

Bayesian approach to detection of treatment-related effects in toxicology studies by borrowing information from historical control animals

Md Yousuf Ali^{1,2}, Kevin Snyder¹

¹U.S. Food and Drug Administration (FDA), Silver Spring, MD;

²Oak Ridge Institute for Science and Education, Oak Ridge, TN.

Md.ali@fda.hhs.gov

Kevin.Snyder@fda.hhs.gov

Nonclinical Toxicological Studies



Control

Low Dose

Medium Dose

High Dose

- Small Group Size
- Statistically Underpowered
- Multiple of Endpoints Assessed

True Effect?

No Response

Response

No Response

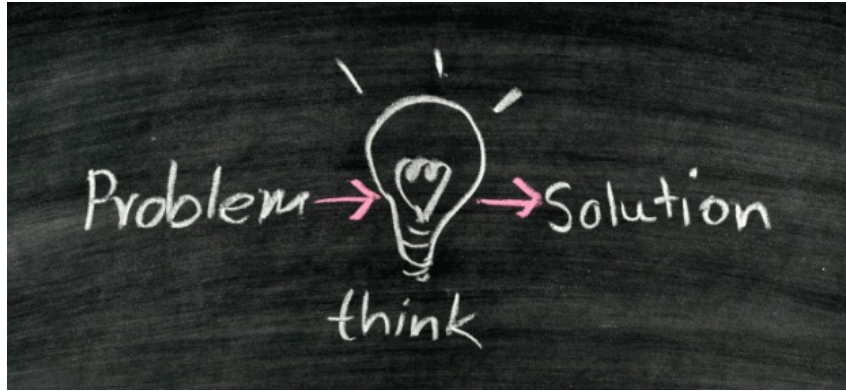
Response



Control Group

Treatment Group





- Historical Control
Animal Information



How to Get Historical Control Animal
Information ?

Standard for Exchange of Nonclinical Data (SEND)

- SEND is a data standard created by CDISC to enable collection and presentation of nonclinical data in a consistent format.
- In December 2014, the FDA finalized a binding guidance requiring that certain clinical and nonclinical studies be submitted with standardized electronic data, formatted in accordance with the standards recognized in FDA Data Standards Catalog, which currently includes SEND versions 3.0 and 3.1.

Electronic study data regulations

- FD&C Act Section 745A(a): Sponsors must use the data standards defined in the **FDA Data Standards Catalog** starting 24-months after final guidance is issued for a specific submission type

Standard	Application type	Dates that standard is <u>required</u> *
SEND 3.0	NDA/BLA/ANDA	12/17/16
	Commercial IND	12/17/17
SEND 3.1	NDA/BLA/ANDA	3/15/19
	Commercial IND	3/15/20

*Requirement dates refer to the nonclinical study *initiation* date (not the date that the study is submitted to the Agency)

