PHASE V

Bayes Bayesian Biostatistics Rockville, MD 2024

To Bayes or not to Bayes

Lessons learned from building an adaptive trial platform

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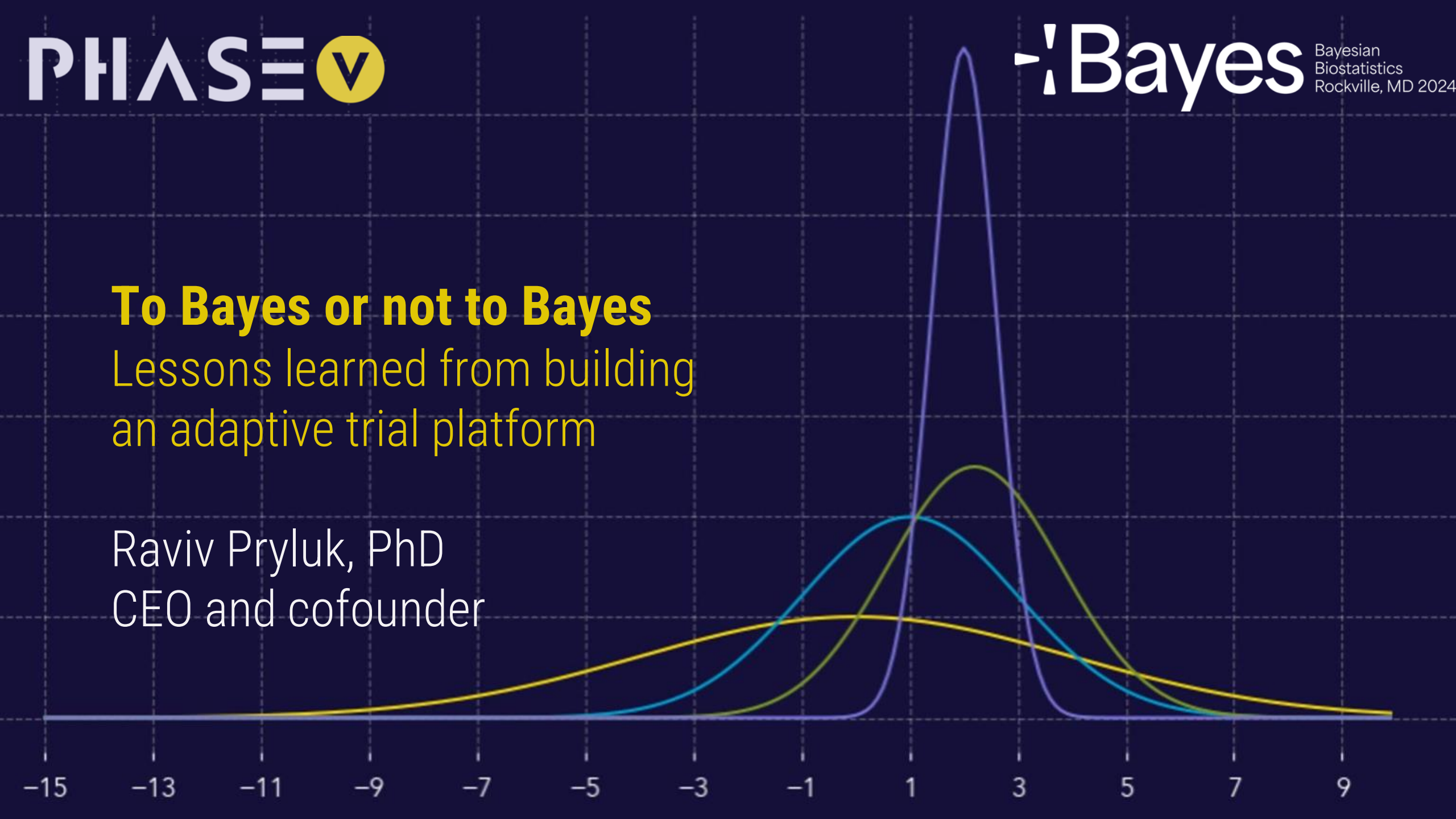
CEO and cofounder



