DESIGN OF EXPERIMENTS FOR NON-LINEAR MODELS

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Model - Design - Analysis

Model

Model of the observation y

$$y = \eta(x, \vartheta) + \varepsilon,$$

x denotes a set of experimental conditions,
$\vartheta = (\vartheta_1, \ldots, \vartheta_p)^{\mathrm{T}}$ denotes a vector of unknown parameters,
ε denotes an observational error, a random variable.

Design tells what experimental conditions x (what levels) should we use in the study.

Analysis is based on the observations y.
Hence, it depends on

- the design (x),
- the properties of the errors (ε),
- the structure of the model function (η).

Linear Models

$$\eta(x,\vartheta) = f_1(x)\vartheta_1 + \ldots + f_p(x)\vartheta_p$$

That is,

$$y = f(x)^{\mathrm{T}}\vartheta + \varepsilon,$$

where

$$f(x)^{\mathrm{T}} = \big(f_1(x),\ldots,f_p(x)\big), \quad \vartheta = \begin{pmatrix} \vartheta_1 \\ \vdots \\ \vartheta_p \end{pmatrix}$$

or in matrix notation (to include all observations)

$$Y = X\vartheta + \epsilon,$$

where

$$Y = \begin{pmatrix} y_1 \\ \vdots \\ y_n \end{pmatrix}, \quad X = \begin{pmatrix} f_1(x_1)\ldots f_p(x_1) \\ \vdots \\ f_1(x_n)\ldots f_p(x_n) \end{pmatrix}, \quad \epsilon = \begin{pmatrix} \varepsilon_1 \\ \vdots \\ \varepsilon_n \end{pmatrix}.$$

Linear Models

Assumption: $\epsilon \sim \mathcal{N}_n(0, V)$

Then, the Maximum Likelihood estimator of ϑ is normally distributed

$$\hat{\vartheta} \sim \mathcal{N}_p(\vartheta, (X^{\mathrm{T}} V^{-1} X)^{-1}).$$

The model assumption about errors and the form of matrix X (design) are involved in the analysis.

Example 1

Growth Rate

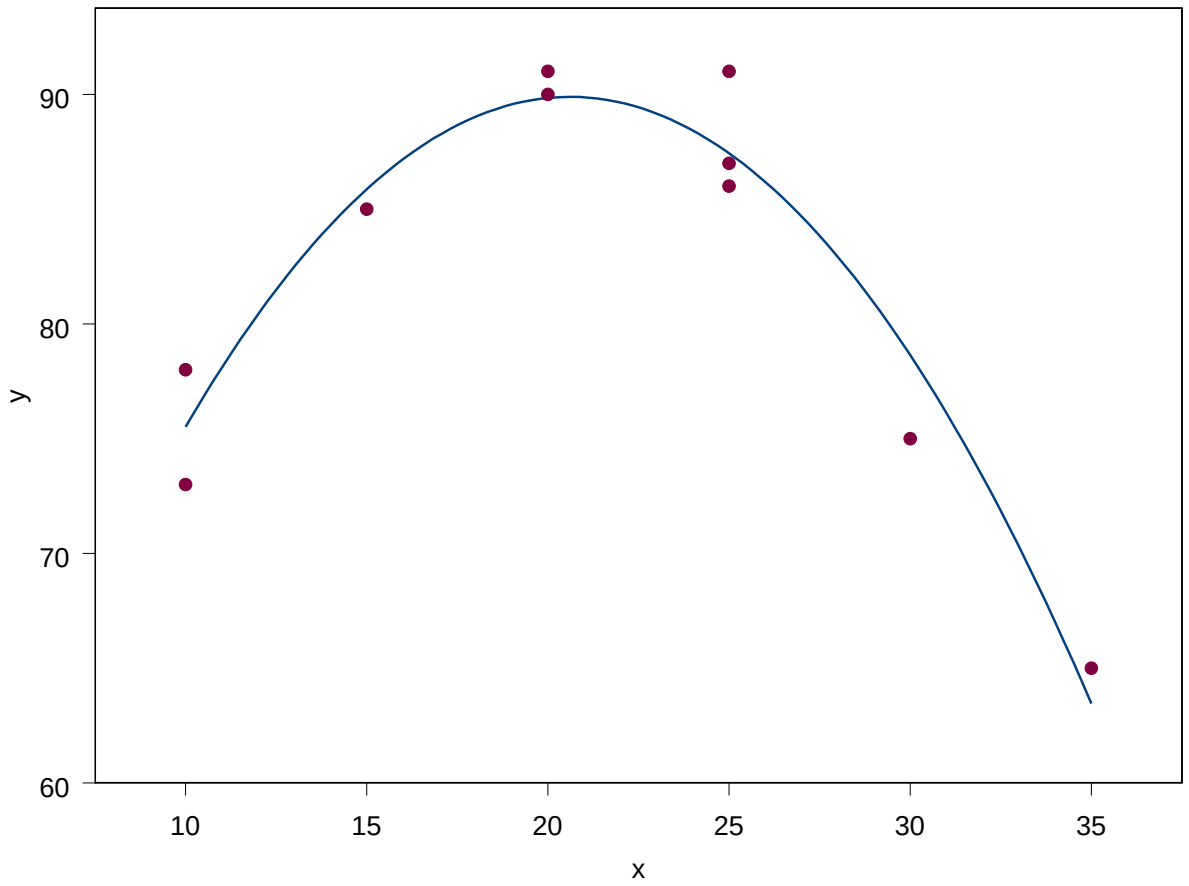
Ten experimental rats were fed with various doses of a dietary supplement and a growth rate was observed. The data are given in the table below.

amount of supplement [g]	growth rate [coded]
10	73
10	78
15	85
20	90
20	91
25	87
25	86
25	91
30	75
35	65

Example 1

Growth Rate

The data and the fitted quadratic polynomial are shown in the figure below.



Example 1

Growth Rate

A few design questions:

1. Why these particular doses were used?
2. What was known about the plausible response before the experiment was performed?
3. Could the doses be selected in a better way?
4. How to decide what doses to select and apply?

Example 1

Growth Rate - Quadratic Regression

$$\eta(x,\vartheta) = \vartheta_1 + \vartheta_2 x + \vartheta_3 x^2 = f(x)^{\mathrm{T}}\vartheta$$

Here,

$$f(x)^{\mathrm{T}} = (1, x, x^2), \qquad \vartheta = \begin{pmatrix} \vartheta_1 \\ \vartheta_2 \\ \vartheta_3 \end{pmatrix}.$$

Then, matrix X is as follows.

$$X = \begin{pmatrix} f(x_1)^{\mathrm{T}} \\ f(x_2)^{\mathrm{T}} \\ \vdots \\ f(x_n)^{\mathrm{T}} \end{pmatrix} = \begin{pmatrix} 1 & x_1 & x_1^2 \\ 1 & x_2 & x_2^2 \\ \vdots & \vdots & \vdots \\ 1 & x_n & x_n^2 \end{pmatrix}.$$

Example 1

Growth Rate - Quadratic Regression

Assuming that $\epsilon \sim \mathcal{N}_n(0, \sigma^2 I)$, the variance-covariance matrix of the ML estimator of ϑ is

$$\begin{aligned}
\mathrm{Var}(\widehat{\vartheta}) &= \left(\frac{1}{\sigma^2} X^{\mathrm{T}} X\right)^{-1} \\
&= \sigma^2 \left\{ \begin{pmatrix} 1 & \dots & 1 \\ x_1 & \dots & x_n \\ x_1^2 & \dots & x_n^2 \end{pmatrix} \times \begin{pmatrix} 1 & x_1 & x_1^2 \\ \vdots & \vdots & \vdots \\ 1 & x_n & x_n^2 \end{pmatrix} \right\}^{-1} \\
&= \sigma^2 \begin{pmatrix} n & \sum_{i=1}^n x_i & \sum_{i=1}^n x_i^2 \\ \sum_{i=1}^n x_i & \sum_{i=1}^n x_i^2 & \sum_{i=1}^n x_i^3 \\ \sum_{i=1}^n x_i^2 & \sum_{i=1}^n x_i^3 & \sum_{i=1}^n x_i^4 \end{pmatrix}^{-1}.
\end{aligned}$$

We would like to make it “somehow small”.

