Bayesian Clinical Trial Software Overview
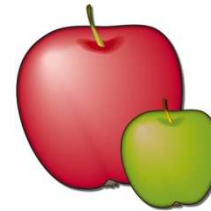
John D. Cook
M. D. Anderson Cancer Center

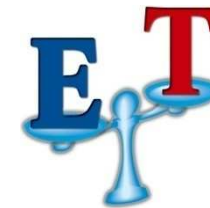# Software outline

Basic utilities

Safety monitoring

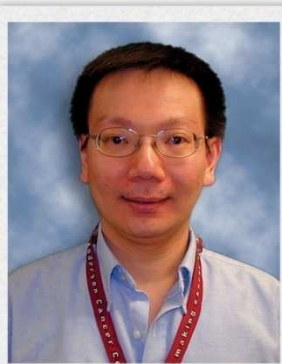Randomized trials

Dose finding

Software developers

Kyle Wathen

Hoang Nguyen

John Cook

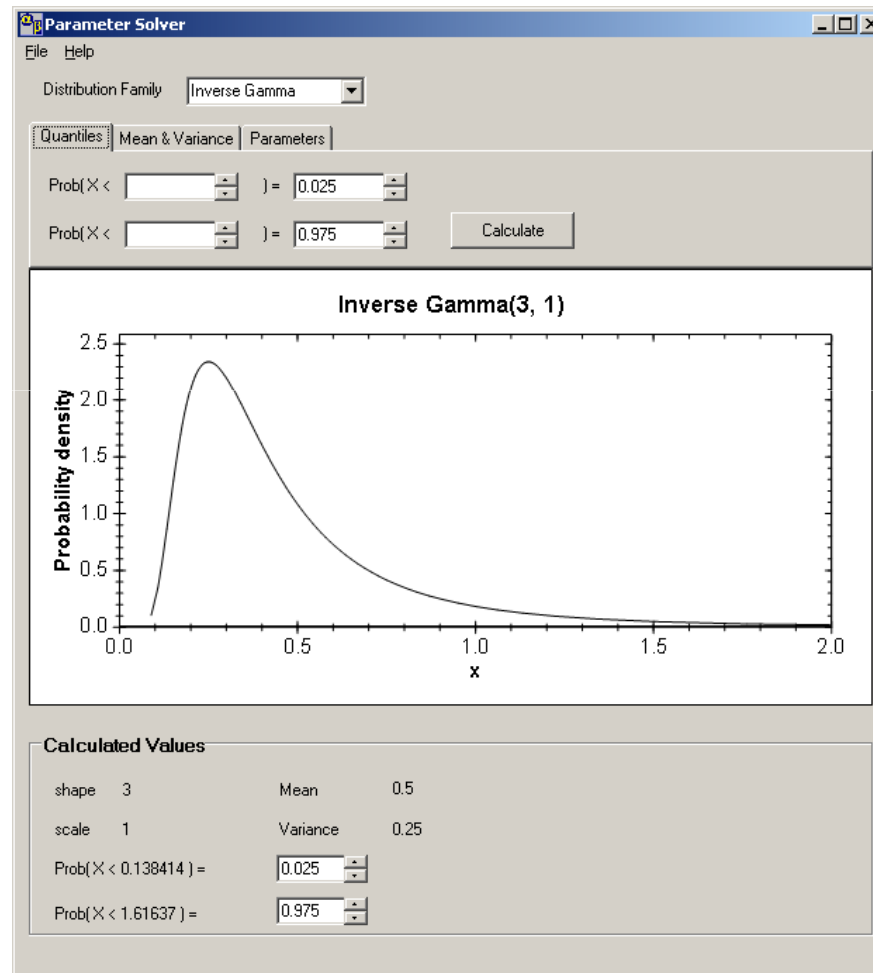Clift Norris

Leiko Wooten

Odis Wooten

Simplest distributions

- Discrete distribution: binary
- Conjugate prior: beta

- Time distribution: exponential
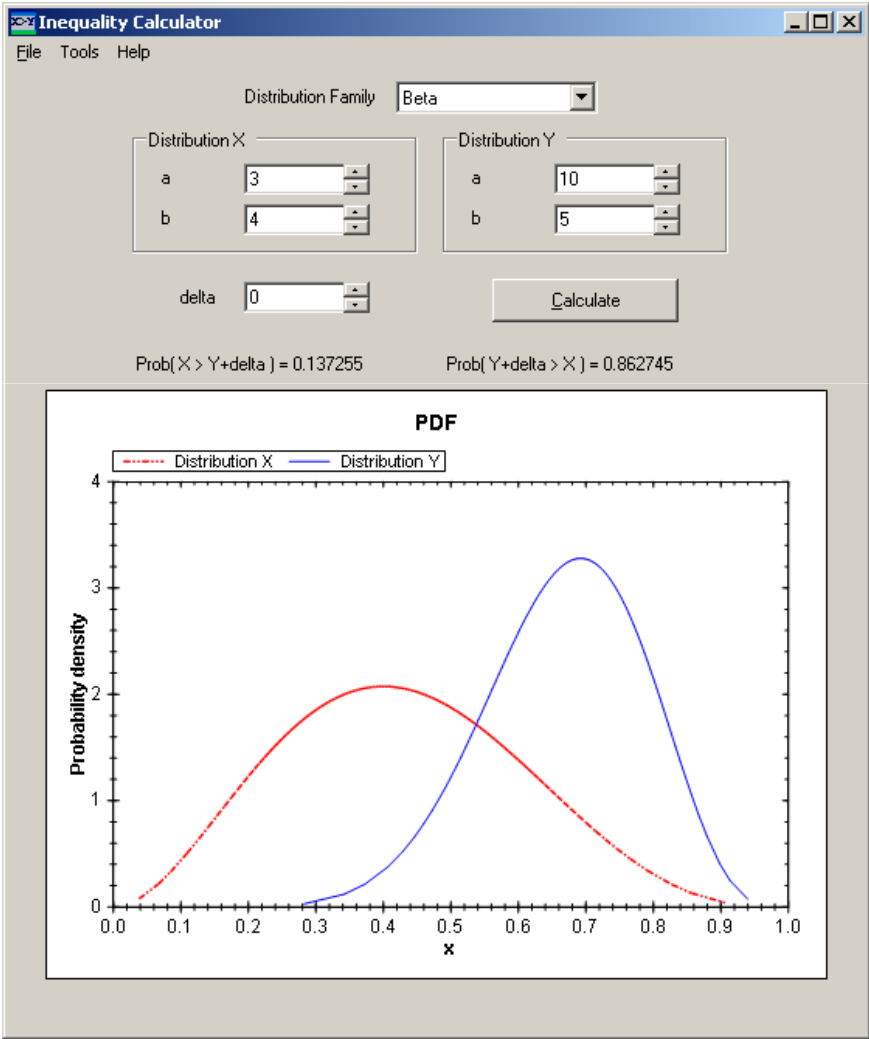- Conjugate prior: inverse gamma

Random inequalities

- $P(X > Y)$
- $P(X > Y + \delta)$
- Proportion: binomial / beta
- Mean time: exponential / inverse gamma
- Randomization probability
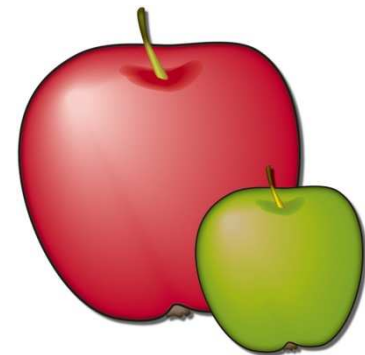- Stopping rule

Parameter solver

Inequality calculator

Multc Lean software

- Original software Multc99, developed by Hsi-Guang Sun
- Greatly simplified, added Windows UI
- Added trial duration simulation

TTEConduct software

- Table allows look-ahead:
  Not just "Should I stop?" but
  "What would cause the trial to stop?"

- NB: design in months, conduct in days

- Simulation software in development

Criticism of exp / IG model

