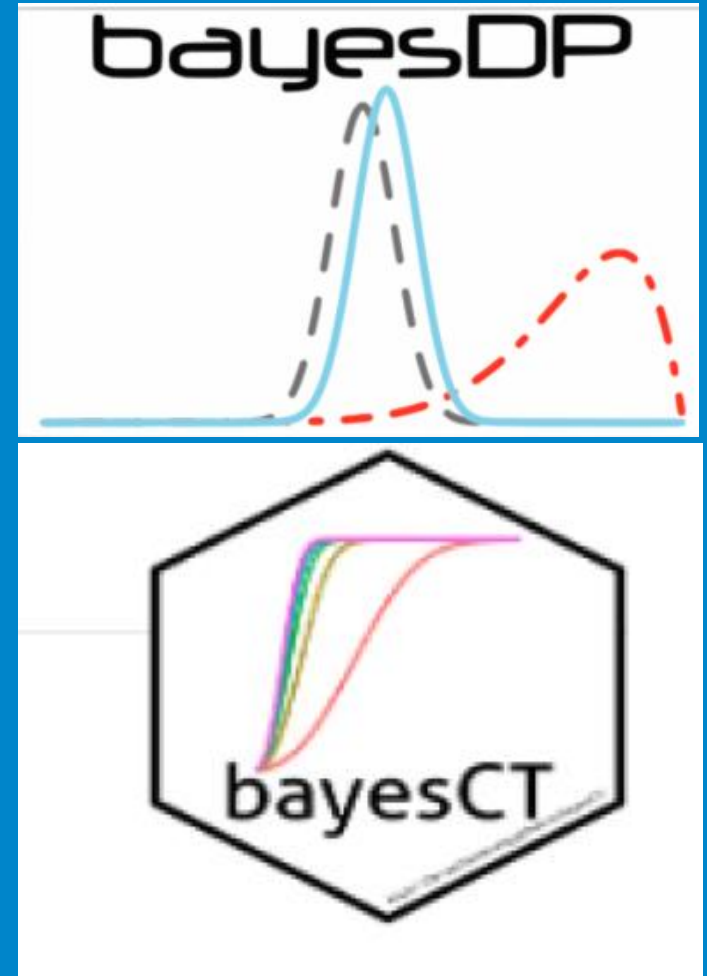
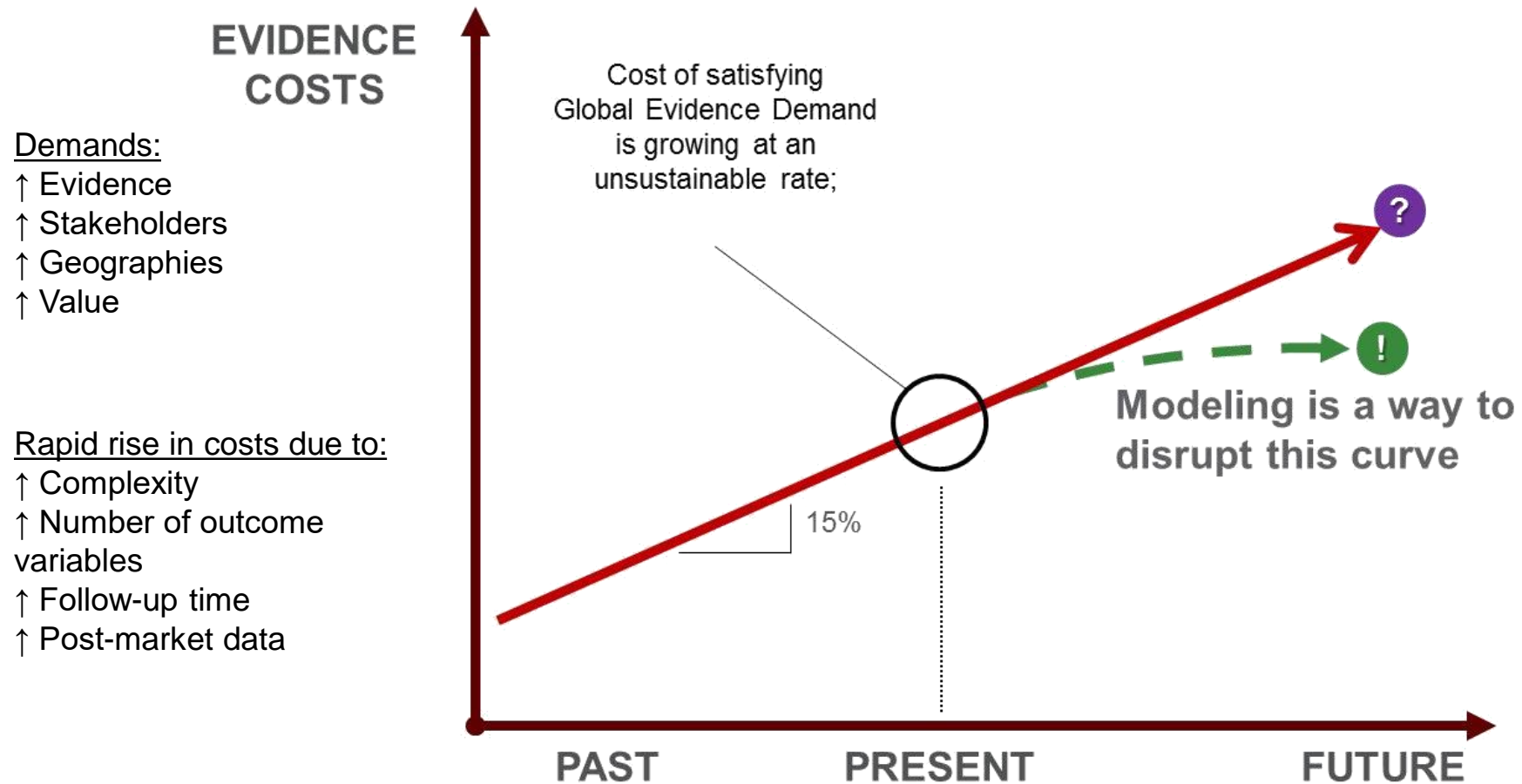


