



Leveraging Bayesian Posterior Probability for Analyzing Treatment Effects in Clinical Trials

A Statistical Programmer's Guide



Meet the Speaker



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Ms. Vismaya Kondassam veedu, Engagement Lead at Zifo RnD Solution has a professional experience of 5 years in the Clinical sector has spearheaded multiple CDISC SDTM, ADaM, and TLFs engagements with many of our top pharma clients. She has been responsible for execution of various clinical studies with team of 15+ people for the customers in Australia. She has led many projects that are prepared for analyses as well as regulatory body submissions for various studies for customers including US, APAC and Europe across various therapeutic areas. She is one of the SMEs and trainer for SDTM within our organization. Also, involved in defining and enhancing the process of team – authorizing DWI, developing & reviewing guidelines and checklists.

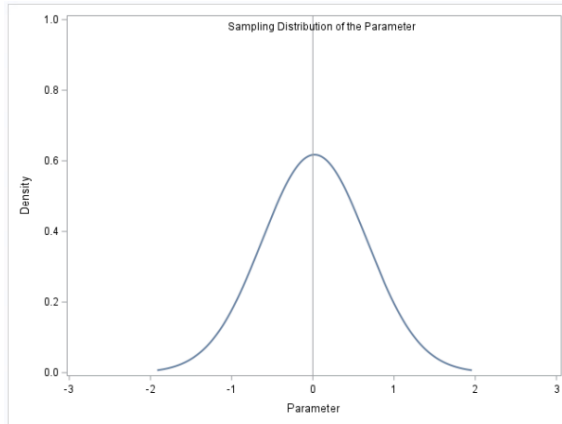
Agenda

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- Concept
 - Case Study
 - Tips and Tricks
 - Merits and Demerits
 - Guideline and References
 - Conclusion

Different Approaches

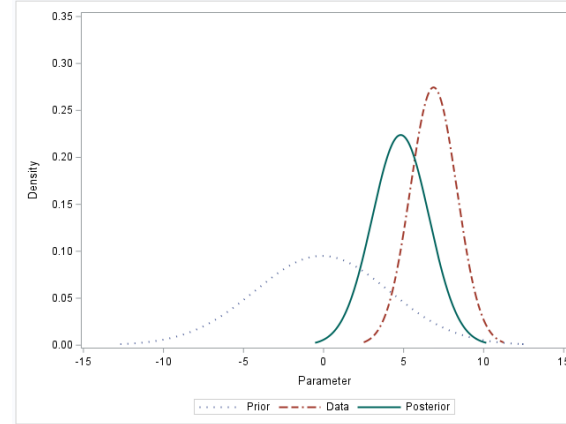
Frequentist

How likely to observe the data given the parameter value



Bayesian

How likely is the parameter value given the data and prior information



Bayes' Theorem (Bayes' rule)



- Bayesian statistics is named after the Reverend Thomas Bayes, whose theorem describes a method to update probabilities based on data and past knowledge.
- A mathematical relationship between the prior probability* and the posterior probability** conditional on data.

$$P(A|B) = \frac{P(A) \cdot P(B|A)}{P(B)}$$

Explanations

Events of interest (A, B)

Prior probability $P(A)$, $P(B)$: Probability of A and B occurring independently.

Posterior probability $P(A|B)$, $P(B|A)$: Probability of A occurring given B is true or vice versa.

* Prior probability: initial probability of an event occurring before any new data is considered.