Note that, the matrix depends on the design variable x.

X is so called **design matrix** and the **design** is the set of x values

$$\xi = \{x_1 \; x_2 \; \ldots \; x_n\} = \left\{ \begin{array}{cccc} x_1 & x_2 & \ldots & x_s \\ \frac{r_1}{n} & \frac{r_2}{n} & \ldots & \frac{r_s}{n} \end{array} \right\},$$

where r_i are **replications** of the **support points** x_i of the design such that

$$\sum_{i=1}^{s} r_i = n, \quad r_i > 0.$$

Example 2

A linear model for an experiment with 5 treatments and 3 blocks of size 4

Let the allocation of treatments to blocks be following

block 1	1	2	3	5
block 2	1	4	3	2
block 3	5	1	4	2

The linear model may be written as

$$y_{ij} = \mu + \tau_i + \beta_j + \varepsilon_{ij},$$

where
μ denotes the general mean,
τ_i denotes an effect of i-th treatment, $i = 1, \ldots, 5$,
β_j denotes an effect of j-th block $j = 1, 2, 3$.

Example 2

A linear model for an experiment with 5 treatments and 3 blocks of size 4

block 1	1	2	3	5
block 2	1	4	3	2
block 3	5	1	4	2

Matrix X and vector ϑ are the of the form

$$Y = \begin{pmatrix} y_{11} \\ y_{12} \\ y_{13} \\ y_{21} \\ y_{22} \\ y_{23} \\ y_{31} \\ y_{32} \\ y_{42} \\ y_{43} \\ y_{51} \\ y_{53} \end{pmatrix}, \quad X = \left(\begin{array}{c|cccc|ccc} 1 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{array}\right), \quad \vartheta = \begin{pmatrix} \mu \\ \tau_1 \\ \tau_2 \\ \tau_3 \\ \tau_4 \\ \tau_5 \\ \beta_1 \\ \beta_2 \\ \beta_3 \end{pmatrix}.$$

Example 2

A linear model for an experiment with 5 treatments and 3 blocks of size 4

block 1	1	2	3	5
block 2	1	4	3	2
block 3	5	1	4	2

The so called **incidence matrix** N indicates the design as well

$$N = \begin{pmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 0 \\ 0 & 1 & 1 \\ 1 & 0 & 1 \end{pmatrix}.$$

Another form of presenting the design is following

$$\xi = \left\{ \begin{array}{cccccccccccc} \binom{1}{1} & \binom{1}{2} & \binom{1}{3} & \binom{2}{1} & \binom{2}{2} & \binom{2}{3} & \binom{3}{1} & \binom{3}{2} & \binom{4}{2} & \binom{4}{3} & \binom{5}{1} & \binom{5}{3} \\ \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} & \frac{1}{12} \end{array} \right\}$$

Non-linear models

$$y_j = \eta(x_j, \vartheta) + \varepsilon_j$$

Taylor series expansion of the model, at a prior ϑ^o, yields

$$\eta(x,\vartheta) = \eta(x,\vartheta^o) + f^{\mathrm{T}}(x,\vartheta^o)(\vartheta - \vartheta^o) + (\vartheta - \vartheta^o)^{\mathrm{T}} f..(x,\vartheta^o)(\vartheta - \vartheta^o) + \ldots$$

where

$$f^{\mathrm{T}}(x,\vartheta^o) = \left(\frac{\partial \eta(x,\vartheta)}{\partial \vartheta_1}, \frac{\partial \eta(x,\vartheta)}{\partial \vartheta_2}, \ldots, \frac{\partial \eta(x,\vartheta)}{\partial \vartheta_p} \right) \Big|_{\vartheta=\vartheta^o}$$

and $f..(x,\vartheta^o)$ is a matrix of second derivatives wrt to the parameters.

Then, a linear approximation of the model is

$$\eta(x,\vartheta) - \eta(x,\vartheta^o) = f^{\mathrm{T}}(x,\vartheta^o)(\vartheta - \vartheta^o)$$

or

$$\eta(x,\vartheta) = const + f^{\mathrm{T}}(x,\vartheta^o)\vartheta$$

Non-linear models

Differences between linear models and linearized non-linear models

1. $\hat{\vartheta} \sim \mathcal{N}_p(\vartheta, (X^{\mathrm{T}} V^{-1} X)^{-1})$ **asymptotically.**

2. Matrix $X = \begin{pmatrix} f(x_1, \vartheta^o)^{\mathrm{T}} \\ f(x_2, \vartheta^o)^{\mathrm{T}} \\ \vdots \\ f(x_n, \vartheta^o)^{\mathrm{T}} \end{pmatrix}$ depends on ϑ^o and on x.

3. The **non-linearity** of the model is ignored.

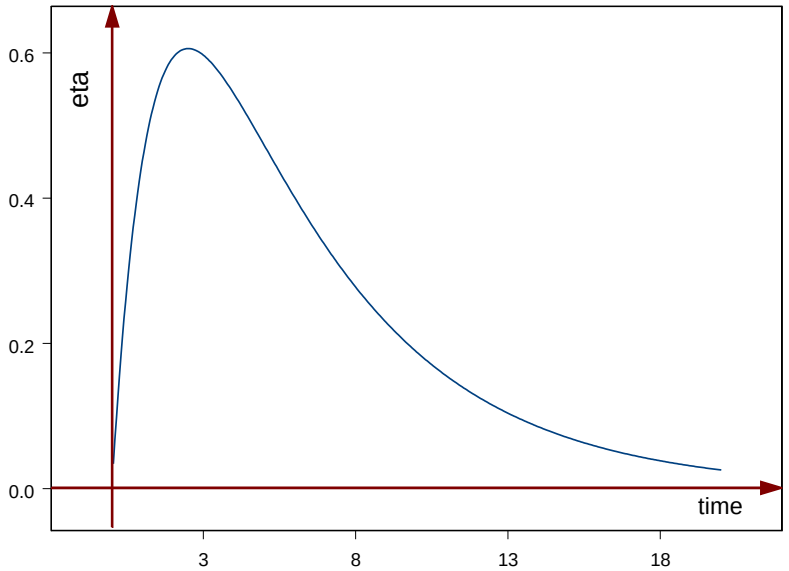
Example 3

One compartment PK model

Concentration of a drug in blood is often expressed in the form:

$$y = \underbrace{\frac{k_a}{(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right)}_{\eta(x,\vartheta)} + \varepsilon,$$

where k_a and k_e denote rates of absorption and elimination of the drug. Here, $x = t$, $\vartheta = (k_a, k_e)^{\mathrm{T}}$.

