Response Adaptive Designs for Phase II Trials with Binary Endpoint Based on Context-Dependent Information Measures

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Introduction

Based on an article that is currently under revision in *Computational Statistics & Data Analysis.*

- Phase II trials are designed to evaluate the drug's effectiveness in people with the disease or condition being studied and to determine the common short-term adverse effects and risks associated with the drug.
- Two objectives: maximising the statistical power and maximising the number of patients responding to the treatment.
- Problem: competing objectives "learn vs earn" trade-off.
- Different approaches: multi-arm bandit (MAB), information- theoretical approaches. In this study, the designs based on the proposed information-theoretical criteria will be compared to alternative dynamic programming based approach: *optimal constrained randomised dynamic programming (CRDP),* since it allows to achieve different balances between statistical power and number of patients allocated to a more efficacious arm, as well as the proposed entropy based design.

The principle of maximum entropy states that the probability distribution which best represents the current state of knowledge is the one with largest entropy, in the context of precisely stated prior data. Principle of maximal entropy is a powerful and universal tool with applications in many spheres, for example in [Kelbert, 2015] it was successfully applied to the producing the earthquakes alarm levels in California.

Introduction

"Learn vs earn" trade-off.
Consider a Phase II clinical trial with two independent treatment arms, A_1 and A_2, associated with unknown efficacy probabilities of a binary response.

- "best intention strategy" – higher number of responses, low statistical power
- "information gain" principle – using "standard" information measures, higher power, low number of responses.

Example:

Assume that a rare disease with 10 patients were assigned to each arm and 4 and 6 responses were observed, respectively.

Assume that the probabilities P_1 and P_2 are considered as random variables with Beta distributions $\mathcal{B}(4,6)$ and $\mathcal{B}(6,4)$, and one uses the mean as the point estimate: $\hat{p}_1 = 0.4$ and $\hat{p}_2 = 0.6$.

For instance, applying the Shannon differential entropy

$$h(f) = -\int_0^1 f(p)\log f(p)\mathrm{d}p, \tag{1}$$

to Beta distributions $f_1(p_1)$, $f_2(p_2)$ as above, one can find that $h(f_1) = h(f_2)$.

Concept of Weighted Information

Definition 1.1

In (Mozgunov and Jaki, 2018) it was proposed to use the information-theoretical criterion based on the weighted Shannon differential entropy (WDE)

$$h^{\phi}(f) = -\int_0^1 \phi(p) f(p) \log(f(p)) \mathrm{d}p \tag{2}$$

where $\phi : \mathbb{R} \mapsto \mathbb{R}^+$ is a positive weight function that answers the question "Which outcomes are more desirable?".

Similarly, other weighted entropy measures can be defined:

Definition 1.2

the weighted Fisher Information (WFI)

$$I^{\phi}(\theta) = \mathbb{E}\left(\phi(P) \left(\frac{\partial}{\partial \theta} \log(f(P, \theta)) \right)^2 \middle| \theta \right), \tag{3}$$

the weighted Renyi Information (WRI)

$$H_{\nu}^{\phi}(f) = \frac{1}{1-\nu} \log \int_0^1 \phi(p)(f(p))^{\nu} \mathrm{d}p, \nu \geq 0, \tag{4}$$

and the weighted Tsallis Information (WTI)

$$T_q^{\phi}(f) = \frac{1}{q-1} \left(1 - \int_0^1 \phi(p)(f(p))^q \mathrm{d}p \right), q \in \mathbb{R}. \tag{5}$$

Concept of Weighted Information

Assume $P \sim \mathcal{B}(\upsilon + 1, \beta - \upsilon + 1)$, $\upsilon > -1, \beta - \upsilon > -1$.

Suppose that an arm was assigned to n patients and x responses were observed.

Then, the posterior PDF of P takes the following form

$$f^{(n)}(p|x) = (n + \beta + 1)\binom{n+\beta}{x+\upsilon} p^{x+\upsilon}(1-p)^{n-x+\beta-\upsilon}. \tag{6}$$

Let us assume $\frac{x}{n} \to \alpha$, implying that the posterior density $f^{(n)}(p|x)$ of r.v. P concentrates in a neighbourhood of a certain point α as the sample size n grows.

Let γ be the target response probability defined by a clinician.

