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CONTENTS

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SANKHYA VIGNAN
સંખ્યા વિજ્ઞાન

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EDITORIAL BOARD

EDITORIAL

HARD WORK PUTS YOU
WHERE GOOD LUCK CAN FIND YOU.

We are extremly happy to present this issue (NSV 15, December 2019, No.2) to our readers. **Incidently Sankhya Vignan completes 15 years** since its inception of New series volume (NSV).We express our sincere thanks to all our contributors, evaluaters, readers and well wishers for their continuous and consistent support which has helped us to achieve our goal.

This issue contains **one article, three research articles, one review article, two research notes, one biography** along with **other items** as usual.

Under the caption of **Management and Statistics, first article** is about a novel idea for modern management in the form of Action Research in Management. This is furnished by **A.C.Brahmbhatt.**

Next article under this caption is a **research article** on managing risks in SC management.This article is presented by **Ajay Aggarwal** and **Dinesh S. Dave**.

Second research article is presented by **Pinakin R. Jani** which is about further discussions on the overview of multiple testing procedure.

Third research article has been furnished by **M.K. Dave** and **Sanjay G. Raval.** It is about TFP studies made for the industrial sectors of India.

One Review Article is provided by **Pinakin R. Jani** discussing statistical analysis in clinical trails. It is intended to give a series of articles under this caption step-by-step.

One Research Note discusses briefly a research area under Poisson Regression model. It is submitted by **H. M. Dixit**.

Another Research Note is furnished by **Pinakin R. Jani** which makes an attempt to brief the readers about some useful statistical softwares.

Biographical sketch of veteran American Mathematician cum Statistician **George Bernard Dantzig,** is furnished by **H. D. Budhbhatti**.

S.V.News letter provides some useful informations about workshops, seminars and conferences. It is provided by **M. B. Thaker.**

Readers Forum provides readers views and suggestions. It is given by **A.M.Patel.**

We are highly indebted to our following referees who have done excellent job of evaluations for the articles / papers submitted in this issue.

(Their names are given one by one in order of their apperance in the journal.)

(1)	**D. S. Dave**	**(2)**	**R. G. Bhatt**
(3)	**C. D. Bhavsar**	**(4)**	**P. H. Thaker**
(5)	**J. R.Purohit**	**(6)**	**M. N. Patel**
(7)	**M. B. Thaker**	**(8)**	**Shailesh Teredesai**

We have started our website since July 2019. You can also meet us on **www.sankhyavignan.org**. We request you to give your feedback and suggestions. We express our sincere thanks to **Shri Ashish Bhatt for website**, **Shree Dinesh Darji for DTP work** and **Shree Mehul Shah for Printing work.**

Digital Copy of this issue will be sent to all our readers whose email ID are with us. Printed copy will follow soon. Our contributors will get offprints of their published articles along with the printed copy and certificate.

WISH YOU A VERY HAPPY, HEALTHY AND PROSPECTIVE COMING NEW YEAR 2020..

Ahmedabad

Date : 31-12-2019

Note : Members of editorial board are in no way concerned with the views, opinions or ideas expressed in this issue. Authenticity responsibility lies solely with the persons presenting them.

SANKHYA VIGNAN

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FROM EDITOR'S DESK

SANKHYA VIGNAN is a peer reviewed refereed Bi-Annually journal that publishes empirical, conceptual and review papers of exceptional quality that contribute to Statistics Theory and enriched Applications of Statistical Techniques in various fields. The objective of the Journal is to disseminate knowledge, which ensures good practice of professional management and its focal point is on research and reflections relevant to academicians and practitioners in the field of **Applied Statistics**.

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MANAGEMENT AND STATISTICS
ARTICLE

ACTION RESEARCH IN MANAGEMENT

A. C. BRAHMBHATT*

ABSTRACT

This article introduces a verstile concept for management research. The concept has been immensely contributed by German-American professor Levin. This naval concept has varied applications in business, education, community projects etc.

KEY WORDS

World Views : Post Positive, Social Constructive, Pragmatic

• • •

Action research is a powerful tool of change management. It is a versatile philosophical world view in the realm of research as distinguished from other three philosophical world views viz. a post-positivist world view that leads to quantitative research, a social constructivist world view leading to qualitative research and a pragmatic world view dictating mixed-methods. Action research is purely change-oriented and participative and collaborative in nature.

Action research provides an opportunity to reflect critically on the things we are doing in our work places and assess as to whether they would have the desired outcomes or not. .It is a useful method for facilitating organizational change by collaborating and involving the client in the entire resolution process of diagnosis, problem identification, experiential learning and problem solving .

It is a cyclical procedure of change — planning ----> Action Taking ----> Evaluation ----> Reflection ----> Feedback ----> Improved planning. The important stage of evaluation assesses the effect of intervention for change in the current situation—has change occurred? If yes, at what pace, at what rate, what is the directionality, do the data provide supporting evidence etc.

Action research is fully employee – centric. The current state is always to be included in the discussion. It should provide empirically demonstrable propositions. Both action and research are simultaneously carried out.

It has several advantages — it is a systematic approach to problem resolutions and dealing with the challenges of business, helps in analysis and development

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of intervention, facilitates a learning culture. In the entire process of Action research , the change agents act as champions of change who effectively take charge of the entire process as process experts, facilitates collaboration, results in improvement in all areas.

German-American professor Kurt Levin , a professor at MIT then ,coined the term 'action research' in 1944. He is famous for his contribution to ' Gestalt Psychology'. In his paper ' Action Research and Minority problems' (1946) ,he described it as a 'comparative research on the conditions and effects of various forms of social action and research leading to social action' that uses ' a spiral of steps, each of which is composed of a circle of planning, action and fact finding about the result of action'.

Action research has varied applications in business, education , community projects etc. It could be applied in the projects like using interactive multimedia to support information system training: System design and learning issues, employee welfare projects, community welfare projects , women empowerment projects etc.

In the field of education, we find numerous applications of action research; for example using drawings to understand second language learner's prior learning experiences, studying student's experiences with science outside of the classroom context, action research by practicing teachers using a wide variety of pedagogies etc.

The author had an opportunity of interacting with DBA program coordinators and supervisors of Laureate university. It is purely action research oriented. Mostly the Vice Presidents and CEOs of corporate world pursue this program. They do not pursue it for any increment in pay package or promotion as it is mostly the purpose behind Ph.D. program scholars. They do it to bring about the visible change in their current practices and procedures, that is achieved by adopting the action research approach.

ACKNOWLEDGEMENTS:

I thank the referee for reviewing my article.

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MANAGEMENT AND STATISTICS
RESEARCH ARTICLE

A REVIEW OF MANAGING RISKS IN SUPPLY CHAINS

Ajay K. Aggarwal[1] and Dinesh S. Dave[2]

ABSTRACT

Supply chains have considerably evolved over the last couple of decades. Factors like Improved technologies, trade agreements, raw material sources, environmental, economic and political concerns, among others, have facilitated the creation of complex, networked, global supply chains. The convenience of procuring products and services from across the globe has its own set of challenges. This paper reviews the issue of risk in supply chains and suggests a conceptual model for risk assessment.

KEY WORDS:

SCM, GSCM, Risk Assessment, AIT

INTRODUCTION:

Wisner (2017) characterized supply chain as a network of companies involved in making goods, services, and associated functions available to consumers. The creation process involves five major flows– product, financial, information, value, and risk (SaiKrishna, 2016). The simple supply chains where lone, local suppliers made and delivered singular finished products to customers have given way to complex, networked, supply chains. The change has been brought about by several factors including improved technologies, trade agreements, raw material sources, environmental, economic and political concerns, among others. While the advanced supply chains exhibit similar flows as their simpler counterpart, the nature of the flow changes considerably. The current study focuses on the flow associated with issue of risk. It reviews the contributions made by others, and proposes a model for managing risk.

Manuj and Mentzer (2008) identified three types of risks in global supply chains

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(rcd. Oct.'19 / rvd. Dec.'19)

– supply risks, demand risk, and operational risks. Supply risks affect inbound supply elements, demand risks affect outbound supply elements, while operational risks affect elements within the supply chain. The four major factors that contribute to risk are stipulated as environmental (natural disaster, extreme weather, pandemic), geopolitical (political instability, trade restrictions, terrorism, corruption, theft and illicit trade), economic (demand shocks, price volatility, border delays, currency fluctuation, energy shortages) and technological (Information and Communications Technology disruptions, infrastructure failures).

Guertler and Spinler (2014) examined the impact of connections within supply networks on supply risk. To improve risk monitoring they associate a level with risk indicators. Risk Level 1 is associated with technological inadequacy, problems with reliability, quality, or cost. Risk Level 2 indicates insufficient product and process knowledge, inflexibility, and disruption in production. Risk Level 3 reflects financial instability, problems in communication, collaboration, and negotiation. Finally, Level 4 is symptomatic of insufficient personnel and materials, and problems with market conditions and exchange rates.

Harland et al. (2003) modeled the impact of complex, global supply chain networks on risk. The authors provided a tool to identify, assess and manage risk. The various risk areas considered by the authors include strategic, operations, supply, customer, asset impairment, competitive, reputation, financial, fiscal, regulatory, and legal. To assess each risk, probability of its realization and the extent of organizational exposure needs to be evaluated considering the organization, its people, and compliance agreements. The potential for several losses – financial, performance, physical, psychological, social, and time have to be considered. The author regard risk assessment as more than a scientific computation since it has to evaluate the risk Impact on intangible, non-physical assets such as credibility, trust, and reputation. To curtail risk, the authors suggest that organizations must carefully design and manage their supplier networks. This includes supplier selection, evaluation, monitoring, risk sharing, rewards, and opportunity. Their model focuses on perceived risk as opposed to existing one. It gives importance to the product life cycle concept and suggests greater risk propensity during early stages of the product life cycle. Their model works iteratively and tends to deliver better performance with greater participation across the network.

Acknowledging the need for risk analysis in supply chains areas such as finance and crisis management, Heckmann et al. (2015) present some terminology and quantitative approaches borrowed from other fields. Kleindorfer and Saad (2005)

impact. The authors use cluster analysis to separate two types of approaches companies have to risk – reactive and proactive. The companies that operated on a preventive stance showed better supply chain performance and were more flexible with better values for safety stocks. The reactive group on the other hand show better disruption resilience, and are able to better control the bullwhip effect.

PROPOSED MODEL

The proposed model builds on the work of previous approaches with some modifications. It features 5 stages like Manuj and Mentzer (2008) with inclusion of product life cycle data at the risk identification stage, artificial intelligence techniques in the technique selection, and a feedback loop to make it work iteratively. The model is shown in Figure 1.

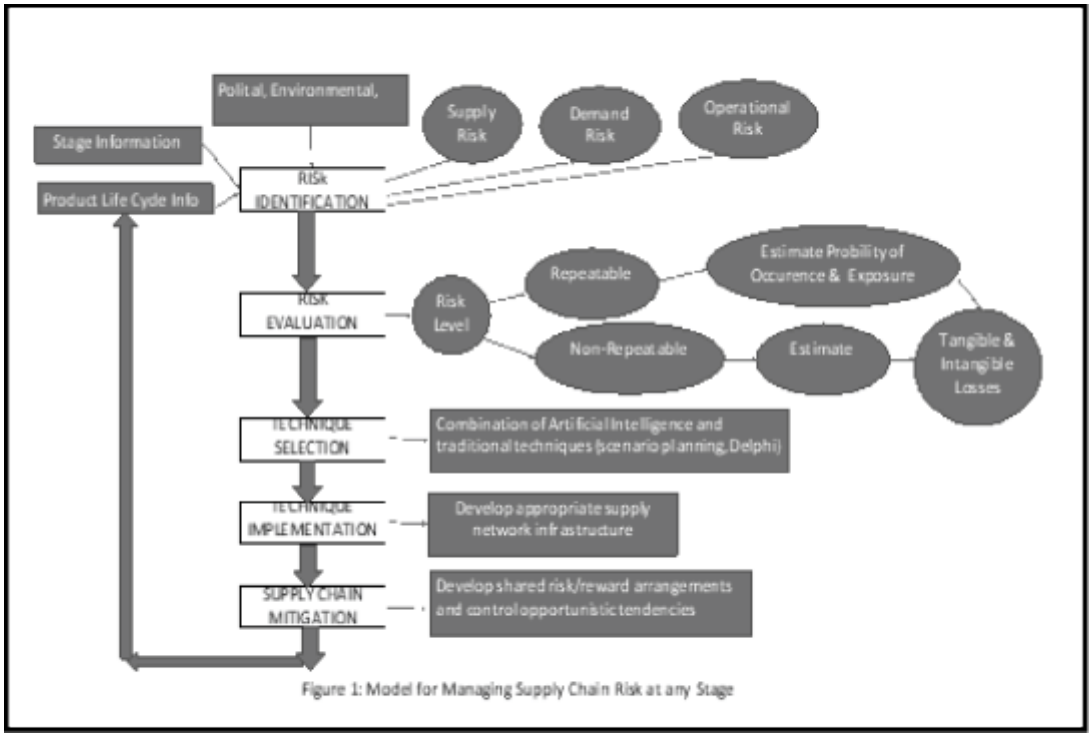

Figure 1: Model for Managing Supply Chain Risk at any Stage

At every stage, the historic stage information, political, environmental, legal, and economic information, along with the product life cycle information is used at the risk identification stage. The risk is identified as associated with supply, demand, or operational. At the risk evaluation stage, the risk level is identified and the tangible and intangible losses estimated depending on the nature of the

mentioned two areas of risks in supply chains – supply-demand coordination and activity disruption. The latter can be caused by factors such as natural disasters, strikes, and terrorism. The authors suggested risk reduction by modifying the management systems design. The new design provides direct new products and processes to a detailed, established, assessment protocol.

Customer demand and competition provides the impetus for global supply chains while opening the door to economic, political, logistical, competitive, cultural, and infrastructural issues (Manuj and Mentzer, 2008). Several sources of risk include supply, operations, demand, security, macro, policy, competition, and resource. Risk is evaluated by two paradigms. For repeatable events, where extreme solutions are possible, the probabilistic choice approach assigns probabilities to good and bad events to assess average behavior. For non-repeated events, the more cautious risk analysis approach operates by minimizing regret, where regret is the difference between the actual and optimal outcomes. Global supply chains are typically evaluated with the probabilistic choice approach. The challenge lies in identifying probabilities due to infrequent occurrences of events. The five steps involved in risk management and mitigation strategy are as follows: risk identification, risk assessment and evaluation, selection of appropriate risk management (avoidance, postponement, speculation, hedging, control, share/ transfer, and security), implementation of supply chain risk management strategy, and mitigation of supply chain risk. The authors suggest that the probability distribution for risk estimation in global supply chains often exhibit non-normal characteristics. A leptokurtic distribution, which is often encountered, is flatter than normal with more data in the tails, indicating higher probability for extreme events.

Tand and Musa (2011) examined the literary contributions associated with material, cash, and information flows. They note the risk focus has shifted from disruptions to proactive system management. Tummala and Schoenherr (2011) presented a structured approach with decision support for managers for assessing and managing supply chain risks. The authors suggested specific techniques for employing the 5-step process proposed by Manuj and Mentzer (2008), with the addition of risk control and monitoring. The risk categories considered by Tummala and Schoenherr (2011) are demand, delay, disruption, inventory, manufacturing process, breakdown, capacity, supply, system, sovereign, and transportation.

