Harvard-MIT Division of Health Sciences and Technology
HST.951J: Medical Decision Support, Fall 2005
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6.873/HST.951 Medical Decision Support
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Survival Analysis

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Outline

- Basic concepts & distributions
  – Survival, hazard
  – Parametric models
  – Non-parametric models
- Simple models
  – Life-table
  – Product-limit
- Multivariate models
  – Cox proportional hazard
  – Neural nets

What we are trying to do

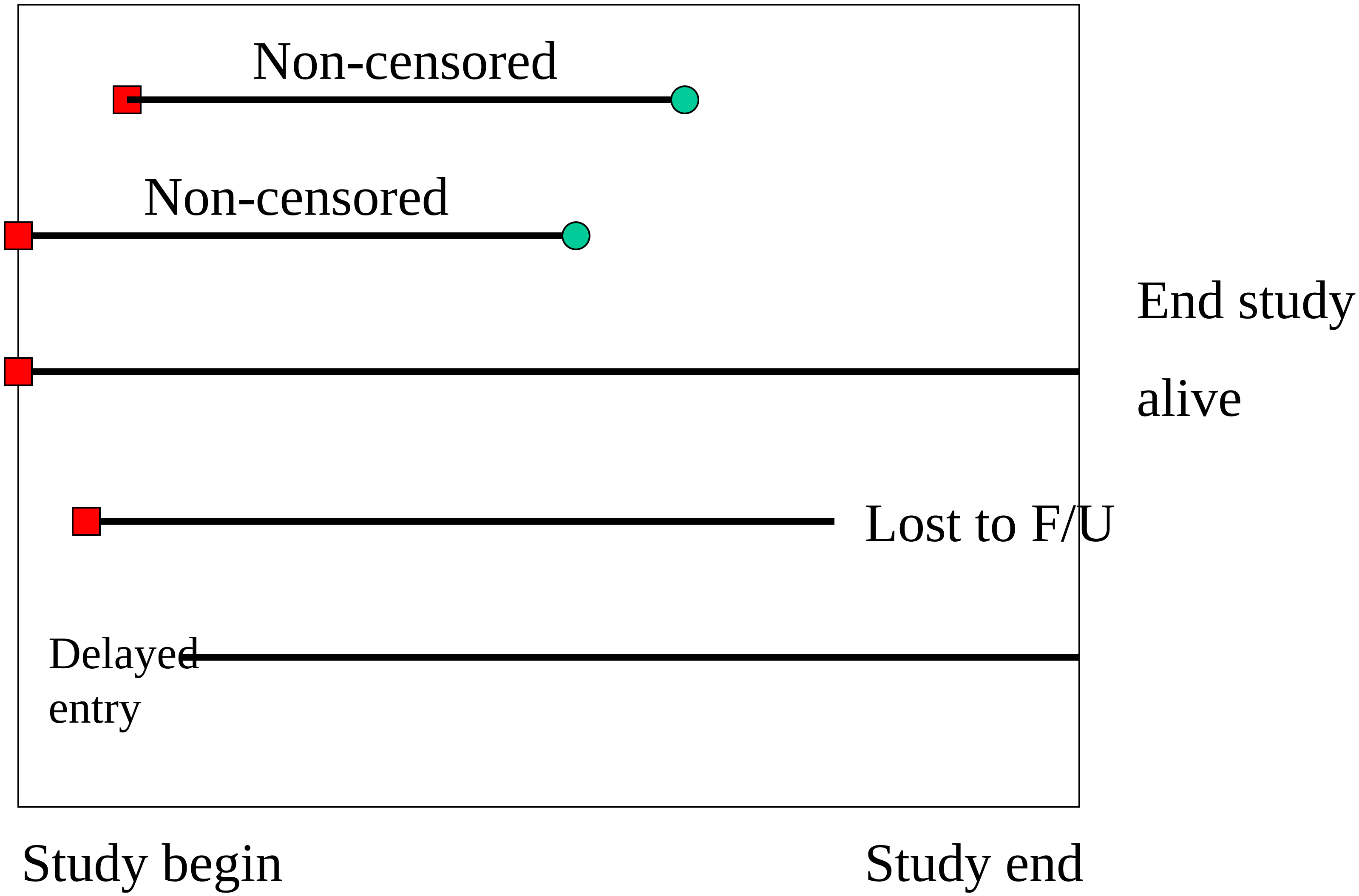
	Variable 1	Variable 2	Years of survival
Case 1	0.7	-0.2	8+
Case 2	0.6	0.5	4
…	-0.6	0.1	2
	0	-0.9	3+
	-0.4	0.4	2
	-0.8	0.6	3
	0.5	-0.7	4

Predict survival (or more frequently predict the probability of at least *n* years of survival)

Using these

- and evaluate performance on new cases
- and determine which variables are important