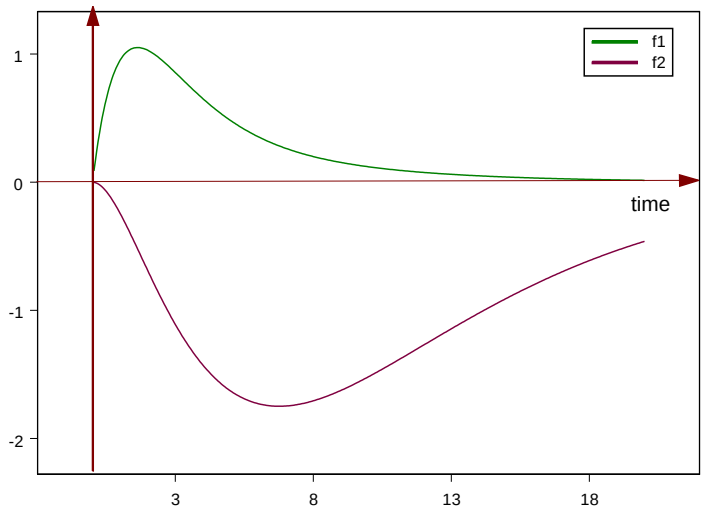


Example 3

One compartment PK model

In our example we have

$$f(x,\vartheta^o) = \begin{pmatrix} \frac{\partial \eta}{\partial k_a} \\ \\ \frac{\partial \eta}{\partial k_e} \end{pmatrix}_{\vartheta=\vartheta^o} = \begin{pmatrix} -\frac{1}{(k_a^o - k_e^o)}\left[\frac{k_e^o}{k_a^o - k_e^o}e^{-k_e^o t} - (tk_a^o + \frac{k_e^o}{k_a^o - k_e^o})e^{-k_a^o t}\right] \\ -\frac{k_a^o}{(k_a^o - k_e^o)}\left[\frac{1}{k_a^o - k_e^o}e^{-k_a^o t} - (t + \frac{1}{k_a^o - k_e^o})e^{-k_e^o t}\right] \end{pmatrix}$$



Partial Derivatives of η with respect to the parameters k_a and k_e at $k_a^o = 0.7$ and $k_e^o = 0.2$.

Example 3

One compartment PK model

Hence, the model can be written as (after linearization and adjusting for a constant)

$$y = k_a f_1(t, \vartheta^o) + k_e f_2(t, \vartheta^o) + \varepsilon,$$

where

$$f_1(t, \vartheta^o) = \frac{\partial \eta}{\partial k_a}\Big|_{\vartheta^o} \text{ and } f_2(t, \vartheta^o) = \frac{\partial \eta}{\partial k_e}\Big|_{\vartheta^o}.$$

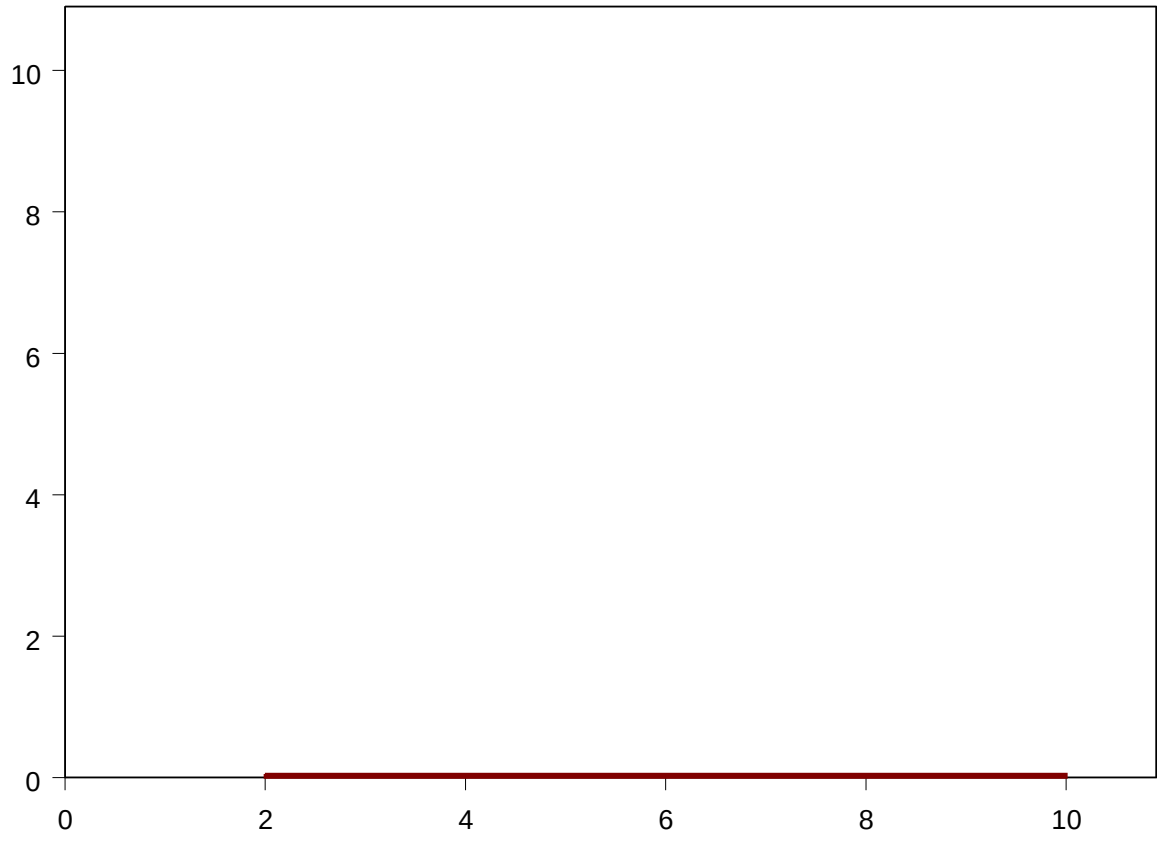
Compare it with a Simple Linear Regression model