Thun and Hoenig (2011) --surveyed sixty-seven manufacturing facilities in the German automotive industry and report their findings. The authors assessed risk by estimating the likelihood of its risky events occurrence and their potential

repeatability of the event. The technique selected for analysis will feature artificial intelligence techniques coupled with traditional statistical approaches. To implement the technique results changes are made to the appropriate supplier infrastructure. To take care of the perceived risk in addition to the realized risk, the mitigation step features risk/reward arrangements achieved with suppliers and a puts tabs on opportunistic behavior (e.g. very large and/or very long-term contracts that yield savings but raise risks substantially).

CONCLUSIONS

The current study examines the role of risk in supply chains. Also, the study discussed the contributions of the previous studies on risk in the supply chains. Building on the previous approaches, the authors proposed a model for risk assessment and mitigation. The proposed a preliminary model that can be applied at any stage in the chain of supply. The study provides an added insight and adds the value to the previous approaches by including product life cycle data, artificial intelligence techniques, and an iterative loop.

ACKNOWLEDGEMENT

We thank the referee for reviewing our paper which has helped in its revision.

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RESEARCH ARTICLE

OVERVIEW OF MULTIPLE TESTING PROCEDURE[1]

Pinakin R. Jani[2]

ABSTRACT

This paper is an overview in continuation to earlier research paper to cover the case studies and some clinical examples, to demonstrate simplicity and ûexibility of the proposed approach covering additional test procedures. After covering introduction to common multiple testing procedure in the previous paper, this paper includes hierarchal test procedure like fixed sequence and fall back procedures, this article also includes closed test procedure and graphical approach for multiple testing.

KEYWORDS:

Hierarchical test procedure, closed test procedure, Graphical Approach.

1. INTRODUCTION:

Multiplicity increases challenging problems which affect almost every decision throughout drug development. Closed test procedure (CTPs) is a general principle to construct powerful multiple test procedures. For structured hypotheses, one can apply the graphical approach, which is based on CTPs. It reflect the difference in importance as well as the relationship between various study objectives and are often applied to clinical trials with structured families of hypotheses and several levels of multiplicity. Proposed graphical method offers the option to, tailor advanced multiple test procedures to structured families of hypotheses. It aids to visualize complex decision strategies in an efficient and easily communicable way. It also benefits to ensure strong FWER control, and approach covers many common multiple test procedures as special cases. (E.g. Holm, fixed sequence, fallback, gatekeeping… etc.)

(1) More methods in continuation to previous research paper, "Overview Multiple testing procedure." SV (NSV15, June19 Issue), email : janipinakin@yahoo.co.in (rcd. Jul'19/ rvd. Nov.'19)

(2) Research Mentor, Ahmedabad, Gujarat, India. (M) 7208069000.

2. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) EXAMPLE BACKGROUNG

Double-blind, parallel-group study to show that drug B is better than drug A in patients which chronic obstructive pulmonary disease (COPD).

Primary endpoint: FEV1 (forced expiratory volume in one second), continuous variable where larger values indicate better efficacy.

Secondary endpoint: Time to exacerbation, time until the event of interest has been observed.

There are two hypotheses corresponding to the two endpoints, thus a multiple test procedure is needed. All of the previous multiple tests in previous research paper can be applied, but this do not reflect the relative importance of the two end points.

For example, the Bonferroni test would treat FEV1 and time to exacerbation as equally important. Note that the stepwise procedures (Holm, Hochberg… and so on) use a data-driven order of the hypotheses. Here we need multiple test procedure that specifies the order of the hypotheses based on the clinical importance (and not based on data).

3. HIERARCHIAL TEST PROCEDURES

If the hierarchy of the hypotheses is specified before data is observed, one can apply a hierarchical test procedure. Two hierarchical test procedures will be introduced.

(i) Fixed sequence procedure
(ii) Fall back procedure

(i) Fixed sequence procedure – General description

Fixed sequence procedures test hierarchically ordered hypotheses in sequence at level α until first non-rejection. Assume m hierarchically ordered hypotheses

$H_1 \rightarrow H_2 \rightarrow \cdots \rightarrow H_m$ with unadjusted p-values $p_1, p_2, \ldots, p_m$

We have the following fixed sequence procedure:

• If $p_1 \leq \alpha$, reject H_1 and continue; else stop

• If $p_2 \leq \alpha$, reject H_2 and continue; else stop

• … so on,

• If $p_i \leq \alpha$, reject H_i and continue; else stop

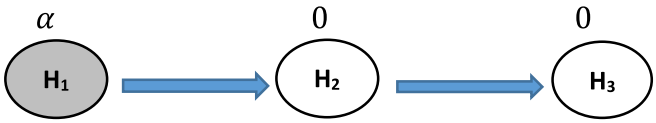
• … so on,

• If $p_m \leq \alpha$, reject H_m

Example with m =3 hypotheses:

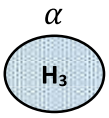
That is, H_1 is more important than H_2, and H_2 is more important than H_3, we have the following fixed sequence procedure for example:

H1 rejected at level α



H_2 rejected at level α

H_3 not rejected at level α



Note: Grey= rejection for H_1 and H_2; Pattern = no rejection (and stop) for H_3

Fixed sequence procedure properties:

Adjusted p-value are given by $q_i = \max\{p_1, p_2, \ldots, p_i\}$, where $i = 1, \ldots, m$.

Advantages:

This is simple procedure. Each test is performed in sequence at level α, it is optimal when early hypotheses in the sequence are related with large effects and perform poorly otherwise.

Disadvantages:

Once a hypothesis is not rejected, no additional testing is permitted, great care needs to be take when postulating the sequence of hypotheses.

(ii) Fall back procedure – General description

Fallback procedures test hierarchically ordered hypotheses in sequence as the fixed sequence procedure, but splits the level α between the hypotheses. Assure m hierarchically ordered hypotheses

$H_1 \rightarrow H_2 \rightarrow \cdots \rightarrow H_m$ with unadjusted p-values $p_1,\ldots, p_m$ and $\alpha = \alpha_1 + \cdots + \alpha_m$

Then the fallback procedure tests H_i at level α_i', where for $i = 2,\ldots, m$.

$\alpha'_i = \alpha_i$, if H_{i-1} is not rejected

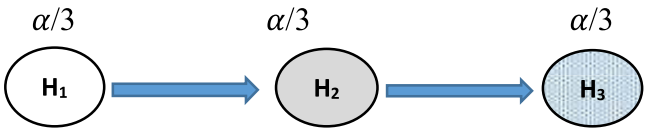
$= \alpha_i + \alpha'_{i-1}$, otherwise

and $\alpha'_1 = \alpha_1$

Example with m = 3 hypotheses

Assume $H_1 \rightarrow H_2 \rightarrow H_3$, and split the significance level as $\alpha_1 = \alpha = \alpha_3 = \alpha/3$.

We could have the following example for the fall back procedure:



Note: Grey = rejection for H_1; pattern= no rejection (and stop) for H_3

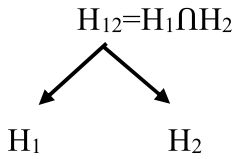
The properties of Fallback procedures are as below:

1) The fixed sequence procedure is obtained as special case from the fallback procedure by setting $\alpha_1 = \alpha$ and $\alpha_i = 0$ for i>1
2) In contrast to the fixed sequence procedure, the fallback procedure tests all the hypotheses in the pre-specified sequence even if the initial hypotheses are not rejected.

4. CLOSED TEST PROCEDURES (CTP):

Closed test procedure is a general principle to construct powerful multiple test procedures, the common procedures are CTP's. The details for operational definition for m = 2, null hypothesis is shown as below:

Schematic diagram for $m = 2$ null hypotheses H_1, H_2, is as below:



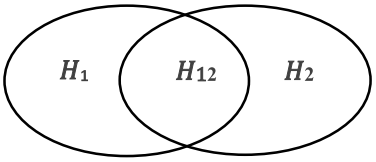
Rejection rule: Reject H_1 (H_2) while controlling the FWER at α, if H_1 (H_2) and H_{12} are rejected, each at local level α.

Operationally:

• Test H_{12} at local level α (using a suitable test): If rejected, proceed; otherwise stop

• Test H_1 and H_2 each at local level α: Reject H_1 (H_2) overall if H_{12} and H_1 (H_2) are rejected locally.

Venn diagram for m=2 null hypothesis:



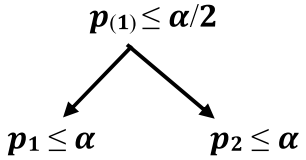
Different parts indicate different null hypotheses as shown in the Venn diagram.

Question: How do we test them?

- Test H_{12} using Bonferroni, Simes, Dunnett, etc. at level α
- Test H_1, H_2 each using a level α test

CTP using Bonferroni, Holm procedure:

- Using Bonferroni to test H_{12}, reject if $p_1 \leq \alpha/2$ or $p_2 \leq \alpha/2$, i.e., if $p_{(1)} \leq \alpha/2$



- If we fail to reject H_{12}, stop as neither H_1 nor H_2 can be rejected according to the CTP.
- If we reject H_{12} then,

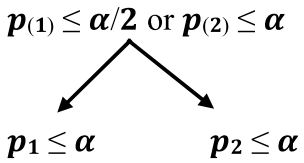
  H_1 is rejected automatically as $p_{(1)} \leq \alpha/2 < \alpha$,

  We only need to test $H_{(2)}$ at level α, i.e., reject $H_{(2)}$ if $p_{(2)} \leq \alpha$

This results exactly in the Holm procedure.

CTP using Simes, Hochberg procedure:

- Using Simes to test H_{12}, reject if $p_{(1)} \leq \alpha/2$ or $p_{(2)} \leq \alpha$.



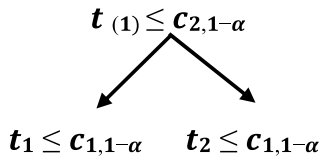
- If we fail to reject H_{12}, stop
- If we reject H_{12} because $p_{(2)} \leq \alpha$, then H_1 , H_2 are rejected automatically as $p_{(1)} \leq p_{(2)} \leq \alpha$, and stop
- If we reject H_{12} because $p_{(1)} \leq \alpha/2$ but $p_{(2)} > \alpha$, we then reject $H_{(1)}$ but fail to reject $H_{(2)}$ and stop.

This results exactly in the Hochberg procedure for m=2.

For $m > 2$ the Hochberg procedure is less powerful than CTP using Simes tests (Hommel procedure)

CTP using Dunnett, Stepwise Dunnett test:

Using Dunnett test to test H_{12}, reject if $t_1 \leq c_{2,\,1-\alpha}$ or $t_2 \leq c_{2,\,1-\alpha}$, i.e., if $t_{(1)} \leq c_{2,\,1-\alpha}$



If we fail to reject H_{12}, stop

If we reject H_{12}, stop

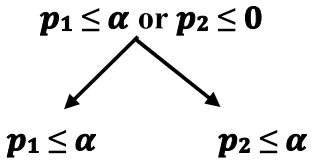
$H_{(1)}$ is rejected automatically as $t_{(1)} \leq c_2$, $1-\alpha \leq c_{1,\,1-\alpha}$

- We only need to test $H_{(2)}$ at level α, i.e., reject $H_{(2)}$ if $t_{(2)} \leq c_{1,\,1-\alpha}$

This results exactly in the step down Dunnett procedure.

CTP using Weighted Bonferroni – fixed sequence procedure

Two ordered hypotheses $H_1 \rightarrow H_2$, using weighted Bonferroni test to test H_{12}, reject if $p_1 \leq \alpha$ or $p_2 \leq 0$



If we fail to reject H_{12}, stop

If we reject H_{12}, then

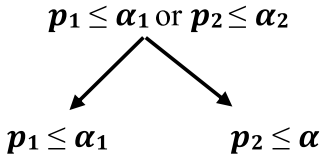
- H_1 is rejected automatically as $p_1 \leq \alpha$
- We only need to test H_2 at level α, i.e., reject H_2 if $p_2 \leq \alpha$

This results exactly in the fixed sequence procedure.

CTP using Weighted Bonferroni – fallback procedure

Two ordered hypotheses $H_1 \rightarrow H_2$

Using weighted Bonferroni test to test H_{12}, reject if $p_1 \leq \alpha_1$ or $p_2 \leq \alpha_2$, weights α_1 and α_2 are such that $\alpha_1 + \alpha_2 = \alpha$

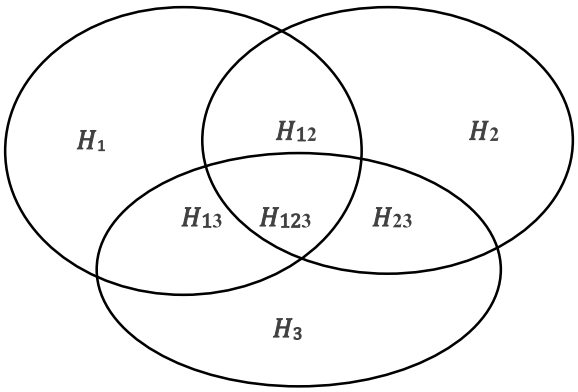


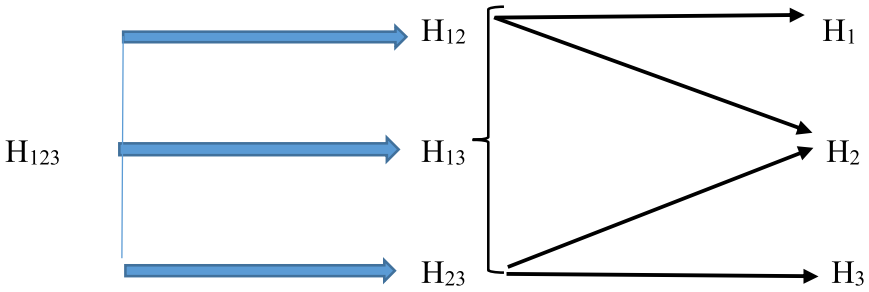
If we fail to reject H_{12}, stop

If we reject H_{12}, then we test H_2 at level α, i.e., reject H_2 if $p_2 \leq \alpha$, H_1 is tested at α_1 level instead of α.

This results exactly in the fallback procedure.

Venn diagram for m=3 null hypothesis:





Similarly for, m null hypotheses, many intersection hypotheses needs to be tested, CTP considers all intersection hypotheses:

$H_J = \cap_{i \in J} H_i, J \subseteq \{1,\ldots, m\}$, any suitable test can be used to test H_J at local level α.

An individual H_i is rejected at level α if all hypotheses H_J formed by intersection with H_i are rejected at local level α.

Overall summary on CTP:

CTP is a general principle to construct powerful multiple test procedures. In a CTP, one rejects an individual null hypothesis Hi at overall level α by rejecting all intersection null hypotheses

$H_J \subseteq H_i$, including $J = \{i\}$, many common multiple test procedures are CTP, including, Holm, Hochberg, step-down Dunnett, etc.

CTPs satisfy certain optimality criteria and there is no reason why not to use a CTP, the number of intersection hypotheses is $2m-1$, for large m, this number increases rapidly and CTPs are in general difficult to apply.

5. GRAPHICAL APPROACH

- Conventions and common multiple test procedures
- Formal description
- COPD example with multiple end points and multiple doses

COPD example:

Study Objective: Show that a new drug is better than a control drug in patients with COPD for two endpoints

• Primary endpoint: FEV1 (forced expiratory volume in one second) - Continuous variable, where larger values indicate better efficacy

• Secondary endpoint: Time to exacerbation - Time until the event of interest has been observed

New drug is available at two doses Dose-1(D_1), Dose-2 (D_2) that are compared with the control C

Two sources of multiplicity

- Comparing two doses with control for each of two endpoints.

