1. Experimental Design Stages
   a) Identifying the factors which may affect the results of an experiment;
   b) Designing the experiment so that the effects of uncontrolled factors are minimized;
   c) Using statistical analysis to separate and evaluate

Factors – any aspect of the experimental conditions which affects the result obtained from an experiment. Can you name a factor?

The relationship between factors and responses can be shown mathematically by:

\[ y = f(x_1, x_2, x_3, ..., x_k) \]

Where \( y \) is the response of interest and \( x \) are the factors that affect the response.

d. Experimental Design Approaches
   a) Full Factorial Designs (two levels per factor)
   b) Fractional Factorial Design
   c) Latin Squares
   d) Greco-Latin Squares
   e) Response Surface Designs (more than two levels for one or more factors)
   f) Box-Behnken Designs
   g) Mixture Designs

The following types of factors can be distinguished:

1) Continuous (e.g. temperature)
2) Discrete (e.g. Experimenter)

- Factors are independent if there is no relationship between them and dependant if a relationship exists.
Experimental Design and Optimization

Why Bother with Experimental Design?

1. Target
2. Maximizing or Minimizing a Response
3. Reducing Variation
4. Making a Process Robust
5. Seeking Multiple Goals
How do we select an experimental design?

- Selected based the objective and the # of factors
  1) Comparative Objective (e.g. one or more factors)
  2) Screening Objective
  3) Response Surface (method)
  4) Optimizing responses
  5) Optimal fitting of a regression model

### Experimental Design and Optimization

<table>
<thead>
<tr>
<th># of Factors</th>
<th>Comparative Objective</th>
<th>Screening Objective</th>
<th>Response Surface Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-factor completely randomized design</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2-4</td>
<td>Randomized block design</td>
<td>Full or fractional factorial</td>
<td>Central composite or Box-Behnken</td>
</tr>
<tr>
<td>5 or more</td>
<td>Randomized block design</td>
<td>Fractional factorial</td>
<td>Screen first to reduce the # of factors</td>
</tr>
</tbody>
</table>

Experimental Design and Optimization

3. Important concepts before we tackle Experimental Design:
   a) Replication – multiple measurements to reduce the experimental error.
      \[ \Rightarrow \text{averaging } \left( \frac{1}{\sqrt{n}} \right) \]
   b) Randomization – running the experiments in a random order
      \[ \Rightarrow \text{obligatory if systematic errors (bias) cannot be avoided} \]
   c) Blocking – Running experiments in blocks that show a minimum variance within one block.
      Ex: An investigation requires 12 experiments, only 4 expts/day
      Then, experiments should be arranged in three blocks w/ 4 expts each day.
      \[ \Rightarrow \text{must be random} \]
   d) Factorial Experiments – varying all factors simultaneously at a limited number of factor levels

Experimental Design and Optimization

Randomization – A closer look
\[ \Rightarrow \text{typically performed by a computer program} \]
Total sample size (# of runs) = \( N = k \times L \times n \)
where \( k = \# \text{ of factors} \), \( L = \# \text{ of levels} \), \( n = \# \text{ of replications} \)

Ex: Completely randomized design
\[ \begin{align*}
  k &= 1 \text{ factor (x1)} \\
  L &= 4 \text{ levels of that factor (called “1”, “2”, “3” and “4”)} \\
  n &= 3 \text{ replications per level} \\
  N &= 4 \text{ levels } * 3 \text{ replications per level = 12 runs}
\end{align*} \]
5. How do we select and scale the Experimental Variables?
   a) Include all important factors
   b) Choose both low and high values
   c) Check for impossible combinations (e.g. low pressure and high gas flows)

Two-level designs help us make this process easier:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Factor 1 (X1)</th>
<th>Factor 2 (X2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>Trial 2</td>
<td>+1</td>
<td>-1</td>
</tr>
<tr>
<td>Trial 3</td>
<td>-1</td>
<td>+1</td>
</tr>
<tr>
<td>Trial 4</td>
<td>+1</td>
<td>+1</td>
</tr>
</tbody>
</table>

“+1” and “-1” represent “high level” and “low level”, respectively for each factor.

