Enrichment Designs for the Development of Personalized Medicines

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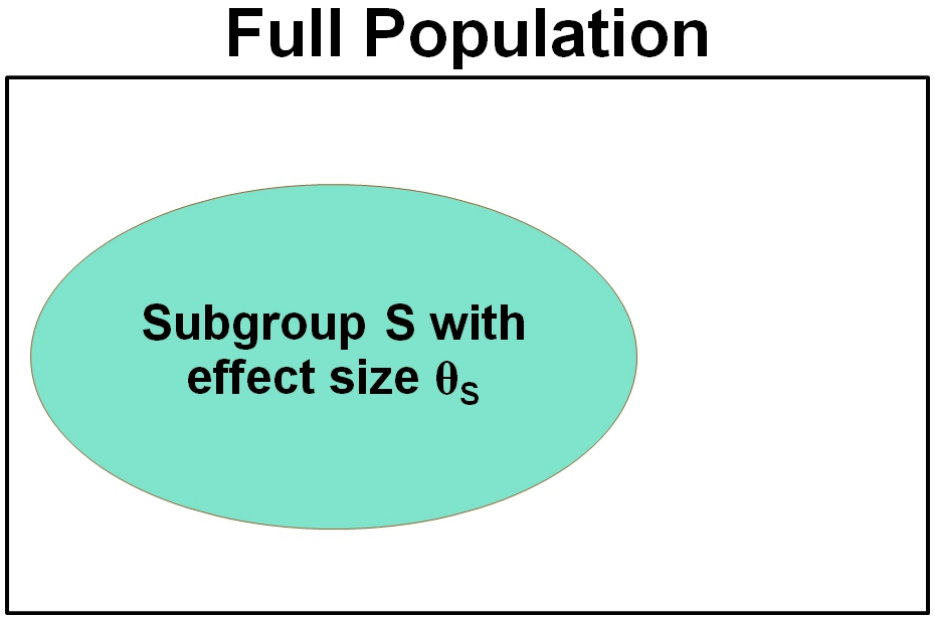
Identifying Target Populations

In recent years, clinical trials with more complex objectives, confirming treatment effects in sub-populations and/or in the overall populations, have raised more and more attention.

- The knowledge on the genetic basis of many diseases is increasing rapidly and therapies are developed that target underlying molecular mechanisms.
- Patients' responses are predicted to targeted treatments based on genetic features or other biomarkers.

Objective: Identify subgroups (based on biomarkers) where the treatment has a positive benefit risk balance.

Example



- Overall treatment effect

$$\theta_F = \lambda\theta_S + (1-\lambda)\theta_{S^c}$$

  where λ is the prevalence of subgroup S.
- Test the null hypotheses $H_F : \theta_F \leq 0$ and $H_S : \theta_S \leq 0$.
- If $\theta_{S^c} \ll \theta_S$ and the prevalence of the subgroup is small, the power to reject H_F is low.

Enrichment and Stratification Design

Enrichment Design: Randomize only patients of subgroup S (say Biomarker +). Patients of the complement S^C are excluded from the trial (Biomarker –).

Stratification Design: Include Biomarker + and Biomarker – patients. Stratify randomization by biomarker status.

- With both designs one can test H_S, i.e., for a treatment effect in the subpopulation.
- With the stratification design one can test in addition H_F.
- With equal overall sample size n, the enrichment design has a larger number of biomarker+ patients.

Testing Problem

- Parallel group comparison of the means of normal distributions.
- Total sample size n is chosen to detect an effect size Δ with a two sample one-sided z-test with $\alpha = 0.025$ and power of about 90%.

Enrichment Design:

- Test H_S with a z-test.

Stratification Design:

- Test H_S with a z-test
- Test H_F with a stratified z-test
- Correct for multiplicity with the Hochberg test.

To Enrich or not to Enrich?

- The power to reject any hypothesis depends on the effect sizes $\Theta = (\theta_S, \theta_{S^c})$
- Assume we suspect that $\theta_{S^c} \leq \theta_S$ but believe that $\theta_{S^c} > \theta_S$ is not plausible.
- Then, the enrichment design (recruiting only patients in S) always leads to the highest power:
  - If $\theta_{S^c} = \theta_S$ the enrichment design has the larger power than the stratification design using a multiple testing procedure.
  - If $\theta_{S^c} < \theta_S$ the enrichment design has larger power.

Thus, is enrichment always preferable?

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Thus, is enrichment always preferable?

Different Gains, different Costs...

The argument results from an oversimplification. The Power to reject any null hypotheses is not the only criteria.

- The stratification design tests the full population $H_F : \theta_F \leq 0$, demonstrating that the treatment works "on average".
- The enrichment design tests a limited null hypothesis $H_S : \theta_S \leq 0$ leading to a limited indication.
- Ethical problem if patients that may benefit are excluded.
- Enrichment maybe costly (e.g. due to longer patient recruitment, ...).

To account for these aspects we may use an approach based on utility functions.

The utility function approach

A sponsor view:

Rejection of	Gain
H_F	G_F
H_S only	G_S
none	0

$G_S \leq G_F$ (for example, $G_S = \lambda G_F$)

$$U_C(\Theta) = G_F P_\Theta(\text{reject } H_F) + G_S P_\Theta(\text{reject only} H_S)$$

A public health view:

θ_S	θ_{S^c}	Rejection of	Gain
+	+	H_F	G_F
+	+	H_S only	G_S
+	0	H_F	G_S
+	0	H_S only	G_S
0	0	H_S, H_F	0
0	0	None	0

$$U_P(\Theta) = G_F 1_{\{\theta_S, \theta_{S^c} > 0\}} P_\Theta(\text{reject } H_F) + G_S 1_{\{\theta_S, \theta_{S^c} > 0\}} P_\Theta(\text{reject only } H_S) + G_S 1_{\{\theta_S > 0, \theta_{S^c} \leq 0\}} P_\Theta(\text{reject } H_F) + G_S 1_{\{\theta_S > 0, \theta_{S^c} \leq 0\}} P_\Theta(\text{reject only } H_S)$$

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Bayesian expected Utility

If $G_S = G_F = 1$ then $U_C = U_P$ is equal to the power of rejecting any hypothesis.

Consider a prior π on $\Theta = (\theta_S, \theta_{S^c})$. Then the expected utilities are

$$U_{\pi,C} = E_\pi(U_C(\Theta)), \quad U_{\pi,P} = E_\pi(U_P(\Theta))$$

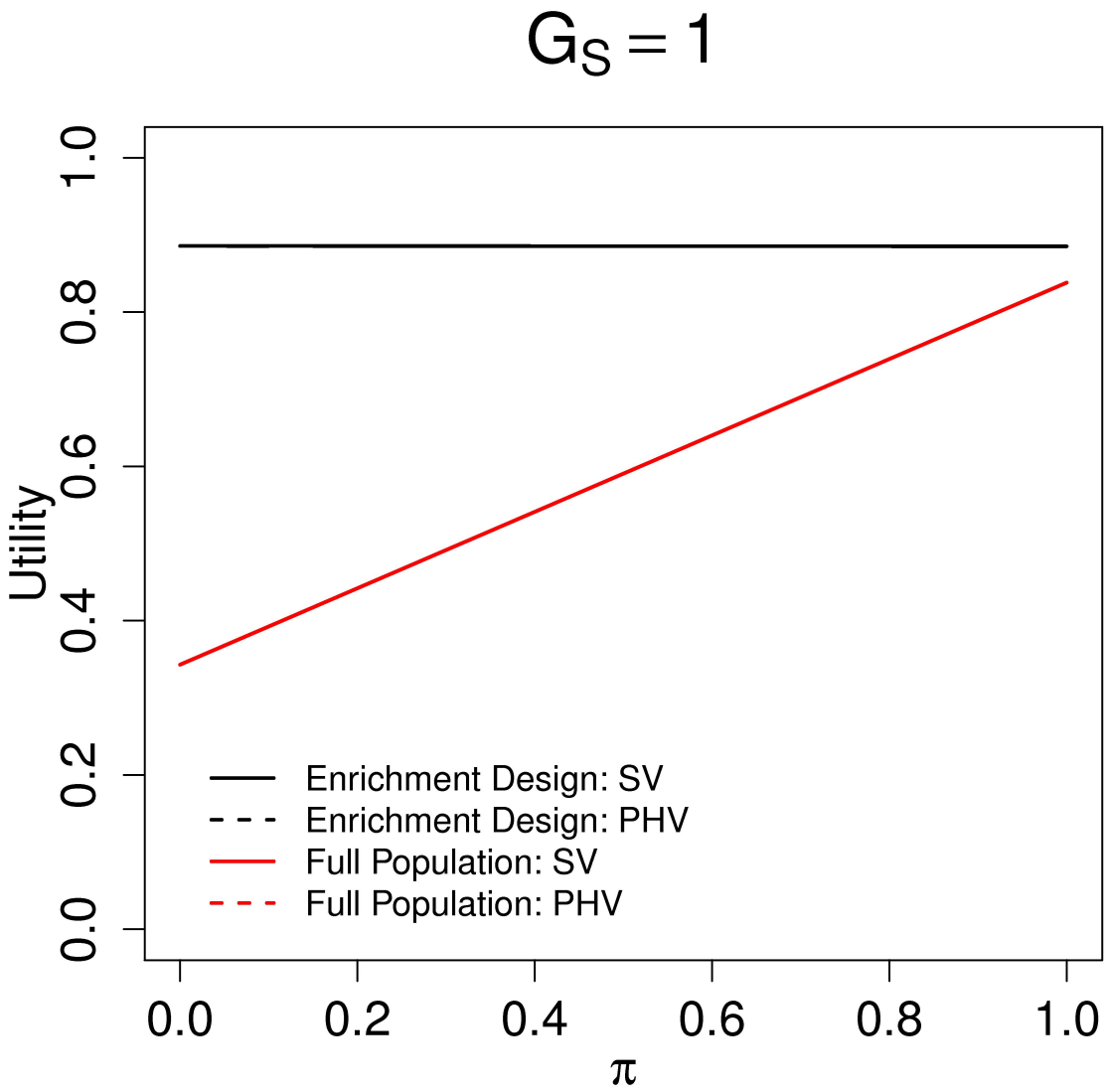
We use the simple prior

$$\begin{aligned} P\{\Theta = (\Delta, \Delta)\} &= \pi \\ P\{\Theta = (\Delta, 0)\} &= (1 - \pi) \end{aligned}$$

setting $G_F = 1$.

Utility for different Priors and Gains G_S

Prevalence $\lambda = 0.3$



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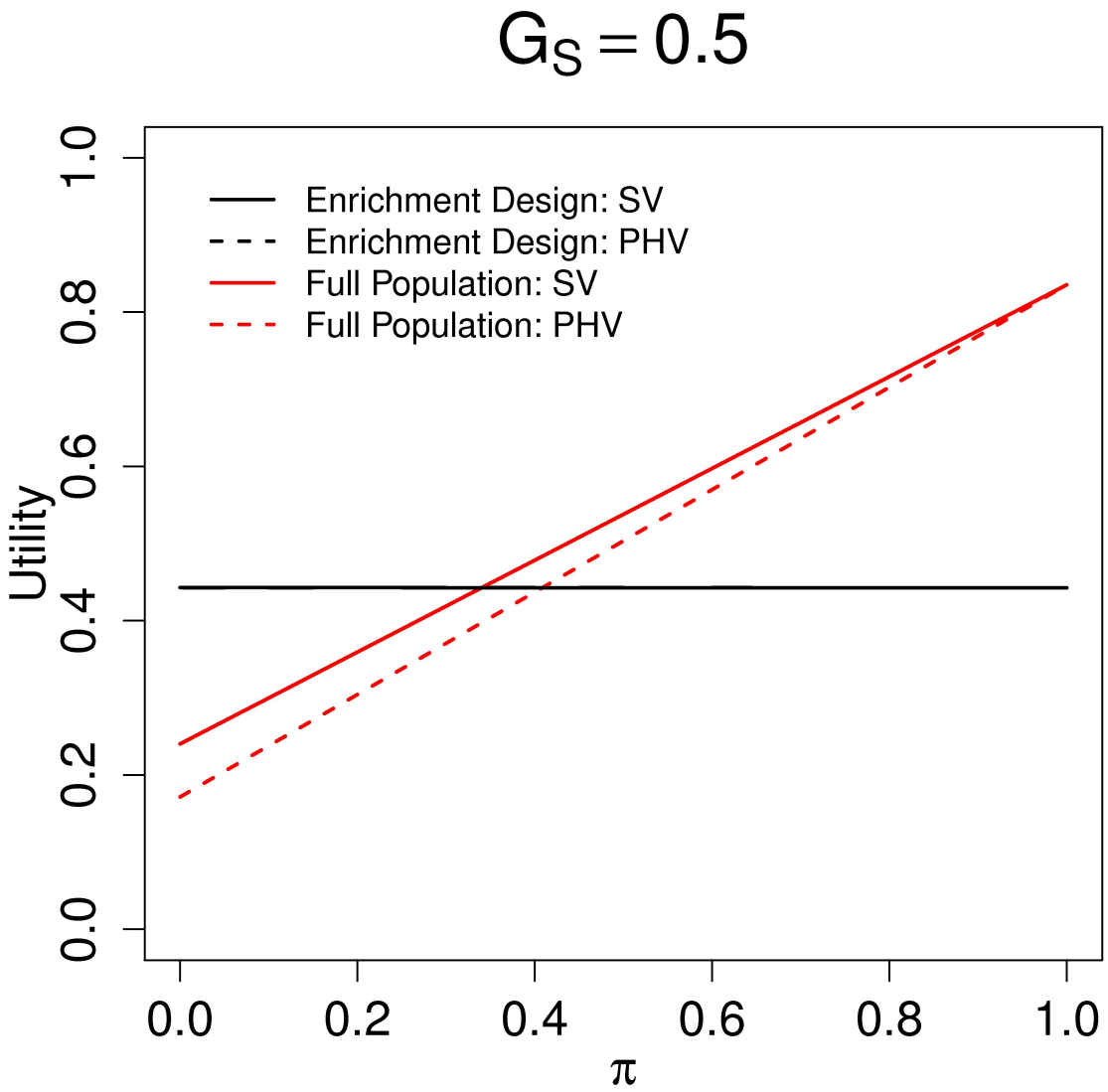