** Posterior probability: updated probability of an event after considering new information.

Scenario 1

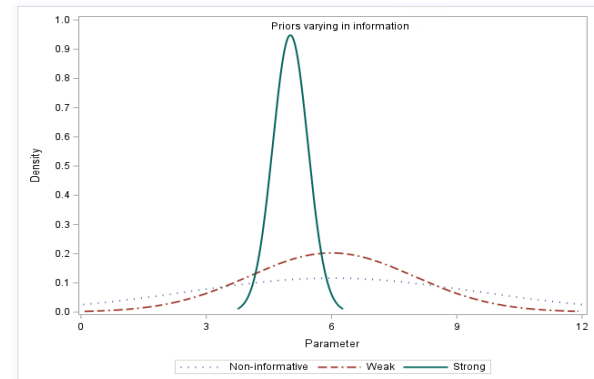
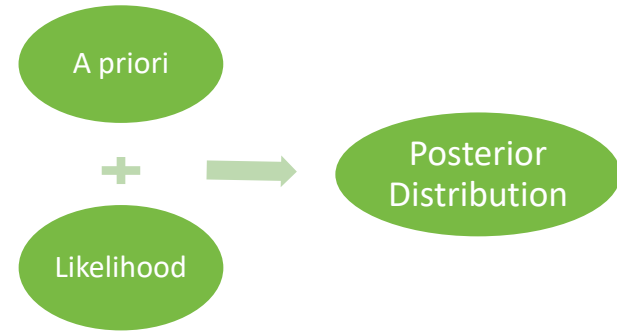
- Given mammogram test results for breast cancer detection and known error rates of the device, you can predict the actual chance of having cancer given a positive test, i.e., how likely is it to have cancer with a positive mammogram result?
- Thus, if E is the event of positive mammogram result and H is the event of having cancer, the Bayes theorem for likelihood of cancer with positive mammogram result can be represented as:

$$\Pr(H|E) = \frac{\Pr(E|H) \Pr(H)}{\Pr(E)}$$

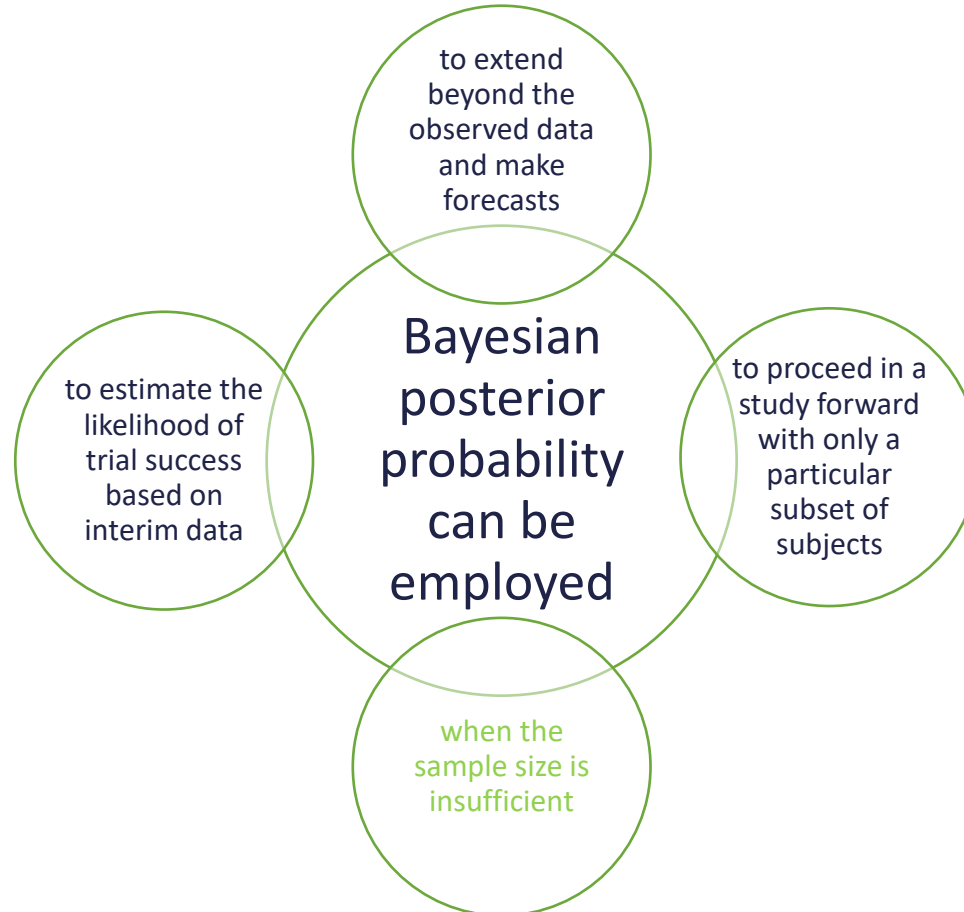
Pr (E) tells us the chance of getting any positive result, whether a true positive in the cancer population or a false positive in the non-cancer population and acts like a weighting factor, adjusting the odds towards the more likely outcome. Here, this is the prior probability.