Note: There are 369,600 ways to run the experiment.
5. Full factorial Designs (Screening Design)
   \[ 2^k \] – designs, where the base 2 stands for the number of factor levels
   and \( k \) expresses the # of factors.
   - with two factors, we can define a visual square.
   - with three factors, we can define a cube.

   → The lower level is usually indicated with a “\( _{-} \)” and
   the upper level a “\( + \)” sign.

Factor combinations:
Ex: \( 2^2 = ? \) experimental conditions
\[ 2^3 = ? \]

Experimental Design and Optimization

Ex: The effects of reaction temperature and pH in determining the
spectrophotometric response of a standard analyte solution.

Experimental matrix:

<table>
<thead>
<tr>
<th>Expt #</th>
<th>Temperature</th>
<th>pH</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-1</td>
<td>-1</td>
<td>( y^1 )</td>
</tr>
<tr>
<td>B</td>
<td>+1</td>
<td>-1</td>
<td>( y^2 )</td>
</tr>
<tr>
<td>C</td>
<td>-1</td>
<td>+1</td>
<td>( y^3 )</td>
</tr>
<tr>
<td>D</td>
<td>+1</td>
<td>+1</td>
<td>( y^4 )</td>
</tr>
</tbody>
</table>

Factor Levels

\(-\) \quad 40˚C \quad pH1
\(+\) \quad 60˚C \quad pH3
Note: The best experimental points in the domain are located in the corners A, B, C and D as follows:

A(40°C, pH1); B(60°C, pH1); C(40°C, pH3); D(60°C, pH3)

If we introduce another variable (e.g. reagent concentration), it is then possible to represent the factors as faces on one or more cubes: $2^3$ design.
6. Latin Square and Related Designs

-Single factor of primary interest (treatment factor) and several nuisance factors (2 for Latin Square).
-Nuisance factors are used as blocking variables.
-Used in experiments where subjects are allocated treatments over a given time period (time is a major factor).
-Allow experiments with a relatively small number of runs.

-Disadvantages:
Assumes there are no interactions between the blocking variables or between the treatments.

“Block what you can, randomize what you cannot”
Experimental Design and Optimization

Ex: Suppose the treatments are labeled A, B, and C. In this case the design would be:

Day 1: A B C
Day 2: C A B
Day 3: B C A

Allows the separation of an additional factor from an equal number of blocks and treatments.

Experimental Design and Optimization

Ex: Four formulations of a drug are to be studied with regard to bioequivalence by treating 4 subjects for 4 periods (4 x 4 Latin Square). Formulations are coded by A, B, C and D.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Period 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>C</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>D</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>A</td>
<td>B</td>
<td>D</td>
</tr>
</tbody>
</table>
Experimental Design and Optimization

7. Greco-Latin Squares

Two Latin Squares that are superimposed on each other (2 treatment factors instead of 1, with 4 factors overall).

<table>
<thead>
<tr>
<th></th>
<th>A₁</th>
<th>A₂</th>
<th>A₃</th>
<th>A₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₁</td>
<td>C₁D₃</td>
<td>C₂D₄</td>
<td>C₃D₁</td>
<td>C₄D₂</td>
</tr>
<tr>
<td>B₂</td>
<td>C₄D₂</td>
<td>C₁D₁</td>
<td>C₂D₃</td>
<td>C₃D₄</td>
</tr>
<tr>
<td>B₃</td>
<td>C₃D₁</td>
<td>C₄D₂</td>
<td>C₁D₃</td>
<td>C₂D₄</td>
</tr>
<tr>
<td>B₄</td>
<td>C₂D₄</td>
<td>C₁D₃</td>
<td>C₃D₂</td>
<td>C₄D₁</td>
</tr>
</tbody>
</table>

Experimental Design and Optimization

Number of runs for a $2^k$ Full Factorial Design

<table>
<thead>
<tr>
<th>Number of Factors</th>
<th>Number of Runs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>128</td>
</tr>
</tbody>
</table>
Experimental Design and Optimization

Note: When the # of factors is 5 or greater...it requires a large number of runs (more time, less efficient!)

