lawless (1981) Statistical Models & Methods for Life time Data, Wiley

Cox, D.R. (1972) Regression Models & Life Tables (with discussion) JRSS B, 187-220

EXAMPLE 1: Pike (1966) Biometrics

TIME IN DAYS TO VAGINAL CANCER MORTALITY FOR RATS GIVEN A CARCINOGEN.

2 PRETREATMENT REGIMENS. ($z=0,1$)

DATA:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $z=0$ | 143 | 164 | 188 | 188 | 190 | 192 | 206 | 209 |
| | 213 | 216 | 220 | 227 | 230 | 234 | 246 | 265 |
| | 304 | 216 | 244 | | | | | |
| $z=1$ | 142 | 156 | 163 | 198 | 205 | 232 | 232 | 233 |
| | 233 | 233 | 233 | 239 | 240 | 261 | 280 | 280 |
| | 296 | 296 | 323 | 204 | 344 | | | |

CENSORED TIMES FOR 4 ANIMALS.

TIME TO DEATH IS KNOWN TO EXCEED THE CENSORING TIME.

RIGHT CENSORING - VERY COMMON

METHODS MUST ACCOMMODATE THIS.

## Example 2: Clinical Trial Data.

Veteran's Administration Lung Cancer Study.

- patients with inoperable lung cancer.

$T$ = time from diagnoses to death.

Standard versus test therapy

$\underset{\sim}{Z}$ {
- time from diagnosis to admission
- age
- prior therapy 0=no 1=yes
- cell type
- performance status.

"fair" treatment comparison.

assess relationship between $T$ and $\underset{\sim}{Z}$.

## Example 3: Accelerated Life Tests.

| | |
|---|---|
| 150°C | 10 × 8064+ |
| 178°C | 1764, 2772, 3444, 3542, 3780 |
| | 4860, 5196, 3× 5448+ |
| 190°C | 408, 408, 1344, 1344, 1440 |
| | 5× 1680+ |
| 220°C | 408, 408, 504, 504, 504, 5×528+ |

Heavily censored.

Assessment of relationship between temperature and time to failure

Extrapolation ~ 130°C is standard operating temperature.

Possibility of time varying covariates.

$z(t)$ = temperature at time $t$

relate failure rate to current and previous values of $z(t)$.

## EXAMPLE 4: COMPETING RISKS

FAILURE MAY BE ANY ONE OF SEVERAL DIFFERENT TYPES.

| |
|---|
| T = time to failure |
| J = type of failure |

e.g. Hoel (1972). Mice given 300 rads of radiation + followed for cancer incidence

Group 0 control

Group 1 germ free.

Three failure types.

i) incidence (diagnosis) of thymic lymphom

ii) " " " reticulum cell sarcoma

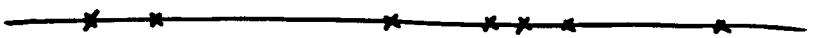
iii) death

How do we construct convenient models?

How does treatment (or other z's) affect failure rate of one type?

## Example 5: Multiple Failure Times.

e.g. attacks of asthma.



may be interested in relating rate of attacks to (e.g.) pollution levels. or to recent history of attacks.

e.g. automobile insurance.

relate accident rate to (e.g.) age, sex, previous accident history, etc.

Want methods which extend to situations like these.

Censoring

Time varying covariates.

Multiple Failure Types.

Multiple Failure Times.

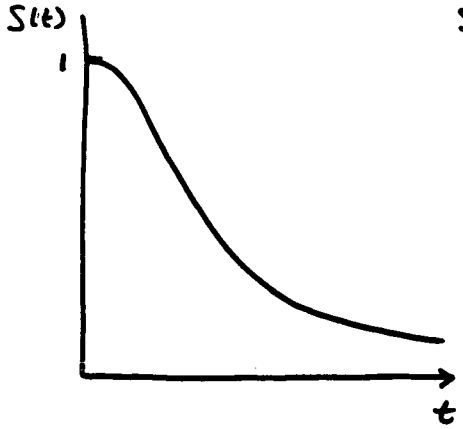
## Failure Time Distributions.

random variable $T$ = time to failure, $T \geq 0$

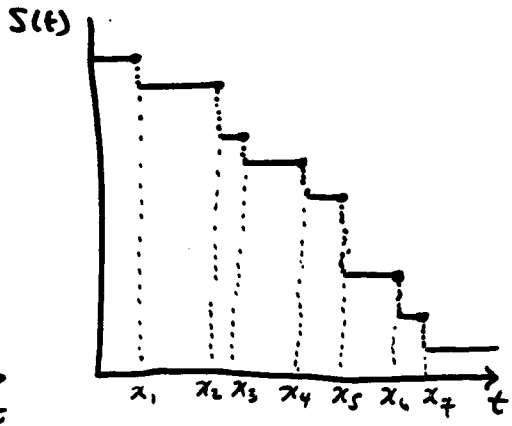
## Survivor Function (Reliability Function)

Def'n $S(t) = \text{pr}\{T \geq t\}$

$S(0) = 1$, $S(\infty) = 0$, non increasing




T continuous




T discrete.

## T (ABSOLUTELY) CONTINUOUS.

PROBABILITY DENSITY FUNCTION (p.d.f.)

$$f(t) = -\frac{d}{dt} S(t)$$

$$= \lim_{\Delta t \to 0^+} pr\{T \in [t, t+\Delta t)\} / \Delta t$$

HAZARD FUNCTION (instantaneous failure rate, force of mortality)

$$\lambda(t) = \lim_{\Delta t \to 0^+} pr\{T \in [t, t+\Delta t) \mid T \geq t\} / \Delta t$$

INTERRELATIONS:

$$\lambda(t) = f(t) / S(t)$$

$$= -\frac{d}{dt} \log(S(t))$$

$$\therefore \boxed{S(t) = \exp\{-\int_0^t \lambda(u)\, du\}}$$

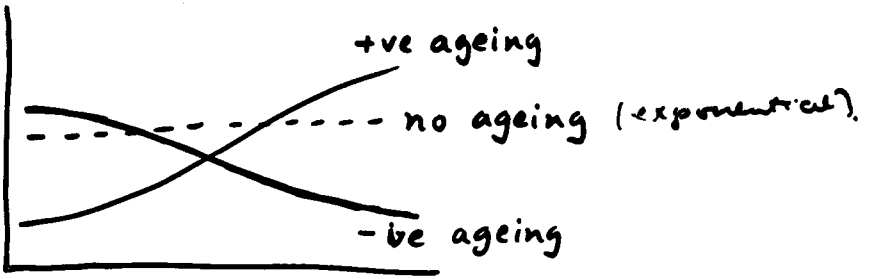
since $S(0) = 1$

Thus $\lambda(t)$ characterizes the distribution of T.

$$\boxed{f(t) = \lambda(t)\, S(t)}$$

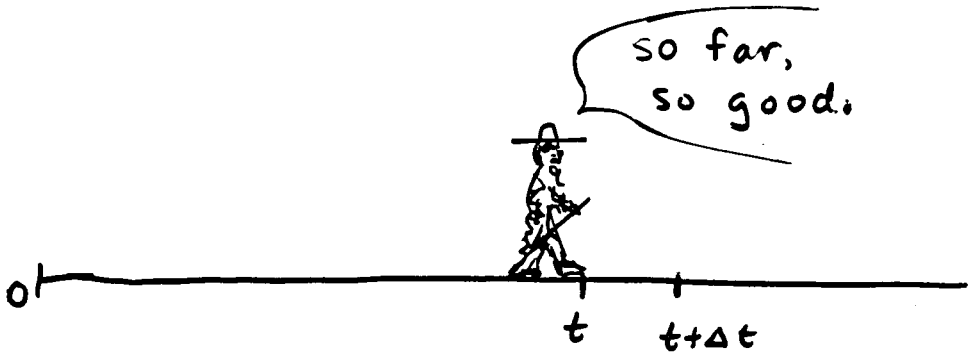
# Why Hazard Modelling.

