Linear regression Nonlinear regression Survival analysis



Biostatistics Course 2024 Lecture 5 Friday, 12 July 2024 2:00pm - 4:00pm Linear regression

Linear regression seeks to explain y as a linear function of x plus Gaussian noise



Parameters are chosen to minimize the sum of squared deviations



 $y_i = a + bx_i + \epsilon_i$

The model "parameters", *a* and *b*, are chosen to minimize this quantity: $\sum_{i} \epsilon_{i}^{2}$.

This can be done mathematically, and one finds that,

$$b = r \frac{\hat{\sigma}_y}{\hat{\sigma}_x}$$
 and $a = \hat{\mu}_y - b\hat{\mu}_x$

Some properties of linear regression



The center of mass point of the data, $(\hat{\mu}_x, \hat{\mu}_y)$, lies on the regression line.

Confidence intervals (shaded region) are curved because of uncertainty in both a and b.

Any reported P-values correspond to the null hypothesis that b = 0.

Linear regression explains a fraction of the variance



model:
$$\hat{y}_i = a + bx_i$$

$$(n-1) \times \text{variance}$$
:



 r^2 is the fraction of variance explained:

$$r^{2} = \frac{\sum_{i} (\hat{y}_{i} - \hat{\mu}_{y})^{2}}{\sum_{i} (y_{i} - \hat{\mu}_{y})^{2}} = 0.593$$

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		23	P value	0.0021		
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- The model is correct, i.e. the expected value for *y* is indeed a linear function of *x* for some correct choice of parameters.
- The noise (i.e. the residuals) is Gaussian and has mean zero.
- The residual for each data point is statistically independent
- The magnitude of the noise (i.e. variance of the Gaussian) is the same at all *x* values.
- Each x_i is known exactly.

As with correlation, many different-looking datasets can have exactly the same regression line



Anscombe's quartet

Anscombe, F. J. (1973). "Graphs in Statistical Analysis". American Statistician. 27 (1): 17–21.

Beware of combining distinct groups into one



Combining two groups into one regression can mislead by creating a strong linear relationship.



Combining two groups into one regression can mislead by hiding a trend.

Beware of reading too much into a regression result

Don't trust regression results that you can't verify by eye



I DON'T TRUST LINEAR REGRESSIONS WHEN IT'S HARDER TO GUESS THE DIRECTION OF THE CORRELATION FROM THE SCATTER PLOT THAN TO FIND NEW CONSTELLATIONS ON IT.

MY HOBBY: EXTRAPOLATING



Don't over-extrapolate

Nonlinear regression

log10_conc	pct_relaxation
-8.0	2.6
-7.5	10.5
-7.0	15.8
-6.5	21.1
-6.0	36.8
-5.5	57.9
-5.0	73.7
-4.5	89.5
-4.0	94.7
-3.5	100.0
-3.0	100.0

Frazier et al (2006) measured the degree to which the neurotransmitter norepinephrine relaxes bladder muscle in rats.

Strips of bladder muscle were exposed to various concentrations of norepinephrine, and percent muscle relaxation was measured.

The data from each rat was analyzed to determine the maximum relaxation and the concentration of norepinephrine that relaxes the muscle half that much (C50)

Example: effect of norepinephrine on muscle relaxation

log10_conc	pct_relaxation
-8.0	2.6
-7.5	10.5
-7.0	15.8
-6.5	21.1
-6.0	36.8
-5.5	57.9
-5.0	73.7
-4.5	89.5
-4.0	94.7
-3.5	100.0
-3.0	100.0

 $x: \log_{10}$ concentration (in M)

y: percent muscle relaxation



 $f(x) = \text{bottom} + \frac{\text{top} - \text{bottom}}{1 + 10^{(\log C50 - x) \cdot \text{hillSlope}}}$

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 $y = \text{Bottom} + \frac{\text{Top} - \text{Bottom}}{1 + 10^{(\text{LogIC50} - x) \cdot \text{HillSlope}}}$

