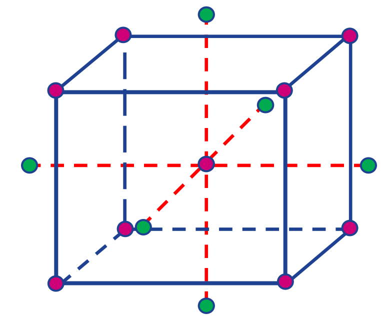
DoE
——Design of Experiments



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GE Healthcare Life Sciences

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Overview of course contents

- Design of Experiments, introduction
- Terminology in DoE
- Transfer Functions (Models) in DoE
- Experimental designs available in UNICORN™ 6
- Evaluation of DoE results in UNICORN™ 6
- Example of DoE
- Summary

Design of Experiments
- Introduction

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What is Design of Experiments (DoE)? 什么是实验设计？

DoE is a systematic way of changing process inputs and analyzing the resulting process outputs in order to quantify the cause and effect relationship between them while using a minimum number of runs.

实验设计是一个系统性方法，它通过同时改变不同的影响因子（输入），分析得到的输出结果，来定量研究它们之间的原因与结果之间的相互关系，运行的试验数量要求往往最少。

Why Design of Experiments?为什么需要实验设计

1. Interactions: Systems influenced by more than one factor are poorly investigated by changing one separate factor at a time (interactions are missed)
交互效应：在单因子法中，系统受多因素的影响很少被研究到(交互效应丢失）

2. Interpretation: Maps of the system may be misleading without using DoE (non-designed experiments often don't cover the complete region of interest) .
诠释：脱离DoE对系统进行诠释很可能导致误解（没有经过设计的实验往往不能涵盖完整的感兴趣区域）

3. Random Noise: Systematic and unsystematic variability (real effects and noise) are difficult to estimate and assess without a designed series of experiments. With DoE, all experiments are also used to quantify the random variability (noise) in the process.
随机噪音：在缺乏设计一系列实验的情况下，系统和非系统变化(真实效应和噪声)是很难被判定和评估的。但是通过DoE, 所有的实验就可以用来量化在过程中的随机变化（噪音）。

4. Time/cost: DoE requires fewer resources for the amount of information obtained, especially as the number of factors increase.
时间/花费：DoE可以通过很少的资源获得的大量信息,特别是在因素增加的情况下。

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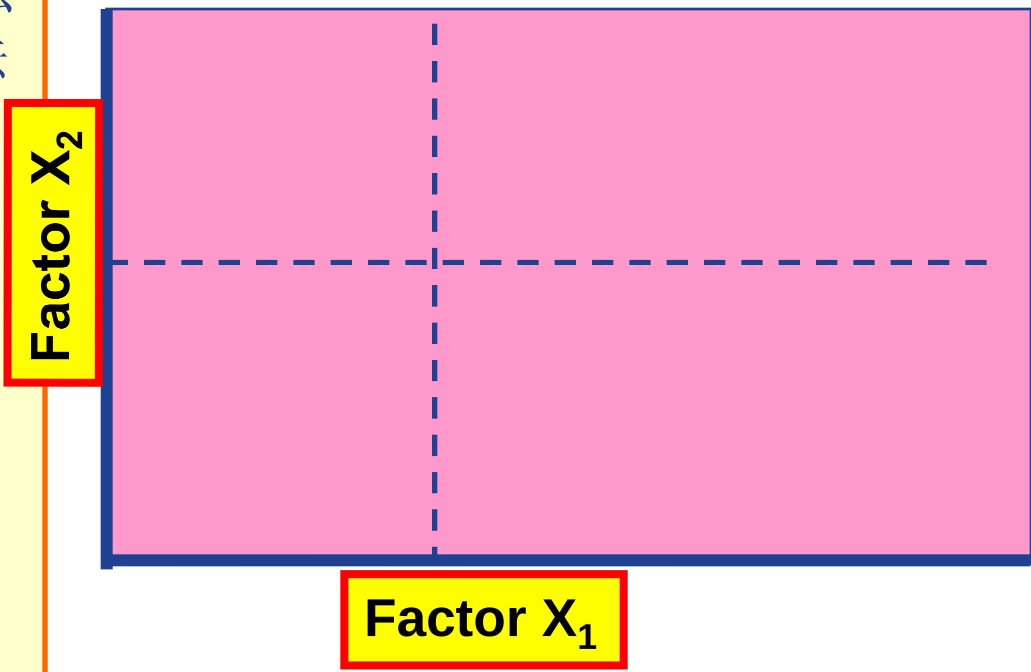
The OFAT approach 单因子法

Classical Approach 经典分析法

OFAT - One Factor at a Time单因子法

- Change one variable, X_1,while holding all others constant.
  固定所有其他因子不变，只变动一个因子（X_1）
- Find the maximum/best setting
  找到最佳的设置
- Hold X_1 at the "maximum effect" level and repeat the process for the other variables.
  固定最佳的X_1水平，对其他因子重复上述步骤



$$Y = a*X_1 + b*X_2 + K$$

Implicit in the OFAT approach is that the system response is a linear combination of the critical factors.
单因子法暗示系统响应是关键因数的一个线性组合

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Example – OFAT investigation

The process：　工艺

- Looking at the Yield of a process
  考虑工艺的产量
- Runs today at 155 °C for 1.5h
  在155°C 操作1.5h
- Possible operating region is 140-180°C and 0.5-2.5h
  可能操作空间在140-180°C，0.5-2.5h

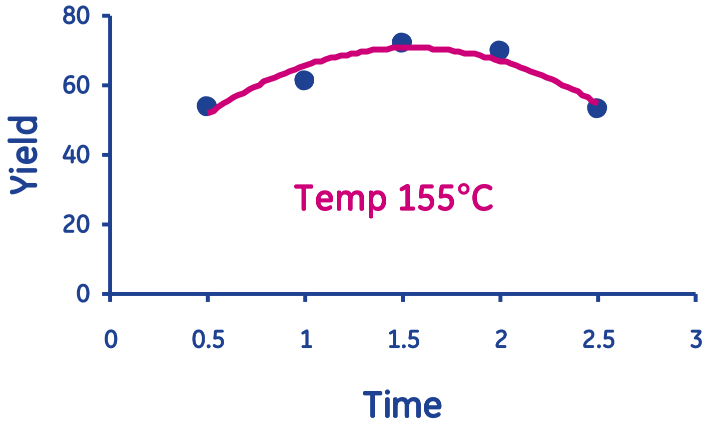
From Past Experience: 借鉴过去的经验

- Time & Temperature influence Yield.
  时间&温度会影响产量
- Cannot be improved... 无法进行改良

One factor changed at the time
每次改变一个因子

- Feels safest and most structured
  感觉最安全而且最具有结构化特质

1)



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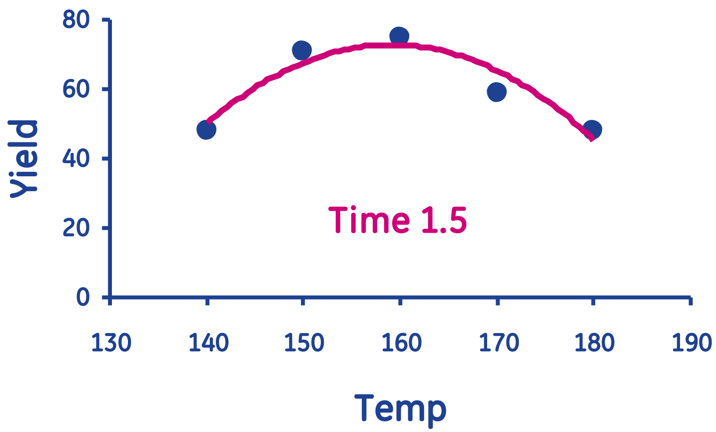

Where would you run? 在哪儿进行操作?
1.5 h, 155-160°C -> Yield 70-75%

What region has actually been explored?
什么区域被真正探索到？

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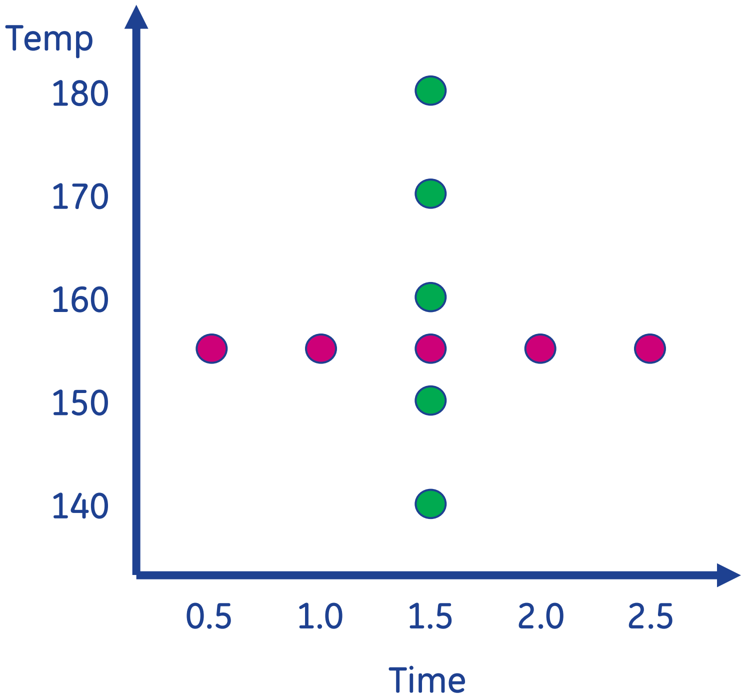
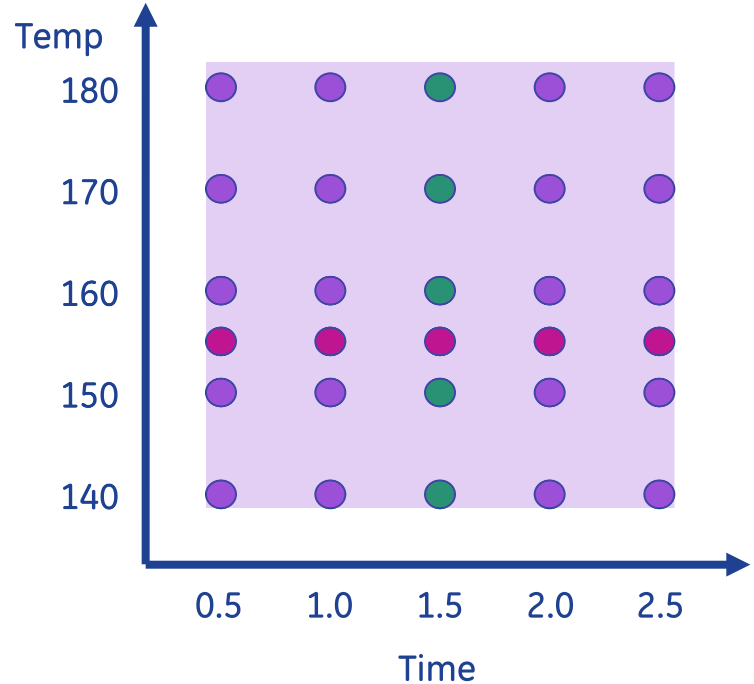
Example continued

This was explored



This could have been explored.
A large area not explored!



The **OFAT** approach (**One Factor At a Time**)

➔ Doesn't explore the whole experimental region!
无法探索整个实验区间

➔ Risk for suboptimization, and/or unpleasant surprises!
存在局部次优化和不愉快的意外风险！

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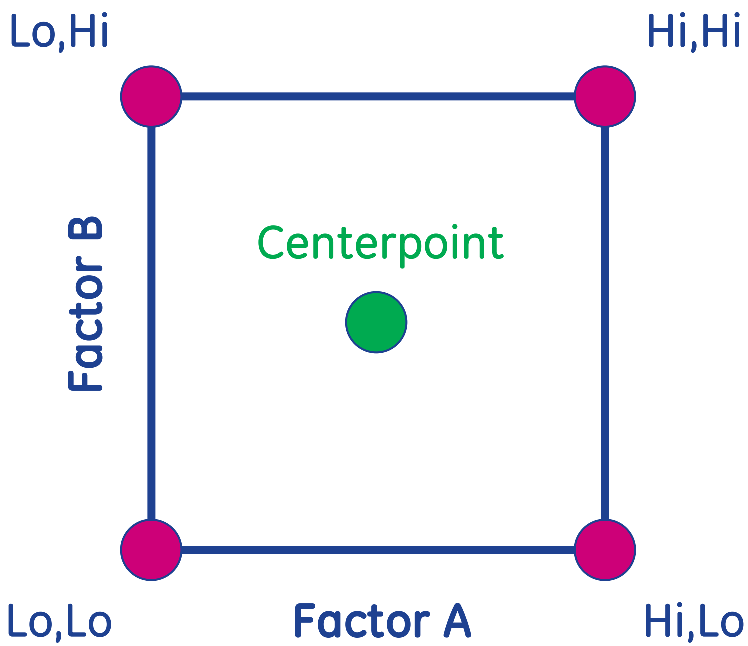
The DoE approach

A *designed set* of experiments where the selected factors are varied (and evaluated) simultaneously!



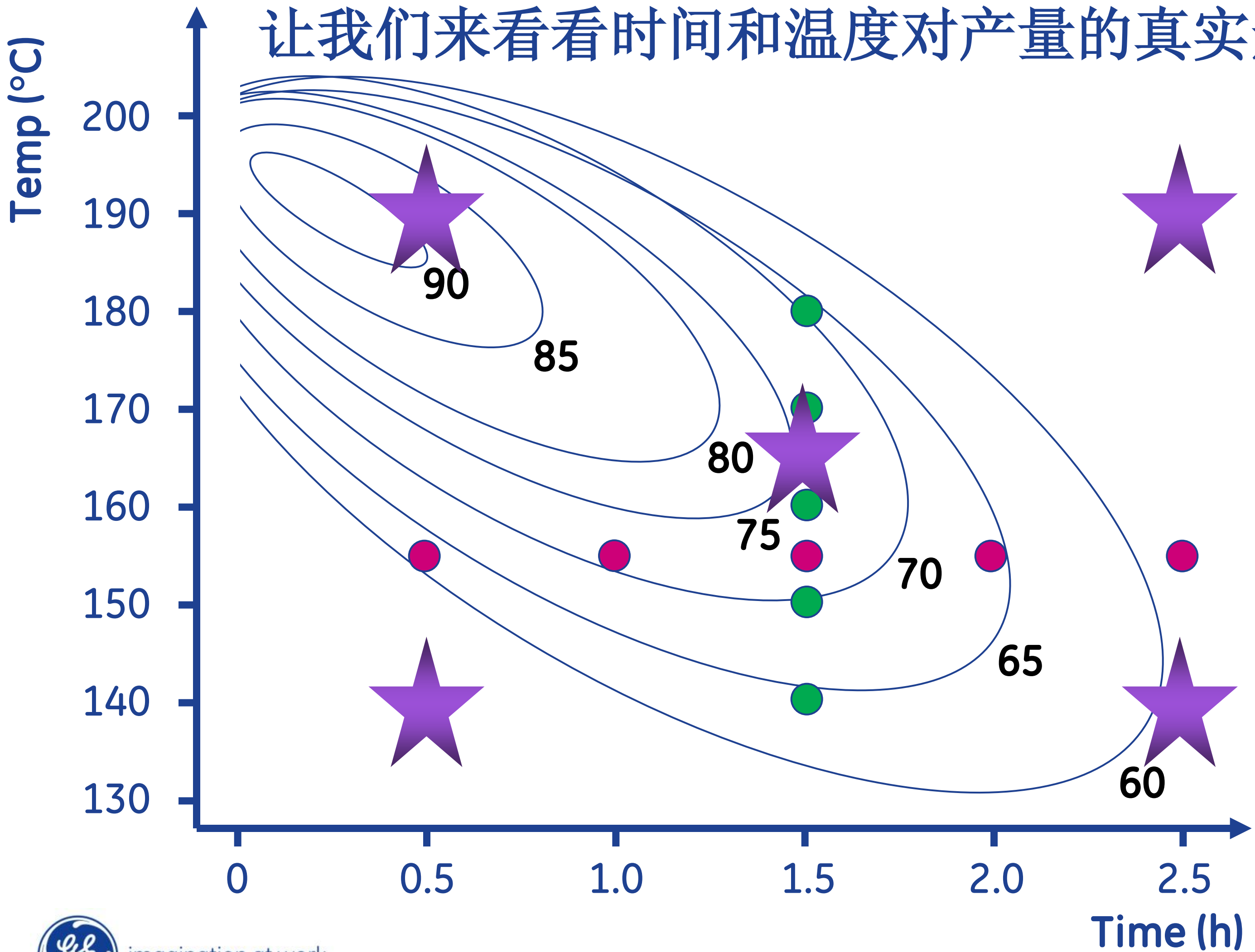
Two factors at two levels

A	B	Result
Lo	Lo	?
Lo	Hi	?
Hi	Lo	?
Hi	Hi	?
Mid*	Mid	?

