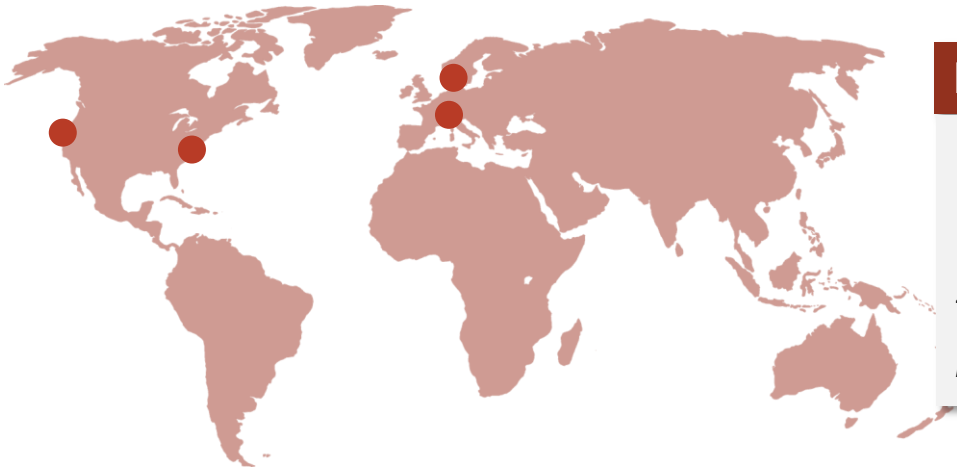
Split-split plot designs in JMP

Stine Fangel, Statistician at Bavarian Nordic

BAVARIAN NORDIC

Bavarian Nordic

Cancer Immunotherapies and Vaccines for Infectious Diseases



FACTS

Founded 1994, IPO 1998

Listed on NASDAQ OMX Copenhagen: BAVA

400 employees worldwide

Market Cap DKK 9.2bn

BAVARIAN NORDIC IN BRIEF

- Vertically integrated multinational biotech company
- Revenue-generating
- Leader in vector-based active immunotherapy
- First product approved in 2013, smallpox
- Commercial scale cGMP manufacturing facility
- Long-term R&D and delivery contracts with the US government

Clinical Pipeline

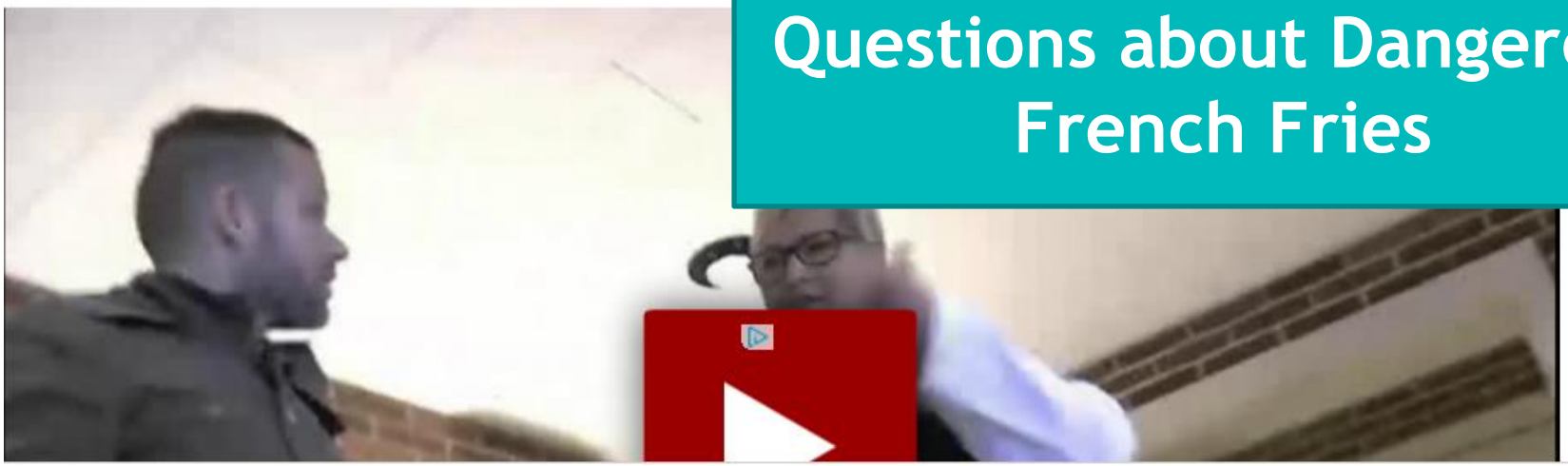
Product	Indication	Partner	Phase 1	Phase 2	Phase 3	Market
IMVANEX/ IMVAMUNE [1-4)]	Smallpox	BARDA				
IMVAMUNE freeze-dried [1)]	Smallpox	BARDA				
PROSTVAC	Prostate Cancer	Bristol-Myers Squibb				
PROSTVAC + enzalutamide	Prostate Cancer	NCI				
PROSTVAC + ipilimumab	Prostate Cancer	NCI				
CV-301 Bladder Combo [1)]	Bladder Cancer	NCI				
MVA-BN Brachyury [1)]	Metastatic Tumors	NCI				
MVA-BN Filo + AdVac® [1)]	Ebola/Marburg	Janssen, NIH				
MVA-BN RSV	RSV		In 2015			