4 parameters: Bottom, Top, LogIC50, HillSlope

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	12	LogIC50	-5.721 to -5.477	
	13	HillSlope	0.5594 to 0.8410	
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 $y = \text{Bottom} + \frac{\text{Top} - \text{Bottom}}{1 + 10^{(\text{LogIC50} - x) \cdot \text{HillSlope}}}$

4 parameters: Bottom, Top, LogIC50, HillSlope



Multiple linear regression and logistic regression

<u>Multiple linear regression</u> (often just called "linear regression") is used to model data where each data point (\vec{x}_i, y_i) consist of an independent variable $\vec{x}_i = (x_{i1}, x_{i2}, ..., x_{iD})$, which is a *D*-dimensional vector, and a dependent variable y_i , which is a single number. Often the entries of the vector \vec{x}_i are called "<u>covariates</u>".

The key assumption is that each dependent variable y_i is related to the corresponding independent variables via

$$y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_D x_{iD} + \epsilon_i$$

where the residual ϵ_i is due to random Gaussian noise.

The covariants that define \vec{x} are often a mixture of continuous and binary variables.

Logistic regression is used to model probabilities that depend on multiple covariates

<u>Logistic regression</u> is used to model data where each data point (\vec{x}_i, y_i) consists of a vector $\vec{x}_i = (x_{i1}, x_{i2}, \dots, x_{iD})$ that represents *D* covariants, and one dependent variable y_i that is **binary**.

The key assumption is that the log odds of y_i is a linear function of \vec{x}_i :

$$\log \text{Odds}_{i} = \log \left[\frac{p(y_{i} = 1 | \vec{x}_{i})}{p(y_{i} = 0 | \vec{x}_{i})} \right] = \beta_{0} + \beta_{1} x_{i1} + \beta_{2} x_{i2} + \dots + \beta_{D} x_{iD}$$

Note that there is no need for a "residual" contribution since the model is inherently probabilistic.

Again, the covariants that define \vec{x} are often a mixture of continuous and binary variables.

Welcome to GraphPad Prism

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NEW TABLE & GRAPH

XY

Column

Grouped

Contingency

Survival

Parts of Whole

Multiple variables

Nested

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Start with sample data to follow a tutorial

Select a tutorial data set:



Aultiple logistic regression



son regression



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Prism Tips

Survival analysis

Uppercase T indicates the time of an individual's death. This is a random variable that changes from individual to individual. Alternatively, T can be the time of some other event an individual can experience once and only once. Not all individuals under study need to experience this event.

Lowercase *t* denotes a time value that we wish to inquire about; it is not specific to any individual.

The survival function S(t) is the probability of survival to time t, i.e.

S(t) = p(T > t)

Here are some properties of the survival function:

- 1. S(0) = 1 (by convention)
- 2. $0 \le S(t) \le 1$ at all times *t*
- 3. S(t) is a non-increasing function of t

The hazard function h(t) is the probability of death per unit time (i.e. death rate) at time t, given that a subject has already survived up until time t.

The hazard function and the survival function are related to each other via

$$S(t) = \exp\left(-\int_0^t dt' h(t')\right) \quad \text{and} \quad h(t) = -\frac{d}{dt}\log S(t).$$

The <u>cumulative hazard function</u> H(t) is the integral of the hazard function:

$$H(t) = \int_0^t dt' \ h(t'),$$

which is related to the survival function via $S(t) = e^{-H(t)}$.

The survival function is usually the primary thing we are interested in estimating from data. Suppose we have *n* individuals who are all alive at time t = 0. Further assume that we observe all death events that do occur. We can then estimate S(t) quite simply as the fraction of these individuals who remain alive at time *t*.

$$\hat{S}(t) = \frac{n(t)}{n(0)}$$

where n(t) is the number of subjects alive at time t.

Survival data is "right-censored" when we know that an individual i survived up to time T_i , but after that we loose track of that individual.

Censoring is usually indicated by an event flag E_i that is 1 if the event is observed or 0 if the event is censored.



Censoring can occur for many different reasons.

