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Factorial Design with Multiple Optimized Randomization Techniques: A Review

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Abstract

The observation of the effects of the variables and their interactions in a given system is thus of the utmost importance. Given the requirement to simultaneously evaluate the effect of a large number of variables and their interactions between them from a limited number of trials, multi variate optimization systems based on factorial design of experiments are a useful and simple alternative. The efficacy of these notions in the study of multivariate systems is demonstrated in this essay by emphasizing their use in studies of many fields of knowledge. Original papers and research on factorial experimental designs commonly used in laboratories in a variety of study topics, including studies and pre-installation already installed, as well as papers in Portuguese, English, and Spanish, were inclusion criteria for articles.

Keywords: *Optimization, Design of experiment, Quality by design, Minitab, Microsoft excel*

1. Introduction

- Multiple components (the researcher-controlled independent variables) are manipulated or allowed to fluctuate in the factorial designs, which are a type of true experiment. They provide researchers two key advantages.
- They firstly enable researchers to concurrently examine the primary effects of two or more distinct independent factors. Secondly, they enable researchers to miss interactions between variables.

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- The major and linking effects between two or more outcome variables can be analyzed using this particular study methodology.
- All mixes that can be created from the various elements are included in the treatments.
- For example, 32 treatments might be produced by an experiment using factors at the 5-2 level.
- When it comes to process and formulation variables, the formulator has direct control over the ingredients. The results of independent variables, such as the responses to study questions or the ensuing drug delivery system, are known as dependent or secondary variables.
- The variable in question is the factor, which can also include concentration, temperature, lubricant, drug-to-polymer ratio, polymer-to-polymer ratio, etc. It is permissible to consider both qualitative and quantitative criteria. An objective quantitative element has a numerical value. Concentration, for instance (1%, 2%, etc.),
- The parameters that cannot be quantified numerically include things like polymer grades, humidity levels, and equipment types.

Quantitative: A numerical factor is assigned to it . Example: Concentration – 1% , 2% , 3% etc.

Qualitative: These are non-numerical, Example – Polymer grade, humidity condition etc.

Factorial and fractional factorial designs are commonly used as an experiment plan to study the impact of several factors on a process.

The main aim of the designing quality formulations is achieved by implementing various optimization technique (OT) like Experimental Design (ED), the terms formulation by Design (FBD) and Quality by Design (QBD) indicates that quality in the product can be developed by various techniques of ED.

Design of Experiment (DoE) primarily has three basic objectives such as screening, optimization and robustness. It major exhibits application in identification of critical variables and their levels, and screening important factors.

2. History

Factorial designs were used in the 19th century by John Bennet Lawes and Joseph Henry Gilbert of the Rothamsted Experimental Station.

Ronald Fisher argued in 1926 that "complex" designs (such as factorial design) were efficient than studying one factor at a time.

Fisher through that a factorial design allows the effect of several factors and even interaction between to be determined with the same number of trials as are necessary to determine any one of the effect by itself with the same degree of accuracy.

The term "factorial" may not have been used in print before 1935, when Fisher used in it his book *The Design of Experiment.*

Experimental designs were first used in the 1920's, mostly in the agricultural domain. Sir Fisher Ronald Aylmer was the first to use mathematical statistics when designing experiments. In 1926 he wrote a paper outlining the principles of experimental design in non- mathematical terms.

Graphic design roots: 15000-3600 BC

Graphic design can be traced all the way back to 15000 BC, when the first known visual communications arose.

These pictographs and symbols are present in the Lascaux caves in southern France. Fast-forward several thousand years, and you'll discover the Blau monument.

A fractional factorial experiment is generated from a full factorial experiment by choosing an alias structure.

The alias structure determines which effects are confounded with each other. For example, The five factor 2^{5-2} can be generated by using a full three factor factorial experiment involving three factors (say A, B and C) and then choosing to confound the two remaining factors D and E with interactions generated by D =A*B and E = A*C.

These two expressions are called the generators of the design. So for example, when the experiment is run and the experimenter estimates the effects for factor D, what is really being estimated is a combination of the main effect of D and the two factor interaction involving A and B.

3. Principle

In a factorial design, each level of a factor (treatment or condition) occurs in combinations with every level of every other factor. Experimental units are assigned randomly to treatment combinations rather than individual treatments.

