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Adaptive Designs for Balancing Complex Objectives

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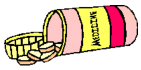
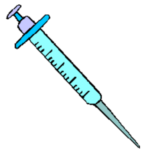
OUTLINE

√ Simple problem of determining the better of two therapies

 ??? 

√ Discuss potential problem constraints — e.g.

- ⋆ Costs for time, subject, failures, errors

√ Present response-adaptive approaches:

- ⋆ using accrued data
- ⋆ incorporating awareness of future decisions
- ⋆ optimization vs. competing goals

√ Describe increasingly *intelligent* designs.

√ Results, references and comments ⟶ done!

Basic Model

Imagine 2 populations of Bernoulli response data that represent patient responses to treatment arms 1 and 2, (T_1, T_2).

From T_1 we get $X_{11}, X_{12}, \ldots \sim B(1, P_1)$ $\searrow$

Independent with $(P_1, P_2) \in \Omega = (0,1) \times (0,1)$

From T_2 we get $X_{21}, X_{22}, \ldots \sim B(1, P_2)$ $\nearrow$

Assume that we know we want a fixed total sample size of n.

What Do We Mean by Design?

- An experimental "design" is an algorithm that specifies how to allocate resources during the study.
- Note that we may require computer algorithms to generate the sampling algorithms that define our designs
- This is the case not only for certain adaptive designs discussed here, but also for such simple considerations as randomization.
- Given a model, an optimal design typically addresses a single *criterion*.
- But $\longrightarrow$ it may be desirable to *evaluate* a design on criteria for which it was not optimized . . .

  We may lose a bit of optimality on 1 criterion to achieve better trade-offs overall.

So What's Analysis?

- ⋆ A main part of analysis is deciding how to treat the resulting data.

- ⋆ A key focus of this talk is to show that one can *design* clinical trials using Bayesian methods, but still *analyze* the data using frequentist perspectives. *(Hardwick and Stout, 1999 "Path Induction")*

- ⋆ More generally, analysis involves evaluating general operating characteristics of a design. *(Error rates, distributions of interesting statistics, robustness to departures from assumptions, etc.)*

Back to our problem ⋯ SIMPLE GOAL

√ Terminal Decision: *Select T_1 or T_2 at end of trial.*

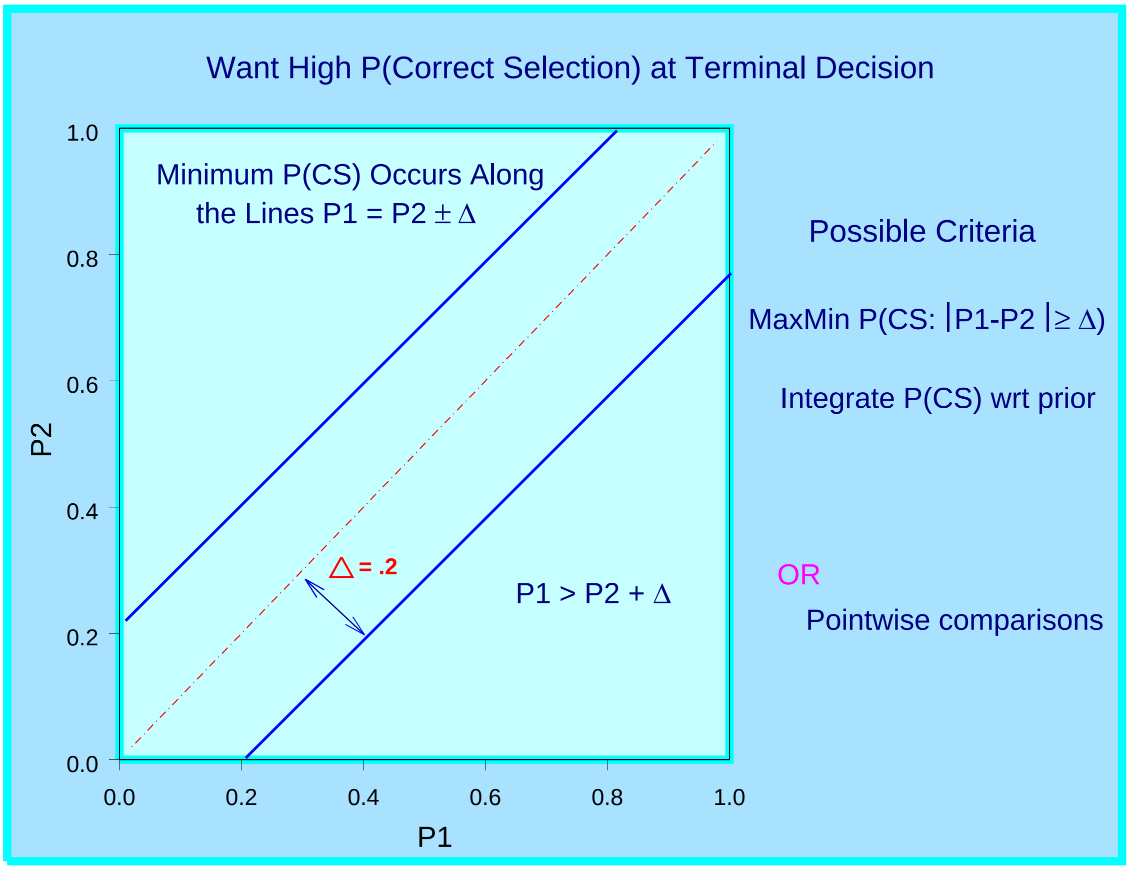
√ Goal: Select correctly for $|P_1 - P_2| \geq \Delta$; $\Delta > 0$ a clinically significant difference.