INDUSTRIAL CONSIDERATIONS FOR STATISTICAL TOOL USED TO SUPPORT SUBMISSIONS

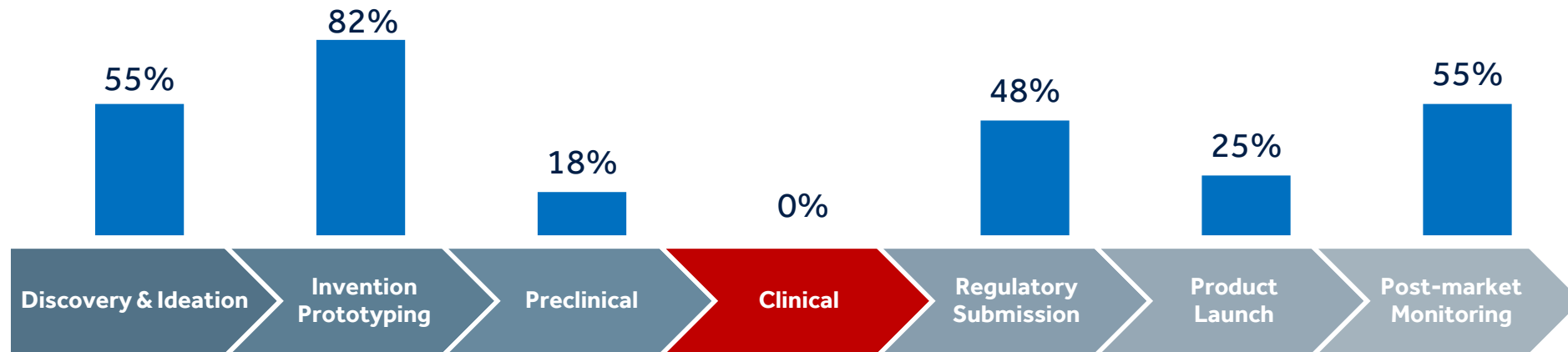
TAREK HADDAD
TED LYSTIG
DONALD MUSGROVE
THEVAA CHANDERENG
GRAEME HICKEY
TIM HANSON



