

# STRATEGIES FOR SUPERSATURATED SCREENING: GROUP ORTHOGONAL AND CONSTRAINED VAR(S+) DESIGNS

---

Maria Weese  
Information Systems & Analytics  
Farmer School of Business  
Miami University  
ENBIS 2021

weeseml@miamioh.edu  
Twitter: @MFWeese

## CO-AUTHORS



**David Edwards**  
VCU  
Richmond, Virginia



**Byran Smucker**  
Miami University  
Oxford, Ohio



**Jon Stallrich**  
NC State  
Raleigh, North Carolina

"I think it is perfectly natural and wise to do some supersaturated experiments."

-John Tukey

(from a discussion of Satterthwaite 1959)

## SSD DEFINITION

Two-level supersaturated designs (SSDs) use  $n < k + 1$  runs to examine  $k$  factors. This design uses  $n = 6$  runs to examine  $k = 9$  factors.

$$D = \begin{pmatrix} -1 & -1 & -1 & 1 & 1 & 1 & 1 & 1 & -1 \\ 1 & 1 & -1 & 1 & 1 & 1 & -1 & -1 & 1 \\ -1 & -1 & 1 & 1 & -1 & -1 & -1 & 1 & 1 \\ 1 & -1 & -1 & 1 & -1 & -1 & 1 & -1 & -1 \\ -1 & 1 & 1 & -1 & -1 & 1 & -1 & -1 & -1 \\ 1 & 1 & -1 & -1 & -1 & 1 & 1 & 1 & 1 \end{pmatrix}$$

## EXAMPLES OF PUBLISHED SSDS



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



Analytica Chimica Acta 524 (2004) 63–71

ANALYTICA  
CHIMICA  
ACTA

[www.elsevier.com/locate/aca](http://www.elsevier.com/locate/aca)

## Application of strategic sample composition to the screening of anti-inflammatory drugs in water samples using solid-phase microextraction

J. Carpinteiro, J.B. Quintana, E. Martínez, I. Rodríguez,  
A.M. Carro, R.A. Lorenzo, R. Cela\*

*Departamento de Química Analítica, Nutrición y Bromatología, Instituto de Investigación y Análisis Alimentario,  
Universidad de Santiago de Compostela, Santiago de Compostela 15782, Spain*

Received 26 November 2003; received in revised form 9 February 2004; accepted 8 March 2004

Available online 8 May 2004

---

### Abstract

The usefulness of the strategically designed sample composition (SSC) methodology for the screening of four anti-inflammatory drugs (ibuprofen, naproxen, tolafenamic acid and diclofenac) in water samples is demonstrated. Assuming that in screening campaigns only a limited number of the samples are contaminated with the analytes, the proposed approach allows the reliable identification of the contaminated specimens and the approximate estimation of their concentrations, with a 50% reduction in the total number of processed samples. To achieve this, a limited number of composite samples are built from the individual specimens. Automatic preparation of composite samples avoids human mistakes during this time-consuming and tedious operation, increasing the reliability of the predictions. In this work, a low-cost automatic device able to mix the individual specimens in the proportions indicated in the composition matrix is used. Moreover, the efficiency of evolutionary algorithms to predict the concentrations of the anti-inflammatory drugs in ultrapure and river water samples, artificially polluted in the laboratory and their robustness against large errors during the analysis of the composite samples, are evaluated.

© 2004 Elsevier B.V. All rights reserved.

**Keywords:** Strategic sample composition; Screening analysis; Anti-inflammatory drugs

---



Contents lists available at ScienceDirect

## Screening of factors influencing the extraction of gelatin from the skin of cuttlefish using supersaturated design



Mourad Jridi<sup>a,\*</sup>, Imen Lassoued<sup>a</sup>, Amel Kammoun<sup>b</sup>, Rim Nasri<sup>a</sup>, Moncef chaâbouni<sup>b</sup>, Moncef Nasri<sup>a</sup>, Nabil Souissi<sup>c</sup>

<sup>a</sup> Laboratoire de Génie Enzymatique et de Microbiologie, Université de Sfax, Ecole Nationale d'Ingénieurs de Sfax, BP 1173-3038 Sfax, Tunisia

<sup>b</sup> Laboratoire de Chimie Industrielle, Université de Sfax, Ecole Nationale d'Ingénieurs de Sfax, BP 1173-3038 Sfax, Tunisia

<sup>c</sup> Laboratoire de Biodiversité et Biotechnologie Marine, Institut National des Sciences et Technologies de la Mer, Centre de Sfax, BP 1035-3018 Sfax, Tunisia

### ABSTRACT

Supersaturated design (SSD) was used for screening the key parameters influencing gelatin extraction yield from cuttlefish (*Sepia officinalis*) skin. Results indicated that among a list of 17 factors only five parameters, namely, alkali (NaOH) concentration, acid reagent (acetic acid), enzyme, thermal treatment temperature and centrifugation time, were factors influencing gelatin yield. The optimal conditions for gelatin extraction were found to be: pretreatment with NaOH 0.03 M for 1 h; treatment with pepsin for 24 h at 4 °C in acetic acid 100 mM; extraction for 14 h at 40 °C. The yield of gelatin extraction was 54.6%. Cuttlefish skin gelatin (CSG) contained protein as the major compound (90.95%) and low fat (0.3%) and ash (0.05%) contents. The physico-chemical properties of the CSG were characterized and compared with those of bovine gelatin (BG). The result of textural properties showed that hardness, elasticity and cohesiveness of CSG were lower than those of BG. Further, the gel strength of CSG (192.01 g) was lower than that of BG (259.65 g), possibly due to lower imino-acid content. The functional properties, including emulsion activity index and foam stability were similar to those of BG. The CSG showed stronger ability of apple juice clarification, than BG without affecting its nutritional values.

