Modern experimental designs in pharmaceutical manufacturing: Overview

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Research & Development: Discovery and Manufacturing Statistics
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Johnson&Johnson

Context

Our mission and scope

From new molecular entity (NME) declaration to full scale manufacturing: efficiently provide defensible and reproducible data-based evidence for informed decision making

NME to FIH	Phase 1 Clinical	Phase 2 Clinical	Phase 3 Clinical	Submission & Launch
API & DP Formulation :	Small scale process	Process scale up	Technology Transfer	Full scale manufacturing
Analytical:	Assay Development	Assay Validation	Method Transfer	Quality Control

Slide courtesy: Tatsiana Khamiakova, Chellafe Ensoy-Musoro

Our expertise

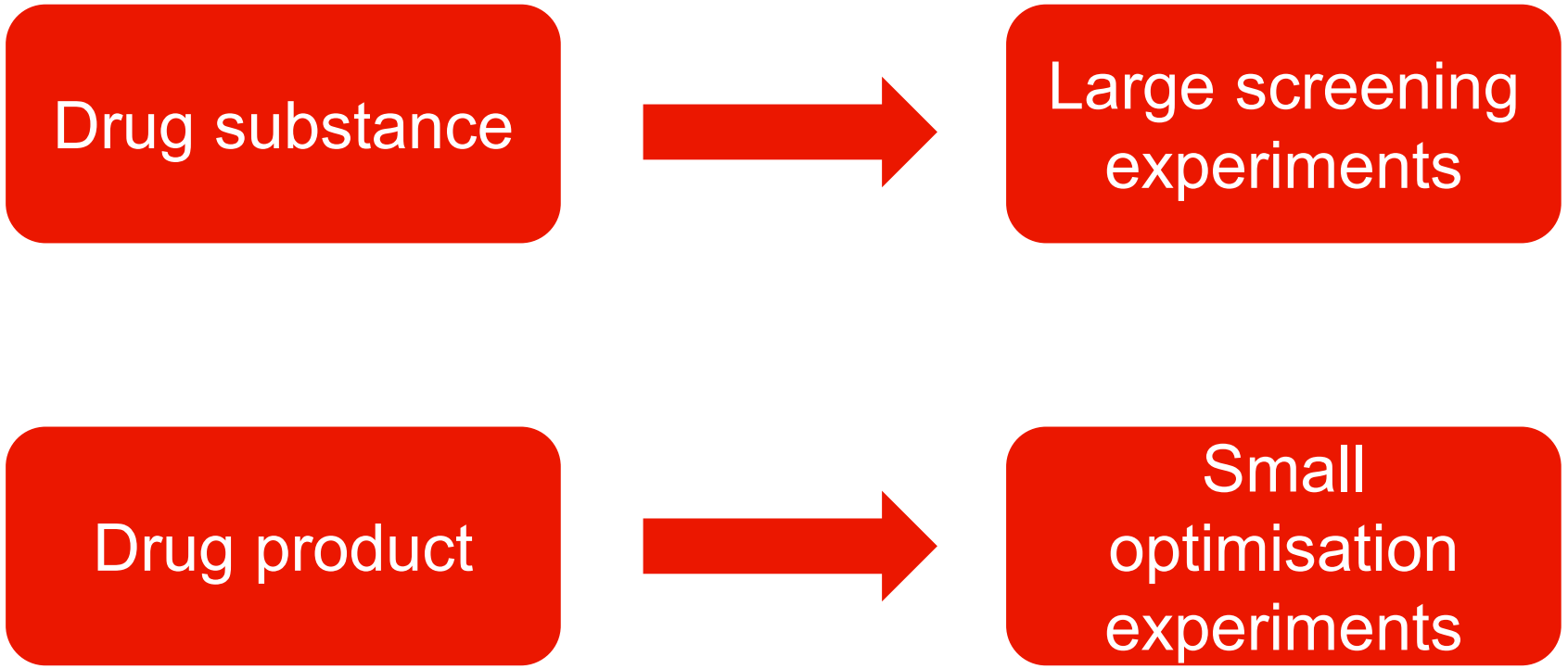
Points of contacts in various application and methodology domains

- Design of Experiments
- Dossier: Justification of Specifications, Stability, Bridging
- Bayesian Analysis
- Machine Learning, Multivariate Data Analysis
- Analytical Methods Development, PAT, Chemometrics
- High Throughput Experimentation data analysis

Slide courtesy: Tatsiana Khamiakova, Chellafe Ensoy-Musoro

Two worlds

Chemistry/biology vs engineering



Desing of Experiment

Jargon for this talk

Design

Pattern	A	B	C
---	-1	-1	-1
--+	-1	-1	1
-+-	-1	1	-1
-++	-1	1	1
+--	1	-1	-1
+-+	1	-1	1
++-	1	1	-1
+++	1	1	1

Jargon for this talk

Design

Run

Factor

Response

Pattern	A	B	C
---	-1	-1	-1
--+	-1	-1	1
-+-	-1	1	-1
-++	-1	1	1
+--	1	-1	-1
+-+	1	-1	1
++-	1	1	-1
+++	1	1	1

Jargon for this talk

Run

Factor

Response

Design

Pattern	A	B	C
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-++	-1	1	1
+--	1	-1	-1
+-+	1	-1	1
++-	1	1	-1
+++	1	1	1

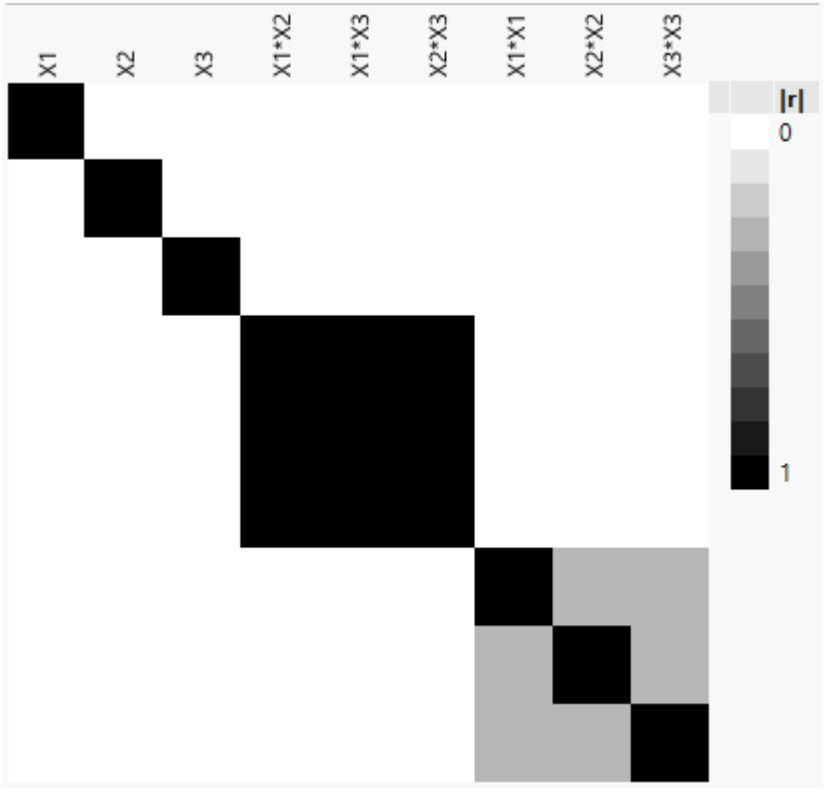
Main effect

Quadratic effect (Curvature)

