tently estimated, however, by the quadratic variation process:

$$[\hat{\Lambda} - \Lambda^*](t) = \int_0^t H^2(s)d[M](s) = \int_0^t d\overline{N}(s)/\overline{Y}^2(s)ds\,, \quad (2.15)$$

which is the Nelson–Aalen variance estimate given earlier (2.4), and justified at that point by an ad hoc Poisson argument.

One could also estimate the integrated hazard by $-\log[\hat{S}_{KM}(t)]$, which, as we have seen, is asymptotically equivalent to the Nelson–Aalen estimator and slightly larger in finite samples. It has a consistent variance estimator given by the well-known Greenwood formula [37, pp. 50–51],

$$\widehat{\text{Var}}\{-\log[\hat{S}_{KM}(t)]\} = \int_0^t \frac{d\overline{N}(s)}{\overline{Y}(s)\{\overline{Y}(s) - \Delta\overline{N}(s)\}}. \quad (2.16)$$

This is slightly larger than the Nelson–Aalen variance estimator in keeping with the larger size of the cumulative hazard estimator. In finite samples, however, the logarithm of the Kaplan–Meier is not a good estimate of the hazard in the tails. In particular, if the last subject in the study dies, the estimator is infinite.

The properties of the estimate then follow directly from the general martingale results. The Nelson–Aalen estimator is uniformly consistent [4, Theorem IV.1.1]; for any $t < \tau$:

$$\sup_{s\in[0,t]} |\hat{\Lambda}(s) - \Lambda(s)| \xrightarrow{P} 0.$$

The variance estimator is also uniformly consistent:

$$\sup_{s\in[0,t]} \left| \int_0^s n d\overline{N}(s)/\overline{Y}^2(s) - \int_0^s \lambda(s)/\pi(s)ds \right| \xrightarrow{P} 0.$$

Under an additional regularity condition that assures that the jumps are becoming negligible [4, Condition B, Theorem IV.1.2], the martingale central limit theorem applies and

$$\sqrt{n}\{\hat{\Lambda}(s) - \Lambda(s)\} \overset{n\to\infty}{\Longrightarrow} W(\alpha(s)) \text{ on } [0,\tau], \quad (2.17)$$

where

$$\alpha(t) = \int_0^t \lambda(s)/\pi(s)ds. \quad (2.18)$$

2.3.2 *Efficiency*

Nonparametric methods are less efficient than parametric methods, sometimes substantially so. For purposes of comparison, Figure 2.5 shows the

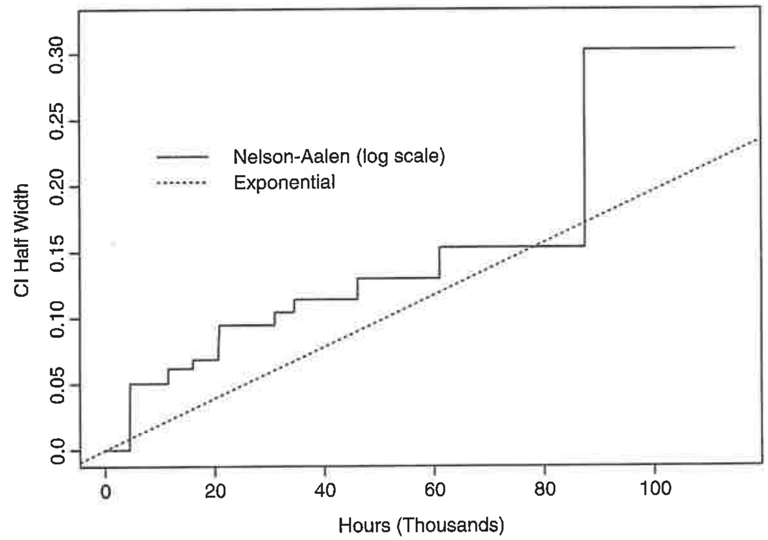

FIGURE 2.5: *Comparison of confidence interval widths*

half-widths of the Nelson–Aalen confidence intervals along with that for the simplest parametric model, exponential failure time. The confidence interval for the parametric estimate is based on the likelihood ratio test using the approximation suggested in Cox and Oakes [37, p. 38]: let $d = \sum_i \delta_i$, the number of failures. Then, $2d\lambda/(\hat{\lambda})$ is distributed approximately as chi-squared on $2d$ degrees of freedom and a $100 \times (1-\alpha)$ confidence interval for the integrated hazard λt is