© 2014 The Institution of Chemical Engineers. Published by Elsevier B.V. All rights reserved.

**Keywords:** Supersaturated design; Gelatin extraction process; Cuttlefish skin; Textural properties; Functional properties; Application



## Supersaturated design for screening factors influencing the preparation of sulfated amides of olive pomace oil fatty acids

F. Rais <sup>a</sup>, A. Kamoun <sup>a</sup>, M. Chaabouni <sup>a,\*</sup>, M. Claeys-Bruno <sup>b</sup>, R. Phan-Tan-Luu <sup>c</sup>, M. Sergent <sup>b</sup>

<sup>a</sup> Laboratoire de Chimie Industrielle, Ecole Nationale d'Ingénieurs de Sfax, BP W 3038 Sfax Tunisia

<sup>b</sup> Aix-Marseille Université, Institut des Sciences Moléculaires de Marseille, ISM2-UMR-CNRS-6263, Equipe AD2EM, Campus St Jérôme, Service D 52, 13397 Marseille Cedex 20, France

<sup>c</sup> LPRAI, 40, boulevard Iradj, 13010 Marseille, France

---

### ARTICLE INFO

**Article history:**

Received 23 May 2009

Received in revised form 20 July 2009

Accepted 25 July 2009

Available online 3 August 2009

---

**Keywords:**

Supersaturated design

Screening

Ridge regression

All-subset regressions

Sulfated fatty amides

Olive pomace oil

---

### ABSTRACT

In a previous paper, we showed that the preparation of sulfated diethanolamide of fatty acids is easy to carry out without organic solvents when using olive pomace oil as starting material; the reaction yield was, however, highly variable as a function of factor levels. The purpose of this research is to look for the optimal experimental conditions. We started by applying a supersaturated experimental design to screen for important factors among a list of 31 potentially influential factors in 18 experiments. Thus, we constructed a two-level supersaturated design as a half fraction of a 36-experiment Hadamard matrix and used it for this screening purpose. Multiple regression methods namely stepwise selection procedure, ridge regression and all-subset regressions were used to analyze the supersaturated design results according to a four step procedure. Results indicated that six factors, namely, molar ratio SO<sub>3</sub>/ester, amidation time, amide addition rate, alkali reagent, alkali concentration, and amidation temperature, were very influential factors. Three other factors were moderately influential: neutralization temperature, sodium methanoate amount, and methanol amount. In future research, these factors will be further studied in order to perform robustness tests of the process.

## WHAT IS SCREENING?

- Screening is the **first stage** of a sequential experimental procedure.
- Screening involves the **choice of a design and analysis** combination.
- Screening aims to **classify factors** into those that should be **further studied** (i.e. “potentially active”) and **those that can be ignored** (i.e. “inactive”).

## BASIC SCREENING MODEL

The most basic screening model includes just the linear main effects:

$$Y_i = \beta_0 + \sum_{j=1}^k \beta_j X_{ij} + \epsilon_i, \quad i = 1, 2, \dots, n \quad (1)$$

where  $n$  is the number of runs,  $\epsilon_i \sim N(0, \sigma^2)$ ,  $X_{ij}$  is the  $j$ -th factor's setting for run  $i$ , and  $\beta_j$  is an unknown parameter.

The model is equivalently written as  $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$ , where  $\mathbf{X}$  is the  $n \times (k + 1)$  model matrix,  $\boldsymbol{\beta}$  is a  $(k + 1)$ -vector of model parameters, and  $\mathbf{Y}$  and  $\boldsymbol{\epsilon}$  are  $n$ -vectors, with  $\boldsymbol{\epsilon} \sim N(\mathbf{0}, \sigma^2 \mathbf{I})$ .

The  $j$ -th factor is considered active if  $|\beta_j| > t$  for some threshold  $t \geq 0$ .

## SCREENING CLASSIFICATION

The screening classification rule depends on the experimenter's willingness to risk classifying an inactive factor as potentially active (type 1 error) and classifying a truly active factor as inactive (type 2 error)

	$ \beta_j  > t$	$ \beta_j  \leq t$
Label: Potentially Active	Correct	Type 1 Error
Label: Inactive	Type 2 Error	Correct

## THE TRADE OFF

A trade-off must be made that depends on the budget for future experimentation and the overall goals:

1. Is it important that few, if any, active factors are omitted, even at the expense of more type 1 errors?
2. Or is the goal to identify as many active factors as possible, while controlling the type 1 error more stringently?

## THE TRADE OFF

A trade-off must be made that depends on the budget for future experimentation and the overall goals:

1. Is it important that few, if any, active factors are omitted, even at the expense of more type 1 errors?
2. Or is the goal to identify as many active factors as possible, while controlling the type 1 error more stringently?

The best choice of supersaturated design (SSD) construction and analysis depends on this practitioner-specified trade-off.

The fundamental principle of experimental design is that the **data collection procedure strongly influences an estimator's statistical properties**, and hence factor classification.

Consider Least Squares (LS) and designs with orthogonal columns.

$\hat{\beta}_{\text{LS}} = (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T \mathbf{Y}$  has good screening properties for a given design if  $\sigma^2(\mathbf{X}^T \mathbf{X})^{-1}$  is “small.”

The ideal matrix,  $\mathbf{X}^T \mathbf{X} = nI_n$ , comes from regular and nonregular fractional factorial designs, having an  $\mathbf{X}$  with settings  $\pm 1$  and mutually orthogonal columns.