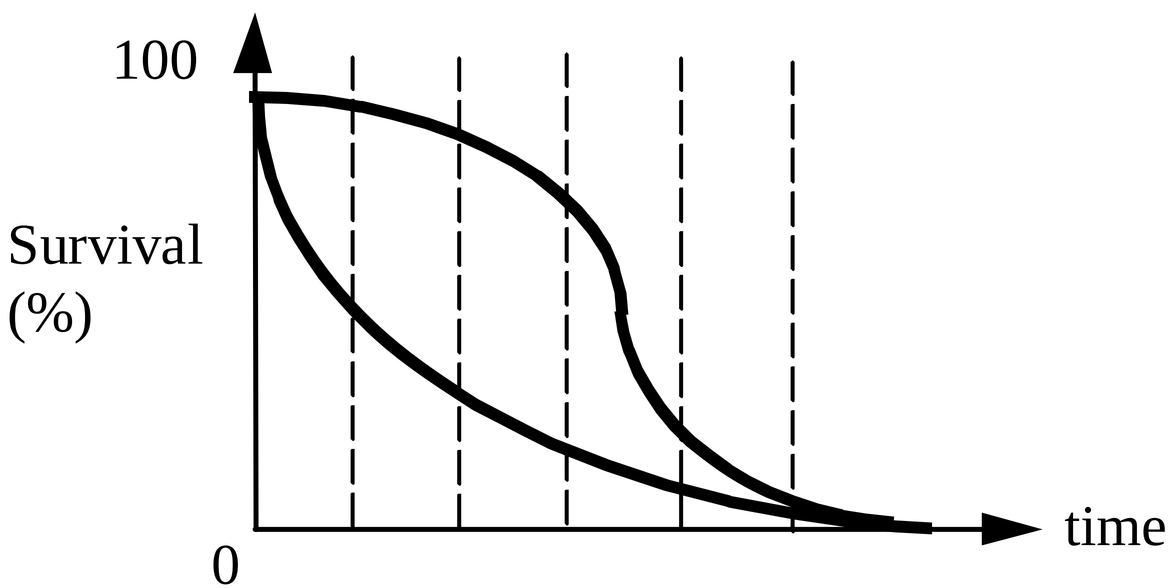
Censoring


Non-censored
Non-censored
End study
alive
Lost to F/U
Delayed
entry
Study begin
Study end

Survival function

Probability that an individual survives at least t, T is patient's survival

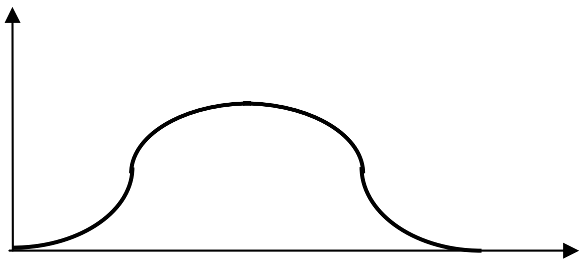
- S(t) = P(T > t) = 1 – F(t)
- Survival is cumulative, non-increasing function
- F(t) is cumulative distribution of death (failure)
- By definition, S(0) = 1 and S(∞)=0

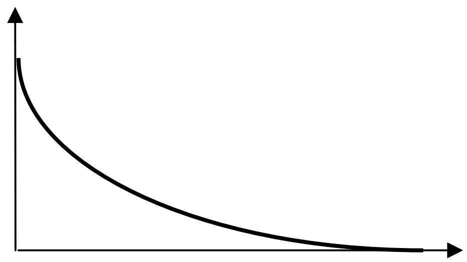


Unconditional failure rate

- pdf of T
- $f(t) = \lim_{\Delta t \to 0} P(\text{individual dies } (t, t+\Delta t)) / \Delta t$
- f(t) always non-negative
- Area below density is 1
- Estimated by

patients dying in the interval/total patients

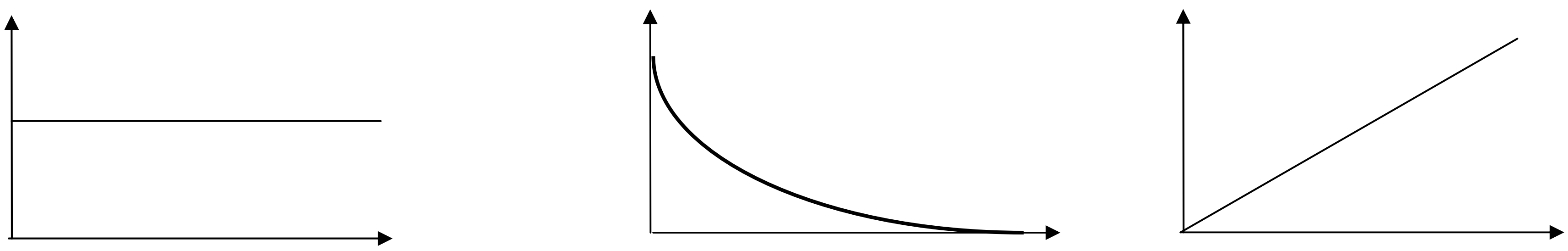




Conditional failure rate

- Hazard function
- $h(t) = \lim_{\Delta t \to 0} P($survivor until t dies $(t, t+\Delta t))/ \Delta t$
- h(t) is conditional instantaneous failure rate
- Estimated by

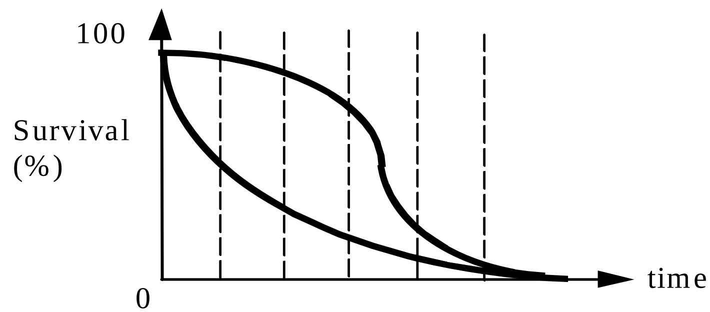
\# patients dying in the interval/survivors at t



Hazard Function

λ

$$f(t) = \partial F(t) / \partial(t)$$
$$F(t) = 1 - S(t)$$
$$f(t) = -\partial S(t) / \partial(t)$$



