DoE for Scale-Up

… using MODDE® and DoE-DiVa®
and a little bit of R

Session 5: Qualitative Dependencies. **01.03. 2023**
(Typically Material Properties)

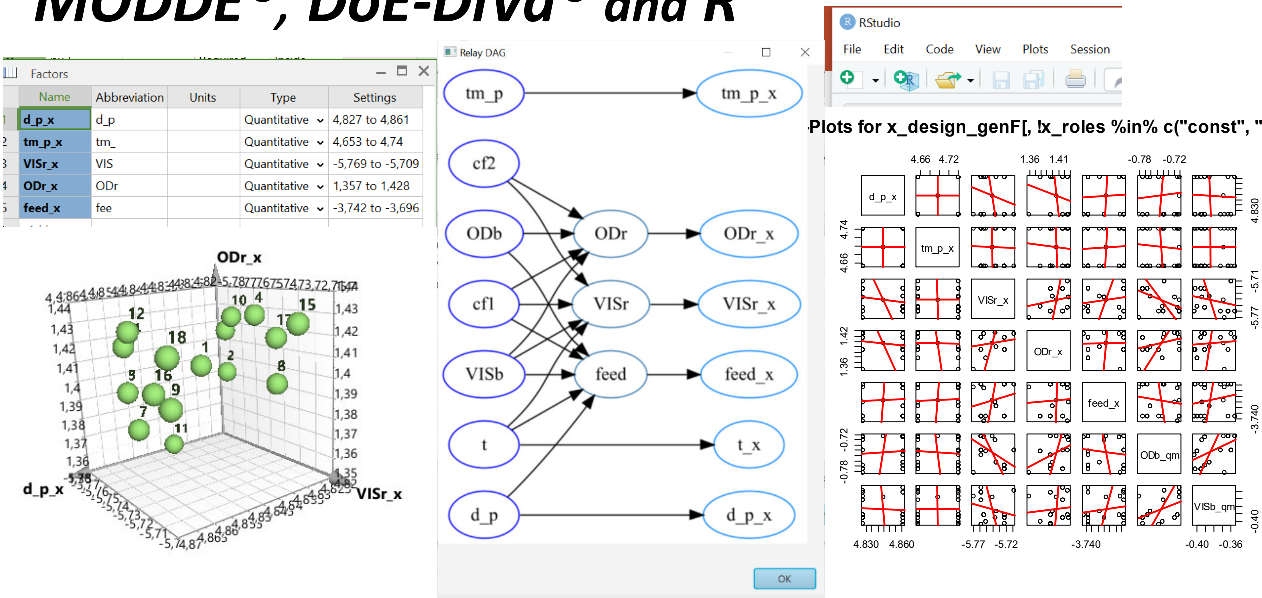
Gefördert durch:
Bundesministerium für Wirtschaft und Klimaschutz
aufgrund eines Beschlusses des Deutschen Bundestages

umesoft **Prof. Dr. Andreas Orth**

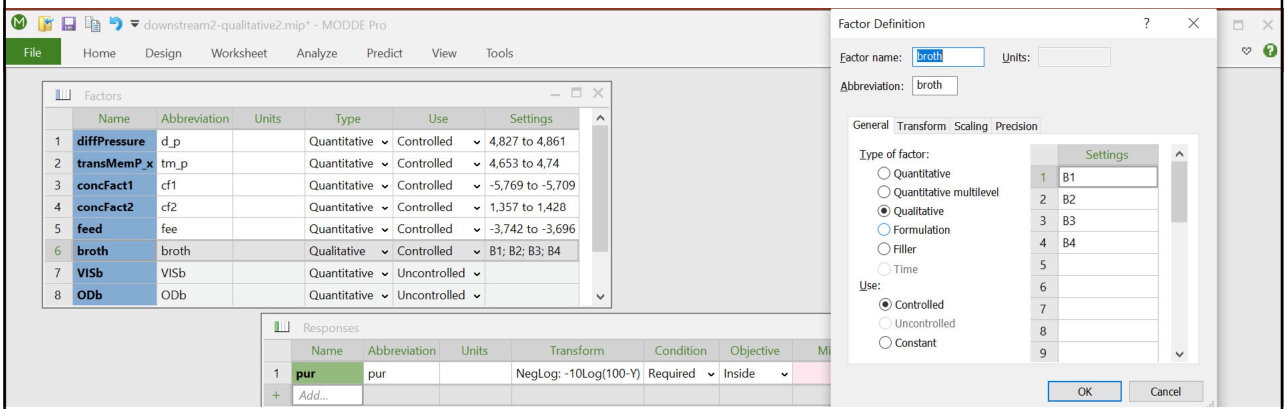
Design of Experiments (DoE)

- ***DoE*** works best for independent and quantitative factors
- ***Real processes*** *are full of* dependencies and discontinuities
- *How to make DoE work better in Real life?*
- *… best idea is to make DoE more flexible!*

MODDE®, DoE-DiVa® and R



MODDE® and qualitative factors



Qualitative factor: fermentation *broth*
with *optical density, Odb,* and *viscosity, VISb*

MODDE®: how *to code* qualitative factors

downstream2-qualitative2.mip* - MODDE Pro

File | Home | Design | Worksheet | Analyze | Predict | View | Tools

Worksheet

	1	2	3	4	5	6	7	8	9	10	11	12	13
	No	Exp	Run	Incl/Ex	diffPress	transMemP	concFa	concFac	feed	broth	VISb	ODb	pur
1	1	N1	10	Incl	4,82686	4,65321	5,76933	1,35702	-3,74178	B1			
2	2	N2	1	Incl	4,86114	4,65321	-5,7092	1,35702	-3,74178	B1			
3	3	N3	8	Incl	4,86114	4,74036	5,76933	1,42806	-3,69603	B1			
4	4	N4	9	Incl	4,82686	4,65321	-5,7092	1,42806	-3,69603	B1			
5	5	N5	11	Incl	4,86114	4,65321	5,76933	1,42806	-3,74178	B2			
6	6	N6	12	Incl	4,82686	4,74036	-5,7092	1,35702	-3,69603	B2			
7	7	N7	2	Incl	4,86114	4,74036	5,76933	1,35702	-3,74178	B3			
8	8	N8	5	Incl	4,82686	4,65321	-5,7092	1,35702	-3,74178	B3			
9	9	N9	4	Incl	4,82686	4,74036	5,76933	1,42806	-3,69603	B3			
10	10	N10	15	Incl	4,86114	4,74036	-5,7092	1,42806	-3,69603	B3			
11	11	N11	7	Incl	4,82686	4,74036	-5,7092	1,42806	-3,74178	B4			
12	12	N12	14	Incl	4,86114	4,65321	5,76933	1,35702	-3,69603	B4			
13	13	N13	13	Incl	4,844	4,69678	5,73926	1,39254	-3,7189	B4			
14	14	N14	6	Incl	4,844	4,69678	5,73926	1,39254	-3,7189	B4			
15	15	N15	3	Incl	4,844	4,69678	5,73926	1,39254	-3,7189	B4			

Design Matrix

	1	2	3	4	5	6	7	8	9
1	Exp No	diffPressu	transMemP_	concFac	concFac	feed	broth(B2)	broth(B3)	broth(B4)
2	1	-1	-1	-1	-1	-1	-1	-1	-1
3	2	1	-1	1	-1	-1	-1	-1	-1
4	3	1	1	-1	1	1	-1	-1	-1
5	4	-1	-1	1	1	1	-1	-1	-1
6	5	1	-1	-1	1	-1	1	0	0
7	6	-1	1	1	-1	1	1	0	0
8	7	1	1	-1	-1	-1	0	1	0
9	8	-1	-1	1	-1	-1	0	1	0
10	9	-1	1	-1	1	1	0	1	0
11	10	1	1	1	1	1	0	1	0
12	11	-1	1	1	1	-1	0	0	1
13	12	1	-1	-1	-1	1	0	0	1
14	13	0	0	0	0	0	0	0	1
15	14	0	0	0	0	0	0	0	1
16	15	0	0	0	0	0	0	0	1

Design matrix computed from worksheet. Regular presentation of qualitative factors.

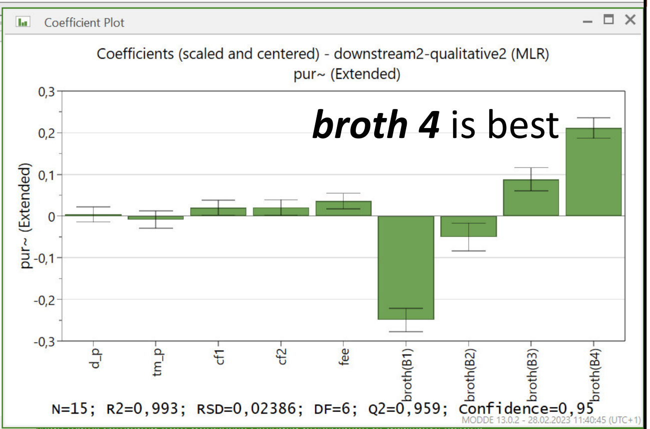
MODDE®: how to *analyse* qualitative factors

downstream2-qualitative2.mip* - MODDE Pro

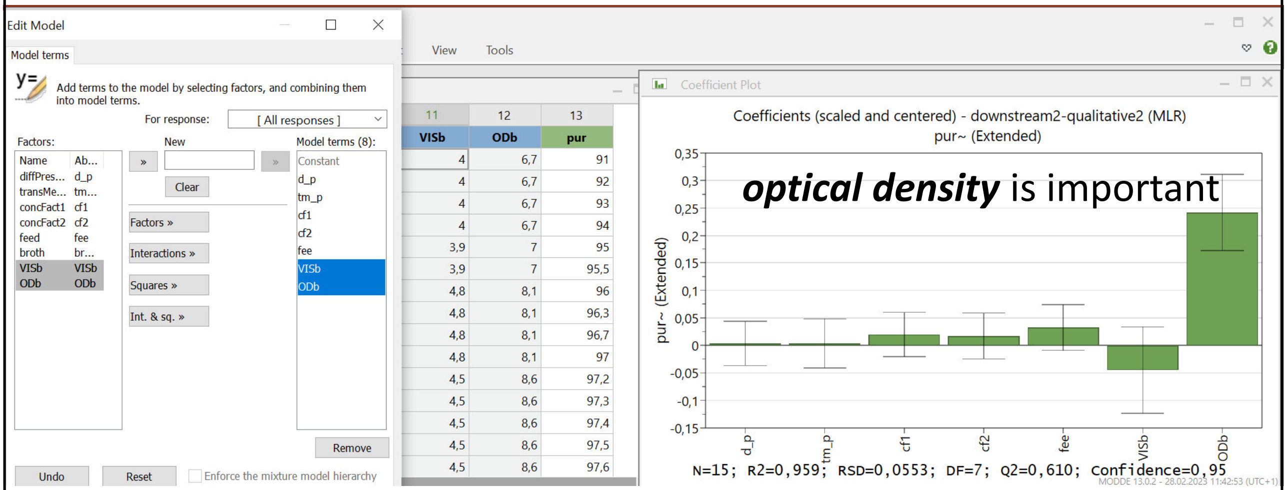
File | Home | Design | Worksheet | Analyze | Predict | View | Tools

