The Dim*-DoE† framework for Scale-Up in Chemical Engineering

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Abstract

In Chemical Engineering Dimensional Analysis (DA) is a useful tool for accomplishing Scale-Up (cf. [6]) of production processes from laboratory to miniplant to pilot plant and then to to production scale. At the same time Design of Experiments (cf. [1] or [4]) is an established method for modelling and optimizing a diversity of production processes in an efficient and systematic way. The aim of this paper is to provide an efficient and applicable way of mergin the two.

It is also highly relevant in pharmaceutical Research and Development which underlies heavy regulation. ICH guidelines Q8(R2) ([3]) and Q11 ([2]) describe QbD[1] and propagate using DoE and Linear Modelling in order to define a so called Design Space in which correct process results can be assured. We argue that, because of the Similarity Principle of DA, this is most efficiently done by combining DoE and DA.

We also propose a solution to the problem of state dependent material properties often needed to define the dimensionless charachteristics.

Keywords: Similarity Principle, Design Space, Quality by Design, D-optimal Designs, Exponent Relaying

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†Design of Experiments
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[1]Quality by Design

1 Introduction

We propose to use ideas from Dimensional Analysis and the associated Similarity Principle to solve problems of Moddelling, Optimization and possibly Scale-Up for a large class of production processes using the techniques Design of Experiments and Linear Modelling for dimensionless factors (such as Reynold's number, Froude number or Newton number) and dimensionless-responses. Assuming a complete relevance list[2] of controlled or constant factors, constant or (state-) dependent material properties and critical or relevant responses can be set up to describe a production process, and assuming the dependency of material properties on other factors is smooth enough, then the proposed methodology will typically reduce the experimental effort required to establish a design space at laboratory scale. At the same time it may allow Scale-Up or at least confirm or disprove the Similarity Principle of DA.

2 Definitions

Let UF be a set of relevent technical factors, (*RT-factors*) or ***u-factors*** that influence the outcome of a process or experimental setup at hand, $uf_1, \ldots, uf_R$. Let $d_1, \ldots, d_R$ be the (row) vectors of dimensions of these factors, expressed as exponents of the SI-system units, so each d_r is a vector with 7 (typically but not necessarily integer) entries, and all of these row vectors form a $R \times 7$-matrix that we shall denote by $\mathbf{D}$.

Denote by XF a the set of dimensionless factors, (*DL-factors*) or ***x-factors***, $xf_1, \ldots, xf_D$, obtained from UF using the exponent matrix

$$\mathbf{V} = \begin{pmatrix} v_{11} & \ldots & v_{1D} \\ \vdots & & \vdots \\ v_{R1} & \ldots & v_{RD} \end{pmatrix}. \tag{1}$$

This means that for a setting $u_1, \ldots, u_R$ of the RT-factors we can obtain a setting $x_1, \ldots, x_D$ of the DL-factors by using the formula:

$x_d = \prod_{r=1}^{R} u_r^{v_{rd}}$, or taking *logs*: $log(x_d) = \sum_{r=1}^{R} log(u_r) v_{rd}$.

[2] as explained in [6]

In the following we assume that all settings of RT-factors are positive and that *logs* can be easily calculated. To simplify things we just substitute $log(u)$ by u for UF and $log(x)$ by x for XF, so that we have $\mathbf{x} = \mathbf{uV}$. Note that only if $D < R$, are there enough degrees of freedom to apply the Similarity Principle.

For $x_1, \ldots, x_D$ to be dimensionless the exponent matrix $\mathbf{V}$ must satisfy the property that $\mathbf{D^T V} = \mathbf{0}$. Please note that the condition $\mathbf{D^T V} = \mathbf{0}$ is not necessary for the functioning of this framework. It is an engineering requirement, needed to justify the Similarity Principle of Dimensional Analysis. Finding a useful matrix $\mathbf{V}$ for a particular problem at hand is a task that requires considerable process know how and some algebraic skills. Engineers call the solution of the homogeneous system of linear equations, $\mathbf{D^T V} = \mathbf{0}$ for $\mathbf{V}$ given $\mathbf{D}$, or the way of solving it the Π-*theorem*. Note that $D = R - rk(\mathbf{D})$, but this is not necessarily useful as amongst the R ***u-factors*** there may be constants and dependent factors.