Three treatments—oral captopril, oral mononitrate, and intravenous magnesium sulphate—were used in the factorial trial ISIS-4. One of two levels could be used to provide each of the three treatments (e.g., placebo, standard dosage). There are eight different treatment combinations (2 x 2 x 2 = 8) that could be used in this investigation. With a probability of 1/8 (12.5%), each patient is randomly assigned to one of the eight pairings. We can assess the interactions or synergistic effects between multiple treatments because each treatment combination is evaluated on a different participant group (e.g., 35-day mortality). Selecting a sample size large enough to discover meaningful interactions with high power or a reasonable statistical probability is a difficult task when using factorial designs.

4. Types of Factorial Design

Factorial designs come in three categories:

1. Full factorial design
2. Fractional factorial design
3. Response surface designs

4.1. Full Factorial Design

The impact of every element and how they interact on the outcome (or outcomes) is examined in a Full Factorial Design (FFD). All input elements are set to have two levels each in a typical experimental design. The terms “high” and “low,” or +1 and 1, respectively, are used to describe these levels. A full factorial design on two levels is one that contains all high/low groups that could be created from all of the input elements. As indicated previously, if there are *k* factors, each with two levels, a full factorial design will consist of 2*k* trials. However, when there are more than five factors, a full factorial design necessitates a sizable number of experimental runs and is ineffective. A fractional factorial design or a Plackett-Burman design would be appropriate as a result.

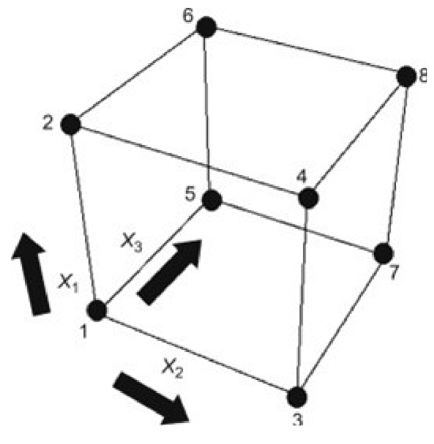

Figure 1: Standard Order of Runs

The arrows show the direction of increase of the factors. The numbers 1 through 8 at the corners of the design box represent the Standard Order of runs as shown in Figure 1.

4.2. *Two Level Full Factorial Design*

For these examples, let's construct an example where we wish to study of the effect of different treatment combinations for cocaine abuse. Here, the dependent measure is severity of illness rating done by the treatment staff. The outcome ranges from 1 to 10 where higher scores indicate more severe illness: in this case, more severe cocaine addiction. Furthermore, assume that the levels of treatment are:

Factor 1: Treatment

- Psychotherapy
- Behavior modification

Factor 2: Setting

- Inpatient
- Day treatment
- Outpatient

Note that the setting factor in this example has three levels.

The first graphic depicts a possible example of an impact for setting an outcome. Higher scores indicate that the patient is performing poorly, thus you must be very cautious when interpreting these data. It is

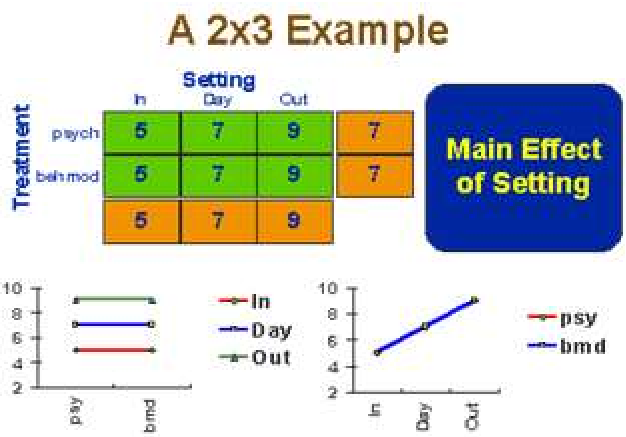

Figure 2: Main Effect of Setting

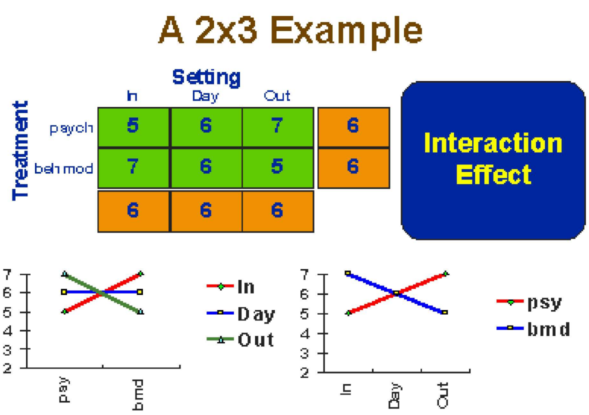

Figure 3: Interaction Effect

obvious that outpatient treatment is the least effective of the three, whereas inpatient treatment has the best results. Additionally, it is obvious that the two treatment modalities (psychotherapy and behavior modification) are equivalent. Despite the fact that both of the graphs in the illustration show the exact same data, I believe the graph on the lower left, where setting is displayed with distinct lines on the graph rather than at different positions along the horizontal axis, makes it easier to notice the main effect for setting.