Interactions

Design assessment

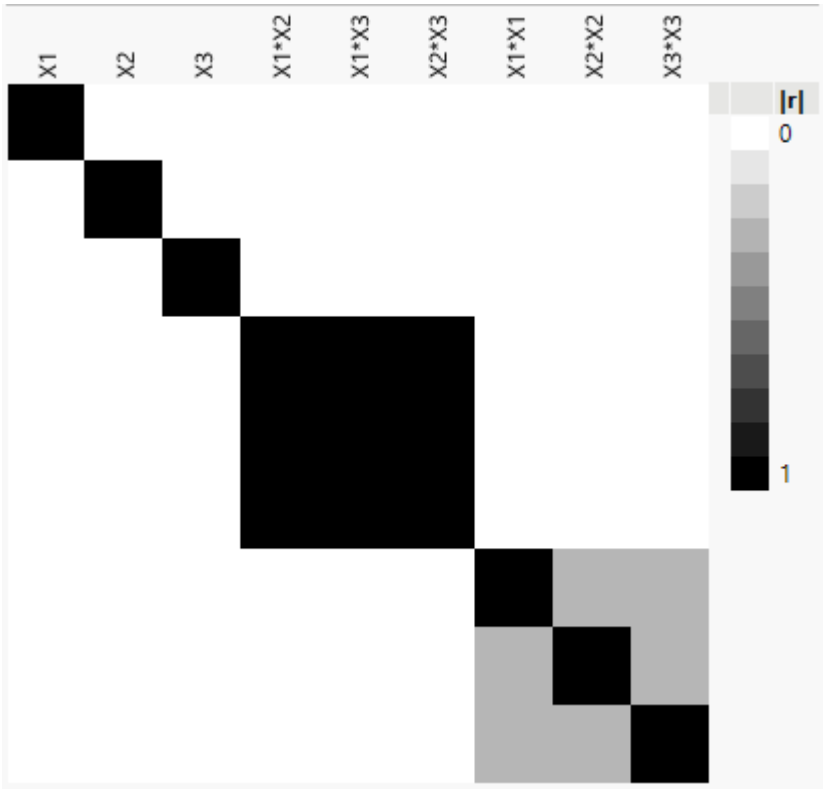
One factor at the time

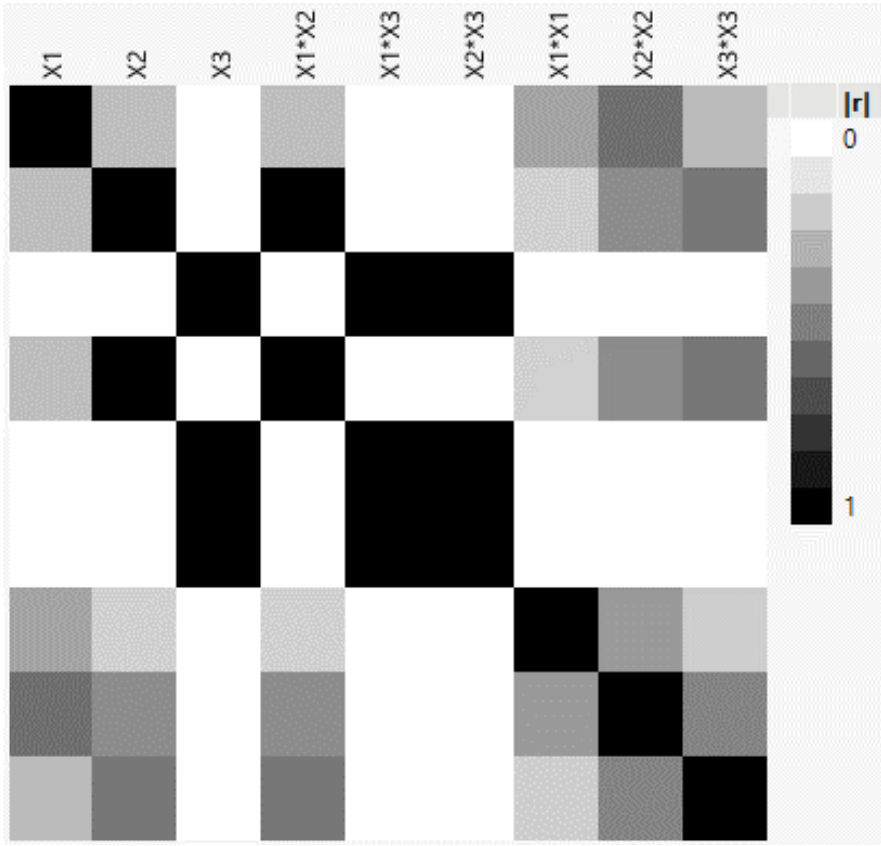


Part	A	B	C
I	-1	0	0
I	0	0	0
I	1	0	0
II	0	-1	0
II	0	0	0
II	0	1	0
III	0	0	-1
III	0	0	0
III	0	0	1

Design assessment

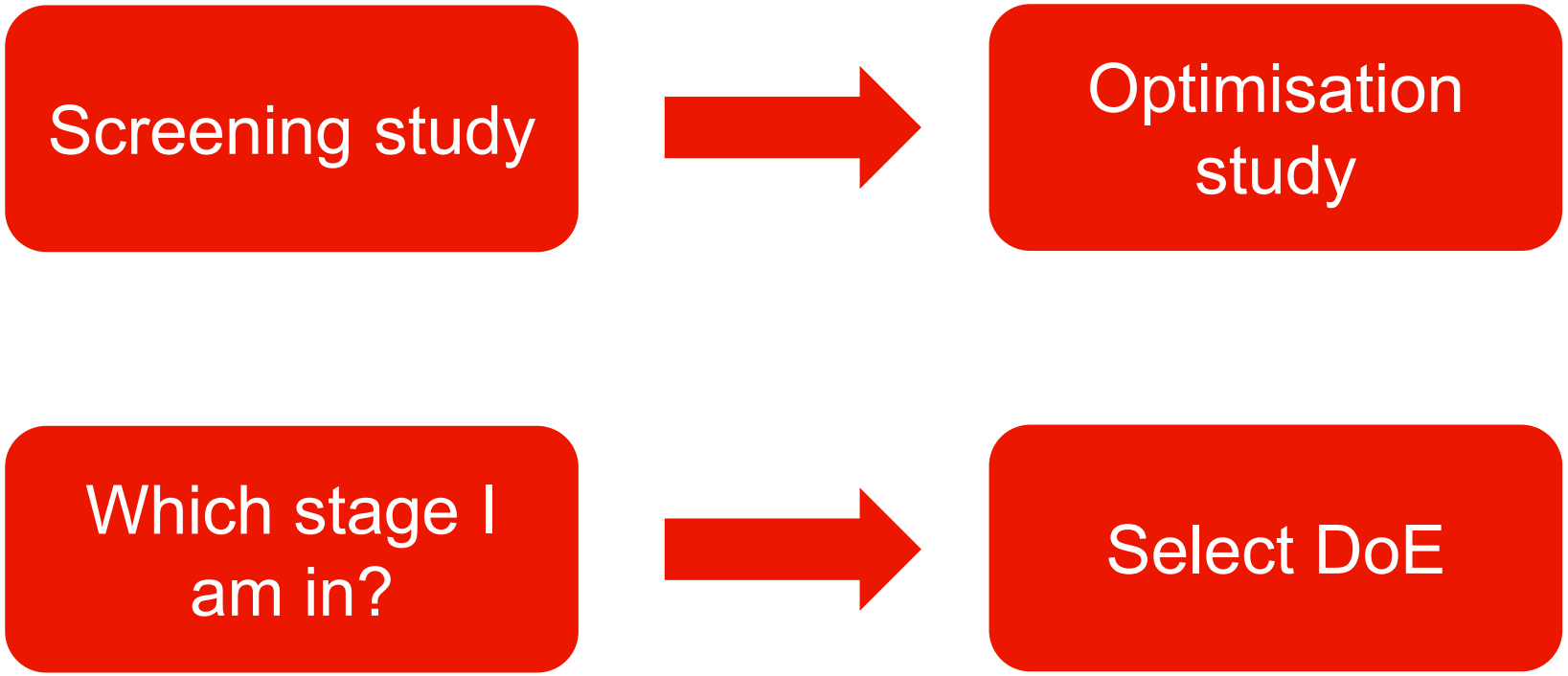
One factor at the time





Traditional strategy

