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**Alternative approaches to regression model, which is almost uniformly applied to many different types of clinical trials.**

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**Abstract:**

This abstract gives special interest to asymptotical properties of risk function of usual LSE depending on the rate of convergence. Though those can be improved by James Stein estimator, most if not all of very many known models of clinical trials use some modifications of standard regression model independently of, if these trails are controlled, cluster, randomized, stepped wedge (gives strict bounds in intervention, as in Ebola vaccination), mixed models, or repeated measures, etc… trails. All of the above models differently apply on the immune system as supported by recent articles. Additional approaches for possible improvement are given by Bayesian inference with nonparametric prior for partially ordered latent observations and rejection sampling on probability measures.

**Keywords:**

Partially ordered latent observations, rejection sampling, immune system.

**INTRODUCTION**

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| --- |
| [**Regression analysis**](https://en.wikipedia.org/wiki/Regression_analysis) |
| [Linear regression.svg](https://en.wikipedia.org/wiki/File:Linear_regression.svg) |

**(Wikipedia in different articles)**

The first clinical trial was conducted 270 years ago (Wikipedia)

(Below is a front page from the following article)

“**Common Industrial Applications of Mixed Models**

Bob Obenchain, Eli Lilly

ABSTRACT

The two types of linear models with random coefficients that I use most frequently

in pharmaceutical applications are (i) models for within and between batch

variation and (ii) random slopes regression models Although *very* simple

conceptually, these basic models illustrate some fundamental distinctions and

computational difficulties that have fueled controversies’ over fixed versus random coefficient models for at least the last 25 years.”

**“1. HISTORICAL PERSPECTIVE.** The following are a number of quotations from

Frank Yates' June 1968 presidential address to the Royal Statistical Society [Yates(l968),

Section 2, Irrelevance of Much Present-Day Statistical Literature]:

''Only when radically new situations arise are extensions of theory necessary."

"A publishes a paper which is irrelevant, or based upon unrealistic premises. This stimulates B and C to further thoughts on the same lines. And in a few years a body of literature is built up."

"In case you think I exaggerate. let me give you an example, that of 'fixed' and 'random' effects in experimental design. This dichotomy has now a considerable vogue in America, and is spreading to this country."

"Differences in formulae, arising from differences in definition. soon intruded, and before long it was represented that tests of significance which could be correctly applied would differ for the two models."

SUMMARY. Because much analytical testing in the pharmaceutical industry is

destructive and, thus, highly variable, the traditional expected mean squares approach to estimation of between-batch variance components in one-way

ANOVA frequently gives negative estimates. Modern likelihood approaches not only avoid this embarrassment but also easily handle cases where data are unbalanced or missing.”

**Partial list of regression models in relation to different types of clinical trials**

**1. Fixed effects model**

**  **

**2.** [**Random effects model**](https://en.wikipedia.org/wiki/Random_effects_model)



**3.[Repeated measures design](https://en.wikipedia.org/wiki/Repeated_measures_design" \o "Repeated measures design)**

**4. Mixed model can be represented as**

y = X β + Z u + ϵ {\displaystyle {\boldsymbol {y}}=X{\boldsymbol {\beta }}+Z{\boldsymbol {u}}+{\boldsymbol {\epsilon }}} 

where

**y** y {\displaystyle {\boldsymbol {y}}} is a known vector of observations, with mean **E(y) = X E ( y ) = X β {\displaystyle E({\boldsymbol {y}})=X{\boldsymbol {\beta }}};**

β {\displaystyle {\boldsymbol {\beta }}} is an unknown vector of fixed effects;

**u {\displaystyle {\boldsymbol {u}}} u** is an unknown vector of random effects, with mean **0**

**E ( u ) = 0 {\displaystyle E({\boldsymbol {u}})={\boldsymbol {0}}}**  var ⁡ ( u ) = G {\displaystyle \operatorname {var} ({\boldsymbol {u}})=G} ϵ {\displaystyle {\boldsymbol {\epsilon }}} is an unknown vector of random errors, with mean E ( ϵ ) = 0 {\displaystyle E({\boldsymbol {\epsilon }})={\boldsymbol {0}}} and variance var ⁡ ( ϵ ) = R {\displaystyle \operatorname {var} ({\boldsymbol {\epsilon }})=R} ;

**X {\displaystyle X} X** and Z {\displaystyle Z} **Z** are known [design matrices](https://en.wikipedia.org/wiki/Design_matrix) relating the observations y {\displaystyle {\boldsymbol {y}}} to **y**  β {\displaystyle {\boldsymbol {\beta }}} and **u** u {\displaystyle {\boldsymbol {u}}}, respectively.

