Basic Quantities and Models

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October 3, 2023

Basic Quantities and Models

The probability density function $f(x)$ is defined as with any continuous distribution. For any short interval of time, it can be thought of as the relative chance that the event will occur in that short interval. The cumulative distribution function is

$$F(x) = \Pr(X \leq x) = \int_0^x f(x)dx$$

For survival data, a more relevant quantity is the *survival function*

$$S(x) = 1 - F(x) = \Pr(X > x) = \int_x^\infty f(x)dx$$

Basic Quantities and Models

$$S(x) = 1 - F(x) = \Pr(X > x) = \int_x^\infty f(x)dx$$

The survival function $S(x)$ is the probability that the event time is later than x. If the event in a clinical trial is death, then this is the fraction of the original population at time 0 that is still alive at time x; that is, the fraction surviving to time x.

The Hazard Function

Another important function is the *hazard function*, which is the probability that the event will occur in the next very short interval, given that it has not occurred yet.

$$h(x) = \lim_{\Delta x \to 0} \frac{\Pr[x \leq X < x + \Delta x | X \geq x]}{\Delta x}$$

The expression in the numerator is the probability of survival until at least time $x + \Delta x$ conditional on surviving until time x. This might be the chance of someone who has just turned 30 still being alive one day later.

The Hazard Function

$$h(x) = \lim_{\Delta x \to 0} \frac{\Pr[x \leq X < x + \Delta x | X \geq x]}{\Delta x}$$

This might be the chance of someone who has just turned 30 still being alive one day later. You can see that this is different than the probability at birth of surviving until age 30 plus one day. The first is the ratio of the number of those who die at age 30 plus one day over the number alive at age 30. The second is a ratio with the same numerator, but with the larger denominator of the number who are born. The latter ratio is smaller.

The Hazard Function

$$\begin{aligned} h(x) &= \lim_{\Delta x \to 0} \frac{\Pr[x \leq X < x + \Delta x | X \geq x]}{\Delta x} \\ &= S^{-1}(x) \lim_{\Delta x \to 0} \frac{\Pr[x \leq X < x + \Delta x]}{\Delta x} \\ &= f(x)/S(x) \end{aligned}$$

The limit takes the difference quotient into a derivative (by definition of the derivative) and the result is because the density $f(x)$ is the derivative of the CDF $F(x)$.

The Hazard Function

Also,

$$
\begin{aligned}
h(x) &= \lim_{\Delta x \to 0} \frac{\Pr[x \leq X < x + \Delta x | X \geq x]}{\Delta x} \\
&= f(x)/S(x) \\
f(x) &= -\frac{dS(x)}{dx} \qquad \text{Because } F' = f \\
h(x) &= -\frac{d \ln(S(x))}{dx} = -S^{-1}(x)\frac{dS(x)}{dx}
\end{aligned}
$$