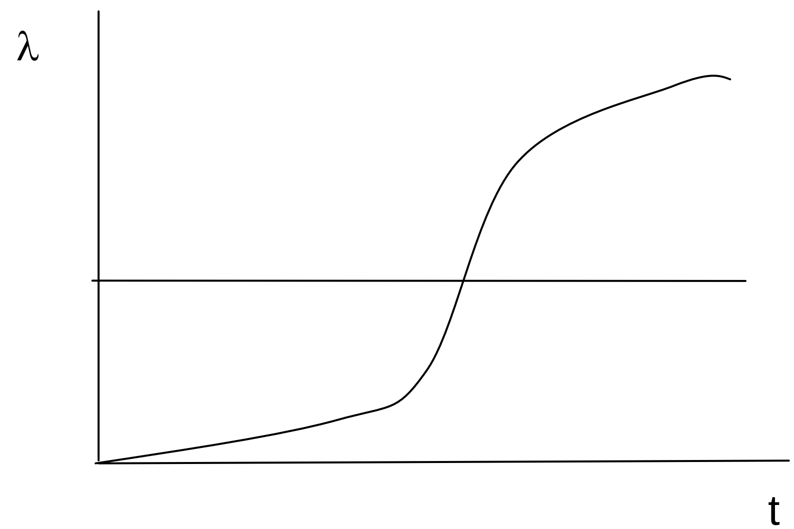
$$\lambda(t) = \lim_{u \to 0} \frac{P\{t < T \le t+u \mid T > t\}}{u}$$

$$\lambda(t) = \lim_{u \to 0} \frac{P\{t < T \le t+u\} \mid P\{T > t\}}{u}$$

$$\lambda(t) = \lim_{u \to 0} \frac{[F(t+u) - F(t)] \mid u}{S(t)}$$

$$\lambda(t) = \frac{\partial F(t) / \partial t}{S(t)}$$

$$\lambda(t) = \frac{f(t)}{S(t)}$$



Cumulative Hazard Function Λ

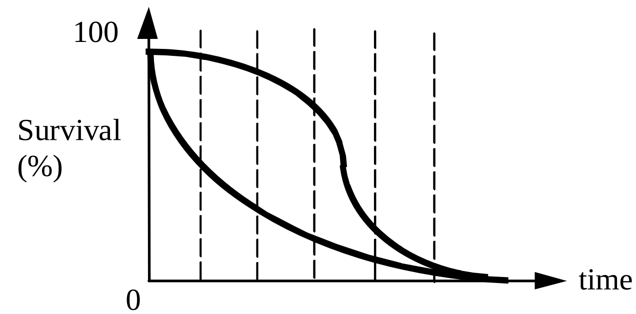
$$\lambda(t) = \frac{f(t)}{S(t)}$$

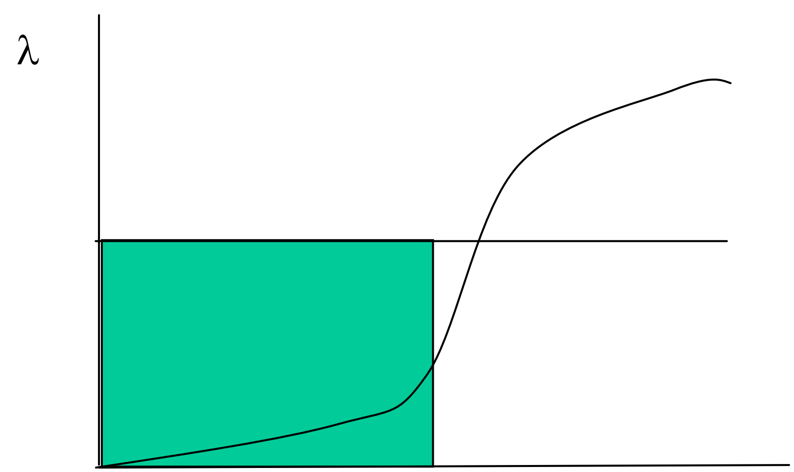
$$\frac{\partial \log S(t)}{\partial t} = \frac{\partial S(t)/\partial t}{S(t)} = -\frac{f(t)}{S(t)}$$

$$\lambda(t) = -\frac{\partial \log S(t)}{\partial t}$$

$$\int_0^t \lambda(v)dv = -\log S(t) = \Lambda(t)$$

$$S(t) = e^{-\Lambda(t)}$$

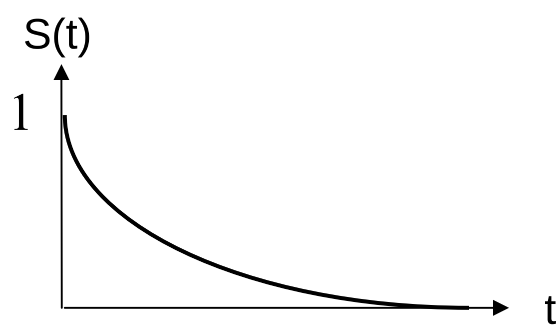


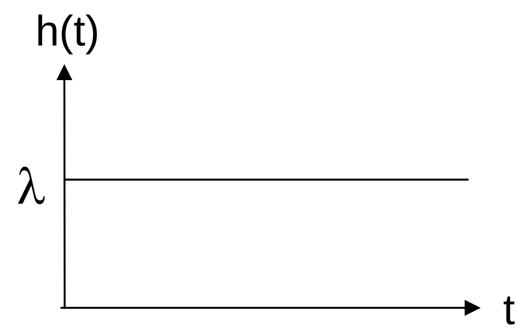


Parametric estimation

Example: Exponential

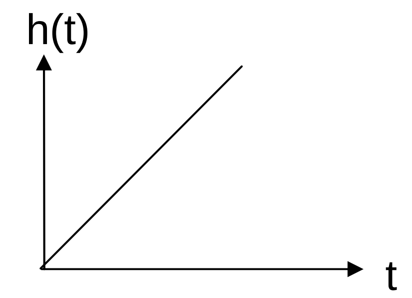
- $f(t) = \lambda e^{-\lambda t}$
- $S(t) = e^{-\lambda t}$
- $h(t) = \lambda$