Toxicology Study Endpoints Modeled in SEND

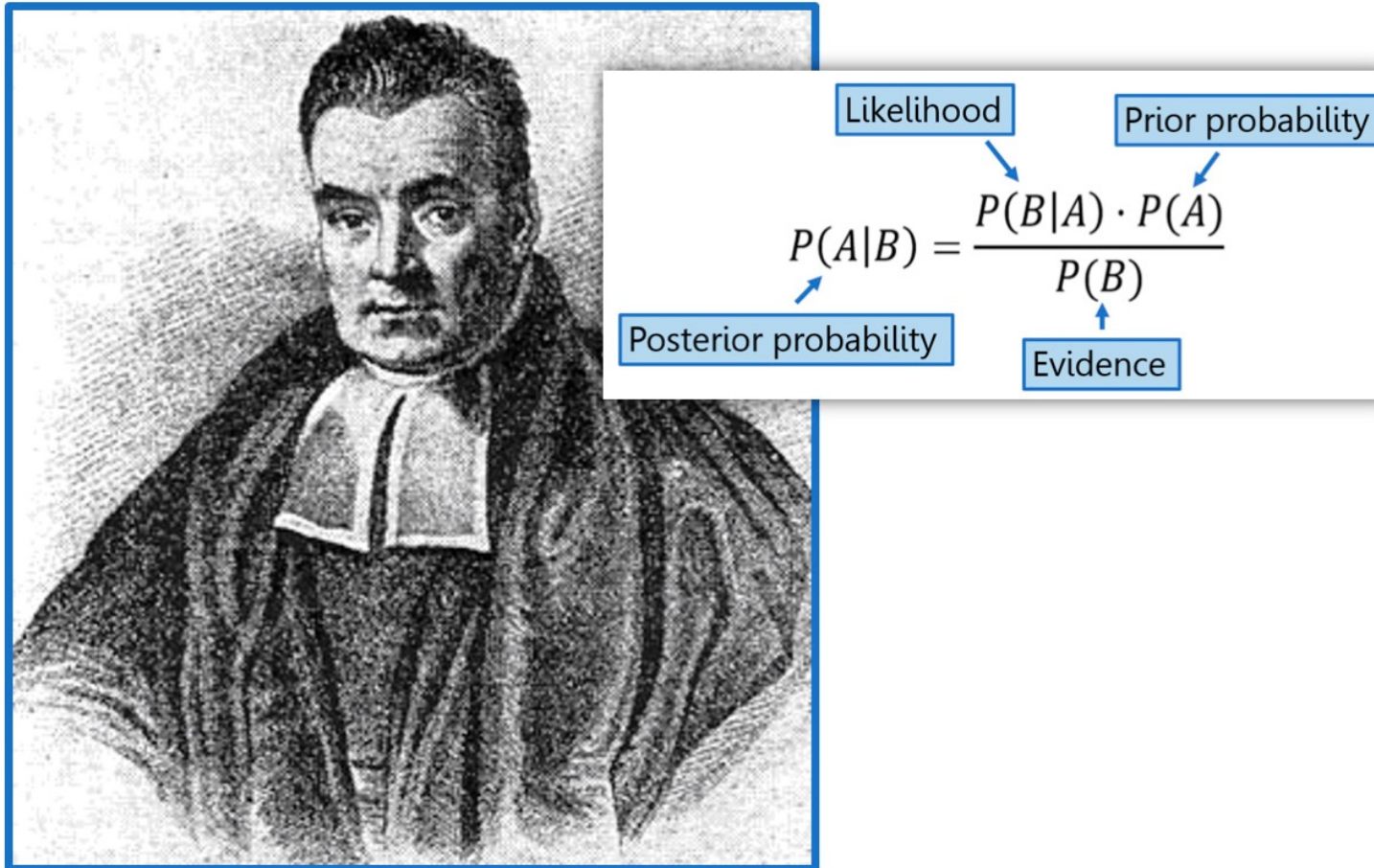
- Mortality (DS)
 - Clinical Signs (CL)
 - Body Weights (BW)
 - Food Consumption (FW)
 - Clinical Pathology (LB)
 - Gross Pathology (MA)
 - Organ Weights (OM)
 - Histopathology (MI)
 - Toxicokinetics (PC and PP)
- Categorical Incidence Data
 - Continuous Numeric Data
 - Not Applicable

R Package: sendigR

- sendigR is an R package developed and maintained by BioCelerate in collaboration with PHUSE nonclinical topics working group.
- sendigR package contains a set of functions to extract and filter data for control animals from a database.
- Historical Incident rate can be extracted using sendigR package.



How to Integrate Historical Control Animal Information ?



