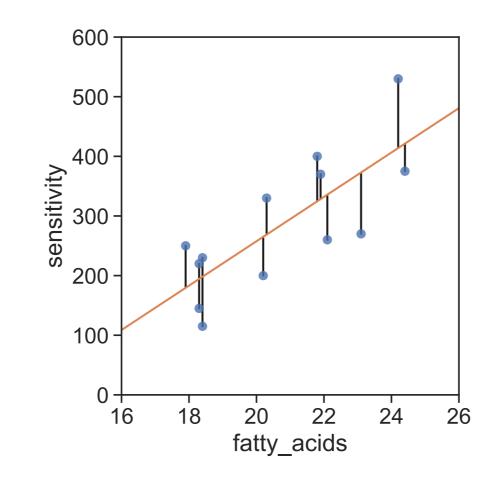
# Linear regression Nonlinear regression Survival analysis



Biostatistics Course 2023 Lecture 5 Thursday, 28 July 2023 1:00pm - 3:00pm



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



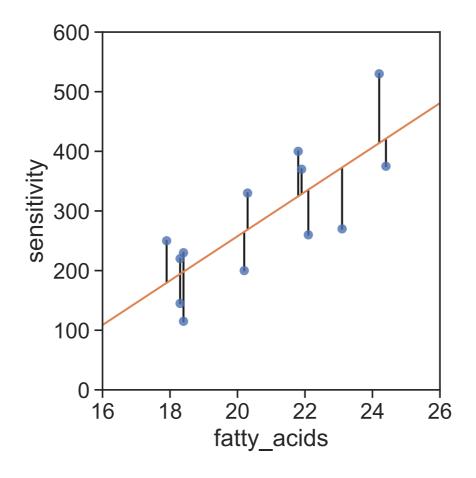
$$y_i = a + bx_i + \epsilon_i$$

*a*: y-intercept

b: slope

 $\epsilon_i$ : the "residuals"

#### Parameters are chosen to minimize the sum of squared deviations



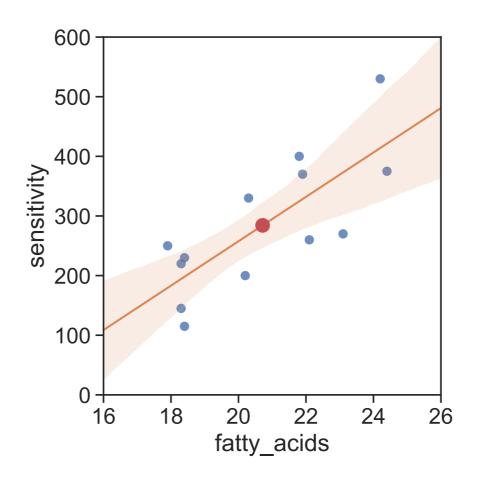
$$y_i = a + bx_i + \epsilon_i$$

The model "parameters", a and b, are chosen to minimize this quantity:  $\sum_i e_i^2$ .

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

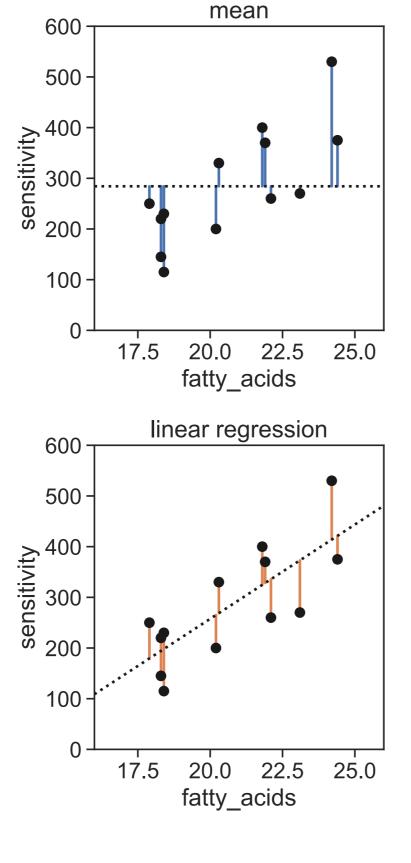


The center of mass point of the data,  $(\hat{\mu}_{\chi}, \hat{\mu}_{\chi})$ , lies on the regression line.

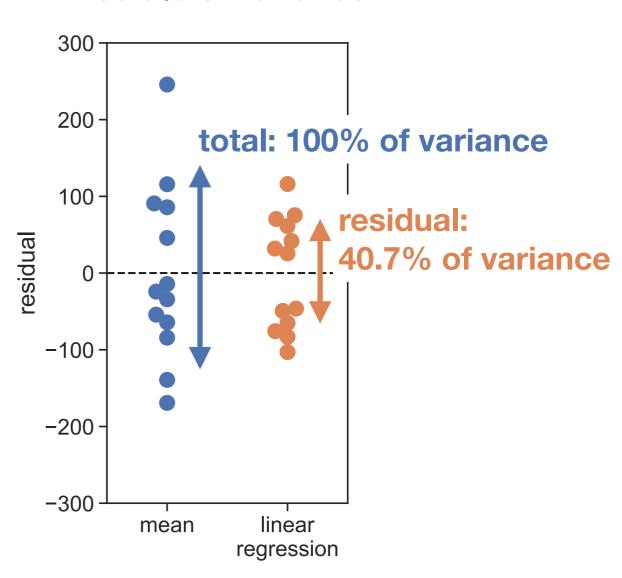
Confidence intervals (shaded region) are curved because of uncertainty in both a and b.