Resulting in four hypotheses of interest

• Two primary hypotheses H_1, H_2 (comparing D_1, D_2 with C for FEV1)

• Two secondary hypotheses H_3, H_4 (comparing D_1, D_2 with C for time to exacerbation)

Note that the four hypotheses are not equally important, suitable multiple test procedure needs to be applied.

• The secondary hypotheses H_3 (H_4) should be tested, only if the corresponding primary hypotheses H_1 (H_2) is rejected.

GRAPHICAL APPROACH

Heuristic

Null hypotheses is defined as $H_1,\ldots, H_m$, with initial allocation of the significance level $\alpha_1 + \cdots + \alpha_m = \alpha$, and unadjusted p-values $p_1,\ldots, p_m$

α–propagation

If a hypothesis H_i can be rejected at level α_i (i.e. $p_i \leq \alpha_i$), propagate its level α_i to the remaining, not yet rejected hypotheses (according to a prefixed rule) and continue testing with the updated α levels.

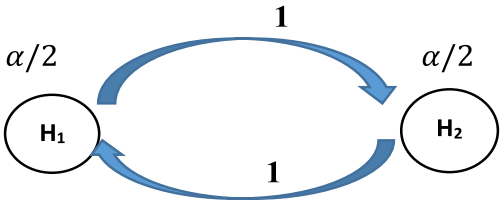
Conventions

Hypotheses $H_1,\ldots, H_m$ represented as nodes

Split of significance level $\alpha_1, \ldots\ldots, \alpha_m$

Bonferroni

"α–propagation" through weighted, direct edges

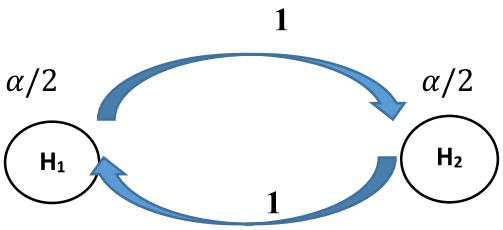


Holm

Graphical Approach - **Bonferroni test and Holm procedure with m=2 hypotheses**

Bonferroni: no α–propagation, i.e. no edges between nodes

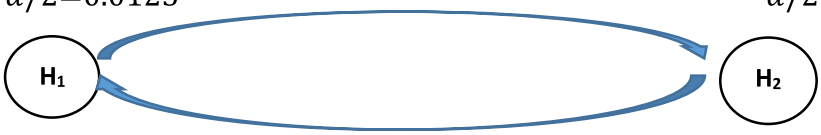
Holm: includes α–propagation and is thus more powerful



Holm procedure: Example with $\alpha = 0.025$

Test H_1 at level $\alpha/2$ **1** Test H_2 at level $\alpha/2$

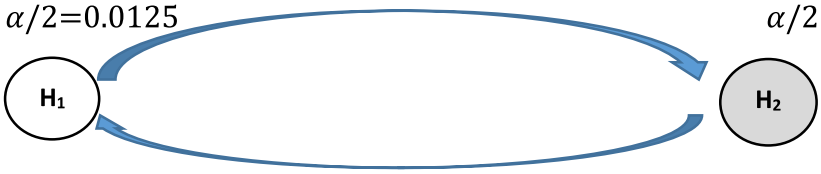
$\alpha/2=0.0125$ $\alpha/2=0.0125$



$p_1=0.4$ **1** $p_2=0.01$

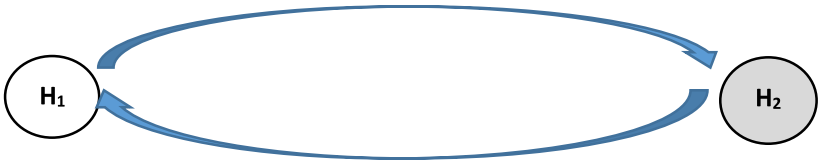
1 $p_2 < \alpha/2 \Longrightarrow$ reject H_2

$\alpha/2=0.0125$ $\alpha/2=0.0125$



$p_1=0.4$ **1** $p_2=0.01$

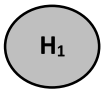
$\alpha=0.025$ **1** Propagate $\alpha/2$



$p_1=0.4$ **1**

Removing node for H_2, test H_1 at level α, $p_1 > \alpha \Longrightarrow$ retain H_1 and stop

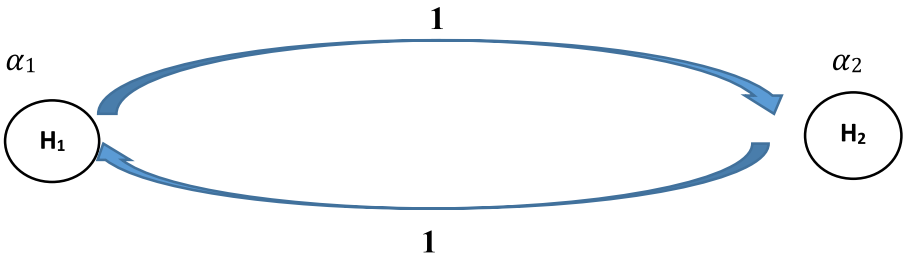
α=0.025



p_1=0.4

Graphical Approach - **Weighted Holm procedure with m=2 hypotheses**

Use α_1, α_2 with $\alpha_1 + \alpha_2 = \alpha$ instead of $\alpha_1 = \alpha_2 = \alpha/2$



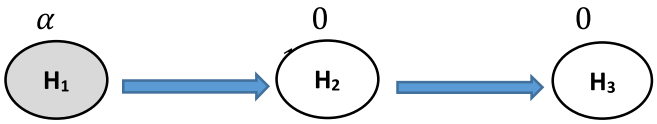
Graphical Approach – **Fixed sequence procedure with m=3 hypotheses**

Assume $H_1 \rightarrow H_2 \rightarrow H_3$

• That is, H_1 is more important than H_2, and H_2 is more important than H_3

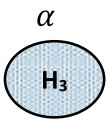
Then we could have, for example, the following fixed sequence procedure:

H_1 rejected at level α



H_2 rejected at level α

H_3 not rejected at level α



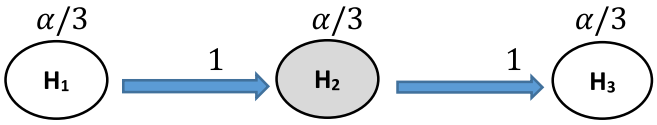
Note: Grey= rejection for H_1 and H_2; pattern= no rejection (and stop) for H_3

Graphical Approach – **Fallback procedure with m=3 hypotheses**

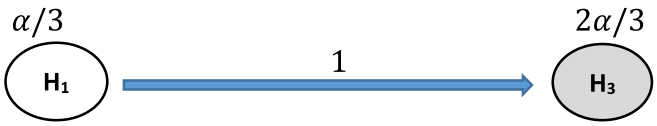
Assume $H_1 \rightarrow H_2 \rightarrow H_3$, and split the significance level as $\alpha_1 = \alpha_2 = \alpha_3 = \alpha/3$

Then we could have, for example, the following fallback procedure:

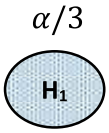
Initial



H_2 rejected at level $\alpha_2 = \alpha/3$



H_3 rejected at level $\alpha_3 = 2\alpha/3$



Graphical Approach – definition:

The graphical approach method is described with, initial levels $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m)$ with,

$$\sum_{i=1}^{m} \alpha_i = \alpha \in 0, 1$$

• $m \times m$ transition matrix $\boldsymbol{G} = (g_{ij})$ where g_{ij} is the fraction of the level of Hi that is propagated to H, with $0 \leq g_{ij} \leq 1$, $g_{ii} = 0$, and

$\sum_{j=1}^{m} g_{ij} \leq 1, \forall i = 1, \ldots, m$, where $\boldsymbol{G}, \boldsymbol{\alpha}$ determine a graph with an associated multiple test

Update Algorithm:

Set $J = \{1, \ldots, m\}$

❶ Select a j such that $p_j \leq \alpha_j$, if no such j exists, stop; otherwise reject H_j

❷ Update the graph:

$J \to J \setminus \{j\}$

$$\alpha_\ell \to \begin{cases} \alpha_\ell + \alpha_j g_{j\ell}, & \ell \in J \\ 0, & \text{otherwise} \end{cases}$$

$$g_{\ell m} \to \begin{cases} \dfrac{g_{\ell m} + g_{\ell j} g_{jm}}{1 - g_{\ell j} g_{j\ell}}, & \ell, m \in J,\ \ell \neq m,\ g_{\ell j} g_{j\ell} < 1 \\ 0, & \text{otherwise} \end{cases}$$

❸ Go to Step 1

The initial levels $\boldsymbol{\alpha}$, the transition matrix $\boldsymbol{G}$, and the algorithm define a unique sequentially rejective test procedure that controls the FWER at level α.

Remarks:

• Any multiple test procedure derived and visualized by a graph $\boldsymbol{G}$, is based on the closed test principle

• The graph $\boldsymbol{G}$, $\boldsymbol{\alpha}$ and the algorithm defines weighted Bonferroni tests for each intersection hypothesis in a CTP

• The algorithm defines a shortcut for the resulting CTP, which does not depend on the rejection sequence

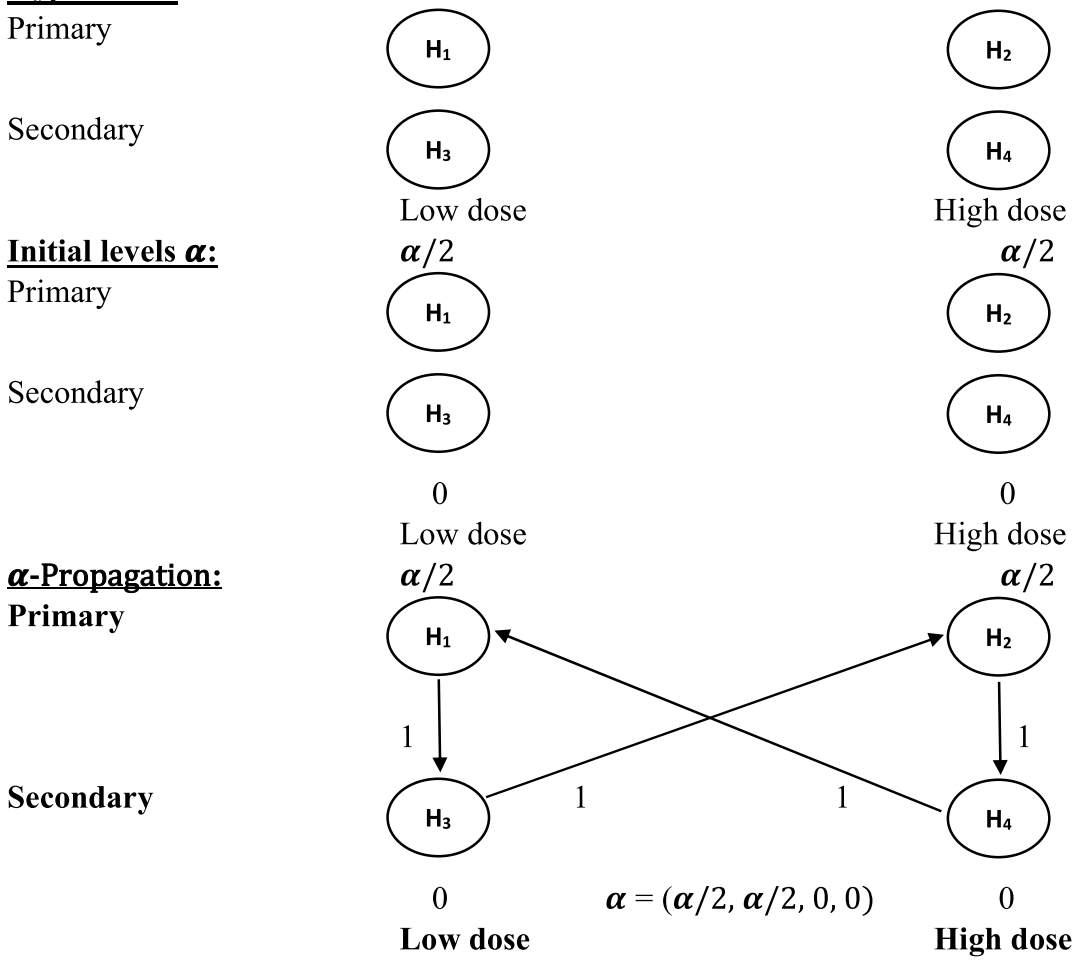
Considering the same COPD example, there is a natural order in that a primary endpoint is more important than a secondary endpoint, thus, we would like to test the primary null hypothesis first; only if that is rejected, we test the secondary hypothesis, both doses are equally important thus, both doses are simultaneously tested against the control.

We have four hypotheses corresponding to the two doses and the two endpoints; a multiple test procedure is needed, standard multiple test procedures could be applied, but do not reflect the relative importance of the two endpoints, for example, the Bonferroni test would treat FEV1 and time-to exacerbation as equally important and doesn't reflect the relative order desired.

We need a multiple test procedure that reflects the relative importance and order of the hypotheses based on clinical importance.

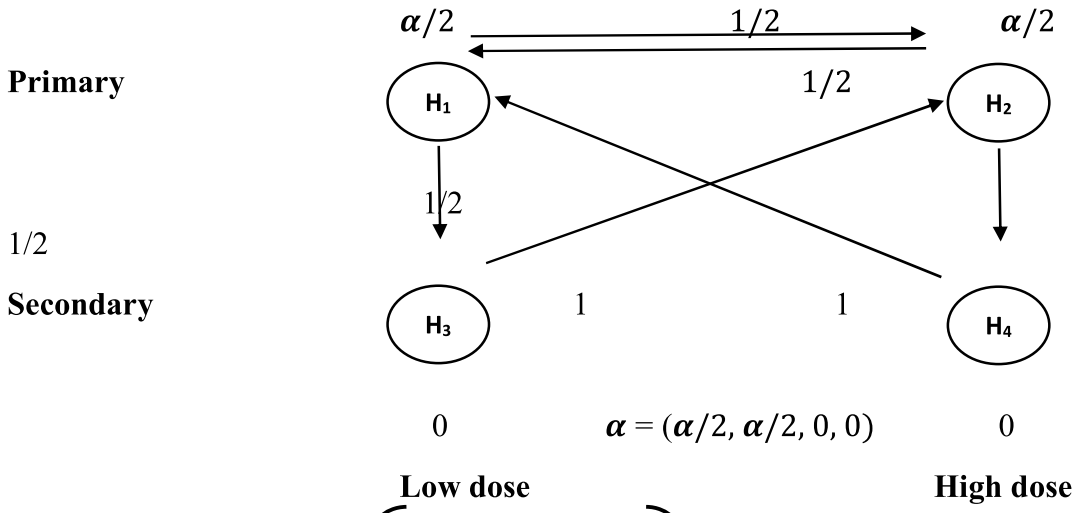
Building a multiple test procedure hypotheses:

Hypotheses:



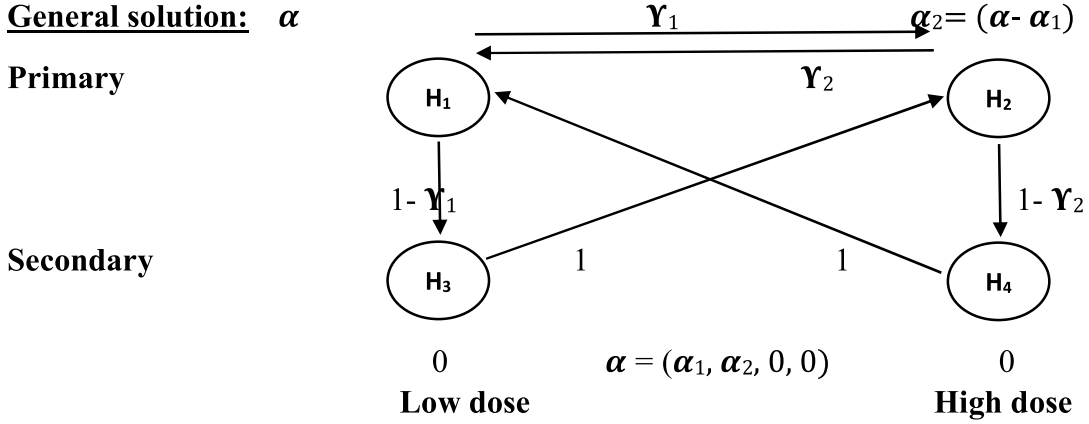
$$\mathbf{G} = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

Alternative α–propagation



$$G = \begin{pmatrix} 0 & 1/2 & 1/2 & 0 \\ 1/2 & 0 & 0 & 1/2 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

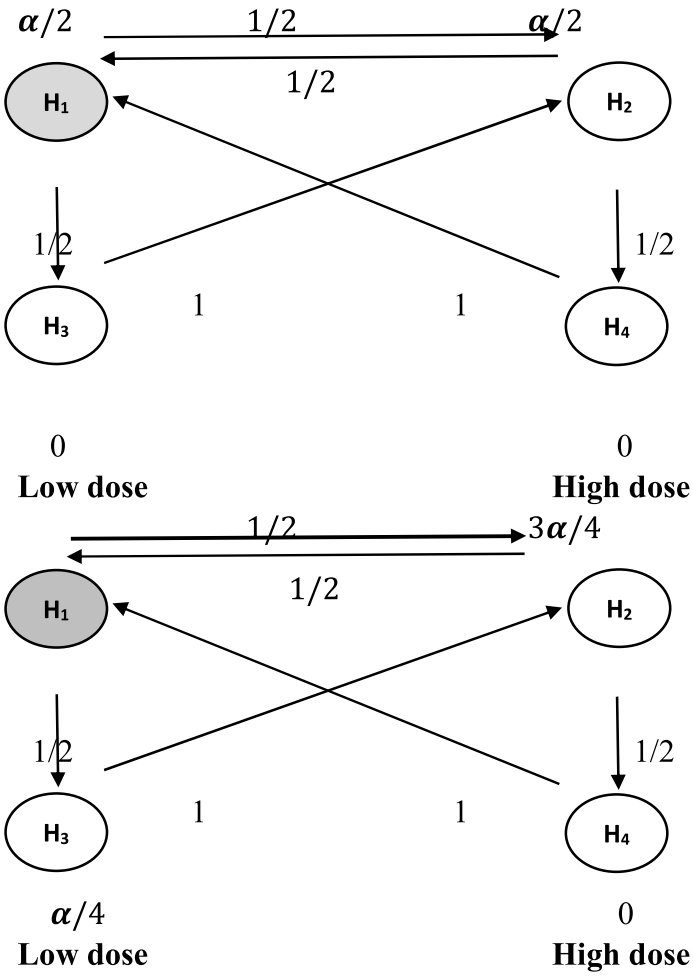
General solution: α

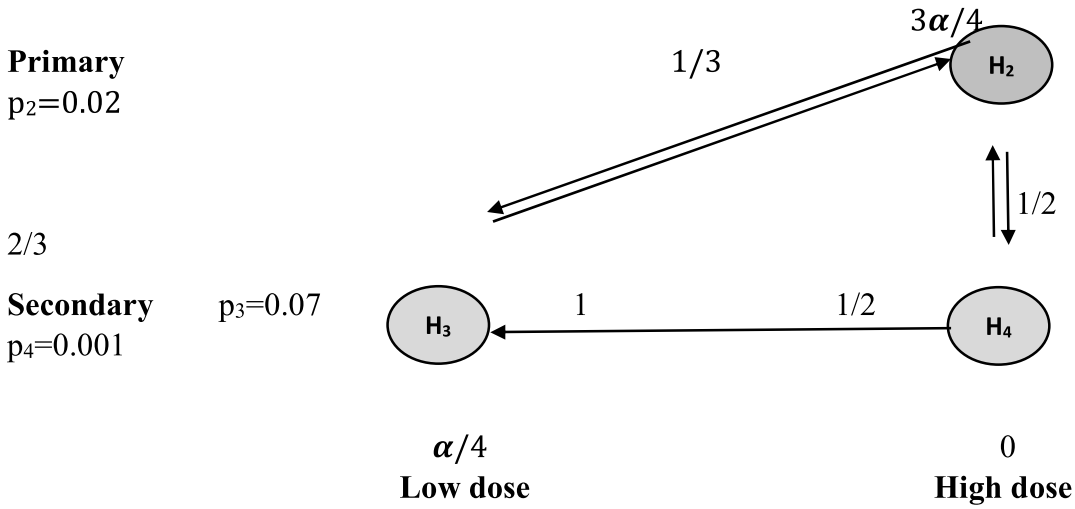


$$\mathbf{G} = \begin{pmatrix} \mathbf{0} & \boldsymbol{\Upsilon}_1 & 1\text{-}\boldsymbol{\Upsilon}_1 & \mathbf{0} \\ \boldsymbol{\Upsilon}_2 & \mathbf{0} & \mathbf{0} & 1\text{-}\boldsymbol{\Upsilon}_2 \\ \mathbf{0} & \mathbf{1} & \mathbf{0} & \mathbf{0} \\ \mathbf{1} & \mathbf{0} & \mathbf{0} & \mathbf{0} \end{pmatrix}$$

Resulting graph depends on only three parameters $\alpha 1$, $\boldsymbol{\Upsilon}_1$, and $\boldsymbol{\Upsilon}_2$ that can be built based on, further clinical considerations, or assumptions about effect sizes, correlations etc.

Example with $\boldsymbol{\alpha}$= 0.025





SAS main function example code:

```
/*****************************************************************
*
 h: indicator whether a hypothesis is rejected (= 1) or not (= 0) (1 x n vector)
a: initial significance level allocation (1 x n vector)
w: weights for the edges (n x n matrix)
p: observed p-values (1 x n vector)
*****************************************************************/
 START mcp (h, a, w, p);
      n = NCOL (h);
      mata = a;
      crit = 0;
      DO UNTIL (crit = 1);
         test = (p < a);
         IF (ANY (test)) THEN DO;
              rej = MIN (LOC (test# (1: n)));

               h[rej] = 1;
              w1 = J (n, n, 0);
             DO i = 1 TO n;
                a [i] = a[i] + a [rej]*w [rej, i];
                IF (w [i, rej] * w [rej, i]<1) THEN DO j = 1 TO n;
```

```
            w1[i,j] = (w[i,j] + w[i,rej]*w[rej,j])/(1 - w[i,rej]*w[rej,i]);
          END;
          w1 [i, i] = 0;
            END;
             w = w1; w [rej,] = 0; w [, rej] = 0; a [rej] = 0;
             mata = mata // a;
      END;
      ELSE crit = 1;
  END;
 PRINT h; PRINT (ROUND (mata, 0.0001)); PRINT (ROUND (w, 0.01));
FINISH;
```

Example call

```
START mcp (h, a, w, p); ……. FINISH;
/*****************************************
 Numerical example
***************************************** ***/
h = {0          0       0       0       };
a = {0.0125     0.0125  0       0       };
w = {0          0.5     0.5     0,
     0.5        0       0       0.5,
     0          1       0       0,
     1          0       0       0       };
 p = {0.01      0.02    0.07    0.001};

RUN mcp (h, a, w, p);
QUIT;
```

Summary

Closed test procedure (CTPs) is a general principle to construct powerful multiple test procedures. For structured hypotheses, one can apply the graphical approach, which is based on CTPs. It is critical to choose the suitable method for a particular problem. There are different types of multiplicity problems that need other methods than those described in this paper:

- Safety data analyses
- Large-scale testing in genetics, proteomics etc.
- Post-hoc analyses / data snooping

•

4. ACKNOWLEDGEMENT

I thank the referee for his comments for reviewing this article which has helped its revision.

5. REFERENCES

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[2] **Bretz, F., Hothorn, T., and Westfall, P. (2010).** Multiple Comparisons with R. Chapman and Hall, Boca Raton.

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[3] **ICH E9 (1998)** on "Statistical principles for clinical trials".

[4] **CPMP (2002)** Points to consider on "Multiplicity issues in clinical trials".

[5] **FDA** draft guidance for industry on "Multiple endpoint analyses" expected for 2014.

RESEARCH ARTICLE

A STUDY OF TOTAL FACTOR PRODUCTIVITY FOR MANUFACTURING INDUSTRIES OF INDIA

M. K. Dave[1] and Sanjay G. Raval[2]

ABSTRACT

In this paper Total Factor Productivity is defined according to Kendrick's universal approach. TFP indices are computed for the industrial sector of Gujarat State as well as India. A non-linear regression model is considered for TFP pertaining to industrial sector of all India during the years 1981-82 to 2017-18.

KEYWORDS : TFP, RTFP, Regression Model.

1. INTRODUCTIOIN

Labour productivity and capital productivity measures are useful for measuring the role of labour and capital inputs over the net value added for any industry. Though these are very useful ratios, they do not measure the over all changes in the productive efficiency, since they are affected by the changes in the composition of inputs such as factor substitution.

A comprehensive measure has been defined by Kendrick which is known as Total Factor Productivity. There are many studies based upon TFP measures in the industrial sector as a whole as well as for particular industries and also for state-wise studies are made to visualise the effect of these measures over a course of time. It may not be possible to give an exhaustive list for all such research done in these areas, however a few of them are quoted in the list of selected references.

In this paper we have made an attempt to find out Total Factor Productivity(TFP)

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(rcd. Nov.'19/rvd. Dec.'19)

based upon Kendrick's approach which is considered to be universal. TFP and TFP indices are computed for the industrial sector of all India as well as Gujarat State. It may also be worthwhile to consider some sort of regression approach for our study.

2. DATA BASE

For our academic study we have used data published in Annual Survey of Industries (ASI) as well as Census of Indian Manufacturers(CIM). The data are pertaining to all the industries in all India as well as all industries of Gujarat State during the years 1981-82 to 2017-18.

3. Methodology

(3.1) Notations

$(TFP)_t$	=	Total Factor Productivity for the year t
V_t	=	Net value added for the year t
N_t	=	Number of workers for the year t
F_t	=	Fixed capital for the year t
S_o	=	Wages and salary for the base year
V_o	=	Net value added for the base year
N_o	=	Number of workers for the base year
F_o	=	Fixed capital for the base year

(3.2) Construction of TFP series and TFP indices

We have obtained Total Factor Productivity (TFP) series during the year t for the industrial sector of Gujarat state and the same for India as a whole by using Kendrick's definition in which the combined effects of the two input factors viz- total productive capital invested and the labour employed are considered. TFP is defined as the ratio of output to the sum of labour and capital inputs, where the wages are weighted by the base year wage rate and fixed capital is weighted by the base year return on capital.

The Total Factor Productivity for year t is denoted by $(TFP)_t$ and it is

calculated from the following formula as given by Kendrick.

$$(TFP)_t = \frac{V_t}{W_0 N_t + R_0 F_t} \quad (1)$$

where $W_0 = \frac{S_0}{N_0}$, $R_0 = \frac{V_0 - S_0}{F_0}$

W_0 and R_0 being the marginal productivities which represents the base year wage rate and base year return on per rupee of the fixed capital for the respective industrial sector as a whole, which can also be interpreted as the weights (which are the base year's remuneration) attached to manpower and the fixed capital employed in the current year respectively.

The indices of the series for $(TFP)_t$ are computed and they are denoted by $TFP(I)_t$ for all industries of all India and $TFP(G)_t$ for all industries of Gujarat with 1981-82 as base year.

In order to compare this measure for the industrial sector of Gujarat State with that for India as a whole, the measure of Relative Total Factor Productivity (RTFP) is found for period 1981-82 to 2017-18 which is denoted by $(RTFP)_t$ and is computed by the following formula.

$$(RTFP)_t = \frac{(TFP)_t \text{ for the industrial secotor of Gujarat state}}{(TFP)_t \text{ for the industrial sector of all India}} \quad (2)$$

This measure may also be referred to as the overall efficiency of the industrial sector of Gujarat State as compared to the same for all India. A comparison can be made as under

(1) If $(RTFP) > 1 \Rightarrow TFP$ for the industrial sector of Gujarat state may be considered as relatively better than the same for the industrial sector of India as a whole.

(2) If $(RTFP) = 1 \Rightarrow TFP$ for the industrial sector of Gujarat state may beconsidered as relatively normal or standard (at par) as compared to the same for India as a whole.

(3) $(RTFP) < 1 \Rightarrow TFP$ for industrial sector of Gujarat state may be considered as relatively below normal with respect to the same for the industrial sector of India as a whole.

(3.3) Regression Analysis

we consider the following regression model for TFP series of the all industries of all India as obtained in (1). The relevant equations are as under.

$$Y_t = \propto \cdot exp\,(\beta_1 t)\; K_t^{\beta_2} L_t^{\beta_3} exp(\beta_4 R_t)\; U_t \qquad (3)$$

where

Y_t = Total Factor Productivity for the year t

K_t = Working capital for the year t

L_t = Labour in terms of wages to workers for the year t

U_t = Disturbance term for the year t

$R_t = \frac{1}{\sqrt{1+\theta_t^2}}$ here $\theta_t = \frac{K_t}{L_t}$ = Capital Labour ratio for the year t

Here $\beta_1, \beta_2, \beta_3, \beta_4$ are the regression co-efficients of the proposed model. The above model takes the form under logarithmic procedure as

$$L_n(Y_t) = A + \beta_1 t + \beta_2 L_n(K_t) + \beta_3 L_n(L_t) + \beta_4 R_t + Z_t \qquad (4)$$

where $A = L_n(\propto)$

$Z_t = L_n(U_t)$

This non-linear regression can be fitted under usual assumptions to estimate the unknown parameters of the model.

4. Statistical Analysis

Table-1 corresponds to TFP and TFP indices for Gujarat State and all India based upon Kendrick's approach given in equation (1). RTFP and their indices are computed from equation (2).