$$y = \vartheta_1 + \vartheta_2 t + \varepsilon$$

in which

$$f_1 = 1, \quad f_2 = t.$$

What would be a good design for a SLR model?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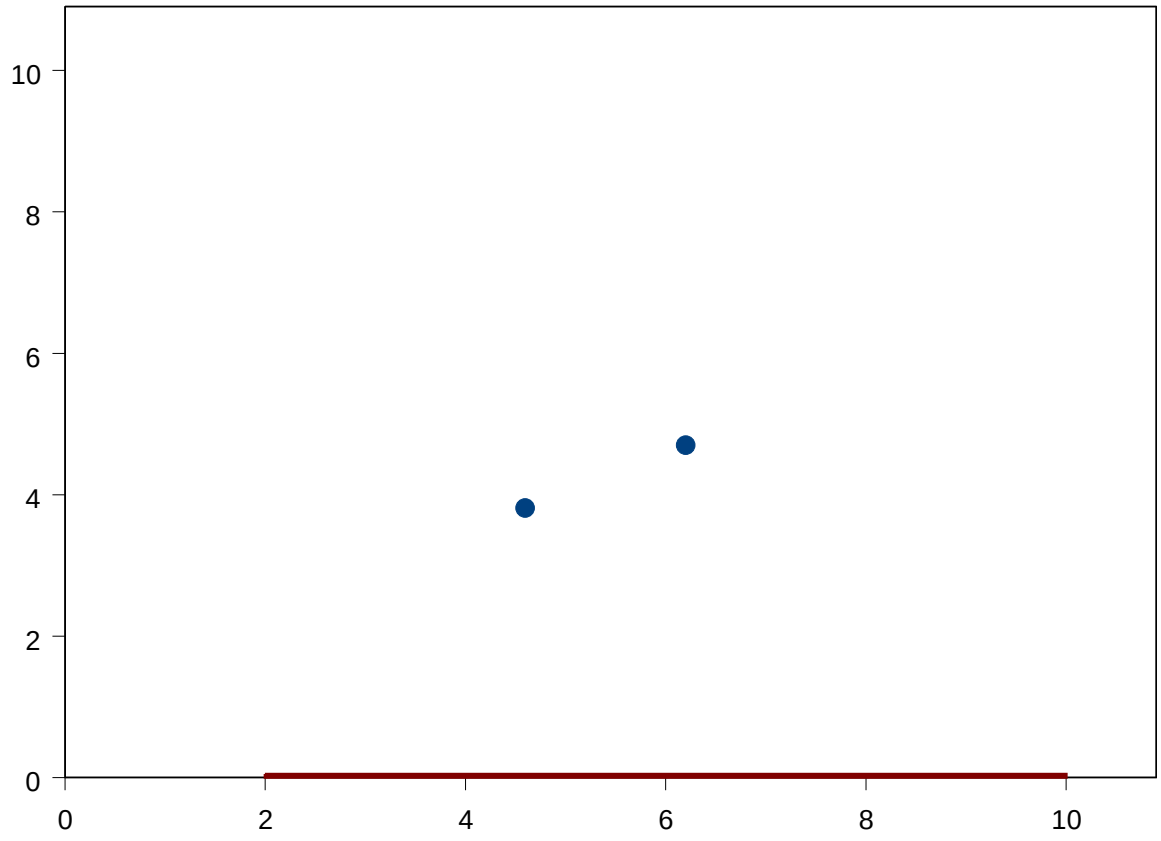
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