TRENDS TRANSFORMING CLINICAL RESEARCH

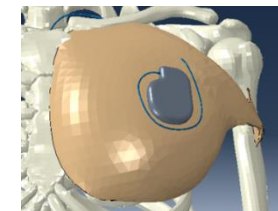
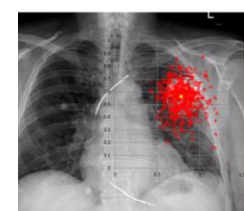
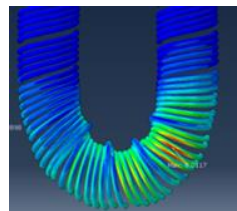
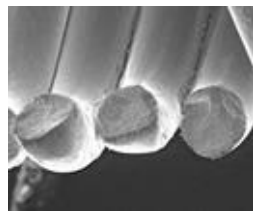
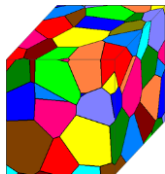


USE OF MODELING ACROSS LIFECYCLE



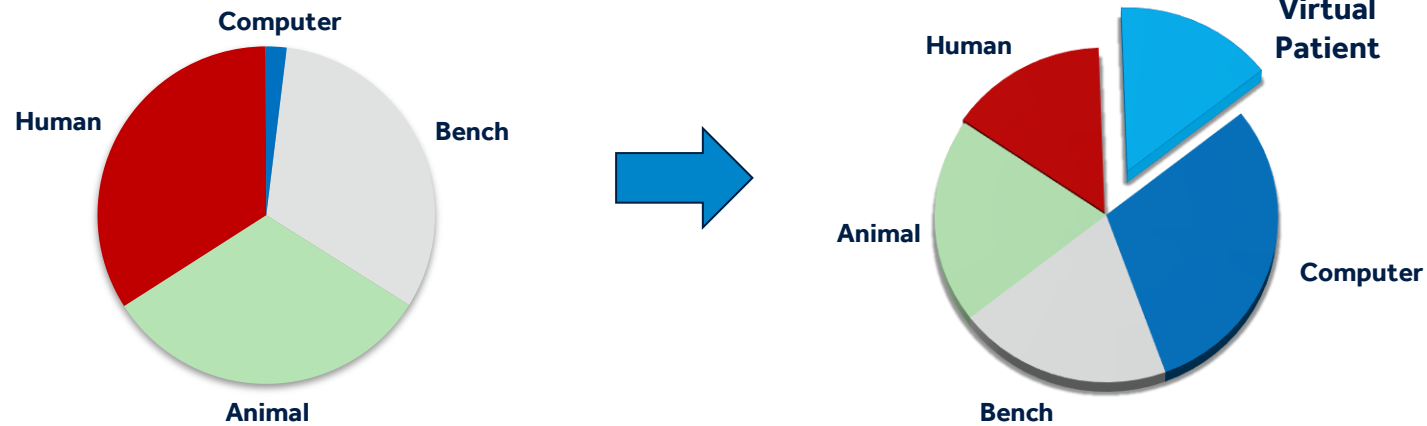
- Animal studies
- Use conditions
- Virtual prototyping
- Material characterization

- Device structure & function
- Systems interaction
- Design optimization
- Failure analysis