√ In classical allocation designs, it is usual to sample equally from the two treatment populations. This is EQUAL ALLOCATION (EA).

√ In general, **no** allocation procedure maximizes power under the alternative $H_A : |P_1 - P_2| \geq \Delta$, for all (P_1, P_2).

√ One approach is to restrict the notion of an optimal design.

- ⋆ $\max \min_{(|P_1 - P_2| \geq \Delta)}$ P(Correct Selection). *[For this EA is optimal.]*
- ⋆ $\mathbf{E}^{\xi}$[P(Correct Selection)], for ξ a prior distribution on (P_1, P_2)



Want High P(Correct Selection) at Terminal Decision
Minimum P(CS) Occurs Along the Lines P1 = P2 ± Δ
Δ = .2
P1 > P2 + Δ
P1
P2
0.0
0.2
0.4
0.6
0.8
1.0
Possible Criteria
MaxMin P(CS: |P1-P2 |≥ Δ)
Integrate P(CS) wrt prior
OR
Pointwise comparisons

Since EA is easy and can be useful for optimizing P(CS) in some special cases $\rightarrow$

$\mathcal{Q}$: Why extend beyond classical schemes?

$\mathcal{A}$: Most clinical trials have multiple objectives and EA rules may perform arbitrarily badly with respect to other trial criteria:

- $\rightsquigarrow$ Incorporate sampling costs: Valuable resources
- $\rightsquigarrow$ Minimize length of study: Time
- $\rightsquigarrow$ Limit patient suffering during the study: Ethics
- $\rightsquigarrow$ Induce balance within groups: Covariates
- $\rightsquigarrow$ Reduce variance of estimators: Inference

Alternatives? $\longrightarrow$ *Adaptive Designs*

$\mathcal{Q}$: What are *adaptive* sampling (allocation) designs?

$\mathcal{A}$: Sampling schemes that allow investigators to adjust resource expenditures *while the experiment is being carried out.*

$\mathcal{Q}$: Why is *adaptive* allocation better?

$\mathcal{A}$:
- $\leadsto$ Most interesting objective functions depend on parameters.
- $\leadsto$ These are unknown or the solution would be trivial.
- $\leadsto$ Adaptive designs use accruing results to estimate parameters and guide future allocations.

$\mathcal{Q}$: Are there problems associated with *adaptive* designs?