PhaseV At A Glance

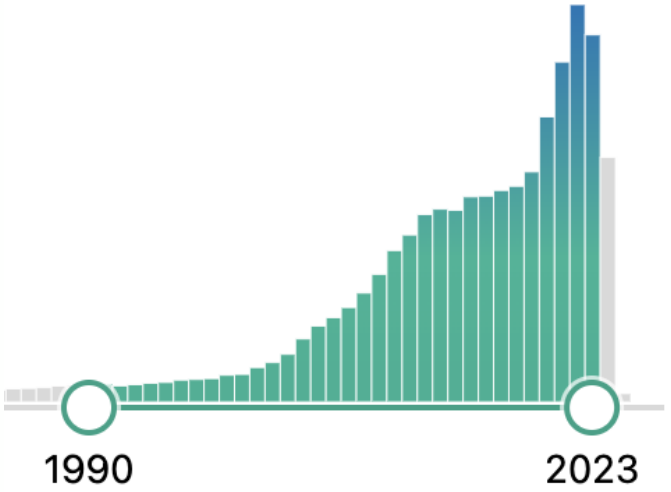
- Multi-disciplinary team of experts in ML, AI, software, biostatistics, and data science, together with pharma and clinical veterans, and adaptive trial leaders - harnessing the latest technological advancements for clinical trial optimization
- HQ in Boston, operating globally
- Products available:
  - Proprietary ML-based platform for the design and execution of adaptive clinical trials
  - Proprietary causal-ML heterogeneity treatment effect pipeline
  - 'Biomarker on the fly' - Causal-ML+Adaptive enrichment
- Expertise and novel predictive disease models in over 20 therapeutic areas, including Immunology, Oncology, Neurology, Endocrinology, Rare Disease, and more

Introduction - Preaching To The Choir :)

- Why are we having this discussion?
  - Trial efficiency
    - Utilize the information from every patient
    - Decreased sample size using informative priors
  - Measure what we care about
    - Probability of “being best” or “tail area”
- Transparency
  - Make assumptions explicit
  - Formalize the decision problem

Trends

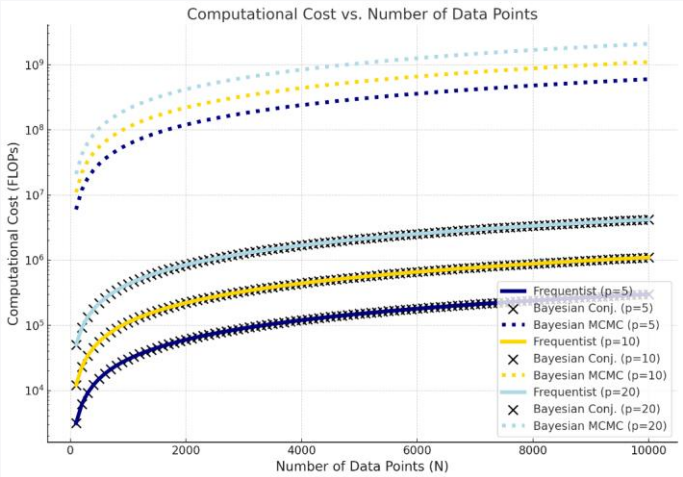
- Key Trends:
  - Low adoption rate in Rare diseases (https://pubmed.ncbi.nlm.nih.gov/34910979/), and this is in the most accepting setting)
  - Regulatory Acceptance:
    - FDA - 2025 Guidance
    - EMA Q&A 2022
  - Most commonly applied:
    - Rare Disease & Pediatrics
    - Early phase (BOIN/CRM)
    - Devices



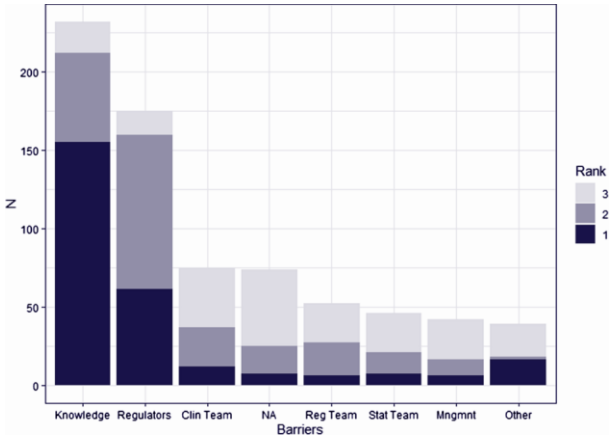
Bayesian Methods - In Pubmed Publications