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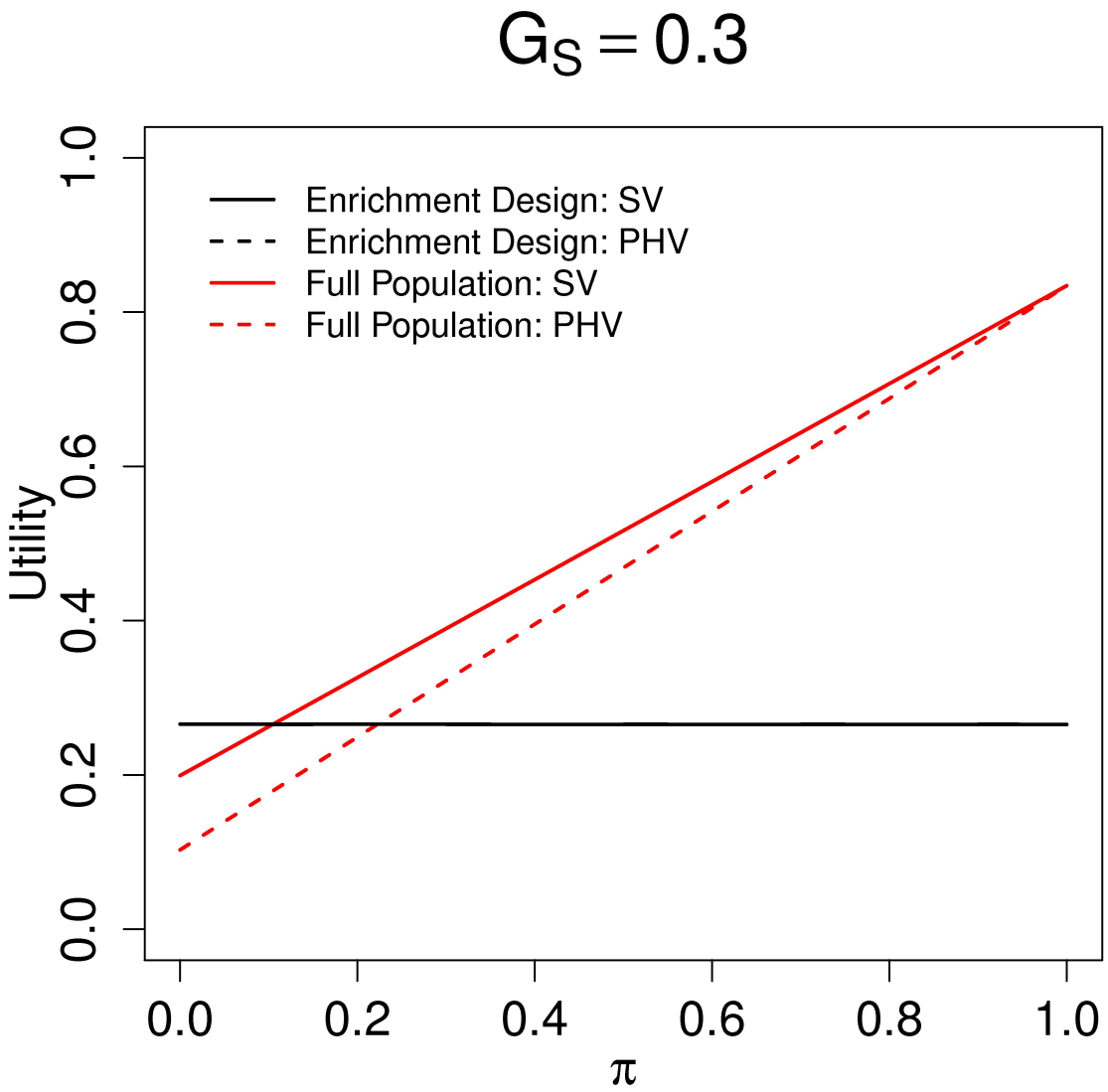
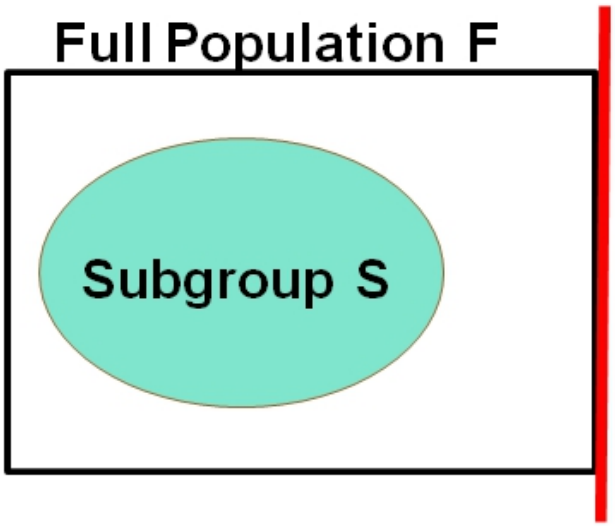


Adaptive Trials with Population Enrichment

Fixed Overall Sample Size: n

Sample size Stage 1:
F: $n_1 = r*n$
S: $\lambda * n_1$



Decision based on interim results:

→ Continue only with S
→ Continue with F
(testing both: F and S)

Interim Analysis
Planning of Second Stage
Subgroup Selection

- First stage data is used to choose the second stage population

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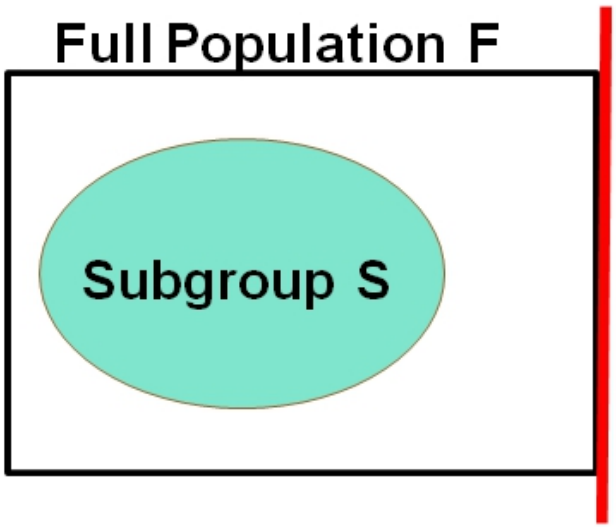

Example:

Decision based on the interim p-value p_{SC} of the Complement S^C

Introducing a „stopping-for-futility"-boundary α_C for S^C

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Adaptive Trials with Population Enrichment

Fixed Overall Sample Size: n

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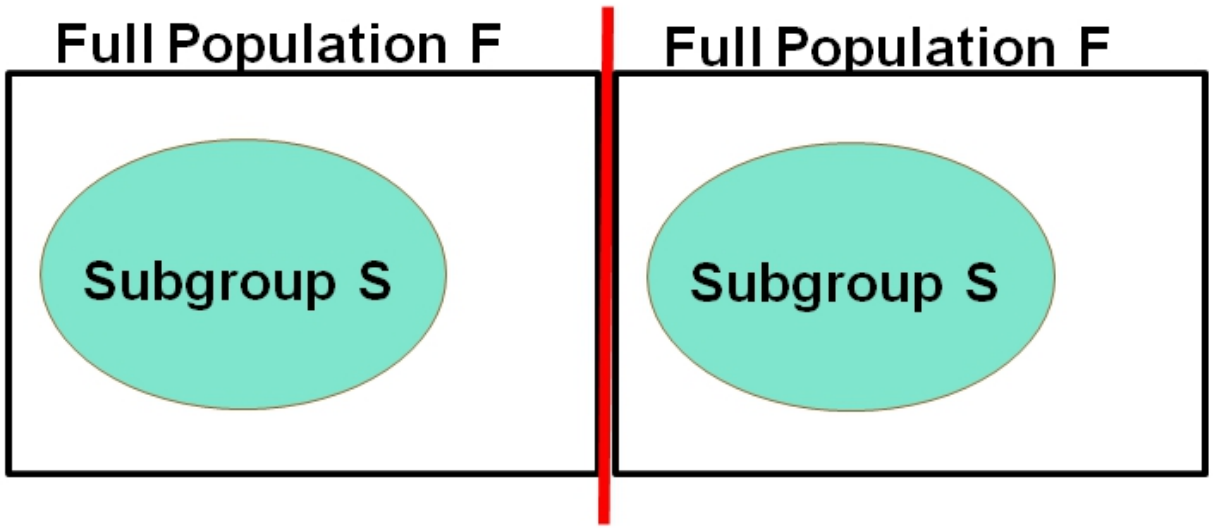
Sample size Stage 2:
F: $n_2 = (1-r)*n$
S: $\lambda * n_2$



- First stage data is used to choose the second stage population
- Efficacy is demonstrated with Stage 1 and 2 data

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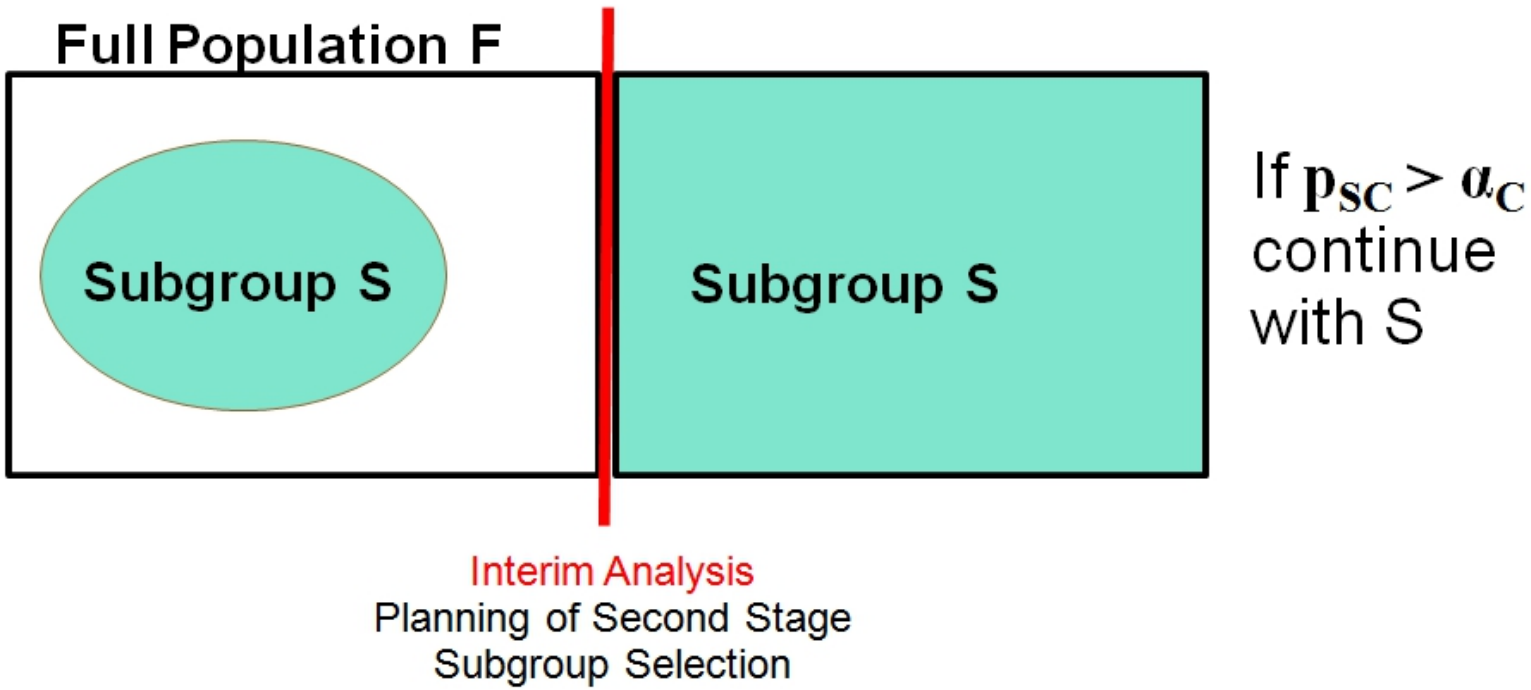

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The Adaptive Closed Test

- To control the family wise error rate apply the closure principle using adaptive combination tests at level α for

$$H_S, \quad H_F, \quad H_{FS} = H_S \cap H_F.$$

(Bauer and Kieser, 1999, Hommel, 2001)

- Reject $H_j, j \in \{S, F\}$ if H_{FS} and H_j are rejected at local level α.

Combination tests for elementary hypotheses H_S, H_F

- Compute stage wise p-values
  - First stage elementary p-values p_S, p_F
  - Second stage elementary p-values q_S, q_F (computed from second stage data only)
- Define a combination function $C(p, q)$ and critical value c such that for independent and uniformly distributed p-values

$$P(C(p, q) \leq c) = \alpha.$$

- Reject H_S if

$$C(p_S, q_S) \leq c$$

- If the trial continues in F, reject H_F if

$$C(p_F, q_F) \leq c,$$

otherwise retain H_F.

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Test of the intersection hypothesis $H_F \cap H_S$

- First stage p-value for $H_F \cap H_S$ with Simes test:

$$p_{FS} = \min[\max(p_F, p_S), 2\min(p_F, p_S)]$$

- Second stage p-value for $H_F \cap H_S$
  - If both populations are continued with Simes test:

$$q_{FS} = \min[\max(q_F, q_S), 2\min(q_F, q_S)]$$

  - If only H_S is selected:

$$q_{FS} = q_S$$

- Final Analysis: Reject H_{FS} if

$$C(p_{FS}, q_{FS}) \leq c$$

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The Adaptive Closed Test

Adaptive Closed Test

Reject $H_i, i \in \{F, S\}$ if

- $C(p_{FS}, q_{FS}) \leq c$ and
- $C(p_i, q_i) \leq c$.

- The population selection rule may depend on the interim data and external data in any way.
- The selection rule needs not to be specified in detail.
- Sample sizes may be adapted based on unblinded interim data
- The familywise error rate is controlled in the strong sense.

Adaptation Rule: Example

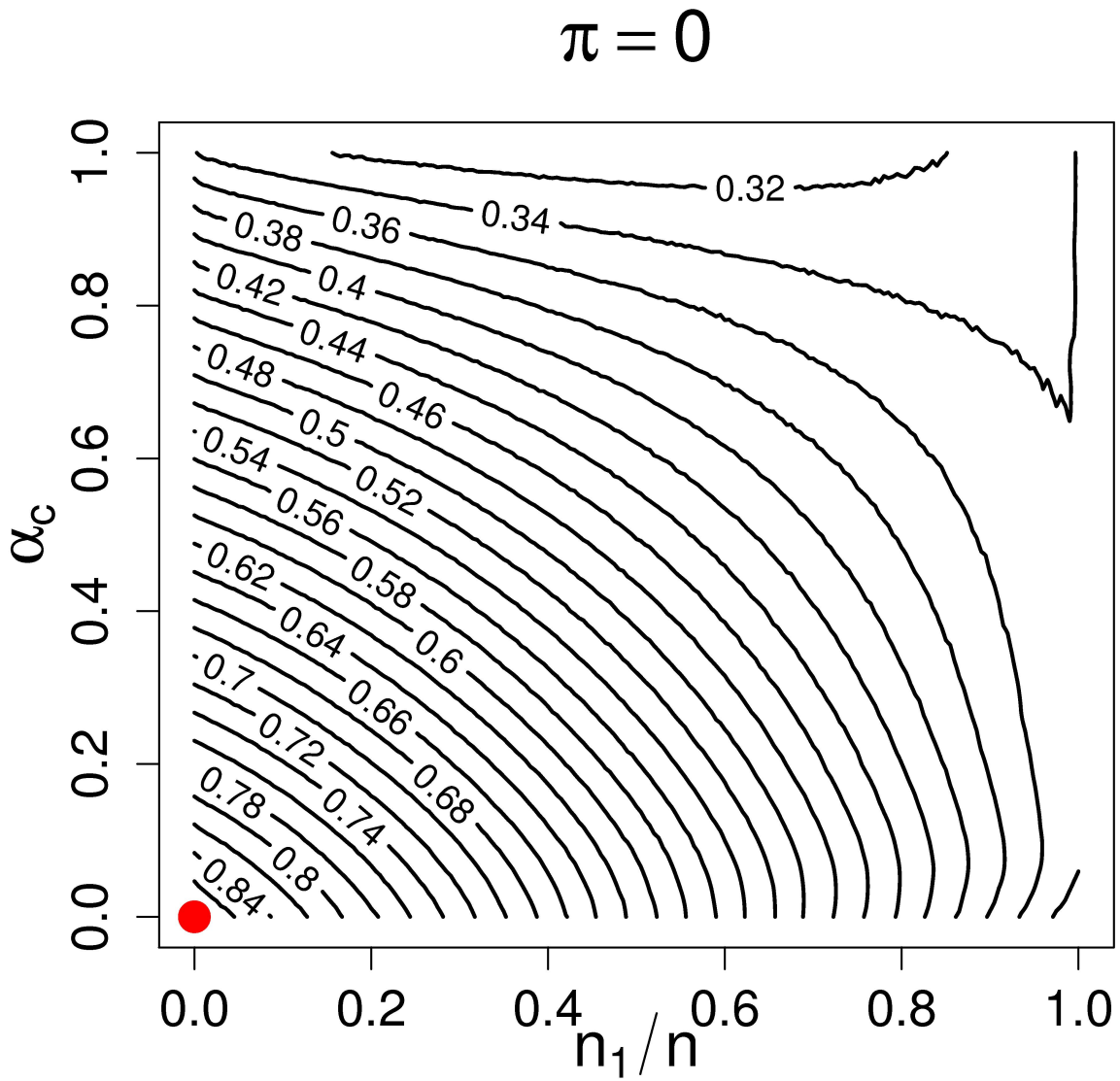
- Selection rule:
  - p_{SC} . . . the interim p-value for the z-test in the complement of the subpopulation.
  - α_C. . . selection threshold
  - Continue with F if $p_{SC} < \alpha_C$, otherwise enrich and continue with S only.
- Two types of adaptation: If the trial continues in the subpopulation only
  - Selection of hypothesis: H_F is dropped.
  - Reassessment of sample size: The sample size for H_S is increased.
- Combination Function: Inverse normal method (Lehmacher and Wassmer, 1999)