* Centerpoint: detection of curvature
* Replicated centerpoint: estimation of noise

Example continued

Let's say this is the true effect on yield…
让我们来看看时间和温度对产量的真实影响



With DoE, we could have explored a broader region in fewer experiments. **And found the TRUE OPTIMUM!**

DoE reduces your cost 实验设计降低开发成本

Design of Experiments allows the maximum amount of information to be obtained from a minimum number of experiments. By improving efficiency, both time and money are saved

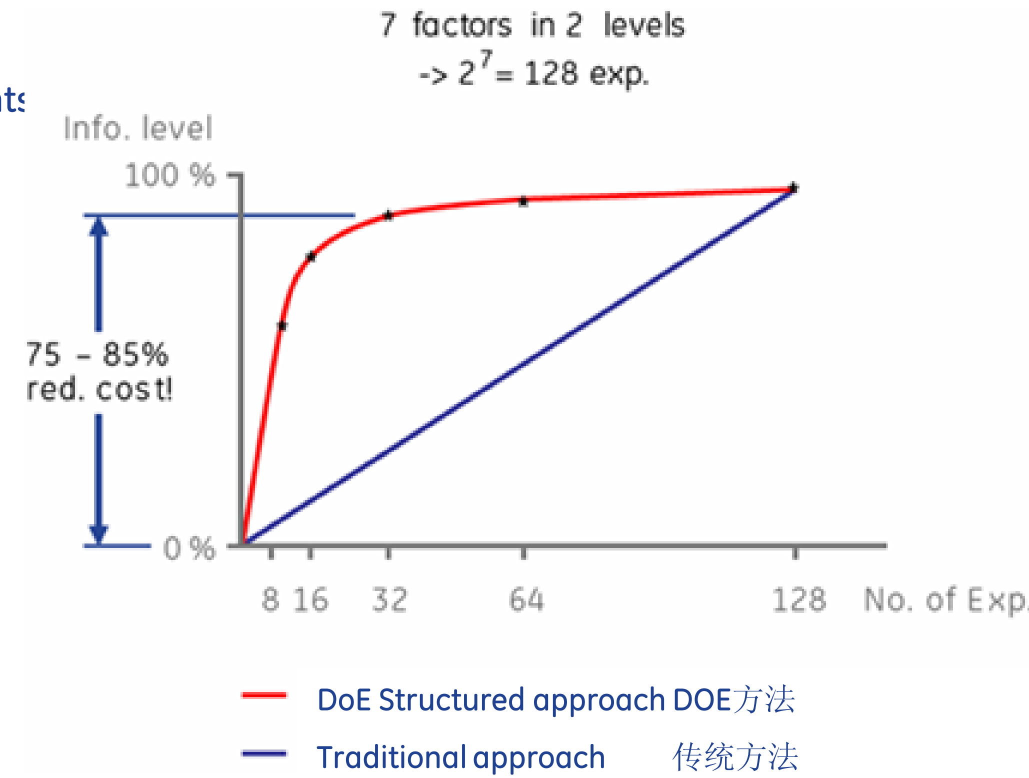
实验设计通过最小的实验数量获得最大的实验信息量。通过提高效率节省金钱和时间。

- Design of Experiments (DoE) is integrated in UNICORN™ 6

  实验设计软件整合到UNICORN™ 6中

- Reach the same result in 16-32 experiments as you would with 128 experiments using the traditional approach!

  用传统的方法进行128个实验得到的结果，采用DOE 只需要进行16-32个实验



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What is Quality by Design?
什么是品质源于设计

Definition of Quality by Design :

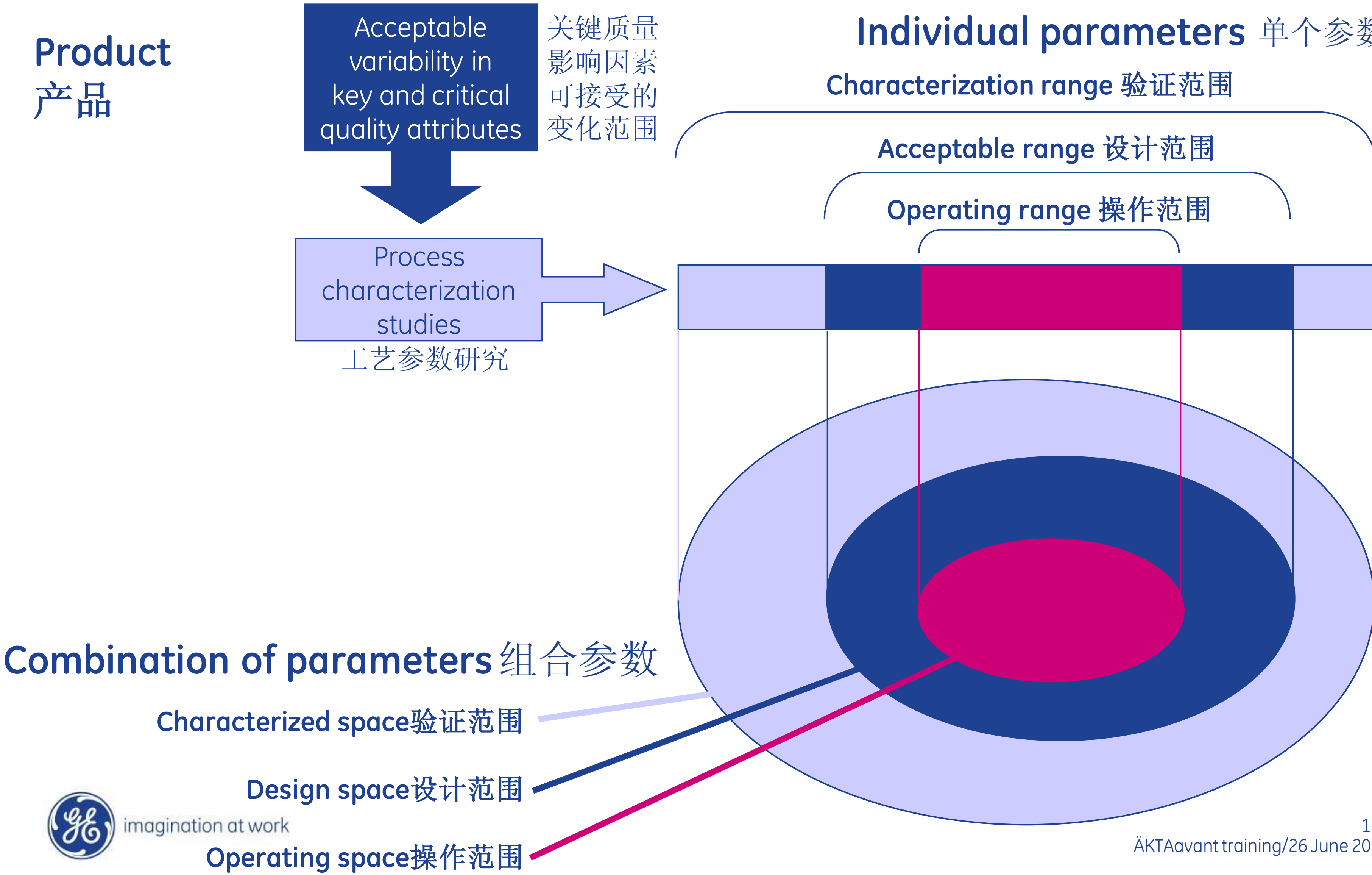
”A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management”.

“一系统性的开发方法。此法基于可靠的科学和质量风险管理之上，预先定义目标以及强调对产品与工艺的理解，和工艺的控制。”

ICH Harmonised Tripartite Guideline, Pharmaceutical Development Q8(R1), November 2008

FDA Guidance for Industry, Q8(R1) Pharmaceutical Development, June 2009

Quality by Design (QbD), Design Space
质量源于设计，设计区域



Defining the Process Design Space
工艺设计空间的定义

Definition of process design space:

”The multidimensional combination of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality”.

“能用于证明质量保证的输入变量（如材料属性）及工艺参数的多维组合及关联。”

Process changes within the design space are not regarded as changes by the regulatory authorities

在设计空间内的操作不被监管机构认作是工艺改变

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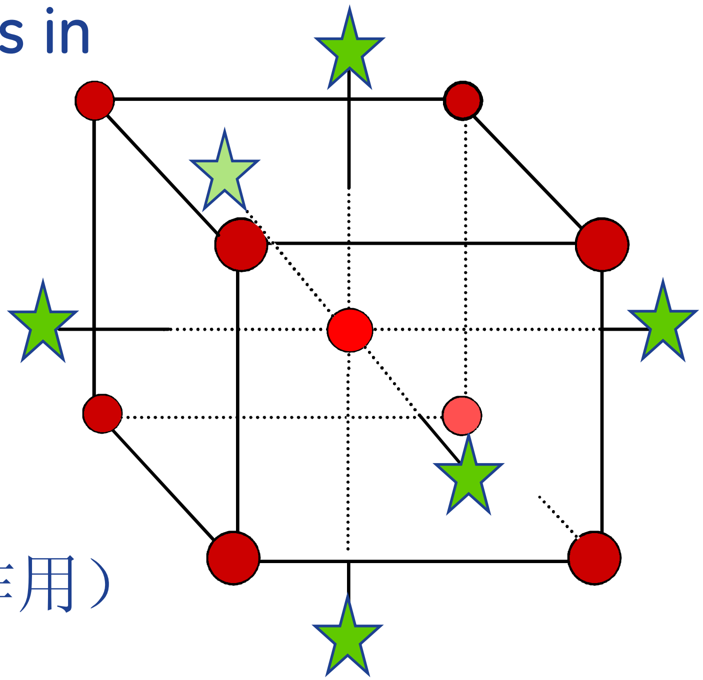
DoE to identify design space
采用DOE 来确定设计空间



- Identify criticality of process parameters in relation to Critical Quality Attributes

确定影响关键质量属性的主要工艺参数

- Understand how the effect of process parameters depend on each other (interactions)

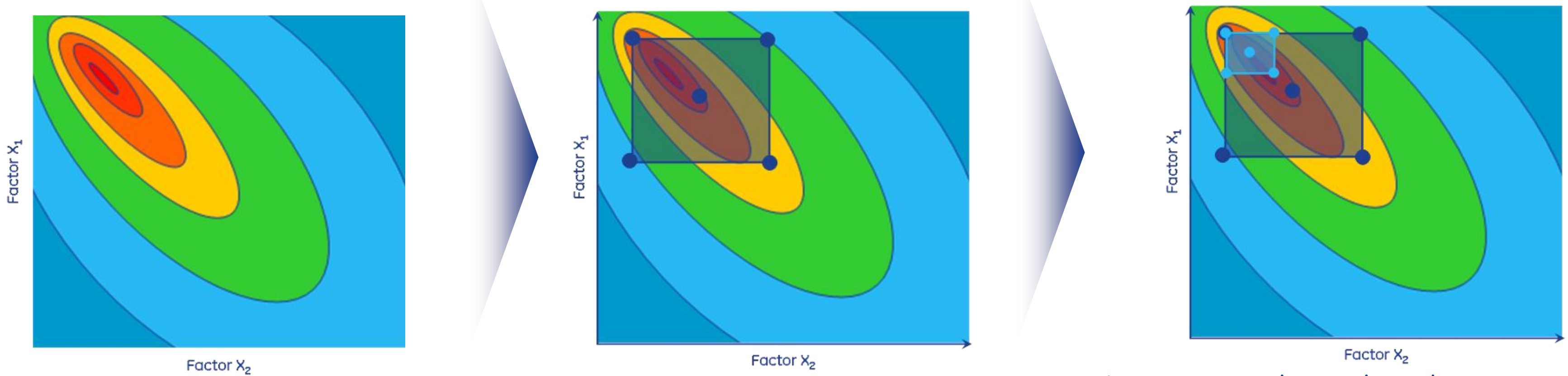
了解工艺参数之间如何相互影响（相互作用）

- Basis for setting acceptable and realistic variability ranges for control space

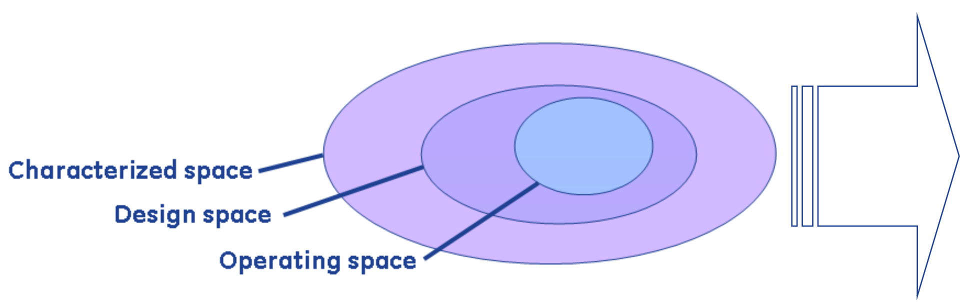
将参数控制区域设定在可接受和可实现的变化范围

DoE and Quality by Design (QbD)
DOE 和质量源于设计

DoE Screening筛选 *DoE Optimization优化* *Operation and DoE Robustness运行和稳健性*



Or in QbD terms...(FDA guidelines)...



Systematic approach to development:
系统性的工艺开发方法

- Begins with predefined objectives
  起始设定好目标
- Emphasizes product and process
  强调产品和工艺
- understanding and process control
  理解和过程工艺控制
- Based on sound science and quality

risk management 以科学和质量风险管理为基础

from ICH Q8(R)

Terminology in Design of Experiments
- Some key concepts

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DoE Glossary术语

Factor（因子、因素、X）

- A parameter (variable) thought to affect the result (e.g. pH, Conductivity)能考虑到的影响实验结果的参数（变量）
- Can usually be controlled, but may also be uncontrolled (measured)通常可被控制，但也可能不可控制（测量）
- Factors are either numerical (e.g. pH) or categorical (e.g. salt type)参数既可是数值(e.g. pH) 或种类(e.g. salt type)

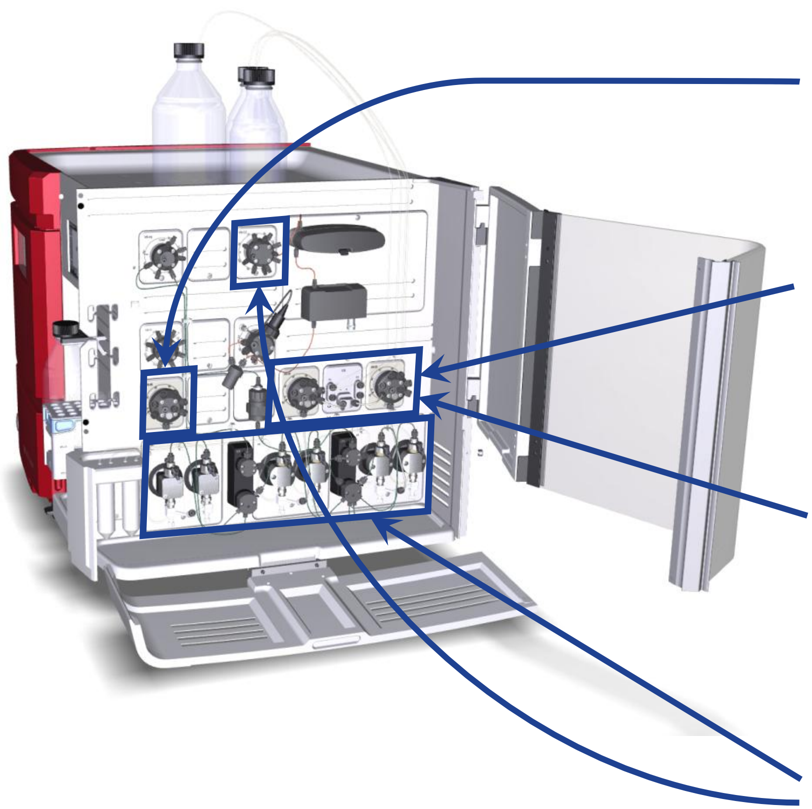
Response（响应，Y）

- One or more measured variables describing the outcome of the experiment一个或多个可测量的变量描述实验结果

Model（模型）

- The equation that best fits the experimental data based on the statistical Analysis of Variance (ANOVA)在变量统计分析的基础上建立最适实验数据方程式
- Usually a second degree polynomial多项性 (quadratic function)通常是二次方程
- Used to predict responses at unmeasured factor levels对不可测量的因子使用预测响应
- Can be represented by model coefficients and Response surface plot可通过模型系数和响应表面图代表

层析过程中因子（X）和响应（Y）的例子



Sample conditions
样品条件

Wash conditions
清洗条件

Elution conditions
洗脱条件

Entire process
整个过程

Factors

- Load pH
- Load conductivity
- Load concentration
- Mass load
- Wash volume
- Wash pH
- Wash conductivity
- Elution pH
- Gradient elution
- Step elution level
- Cut OD
- Elution Additive
- Media type
- Column size
- Bed Height
- Flow rate
- Residence time

Responses

External data:

- Capacity
- DBC (Frontal analysis)
- Yield
- Purity/Selectivity
- Molecular weight
- Activity
- HCP
- DNA
- Aggregates
- Protein A

Peak Data:

- Area
- Concentration
- Amount
- Resolution
- Asymmetry
- Plates per meter

General DoE scenarios

Screening实验参数的筛选

- Which factors are most important, i.e. affect the response?
- 那些因素是最重要的
- How much should we change the factors to see an effect?
- 因子变化多大才可看到影响结果

Optimization实验参数的优化

- Can we find optimal settings for the important factors?
- 对于重要的因子，我们能找到最适的设计吗？
- If we have more than one response, can we find common factor settings that satisfy all responses, or do we need to compromise?
- 如果有多于一个的响应结果，我们能够否找到满足所有响应结果的普通的因子设定，或我们需要作一个比较？

Robustness testing工艺的稳健性

- Is the process robust, i.e. unaffected by typical process variations?
- 过程是否经得住考验？
- How much will the product specifications vary due to process variations?
- 产品特质的变化有多少是因为过程变化引起的？

Models / transfer functions模型/函数

DoE relies on Models (Transfer Functions) for mathematical and statistical descriptions of the relation between process factors (X's) and process responses (Y's).

$Y = f(X) + e$

$f(X)$: The transfer function (model). Describes cause-effect relationships between factors and responses.

e: The residuals, variation in Y not described by the model. Represents the random variation inherent in the process.