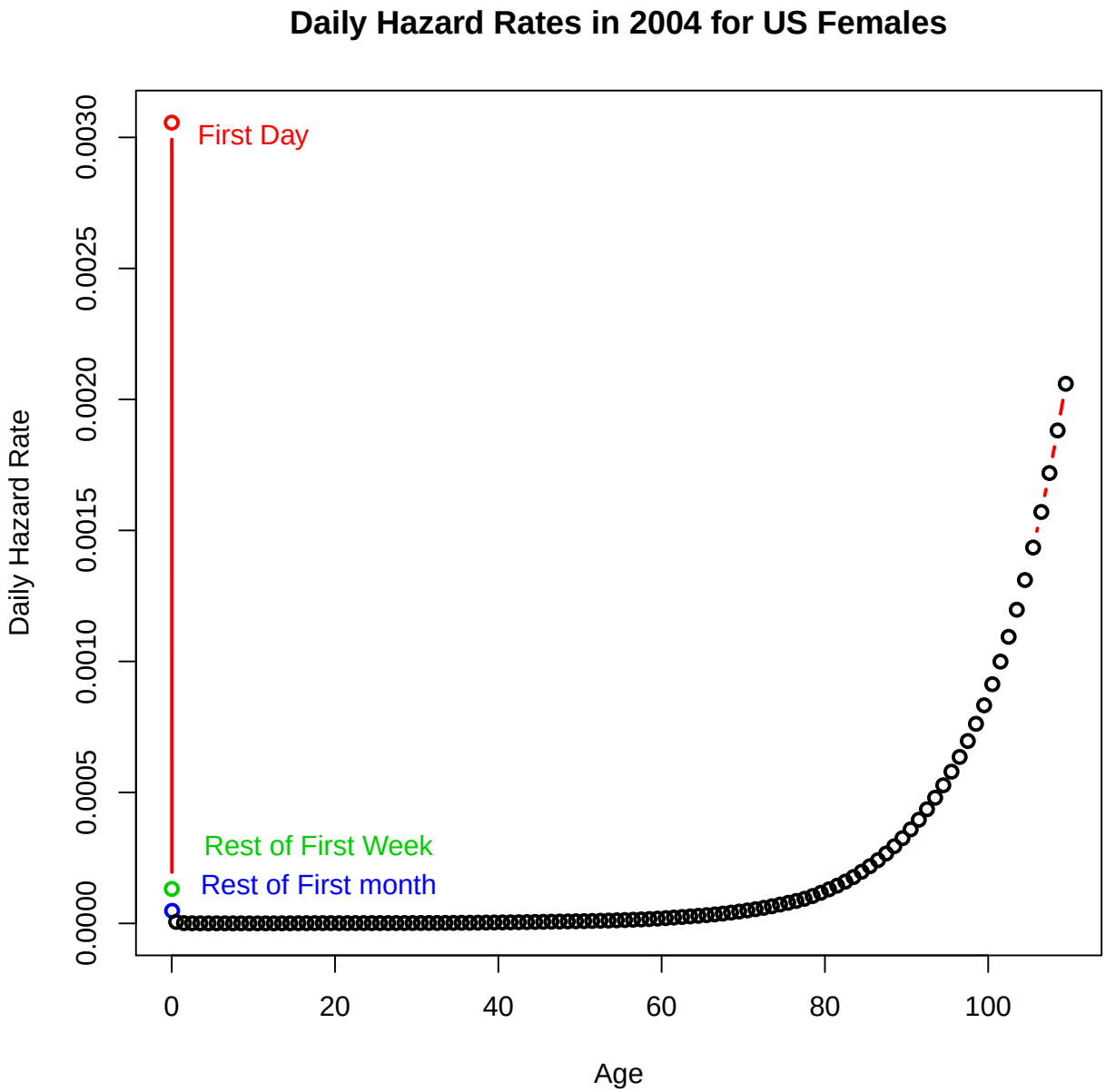
Cumulative Hazard

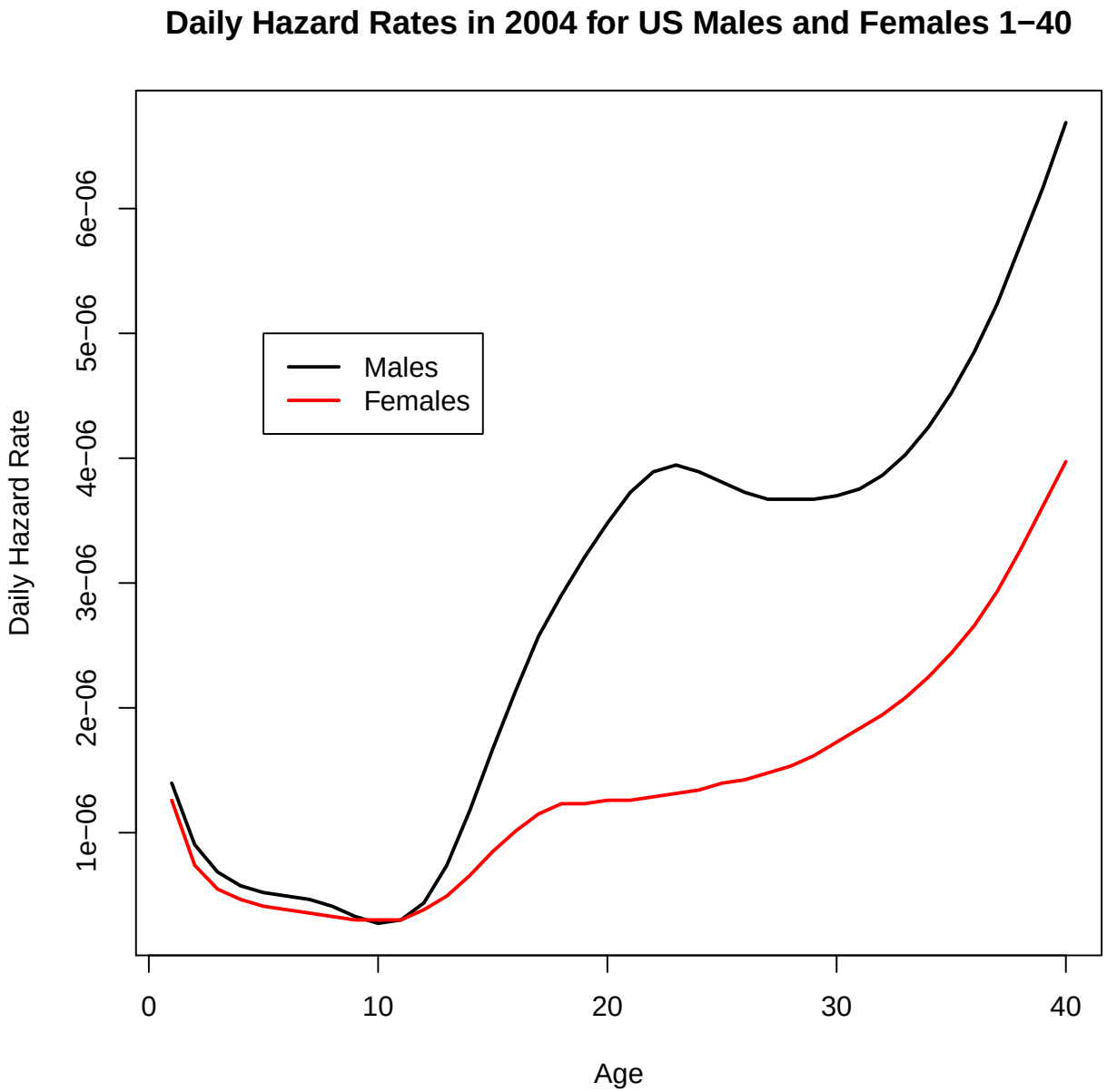
$$h(x) = -\frac{d \ln(S(x))}{dx}$$

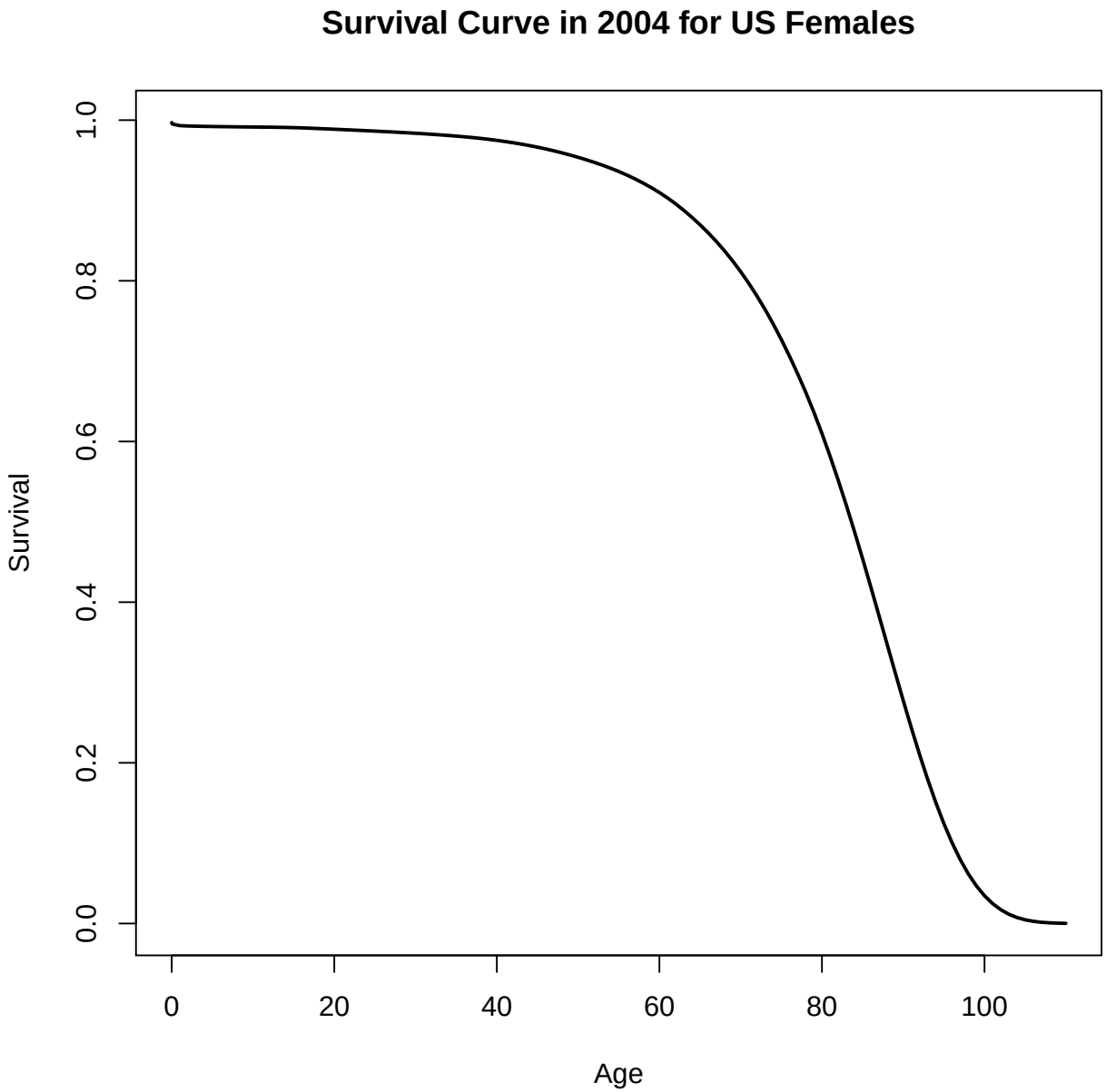
The cumulative hazard function is

$$H(x) = \int_0^x h(t)dt = -\ln(S(x))$$

This function is easier to estimate than the hazard function, and we can then approximate the hazard function by the approximate derivative of the cumulative hazard.


Daily Hazard Rates in 2004 for US Females
First Day
Rest of First Week
Rest of First month
Daily Hazard Rate
0.0000
0.0005
0.0010
0.0015
0.0020
0.0025
0.0030
0
20
40
60
80
100
Age


Daily Hazard Rates in 2004 for US Males and Females 1−40
Daily Hazard Rate
1e−06
2e−06
3e−06
4e−06
5e−06
6e−06
Males
Females
0
10
20
30
40
Age


Survival Curve in 2004 for US Females
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Age

Exponential Distribution

- The exponential distribution is the base distribution for survival analysis.
- The distribution has a constant hazard λ which makes it the simplest survival distribution in that sense.
- The mean survival time is λ^{-1}

$$