To emphasize the desirable values of the response probability (a neighbourhood of the target γ), the weight function in a Beta form can be used

$$\phi_\kappa^{(n)}(p) = \bar{\Lambda}(\gamma, x, n, \upsilon, \beta, \kappa) p^{\gamma n^\kappa}(1-p)^{(1-\gamma)n^\kappa} \tag{7}$$

where κ is the sensitivity parameter and $\bar{\Lambda}$ is a constant satisfying the normalisation condition

$$\int_{\mathbb{R}} \phi_\kappa^{(n)} f^{(n)} \mathrm{d}p = 1. \tag{8}$$

To preserve the asymptotically unbiased estimation of the probability, the weight function is restricted to satisfy

$$\lim_{n\to\infty} \int_0^1 p \phi_\kappa^{(n)} f^{(n)} \mathrm{d}p = \alpha.$$

Derivation of the Asymptotic Criteria

Following the entropy gain principle

$$\delta_R^{(\kappa)}(\gamma, n, x, \beta, \upsilon) = H_\nu^{\phi_\kappa}(f_x^{(n)}) - H_\nu(f_x^{(n)}), \tag{9}$$

$$\delta_T^{(\kappa)}(\gamma, n, x, \beta, \upsilon) = T_\nu^{\phi_\kappa}(f_x^{(n)}) - T_\nu(f_x^{(n)}), \tag{10}$$

$$\delta_F^{(\kappa)}(\gamma, n, x, \beta, \upsilon) = I^{\phi_\kappa}(f_x^{(n)}) - I(f_x^{(n)}), \tag{11}$$

$$\delta_S^{(\kappa)}(\gamma, n, x, \beta, \upsilon) = h^{\phi_\kappa}(f_x^{(n)}) - h(f_x^{(n)}), \tag{12}$$

are used as "exact" entropy criteria for the allocation of patients.

In (Mozgunov and Jaki, 2018) the leading term of the information gain *asymptotic expansions*

$$\delta_S = h^{\phi}(f) - h(f) \tag{13}$$

was proposed as the **selection criterion** to be used for the allocation of patients.

Precisely, it was obtained that the leading term of the difference between the weighted and standard Shannon differential entropy for a r.v. with density (6) and the weight function (7) takes the form

$$\frac{(\alpha-\gamma)^2}{2\alpha(1-\alpha)}(n+\beta+2)^{2\kappa-1}.$$

Derivation of the Asymptotic Criteria

Let $\phi_\kappa^{(n)}$ be the weight function given in (7), $0 < \kappa < 1$, and $\lim_{n\to\infty} \frac{x}{n} = \alpha$. Consider a r.v. $Z_x^{(n)}$ with PDF (6). Then the following limits hold for the difference in the weighted and standard differential entropies of r.v. $Z_x^{(n)}$ for:

(*i*) the Renyi entropy

$$\lim_{n\to\infty}\left[H_\nu^{\phi_\kappa}(f_x^{(n)}) - H_\nu(f_x^{(n)}) - \frac{1}{1-\nu}\omega(\nu,\alpha,\kappa,n,\gamma)\right] = 0 \qquad (14)$$

$$\text{where}\quad \omega(\nu,\alpha,\kappa,n,\gamma) = \sum_{i=1}^{\lfloor\frac{\kappa}{1-\kappa}\rfloor}(-1)^{i-1}\frac{1}{i(i+1)}\left(\gamma^{i+1}\frac{1-\nu^i}{(\nu\alpha)^i} + \right.$$
$$\left. + \ (1-\gamma)^{i+1}\frac{1-\nu^i}{(\nu(1-\alpha))^i} \ + \ \frac{\nu^i-1}{\nu^i}\right) n^{(i+1)\kappa-i}.$$

(*ii*) the Tsallis entropy

$$\lim_{n\to\infty}\left[T_q^{\phi_\kappa}(f_x^{(n)}) - \exp\left\{\omega(q,\alpha,\kappa,n,\gamma)\right\}T_q(f_x^{(n)})\right] = 0. \qquad (15)$$

(*iii*) the Fisher information

$$\lim_{n\to\infty}\left[I^{\phi_\kappa}(f_x^{(n)}) - I(f_x^{(n)}) - \sum_{m_1,m_2\in\mathbb{N}:\, m_1+m_2\le\lfloor\frac{2}{1-\kappa}\rfloor}\frac{(-1)^{m_1+m_2-2}}{m_1 m_2}\right.$$
$$\left(\left(\frac{\gamma}{\alpha}\right)^{m_1} - \left(\frac{1-\gamma}{1-\alpha}\right)^{m_1}\right)\left(\left(\frac{\gamma}{\alpha}\right)^{m_2} - \left(\frac{1-\gamma}{1-\alpha}\right)^{m_2}\right) n^{(m_1+m_2)\kappa-(m_1+m_2)+2} -$$
$$\left. - 2\sum_{m=1}^{\lfloor\frac{\kappa}{1-\kappa}\rfloor}\left(\left(\frac{\gamma}{\alpha}\right)^{m} - \left(\frac{1-\gamma}{1-\alpha}\right)^{m}\right)\left(\frac{1-2\gamma}{2\alpha(1-\alpha)}\right) n^{(m+1)\kappa-m}\right] = 0. \qquad (16)$$

Derivation of the Asymptotic Criteria

Using the same idea using other weighted generalisation of the well-established information measures, namely, the Renyi, Tsallis and Fisher informations are elaborated.