Transfer functions (models) used in DoE

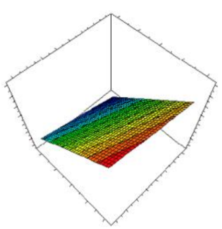
The Model

X: known input - experimental settings, factors

Y: measured - response

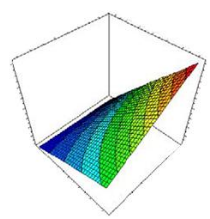
b: unknown constant - determined by the regression model

$$Y = \overbrace{b_0}^{\text{Constant Term = response of } Y \text{ when factors are 0}} + \underbrace{b_1X_1 + b_2X_2 + b_3X_3}_{\text{Linear Terms = main effects}} + \underbrace{b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3}_{\text{Two-way Interaction Terms}} + \underbrace{b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2}_{\text{Quadratic Terms}}$$



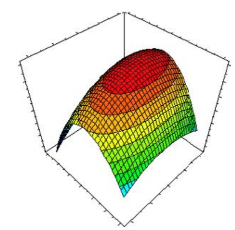
Fractional factorial design

Screening or Robustness testing



Full or Fractional factorial design

Screening



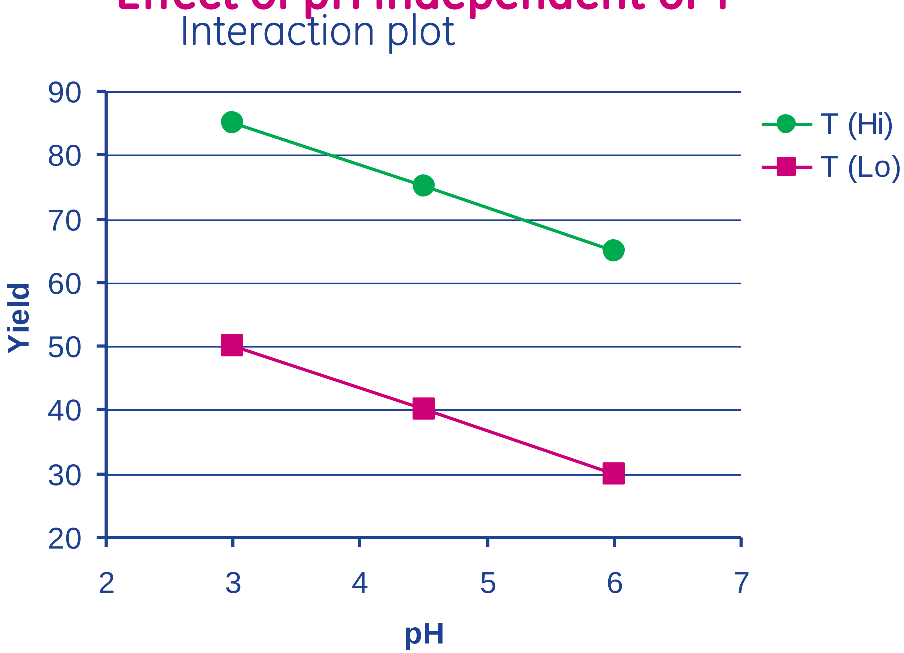
Composite design

Optimization

工艺参数之间相互作用 (Linear线性)

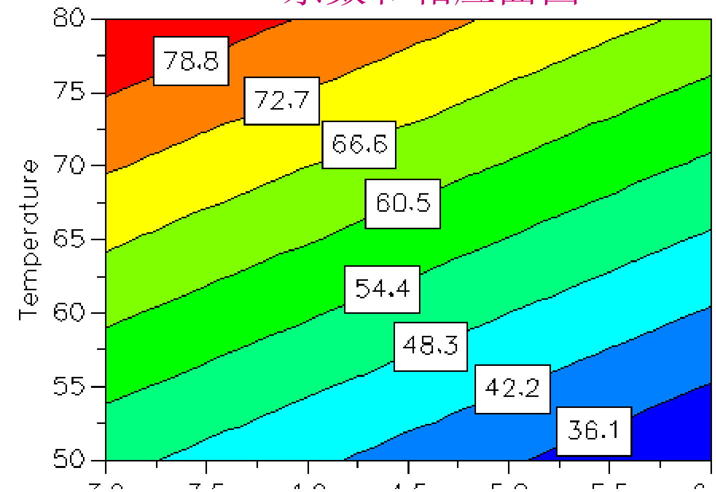
Example - No interaction

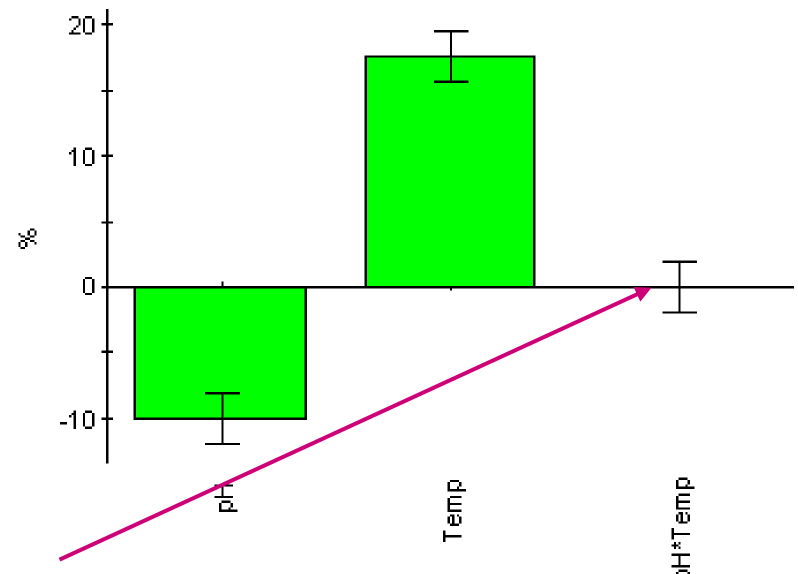
Effect of pH independent of T



$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

Coefficient and Response Surface Plot
系数和相应面图





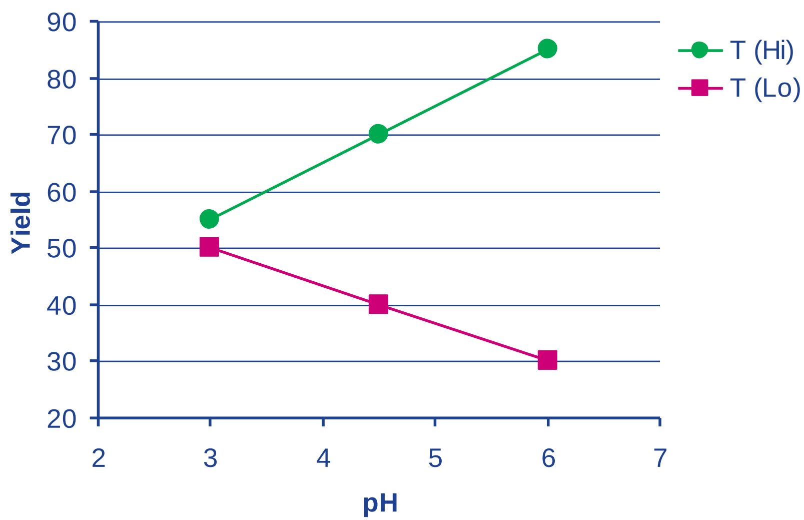
- Non-significant terms are identified by checking the confidence intervals (the noise contained in the confidence intervals). If the confidence interval covers zero the term is not significant.

工艺参数之间相互作用 (Interaction相互影响)

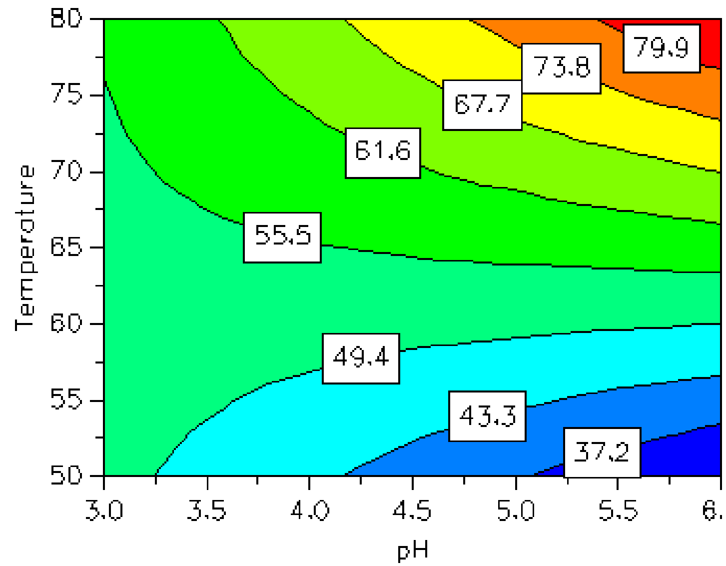
Example - Strong interaction

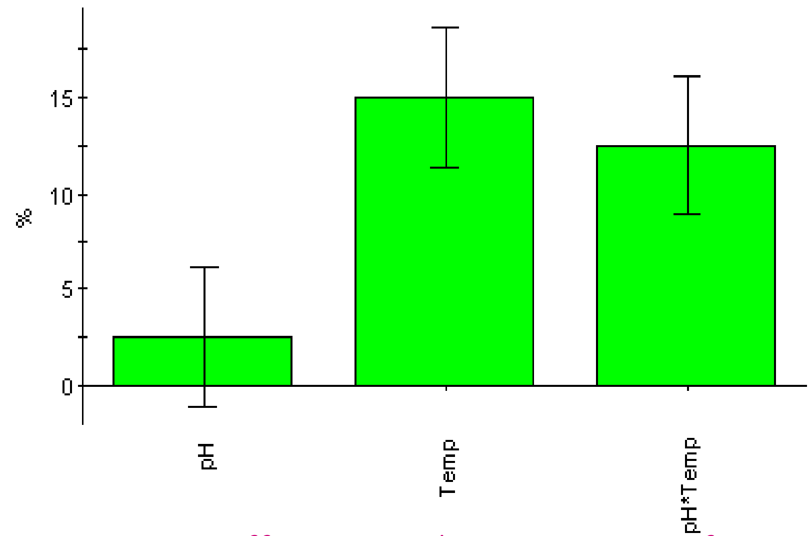
Effect of pH reversed at high T

Interaction plot



$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2$$





Coefficient and Response Surface Plot
系数和相应面图

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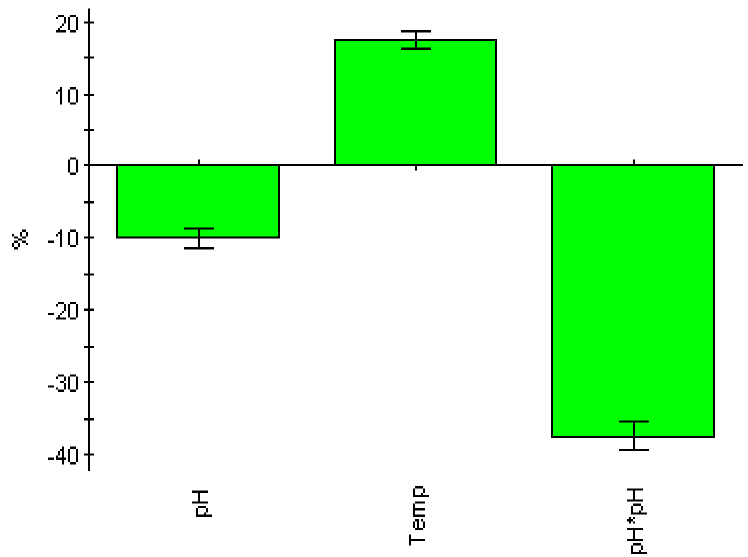
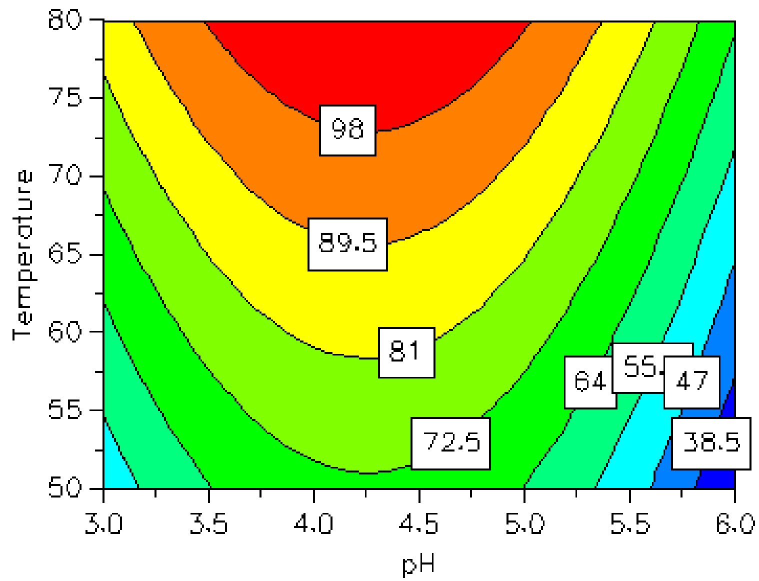
Coefficient and Response Surface Plot (Curvature曲率)





Regression equation $y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{22} x_2 x_2$

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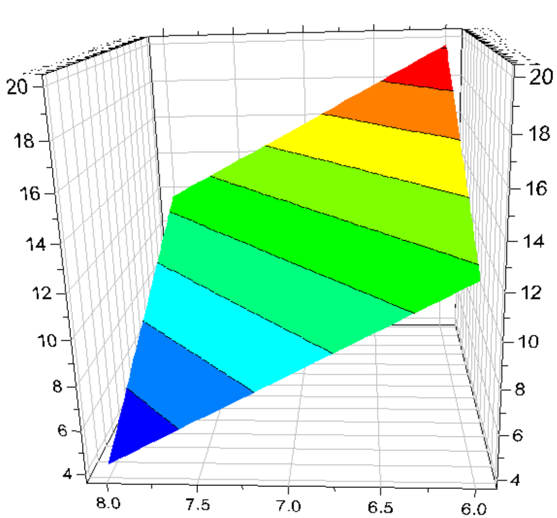
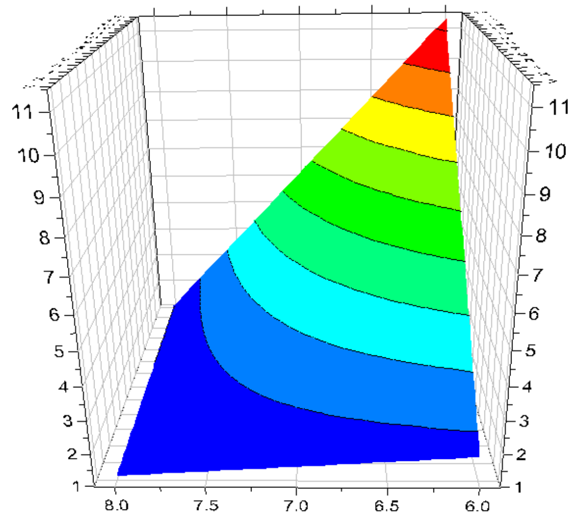
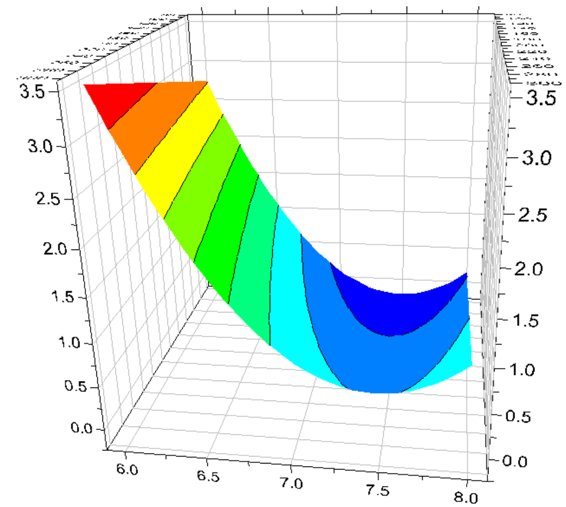
DoE transfer functions

Three types of transfer functions commonly used



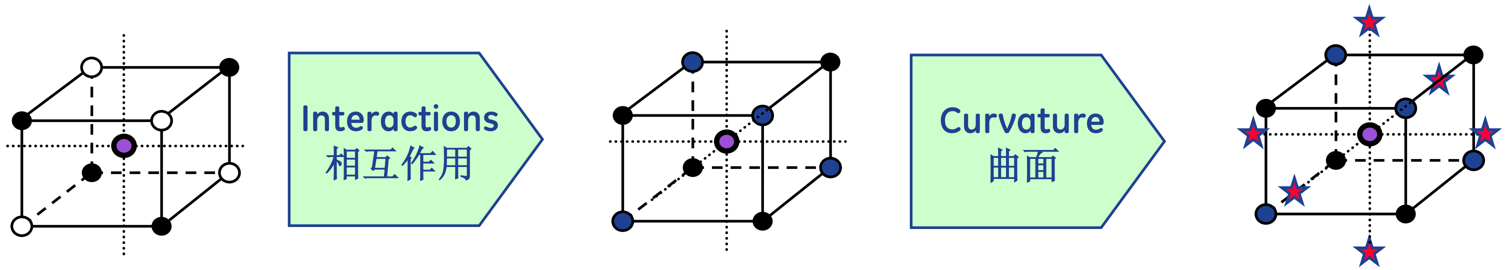




Linear: a+b
Screening (Res IV)
Robustness Testing (Res III or IV)

Interaction (2FI): a+b+ab
Screening (Res V)

Quadratic:a+a^2+b+b^2+ab
Optimization
(Res V + Star points)



An iterative, building block DoE approach

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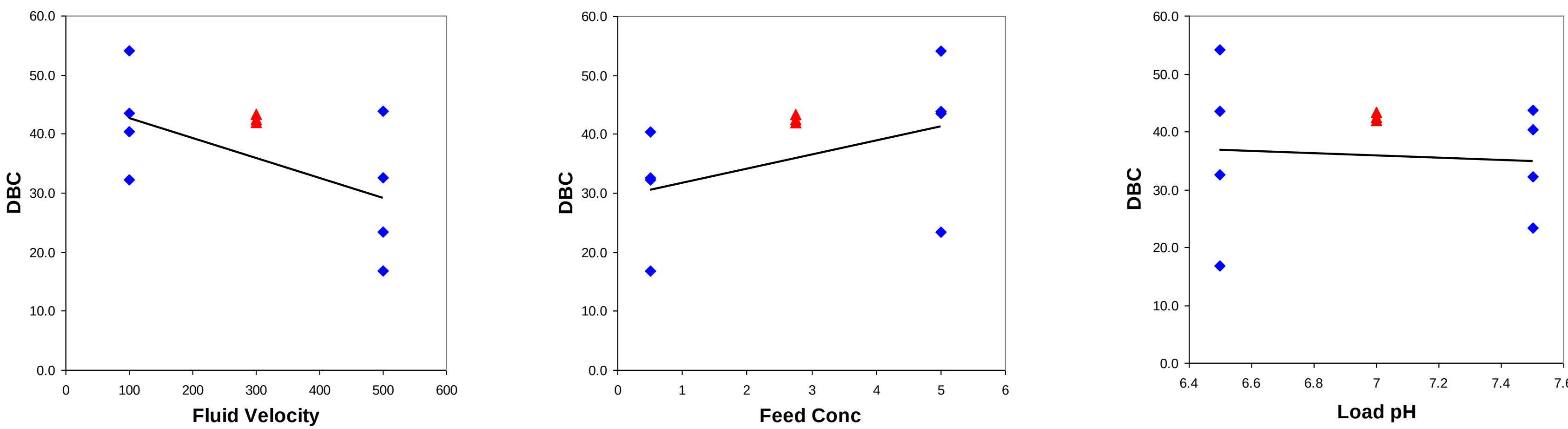
The important role of center points
中心点的重要作用