- 1. Subjects enroll in a clinical trial on a rolling basis, and survival time is computed from the date of enrollment. When the trial ends, the subjects how still survive will have survived for different periods of time.
- 2. Subjects in a clinical trial leave because they don't want to participate anymore, they require protocol-breaking treatment, or they are lost to follow-up.
- 3. In an animal study, animals become available for experimentation at different times.
- 4. An animal in a study is subject to some unexpected mishap (lost, etc.)

Do not throw away censored data! This will invalidate your entire analysis.

Let T_1, T_2, \ldots, T_K , be the times, in increasing order at which individuals either die or are censored. We allow for multiple individuals dying and/or being censored at the same time.

Let n_i denote the number of individuals <u>at risk</u> at time T_i .

Let d_i denote the number of individuals that actually die at time T_i .

The Kaplan-Meier estimate $\hat{S}(t)$ for the survival curve is given by:

$$\hat{S}(t) = \prod_{i: T_i < t} \frac{n_i - d_i}{n_i}.$$

The <u>log-rank</u> test is (also called the <u>Mantel-Cox</u> test) is the standard test used to compare survival curves for two distinct groups

Null hypothesis: the two populations are governed by the same survival curve and hazard rate

How it works: computes a summary statistic that quantifies how evenly distributed deaths are across the populations in question. Under the null hypothesis, this statistic approximately follows a χ^2 distribution with 1 degree of freedom.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Save this study

Lymph Node Removal in Treating Women Who Have Stage I or Stage IIA Breast Cancer

The safety and scientific validity of this study is the responsibility of
 the study sponsor and investigators. Listing a study does not mean it
 has been evaluated by the U.S. Federal Government. Read our
 disclaimer for details.

ClinicalTrials.gov Identifier: NCT00003855

Recruitment Status ①: Completed First Posted ①: January 27, 2003 Last Update Posted ①: April 29, 2020

Go to

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Study Description

Brief Summary:

RATIONALE: Surgery to remove lymph nodes in the armpit may remove cancer cells that have spread from tumors in the breast.

PURPOSE: Randomized phase III trial to determine the effectiveness of removing lymph nodes in the armpit in treating women who have stage I or stage IIA breast cancer.

Condition or disease 0	Intervention/treatment 0	Phase 0
Breast Cancer	Procedure: axillary lymph node dissection	Phase 3
	Radiation: whole breast irradiation	

Detailed Description:

OBJECTIVES:

Primary objectives:

Long term: To assess whether overall survival for patients randomized to Arm 2 (no immediate ALND) is essentially equivalent to (or better than) than that for patients assigned to Arm 1 (completion ALND).

Short term: To quantify and compare the surgical morbidities associated with SLND plus ALND versus SLND alone.

OUTLINE: This is a randomized study. After segmental mastectomy and sentinel lymph node dissection, patients are stratified according to age (50 and under vs over 50), estrogen receptor status (positive vs negative), and tumor size (no greater than 1 cm vs greater than 1 cm but no greater than 2 cm vs greater than 2 cm). Patients are randomized to one of two treatment arms.

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XY

Column

Grouped

Survival

Nested

EXISTING FILE

Open a File

LabArchives

Clone a Graph

Graph Portfolio

Contingency

Parts of Whole

Multiple variables

Welcome to GraphPad Prism



Survival tables: Each row tabulates the survival or censored time of a subject



Prism Tips

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Survival curve	
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27 95% CI of ratio 0.5269 to 1.183 0.8454 to 1.898	
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Suppose that each individual *i* has, in addition to an event time t_i and event flag, has a set of *D* covariants $x_{i1}, x_{i2}, \ldots, x_{iD}$, which can be either real numbers or binary.