Case

Tv: Kartoffeldronning flygter fra spørgsmål om farlige fritter

Flensteds direktør er afsløret i at producere farlige pomm[illegible]ittes, men stikker af fra Ekstra Bladet

Af: **Christian Kloster**



Potato Queen Runs from Questions about Dangerous French Fries

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Case

How would I suggest this analysis was done?

- **Temperature**: 175°C, 187.5°C, 200°C (hard-to-change)
- **Types of Potato** organic, non organic
- T**wo Days** (block)

- Responses: **Acrylamide** and **Taste**

One oven with room for two baking trays

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Requests

- Balanced design
- Estimations of block variation

- Montgomery, Design and Analysis of Experiments, eq. 13-16 ed. 5th.

Block Whole plot error

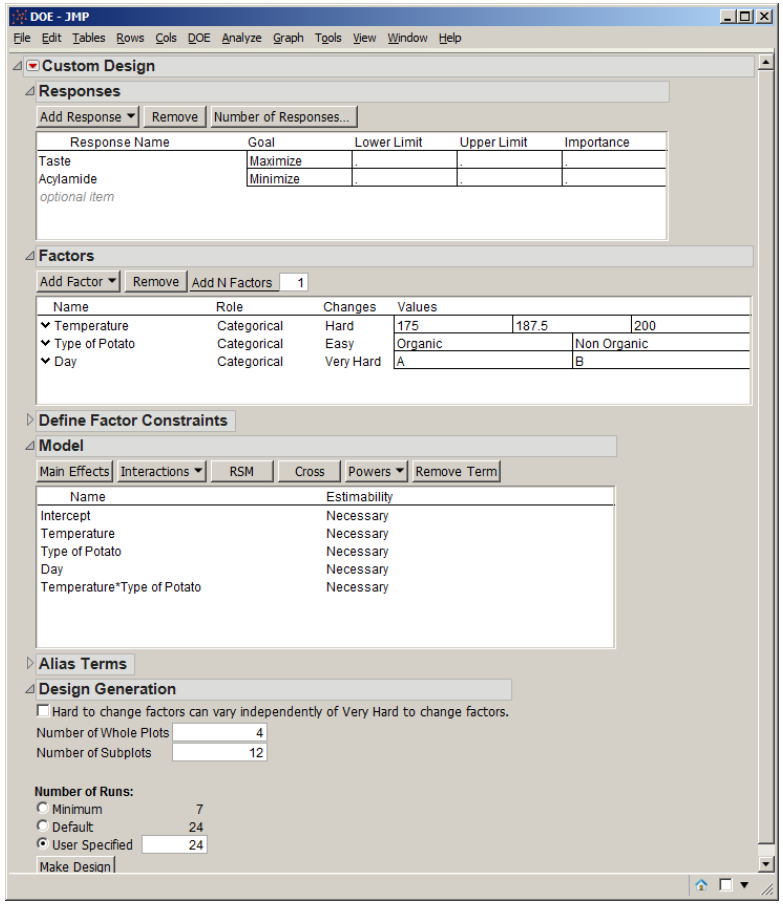
$$y_{ijk} = \mu + Day_i + Temp_j + (Day \cdot Temp)_{ij} + Type_k + (Temp \cdot Type)_{jk} + \epsilon_{ijk}$$

$$\begin{cases} i = A, B \\ j = 175, 187.5, 200 \\ k = Organic, Non\ Organic \end{cases}$$