\begin{aligned}
f(x;\lambda) &= \lambda e^{-\lambda x} \quad \text{density} = \text{likelihood} \\
\ln(f(x;\lambda)) &= \ln\lambda - \lambda x \quad \text{log likelihood} \\
\frac{\partial}{\partial\lambda}\ln(f(x;\lambda)) &= \lambda^{-1} - x \\
F(x) &= 1 - e^{-\lambda x} \\
S(X) &= e^{-\lambda x} \\
\ln(S(x)) &= -\lambda x \\
h(x) &= -\frac{d}{dx}\ln(S(x)) \\
&= -\frac{d}{dx}(-\lambda x) \\
&= \lambda
\end{aligned}
$$

Estimation of λ

- Suppose we have m exponential survival times of $t_1, t_2, \ldots, t_m$ and k right-censored values at $u_1, u_2, \ldots, u_k$.
- A survival time of $t_i = 10$ means that subject i died at time 10. A right-censored time $u_i = 10$ means that at time 10, subject i was still alive and that we have no further follow-up.
- For the moment we will assume that the survival distribution is exponential and that all the subjects have the same parameter λ.

Estimation of λ

- A naive estimate of λ is the average of the survival times of the of those subjects who died, $m^{-1} \sum t_i$, but this is not correct because it ignores the k subjects that are still alive.
- Suppose one subject died at 1 day, and the rest were still alive at 10 years. One day is a poor estimate of average survival (although this is often the first thing that statistically naive investigators think of).
- This estimate of average survival could be too small or too large.

Estimation of λ

- Another naive estimate of λ is the average of the times of all the subjects, $(m+k)^{-1}[\sum t_i + \sum u_i]$, but this is not correct either because it treats the subjects who are still alive as though they had just died.
- This estimate of average survival is too small if any of the subjects are censored.

Estimation of λ

- Suppose we have m exponential survival times of $t_1, t_2, \ldots, t_m$ and k right-censored values at $u_1, u_2, \ldots, u_k$.
- A survival time of $t_i = 10$ means that subject i died at time 10. A right-censored time $u_i = 10$ means that at time 10, subject i was still alive and that we have no further follow-up.
- For the moment we will assume that the survival distribution is exponential and that all the subjects have the same parameter λ.

