

# Analysis of Clinical Trials with Biologics Using Dose-Time- Response Models



**Group 2**

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# Agenda

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- ❖ Background
- ❖ Methodology
- ❖ Dose-Time-Response Model
- ❖ Simulation
- ❖ Clinical Trail
- ❖ Evaluations

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# **Background**

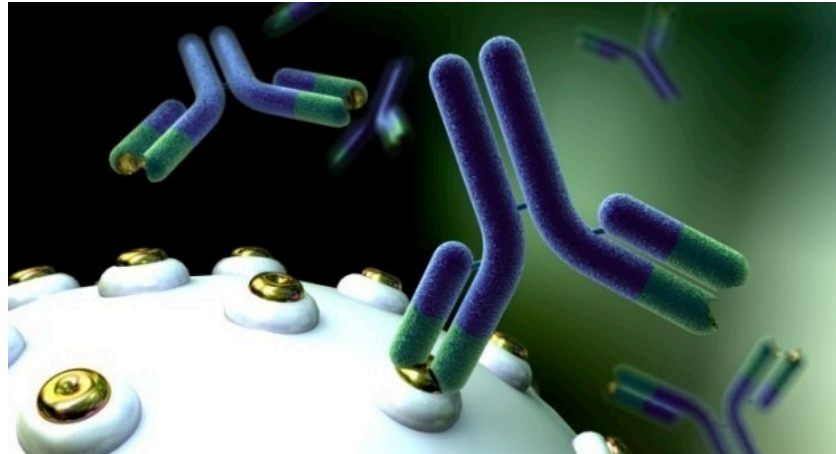
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# Background

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## Monoclonal Antibodies (mAbs)





# Background

## Clinical trial: Conventional Drug VS mAbs

### ❖ Conventional Drug

- ❖ Small and fixed interval
- ❖ Only optimize dose
- ❖ Fast effect

### ❖ mAbs

- ❖ Long and Flexible interval
- ❖ Both dose and time need to be optimized
- ❖ Slow and Long Term effect

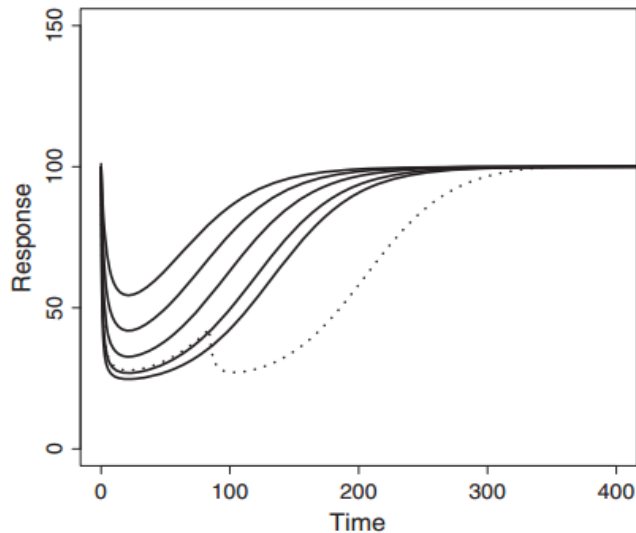




# Background

## Main Idea

The proposed approach uses nonlinear regression models to describe and predict the time-changing response for complex dosing regimens.



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# **Methodology**

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# Methodology

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## Bayesian Inference

$$P(\textit{Model}|\textit{Data}) = \frac{P(\textit{Data}|\textit{Model})P(\textit{Model})}{P(\textit{Data})}$$

- ❖  $P(\textit{Data} | \textit{Model})$ : prior model  $\Rightarrow$  data
- ❖  $P(\textit{model} | \textit{data})$ : data  $\Rightarrow$  posterior model