**5.** [Generalized linear mixed model](https://en.wikipedia.org/wiki/Generalized_linear_mixed_model) as modification of

6. [Generalized linear model](https://en.wikipedia.org/wiki/Generalized_linear_mixed_model), where **Y** is dependent on **X** from exponential family

**E(Y) = g-1(X)**

**7. Randomized controlled trials**

**(All of the above are taken from the different articles in Wikipedia to focus an attention that those studies are very common with numerous publications)**

**8. And mixed models repeated measures have procedures** PROC **MIXED** with **REPEATED in SAS and** lmer in R

For the introduction of mixed models repeated measures can be used as introduction: “My motivation for this document came from a question asked by Rikard Wicksell at Karolinska University in Sweden. He had a randomized clinical trial with two treatment groups and measurements at pre, post, 3 months, and 6 months. His problem is that some of his data were missing. He considered a wide range of possible solutions, including "last trial carried forward," mean substitution, and listwise deletion. In some ways listwise deletion appealed most, but it would mean the loss of too much data. One of the nice things about mixed models is that we can use all of the data we have. If a score is missing, it is just missing. It has no effect on other scores from that same patient.” (Mixed Models for Missing Data With Repeated Measures Part 1 David C. Howell)

**The model**

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There are certainly more models of clinical trials that can be modeled by some kind of linear regression model.

And one of them is Stepped Wedge Design.

“More than a year from now and right after the last Ebola outbreak in Sierra Leone, when in the mid January of the last year WHO made an urgent statement indicating that Guinea, Liberia and Sierra Leone continued to remain at high risk of additional small outbreaks of Ebola in the coming months due to the virus persisting in survivors after recovery, I was invited to make a Poster Presentation at the First International Conference on Stepped Wedge Trails Design in York University, UK that was held in the beginning of March.

While I was working on my Presentation [18], I found that previous Ebola outbreak WHO at high-level Emergency Meeting on Ebola vaccination and financing convened at the request of several governments and representatives of the pharmaceutical industry stressed that though” Randomized Controlled Trials remain the “gold standard”, however, many agreed on the appropriateness of using stepped-wedge designs as well.” Though the statement could be understood as optional, which approach could be taken. However, the statistics of vaccination, in which only these individuals, who immediately after reminder of a doctor made the vaccination were safe from contracting Ebola virus, and those who waited had a risk of contracting Ebola, which increased with waiting time, suggests that only Stepped Wedge Trails Design was applied without exceptions.

Most of the literature (some of them are mentioned in [18] ) on the Stepped Wedge Trails Design including even different Encyclopedias compare the stepped wedge to randomized control trails, or as in ( [34,35]in [18]) list it as a variation of the crossover design for randomized controlled trials. However, the approaches are definitely different in that the stepped wedge design uses the constraints under which policy makers and service managers operate and which themselves are in the need for rigorous scientific evaluations. And though researchers may believe an evaluation of an intervention is required, only the decision makers (that is, politicians and managers) are in control resources for system change ([32] in [18]). This implies that **SWTD was widely used previously for political measures**

**Combination of health policy measures with political and investment strategies.**

The last measures are the kind of measures and strategies that we are looking **for the defense or prophylactic strategy** in solving the complication of the cyber problem mentioned in the Paper.