Key Concepts (Summary)

- Bayes' theorem provides a mathematical method for integrating the prior and the likelihood to derive the posterior distribution.
- Priors outline the plausible values and the associated uncertainty of the parameters of interest. Based on the amount of information available, priors can vary from non-informative (no information) to highly informative.
- Likelihood represents the information available in the data
- The posterior distribution represents the probability distribution of the parameters of primary interest, based on the likelihood and prior information.



Application of Bayesian in Clinical Trials



Case study

Consider a clinical trial evaluating the efficacy of study treatment compared to placebo in reducing disease-associated pain. Due to the rarity of the disease, there are very few subjects to study the treatment effect. Bayesian posterior probability proves to be a better choice for analysis in this case (i.e., small sample size).

Analysis:

- The change from baseline to Week 7, Week 13 etc., in FPS-R score is compared between treatment and placebo using MMRM model.
- The MMRM model includes factors for treatment group (Treatment, Placebo), time (Week 7, 13, 25), and treatment by-time interaction. Random effect for subject is also added.



- **Bayesian posterior probabilities** that the mean **improvement due to treatment exceeds 0%, 10% and 20%** are also computed.

Data

A sample of the data used for analysis

SUBJID	AVISIT	AVAL	BASE	CHG	FASFL	TRTA	AGE
10001	Week 25	8.86	6.29	2.57	Y	Treatment	29
10002	Week 7	3.42	6.29	-2.87	Y	Placebo	22
10002	Week 13	4.57	6.29	-1.72	Y	Placebo	22
10002	Week 25	4	6.29	-2.29	Y	Placebo	22
10003	Week 7	3.14	4.86	-1.72	Y	Treatment	50
10003	Week 13	3.71	4.86	-1.15	Y	Treatment	50
10003	Week 25	0.86	4.86	-4	Y	Treatment	50

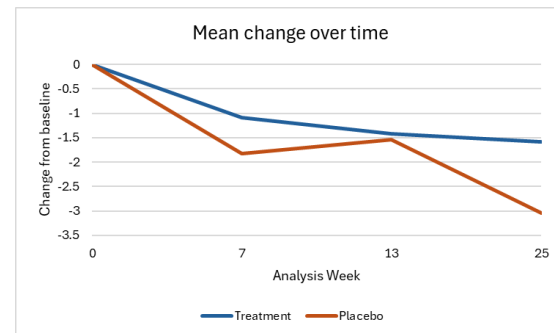
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AVAL – The average FPS-R score of the Week

BASE – The FPS-R score at Baseline

CHG - Change from Baseline

FASFL – Full Analysis Set (whether a subject belongs to the population of analysis)



Analysis algorithm with sample SAS codes

LS-mean and 95% CI estimates of change from baseline at each visit from PROC MIXED

```
proc mixed maxiter = 1000 maxfunc = 5000 data = input_data;  
class TRTA AVISIT SUBJID;  
model CHG = TRTA AVISIT TRTA*AVISIT / solution;  
repeated AVISIT/ type=un /*Unstructured covariance matrix*/ subject = SUBJID;  
random SUBJID;  
lsmeans TRTA*AVISIT/ pdiff cl e;  
ods output lsmeans=lsmeans diffs=lsmean_diff(where=(TRTA ne _TRTA and AVISIT eq _AVISIT))  
coef=coef convergencestatus=cs;  
run;
```

Note: Above are sample SAS codes and do not contain the full structure.