Worksheet

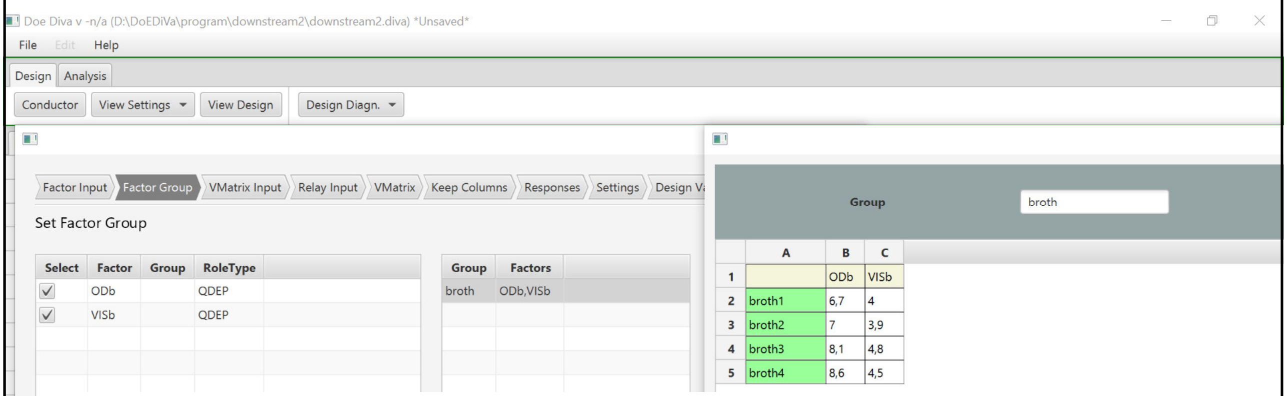
	1	7	8	9	10	11	12	13
	Exp No	concFact1	concFact2	feed	broth	VISb	ODb	pur
1	1	-5,76933	1,35702	-3,74178	B1	4	6,7	91
2	2	-5,7092	1,35702	-3,74178	B1	4	6,7	92
3	3	-5,76933	1,42806	-3,69603	B1	4	6,7	93
4	4	-5,7092	1,42806	-3,69603	B1	4	6,7	94
5	5	-5,76933	1,42806	-3,74178	B2	3,9	7	95
6	6	-5,7092	1,35702	-3,69603	B2	3,9	7	95,5
7	7	-5,76933	1,35702	-3,74178	B3	4,8	8,1	96
8	8	-5,7092	1,35702	-3,74178	B3	4,8	8,1	96,3
9	9	-5,76933	1,42806	-3,69603	B3	4,8	8,1	96,7
10	10	-5,7092	1,42806	-3,69603	B3	4,8	8,1	97
11	11	-5,7092	1,42806	-3,74178	B4	4,5	8,6	97,2
12	12	-5,76933	1,35702	-3,69603	B4	4,5	8,6	97,3
13	13	-5,73926	1,39254	-3,7189	B4	4,5	8,6	97,4
14	14	-5,73926	1,39254	-3,7189	B4	4,5	8,6	97,5
15	15	-5,73926	1,39254	-3,7189	B4	4,5	8,6	97,6



MODDE®: *alternative* analysis (*edit model*)



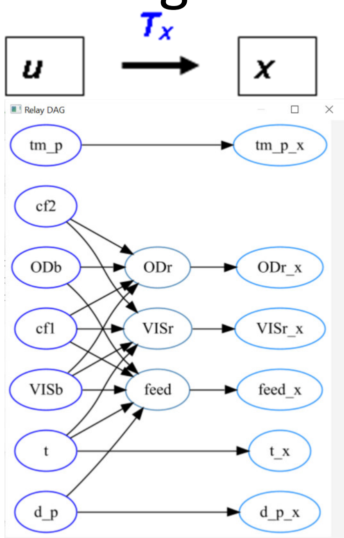
DoE-DiVa® can ***design*** *for ODb and VISb*



Group factor: fermentation *broth*

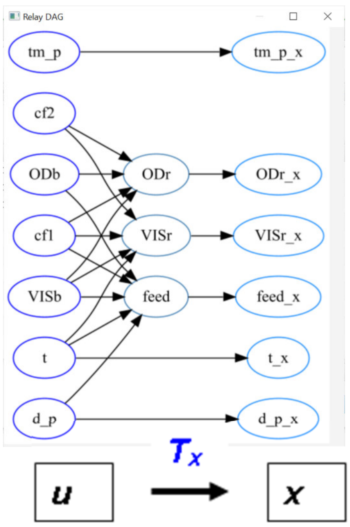
QDEP-u-factors: *optical density, Odb,* and *viscosity, VISb*

How ***DoE-DiVa*** and ***MODDE®*** work together



- ***DoE-DiVa*** prepares the dependencies
- ***& either*** *generates an **x**-design and* ***MODDE®*** does *Analyze* and *Optimize*
- ***or DiVa*** *generates an **x**-candidate set and **MODDE®*** generates a *D-optimal, and then does Analyze and Optimize*

How this works *technically …*



x**-factors* are just *factors* in ***MODDE®,
***u**-factors* become *derived responses*

Factors

	Name	Abbreviation	Units	Type	Use	Settings
1	**d_p_x**	d_p		Quantitative	Controlled	4,827 to 4,861
2	**tm_p_x**	tm_		Quantitative	Controlled	4,653 to 4,74
3	**VISr_x**	VIS		Quantitative	Controlled	-5,769 to -5,709
4	**ODr_x**	ODr		Quantitative	Controlled	1,357 to 1,428
5	**feed_x**	fee		Quantitative	Controlled	-3,742 to -3,696
6	**ODb_q**	ODb		Quantitative	Uncontrolled	

Responses

Name	Abbreviation	Units	Type	Condition	Objective
pur	pur		Regular	Required	Inside
pur_y	pu2		Regular	Required	Inside
cf1_C	cf1		Derived: (10^(1.12083018528585*v1+0.839826684321736*v3 - 0.5190447	Observed	Predicted
cf2_C	cf2		Derived: (10^(0.799356*v1+0.692646*v3 - 0.478962*v4 - 0.927826*v5 - 6.	Observed	Predicted
d_p_C	d_2		Derived: (10^(v1))/100000	Observed	Predicted

ouble-click or press return to edit the response

DoE-DiVa® can even *design for ODr and VISr, where „r“ stands for „retentate“*

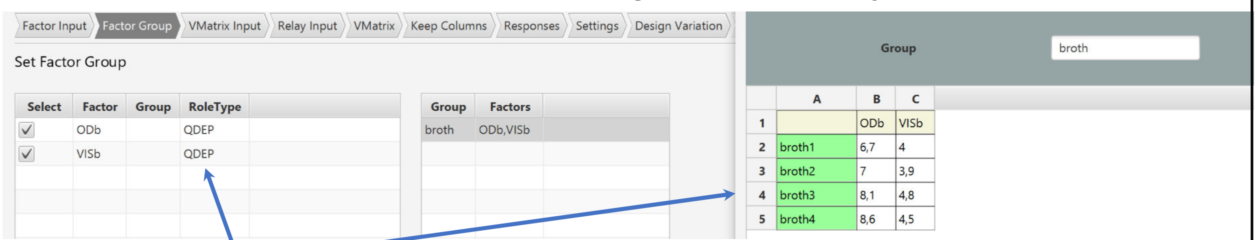
Key	Name	Low	High	Role	Unit	Transformation
VISr	viscosity of retentate	1.0	1.0	CDEP	mm?/s	LOG
ODr	OD of retentate	1.0	1.0	CDEP	AU	LOG
feed	feed flow rate	1.0	1.0	CDEP	l/m?h	LOG
ODb	broth	6.7	8.6	QDEP	AU	LOG
VISb	broth	3.9	4.8	QDEP	mm?/s	LOG

Group: broth

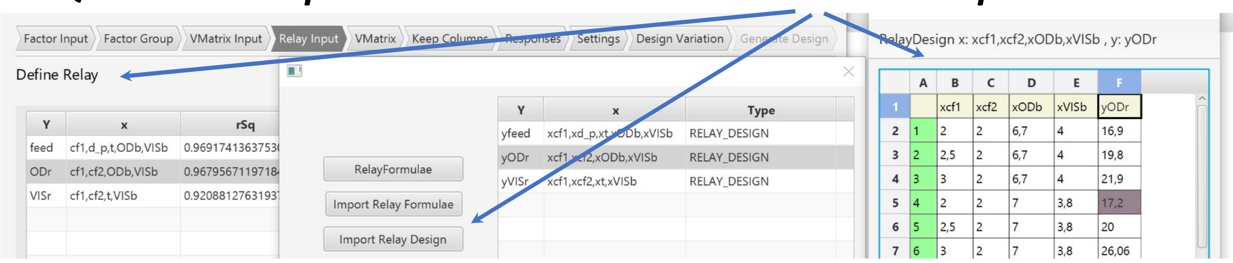
	A	B	C
1		ODb	VISb
2	broth1	6,7	4
3	broth2	7	3,9
4	broth3	8,1	4,8
5	broth4	8,6	4,5

Group factor: fermentation *broth*
QDEP-u-factors: *optical density, Od**b***, and *viscosity, VIS**b***
CDEP-u-factors: *optical density, Od**r***, and *viscosity, VIS**r***

How ***DoE-DiVa*** handles *factor dependencies*

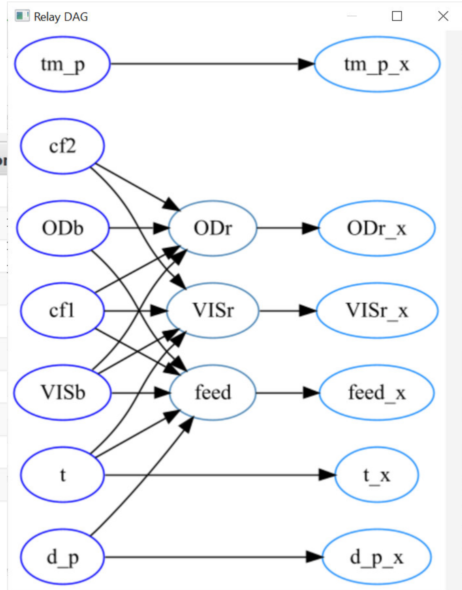


***Qualitative dep**endencies* ***Continuous dep**endencies*



Factor dependencies in Downstream Filtration

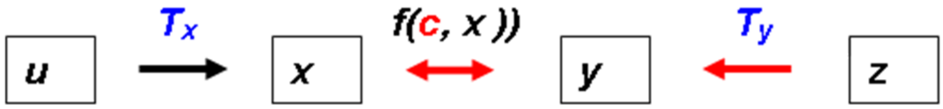
Key	Name	Low	High	Role	Unit	Transformatio
cf1	conc-factor1	2.0	3.0	CONTR	mg/l	LOG
cf2	conc-factor2	2.0	3.0	CONTR	mg/l	LOG
d_p	differential pressure	0.65	0.75	CONTR	bar	LOG
tm_p	transmembrane pressure	0.45	0.55	CONTR	bar	LOG
t	storage time	6.0	12.0	CONTR	h	LOG
VISr	viscosity of retentate	1.0	1.0	CDEP	mm?/s	LOG
ODr	OD of retentate	1.0	1.0	CDEP	AU	LOG
feed	feed flow rate	1.0	1.0	CDEP	l/m?h	LOG
ODb	broth	6.7	8.6	QDEP	AU	LOG
VISb	broth	3.9	4.8	QDEP	mm?/s	LOG