$$\frac{\hat{\lambda} t c^*_{2d,1-\alpha/2}}{2d} < \lambda t < \frac{\hat{\lambda} t c^*_{2d,\alpha/2}}{2d},$$

where $c^*_{p,\alpha}$ is the upper α point of the chi-squared distribution with p degrees of freedom. Over much of the range, the confidence intervals for the Nelson–Aalen are about 1.8 times as wide.

We can compute the asymptotic relative efficiency (ARE) in closed form for a simple case. Suppose T^* and C^*, the true survival and censoring times, are distributed exponentially with parameters λ and γ, respectively. Then the observed time $T = T^* \wedge C^*$ is exponential with parameter $\lambda + \gamma$, and $\pi(t) = e^{-(\lambda+\gamma)t}$ is the expected proportion of subjects still at risk at time t. Applying equations (2.17) and (2.18), the scaled Aalen estimate $\sqrt{n}\{\hat{\Lambda}_a(t) - \Lambda(t)\}$ has asymptotic variance

$$\alpha(t) = \frac{\lambda\{\exp[(\lambda+\gamma)t] - 1\}}{\lambda+\gamma}.$$

$P(T>t) = P(T^* \wedge C^* > t)$
$= P(T^*>t \text{ and } C^*>t)$
$= P(T^*>t)P(C^*>t)$
$= e^{-(\lambda+\nu)t}$

$\alpha(t) = \int_0^t \lambda \cdot e^{(\lambda+\nu)u}du$
$= \frac{\lambda}{\lambda+\nu} \exp((\lambda+\nu)u)\Big|_0^t$

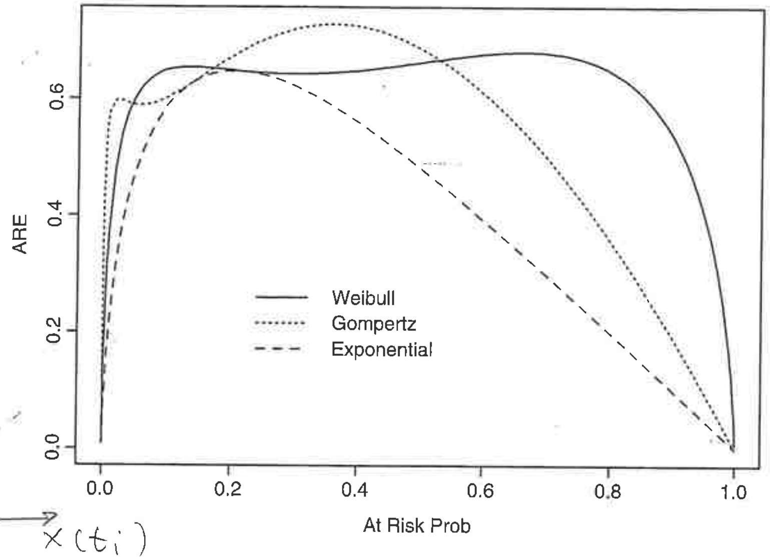

FIGURE 2.6: *Asymptotic relative efficiency when both failure and censoring are exponential*

$E(-\ddot{\ell}) = \frac{1}{\lambda^2} \cdot E\delta_i = \frac{1}{\lambda^2} \cdot P(T_i < C_i)$