# Methodology

## Bayesian VS Frequentist

### Where is the ringing phone?

- ❖ Frequentist Reasoning

- ✧ Judgment from listening

- ❖ Bayesian Reasoning

- ✧ Judgment from listening
- ✧ Previous knowledge of phone location





# Methodology

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## Maximum Likelihood

$$\text{lik}(\theta) = f_D(x_1, \dots, x_n \mid \theta)$$

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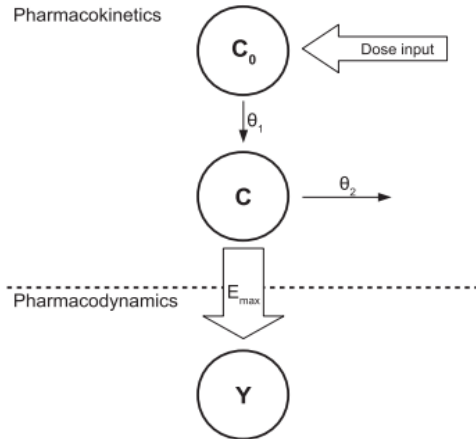
## **Dose-Time-Response Model**



# Dose-Time-Response Model

## Basic Model

pharmacokinetic–pharmacodynamic (PKPD) model



$$\frac{dC_0(t)}{dt} = -\theta_1 C_0(t)$$

$$\frac{dC(t)}{dt} = -\theta_2 C(t) + \theta_1 C_0(t).$$



# Dose-Time-Response Model

Direct-Response  $E_{\max}$ -model

$$g(C(t)) = \theta_5 + \frac{\theta_4 \cdot C(t)}{\theta_3 + C(t)}.$$

The Basic Model

$$y_{ij} = \theta_5 + \frac{\theta_4 D_i (e^{-\theta_2 t_j} - e^{-\theta_1 t_j})}{\theta_3 (1 - \theta_2/\theta_1) + D_i (e^{-\theta_2 t_j} - e^{-\theta_1 t_j})} + \epsilon_{ij}$$



# **Dose-Time-Response Model**

## **Model Extension**

- ❖ Placebo response
- ❖ Baseline covariates
- ❖ Multiple doses
- ❖ Route of administration
- ❖ Residual error
- ❖ Indirect-response models and turnover models

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# **Simulation**

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## Simulation

To estimate the operating characteristics of the basic model

$$y_{ij} = \theta_5 + \frac{\theta_4 D_i (e^{-\theta_2 t_j} - e^{-\theta_1 t_j})}{\theta_3 (1 - \theta_2 / \theta_1) + D_i (e^{-\theta_2 t_j} - e^{-\theta_1 t_j})} + \epsilon_{ij}$$

- ❖ A mAb is administered by subcutaneous injection
- ❖ 1000 datasets generated using a multivariate normal distribution
- ❖  $E_{\max}$  model is used to assess the expected value





# Simulation

## Summary of the simulation results

**Table I.** Summary results of the clinical trial simulations (CI=confidence interval, PI=probability interval).

Parameter	True value	Likelihood analysis		Bayesian analysis	
		Median of maximum likelihood-estimate	95% CI coverage (in %) *	Median of posterior median	95% PI coverage (in %) *
$\theta_1$	0.07	0.067	90.7	0.087	94.8
$\theta_2$	0.03	0.032	91.2	0.028	97.2
$\theta_3$	10.00	9.67	97.4	13.23	92.1
$\theta_4$	-80.00	-80.7	99.7	-82.16	92.5
$\theta_5$	100.00	100.0	91.9	98.92	93.6
Time					
0	100.00	100.0	91.9	98.92	93.6
10	28.38	27.9	99.8	26.80	95.3
50	30.32	30.5	99.9	31.32	94.6
100	26.18	25.4	100.0	24.44	93.5
200	57.13	57.0	98.4	57.49	94.3
300	95.61	94.8	94.6	92.21	90.5

\* Monte Carlo standard error: 0.7%



# Simulation

## Simulation results

- ❖ Point estimates near to the true parameter values
- ❖ ML estimates close to the true values on average
- ❖ Acceptable confidence and probability interval coverage
- ❖ Slightly better Bayesian probability interval coverage