$\mathcal{A}$: $\rightsquigarrow$ Analytically, the data that arise from adaptive designs are less friendly than those we get from fixed sampling designs.

$\rightsquigarrow$ Sample sizes tend to be random variables and the obs are not necessarily independent $\Longrightarrow$ unknown sampling distributions for standard statistics.

$\rightsquigarrow$ Historically, analysis of adaptive designs has been based on asymptotic approximations $\Longrightarrow$ may not apply well in practice.

$\rightsquigarrow$ In our work, we generally use computers to carry out exact evaluations of interesting quantities *(Hardwick and Stout, 1995)*.

$\rightsquigarrow$ However, simulations are becoming more and more popular as methods for evaluating *(and even designing)* adaptive designs. *[V. Dragalin's Sim Toolkit!]*

A Simple Adaptive Design

- ⋆ Suppose we're interested in a secondary criterion of *patient survival* during the trial.
- ⋆ Measure this by E[Successes Lost]=$[n \times \max\{P_1, P_2\} - \#\ \mathit{Failures}]$
- ⋆ This suggests sampling more often from the better treatment.
- ⋆ An intuitive way to do this is to Play the Winner (PW): If the last response was a success, allocate the next patient to the same treatment, otherwise switch.
- ⋆ Note that PW uses only the information in the last observation to make the next decision.

Using More Information

- Another intuitive strategy is called Myopic: Estimate the unknown parameters using all observed data and allocate the next patient to the treatment that has the highest *expected success rate*.
- Myopic rules are *aka* One Stage Look Ahead (1SLA) rules.
- Both Myopic and PW strategies have the advantage of being simple to compute.
- But we can do better if we think about the future as well as the past.

Two-Arm Bandit Problem

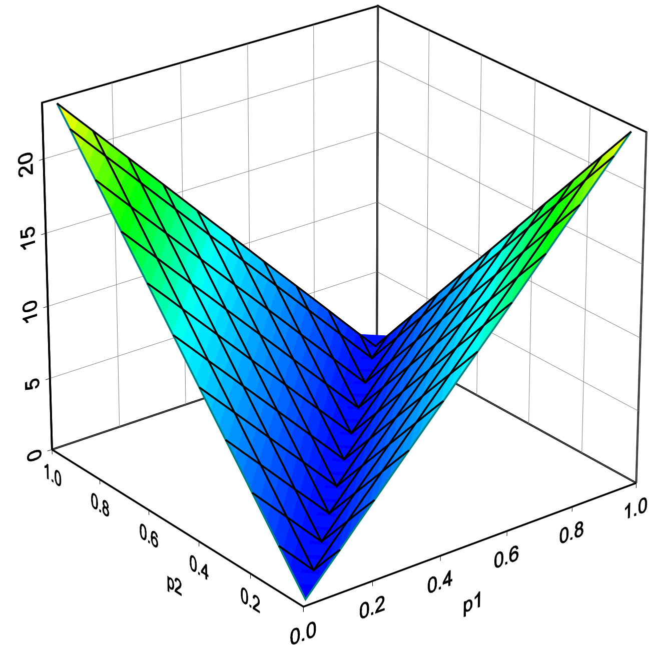
This is basically a problem in optimal learning theory.

- √ Slot machine with two arms
- √ At pull i, you win $r_i = 0$ or 1
- √ Win w.p. P_1 on Arm 1 & P_2 on Arm 2
- √ You get n pulls