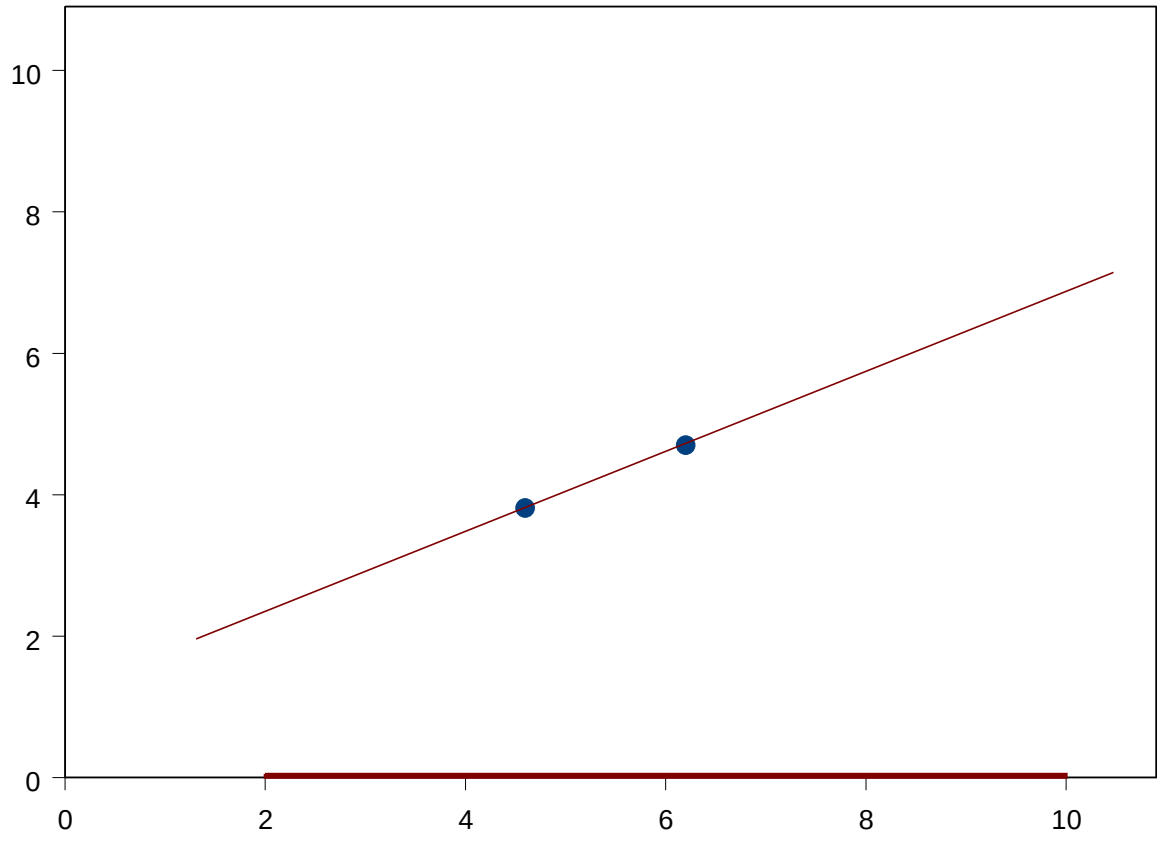
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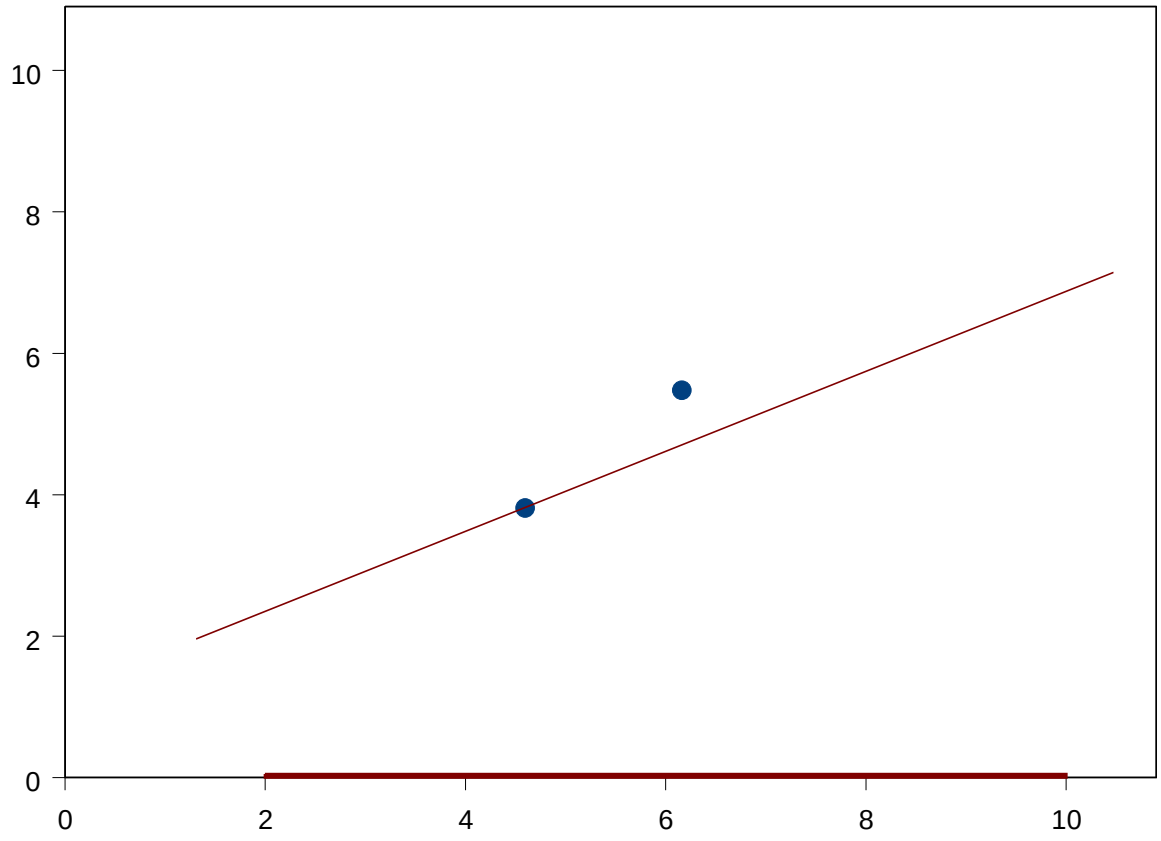
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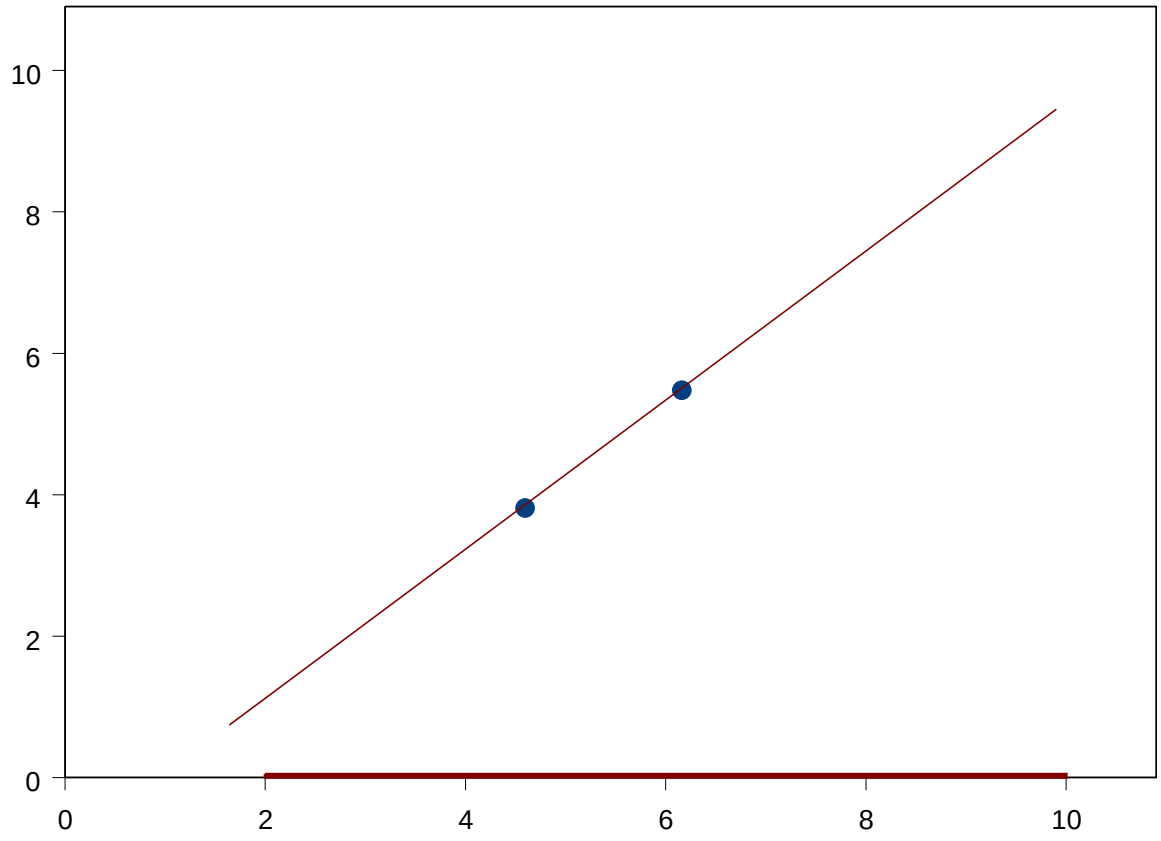