- Replication 重复试验
  - The center points are many times the only replicated experiments in an experimental design, providing information on the process reproducibility.
  - 试验设计只在中心点安排多次的重复试验，以提供工艺的复现性信息。

- Identify if you have 2nd degree Curvature or not 识别是否具有二次项曲率
  - If the center points do not fit to a DoE model with only linear and interaction terms, we might need to extend the DoE to also support quadratic terms for quantifying the curvature effect. 如果中心点在只有线性和交互效应的DoE模型中无法拟合，我们可能需要对模型进行扩展来支持量化曲率的二次项效应



Example: The center points deviate from corner point regression line -> There is 2nd degree curvature! 这些中心点偏离了拐点的回归线-> 存在二次项曲率

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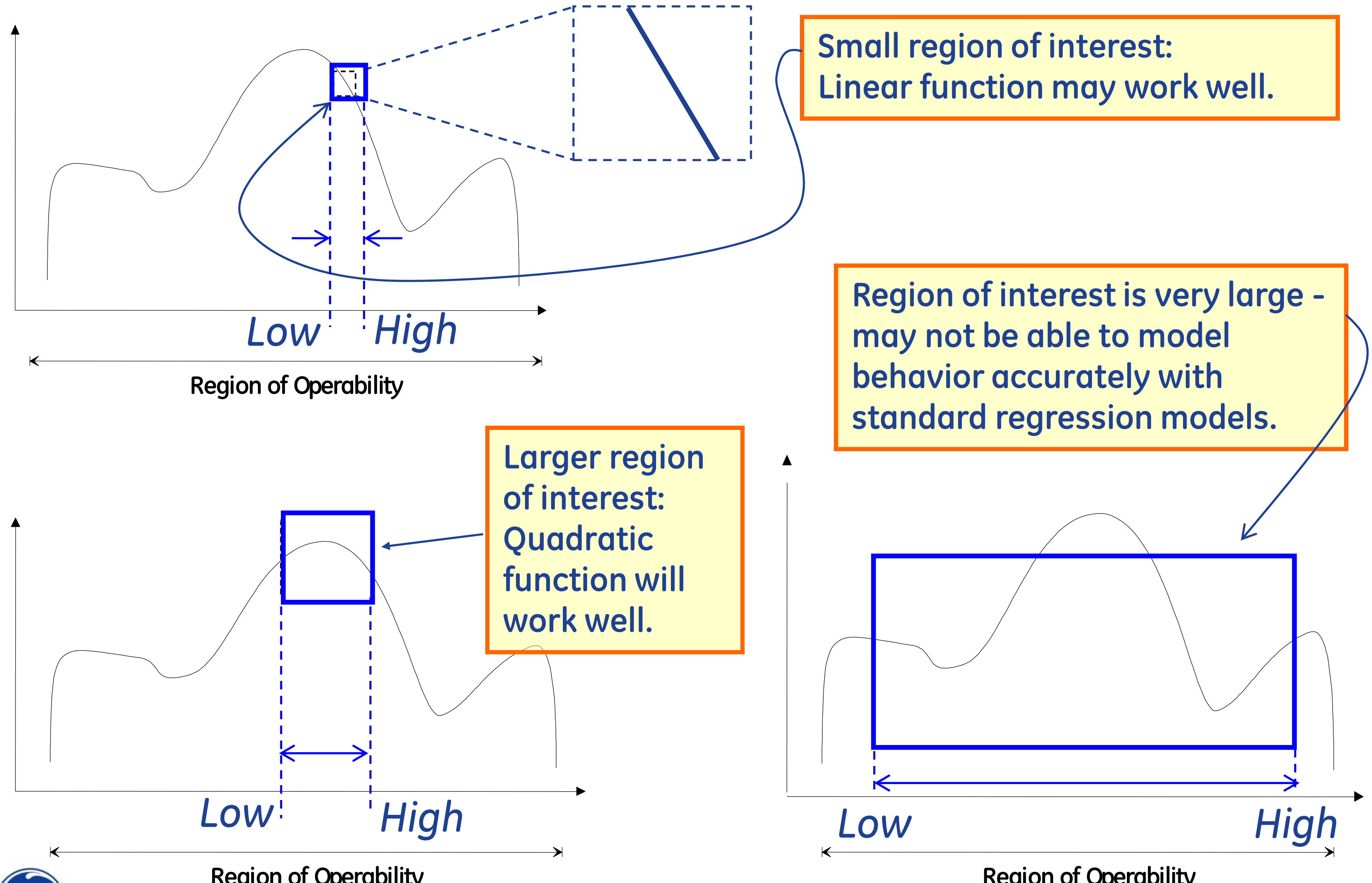
为什么(仅)使用线性或者二次方拟合



Experimental designs available in UNICORN™ 6

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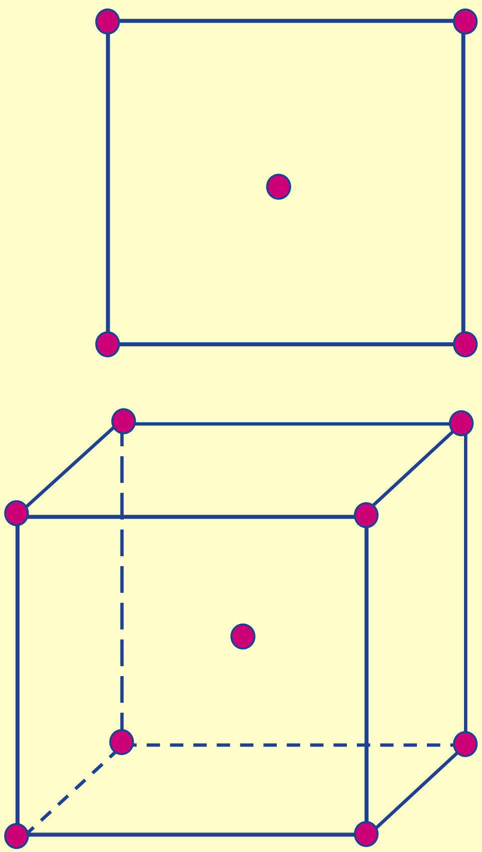
Screening and robustness testing

- Full factorial designs
  - Support for linear effects and all interactions反映线性以及相互作用
- Fractional factorial designs
  - Support for linear and interaction effects, degree of support depends on resolution of design线性、相互作用以及次方的变化
- Plackett-Burman designs
  - Support for linear effects only, useful for robustness testing up to (4*k – 1) parameters in (4*k) experimental runs仅反映线性关系，对于稳定性实验非常有用
- Rechtschaffner screening designs
  - Full support for linear effects and two-factor interactions in a minimal number of runs使用最小的实验数量得到线性和两个因子相互作用
- L9, L27 and L35 designs
  - Support for linear and quadratic effects but not for interactions对于相互作用不适合，寻找二次方的数据

Full Factorial Designs完全因子设计

Full Factorial Designs



2 factors:
4+1 exp

3 factors:
8+1 exp

The number of experiments in a full factorial design increases rapidly with the number of factors

No of factors

$$\# = 2^k + 3$$

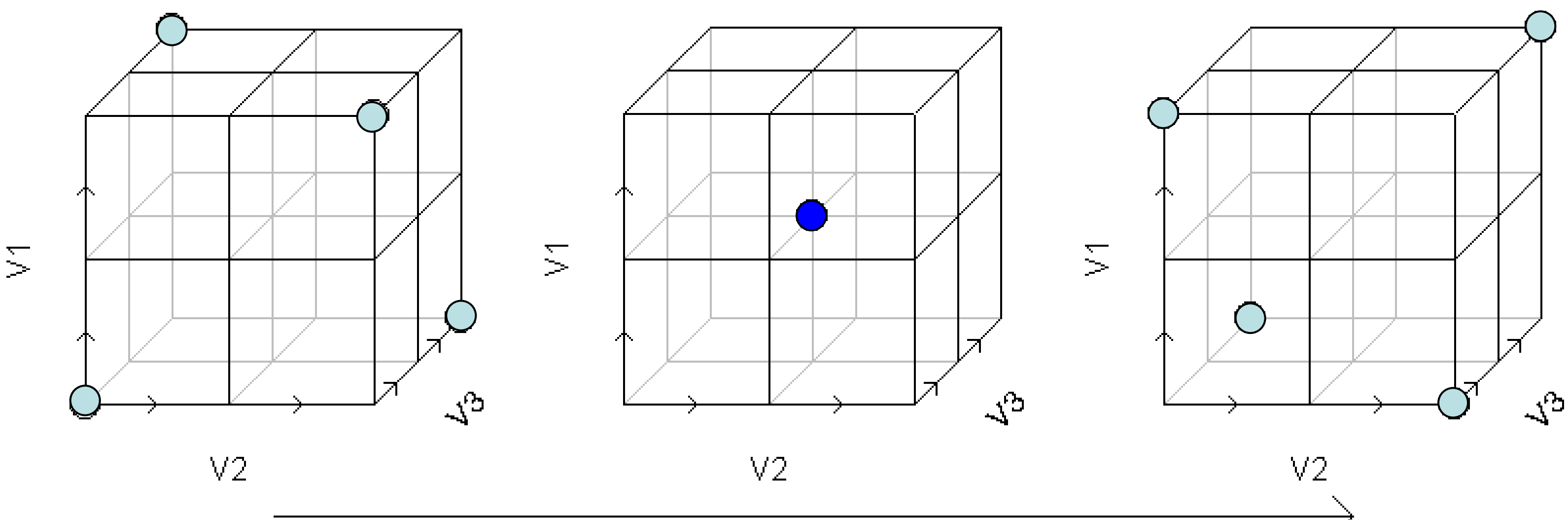
2 levels

Centerpoints
- detection of curvature
- Usually replicated to estimate noise

7 factors -> 128 experiments in a full factorial!

Fractional Factorial Designs部分因子设计

Fractional factorial designs allow testing of many factors with few experiments. So called Resolution V Fractional Factorials allow quantification of interaction effects.



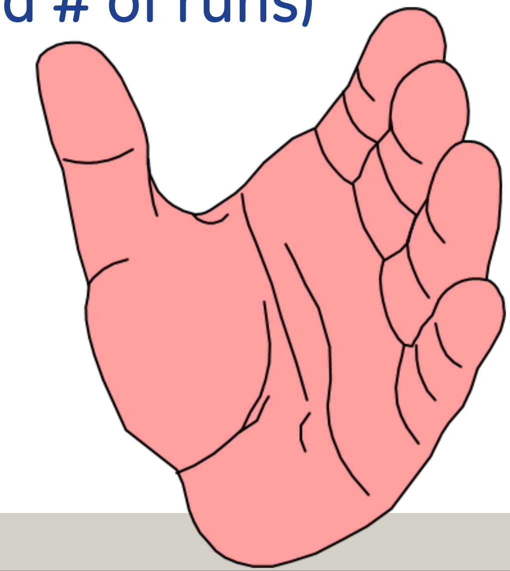
V4 low

V4 center

V4 high

Full and fractional factorial designs

Resolution分辨率级别= f (# of Factors and # of runs)



Factors

Runs	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4	Full	III												
8		Full	IV	III	III	III								
16			Full	V	IV	IV	IV	III	III	III	III	III	III	III
32				Full	VI	IV	IV	IV	IV	IV	IV	IV	IV	IV
64					Full	VII	V	IV	IV	IV	IV	IV	IV	IV
128						Full	VIII	VI	V	V	IV	IV	IV	IV

Plackett Burman screening designs
Plackett Burman 筛选设计

- Designs with resolution III using N=4*k number of runs to investigate up to (N-1) X factors.
- 用分辨度III进行设计，采用4*k次实验能够检测多达（N-1）个因素
- Support only linear effects. However, these are in general heavily confounded with interaction effects.
- 只适用于线性效应。然而，这通常与交互效应严重混淆
- Can be used to economically detect large main effects, assuming interactions are negligible.
- 在交互效应较小时，该设计可以经济的运用于检测数量众多的主要效应
- Highly useful as robustness testing designs for many X factors
- 特别适用于众多因子的稳定性分析设计

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Plackett-Burman 12 run design

- Allows testing up to 11 factors for main effects in 12 runs + center points, assuming interaction effects are negligible.
- Useful for robustness testing (control space verification) of up to 11 factors in 12 runs + center points.

Exp No	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11
1	1	-1	1	-1	-1	-1	1	1	1	-1	1
2	1	1	-1	1	-1	-1	-1	1	1	1	-1
3	-1	1	1	-1	1	-1	-1	-1	1	1	1
4	1	-1	1	1	-1	1	-1	-1	-1	1	1
5	1	1	-1	1	1	-1	1	-1	-1	-1	1
6	1	1	1	-1	1	1	-1	1	-1	-1	-1
7	-1	1	1	1	-1	1	1	-1	1	-1	-1
8	-1	-1	1	1	1	-1	1	1	-1	1	-1
9	-1	-1	-1	1	1	1	-1	1	1	-1	1
10	1	-1	-1	-1	1	1	1	-1	1	1	-1
11	-1	1	-1	-1	-1	1	1	1	-1	1	1
12	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0

Rechtschaffner screening designs
Rechtschaffner 筛选设计

- Designs with resolution V using a minimum number of runs
- 用最少的实验次数进行分辨度V级的设计
- Supports linear and interaction effects for all model terms
- 适用于各种线性和交互效应
- May have some degree of correlation between model terms, but still ok condition number
- 在不同的模型中具有一定程度的关联，但。。。。
- Can be used if # of experiments needs to be as low as possible
- 可以用于尽可能减少实验数

Reference: Saturated fractions of 2^n and 3^n factorial designs, Technometrics 9, 569–576 (1967)

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L9 – L27 – L36 designs
L9 – L27 – L36 设计

- Family of designs that support linear and quadratic model terms, but not all interactions
- 适用于线性和二次模型的设计，但并不适用于所有的互作效应
- Not recommended as a suitable first choice in downstream optimization studies since interaction effects often are present
- 不推荐作为下游优化研究的第一选择，因为经常出现互作效应

- L9 designs: Up to 4 factors in 9 experiments
- L9设计：9次实验可检测多达4因素
- L27 designs: Up to 13 factors in 27 experiments
- L27设计：27次实验可检测多达13因素
- L36 designs: Up to 13 factors in 36 experiments
- L36设计：13次实验可检测多达36因素

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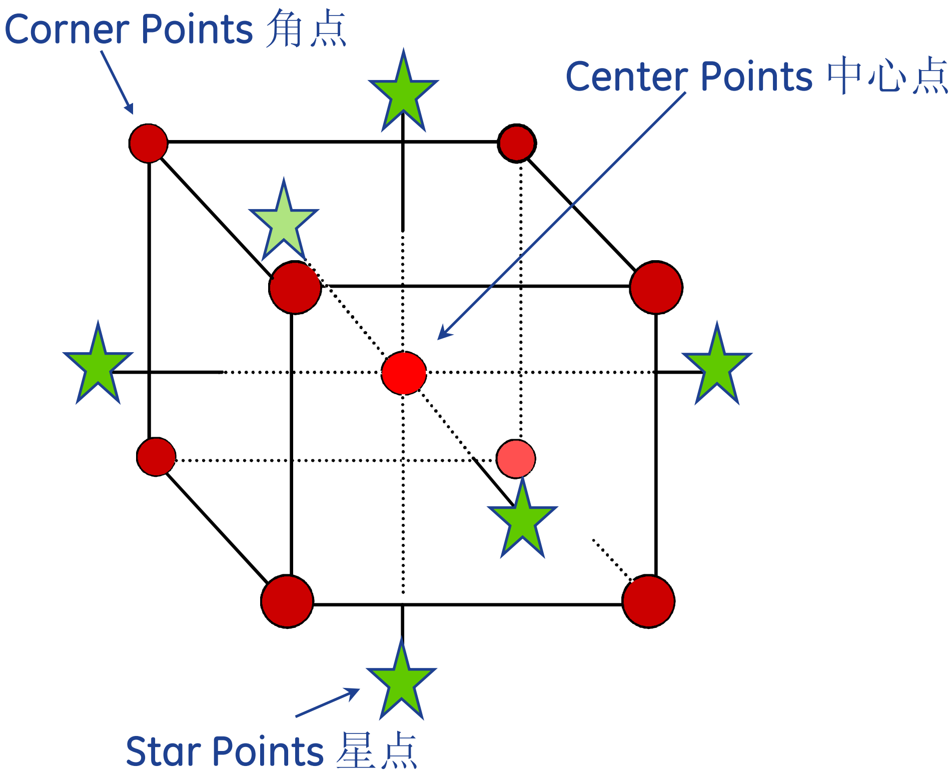
Experimental designs for optimization and response surface modeling (RSM)

- Central composite designs中心复合设计
    - Consist of one factorial part (full or fractional of resolution V) and two star points for each X parameter
- Rechtschaffner RSM designs
    - D-optimal optimization RSM designs, minimal number of runs with support for linear effects, two-factor interactions and qurvature
- Box-Behnken designs
    - RSM designs with experiments located on the edges of the N-dimensional hypercube instead of the corners
- Doehlert RSM designs
    - RSM designs suitable for explorative DoE, can easily be extended in any direction. New factors can be added to an existing design, keeping all previous runs.