Cookbook-like approaches



Optimisation designs

Central composite: orthogonal

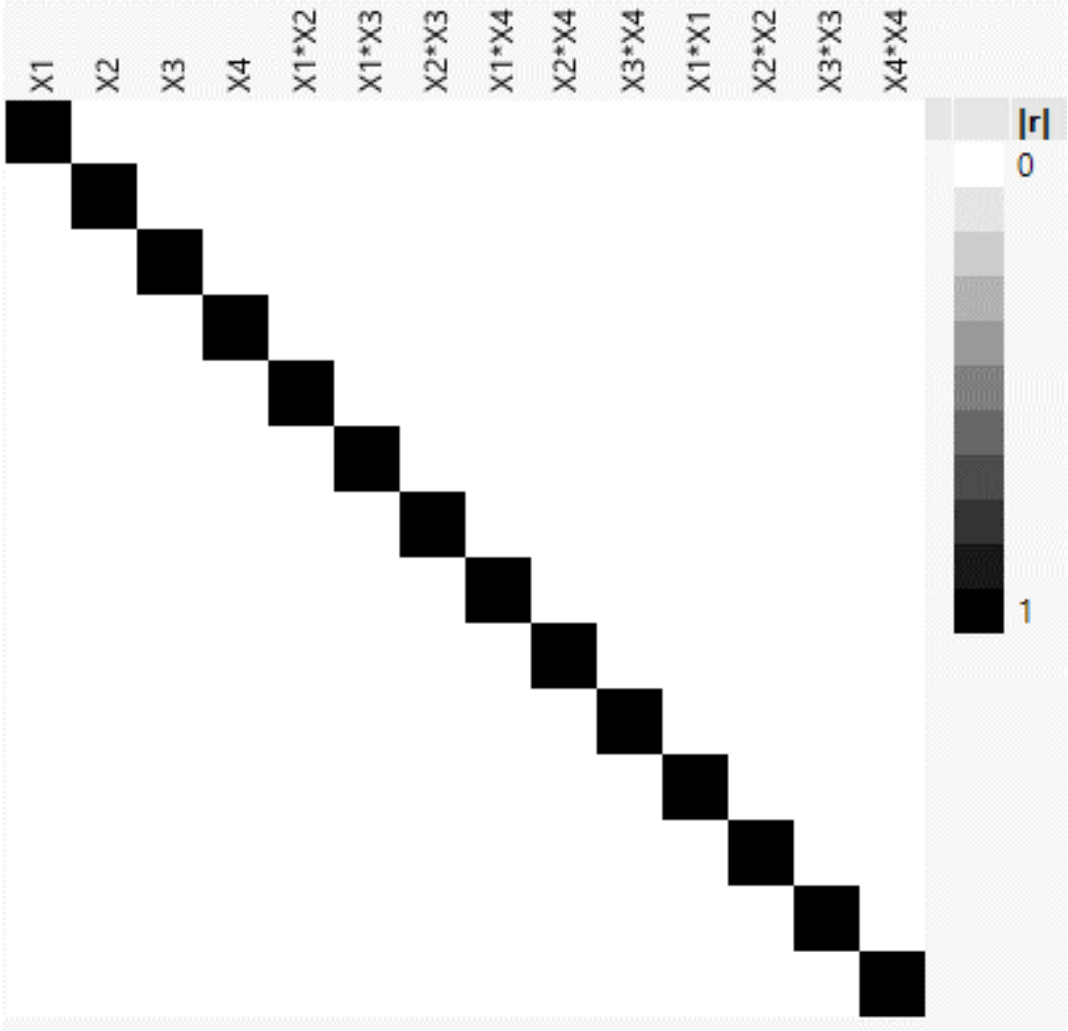
Ideal case mathematically: 26R

Great design properties

Large

Inflexible size

Issue with experimental range



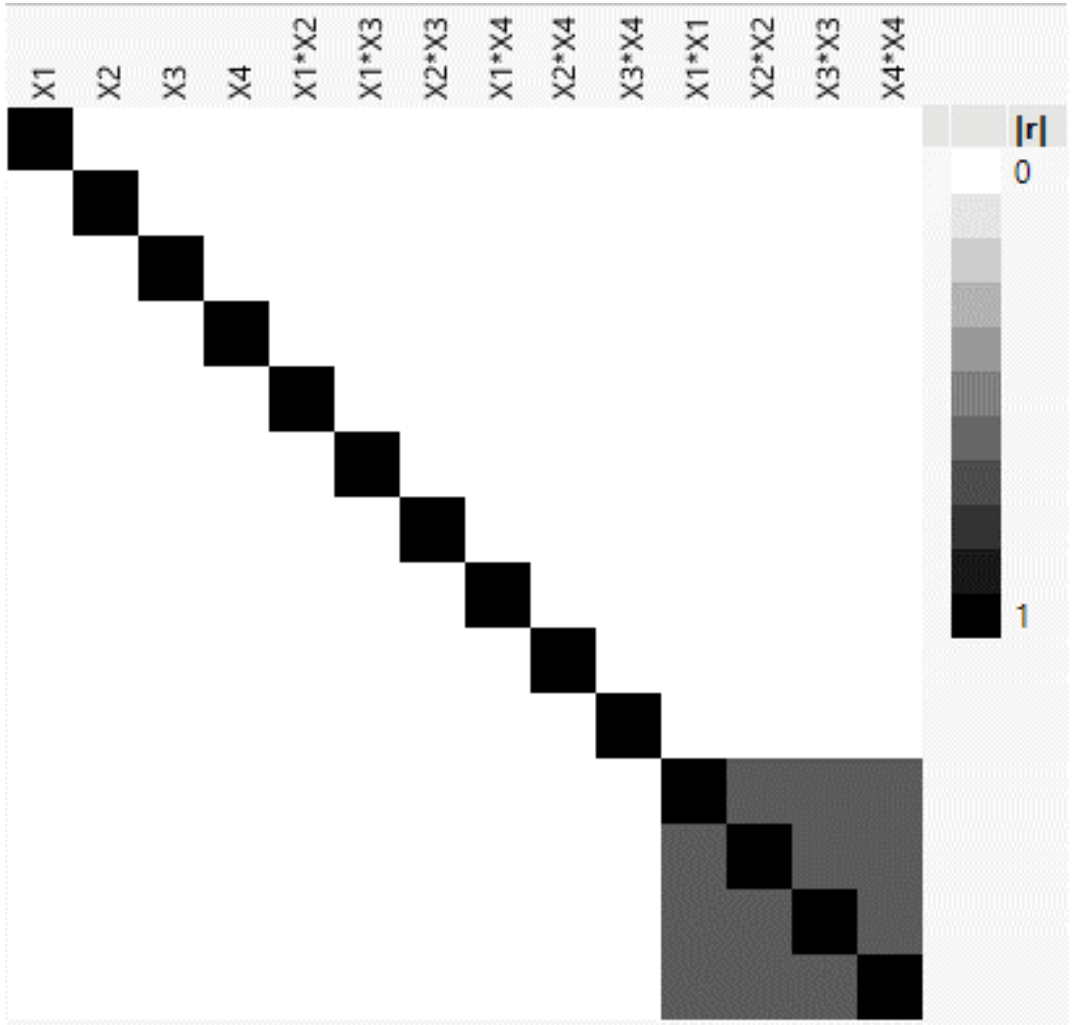
Central composite: on face

Ideal case practically: 26R

Problems with separation of curvatures