For the first type of designs, using the leading term of the asymptotic expansion for difference between the weighted and standard Shannon (17) and Fisher (18) informations results in the following "asymptotic" criteria for the treatment selection

$$\bar{\delta}_S^{(\kappa)}(\gamma, \alpha, n, \beta) = \frac{2(\alpha-\gamma)^2}{\alpha(1-\alpha)}(n+\beta+2)^{2\kappa-1},\ \kappa \in [0.5, 1) \tag{17}$$

and

$$\bar{\delta}_F^{(\kappa)}(\gamma, \alpha, n, \beta) = \frac{(\alpha-\gamma)^2}{\alpha^2(1-\alpha)^2}(n+\beta+2)^{2\kappa},\ \kappa \in (0, 1), \tag{18}$$

respectively. The term $(n+\beta+2)$ plays the role of "total" number of actual (n) and prior $(\beta+2)$ observations. Note that the leading terms for the Renyi and Tsallis entropies are not considered as they are monotonic transformations of the leading term of the difference for the Shannon entropies (17).

For asymptotic designs the experiment starts with the arm that minimises either the criterion (17) or the criterion (18) based on the prior distribution:
$\inf_{j\in\{1,\dots,k\}}\{\bar{\delta}_i^{(\kappa)}(\gamma, \hat{\alpha}_j, 0, \beta_j)\}$, $i \in \{S, F\}$, $\hat{\alpha}_j = \frac{\upsilon_j+1}{\beta_j+2}$.
During the experiment the plug-in estimator is recomputed on each iteration $\hat{\alpha}_j = \frac{x_n+\upsilon_j+1}{n_j+\beta_j+2}$ and the information gains $\bar{\delta}_i^{(\kappa)}(\gamma, \hat{\alpha}_j, n_j, \beta_j)$ are recomputed.

Algorithm for Arm Selection

Consider k alternative treatment arms $\{A_1, \ldots, A_k\}$. Denote by α_j,υ_j,β_j,n_j and $\hat{\alpha}_j$ parameters for the arm A_j.

The algorithm for Arm Selection using the exact entropy criteria:

- The experiment starts with the arm that minimises one of the quantities (9-12), depending on the information measure used, based on prior distribution: $\inf_{j\in\{1,\ldots,k\}}\{\delta_i^{(\kappa)}(\gamma, 0, 0, \beta_j, \upsilon_j)\}$, $i \in \{R, T, S, F\}$.

- Once the outcomes for the previous $n = n_1 + \cdots + n_k$ patients are observed and the information gain $\delta_i^{(\kappa)}(\gamma, n_j, x_j, \beta_j, \upsilon_j)$ is recomputed with an updated number of responses, the target arm for the next patient is being chosen by the rule: $\inf_{j\in\{1,\ldots,k\}}\{\delta_i^{(\kappa)}(\gamma, n_j, x_j, \beta_j, \upsilon_j)\}$.

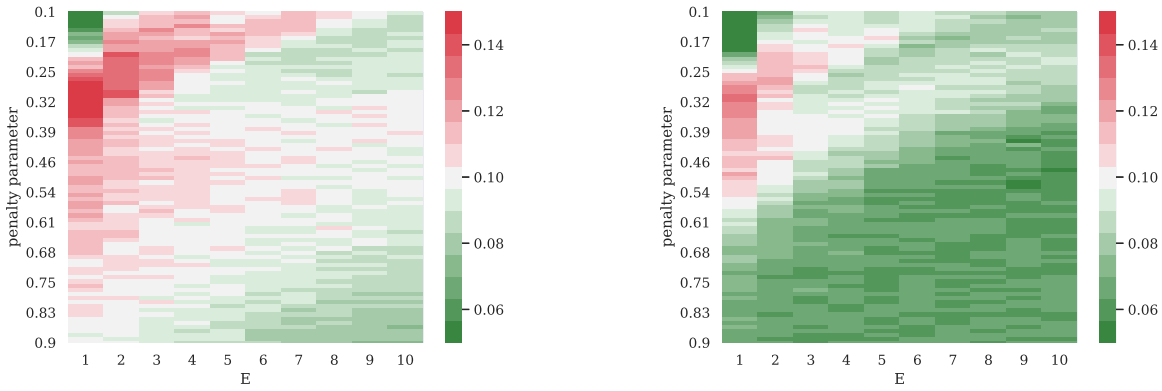
- The procedure repeats until the total number of N observations is attained. At the end of the experiment as for the asymptotic criteria, the target arm is defined with κ_f which minimises leading term of the asymptotic: $\kappa_f = \frac{1}{2}$ for the Renyi, Tsallis and Shannon criteria and $\kappa_f \approx 0$ for the Fisher criterion.