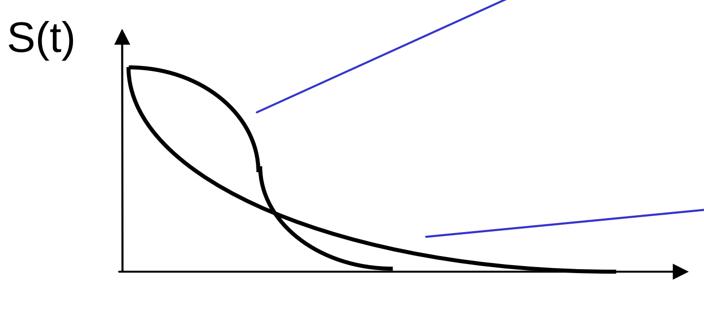


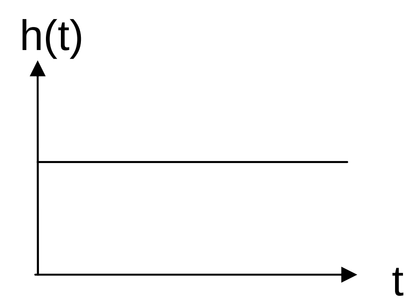


Weibull distribution

- Generalization of the exponential
- For $\lambda,\gamma > 0$
- $f(t) = \gamma\lambda(\lambda t)^{\gamma-1}\, e^{-\lambda t^{\gamma}}$
- $S(t) = e^{-\lambda t^{\gamma}}$
- $h(t) = \gamma\lambda(\lambda t)^{\gamma-1}$



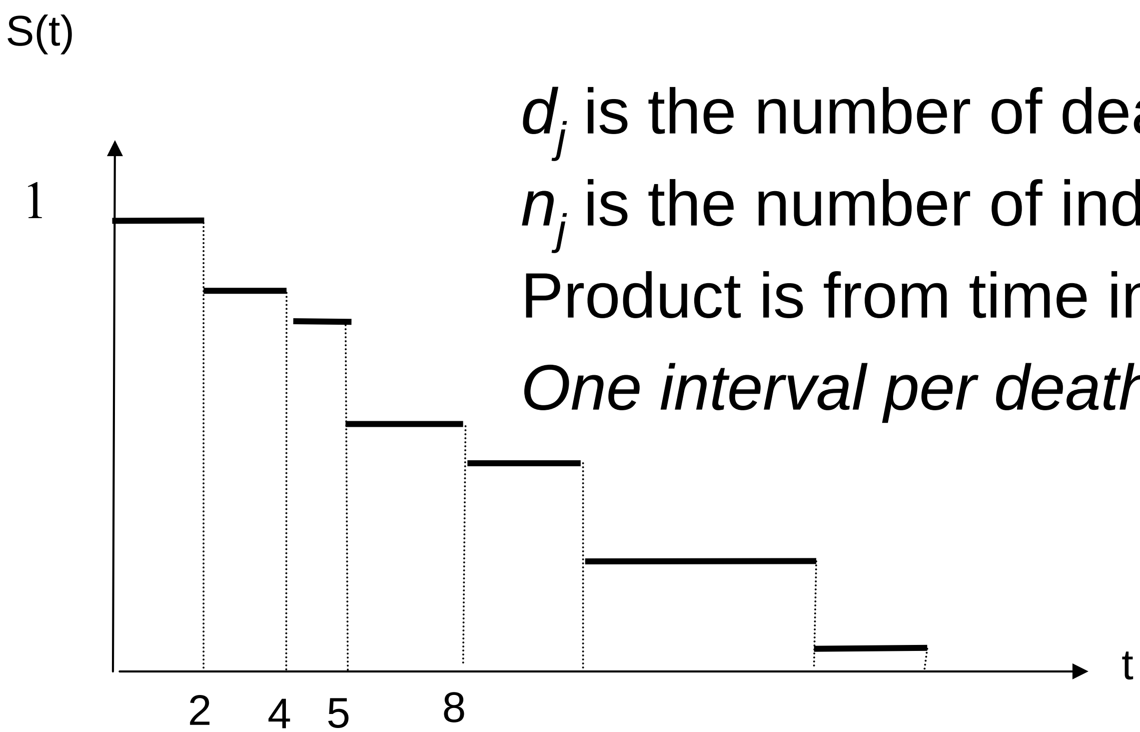




Non-Parametric estimation

Product-Limit (Kaplan-Meier)