Large

Inflexible size



D/I-optimality

Balancing: 18 runs D-optimal

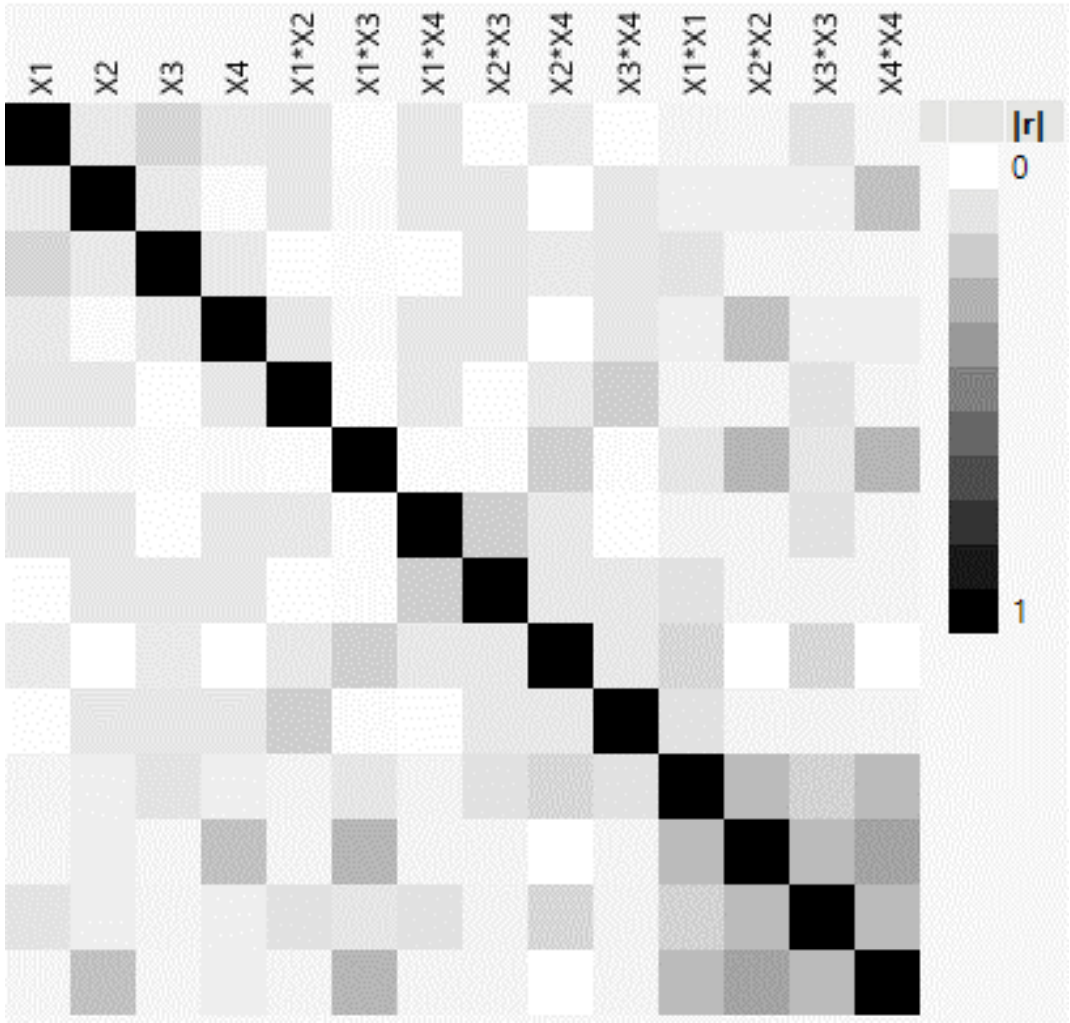
Flexible size

Flexible quality

Losing orthogonality

Is correlation 0.36 “too much”?

Rounding

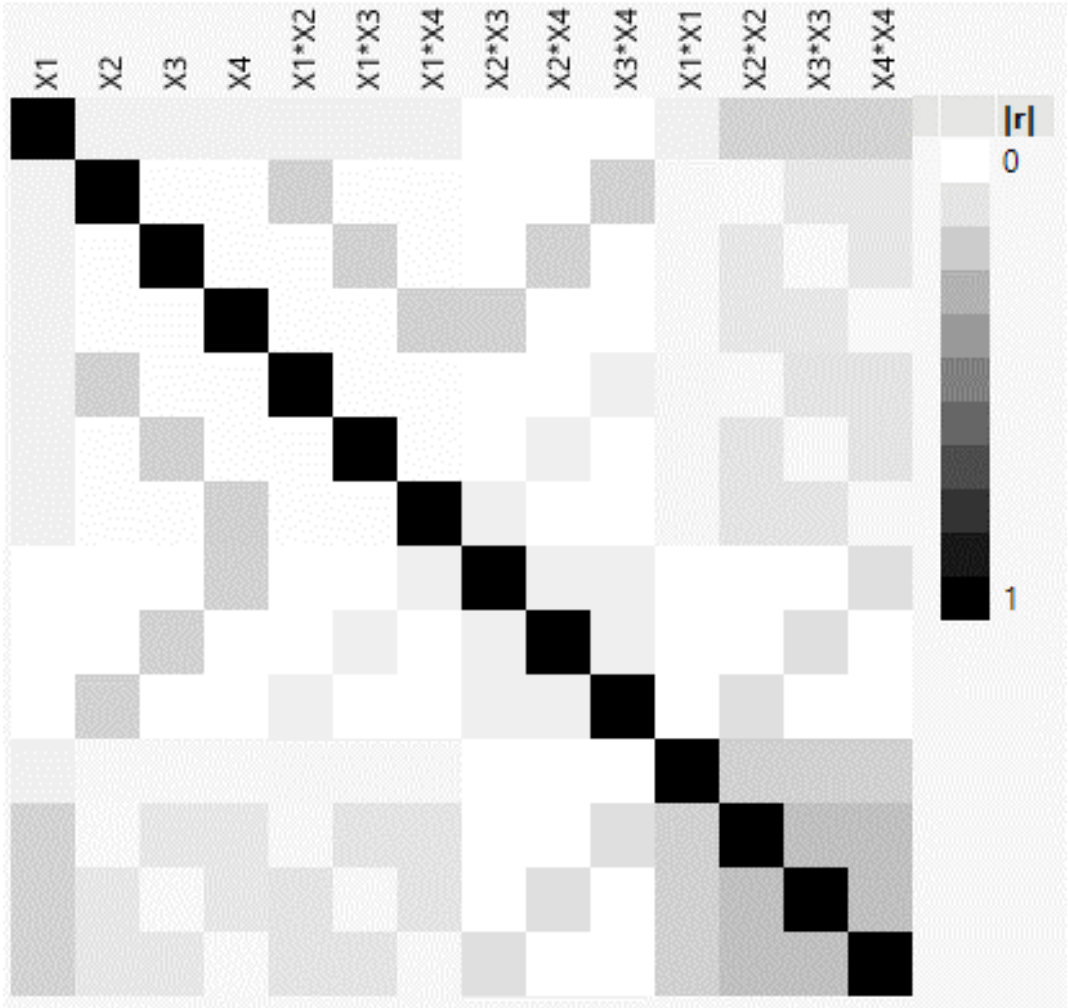


D/I-optimality

Balancing: 24 runs I-optimal

Is reduction to correlation 0.24 worth it?