The Cox proportional hazards model assumes that subjects are governed by a hazards function that has the following form.

$$h_i(t) = h_0(t) \times \exp \left[\beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_D x_{iD}\right]$$

Each coefficient β_j is the "effect size" for the corresponding covariate x_{j} . If the value for β_j is significantly different than 0, it means that the covariate x_{j} effects survival.

lifelines.datasets.load_rossi(**kwargs)

This data set is originally from Rossi et al. (1980), and is used as an example in Allison (1995). The data pertain to 432 convicts who were released from Maryland state prisons in the 1970s and who were followed up for one year after release. Half the released convicts were assigned at random to an experimental treatment in which they were given financial aid; half did not receive aid.:

Size: (432,9)	
Example:	
week	20
arrest	1
fin	0
age	27
race	1
wexp	0
mar	0
paro	1
prio	3

References

Rossi, P.H., R.A. Berk, and K.J. Lenihan (1980). Money, Work, and Crime: Some Experimental Results. New York: Academic Press. John Fox, Marilia Sa Carvalho (2012). The RcmdrPlugin.survival Package: Extending the R Commander Interface to Survival Analysis. Journal of Statistical Software, 49(7), 1-32.

https://lifelines.readthedocs.io/en/latest/lifelines.datasets.html#lifelines.datasets.load_rossi

Example: Rossi recidivism dataset

A data frame with 432 observations on the following 62 variables.

week

week of first arrest after release or censoring; all censored observations are censored at 52 weeks.

arrest

1 if arrested, 0 if not arrested.

fin

financial aid: no yes.

age

in years at time of release.

race

black Or other.

wexp

full-time work experience before incarceration: no or yes.

mar

marital status at time of release: married or not married.

paro

released on parole? no or yes.

prio

number of convictions prior to current incarceration.

educ

level of education: 2 = 6th grade or less; 3 = 7th to 9th grade; 4 = 10th to 11th grade; 5 = 12th grade; 6 =some college.

Example: Rossi recidivism dataset

- 1 **#** Load and preview Rossi dataset
- 2 **from** lifelines.datasets **import** load_rossi
- 3 rossi_df = load_rossi()
- 4 rossi_df.head()

	week	arrest	fin	age	race	wexp	mar	paro	prio
0	20	1	0	27	1	0	0	1	3
1	17	1	0	18	1	0	0	1	8
2	25	1	0	19	0	1	0	1	13
3	52	0	1	23	1	1	1	1	1
4	52	0	0	19	0	1	0	1	3

week: survival time
arrest: 1 if arrested (event), 0 if not arrested (censored)

The results of Cox Regression is a statement about the effect size and significance of each variable

		exp(coef)	exp(coef)	lower 95%	exp(coef)	upper 95%
	fin	0.68		0.47		1.00
	age	0.94		0.90		0.99
effect size	race	1.37		0.75		2.50
(hazard)	wexp	0.86		0.57		1.30
	mar	0.65		0.31		1.37
	paro	0.92		0.63		1.35
	prio	1.10		1.04		1.16

	Z	р	-log2(p)
fin	-1.98	0.05	4.40
age	-2.61	0.01	6.79
race	1.02	0.31	1.70
wexp	-0.71	0.48	1.06
mar	-1.14	0.26	1.97
paro	-0.43	0.66	0.59
prio	3.19	<0.005	9.48
	fin age race wexp mar paro prio	z fin -1.98 age -2.61 race 1.02 wexp -0.71 mar -1.14 paro -0.43 prio 3.19	z p fin -1.98 0.05 age -2.61 0.01 race 1.02 0.31 wexp -0.71 0.48 mar -1.14 0.26 paro -0.43 0.66 prio 3.19 <0.005

Log-likelihood ratio test = 33.27 on 7 df, -log2(p)=15.37

The likelihood ratio test is an extremely general way of comparing two models. It is an approximate test, though, valid only in the large data regime.

Likelihood ratio test uses a statistic given by:

$$\chi^2 = 2 \log \left(\frac{\text{Likelihood}_{\text{alt}}}{\text{Likelihood}_{\text{null}}} \right)$$

Under the null hypothesis, χ^2 follows a chi square distribution where the number of degrees of freedom is:

DOF = (# alt model parameters) - (# null model parameters)

It tests the necessity of all parameters; it does not say whether individual parameters are required.

10:00a - 12:00p. Finished right on time, though rather rushed at the end.