The second image depicts a primary impact for treatment, with psychotherapy outperforming behavior modification across all conditions (note the movement of the outcome variable). The graph on the lower right, where therapy levels are used to draw the lines, makes the effect more obvious. There are no contact effects, as can be seen by the parallel lines in all of the graphs displayed in the prior picture.

Let's now examine a few potential interaction effects. We can see from the first instance that a single therapy is never the greatest option. Additionally, we observe that behavioural modification is most effective with outpatient care while psychotherapy is most effective with inpatient care.

The second interaction effect illustration is a little trickier. Although the interaction may have some main effects, it is crucial to note that inpatient psychotherapy represents a special confluence of degrees of elements that stands out as superior. When we find a "best" combination like this, of degrees of elements that stands out as superior. When we find a "best" combination like this, the state of the principal impacts almost becomes unimportant.

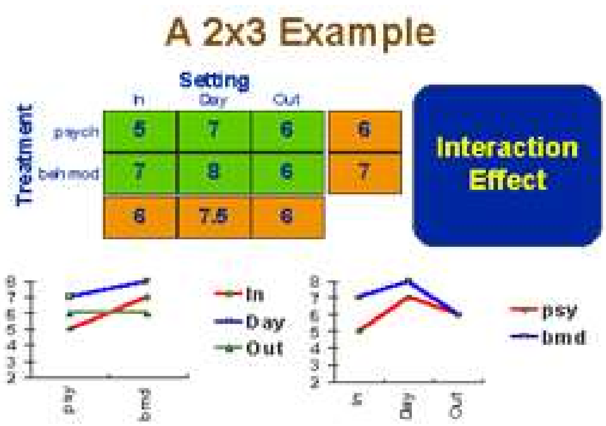

Figure 4: Interaction Effect of 2x 3 Example

4.3. *Three-Factor Example*

Now let's examine what a three-factor study might look like. We'll use the same factors as above for the first two factors. But here we'll include a new factor for dosage that has two levels. The factor structure in this 2x2x3 factorial experiment is:

Factor 1: Dosage

- 100 mg
- 300 mg

Factor 2: Treatment

- Psychotherapy
- Behavior modification

Factor 3: Setting

- Inpatient
- Day treatment
- Outpatient

Figure 5: A Three Factor Level Example

This design has 2x2x3=12 groups. Factor studies are tempting to add more factors, but the number of groups is always multiplicative (is that a true word?). Also note that to display a table of means, you need a table that shows the relationship between the two elements, each one. Also, graphing the results of such studies is difficult due to the large number of different graphs. Statistical analysis can examine the main effects and three interactions (e.g., treatment-dose, treatment-treatment) for each of the three factors. Attitude vs. Attitude vs. Dosage), one can see a three-way interaction. Whatever else happens, it is clear that the best combination of these three levels is: 300 mg. and psychotherapy in hospitalized patients. Therefore, a three-way interaction takes place in this study. As administrators, if we have to choose between different treatment combinations, it is best to choose them (assuming patients and circumstances are comparable to those in this study).

4.4. *Fractional Factorial Design*

A fractional factorial design in statistics is a design consisting of a carefully selected subset (fraction) of runs of a full factorial design (Green *et al.*, 2002). The subsets are chosen to reveal information about the most

Treatment combinations for a 2^{5-2} design

Treatment combination	I	A	B	C	D = AB	E = AC
de	+	−	−	−	+	+
a	+	+	−	−	−	−
be	+	−	+	−	−	+
abd	+	+	+	−	+	−
cd	+	−	−	+	+	−
ace	+	+	−	+	−	+
bc	+	−	+	+	−	−
abcde	+	+	+	+	+	+

Figure 6: Treatment Combinations of a Fractional Factorial Design

important features of the problem under study using the principle of sparsity of effects, but with the effort of full factorial design in terms of experimental execution and resources. In other words, we take advantage of the fact that many experiments in full factorial design are often redundant and provide little or no new information about the system.