Fractional Replication

# of experiments is reduced by a number \( p \) according to \( 2^{k-p} \),
With the most common being \((p=1)\)

**Ex:** A design with \( 2^3 \) (8 treatment combinations) can be run a \( 2^{3-1} = 4 \) treatment combinations

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Experimental Design and Optimization

Fractional Factorial is based on an algebraic method of calculating the contributions of factors to the total variance with less than a full factorial # of expt's.

**Ex:** Measuring the scaled absorbance for a fixed amount of analyte as a function of pH, dielectric constant and mg L\(^{-1}\) of catalyst.

\[
Y_{1i} = b_0 + b_1x_{1i} + b_2x_{2i} + b_3x_{3i} + e_{1i} \quad \text{Eq. 1}
\]

\[
\begin{array}{ccc|c}
D & 8 & 72 & 4 & 0.5 \\
8 & 78 & 8 & 7.5 \\
10 & 72 & 8 & 3.5 \\
10 & 78 & 4 & 8.5 \\
\end{array}
\]
The model represented by Eq. 1 may be fit using:

$$X = \begin{bmatrix}
1 & 8 & 72 & 4 \\
1 & 8 & 78 & 8 \\
1 & 10 & 72 & 8 \\
1 & 10 & 78 & 4
\end{bmatrix}$$

Fitted model: $y_1 = -80.5 + 1.00x_1 + 1.00x_2 + 0.250x_3$

For the # of runs:

$$r = 2^{k-p} + 2k + n_0$$

$k$=# factors, $p$=# for reduction of the full design and $n_0$ = # of experiments in the center of the design
Experimental Design and Optimization

Diagram of Central Composite Design generation for 2 factors.
- Start points are at some distance \( \alpha \) from the center, with \( \alpha \) depending on the number of factors in the factorial part of the design.


Experimental Design and Optimization

Diagram of Central Composite Design consisting of a full factorial 2-level and star design.
### Central Composite Design Type

<table>
<thead>
<tr>
<th>Central Composite Design Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscribed (CCC)</td>
<td>Original form, the star points establish new extremes for both low and high factor settings.</td>
</tr>
<tr>
<td>Inscribed (CCI)</td>
<td>A scaled down version of the CCC with factor levels % α</td>
</tr>
<tr>
<td>Face Centered (CCF)</td>
<td>Requires 3 levels of each factor, α=+/- 1</td>
</tr>
</tbody>
</table>

CCC explores the largest process space and the CCI explores the smallest process space.

Both the CCC and CCI are rotatable designs, but the CCF is not.

In the CCC design, the design points describe a circle *circumscribed* about the factorial square.

For three factors, the CCC design points describe a sphere around the factorial cube.
9. Box-Behnken Designs – alternative to common CC designs

- Has three levels per factor, but avoids the corners of the space
- Fills the combinations of center and extreme levels
- Combines a fractional factorial with incomplete block designs to avoid extreme vertices & to present a “rotatable” design.

- Not useful when the experimenter is interested in predicting extreme responses.

<table>
<thead>
<tr>
<th>Run</th>
<th>Factors</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$x_1$</td>
<td>$x_2$</td>
</tr>
<tr>
<td>1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>2</td>
<td>+1</td>
<td>-1</td>
</tr>
<tr>
<td>3</td>
<td>-1</td>
<td>+1</td>
</tr>
<tr>
<td>4</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>5</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>13,14,15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Box-Behnken design with 3-levels per factor.