In fact in practice RT-factors may be

- state variables like temperature and pressure,
- process parameters like stirrer or screw speeds (rotation number or tip speed), dosage speeds, feed rates etc.
- reaction parameters like molar or mass concentrations or simply molar, mass or volume ratios of starting materials (ratios are typically already dimensionless),
- material properties, like density, viscosity, heat or electrical conductivity and heat or electrical capacity, maybe dependent on state variables or reaction parameters (particularly in gases this dependency may span several orders of magnitude).
- geometric parameters like stirrer diameter, reactor volume, tube length, catalyst grain size, etc. that will typically act as Scale-Up parameters,
- constants that are needed to define DL-factors, such as constant of gravity, gas constant, Avogadro's number etc.

3 Assumption and Idea

The basic assumption is the Similarity Principle of Dimensional Analysis, which states that physical and chemical systems that are described by the same settings of the correctly chosen dimensionless ***x-factors*** are equivalent in their behaviour and will yield the same settings for the dimensionless — let us call them — ***y-responses***. From these ***y-responses*** relevent technical responses that we consequentially call ***z-responses*** can be recovered. This principle will be demonstrated in section 12 and used for Scale-Up of a defoamer.

The second idea is to dualize the Similarity Principle and to postulate that the greatest change in a system is induced, *when the dimensionless factors are changed*. This is motivation to devise efficient experiments by using designs for these ***x-factors*** rather than for the original ***u-factors***. These designs will typically be less elaborate and the associated models simpler in structure — with less interaction terms — than comparable designs and models in the ***u-factors***. In the pharmaceutical context of finding a Design Space according to Q8 (R2), an experimental design should — in the author's opinion — always be made for dimensionless ***x-factors*** because following the dualized version of the Similarity Principle, these will have the most effect on the process, and the proof that critical quality attributes are unaffected by extremes of ***x-factors*** immediately translates into the proof that this is also the case for all ***u-factors***!

It is important to understand that applying the Similarity Principle is not the same thing as extrapolation. In the example in section 12 we recognize this difference and see at the same time that extrapolation is much less efficient for Scale-Up. At the same time it may be the aim of experimentation to establish that this principle is true for a process at hand, so that in future investigations it can be assumed and applied.

4 Method: Transferring an *x-design* to a *u-design*

A design for the ***x-factors*** must be converted into a design for the ***u-factors*** in order to be performed. Of course in general due to the fact that $D < R$, this "back-"transform is not unique. In fact it is this non-uniqueness that gives the necessary degrees of freedom for Scale-Up. In order to back-transform, we must find a generalized (in this case a left-)

inverse of $\mathbf{V}$, best by calculating: $\mathbf{W} = (\mathbf{V^T V})^{-1}\mathbf{V^T}$, for assuming the list of DL-factors is minimal, the rank of $\mathbf{V}$ will be D and and $\mathbf{V^T V}$ will be invertible. Obviously $\mathbf{WV} = \mathbf{id_{DxD}}$.

At this stage we need to differentiate between controlled, constant and dependent ***u-factors*** — remembering that dependent factors are typically material properties that may depend on state variables like temperature and pressure and that are required to define dimensionless variables. Assume $R = R_{contr} + R_{const} + R_{dep}$. Then if $D > R_{contr}$ not all ***x-factors*** can be varied independently, as would be required by a DoE. But it will be possible to define $\mathbf{V}$ in such a way, that only R_{contr} of the D ***x-factors*** depend on controlled ***u-factors*** and the remaining $D - R_{contr}$ ***x-factors*** only depend on constant and dependent ***u-factors***.

If $D > R_{contr}+R_{const}$ Scale-Up will not be possible because only R_{contr} ***x-factors*** can be systematically varied in the design, R_{const} further ones can be held constant, but $D-R_{contr}+R_{const}$ ***x-factors*** will vary depending on other ***x-factors***. In Dimensional Analysis, this phenomenon is well known as *Partial Similarity*. Following a naming sometimes used for filler variables in mixture designs, we call these dependent ***x-factors*** *slack variables*. Their effect can not be quantified without bias unless using adjustments methods known from Causality Theory $referencemissing$. These may however, due to collinearities, introduce high variance.