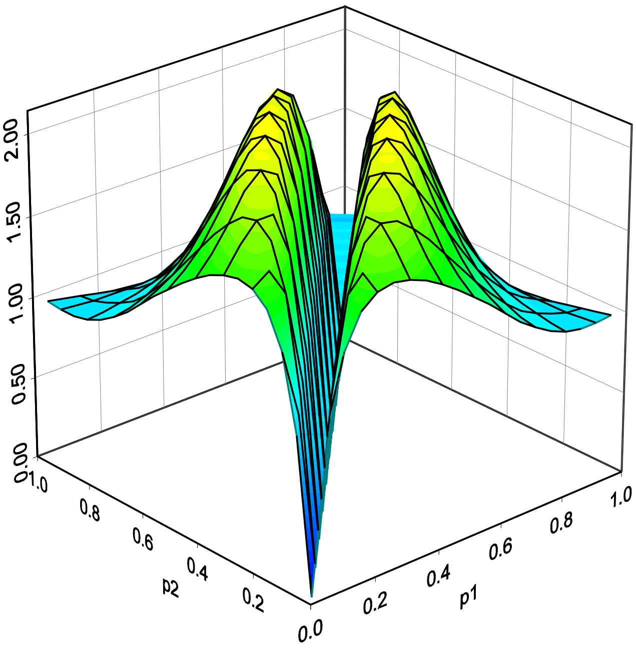
Pull Arm 1 or Arm 2 ??

Bandit solution is the optimal solution to the problem of choosing the arms to *maximize* your $\rightarrow$ E(total reward) = $E(\Sigma_1^n r_i)$

E(Successes Lost | EA)

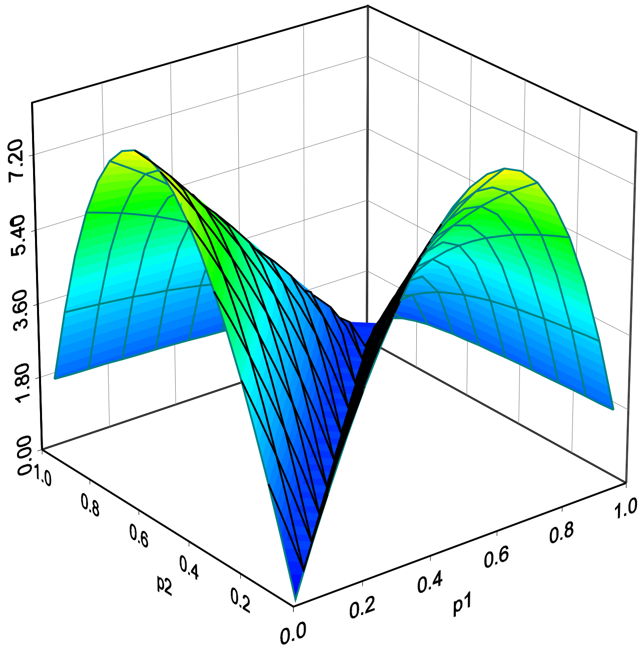


E(Successes Lost | B)

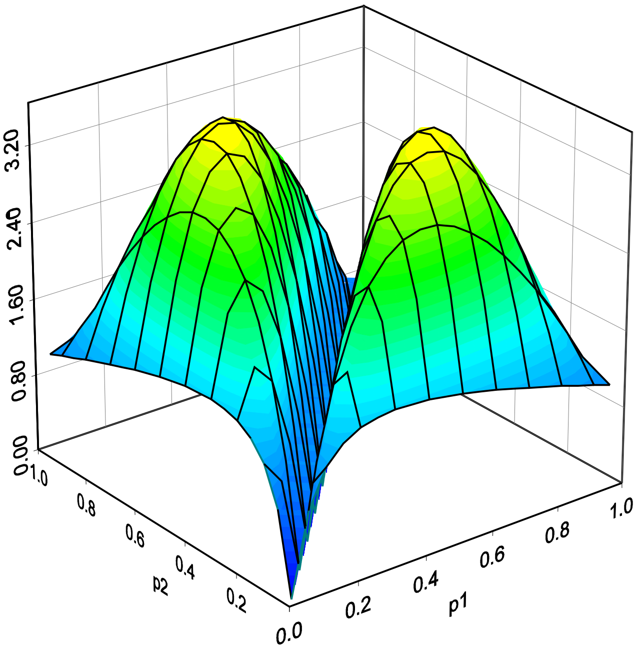


Uniform Priors for Bandit; n=50

E[Successes Lost | PW]



E[Successes Lost | MY]



n=50

Technicalities

Formulate as Bayesian decision theoretic problem.