Table : 1 Total Factor Productivity for all India and Gujarat state

Year	TFP(I)	TFP(I) INDICES	TFP(G)	TFP(G) INDICES	RTFP	RTFP INDICES
1981-82	1.00	100.00	1.00	100.0	1.00	100
1982-83	1.01	101.00	0.98	98.00	0.97	97
1983-84	1.08	108.00	1.22	122.00	1.13	113
1984-85	1.02	102.00	0.65	65.00	0.64	64
1985-86	1.04	104.00	1.05	105.00	1.01	101
1986-87	1.07	107.00	1.09	109.00	1.01	101
1987-88	1.04	104.00	1.02	102.00	0.98	98
1988-89	1.14	114.00	1.67	167.00	1.46	146
1989-90	1.19	119.00	1.09	109.00	0.91	91
1990-91	1.18	118.00	1.06	106.00	0.89	89
1991-92	1.12	112.00	0.88	88.00	0.79	79
1992-93	1.17	117.00	1.22	122.00	1.05	105
1993-94	1.26	126.00	1.43	143.00	1.14	114
1994-95	1.26	126.00	1.33	133.00	1.05	105
1995-96	1.30	130.00	0.95	95.00	0.73	73
1996-97	1.35	135.00	1.08	108.00	0.80	80
1997-98	1.29	129.00	0.99	99.00	0.77	77
1998-99	1.22	122.00	0.84	84.00	0.68	68
1999-00	1.27	127.00	0.76	76.00	0.60	60
2000-01	1.19	119.00	0.72	72.00	0.60	60
2001-02	1.11	111.00	0.72	72.00	0.65	65
2002-03	1.28	128.00	0.86	86.00	0.67	67
2003-04	1.42	142.00	1.04	104.00	0.73	73
2004-05	1.68	168.00	1.27	127.00	0.76	76
2005-06	1.71	171.00	1.24	124.00	0.72	72
2006-07	1.84	184.00	1.13	113.00	0.61	61
2007-08	1.91	191.00	1.32	132.00	0.69	69
2008-09	1.68	168.00	1.08	108.00	0.65	65
2009-10	1.48	148.00	1.56	156.00	1.05	105
2010-11	1.48	148.00	1.17	117.00	0.79	79
2011-12	1.33	133.00	1.18	118.00	0.88	88
2012-13	1.32	132.00	0.49	49.00	0.37	37
2013-14	1.28	128.00	0.93	93.00	0.73	73
2014-15	1.34	134.00	0.73	73.00	0.54	54
2015-16	1.29	129.00	0.34	34.00	0.26	26
2016-17	1.22	122.00	0.28	28.00	0.23	23
2017-18	1.28	128.00	0.40	40.00	0.31	31

Conclusion : From the above table it is observed that TFP indices for all India increase from year 1981-82 up to the year 1989-90. Thereafter it reduces for three further years and then almost increases reaching to 191 as maximum in year 2007-2008 thereafter it reduces and for the year 2017-18 it reaches to 128.

Simillarly, TFP indices for Gujarat state also shows fluctuations from the year 1981-82 and it reaches to 143 in 1993-94. Thereafter it reduces but it becomes maximum of 105 during the year 2009-10 and then reduces and becoming 40 as lowest in the 2017-18. Both the series observe fluctuations but in Gujarat state this variation is more as compared to TFP indices for all India.

RTFP indices indicate relative performance for all industries in Gujarat state as compared to that for all India which are given in the last column of Table:1 We find that this series also has fluctuations and becoming 146 in the year 1988-89 and it is lowest as 23 in the year 2016-17. This fluctuation is observed from our analysis of RTFP indices. It may be concluded that the relative performance of TFP for Gujarat state as compared to all India for all industries cannot be considered to be satisfactory.

Based upon the TFP values and their indices and RTFP values and their indices, graphical presentation is shown in diagrams 1, 2 and 3.

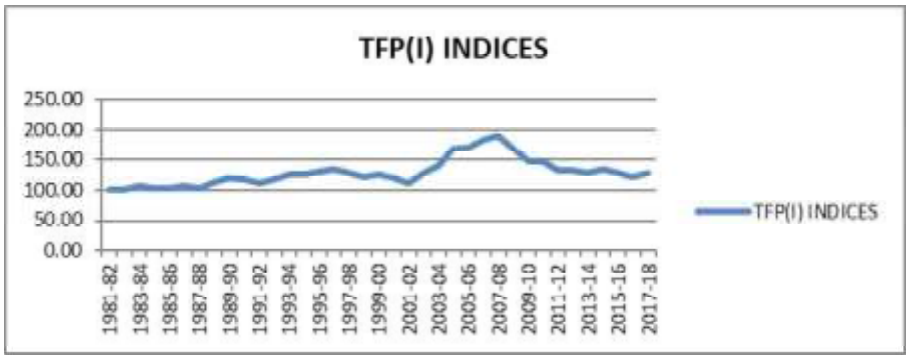

Diagram : 1 TFP Indices for all industries of all India.

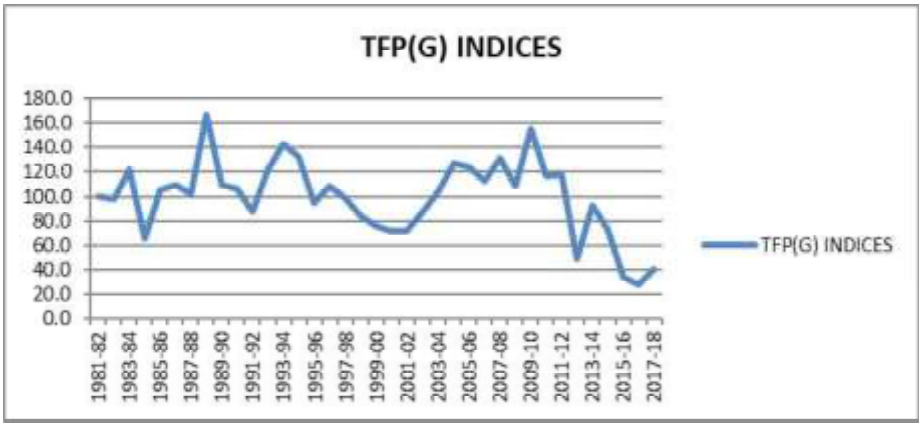

Diagram : 2 TFP Indices for all industries of Gujarat State.

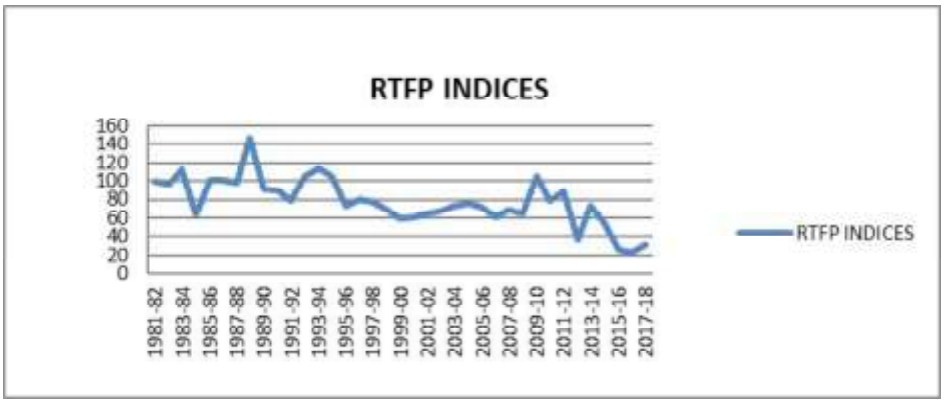

Diagram : 3 RTFP Indices for all industries of Gujarat State.

5. REGRESSION ANALYSIS

Using TFP values as computed in table 1 above, an attempt is made to consider regression analysis based upon equation (4). The results obtained are as shown in table 2 below.

Table : 2

Regression Analysis for all Industries of All India

Model : $L_n(Y_t) = A + \beta_1 t + \beta_2 L_n(K_t) + \beta_3 L_n(L_t) + \beta_4 R_t + Z_t$

Regression Statistics	
Multiple R	0.83104692
R Square	0.69063898
Adjusted R Square	0.65196885
Standard Error	0.09742162
Observations	37

ANOVA					
	df	SS	MS	F	Significance F
Regression	4	0.678025707	0.169506427	17.8597545	8.48095E-08
Residual	32	0.303711099	0.009490972		
Total	36	0.981736806			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	4.1630007	1.708175361	2.437103823*	0.02054534	0.683561369	7.642440038	0.68356137	7.642440038
Time t	0.02382875	0.009419177	2.52981244*	0.01653382	0.004642516	0.043014988	0.00464252	0.043014988
Capital	-0.3878959	0.189384006	-2.04819779*	0.04881947	-0.7736585	-0.00213331	-0.7736585	-0.00213331
Labour	0.18545498	0.112674523	1.645935312	0.10956538	-0.04405552	0.414965469	-0.0440555	0.414965469
R_t	-3.2906881	1.040217586	-3.16346137*	0.00340681	-5.40954203	-1.17183427	-5.409542	-1.17183427

(* Indicates significance at 5% level)

From the above analysis, we find that about 69% of the variation is explained by the model. Value of R^2 is highly significant. All the regression coefficients are also significant at 5% level except the coefficient for labour. In order that we may employ this model for prediction purpose during the subsequent years, we modify this model by omitting the insignificant component (i.e. labour) and run the modified model pertaining to all industries of all India.

Modified Model

Model : $L_n(Y_t) = A + \beta_1 t + \beta_2 L_n(K_t) + \beta_3 R_t + Z_t$

Table 3 gives the analysis based upon this model

Table : 3

Regression Analysis

Regression Statistics	
Multiple R	0.815137192
R Square	0.664448641
Adjusted R Square	0.633943972
Standard Error	0.099912556
Observations	37

ANOVA					
	df	SS	MS	F	Significance F
Regression	3	0.652313687	0.2174379	21.7818669	5.79785E-08
Residual	33	0.329423119	0.0099825		
Total	36	0.981736806			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	1.996190403	1.116312699	1.7882	0.08292934	-0.274964848	4.267345653	-0.274964848	4.267345653
Time t	0.014831343	0.007866781	1.8853128	0.06821792	-0.001173744	0.030836429	-0.001173744	0.030836429
Capital	-0.0996967	0.074005681	-1.347149	0.18711049	-0.250262386	0.050868993	-0.250262386	0.050868993
R_t	-1.6784786	0.359115179	-4.673928	4.806E-05	-2.409103922	-0.94785328	-2.409103922	-0.94785328

We find from our analysis that about 66.45 % of the variation is explained by the model. Value of R^2 is found to be highly significant. All the regression coefficients are now statistically significant at 5% level of significance. Thus this modified version of the model is found to be appropriate for data of all industries in all India.

It may be noted that when we fit these models for all industries of Gujarat state all the coefficients are not found to be significant, as well as R^2 is very poor. Hence we have not presented this approach for Gujarat state.

.6. CONCLUDING REMARKS.

(6.1) In this paper we have made an effort for computing TFP, their indices as well as RTFP indices. We may conclude from our analysis that TFP for all India may be considered as satisfactory (above par) on an average, but the same for Gujarat State is not found to encouraging. This is also reflected in RTFP indices. Hence steps should be taken for monitoring the situation so that Gujarat State may come to above par level compared to all India.

(6.2) Regression approach for all India can be considered to be satisfactory as viewed by the modified version of the regression model. It is interesting to note that the component R_t which is based upon capital-labour ratio for the relevant year is found to be significant at 5% level for the modified model. This also suggests that change in capital-labour ratio may become affected for TFP.

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REVIEW ARTICLE

STATISTICAL ANALYSIS IN CLINICAL TRIALS - (I)

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ABSTRACT

This paper covers introduction and basics on statistical methods applied in clinical trials. We will make an effort to highlight the common statistical methods for clinical research with examples. The details will help the beginners to get insights in the clinical trial data and statistical application.

KEYWORDS:

Clinical trials, CDISC data standards, Study Data Tabulation Model, Analysis Dataset Model.

1. INTRODUCTION

The purpose of the field "Statistics" is to characterize a population based on the information contained in a sample taken from that population. The sample information is conveyed by function of the observed data, which are called statistics. The field of Statistics is a discipline the endeavors to determine which functions are the most relevant in the characterization of the various populations. The concept of 'populations', 'samples' and 'characterization' are discussed in this paper. For example, the arithmetic mean might be most appropriate statistics to help characterize certain populations, while the median might be more appropriate for others. Statistician use statistical and probability theory to develop new methodology and apply the methods best suited for different types of the datasets. Applied statistics can be viewed as a set of methodologies used to help carry out scientific experiments. In keeping with the scientific method, applied statistics consists of developing a hypothesis, conducting the experiment, observing the results, and making conclusions. The statistician's responsibilities includes protocol

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inputs viz. study design, sample size calculation, randomization plan, data collection, data imputations, and statistical methods etc. Statisticians are also responsible to prepare statistical analysis plan (SAP), mock shells (TLF shells) for the outputs which includes tables, listings and figures. Statisticians are also involved in statistical analysis, and they support in making appropriate inferences from data, they assist medical writing team to draft statistical section of clinical study report (CSR) which usually gets submitted to health authorities. Statistician should ideally have programming skills and knowledge of the Clinical Data Interchange Standards Consortium (CDISC), which includes Study Data Tabulation Models (SDTM) and Analysis Dataset (ADaM). Statisticians usually works closely with clinical team to gain insights on therapeutic area, trail objective, regulatory or health authority requirements etc.

2. CLINICAL TRIALS

Clinical trials are experiments or observations done in clinical research. Such prospective biomedical or behavioral research studies on human participants are designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on safety and efficacy. They are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for vetting the risk/benefit ratio of the trial – **their approval does not mean that the therapy is 'safe' or effective, only that the trial may be conducted.**

Depending on product type and development stage, investigators initially enroll volunteers or patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. Clinical trials can vary in size and cost, and they can involve a single research center or multiple centers, in one country or in multiple countries. Clinical study design aims to ensure the scientific validity and reproducibility of the results. Costs for clinical trials can range into the billions of dollars per approved drug. The sponsor may be a governmental organization

or a pharmaceutical, biotechnology or medical device company. Certain functions necessary to the trial, such as monitoring and lab work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory. It may be noted that only 10 percent of all drugs started in human clinical trials become approved drugs.

3. PHASES OF CLINICAL TRIALS

The phases of clinical research are the steps in which scientists do experiments with a health intervention in an attempt to find enough evidence for a process which would be useful as a medical treatment. In the case of pharmaceutical study, the phases start with drug design and drug discovery then proceed on to animal testing. If this is successful, they begin the clinical phase of development by testing for safety in a few human subjects and expand to test in many study participants to determine if the treatment is effective.

Pre-clinical studies

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies. These involve in vitro (test tube or cell culture) and animal experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.

Phase 0

Phase 0 is a recent designation for optional exploratory trials conducted in accordance with the United States Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational new drug (IND) studies. Phase 0 trials are also known as human micro dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies. Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (what the body does to the drugs).

Summary of clinical trial phases

Phase	Primary goal	Dosa	Patient monitor	Typical number of participants	Success rate	Notes
Preclinical	Testing of drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information	Unrestricted	scientific researcher	not applicable (in vitro and animal studies only)		
Phase 0	Pharmacokinetics and safety, oral bioavailability and half-life of the drug	very small, sub-therapeutic	clinical researcher	10 people		often skipped for phase I
Phase I	Testing of drug on healthy volunteers for safety; involves testing multiple doses dose-ranging	often sub-therapeutic but with ascending doses	clinical researcher	20–100 normal healthy volunteers (or for cancer drugs, cancer patients)	approximately 70%	determines whether drug is safe to check for efficacy
Phase II	Testing of drug on patients to assess efficacy and side effects	therapeutic dose	clinical researcher	100–300 patients with specific diseases	approximately 33%	determines whether drug can have any efficacy; at this point, if the drug is no presumed to have any therapeutic effect whatsoever
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety	therapeutic dose	clinical researcher and personal physician	300–3,000 patients with specific diseases	25–30%	determines a drug's (lesser) side effect; at this point, the drug is presumed to have some effect
Phase IV	Post-marketing surveillance – watching drug rate in public	therapeutic dose	personal physician	anyone seeking treatment from their physician	N/A	watch drug's long-term effects

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

Phase I

Phase I trials were formerly referred to as "first-in-man studies" but the field generally moved to the gender-neutral language phrase "first-in-humans" in the 1990s; these trials are the first stage of testing in human subjects. They are designed

to test the safety, side effects, best dose, and formulation method for the drug.