Power calculations?



Ruining orthogonality

Asymmetry

Special runs

Replicates

Screening designs

Fractional factorial: 19 runs

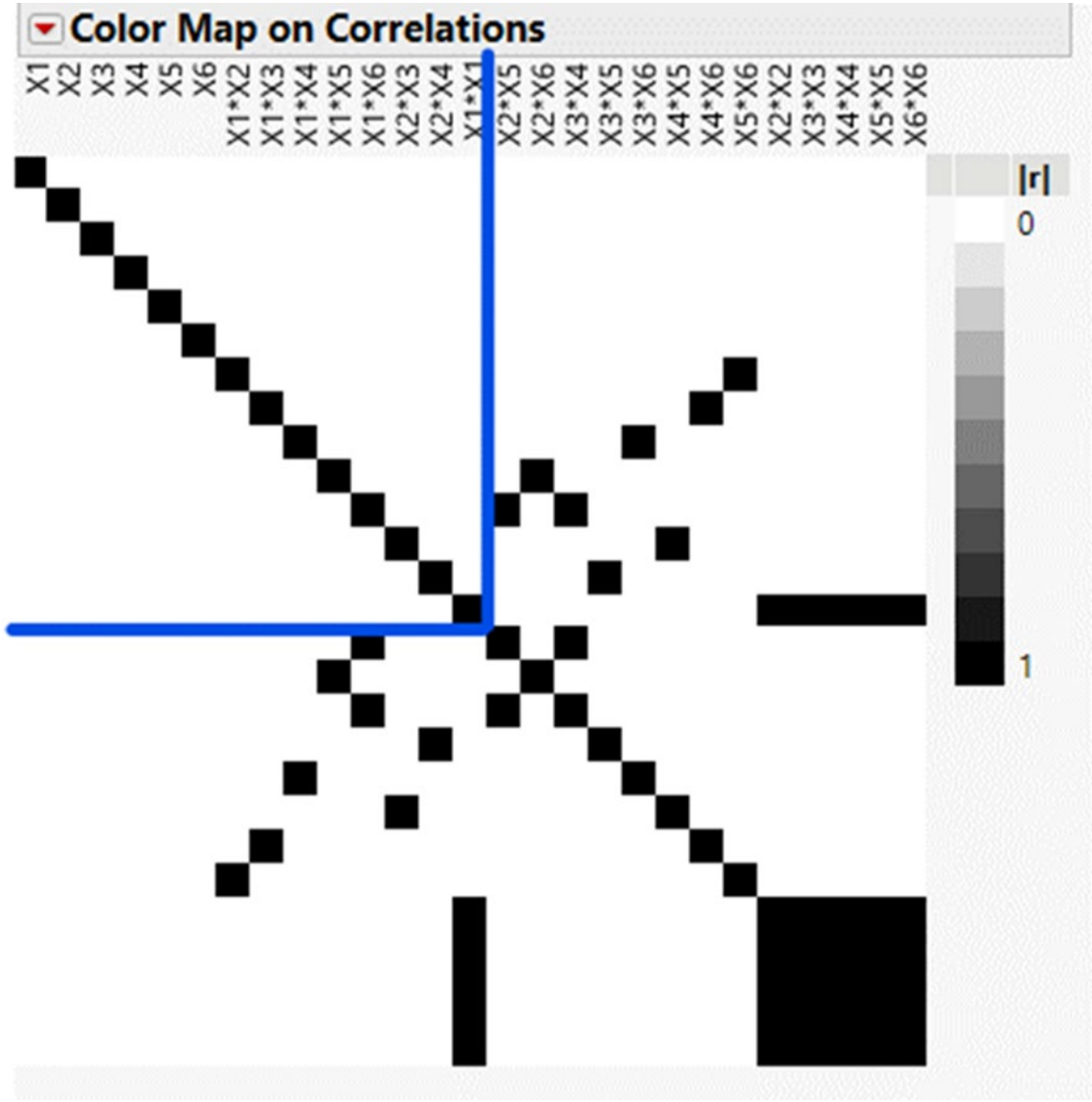
Schoolbook example

Works fine for main effects

Only overall curvature explored

Zero information on individual curvatures

Confounding of some interactions



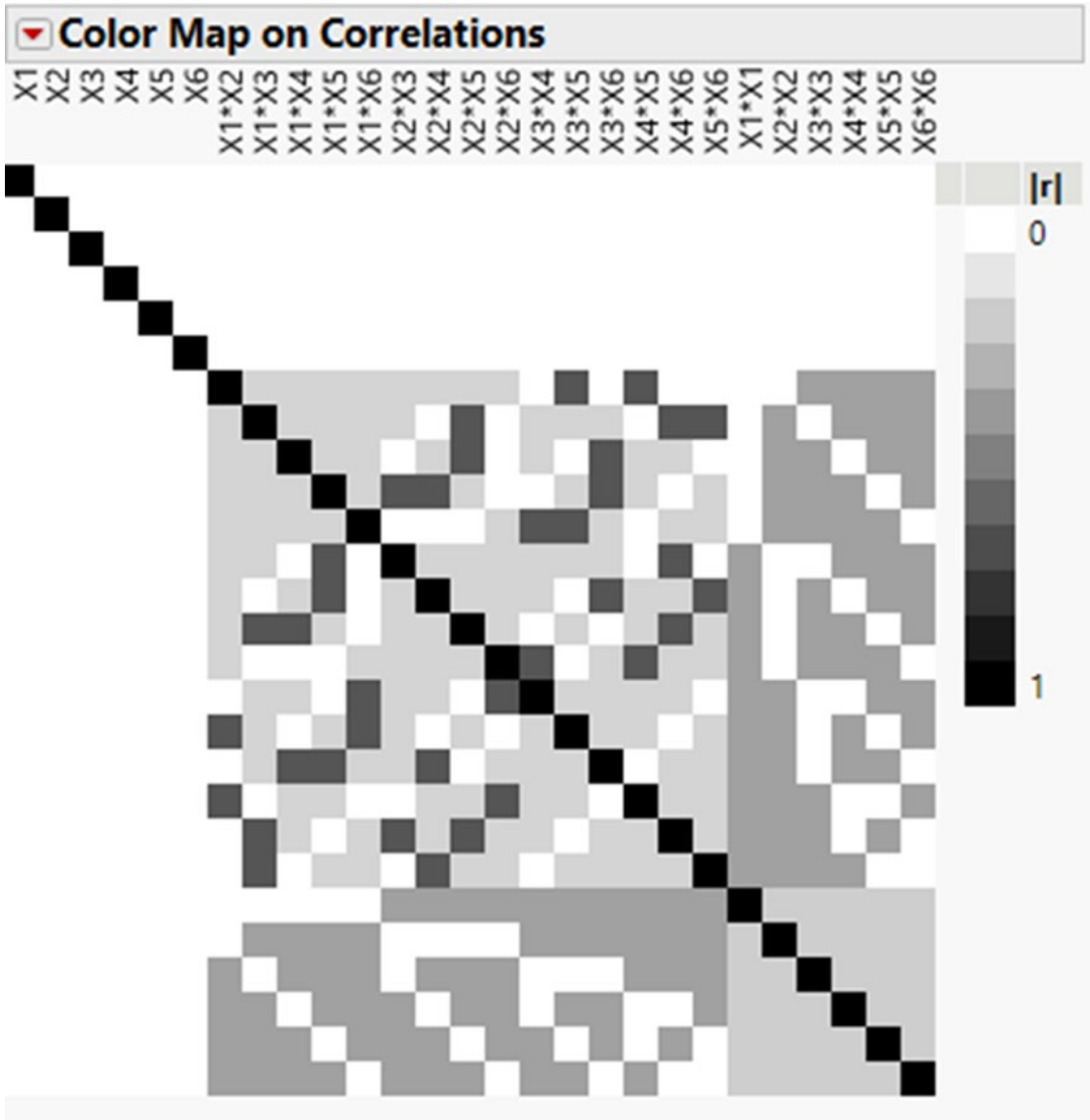
Definitive screening design: 17 runs

Recent and not yet “definitive”

Screening for main effects