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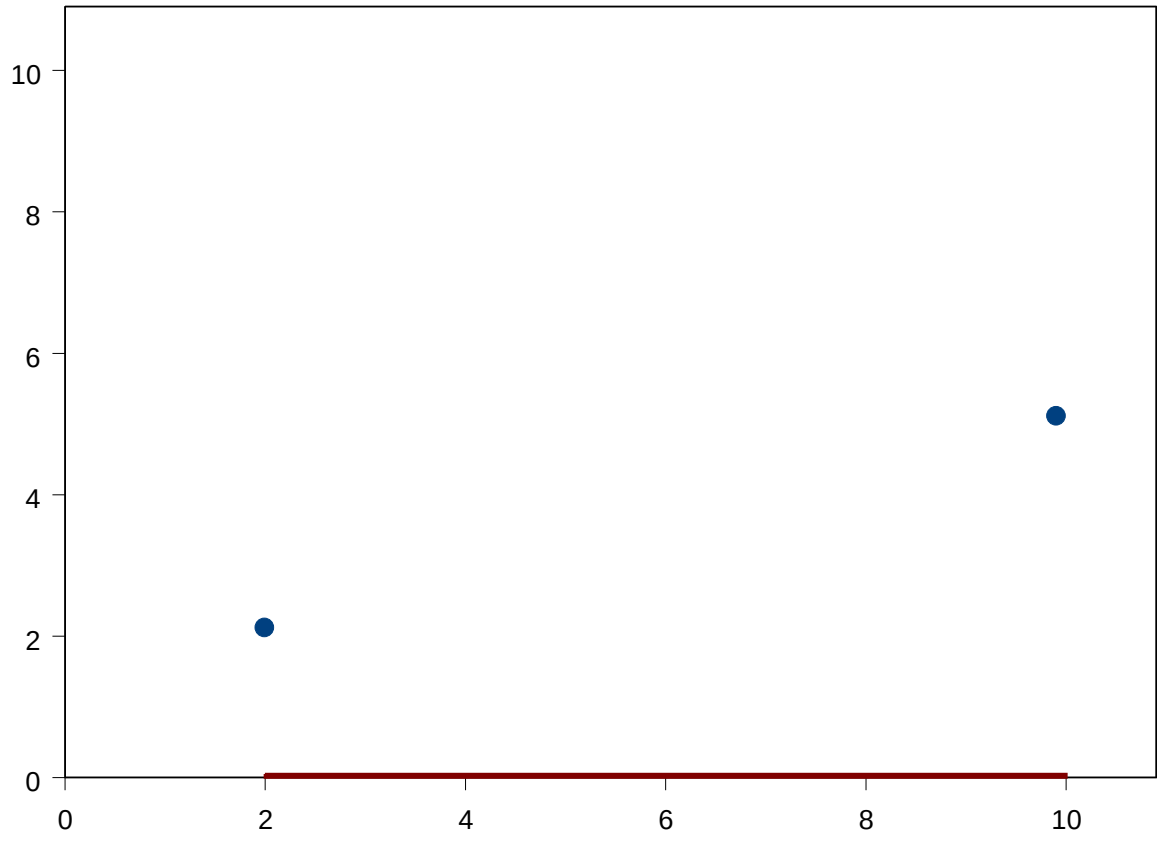
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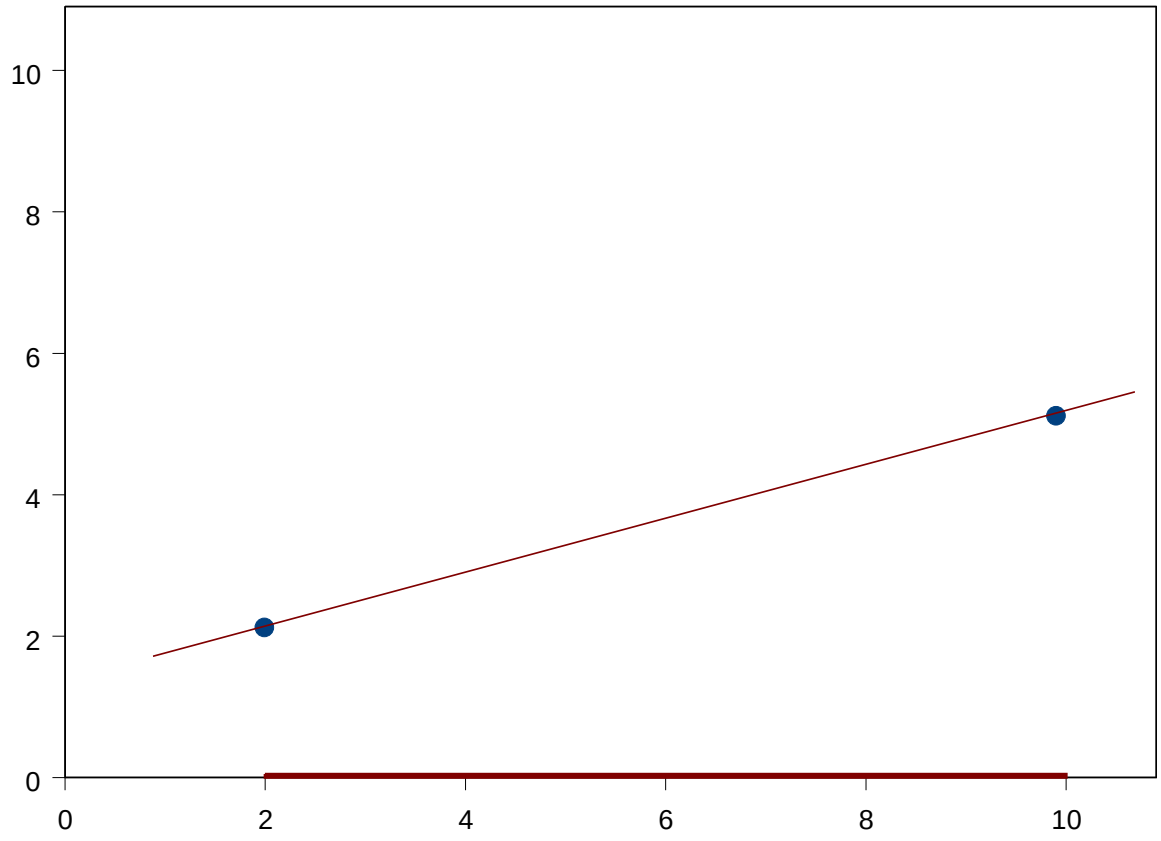
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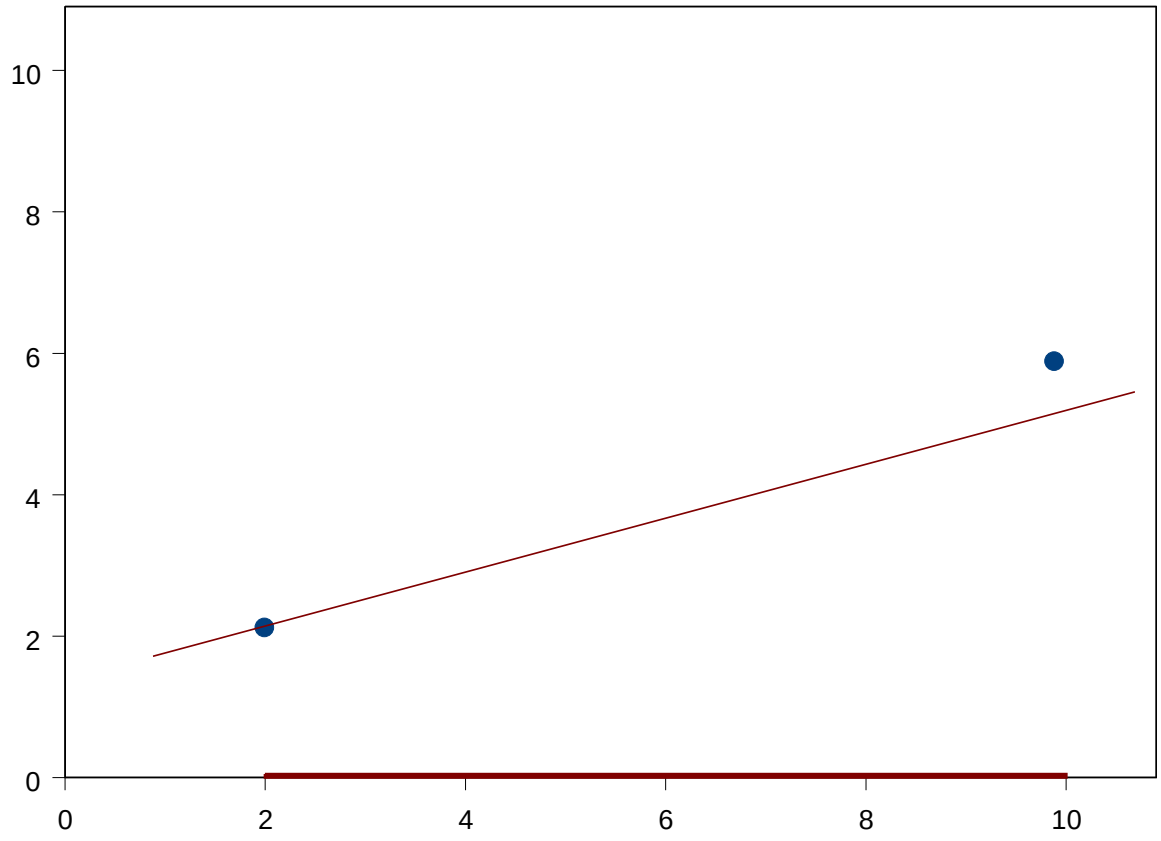