The scaled parametric estimate $\sqrt{n}(\hat{\Lambda}_p - \Lambda) = \sqrt{n}(\hat{\lambda} - \lambda)t$ has asymptotic variance $t^2/E[-\ddot{\ell}] = t^2\lambda(\lambda+\gamma)$, where $\ell(\lambda) = \delta_i \log(\lambda) - \lambda T_i$ the loglikelihood for a single observation, $\dot{\ell}$ and $\ddot{\ell}$ are the first and second derivatives wrt λ, and $E[-\ddot{\ell}]$ is the Fisher (expected) information. The ARE is the ratio of the asymptotic variances:

$$\text{ARE} = \frac{(\lambda+\gamma)^2 t^2}{\exp[(\lambda+\gamma)t] - 1}.$$

$= \frac{1}{\lambda^2}\int_0^\infty \left(\int_x^\infty \gamma e^{-\gamma y}\,dy\right) \cdot \lambda e^{-\lambda x}\,dx$

$= \frac{\lambda}{\lambda^2}\int_0^\infty e^{-\gamma x} \cdot e^{-\lambda x}\,dx$

This is identical to the ARE derived by Miller in his paper "What price Kaplan–Meier", for comparing the exponential and non-parametric estimates [109, equation (7)]. Considered as a function of the probability of being at risk, $\pi = \pi(t) = \exp[-(\lambda+\gamma)t]$, the ARE becomes

$= \frac{1}{\lambda(\lambda+\gamma)}$

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$$\text{ARE} = \frac{\pi(\log \pi)^2}{1 - \pi},$$

a concave function attaining its maximum of 0.648 at $\pi = 0.203$; see Figure (2.6).

The efficiency is not very impressive; but the poor showing of the nonparametric estimator should not be a surprise. The asymptotic efficiency relative to the exponential model effectively compares the variability in fitted values between a one-parameter and a (# deaths)-parameter model. The Nelson–Aalen estimator does better when compared to the fit from

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a model with more parameters. We consider two different two-parameter distributions, the Weibull, $\lambda(t) = \alpha\lambda^\alpha t^{\alpha-1}$ and the Gompertz, $\lambda(t) = \lambda\exp(\alpha t)$; each reduces to the exponential for particular values of α. Using the same likelihood expansion method

$$\text{ARE(Gompertz)} = \text{ARE(exp)}\{1 + \frac{[(\lambda+\gamma)t - 2]^2}{4}\}$$

$$\text{ARE(Weibull)} = \text{ARE(exp)}\{1 + \frac{6\,[1 - c - \log((\lambda+\gamma)t)]^2}{\pi^2}\},$$

where c denotes Euler's constant 0.577215.... As with the exponential model, these AREs are functions of the probability of being at risk and so can be superimposed on Figure 2.6. The range over which efficiency < .5 has been substantially decreased, but still the ARE barely exceeds 60% over the range of likely values. These efficiencies are comparable to those of some other widely used nonparametric estimators; for (noncensored) Gaussian data, the median has ARE $2/\pi = 0.637$ relative to the sample mean [67], and the MAD and interquartile range both have ARE 0.735, relative to the sample standard deviation [70, Chap. 5, Exhibit 5.7.3].

2.4 Tied data

So far, we have assumed that each event time corresponds to exactly one event, an assumption required by an absolutely continuous integrated hazard function. However, tied event times are the rule rather than the exception; they exist in nearly every data set used in this book.

There are two conceptually different approaches to dealing with ties. The first, which we call the grouped approach, views the presence of tied data as an artifact of the imprecision of real world measurement. Ties happen because of intermittent observation and/or rounded event times. The AML study had both; clinical assessment for remission occurred only at certain times and remission and censoring times are recorded to the nearest week. The failure and censoring times of the generator data were rounded to the nearest hundred hours.

If ties result from imprecision, then the obvious approach is to break the ties randomly, reconstructing, in some sense, what the data "would have been" without the imprecision. If the rounding is small this recovery is essentially perfect. For instance, if followup time is recorded in days and data accuracy is such that an event recorded as day 44 really preceded an event at day 45, then the only issue is breaking ties within a day. The computed result for $\hat{\Lambda}(t)$ (i.e., cumulative hazard through the end of day t) is invariant to the order in which the ties are broken, and can be written