Least Squares Means										
Effect	TRTA	AVISITn	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
TRTA*AVISITn	Placebo	7	-1.8286	0.7588	11	-2.41	0.0346	0.05	-3.4986	-0.1585
TRTA*AVISITn	Placebo	13	-1.5429	0.8881	11	-1.74	0.1102	0.05	-3.4975	0.4118

Analysis algorithm with sample SAS codes

Obtaining Posterior Distribution using BGLIMM procedure:

BGLIMM uses similar syntax as that of PROC MIXED and GENMOD

```
proc bglimm data = input_data nmc=11000 seed=8654286 outpost=pr_out;
  class TRTA AVISIT SUBJID;
  model CHG = TRTA AVISIT TRTA*AVISIT/ coeffprior=constant;
  repeated AVISIT/ type=un subject=SUBJID;
  random SUBJID;

  /*Estimating LSMEANS for Treatment group and Placebo group at respective visits*/
  estimate 'Treatment_at_Week_7' intercept 1 TRTA 1 0 AVISIT 1 0 0 TRTA*AVISIT 1 0 0 0 0 0;

  estimate 'Placebo_at_Week_7' intercept 1 TRTA 0 1 AVISIT 1 0 0 TRTA*AVISIT 0 0 0 1 0 0;
  . . .
run;
```

Note: Above are sample SAS codes and do not contain the full structure.

Analysis algorithm with sample SAS codes

Specifying Prior distribution:

- **COEFFPRIOR=CONSTANT** provided in the above SAS code instructs the procedure to use non-informative flat prior for fixed effect coefficients in estimating the posterior distribution. This is the default prior for fixed effect coefficients in the BGLIMM procedure and it assigns equal likelihood for all possible values of the coefficients.
- Priors for covariance matrices can be provided using **COVPRIOR options in the RANDOM and REPEATED** statements. Scale/shape parameters can be varied like **COVPRIOR=IG (3, 0.5)** based on the information at hand

Priors for Fixed Effects	
Parameter	Prior
Intercept	Constant
TRTA Placebo	Constant
AVISITn 7	Constant
AVISITn 13	Constant
TRTA Placebo*AVISITn 7	Constant
TRTA Placebo*AVISITn 13	Constant

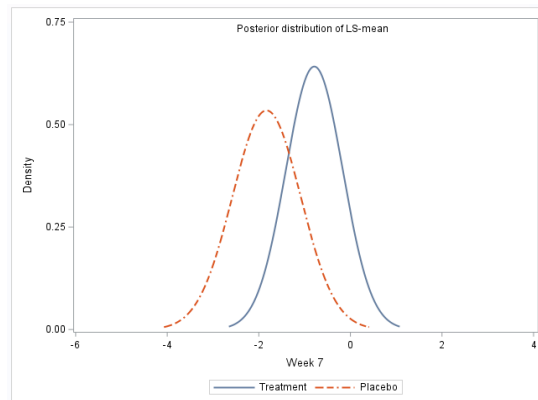
Priors for Scale and Covariance Parameters	
Parameter	Prior
Residual Cov	Inverse Wishart (DF=6, Scale=6)

LS-means from the Posterior distribution

Estimating the LS-means from posterior distribution to evaluate the mean improvement due to treatment. Unlike, the PROC mixed or other GLM procedure BGLIMM does not support LSMEANS statement. Hence, we rely on estimate statement for calculating the LS-means.

```
/*Estimating LSMEANS for Treatment group and Placebo group at respective visits*/  
estimate 'Treatment_at_Week_7' intercept 1 TRTA 1 0 AVISIT 1 0 0 TRTA*AVISIT 1 0 0 0 0 0;  
  
estimate 'Placebo_at_Week_7' intercept 1 TRTA 0 1 AVISIT 1 0 0 TRTA*AVISIT 0 0 0 1 0 0;
```

Note: Above are sample SAS codes and do not contain the full structure.



Continued...