TODAY: QDEP: qualitative dependency

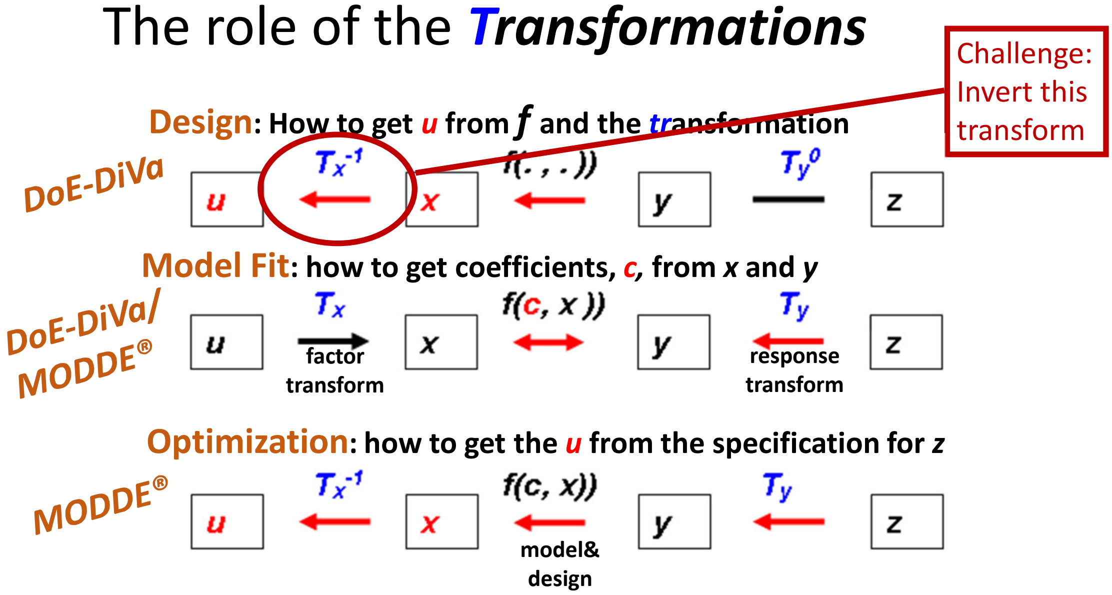
1. ***The DoE-Diva approach***
2. Example: Membrane Filter
3. Factorial ***x***-design using DoE-DiVa
4. Preparing a Candidate Set for ***MODDE®***

The *DoE-DiVa*-approach



***u: U**ser-factor,* to be set in the experiment, e.g. *Temp, pressure etc.*
***x:** e**X**plaining-factor,* to be used in the model, e.g. *a force-ratio*
T_x**: transformation* to get from ***u to ***x***, e.g. *ratio, dimensionless variable*
c:** coefficients or parameters in the model,* ***f, *to be determined by model FIT*
***z:** measured response value*
y:** transformed response value, e.g. ratio or product of a **z** and some **u
T_y**: transformation* to get from ***z to ***y***, *may also just be log or neg-log*

The role of the *Transformations*

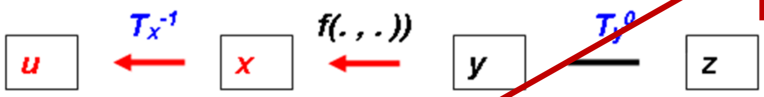


The *Approximation* Trick to get T_x^{-1}

Session 3

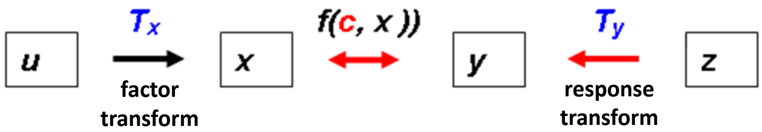
Response to the Challenge:

Design: To get u from x, T_x has to be inverted



Inverting a non-linear T_x may be difficult or impossible, so T_x is approximated by a linear T_{approx} and *when we write* T_x^{-1} *we mean* T_{approx}^{-1}

Model Fit: To get *x* from *u* for Fit, T_x need not be inverted, T_{approx} is not needed.

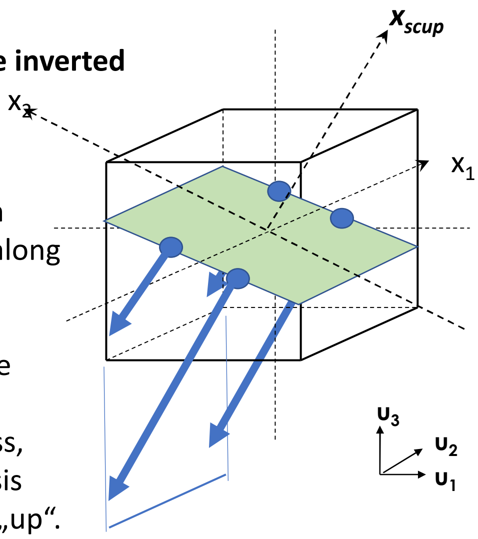


„*Simple*" ***Scale Up*** using Similarity

Session 2

Design: To get u from x, T_x has to be inverted

If there are fewer ***x**-factors* than ***u**-factors*, then there is an orthogonal x_{scup}-"***slider***"-direction, along which both ***x***-coordinates stay the same. T_x^{-1} (respectively T_{approx}^{-1}) then depends on the „sliding-direction", „down" or „up". If the ***x****'s* are dimensionless, and if ***u*** gives a „complete" description of all relevant aspects of the process, the Similarity Principle of Dimensionless Analysis permits the transfer of results from „down" to „up".



*Complex" **Scale Up*** using „All that one knows"

„A-t-o-k approach"

Session 4

Design: To get u from *x*, T_x has to be inverted

T_x^{-1} *at high Scale*

u ← *x*

Challenge: They may be different

The back transform, T_x^{-1} (respectively T_{approx}^{-1}), may be ***much more different*** at *Low Scale* than at *High Scale* ***than just a different „slider position"***, particularly if there are

- *differing low/high intervals* for (geometrical) ***u**-factors,*
- *different **u**-factor* variables altogether (=> a different dimension(!)),
- *different formulae* or *data* relating relevant ***u**- and **x**-factor* variables.

T_x^{-1} *at low Scale*

u ← *x*

Coping with ***qualitative factors***

quantitative approach

TODAY:

Outset: A ***qualitative factor*** (like *broth*) can be described by ***numeric factor variables,*** we call them ***QDEP-factors***, like (*Odb* and *VISb*).

Typically these factor variables and ***interdependent*** and ***discrete***

discrete: Odb can take values 6.7, 7, 8.1 and 8.6

VISb can take values 3.9, 4, 4.5 and 4.8

interdependent: not all combinations are possible,

values come in pairs: B1 → 6.7 and 4 (… or triples etc.)

B2 → 7 and 3.9

B3 → 8.1 and 4.8

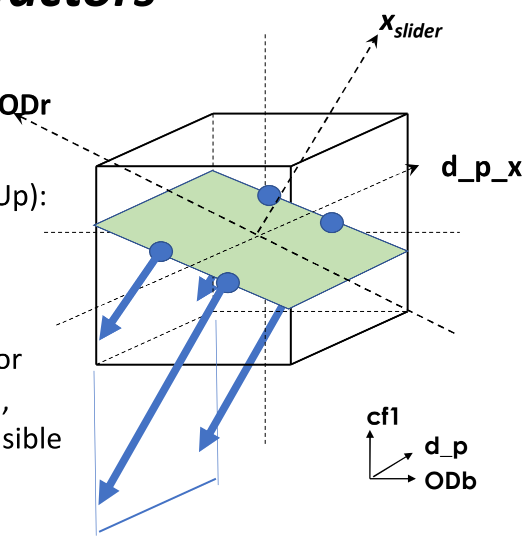
B4 → 8.6 and 4.5

Coping with *qualitative factors*

TODAY:

Variant 1: There are ***enough*** *independent* ***controlled*** *factors* that can influence these **numeric factors** to allow ***„Sliding“*** (as in simple Scale-Up):

Concentration factor, ***cf1,*** influences ***Optical Density*** *in the* ***retentate, ODr,*** so that the ***x****-design* can be made for ***ODr*** and ***d_p_x*** (***differential pressure***), and ***cf1*** can be used to „***slide***“ to a feasible ***ODb***-setting, that corresponds to an existing *broth*.



Coping with *qualitative factors*

TODAY:

Variant 2: Maybe there are ***not enough*** controlled factors for **„Sliding“**, or the ***interdependent*** and ***discrete*** describing factor variables need to be ***used directly*** without being influenced by other controlled factors.

In this case the ***interdependency*** defines ***discrete contraints***, that should be reflected in a ***candidate set*** of potential experimental runs, from which a D-optimal design can be generated.

MODDE® perfectly handles continuous contraints, the ***DoE-DiVa®*** can – soon (not in the current version) – supply corrresponding *candidates sets*.

1. The DoE-Diva approach
2. ***Example: Membrane Filter***
3. Factorial ***x***-design using DoE-DiVa
4. Preparing a Candidate Set for ***MODDE®***

u-factors for membrane-filter example

	Name	Abbr	Group	Role	userunit	transform	userlow	userhigh	offset	gradient
1	conc-factor1	cf1	cf1	contr	mg/l	log	2	3	0	0,001
2	conc-factor2	cf2	cf2	contr	mg/l	log	2	3	0	0,001
3	differential pressure	d_p	d_p	contr	bar	log	0,65	0,75	0	100000
4	transmembrane pressure	tm_p	tm_p	contr	bar	log	0,45	0,55	0	100000
5	storage time	t	t	contr	h	log	6	12	0	3600
6	viscosity of retentate	VISr	VISr	cdep	mm²/s	log	1	1	0	0,000001
7	OD of retentate	ODr	ODr	cdep	AU	log	1	1	0	1
8	feed flow rate	feed	feed	cdep	l/m²h	log	1	1	0	2,78E-07
9	broth	ODb	broth	qdep	AU	log	6,7	8,6	0	1
10	broth	VISb	broth	qdep	mm²/s	log	3,9	4,8	0	0,000001

u-dependencies

	xcf1	xcf2	xt	xVISb	yVISr
1	2	2	6	4	1,11
2	2,5	2	6	4	1,29
3	3	2	6	4	1,29
4	2	2	6	3,9	1,11
5	2,5	2	6	3,9	1,2
6	3	2	6	3,9	1,37
7	3	2	6	3,9	1,34
8	2	2	6	4,8	1,6
9	2,5	2	6	4,8	1,86
10	3	2	6	4,8	2,29
11	2	2,5	6	4	1,21
12	2,5	2,5	6	4	1,39

	xcf1	xcf2	xODb	xVISb	yODr
1	2	2	6,7	4	16,9
2	2,5	2	6,7	4	19,8
3	3	2	6,7	4	21,9
4	2	2	7	3,8	17,2
5	2,5	2	7	3,8	20
6	3	2	7	3,8	26,06
7	2	2	8,1	4,8	23,9
8	2,5	2	8,1	4,8	27,5
9	3	2	8,1	4,8	31,5
10	2	2,5	6,7	4	18,4
11	2,5	2,5	6,7	4	21,3
12	3	2,5	6,7	4	23,4

	xcf1	xd_p	xt	xODb	xVISb	yfeed
1	2	0,7	9	6,7	4	740
2	2,5	0,7	9	6,7	4	700
3	2,5	0,65	9	6,7	4	655
4	2,5	0,7	9	6,7	4	700
5	2,5	0,7	9	6,7	4	705
6	2,5	0,75	9	6,7	4	720
7	2,5	0,7	9	6,7	4	675
8	2,5	0,7	9	6,7	4	710
9	3	0,7	9	6,7	4	675
10	2	0,65	12	7	3,9	775
11	2	0,75	12	7	3,9	864
12	2	0,65	12	7	3,9	778
13	2	0,75	12	7	3,9	867