For asymptotic designs:
The information gains $\bar{\delta}_i^{(\kappa)}(\gamma, \hat{\alpha}_j, n_j, \beta_j)$ are recalculated using a plug-in estimator $\hat{\alpha}_j = \frac{x_n+\upsilon_j+1}{n_j+\beta_j+2}$

Criteria for Performance Evaluation and calibration

Prior distribution is reparametrised: $\mathcal{B}(E \times \eta, E - E \times \eta)$. $E > 0$ and $\eta \in (0, 1)$ called the strength of prior and prior probability, respectively.

1. **Type I error rate.** The proportion of times H_0 is incorrectly rejected under scenario $\theta_a = \theta_b = 0.5$. The type I error rate is required to be controlled under 10%.



The effect of E on type I error rate for the AF for the designs with $\delta = 0.085$ and $\delta = 0.1$. Type I error, calculated for all of the designs with various penalty parameter $\kappa \in \{0.1, 0.11, \ldots, 0.99\}$ (top to bottom) and prior parameter $E \in \{1, 2, \ldots, 10\}$ (left to right), is represented by a color in a range from 15% (brightest red) to 5% (darkest green), with target values less than 10% (white).

Table: Calibrated values of E and δ for each entropy criteria, namely the Shannon (S), Fisher (F), Tsallis (T), Renyi (R).

	AS	AF	S	F	T	R
E	7	6	9	4	9	8
δ	0.09	0.085	0.085	0.09	0.09	0.09

A – asymptotic criteria, no letter – exact criteria.

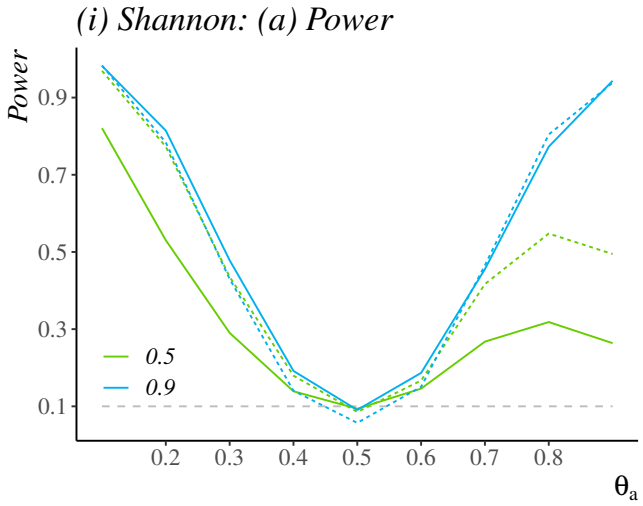
Calibrated values of additional parameters: $q = 0.35$ for the Tsallis entropy and $\nu = 0.75$ for the Renyi entropy.

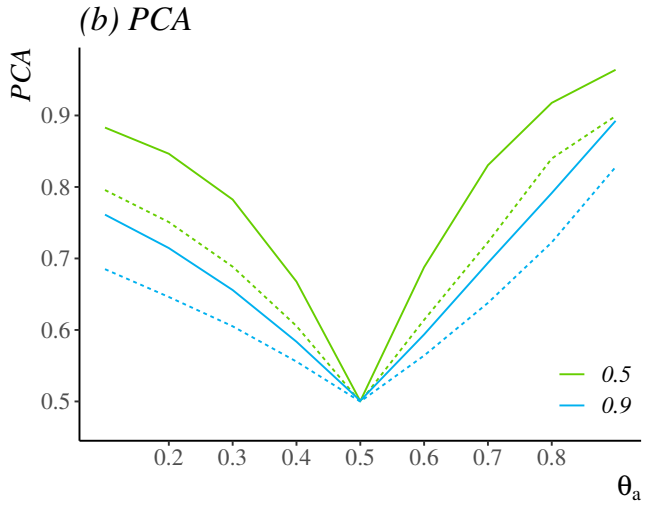
Criteria for Performance Evaluation and calibration

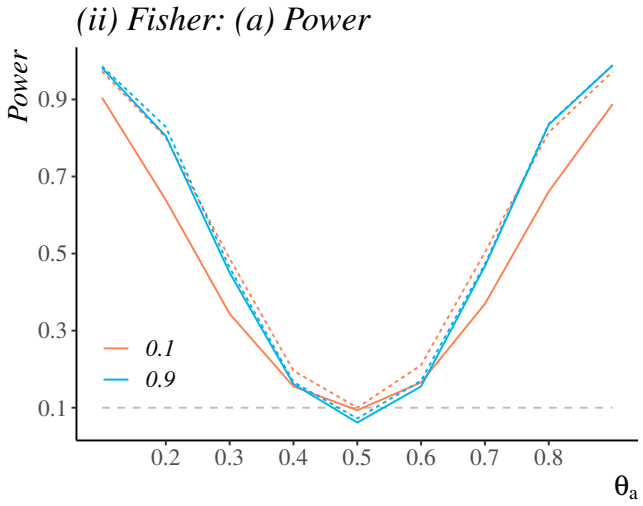
1. **Type I error rate.** The proportion of times H_0 is incorrectly rejected under scenario $\theta_a = \theta_b = 0.5$. The type I error rate is required to be controlled under 10%.
2. **Power.** The proportion of times H_0 is correctly rejected under scenarios $\theta_a \neq \theta_b$.
3. **Proportion of correctly allocated patients (PCA).** The proportion of patients on a superior treatment.
4. **Probability of correct selections (PCS).** The proportion of times when the truly superior arm was correctly recommended by the design.