$\rightarrow$ $r = 0, \alpha_C = 0$ Fixed Sample Trial in S only

$\rightarrow$ $0 < r, \alpha_C < 1$ Adaptive Design integrating both phases

$\rightarrow$ $r = 1, \alpha_C = 1$ Fixed Sample Trial in F

Utility $U_{\pi,C} = U_{\pi,P}$ for $\mathbf{G_S = 1}$



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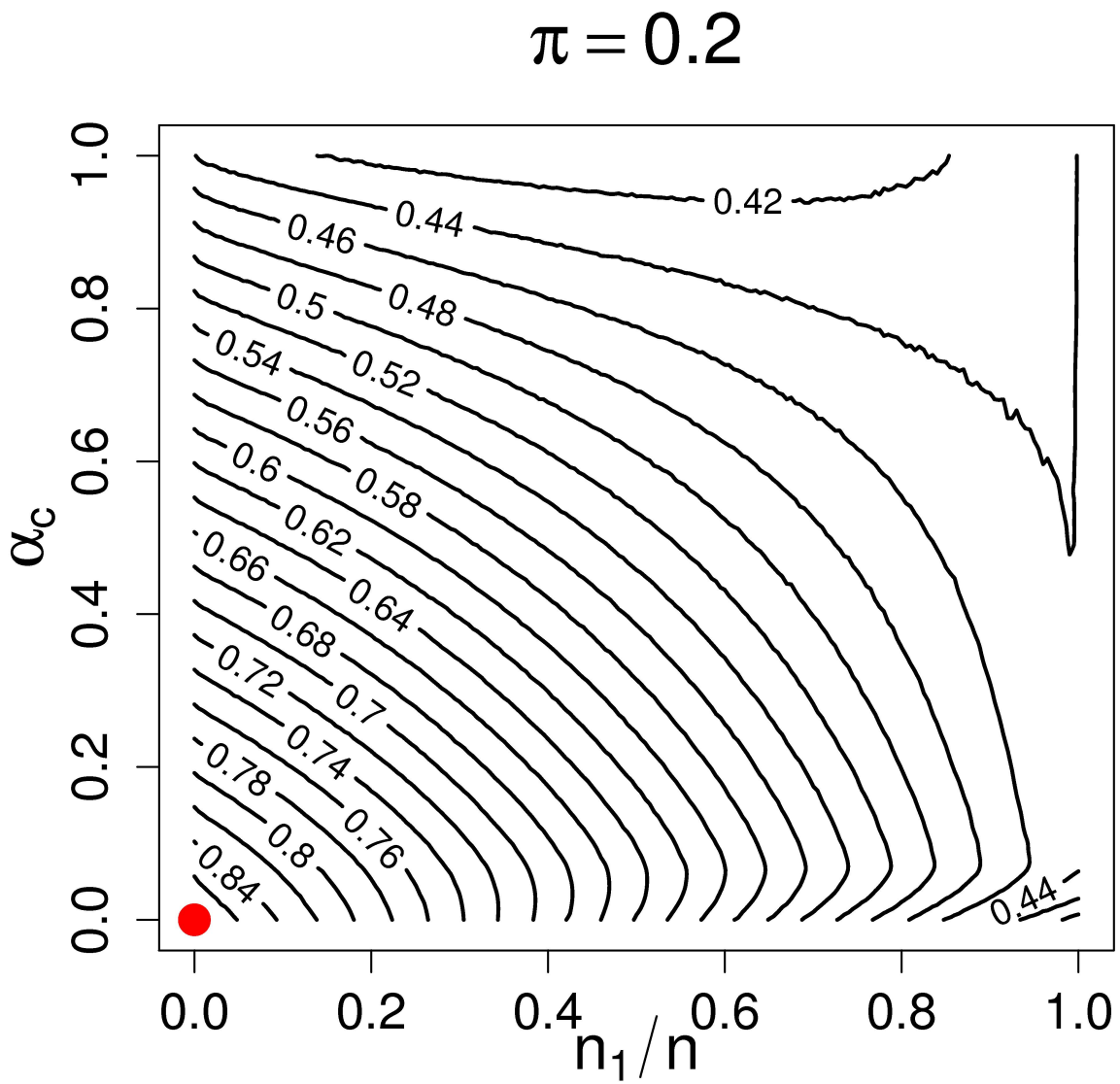

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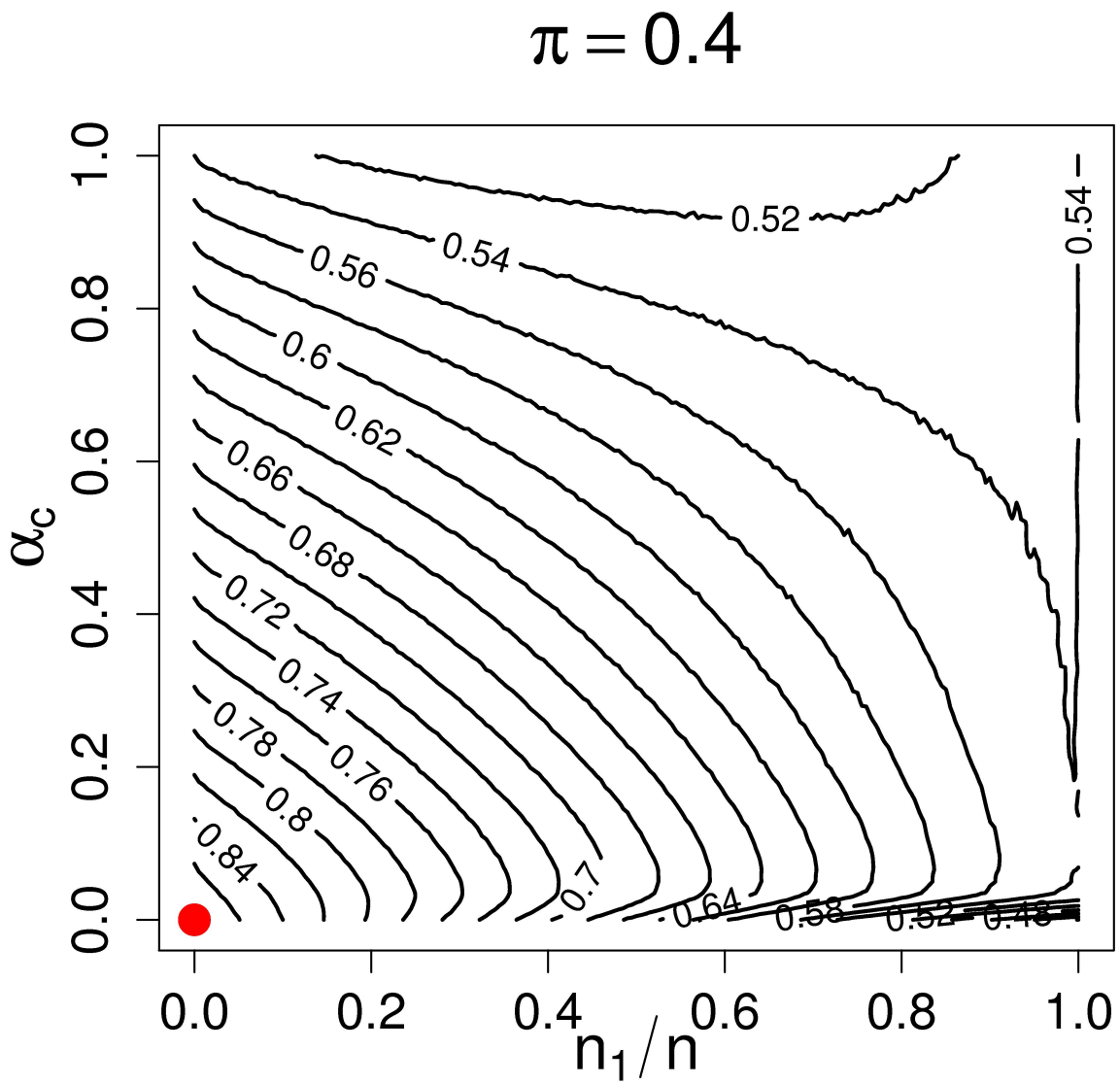

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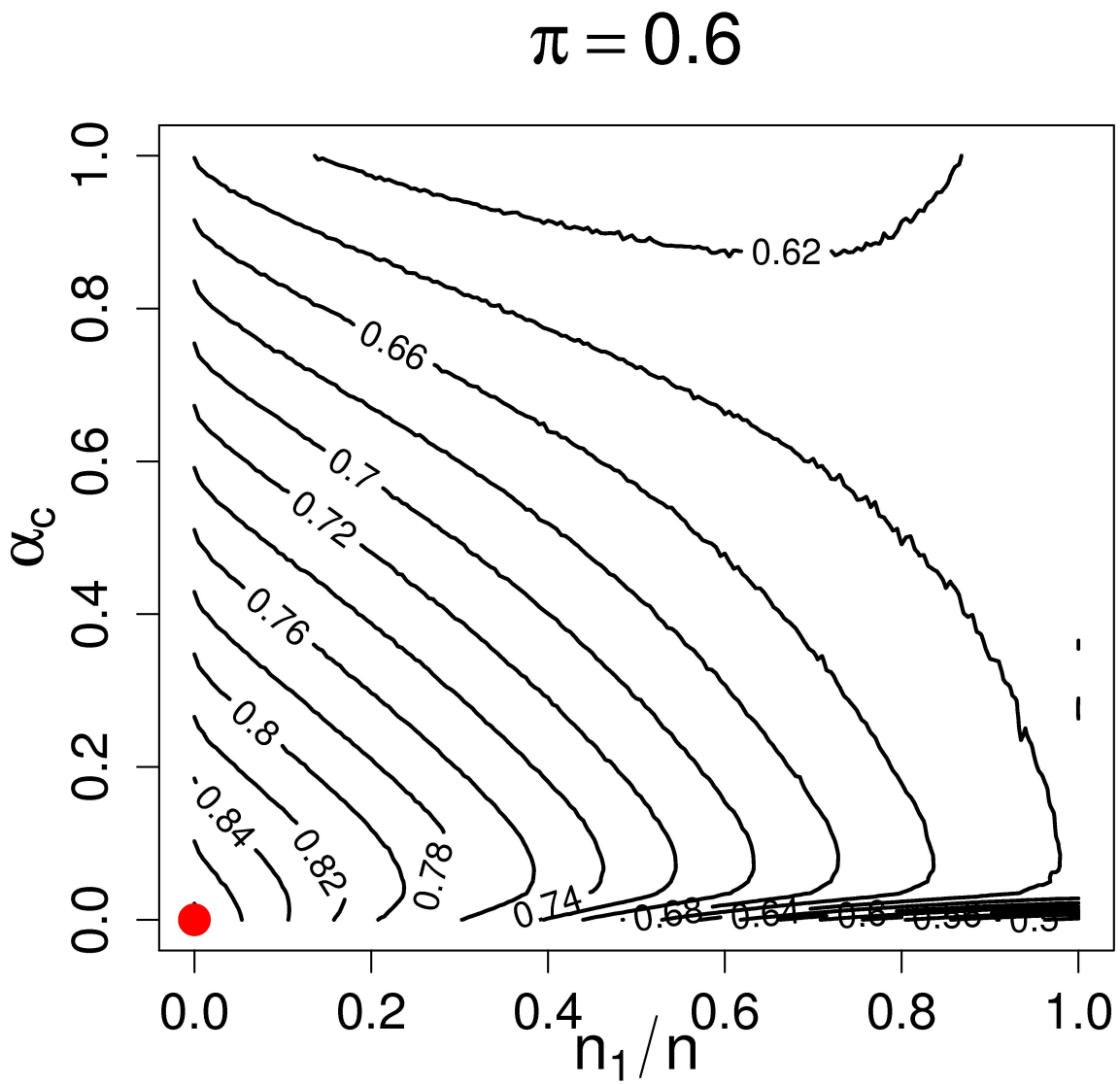

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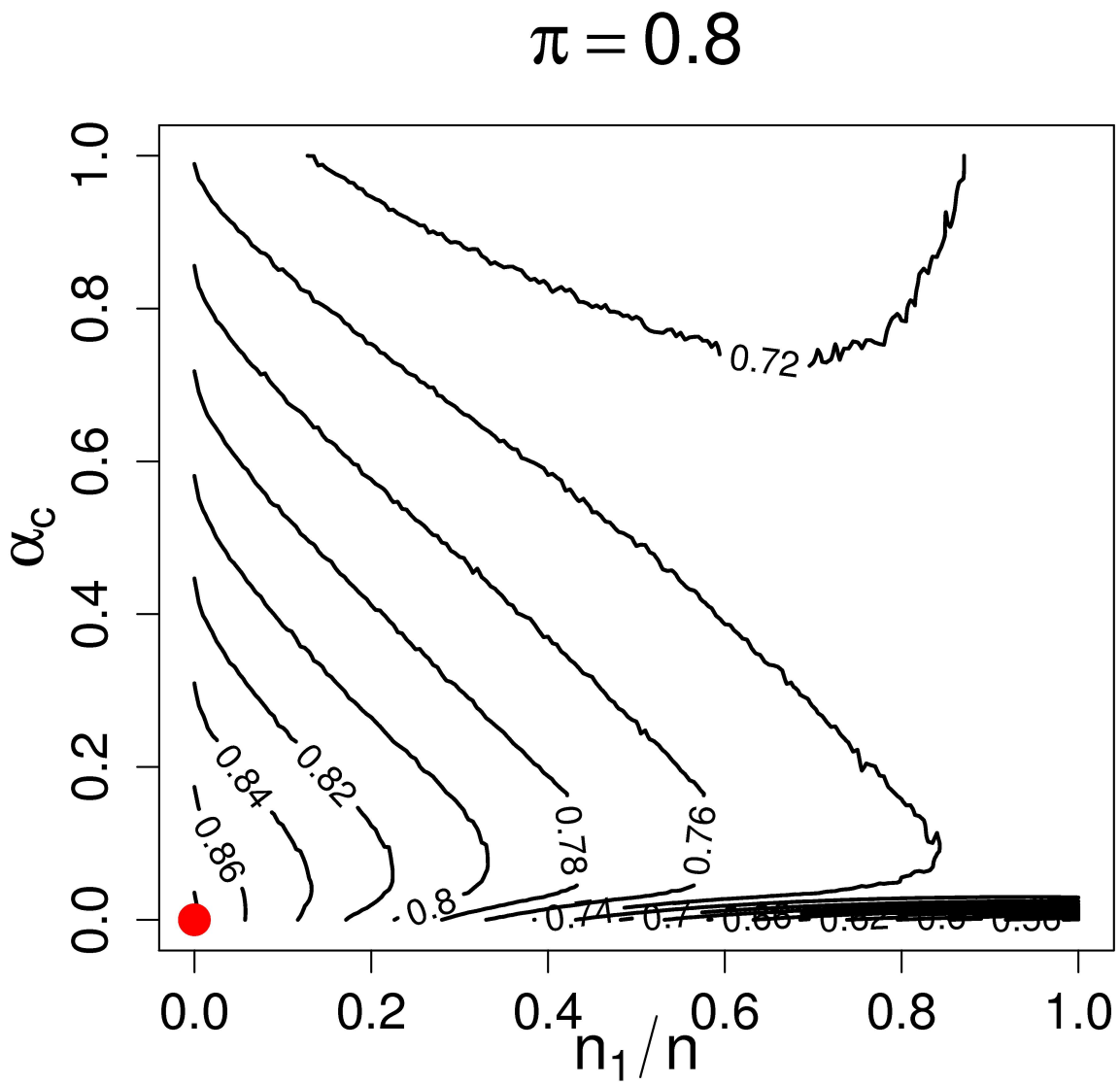