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## **Clinical Trail**

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# Clinical Trail

## Dose-time-response models used to analyze the clinical trail

- ❖ The effects of canakinumab subcutaneous injection were examined
- ❖ 24 weeks, 400 patients
- ❖ Participants randomly divided into seven groups
  - ✧ Five groups received single doses (either 25 mg, 50 mg, 100 mg, 200 mg, or 300 mg at day 1)
  - ✧ One group received multiple doses (50 mg at day 1, 50 mg at week 4, 25 mg at week 8, and 25 mg at week 12)
  - ✧ The last group as the placebo
- ❖ The logarithm of C-reactive protein (CRP) levels as a proxy of the response
  - ✧ CRP is a biomarker signaling the severeness of the disease



# Clinical Trail

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## Objectives

- ❖ To evaluate the fitness of the dose-time-response model in the clinical trail
- ❖ To evaluate the accuracy of the dose-time-response model predictions of the untested treatment regimens response



# Clinical Trail

## Bayesian analysis for the five single-dose groups

**Table II.** Bayesian analysis for data from the five single-dose treatment groups.

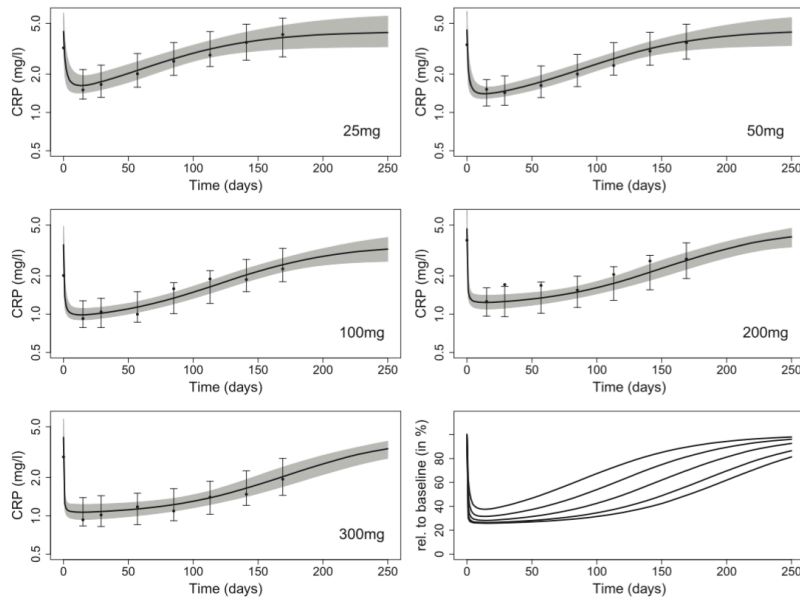
	Posterior median	95% probability interval	
$\theta_1$	0.177	0.077	0.293
$\theta_2$	0.022	0.016	0.031
$\theta_3$	8.07	3.44	15.19
$\theta_4$	-1.41	-1.82	-1.06
$\theta_5$	0.934	0.65	1.29
$\theta_6$	0.431	0.38	0.53

$\theta_6$  is added to the basic model to measure the effect of the baseline CRP levels ( $X_0$ )



# Clinical Trail

## Comparison of observed values and the fitted Bayesian model



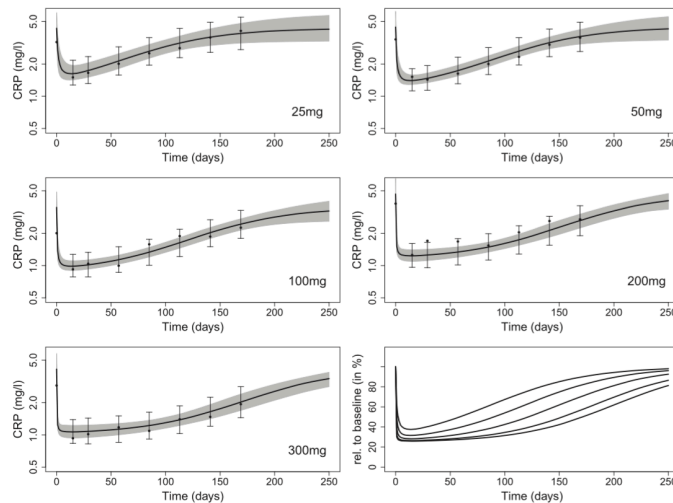
- ✧ Dots: CRP mean
- ✧ Solid curve: CRP median
- ✧ Grey area: 95% posterior probability interval
- ✧ Vertical lines: 95% prediction probability interval
- ✧ Last plot: all posterior median curves relative to their baseline value