$S(t_i) = \Pi \, (n_j - d_j)/ n_j$



d_j is the number of deaths in interval j

n_j is the number of individuals at risk

Product is from time interval 1 to j

One interval per death time

Kaplan-Meier

- Example
- Deaths: 10, 37, 40, 80, 91,143, 164, 188, 188, 190, 192, 206, …

Life-Tables

- AKA actuarial method

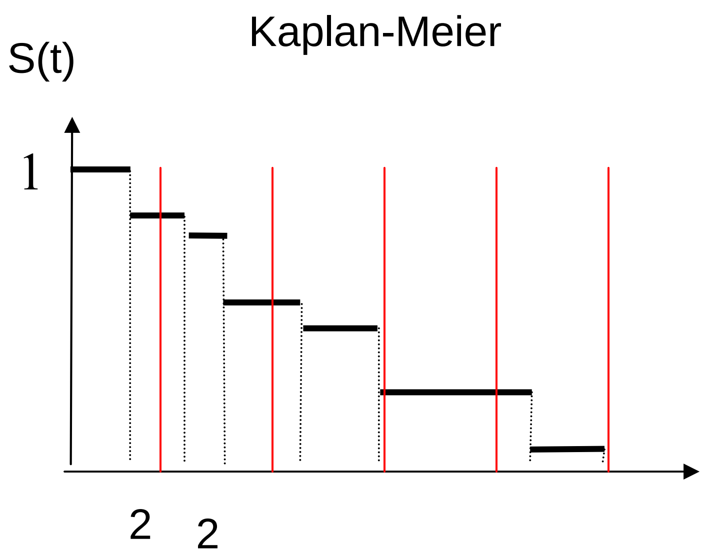
$S(t_i) = \Pi\ (n_j - d_j)/\ n_j$

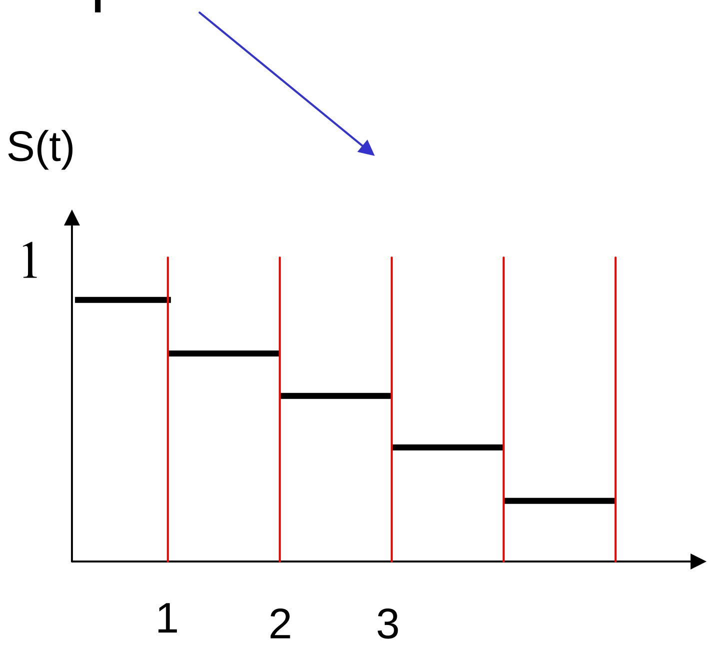
d_j is the number of deaths in interval j

n_j is the number of individuals at risk

Product is from time interval 1 to j

- Pre-defined intervals j are independent of death times





Life-Table

hazard

survival

density

Simple models

Multiple strata

Multivariate models

- Several strata, each defined by a set of variable values
- Could potentially go as far as “one stratum per case”?
- Can it do prediction for individuals?

Cox Proportional Hazards

- Regression model
- Can give estimate of hazard for a particular individual relative to baseline hazard at a particular point in time
- Baseline hazard can be estimated by, for example, by using survival from the Kaplan-Meier method or parametrically

Proportional Hazards

$$\lambda_i = \lambda\, e^{\beta x_i}$$

where λ is baseline hazard (ie, for the “baseline” – usually the most common patient) and x_i is covariate vector for a specific patient i

Cox proportional hazards

$$h_i(t) = h_0(t)\, e^{\beta x_i}$$

- Survival

$$S_i(t) = [S_0(t)]^{e^{\beta x_i}}$$

Cox Proportional Hazards

$$h_i(t) = h_0(t)\, e^{\beta x_i}$$

- From the set of m individuals at risk at time **j** (R_j), the probability of picking exactly the one who died is

$$\frac{h_0(t)\, e^{\beta x_i}}{\Sigma_m\, h_0(t)\, e^{\beta x_m}}$$

- Then likelihood function to maximize to all j is
- $L(\beta) = \Pi_j \left(e^{\beta x_i} / \Sigma_m e^{\beta x_m}\right)$
- MLE uses LogLikelihood