Normally, a small group of 20–100 healthy volunteers will be recruited. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organization (CROs) who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. Phase I trials normally include dose-ranging, also called dose escalation studies, so that the best and safest dose can be found and to discover the point at which a compound is too poisonous to administer. The tested range of doses will usually be a fraction [quantify] of the dose that caused harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when clinical patients are used, such as patients who have terminal cancer or HIV and the treatment is likely to make healthy individuals ill. These studies are usually conducted in tightly controlled clinics called CPUs (Central Pharmacological Units), where participants receive 24-hour medical attention and oversight. In addition to the previously mentioned unhealthy individuals, "patients who have typically already tried and failed to improve on the existing standard therapies" may also participate in phase I trials. Volunteers are paid a variable inconvenience fee for their time spent in the volunteer center.

Before beginning a phase I trial, the sponsor must submit an Investigational New Drug application to the FDA detailing the preliminary data on the drug gathered from cellular models and animal studies.

Phase I trials can be further divided:

Single ascending dose (Phase Ia)

In single ascending dose studies, small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time to confirm safety. Typically, a small number of participants, usually three, are entered sequentially at a particular dose. If they do not exhibit any adverse side effects,

and the pharmacokinetic data are roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. If unacceptable toxicity is observed in any of the three participants, an additional number of participants, usually three, are treated at the same dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the maximum tolerated dose (MTD)). If an additional unacceptable toxicity is observed, then the dose escalation is terminated and that dose, or perhaps the previous dose, is declared to be the maximally tolerated dose. This particular design assumes that the maximally tolerated dose occurs when approximately one-third of the participants experience unacceptable toxicity. Variations of this design exist, but most are similar.

Multiple ascending dose (Phase Ib)

Multiple ascending dose studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of the drug, looking at safety and tolerability. In these studies, a group of patients receives multiple low doses of the drug, while samples (of blood, and other fluids) are collected at various time points and analyzed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level.

Food effect

A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug while fasted, and after being fed.

Phase II

Once a dose or range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect. Phase II trials are performed on larger groups (100–300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rate. When the development process for a new drug fails,

this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB. There is no formal definition for these 2 sub-categories, but generally:

Phase IIA studies are usually pilot studies designed to demonstrate clinical efficacy or biological activity ('proof of concept' studies)

Phase IIB studies look to find the optimum dose at which the drug shows biological activity with minimal side-effects ('definite dose-finding' studies).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Trial design

Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized controlled trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

Example of Cancer Design

In the first stage, the investigator attempts to rule out drugs which have no or little biologic activity. For example, the researcher may specify that a drug must have some minimal level of activity, say, in 20% of participants. If the estimated activity level is less than 20%, the researcher chooses not to consider this drug further, at least not at that maximally tolerated dose. If the estimated activity level exceeds 20%, the researcher will add more participants to get a better estimate of the response rate. A typical study for ruling out a 20% or lower response rate enters 14 participants. If no response is observed in the first 14 participants, the drug is considered not likely to have a 20% or higher activity level. The number of additional participants added depends on the degree of precision desired, but ranges from 10 to 20. Thus, a typical cancer phase II study might include fewer than 30 people to estimate the response rate.

Efficacy vs. Effectiveness

When a study assesses efficacy, it is looking at whether the drug given in the specific manner described in the study is able to influence an outcome of

interest (e.g. tumor size) in the chosen population (e.g. cancer patients with no other ongoing diseases). When a study is assessing effectiveness, it is determining whether a treatment will influence the disease. In an effectiveness study it is essential that patients are treated as they would be when the treatment is prescribed in actual practice. That would mean that there should be no aspects of the study designed to increase patient compliance above those that would occur in routine clinical practice. The outcomes in effectiveness studies are also more generally applicable than in most efficacy studies (for example does the patient feel better, come to the hospital less or live longer in effectiveness studies as opposed to better test scores or lower cell counts in efficacy studies). There is usually less rigid control of the type of patient to be included in effectiveness studies than in efficacy studies, as the researchers are interested in whether the drug will have a broad effect in the population of patients with the disease.

Some researchers argue that phase II studies are generally smaller than they ought to be.

Phase III

This phase is designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice. Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. Phase III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. This is sometimes called the "pre-marketing phase" because it actually measures consumer response to the drug.

It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include

attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as "Phase IIIB studies."

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (USA), or the EMA (European Union).

Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines through a New Drug Application (NDA) containing all manufacturing, pre-clinical, and clinical data. In case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.

Phase IV

A Phase IV trial is also known as post marketing surveillance trial, or informally as a confirmatory trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold (e.g. after approval under the FDA Accelerated Approval Program). Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for

interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials).

The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses. The minimum time period mandatory for Phase IV clinical trials is 2 years.

4. INTRODUCTION AND BASICS – STATISTICAL METHODS

Population – A *population* is a universe of entities to be characterized but is too vast to study in its entirety. The population in a clinical trial would be defined by its limiting conditions, usually specified via study inclusion and exclusion criteria.

Sample – You can describe population by describing some representative entities in it. Measurements obtained from sample entities tend to characterize the entire population through inference. The degree of representation of the entities in a sample that is taken from the population if interest depends on the sampling plan used.

Characterization – Statistical methods used to characterize population can be classified as descriptive or inferential.

Descriptive statistics are used to describe the distribution of the population measurements by providing the estimates of the central tendency and measures of variability, or by using graphical techniques such as histograms.

Inferential methods use probability to express the level of certainty about estimates and to test specific hypothesis.

Exploratory analyses represent third type of statistical procedure used to characterize the populations. Although exploratory methods use both descriptive and inferential techniques, conclusions cannot be drawn with same level of certainty because hypotheses are not pre-planned. Given a large dataset it is very likely that at least one statistically significant results can be found by using exploratory analysis. Such results are “hypothesis generating” and often lead to new studies prospectively designed to test these new hypothesis.

Two main inferential methods are - confidence interval estimation and hypothesis testing.

Probability Distributions

Each outcome of a statistical experiment can be mapped to a numeric-valued function called a "random variable". Some values of the random variable might be more likely to occur than others. The probability distribution associated with the random variable X describes the likelihood of obtaining certain values or ranges of values of the random variable.

For example, consider two cancer patients, each having a 50-50 chance of surviving at least 3 months. Three months later, there are 4 possible outcomes which are as below:

Probability distribution of number of survivors (n=2)

Outcome	Patient 1	Patient 2	Random Variable X	Probability
1	Died	Died	0	0.25
2	Died	Survived	1	0.25
3	Survived	Died	1	0.25
4	Survived	Survived	2	0.25

Each outcome can be mapped to the random variable X, which is defined as the number of patients surviving at least 3 months. X can take the values 0, 1, 2 with the probabilities 0.25, 0.5 and 0.25 respectively, because each outcome is equally likely.

Discrete Distributions

The above example is a discrete probability distribution, because the random variable X can only take discrete values (i.e. 0, 1 and 2).

Binomial distribution is most commonly used discrete distribution in clinical biostatistics. The distribution is used to model experiments involving "n" independent trials, each with 2 possible outcomes, say, "event" or "non-event", and the probability of an "event", p, is same for all "n" trials. The above example involves two cancer patients, is an example of binomial distribution in which n=2 (patients), p=0.5, and "event" is survival of at least 3 months.

Other common discrete distributions include Poisson and Hypergeometric distributions etc.

Continuous Distributions

If a random variable can take any values within an interval or continuum, it is called a continuous random variable. Height, weight, blood pressure, and cholesterol level are some examples of continuous random variables because they can take any value within certain interval, even though the observed measurement is limited the accuracy of the measuring device.

The probability distribution for a continuous random variable cannot be specified in a simple form as it is in the discrete example above.

Continuous distributions are most convenient approximated by functions of the random variable X, such as P_x. Examples of such function are

$P_x = 2x$ for $0 < x < 1$

$P_x = ae^{-ax}$ for $0 < x < \infty$

The normal distribution is the most commonly used continuous distribution in clinical research statistics. Many naturally occurring phenomena follow the normal distribution, which can be explained by powerful results from probability theory known as the Central Limit Theorem.

Other common continuous distributions are exponential distribution, Chi-square distribution, F-distribution and Student t-distribution etc.

Central Limit Theorem

The central limit theorem states, that regardless of the distribution of the measurements, sums and averages of a large number of like measurements tend to follow the normal distribution. Because many measurements related to growth, healing, or disease progression might be represented by a sum or an accumulation of incremental measurements over period of time, the normal distribution is often applicable to clinical data for large samples.

Example of central limit theorem:

A placebo (dummy pill) is given to "n" patients, followed by an evaluation one hour slater. Suppose that each patient's evaluation can result in "improvement" coded as +1, "no change" (0), or deterioration (-1), with each result equal probable. Let X_1, X_2, ……,X_n represents the measurements for the n patients, and define

Z to be a random variable that represents the sum of these evaluation scores for all "n" patients.

$Z= X_1+X_2+ \ldots\ldots+X_n$

For n=1, the probability distribution of Z, is the same as X, which is constant for all possible values of X. this is called "uniform" distribution.

Probability distribution for $Z=X_i$

Z	P_z
-1	1/3
0	1/3
+1	1/3

For n=2, there are 9 equal probable outcomes resulting in 5 possible, distinct value for Z, as shown in table below.

Patient 1	Patient 2	Z	Prob.
-1	-1	-2	1/9
-1	0	-1	1/9
0	-1	-1	1/9
-1	+1	0	1/9
0	0	0	1/9
+1	-1	0	1/9
0	+1	+1	1/9
+1	0	+1	1/9
+1	+1	+2	1/9

The resulting probability distribution for $Z=X_1+X_2$ is shown below:

Z	P_z
-2	1/9
-1	2/9
0	3/9
+1	2/9
+2	1/9

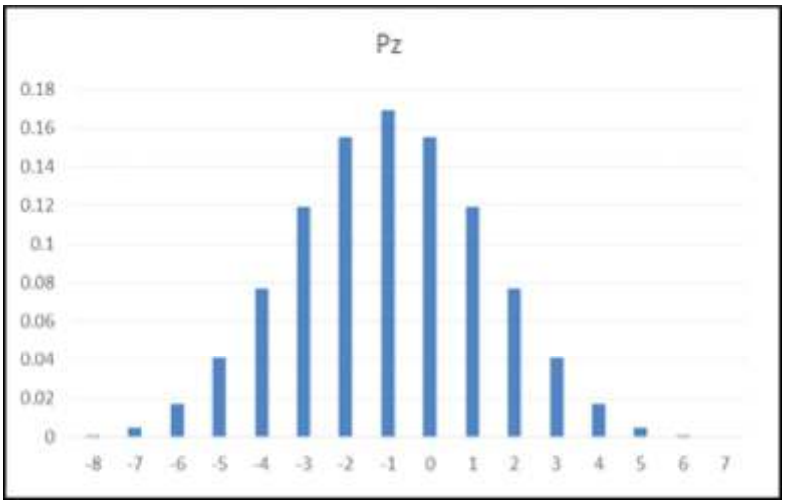
For n=3, Z can take values from -3 to +3, probability distribution for $Z= X_1+X_2+X_3$ is shown below:

Z	P_z
-3	1/27
-2	3/27
-1	6/27
0	7/27
+1	6/27
+2	3/27
+3	1/27

It may be observed that as "n" becomes larger the distribution of Z gradually takes on characteristic of the normal distribution. While the probability distribution of the measurements (x) is "uniform", the sum of these measurements (Z) is a random variable that trends towards a normal distribution as "n" increases. The central limit theorem states that this will be the case regardless of the distribution of the X measurements, since the sample mean, is the sum of measurements (multiplied by a constant, 1/n), the central limit theorem implies that sample mean has an approximate normal distribution for large "n" regardless of the probability distribution of the measurements that comprise the sample mean.

Probability distribution for $Z= X_1+X_2+X_3+X_4+X_5+X_6+X_7+X_8$

Z	P_z
-8	0.000
-7	0.001
-6	0.005
-5	0.017
-4	0.041
-3	0.077
-2	0.119
-1	0.155
0	0.169
+1	0.155
+2	0.119
+3	0.077
+4	0.041
+5	0.017
+6	0.005
+7	0.001
+8	0.000



Study Design

It is very important that study plan is well thought and accompanied by appropriate data collection methods which is key for sound statistical results. If the study is flawed, even most of statistical tests might not lead to valid inference or appropriate characterization of the population. Therefore, it is vital that statistical design considerations be addressed in the clinical studies during protocol development.

There are many statistical design consideration that go in to the planning stage of the new study. The probability distribution of the primary response variables will help to predict how the measurements will vary. Since greater variability of the measurements requires a larger sample size, distributional assumptions enable the computation of sample size requirements to differentiate the trend from statistical variations.

Methods to help reduce response variability can also be incorporated into the study design. Features of controlled clinical trials such as randomization and blinding and statistical 'noise-reducing' techniques (such as use of covariates, stratification or blocking factors, and the use of within-patient controls) are ways to help control the peripheral variability and focus on the primary response measurements.

Controlled Studies

A controlled study uses known treatment, which is called a 'control', along with the test treatments. A control may be inactive (e.g. placebo or it may be another active treatment, perhaps marketed product).

A study that uses separate, independent group of patients in the control group is called a parallel-group study. A study that gives both the test treatment and the control to the same patients is called a within-patient control study.

Randomization

Randomization is means of objectively assigning experimental units or patients to treatment groups. In clinical trials, this is done by means of a randomization schedule generated prior to starting the patient enrollment.

Randomization filters out the selection bias and helps establish the baseline comparability among the treatment groups. Randomization provides a basis for unbiased comparisons of the treatment groups. Omitting specific response from the analysis is the form of tampering with this randomization and will probably bias the results if the exclusions are made in non-randomized fashion. For this reason, the primary analysis of a clinical trial is often based on the 'intent-to-treat' principle, which includes all randomized patients in the analysis even though some might not comply with protocol requirements.

Blinded Randomization

Blinded (or masked) randomization is one of the most important features of a controlled study. There are different types of blinding viz. single blind, double blind and even triple blind studies are common among the clinical trials.

Single blind is one in which patients are not aware of which treatment they receive. Double blind is a common and important feature of a controlled clinical trials, especially when evaluations are open to some degree of subjectivity. However, double blinding is not always possible or practical. For example, test and control treatment might not be available in the same formulation. In such cases, treatment can sometimes be administered by one investigator and the evaluations performed by a co-investigator at the same center is an attempt to maintain some sort of masking of the investigator.

Studies can be triple blind, wherein patient, investigator and clinical project team (including statistician) are not aware of the treatment administered until the statistical analysis is complete. This reduces the third level of potential bias. Usually blinded analysis is planned and lastly after data base lock, the un-blinding happens and later final submissions are done on the actual treatment administered, more often we see that separate teams work on both blinded and unblended analysis during interim study milestones.

Selection of Statistical Methods

Features of controlled clinical trials, such as randomization and blinding helps to limit bias when making statistical inference. The statistical methods themselves might also introduce bias if they are 'data-driven', that is the method selected based on the study outcome. In most of the trials, study design and objectives will point to the most appropriate statistical methods for the primary objective analysis. The methods are usually detailed in the formal statistical analysis plan prepared prior to the data collection and, therefore, represent the best 'theoretical' methodology not influenced by the knowledge of data. A different statistical method might be required for each objective in the clinical study. The study objective must be clear before the statistical method can be selected.

Descriptive Statistics

Descriptive statistics describe the probability distribution of the population. This is done by using the histograms to depict the shape of the distribution, by estimating the distributional parameters, and by computing various measure of the central tendency and dispersion. These methods are often the only approach that can be used for analyzing the results of pilot studies or Phase I clinical trials. Due to small sample sizes, the lack of blinding, or the omission of the other features

of a controlled trial, statistical inference might not be possible. However, trends or patterns observe the data by using descriptive or exploratory methods will often help in building hypotheses and identifying the cofactors. These new hypotheses can be then tested in a more controlled manner in subsequent studies, where in inferential methods would be more appropriate.