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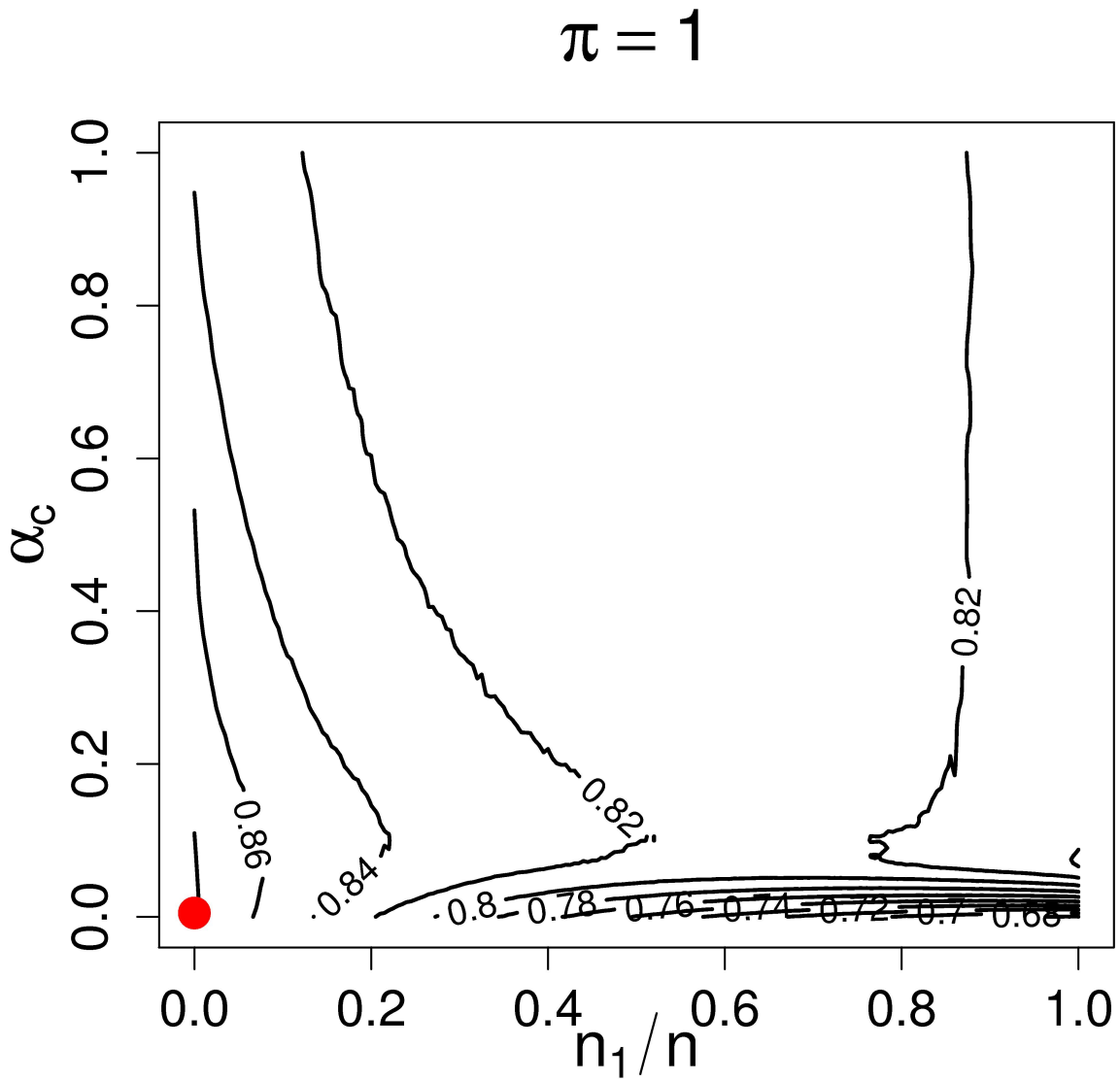

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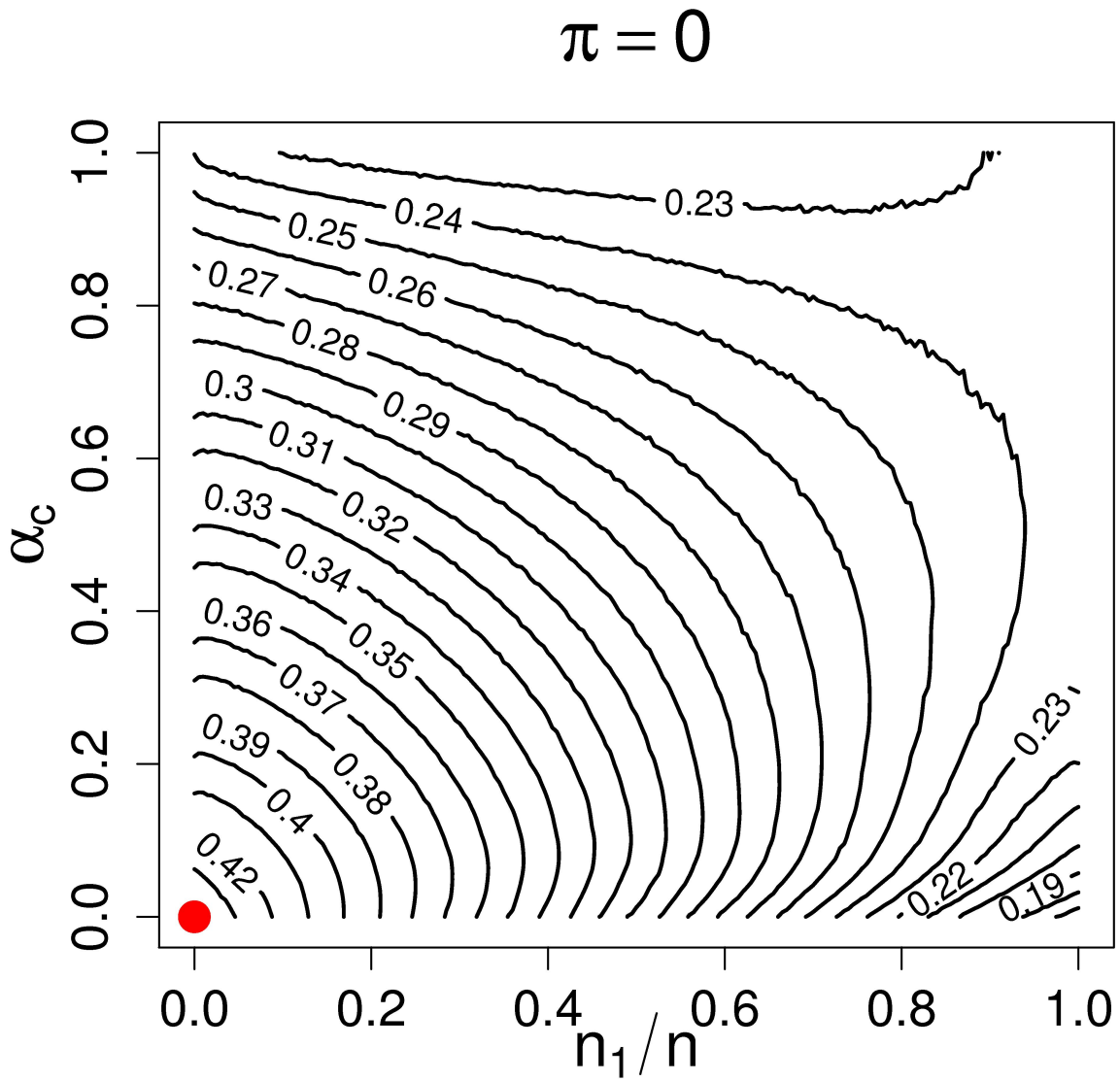

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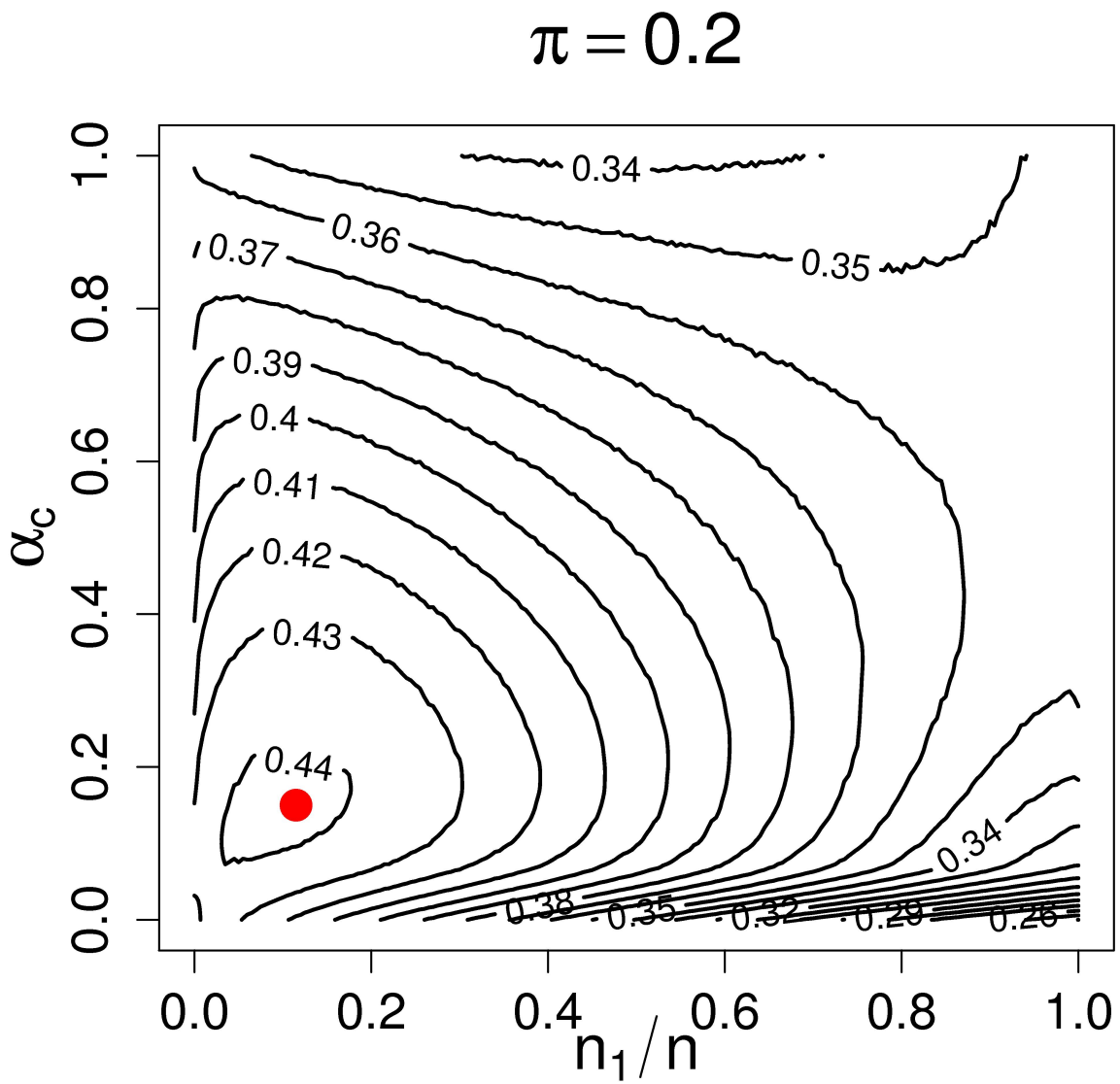

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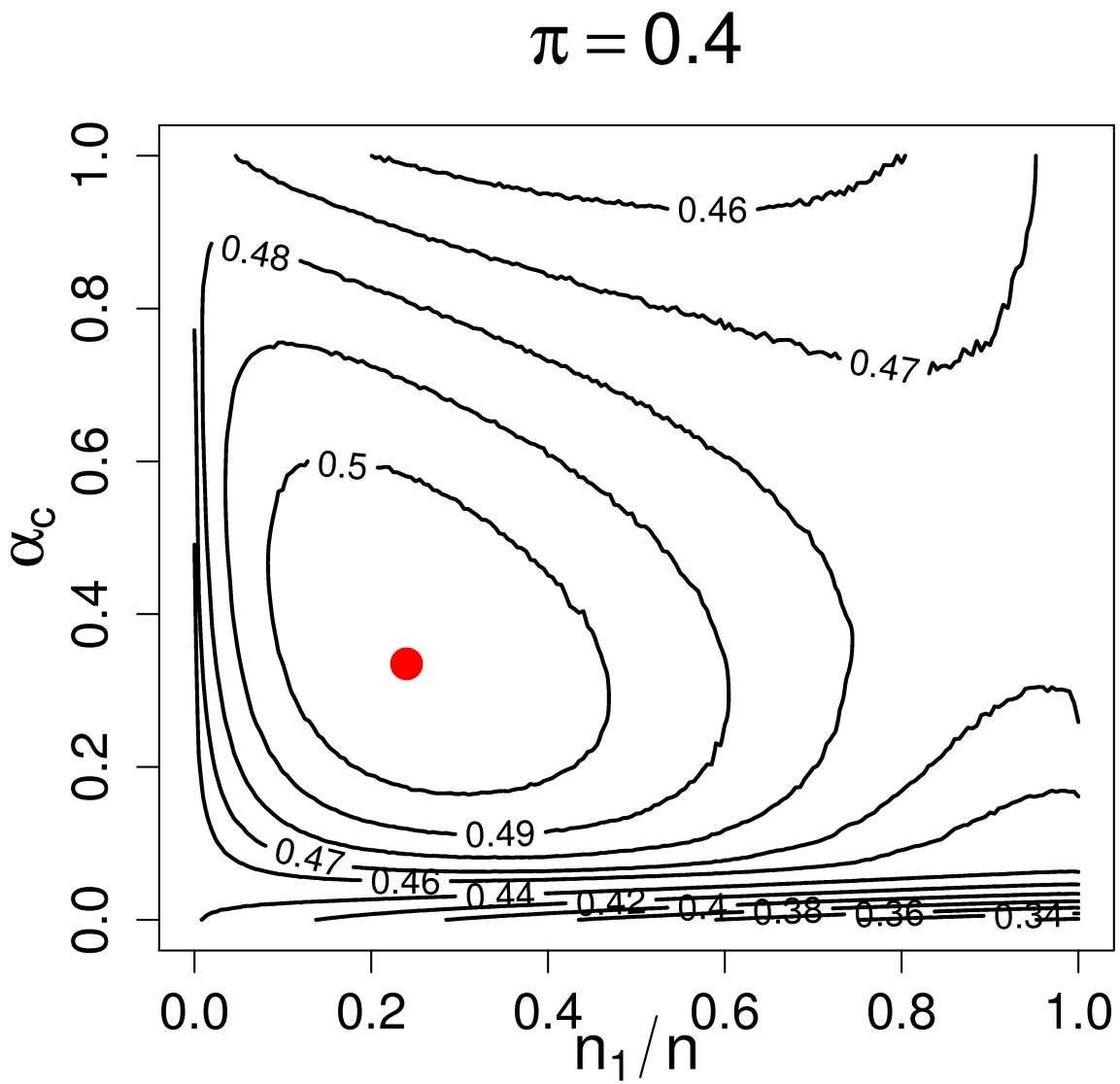

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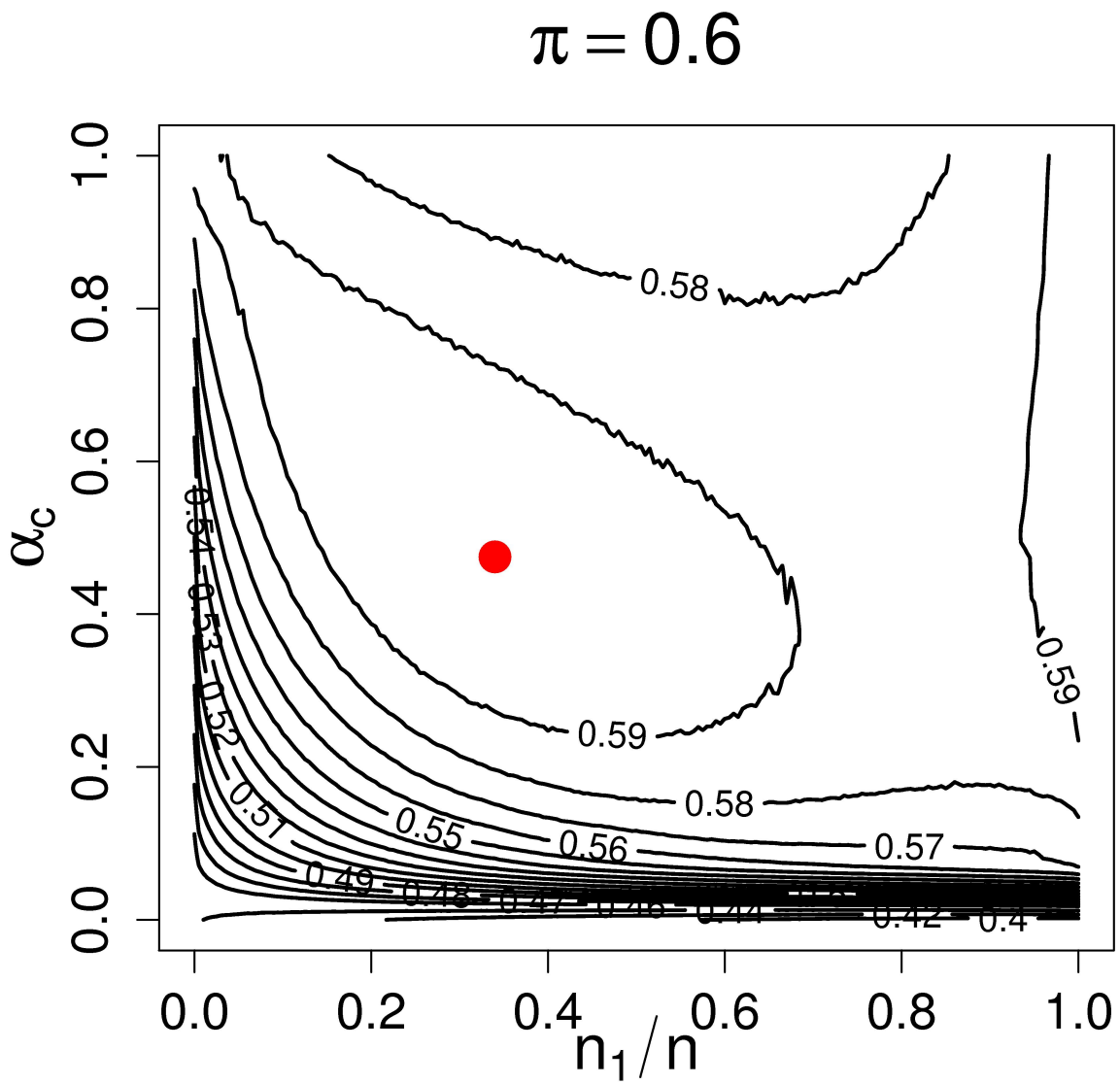