## TRADITIONAL SSD CONSTRUCTION

SSDs have been constructed via heuristic measures of orthogonality based on the off-diagonals of  $\mathbf{X}^T \mathbf{X} = (s_{ij})$ .

For example, the **E( $s^2$ )-criterion** forces  $s_{0j} = 0$  and minimizes  $E(s^2) = \binom{k}{2}^{-1} \sum_{1 \leq i < j \leq k} s_{ij}^2$ .

The **unconditional E( $s^2$ )-criterion, or UE( $s^2$ )-criterion** (Jones and Majumdar 2014; Weese et al. 2015) is similarly defined, but does not require  $s_{0j} = 0$ ; that is,

$$UE(s^2) = \frac{2}{k(k+1)} \sum_{0 \leq i < j \leq k} s_{ij}^2.$$

Such criteria intend to approximate the ideal structure  $\mathbf{X}^T \mathbf{X} = n \mathbf{I}_n$  as closely as possible.

For SSDs, **the ideal X cannot exist** and, even worse, **the main-effect model is not least-squares estimable.**

For SSDs, **the ideal X cannot exist** and, even worse, **the main-effect model is not least-squares estimable.**

There has been no clear consensus about the optimal pairing of SSD construction criteria and analysis strategy.

This may partially explain why practitioners are hesitant to adopt SSDs for screening.

# SSDs AS A DESIGN AND ANALYSIS COMBINATION

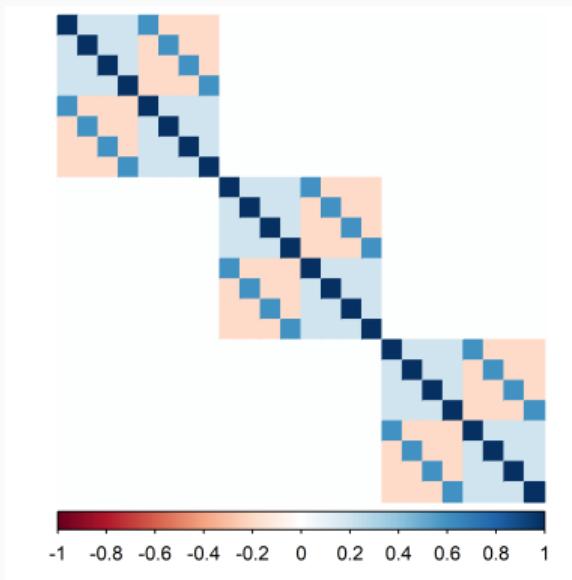
## SSD+ANALYSIS COMBINATIONS

There are two recent works which pair analysis method and SSD construction.

1. GO-SSDs (Jones et al. (2019))
2. Var(s+) (Weese et al. (2017))

## GROUP ORTHOGONAL SUPERSATURATED DESIGNS

- GO-SSDs (Jones et al. (2019)) include “fake” factor columns to estimate  $\sigma^2$ .
- The true factor columns are partitioned into mutually-orthogonal groups.
- GO-SSDs are generated using a Kronecker product of a Hadamard matrix,  $H_m$  and a small generating SSD



$n = 20, k = 24$  GO-SSD

## GO-SSDS CONSTRUCTION

To construct the  $n = 20$ ,  $k = 24$  design GO-SSD:

1. Create a Hadarmard matrix with  $m = 4$ .
2. Construct  $\mathbf{T}_{w=5 \times p=8}$  using the first 5 rows of a Hadarmard matrix with  $m = 8$ .
3. Take the Kronecker product of  $\mathbf{H}_4$  and  $\mathbf{T}_{5 \times 8}$  giving  $n = 4 \times 5 = 20$  and  $k^* = 4 \times 8 = 32$ .
4. This GO-SSD has a group size  $p = 8$  and 4 groups. Each column group will have equal rank,  $r < p$ , equal to the rank of  $\mathbf{T}$ .
5. The first group contains the intercept column and the  $p - 1 = 7$  “fake” factor columns for estimating  $\sigma^2$ . This group is not shown in the correlation plot on slide 17.

## GO-SSDS CONSTRUCTION

To construct the  $n = 20$ ,  $k = 24$  design GO-SSD:

1. Create a Hadarmard matrix with  $m = 4$ .
2. Construct  $T_{w=5 \times p=8}$  using the first 5 rows of a Hadarmard matrix with  $m = 8$ .
3. Take the Kronecker product of  $H_4$  and  $T_{5 \times 8}$  giving  $n = 4 \times 5 = 20$  and  $k^* = 4 \times 8 = 32$ .
4. This GO-SSD has a group size  $p = 8$  and 4 groups. Each column group will have equal rank,  $r < p$ , equal to the rank of  $T$ .
5. The first group contains the intercept column and the  $p - 1 = 7$  “fake” factor columns for estimating  $\sigma^2$ . This group is not shown in the correlation plot on slide 17.

In general GO-SSDs screen  $k = (m - 1)p$  factors in  $n = mw$  runs.

### Stage 1: Group Testing

1. Using the fake factor columns obtain an estimate for  $\sigma^2$ .
2. Test the significance of each group (recall the groups are orthogonal) using the error estimate obtained in step 1.
3. Pool the degrees of freedom for any non-significant groups.

## Stage 1: Group Testing

1. Using the fake factor columns obtain an estimate for  $\sigma^2$ .
2. Test the significance of each group (recall the groups are orthogonal) using the error estimate obtained in step 1.
3. Pool the degrees of freedom for any non-significant groups.