It was also very much believed that during 3 last years of introduction by WHO of control and intervention trails for Ebola vaccination gave significant reduction in deaths numbers, following contraction of the disease virus. On 11/7/15, WHO declared Sierra Leone free of Ebola virus transmission after two incubation periods, but on 11/10/15, CDC changed the country classification for Sierra Leone to a country with former widespread transmission and current, established control measures. It can be said that their decision was based on suspicion ***in the immune system of the population, which was based on the previous measures taken.***”(Michael Fundator “SBS Decadal Survey” National Academy Publication)

1. Why this study is important:

“There were more than 2.7 million deaths (in the United States), or about 86,000 more than the previous year. The notion that the life expectancy in the United States has mostly risen since World War II may sound as some kind of alarm and is certainly a basis for the analysis. Average life expectancy declined for men, falling by more than two months, to 76 years and 3 ½ months in 2015. It fell by about one month for women, to 81 years and 2 ½ months according to the CDC report. The increase was led by an unusual upturn in the death rate from the nation's leading killer, heart disease. Death rates also increased for chronic lower lung disease, accidental injuries, stroke, Alzheimer's disease, diabetes, kidney disease, etc..Researchers at Penn State Health Milton S. Hershey Medical Center linked the causes to ***lifestyle choices and obesity***.”(Michael Fundator “SBS Decadal Survey” National Academy Publication,[17])

2. How it can be understood that the use of Stepped Wedge Design can increase the risk of the whole study.

“I was honored to make a Presentation at the 11th International Conference on Health Policy Statistics in Providence, RI in October, where I introduced the following ideas:

1. Reduction of infinite dimensional model to finite dimensional model that remains multidimensional model allows us to view the data of the epidemics outbreaks as related to changes ***in the immune system of the population.*** The examples are: Ebola virus, cancer, smallpox, etc... .It also sheds light on how to approach such problematic deceases, as Tuberculosis (TB), HIV, and diabetes mellitus, and there are certainly other diseases, where different stages of development, treatment, and vaccinations are related to immune system. It was certainly in the good agreement with Good’s Article “Multivariate Tests after dimensionality reduction”. (Michael Fundator “SBS Decadal Survey” National Academy Publication)

There are number of recent articles connecting immune system with vaccination, to mention a few:

1. Follmann, D, Fay, M (2012). Bounds on the effect of vaccine induced immune response on outcome. *International Journal of Biostatistics* Vol 8, Iss. 2, Article 3. *“Repeatedly are case reports and studies which indicate that vaccinations may exacerbate or trigger an autoimmune illness.* (2. FOURNEAU JM. MOL IMMUNOL 2004;40(14-15):1095-102 , 3. HERNAN MA. Neuology 2004;63:772-3 , 3. RAVEL G. TOXICOLOGY 2004;196(3)211-6 , 4. WRAITH DC. LANCET 2003;462(9396):1659-66 , 5. BORCHERS AT. J INVESTIG ALLERGOL CLIN IMMUNOL 2002;12(3):155-68 , SAADOUN, D. REV MED INTERNE 2001 FEB;22(2):172-6 , 6. OLDER, SA. SEMIN Arthritis 7. RHEUM 1999 DEC;29(3):131-9 , NEUSTAEDTER, R. THE VACCINE GUIDE. BERKELEY 1996 , KALDEN JR. DMW 1992, 117, 1259 ,)*.” (****More transparency on vaccines, vaccinations and vaccine injuries*** *http://www.vaccineinjury.info/vaccinations-in-general/vaccines-and-immune-system.html)*

**In such a case special attention should be paid to decisions in relation to risk function. However, dependence of risk function as a function of estimators varies and is not smooth, and sometimes differs highly even with the slight variation in estimator value depending on number of dimensions considered.**

Below is the discussion of James –Stein estimators

“ For regression model, **Y = XC + e**, where **Y** is a N x 1 vector of N observations on the variable to be explained, X is a N x K full-column-rank matrix of N observations on K fixed explanatory variables, **C** is a column vector of regression coefficients, and **e** is a N x 1 error vector with a multivariate normal distribution with mean vector 0 and variance-covariance matrix **I**N, with 2 unknown. The least-squares (LS) estimator for **C** is LS = (**X’X)-1 X'Y**, and Stein’s estimator

is SE= **C**, where L is a scalar, n= N-K, **S2 =/**n

Though SE is also baised it dominates LS so as

E[**SE – C**)’ **X’XSE – C**)] < E[LS **– C**)’ **X’X**LS **– C**)], and 0<L<, K> 2.