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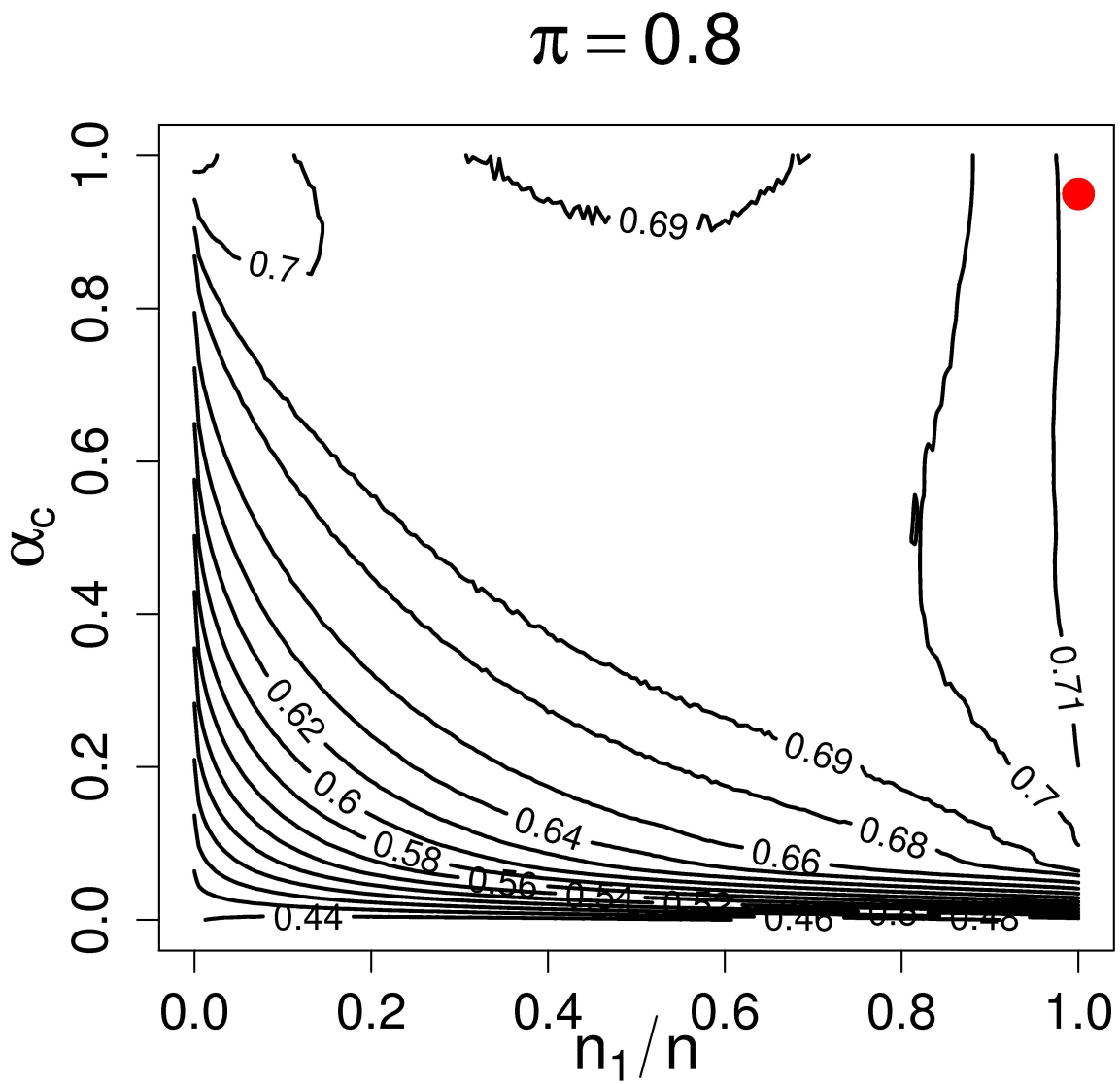

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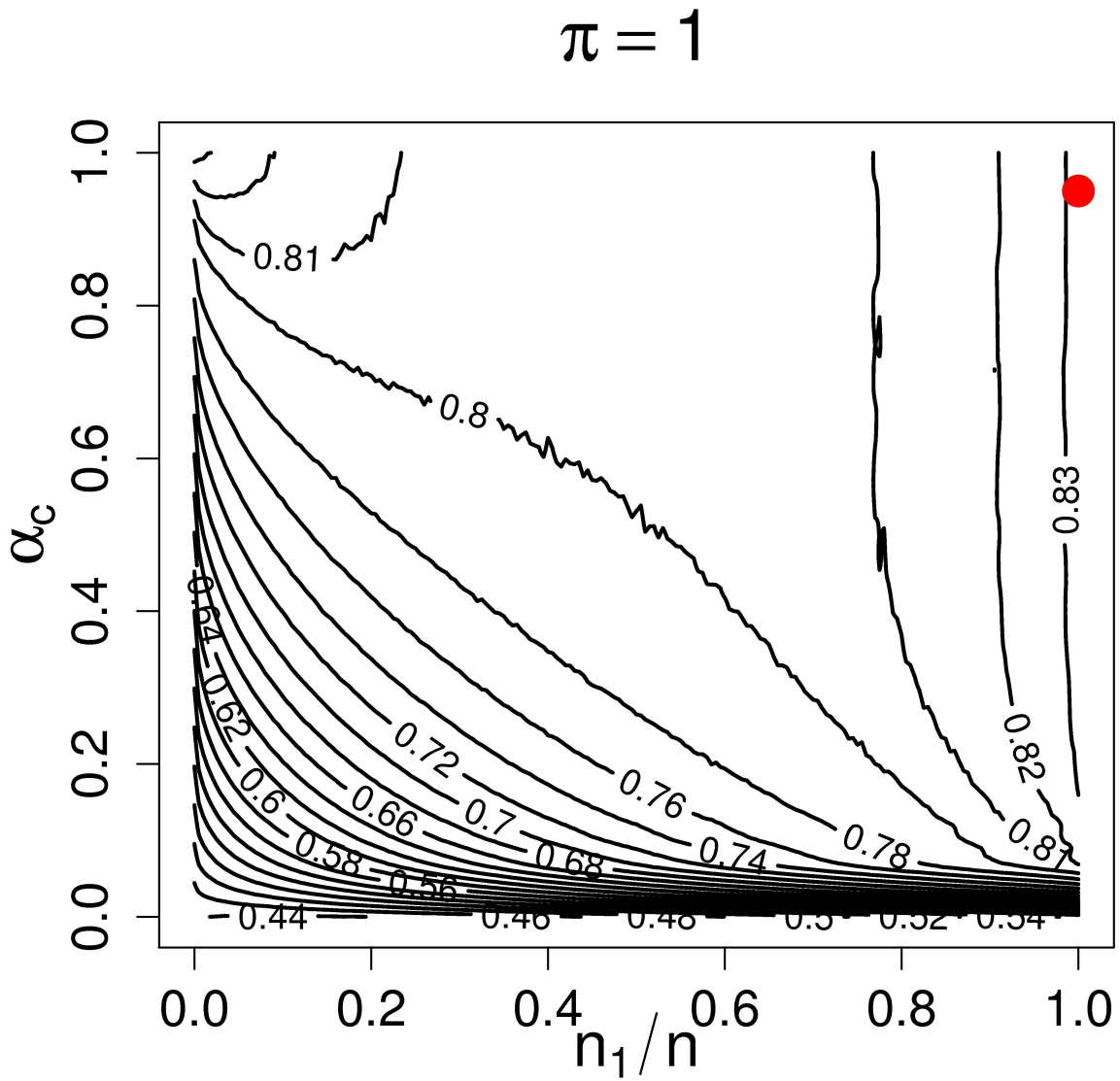

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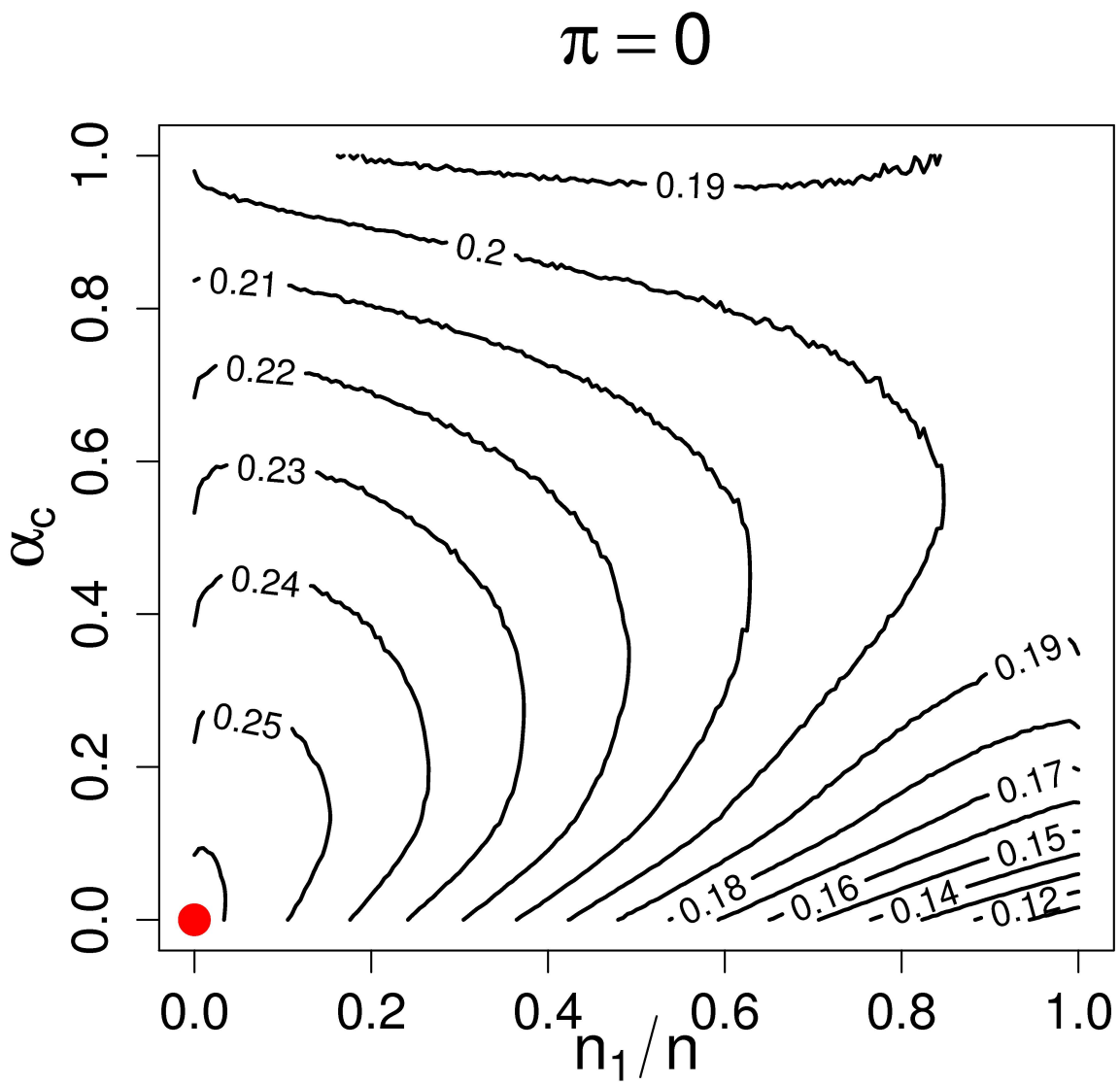

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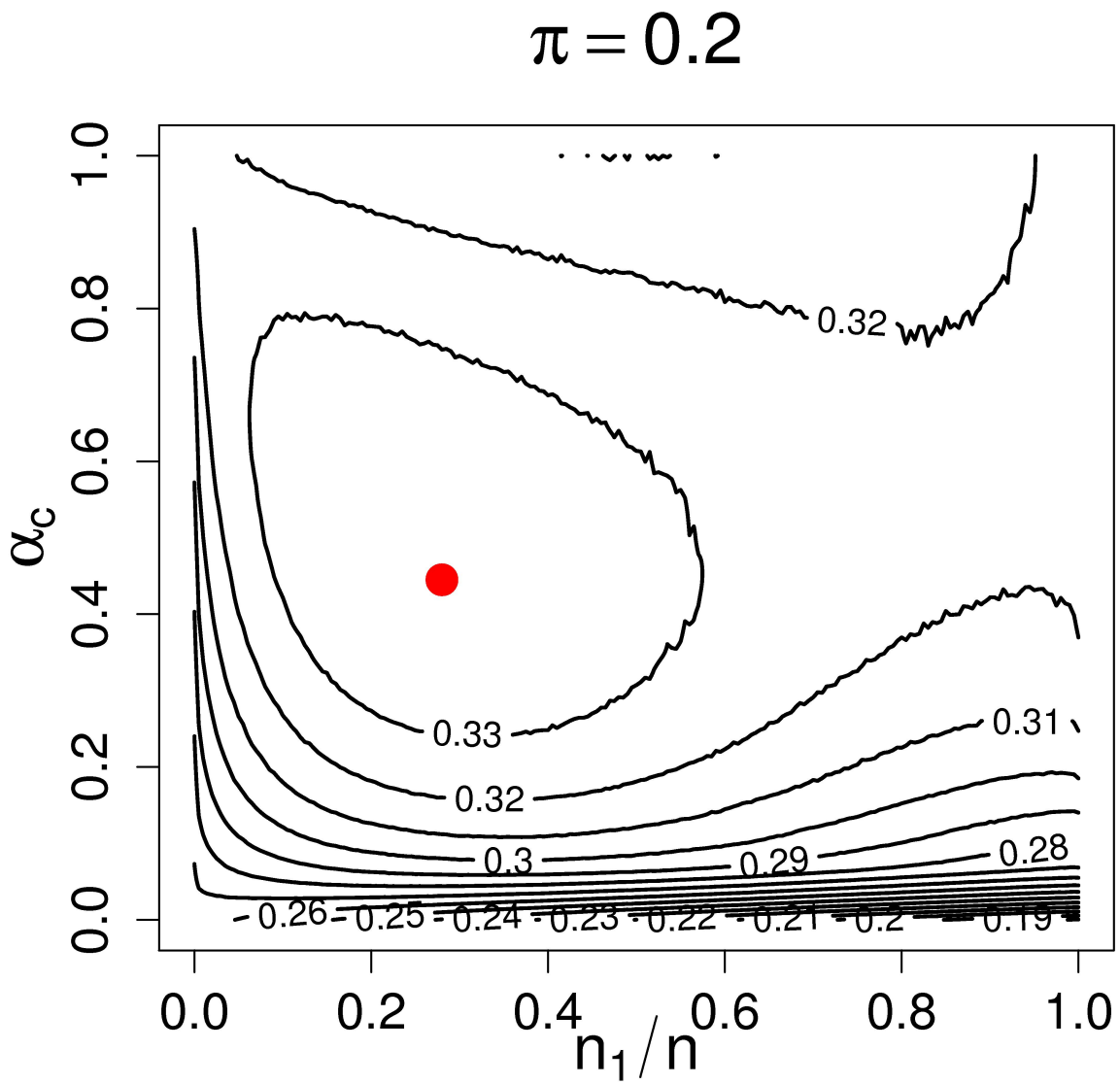