Fractional plans are expressed using the notation *lk – p*. where *l* represents the number of levels of each factor examined, *k* the number of factors examined, and *p* the size of the full factorial fraction used. Formally, *p* is a generator, the number of imputations, which effects or interactions are falsified, i.e., cannot be estimated independently of each other (see below). A design with *p* such generators is the 1/(*lp*) = *l – p* part of the full factorial design. For example, a 25 – 2 design is a quarter of a 2-level, 5 factorial design. Instead of the 32 runs required for a full 25 factorial experiment, this experiment requires only 8 runs.

The broken design is I = ABD = ACE = BCDE. A defining relationship can determine a design alias pattern.

4.5. Response Surface Design

The experimental design subject deals with the statistical methodology necessary to draw conclusions about treatment effects based on responses (univariate or multivariate) collected during a designed experiment. In agriculture, horticulture and related sciences, experiments involving several factors simultaneously are performed to address the development and analysis of methods to study the mechanisms of variable systems. Data from experiments using concentrations or combinations of concentrations of one or more factors as treatments are typically examined to compare the effects of the factors and their interactions. However, such studies are useful for objectively assessing the effects of levels actually tested in experiments. This seems particularly inadequate when the factors are of a quantitative nature. In such cases, it is more practical and meaningful to conduct research with two objectives: To determine and to quantify the relationship between the response and the settings of a group of experimental factors.

To find the settings of the experimental factors that produces the best value or the best set of values of the responses.

Example: A researcher estimating the effects of independent variables like temperature and pressure influences the yield.

4.5.1. Advantages of Factorial Designs

Many people examine the effect of only a single factor or variable. Compared to such one-factor-at-a-time (OFAT) experiments, factorial experiments offer several advantages.

- Factorial designs are more efficient than OFAT experiments. They provide more information at similar or lower cost. They can find optimal conditions faster than OFAT experiments.
- Factorial designs allow additional factors to be examined at no additional cost.
- When the effect of one factor is different for different levels of another factor, it cannot be detected by an OFAT experiment design. Factorial designs are required to detect such interactions.