Works fine for curvatures

Can detect some interactions, but needs usually augmentation of **quite some** extra runs for full optimization (e.g. for reliable design space)



OMARS: 13 runs

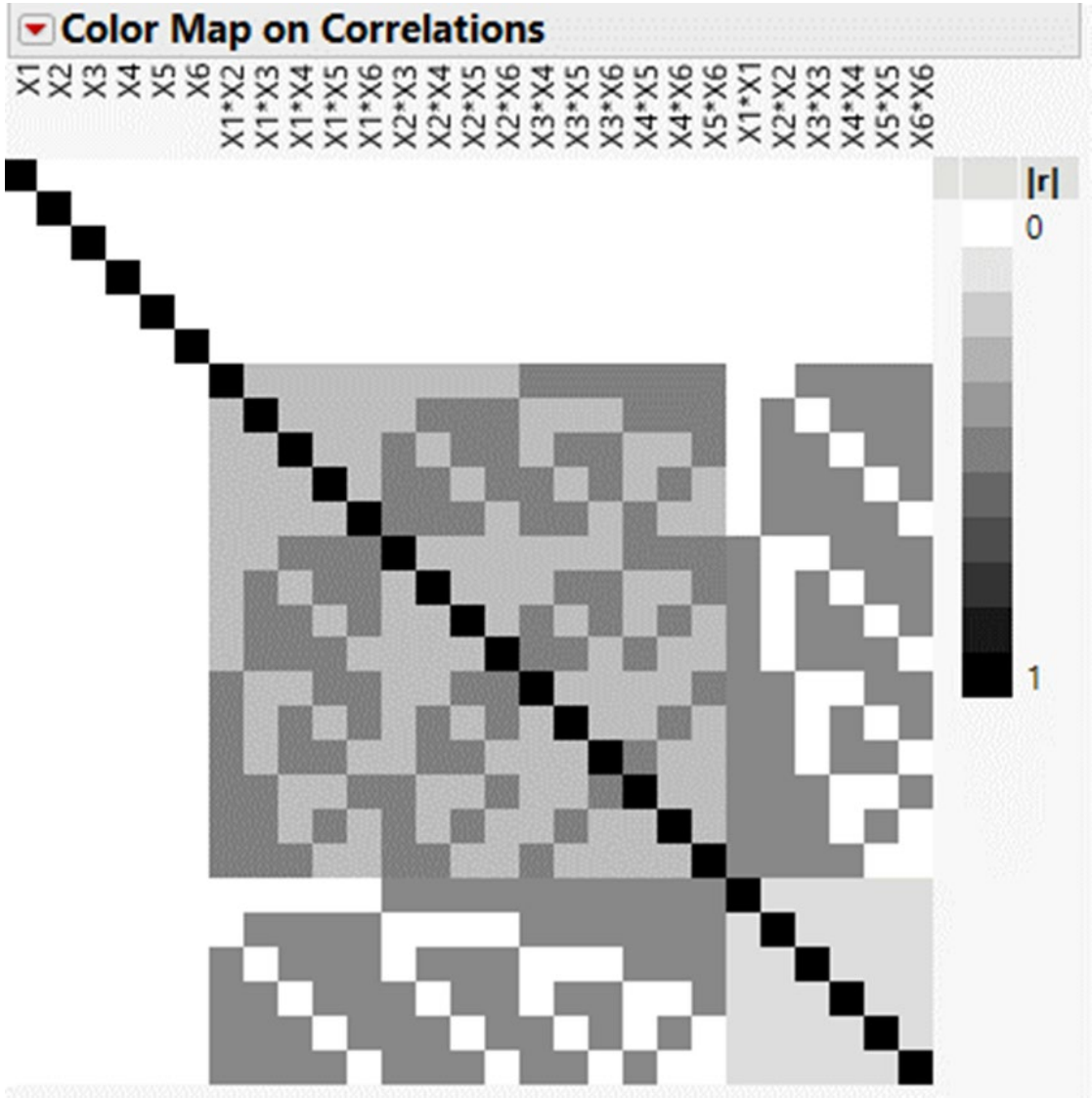
The most recent and possibly definitive

Screening for main effects

Works fine for curvatures

Control of correlation

Can detect some interactions, but needs usually augmentation of some **(few)** extra runs for full optimization (e.g. for reliable design space)