## Stage 2: Factor Testing

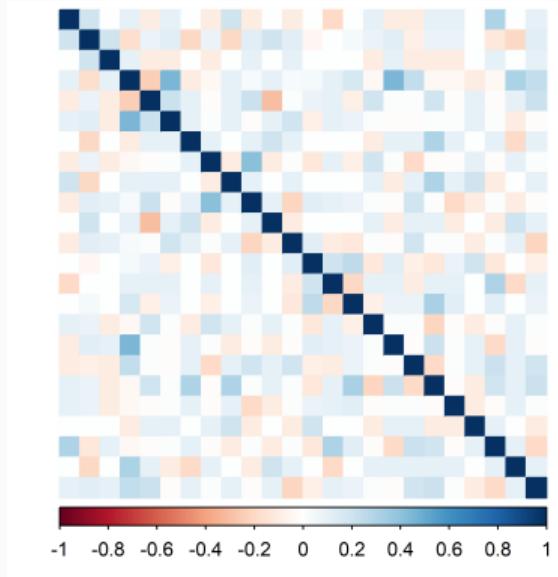
1. For the factors in the groups identified in stage 1, test all models of size 1 then 2...etc. We collect all models for a given size with a significant F-test and classify all the factors in these models as potentially active.
2. Repeat for models of up to size  $[r/2]$ .
3. If all models of rank  $[r/2]$  are significant, designate all factors in the group as “potentially active”.

## CONSTRAINED VAR(s+) SUPERSATURATED DESIGNS

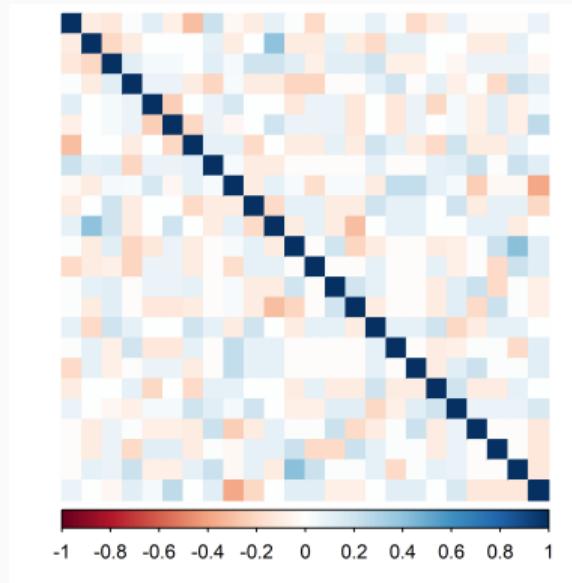
- The Var(s+) criterion (Weese et. al (2017)) minimizes the variance of the off-diagonal  $s_{ij}$ 's subject to some constraints.

$$\text{Var}(s+) = \text{UE}(s^2) - \text{UE}(s)^2 \text{ s.t. } \frac{\text{UE}^*(s^2)}{\text{UE}(s^2)} > c \text{ and } \text{UE}(s) > 0$$

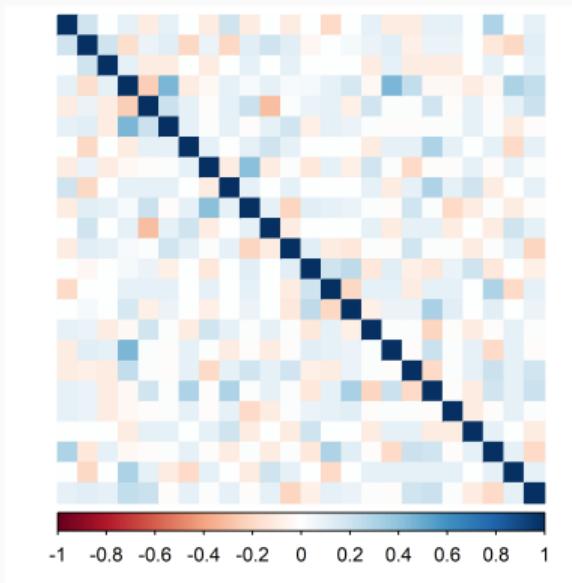
- This criterion allows the  $s_{ij}$ 's to be, on average, more positive than those in the approximately  $\text{UE}(s^2)$ -optimal design, but with less variability.



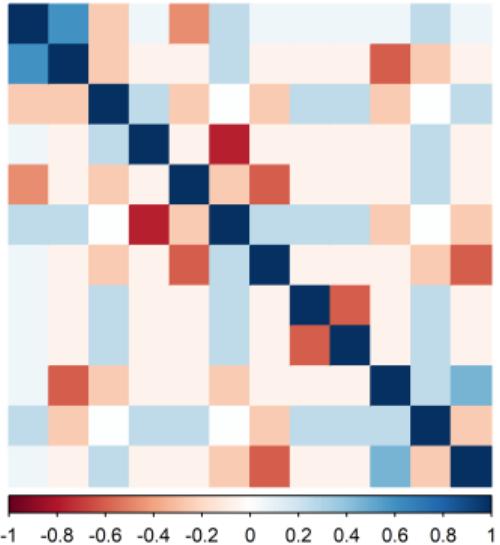
$n = 20, k = 24$  Var(s+) SSD



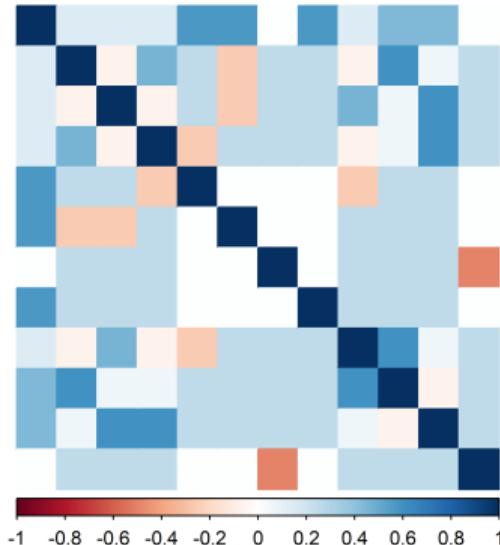
$n = 20, k = 24$   $\text{UE}(s^2)$  SSD