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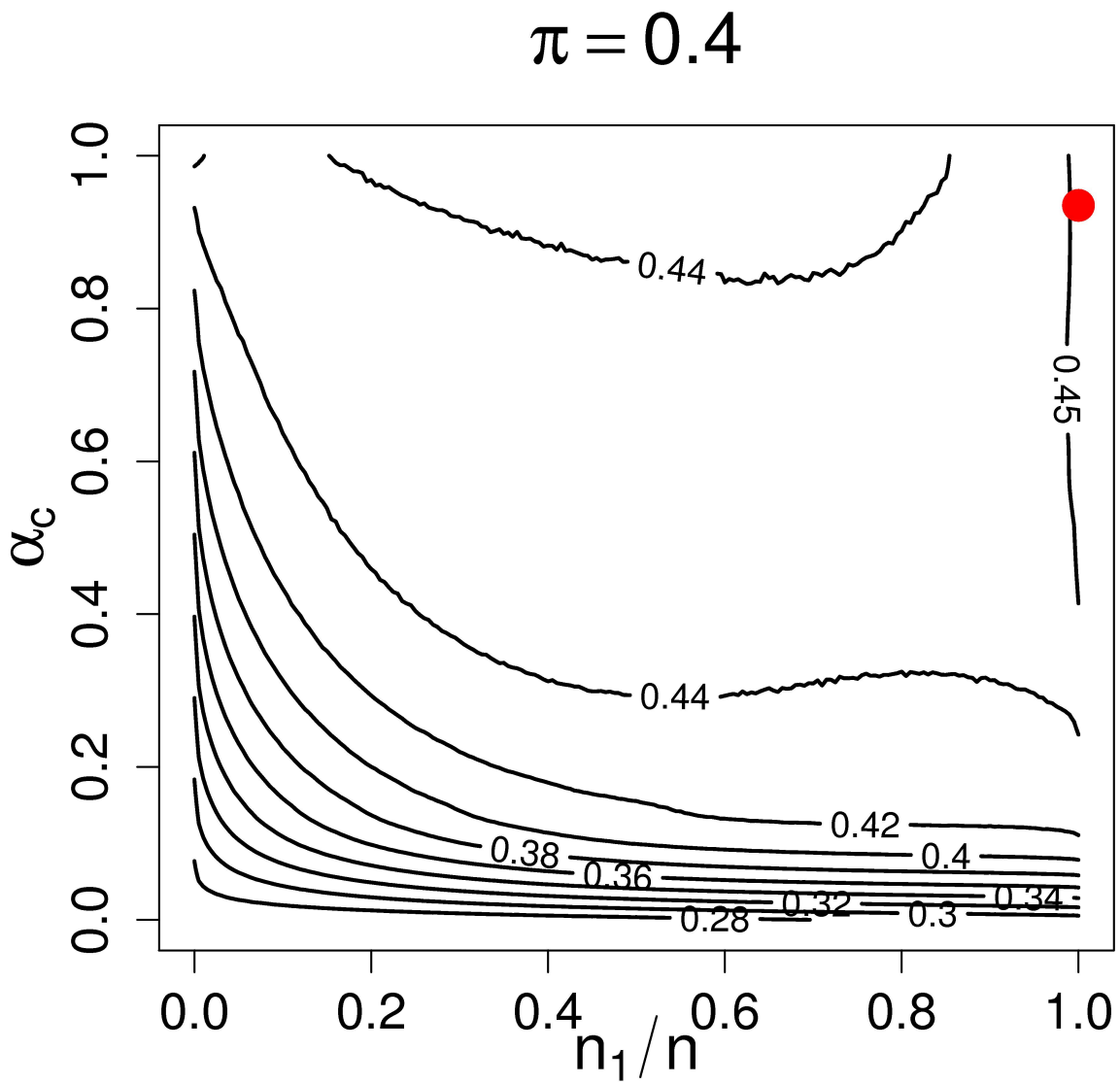
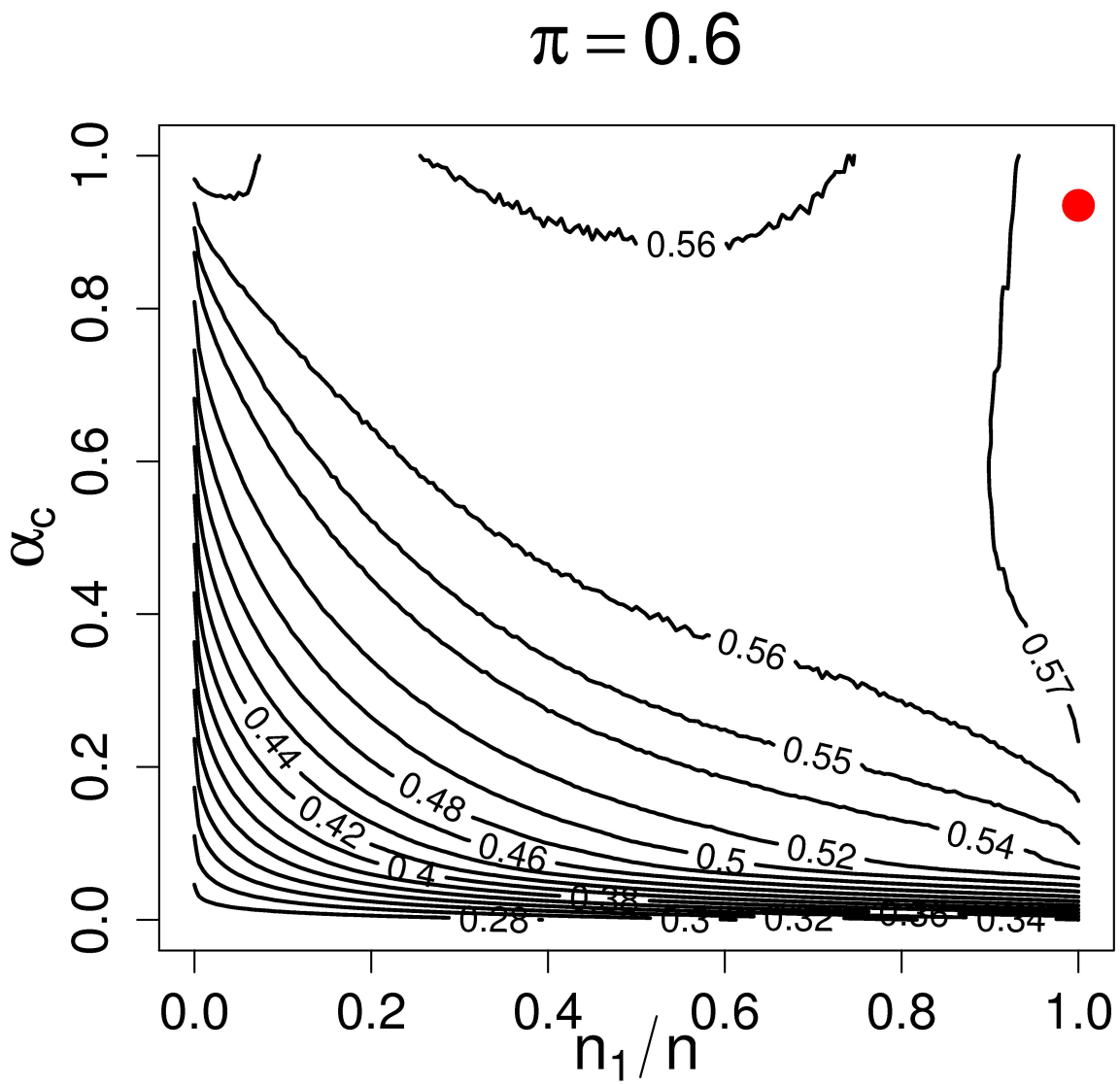
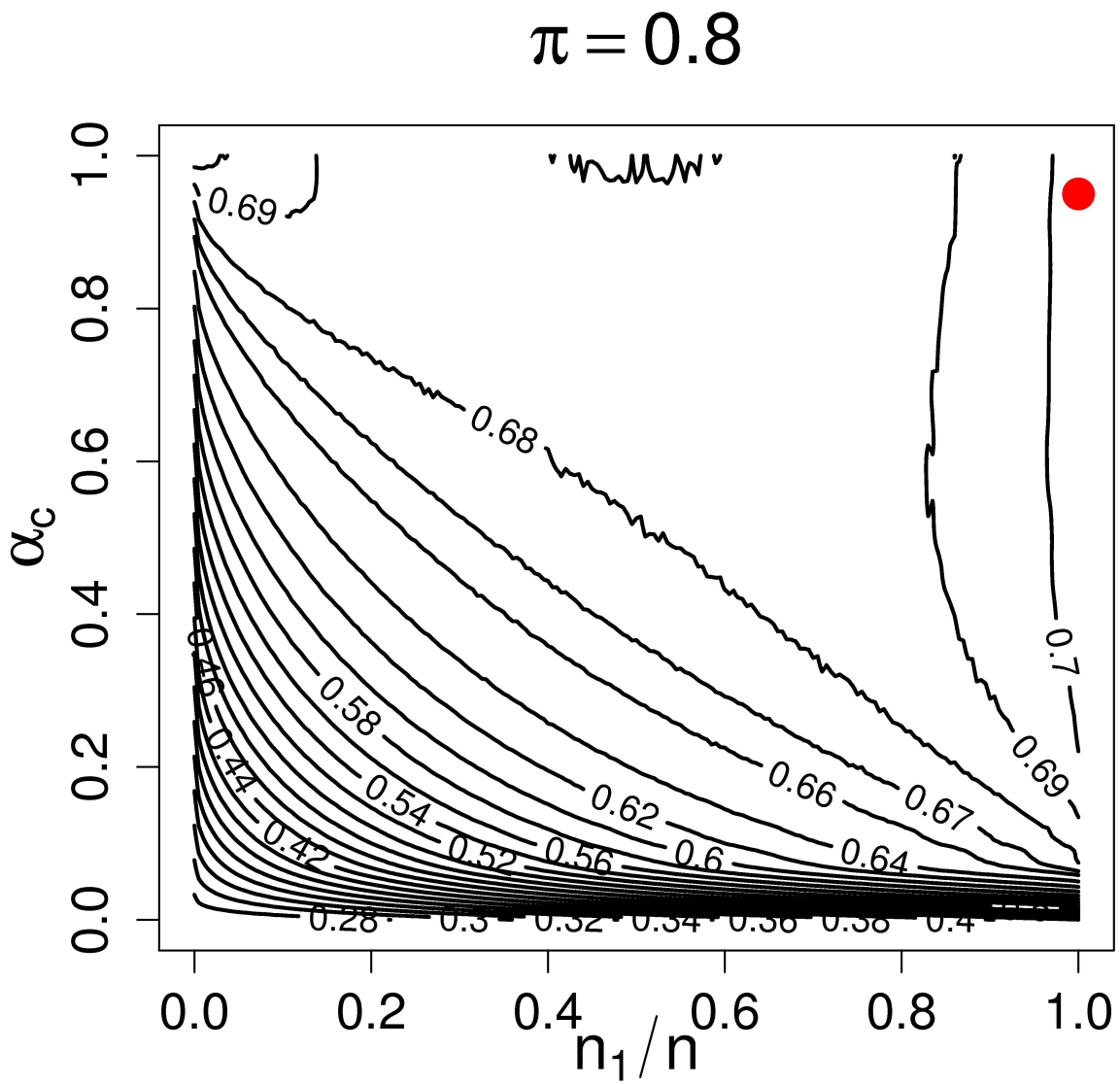


Utility $U_{\pi,C}$ for $\mathbf{G_S = .3}$



Utility $U_{\pi,C}$ for $\mathbf{G_S = .3}$



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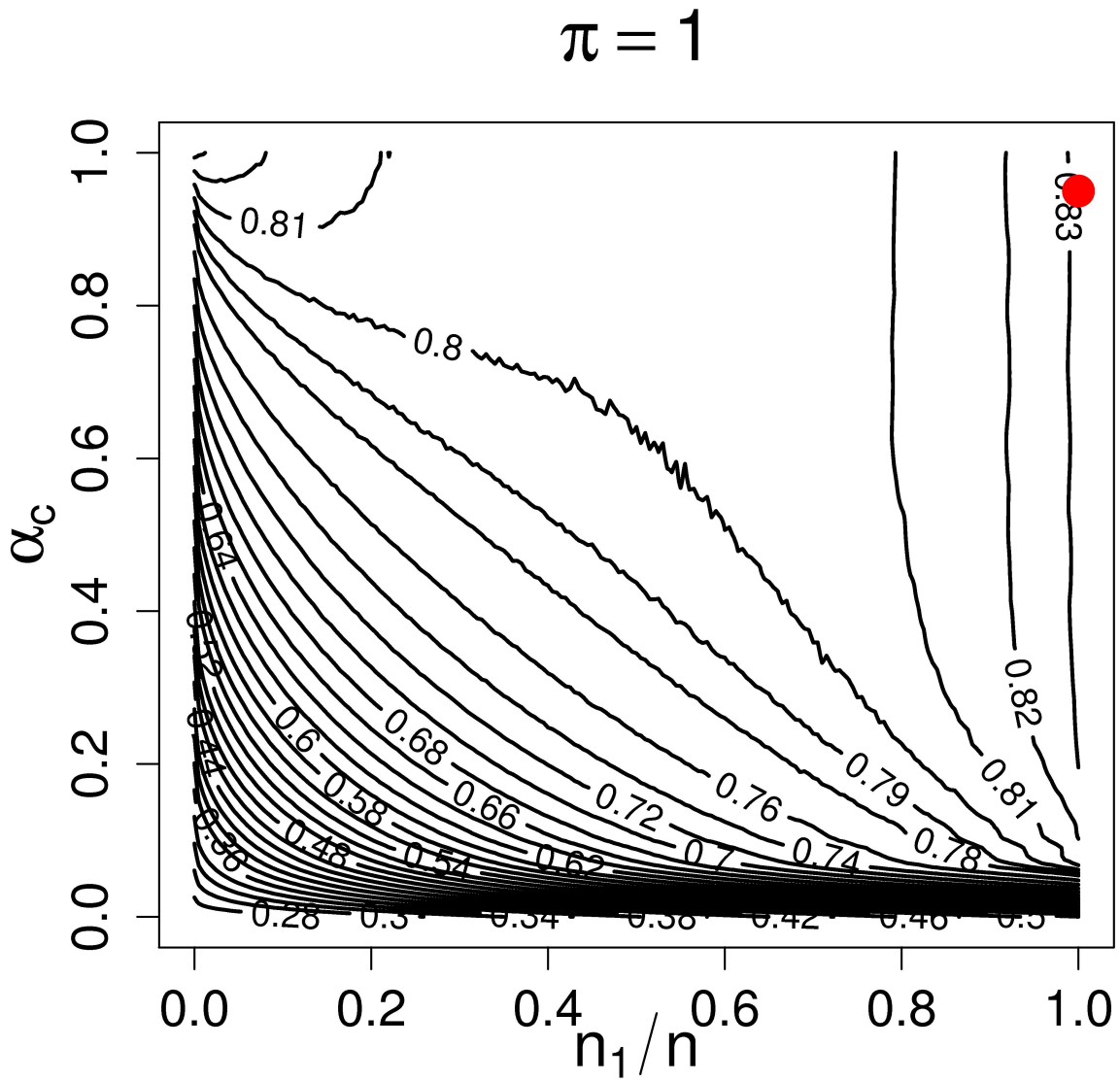
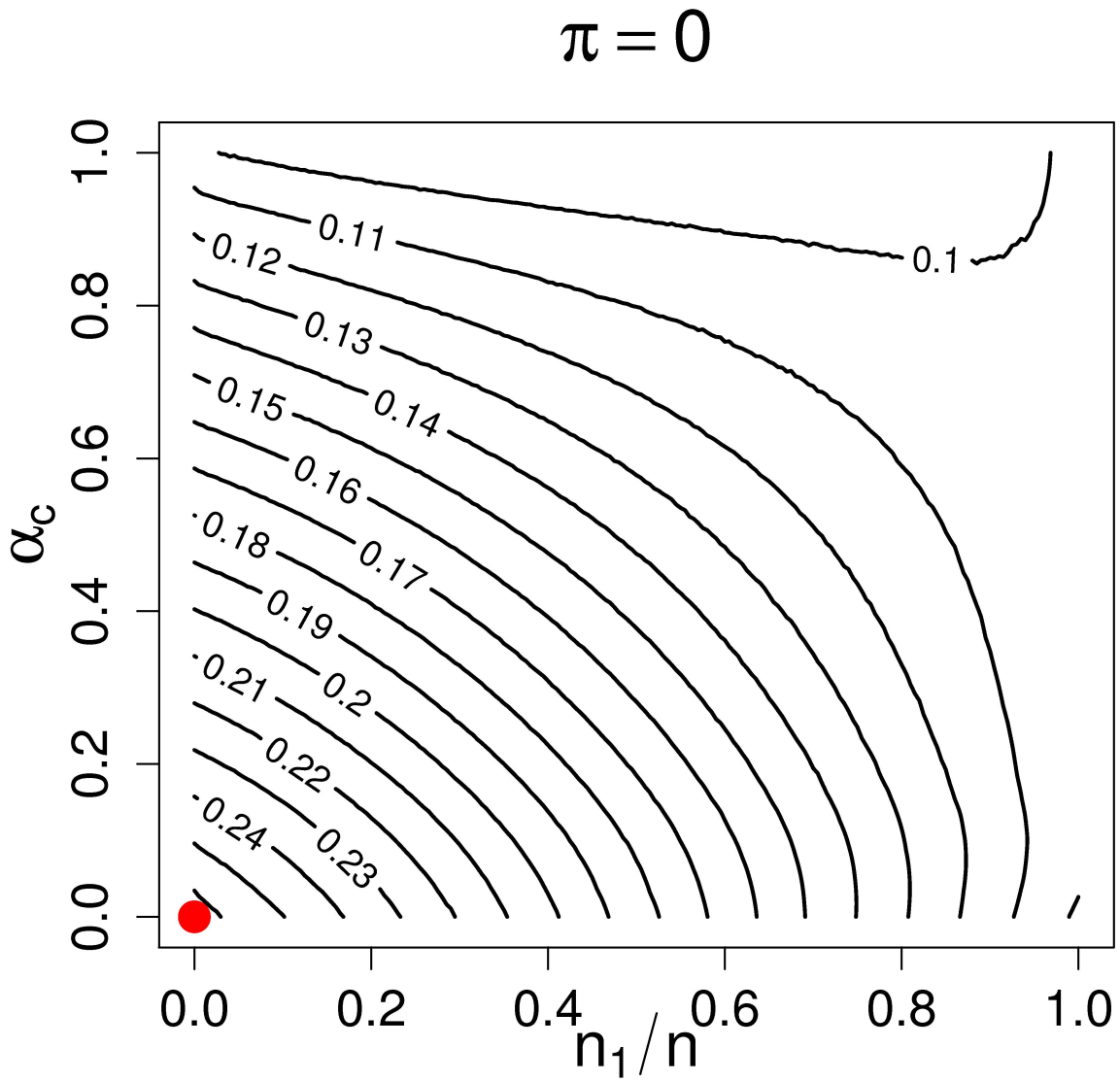
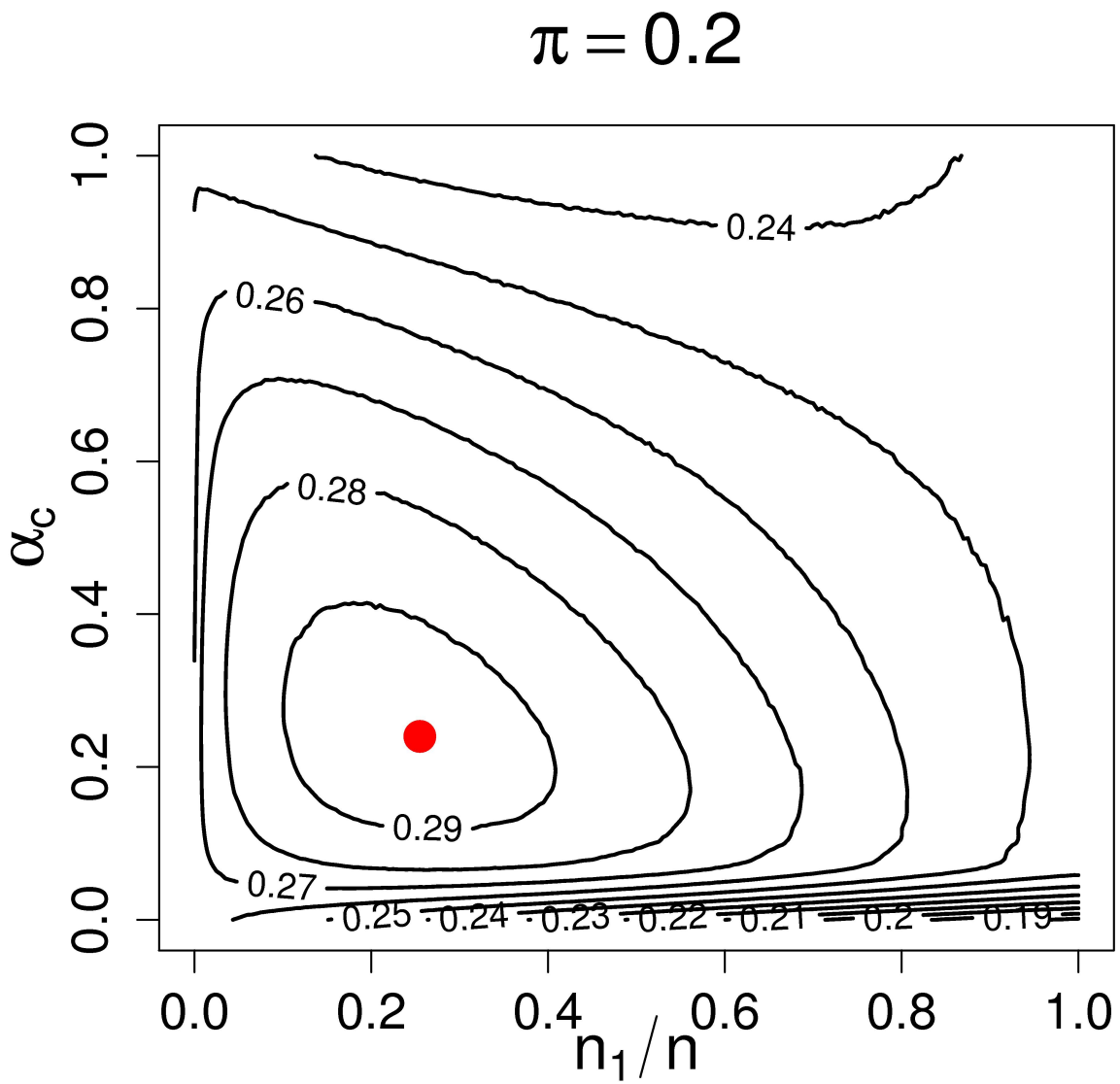