## ① Ease of Interpretation



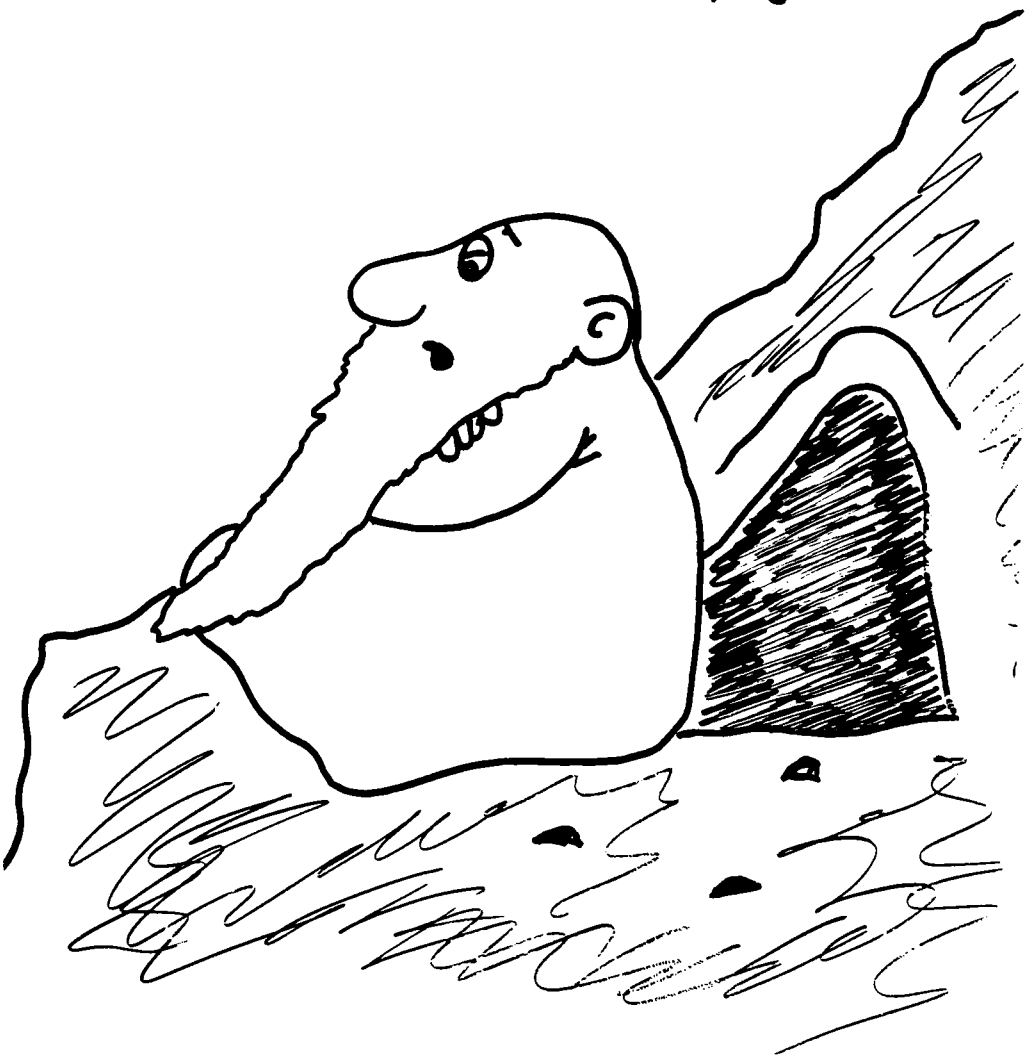

## ② Invites Sequential Interpretation

Time dep't covariates.
Likelihood construction
Partial likelihood.




Interpretation of right censoring.

LIFE IS A SEQUENCE OF BERNOULLI TRIALS



## T DISCRETE

$S(t)$ step fcn

discontinuities at $x_1 < x_2 < x_3 < \cdots$

PROBABILITY FUNCTION:

$$f(x_j) = \text{pr}\{T = x_j\} \qquad j = 1, 2, \cdots$$

HAZARD FUNCTION:

$$\lambda_j = \text{pr}\{T = x_j \mid T \geq x_j\} = f(x_j)/S(x_j) \qquad j = 1, 2, \cdots$$

INTER RELATIONS: $(\lambda_0 = 0)$

$$S(x_j) = (1-\lambda_0)(1-\lambda_1)\cdots(1-\lambda_{j-1})$$

$$= \prod_{j | x_j < t} (1-\lambda_j) \qquad *$$

$$f(x_j) = \lambda_j S(x_j) \qquad j = 1, 2, \cdots$$

* THE LIFE TABLE IS BASED ON THIS RELATIONSHIP.

# SURVIVOR FUNCTION ESTIMATION

**LIFE TABLE:**

| | at risk | deaths | losses (withdrawals) |
|---|---|---|---|
| $[b_0=0, b_1)$ | $N_1$ | $D_1$ | $C_1$ |
| $[b_1, b_2)$ | $N_2$ | $D_2$ | $C_2$ |
| $[b_2, b_3)$ | $N_3$ | $D_3$ | $C_3$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ |
| $[b_{k-1}, b_k)$ | $N_k$ | $D_k$ | $C_k$ |

$$\lambda_j = pr\{T \in [b_{j-1}, b_j) \mid T \geq b_{j-1}\}$$

Estimate

$$\hat{\lambda}_j = \frac{D_j}{N_j - C_j/2} = \frac{D_j}{N_j'}, \quad j=1,\cdots,k$$

The corresponding estimate of the survivor function is

$$\hat{S}(b_j) = \prod_{\ell=1}^{j} (1-\hat{\lambda}_\ell) = \prod_{\ell=1}^{j} \left(1 - \frac{D_\ell}{N_\ell'}\right)$$

NOTE: Grouped data — if actual times of failures & censorings are known, there are better estimates.

# The Kaplan Meier (Product Limit) Estimate

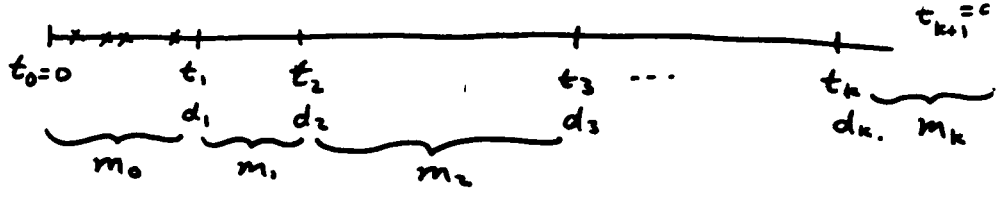
Censored sample from $S(t) = pr\{T \geq t\}$.

Failure times are $t_1 < t_2 < \cdots < t_k$

$d_i$ individuals fail at $t_i$

Censored times

$m_j$ individuals are censored in $[t_{j*}, t_{j+1})$ at $t_{j1}, \cdots, t_{jm_j}$




Let $n_j = d_j + m_j + \cdots + d_k + m_k$

$= \#$ at risk at $t_j - 0$

Estimate discrete hazard components

$\hat{\lambda}_1, \cdots, \hat{\lambda}_k$ at $t_1, \cdots, t_k$

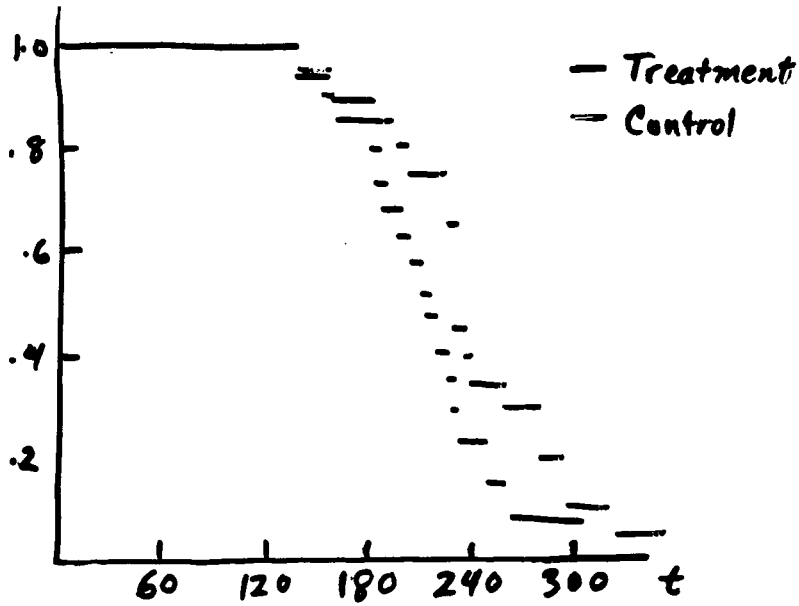
$$\hat{\lambda}_j = d_j / n_j = \frac{\#\text{ failing}}{\#\text{ at risk}}$$