Central Composite Designs (CCD's)

Classical designs for response surface modelling (RSM)

中心复合实验设计，经典的响应曲面模型设计方法（RSM)



Corner Points 角点
The factorial part of the design. For the assessment of linear and 2-way interaction terms. 用于评估线性和两-两相互作用的因子部分

Center Points 中心点
Used to detect curvature.
用来评估弯曲效应
Replicated to estimate pure error
重复实验用于评估系统性误差

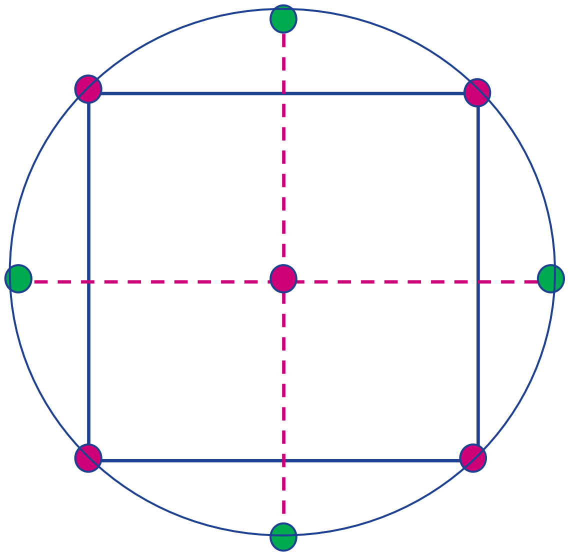
Star Points 星点
For the assessment of quadratic terms. At face or outside the factorial part (corner points). 用于估算2次方程影响，在角点的表面或外部

The CCD's builds upon the traditional factorial designs, and contains additional points for capturing significant curvature effects in the design space. 中心复合实验设计是基于经典的因子设计方法，并用额外的星点来获得重要的曲面效应信息

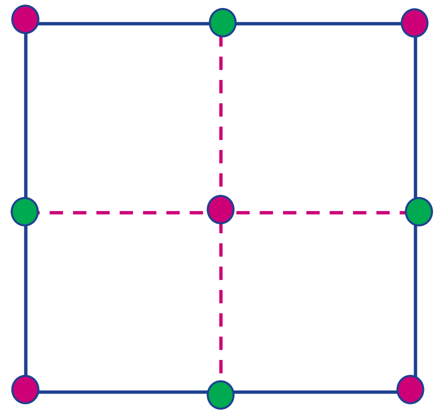
# Runs = Factorial (Full or res V+) + 2n + # of center points
n= # of factors

Central Composite Designs

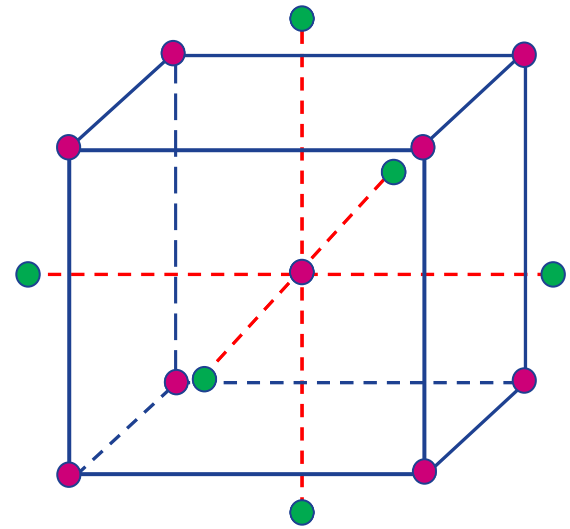
Consist of a factorial part + additional points to quantify curvature effects.包括一个



CCC Design
Central Composite
Circumscribed
中心复合有界设计



CCF Design
Central Composite
Face Centered
中心复合表面设计



CCC Design
Central Composite
Circumscribed

The factorial part in a CC design can be either full or fractional.

Rechtschaffner RSM designs
Rechtschaffner 响应曲面设计

• Designs with resolution V and support for 2nd degree curvature using a minimum number of runs

采用最小的实验次数，具有分辨度V，并且支持2级曲率分析

• Supports linear, interaction and quadratic effects for all model terms

可适用于所有模型的线性，互作和二次效应

• May have some degree of correlation between model terms, but still ok condition number

在一些模型之间有一定程度的交互作用，但条件数可接受

• Can be used if number of experiments needs to be as low as possible

如果想把实验数控制到最低，则采用该方法

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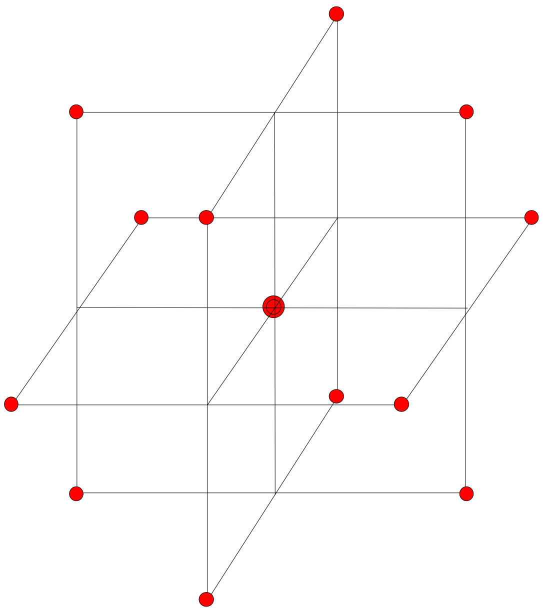
Box Behnken optimization designs
Box behnken优化设计



- Designs that avoid the corner settings with all factors at high/low at the same time
- 该设计避免了拐点处的设置同一时间设置高低值
- Supports linear, interaction and quadratic effects for all model terms
- 可运用于所有模型的线性，互作和二次效应
- Exist for 3-7 factors, especially useful for investigating many (5-7) X parameters
- 具有3-7因子，尤其适用于X参数多（5-7）的研究
- Also suitable for the situation when some corners are not feasible due to process limitations. For example, if temperature, pressure and time are factors, it may not be possible to simultaneously set all three at their high levels.
- 也适用于一些拐角点由于过程限制而不用的情况。比如，如果温度，压力和时间是因子，也许同时设置所有3因子都在高值是不可行的。

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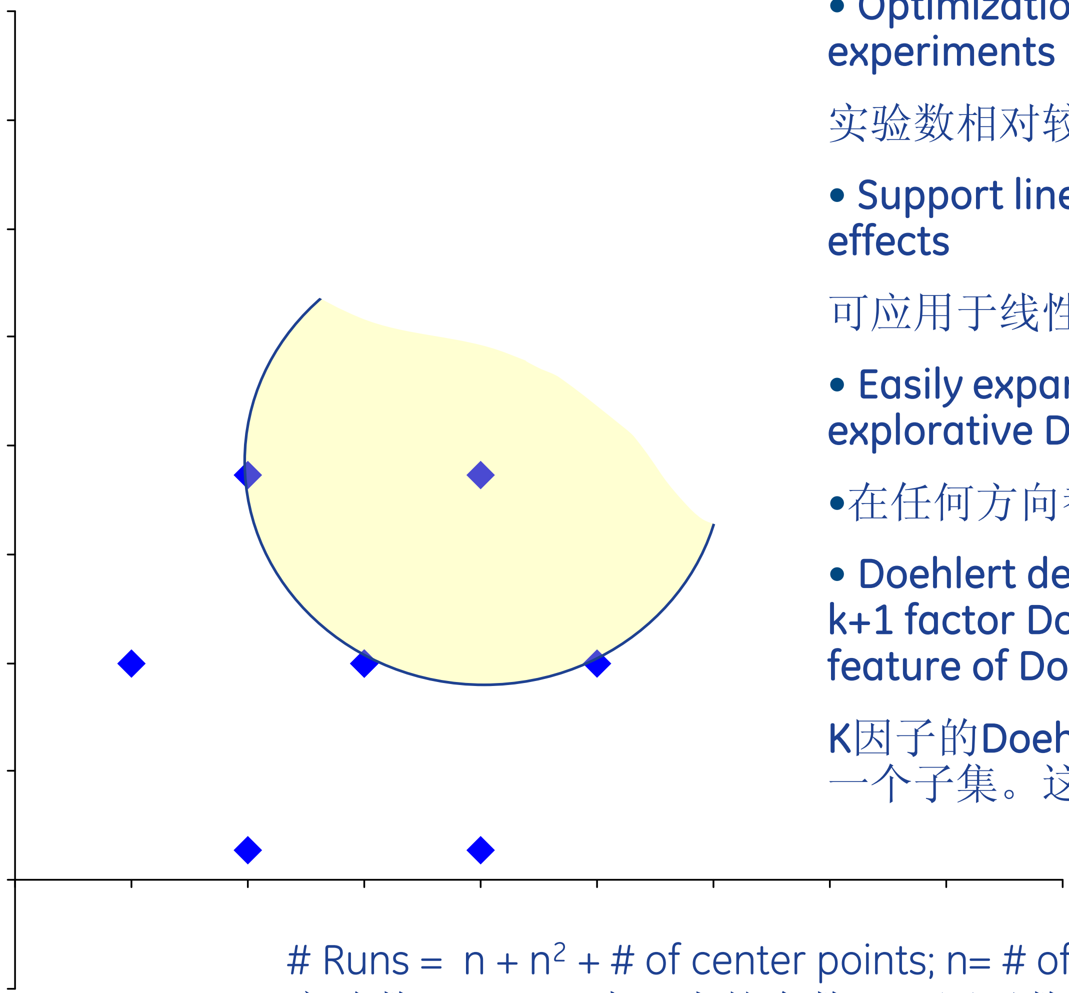
Doehlert optimization designs
Doehlert优化设计



- Optimization designs using relatively few experiments

实验数相对较少的优化设计

- Support linear, interaction and curvature effects

可应用于线性，互作和曲率效应

- Easily expandable in any direction = good for explorative DoE's

•在任何方向都易于扩展=有利于DoE的扩展

- Doehlert design for k factors is a subset of the k+1 factor Doehlert design. This is a unique feature of Doehlert designs.

K因子的Doehlert设计是k+1因子Doehlert设计的一个子集。这是Doehlert设计独有的特点。

Runs = $n + n^2$ + # of center points; n= # of factors)
实验数= $n + n^2$ + 中心点的个数；n=因子数

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Overview of experimental designs

2-7 X parameters, # of runs including three center points

# of runs = f (design type and # of X parameters)	Number of X parameters					
	2	3	4	5	6	7
Full factorial	7	11	19	35	65	131
Fractional factorial res III	--	7	--	11	11	11
Fractional factorial res IV	--	--	11	--	19	19
Fractional factorial res V	--	--	--	19	35	65
Rechtschaffner res V	--	10	14	19	25	32
L9 / L27	9	9	9	27	27	27
Central composite RSM	11	17	27	29	47	81
Rechtschaffner RSM	--	13	18	24	31	39
Box-Behnken RSM	--	15	27	43	51	59
Doehlert RSM	9	15	23	33	45	59

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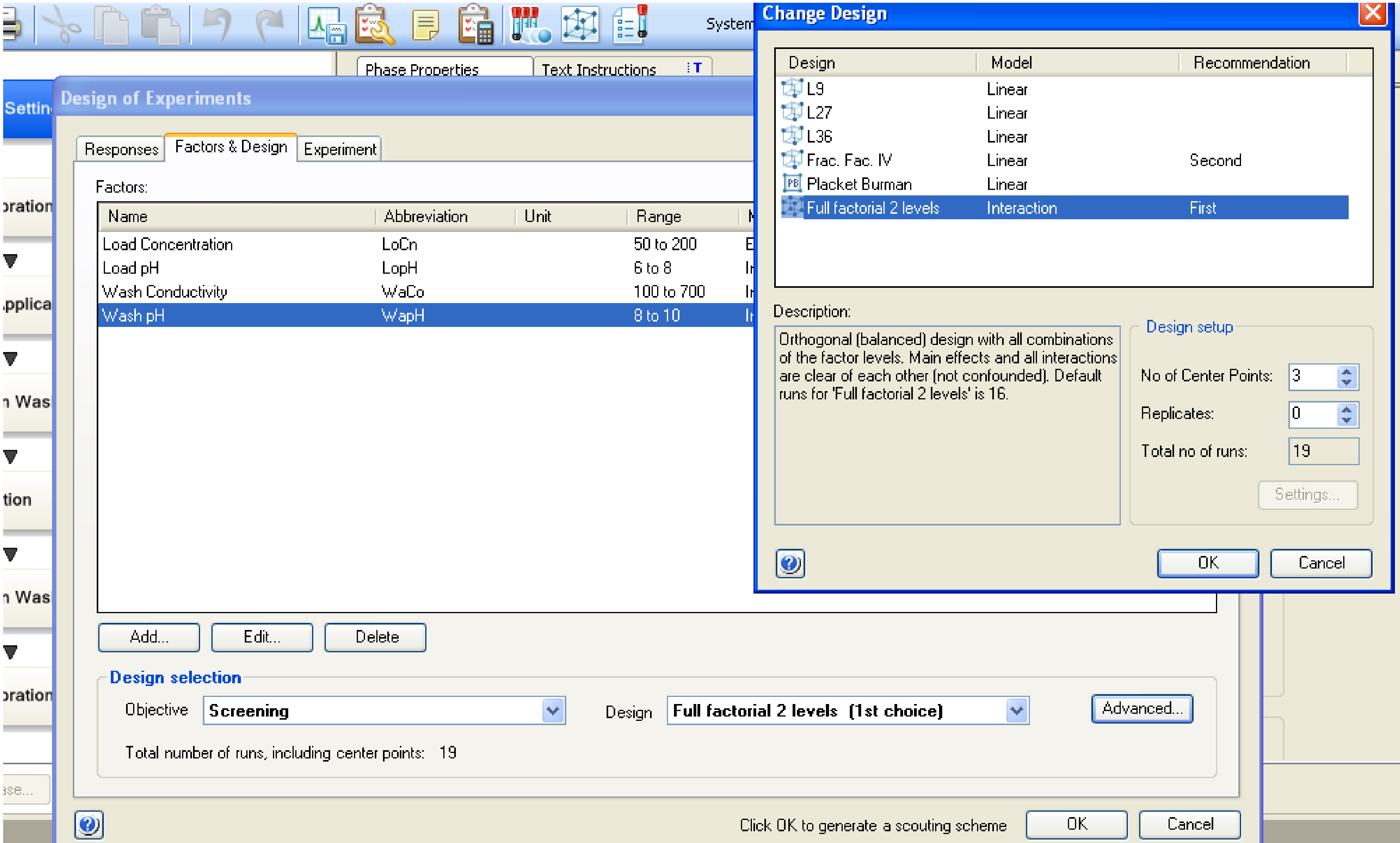
How to choose experimental designs



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Evaluation of results from DoE investigations in UNICORN™ 6

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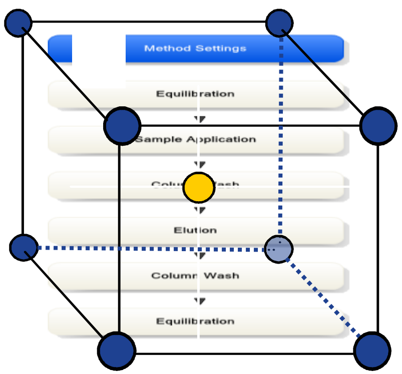
The DoE workflow

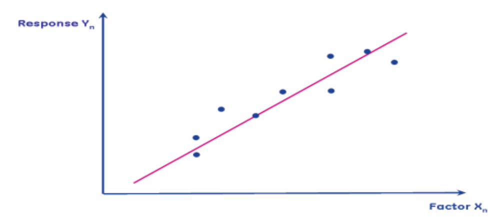
Let UNICORN™ guide you

DoE method scheme

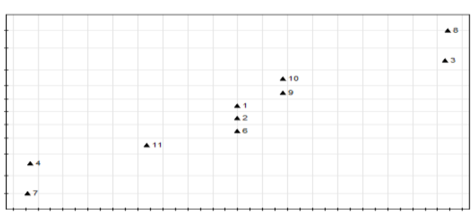


Scouting run

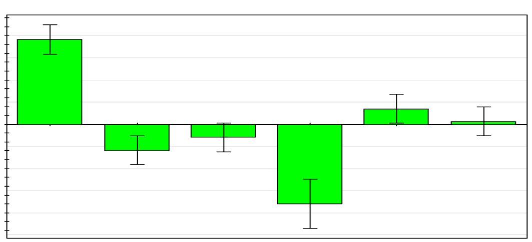
Model creation



Model validation



Decision using model



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Three stages of data analysis