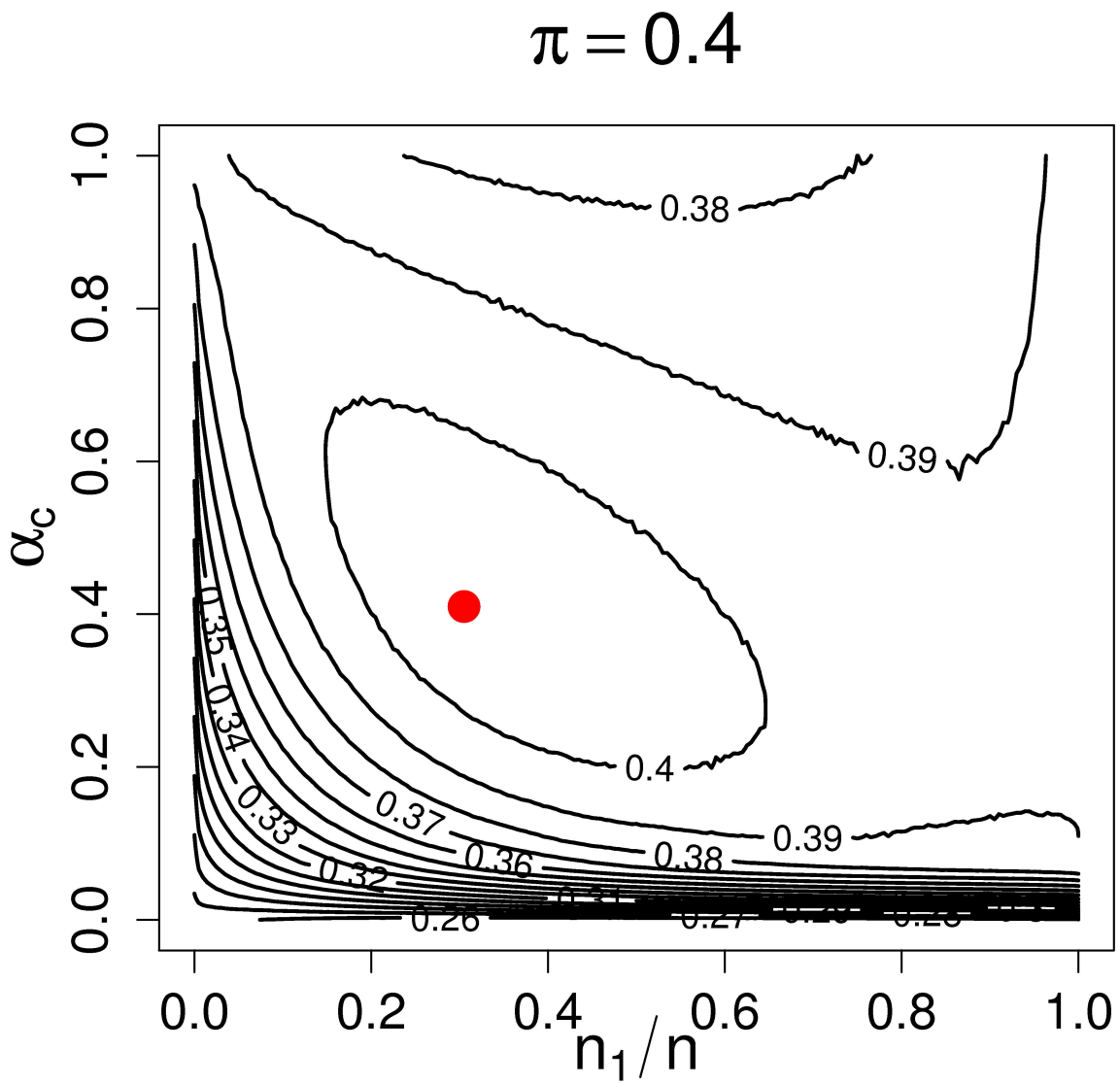
Utility $U_{\pi,P}$ for $\mathbf{G_S = .3}$



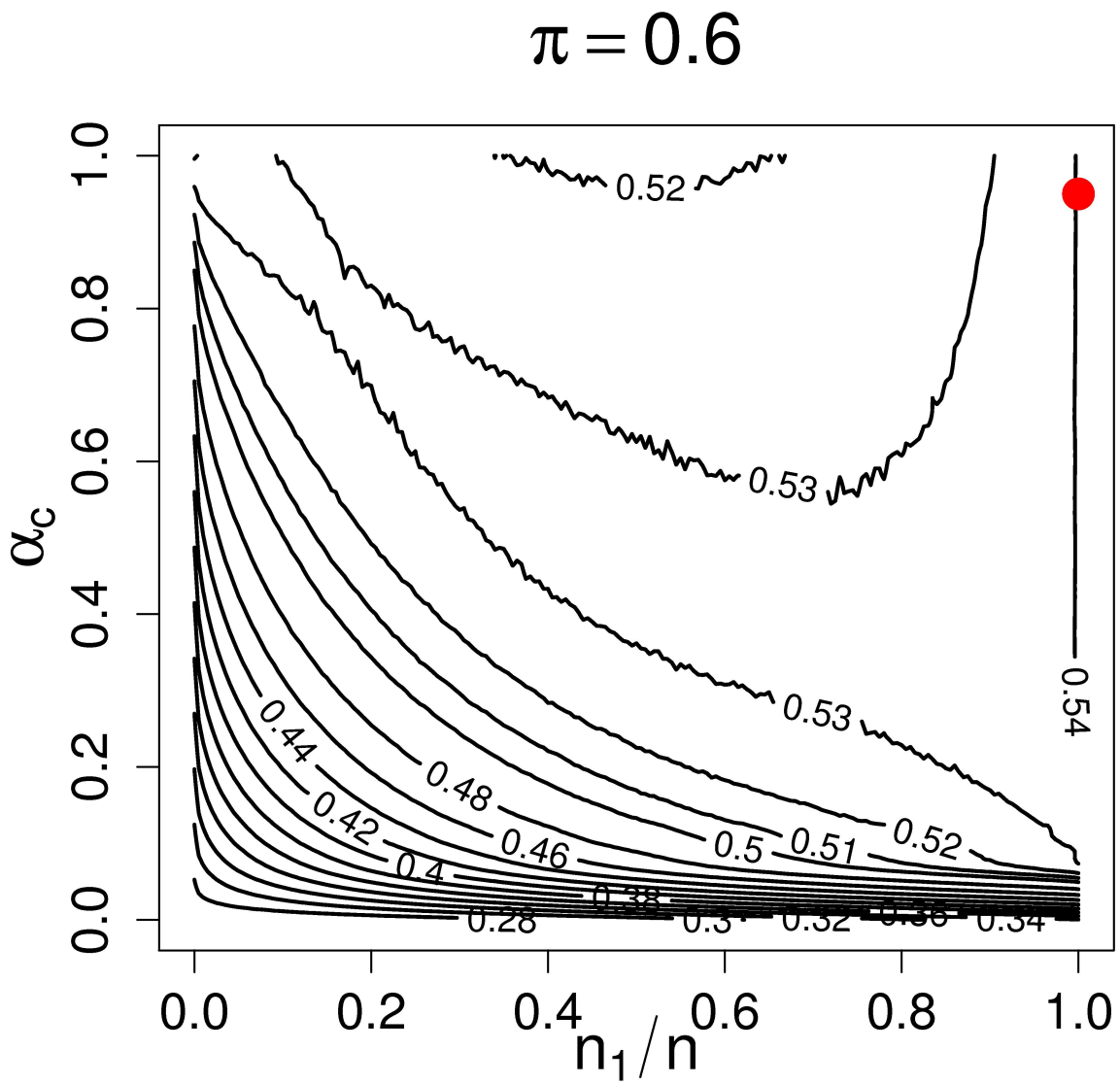
Utility $U_{\pi,P}$ for $\mathbf{G_S = .3}$