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

#### Linear regression explains a fraction of the variance



# model: 59.3% of variance



#### Linear regression explains a fraction of the variance

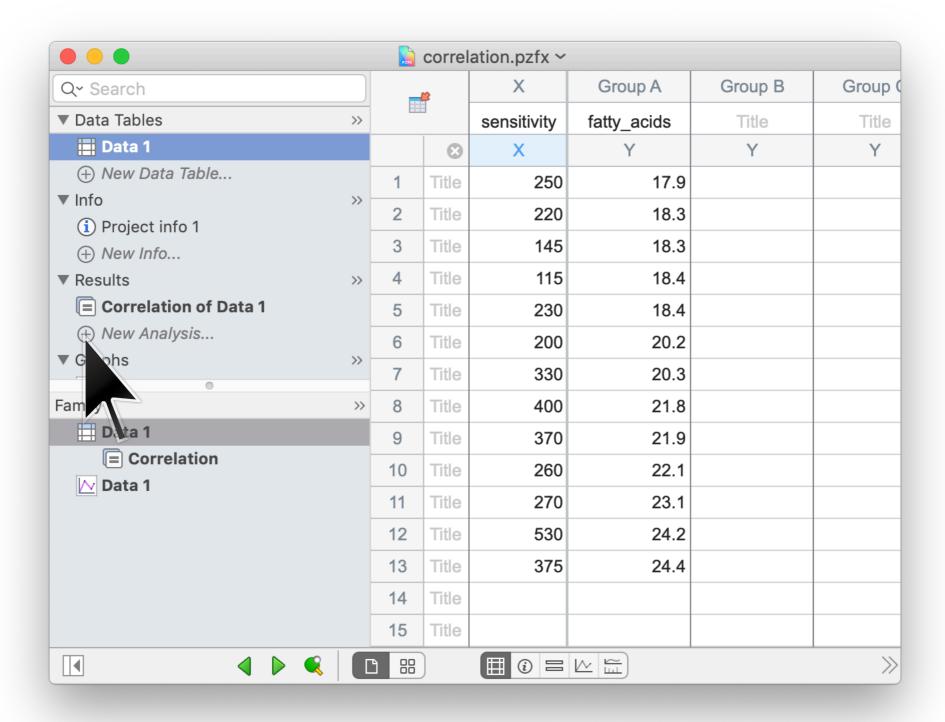
model: 
$$\hat{y}_i = a + bx_i$$

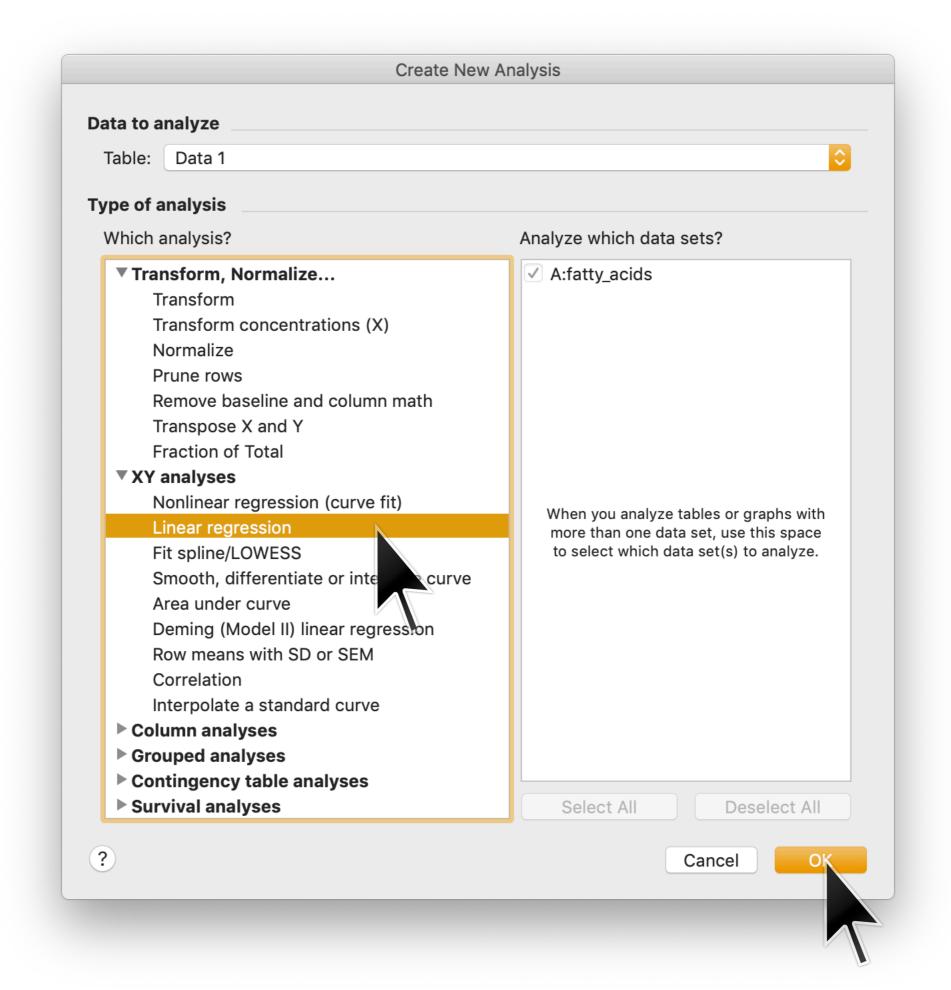
$$(n-1) \times \text{variance}$$
:

$$\sum_{i} (y_i - \hat{\mu}_y)^2 = \sum_{i} (y_i - \hat{y}_i)^2 + \sum_{i} (\hat{y}_i - \hat{\mu}_y)^2$$
total: residual: model: 40.7% 59.3%

 $r^2$  is the fraction of variance explained:

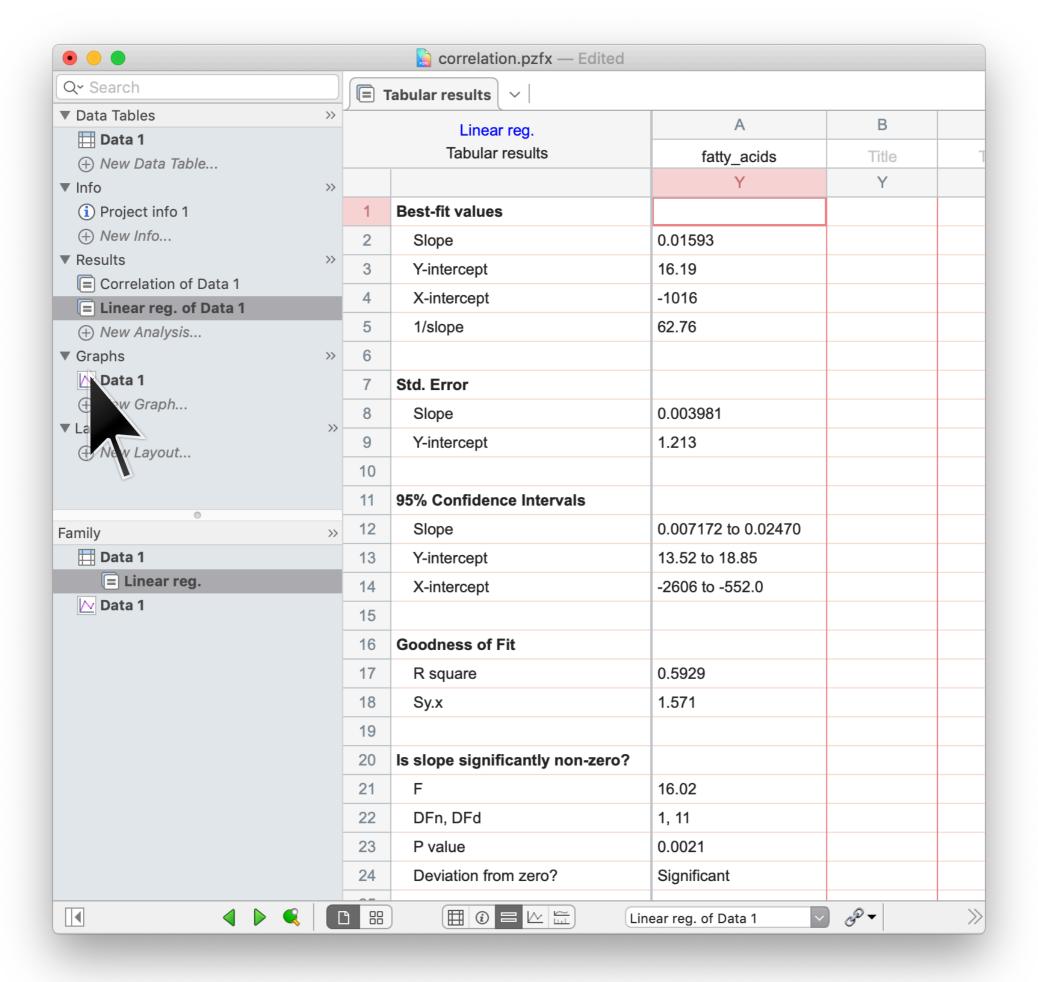
$$r^{2} = \frac{\sum_{i} (\hat{y}_{i} - \hat{\mu}_{y})^{2}}{\sum_{i} (y_{i} - \hat{\mu}_{y})^{2}} = \mathbf{0.593}$$