1. Evaluation of raw data准确的原始数据

- *done to understand and clean data, and speed up modelling*

2. Regression analysis and model interpretation

回归分析——模型是否准确

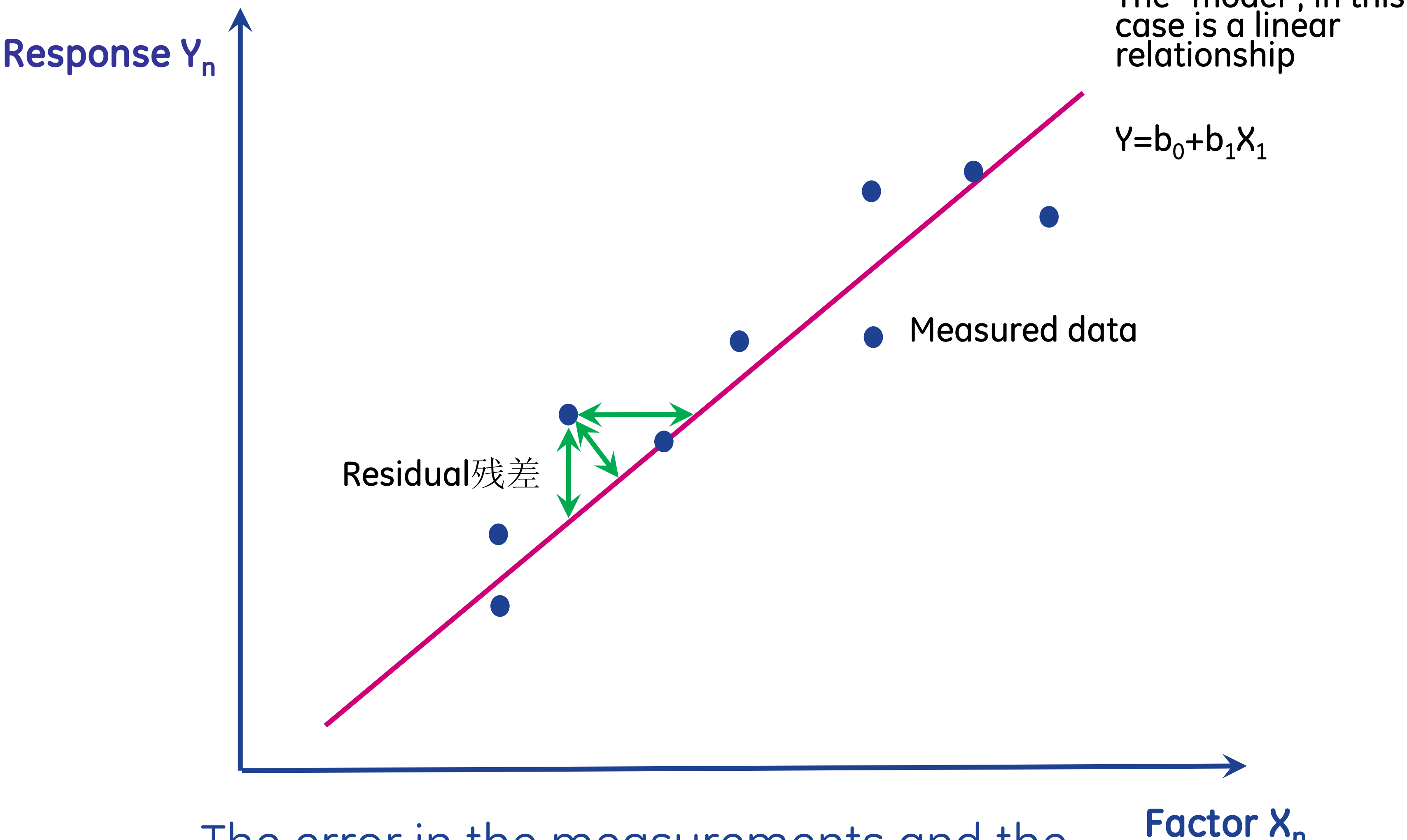
- *done to derive the predictively most relevant model*

3. Use of model 使用模型

- *done to find out the impact of the model: What does it mean? Where should new experiments be positioned?*

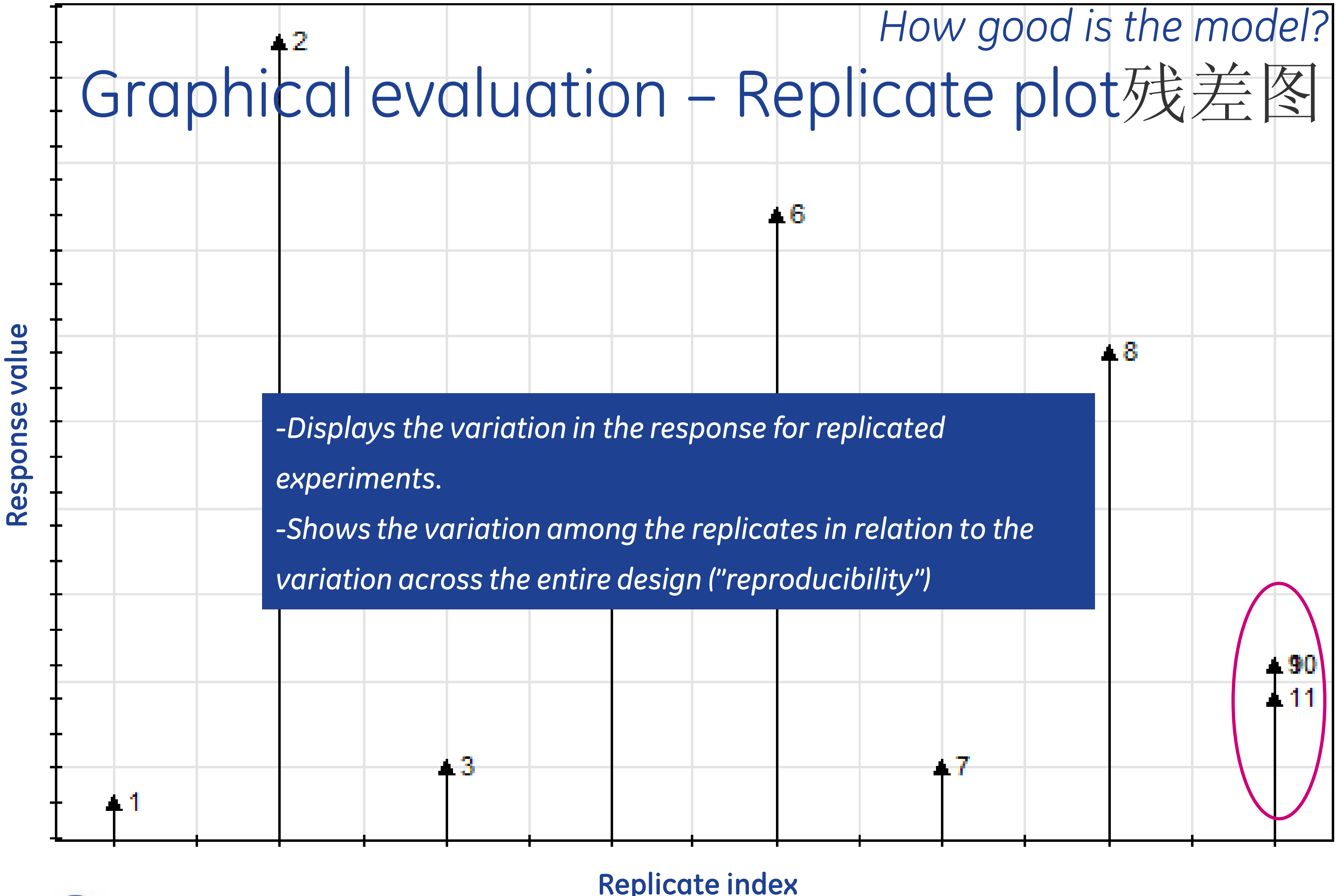
Remember to validate the results!

A model explained



The error in the measurements and the deviations from the model we call residuals.
残差是指实际观察值与回归估计值的差。

Graphical evaluation – Replicate plot残差图



-Displays the variation in the response for replicated experiments.

-Shows the variation among the replicates in relation to the variation across the entire design ("reproducibility")

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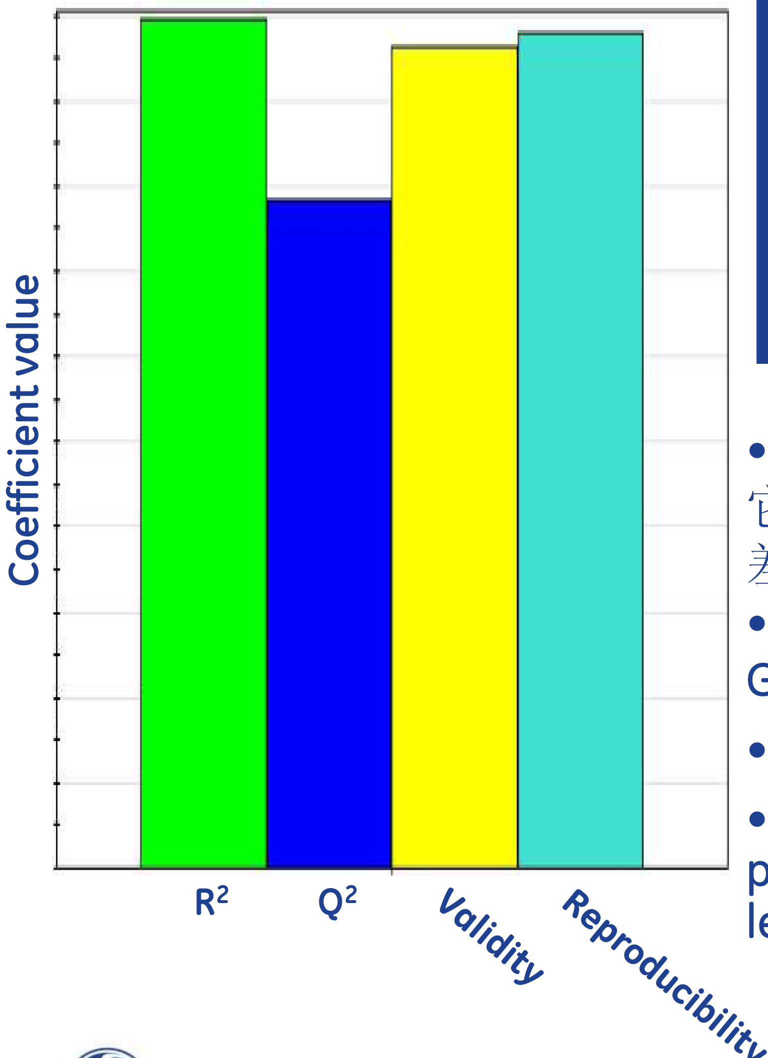
Graphical evaluation– Summary of fit plot



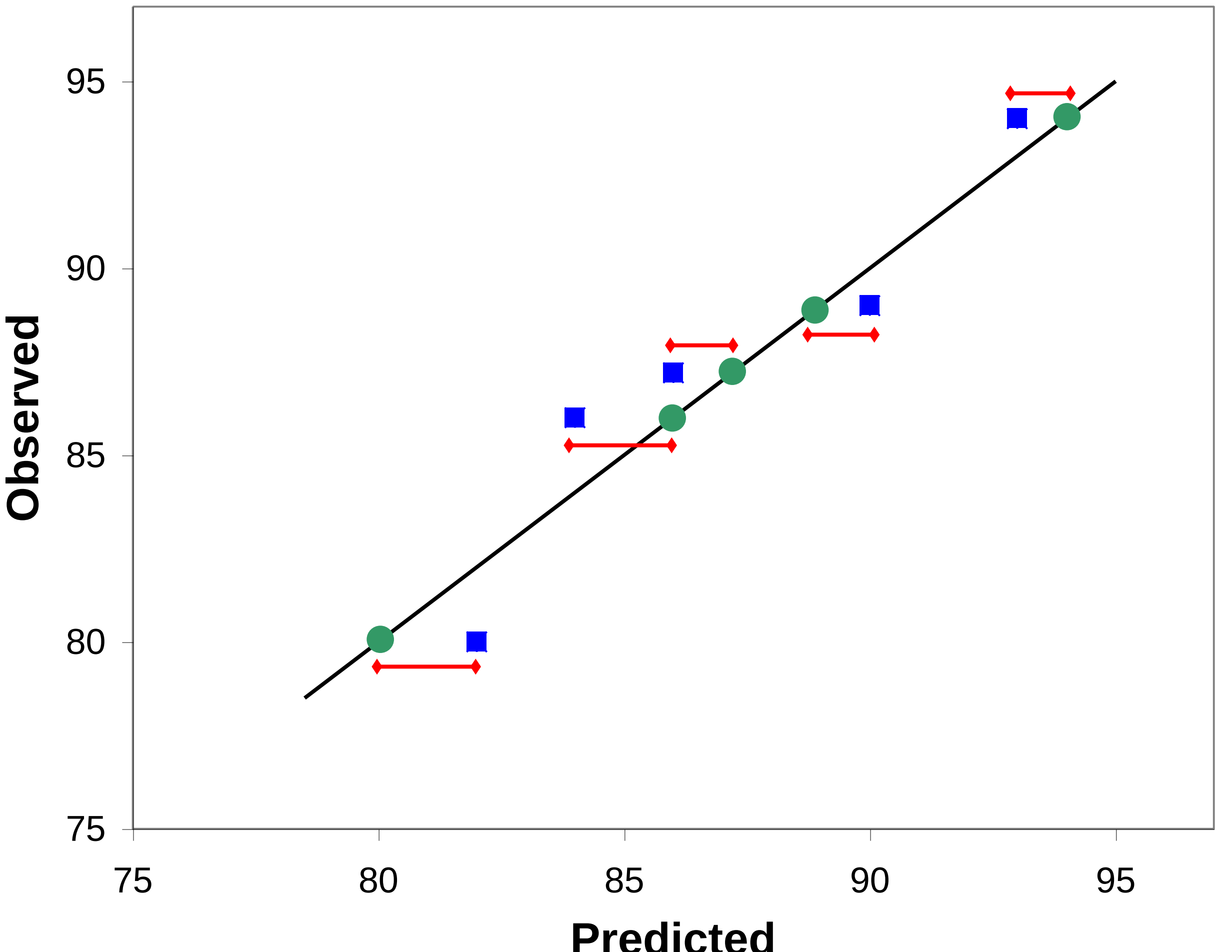
- *R^2 Model fit*
- *Q^2 predictive power*
- *Model validity*
- *Reproducibility (replicate variation).*

-R^2 Q^2 is based on model, external validation needed

- R2叫判定系数,是回归直线拟合直线程度的综合度量,它的范围是0-1,越接近1,就说明可用x变化来解释 y值变差的部分就越多,拟合程度就越高.反之亦然
- Q2揭露模型是否可以预测未来的实验结果： Q2>0.5 Good, Q2>0.9 Excellent!
- 模型有效性 >0.25 indicates a good model
- 重复性 is below 0.5 you have a large pure error and poor control of the experimental procedure (high noise level)

R^2 Model Statistic

How well does the model fit my data?



Obs vs Pred

Perfect Fit（完美拟合）

Residuals（残差）

Total Variation =
= Variation Explained by Model + Residual Variation

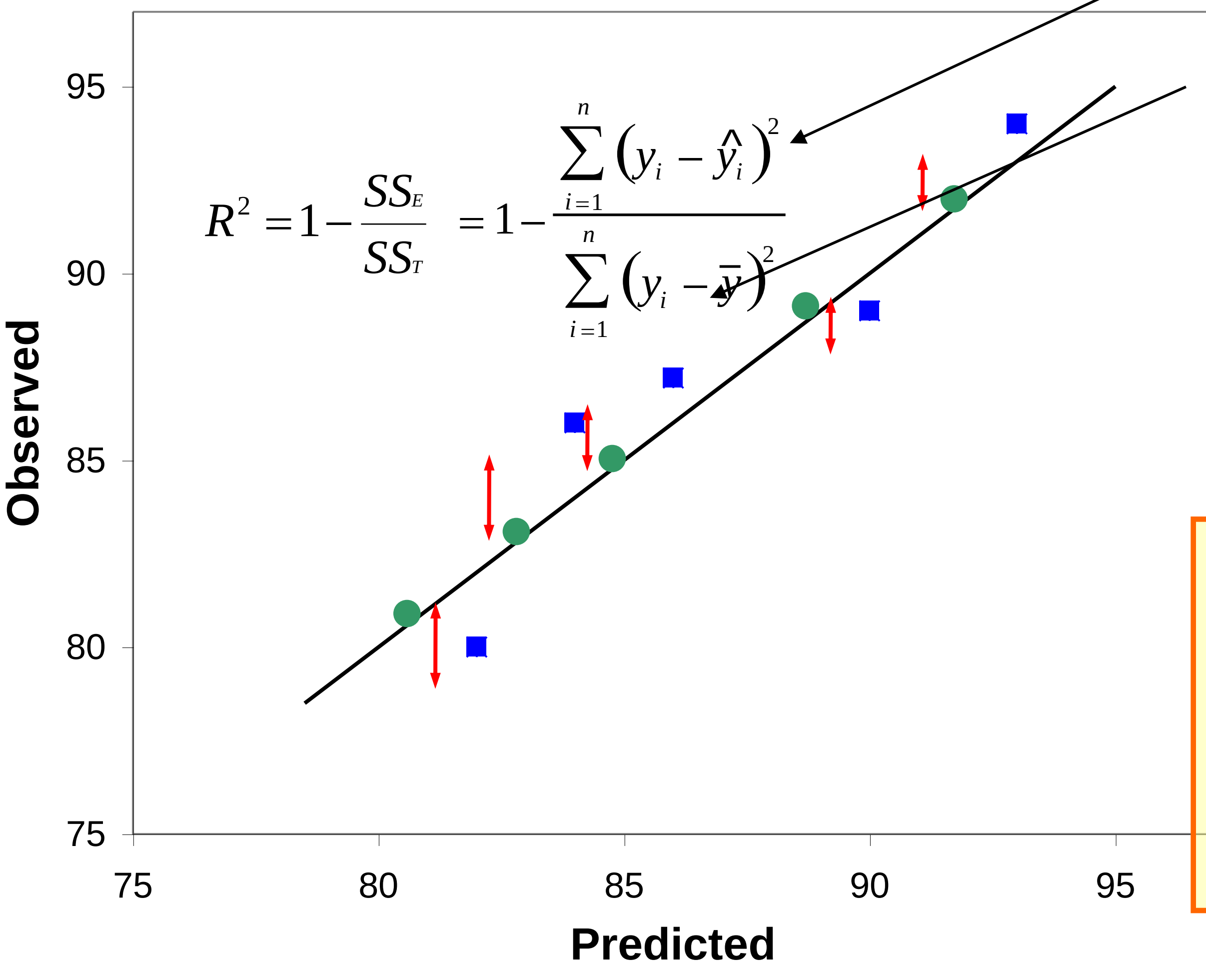
R^2 Model Statistic R^2 模型统计

How well does the model fit my data? 模型和我得数据拟合度如何？

Sum of squares of the residuals
残差平方的总和

Total sum of squares 平方的总和

$$R^2 = 1 - \frac{SS_E}{SS_T} = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (y_i - \bar{y})^2}$$



Obs vs Pred

Perfect Fit

Residuals

观察值vs预测值

完美拟合

残差

R2 = the fraction of total variation explained by the model

R^2 > 0.75 is generally considered OK.