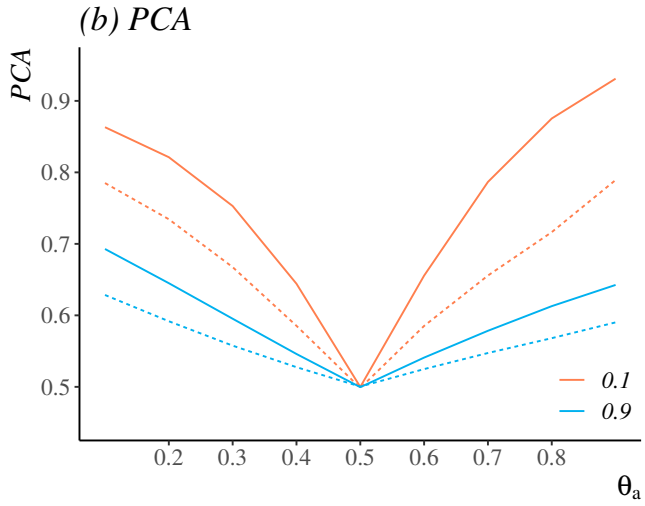
In actual clinical trials, the true probabilities of response θ_a and θ_b are unknown. Hence, it is important to take into account an average performance in terms of power and PCA over the set of all scenarios $\Theta'_a = \Theta_a \backslash \{0.5\}$, except for the $\theta_a = \theta_b$.

The Effect of Penalty Parameter κ



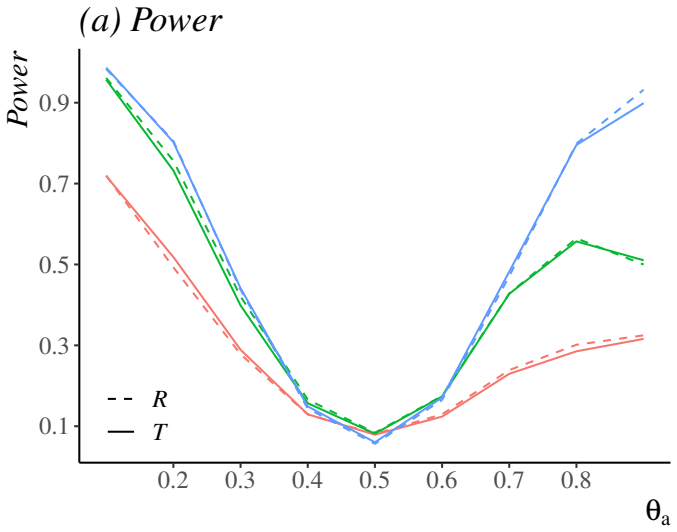


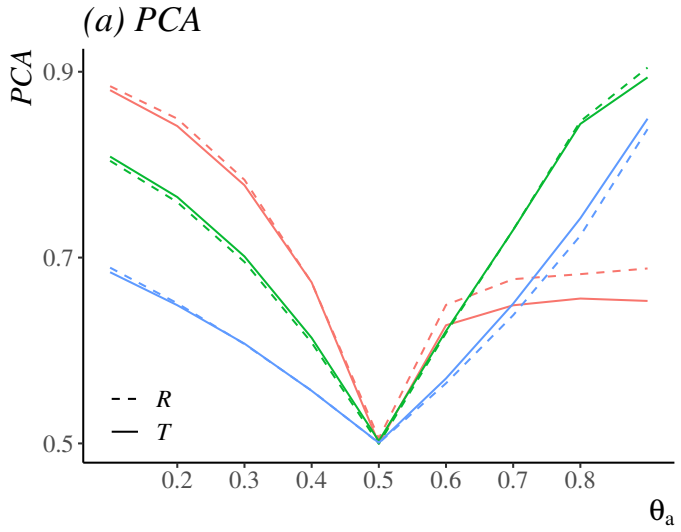




Power and PCA for the Shannon and Fisher criteria with different values of κ: $\kappa = 0.1$ (red line), $\kappa = 0.5$ (green line), $\kappa = 0.9$ (blue line); the asymptotic criteria AS, AF, and T are denoted by solid lines, and the exact criteria S and F by the dashed line.

Renyi vs Tsallis entropy





Comparison of Renyi criterion with respect to Tsallis criterion in terms of power and PCA: solid line – Tsallis criteria; dashed line – Renyi criteria; red line, $\kappa = 0.1$; green line, $\kappa = 0.5$; blue line, $\kappa = 0.9$.
The calibrated values of the additional parameters are $q = 0.35$ for the Tsallis entropy and $\nu = 0.75$ for the Renyi entropy.