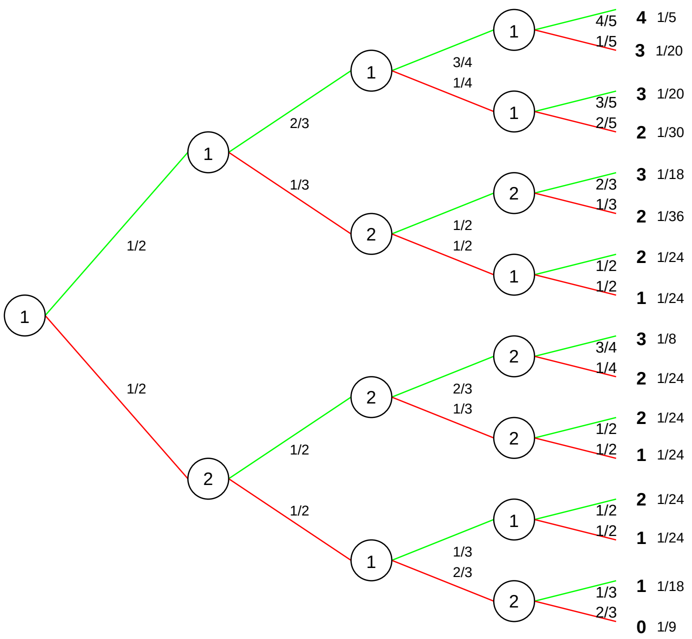
Here use beta prior distributions on (P_1, P_2).

Solution is obtained using Dynamic Programming (DP)

For k arms, DP solution requires computational space and time of $\frac{n^{2k}}{(2k)!}$

Looking Forward

For a sample of size n: bandit solution $\equiv$ $n-$SLA rule. For $n = 4$:



Solving Bandit Problems

$$\text{Bandit Strategy} = \text{Black Box}\ ?$$

Heuristically $\longrightarrow$ Balancing immediate gain (myopic) vs. information gathering (exploration for potential future gain)

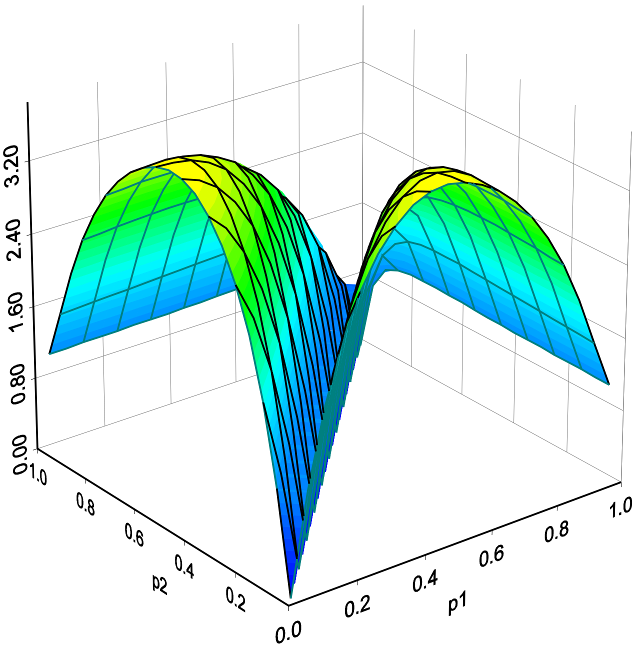
So, bandits minimize total harm to trial subjects $\longrightarrow$

But bandits become myopic near the end of a trial, maximizing successes but ignoring desire to also make good decision for post-trial patients.