**Kaplan-Meier Estimate is**

$$\hat{F}(t) = \prod_{j | t_j < t} \left(1 - \frac{d_j}{n_j}\right)$$

EXAMPLE: CARCINOGENESIS.

| $t_j$ | $d_j$ | $n_j$ | $(1-\hat{\lambda}_j)$ | $\hat{F}(t_j+0)$ | |
|---|---|---|---|---|---|
| 142 | 1 | 21 | 20/21 | .952 | |
| 156 | 1 | 20 | 19/20 | .905 | $(= .952 \times \frac{19}{20})$ |
| 163 | 1 | 19 | 18/19 | .857 | |
| 198 | 1 | 18 | 17/18 | .810 | |
| 205 | 1 | 16 | 15/16 | .759 | |
| 232 | 2 | 15 | 13/15 | .658 | |
| 233 | 4 | 13 | 9/13 | .455 | |
| 239 | ⋮ | ⋮ | ⋮ | ⋮ | |
| 240 | | | | | |
| 261 | | | | | |



## COMPARISON OF TWO POPULATIONS:

Censored samples available from two populations with survivor fcns $S_1(t)$ and $S_2(t)$.

We wish to test the hypothesis $S_1(t) = S_2(t)$, $0 < t < \infty$.

## LOG RANK TEST (MANTEL HAENSZEL TEST)

- MANTEL (1966) JNCI
- PETO & PETO (1972) JRSS A

Data organization:

- pool samples and let

$$t_1 < t_2 < \cdots < t_k$$

be the distinct failure times.

| | $t_1$ | $t_2$ | $\cdots$ | $t_k$ |
|---|---|---|---|---|
| # failing at $t_j$ | $d_1$ | $d_2$ | | $d_k$ |
| # at risk at $t_j - 0$ | $n_1$ | $n_2$ | | $n_k$ |

View sequentially and test $\lambda_1(t) = \lambda_2(t)$ (equality of failure rates)

Let $d_{ij}$ ($n_{ij}$) be the # of failures at $t_j$ (# at risk at $t_j - 0$) in Sample $i$, $i=1,2$

At $t_j$, set up a 2x2 Contingency Table

| Sample | Failures | Survivors | At Risk |
|---|---|---|---|
| 1 | $d_{1j}$ | $n_{1j} - d_{1j}$ | $n_{1j}$ |
| 2 | $d_{2j}$ | $n_{2j} - d_{2j}$ | $n_{2j}$ |
| | $d_j$ | $n_j - d_j$ | $n_j$ |

Under the null hypothesis ($\lambda_1(t) = \lambda_2(t)$) and given $C_j = (d_j, n_{1j}, n_{2j})$, the probability fcn. of $d_{1j}$ is

$$p(d_{1j} | C_j) = \binom{n_{1j}}{d_{1j}} \binom{n_{2j}}{d_j - d_{1j}} \Big/ \binom{n_j}{d_j}$$

The corresponding (conditional) mean & variance are

$$e_{1j} = E(d_{1j} | C_j) = n_{1j} d_j / n_j$$

$$V_{1j} = \text{var}(d_{1j} | C_j) = n_{1j} n_{2j} d_j (n_j - d_j) n_j^{-2} (n_j - 1)^{-1}$$

Let $v_j = d_{1j} - e_{1j}$

The log rank statistic is

$$v = \sum_{j=1}^{k} v_{1j} = O_1 - E_1$$

which can be shown to ~~have~~ be approximately normal with mean 0 and variance estimated by

$$V = \sum_{j=1}^{k} V_{1j}$$

Comparison of $v/\sqrt{V}$ with $N(0,1)$ tables provides the test.

Notes:

i) $O_1$ = obs'd # of deaths in sample 1

$E_1$ = (sum of conditionally) expected # of deaths in sample 1.

ii) The test exploits the sequential nature of the failure time mechanism.

iii) The test is applicable both to grouped data and to "continuous" data.

EXAMPLE:

Discrete (grouped) failure time data.
Censoring at end of intervals.

Time to recurrenee after initial 90 day treatment period.

| | 0-3mon. | 3-6mos. | 6-9moo | 9-12moo. | >12 |
|---|---|---|---|---|---|
| Rad | $d_{11}=10$ | $d_{12}=8$ | $d_{13}=12$ | $d_{14}=8$ | 12 |
| | $n_{11}=65$ | $n_{12}=54$ | $n_{13}=40$ | $n_{14}=22$ | |
| MTX+Rad | $d_{21}=5$ | $d_{22}=8$ | $d_{23}=8$ | $d_{24}=4$ | 20 |
| | $n_{21}=70$ | $n_{22}=62$ | $n_{23}=44$ | $n_{24}=28$ | |

View sequentially - each interval is a separate trial

e.g. 2nd interval

| sample | fail | surv. | atrisk |
|---|---|---|---|
| 1 | 8 | 46 | 54 |
| 2 | 8 | 54 | 62 |
| | 16 | 100 | 116 |

$$r_{12} = d_{12} - e_{12} = 8 - 7.45 = .55$$
$$V_{12} = 3.46$$

Find $\frac{r}{\sqrt{V}} = 2.37$ S.L. $\cong .02$

Some indication that MTX + Rad is the preferable therapy.

Example: Ungrouped data. Carcinogenesis.

Grp 1: 143, 164, 188, 188, 190, 192, ...

Grp 2: 142, 156, 163, 198, 205, 232, 232, ...

Same procedure

e.g. at $t_j = 188$

$n_{1j} = 17 \quad d_{1j} = 2$

$n_{2j} = 18 \quad d_{2j} = 0$

| sample | fail | surv | risk |
|---|---|---|---|
| 1 | 2 | 15 | 17 |
| 2 | 0 | 18 | 18 |
| | 2 | | 35 |

Calculate $v_{ij}$, $V_{ij}$

Carry out computations for each failure time

142, 143, 156, 163, 164, 188, 190, 192, ...

In this case

$$\frac{v}{\sqrt{V}} = 1.77 \qquad \text{S.L.} \cong .08$$

$v = D_1 - E_1 > 0 \Rightarrow$ sample 1 has somewhat poorer experience. Differences are not significant.

## REGRESSION MODELS:

- relate time to failure to covariates $\underset{\sim}{z}$
  $\underset{\sim}{z} = (z_1, \ldots, z_a)$
- allow quantification of "risk" associated with various subgroups indicated by levels of $\underset{\sim}{z}$.

Consider simplest case first.
$z = 0, 1$ sample indicator. $a = 1$

Let

$$\lambda(t; z) = \lim_{\Delta t \to 0^+} pr\{T \in [t, t+\Delta t) \mid T \geq t, z\} / \Delta t$$

be the hazard function for $z = 0, 1$.