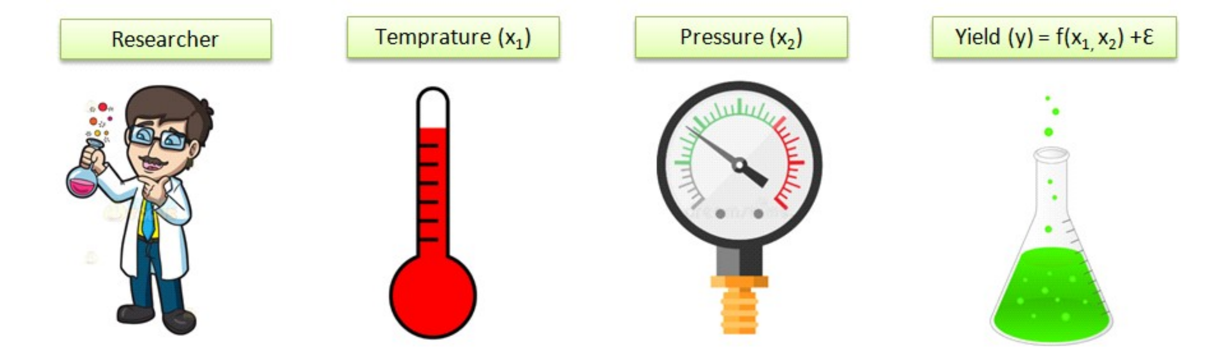

Figure 7: Independent Variables

- Use of OFAT when interactions are present can lead to serious misunderstanding of how the response changes with the factors.
- Factorial designs allow the effects of a factor to be estimated at several levels of the other factors, yielding conclusions that are valid over a range of experimental conditions.
- Some experiments are designed so that two or more treatments (independent variables) are explored simultaneously. Such experimental designs are referred to as factorial designs. In factorial designs, every level of each treatment is studied under the conditions of every level of all other treatments.
- Factorial designs can be arranged such that three, four, or *n* treatments or independent variables are studied simultaneously in the same experiment. If two independent variables are analyzed by using a completely randomized design, the effects of each variable are explored separately (one per design).
- Thus, it takes two completely randomized designs to analyze the effects of the two independent variables. By using a factorial design, the business researcher can analyze both variables at the same time in one design, saving the time and effort of doing two different analyses and minimizing the experiment-wise error rate.
- Some business researchers use the factorial design as a way to control confounding or concomitant variables in a study. By building variables into the design, the researcher attempts to control for the effects of multiple variables in the experiment.
- With the completely randomized design, the variables are studied in isolation. With the factorial design, there is potential for increased power over the completely randomized design because the additional effects of the second variable are removed from the error sum of squares.
- The researcher can explore the possibility of interaction between the two treatments variables in a two-factor factorial design if multiple measurements are taken under every combination of levels of the two treatments. Factorial designs with two treatments are similar to randomized block designs.

5. Industrial and Clinical Trails: Statistical Softwares

5.1. Microsoft Excel

It is used to design and perform experiments with multiple variables can be tricky and hard to analyze. There is always the option of changing one variable at a time while keeping the other factors constant. It might requires too many experiments or even lead to a “pseudo-optimal point”. Hence a proper Design of Experiment (DoE) should be carried out to attain the best results with least number of experiments and the highest accuracy.

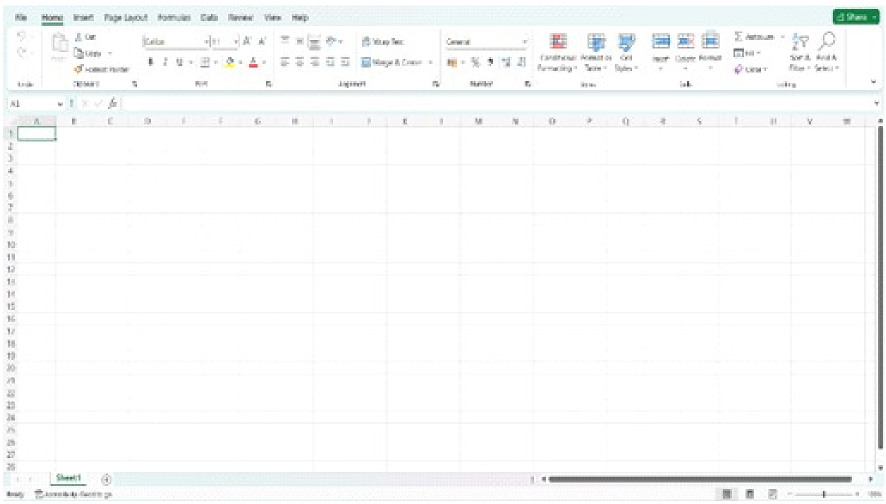

Figure 8: Microsoft Excel

Experimental systems can be modeled and optimized considering it as a black-box just a correlation between the variables (what is controlled) and the response (what is observed) without knowing the physical and chemical principles governing the process.

5.2. Designing of Experiment Performing in Excel

- In design of experiment we talk about "confounding" which simply means that one factor affects another. Microsoft excel has some powerful data analysis tools which I have successfully used for DOE.
- When it comes to analyze cause and effect we want to know what process factors affect our outputs. Correlation and Regression could give us an indication of the main factors and the extent they affect.
- In some cases there may be interaction among the different factors or the mathematical relation between factors and outputs may be linear.

Loss	pH	Temp	Pres	Temp*Pres
20	-1	-1	-1	1
28	1	-1	-1	1
23	-1	-1	-1	1
34	1	-1	-1	1
4	-1	1	-1	-1
21	1	1	-1	-1
11	-1	1	-1	-1
23	1	1	-1	-1
7	-1	-1	1	-1
24	1	-1	1	-1
10	-1	-1	1	-1
29	1	-1	1	-1
18	-1	1	1	1
31	1	1	1	1
16	-1	1	1	1
28	1	1	1	1
17	0	0	0	0
19	0	0	0	0

Regression Statistics	
Multiple R	0,95
R Square	0,90
Adjusted R Square	0,87
Standard Error	3,09
Observations	18

ANOVA

	df	*SS*	*MS*	*F*
Regression	4	1093	273	29
Residual	13	124	10	
Total	17	1218		

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	20,24	0,73	27,78	0,00
pH	6,85	0,77	8,86	0,00
Temp	-1,40	0,77	-1,82	0,09
Pres	-0,06	0,77	-0,08	0,94
Temp*Pres	4,41	0,77	5,70	0,00

Figure 9: Experimental Design in Excel

5.3. Factorial Experiment Example

We want to minimize process loss and after some brainstorming among the process specialists we concluded that 5 factors may affect loss. Based on their current factor levels we have selected the foolowing levels to experiment.