OMARS: 25 runs

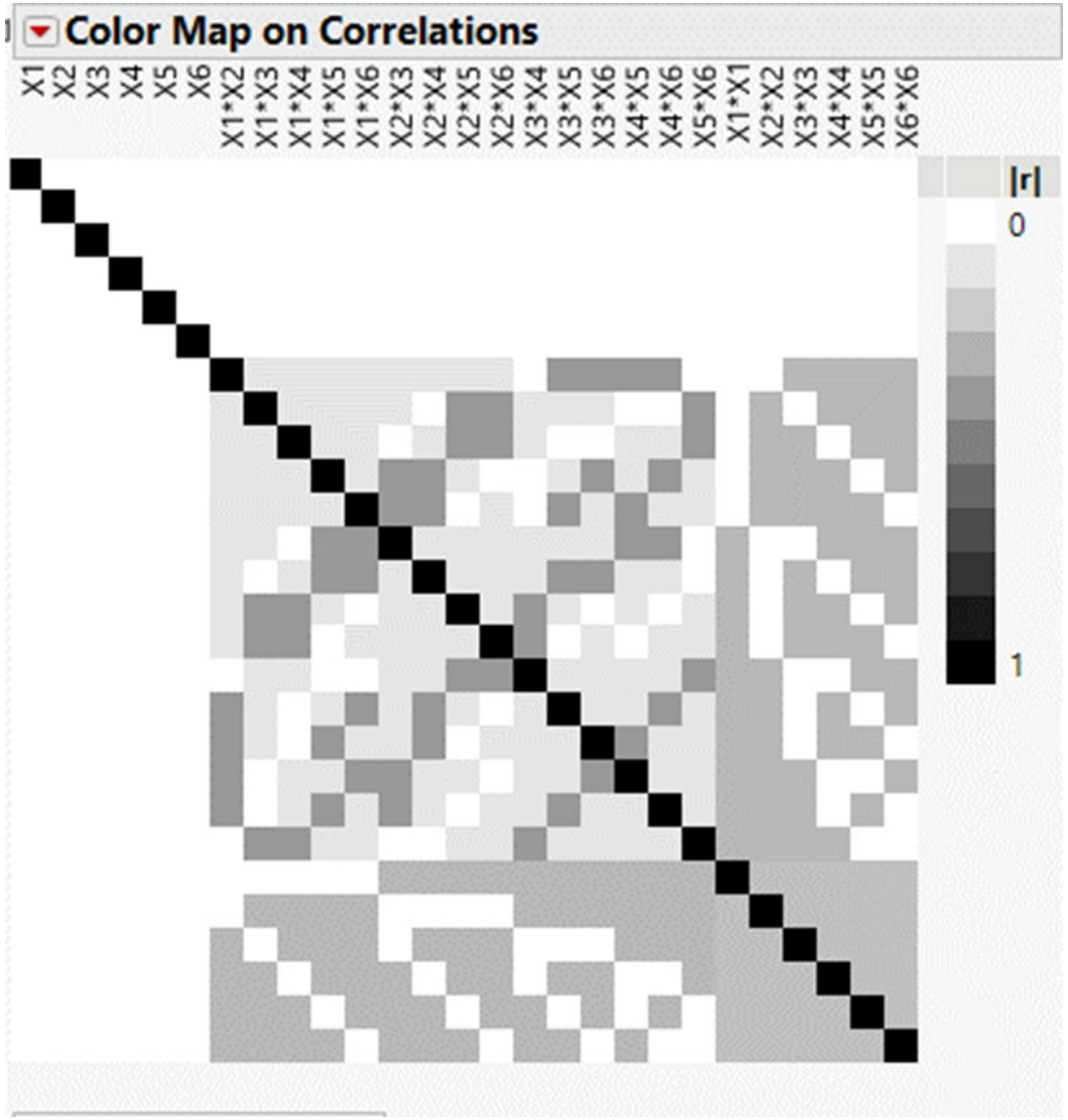
Getting closer to full optimisation design

Screening for main effects

Works fine for curvatures

Control of correlation; lower correlation than 13 run OMARS

If some factors are removed during data analysis, it can be directly used as Optimisation design



Augmentation

Saving resources

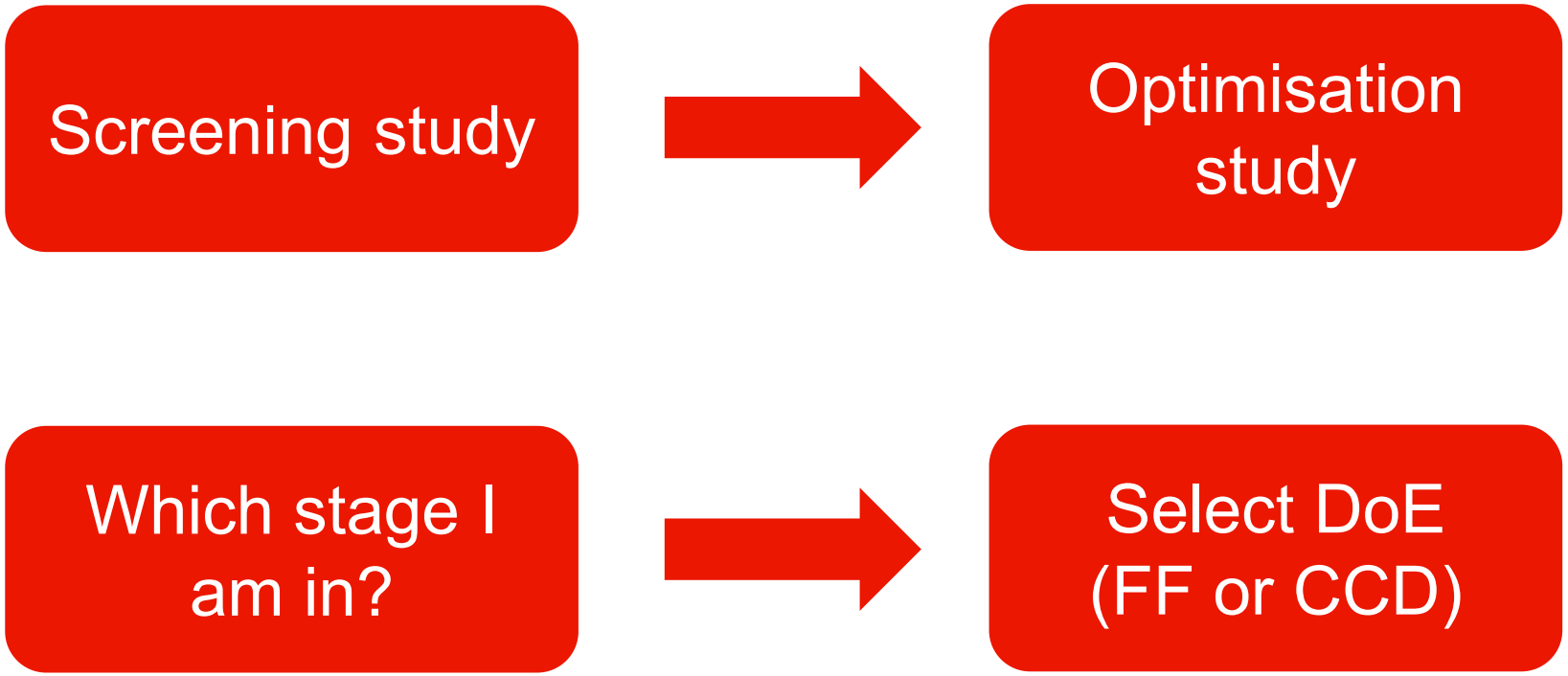
Why discard the information from screening stage?

Use the screening runs and only generate what to add to have good “Optimal design”