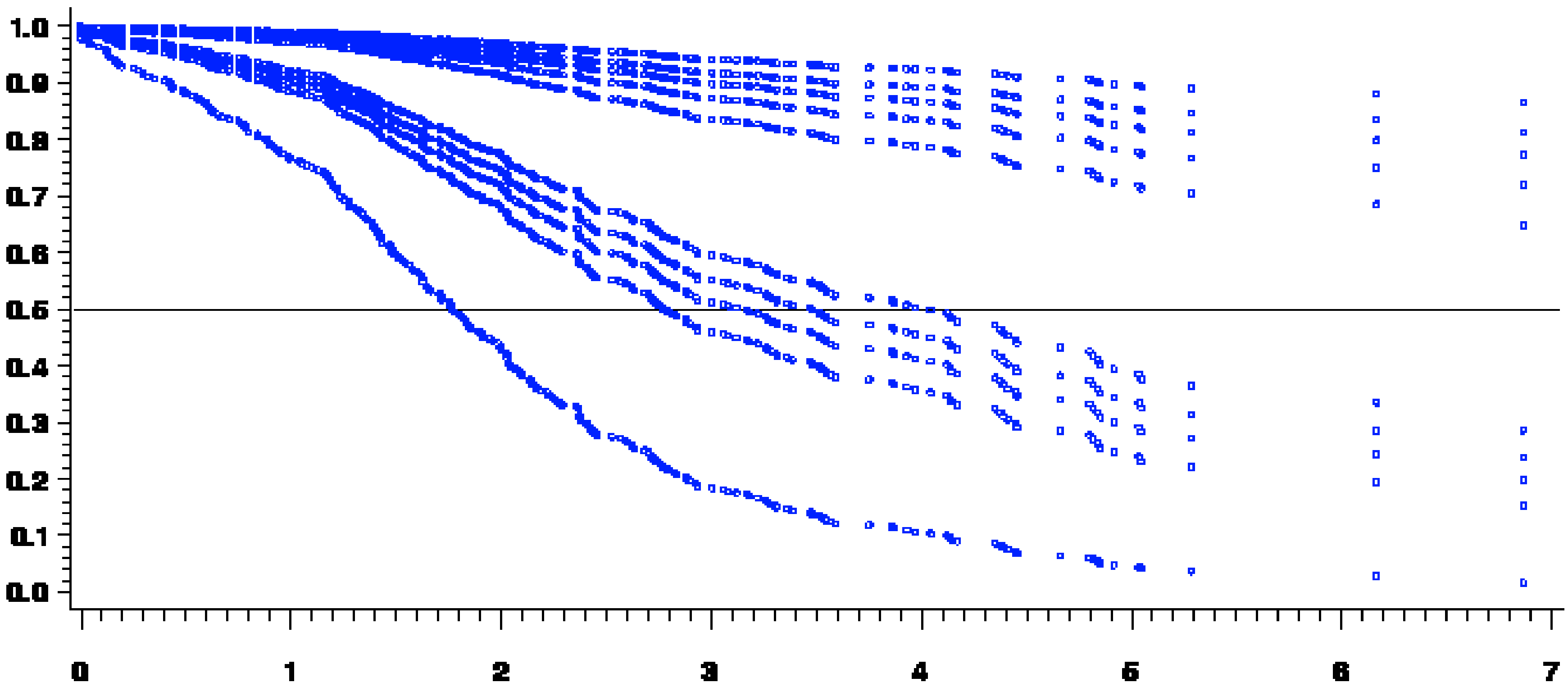
Important details

- Survival curves can't cross if hazards are proportional
- There is a common baseline h_0, but we don't need to know it to estimate the coefficients
- Ie, we don't need to know the shape of hazard function
- Cox model is commonly used to interpret importance of covariates (amenable to variable selection methods)
- It is the most popular multivariate model for survival
- Testing the proportionality assumption is difficult and hardly ever done

Estimating survival for a patient using the Cox model

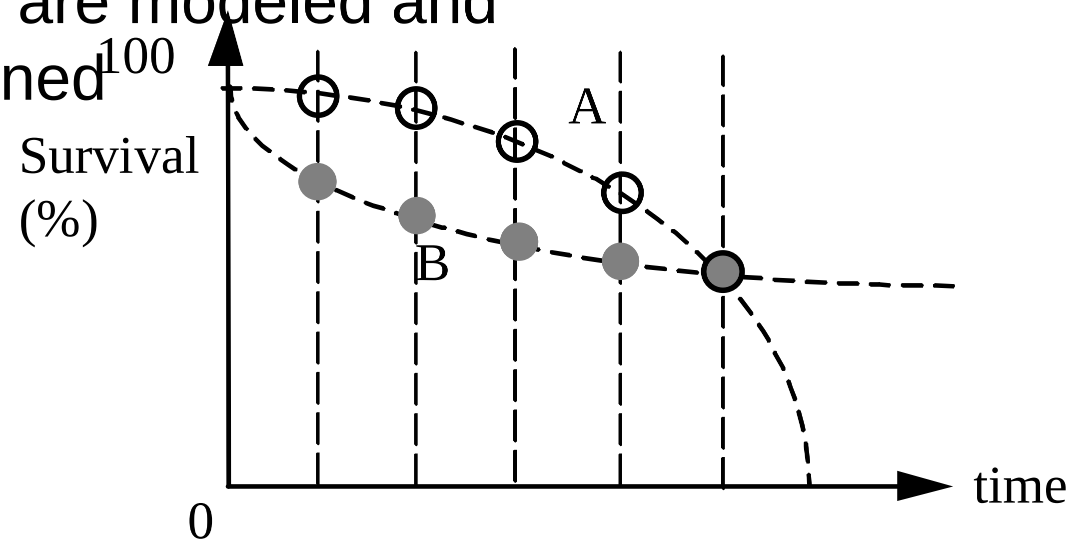
- Need to estimate the baseline
- Can use parametric or non-parametric model to estimate the baseline
- Can then create a continuous “survival curve estimate” for a patient
- Baseline survival can be, for example:
  - Kaplan-Meier estimate