Leaving constant and slack ***x-factors*** out of consideration, we may assume without loss of generality that $D \leq R_{contr}$. However, since constant ***u-factors*** are needed for defining dimensionless factors, these can not be left out of consideration and the $\mathbf{V}$-matrix must be augmented by R_{const} columns each containing just an entry of 1 to indicate which is the row of the respective constant. This augmented $\mathbf{V}$ is (left-)inverted using $\mathbf{W} = (\mathbf{V^T V})^{-1}\mathbf{V^T}$.

If $D < R_{contr}$, in order to capitalize on this dimensional freedom, calculate $R_{contr} - D$ residual vectors using $\mathbf{r_j} = \mathbf{s_j} - \mathbf{s_j} \cdot \mathbf{V} \cdot \mathbf{W}$. $\mathbf{V} \cdot \mathbf{W}$ is a projection matrix (often called "Hat"-matrix) of ***u-factors***-space onto that sub-space spanned by the columns in $\mathbf{V}$. So $\mathbf{r_j V} = 0$ for all $j = 1, \ldots, R_{contr} - D$. $\mathbf{s_j}$ can be any vector in ***u-factor***-space that is not linear combination of the columns of $\mathbf{V}$; typically it is a basis vector representing a factor to be used for Scale-Up (i.e. a unit vector $(0, \ldots, 0, 1, 0, \ldots, 0)$,with a 1 at the position of of the said factor). Let **RES** be the matrix of residual vectors, **VRES** the concatenation of

(the augmented) **V** and **RES**. **VRES** and its inverse, **WRES** can now be used to convert a ***u-design*** into an ***x-design*** and vice versa, and **RES** can be used to deal with Scale-Up requirements, as will be explained in the next section.

5 Implementing Scale-Up and Checking the Similarity Principle

We define a *Scale-Up factor* to be a ***u-factor*** whose associated $\mathbf{s_j}$ is not a linear combination of the columns of **V**. This implies that it can be set to one constant in the ***u-design*** and to another constant for (later) prediction purposes, without leaving the domain of the design for the ***x-factors***. Scale-Up factors by our definition can be either used by an engineer for the Scale-Up of his process or for the verification of the Similarity Principle. However if an engineer wants to do Scale-Up for a factor that does not satisfy our condition, then these endeavours will fail. Even if the condition is fulfilled, but the correlation (cosine) between $\mathbf{s_j}$ and its projection onto the columns of **V** is large, then Scale-Up may be difficult, as is shown in the example in section 12).

Given the **RES**-matrix with its columns $\mathbf{r_j}$, any two settings of the ***u-factors*** that differ by only a linear combination of the $\mathbf{r_j}$ are similar in the sense of the Similarity Principle. So if **sli** is a row vector of $R_{contrl} - D$ multiplication factors (imagine *"slider settings"*) then $\mathbf{sli} \cdot \mathbf{RES^T}$ is such a linear combination. Having orthogonolized the $\mathbf{r_j}$ vectors gives the freedom to choose slider settings for $j = 1, \ldots, R_{contrl} - D$ of Scale-Up-factors at low scale in the design phase, but to change slider settings later in the prediction phase and use "scaled-up" values for these same factors without changing the settings of the ***x-design*** or of the constant factors. Remark: Dependent factors should at this stage be treated as constants. Resolving the dependency on controlled factors will be the topic of sections 8 and 9.

Let

$$\mathbf{U_W} = \boldsymbol{x\text{-}design} \cdot \mathbf{W} \tag{2}$$

, where the ***x-design*** has N rows for N experimental runs. Also let **SLI** be a $N \times (R_{contr} - D)$-matrix of slider settings – one vector for each run – then $\mathbf{U_W}$ and $\mathbf{U_W} + \mathbf{SLI} \cdot \mathbf{RES^T}$

are to be considered as equivalent designs and the matrix **SLI** represents the freedom of the user to set his Scale-Up factors to a low setting in the design for the laboratory experiments and to a high setting for prediction of the production process.