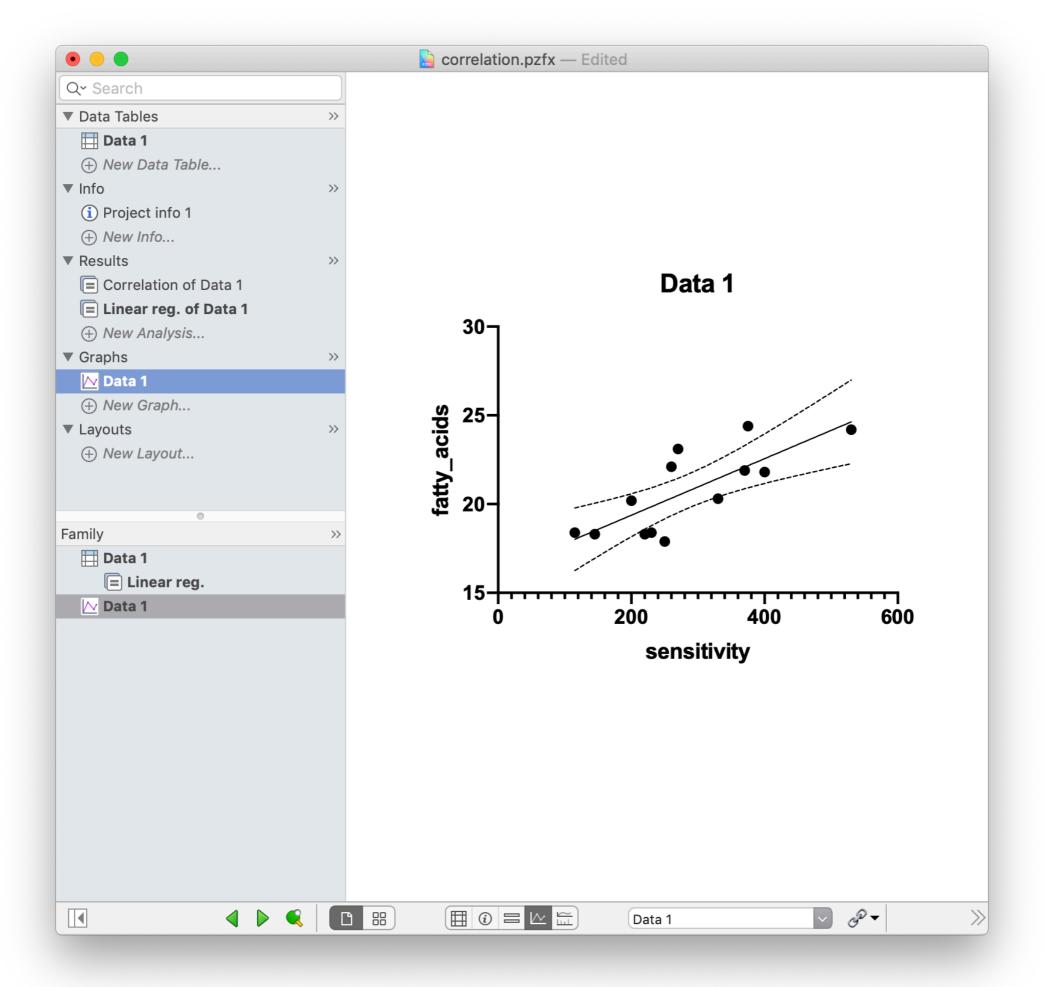




| Parameters: Linear Regression   |  |  |  |  |
|---|--|--|--|--|
| Interpolate  Interpolate unknowns from standard curve                                 |  |  |  |  |
| Compare   |  |  |  |  |
| Test whether slopes and intercepts are significantly different                        |  |  |  |  |
| Graphing options  |  |  |  |  |
| Show the 95% confidence bands of the best-fit line                                    |  |  |  |  |
| sidual plot   |  |  |  |  |
| Col dain  |  |  |  |  |
| Force the line to go through X =  |  |  |  |  |
| Replicates  |  |  |  |  |
| Consider each replicate Y value as individual point                                   |  |  |  |  |
| Only consider the mean Y value of each point  |  |  |  |  |
| Also calculate  |  |  |  |  |
| Test departure from linearity with runs test  |  |  |  |  |
| ✓ 95% confidence interval of Y when X = 0   |  |  |  |  |
| ✓ 95% confidence interval of X when Y = 0   |  |  |  |  |
| Range   |  |  |  |  |
| Start regression line at: End regression line at:                                     |  |  |  |  |
| O Auto  |  |  |  |  |
| $\bigcirc X = 115$ $\bigcirc X = 530$ $\bigcirc X = 530$                              |  |  |  |  |
| Output options  |  |  |  |  |
| Show this many significant digits (for everything except P values): 4                 |  |  |  |  |
| P Value Style: GP: 0.1234 (ns), 0.0332 (*), 0.0021 (**), 0.0002 (***), <0.0001 (****) |  |  |  |  |
| Make these choices as default for future regressions                                  |  |  |  |  |
| ? More choices Cancel   |  |  |  |  |

A

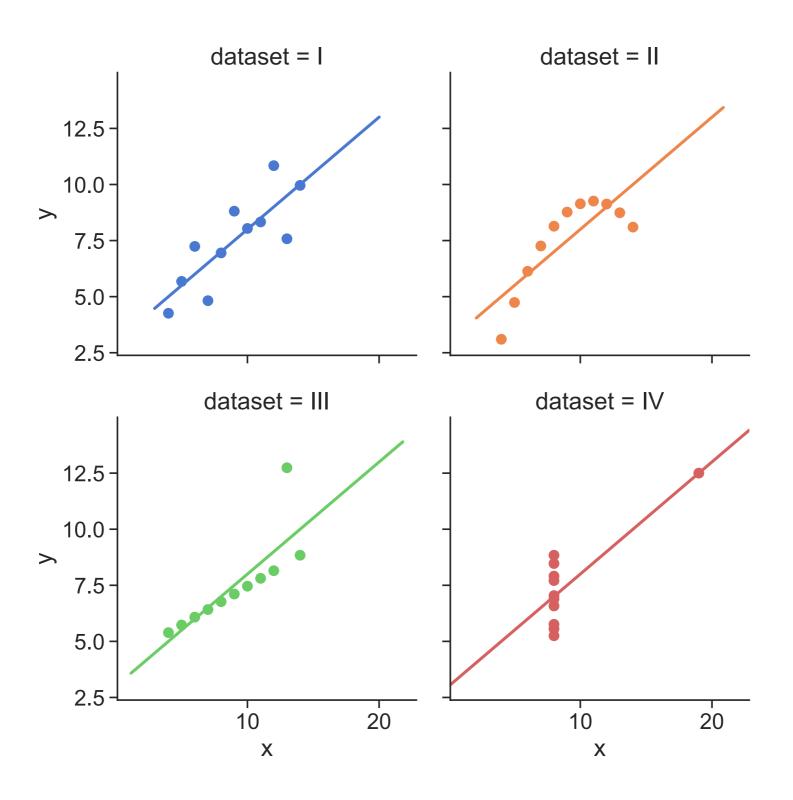




#### **Linear regression assumptions**

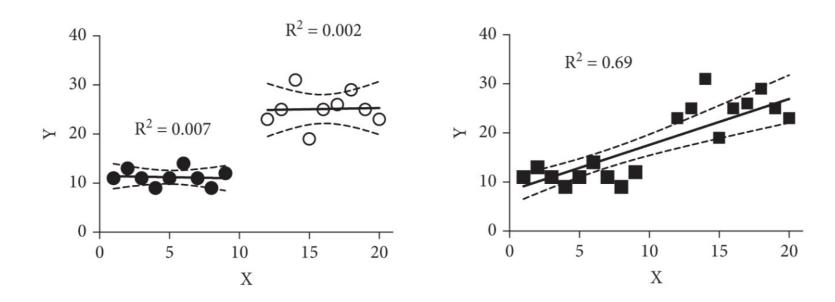
- The model is correct, i.e. the expected value for *y* is indeed a linear function of *x* for some correct choice of parameters.
- The noise (i.e. the residuals) is Gaussian and has mean zero.
- The residual for each data point is statistically independent
- The magnitude of the noise (i.e. variance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

#### Anscombe's quartet

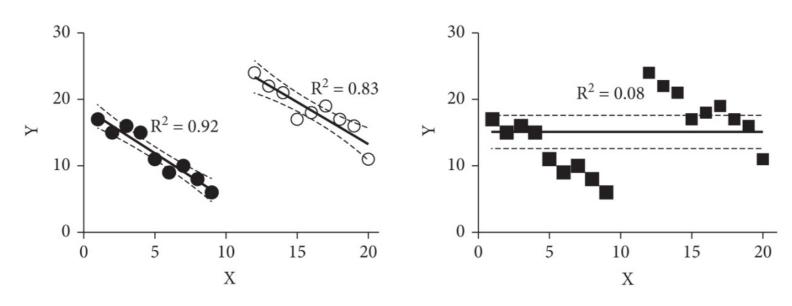


Anscombe, F. J. (1973). "Graphs in Statistical Analysis". American Statistician. 27 (1): 17–21.

#### Beware of combining distinct groups into one



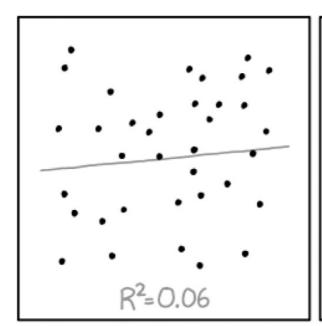
Combining two groups into one regression can mislead by creating a strong linear relationship.