Example of survival estimates



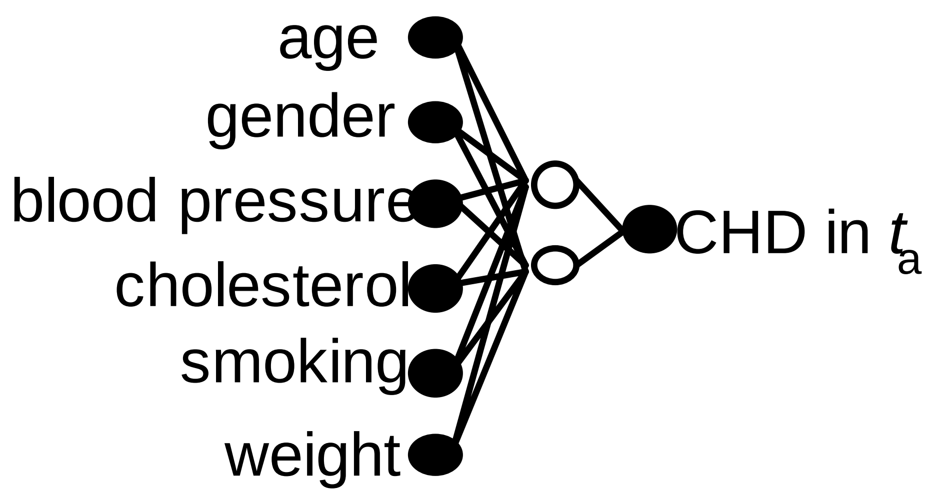
What if the proportionality assumption is not OK?

- Survival curves may cross
- Other multivariate models can be built
- Survival at certain time points are modeled and combined



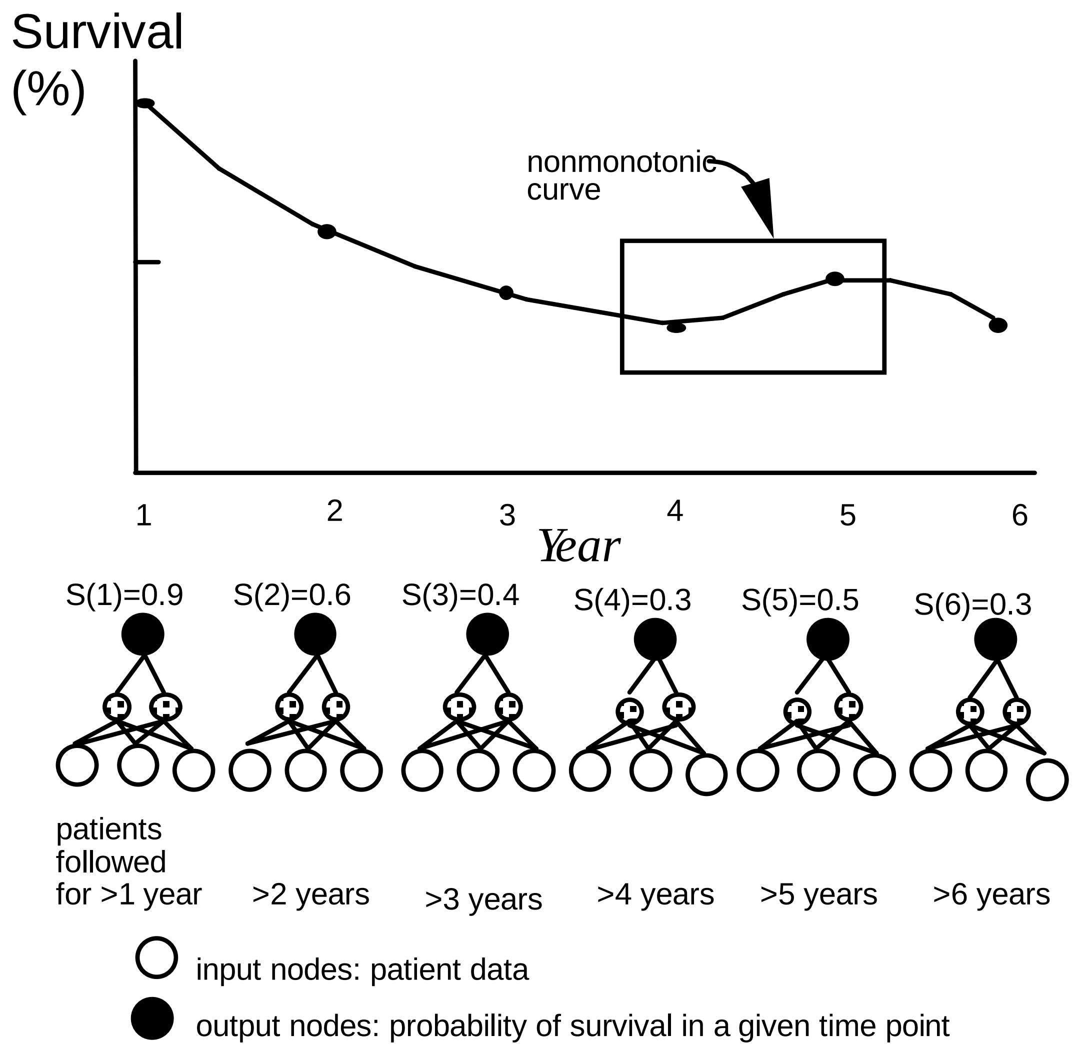
Single-point models

- Logistic regression
- Neural nets



Problems

- Dependency between intervals is not modeled (no links between networks)
- Nonmonotonic curves may appear
- How to evaluate?