Deriving the mean improvement from the posterior samples

```
/*Calculating mean improvement*/
data nmc;
  set pr_out;
  n = _n_ - 1000;
  if n>=1; *discarding first 1000 samples;

  mean_imp_1 = (Treatment - Placebo)*100/ Placebo;
  if Treatment lt 0 and Placebo _ lt 0 then dup = mean_imp_1;
  else if Treatment lt 0 and Placebo _ gt 0 then dup = -1* mean_imp_1;
  else if Treatment gt 0 and Placebo _ lt 0 then dup = -10; *Since this will always be
less than 0% improvement hard coding this as -10;
  else if Treatment gt 0 and Placebo _ gt 0 then dup = -1* mean_imp_1; *Since negative
changes are preferred directions are changed;

/*Week 7*/
  ind1_0 = ifn(dup > 0,1,0);
  ind1_10 = ifn(dup > 10,1,0);
  ind1_20 = ifn(dup > 20,1,0);
run;
```

Note: Above are sample SAS codes and do not contain the full structure.

Posterior Probability

The posterior probability of our parameters of interests, which is mean improvement $>0\%$, $>10\%$ and $>20\%$, is obtained from the posterior distribution.

In this case, the posterior probability is the proportion of samples that has mean improvement over 0% , 10% and 20% respectively.

```
/*Posterior probabilities for Mean improvement over 0%, 10% and 20%*/  
proc freq data = nmc;  
/*Week 7*/  
    table ind1_0 / out = week7_0 binomial(cl=exact level='1'); *to get the proportion (which  
is same as the posterior probability) of cases where improvement > 0%;  
    tables ind1_10 / out = week7_10 binomial(cl=exact level='1'); *to get the proportion of  
cases where improvement > 10%;  
    tables ind1_20 / out = week7_20 binomial(cl=exact level='1'); *to get the proportion of  
cases where improvement > 20%;  
run;
```

Note: Above are sample SAS codes and do not contain the full structure.

Output

Table
MMRM for Change from baseline in Mean Pain Intensity Measured by FPS-R

Visit	Parameter Statistic	Treatment (N=XX)	Placebo (N=XX)	Treatment Difference (N=XX)
Week 7	Change from Baseline			
	n	7	5	
	Mean	-1.082	-1.829	0.747
	LS Means (95% CI)	-0.7366 (-2.094, 0.6209)	-1.8286 (-3.4986, -0.1585)	-1.0920 (-3.2442, 1.0602)
	Posterior probability ¹			
	>0%			0.0939
	>10%			0.0936
	>20%			0.0935
Week x	...			

Note: Change from Baseline = Result at Visit X - Result at Baseline.

MMRM Model: Change from Baseline = Baseline + Treatment + Visit + Treatment*Visit + Baseline*Visit + Age.

¹ Bayesian posterior probability that the TRUE mean improvement is >0%, >10% and >20%. Non-informative priors are assumed for the model coefficients and the posterior distribution is generated using MCMC method.

Interpretation

- We assumed a non-informative prior for the model coefficients which means the probability that the true mean treatment is $>0\%$ (or $>10\%$, or $>20\%$) is equally like (i.e., 50-50 chance).
- The posterior probability for mean improvements $>0\%$, $>10\%$ and $>20\%$ are 0.0939, 0.0936, and 0.0935 respectively, indicating that the chances for mean improvement to be $>0\%$ have notably worsened.

Tips & Tricks

- As the procedure involves generating random samples, establishing the **seed number**, determining the **number of iterations for MCMC**, etc., will ensure reproducibility of the results.
- Standard caution like using **numeric variables (for e.g., AVISITN)** in place character variables as needed, specifying the **reference levels for the class variables** (for e.g., TRTA(ref="Placebo")), **confirming/agreeing up on the covariance structure or the order** in which the covariance structures are to be used in the model in case of convergence issues, etc., shall be exercised.
- Few incorrect results can be identified, **based on the prior information and data at hand**:
 - While using non-informative priors, Bayesian results are generally similar to results obtained from frequentist approach. There is very limited chance for a discrepancy.
 - In case of strong priors, either posterior distribution should resemble the prior distribution (if the likelihood is similar to prior) or should have results that lie between the prior and likelihood (if the likelihood differs markedly from the prior)
 - In case of weak or flat priors, the posterior distributions are bound to be similar to likelihood.