# Clinical Trail

## Accuracy evaluation

- ❖ The dose-time-response model describes the single-dose data well with  $R^2 = 0.82$

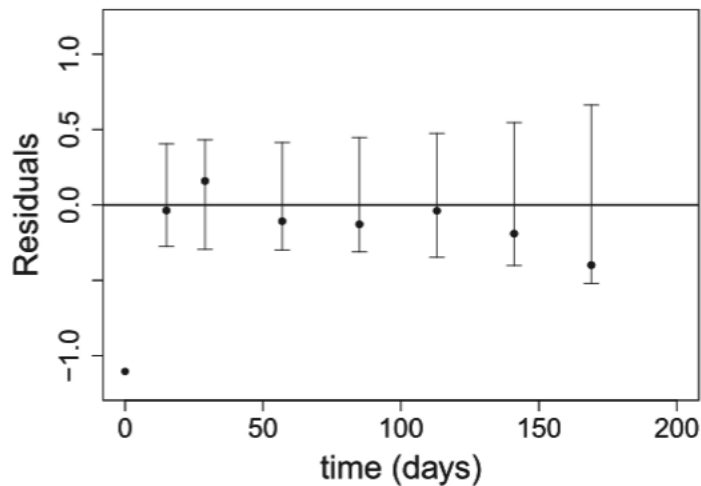
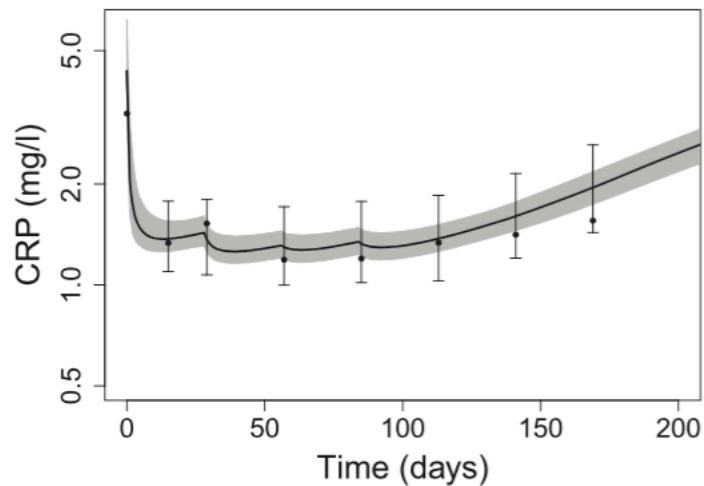






# Clinical Trail

## Bayesian prediction for the multiple dose treatment

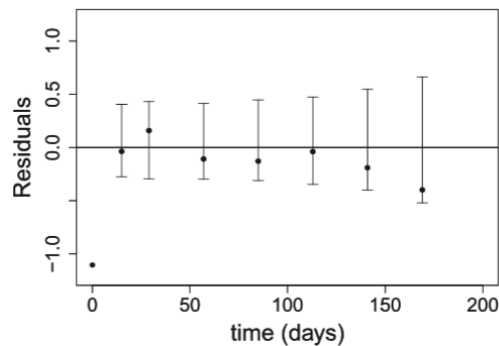
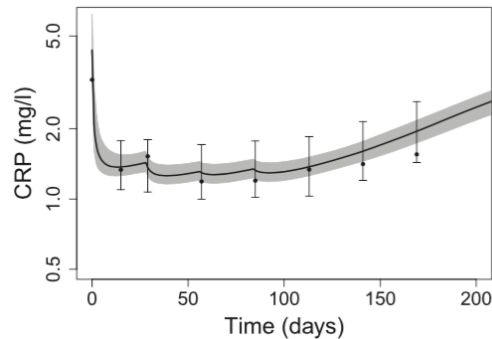