R^2 = 模型所解释的总变异的部分

R^2 >0.75时总体上认为OK

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Total Variation =
= Variation Explained by Model + Residual Variation
总变异=模型所解释的变异+残差变异

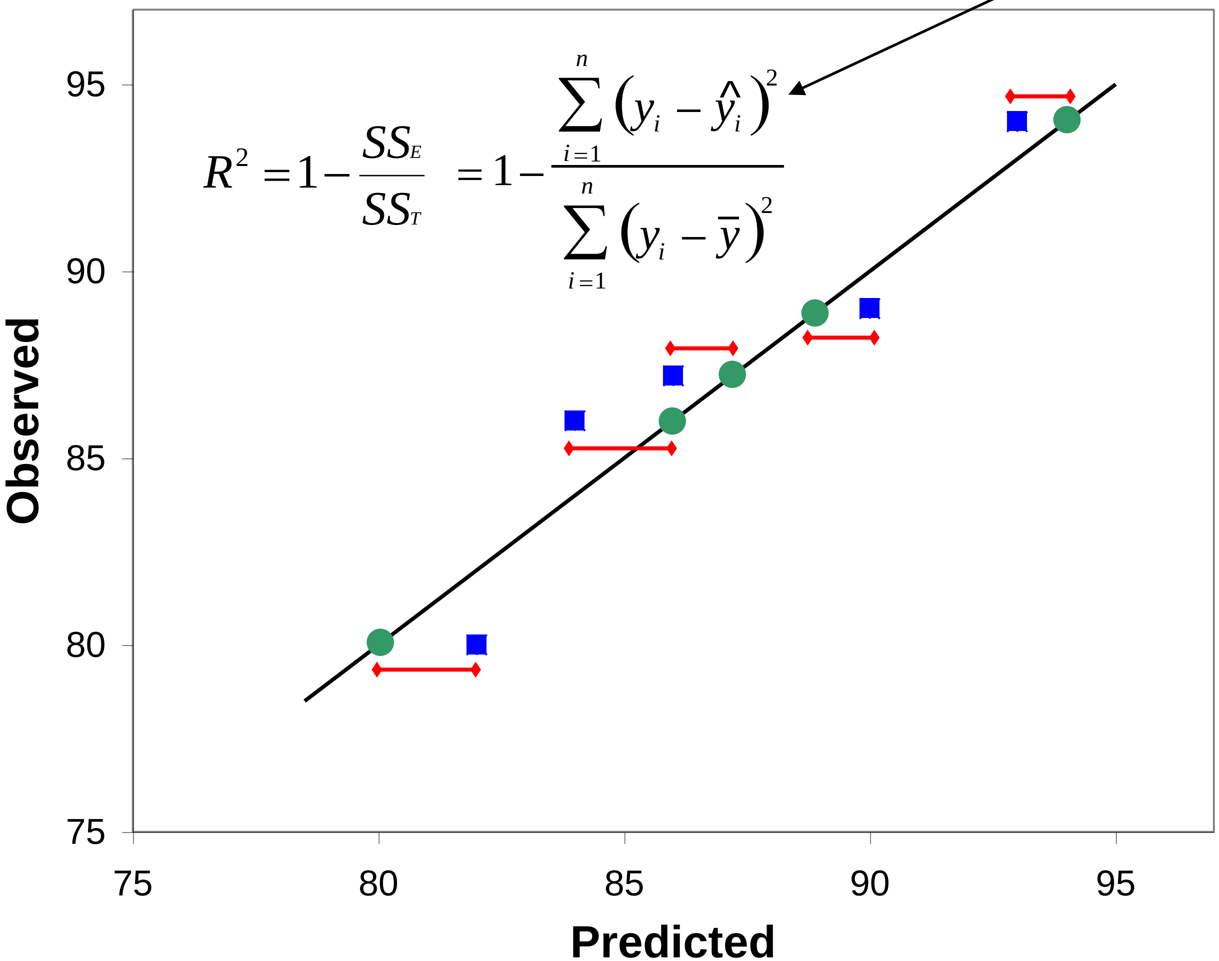
R^2 Model Statistic

How well does the model fit my data?

Sum of squares of the residuals
残差平方的总和

Total sum of squares 平方的总和

$$R^2 = 1 - \frac{SS_E}{SS_T} = 1 - \frac{\sum_{i=1}^{n}\left(y_i - \hat{y}_i\right)^2}{\sum_{i=1}^{n}\left(y_i - \bar{y}\right)^2}$$



Obs vs Pred

Perfect Fit

Residuals

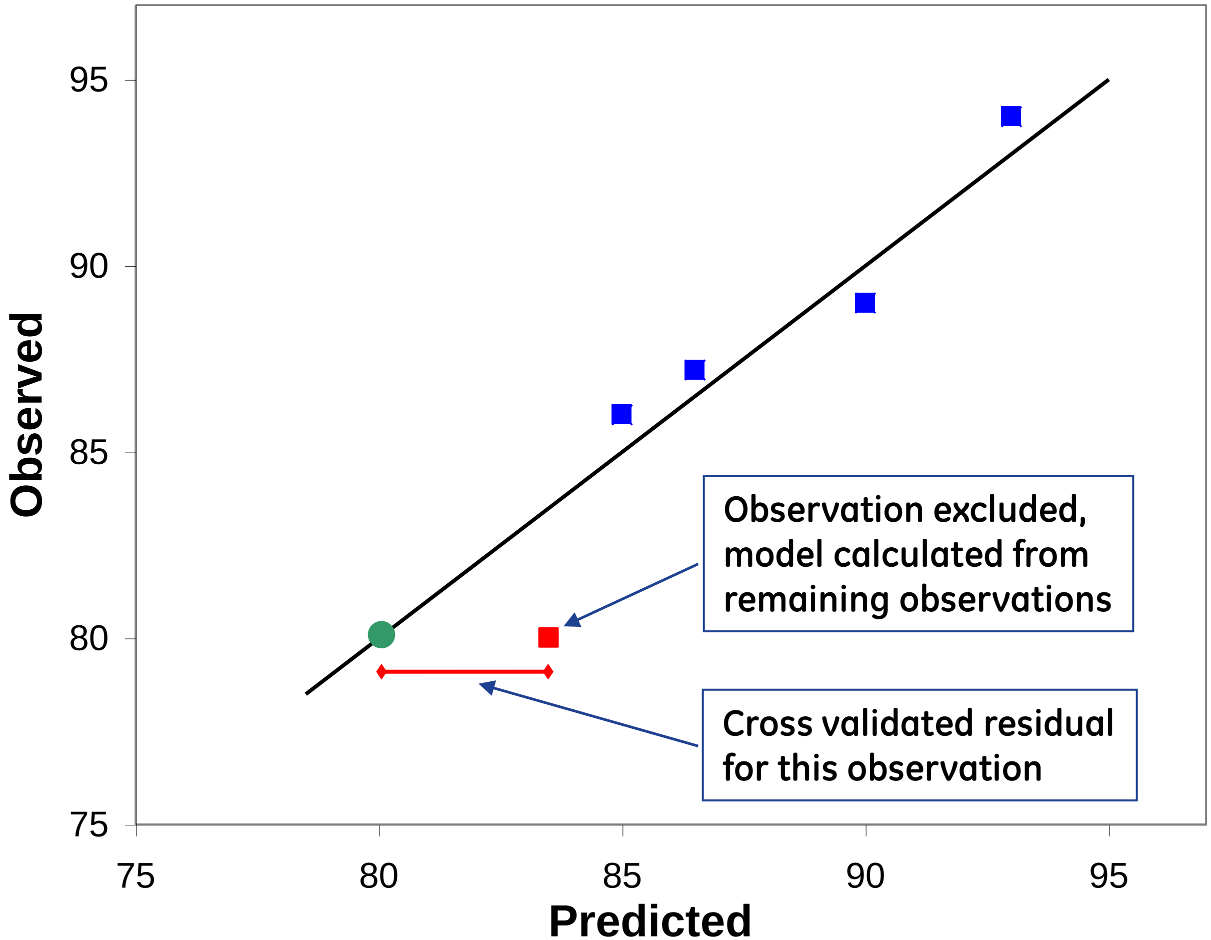
R^2 = the fraction of total variation explained by the Model

$R^2 > 0.75$ is generally considered OK.

Total Variation =
= Variation Explained by Model + Residual Variation

Q^2 Model Statistic

How well will the model work in future predictions?



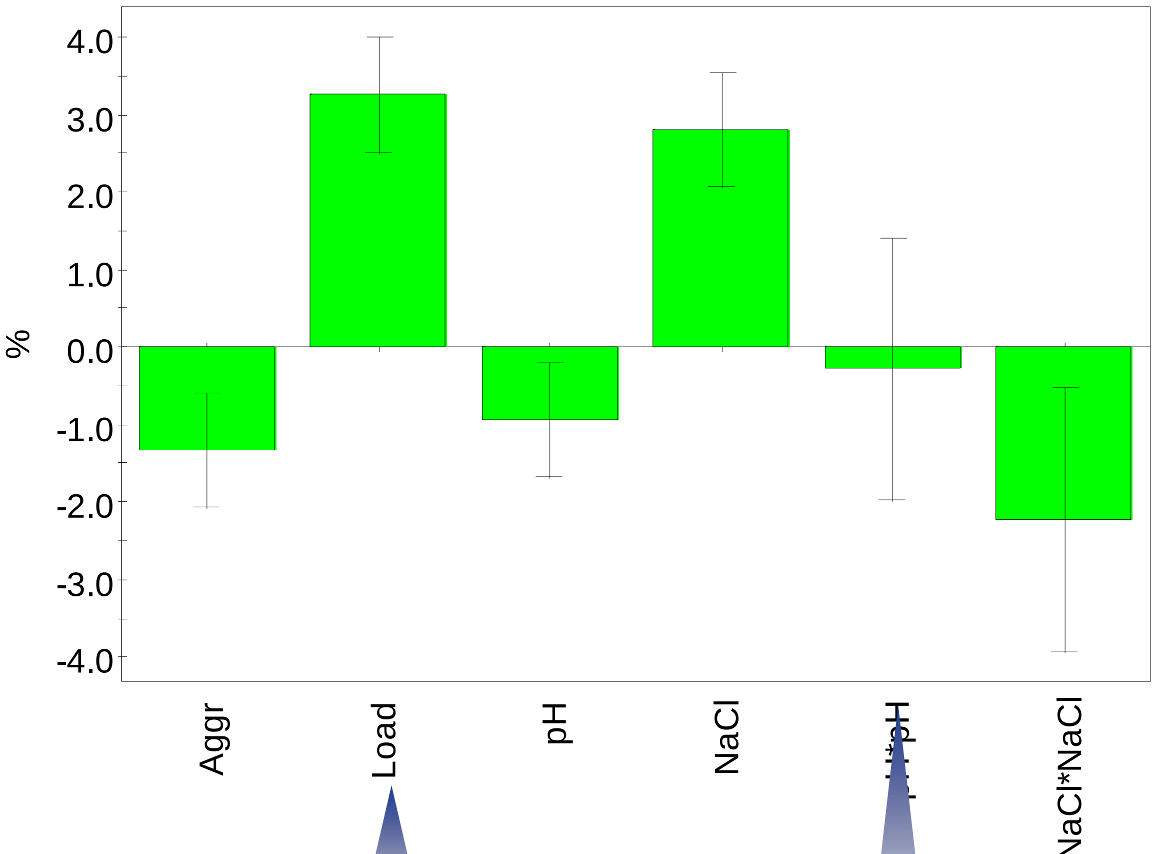
Q^2 is calculated using cross-validation to estimate predictive power

1. Exclude observation
2. Fit model to remaining observations
3. Predict and calculate residual for excluded observation.
4. Include observation and exclude another.
5. Repeat from 1. Until all observations have been excluded exactly once.

Comment: Q^2 is also called R^2 predicted.

Model Coefficient Plot模型的系数图

Which parameters have a significant impact on the responses?



Estimates the real effects

Non-signficant term!

The plot shows the transfer function coefficients and their confidence intervals
显示转换方程的系数和置信区间.

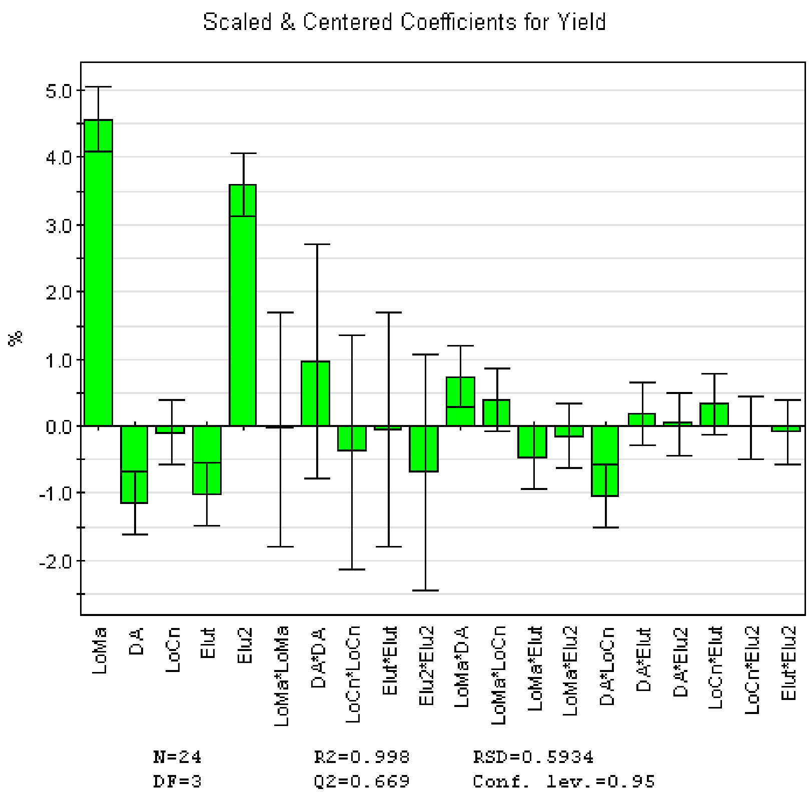
Useful when refining model by removal of insignificant terms.精简模型时去除不重要的方程项

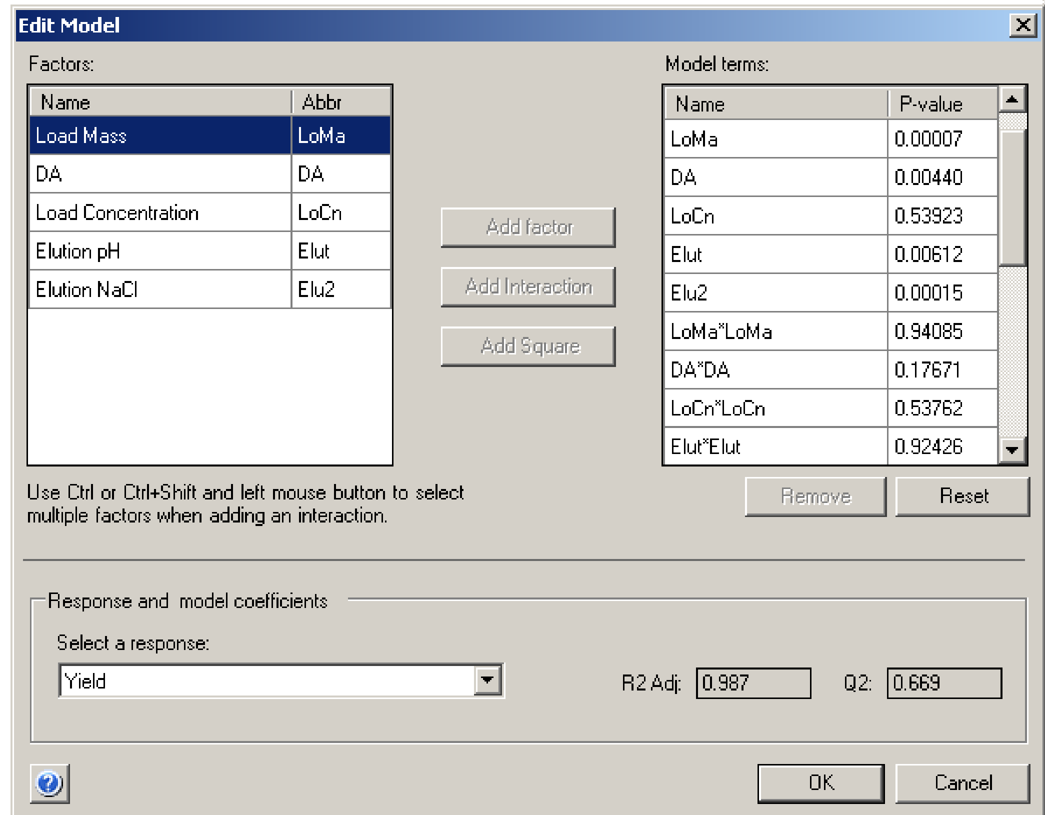
Shows the relative impact of the different Factors.
显示不同因子之间的相互影响

Interpretation from this plot can be tricky when interactions or curvature are present.

Model coefficient lists with p-values

p-value = probability that model term is NOT significant





Edit model dialogue in UNICORN™ 6 above, determine statistical significance by p-values and/or coefficient plot.