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

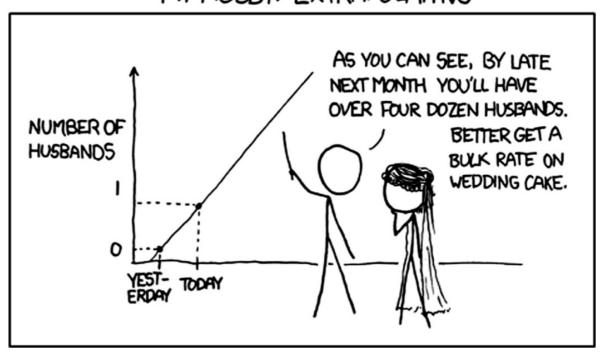


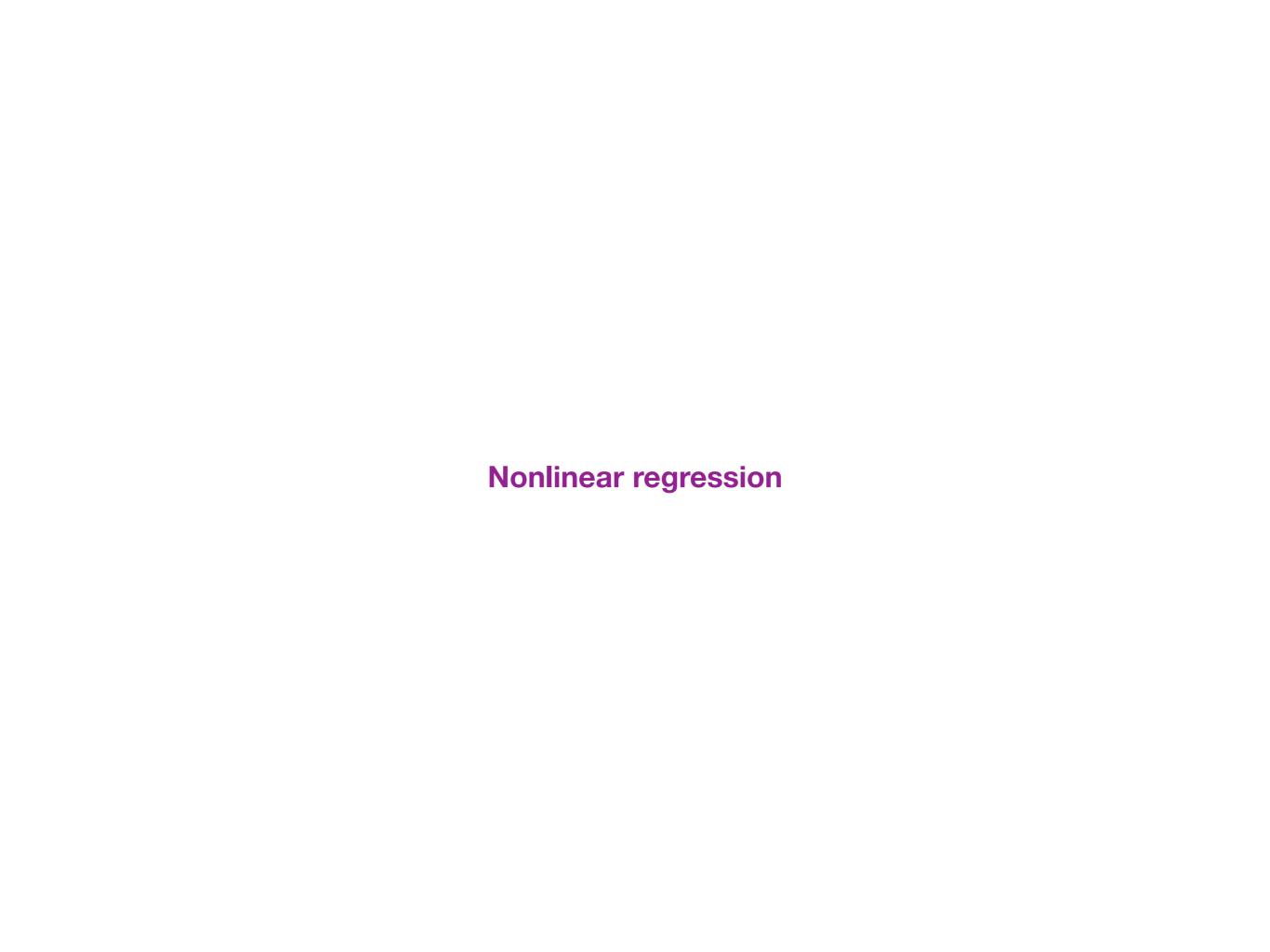


I DON'T TRUST LINEAR REGRESSIONS WHEN IT'S HARDER TO GUESS THE DIRECTION OF THE CORRELATION FROM THE SCATTER PLOT THAN TO FIND NEW CONSTELLATIONS ON IT.

Don't over-extrapolate

MY HOBBY: EXTRAPOLATING





#### 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          |

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.

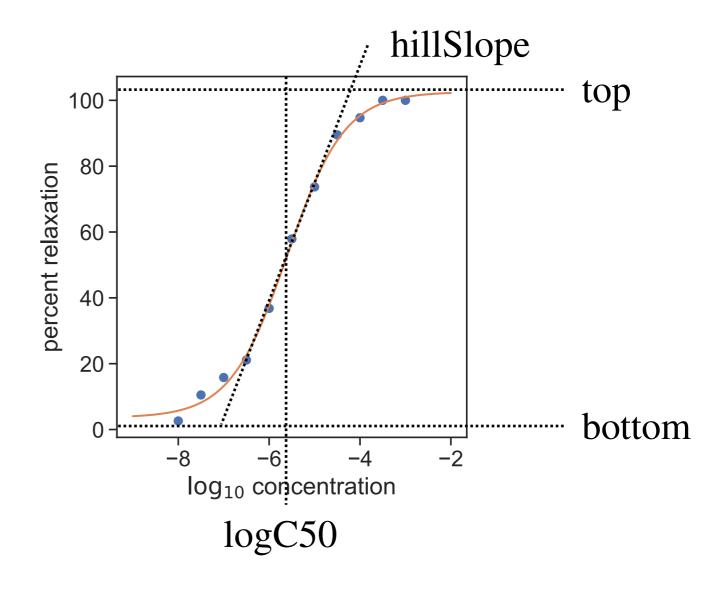
The data from each rat was analyzed to determine the maximum relaxation and the concentration of norepinephrine that relaxes the muscle half that much (C50)

#### Example: effect of norepinephrine on muscle relaxation

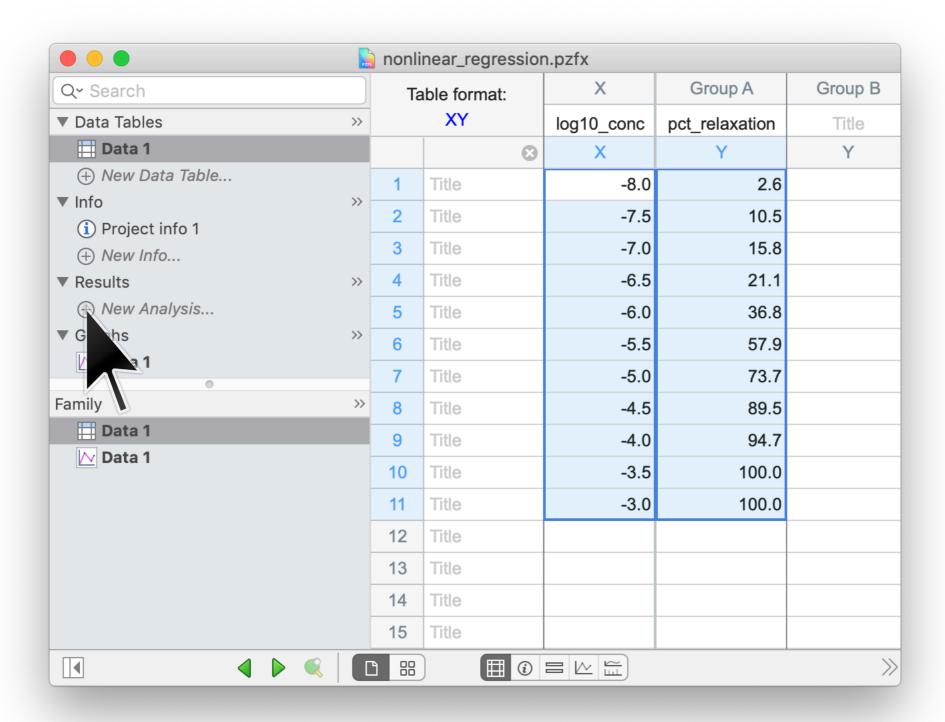
| log10_conc | pct_relaxation |  |
|------------|----------------|--|
| -8.0       | 2.6            |  |
| -7.5       | 10.5           |  |
| -7.0       | 15.8           |  |
| -6.5       | 21.1           |  |
| -6.0       | 36.8           |  |
| -5.5       | 57.9           |  |
| -5.0       | 73.7 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

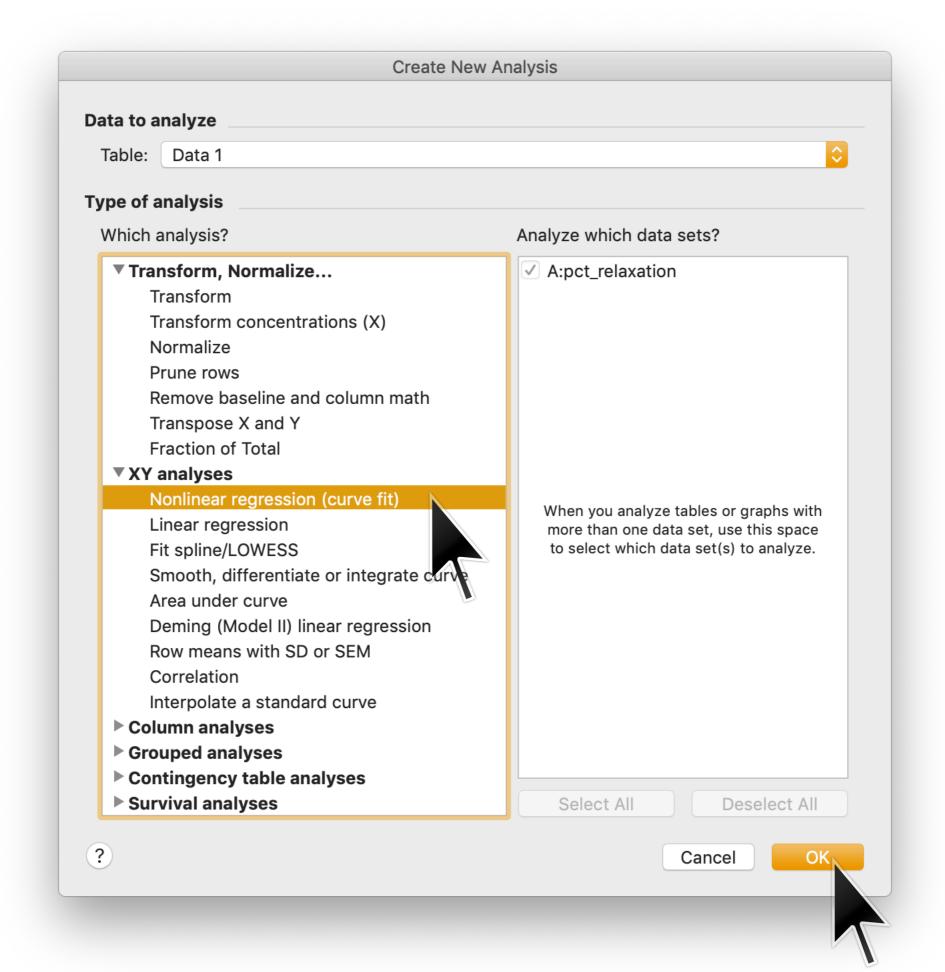
x:  $log_{10}$  concentration (in M)