The *Proportional hazards model*

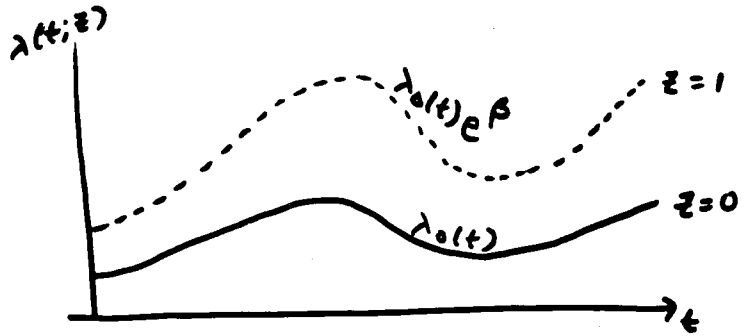
specifies $\boxed{\lambda(t; z) = \lambda_0(t)\, e^{z\beta}}$

for some unknown parameter $\beta$ and arbitrary unspecified hazard $\lambda_0(t)$.

Thus

$$\lambda(t; 0) = \lambda_0(t) \qquad (z = 0)$$
$$\lambda(t; 1) = \lambda_0(t)\, e^{\beta} \qquad (z = 1)$$

$e^{\beta}$ = "relative risk".




Effect of the covariate is to act multiplicatively on the hazard.

$$\frac{\lambda(t;1)}{\lambda(t;0)} = e^{\beta} = \text{relative risk}$$

(indep't of time).

GENERAL

$\underset{\sim}{z} = (z_1, \ldots, z_p)$ vector of $p$ covariates.

$$\lambda(t;\underset{\sim}{z}) = \lambda_0(t)\, e^{\underset{\sim}{z}\underset{\sim}{\beta}}$$
$$= \lambda_0(t)\, e^{z_1\beta_1 + \cdots + z_p\beta_p}$$

where $\underset{\sim}{\beta} = \begin{pmatrix} \beta_1 \\ \vdots \\ \beta_p \end{pmatrix}$ and $\lambda_0(\cdot)$ is arbitrary.

Note $\dfrac{\lambda(t;\underset{\sim}{z}^*)}{\lambda(t;\underset{\sim}{0})} = e^{\underset{\sim}{z}^*\underset{\sim}{\beta}}$ is the "relative risk" associated with $\underset{\sim}{z} = \underset{\sim}{z}^*$ compared to $\underset{\sim}{z} = \underset{\sim}{0}$.

PROBLEMS:

1. TESTS FOR MODEL ADEQUACY.

2. ESTIMATION OF $\underset{\sim}{\beta}$ AND HENCE OF RELATIVE RISKS.

3. ESTIMATION OF $\lambda_0(\cdot)$

We shall deal mostly with 2.

Note again the model

$$\lambda(t;\underset{\sim}{z}) = \lambda_0(t)\, e^{\underset{\sim}{z}\underset{\sim}{\beta}}$$

This is a regression model for the failure rate at time $t$

Postulates no direct relationship between

$T$: time to failure and $\underset{\sim}{z}$.

LIFE IS A SEQUENCE OF BERNOULLI TRIALS.

## Estimation of $\beta$.

**Model:**

$$\lambda(t; \underset{\sim}{z}) = \lambda_0(t) e^{\underset{\sim}{z}\underset{\sim}{\beta}}$$

**Data:**

$$(t_i, \delta_i, \underset{\sim}{z}_i) \quad i = 1, \ldots, n$$

$t_i$ = time to failure or censoring

$\delta_i = 1$ failure

$0$ censored.

$\underset{\sim}{z}_i = (z_{1i}, \cdots, z_{pi})$ covariates for ith individual.

**Problem:** Estimate $\underset{\sim}{\beta}$

Three approaches:

1. Marginal Likelihood
2. Partial Likelihood *
3. Pseudo Maximum Likelihood.

All are in essential agreement.

**Note:** Standard asymptotic results for maximum likelihood estimation do not apply with arbitrary $\lambda_0(\cdot)$ in the model.

Before continuing, it is convenient to rewrite the data — organize them in a sequential way.

Let the observed failure times be

$$t_{(1)}, t_{(2)}, \cdots, t_{(k)}$$

where $0 < t_{(1)} < t_{(2)} < \cdots < t_{(k)}$.

In addition, let $R(t)$ be the set of items atrisk (i.e. not censored and at risk of failure ) at $t-0$.

$\underset{\sim}{Z}_{(i)}$ is the covariate vector of the item that fails at $t_{(i)}$.

Method involves comparing the $\underset{\sim}{Z}_{(i)}$ of the item that fails at $t_{(i)}$ with $\underset{\sim}{Z}_{\ell}$, $\ell \in R(t_{(i)})$ which are the $\underset{\sim}{Z}$ values of the items at risk at $t_{(i)}$.

## PARTIAL LIKELIHOOD (NO TIES)

Consider 2 sample problem first

$\lambda_0(t)$ hazard for sample 0

$\lambda_1(t)$ hazard for sample 1

Proportional hazards $\boxed{\lambda_1(t) = \lambda_0(t) e^{\beta}}$

**Data:** $t_{(1)} < t_{(2)} < \cdots < t_{(k)}$ failure times

At $t_{(i)}-0$, $n_i$ are at risk, of which one fails. If failure at $t_{(i)}$ is S1 failure, can form a 2x2 table

| | fail | surv. | at risk |
|---|---|---|---|
| S1 | 1 | $n_{1i}-1$ | $n_{1i}$ |
| S0 | 0 | $n_{0i}$ | $n_{0i}$ |
| | 1 | | $n_i$ |

$$\text{pr}\{(i) \text{ fails} \mid R(t_{(i)}), \text{ failure at } t_{(i)}\}$$

$$= \frac{\lambda_1(t_{(i)})\, dt_{(i)}}{n_{0i}\lambda_0(t_{(i)})\, dt_{(i)} + n_{1i}\lambda_1(t_{(i)})\, dt_{(i)}} + \Theta(dt_{(i)})$$

$$= \frac{e^{\beta}}{n_{0i} + n_{1i} e^{\beta}}$$

$R(t_{(i)})$ ~ risk set ~ labels of items at risk at $t_{(i)}-0$

Similarly, if (i) is in sample 0

$$\text{pr}\{i) \text{ fails} \mid R(t_{(i)}), \text{ failure at } t_{(i)}\} = \frac{1}{n_{0i} + n_{1i} e^{\beta}}$$

If $z_{(i)} = \begin{cases} 1 & \text{sample } 1 \\ 0 & \text{sample } 0 \end{cases}$

and $z_\ell = 1$ or $0$ similarly for items in $R(t_{(i)})$,

the term arising at $t_{(i)}$ is

$$\frac{e^{z_{(i)}\beta}}{\sum_{\ell \in R(t_{(i)})} e^{z_\ell \beta}}$$

Combine "indep't" exp'ts to obtain the

Partial Likelihood of $\beta$

$$L(\beta) = \prod_{i=1}^{k} \frac{e^{z_{(i)}\beta}}{\sum_{\ell \in R(t_{(i)})} e^{z_\ell \beta}}$$

Note: $L(\beta)$ is not a likelihood in usual sense. It has been shown, however, that the usual asymptotic properties of likelihoods apply to $L(\beta)$ under mild restrictions on covariates $z$ and censoring.

General case: (no ties)

$t_{(1)}, \ldots, t_{(k)}$ failure times.

$\underset{\sim}{z}_{(1)}, \ldots, \underset{\sim}{z}_{(k)}$ corresp. covariate vectors

$\underset{\sim}{z}_\ell$ covariate vector of $\ell$'th individual

$R(t)$ as before

Model: $\lambda(t; \underset{\sim}{z}) = \lambda_0(t) e^{\underset{\sim}{z}\underset{\sim}{\beta}}$

At $t_{(i)}$,

$$\text{pr}\{\text{item } (i) \text{ fails} \mid R(t_{(i)}), \text{ one item fails at } t_{(i)}\}$$

$$= \frac{\lambda(t_{(i)}; \underset{\sim}{z}_{(i)})}{\sum_{\ell \in R(t_{(i)})} \lambda(t_{(i)}; \underset{\sim}{z}_\ell)}$$

$$= \frac{\exp(\underset{\sim}{z}_{(i)} \underset{\sim}{\beta})}{\sum_{\ell \in R(t_{(i)})} \exp(\underset{\sim}{z}_\ell \underset{\sim}{\beta})}$$

Product over indep't exp'ts gives.

$$L(\underset{\sim}{\beta}) = \prod_{i=1}^{k} \frac{e^{\underset{\sim}{z}_{(i)} \underset{\sim}{\beta}}}{\sum_{\ell \in R(t_{(i)})} e^{\underset{\sim}{z}_\ell \underset{\sim}{\beta}}}$$

Cox likelihood for case of no ties.