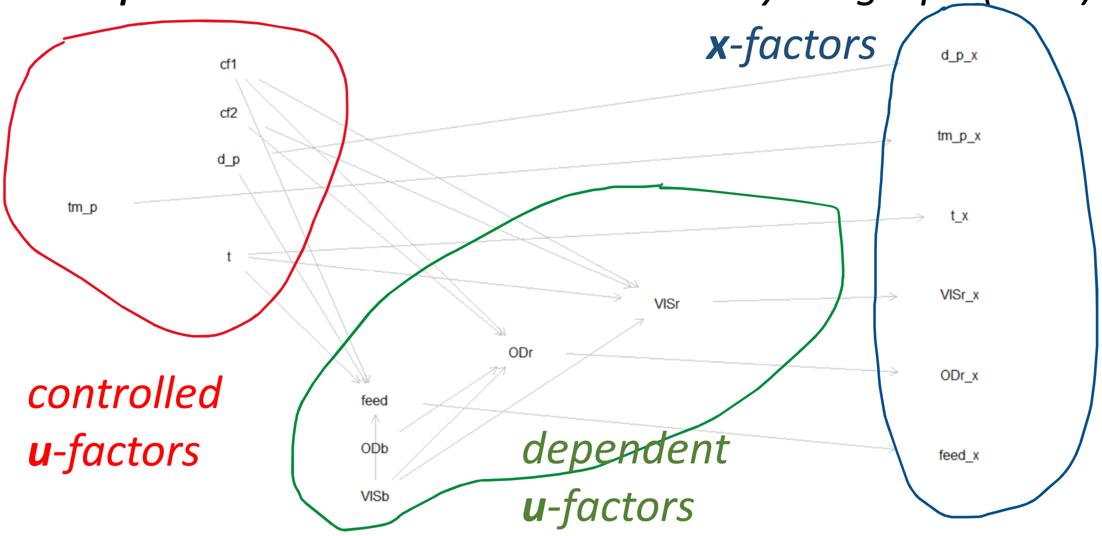
6	viscosity of retentate	VISr	VISr	cdep
7	OD of retentate	ODr	ODr	cdep
8	feed flow rate	feed	feed	cdep
9	broth	ODb	broth	qdep
10	broth	VISb	broth	qdep

broth	ODb	VISb
broth1	6,7	4
broth2	7	3,9
broth3	8,1	4,8
broth4	8,6	4,5

… as *data tables*

u-dependencies

… as *directed acyclic graph (DAG)*



1. The DoE-Diva approach
2. Example: Membrane Filter
3. ***Factorial x-design using DoE-DiVa***
4. Preparing a Candidate Set for ***MODDE®***

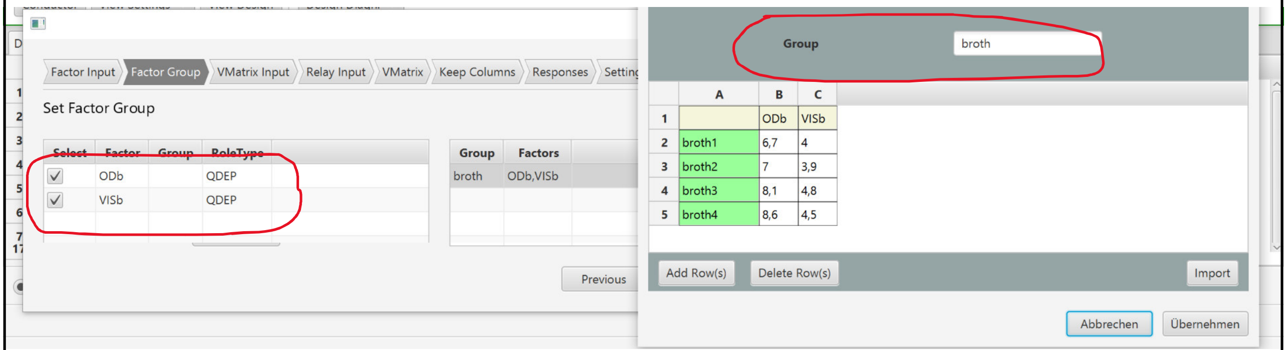
Step 1: *u-factors*

Factor Input | Factor Group | VMatrix Input | Relay Input | VMatrix | Keep Columns | Responses | Settings | Design Variation | Generate Design

Define Factors

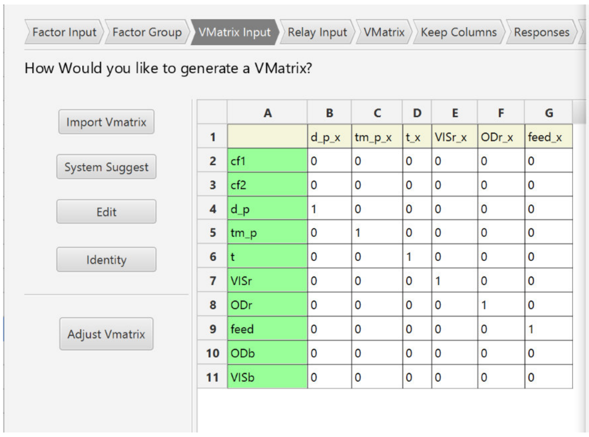
Key	Name	Low	High	Role	Unit	Transformation	Dimension
cf1	conc-factor1	2.0	3.0	CONTR	mg/l	LOG	noName
cf2	conc-factor2	2.0	3.0	CONTR	mg/l	LOG	noName
d_p	differential pressure	0.65	0.75	CONTR	bar	LOG	noName
tm_p	transmembrane pressure	0.45	0.55	CONTR	bar	LOG	noName
t	storage time	6.0	12.0	CONTR	h	LOG	noName
VISr	viscosity of retentate	1.0	1.0	CDEP	mm?/s	LOG	noName
ODr	OD of retentate	1.0	1.0	CDEP	AU	LOG	noName
feed	feed flow rate	1.0	1.0	CDEP	l/m?h	LOG	noName
ODb	broth	6.7	8.6	QDEP	AU	LOG	noName
VISb	broth	3.9	4.8	QDEP	mm?/s	LOG	noName

Step 2: ***u-factor* qualitative** *dependencies*

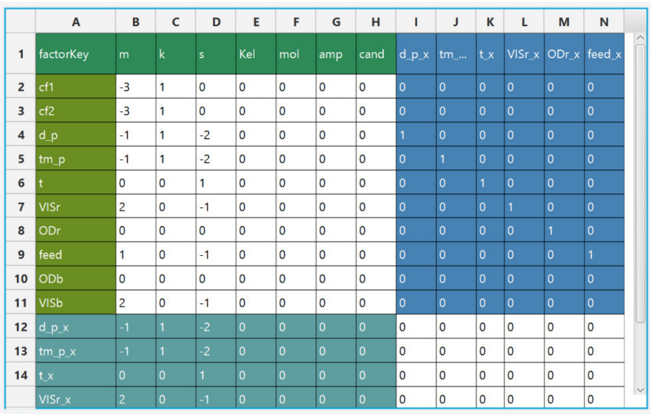


	A	B	C
1		ODb	VISb
2	broth1	6,7	4
3	broth2	7	3,9
4	broth3	8,1	4,8
5	broth4	8,6	4,5

Step 3: ***x-factors***



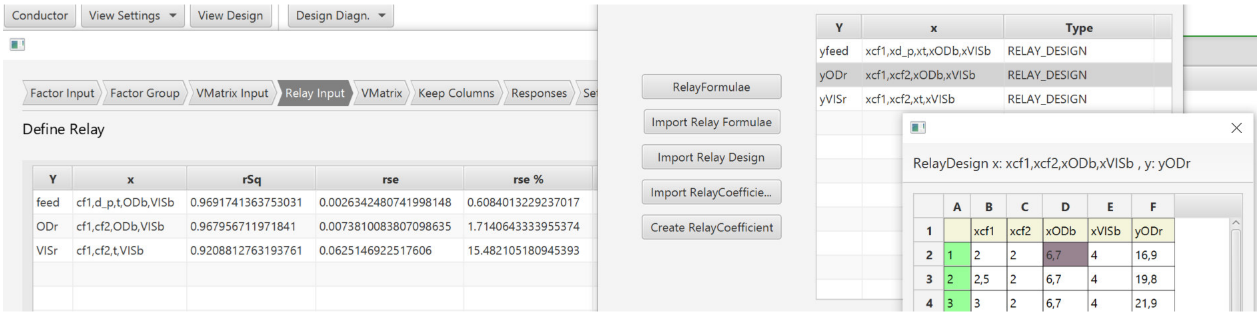
	A	B	C	D	E	F	G
1		d_p_x	tm_p_x	t_x	VISr_x	ODr_x	feed_x
2	cf1	0	0	0	0	0	0
3	cf2	0	0	0	0	0	0
4	d_p	1	0	0	0	0	0
5	tm_p	0	1	0	0	0	0
6	t	0	0	1	0	0	0
7	VISr	0	0	0	1	0	0
8	ODr	0	0	0	0	1	0
9	feed	0	0	0	0	0	1
10	ODb	0	0	0	0	0	0
11	VISb	0	0	0	0	0	0



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	factorKey	m	k	s	Kel	mol	amp	cand	d_p_x	tm_...	t_x	VISr_x	ODr_x	feed_x
2	cf1	-3	1	0	0	0	0	0	0	0	0	0	0	0
3	cf2	-3	1	0	0	0	0	0	0	0	0	0	0	0
4	d_p	-1	1	-2	0	0	0	0	1	0	0	0	0	0
5	tm_p	-1	1	-2	0	0	0	0	0	1	0	0	0	0
6	t	0	0	1	0	0	0	0	0	0	1	0	0	0
7	VISr	2	0	-1	0	0	0	0	0	0	0	1	0	0
8	ODr	0	0	0	0	0	0	0	0	0	0	0	1	0
9	feed	1	0	-1	0	0	0	0	0	0	0	0	0	1
10	ODb	0	0	0	0	0	0	0	0	0	0	0	0	0
11	VISb	2	0	-1	0	0	0	0	0	0	0	0	0	0
12	d_p_x	-1	1	-2	0	0	0	0	0	0	0	0	0	0
13	tm_p_x	-1	1	-2	0	0	0	0	0	0	0	0	0	0
14	t_x	0	0	1	0	0	0	0	0	0	0	0	0	0
	VISr_x	2	0	-1	0	0	0	0	0	0	0	0	0	0

The u-factors, *cf1*, *cf2*, *Odb* and *VISb* are not required as x-factors.