Challenges

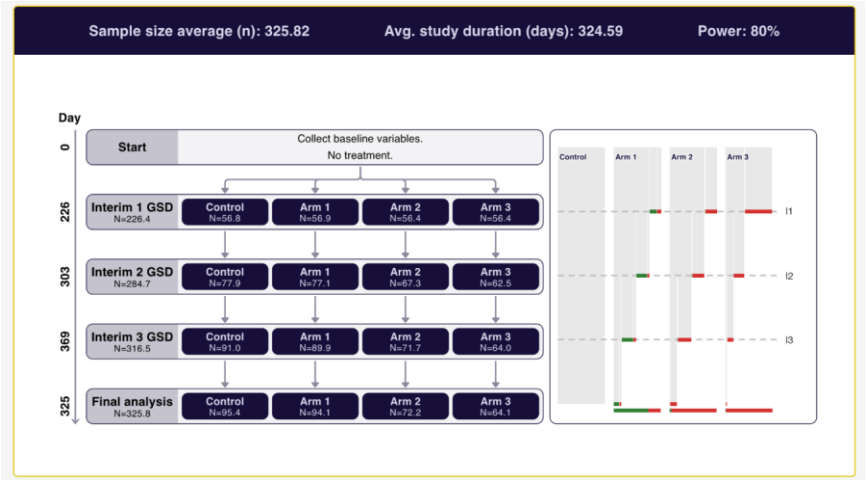
Computation



Knowledge and Trust

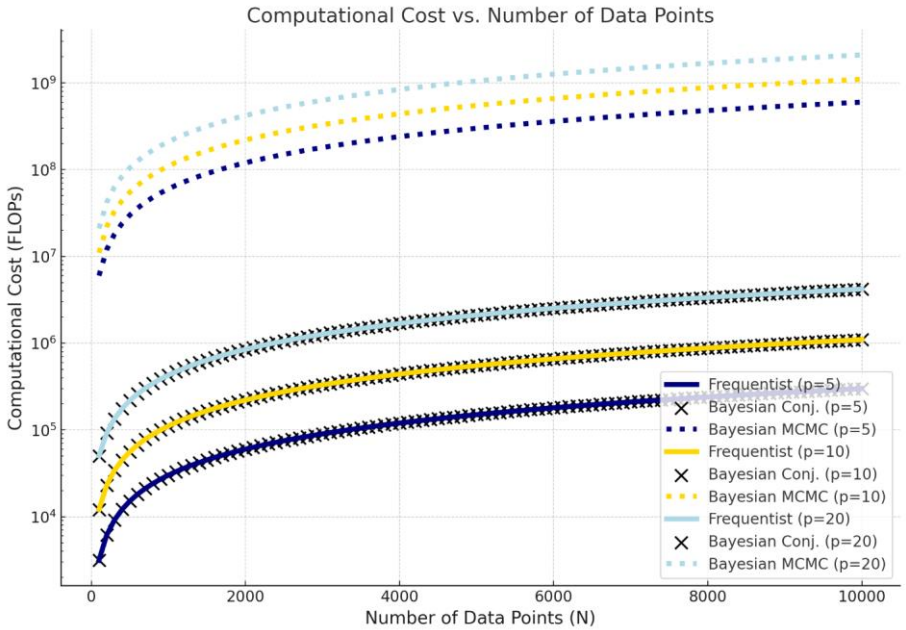


Tools



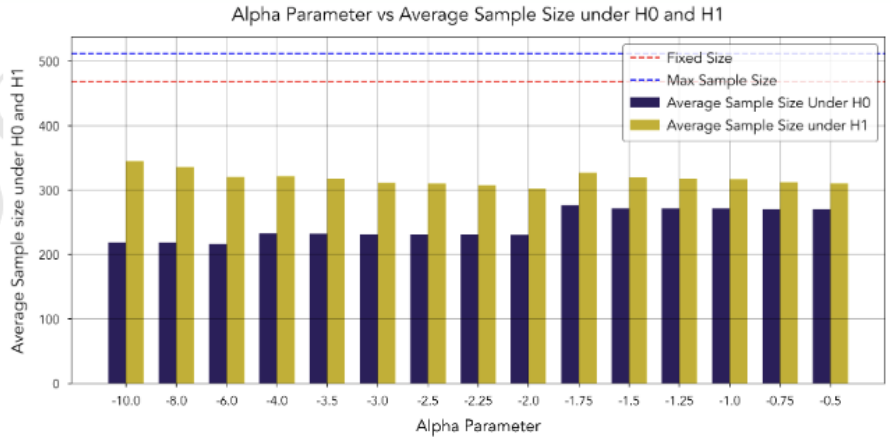
Computation

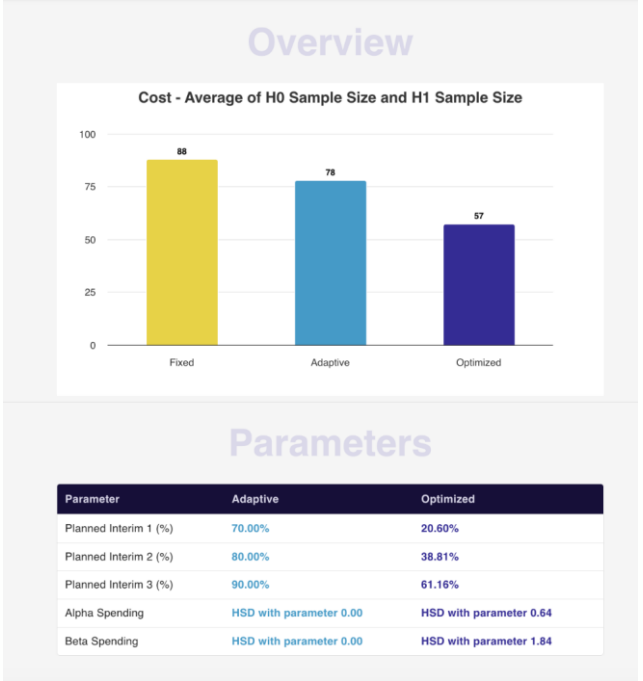
- Many Bayesian designs are not analytically tractable
  - Even “simple” models like the difference of two binomial variables
- Require extensive simulation using MCMC
  - Computationally taxing
  - Sequential (difficult to parallelize)
  - Not directly amenable to recent computation improvements ⟶ GPUs



Computation

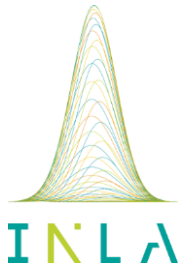
- Should we care?
  - No - the cost and time are negligible in the grand scheme
  - Of Course - prevents us from using in practical settings
    - Iterative process
    - Changing data
    - Optimization

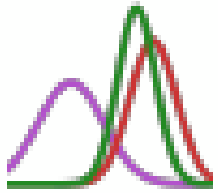




Computation - Cont.

- Potential solutions:
  - Stan/Turing/Pymc:
    - Algorithms - HMC, NUTS etc.
    - Code - technical innovation
    - Stochastic Gradient MCMC
  - Approximate Bayesian inference
    - INLA
    - Others
  - Machine learning
    - New methods using ML to optimize MCMC



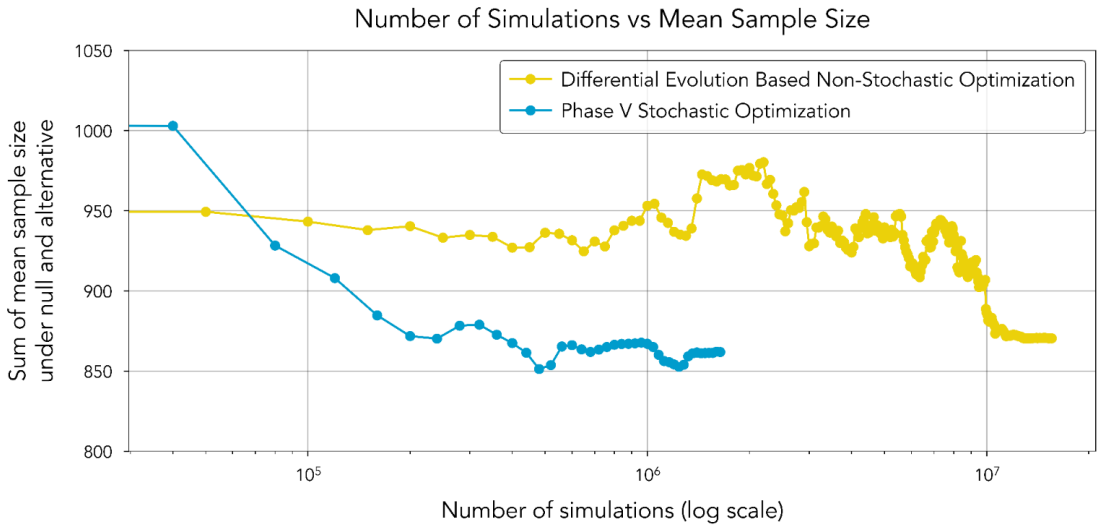


PhaseV Stochastic Optimizing Algorithm for Bayesian Designs

- Complex Bayesian trial designs have many possible tunable parameters (sample sizes for various trial stages, efficacy and futility stop criteria, etc.).
- Goal: Find parameters satisfying both frequentist (e.g., type I error rate) and bayesian operating characteristics, while minimizing the trial cost (e.g., mean sample size).
- Calculation is based on heavy simulation, limiting the search space.
- PhaseV stochastic optimization algorithm utilises local information to find close to optimal design parameters, while minimizing the number of simulations.