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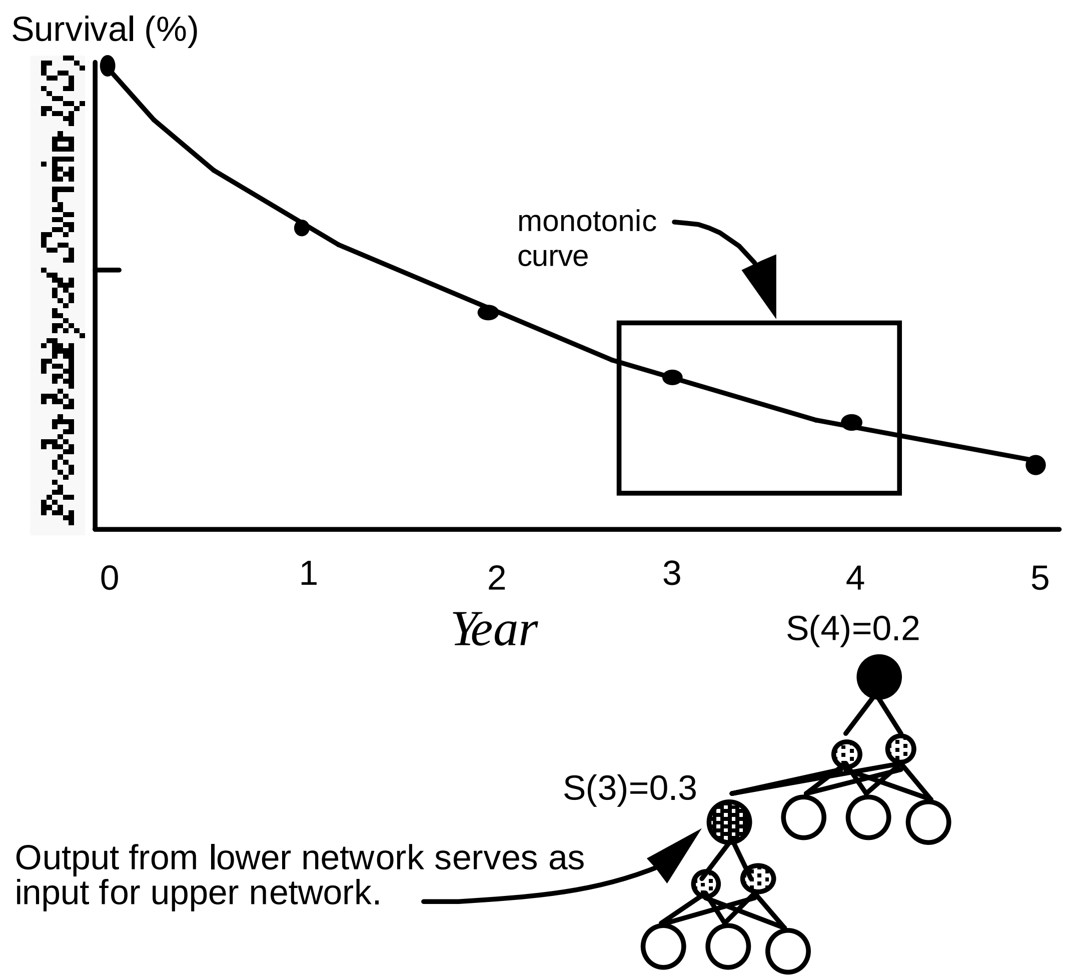
Please see Tables III, V, VI and figures 6, 8, and 10 in:

Ohno-Machado, Lucila, and Mark A. Musen. "Modular Neural Networks for Medical Prognosis: Quantifying the Benefits of Combining Neural Networks for Survival Prediction." *Connection Science* 9, no. 1 (March 1997): 71-86.

Accounting for dependencies

- “Link” networks in some way to account for dependencies



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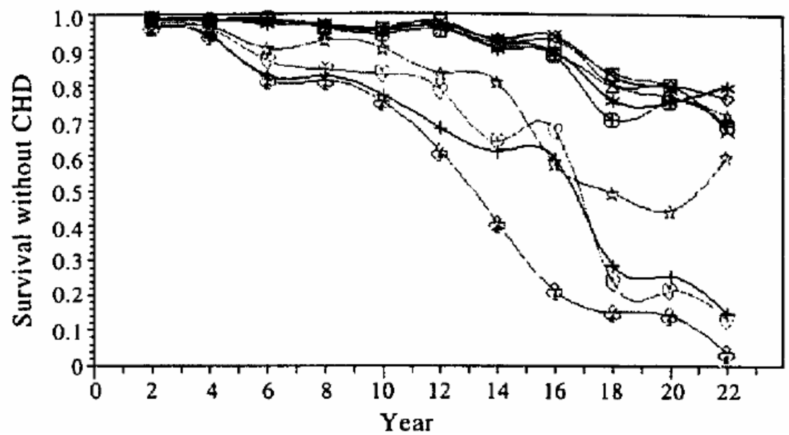
Survival without Coronary Disease

Year of follow-up	Test set χ^2	Test set p
2	15.0118	0.0589
4	11.1389	0.1939
6	19.6175	0.0118
8	30.3247	0.0001
10	23.6363	0.0026
12	11.6443	0.1677
14	9.3273	0.3154
16	6.7588	0.5628
18	26.1660	0.0009
20	22.3739	0.0042
22	12.7683	0.1200

Test set Area under the ROC curve	*standard error*
0.7038	0.0242
0.7117	0.0190
0.7352	0.0152
0.7337	0.0138
0.7333	0.0130
0.7448	0.0123
0.7752	0.0121
0.8059	0.0119
0.8275	0.0122
0.8374	0.0122
0.8324	0.0163



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Ohno-Machado, Lucila, and Mark A. Musen. "Sequential versus standard neural networks for pattern recognition: an example using the domain of coronary heart disease." *Comput Biol Med* 27, no. 4 (Jul 1997): 267-81.

Summary

- Kaplan-Meier for simple descriptive analysis
- Cox Proportional for multivariate prediction if survival curves don’t cross
- Other methods for multivariate survival exist: logistic regression, neural nets, CART, etc.