Renyi vs Tsallis entropy

1. **Type I error rate.** The proportion of times H_0 is incorrectly rejected under scenario $\theta_a = \theta_b = 0.5$. The type I error rate is required to be controlled under 10%.
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4. **Probability of correct selections (PCS).** The proportion of times when the truly superior arm was correctly recommended by the design.

In actual clinical trials, the true probabilities of response θ_a and θ_b are unknown. Hence, it is important to take into account an average performance in terms of power and PCA over the set of all scenarios $\Theta'_a = \Theta_a \backslash \{0.5\}$, except for the $\theta_a = \theta_b$.

Consider average percentage performance of a design X over the set of scenarios Θ'_a in terms of power relative to the FR

$$\overline{\psi}_X := \frac{100}{|\Theta'_a|} \sum_{i \in \Theta'_a} \frac{\psi_{X,i} - \psi_{FR,i}}{\psi_{FR,i}} , \tag{19}$$

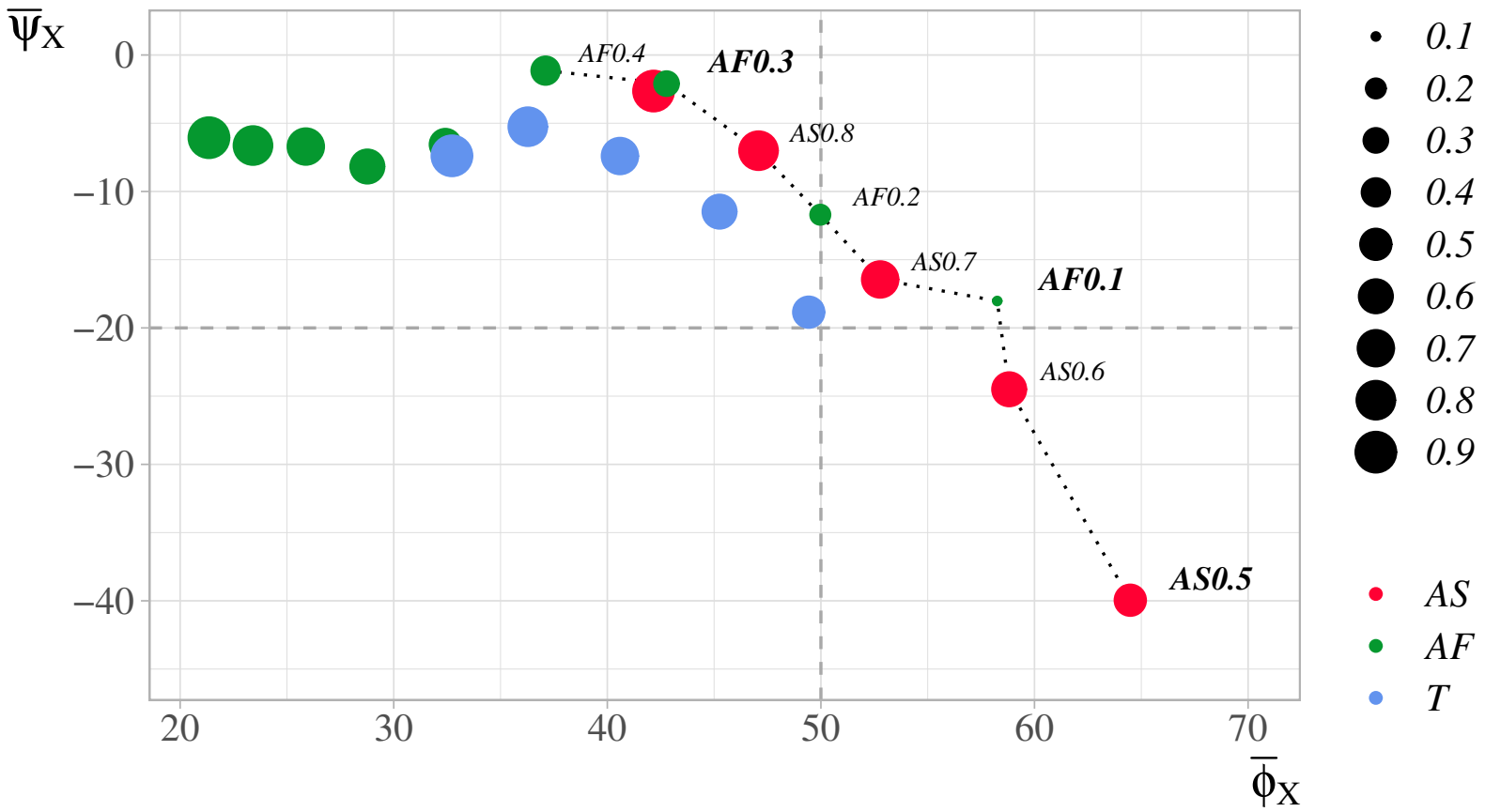
and similarly defined average percentage performance in terms of PCA

$$\overline{\phi}_X := \frac{100}{|\Theta'_a|} \sum_{i \in \Theta'_a} \frac{\phi_{X,i} - \phi_{FR,i}}{\phi_{FR,i}} \tag{20}$$

where $\psi_{X,i}$, $\phi_{X,i}$ are power and PCA for design X in a scenario i, respectively.