Subplot error

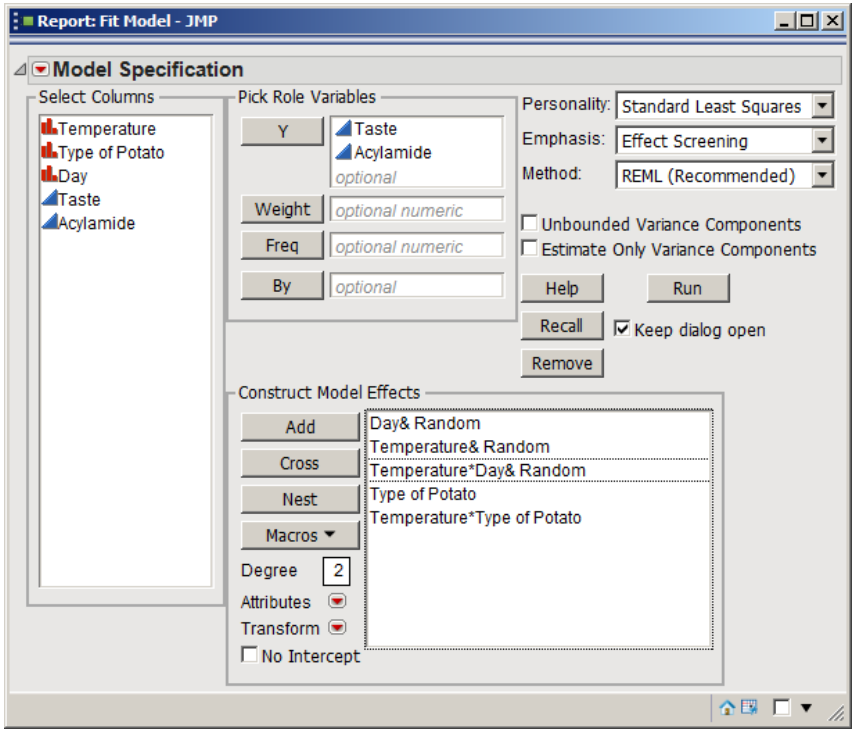
Design in JMP

The trick is to ask for twice as many runs, twice as many whole plots and twice as many subplots as needed



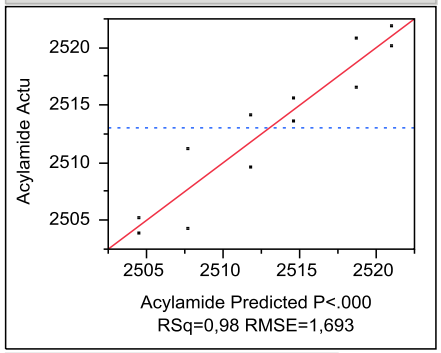
7/0 Cols / 24/12	Whole Plots	Subplots	Temperature	Type of Potato	Day
1	1	1	187.5	Organic	A
2	1	1	187.5	Non Organic	A
3	1	2	200	Organic	A
4	1	2	200	Non Organic	A
5	1	3	175	Non Organic	A
6	1	3	175	Organic	A
7	2	4	175	Organic	B
8	2	4	175	Non Organic	B
9	2	5	187.5	Organic	B
10	2	5	187.5	Non Organic	B
11	2	6	200	Organic	B
12	2	6	200	Non Organic	B
13	3	7	200	Non Organic	A
14	3	7	200	Organic	A
15	3	8	187.5	Non Organic	A
16	3	8	187.5	Organic	A
17	3	9	175	Organic	A
18	3	9	175	Non Organic	A
19	4	10	200	Organic	B
20	4	10	200	Non Organic	B
21	4	11	175	Organic	B
22	4	11	175	Non Organic	B
23	4	12	187.5	Organic	B
24	4	12	187.5	Non Organic	B

Model specified in JMP



Response Acylamide

Actual by Predicted Plot



Summary of Fit

RSquare	0,975025
RSquare Adj	0,954212
Root Mean Square Error	1,693529
Mean of Response	2513,036
Observations (or Sum Wgts	12