# Clinical Trail

## Results of the Bayesian prediction

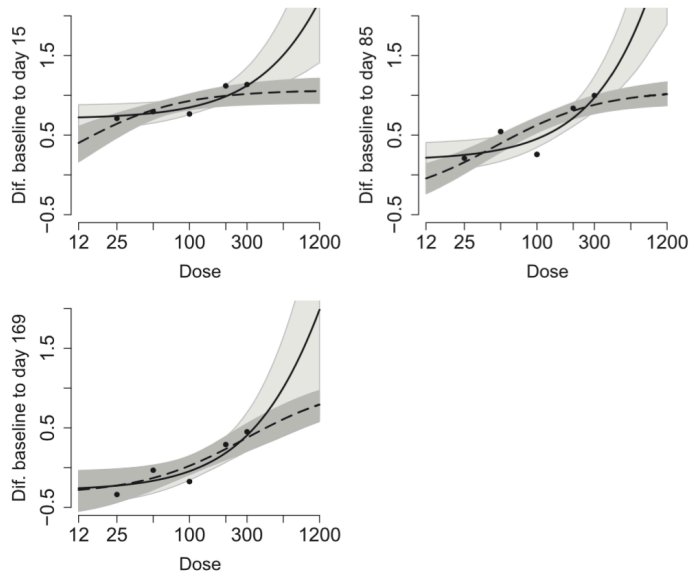
- ❖ All data points within the 95% prediction intervals
- ❖ Good accuracy of the dose-time-response model predictions of the response over time for the multiple dose treatment





# Clinical Trail

## Dose-time-response model VS Standard $E_{\max}$ model



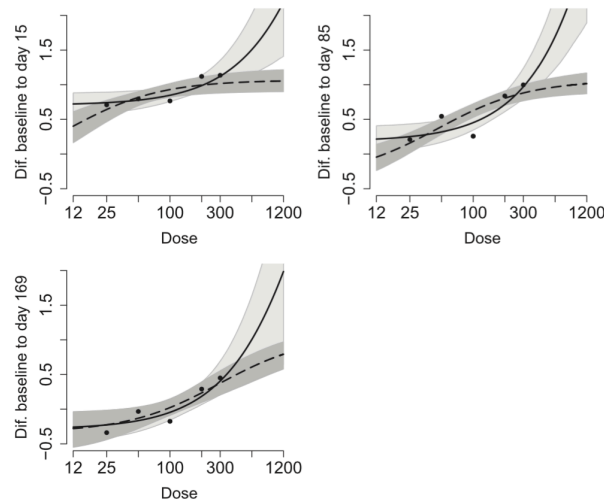
- ✧ Dots: CRP mean
- ✧ Solid line: fitted  $E_{\max}$  model
- ✧ Dashed line: fitted dose-time-response model
- ✧ Light/Dark grey area: respective 95% confidence bands of the expected response



# Clinical Trail

## Results of Comparison

- ❖ Similar fits of data for both models
- ❖ More accurate predictions for higher doses in the dose-time-response



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# **Evaluations**

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# Evaluations

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## Limitations

- ❖ ML methods may not be valid for small samples in the experiments
- ❖ Bayesian framework may cause unintended informative prior problems
- ❖ Sample generated using MCMC methods are subject to the validity problem
- ❖ In the clinical trial, data may not be complete enough to achieve the accuracy of the model evaluation



# Evaluations

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## Issues & Challenges

- ❖ Challenging to ensure the fitness of nonlinear regression models
- ❖ Bayesian analysis requires MCMC algorithms, which is computer-intensive and time-consuming



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# **Thanks!**

***Any questions ?***





# Maximum Likelihood

- ❖ Maximum likelihood is the procedure of finding the value of one or more **parameters** for a given statistic which makes the **known likelihood distribution** a **maximum**.
- ❖ <http://mathworld.wolfram.com/MaximumLikelihood.html>
- ❖ <http://statweb.stanford.edu/~susan/courses/s200/lectures/lect11.pdf>



# MLE

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- ❖ **Maximum-likelihood estimation** (MLE) is a method of estimating the parameters of a statistical model given data.
- ❖ In general, for a fixed set of data and underlying statistical model, the method of maximum likelihood selects the set of values of the model parameters that maximizes the likelihood function.