## THE CASE OF TIES:

COX SUGGESTS A DISCRETE MODEL FOR THE HAZARD.

$$\lambda_i = P\{T = t_{(i)} \mid \underline{z} = \underline{0}\} \{T \geq t_{(i)}\}$$

$$\lambda_i(\underline{z}) = P\{T = t_{(i)} \mid \underline{z}, T \geq t_{(i)}\}$$

$$= \frac{\lambda_i e^{\underline{z}\underline{\beta}}}{1 + \lambda_i e^{\underline{z}\underline{\beta}} - \lambda_i} = \frac{e^{\alpha_i + \underline{z}\underline{\beta}}}{1 + e^{\alpha_i + \underline{z}\underline{\beta}}}$$

where $\alpha_i = \log \frac{\lambda_i}{1-\lambda_i}$ "BINARY LOGISTIC MODEL".

NOTE:

$$\log \frac{\lambda_i(\underline{z})}{1-\lambda_i(\underline{z})} = \log \frac{\lambda_i}{1-\lambda_i} + \underline{z}\underline{\beta}$$

covariates act additively on log odds.

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ASIDE: Let

$$\lambda_0(t) = \sum \lambda_i \, \delta(t - t_{(i)})$$

$$\lambda(t; \underline{z}) = \sum \lambda_i(\underline{z}) \, \delta(t - t_{(i)})$$

$$\frac{\lambda(t;\underline{z})\,dt}{1 - \lambda(t;\underline{z})\,dt} = \frac{\lambda_0(t)\,dt}{1 - \lambda_0(t)\,dt} e^{\underline{z}\underline{\beta}}$$

specifies both discrete + continuous models.

DATA: $t_{(1)}, t_{(2)}, \ldots, t_{(k)}$ distinct failure times

$d_1, d_2, \ldots, d_k$ multiplicities.

$\mathcal{D}_i$ = set of items failing at $t_{(i)}$.

Consider again the conditional terms.

$$P\{\text{items in } \mathcal{D}_i \text{ fail} \mid R(t_{(i)}), d_i \text{ failures at } t_{(i)}\}$$

$$= \frac{\prod_{\ell \in \mathcal{D}_i} \lambda_\ell e^{\underset{\sim}{z}_\ell \underset{\sim}{\beta}} \prod_{\ell \in R(t_{(i)})} \lambda_\ell e^{\underset{\sim}{z}_\ell \underset{\sim}{\beta}} - \lambda_i)^{-1} \prod_{\ell \in R_{d_i}} (1-\lambda_i)}{\sum_{\rho \in R_{d_i}(t_{(i)})} \prod_{\ell \in \rho} \lambda_\ell e^{\underset{\sim}{z}_\ell \underset{\sim}{\beta}} \prod_{\ell \in R(t_{(i)})} ( \quad \cdot \cdot \quad )^{-1} \prod_{\ell \in R_{d_i}} (1-\lambda_i)}$$

$$= \frac{e^{\underset{\sim}{\Delta}_{(i)} \underset{\sim}{\beta}}}{\sum_{\rho \in R_{d_i}(t_{(i)})} e^{\underset{\sim}{\Delta}_\rho \underset{\sim}{\beta}}}$$

where $\underset{\sim}{\Delta}_{(i)} = \sum_{\ell \in \mathcal{D}_i} \underset{\sim}{z}_\ell$

$\underset{\sim}{\Delta}_\rho = \sum_{\ell \in \rho} \underset{\sim}{z}_\ell$

and $R_{d_i}(t_{(i)})$ is the set of all subsets of $d_i$ items chosen from the risk set without replacement.

THE PARTIAL LIKELIHOOD IS THEN

$$\prod_{i=1}^{k} \frac{e^{\underset{\sim}{A}_{(i)}\underset{\sim}{\beta}}}{\sum_{\ell \in R_{d_i}(t_{(i)})} e^{\underset{\sim}{A}_{\ell}\underset{\sim}{\beta}}}$$

APPROXIMATION:

CHANGE "WITHOUT REPLACEMENT" TO "WITH REPLACENT"

$$\prod_{i=1}^{k} \left\{ \frac{e^{\underset{\sim}{A}_{(i)}\underset{\sim}{\beta}}}{\sum_{\ell \in R(t_{(i)})} e^{\underset{\sim}{A}_{\ell}\underset{\sim}{\beta}}} \right\}^{d_i} = L(\underset{\sim}{\beta})$$

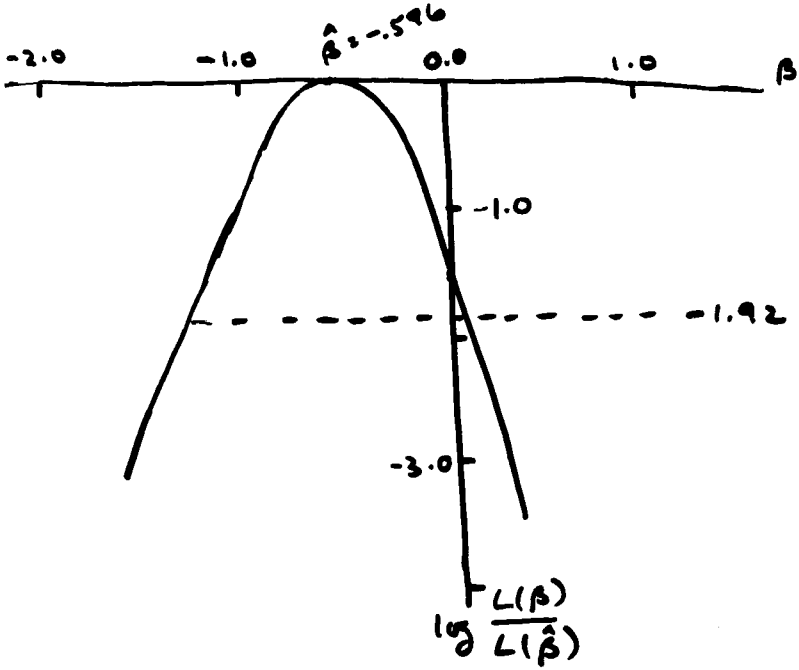
"THE COX LIKELIHOOD".

EXAMPLE: CARCINOGENESIS

| $i$ | $t_{(i)}$ | $d_i$ | $z_i$ failures | censored | contin to likelihood. |
|---|---|---|---|---|---|
| 1 | 142 | 1 | 1 | | $e^{\beta}/(19+21e^{\beta})$ |
| 2 | 143 | 1 | 0 | | $1/(19+20e^{\beta})$ |
| ⋮ | ⋮ | ⋮ | ⋮ | | ⋮ |
| 6 | 188 | 2 | 0,0 | | $1/(17+18e^{\beta})^2$ |
| ⋮ | ⋮ | ⋮ | ⋮ | | ⋮ |
| 9 | 198 | 1 | 1 | 1(204) | $e^{\beta}/(13+18e^{\beta})$ |
| 10 | 205 | 1 | 1 | | $e^{\beta}/(13+16e^{\beta})$ |
| ⋮ | ⋮ | ⋮ | ⋮ | | ⋮ |
| 19 | 233 | 4 | 1,1,1,1 | | $e^{4\beta}/(5+13e^{\beta})^4$ |
| ⋮ | ⋮ | ⋮ | ⋮ | | ⋮ |
| 28 | 304 | 1 | 0 | | $1/(1+2e^{\beta})$ |
| 29 | 323 | 1 | 1 | 1(344) | $e^{\beta}/2e^{\beta}$ |

Notes: 1. $z=\begin{cases}0 & \text{sample 1}\\ 1 & \text{sample 2}\end{cases}$

2. Unecessary to use tied failure time approx. since all tied values occur at common $z$ values.




Log partial likelihood fcn of β for Carcinogenesis data.

