The Analysis of Failure Times in the Presence of Competing Risks

Prentice et al. (1978)

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Motivations for Competing Risks

- Single cause vs multiple causes for failure process
- Competing Risks analysis on:
  (1) inference on the effects of treatment/exposure on specific types of failure
  (2) interrelations among failure types
  (3) failure rates for some causes given "removal" of some/all other causes
- Example:
  Acute Leukemia Bone marrow transplantation:(i) recurrence, (ii) GVHD, (iii) pneumonia

(1) inference on the effects of treatment/exposure on specific types of failure:

$T >= 0$, the time of failure, which may be right censored

$J \in \{1, 2, ...m\}$, the type of failure, which will be unknown if T is censored

$\mathbf{z} = (z_1, ..., z_p)$, regression vector

(1) inference on the effects of treatment/exposure on specific types of failure:

Overall hazard function (Cox 1972):

$$\lambda(t; \mathbf{z}) \tag{1}$$

Cause-specific hazard function (Prentice and Breslow 1978):

$$\lambda_j(t; \mathbf{z}) \tag{2}$$

(1) inference on the effects of treatment/exposure on specific types of failure:

Conclusion: The likelihood factor for $\lambda_j(t;\mathbf{z})$ is precisely the same as

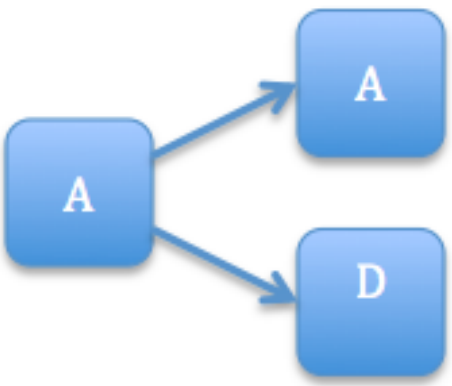
would be obtained by regarding all failure types other than j as censored at the individual's failure time. Thus, any of the standard methods for estimating $\lambda(t;\mathbf{z})$ can be applied for inference on $\lambda_j(t;\mathbf{z})$.

(1) inference on the effects of treatment/exposure on specific types of failure:

Bone marrow transplantation example:
(1)recurrence : j=1;
(2)GVHD: j=2;
(3)pheumonia: j=3

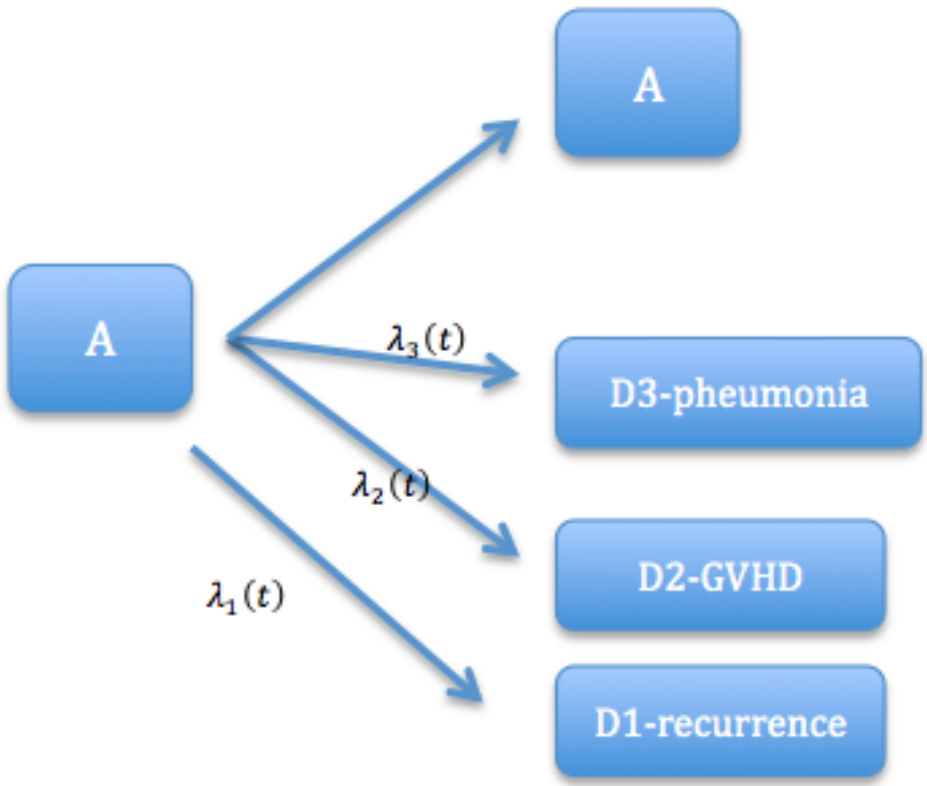
Recurrence-specific Hazard Function $\lambda_1(t; \mathbf{z})$ could be obtained by treating GVHD and pheumonia failure as consored.