Estimation of λ

We have m exponential survival times of $t_1, t_2, \ldots, t_m$ and k right-censored values at $u_1, u_2, \ldots, u_k$. The log-likelihood of an observed survival time t_i is

$$\ln\left(\lambda e^{-\lambda t_i}\right) = \ln\lambda - \lambda t_i$$

and the likelihood of a censored value is the probability of that outcome (survival greater than u_j) so the log-likelihood is

$$\log(e^{-\lambda u_j}) = -\lambda u_j.$$

Let $T = \sum t_i$ and $U = \sum u_j$. Then the log likelihood is

$$\sum_{i=1}^{m}(\ln \lambda - \lambda t_i) + \sum_{j=1}^{k}(-\lambda u_j) = m \ln \lambda - \lambda(T + U)$$

$$m \ln \lambda - \lambda(T + U)$$

is maximized when the derivative wrt λ is 0, that is when

$$\begin{aligned} 0 &= m/\hat{\lambda} - (T + U) \\ \hat{\lambda} &= m/(T + U) \\ 1/\hat{\lambda} &= (T + U)/m \end{aligned}$$

Thus, the estimated mean survival is the total of the times, exact and censored, divided by the number of exact times. It can be show that the variance of $\hat{\lambda}$ is asymptotically λ^2/m, depending only on the number of uncensored observations. This is generally true.

Suppose that we have two groups with m items in each group, where the mean time in each group is $\bar{x}$. If the times in group 1 are failures and the times in group 2 are censored, vs. both are failures, then

$$\begin{aligned} 1/\hat{\lambda} &= (m\bar{x} + m\bar{x})/m \\ &= \bar{x} + \bar{x} = 2\bar{x} \\ \hat{V}(\hat{\lambda}) &= \hat{\lambda}^2/m \end{aligned}$$

$$\begin{aligned} 1/\hat{\lambda} &= (m\bar{x} + m\bar{x})/(2m) \\ &= (\bar{x} + \bar{x})/2 = \bar{x} \\ \hat{V}(\hat{\lambda}) &= \hat{\lambda}^2/(2m) \end{aligned}$$

The Score and the Fisher Information

The log likelihood is

$$\ell\ell = m \ln \lambda - (T + U)\lambda$$

and its derivative, called the *score*, is

$$\ell\ell' = m/\lambda - (T + U)$$

Under certain conditions, the negative derivative of the score, called the *Fisher Information*, estimates the reciprocal of the variance of the MLE.

The score is

$$\ell\ell' = m/\lambda - (T + U)$$

(which is 0 evaluated at the MLE) and the observed Fisher information is

$$-\ell\ell'' = m/\hat{\lambda}^2$$

and its reciprocal is

$$\hat{\lambda}^2/m$$

Although the value of $\hat{\lambda}$ depends on both the uncensored data and the censored data, the variance depends only on the uncensored sample size.

- The (expected value of the) score statistic is zero when evaluated at the MLE.
- The larger the second derivative of the log likelihood is, the steeper the fall-off from the MLE and the more certainly we know the true parameter.
- The multivariate generalization of the Fisher information is most times the method of determining the variance covariance matrix for Wald tests.
- Or we can use the likelihood ratio chi-squared test and interval from inverting this test (profile likelihood).

Multivariate Generalization

- If there are p parameters, then the score is the gradient vector of length p of partial derivatives of the log likelihood. This determines the estimates by solving p equations in p unknowns setting the score vector to the zero vector.
- The Hessian H is the matrix of second partials and its negative inverse evaluated at the MLE's estimates the variance covariance matrix of the estimated parameters.