## Asymptotic Results:

The Partial Likelihood is not a likelihood in usual sense.

It has been shown, however, that usual asymptotic properties hold.

ie. if $\hat{\underset{\sim}{\beta}}$ is the maximum partial likelihood estimate, then under relatively mild regularity conditions:

i) $\hat{\underset{\sim}{\beta}}$ is unique solution to

$$\frac{\partial}{\partial \underset{\sim}{\beta}} \log L(\beta) = 0$$

ii) $\hat{\underset{\sim}{\beta}}$ is asymptotically normally distributed with mean $\underset{\sim}{\beta}$ and covariance matrix estimated by

$$I^{-1}(\hat{\beta})$$

where $$I(\underset{\sim}{\beta}) = \left( - \frac{\partial^2 \log L(\underset{\sim}{\beta})}{\partial \beta_i \partial \beta_j} \right)_{p \times p}$$

Tsiatis (1980, Aof. Stat.)
Andersen & Gill (1982, Ann. of. Stat.)

EXAMPLE: CARCINOGENESIS DATA

$\hat{\beta} = -.596$

$$I(\hat{\beta}) = -\frac{\partial^2}{\partial \beta^2} \log L(\beta)\Big|_{\beta=\hat{\beta}} = 8.237$$

1. Wald / m.l.e. results.

s.e. of $\hat{\beta}$ is estimated by $\frac{1}{\sqrt{I(\hat{\beta})}} = .35$

95% C.I. for $\beta$

$\hat{\beta} \pm 1.96(.35) = (-1.28, .09)$

$H_0: \beta = 0$

$$\hat{\beta}\sqrt{I(\hat{\beta})} = \frac{-.596}{.35} = -1.71 = -\sqrt{2.92}$$

Note: relative risk $\rho = e^{\beta}$ $\quad \hat{\rho} = e^{\hat{\beta}} = .551$

95% C.I. is $(e^{-1.28}, e^{.09}) = (.28, 1.09)$

2. Likelihood Ratio

$H_0: \beta = 0$ $\quad -2\log\left\{\frac{L(0)}{L(\hat{\beta})}\right\} = 2.86$ compare $\chi^2_{(1)}$

95% C.I. $= \left\{\beta : -2\log\frac{L(\beta)}{L(\hat{\beta})} \leq 3.84\right\} = (-1.27, .11)$

3. Rao / Score Tests.

$H_0: \beta = 0$ $\quad U(0) = 4.763$, $I(0) = 7.560$

(cut put from first step in Newton Raphsen)

$U(0)^2 I(0)^{-1} = 3.00$

N.B. $U(0) = O - E$ is the log rank statistic

# THE SCORE TEST AND THE LOGRANK TEST

$$\underset{\sim}{U}(0) = \partial \log L(\beta)/\partial \beta \,|_{\beta=0}$$

$$= \sum_{i=1}^{k} \left\{ s_{(i)}' - d_i\, n_i^{-1} \sum_{\ell \in R(t_{(i)})} \underset{\sim}{z}_\ell' \right\}$$

where $n_i$ = # of elts in $R(t_{(i)})$

$s_{(i)}'$ = obs'd sum of $z$'s for failures at $t_{(i)}$.

$d_i n_i^{-1} \sum_{R(t_{(i)})} \underset{\sim}{z}_\ell'$ = conditionally expected sum of $\underset{\sim}{z}$'s

**Special case:** s+1 sample problem

$\underset{\sim}{z}_i = (z_{1i}, \ldots, z_{si})$ $\qquad z_{ji} = \begin{cases} 1 & \text{ith subj in jth sample} \\ 0 & \text{else} \end{cases}$

$\underset{\sim}{U}(0) = \underset{\sim}{O} - \underset{\sim}{E}$ $\qquad \underset{\sim}{O} = s_{(1)}' + \cdots + s_{(k)}'$ = obs'd # failures

$\underset{\sim}{E} = \sum_{1}^{k} d_i n_i^{-1} \sum_{R(t_{(i)})} \underset{\sim}{z}_\ell$ = sum of cmd. exp.

**Variance estimation:**

From Cox likelihood use $I(0)$
involves approx for ties.

Earlier estimate $V$ involves no approx.
& arises directly from partial likelihood with discrete logistic model.

Can be shown that

$$\underset{\sim}{U}(0)' I(0)^{-1} \underset{\sim}{U}(0) \le \underset{\sim}{U}(0)' V^{-1} \underset{\sim}{U}(0)$$

## Example: Lung Cancer Trial

$z_1$ = Karnofsky score  0, 10, ---, 100

$z_2$ = age

$z_3, z_4, z_5$ } cell type  Squamous vs. large; small vs. large; adeno. vs. large.

$z_6$ treatment.  1 = test; 0 = standard.

$$\lambda(t; \underset{\sim}{z}) = \lambda_0(t)\, e^{\underset{\sim}{z}\underset{\sim}{\beta}}$$

| Variable | $\hat{\beta}$ | $\chi^2$ (Likelihood ratio) | |
|---|---|---|---|
| $z_1$ | -.033 | 35.08 | |
| $z_2$ | -.0086 | .85 | |
| $z_3$ | -.4087 | 18.15 | Compare $\chi^2_{(3)}$ |
| $z_4$ | .4597 | | |
| $z_5$ | .7879 | | |
| $z_6$ | -.298 | 2.07 | |

Estimation of relative risk

$z_1 = 100$ vs $z_1 = 50$

estimate $\hat{r} = e^{(50)(-.033)} \tilde{=} .22$

Could specify subgroups ~~with approximate uniform risk~~ within which the risk is nearly constant.

## ESTIMATION OF $\lambda_0(\cdot)$

Model: $\lambda(t;\underset{\sim}{z}) = \lambda_0(t)\, e^{\underset{\sim}{z}\underset{\sim}{\beta}}$

$\underset{\sim}{\beta}$ can be estimated using the Partial Likeliho

Require now an estimate of $\lambda_0(\cdot)$.

## General approach

Take $\underset{\sim}{\beta} = \hat{\underset{\sim}{\beta}}$ and generalize life table or Kaplan Meier Estimates to allow for weighted failure rates.

Resulting estimate is of

$$S_0(t) = pr\{T \geq t\,;\, z=0\} = e^{-\int_0^t \lambda_0(u)\,du}.$$

can obtain from this estimates of

$$S(t;z) = pr\{T \geq t;\, z\} = e^{-\int_0^t \lambda_0(u)\,du\, e^{z\beta}}$$

$$= \{S_0(t)\}^{\exp(z\beta)}$$

Example: Generalization of the life table.

Let $[b_0=0, b_1), [b_1, b_2), \ldots, [b_{k-1}, b_k)$ be a partition of the interval $[0, b_k)$.

Note that

$$\Pr\{T \in [b_{i-1}, b_i) \mid T \geq b_{i-1}, z\} = \exp\{-\int_{b_{i-1}}^{b_i} \lambda_0(u)\,du\, e^{z\beta}\}$$

$$= q_i^{\exp(z\beta)}, \quad i = 1, 2, \ldots, k.$$

where $q_i = \exp\{-\int_{b_{i-1}}^{b_i} \lambda_0(u)\,du\}$.

The baseline survivor fcn at $b_i$ is

$$S(b_i) = \prod_{j=1}^{i} (1 - q_j) \qquad \hat{S}(b_i) = \prod_{1}^{i} (1 - \hat{q}_j)$$

Divide $R(b_{i-1})$ into 3 components

$\mathcal{D}_i$ = set of individuals failing in $[b_{i-1}, b_i)$

$\mathcal{C}_i$ = set of individuals surviving $b_i$

$\mathcal{L}_i$ = set of individuals censored in $[b_{i-1}, b_i)$

| Interval | failures | survivors | withdrawals |
|---|---|---|---|
| $[b_{i-1}, b_i)$ | $z_\ell, \ell \in \mathcal{D}_i$ | $z_\ell, \ell \in \mathcal{C}_i$ | $z_\ell, \ell \in \mathcal{L}_i$ |

Form a likelihood to estimate $q_i$:

$$L = \prod_{\ell \in \mathcal{D}_i} q_i^{\exp(z_\ell \beta)} \prod_{\ell \in \mathcal{C}_i} (1 - q_i^{\exp(z_\ell \beta)}) \prod_{\ell \in \mathcal{L}_i} (1 - q_i^{\exp(z_\ell \beta)})^{\frac{1}{2}}$$

$\Rightarrow$ estimate $q_i$ using maximum likelihood.