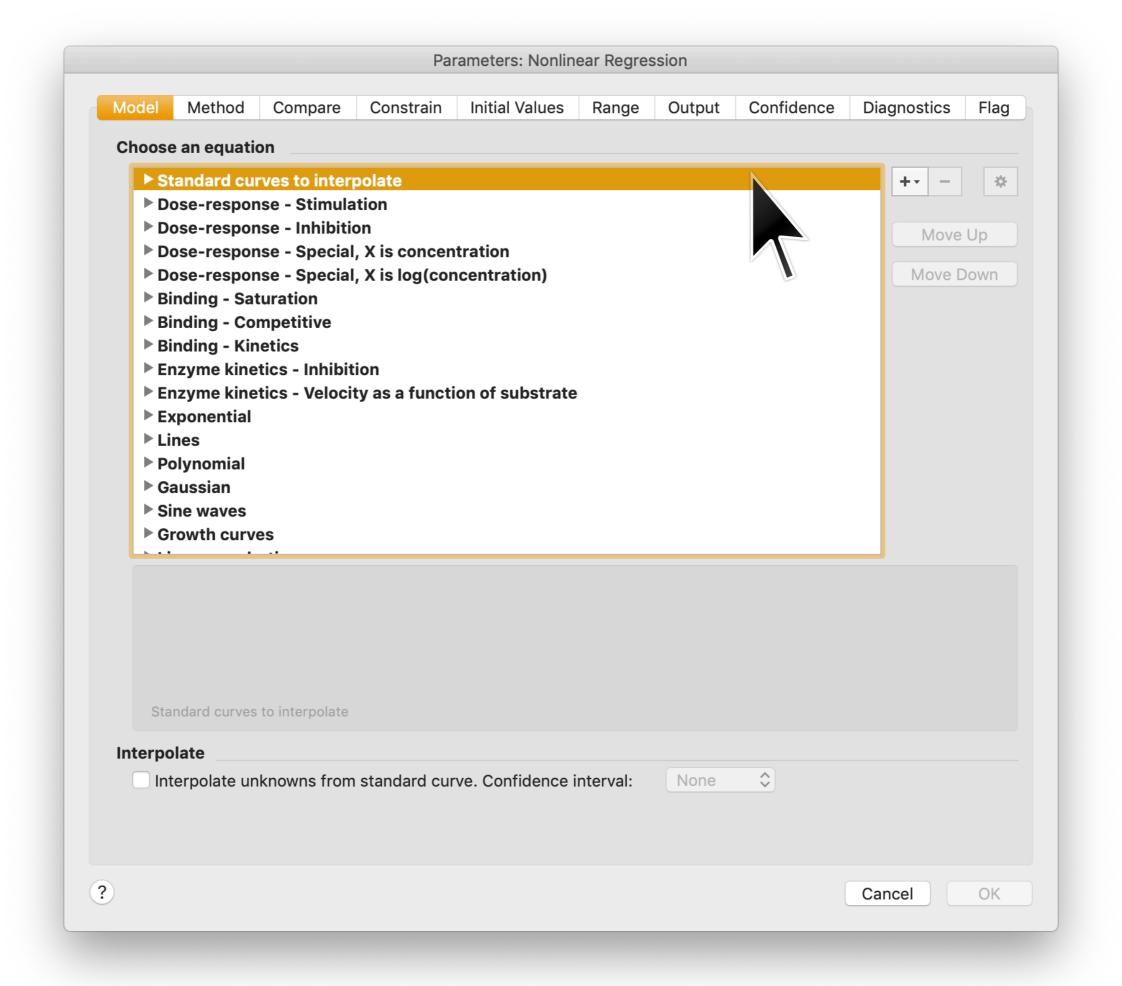
y: percent muscle relaxation

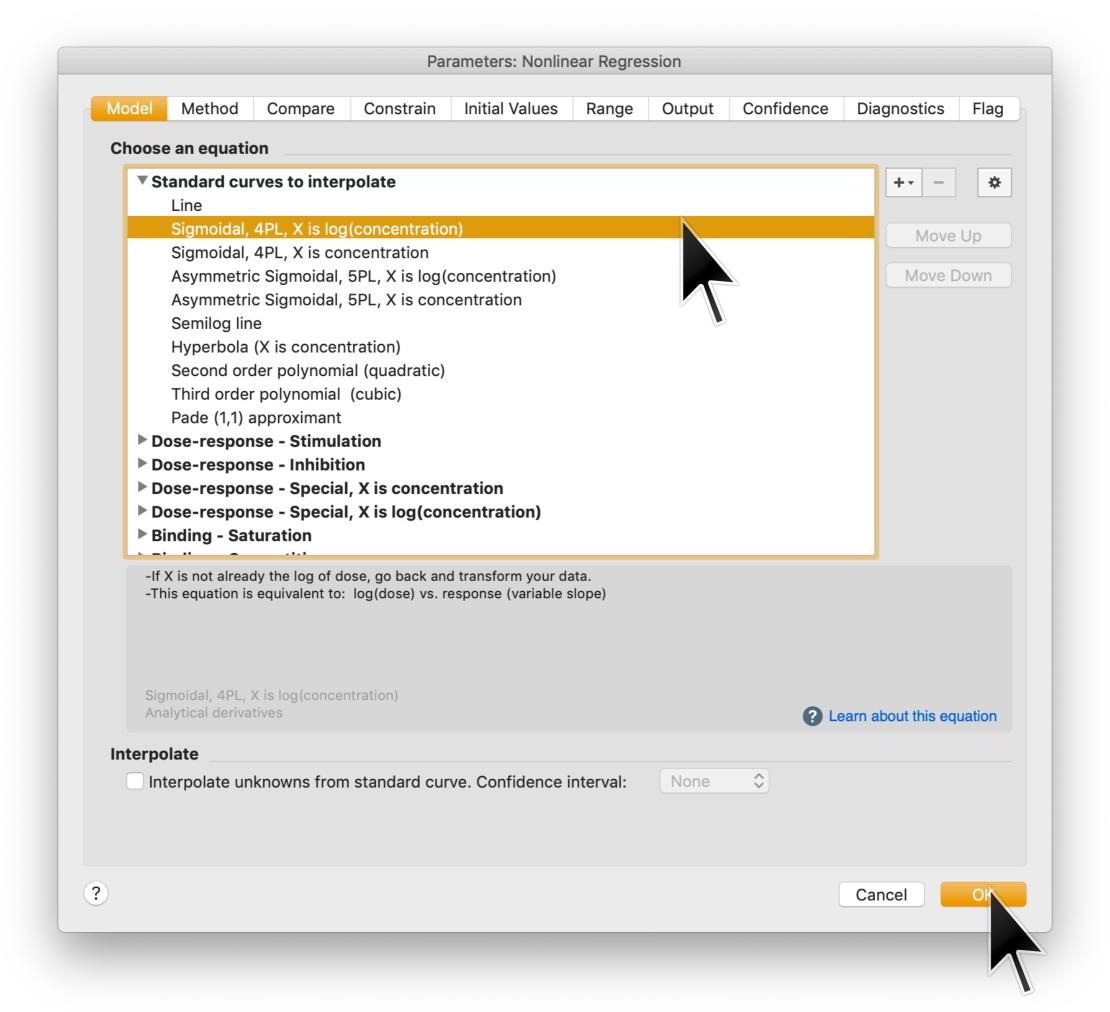


$$f(x) = bottom + \frac{top - bottom}{1 + 10^{(\log C50 - x) \cdot hillSlope}}$$



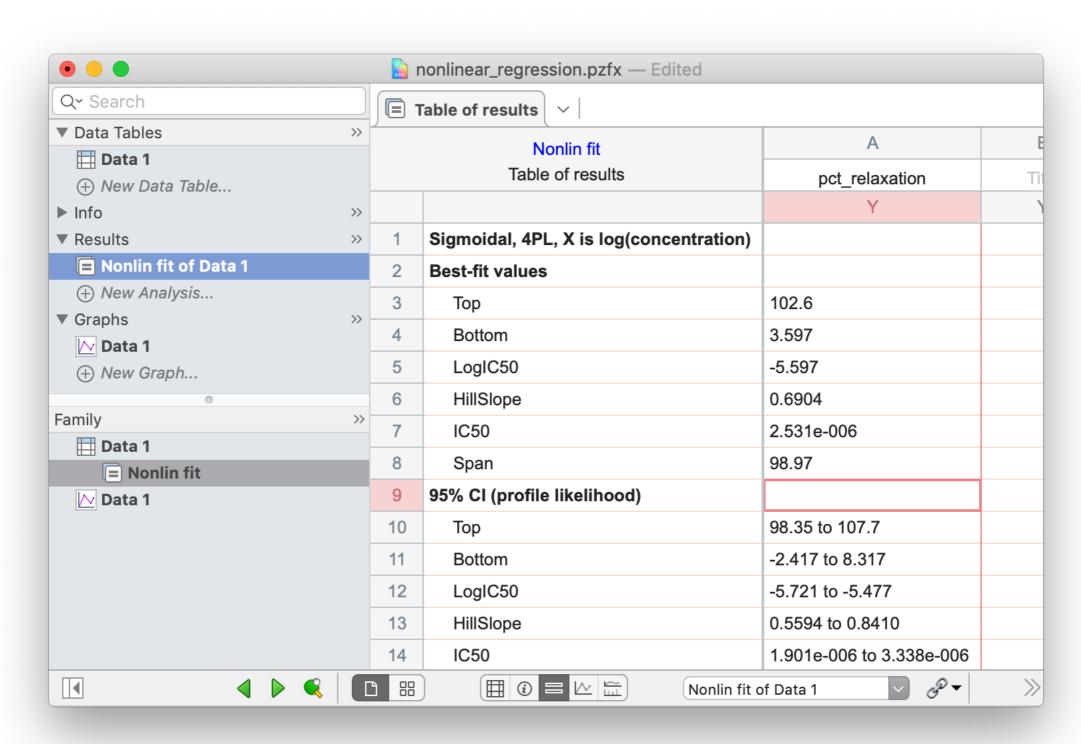






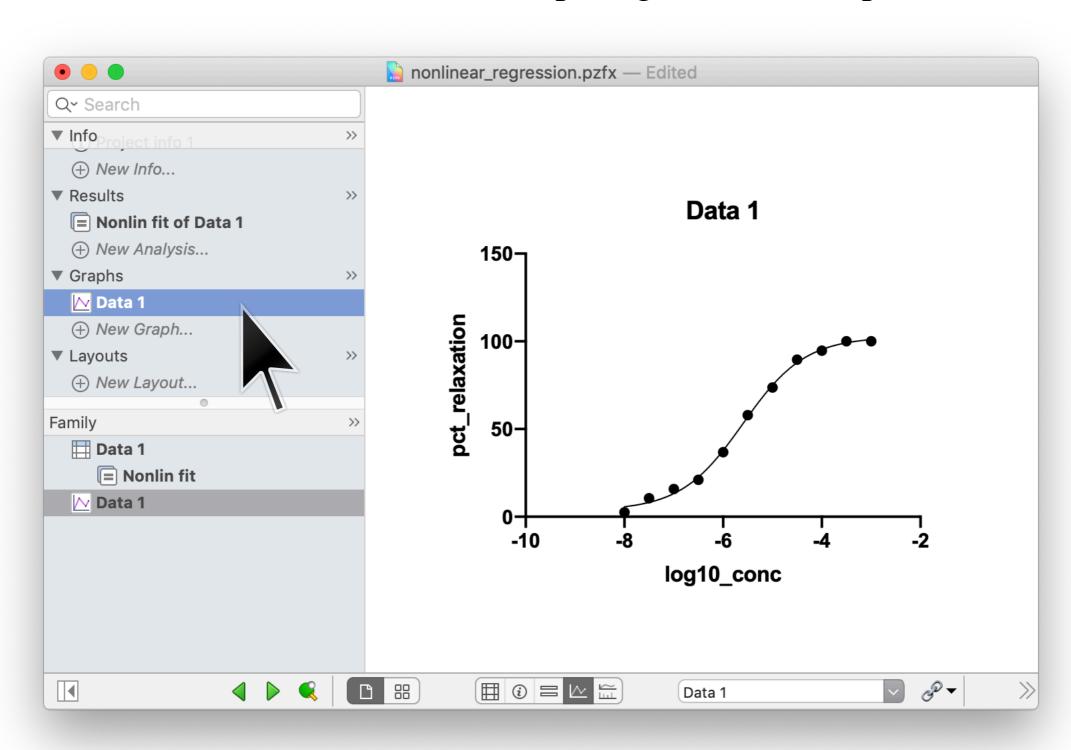
$$y = Bottom + \frac{Top - Bottom}{1 + 10^{(LogIC50 - x) \cdot HillSlope}}$$

## 4 parameters: Bottom, Top, LogIC50, HillSlope



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

4 parameters: Bottom, Top, LogIC50, HillSlope





# Multiple linear regression is used to model a <u>continuous number</u> that depends on <u>multiple covariates</u>

Multiple linear regression (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 "covariates".

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  $\epsilon_i$  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 <u>probabilities</u> 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  $\vec{x}_i = (x_{i1}, x_{i2}, ..., x_{iD})$  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  $\vec{x}_i$ :

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

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.



#### **NEW TABLE & GRAPH**

XY

. .

Column

Grouped

Contingency

Survival

Parts of Whole

Multiple variables

Nested

#### **EXISTING FILE**

Open a File

LabArchives

Clone a Graph

**Graph Portfolio** 

Multiple variable tables: Each column represents a different variable. Each row represents a different individual or experimental unit