DISRUPTING CLINICAL TRIAL DESIGN WITH VIRTUAL PATIENTS

Sources of Evidence

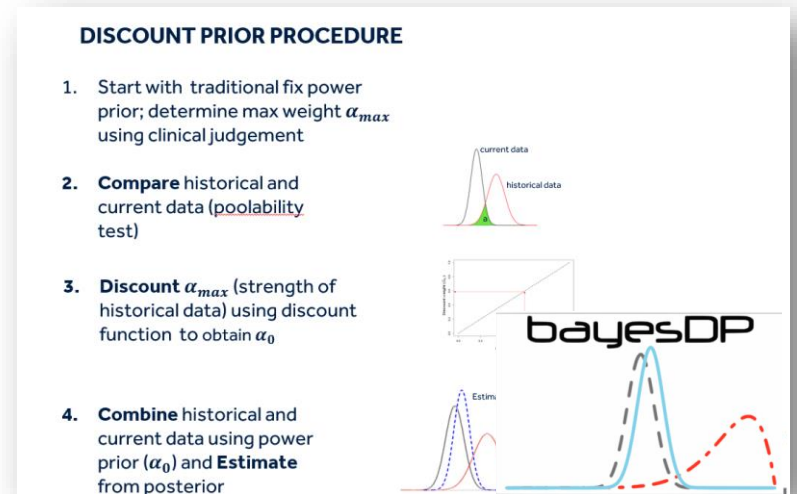


- Combine physical and probabilistic models to simulate clinically relevant outcomes in virtual patients
- Use Bayesian methods to integrate virtual patients into clinical trial
- Maintain clinical endpoints with reduced sample size

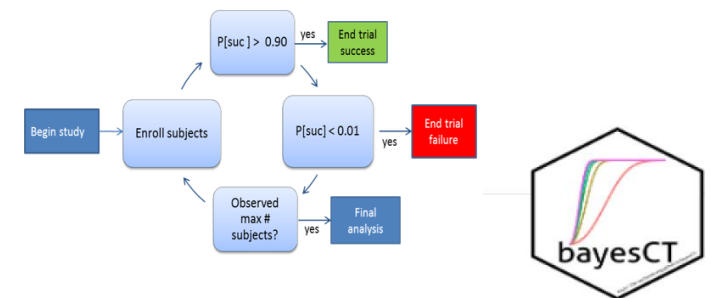
INCORPORATION OF VIRTUAL PATIENTS IN ADAPTIVE BAYESIAN CLINICAL TRIALS USING INFORMATIVE PRIOR

TWO R PACKAGE

- Some statisticians were uncomfortable with non-standard methods and with coding it up
- Regulatory: more work to read custom code
- Code that are simple to understand (Think SAS Proc mixed)
 - Universal language used for describing Bayesian adaptive trials.
 - Ease of developing an entire adaptive trial using these packages.
- Fast implementation: days and weeks → hours and min
- Employable for multiple trials with most common data types.
- Ability for a smaller company with a single statistician to be able to develop an entire adaptive clinical trial code



ADAPTIVE STUDY DESIGNS WITH DP



PACKAGE DEVELOPMENT

- Fast implementation
 - Copied standard input & outputs (lm)
 - dplyr bayesCT
 - Meeting R's requirements for packages
-
- Documentation
 - Lots of documentation → Vignettes!!
 - Credibility
 - Method credibility → Publications & conferences
 - Regulatory workshops
 - Validation → External validation (re-coding)

Journal of Biopharmaceutical Statistics >
Volume 27, 2017 - Issue 6

Submit an article | Journal homepage

2,702 Views
23 CrossRef citations to date
6 Altmetric

Original Articles

Incorporation of stochastic engineering models as prior information in Bayesian medical device trials

Tarek Haddad, Adam Himes, Laura Thompson, Telba Irony, Rajesh Nair & on Behalf of MDIC Computer Modeling and Simulation Working Group Participants

Pages 1089-1103 | Received 04 Apr 2016, Accepted 23 Feb 2017, Accepted author version posted online: 10 Mar 2017, Published online: 21 Mar 2017

bayesCT: An R package for Simulation in Adaptive Bayesian Clinical Trials

Thevaa Chandereeng, Donald Musgrove, Tarek Haddad, Graeme Hickey, Timothy Hanson, Theodore Lystig