- Exponential survival time model is usually a poor fit to reality. Hazard not constant.

- Exp / IG model chosen for convenience (conjugate, trivial posterior calculation)

- Nevertheless, model robust in practice (Thall and Wooten)

What's going on?

- We're not modeling survival per se, we're making a stop/go decision.

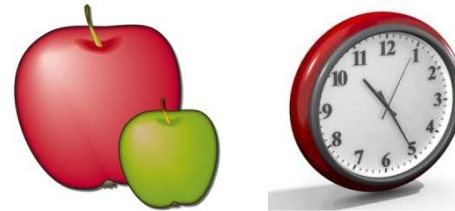- Survival isn't exponential but a continuous mixture of exponentials.

Monitoring with Bayes factors

- Not based on random inequalities
- Alternative must really be alternative
- Better operating characteristics
- Command line software

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Stop for futility:
Predictive Probability

- Binary and time-to-event outcomes

- Three decisions: A, B, neither

- If P(neither) is large, stop for futility

Pred Probs

Adaptive Randomization

- Randomize, but not equally
- Increase the probability of assigning what appears to be the best treatment
- Compromise between equal randomization and myopic optimization

Tuning parameter c

Let $p_A = P(\pi_A > \pi_B)$ and $p_B = P(\pi_B > \pi_A)$.

Assign treatment A with probability

$$\rho = \frac{p_A^c}{p_A^c + p_B^c}$$

Special values of c

- If $c = 0$, $\rho = 0.5$.
  Equal randomization

- If $c = 1$, $\rho = p_A$.
  Common choice (proposed in 1933!)