$$\log(\hat{\bar{n}}) + C_1(\hat{\alpha} - \alpha)^2 + C_1(\hat{\beta} - \beta)^2 + C_2 I_{\hat{\alpha}>\alpha} + C_2 I_{\hat{\beta}>\beta}$$

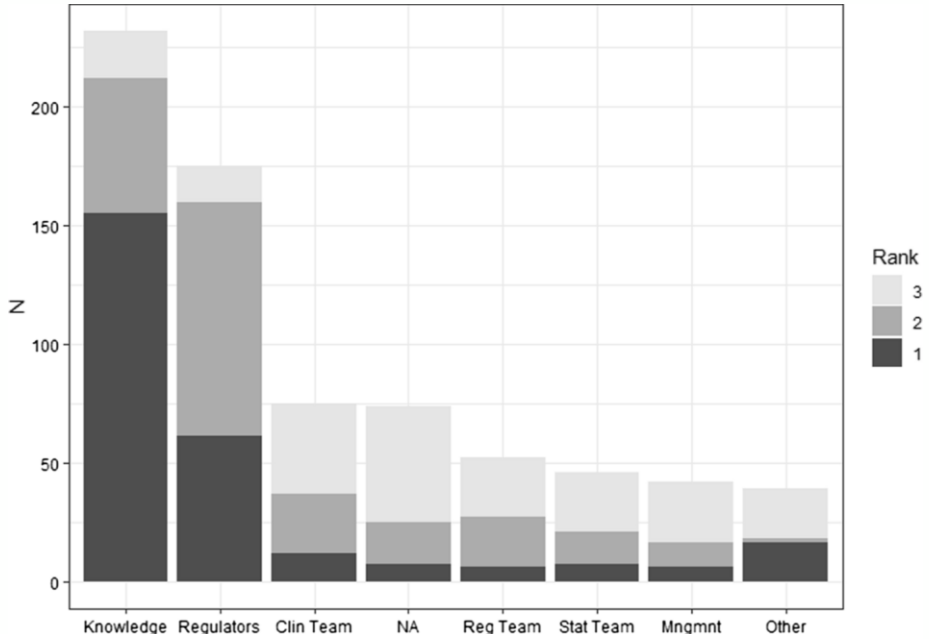
$\hat{\bar{n}}$: predictive mean sample size, $\hat{\alpha}$: predictive type I error, $\hat{\beta}$: predictive type II error



Knowledge & Trust

"*All these Bayesian experiments… Nobody understands whats going on in them. Give me bigger simpler trials.*", Josh Angrist

- Surveys on Bayesian methods have repeatedly identified knowledge and familiarity as the key challenges in adopting Bayesian methodology
- Even among most statisticians (let alone clinicians), Bayesian methods are not well understood and practical experience is limited



Why are not There More Bayesian Clinical Trials? Perceived Barriers and Educational Preferences Among Medical Researchers Involved in Drug Development. *Ther Innov Regul Sci* **57**, 417–425 (2023).

Knowledge & Trust

- What can be done:
  - Educational resources:
    - Conferences and Workshops
    - Tutorial papers
    - BLOG posts (Gelman, Harrell…)