Modern part

Traditional strategy: standard approach

Cookbook-like approaches



Holistic strategy: tailor-made approach

We are not DoE generating software

No DoE?
Confirmatory
Exploratory

Traditional
2-stage

Direct
optimisation

Augmentation

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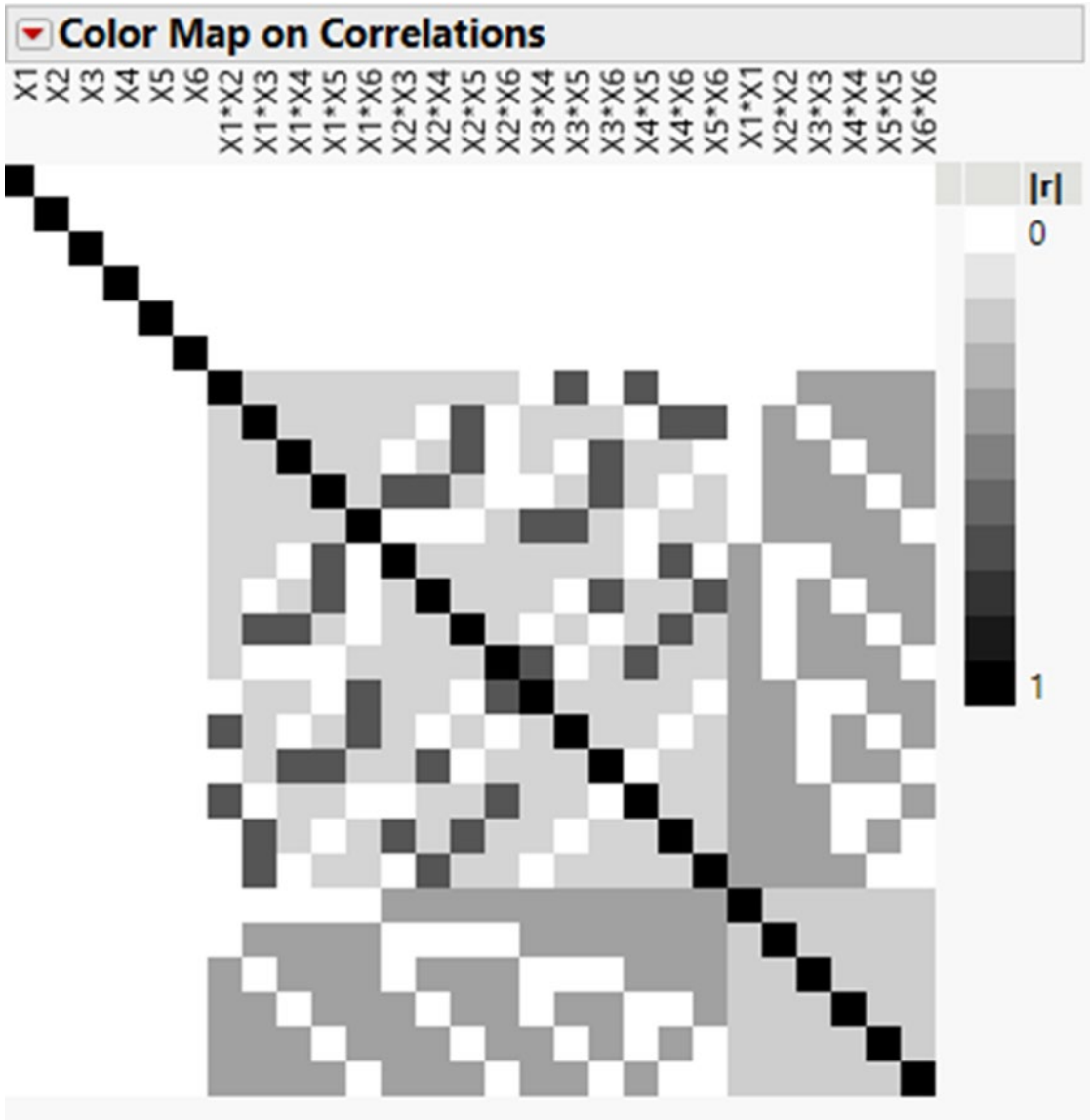

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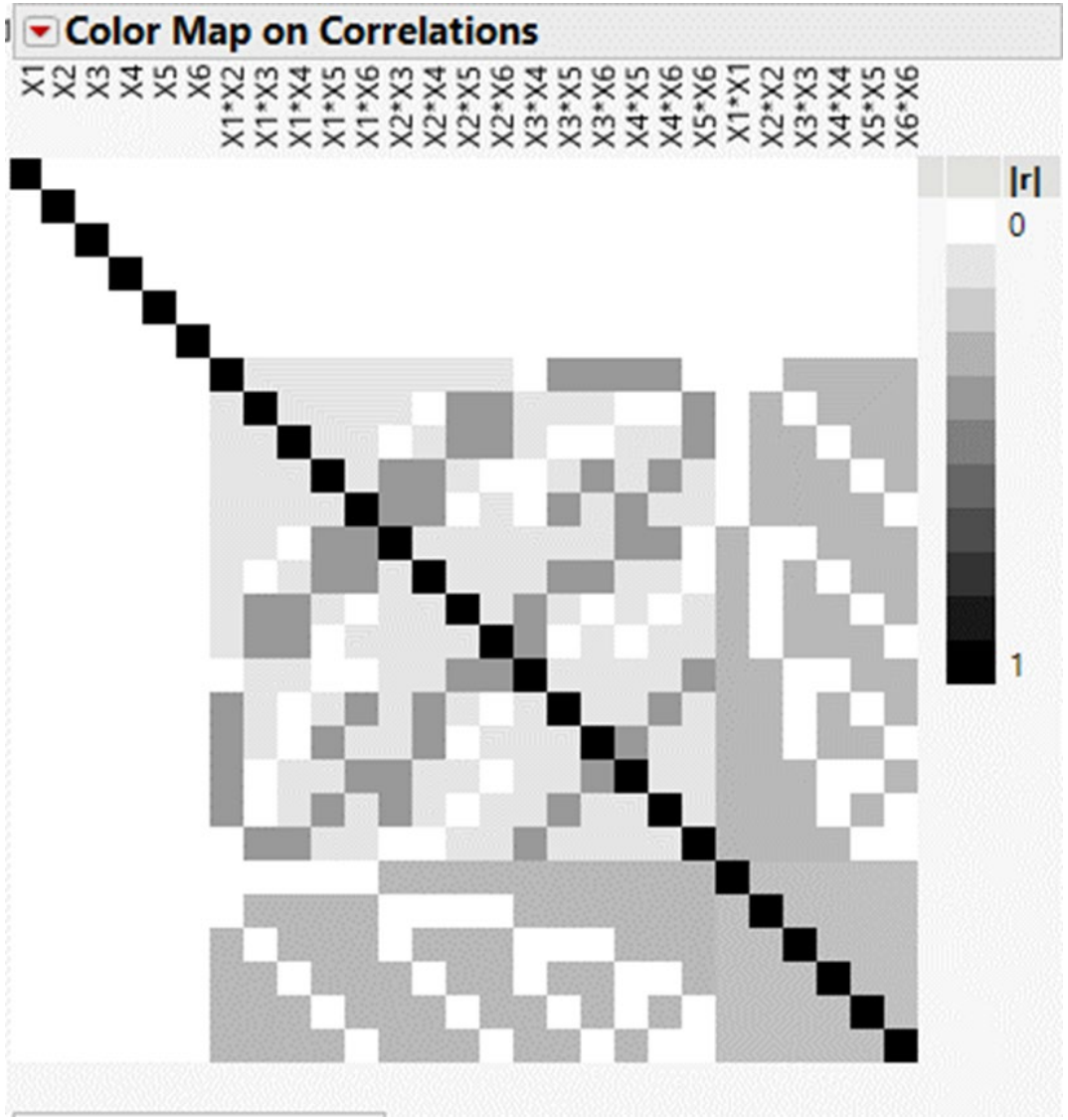

Extras

Additional considerations

Complicate “traditional designs”

Blocking

Split-plot

Special methodologies

Often purpose specific

Mixtures

Bayesian optimisation

Non-linear designs

New optimisation criteria

Thank you

Jones B, Nachtsheim CJ
Definitive Screening Designs with Added Two-Level Categorical Factors.
Journal of Quality Technology 2013, 45(2): 121–129. https://doi.org/10.1080/00224065.2013.11917921

Otava M, Mylona K
Communicating statistical conclusions of experiments to scientists.
Qual Reliab Engng Int. 2020, 36: 2688-2698. https://doi.org/10.1002/qre.2697

Núñez Ares J, Schoen ED, Goos P
Orthogonal minimally aliased response surface designs for three-level quantitative factors and two-level categorical factors
Statistica Sinica 2023, 33: 107-126

NCS2024 (https://ncs-conference.org/ncs-2024/)
Ying Chen et al.: *Optimal Experimental Designs for Process Robustness Studies*
Leonie Hezler et al.: *Experimental designs for preclinical dose response experiments*

If you have more questions, please contact:
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