- Introduction
- Running bayesCT
- Recruitment
- Randomization Scheme
- Incorporation of Historical Data
- Early Stopping for Futility or Success
 - Success
 - Futility

Introduction

Randomized controlled trials (RCT) are the gold standard of pharmaceutical and medical device clinical studies. In a two-armed RCT, subjects are randomized to an intervention arm, with the standard framework being the comparison of a new treatment to an alternative treatment (or no treatment at all). The majority of research in the design of RCTs and their application is based on the frequentist paradigm. In recent years, the adaptive Bayesian trial design approach has gained attention.

Adaptive Bayesian trials provide added flexibility compared to conventional frequentist approaches in terms of the design and analysis of a clinical trial. Notably, adaptive Bayesian trials can:

- Incorporate historical data, helping to reduce the sample size
- Easily carry out interim analyses to facilitate stopping early for success or futility
- Work with multiple treatment arms (versus a single control), allowing for dropping of demonstrably unsuccessful treatments
- Alter the randomization ratio (e.g., treatment to control ratio) to improve trial efficiency or even to increase trial recruitment

A fundamental requirement of an adaptive trial is the a priori and interim evaluation of the operating characteristics, e.g., power and type 1 error. In adaptive trials, these operating characteristics generally do not

BayesDP

Donnie Musgrove

2017-12-07

- Introduction
- Estimation of the historical data weight
 - Discount function
- Estimation of the posterior distribution of the current data, conditional on the historical data
- Estimation of the posterior treatment effect, treatment versus control
- Function inputs
- Examples
 - One-arm trial
 - Two-arm trial

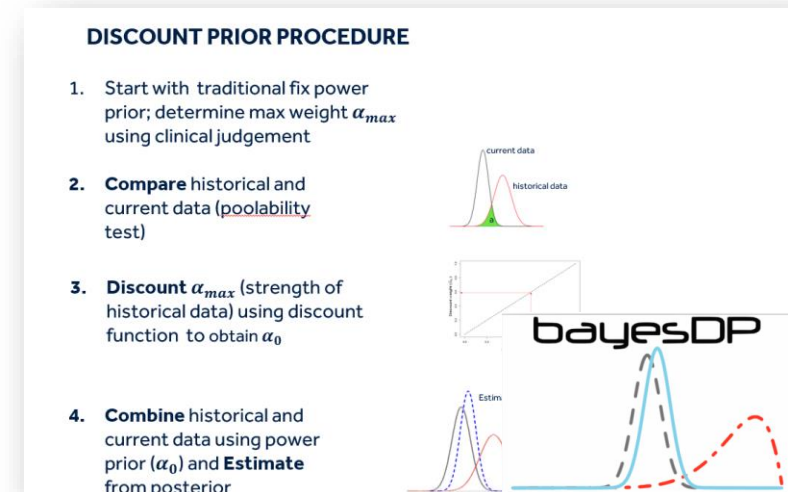
Introduction

The purpose of this vignette is to introduce the `bayesDP` function `bayesDP()` is used for estimating posterior samples from a Binomial event rate outcome for clinical trials where an informative prior is used. In the parlance of clinical trials, the informative prior is derived from historical data. The weight given to the historical data is determined using what we refer to as a discount function. There are three steps in carrying out estimation:

1. Estimation of the historical data weight, denoted $\psi(\text{that}(\alpha))$, via the discount function
2. Estimation of the posterior distribution of the current data, conditional on the historical data weighted by $\psi(\text{that}(\alpha))$
3. Estimation of the posterior treatment effect, treatment versus control

CONSIDERATIONS

- Package Management:
 - Not necessarily a software organization → management of the package
 - Package owner vs Package developer
 - Continued package maintenance
 - Implementation errors
 - Modifications on the Fly
 - Data preprocessing → Centering the data
 - Protocol modifications



Thank you
Questions?