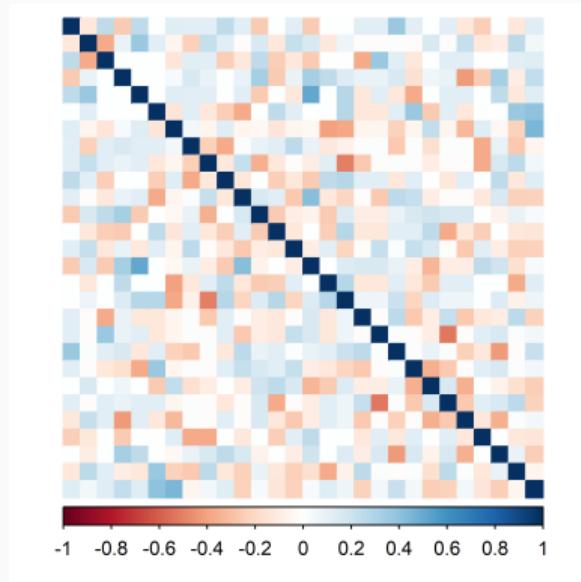
$n = 20, k = 24$   $\text{Var}(s+)$  SSD



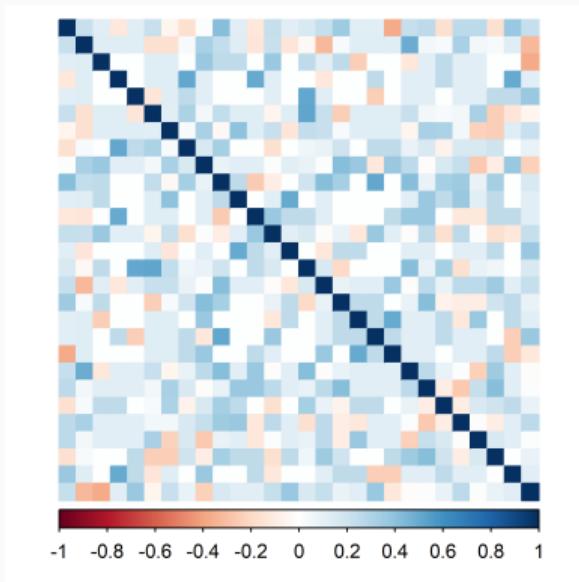
$n = 8, k = 12$  UE( $s^2$ ) SSD



$n = 8, k = 12$  Var( $s^+$ ) SSD



$n = 16, k = 28$   $\text{UE}(s^2)$  SSD



$n = 16, k = 28$   $\text{Var}(s+)$  SSD

## $\text{var}(s+)$ : DANTZIG SELECTOR

Weese et al. (2017) showed that  $\text{Var}(s+)$  designs are superior to  $\text{UE}(s^2)$ -optimal and Bayesian D-optimal designs when effect directions were correctly specified in advance:

1.  $\text{Var}(s+)$  designs have higher power
2.  $\text{Var}(s+)$  designs do not elevate type 1 error

## $\text{var}(s+)$ : DANTZIG SELECTOR

Weese et al. (2017) showed that  $\text{Var}(s+)$  designs are superior to  $\text{UE}(s^2)$ -optimal and Bayesian D-optimal designs when effect directions were correctly specified in advance:

1.  $\text{Var}(s+)$  designs have higher power
2.  $\text{Var}(s+)$  designs do not elevate type 1 error

This effect was particularly pronounced when  $\text{Var}(s+)$  designs were analyzed with the Dantzig selector.

## $\text{var}(s+)$ : DANTZIG SELECTOR

Weese et al. (2017) showed that  $\text{Var}(s+)$  designs are superior to  $\text{UE}(s^2)$ -optimal and Bayesian D-optimal designs when effect directions were correctly specified in advance:

1.  $\text{Var}(s+)$  designs have higher power
2.  $\text{Var}(s+)$  designs do not elevate type 1 error

This effect was particularly pronounced when  $\text{Var}(s+)$  designs were analyzed with the Dantzig selector.

Even when the effect directions were misspecified, the  $\text{Var}(s+)$  designs fared no worse than the  $\text{UE}(s^2)$  and Bayesian D-optimal SSDs.

## DANTZIG SELECTOR

The Dantzig selector is a regularization method that constrains an  $\ell_1$ -estimator:

$$\hat{\beta}_{DS} = \arg \min_{\tilde{\beta}} \|\tilde{\beta}\|_1 \text{ subject to } \|X^\top(y - X\tilde{\beta})\|_\infty \leq \delta. \quad (2)$$

In practice, estimates are generated for many values of  $\delta > 0$ , generating a profile plot of estimates. We **strongly recommend screening decisions be made with respect to this profile plot**, but this somewhat subjective process cannot be carried out in a simulation study.