Utility $U_{\pi,P}$ for $\mathbf{G_S = .3}$



Utility $U_{\pi,P}$ for $\mathbf{G_S = .3}$



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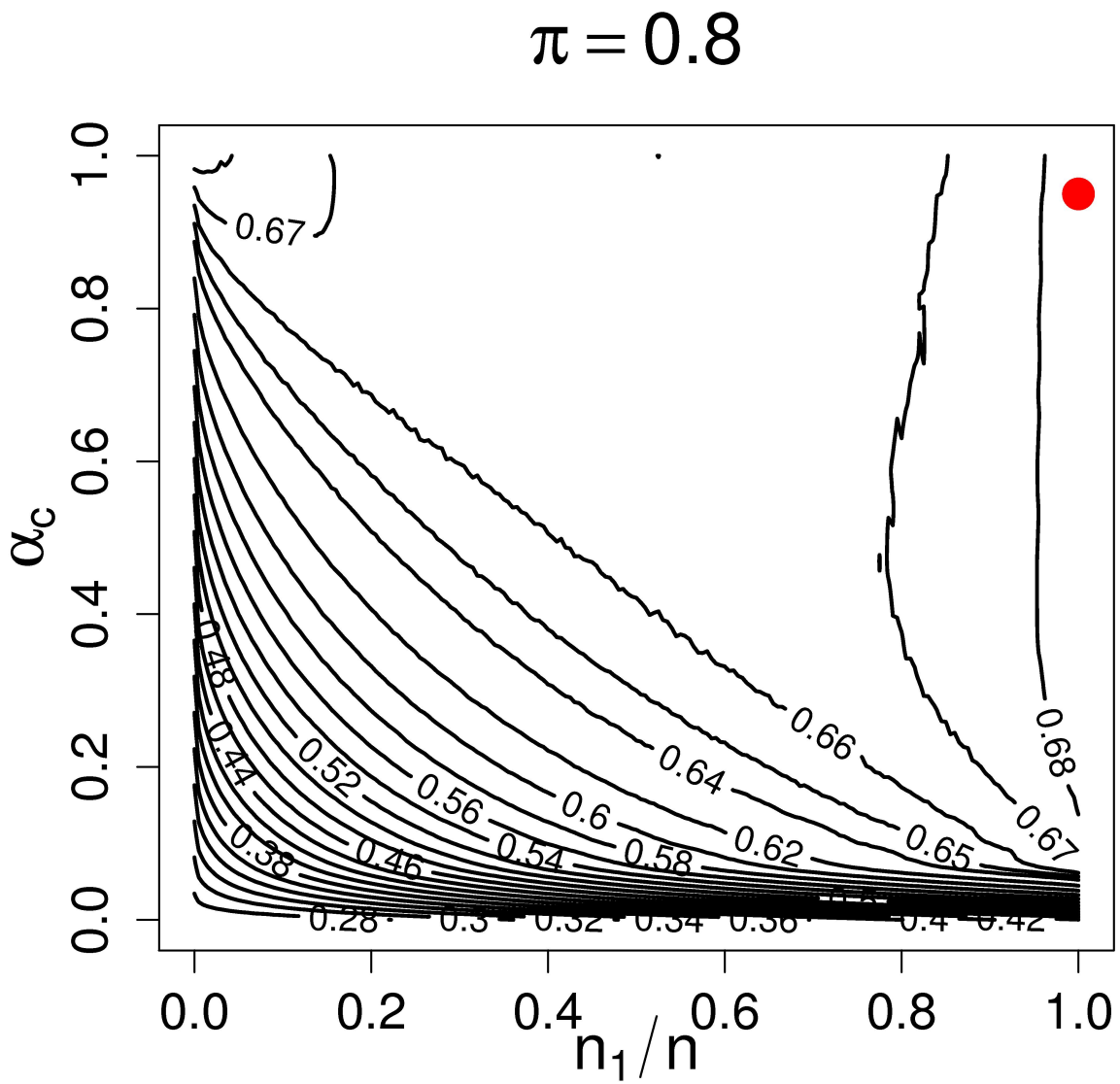
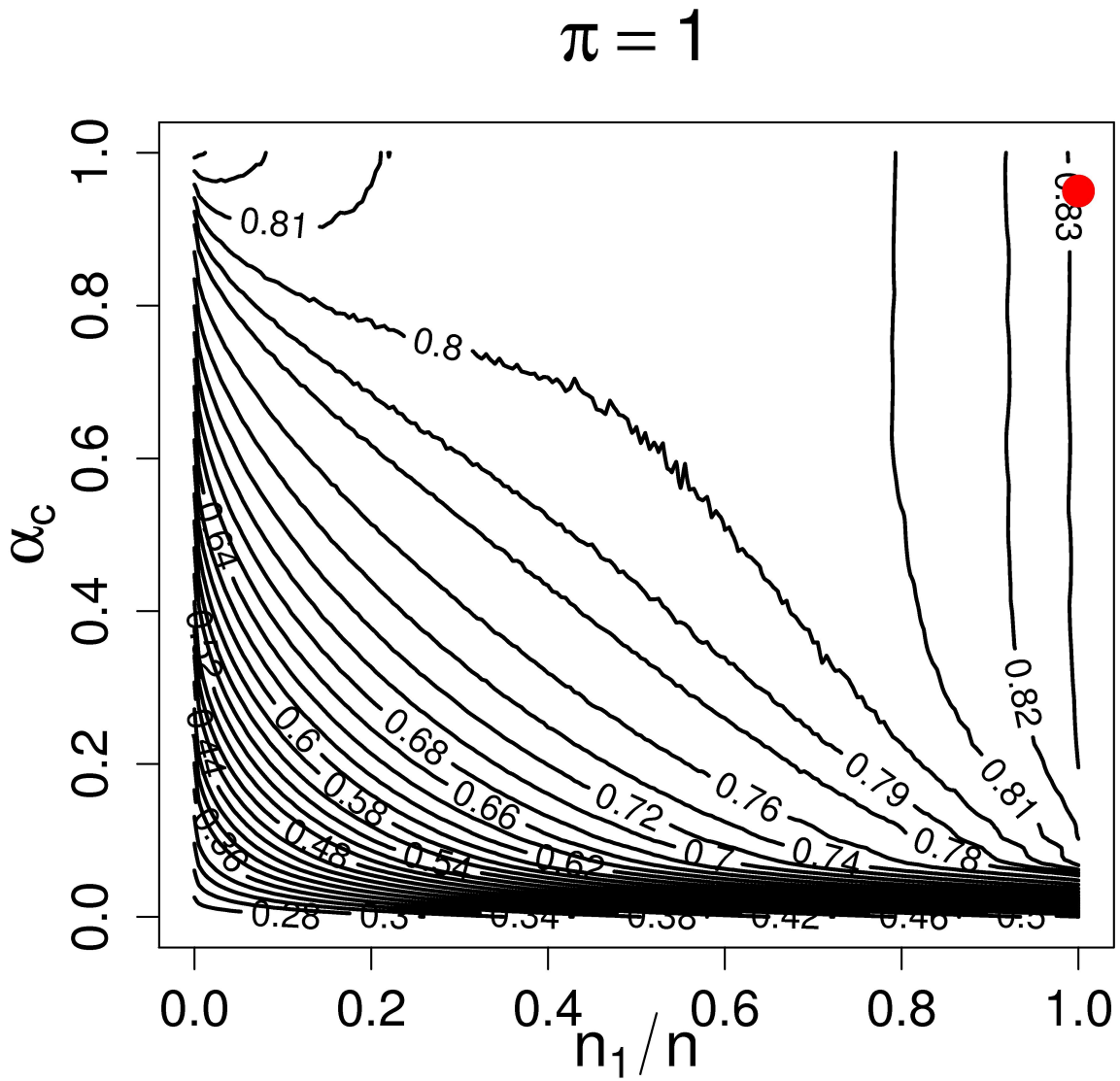
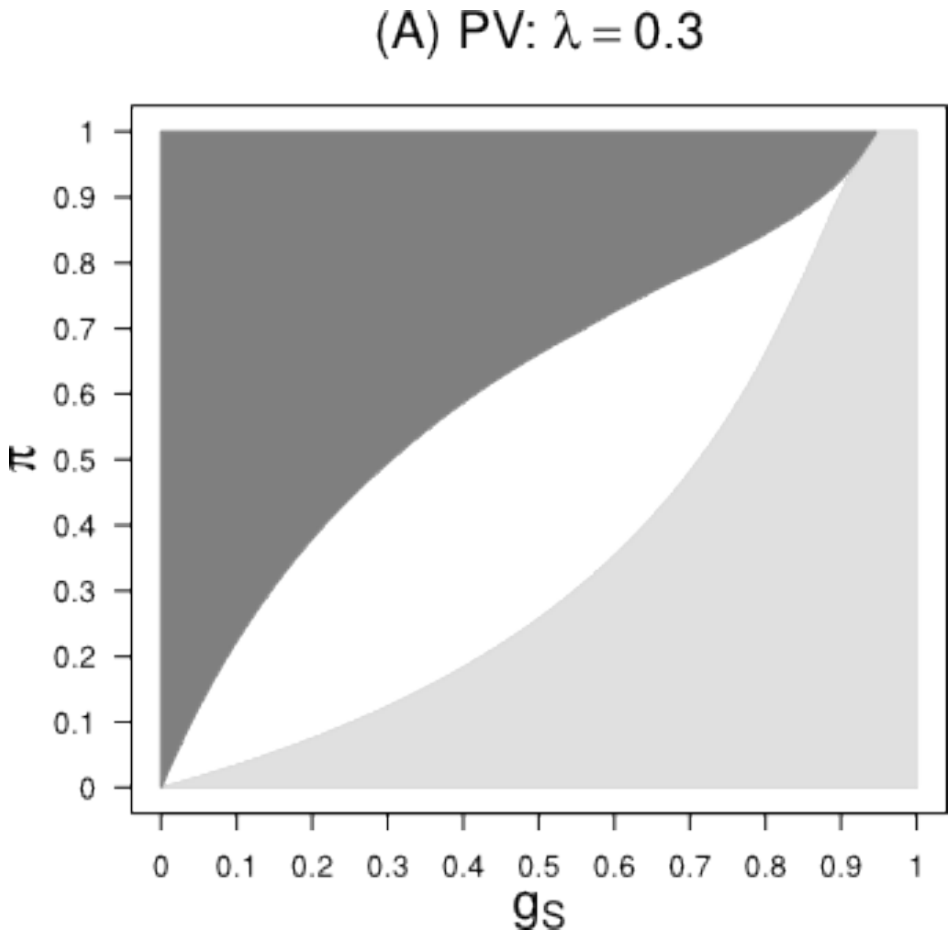


Utility $U_{\pi,P}$ for $\mathbf{G_S = .3}$



Which Design is best?

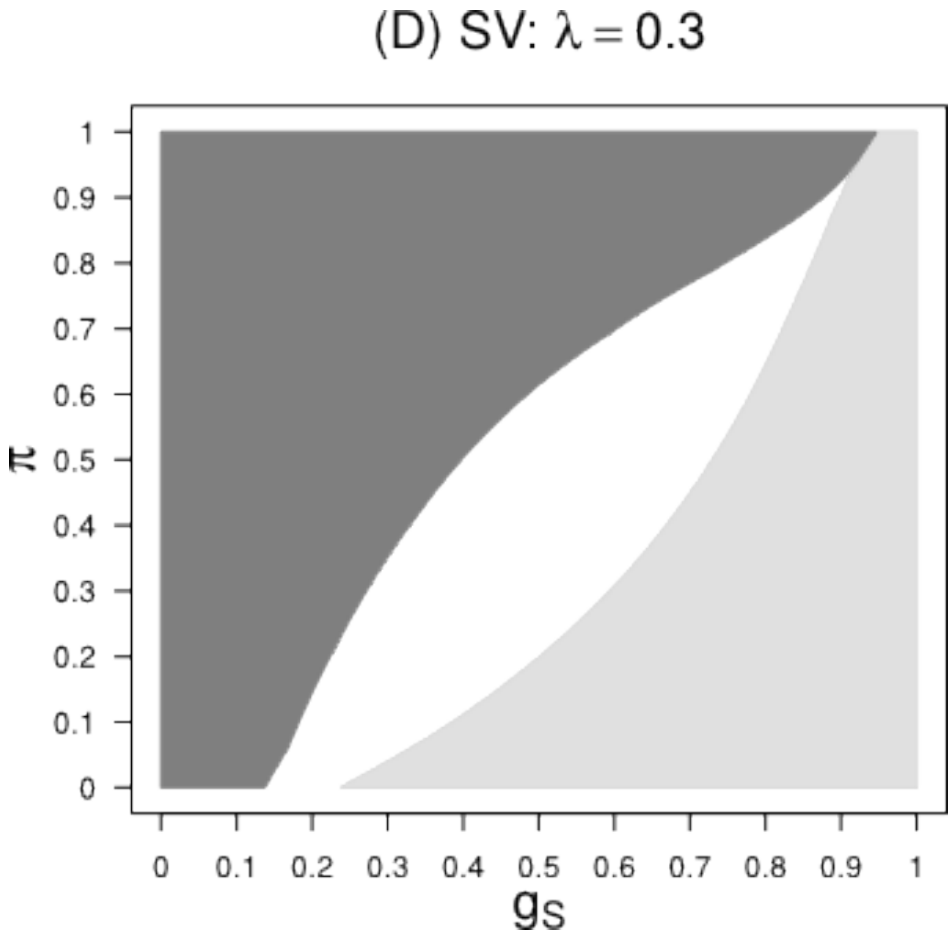
Public View Utility Function



■ Stratification □ Adaptive ■ Enrichment

Which Design is best?

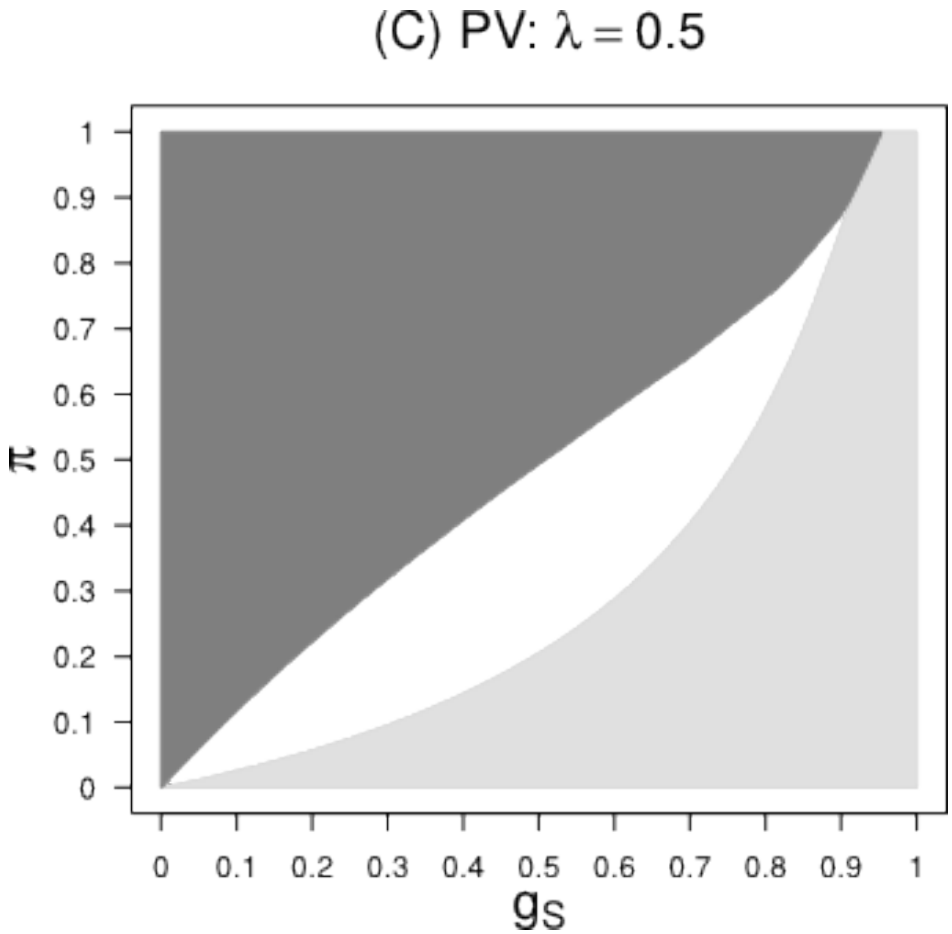
Sponsor View Utility Function



■ Stratification □ Adaptive ■ Enrichment

Which Design is best?

Public View Utility Function



■ Stratification □ Adaptive ■ Enrichment

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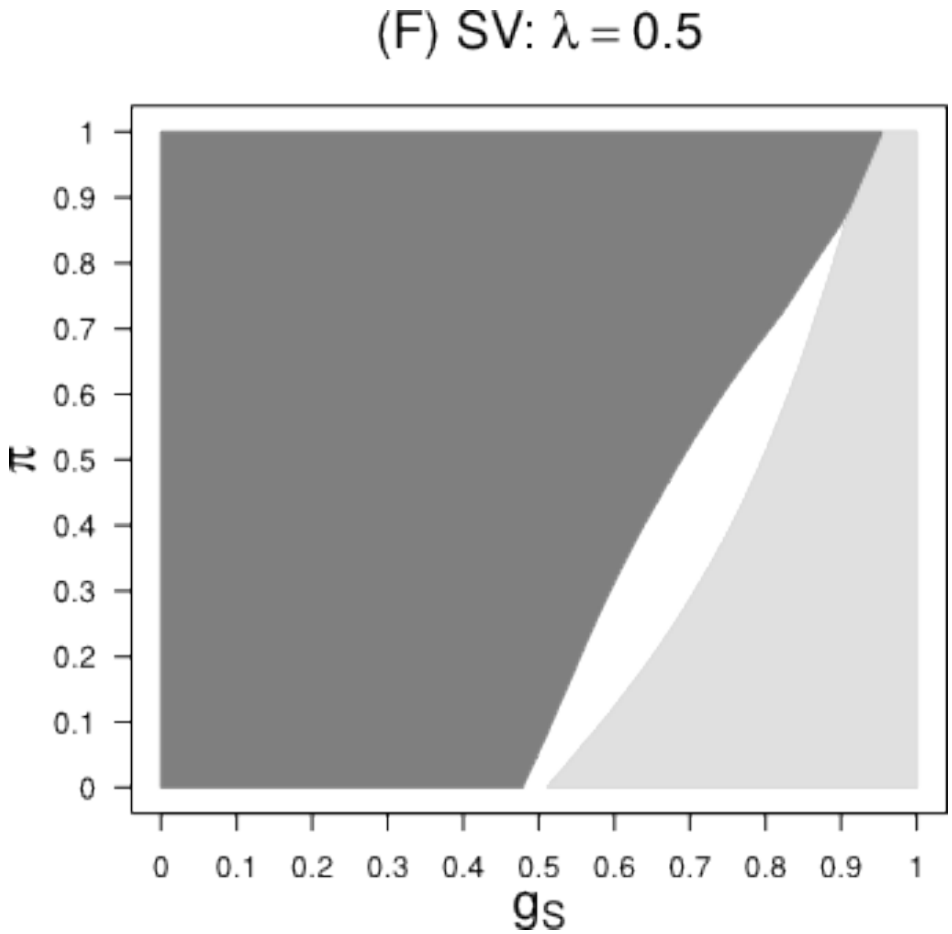
Sponsor View Utility Function



■ Stratification □ Adaptive ■ Enrichment

Summary and Limitations

- For enrichment designs investigating the power to reject any null hypothesis may not be sufficient.
- The optimized design depends critically on the prior.
- We investigated a very simple adaptation rule, that depended on the effect size of the complement of S only.
- Designs can be extended to optimize the conditional expected utility, taking into account also the effect size S.
- The loss resulting from false positive rejections of H_S and H_F is accounted for only through the multiple testing procedure but not included in the utility function.

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