Let the residual matrix **RES** have the form:

$$\mathbf{RES} = \begin{pmatrix} r_{11} & \dots & r_{1,R_{const}-D} \\ \vdots & & \vdots \\ r_{R1} & \dots & r_{R,R_{const}-D} \end{pmatrix}. \tag{3}$$

Without loss of generality we assume that the Scale-Up factors correspond to the last $R_{contr} - D$ rows of $\mathbf{V}$ (and hence **RES**). Then by construction $\mathbf{RES_{red}}$, defined as the last $R_{contr} - D$ rows of **RES** is invertible, as is its transpose, $\mathbf{RES^T_{red}}$.

For the $R_{contr} - D$ Scale-Up factors we would like

$$\mathbf{U_W} + \mathbf{SLI} \cdot \mathbf{RES^T} = \mathbf{u_{given}} \tag{4}$$

So it suffices to set

$$\mathbf{SLI} = (\mathbf{u_{given}} - \mathbf{U_{Wred}}) \cdot (\mathbf{RES^T_{red}})^{-1}. \tag{5}$$

Here $\mathbf{U_{Wred}}$ are the last $R_{const} - D$ columns of $\mathbf{U_W}$.

Note that although both **RES** and **SLI** matrices depend on the choice of residual vectors $\mathbf{r_j}$ derived from the $\mathbf{s_j}$ as described above, the product $(\mathbf{RES^T_{red}})^{-1} \cdot \mathbf{RES^T}$ and hence the final ***u-factors***-matrix for the ***u-factors***

$$\mathbf{U} = \mathbf{U_W} + \mathbf{SLI} \cdot \mathbf{RES^T} \tag{6}$$

do not.

This can be seen as follows: Any two sets of generating basis vectors $\mathbf{s_j}$, as introduced above, that lead to nondegenerate $\mathbf{r_j}$, can be mapped into each other by unitary $(R_{const} - D) \times (R_{const} - D)$ matrix **UMAT**. Then the corresponding residual matrix, **RES**, must be replaced by $\mathbf{RES} \cdot \mathbf{UMAT}$. Replacing this in the expression $(\mathbf{RES^T_{red}})^{-1} \cdot \mathbf{RES^T}$ resulting from (4) and (5) and using the rules for matrix transposition and inversion show that the expression indeed remains invariant.

If the aim of an investigation is to test the validity of the Similarity Principle and not to apply it for Scale-Up, then typically the Scale-Up factors as defined above, or a

selection thereof, can be included in the ***x-design*** together with the dimensionless factors and low and high settings can be implemented for the residual vectors by using the "slider"-technique described above.

6 Dimensionless Responses

We assume that the process result is described by a set of Q relevant technical responses, we call them ***z-responses***, $z_1, \ldots, z_Q$ and that matching these there are Q dimensionless responses, we call them ***y-responses***, $y_1, \ldots, y_Q$, that are calculated from ***z-responses*** and ***u-factors*** in a similar way as ***x-factors*** are calculated from ***u-factors***. Instead of the $R \times D$ dimensional $\mathbf{V}$-matrix, a $(R+Q) \times Q$ dimensional exponent matrix $\mathbf{V_{resp}}$, is used, where the lower part,

$$\mathbf{VZ_{resp}} = \begin{pmatrix} v_{resp,(R+1)1} & \cdots & v_{resp,(R+1)Q} \\ \vdots & & \vdots \\ v_{resp,(R+Q)1} & \cdots & v_{resp,(R+Q)Q} \end{pmatrix} \tag{7}$$

must be invertible, ideally it is the identity matrix. Then at modelling time ***y-responses*** can be calculated (logarithms or negative logarithms of all variables have been assumed to be taken) using

$$\mathbf{Y} = \mathbf{Z} \cdot \mathbf{VZ_{resp}} + \mathbf{U} \cdot \mathbf{VZ_{fact}}, \tag{8}$$

where U is as in equation 6 and

$$\mathbf{VZ_{fact}} = \begin{pmatrix} v_{resp,11} & \cdots & v_{resp,1Q} \\ \vdots & & \vdots \\ v_{resp,R1} & \cdots & v_{resp,RQ} \end{pmatrix} \tag{9}$$

is the top part of the $\mathbf{VZ}$-matrix.