(1) inference on the effects of treatment/exposure on specific types of failure:



t $t + \Delta t$

Overall $\lambda(t)$



Cause-Specific $\lambda_j(t)$

(2) Interrelations among failure types:

- With data of the type $(T, J; \mathbf{z})$, interrelation among failure types is nonidentifiable. Therefore, with z being time independent, we can not study the interrelation, or even test for independence among competing failure modes.

- For example, we can not distinguish between an independent competing risk model, where the different causes are independent of each other, or an dependent model, where the causes are correlated, but which rise to the same Hazard functions.

(2) Interrelations among failure types:

Example:

Define latent(potential) failure times $Y_1, Y_2, ..., Y_m$

Then $T = min(Y_1, Y_2, ..., Y_m)$.

Define joint survival function:
$Q(y_1, ..., y_m; \mathbf{z}) = P(Y_1 > y_1, ..., Y_m > y_m; \mathbf{z})$.

(2) Interrelations among failure types:

Model1:

$$Q(y_1, y_2) = exp[1 - \alpha_1 y_1 - \alpha_2 y_2 - exp\{\alpha_{12}(\alpha_1 y_1 + \alpha_2 y_2)\}] \quad (3)$$

parameter α_{12} measures dependence between Y_1 and Y_2.

Model2:

$$Q^*(y_1, y_2) = exp[1-\alpha_1 y_1 - \alpha_2 y_2 - \sum_{j=1}^{2} \alpha_j exp\{\alpha_{12}(\alpha_1 + \alpha_2) y_j\} (\alpha_1 + \alpha_2)^{-1}] \quad (4)$$

Corresponding cause-specific hazard function for both models are:
$\lambda_j(t) = \alpha_j[1 + \alpha_{12} exp\{\alpha_{12}(\alpha_1 + \alpha_2)t\}], j = 1, 2$

(2) Interrelations among failure types:

- Interrelation among failure types is nonidentifiable.
- One promising approach to study the relationship among failure types involves the definition of risk-indicator variables as time-dependent covariates.

(2) Interrelations among failure types:

Burn Wound Infection example:

Endpoint: (1)Infection (2)Wound eschar excision
$\mathbf{z}$(time-independent): treatment group, gender, race, percentage of body surface burned.

Define a risk-indicator for Wound eschar excision $z(t)$, that takes value 0 between $t = 0$ and the excision and value 1 after.

Positive Responses Rates and Sample Standard Deviations

Table : Cox model Results

No. of subjects = 154; No. of failures = 48

Variable	Coef	exp(Coef)	Std. Err.	z	$P(>\|z\|)$
Treatment	-.54	0.58	.30	-1.81	0.071
Excision Risk Indicatior	-.48	0.62	.46	-1.04	0.299
Female	-.57	0.57	.39	-1.46	0.143
White	2.13	8.41	1.01	2.10	0.035
pBurned	0.0036	1.0036	0.0070	0.51	0.613

$\widehat{\beta} = -.48$ for Excision Risk Indicator, which suggests that the infection rate is reduced by an estimated multiplicative factor $exp(\widehat{\beta}) = .62$

(3) Failure rate estimation following cause removal:

Estimation of failure probabilities given the removal of some or all other causes:

- Not well defined until mechanism for cause removal is clearly specified.
- Strong assumptions on study conditions.

(3) Failure rate estimation following cause removal:

Bone marrow translantation example:

Mechanism to remove GVHD: strengthening donor-recipient matching criteria

Recurrent leukemia relapse rates would increase.

Mechanism to remove GVHD: treatment to control GVH reaction.

If the treatment has antileukemia potential, recurrent leukemia relapse rates would decrease.