# Bayesian Analysis

- ❖ Bayesian analysis is a statistical procedure which endeavors to estimate parameters of an underlying distribution based on the observed distribution
- ❖ prior distribution  $\rightarrow$  observed distribution  $\rightarrow$  posterior distribution
- ❖ Bayesian analysis is somewhat controversial because the validity of the result depends on how valid the prior distribution is, and this cannot be assessed statistically.
- ❖ <http://mathworld.wolfram.com/BayesianAnalysis.html>



# Bayesian Inference

- ❖ A method of statistical inference in which **Bayes' theorem** is used to update the probability for a hypothesis as more evidence or information becomes available.
- ❖ Bayesian updating is particularly important in the **dynamic analysis** of a sequence of data.

$$P(\textit{Model}|\textit{Data}) = \frac{P(\textit{Data}|\textit{Model})P(\textit{Model})}{P(\textit{Data})}$$



# Monte Carlo Method

- ❖ Any method which solves a problem by generating **suitable random numbers** and observing that fraction of the numbers obeying some property or properties.
- ❖ The method is useful for obtaining numerical solutions to problems which are too **complicated** to solve analytically.
- ❖ Monte Carlo methods are mainly used in three distinct problem classes: optimization, numerical integration, and generating draws from a probability distribution.
- ❖ <http://mathworld.wolfram.com/MonteCarloMethod.html>



# Monte Carlo Integration

- ❖ In mathematics, Monte Carlo integration is a technique for numerical integration using random numbers.
- ❖ Many algorithms usually evaluate the integrand at a regular grid, Monte Carlo randomly choose points at which the integrand is evaluated. This method is particularly useful for higher-dimensional integrals.

$$\int f dV \approx V \langle f \rangle \pm V \sqrt{\frac{\langle f^2 \rangle - \langle f \rangle^2}{N}}, \text{ where } \langle f \rangle \equiv \frac{1}{N} \sum_{i=1}^N f(x_i) \quad \langle f^2 \rangle \equiv \frac{1}{N} \sum_{i=1}^N f^2(x_i)$$

- ❖ <http://mathworld.wolfram.com/MonteCarloMethod.html>



# MCMC Method

- ❖ Markov chain Monte Carlo (MCMC) methods are a class of algorithms for sampling from a probability distribution based on constructing a Markov chain that has the desired distribution as its equilibrium distribution.
- ❖ The state of the chain after a number of steps is then used as a sample of the desired distribution.
- ❖ Markov chain is collection of random variables  $\{X_t\}$  ( $t = 0, 1, \dots$ ) having the property that, given the present, the future is conditionally independent of the past. i.e.

$$P(X_t = j | X_0 = i_0, X_1 = i_1, \dots, X_{t-1} = i_{t-1}) = P(X_t = j | X_{t-1} = i_{t-1}).$$



# Multivariate Normal Distribution

- ❖ A generalization of the one-dimensional (univariate) normal distribution to higher dimensions
- ❖ A random vector is said to be k-variate normally distributed if every linear combination of its k components has a univariate normal distribution
- ❖ The probability density function of the d-dimensional multivariate normal distribution is given by

$$y = f(x, \mu, \Sigma) = \frac{1}{\sqrt{|\Sigma|(2\pi)^d}} e^{-\frac{1}{2}(x-\mu)' \Sigma^{-1}(x-\mu)}$$

- ❖ <http://www.mathworks.com/help/stats/multivariate-normal-distribution.html>