REML Variance Component Estimates

Random Effect	Var Ratio	Var Component	Std Error	95% Lower	95% Upper	Pct of Total
Day	0,998062	2,8624833	5,8899104	-8,681529	14,406495	36,071
Temperature*Da	0,7688405	2,2050667	3,8228133	-5,28751	9,6976431	27,787
Residual		2,8680417	2,3417462	0,9203844	39,871701	36,141
Total		7,9355917	6,3620993	2,5840847	102,3942	100,000

-2 LogLikelihood = 40,066882331

Note: Total is the sum of the positive variance components

Total including negative estimates = 7,9355917

Fixed Effect Tests

Source	Nparm	DF	DFDen	F Ratio	Prob > F
Temperature	2	2	2	0,0203	0,9801
Type of Potato	1	1	3	06,3165	0,0019 *
Temperature*Type of Potat	2	2	3	10,7392	0,0429 *

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Check the design

- Can I estimate what I want?
- I usually also take a look at VIF (variance inflations factor)
- VIF describes how much multicollinearity (correlation between predictors) exists in a regression analysis

Demo in JMP

Case: Time added to the design

- **Temperature:** 175°C, 187.5°C, 200°C (very-hard to change)
- **Types of Potato** organic, non organic
- **Time** 25 minutes and 30 minutes (hard-to-change)
- **Two Days** (block factor)

- Responses: **Acrylamide** and **Taste**

One oven with room for two plates

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Requests

- Balanced design
- Estimations of block variation

- Montgomery, Design and Analysis of Experiments, paragraph 13-5.2, reduced

Block Whole plot error Subplot error

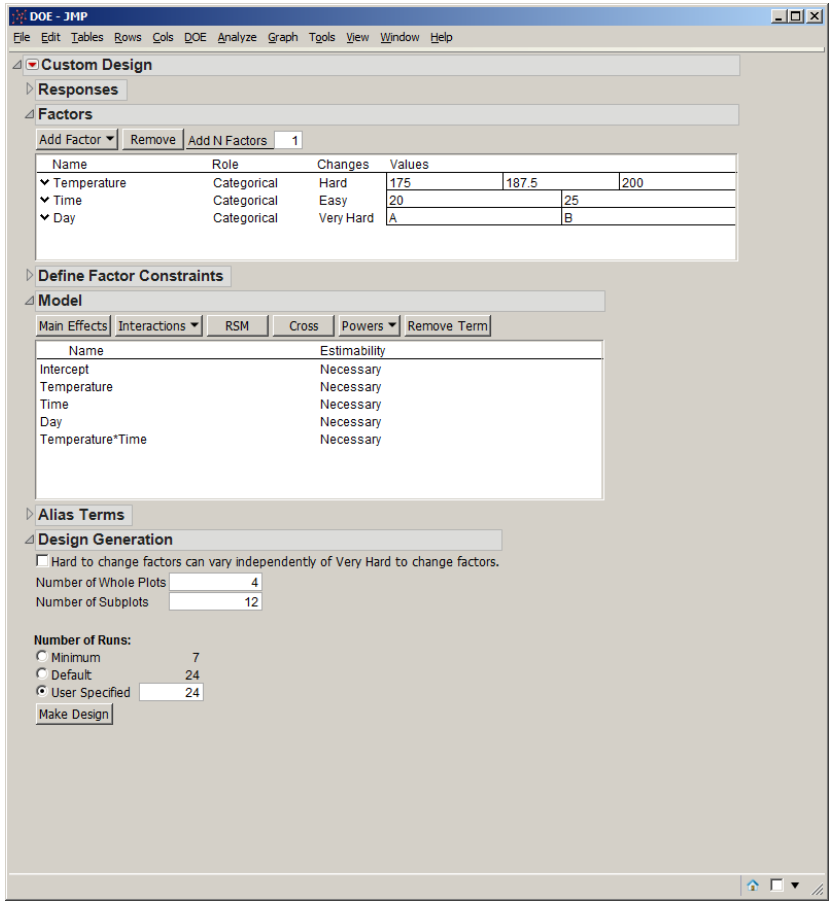
$$y_{ijk} = \mu + Day_i + (Day \cdot Temp)_{ij} + (Day \cdot Temp \cdot Time)_{ijl} + Temp_j + Time_l + Type_k + (Temp \cdot Type)_{jk} + (Temp \cdot Time)_{jl} + (Time \cdot Type)_{jl} + (Temp \cdot Time \cdot Type)_{jkl} + \epsilon_{ijlk}$$