An unbiased estimator of **SE** is CUB = **SE -** LS = - L

Z = (**X’X)1/2** and ***N***(,**I**K) with (/) .

To test null hypothesis **H0** : **C** **= 0** against alternative hypothesis **H1** : **C**  **0**

The uniformly most powerful invariant test statistic is **F** = **(** ĈLS’**X’X**ĈLS)/KS2,

**F**  K, n an F-distribution with K and n degrees of freedom and noncentrality parameter,

D = **C’X’XC/**2

And for F-ratio based on **SE** statistic = **SE’[S2(X’X)-1]-1SE = F(1 –** nL/K**F)2.** Since is a function of of **F**, thoughnonmonotonic, and some authors proposed to use it is invariant to the same linear and orthogonal transformations, as F is.

The above analysis was developed since mid 50-ties and greatly contributed to the theory of multihypotheses testing and FDR analysis”(Michael Fundator [Testing Statistical Hypothesis in Light of Mathematical Aspects in Analysis of Probability](https://www.preprints.org/manuscript/201607.0069/v1))

And therefore, Stein or James-Stein estimators are better then usual least squares estimators for dimensions 3.

**To get some sense how it works with risk functions**

“To estimate unknown mean of a k 3 dimensional random vector X with a known variance matrix2I with known observations X and S, S/ 2 has a chi-squared distribution with n degrees of freedom. For c= 2/22, the Loss function L(’,)= 2/a2, define t = t(U) to be absolutely continuous with derivative t’

Consider estimators of the form

’t = (1- (t(U)+ 1)/U)X, where U = [ 2/(k – 2)]/[S/(n+2)]

Theorem(Efron &Morris extention of Stein Theorem)

There is a unique unbiased estimator based on U for risk Rt(c) given by

Rt’(U) = k-[(k-2)/U](1-t2(U)) – 4t’(U)(1+d+dt(U)), where d=(k-2)/(n+2),

When d 0 the expectation of each term in (1) does not exist if

t-1(U) = O(U-(n+2)/4) , as U , or t-1(U) = O(U-(k-2)/4) ,as U 0”

(T. Moore et al Risk optimality of J-S estimators Annl Stat 6, 4 917-919)

To get more sense from “Blyth’s method for admissibility using limiting Bayes argument.

**Theorem** Suppose Rn is open and R(’,) is continuous on ’ for all .

Let be an estimator and {pi} be a sequence of measures such that for any open ball0

0 as i , then is admissible

The admissibility conditional on existence of estimator that dominates X means and an open ball B : R(’,X) – R(’,)> B implies for = d’)(B)

If goes to zero very fast (e.g. faster than

the probability of any set *B*) , then in a sense ***X*** would have to be doing well

everyhwere, and would not be able to be dominated - this is Blyth's method for

showing admissibility.

For n *>* 2, the probability (B) open set *B* is going to zero much faster than the Bayes

risk difference, leaving a large enough gap" for some other estimator (such as J-S)

to do better.”( Peter Hoff Shrinkage estimators)

And in the sense of the above discussion the behavior of the risk function depends on the rate of convergence conditional on Bayes sequence of measures.

**There are possible methods to deal with this problem that can pay attention to dimensionality**

**1. Partial stochastic ordering.**

”It may be of interest to impose a partial stochastic ordering on several probability measures.For example, if two treatments *a* and *b* are considered beneficial in increasing plant height, then we might impose the partial ordering Pnone *(Pa, Pb)*  *Pab* on distributions of plant height, where the subscripts on the measures indicate the treatments present. Dykstra and Feltz (1989) give a method

for maximum likelihood estimation subject to such partial stochastic orderings, and an alternative maximum likelihood estimation method is given in Hoff (2000)

The next step is to introduce the lattent variable . the construction is the following for real valued observations from k groups labeled by the elements from an indexing set A={a1, a2,…,ak} that are from unknown dist P with support X. We have partial ordering on A Pa1  Pa2 for a1 a2