Code	pH	Time	Temp	Pres	Flow
-1	2	7	120	1	3
1	12	15	150	1,5	5

Figure 10: Example of Factorial Experiment

6. Advantages of Excel Software

Excel software, developed by Microsoft, is a widely used spreadsheet application that offers numerous advantages in various domains. Here are some key advantages of Excel:

1. Spreadsheet Functionality: Excel provides powerful spreadsheet functionality, allowing users to organize, analyze, and manipulate large amounts of data efficiently. It supports mathematical calculations, statistical analysis, data visualization, and complex formulas, making it suitable for financial modelling, budgeting, data analysis, and more.

2. User-Friendly Interface: Excel has a user-friendly interface that is relatively easy to navigate, making it accessible to both novice and advanced users. It offers a range of features, such as customizable toolbars, shortcuts, and intuitive menus, enhancing user productivity and ease of use.
3. Data Organization and Management: Excel enables users to organize data effectively in rows and columns, making it easy to sort, filter, and format data. It also allows the creation of multiple worksheets within a single workbook, enabling users to manage large datasets efficiently.
4. Formula and Calculation Capabilities: Excel's formula and calculation capabilities are robust and versatile. Users can perform simple arithmetic calculations, use built-in functions, create complex formulas, and perform iterative calculations. These capabilities make Excel suitable for financial analysis, modeling, forecasting, and other data-intensive tasks.
5. Data Visualization: Excel offers various tools for data visualization, including charts, graphs, and conditional formatting. Users can create visually appealing representations of their data, making it easier to understand and interpret trends, patterns, and relationships.
6. Automation and Customization: Excel provides powerful automation features, such as macros and Visual Basic for Applications (VBA), which allow users to automate repetitive tasks, streamline workflows, and create custom functions. This flexibility enables users to tailor Excel to their specific needs and improve overall productivity.
7. Integration with Other Applications: Excel seamlessly integrates with other Microsoft Office applications, such as Word and PowerPoint, as well as external data sources, including databases and web services. This integration allows users to import and export data, share information across applications, and enhance collaboration and reporting capabilities.
8. Wide Availability and Support: Excel is widely used and supported, with a vast user community and abundant online resources, tutorials, and forums. Finding assistance, troubleshooting issues, and learning new features and techniques are relatively easy, ensuring users have ample support in utilizing the software effectively.

These advantages make Excel a versatile and valuable tool for a wide range of industries and tasks, from financial analysis and project management to inventory tracking and data reporting.

7. Minitab

A statistical software programme called Minitab is made for data analysis and quality control. It offers a selection of features and tools that let users visualize, understand, and analyse data. Numerous industries, including manufacturing, engineering, pharmaceuticals, healthcare, and academics, use Minitab extensively.

Here are some key features and functionalities of Minitab:

1. Data Analysis: Minitab provides a full range of statistical tools for data analysis. The Design of Experiments (DOE), regression analysis, Analysis of Variance (ANOVA), control charts, and descriptive statistics are all included.
2. Graphical Tools: Using Minitab, users can construct a number of different graphical data visualizations, such as scatter plots, histograms, boxplots, and Pareto charts. Understanding patterns, trends, and correlations in the data is made easier by these visualizations.
3. Quality Improvement: Minitab offers tools for projects like Six Sigma and Lean Six Sigma that focus on improving the quality of products. It contains features including Statistical Process Control (SPC) charts, Measurement Systems Analysis (MSA), and process capability analysis.
4. DOE and Optimization: Minitab gives users the ability to create and evaluate experiments to improve procedures and goods. To assist users in locating important variables and their interactions, it supports factorial designs, response surface techniques, and mixed designs.