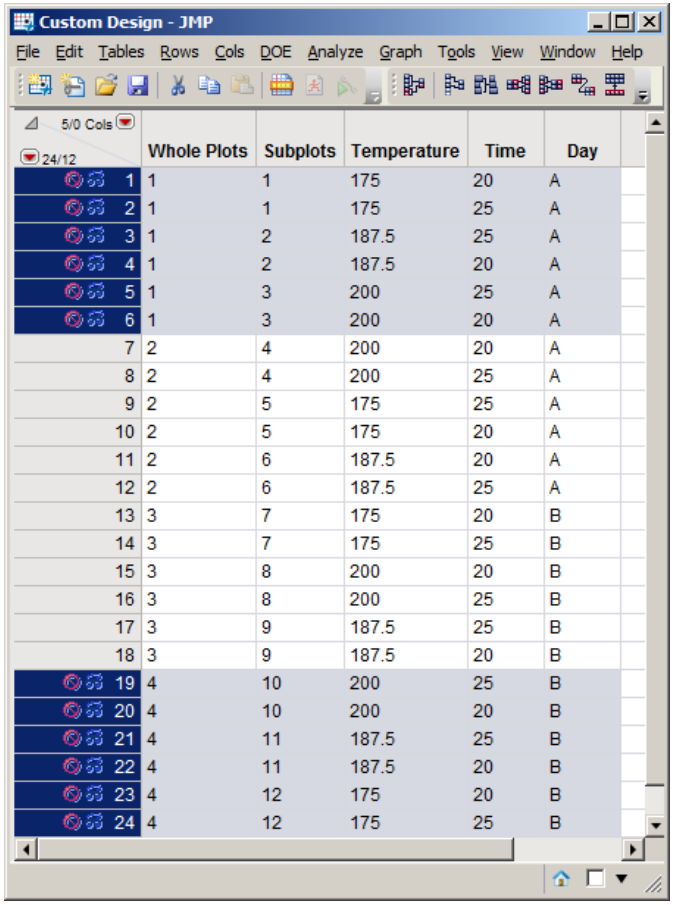
$$\begin{cases} i = A, B \\ j = 175, 187.5, 200 \\ k = Organic, Non\ Organic \\ l = 20, 25 \end{cases}$$

Sub-subplot error

Reference: http://www.public.iastate.edu/~dnett/S402/wsplit2plotwpblock.pdf

2nd Design in JMP





	Whole Plots	Subplots	Temperature	Time	Day
1	1	1	175	20	A
2	1	1	175	25	A
3	1	2	187.5	25	A
4	1	2	187.5	20	A
5	1	3	200	25	A
6	1	3	200	20	A
7	2	4	200	20	A
8	2	4	200	25	A
9	2	5	175	25	A
10	2	5	175	20	A
11	2	6	187.5	20	A
12	2	6	187.5	25	A
13	3	7	175	20	B
14	3	7	175	25	B
15	3	8	200	20	B
16	3	8	200	25	B
17	3	9	187.5	25	B
18	3	9	187.5	20	B
19	4	10	200	25	B
20	4	10	200	20	B
21	4	11	187.5	25	B
22	4	11	187.5	20	B
23	4	12	175	20	B
24	4	12	175	25	B