**Theorem** *Let A be a partially ordered set with K elements. A collection P is in* C*A if and only if there exists a measure Q on (Ya1,…* , *YaK) such that Ya1*  *Ya2 with probability one for all* al *a2, and Q(Ya* E .) = *Pa(·) for all a* E *A.*

This **Theorem** can also be seen as a corollary of Choquet's theorem in the following sense: C*A* is a closed convex set, and its extreme points are collections of point-mass measures 0s *{0sa ,a* E *A}* for which *Sa1 Sa2* for all al *a2.* Thus the extreme points can be indexed by vectors *s* which lie in a subset *S* of *K* -dimensional Euclidean space and sampling and observation y from dist P is equivalent to sampling s from Q and noting y =s

The collection *S* = *{sa, a* E *A}* can be interpreted as a set of latent observations, and *Y Sa* the realized observation. The set *{Sb/ b* E *A, b =I a}* can be thought of as counterfactual or missing observations

Prior Formulation and Interpretation fornonparametric Bayesian

*{Pa : a* E *A}* == *P pcA*

for each *a* E *A, {Yi* : *Xi* = *a }IPa* independent draws from *Pa ,*where pCAhas full support on *CA,* relative to some topology. Such a prior for *P* can be constructed

via a prior for a representing measure *Q:* If pQ has support on Q, the space of measures on S, then the marginals of *Q* will lie in *CA.*

There are Dirichlet, Poisson, and Binomial that can be considered as priors.

Measure *Q* on ordered latent observations doesn't imply that latent observations actually exist or represent counterfactuals, i.e. what would have been observed under different conditions. The construction of *Q* is primarily a computational

convenience, allowing us to work in an unconstrained space of representing measures rather than a constrained space of ordered measures.

**Corollary** *Given continuous PI, P2* : *PI P2 and an integrable function T(X, y) on* S, *there is a unique Q on* S *having marginals PI, P2 and local dependence functio*n T.

**Proposition** *Let aQo be a positive measure on {i,* j E (1, ... *,K)2* : i :s: j}J *and let Q* dist *D(aQo). Let* P1 *P2 be the first and second marginals of Q and let 'T be the local dependence* *function. Then'T is independent of*P1 *'T is independent of P2 but'T is not independent of* (P1, *P2).*”( Peter D. Hoff Bayesian methods for Partial Stochastic Orderings)

There are different algorithms for construction based on assumptionIf the sample space *S* is discrete, then *Q* is finite dimensional such as Gibbs sampling, Metropolis-Hastings algorithm, which allows clustering.

**2. Rejection sampling** also gives some possible attention to multidimensionality

The method going back to Comte de Buffon and John von Neumann for checking if a sample from dist Y with density g is from sample from dist X with density f by obtaining sample from uniform dist U and comparing if u< f(y)/Mg(y)

“Adaptive rejection sampling involves method of defining envelop function for domain D and introduction of tangents lines at points xk.”( Peter D. Hoff Bayesian methods for Partial Stochastic Orderings)

**3 Survival Analysis methods and Actuarial Sciences**(**Michael Fundator** Survival Analysis Applied and Studied by Multidimensional Time Model for Probability Cumulative Function along with Different Methods for Approximation of Survival Function of Random Trees and Forests Including Maximum Entropy and Saddle Point Approximations. **Survival Analysis Conference Leicester, UK 4/5-6/17)**

Let Г(ai, λ), ai, λ > 0, where Г(ai, λ) is for gamma distribution function, then

Г ( , λ) = =f(t) for t>0, where = = m

Let with Ti having parameters ai and I for S= can be used convolution Theorem (Feller)

*S* *f*(*t*;*m*1*,*) \* *f*(*t*;*m*2*,*) \**….* \* *f*(*t*;*m*n*,*), where \* denotes convolution

G(t) \*H(t) =

The variety of different methods and types of bivariate exponential and Gamma distribution allow flexible approach for the evaluation of data. Only for Poisson distribution there are at least 20 different procedures for finding confidence intervals.