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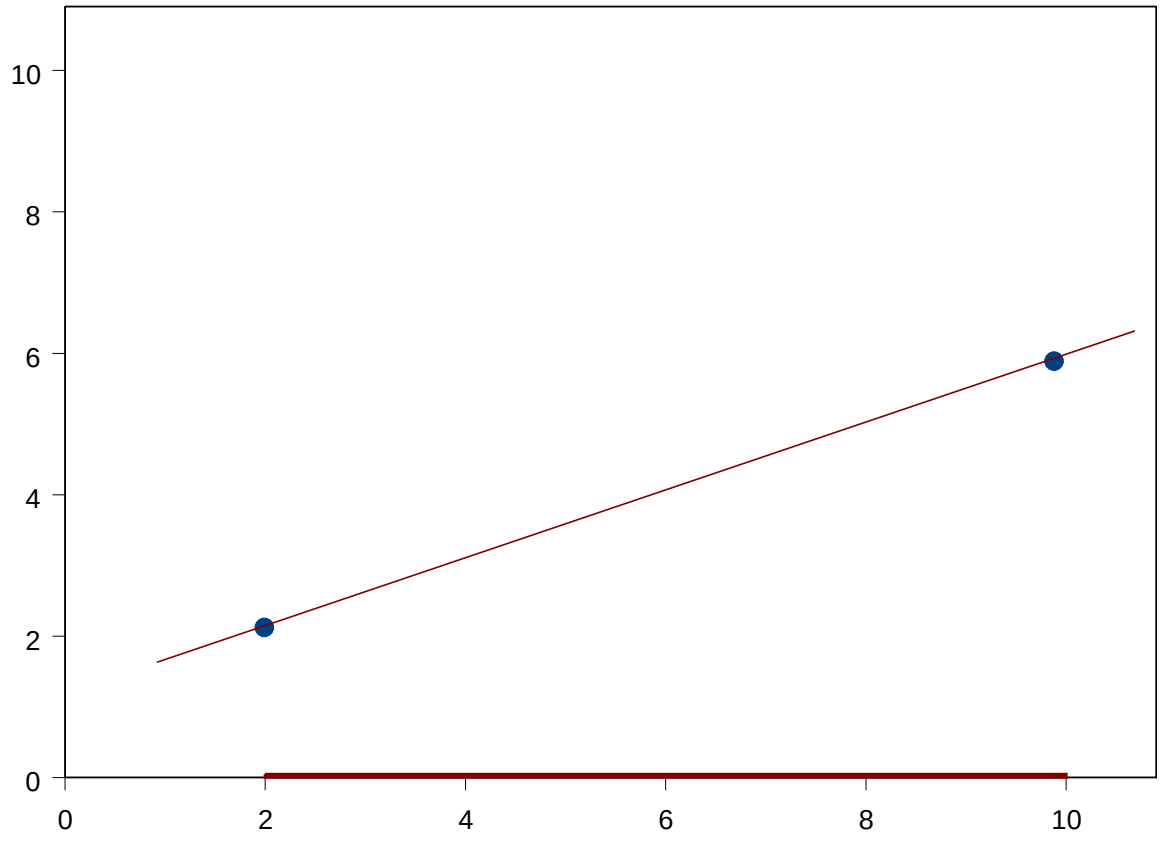
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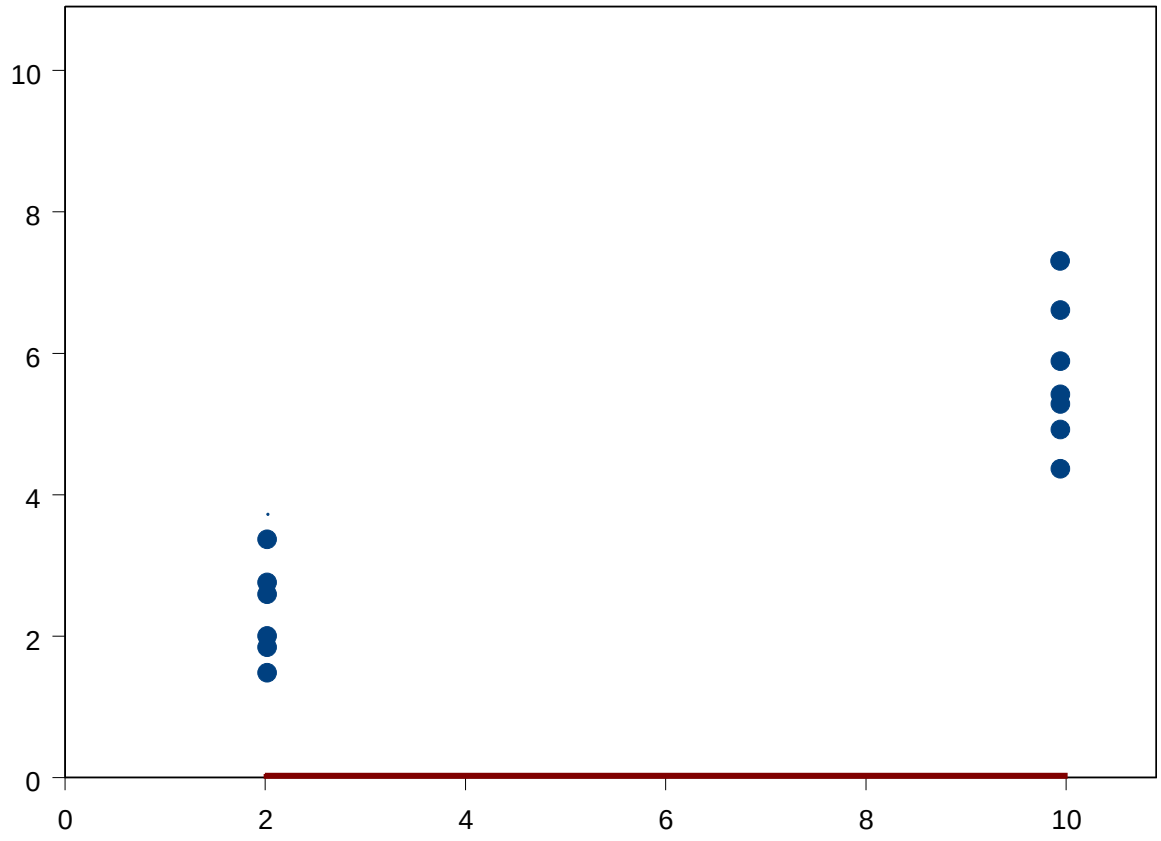
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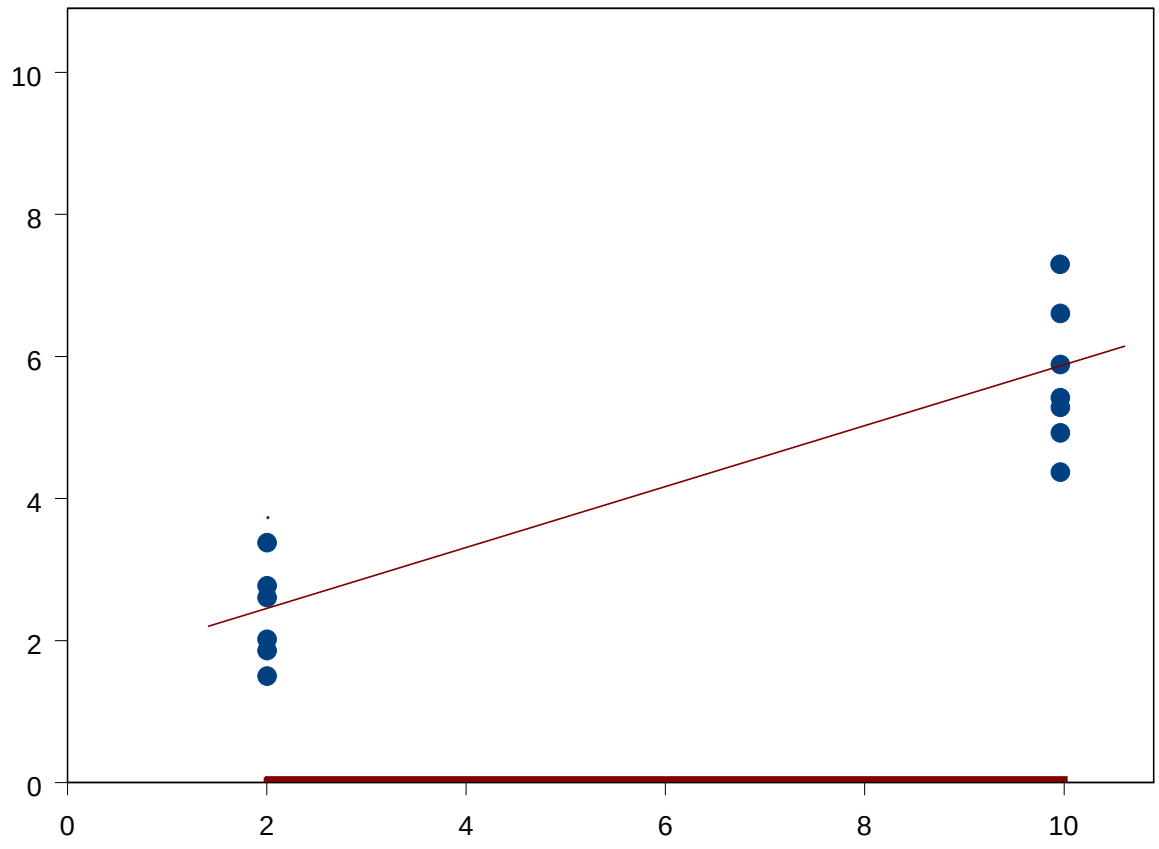