In our simulations we followed the non-graphical approach by Phoa et al. (2009)

1. Center  $\mathbf{y}$ , and center and scale the columns of  $\mathbf{X}$  to have mean 0 and unit variance.  
Drop the intercept column from  $\mathbf{X}$ .
2. Solve (2) for  $d$  values of  $\delta$  between 0 and  $\max_j |\mathbf{x}_j^T \mathbf{y}|$ ,  $j = 1, 2, \dots, p$ . Denote the  $d$  estimates by  $\hat{\boldsymbol{\beta}}_{DS}(\delta)$ .
3. For each  $\hat{\boldsymbol{\beta}}_{DS}(\delta)$ , set all  $|\hat{\beta}_j(\delta)| < \gamma$  to 0 for some threshold  $\gamma > 0$ . Denote this by  $\hat{\boldsymbol{\beta}}_{DS}(\delta, \gamma)$ .
4. For each  $\hat{\boldsymbol{\beta}}_{DS}(\delta, \gamma)$ , calculate the least-squares estimates (also known as Gauss-Dantzig estimates) using only predictors with nonzero  $\hat{\beta}_j(\delta, \gamma)$  and compute  $BIC = n \ln(SSE/n) + k \ln(n)$  where SSE is the sum-of-squared errors.
5. For  $\hat{\boldsymbol{\beta}}_{DS}(\delta, \gamma)$  with the smallest BIC from step 4, factors with nonzero  $\hat{\beta}_j(\delta, \gamma)$  are classified as potentially active; otherwise a factor is inactive.

## THE THRESHOLD VALUE, $\gamma$

The choice of  $\gamma$  is obviously important to the power and type I error rates.

In order to compare strategies between Var(s+)/Dantzig and GO-SSD/Maxpower we used a data driven threshold value (Phoa et al. (2009)):

$$\gamma = 0.1 \times \max |\hat{\beta}_j|,$$

where the  $\hat{\beta}_j$ 's are estimates when  $\delta = 0$ .

# SSD COMPARISON

## SIMULATION PROTOCOL

For several SSD  $(n, k)$  sizes, each SSD we generated 5000 responses according to model (1) by:

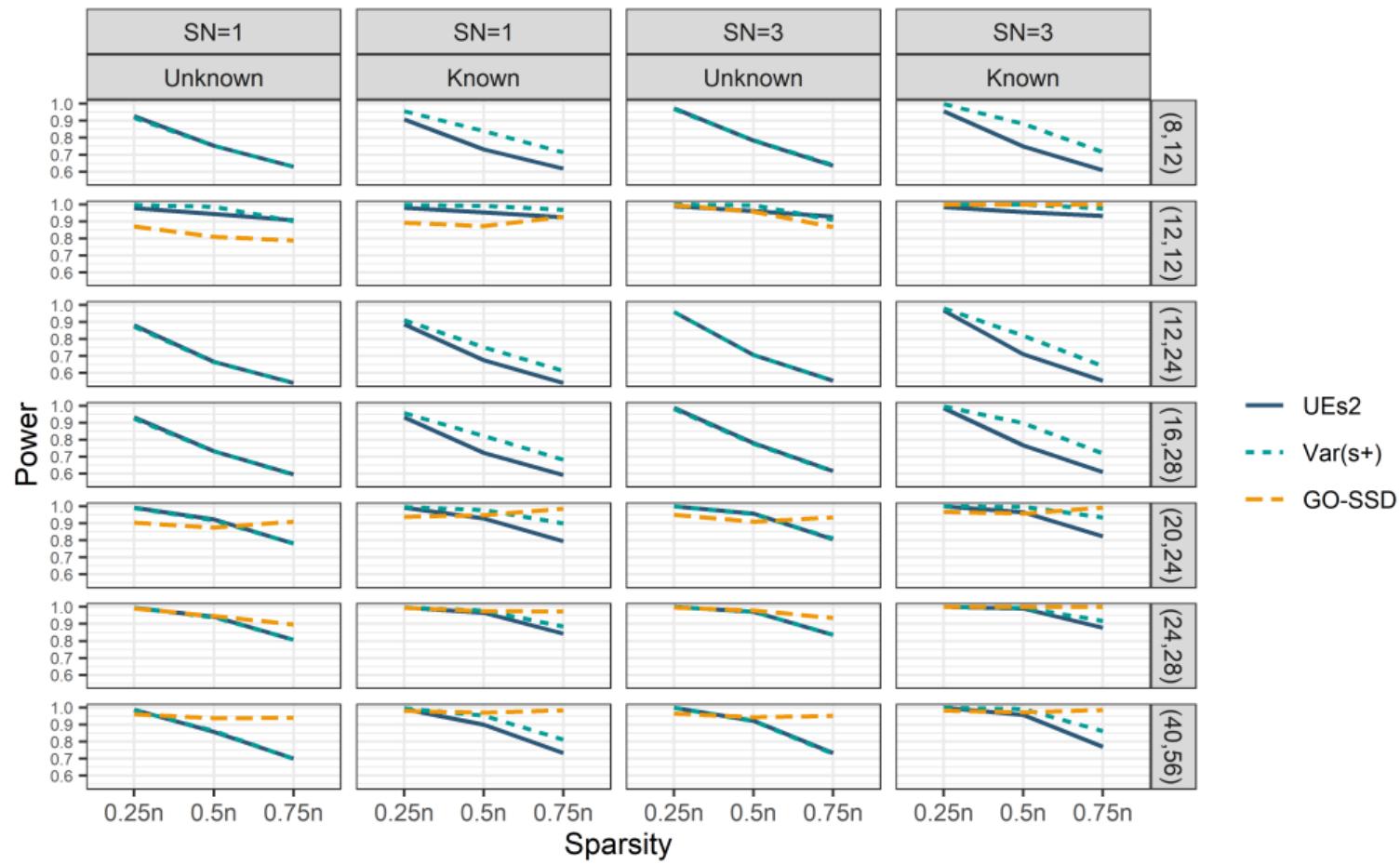
1. Randomly assigning columns to be active based on effect sparsity levels:  $0.25n$ ,  $0.5n$ , and  $0.75n$ .
2. Assigning the magnitude of the active effects generated randomly from  $\text{Exp}(1) + SN$ , where  $SN$ , meaning signal-to-noise ratio, was set to either 1 or 3.
3. Assigning the remaining inactive columns a coefficient from  $N(0, 6^{-2})$ .
4. Adjusting the signs of all coefficients to either be all positive (directions known) or mixed positive and negative (directions unknown).