**Variety of methods of linear combinations and ratios of random variables.**

Five methods of the theory and applications of linear combinations and ratios of random variables:

1. Ratios of normal random variables appear as sampling distributions in single equation models, in simultaneous equations models, as posterior distributions for parameters of regression models
2. Weighted sums of uniform random variables
3. Ratio of linear combinations of chi-squared random variables multivariate linear functional relationship model Sums of independent gamma random variables
4. Linear combinations of inverted gamma random variables for the Behrens-Fisher problem and variance components in balanced mixed linear models Beta distributions their linear combinations
5. Linear combinations of the form T = , where tf denotes the Student t random variable based on f degrees of freedom and weighted sums of the Poisson parameters.

**Five types of the bivariate exponential distribution**

1. = F(x; y) = 1 − exp(−a1x –a2y− a12max(x, y)).x,y 0. for Marshal and Olkin model.
2. F(x,y)=1-exp(-x) –exp(-y) + exp(-x-y-axy); x,y>0, 0 for Gumbel model.
3. X = + Y = + with with (U1, U3) independent from (U2, U4), but have the same joint normal with zero means, variances ½, and corr r(0) for Moran model.
4. For Freund model component 1 and component 2 are dependent in that a failure of either component changes the parameter of the life distribution of the other component.
5. Block and Basu considered a bivariate distribution whose marginals are mixtures of exponentials and having an absolutely continuous joint distribution.

**Five types of bivariate gamma distributions.**

In univariate case the gamma distributions is generalization of Erlang distribution, which is the sum of i.i.d. exponentially distributed random variables:

*1. McKay’s bivariate gamma distribution given by the joint pdf*

*f (x, y) =(ap+q /* Г *(p)* Г *(q))xp-1(y – x)q-1exp(−ay) , , for y >x >0, a >0, p >0 and q >0.*

*2. Cherian’s bivariate gamma distribution given by the jointpdf*

*f(x, y)=(exp(−x−y)/* Г *(θ1)* Г *(θ2)* Г *(θ3))exp(z)dz for x >0, y >0, θ1 >0, θ2 >0 and θ3 >0.*

*3.Kibble’s bivariate gamma distribution given by the joint pdf f(x, y) = exp(-)(), where If(.) denoted modified Bessel function of the first kind of order f.*

*4. the Beta Stacy distribution is given by the joint pdf* f(x, y) =xp-1(y-x)q-1ybc-p-qexp{-(y/a)c}, where B(.,.) is Beta distribution function for y >x >0, a >0, b >0, c >0, p >0 and q >0.

5. Becker and Roux’s bivariate gamma distribution f(x, y)= xa-1{}b-1exp{- },if yor yb-1{}a-1exp{- },if y

for x >0, y >0, a >0, b >0, α >0, β >0, α’ >0 and β’ >0.

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**3. Different methods of approximating probability distributions.**

**3.1 Method of maximum entropy.**

According to the **Principle of Maximum Entropy** the best approximating model probability distribution with exactly known prior data is with the largest entropy.

Entropy of a discrete rv X is defined as

H(X) = E (-lnP(X)) = E (I(X)) = )I() = - )ln(P())

Where I(X) is an Information,

Conditional Entropy of a rv X conditional on Y is H(X/Y) = )

For discrete rv X with values in {*x1*, *x2*,..., *xn*} the Information I has the form of *m* constraints on the expectations of the functions *fk*. The probability distribution subject to constrains is

P(xi/I) = [()+….+)], with condition =1

Where the normalization constant Z = [()+….+)]

Fk = , where the are the Lagrange multipliers and the system of equations can be solved with numerical methods

And for conditional or Bayesian model would became

p(x=xi/Y) =

**3.2 Method of Saddle Point Approximations. [20]**

For cumulant generating function K(t)= log(M(t)), where M(t)is the moment generating function then the saddlepoint approximation to the PDF and CDF of a distribution is given by

(x) = exp ( - x)

(x)= ) + )( - ) for x E(x)

+ for x E(x)

Where is a solution to = x, =sgn and = )

This can be applied to hazard function that can be approximated by (x) =

The philosophy of application of saddle point approximation as approximation of probability density function of continuing functioning of k components out of n with intractable distribution functions is coming from common multidimensional retrospective approach.[20]

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