Step 4: ***u-factor*** ***continuous*** *dependencies*



Y	x	rSq	rse	rse %
feed	cf1,d_p,t,ODb,VISb	0.9691741363753031	0.0026342480741998148	0.6084013229237017
ODr	cf1,cf2,ODb,VISb	0.967956711971841	0.0073810083807098635	1.7140643333955374
VISr	cf1,cf2,t,VISb	0.9208812763193761	0.0625146922517606	15.482105180945393

Y	x	Type
yfeed	xcf1,xd_p,xt,xODb,xVISb	RELAY_DESIGN
yODr	xcf1,xcf2,xODb,xVISb	RELAY_DESIGN
yVISr	xcf1,xcf2,xt,xVISb	RELAY_DESIGN

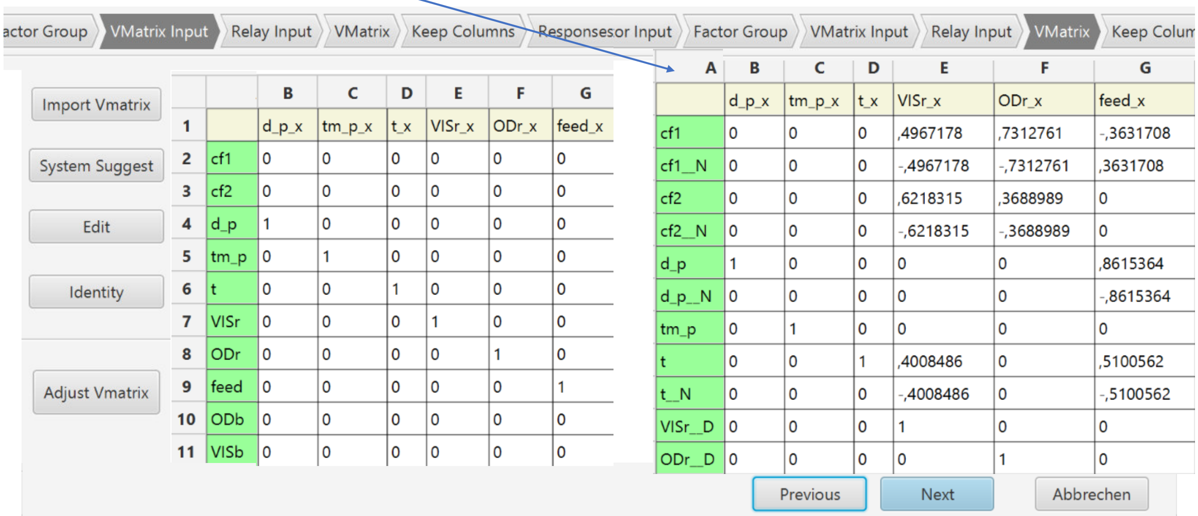
	A	B	C	D	E	F
1		xcf1	xcf2	xODb	xVISb	yODr
2	1	2	2	6,7	4	16,9
3	2	2,5	2	6,7	4	19,8
4	3	3	2	6,7	4	21,9

Approximation quality:

*R^2 is 0.969 for **feed**, 0.968 for **ODr** and 0.921 for **VISr***

*relative deviation is 0.608 % for **feed**, 1.71% for **ODr** and 15.48% for **VISr***

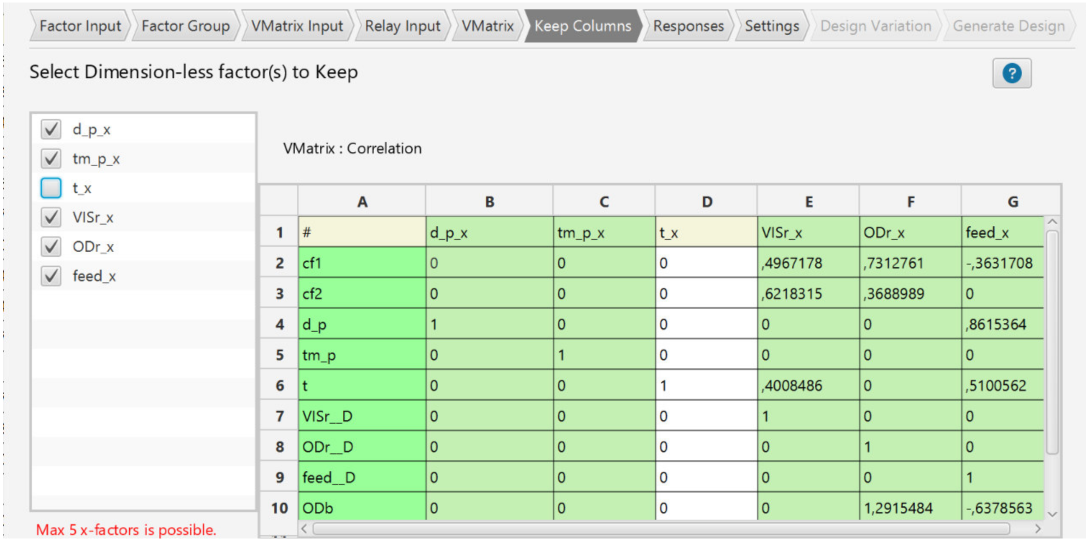
Info: T_{approx} – *transformation as a matrix*



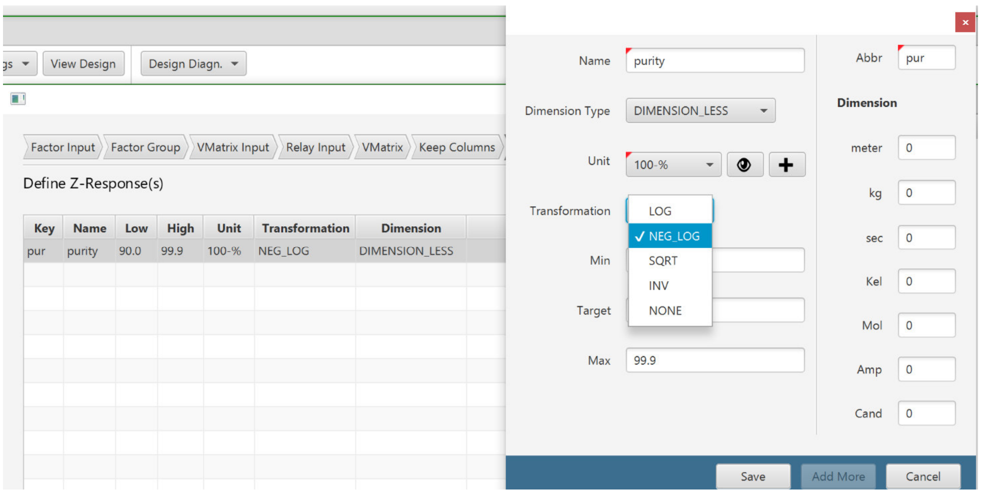
		B	C	D	E	F	G
1		d_p_x	tm_p_x	t_x	VISr_x	ODr_x	feed_x
2	cf1	0	0	0	0	0	0
3	cf2	0	0	0	0	0	0
4	d_p	1	0	0	0	0	0
5	tm_p	0	1	0	0	0	0
6	t	0	0	1	0	0	0
7	VISr	0	0	0	1	0	0
8	ODr	0	0	0	0	1	0
9	feed	0	0	0	0	0	1
10	ODb	0	0	0	0	0	0
11	VISb	0	0	0	0	0	0

A	B	C	D	E	F	G
	d_p_x	tm_p_x	t_x	VISr_x	ODr_x	feed_x
cf1	0	0	0	,4967178	,7312761	-,3631708
cf1__N	0	0	0	-,4967178	-,7312761	,3631708
cf2	0	0	0	,6218315	,3688989	0
cf2__N	0	0	0	-,6218315	-,3688989	0
d_p	1	0	0	0	0	,8615364
d_p__N	0	0	0	0	0	-,8615364
tm_p	0	1	0	0	0	0
t	0	0	1	,4008486	0	,5100562
t__N	0	0	0	-,4008486	0	-,5100562
VISr__D	0	0	0	1	0	0
ODr__D	0	0	0	0	1	0

Step 5: ***choose x-factors to use in the design***



Step 6: ***define z-response(s)*** *(no relevance today)*



Info: *view T_{approx} and its inverse T_{approx}^{-1}*

atrix | x-Settings | u-Settings | VRes | Wres | y-response(s

A	B	C	D	E	F
	d_p...	tm_...	VISr_x	ODr_x	feed_x
cf1	0	0	,4967178	,7312...	-,363...
cf1__N	0	0	-,49671...	-,731...	,3631...
cf2	0	0	,6218315	,3688...	0
cf2__N	0	0	-,62183...	-,368...	0
d_p	1	0	0	0	,8615...
d_p__N	0	0	0	0	-,861...
tm_p	0	1	0	0	0
t	0	0	,4008486	0	,5100...
t__N	0	0	-,40084...	0	-,510...

atrix | x-Settings | u-Settings | VRes | Wres | y-response(s)

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
	cf1	...	cf2	...	...	...	...	t	...	...	...	f...	ODb	...	VISb
d_p_x	1,1208...	0	,79935...	0	1	0	0	-1,333...	0	0	0	0	-,7907...	0	-,278...
tm_p_x	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
VISr_x	,8398267	0	,69264...	0	0	0	0	-,8465...	0	0	0	0	-,7417...	0	,2636...
ODr_x	-,5190...	0	-,4789...	0	0	0	0	,89682...	0	0	0	0	1,1776...	0	,1052...
feed_x	-1,300...	0	-,9278...	0	0	0	0	1,5481...	0	0	0	0	,9177957	0	,3232...
cf1__N	,510065	1	,33075...	0	0	0	0	-,3269...	0	0	0	0	,1594584	0	,09052
cf2__N	,3307556	0	,25402...	1	0	0	0	-,1955...	0	0	0	0	-,0267...	0	,2027...
d_p__N	-1,120...	0	-,7993...	0	0	1	0	1,3337...	0	0	0	0	,7907144	0	,2785...
t__N	-,3269...	0	-,1955...	0	0	0	0	,45027...	1	0	0	0	,1708116	0	,2705...
VISr__D	-,8398...	0	-,6926...	0	0	0	0	,84658...	0	1	0	0	,7417159	0	-,263...

These tables can be used later, if it becomes necessary to adapt *low/high settings* of ***u**-factors*.