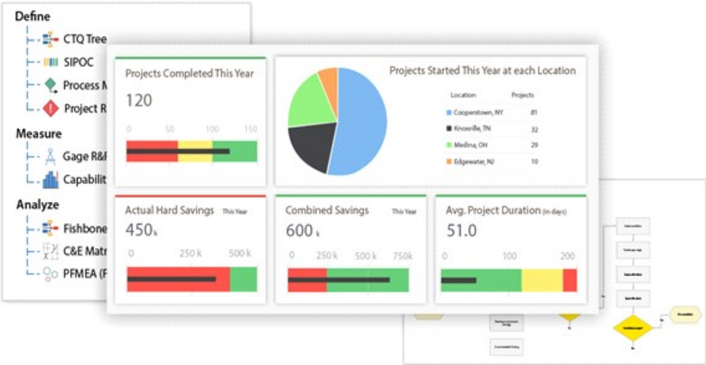

Figure 11: Minitab

5. Time Series Analysis: Minitab has tools for studying and predicting data from time series. To find patterns and predict outcomes, users can do forecasting, decomposition, autocorrelation, and other time series studies.
6. Reliability Analysis: Using techniques like reliability charts, Weibull analysis, and accelerated life testing, Minitab enables users to evaluate the dependability and durability of items.
7. Statistical Process Control (SPC): Minitab provides a variety of SPC tools to track and manage operations. To assure quality control, users can build control charts, carry out process capability analysis, and run hypothesis tests.

Both novice and seasoned statisticians can use Minitab because of its user-friendly design. To help customers get the most of its features, it offers tutorials, step-by-step instructions, and online resources.

8. Advantages of Minitab Software

Minitab is a statistical software package that offers several advantages for data analysis and statistical modeling. Here are some key advantages of Minitab software:

1. Statistical Analysis Capabilities: Minitab provides a comprehensive set of statistical tools and techniques, allowing users to perform a wide range of analyses. It supports descriptive statistics, hypothesis testing, regression analysis, ANOVA, DOE, control charts, reliability analysis, and more. These capabilities make it an excellent choice for researchers, quality professionals, and statisticians.
2. User-Friendly Interface: Minitab has an intuitive and user-friendly interface that simplifies the process of data analysis. The software provides step-by-step guidance and prompts, making it accessible to users with varying levels of statistical knowledge. Its graphical interface allows users to import data easily, perform analyses, and interpret results efficiently.
3. Data Visualization: Minitab offers a wide range of graphical tools for data visualization. Users can create various types of charts, such as histograms, scatterplots, boxplots, and control charts, to explore and present data visually. These visualizations help users identify patterns, trends, outliers, and relationships in their data.
4. Quality Improvement Tools: Minitab is widely used in quality improvement initiatives, such as Six Sigma. It provides specific tools like capability analysis, process mapping, Gage R&R (Repeatability and Reproducibility), DOE, and Statistical Process Control (SPC). These tools help organizations identify and reduce process variability, enhance quality, and optimize processes.
5. Efficiency and Automation: Minitab offers features that enhance productivity and efficiency in data analysis. It supports batch processing and automation through scripts, allowing users to perform repetitive tasks or conduct analyses on multiple datasets simultaneously. This capability saves time and improves workflow efficiency.

6. Data Management and Manipulation: Minitab provides a variety of data manipulation capabilities. Users can import data from different file formats, clean and prepare data, and transform variables. The software also offers powerful data management tools, such as sorting, filtering, recoding, and merging datasets.
7. Collaboration and Reporting: Minitab facilitates collaboration and reporting by allowing users to export analysis results and graphs to various formats, including Microsoft Word and PowerPoint. This enables users to share findings and insights easily with colleagues, clients, or stakeholders.
8. Statistical Learning and Support: Minitab offers extensive resources and support for users to enhance their statistical knowledge and proficiency. It provides built-in help documentation, tutorials, sample datasets, and a large user community. Additionally, Minitab offers training courses and certifications to help users develop their statistical analysis skills.

Overall, Minitab is a powerful statistical software package that combines ease of use with advanced analytical capabilities. Its extensive range of statistical tools, data visualization options, and quality improvement features make it a valuable tool for professionals in various industries, including manufacturing, healthcare, finance, and research.

9. Conclusion

To sum up, factorial design is a potent and adaptable experimental design strategy that has a number of advantages for study and testing. Factorial design enables researchers to study the primary impacts and interactions among factors by methodically adjusting numerous factors at the same time, offering insightful information on the relationship between variables.

Factorial designs provide the potential to examine complex interactions, make better use of resources, have higher statistical power, and have better generalizability. Researchers can determine the individual and combined effects of these factors on the outcome of interest by altering several factors in a factorial design, leading to a more thorough knowledge of the underlying phenomenon.

References

Allore, H.G. and Murphy, T.E. (2008). An Examination of Effect Estimation in Factorial and Standardly-Tailored Designs. *Clin. Trials.*, 5(2), 121-30. doi: 10.1177/1740774508089278. PMID: 18375650; PMCID: PMC3477845.