A well designed experimental data for fitting a SLR model.

Big Question

What is the best choice of the design points when the model is non-linear?

Purpose of an experiment - stats point of view

- estimation of the parameters and their functions (i.g. contrasts) and further testing statistical hypothesis (we know the family of models),
- model building (no information about the family of models),
- model discrimination (there are two or more plausible families of models),
- a combination of estimation and model discrimination,
- other.

What is a Design of Experiment?

A plan showing where/when to take observations during an experiment.

- Classical (combinatorial) design
  - way of allocating treatments to experimental units,
  - usually applied for linear models of observations,
  - treatment structure and unit structure have to be defined and matched.

What is a Design of Experiment?

- Continuous (approximate) design

$$\xi = \left\{ \begin{array}{cccc} x_1 & x_2 & \dots & x_s \\ w_1 & w_2 & \dots & w_s \end{array} \right\}$$

where

$$w_i > 0, \quad \sum_{i=1}^{s} w_i = 1.$$

  - probability measure on a discrete set of points,
  - usually applied to regression models, linear or non-linear,
  - treatments and units may not be so clear as they are in the combinatorial design.

Optimum Design of Experiments

- A **criterion** of design optimality has to be specified.
- The criterion will depend on the **purpose of the experiment** and on the **model**.
  - **When a general form of the model is known, then**
    - Purpose: estimation of unknown parameters or their functions, or hypothesis testing.
    - Design for **precision of estimation**.

How can we measure the precision of estimation?

- via variance and bias of the estimator

Optimum Design of Experiments

- **When there are several competing models, then**
  - Purpose:
    - **discrimination** between the models,
    - **estimation of the parameters and discrimination**.
  - Design: to optimize for most powerful discrimination and for precise estimation.
- **When there is no information about the model at all, then**
  - Purpose: to identify the model or some specific values of interest,
  - Design: to optimize for the specific objective.

Optimum Design of Experiments

Problems

- In linear models a combinatorial optimum design for a particular treatment and unit structures may not exist.
- In non-linear models it is possible to find an approximate (continuous) optimum design but it depends on
  - prior values of the unknown parameters,
  - curvature of the assumed model,
  - usually, there are no close form solutions.
- In any case, the optimum design depends on the assumptions regarding the variability and correlation of the observed response.

Criteria of design optimality

For parameter estimation

Most of the criteria for parameter estimation were introduced for linear models and are functions of the Fisher Information Matrix (FIM):

$$M = \left\{ \mathrm{E}\left(\frac{\partial L}{\partial \vartheta_i} \frac{\partial L}{\partial \vartheta_j} \right) \right\}_{i,j=1,\ldots,p},$$

where $L = \ln h(\vartheta; y)$ and $h(\vartheta; y)$ is the likelihood function for ϑ given y.

This comes from the (asymptotic) properties of ML estimators:

$$\widehat{\vartheta} \underset{approx.}{\sim} \mathcal{N}\left(\vartheta, M^{-1}\right).$$

Criteria of design optimality

For parameter estimation

For a normal linear model of observations

$$y \sim \mathcal{N}(X\vartheta, V),$$

the likelihood function is

$$h(\vartheta; y) = \frac{1}{(2\pi)^{n/2}\sqrt{|V|}} \exp\left\{-\frac{1}{2}(y - X\vartheta)^{\mathrm{T}} V^{-1}(y - X\vartheta)\right\}.$$

Hence,

$$L = const - \frac{1}{2}(y - X\vartheta)^{\mathrm{T}} V^{-1}(y - X\vartheta),$$

$$\frac{\partial L}{\partial \vartheta} = X^{\mathrm{T}} V^{-1}(y - X\vartheta),$$

and

$$M = \mathrm{E}\left[\frac{\partial L}{\partial \vartheta}\left(\frac{\partial L}{\partial \vartheta}\right)^{\mathrm{T}}\right] = \mathrm{E}\left[X^{\mathrm{T}} V^{-1}(y - X\vartheta)(y - X\vartheta)^{\mathrm{T}} V^{-1} X\right] = X^{\mathrm{T}} V^{-1} X.$$

Criteria of design optimality

For parameter estimation

For a nonlinear model of observations we have

$$X = \begin{bmatrix} f^{\mathrm{T}}(t_1, \vartheta^o) \\ \vdots \\ f^{\mathrm{T}}(t_n, \vartheta^o) \end{bmatrix}, \quad f^{\mathrm{T}}(t_i, \vartheta^o) = \left(\begin{array}{ccc} \frac{\partial \eta(t_i, \vartheta^o)}{\partial \vartheta_1} & \cdots & \frac{\partial \eta(t_i, \vartheta^o)}{\partial \vartheta_p} \end{array} \right)$$

$$\frac{\partial \eta(t_i, \vartheta)}{\partial \vartheta_j}, \quad \text{for } j = 1, \ldots, p, \ i = 1, \ldots, n$$

is called the parameter sensitivity.

Criteria of design optimality

For parameter estimation

Common Criteria (functions of FIM) introduced by Wald (1943), Elving (1952), Kiefer (1959), Kiefer (1975)

- **A** - minimises the average variance of contrasts of treatment effects
- **D** - minimises the volume of confidence ellipsoid for the unknown model parameters
- **E** - minimises the longest confidence interval among confidence intervals for all parameters
- **G** - minimises the variance of prediction of the model function
- **c** - minimises variance of a function of the parameters (i.e., AUC)
- Φ_p - a general class of criteria which includes A, D and E
- **Universal** - a very general convex function, includes even wider class of criteria.