- As $c \rightarrow \infty$, $\rho \rightarrow [\, p_A > p_B \,]$
  Myopic optimization

- See tech report for all values of c

Adaptive Randomization software

- Supports binary and TTE outcomes
- Up to 10 arms
- Equal randomization special case

CRMSimulator software

- Emphasis on ease-of-use, not generality

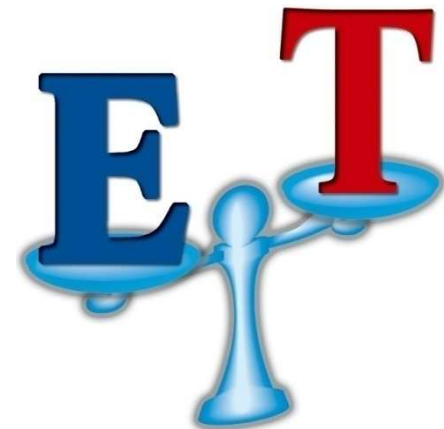- Contains features commonly used at MDACC, and no more
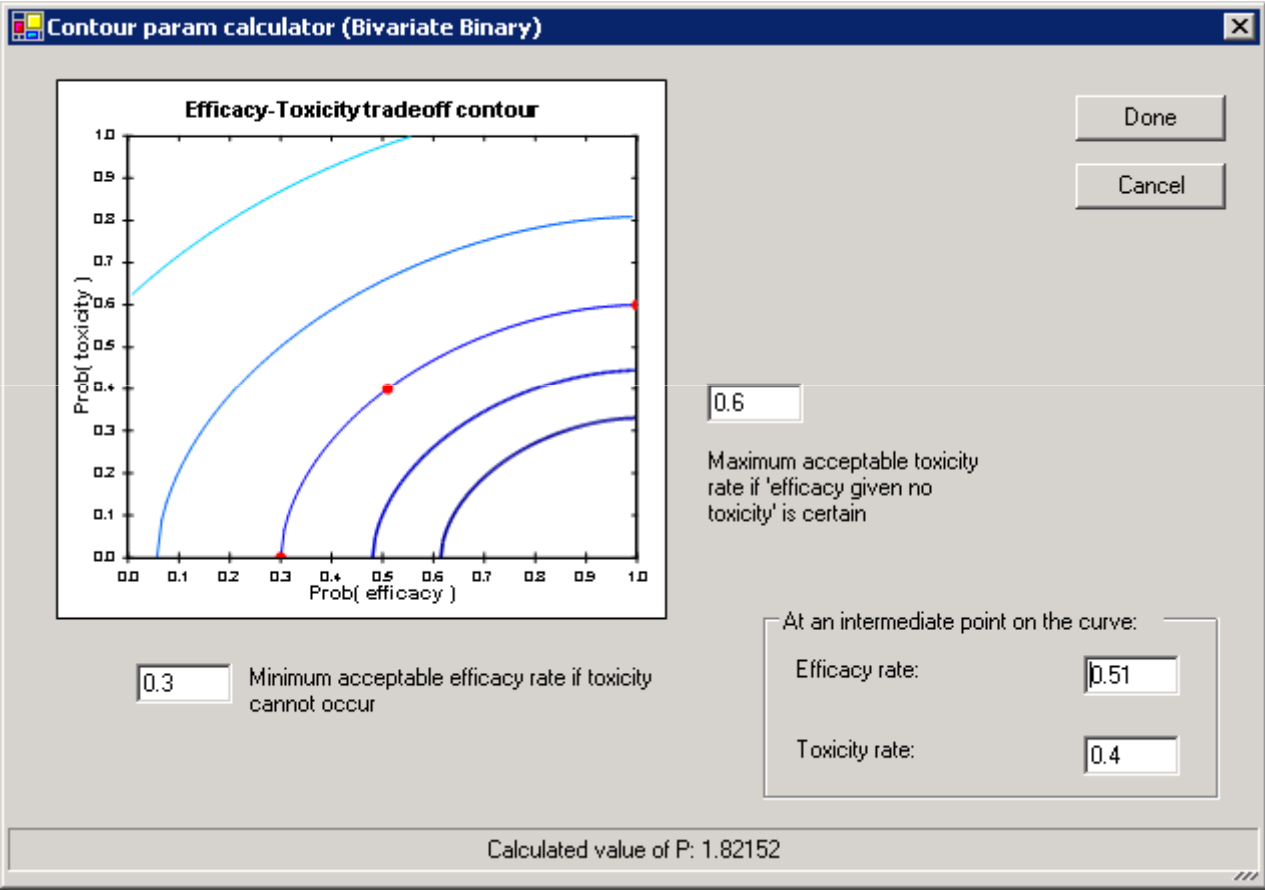
CRM misunderstandings

- Not "dose *escalation*"

- Law of small numbers

- Doesn't fit 3+3 expectations

EffTox dose-finding

- Minimize toxicity, maximize efficacy

- Investigator specifies trade-off

- Uses twice as much data per patient

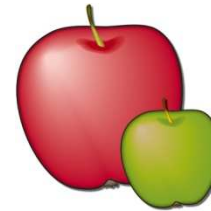- Uses dose *values*, not just dose *order*
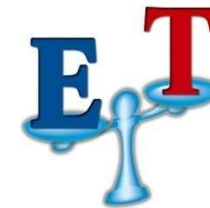
Heart of the method

Software summary

Basic utilities

Safety monitoring

Randomized trials

Dose finding

Links

- https://biostatistics.mdanderson.org/ SoftwareDownload/

- http://www.JohnDCook.com