In additional to distributional parameters, you sometimes want to estimate parameters associated with statistical model, if an unknown response can be modeled as function of known or controlled variables, you can often obtain valuable information regarding the response by estimating the weights or coefficients of each of these known variables. These coefficients are called model parameters. They are estimated in a way that results in greater consistency between the model and the observed data.

Common Descriptive Statistics:

Measure of 'Central Tendency'

Arithmetic Mean	Sum of all observations/ Number of observations = $\bar{X} = (\sum x_i)/n = (X_1+X_2+X_3+X_4+X_5+\ldots\ldots\ldots+X_n)/n$
Median	The middle value, if 'n' is odd, the average of the two middle values if 'n' is even then (50^{th} percentile)
Mode	The most frequently occurring value
Geometric Mean	$(\pi X_i)^{1/n} = (X_1.X_2.X_3.X_4.X_5\ldots\ldots\ldots\ldots...X_n)^{1/n}$
Harmonic Mean	$n\left(\sum \frac{1}{X_i}\right)^{-1} = n\{(1/X_1)+(1/X_2)+\ldots\ldots+(1/X_n)\}^{-1}$
Weighted Mean	$X_w = (\sum w_i x_i)/W$, where $W=\sum w_i$
Trimmed Mean	Arithmetic mean omitting the largest and smallest observation.
Winsorized Mean	Arithmetic mean after replacing outliers with the closest non-outlier values.

Measure of 'Dispersion'

Variance	$s^2 = \sum (x_i - x)^2 / (n-1)$
Standard Deviation	s = Positive square root of the variance
Standard Error (of the mean)	$(s^2/n)^{1/2}$
Range	Largest value – Smallest value
Mean Absolute Deviation	$(\sum |x_i - x|)/n$
Inter-Quartile Range	75^{th} percentile – 25^{th} percentile
Coefficient of variation	$s/\bar{x}$

Inferential Statistics

The two primary methods of making inferences are confidence interval estimation and hypotheses testing.

Confidence Intervals – Population parameters, such as mean (μ) or the standard deviation (σ), can be estimated by using point estimate such as sample mean or the sample standards deviation. A confidence interval around the point estimate that contains the parameter with specific high probability or confidence level. A 95% confidence interval for mean (μ) can be constructed from the sample data with the following interpretation: If the same experiment were conducted large number of times and confidence intervals were constructed for each, approximately 95% of those intervals would contain the population mean (μ). The general form of the confidence interval is $[r_L, r_U]$, where r_L represents the lower limit and r_U represents the upper limit of the interval. **Hypotheses Testing** – is the means of formalising the inferential process for decision making. It is a statistical approach for testing hypothesized statements about population parameter based on the logical argument. To understand the concept behind the hypothesis test, let's examine a form of deductive argument from logic, using following example.

If you have drug A, you do not have drug B. You have drug B, therefore you do not have drug A.

The first two statement of the argument are premise and the third is the conclusion. The conclusion is logically deduced from the two premises, and its truth depends on the truth of the premises.

If P represents the first premise and Q represents the second premise, the argument may be formulated as below:

if P then not Q (conditional premise)

Q (premise)

Therefore, not P (conclusion)

This is deductively valid argument of logic that applied in any two statements, P and Q, whether true or false. Note if you have both drug A and drug B, the conditional premise would be false, which makes the conclusion false because

argument is still valid.

Statistical argument takes the same form as this logical argument, but statistical argument must account for random variations in statements that might not be known to be completely true. A statistical argument might be paraphrased from the logic argument above as

if P then probably not Q (conditional premise)

Q (premise)

Therefore, probably not P (conclusion)

Example:

Statements:

P=Drug A has no effect on cancer

Q=from sample of 25 patients, 23 showed improvement in their cancer after taking Drug A.

Argument:

If Drug A has no effect on cancer, you would probably not see improvement in 23 or more of the same of 25 cancer patients treated with Drug A. You observe improvement in the 23 of the sample of 25 cancer patients treated with Drug A, therefore Drug A is probably effective for cancer.

Hypothesis testing can be set forth in an algorithm with 5 parts

- the null hypothesis (abbreviated as H_0)
- the alternative hypothesis (abbreviated as H_1)
- the test criterion
- the decision rule
- the conclusion

The decision rule results in the rejection of the null hypothesis if unlikely value of the test statistics are observed when assuming the test statistic is true. To determine a decision rule, the degree of such "unlikeliness" needs to be specified. This is referred to as the significance level of the test (denoted by α) and, in clinical trials, is often (but not always) set to 0.05 (i.e. 5% level of significance). By knowing the probability distribution of the test statistics when

the null hypothesis is true, you can identify the most extreme 100α% of the values as a rejection region. The decision rule is simply, reject H_0 when the test statistics fall in the rejection region.

5. SUMMARY

The review article highlights the details on clinical study and clinical phases, roles and responsibilities of the biostatistician, industry data standards etc. The paper also covers some basic concepts of statistics, given an overview of statistics in a scientific discipline, and shows that the results of statistical analysis can be no better than the data collected, emphasize the correct application of the statistical techniques in the study design and data collection as well as analysis stage.

6. ACKNOWLEDGEMENT

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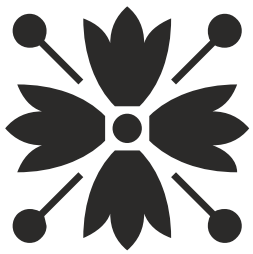

RESEARCH NOTE

POISSON REGRESSION MODEL

H. M. Dixit[1]

ABSTRACT

This paper introduces an interesting research area as an externsion of categorial variables data models. Using property of equidispersions, PR model is highlighted with its limitations and further possible extensions.

KEY WORDS

PRM, ML, LR, NBRM, MNRM

1. INTRODUCTION

In the terminology of econometrics, the dependent or endogenous variable is called **regressand** and the independent or explanatory variable is called **regressor.**

In some specific situation, the regression is of **count type.** e.g. number of visits to riverfront in a month, the number of patents received by a firm in a year, the number of visits for medical checkup in a year, the number of cars passing through a toll booth in a span of 10 minutes, and so on

The underlying variable in each case is discrete taking only a finite number of non-negative values. Sometimes such count data may also include rare or infrequent occurrences such as having one or more traffic accidents in a day, number of dharna made by a political party in a month, number of suicides found by jumping in a river from the bridge and so on.

A unique feature of all these examples is that they take a finite number of non-negative integers or count values. Each count varibale is measured over a certain finite time period.

For modelling such phenomena, we need a probability distribution which takes into account the **unique feature of count data.** One such distribution is **Poisson distribution** and the regression model based upon Poisson distribution can be called **POISSION REGRESSION MODEL (PR MODEL).**

2. PR MODEL

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(rcd. July'19 / rvd. Dec.'16)

Let us consider a discrete random variable Y following poisson distribution. We can write this as

$$f(Y/y_i)=\frac{e^{-\lambda_i}\lambda_i^{y_i}}{y_i!} \quad \ldots\ldots\ldots\ldots\ldots y_i=0,1,2.... \quad \lambda_i>0 \text{ for all i} \tag{1}$$

A unique feature of Poison distribution is that

Mean = Variance

i.e. $E(y_i)=\lambda_i$ (2)

$V(y_i)=\lambda_i$ (3)

This property is called equidispersion.

(In practice, often variance is greater than mean, which is called Over dispersion)

From this we write PR model as

$$y_i=E(y_i)+u_i=\lambda_i+u_i \tag{4}$$

Where Y's are independly distributed Poisson Variable with $E(y_i)=\lambda_i$

For each individual, λ_i can be expresed as

$$\lambda_i=E(y_i/X_i)=\exp\left[B_1+B_2X_{2i}+\ldots\ldots\ldots+B_kX_{ki}\right]$$

Thus $\lambda_i=\exp[\underline{B}'\underline{X}]$ (5)

where $X'=(1,X_{2i},X_{3i},\ldots\ldots\ldots\ldots\ldots X_{ki})$

$$B=\begin{pmatrix}B_1\\B_2\\\ldots.\\B_k\end{pmatrix}$$

The $\underline{X}$ variables are the regressors that may determine the mean value of the regressand. Due to the property of Poisson distribution it also determines the variance value (and hence its standard errors) if PR model is appropriate.

(e.e. If the count variable is number of visits for medical checkup in a big hospital in a year, it will depend upon the hospital admission charges, income of the individual, number of appointments given by doctors, distance for the person for travelling from his homespace to the hospital, parking fees, etc.)

It may be noted that due to exponential term exp ($\underline{B}'\underline{X}$) in equation (5), it will ensure that λ_i will be positive.

Once the co-efficients B are estimated,

We can have $\hat{\lambda}_i = \exp(\underline{\hat{B}}'\underline{X})$ (6)

and hence we have $Ln\left(\hat{\lambda}_i\right) = \underline{\hat{B}}'\underline{X}$ (7)

PR model as expressed above is non linear in parameters, which needs nonliner regression estimation.

This is accomplished by the method of maximum likelihood. Software such as stata can be used for computation purposes.

It may be noted that in non-liner models like PRM, R^2 is not particularly meaningful. It is the likelihood ratio (LR) statistic which may be important for judging the importance of explanatory variables in explanining the conditional mean values λ_i.

3. LIMITATIONS OF PR MODEL

As stated above, PRM assumes that the conditional mean and the conditional variance of the distribution, given the values of the X regressors are the same, it is critical to check this assumption of equidispersion.

A test suggested by cameron and Trivedi can be used to test for overdispersion.

4. Further Extensions

PRM can be expanded further (in the case of overdispersion) by Negative Binomial Regression model (NBRM). Similarly a further extension may also be possible by considering Multinomial Regression Model (MNRM). A number of other related studies can be possible by using the truncated distributions. Sophisticated statistical softwares can be helpful in the computational procedures.

5. Acknowledgements

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RESEARCH NOTE

OVERVIEW OF STATISTICAL SOFTWARES USED IN CLINICAL TRIALS

Pinakin R. Jani[1]

INTRODUCTION

Background

We are highlighting some statistical software used in the clinical trials. Ideally it is very important for biostatistician to have knowledge with regards to these tools, since they are usually involved in analysis of data, interpretation of data and support towards preparing regulatory submission packages.

These software should ideally be covered during undergraduate and graduate education. This will support students to become market ready, where they will have opportunity to get jobs in the industry. There is lots of support available towards statistical analyses, including this online course, biostatistical consultants, websites, YouTube tutorials, and even massive open online course (MOOC) courses.

If you would like face-to-face assistance, then information about biostatistical support can be found here: http://www.unisa.edu.au/Health-Sciences/Research/Biostatistical-and-epidemiological-support/

In addition, there are a multitude of statistical software packages available that can do a lot of the work for you – and these are the focus of this current module. However, before we start looking at these, a question that often arises is "How do I get my data into a statistical package?".

The good news is that most statistical software can read data directly from an Excel spreadsheet, so using Excel is often the easiest solution. Secondly, you can always enter data directly into a statistical package, since they nearly all have some form of inbuilt spreadsheet, apart from this some software needs data is specific readable file format.

Another solution is to use software like SurveyMonkey (https://

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(rcd. Oct.'19 / rvd. Nov.'16)

www.surveymonkey.com/) to collect the data. Survey Monkey has the facility to convert the data into an Excel spreadsheet or SPSS format. A final solution is to use specialized data entry software. This has the advantage of being able to put things like range checks on data entry fields, so for example, if a data entry field should only have a 0 or 1 entered, if you try and put anything else, it won't let you. A really good and free data entry program is EpiData Entry provided by CDC Atlanta. It is available from here: http://www.epidata.dk/download.php

There are also many websites where you can undertake online statistical analyses. A good starting place is: http://statpages.info/

There are also many specialized software programs for things like graphs, sample size calculations, and genetic analyses. Some of these software are commercial and licensed while some are open source which can be downloaded and used. In fact the diversity and number of software packages and available websites is so large, that reviewing all of them is really challenging, so the key is to understand what kind of task you are undertaking which needs statistical analysis, example if its publication or PHD thesis etc. then normal free software can be used, while is its regulatory submission to authorities, government surveys or analysis or any other commercial usage which is governed by regulations then ideally the licensed versions must be used. However, there are some software packages that are readily available and often used, it includes Microsoft Excel, SPSS, WinNonlin, SAS, Stata and R, which will briefly overviewed here. There are other statistical software which are used for statistical application across different domains. (e.g., engineering, finance, marketing, quality control etc.).

Introduction to Statistical Software

Microsoft Excel

This is part of the Microsoft Office suite of programs. Excel version 1.0 was first released in 1985, we have latest office versions available in market.

Advantage

- Extremely easy to use and interchanges nicely with other Microsoft products
- Excel spreadsheets can be read by many other statistical packages
- Add on module which is part of Excel for undertaking basic statistical analyses
- Can produce very nice graphs

Disadvantage

- Excel is designed for financial calculations, although it is possible to use it for many other things
- Cannot undertake more sophisticated statistical analyses without purchase of expensive commercial add-ons.

SPSS

SPSS stands for Statistical Package for the Social Sciences. It was one of the earliest statistical packages with Version 1 being released in 1968, well before the advent of desktop computers. It is now on Version 23.

Advantage

- Very easy to learn and use
- Can use either with menus or syntax files
- Quite good graphics
- Excels at descriptive statistics, basic regression analysis, analysis of variance, and some newer techniques such as Classification and Regression Trees (CART)
- Has its own structural equation modelling software AMOS, that dovetails with SPSS

Disadvantage

- Focus is on statistical methods mainly used in the social sciences, market research and psychology
- Has advanced regression modelling procedures such as LMM and GEE, but they are awful to use with very obscure syntax
- Has few of the more powerful techniques required in epidemiological analysis, such as competing risk analysis or standardized rates

WINNONLIN

Phoenix® WinNonlin® is the industry standard for non-compartmental analysis (NCA), pharmacokinetic/pharmacodynamics (PK/PD), toxicokinetic (TK) modelling. Integrated tools for data processing, post analysis processing, tables creation, graphics and compliance create an all in one collaboration workbench used by scientists, reviewers, medical writers, and quality assurance staff for drug development projects.

Advantage

- NCA and individual PK/PD modeling engine and statistical analysis tools can be used for a wide range of studies and analyses.

- The powerful NCA engine automatically outputs NCA parameters for plasma and urine to save time, reduce errors, provide higher transparency for regulatory agencies.
- Organizations can set strict criteria with user-defined parameters for calculating the terminal slope in NCA.
- NCA ratios are automatically calculated increasing efficiency and saving time.
- Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) is usually done for the software at the time of installation and renewals.
- Powerful software, it has audit trails and acceptance by regulatory agencies.

Disadvantage

- No major disadvantage, user guide is available which helps step by step application.

SAS®

SAS® stands for Statistical Analysis System. It was developed at the North Carolina State University in 1966, so is contemporary with SPSS. This is extensively used in the clinical industry for statistical analysis by Biostatisticians and Statistical Programmers.

Advantage

- Can use either with menus or syntax files
- Much more powerful than SPSS
- Commonly used for data management in clinical trials
- Accepted by regulatory agencies
- There are certification exams and an individual can be certified user for this SAS application.

Disadvantage

- Harder to learn and use than SPSS, individual needs to invest some reasonable time to learn the same and practice more to get desired grip on the application.