Bayes

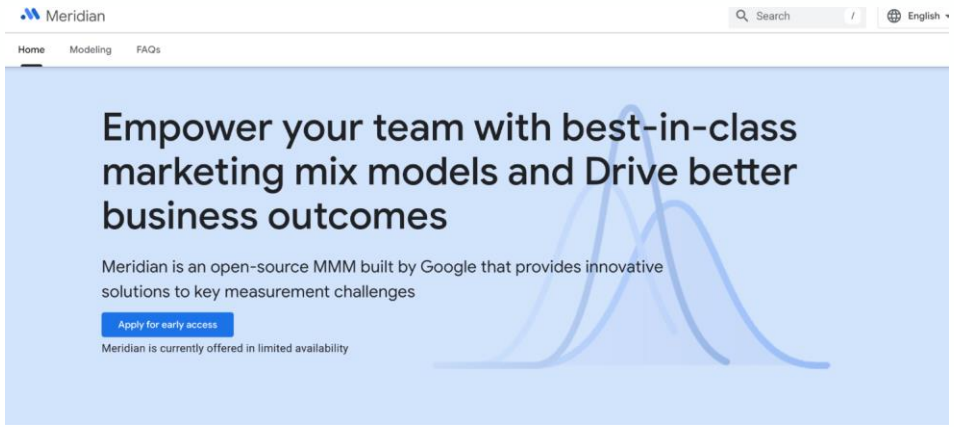
Application of Bayesian approaches in drug development: starting a virtuous cycle

Stephen J. Ruberg,[1] Francois Beckers,[2] Rob Hemmings,[3] Peter Honig,[4] Telba Irony,[5] Lisa LaVange,[6] Grazyna Lieberman,[7] James Mayne,[8] and Richard Moscicki[8]

A Tutorial on Modern Bayesian Methods in Clinical Trials

Natalia Muehlemann,[1] Tianjian Zhou,[2] Rajat Mukherjee,[3] Munshi Imran Hossain,[1] Satrajit Roychoudhury,[4] and Estelle Russek-Cohen[5]

  - Software & Tools
    - Useful and intuitive tools can make a substantial difference
      - Approachable by a wide range of Users

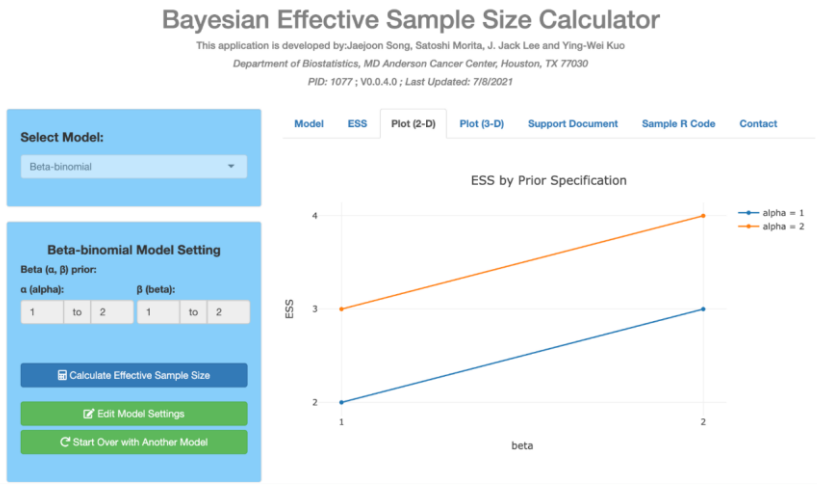


Google Meridian

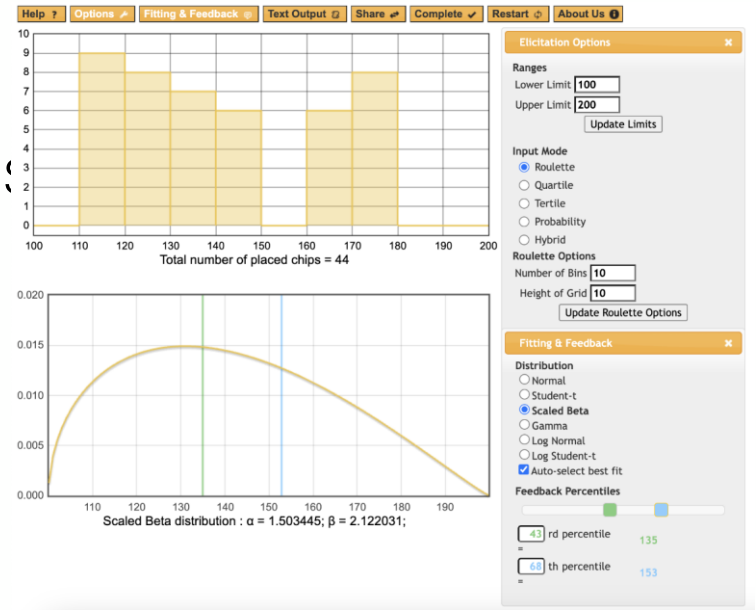
Tools

- Lack of easy to use tools across the board:
  - Prior Solicitaion
  - Sample Size Calculation
  - Result Analysis