Comparison of the Entropy-based Designs

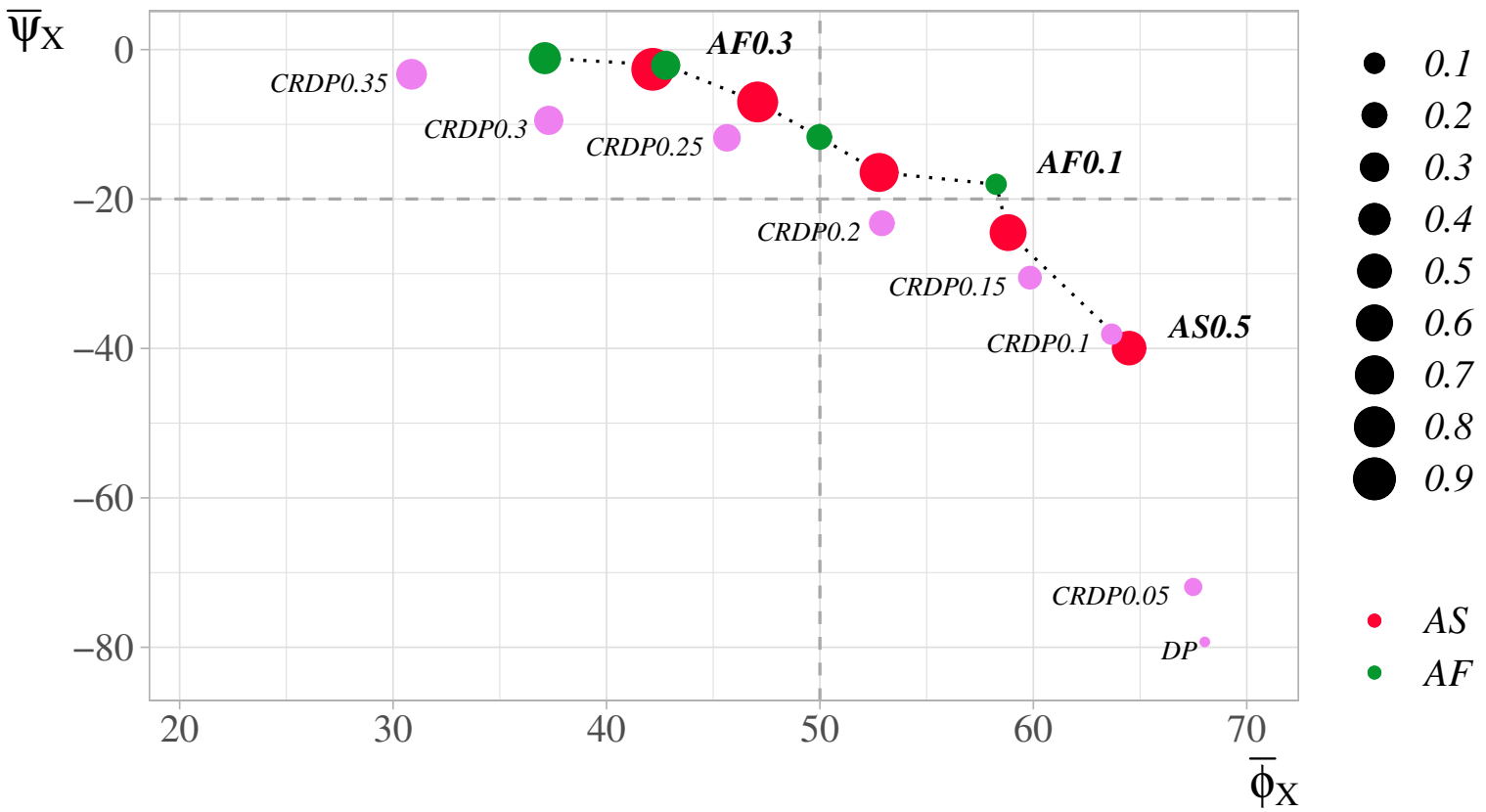
- $AF0.4$, $AF0.3$ and $AS0.8$ with a balance "shifted" towards power;
- $AS0.7$ and $AF0.1$ with an "intermediary" balance;
- $AS0.5$ and $AS0.6$ with a balance "shifted" towards PCA.