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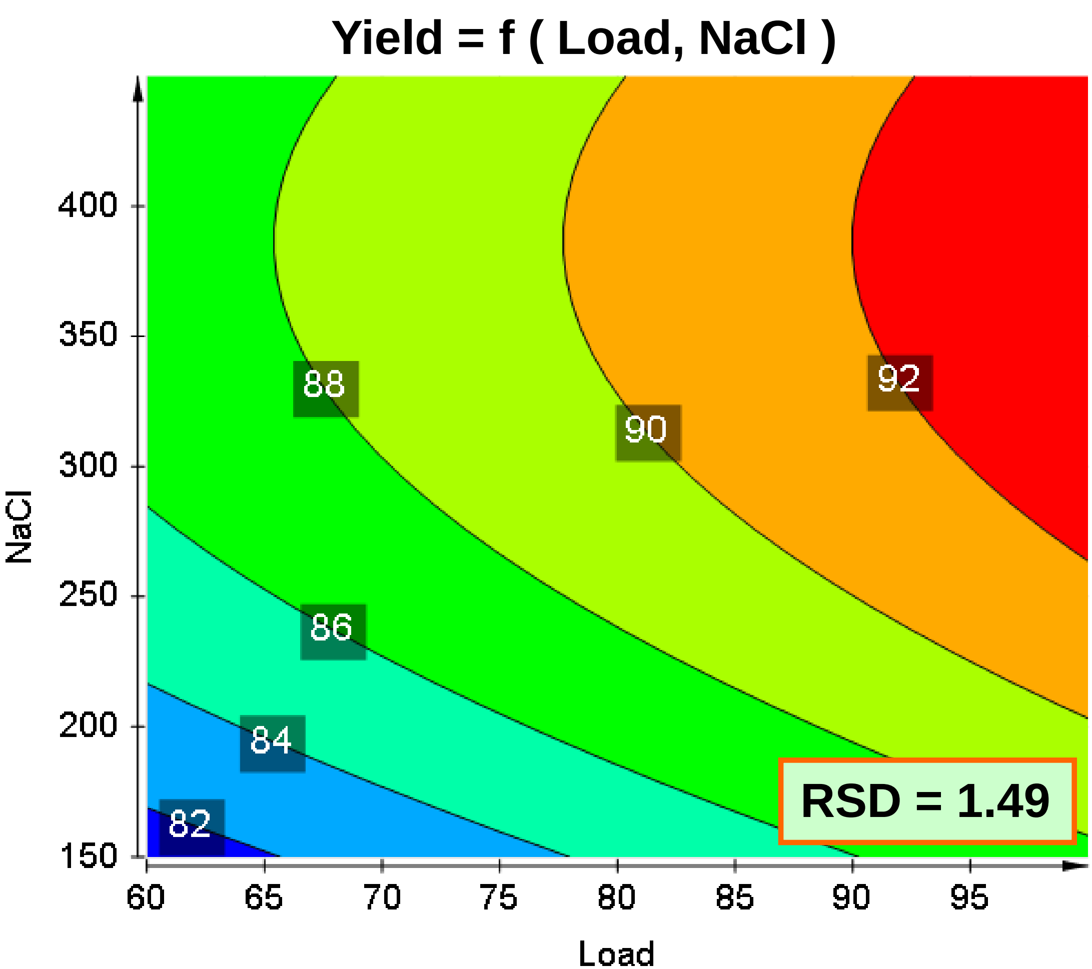
Response Surface Plots响应面



Response Surface Plots are very useful to visualise the combined effect from 2-4 factors.

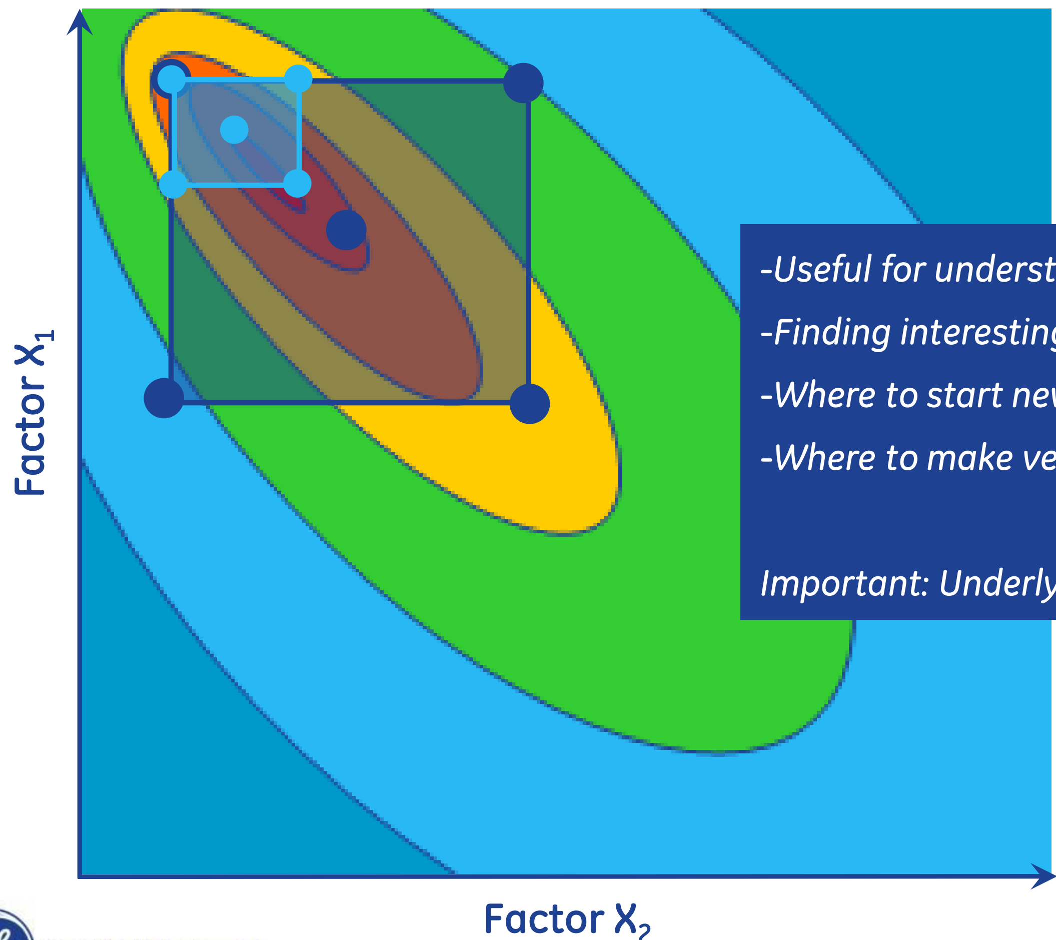
Great tool for interpretation of interactions and curvature effects. Domain knowledge - effects should always make sense!

Always consider RSD when looking at these plots. Model uncertainty is approx. +/- 2*RSD.

Map of the process (response contour plot)

-DoE could play an important role in decision making!

-Convert modeling results into actions!



-Useful for understanding the impact of large interactions

-Finding interesting area

-Where to start new investigation

-Where to make veryfing experiments

Important: Underlying model must be good (high Q2) !!!

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The ANOVA Table 1:4

Yield	DF	SS	MS (variance)	F	p
Total	30	228469	7615.62		
Constant	1	227993	227993		
Total Corrected	29	475.609	16.4003		
Regression	5	422.363	84.4727	38.075	**0.000**
Residual	24	53.2461	2.21859		
Lack of Fit (Model Error)	21	50.9661	2.42696	3.19335	**0.184**
Pure Error (Replicate Error)	3	2.28001	0.760002		
	N = 30	Q2 =	0.807	Cond. no. =	2.924
	DF = 24	R2 =	0.888	RSD =	1.489
		R2 Adj. =	0.865		

The ANOVA table is a classical regression analysis tool that answers two questions:

Q1:
Is the model as a whole statistically significant?统计学上是否有意义？

Q2: Compared with the variation between replicates, is the size of the residual variation ok or too large , i.e. does the model suffer from lack of fit or not?

方差分析（ANOVA）又称“变异数分析”或“F检验”，是R.A.Fister发明的，用于两个及两个以上样本均数差别的显著性检验。

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The ANOVA Table 2:4

Is the model as a whole statistically significant?

Yield	DF	SS	MS (variance)	F	p
Total	30	228469	7615.62		
Constant	1	227993	227993		
Total Corrected	29	475.609	16.4003		
Regression	5	422.363	84.4727	38.075	**0.000**
Residual	24	53.2461	2.21859		
Lack of Fit	21	50.9661	2.42696	3.19335	**0.184**
(Model Error)					
Pure Error	3	2.28001	0.760002		
(Replicate Error)					
	N = 30	Q2 =	0.807	Cond. no. =	2.924
	DF = 24	R2 =	0.888	RSD =	1.489
		R2 Adj. =	0.865		

Variance explained by model

Residual variance

F-value: Ratio Model/Residuals

p for F-value =
= Probability of model being non-significant.

P < 0.05 = OK

对应回归项（Regression）的p-value <0.05, 则表明应拒绝原假设,本模型总的说来是有效的. 对应回归项的p-value >0.05, 则表明无法拒绝原假设, 即可以判定, 本模型总的说来是无效的.

The ANOVA Table 3:4

Is there any significant lack of fit?

Yield	DF	SS	MS (variance)	F	p
Total	30	228469	7615.62		
Constant	1	227993	227993		
Total Corrected	29	475.609	16.4003		
Regression	5	422.363	84.4727	38.075	0.000
Residual	24	53.2461	2.21859		
Lack of Fit (Model Error)	21	50.9661	2.42696	3.19335	**0.184**
Pure Error (Replicate Error)	3	2.28001	0.760002		
	N = 30	Q2 =	0.807	Cond. no. =	2.924
	DF = 24	R2 =	0.888	RSD =	1.489
		R2 Adj. =	0.865		

Residual variance excluding replicates

Replicate variance

F-value: Ratio Model/Residuals

p for F-value =
= Probability of no Lack of Fit.

P > 0.05 = OK

The ANOVA Table 4:4

Some additional model statistics are also included

Yield	DF	SS	MS (variance)	F	p
Total	30	228469	7615.62		
Constant	1	227993	227993		
Total Corrected	29	475.609	16.4003		
Regression	5	422.363	84.4727	38.075	**0.000**
Residual	24	53.2461	2.21859		
Lack of Fit	21	50.9661	2.42696	3.19335	**0.184**
(Model Error)					
Pure Error	3	2.28001	0.760002		
(Replicate Error)					
	N = 30	Q2 = 0.807		Cond. no. = 2.924	
	DF = 24	R2 = 0.888		RSD = 1.489	
		R2 Adj. = 0.865			

Condition number, measures how orthogonal the design is, lower is better.
Screening DoE's < 6
Curvature DoE's < 12

Residual Standard Deviation, should be in agreement with measurement error

R^2 = fraction of variance explained by model.
Q^2 = estimate of model's predictive power

$R^2_{adjusted} = R^2$ corrected for degrees of freedom lost when calculating model

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Use the model - Prediction list

- *Predict the responses for "new" factor settings using the model*

Prediction

Load Mass	Load Conductivity	Load pH	HCP Content	Lower	Upper	Recovery MassOut/MassIn	Lower	Upper	Aggregate Content	Lower	Upper
125	15	6.25	8.420884	7.253068	9.5887	86.4017	84.06287	88.74052	0.5378709	0.3989147	0.6768271
150	20	6.5	9.153082	8.097614	10.20855	89.05223	86.93841	91.16605	0.6624237	0.5368357	0.7880117
175	25	6.75	11.19658	10.01753	12.37564	90.25169	87.89036	92.61303	0.7736544	0.6333611	0.9139477

Use the model - Optimizer

- When moving the experimental region to a optimum

Goal: Adequate re-positioning of the experimental region

Optimization Criteria

Factors

Factor	Role	Value	Low Value	High value
Load Mass	Free		100	300
Load Conductivity	Free		10	30
Load pH	Free		6	7.5

Responses

Response	Criteria	Weight	Min	Target	Max
HCP Content	Minimize	1		10	50
Recovery MassO...	Maximize	1	75	90	
Aggregate Content	Minimize	1		0.3	1.5

Result

Calculate Optimal Settings | Clear

Factor | Response

Experiment

Load Mass	Load Conductivity	Load pH	HCP Content	Recovery MassOut/MassIn	Aggregate Content	Iter	Log(D)
136.667	29	6.5	8.2452	84.0381	0.6364	13	-1.1031
260	10	6	26.5124	94.7974	0.6149	0	-1.0982
100	10	7.2	3.2458	85.1485	0.5365	0	-1.3204
260	28	7.5	25.0749	88.3417	0.8848	0	-0.8841
200	20	6.75	13.4821	94.3314	0.8028	0	-1.2144
282	10	7.5	26	92.8999	0.65	0	-1.0878
192	20	6.75	12.6667	93.5666	0.7867	0	-1.2494
192	20	6.75	12.6667	93.5666	0.7867	0	-1.2494

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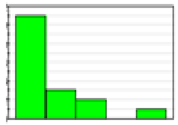
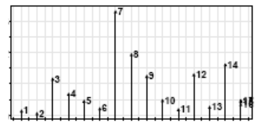
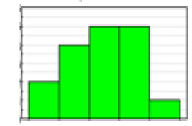
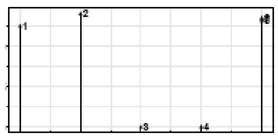
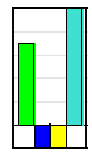
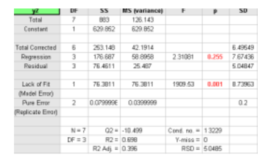
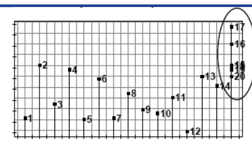
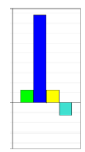
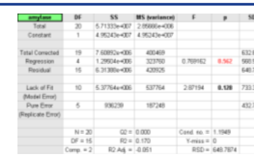
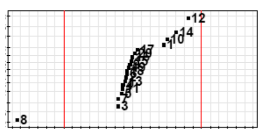
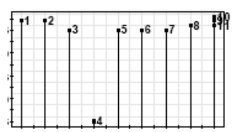
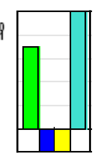
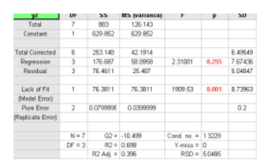
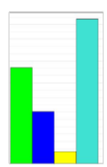
How to deal with bad models

Causes of bad model<	Primary Detection Tools	Action
Skew response distribution (e.g. Low conc)	Histogram or replicate plot  	Log transformation 
Curvature	Replicate plot Low Q2 & Model Validity LoF (ANOVA)   	removal of non significant two-factor interaction addition of quadratic terms refitting of model
Bad replicates	Replicate plot ANOVA table Reproducibility   	New experiments?
Deviating experiments	N-Plot of residual Replicate plot Model validity Lack of fit in ANOVA    	Data entered wrongly? Incorrect experiment? Correct result => Model inappropriate for the area
Missing factors	Model with moderate R2 (~0.6) and Q2 (~0.4) 	Uncontrolled continous or uncontrolled discrete More experiments?

Summary

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Summary

DoE addresses three experimental situations:

- Screening
- Optimization
- Robustness testing

DoE solves problems where the “COST”-approach fails:

- Interaction effects can be detected and quantified
- True effects can be separated from noise
- You can afford to investigate more factors
- Truly optimal conditions can be found, even in the presence of several objectives (responses) with conflicting requirements
- More knowledge is generated during process development

DoE is a cornerstone for the FDA PAT initiative!

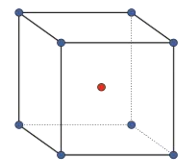
The DoE workflow DOE工作流程

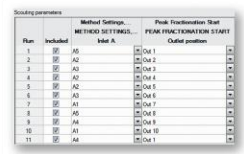
Unicorn编辑方法
UNICORN method

实验设计输入
Design input

- Definition of factors, factor types and settings
- Definition of objective for creating the design

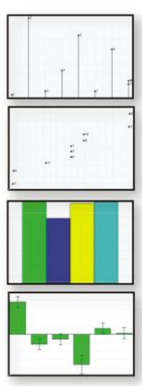
实验设计和工艺探索
Design and scouting

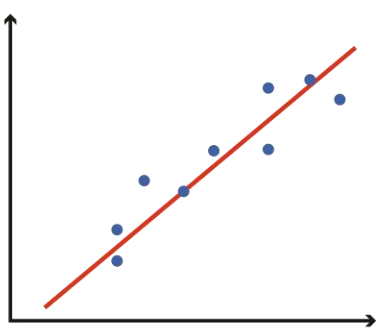




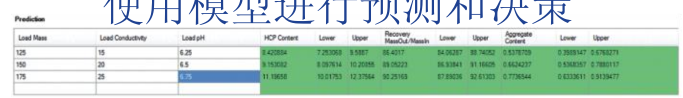
运行
Run

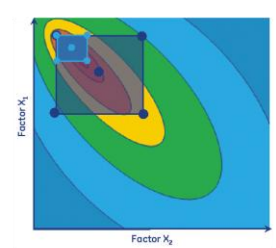
Model evaluation
模型评估

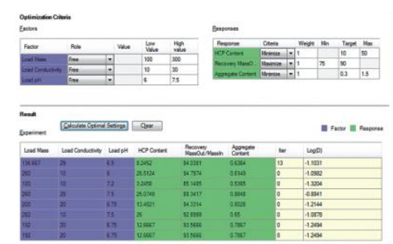




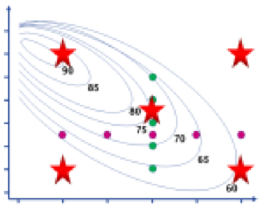
Use of model for prediction and decisions
使用模型进行预测和决策





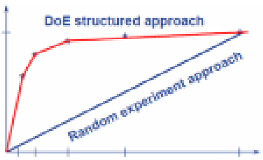


DoE benefits

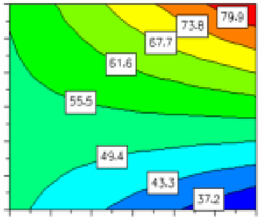


Truly optimal conditions are found allowing better processes（通过

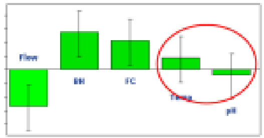
优化工艺找到真实地最优操作条件）



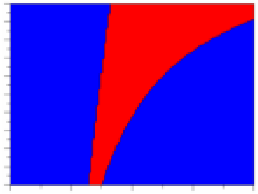
More knowledge is generated in less time, time to market is shortened（花费更少的时间得到更多的信息，从而缩短产品上市周期）



Interaction effects can be detected and quantified : robustness of processes is better controlled（确定和量化互相影响的因子，从而更好地控制工艺的稳定性）



DoE discriminates non-significant from reliable information for more confidence.（DoE能够从真实的信息中区别不重要的信息）



Outcome is highly valuable and easily usable, directly translating into process improvement.（结果更有价值更容易得到，直接转化为工艺的提高）

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Thank you

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