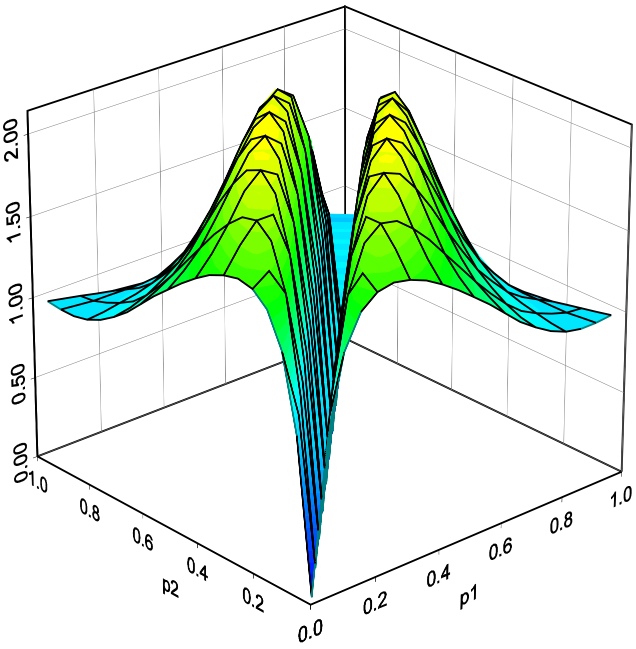
Incorporating Future Patients

- ⋆ To improve decision making, incorporate reward for future patients.
- ⋆ Assume patient k in the future is "worth" β^k, for some $0 < \beta < 1$
- ⋆ Elegant theory for maximizing the total "discounted" reward: $\mathrm{E}(\Sigma_1^\infty \beta^i r_i)$
- ⋆ **Theorem:** For each arm, given prior and observations to date, compute its *Gittins Index* (GI) , pull arm of highest index. *(Gittins and Jones, 1974)*
- ⋆ GI is infeasible to compute. Lower bound works well in practice even when applied to finite sample size problems: β acts as control parameter for n.
- ⋆ Allocation based on the approximate GI is $\rightarrow$ Modified Bandit (MB) *(Hardwick, 1986, 1995)*

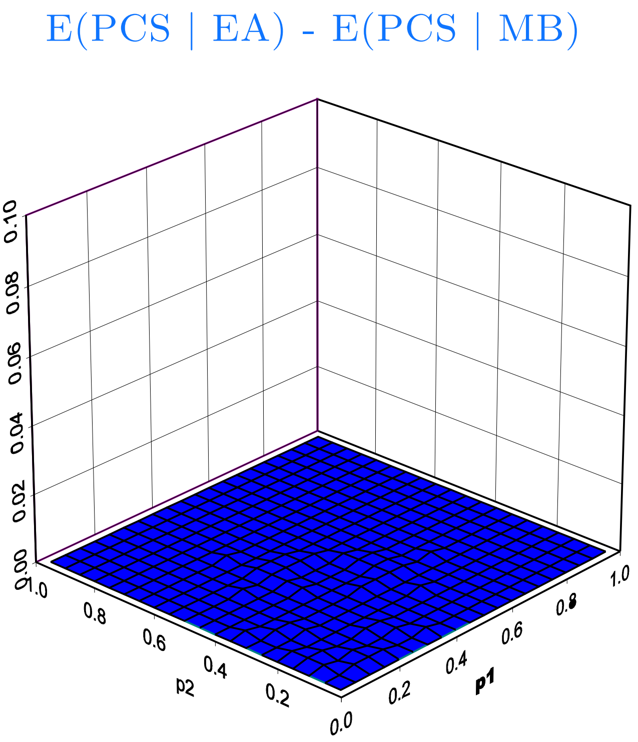
E(Successes Lost | MB)