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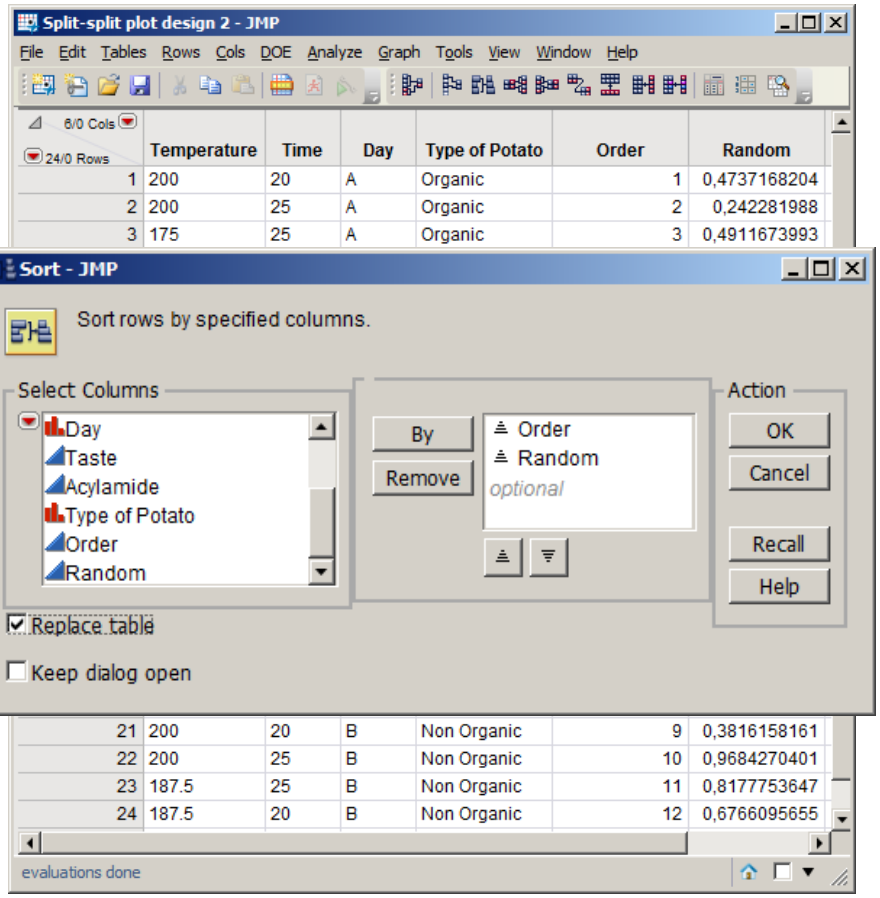
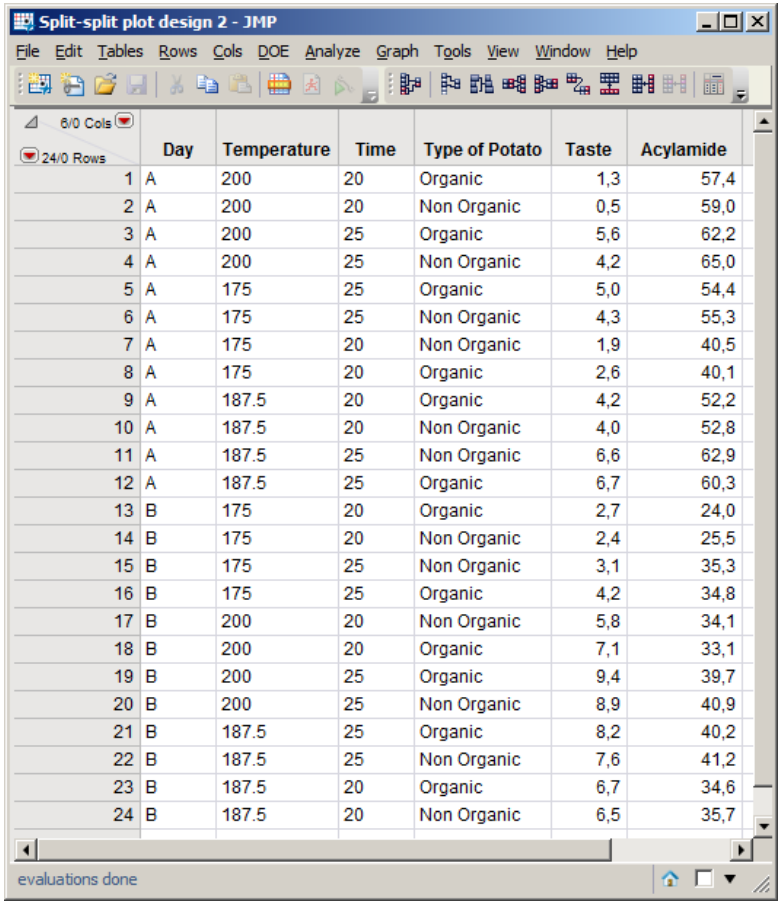
Add *Type of Potato* to the design, double and then randomize