EXTENSIONS:

① TIME VARYING COVARIATES.

② COMPETING RISKS (MULTIPLE FAILURE TYPES)

③ MULTIPLE FAILURE TIMES.

TIME VARYING COVARIATES:

All of the earlier material extends to the case in which the covariates vary with time.

$\underset{\sim}{z}(t)$ covariate value at time $t$

$$\underset{\sim}{Z}(t) = \{ \underset{\sim}{z}(A) : 0 < A < t \}$$

$$\lambda(t; \underset{\sim}{Z}(t)) = \lim_{\Delta t \to 0^+} pr\{T \in [t, t+\Delta t) \mid \underset{\sim}{Z}(t), T \geq t\} / \Delta t$$

$$= \lambda_0(t)\, e^{\underset{\sim}{z}(t)\underset{\sim}{\beta}}$$

where dependence is on the current value $\underset{\sim}{z}(t)$ only

PARTIAL LIKELIHOOD EXTENDS IMMEDIATELY.

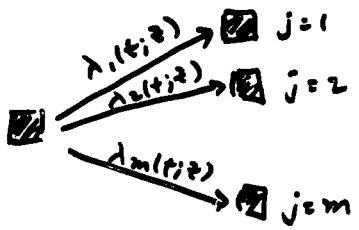
$$pr\{(i) \text{ fails} \mid R(t_{(i)}), \text{a failure at } t_{(i)}\}$$

$$= \frac{e^{z_{(i)}(t_{(i)})\beta}}{\sum_{\ell \in R(t_{(i)})} e^{z_\ell(t_{(i)})\beta}}$$

## COMPETING RISKS (MULTIPLE FAILURE TYPES)

$T$ = time to failure
$J$ = type of failure $\quad J = 1, 2, \ldots, m$
relate to covariates $\underline{z} = (z_1, \ldots, z_p)$

How should this be modelled?




**Def'n:**

$$\lambda_j(t;\underline{z}) = \lim_{\Delta t} \Pr\{T \in [t, t+\Delta t), J=j \mid T \geq t, \underline{z}\} / \Delta t \qquad j=1,\ldots,m$$

"CAUSE SPECIFIC" or "CRUDE" hazard.

Note that the total hazard is

$$\lambda(t;\underline{z}) = \sum_{j=1}^{m} \lambda_j(t;\underline{z})$$

"LIFE IS A SEQUENCE OF MULTINOMIAL TRIALS"

**EXAMPLE**: Mice given 300 rads of radiation "therapy"

randomized — Control
randomized — germ free

Three types of failure

$j=1$ incidence of thymic lymphoma

$j=2$ " " reticulum cell sarcoma

$j=3$ death by other causes.

Time ~ measured in days.

**Data**:
- $t_i$ = time to failure or censoring
- $\delta_i$ = 1 (failure) 0 (censored)
- $z_i$
- $j_i$ = type of failure.

PROBLEMS

1. How do covariates relate to rates failure by various types?

2. Are the failure types interrelated?
   "independent" risks

3. What is the effect of removing one or several causes of failure?

3 is often called **THE** problem of competing risks.

PROBLEMS (CONT'D)

1. ESTIMATION OF RELATIONSHIPS BETWEEN COVARIATES $\underline{z}$ AND FAILURE RATES.
   - e.g. effect of germ free environment on death rate by reticulum cell sarcoma.
   - e.g. University Group Diabetes Program.
2. Interrelationships between different failure types
   "If on one individual is at unusually high risk of failure of one type, is she correspondingly at high (low) risk of failure of another type?"
   - Bone Marrow Transplantation in trt of Acute Leukemia
     Acute graft versus host disease
     Recurrent Leukemia.
   - Dependent Censoring.
3. Estimation of failure rates for remaining types if some types are removed.
   - Gorrouchi - smallpox
     = Weibirthaum (1975)
   - elimination of A.C.V.H.D - what effect on recurrent leukemia

## NOTATION

Total hazard: $\lambda(t;\underset{\sim}{z}) = \sum_{j=1}^{m} \lambda_j(t;\underset{\sim}{z})$

Survivor function:

$$F(t;\underset{\sim}{z}) = pr\{T \geq t \mid \underset{\sim}{z}\} = \exp\left\{-\int_0^t \lambda(u;\underset{\sim}{z})\,du\right\}$$

Sub density function for jth ~~cause~~ type:

$$f_j(t;\underset{\sim}{z}) = \lim pr\{T \in [t, t+\Delta t), J = j \mid \underset{\sim}{z}\}/\Delta t$$

$$= \lambda_j(t;\underset{\sim}{z})\, F(t;\underset{\sim}{z})$$

Cumulative Incidence for jth type:

$$I_j(t;\underset{\sim}{z}) = pr\{T \leq t, J = j \mid \underset{\sim}{z}\}$$

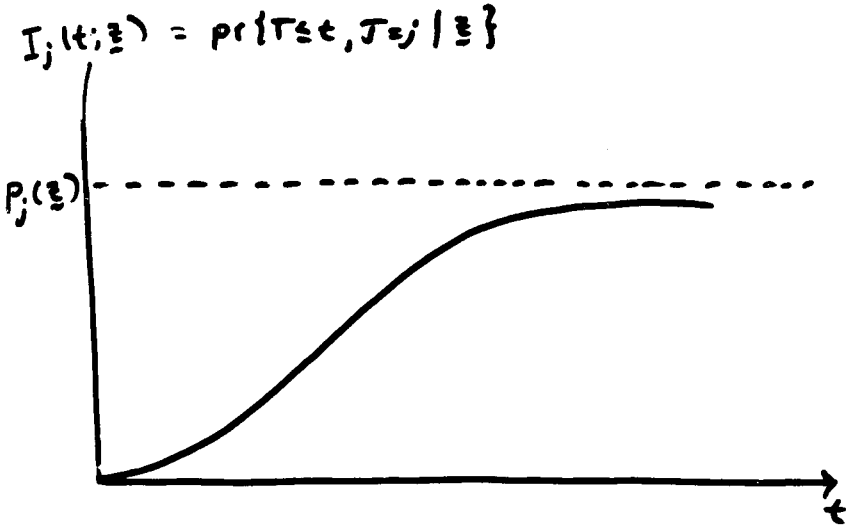
$$= \int_0^t f_j(u;\underset{\sim}{z})\,du$$

Pseudo Survivor Function for jth type

$$F_j(t;\underset{\sim}{z}) = \exp\left\{-\int_0^t \lambda_j(u;\underset{\sim}{z})\,du\right\}.$$

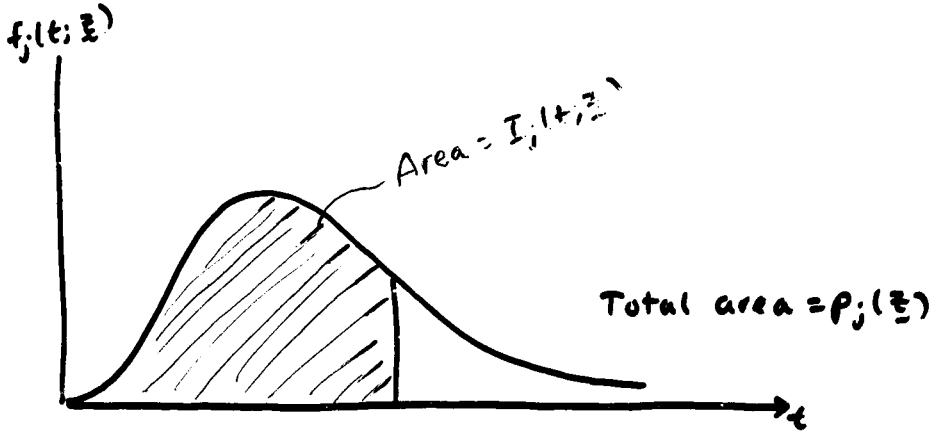
Note: $F_j(t;\underset{\sim}{z})$ has no probabilistic interpretation in general

EACH OF THESE CAN BE WRITTEN ENTIRELY IN TERMS OF THE CAUSE SPECIFIC HAZARDS $\lambda_j(t;\cdot)$




Cumulative incidence for jth cause.

$$P_j(\underline{z}) = \lim_{t\to\infty} I_j(t;\underline{z}) = pr\{J=j \mid \underline{z}\}.$$




Sub density (or incidence) function for jth type.