Baker, T.B., Smith, S.S., Bolt, D.M., Loh, W.Y., Mermelstein, R., Fiore, M.C., Piper, M.E. and Collins, L.M. (2017). Implementing Clinical Research Using Factorial Designs: A Primer. *Behav Ther.*, 48(4), 567-580. doi: 10.1016/j.beth.2016.12.005. Epub 2017 Jan 7. PMID: 28577591; PMCID: PMC5458623.

Byth, K. and Gebski, V. (2004). Factorial Designs: A Graphical Aid for Choosing Study Designs Accounting for Interaction. *Clin. Trials.*, 1(3), 315-25. doi: 10.1191/1740774504cn026oa. PMID: 16279257.

Couper, D.J., Hosking, J.D., Cisler, R.A., Gastfriend, D.R. and Kivlahan, D.R. (2005). Factorial Designs in Clinical Trials: Options for Combination Treatment Studies. *J. Stud. Alcohol. Suppl.*, (15), 24-32; discussion 6-7. doi: 10.15288/jsas.2005.s15.24. PMID: 16223053.

Dakin, H. and Gray, A. (2017). Economic Evaluation of Factorial Randomised Controlled Trials: Challenges, Methods and Recommendations. *Stat. Med.*, 36(18), 2814-2830. doi: 10.1002/sim.7322. Epub 2017 May 3. PMID: 28470760; PMCID: PMC5599939.

Dakin, H.A., Gray, A.M., MacLennan, G.S., Morris, R.W. and Murray, D.W. (2018). Partial Factorial Trials: Comparing Methods for Statistical Analysis and Economic Evaluation. *Trials*, 19(1), 442. doi: 10.1186/s13063-018-2818-x. PMID: 30115104; PMCID: PMC6097309.

Freidlin, B. and Korn, E.L. (2017). Two-by-Two Factorial Cancer Treatment Trials: Is Sufficient Attention Being Paid to Possible Interactions?. *J. Natl. Cancer Inst.*, 109(9), djx146. doi: 10.1093/jnci/djx146. PMID: 28954288; PMCID: PMC6059117.

Green, S., Liu, P.Y. and O'Sullivan, J. (2002). Factorial Design Considerations. *J. Clin. Oncol.*, 20(16), 3424-30. doi: 10.1200/JCO.2002.03.003. PMID: 12177102.

Kahan, B.C., Tsui, M., Jairath, V., Scott, A.M., Altman, D.G., Beller, E. and Elbourne, D. (2020). Reporting of Randomized Factorial Trials was Frequently Inadequate. *J. Clin. Epidemiol.* 117(January), 52-59. doi: 10.1016/j.jclinepi.2019.09.018. Epub 2019 Oct 1. PMID: 31585174.

Korn, E.L. and Freidlin, B. (2016). Non-factorial Analyses of Two-by-two Factorial Trial Designs. *Clin. Trials.* 13(6), 651-659. doi: 10.1177/1740774516659472. Epub 2016 Jul 19. PMID: 27439306.

Montgomery, A.A., Peters, T.J. and Little, P. (2003). Design, Analysis and Presentation of Factorial Randomised Controlled Trials. *BMC Med. Res. Methodol.*, 3(Nov), 26. doi: 10.1186/1471-2288-3-26. PMID: 14633287; PMCID: PMC305359.

Pandis, N., Walsh, T., Polychronopoulou, A., Katsaros, C. and Eliades, T. (2014). Factorial Designs: An Overview with Applications to Orthodontic Clinical Trials. *Eur. J. Orthod.*, 36(3), 314-20. doi: 10.1093/ejo/cjt054. Epub 2013 Jul 24. PMID: 23885023.

Stampfer, M.J., Buring, J.E., Willett, W., Rosner, B., Eberlein, K. and Hennekens, C.H. (1985). The 2 x 2 Factorial Design: Its Application to a Randomized Trial of Aspirin and Carotene in U.S. Physicians. *Stat. Med.*, 4(2), 111-6. doi: 10.1002/sim.4780040202. PMID: 4023472.

Whelan, D.B., Dainty, K. and Chahal, J. (2012). Efficient Designs: Factorial Randomized Trials. *J. Bone Joint Surg. Am.*, Jul 18; 94 Suppl 1: 34-8. doi: 10.2106/JBJS.L.00243. PMID: 22810445.

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