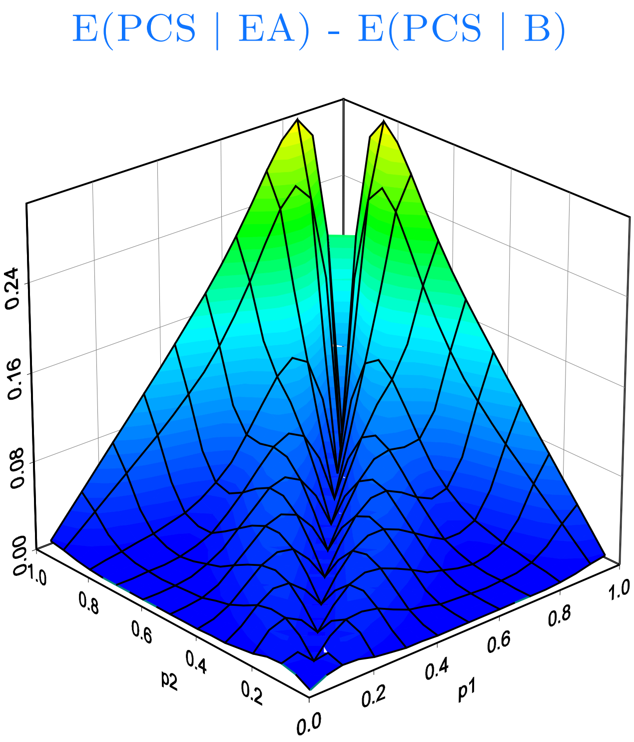


E(Successes Lost | B)



Uniform Priors for Bandits; n=50, $\beta = 0.99999999$





Uniform Priors for Bandits; $\beta = .99999999$ for MB; $n = 50$

Summary of Design Objectives

Equal Allocation Maximize information about both arms (maximin), no notion of reward nor of when trial stops

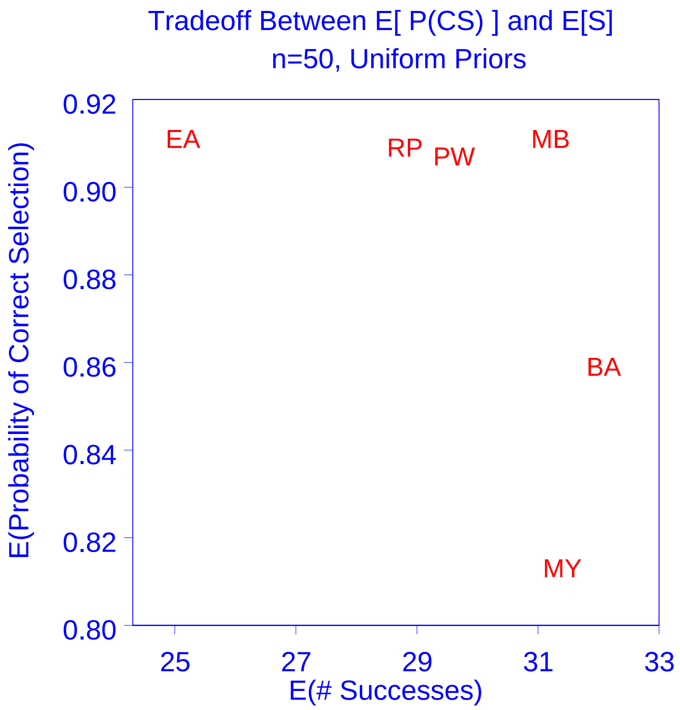
Myopic Maximize reward assuming trial stops immediately. No need to gather information.

Bandit Maximize reward assuming trial is all. Gather enough information to insure greatest total reward in n trials.

Modified Bandit Maximize reward assuming trial goes on forever, as if to gather information for an infinite future.

Summary Measures

Values shown are integrated wrt uniform priors



EA Equal Allocation

PW Play the Winner

MY Myopic

RP Randomized PW

BA Bandit

MB Modified Bandit

COMMENTS/FUTURE RESEARCH

Adaptation is good.

- √ Does extremely well on more than one objective when not seeking *complete* optimization on one of them.
- √ There are numerous ways to approach problems adaptively.
- √ Often worth it to trade off optimality for better intuition and design simplicity.
- √ Useful to evaluate the designs for robustness.

⟶ Designs are applicable for many problems. Examples we have worked on include adaptive designs to handle

- ⋆ Delayed responses
- ⋆ Censored data
- ⋆ Sampling in stages
- ⋆ Dose response models
- ⋆ Screening models

⟶ Future research to focus more on developing adaptive designs to handle

- √ classical hypothesis testing problems
- √ correlated arms — as in dose response models
- √ generally more complex models

Some Related Literature

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