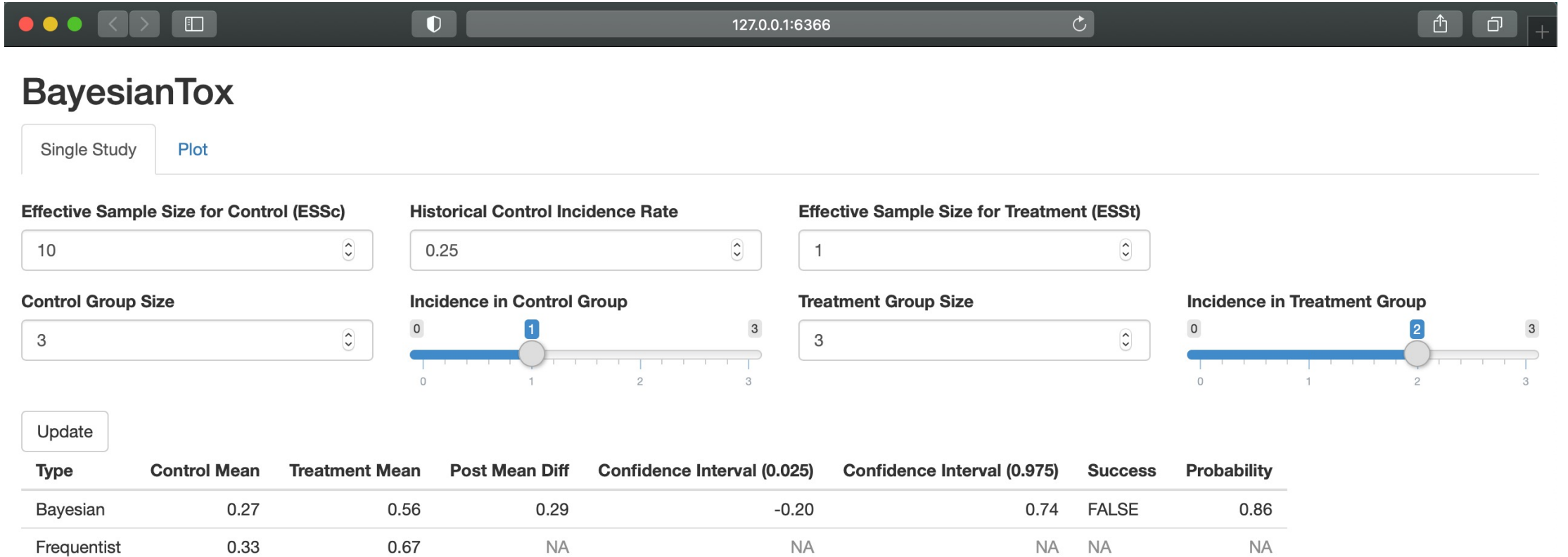
The Rev. Thomas Bayes, whose simple and fairly narrow formula eventually inspired a vast new field of statistics.

Bayesian Beta-Binomial Distribution

- Binomial likelihood, $L(D|\theta) := \binom{n}{x} \theta^x (1 - \theta)^{n-x}$
- Beta prior, $p(\theta) := \frac{\theta^{\alpha-1} (1-\theta)^{\beta-1}}{B(\alpha, \beta)}$,
- Posterior $p(\theta|D) \propto L(D|\theta) * p(\theta)$ Ignoring the normalizing constant $p(D)$
 $\propto \theta^x (1 - \theta)^{n-x} * \theta^{\alpha-1} (1 - \theta)^{\beta-1}$ Ignore $\binom{n}{x}$ and $B(\alpha, \beta)$ as they don't depend on θ .
 $= \theta^{(\alpha+x-1)} (1 - \theta)^{(\beta+n-x-1)}$
 $\Rightarrow \text{Beta}(\alpha + x, \beta + n - x)$

Not knowledgeable of
Bayesian Statistics or in
R programming?

BayesianTox Shiny App



Future Direction

- In more complex cases (non-conjugate), may need to rely on Markov-Chain Monte-Carlo to draw samples from the posterior.
- Build Logistic Regression model to add more data points in the model.
- Improve User Interface of the App and add visualization.

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