Stata

Stata is a more recent statistical package with Version 1 being released in 1985. Since then, it has become increasingly popular in the areas of epidemiology and economics, and probably now rivals SPSS and SAS in it user base.

Advantage

- Can use either with menus or syntax files

- Much more powerful than SPSS – probably equivalent to SAS
- Excels at advanced regression modelling
- Has its own in-built structural equation modelling
- Has a good suite of epidemiological procedures
- Researchers around the world write their own procedures in Stata, which are then available to all users

Disadvantage

- Harder to learn and use than SPSS
- Does not yet have some specialized techniques such as CART or Partial Least squares regression

R

S-plus is a statistical programming language developed in Seattle in 1988. R is a free version of S-plus developed in 1996. Since then the original team has expanded to include dozens of individuals from all over the globe. Because it is a programming language and environment, it is used by giving the software a series of commands, often saved in the text document called syntax files or scripts, rather than having a menu-based system. Because of this, it is probably best used by people already reasonably expert at statistical analysis. This is becoming more popular and extensively used for validation.

Advantage

- Free and Very powerful – easily matches or even surpasses many of the models found in SAS or Statas.
- Researchers around the world write their own procedures in R, which are then available to all users

Disadvantage

- Much harder to learn and use than SAS or Stata

ACKNOWLEDGEMENT

I thank the referee for reviewing this article.

BIOGRAPHY

GEORGE BERNARD DANTZIG[1]

H. D. BUDHBHATTI[2]

American statistician George Bernard Dantzig affected the world enormously by his mathematical discovery of the simplex method. It is used by industry and governments to identify the best possible solutions to the problems with many variables.

Simplex method is useful in the problems of resource allocation, worker scheduling and production planning. Airlines use it to co-ordinate routes for commercial flights and governments use this algorithm schedule refuse collection.

A humble attempt is made here to give a brief biographical sketch of this versatile personaltiy.

(1) Life

Born in Portland, Oregon, on November 8, 1914 George Bernard Dantzig was named after George Bernard Shaw, the Irish writer. Born to Jewish parents, his father, Tobias Dantzig, was a mathematician and linguist, and his mother, Anja Dantzig, was a linguist of French Jewish origin. Dantzig's parents met during their study at the University of Paris, where Tobias studied mathematics under Henri Poincaré, after whom Dantzig's brother was named. The Dantzigs immigrated to the United States, where they settled in Portland, Oregon.

Early in the 1920s the Dantzig family moved from Baltimore to Washington. His mother became a linguist at the Library of Congress, and his father became

(1) Adapted from wikipedia (the free encyclopedia) and other related source. We express our sincere thanks and gratitude for this assitance.

(2) Ex. CSO, Head, Statistics Dept. GSRTC, Ahmedabad. (Thanks to the refereee for reviewing this article) (rcd. Oct.'19 / rvd. Nov.'19)

a math tutor at the University of Maryland, College Park. Dantzig attended Powell Junior High School and Central High School.By the time he reached high school he was already fascinated by geometry, and this interest was further nurtured by his father, challenging him with complicated problems, particularly in projective geometry.

George Dantzig received his B.S. from University of Maryland in 1936 in mathematics and physics, which is part of the University of Maryland College of Computer, Mathematical, and Natural Sciences. He earned his master's degree in mathematics from the University of Michigan in 1938. After a two-year period at the Bureau of Labor Statistics, he enrolled in the doctoral program in mathematics at the University of California, Berkeley, where he studied statistics under Jerzy Neyman.

With the outbreak of World War II, Dantzig took a leave of absence from the doctoral program at Berkeley to work as a civilian for the United States Army Air Forces. From 1941 to 1946, he became the head of the combat analysis branch of the Headquarters Statistical Control for the Army Air Forces. In 1946, he returned to Berkeley to complete the requirements of his program and received his Ph.D. that year. Although he had a faculty offer from Berkeley, he returned to the Air Force as mathematical advisor to the comptroller.

In 1952 Dantzig joined the mathematics division of the RAND Corporation. By 1960 he became a professor in the Department of Industrial Engineering at UC Berkeley, where he founded and directed the Operations Research Center. In 1966 he joined the Stanford faculty as Professor of Operations Research and of Computer Science. A year later, the Program in Operations Research became a full-fledged department. In 1973 he founded the Systems Optimization Laboratory (SOL) there. On a sabbatical leave that year, he headed the Methodology Group at the International Institute for Applied Systems Analysis (IIASA) in Laxenburg, Austria. Later he became the C. A. Criley Professor of Transportation Sciences at Stanford, and kept going, well beyond his mandatory retirement in 1985.

He was a member of the National Academy of Sciences, the National Academy

of Engineering, and the American Academy of Arts and Sciences. Dantzig was the recipient of many honors, including the first John von Neumann Theory Prize in 1974, the National Medal of Science in 1975, an honorary doctorate from the University of Maryland, College Park in 1976. The Mathematical Programming Society honored Dantzig by creating the George B. Dantzig Prize, bestowed every three years since 1982 on one or two people who have made a significant impact in the field of mathematical programming. He was elected to the 2002 class of Fellows of the Institute for Operations Research and the Management Sciences.

Dantzig died on May 13, 2005, at the age of 90 years in his home in Stanford, California, of complications from diabetes and cardiovascular disease.

At his death, Dantzig was the Professor Emeritus of Transportation Sciences and Professor of Operations Research and of Computer Science at Stanford University.

(2) Work

George Bernard Dantzig was an American mathematical scientist who made contributions to industrial engineering, operations research, computer science, economics, and statistics.

Dantzig is known for his development of the simplex algorithm, an algorithm for solving linear programming problems, and for his other work with linear programming. In statistics, Dantzig solved two open problems in statistical theory, which he had mistaken for homework after arriving late to a lecture by Jerzy Neyman.

Dantzig's work allows the airline industry, for example, to schedule crews and make fleet assignments. Based on his work tools are developed "that shipping companies use to determine how many planes they need and where their delivery trucks should be deployed. The oil industry long has used linear programming in refinery planning, as it determines how much of its raw product should become different grades of gasoline and how much should be used for petroleum-based byproducts. It is used in manufacturing, revenue management, telecommunications, advertising, architecture, circuit design and countless other areas".

Mathematical statistics

An event in Dantzig's life became the origin of a famous story in 1939, while he was a graduate student at UC Berkeley. Near the beginning of a class for which Dantzig was late, professor Jerzy Neyman wrote two examples of famously unsolved statistics problems on the blackboard. When Dantzig arrived, he assumed that the two problems were a homework assignment and wrote them down. According to Dantzig, the problems "seemed to be a little harder than usual", but a few days later he handed in completed solutions for the two problems, still believing that they were an assignment that was overdue

Six weeks later, Dantzig received a visit from an excited professor Neyman, who was eager to tell him that the homework problems he had solved were two of the most famous unsolved problems in statistics He had prepared one of Dantzig's solutions for publication in a mathematical journal. As Dantzig told it in a 1986 interview in the College Mathematics Journal:

A year later, when I began to worry about a thesis topic, Neyman just shrugged and told me to wrap the two problems in a binder and he would accept them as my thesis.

Years later another researcher, Abraham Wald, was preparing to publish an article that arrived at a conclusion for the second problem, and included Dantzig as its co-author when he learned of the earlier solution.

Linear programming

Linear programming is a mathematical method for determining a way to achieve the best outcome (such as maximum profit or lowest cost) in a given mathematical model for some list of requirements represented as linear relationships. Linear programming arose as a mathematical model developed during World War II to plan expenditures and returns in order to reduce costs to the army and increase losses to the enemy. It was kept secret until 1947. Postwar, many industries found its use in their daily planning.

The founders of this subject are Leonid Kantorovich, a Russian mathematician who developed linear programming problems in 1939, Dantzig, who published

the simplex method in 1947, and John von Neumann, who developed the theory of the duality in the same year.

Dantzig's original example of finding the best assignment of 70 people to 70 jobs exemplifies the usefulness of linear programming. The computing power required to test all the permutations to select the best assignment is vast; the number of possible configurations exceeds the number of particles in the universe. However, it takes only a moment to find the optimum solution by posing the problem as a linear program and applying the Simplex algorithm. The theory behind linear programming drastically reduces the number of possible optimal solutions that must be checked.

In 1963, Dantzig's Linear Programming and Extensions was published by Princeton University Press. Rich in insight and coverage of significant topics, the book quickly became "the bible" of linear programming.

(3) Publications

Books by George Dantzig:

* (1953) Notes on linear programming. RAND Corporation.
* (1956) Linear inequalities and related systems. With others. Edited by H.W. Kuhn and A.W. Tucker. Princeton University Press.
* (1963) Linear programming and extensions. Princeton University Press and the RAND Corporation. pdf from RAND
* (1966) On the continuity of the minimum set of a continuous function. With Jon H. Folkman and Norman Shapiro.
* (1968) Mathematics of the decision sciences. With Arthur F. Veinott, Jr. Summer Seminar on Applied Mathematics 5th : 1967 : Stanford University. American Mathematical Society.
* (1969) Lectures in differential equations. A. K. Aziz, general editor. Contributors: George B. Dantzig and others.
* (1970) Natural gas transmission system optimization. With others.
* (1973) Compact city; a plan for a liveable urban environment. With Thomas L. Saaty.
* (1974) Studies in optimization. Edited with B.C. Eaves. Mathematical Association of America.
* (1985) Mathematical programming : essays in honor of George B. Dantzig.

Edited by R.W. Cottle. Mathematical Programming Society.

* (1997) Linear programming 1: Introduction. G.B.D. and Mukund N. Thapa. Springer-Verlag.

* (2003) Linear programming 2: Theory and Extensions. G.B.D. and Mukund N. Thapa. Springer-Verlag.

* (2003) The Basic George B. Dantzig. Edited by Richard W. Cottle. Stanford Business Books, Stanford University Press, Stanford, California.[12]

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[11] **Dantzig, George; Wald, Abraham (1951).** "On the Fundamental Lemma of Neyman and Pearson". The Annals of Mathematical Statistics. 22: 87–93. Retrieved 14 October 2014.

[12] **Todd, Michael J. (2011).** "Review: The Basic George B. Dantzig, by Richard W. Cottle". Bull. Amer. Math. Soc. (N.S.). 48 (1): 123–129.

SV NEWS LETTER

M. B. Thaker*

Some of the conference / Seminar / Workshop programmes that may take place very shortly are shown briefly as below :

* ***Vishwakarma University*** is organising a National Level competition for B.Sc. students in Statistics on 31st January 2020.
  Place : Faculty of Science and Technology, Vishwakarma University, PUNE
  Contact : http : //www.vupune.ac.in/sankhyakriti
* **C. R. Rao Advanced Institute of Mathematics, Statistics and computer science**, is organising 12th Statistics olympliad for college and Univesity Students on 19th Jan. at University of Hyderabad-5000461.
* 52nd Annual convention of **ORSI and International conference** is organised at I.T.M., AHmedabad during Dec. 15-18, 2019.
  Contact : http://conference.iima.ac.in/orsi2019/
* Second International conference on Frontiers of OR and Business Studies **(FORBS 2019)** is organised during Dec. 27-28, 2019 at Calcutta Business School, Kolkata.
  contact : http://www.calcuttabusinesschool.org/FORBS 2019
* **INDSTAT 2019**, International ISA conference on Innovations in Data and Statistical Science is organised during 26-30 Dec. 2019, at Victroia Menezes Convention Center, IIT Bombay.
  Contact : IISA2019@intindstat.org
* The Econometrics society of India **(TIES)** is organising 56th annual conference at School of Economics, Madurai Kamraj University, Madurai during January 8-10, 2020.
* Fourth International Conference on **Computer applications and Image Processing** is to be organised during 15th May, 2019 at University of

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Rajasthan, Jaipur.

* Fourth International Conference on **Computer Interactions and Network** is organised by CINE during Feb. 27-29, 2020 at ISI, Kolkata
  Contact : rajdeeppfcs@kitt.ac.in
* **IAPR** is organising International conference on Biometrics during June 11-13, 2020 at Tezpur, India.
* International conference on Business Management and Social Science is Organised **(ICBMSS 2019)** at Thiruvananthapuram, Kerala, India.
  Contact : info.irfconference@gmail.com

+ + + + +

* A very useful reference book is published by Prof. Kirtan Parmar and Prof. Atmaram on the subject. **A study for social sciences theory and practice using SPSS.** It is published by McMillan Co. (2019)
* Prof. A.C.Brahmbhatt has published a book entitled-**Paradigm shift in Management Philosopy,** it is published by Mc.Millan Co. (2019) and it may be solf by Amazone Company.

READERS FORUM

A. M. PATEL*

(Readers are requested to feel free for sending their views and constructive suggestions for this section.)

* **C.D. Bhavsar (Ahmedabad)**
My heartly congratulations to S V team for continuing this research oriented efforts since last 15 years. My best wishes for the work ahead.

* **Gaurang Trivedi (Gandhinagar)**
Last issue of SV (NSV 15, June 2019, No. 1) contained a very interesting paper on Human Development Index (HDI) and related areas. It was really praiseworthy. SV team does good work for promoting research work. Congrats and best wishes.

* **H. S. Modi (Ahmedabad)**
NSV last issue contained a paper by P. R. Jani discussing overview for multiple testing procedures. It was very nicely presented by the author. We need still further such throught provoking articles.

* **K. S. Shah (Bharuch)**
SV last issue contained LP application study. There were two printing mistakes found. I had requested to correct them. My best wishes for further progress of this team work.

* **Hemal Pandya (Ahmedabad)**
SV issues contain two useful informations. First is about some biographies of eminent personalities of the field. Second one is the book review for some useful books. My best wishes for further work a head.

* **V. H. Bajaj (Aurangabad)**
Congrats to the SV team for accomplishing this task for 15 years. Please go ahead with more progress and spirits, my best wishes.

* Rtd. Principal, H. K. Commerce College, Ahmedabad
and Ex. Secretary, Gujarat Vidyasabha and Brahmachariwadi Trust, Ahmedabad.

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THINK TANK

GEORGE BERNARD DANTZIG*

George Bernard Dantzig was born on **Nov. 8, 1914** in Portland, Oregon. He lived for 90 years and passed away on May 13, 2005 in his home in Stanford, California. Dantzig received B.S. from University of Maryland in 1936 in Mathematics and Physics. He received Master's degree from University of Michigan in 1938. He worked for his doctoral programme in Mathematics at the University of California, Berkeley where he studied under **J. Neyman.** By 1960, he became a professor in the Dept. of Industrial Engineering at U C Berkeley and established OR Center. He had worked with US Airforce office of Statistical Control, Rand Corporation, Stanford University etc.

His work areas were **Mathematics, OR, Industrial Engineering, Computer Science, Economics and Statistics**. **This great American Mathematician cum Statistician produced 50 doctoral students, many of whom became leaders in their fields.**

Dantzig is best known for his works like **(1) Linear Programming (2) Simplex Algorithm (3) Dantzig - Wolfe decomposition Principle (4) Generalised Linear Programming (5) Generalised Upperbounding (6) Max-flow min-cut theorem of networks. (7) Quadratic Programming (8) Complementary Pivot Algorithms (9) Stochastic Programming etc.**

Dantzig received numerous prestigious awards like *** John Von Neuman Theory Pirze (1975), * National Medal of sciences in Mathematical, Statistical and Computational Science (1975), * Harvey Prize (1985), * Harold Pendue Award (1995)**

***(Brief Biographical sketch is given inside the journal)**

This page is specially donated by Prof. Shailesh Teredesai (Ex. Head), Statistics Dept., S. M. Patel Insitute of Commerce, GLS, Ahmedabad-380 009.

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