Lagakos & Mosteller (1980) model using $p_j(\underline{z})$ and

$$\lambda_j^*(t;\underline{z}) = \lim pr\{T\in[t,t+\Delta t) \mid \underline{z}, J=j, T\ge t\}/\Delta t.$$

## REGRESSION MODELS:

PARAMETRIC:

e.g. $\lambda_j(t;\underset{\sim}{z}) = \lambda_j \rho_j (\lambda_j t)^{\rho_j - 1} e^{\underset{\sim}{z}\underset{\sim}{\beta_j}}$

- Substitute in likelihood - find $\hat{\lambda}_j, \hat{\rho}_j, \hat{\beta}_j$
- use asymptotic theory for estimation & testing.

SEMI PARAMETRIC: proportional hazards

$$\lambda_j(t;\underset{\sim}{z}) = \lambda_{0j}(t)\, e^{\underset{\sim}{z}\underset{\sim}{\beta_j}} \qquad j=1,\ldots,m \qquad *$$

Data: suppose $k_j$ failures of type $j$ at ordered times $t_{j1}, \ldots, t_{jk_j}$ (no ties)

Partial Likelihood

pr{item $j_i$ has type $j$ failure at $t_{ji}$ | $R(t_{ji})$ & one type $j$ failure at $t_{ji}$}

$$= \frac{\lambda_j(t_{ji};\underset{\sim}{z}_{ji})}{\sum_{\ell \in R(t_{ji})} \lambda_j(t_{ji};\underset{\sim}{z}_{\ell})}$$

Substitute * & product over failure times

$$L(\underset{\sim}{\beta}_1,\ldots,\underset{\sim}{\beta}_m) = \prod_{j=1}^{m} \prod_{i=1}^{k_j} \frac{\exp(\underset{\sim}{z}_{ji}\underset{\sim}{\beta}_j)}{\sum \exp(\underset{\sim}{z}_{\ell}\underset{\sim}{\beta}_j)}$$

PRODUCT OF $m$ FACTORS. $j$TH FACTOR IS SAME AS BEFORE WITH ALL BUT TYPE $j$ FAILURES TAKEN AS CENSORED.

EXAMPLE: DAYS UNTIL OCCURRENCE OF CANCER FOR IRRADIATED MALE MICE.

$$z = \begin{cases} 0 & \text{control} \\ 1 & \text{germ free.} \end{cases}$$

$$\lambda_j(t; \underline{z}) = \lambda_{0j}(t)\, e^{z\beta_j} \qquad j = 1, 2, 3.$$

$j=1$ Thymic Lymphoma

$$\hat{\beta}_1 = .295 \qquad I(\hat{\beta}_1)^{-1} = .0821$$

$$SL \cong .30$$

$j=2$ Reticulum cell sarcoma

$$\hat{\beta}_2 = -2.018 \qquad \widehat{var}(\hat{\beta}_2) = .1199$$

$$SL << .001$$

$j=3$ Other Causes

$$\hat{\beta}_3 = -1.188 \qquad \widehat{var}(\hat{\beta}_3) = .0889$$

$$SL << .001$$

No evidence of an effect of germ free environment on Thymic Lymphoma rates.

- marked decrease due to germ free environment for $j=2, 3$ relative risks $e^{-\hat{\beta}_2} = 7.52$

$$e^{-\hat{\beta}_3} = 3.28$$

## 2. INTERRELATIONS BETWEEN FAILURE RATES.

Classical Approach.

Multiple Decrement Function:

$\tilde{T}_1, \tilde{T}_2, \ldots, \tilde{T}_m$ conceptual (latent) failure times.

Observe $T = \min(\tilde{T}_1, \ldots, \tilde{T}_m)$

$$J = \{j \mid \tilde{T}_j \le \tilde{T}_k, k = 1, \ldots, m\}$$

The multiple decrement function is

$$Q(t_1, \ldots, t_m; \underset{\sim}{\Xi}) = pr\{\tilde{T}_1 \ge t_1, \ldots, \tilde{T}_m \ge t_m; \underset{\sim}{\Xi}\}$$

Marginal Survivor Function of $\tilde{T}_j$:

$$Q_j(t_j; \underset{\sim}{\Xi}) = Q(0, \ldots, 0, t_j, 0, \ldots, 0)$$

$$= pr\{\tilde{T}_j \ge t_j; \underset{\sim}{\Xi}\}$$

The corresponding hazard is called the net hazard

$$h_j(t)^{\underset{\sim}{\Xi}} = -\frac{d}{dt} \log Q_j(t)^{\underset{\sim}{\Xi}} = \lim pr\{\tilde{T}_j \in [t, t+dt) \mid \tilde{T}_j \ge t_j$$

One formulation: The risks are independent iff $Q(t_1, \ldots, t_m; \underset{\sim}{\Xi}) = \prod_{j=1}^{m} Q_j(t_j; \underset{\sim}{\Xi})$

BUT, THERE IS A PROBLEM!

The data $(t_i, \delta_i, j_i, \underset{\sim}{z}_i)$ are sufficient to identify only the <u>cause specific hazards</u>

$$\lambda_j(t;\underset{\sim}{z}) = \lim_{\Delta t \to 0} pr\{T \in [t, t+\Delta t), J=j \mid \underset{\sim}{z}, T \geq t\}/\Delta t.$$

$$= -\frac{\partial}{\partial t_j} \log Q(t_1, \ldots, t_m; \underset{\sim}{z})\Big|_{t_1 = \cdots = t_m = t}.$$

$Q(t_1, \ldots, t_m)$ and $Q_j(t_j)$, $j = 1, \ldots, m$ are not identifiable – further assumptions needed.

THE HYPOTHESIS

$H_0$: $Q(t_1, \ldots, t_m) = \prod Q_j(t_j)$ is wholly untestable without further assumption.

## 3 Cause Removal

Non statistical Questions
What is the mechanism of removal?

### Classical Approach

multiple decrement $Q(t_1, \ldots, t_m)$
After removal of all but jth cause

$$Q_j(t_j) = Q(0, \ldots, 0, t_j, 0, \ldots, 0)$$
$$= pr\{\tilde{T}_j \geq t_j\}$$

Assumptions of independence or of parametric models that cannot be tested.

① Removal $\Leftrightarrow$ Marginalization ?
No prior validity Makeham (1874)

② Usually answers to questions of cause removal require specialized models that account for the mechanics of the failure types and the method of removal.

## MULTIPLE FAILURE TIMES

The statistical methods outlined above conveniently generalize to problems involving multiple failure times.

e.g. Asthma attacks and pollution levels.


x ≡ attack

n individuals are followed + the times of attack are recorded.
Want to relate rate of attacks to (e.g.) pollutim levels. Let $z(t)$ be a measure of pollution at time $t$

$\lambda(t; z(t))$ – rate at which events occur at time $t$ given current level $z(t)$

$$\lambda(t; z(t)) = \lambda_0(t)\, e^{z(t)\beta}$$

More generally, models can allow for dependence of rate on frequency of previous attacks, on time since last attack, etc.