Merits

- We can make use of the relevant **prior information** in analysis and thereby incorporating prior information **in decision making**.
- Bayesian methods can provide **reliable estimates even for small samples** when appropriate prior information is available, whereas frequentist methods often require larger samples for reliable estimates.
- Bayesian methods are found to offer **more flexibility in designing adaptive trials**.
- Bayesian methods also allow for **great flexibility in dealing with missing data**.

Challenges

- Selecting a **universally accepted prior** is difficult due to the subjective nature of the prior beliefs. Even widely known methods for selecting priors like expert opinion and historical data suffer from drawbacks like **personal biases and relevance/quality of data** respectively.
- The extend of pre-planning the primary analysis will contribute to the degree of confidence in the results. Hence choice of priors, method of obtaining the posterior, etc., **should be decided before the commencement of the trials**.
- **Computationally intense** as it involves extensive mathematical modelling. Greater complexity also introduces **greater chance for error**.

Guidelines & References

Though Bayesian analysis is being widely used there are very few regulatory guidance on the use of it in clinical trials.

1. FDA Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (2010)
2. FDA Guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics (2019)

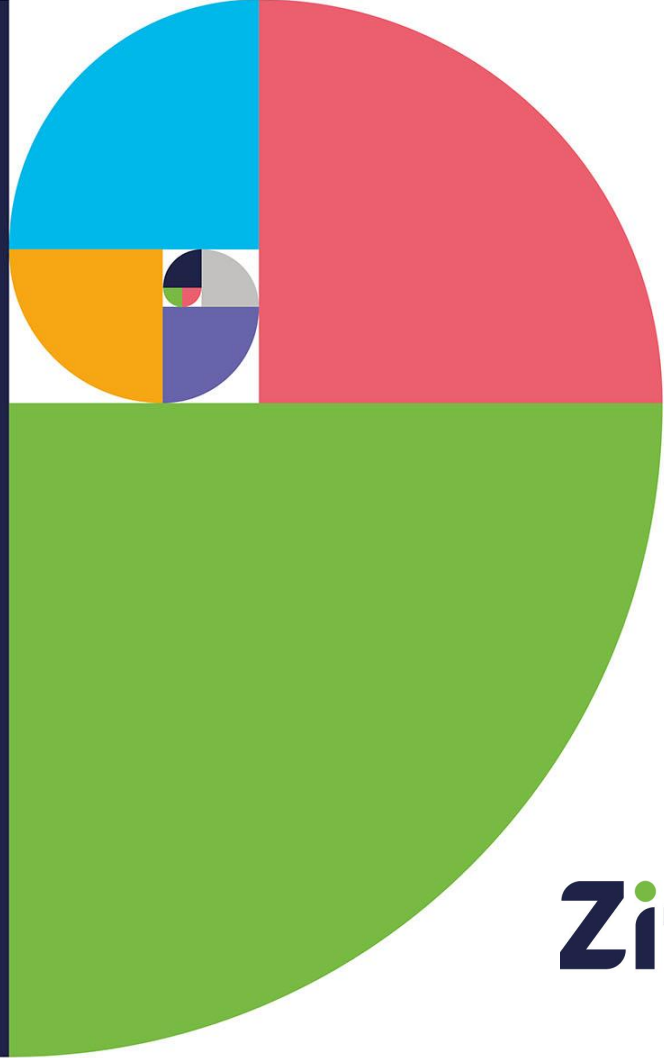
Some more references:

- 1) https://documentation.sas.com/doc/en/statcdc/14.2/statug/statug_introbayes_sect015.htm
- 2) <https://users.metu.edu.tr/ozancan/BayesLectureNotes.pdf>
- 3) <https://online.stat.psu.edu/stat509/lesson/9/9.4>
- 4) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10117244/#CR13>

To sum up..

Considering the limited exploration of Bayesian posterior probability in clinical analysis, our objective was to elucidate its core principles and demonstrate its application in clinical trial evaluations. We applied Bayesian posterior probability in a case study to provide practical insights and analyzed the outcomes comprehensively. Additionally, we outlined best practices and strategies for implementing Bayesian analysis, along with potential challenges that may arise.

THANK YOU



Zifo.