| ₫ |       | Variable A | Variable B | Variable C |
|---|-------|------------|------------|------------|
|   |       | Sales      | Income     | Avg        |
|   |       | Y          | Y          | Y          |
| 1 | Title |            |            |            |
| 2 | Title |            |            |            |
| 3 | Title |            |            |            |

? Learn more

#### Data table:

- Enter or import data into a new table
- Start with sample data to follow a tutorial

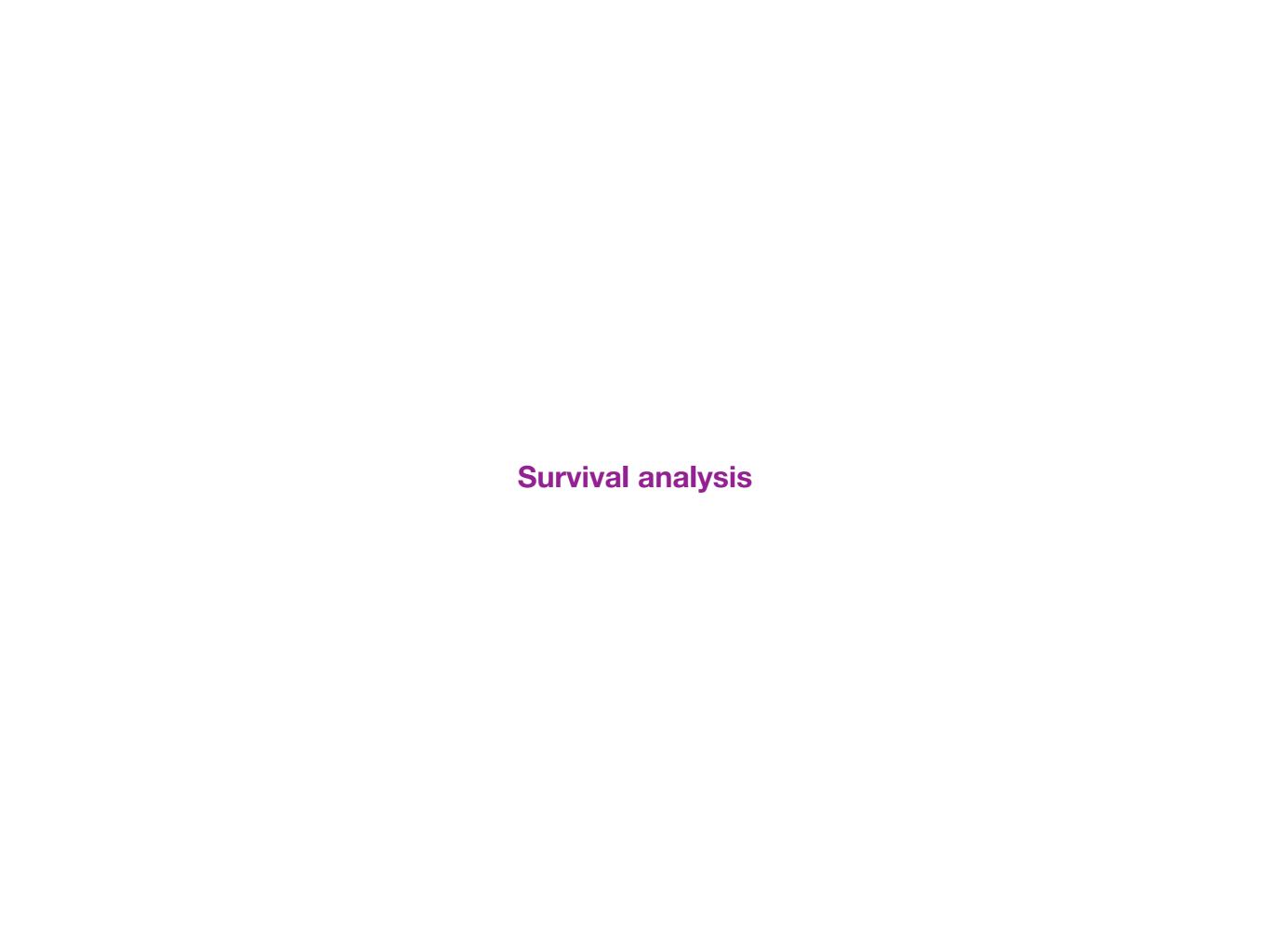
#### Select a tutorial data set:

Multiple linear regression
Multiple logistic regression
Son regression
Cyrrelation matrix

Prism Tips

Cancel

Create



## The Survival function S(t)

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 <u>hazard function</u> 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

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

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  $S(t) = e^{-H(t)}$ .

#### Estimating the survival function: no censoring

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.

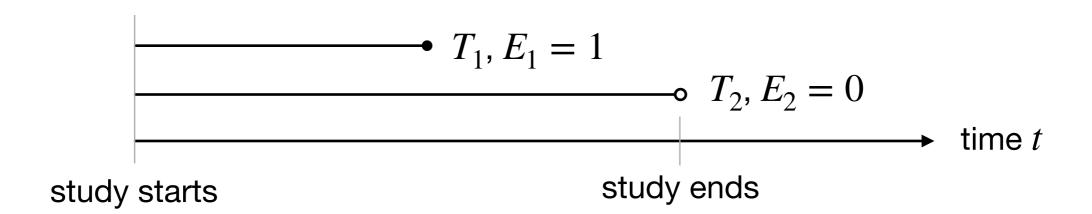
$$\hat{S}(t) = \frac{n(t)}{n(0)}$$

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

#### **Right censoring**

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 occurs for many different reasons**

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.