→ Multiple R Shiny apps lacking unified tool and standards



Bayesian Effective Sample Size Calculator, MD Anderson



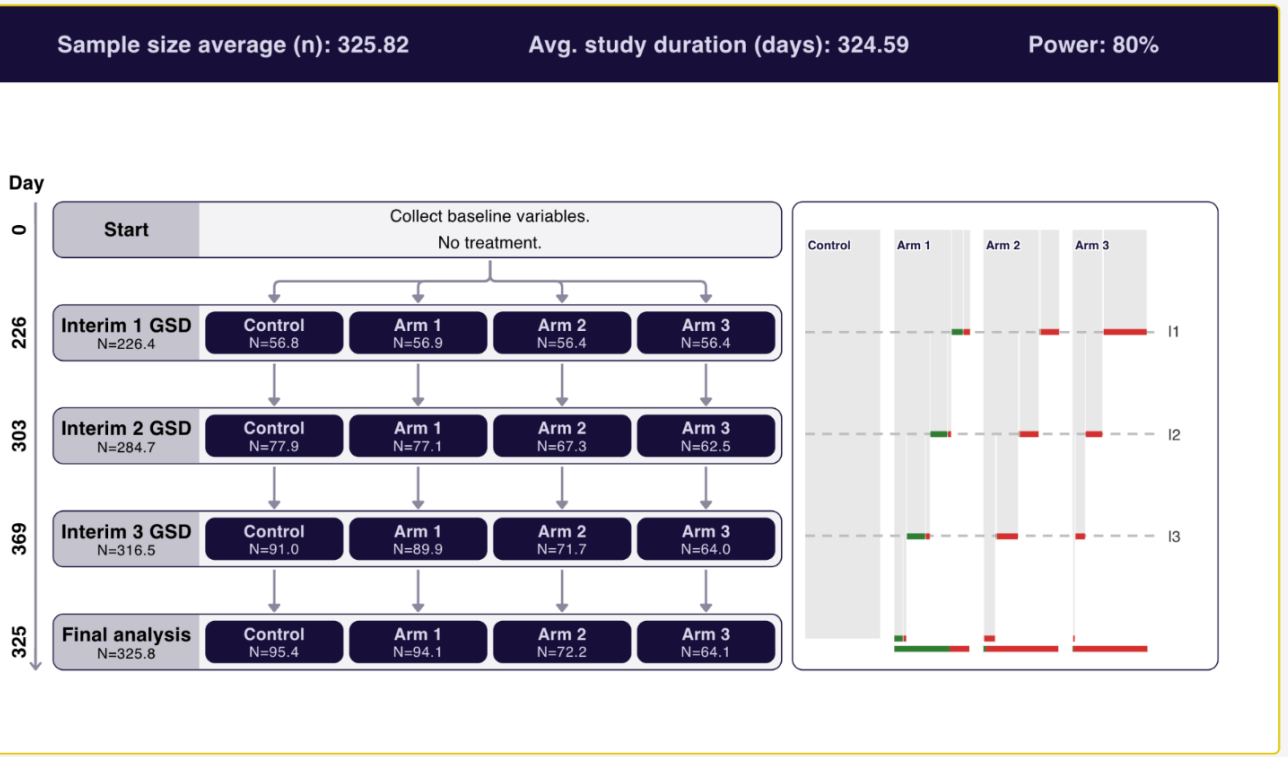
MATCH Uncertainty Elicitation Tool, Nottingham University

Tools - Cont.

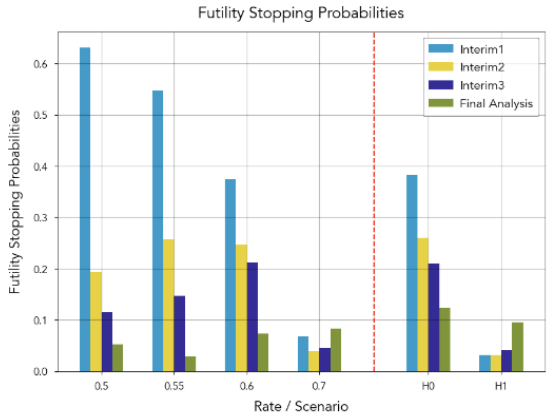
- Our challenges:
  - User Unterface (UI):
    - Expressivness - How much freedom should we give the user? What about non-experts?
    - BYOD - Bring your own data - Support customer data as input (informative prior)
    - Results visualization - should we / how to maintain frequentist / bayesian duality?
  - Intreactivity and Realtime:
    - Rapid iteration - maintain realtime interactive interface - make changes together in realtime
    - Optimization - search the parameter space