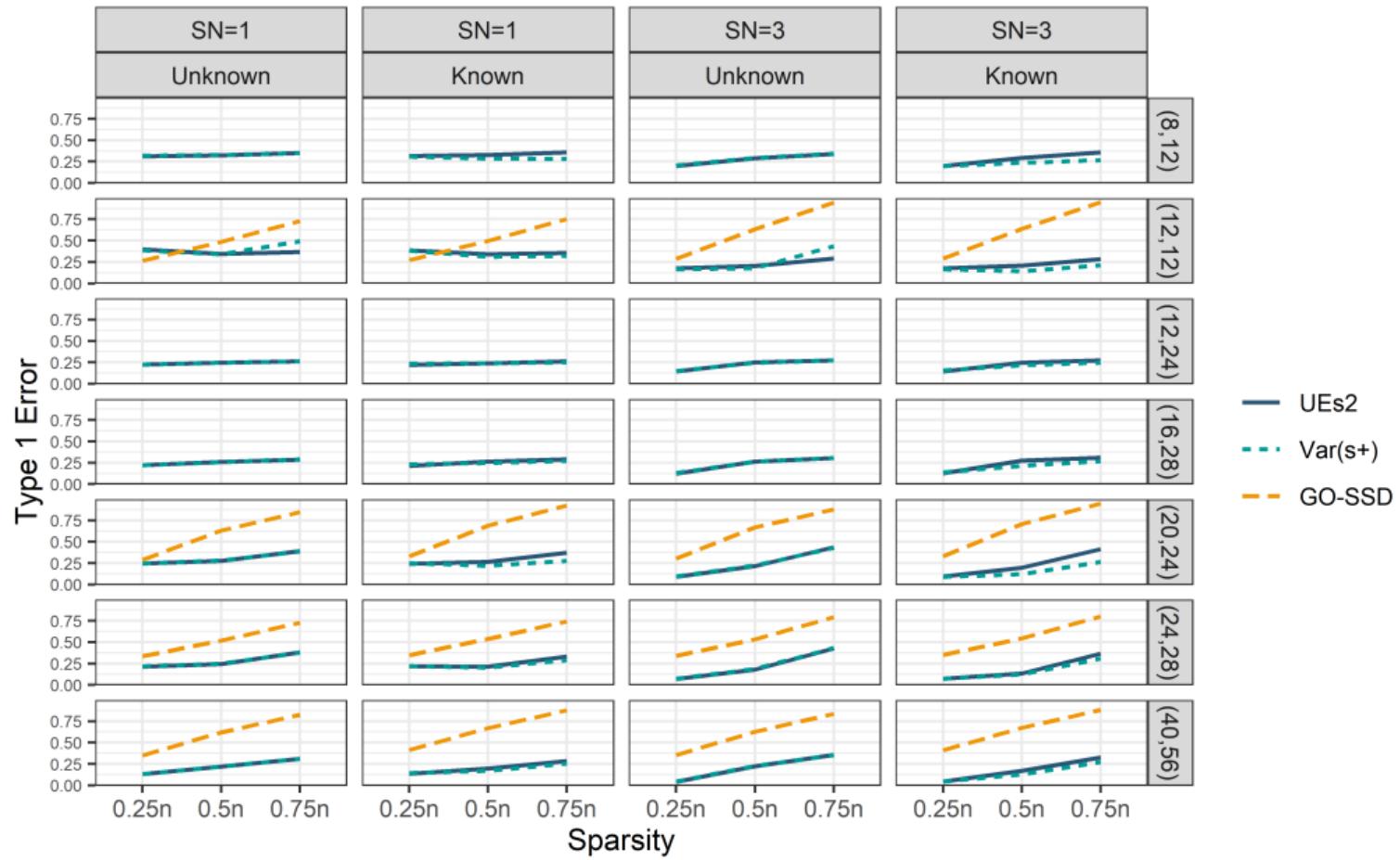
## SIMULATION PROTOCOL, CONT.

For each SSD and analysis combination,

1. GO-SSD and MaxPower,
2.  $\text{Var}(s^+)$  and the Automated Dantzig selector,
3.  $\text{UE}(s^2)$  and the Automated Dantzig selector,

we report the average (1) the power (proportion of effects correctly classified as potentially active) and (2) type 1 error (proportion of inactive effects classified as potentially active).