#### The Kaplan-Meier estimator is the standard way to estimate survival curves

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 at risk 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:

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

## Use the log-rank test to compare two survival curves

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  $\chi^2$  distribution with 1 degree of freedom.

Search Results > Study Record Detail ☐ Save this study Home >

#### 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 6 : Completed First Posted 1 : January 27, 2003 Last Update Posted 3: April 29, 2020

Study Description

Go to

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 | Intervention/treatment ①                  | Phase 1 |
|----------------------|---|---------|
| 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.



#### **NEW TABLE & GRAPH**

XY

. .

Column

Grouped

Contingency

Survival

Parts of Whole

Multiple variables

Nested

#### **EXISTING FILE**

Open a File

LabArchives

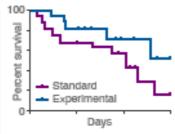
Clone a Graph

**Graph Portfolio** 

#### Welcome to GraphPad Prism

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

| Table format |        | X    | A        |  |
|--------------|--------|------|----------|--|
| Su           | rvival | Days | Standard |  |
|              |        | X    | Υ        |  |
| 1            | Title  |      |          |  |
| 2            | Title  |      |          |  |
| 3            | Title  |      |          |  |
| 4            | Title  |      |          |  |



? Learn more

#### Data table:

- Enter or import data into a new table
- O Start with sample data to follow a tutorial

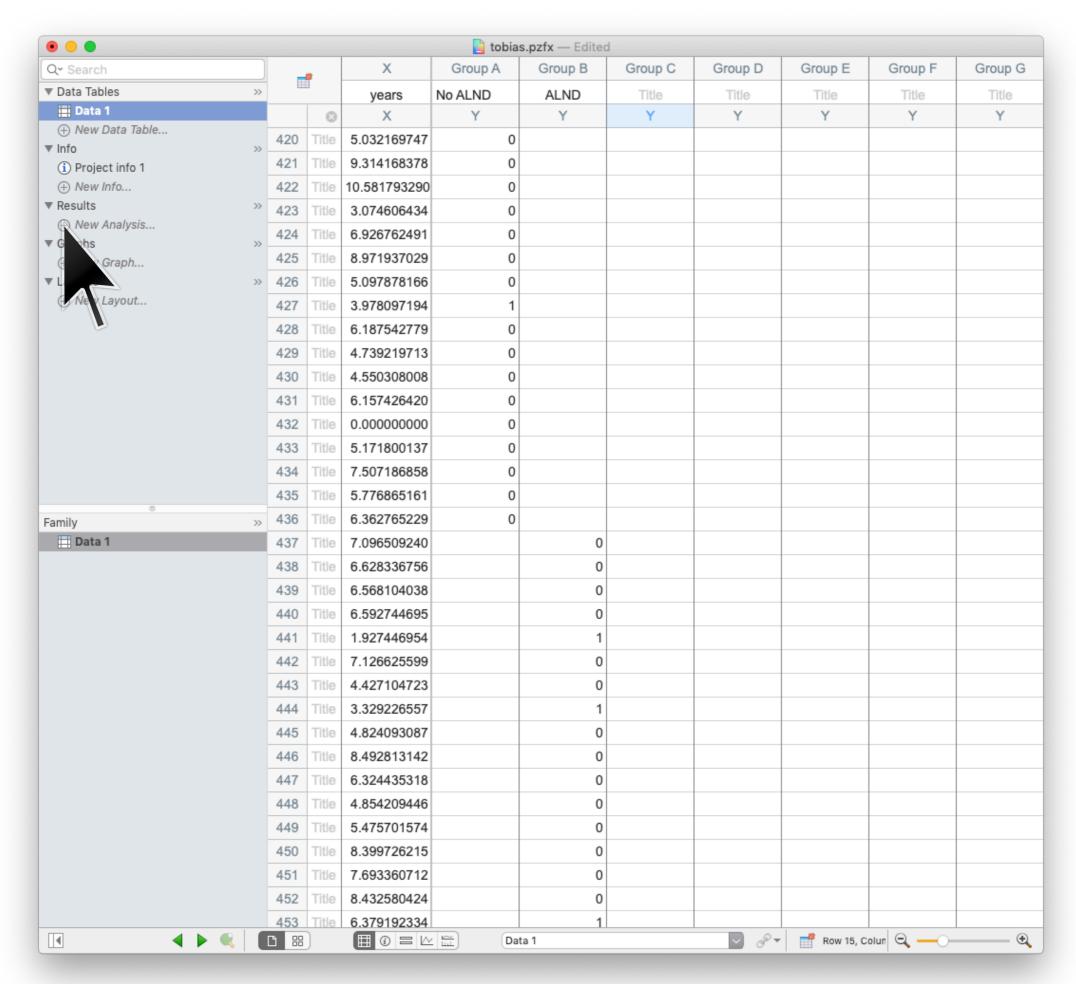
#### Select a tutorial data set:

- O Comparing two groups
- Three groups

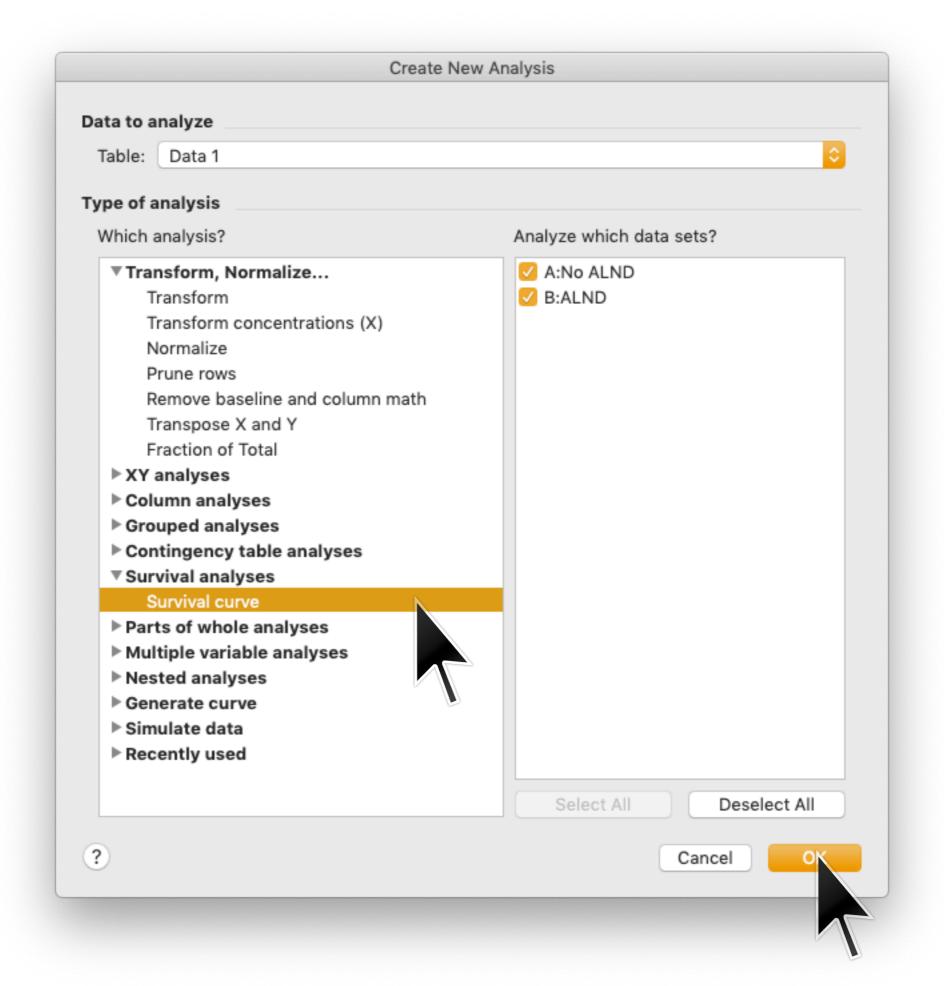
Prism Tips

Cancel

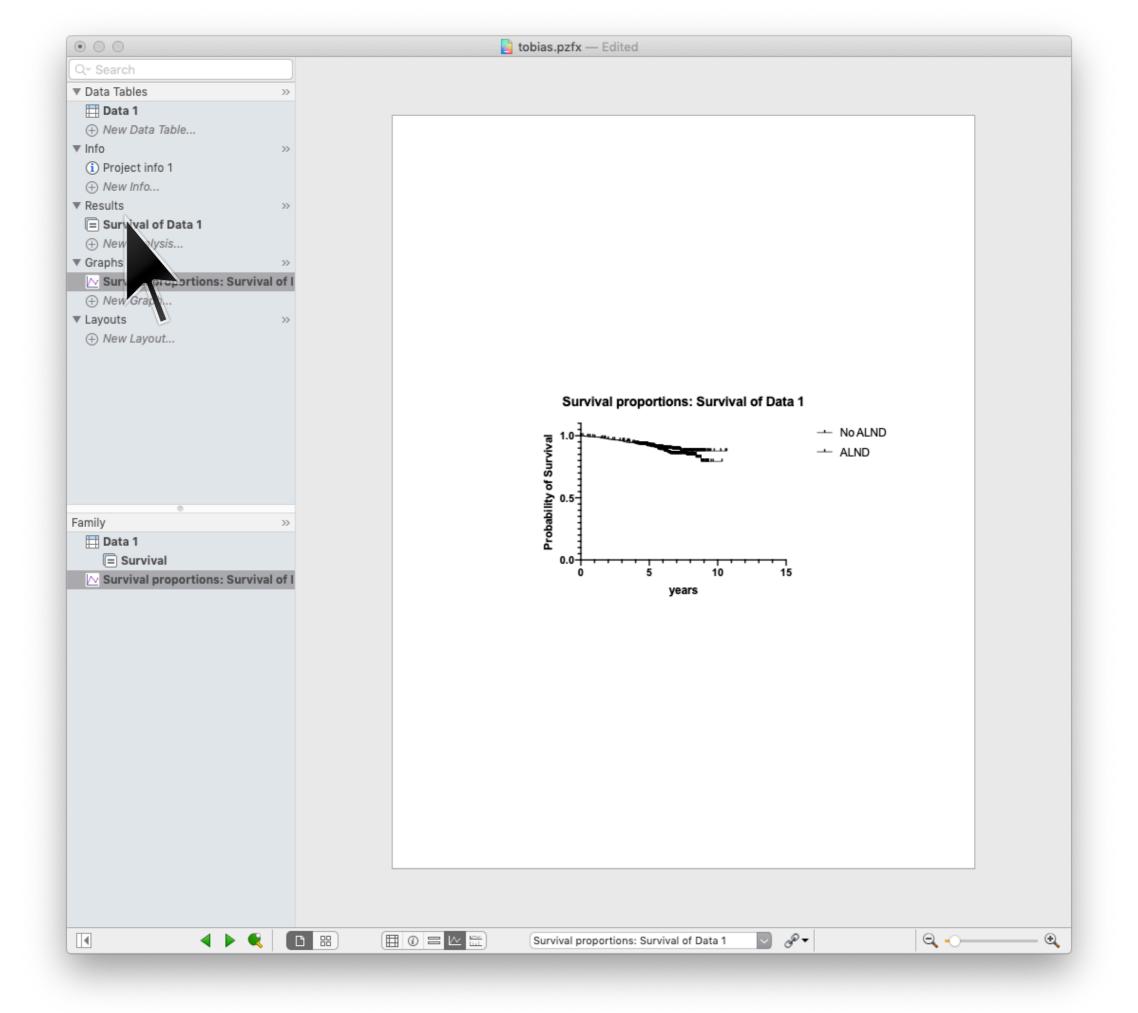
Create

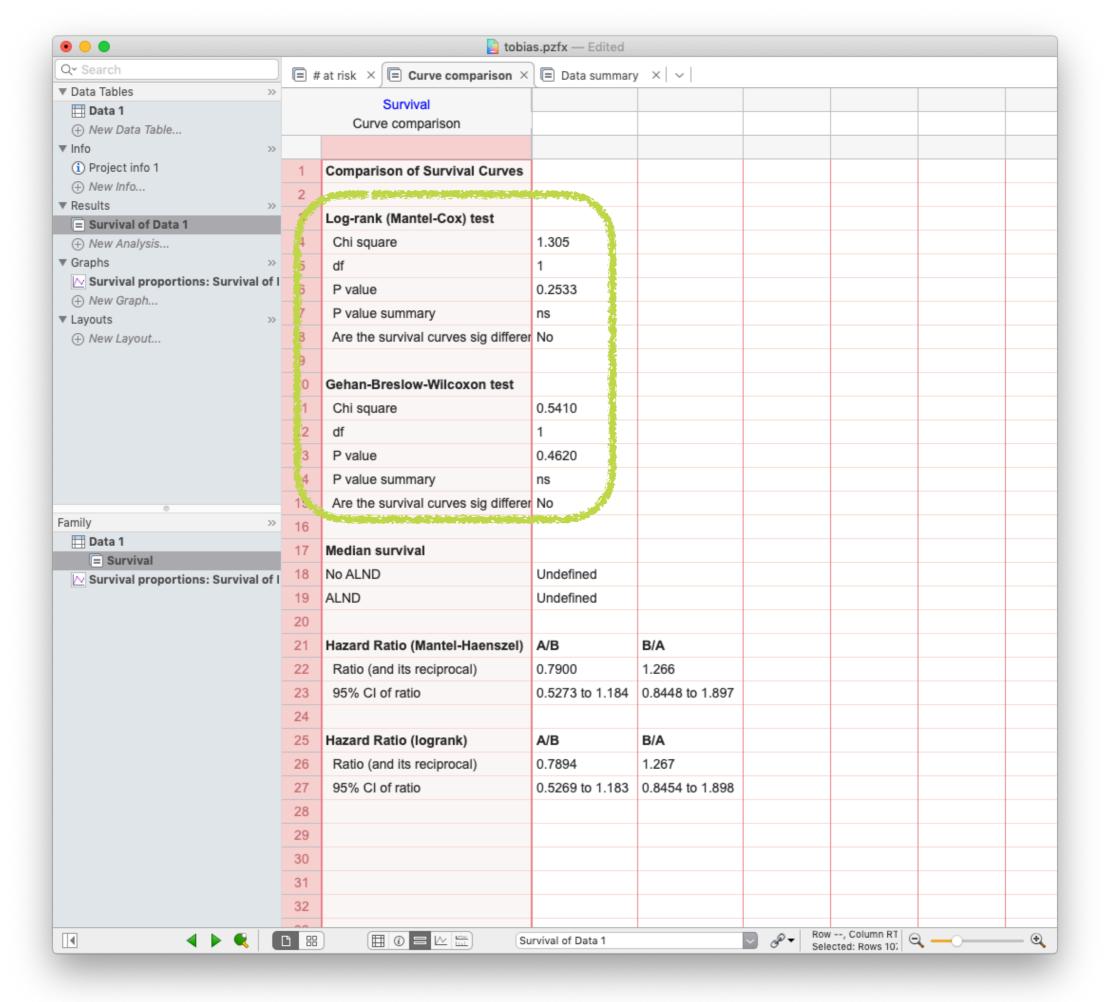


(data curtsey of Tobias Janowitz)



| Parameters: Survival Curve  |   |  |  |  |  |  |  |  |
|---|---|--|--|--|--|--|--|--|
| Innut   |   |  |  |  |  |  |  |  |
| The X values are time. The Y values are coded as follows:                     |   |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |
| Death/Event: 1  |   |  |  |  |  |  |  |  |
| Note: All other Y values are ignor  | Censored subject:                                     |  |  |  |  |  |  |  |
| _   | eu  |  |  |  |  |  |  |  |
| Curve comparison  |   |  |  |  |  |  |  |  |
| Calculations to compare two U Logrank (Mantel-Cox te                          |   |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |
|   | on test (extra weight for early time points)          |  |  |  |  |  |  |  |
| Calculations to compare thre  Logrank   | Match SPSS and SAS (recommended)                      |  |  |  |  |  |  |  |
| ✓ Logrank test for trend  |   |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |
|   | on test (extra weight for early time points)          |  |  |  |  |  |  |  |
| Style   |   |  |  |  |  |  |  |  |
|   | urvival (Percent)                                     |  |  |  |  |  |  |  |
| Express fraction survival erro  | or bars as:   |  |  |  |  |  |  |  |
|   | SE  SE  SE  Asymmetrical (more accurate; recommended) |  |  |  |  |  |  |  |
| None  |   |  |  |  |  |  |  |  |
| Show censored subjects of   |   |  |  |  |  |  |  |  |
|   | on graph.   |  |  |  |  |  |  |  |
| Output  Show this many significant di   | gits (for everything except P values): 4              |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |
| P Value Style: GP: 0.1234 (ns), 0.0332 (*), 0.0021 (**), 0.0002 (***), <0.000 |   |  |  |  |  |  |  |  |
| Use these settings as the default for future survival analyses                |   |  |  |  |  |  |  |  |
| ? Cancel OK   |   |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |





## The Cox proportional hazards model is the most common way to analyze how different variables influence survival

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  $\beta_j$  is the "effect size" for the corresponding covariate  $x_{\cdot j}$ . If the value for  $\beta_j$  is significantly different than 0, it means that the covariate  $x_{\cdot j}$  effects survival.

## **Example: Rossi recidivism dataset**

#### 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
               27
    age
               1
    race
    wexp
    mar
    paro
                3
    prio
```

#### 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.

## **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**

```
# Load and preview Rossi dataset
from lifelines.datasets import load_rossi
rossi_df = load_rossi()
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(coe      | f) 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            |           |           |
| statistical  | race 1.02    | 0.31    | 1.70            |           |           |
| significance | wexp $-0.71$ | 0.48    | 1.06            |           |           |
| e.g          | mar -1.14    | 0.26    | 1.97            |           |           |
|              | paro -0.43   | 0.66    | 0.59            |           |           |
|              | prio 3.19 <  | 0.005   | 9.48            |           |           |

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,  $\chi^2$  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.