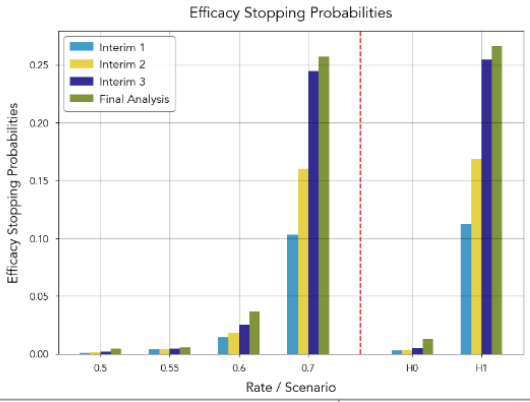
Use Case - Bayesian GSD with Multiple Arms

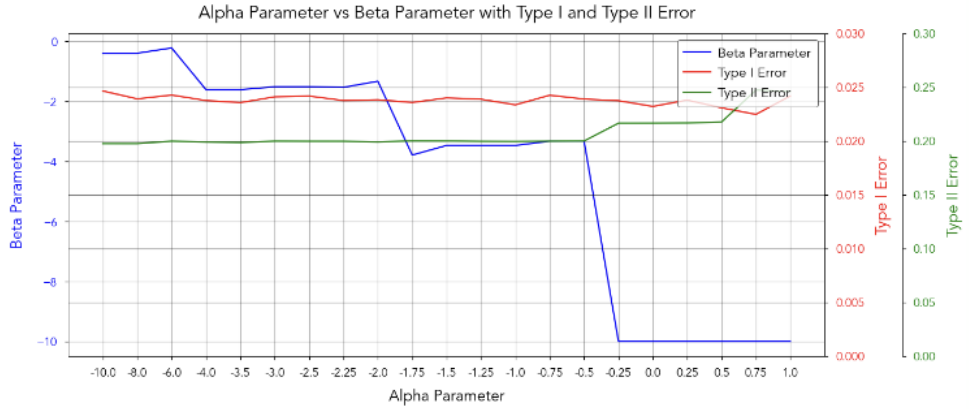
- Control - response 0.5
- 3 Treatment arms - 0.7, 0.6, 0.55
- Conjunctive Power (any arm)
- No Delay
- 3 Interims - 40%, 60%, 80%

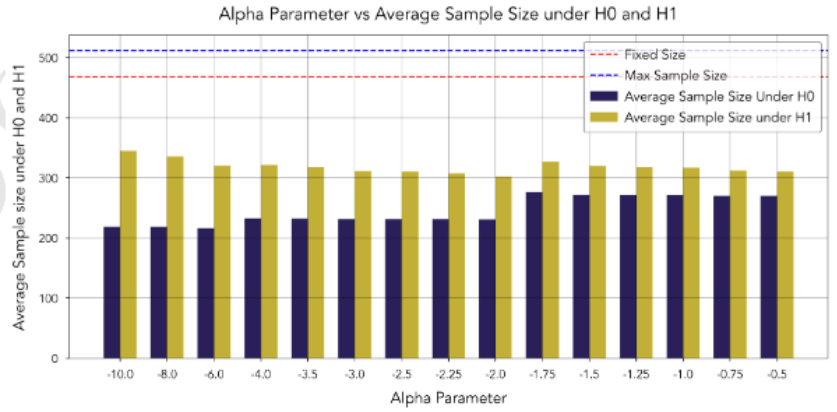


Use Case - Bayesian GSD With Multiple Arms









	Bayesian Design	Frequentist Design	Fixed
Sample Size | H1	302	325	480

Summary

- Bayesian Clinical Trials are growing in popularity
- Nonetheless there are still significant hurdles to overcome to support wide application
- Key challenges are:
  - Knowledge and familiarity
  - Computation and runtime
  - Existing tools and standardisation
- The challenges are strongly related:
  - Runtime and computation are key blockers to developing good tools
  - Good software can help dramatically with familiarity, knowledge and trust
- PhaseV is tackling the challenge on both ends:
  - Intuitive, responsive user friendly software
  - Technical innovation to decrease runtime and improve performance