Step 7: *view and edit x-settings to use*

Vmatrix | x-Settings | u-Settings | VRes | Wres | y-response(s)

#	Weight	Outer Low	User Low	Inner Low	Mean	Inner High	User High	Outer High
d_p_x	1.0	0.65	0.671192	0.671192	0.6982...	0.72632	0.72632	0.75
tm_p_x	1.0	0.450001	0.450001	0.450001	0.4974...	0.55	0.55	0.55
VISr_x	1.0	1.0382	1.7413	1.7413	1.8162	1.8942	1.8942	3.177
ODr_x	1.0	16.771156	24.833561	24.833561	25.5004	26.185146	26.185146	38.772875
feed_x	1.0	414.56259	657.685252	657.685252	680.43...	703.965108	703.965108	1116.791727
cf1__N	0.0	2.449492	2.449492	2.449492	2.4494...	2.449492	2.449492	2.449492
cf2__N	0.0	2.449492	2.449492	2.449492	2.4494...	2.449492	2.449492	2.449492
d_p__N	0.0	0.698212	0.698212	0.698212	0.6982...	0.698212	0.698212	0.698212

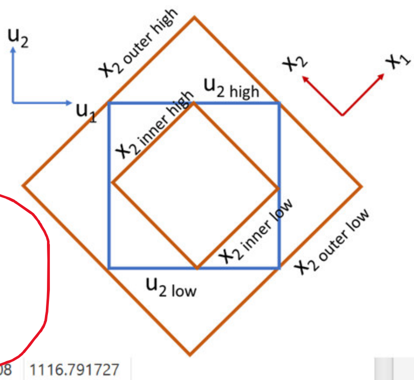
Transformation: LOG / back-transform (selected)

Use: Inner (selected) / Outer / Inbetween / User

Setting

Generate x-Settings

Step 7f: *x-settings*



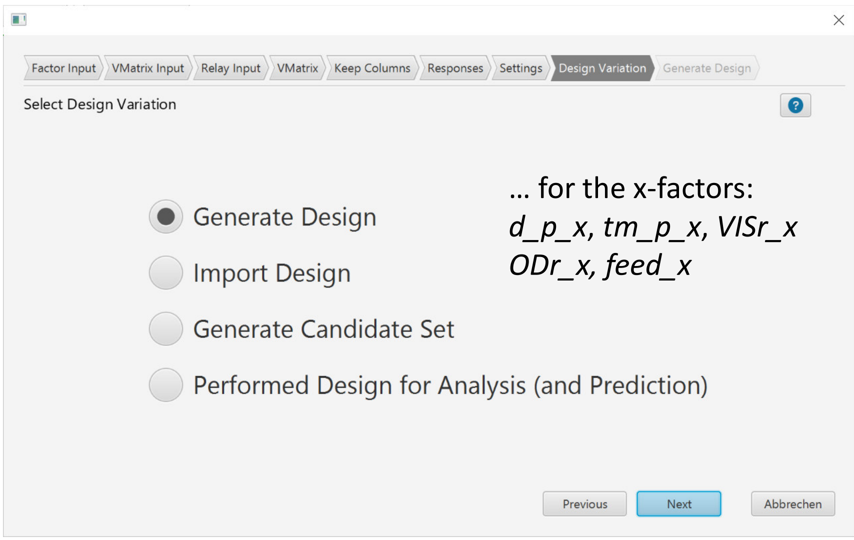
Vmatrix | x-Settings | u-Settings | VRes | Wres | y-response(s)

#	Weight	Outer Low	User Low	Inner Low	Mean	Inner High	User Hi	
d_p_x	1.0	0.65	0.671192	0.671192	0.6982...	0.72632	0.72632	
tm_p_x	1.0	0.450001	0.450001	0.450001	0.4974...	0.55	0.55	
VISr_x	1.0	1.0382	1.7413	1.7413	1.8162	1.8942	1.8942	
ODr_x	1.0	16.771156	24.833561	24.833561	25.5004	26.185146	26.18514	
feed_x	1.0	414.56259	657.685252	657.685252	680.43...	703.965108	703.965108	1116.791727
cf								49492
cf								49492
d								98212

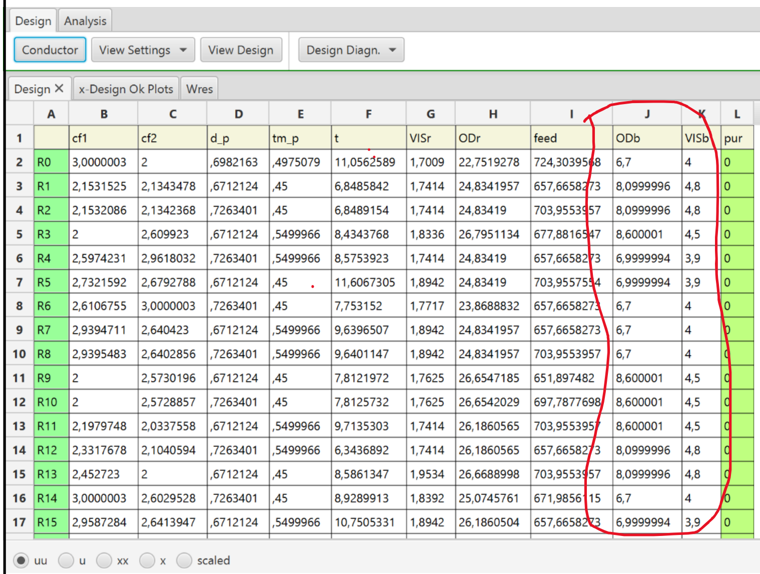
In this example ***inner limits*** and ***outer limits*** are ***different*** for all ***x**-factors*

Transformation: LOG / back-transform (selected)
Use: Inner (selected) / Outer / Inbetween / User
Setting | Generate x-Settings

Step 8: *select the design variation*



... for the x-factors:
d_p_x, tm_p_x, VISr_x
ODr_x, feed_x

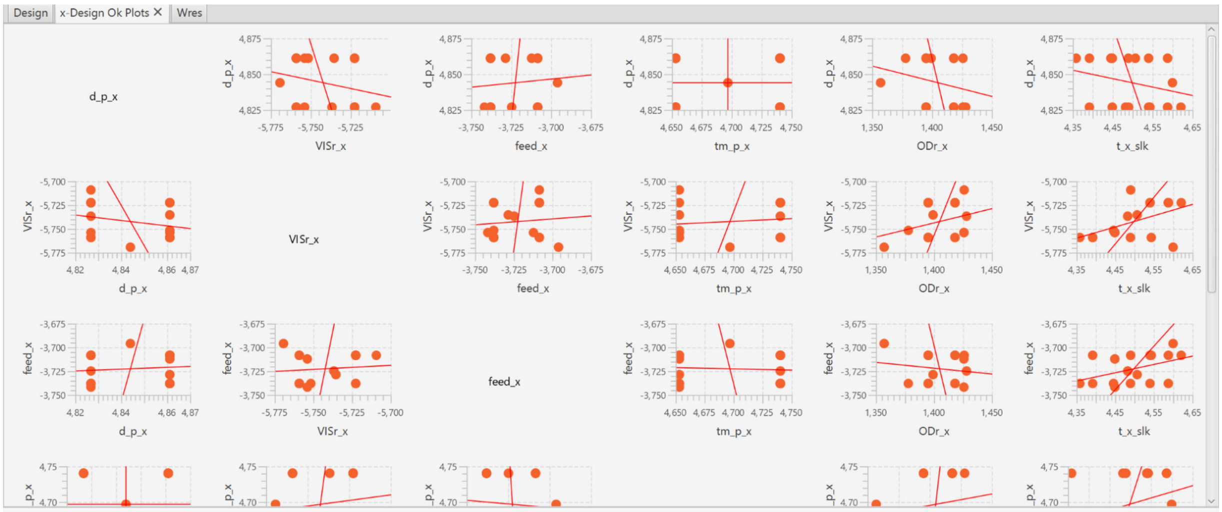


	A	B	C	D	E	F	G	H	I	J	K	L
1		cf1	cf2	d_p	tm_p	t	VISr	ODr	feed	ODb	VISb	pur
2	R0	3,0000003	2	,6982163	,4975079	11,0562589	1,7009	22,7519278	724,3039568	6,7	4	0
3	R1	2,1531525	2,1343478	,6712124	,45	6,8485842	1,7414	24,8341957	657,6658273	8,0999996	4,8	0
4	R2	2,1532086	2,1342368	,7263401	,45	6,8489154	1,7414	24,83419	703,9553957	8,0999996	4,8	0
5	R3	2	2,609923	,6712124	,5499966	8,4343768	1,8336	26,7951134	677,8816547	8,600001	4,5	0
6	R4	2,5974231	2,9618032	,7263401	,5499966	8,5753923	1,7414	24,83419	657,6658273	6,9999994	3,9	0
7	R5	2,7321592	2,6792788	,6712124	,45	11,6067305	1,8942	24,83419	703,9557554	6,9999994	3,9	0
8	R6	2,6106755	3,0000003	,7263401	,45	7,753152	1,7717	23,8688832	657,6658273	6,7	4	0
9	R7	2,9394711	2,640423	,6712124	,5499966	9,6396507	1,8942	24,8341957	657,6658273	6,7	4	0
10	R8	2,9395483	2,6402856	,7263401	,5499966	9,6401147	1,8942	24,8341957	703,9553957	6,7	4	0
11	R9	2	2,5730196	,6712124	,45	7,8121972	1,7625	26,6547185	651,897482	8,600001	4,5	0
12	R10	2	2,5728857	,7263401	,45	7,8125732	1,7625	26,6542029	697,7877698	8,600001	4,5	0
13	R11	2,1979748	2,0337558	,6712124	,5499966	9,7135303	1,7414	26,1860565	703,9553957	8,600001	4,5	0
14	R12	2,3317678	2,1040594	,7263401	,5499966	6,3436892	1,7414	26,1860565	657,6658273	8,0999996	4,8	0
15	R13	2,452723	2	,6712124	,45	8,5861347	1,9534	26,6688998	703,9553957	8,0999996	4,8	0
16	R14	3,0000003	2,6029528	,7263401	,45	8,9289913	1,8392	25,0745761	671,9856115	6,7	4	0
17	R15	2,9587284	2,6413947	,6712124	,5499966	10,7505331	1,8942	26,1860504	657,6658273	6,9999994	3,9	0

Step 8f: ***Look at the design (uu-design)***

... and verify that only ***existing broth-properties*** are being used in the *design*!

Step 8ff: ***ok-plot for u-design***



Step 8ff: *ok-plot for x-design*

(should be orthogonal)

1. The DoE-Diva approach
2. Example: Membrane Filter
3. Factorial ***x***-design using DoE-DiVa
4. ***Preparing a Candidate Set for MODDE®***

Step 1: ***u-factors***

Only one contr-factor to influence *Odr* and *VISr*

Factor Input

Define Factors

Key	Name	Low	High	Role	Unit	Transformation	Dimension
cf	concentration factor	2.5	3.5	CONTR	mg/l	LOG	DENSITY
dp	differential pressure	0.65	0.75	CONTR	bar	LOG	PRESSURE
TMP	transmembrane pressure	0.45	0.55	CONTR	bar	LOG	PRESSURE
t	storage time	10.0	17.0	CONTR	h	LOG	TIME
VISr	viscosity of retentate	1.0	1.0	CDEP	mm^2/s	LOG	VISCOSITY_KINETIC
ODr	OD of retentate	1.0	1.0	CDEP	SI	LOG	DIMENSION_LESS
feed	feed flow rate	1.0	1.0	CDEP	l/m?h	LOG	SPEED
ODb	OD before storage	6.7	8.6	QDEP	SI	LOG	DIMENSION_LESS
VISb	viscosity before storage	3.9	4.8	QDEP	mm^2/s	LOG	VISCOSITY_KINETIC

Step 2: ***u-factor qualitative** dependencies*

Same dependency of *Odb* and *VISb on broth*

Factor Input | Factor Group | VMatrix Input | Relay Input | VMatrix | Keep Columns | Responses | Setting

Set Factor Group

Select	Factor	Group	RoleType
✓	ODb		QDEP
✓	VISb		QDEP

Group	Factors
broth	ODb,VISb

Previous

Group: broth

	A	B	C
1		ODb	VISb
2	broth1	6,7	4
3	broth2	7	3,9
4	broth3	8,1	4,8
5	broth4	8,6	4,5