Once the model has been fitted for the ***y-responses*** with ***x-factors*** acting as predictors, and predictions are available for DL-responses, predictions for ***z-responses*** can be obtained by inverting $\mathbf{VZ_{resp}}$ and calculating

$$\mathbf{Z_{pred}} = \mathbf{VZ_{resp}^{-1}}(\mathbf{Y_{pred}} - \mathbf{U} \cdot \mathbf{VZ_{fact}}). \tag{10}$$

Just as in linear modelling the dependency of predicted ***z-responses*** can be plotted graphically and the formula (10) can be used in an optimization algorithm directly or via the intermediate of a desirabilty function. In this context it is important to note that according to the underlying Similarity Principle of Dimensional Analysis, predictions for both **y** and **z** do not depend on slider settings, and the latter can be set in a way so that Scale-Up factors take the level that corresponds to production scale, even if experiments were only done on laboratory or pilot plant scale.

7 Fitting, Diagnosing and Interpreting the model

When fitting the model for the ***y-responses*** as a functions of ***x-factors*** and — when the additional objective is to verify the Similarity Priniciple — Scale-Up factors, it may be argued that scaling is not necessary as all predictors are of the same dimension, namely dimensionless. In any case centring is useful particularly if quadratic and other terms are to be used.

Assuming NID errors for the above model, model diagnostics is also performed for ***y-responses*** and ***x-factors***.

An interesting aspect of analysis that will not be explicated further here is the question of whether one or several ***u-factors*** have direct influence on the responses, i.e. not all its influence can be "caught" by the dimensionless variables. This would not only place heavy doubt on the validity of the Similarity Prinicple but also lead to a bias on the estimates of coefficients for the ***x-factors***, because — in the language of Causal Inference — these ***u-factors*** would act as confounders. To decrease this bias, they would have to be taken up as predictors in the linear model in the sense of *adjustment variables*, side by side with the ***x-factors***. This adjustment question is also relevent when discussing the influence of dependent factors as elaborated in sections 8 and 9.

8 State dependent Material Properties

As mentioned in section 2 material properties like densities, viscosities and conductivities may heavily depend on state variables like pressure and temperature. There is a natural

way of modelling this dependancy so that the Dim-DoE-framework can be easily applied even if properties vary by an order of magnitude as may be the case when gases are involved in a reaction.

For simplicity we assume that we are interested in the dependency of density, ρ, as a function of temperature, T. If density occurs in an ***x-factors***, say x, with exponent v and density depends on temperature in the following way: $log(\rho(T)) = f(log(T))$, then a linear approximation is obtained by

$$log(\rho(T)) \approx f(log(T_N)) + f'(log(T_N) log(T/T_N) = log(\rho(T_N)) + f'(log(T_N) log(T/T_N). \quad (11)$$

This means that in addition to T, T_N is taken up as ***u-factors***, T is controlled and T_N is constant, and the factor and ρ is replaced by $\rho_N := \rho(T_N)$ in the ***u-factor***-list which will also be constant. T_N will typically be the geometric mean of the lower and upper levels of T. The exponent matrix $\mathbf{V}$ will be modified in the following way: In those ***x-factors***, in which ρ occured with exponent v, this v will now be at the position of the ***u-factor*** ρ_N. The exponent for temperature T will be augmented by $vf'(log(T_N)$ and that of T_N by $-vf'(log(T_N)$. In ideal gases, governed by the gas equation $pV = nRT$, where ρ is proportional to $1/T$, $f'(log(T_N)$ can easily seen to be just -1. Relaying the dependency of ***x-factor*** from dependent factors onto controlled factors in this way leaves the original ***x-factor*** dimensionless.

If a ***u-factor*** depends on other state variables like pressure, p, the same scenario will work. If more than one dependent factor load into an ***x-factor*** (for example density and dynamic viscosity into Reynolds number), the exponent for – say – temperature, T, will just be augmented by the sum of two or more terms of the type $vf'(log(T_N)$ and for T_N respectively $-vf'(log(T_N)$. And if T itself is not a controlled factor but dependent on other reaction conditions, then the exponents in the $\mathbf{V}$-matrix can be relayed ont to the factors T may depend on.