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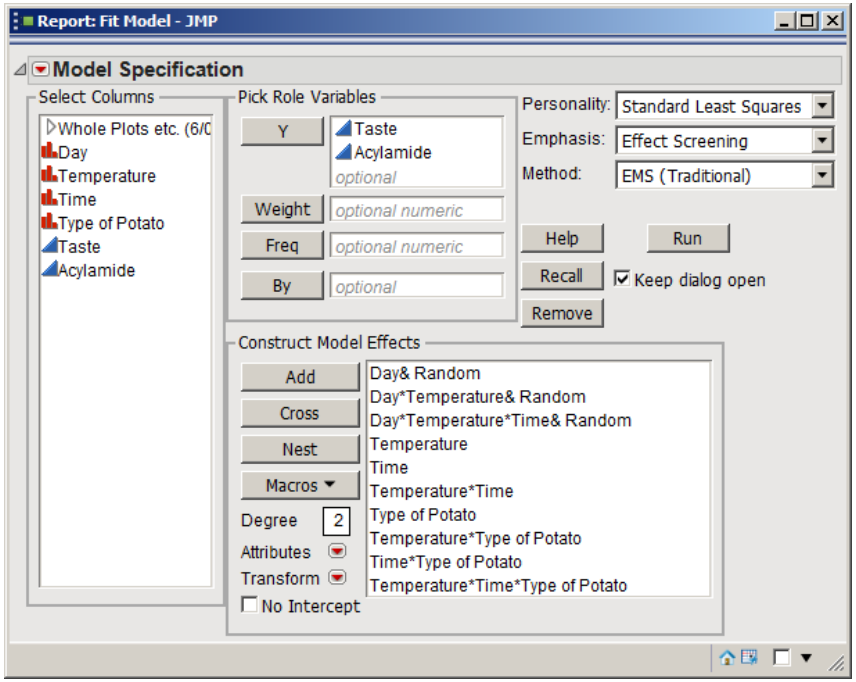
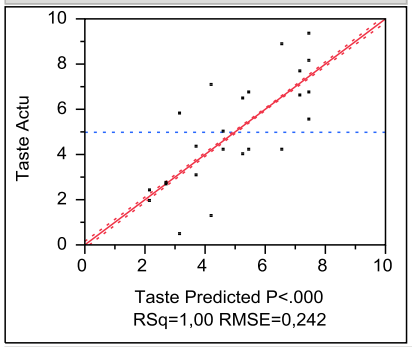
Model specified in JMP



Response Taste

Actual by Predicted Plot



REML Variance Component Estimates

Random Effect	Var Ratio	Var Component	Std Error	95% Lower	95% Upper	Pct of Total
Day	18,584761	1,0930056	3,4056578	0,1128147	6,62e+14	22,544
Day*Temperature	55,897805	3,2874577	3,5111957	0,84172	202,89929	67,808
Day*Temperature*Tim	6,9534062	0,4089432	0,3583131	0,123914	7,7916059	8,435
Residual		0,0588119	0,0339551	0,0244212	0,2851846	1,213
Total		4,8482186	3,9660612	1,553479	67,934185	100,000

-2 LogLikelihood = 58,984486717

Note: Total is the sum of the positive variance components

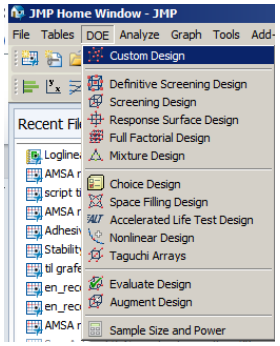
Total including negative estimates = 4,8482186

Fixed Effect Tests

Source	Nparm	DF	DFDen	F Ratio	Prob > F
Temperature	2	2	2	1,3599	0,4237
Time	1	1	3	37,4461	0,0088 *
Temperature*Time	2	2	3	1,7288	0,3167
Type of Potato	1	1	6	43,4652	0,0006 *
Temperature*Type of Potato	2	2	6	4,1577	0,0736
Time*Type of Potato	1	1	6	0,3175	0,5935
Temperature*Time*Type of Potat	2	2	6	0,5645	0,5962

Demo in JMP

Summary / Conclusion



- I have very often used these text books designs, also at different workplaces
- And yes you do have less power, for the factor you split on, however, not less power for the interactions

Wish list for developments in JMP DOE menu

- Possibility to add hierarchy block factors, so these workarounds are not necessary

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