Add Row(s) | Delete Row(s) | Import

Abbrechen | Übernehmen

Info: T_{approx} – *transformation as a matrix*

A	B	C	D	E	F	G
	d_p_x	tm_p_x	t_x	VISr_x	ODr_x	feed_x
cf1	0	0	0	,4967178	,7312761	-,3631708
cf1_N	0	0	0	-,4967178	-,7312761	,3631708
cf2	0	0	0	,6218315	,3688989	0
cf2_N	0	0	0	-,6218315	-,3688989	0
d_p	1	0	0	0	0	,8615364
d_p_N	0	0	0	0	0	-,8615364
tm_p	0	1	0	0	0	0
t	0	0	1	,4008486	0	,5100562
t_N	0	0	0	-,4008486	0	-,5100562
VISr_D	0	0	0	1	0	0
ODr_D	0	0	0	0	1	0

	A	B	C	D	E	F	G	H
1		cf_x	dp_x	TMP_x	t_x	VISr_x	ODr_x	feed_x
2	cf	1	0	0	0	,5590938	,8765757	-,4369306
3	cf_N	0	0	0	0	-,5590938	-,8765757	,4369306
4	dp	0	1	0	0	0	0	,8609632
5	dp_N	0	0	0	0	0	0	-,8609632
6	TMP	0	0	1	0	0	0	0
7	t	0	0	0	1	0	0	,6542207
8	t_N	0	0	0	0	0	0	-,6542207
9	VISr_D	0	0	0	0	1	0	0
10	ODr_D	0	0	0	0	0	1	0
11	feed_D	0	0	0	0	0	0	1
12	ODb	0	0	0	0	0	1,2651497	-,6211727

Only one contr-factor to influence *Odr* and *VISr*

Step 5: *choose x-factors to use in the design*

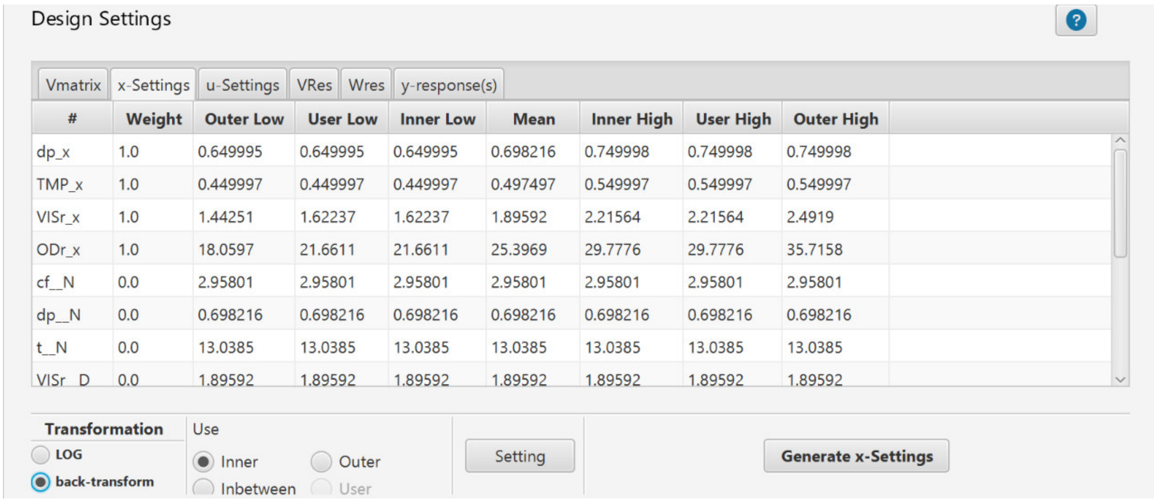
Select Dimension-less factor(s) to Keep

- [ ] cf_x
- [x] dp_x
- [x] TMP_x
- [ ] t_x
- [x] VISr_x
- [x] ODr_x
- [ ] feed_x

VMatrix : Correlation

	A	B	C	D	E	F	G
1	#	cf_x	dp_x	TMP_x	t_x	VISr_x	ODr_x
2	cf	1	0	0	0	,5590938	,8765757
3	dp	0	1	0	0	0	0
4	TMP	0	0	1	0	0	0
5	t	0	0	0	1	0	0
6	ODb	0	0	0	0	0	1,2651497
7	VISb	0	0	0	0	1,7267847	,3425799

Step 7: ***view and edit x-settings to use***

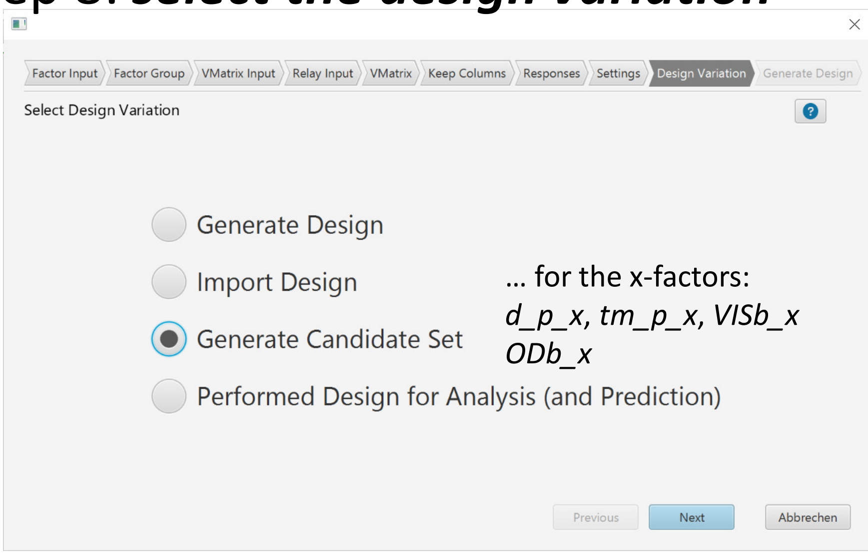


Design Settings

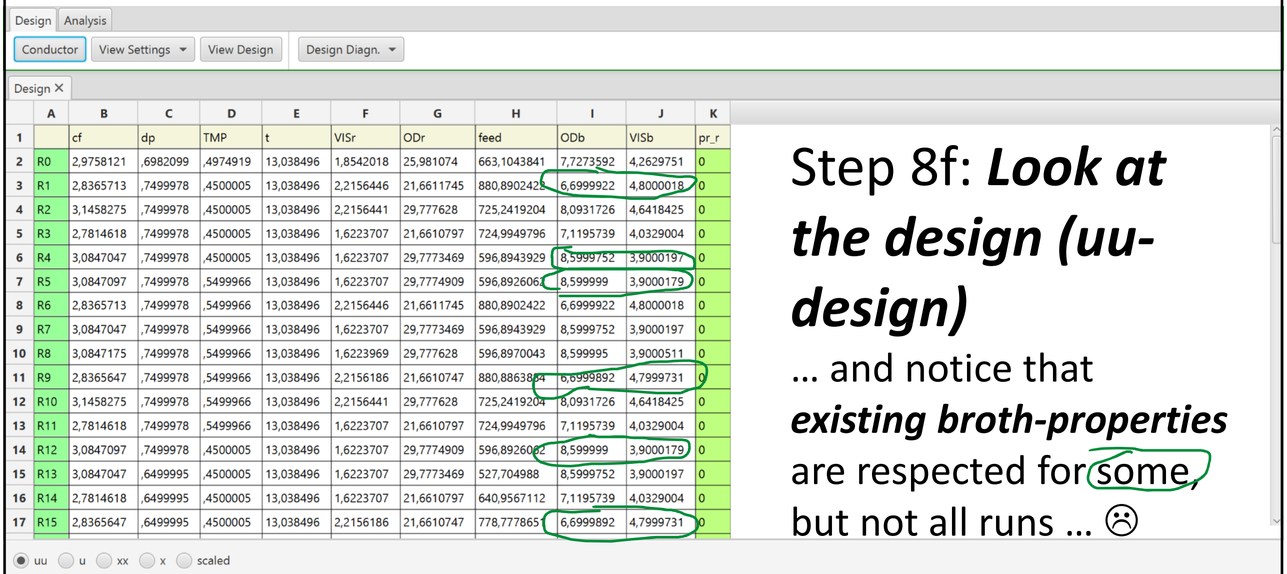
Vmatrix | x-Settings | u-Settings | VRes | Wres | y-response(s)

#	Weight	Outer Low	User Low	Inner Low	Mean	Inner High	User High	Outer High
dp_x	1.0	0.649995	0.649995	0.649995	0.698216	0.749998	0.749998	0.749998
TMP_x	1.0	0.449997	0.449997	0.449997	0.497497	0.549997	0.549997	0.549997
VISr_x	1.0	1.44251	1.62237	1.62237	1.89592	2.21564	2.21564	2.4919
ODr_x	1.0	18.0597	21.6611	21.6611	25.3969	29.7776	29.7776	35.7158
cf__N	0.0	2.95801	2.95801	2.95801	2.95801	2.95801	2.95801	2.95801
dp__N	0.0	0.698216	0.698216	0.698216	0.698216	0.698216	0.698216	0.698216
t__N	0.0	13.0385	13.0385	13.0385	13.0385	13.0385	13.0385	13.0385
VISr__D	0.0	1.89592	1.89592	1.89592	1.89592	1.89592	1.89592	1.89592