- If we have a null hypothesis for the exponential parameter λ

$$H_0 : \lambda = \lambda_0$$

then the log likelihood at the MLE is

$$\ell\ell = m \ln(m/(T+U)) - m$$

and at the null hypothesis is

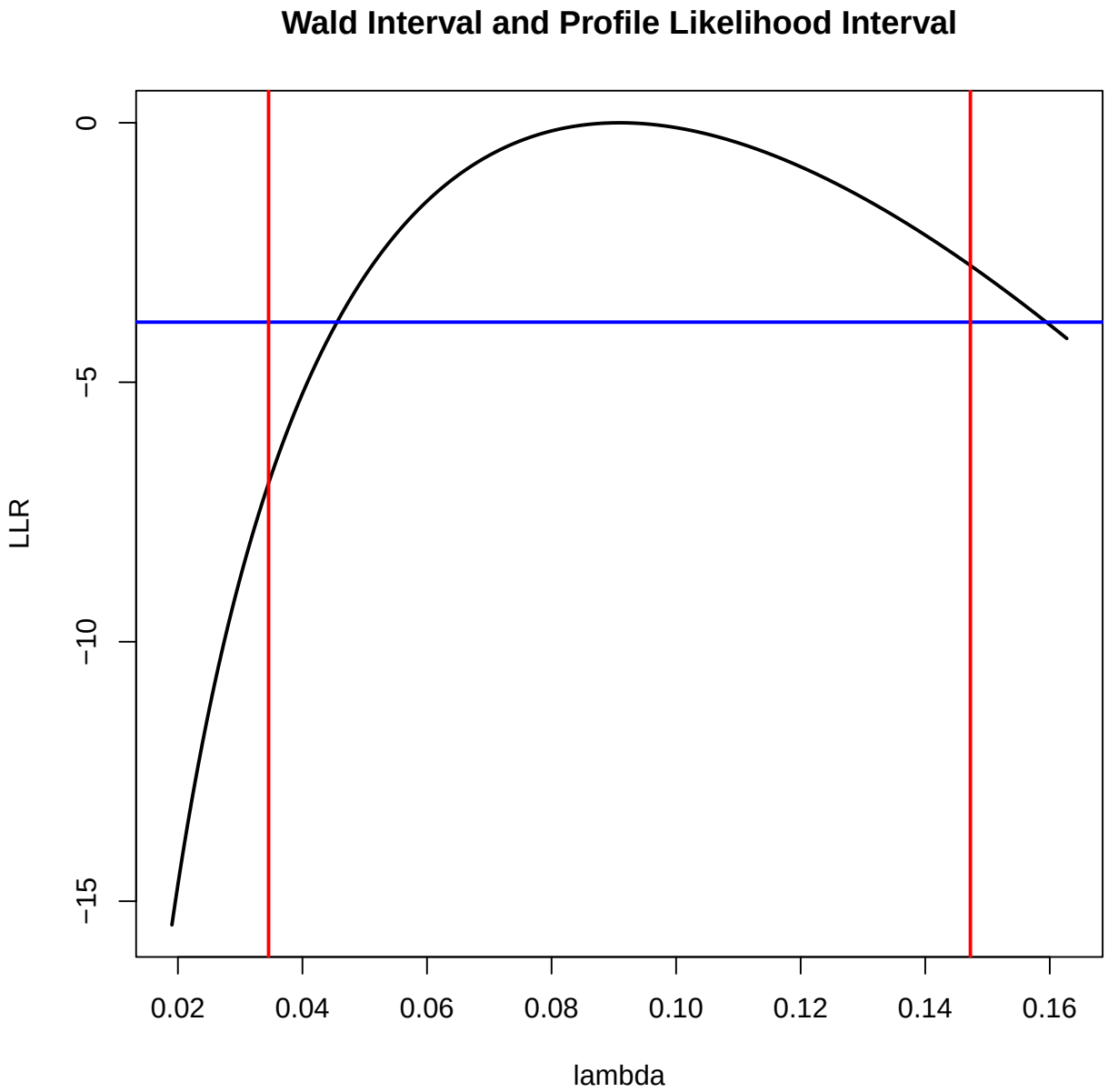
$$\ell\ell = m \ln \lambda_0 - (T+U)\lambda_0$$

- The likelihood ratio statistics is the negative of twice the difference between the log likelihood at the null and the log likelihood at the MLE.

- We can construct a confidence interval for λ in two ways: using the asymptotic normal approximation or the likelihood ratio statistics.
- The plot on the next slide is for $m = 10, k = 5, T = 100, U = 10$ with

$$\begin{aligned} \hat{\lambda} &= 0.0909 \\ \hat{se}(\lambda) &= 0.02875 \end{aligned}$$

- The red lines are at ± 1.96 standard errors away from the MLE.
- The blue line is at the chisquare statistic with 5% in the tail and 1 df and intersects the likelihood curve to form another interval.


Wald Interval and Profile Likelihood Interval
LLR
0
−5
−10
−15
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
lambda

- The Wald test/interval and the LLR test/profile likelihood interval are both asymptotically accurate subject to assumptions.
- Frequently, the convergence of the LLR procedures to asymptopia is faster than that of the Wald procedures.
- We could check this by simulation under the assumptions.
- Also, the profile likelihood procedures are unchanged by transformations in the parameter—the same for λ as for the mean λ^{-1}; this is not true of the Wald procedures.