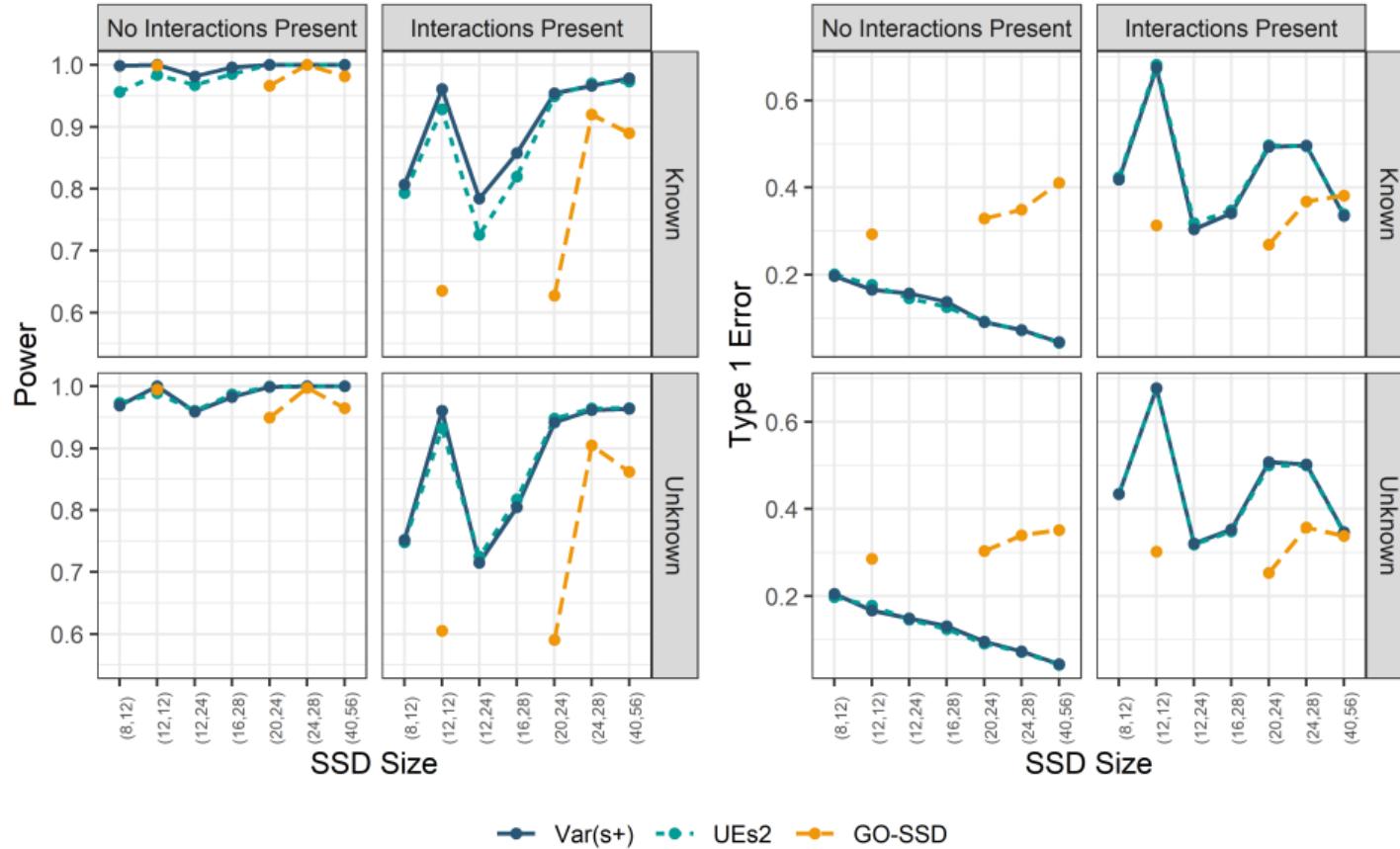


## SIMULATION WITH UNKNOWN INTERACTIONS

We consider the case where interactions are present in the true model, but ignored in the analysis.

$$Y_i = \beta_0 + \sum_{j=1}^k \beta_j X_{ij} + \sum_{j=1}^{k-1} \sum_{l=j+1}^k \beta_{jl} X_{ij} X_{il} + \epsilon_i, \quad i = 1, 2, \dots, n \quad (3)$$

1. We generated 5000 responses using (3) containing two interaction effects exhibiting weak heredity with the active main-effect columns
2. We fixed the factor sparsity to  $0.25n$  for the main effects.
3. Both main and interaction effects were assigned SN = 3.
4. We considered both known and unknown effect directions.



## RECOMMENDATIONS

### GO-SSD+MaxPower

1. Conservative screening
2. Measure of sparsity
3. Easy construction
4. Limited design sizes
5. Less robust to interactions

### Var(s+)+Dantzig Selector

1. More aggressive screening
2. Algorithmically constructed
3. Flexible design sizes
4. More robust to interactions

## CONCLUSION

SSDs should be considered on their own terms, with experimental goals and analysis methods specified and effectively exploited.

## REFERENCE AND CONTACT INFORMATION

Weese, M. L., Stallrich, J. W., Smucker, B. J., Edwards, D. J. (2020). Strategies for Supersaturated Screening: Group Orthogonal and Constrained Var (s) Designs. *Technometrics*, 1-13. doi:10.1080/00401706.2020.1850529

## REFERENCE AND CONTACT INFORMATION

Weese, M. L., Stallrich, J. W., Smucker, B. J., Edwards, D. J. (2020). Strategies for Supersaturated Screening: Group Orthogonal and Constrained Var (s) Designs. *Technometrics*, 1-13. doi:10.1080/00401706.2020.1850529

Maria Weese  
weeseml@miamioh.edu  
Twitter: @MFWeese

## OTHER REFERENCES

- Jones, B., Majumdar, D. (2014). Optimal supersaturated designs. *Journal of the American Statistical Association*, 109(508), 1592-1600.
- Jones, B., Lekivetz, R., Majumdar, D., Nachtsheim, C. J., Stallrich, J. W. (2019). Construction, Properties, and Analysis of Group-Orthogonal Supersaturated Designs. *Technometrics*, 62(3), 403-414.
- Weese, M. L., Smucker, B. J., Edwards, D. J. (2015). Searching for powerful supersaturated designs. *Journal of Quality Technology*, 47(1), 66-84.
- Weese, M. L., Edwards, D. J., Smucker, B. J. (2017). A criterion for constructing powerful supersaturated designs when effect directions are known. *Journal of Quality Technology*, 49(3), 265-277.