Step 8: ***select the design variation***



… for the x-factors:
d_p_x, tm_p_x, VISb_x ODb_x



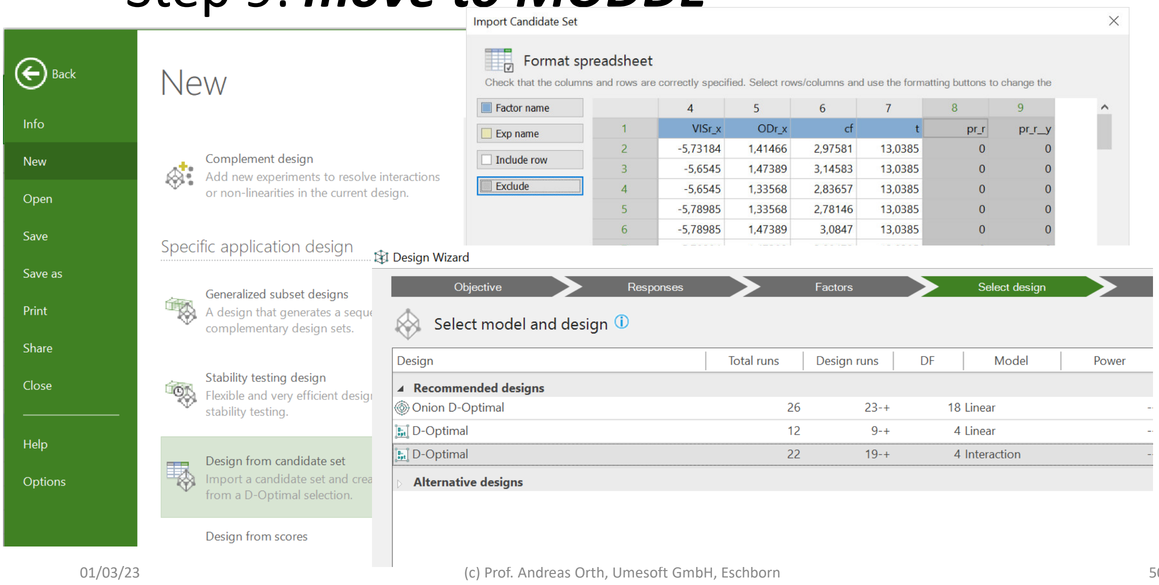
	A	B	C	D	E	F	G	H	I	J	K
1		cf	dp	TMP	t	VISr	ODr	feed	ODb	VISb	pr_r
2	R0	2,9758121	,6982099	,4974919	13,038496	1,8542018	25,981074	663,1043841	7,7273592	4,2629751	0
3	R1	2,8365713	,7499978	,4500005	13,038496	2,2156446	21,6611745	880,8902422	6,6999922	4,8000018	0
4	R2	3,1458275	,7499978	,4500005	13,038496	2,2156441	29,777628	725,2419204	8,0931726	4,6418425	0
5	R3	2,7814618	,7499978	,4500005	13,038496	1,6223707	21,6610797	724,9949796	7,1195739	4,0329004	0
6	R4	3,0847047	,7499978	,4500005	13,038496	1,6223707	29,7773469	596,8943929	8,5999752	3,9000197	0
7	R5	3,0847097	,7499978	,5499966	13,038496	1,6223707	29,7774909	596,8926062	8,599999	3,9000179	0
8	R6	2,8365713	,7499978	,5499966	13,038496	2,2156446	21,6611745	880,8902422	6,6999922	4,8000018	0
9	R7	3,0847047	,7499978	,5499966	13,038496	1,6223707	29,7773469	596,8943929	8,5999752	3,9000197	0
10	R8	3,0847175	,7499978	,5499966	13,038496	1,6223969	29,777628	596,8970043	8,599995	3,9000511	0
11	R9	2,8365647	,7499978	,5499966	13,038496	2,2156186	21,6610747	880,8863884	6,6999892	4,7999731	0
12	R10	3,1458275	,7499978	,5499966	13,038496	2,2156441	29,777628	725,2419204	8,0931726	4,6418425	0
13	R11	2,7814618	,7499978	,5499966	13,038496	1,6223707	21,6610797	724,9949796	7,1195739	4,0329004	0
14	R12	3,0847097	,7499978	,4500005	13,038496	1,6223707	29,7774909	596,8926062	8,599999	3,9000179	0
15	R13	3,0847047	,6499995	,4500005	13,038496	1,6223707	29,7773469	527,704988	8,5999752	3,9000197	0
16	R14	2,7814618	,6499995	,4500005	13,038496	1,6223707	21,6610797	640,9567112	7,1195739	4,0329004	0
17	R15	2,8365647	,6499995	,4500005	13,038496	2,2156186	21,6610747	778,7778651	6,6999892	4,7999731	0

uu u xx x scaled

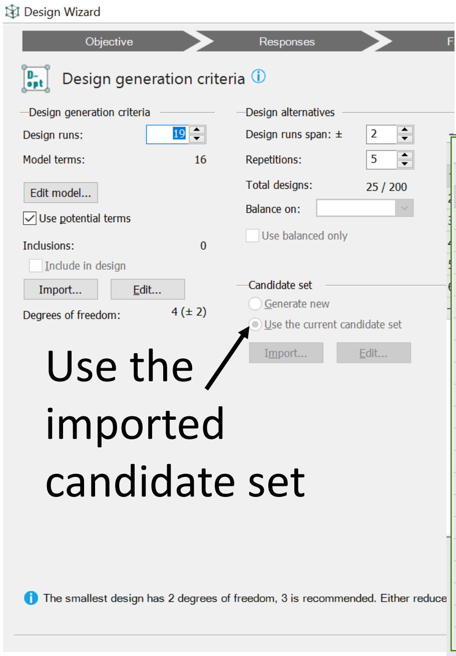
Step 8f: ***Look at the design (uu-design)***

… and notice that ***existing broth-properties*** are respected for some, but not all runs … ☹

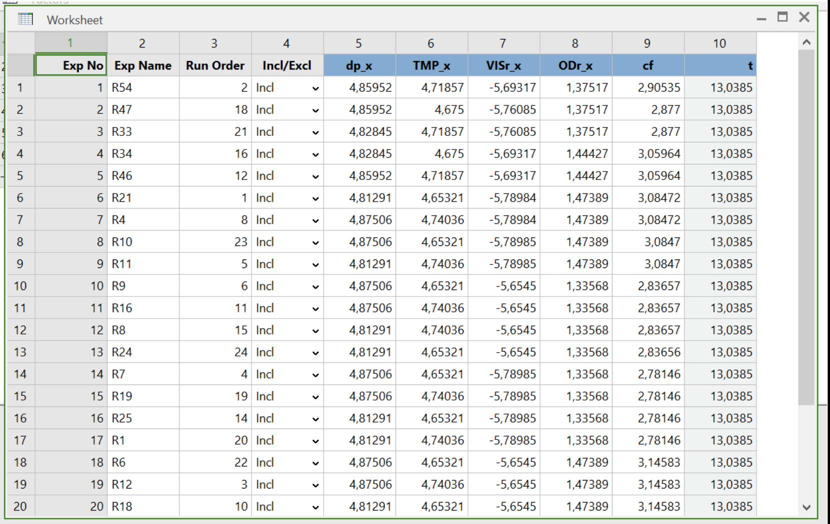
Step 9: ***move to MODDE***



Step 9f: ***design in MODDE***



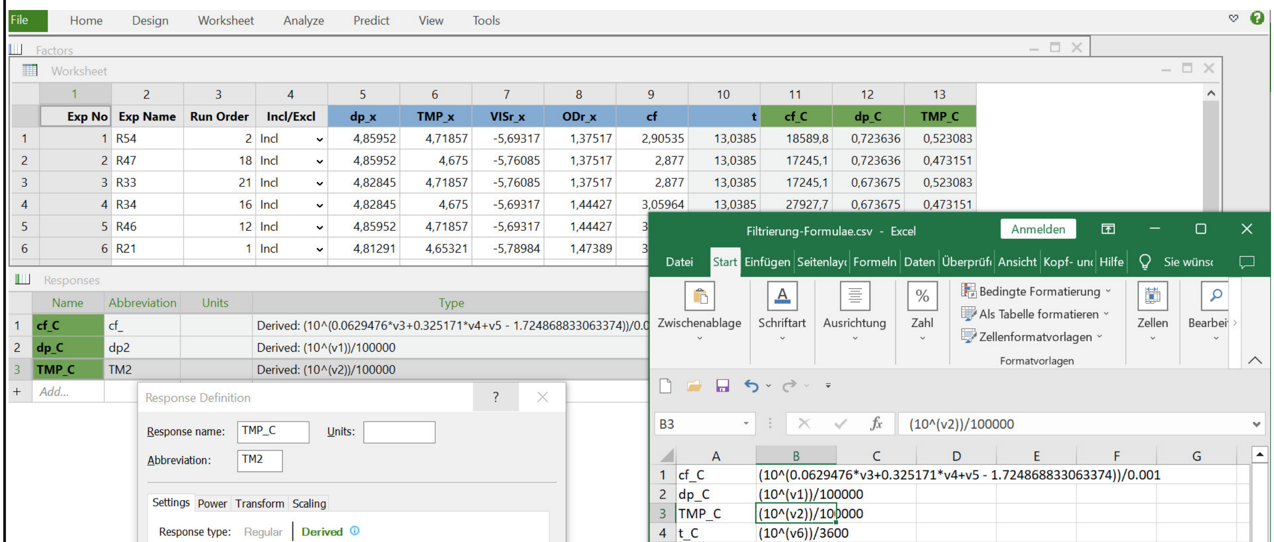
Use the imported candidate set



Worksheet

	Exp No	Exp Name	Run Order	Incl/Excl	dp_x	TMP_x	VISr_x	ODr_x	cf	t
1	1	R54	2	Incl	4,85952	4,71857	-5,69317	1,37517	2,90535	13,0385
2	2	R47	18	Incl	4,85952	4,675	-5,76085	1,37517	2,877	13,0385
3	3	R33	21	Incl	4,82845	4,71857	-5,76085	1,37517	2,877	13,0385
4	4	R34	16	Incl	4,82845	4,675	-5,69317	1,44427	3,05964	13,0385
5	5	R46	12	Incl	4,85952	4,71857	-5,69317	1,44427	3,05964	13,0385
6	6	R21	1	Incl	4,81291	4,65321	-5,78984	1,47389	3,08472	13,0385
7	7	R4	8	Incl	4,87506	4,74036	-5,78984	1,47389	3,08472	13,0385
8	8	R10	23	Incl	4,87506	4,65321	-5,78985	1,47389	3,0847	13,0385
9	9	R11	5	Incl	4,81291	4,74036	-5,78985	1,47389	3,0847	13,0385
10	10	R9	6	Incl	4,87506	4,65321	-5,6545	1,33568	2,83657	13,0385
11	11	R16	11	Incl	4,87506	4,74036	-5,6545	1,33568	2,83657	13,0385
12	12	R8	15	Incl	4,81291	4,74036	-5,6545	1,33568	2,83657	13,0385
13	13	R24	24	Incl	4,81291	4,65321	-5,6545	1,33568	2,83656	13,0385
14	14	R7	4	Incl	4,87506	4,65321	-5,78985	1,33568	2,78146	13,0385
15	15	R19	19	Incl	4,87506	4,74036	-5,78985	1,33568	2,78146	13,0385
16	16	R25	14	Incl	4,81291	4,65321	-5,78985	1,33568	2,78146	13,0385
17	17	R1	20	Incl	4,81291	4,74036	-5,78985	1,33568	2,78146	13,0385
18	18	R6	22	Incl	4,87506	4,65321	-5,6545	1,47389	3,14583	13,0385
19	19	R12	3	Incl	4,87506	4,74036	-5,6545	1,47389	3,14583	13,0385
20	20	R18	10	Incl	4,81291	4,65321	-5,6545	1,47389	3,14583	13,0385

Step 9ff: ***copy/paste the formulae***



Worksheet

	Exp No	Exp Name	Run Order	Incl/Excl	dp_x	TMP_x	VISr_x	ODr_x	cf	t	cf_C	dp_C	TMP_C
1	1	R54	2	Incl	4,85952	4,71857	-5,69317	1,37517	2,90535	13,0385	18589,8	0,723636	0,523083
2	2	R47	18	Incl	4,85952	4,675	-5,76085	1,37517	2,877	13,0385	17245,1	0,723636	0,473151
3	3	R33	21	Incl	4,82845	4,71857	-5,76085	1,37517	2,877	13,0385	17245,1	0,673675	0,523083
4	4	R34	16	Incl	4,82845	4,675	-5,69317	1,44427	3,05964	13,0385	27927,7	0,673675	0,473151
5	5	R46	12	Incl	4,85952	4,71857	-5,69317	1,44427	3				
6	6	R21	1	Incl	4,81291	4,65321	-5,78984	1,47389	3				

Responses

	Name	Abbreviation	Units	Type
1	cf_C	cf_		Derived: (10^(0.0629476*v3+0.325171*v4+v5 - 1.724868833063374))/0.0
2	dp_C	dp2		Derived: (10^(v1))/100000
3	TMP_C	TM2		Derived: (10^(v2))/100000

	A	B
1	cf_C	(10^(0.0629476*v3+0.325171*v4+v5 - 1.724868833063374))/0.001
2	dp_C	(10^(v1))/100000
3	TMP_C	(10^(v2))/100000
4	t_C	(10^(v6))/3600

Vielen Dank!

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des Deutschen Bundestages

ganz besonders an:

Chhawang Lama
Anthony Orth