An average percentage power loss $\bar{\psi}_i$ vs an average percentage PCA gain $\bar{\phi}_i$ for design X in comparison to the FR approach for the AS (red dots), AF (green dots), T (blue dots).

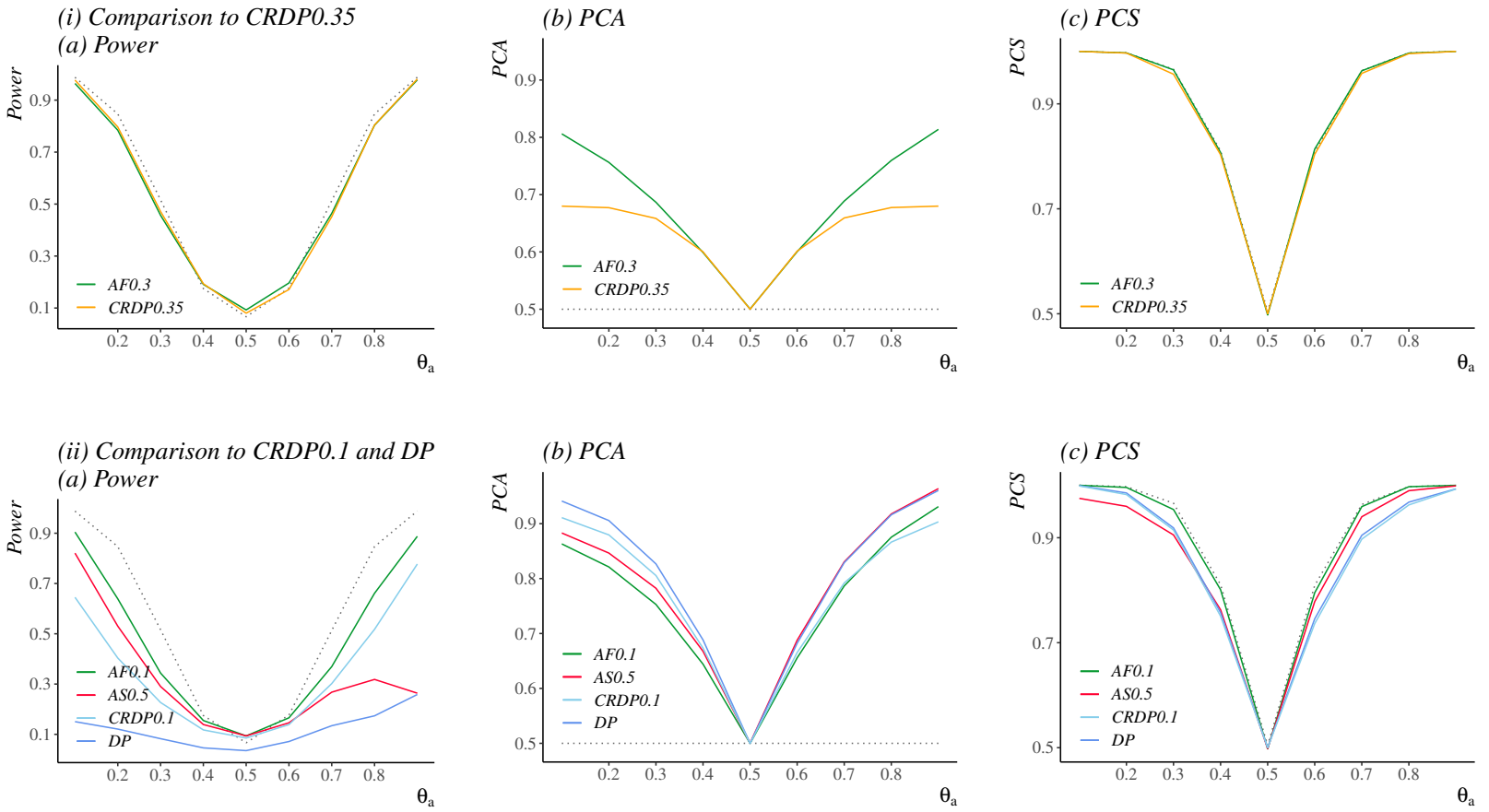
Comparison to the Dynamic Programming Designs

- $AF0.3$ – a design with a balance "shifted" towards power;
- $AF0.1$ – a design with an "intermediary" balance;
- $AS0.5$ – a design with a balance "shifted" towards PCA.



An average percentage power loss $\bar{\psi}_i$ vs an average percentage PCA gain $\bar{\phi}_i$ for winning entropy-based designs X and dynamic programming designs (pink dots) in comparison to the FR approach.

Comparison to the Dynamic Programming Designs



Comparison of the novel designs, namely $AF0.1$ (green line), $AF0.3$ (green line) and $AS0.5$ (red line), to the alternative approaches, namely $CRDP0.35$ (orange line), $CRDP0.1$ (light blue line), the DP (blue line), the FR (grey dotted line), in terms of power, PCA and PCS.