It may be necessary to do independent experiments at laboratory scale to determine the exponents $f'(log(T_N)$ — although often enough this information is available in the internet or in other published form, for example VDI-Waermeatlas — and of course in general they can be assumed to be scale independent, so that these additional experiments need not be done at production scale. From a designed experiment the exponents, $f'(log(T_N)$, can

be determined as coefficients of a linear mid-range scaled model for the material property and the constant value for the material property will just be the constant coefficient of this model. It is however a little tricky to get the correct $low/high$ ranges for the dependent factors, and these are needed to get the ranges of the ***x-factors***. If there are chained dependencies as described for temperature above, it is useful to construct a directed acyclic graph (DAG) to describe these, and then to determine the ranges by traversing the graph going from parents, i.e. the controlled factors, to children, i.e. the dependent factors and then the dimensionless factors, while calculating exponents traversing in the opposite direction from children to parents. Once such a DAG is available it can also be used in analysis to obtain unbiased estimators for dependent factor effects by constructing valid adjustment sets.

9 Temperature dependent Reaction Rates

Chemical reaction rates usually depend in a sensitive manner on temperature. The relation is essentially described by the equation

$$k_{eff}(T) = k_\infty exp(-E/RT), \tag{12}$$

where k_∞ is Arrhenius constant, E the activation energy, R the universal gas constant and T temperature. A dimensionless number that is usually associated with reaction rate - at least for first order reactions - is its product with residence time, τ, namely $k_{eff}\tau$.

Following the same idea as in section 8 and taking $logs$ of equation (12) we have

$$\begin{aligned} log(k_{eff}) &= log(k_\infty) - log(e)E/RT \\ &= log(k_\infty) - log(e)\tfrac{E}{R}exp(-ln(T)) \\ &\approx log(k_\infty) - log(e)\tfrac{E}{RT_N} + log(e)\tfrac{E}{RT_N}ln(T/T_N) \\ &= log(k_N) + \tfrac{E}{RT_N}log(T/T_N). \end{aligned} \tag{13}$$

where $k_N = k_\infty exp(-E/RT_N)$.

As in section 8 we just need to take up the correct ***u-factors***, T, T_N and k_N, the latter both being constant, and use the exponent $\frac{E}{RT_N}$ as exponent for T in the exponent matrix for $k_{eff}\tau$. Similarly $-\frac{E}{RT_N}$ is the exponent for the constant ***u-factors*** T_N.

Again experimentation should be done at laboratory scale to determine the activation energy, E, which will in practice of course not only depend on the reaction itself, but also on the properties of possible catalysts in use.

10 Qualitative Factors

In Chemical Engineering and other DoE applications not all input factors can be formulated in a quantitative way. Some factors like stirrer type, baffler geometry, catalyst type or solvent type can only be specified in a qualitative way just using text. Qualitative factors by their nature are dimensionless and will hence be taken up in both the ***u-*** and the ***x-factor***-lists. However they may influence other factors. We differentiate three cases:

(a) The qualitative factor has no relation to other ***u-factors*** at all and the levels of the other ***x-factors*** are independent of the setting of the qualitative factor.

(b) There are other ***u-factors*** that depend on the qualitative factor; for example a radius to be used as characteristic length in a Reynold's number may depend on a stirrer type. Or viscosity, density or heat conductivity may depend on the type of a solvent.

(c) The most extreme dependency is if even the exponents in the $\mathbf{V}$-matrix depend on the setting of the qualitative factor. This is the case in chemical reactions where temperature is varied and reaction rates depend on temperature and the activation energy which in turn is determined by the type of catalyst used. In this case typically case (b) is included, since catalyst may additionally be described by quantitative variables like bead size or filament diameter or surface to mass ratio or the like, which may in turn load into an ***x-factor***.

In case (a) the qualitative factor with, say, K settings is typically coded by using $K-1$ contrast variables, the first setting being coded as $(-1,\ldots,-1)_{1\times K-1}$, the other $K-1$ settings, for $k=2,\ldots,K$, as $e_{k-1}=(0,\ldots,1,\ldots,0)_{1\times K-1}$, where the 1 as at position $k-1$. Then the entries in the $\mathbf{V}$-matrix for these contrast factors (that appear in both the ***u-*** and ***x-factor***-lists) will be a $K-1$-diagonal of 1s.

In case (b) the coding of the qualitative factor and the way the contrast factors appear in ***u-*** and ***x-factor***-space are unchanged. However, quantitative factors associated to the settings are now dependent, quantitative and multilevel settings and in the final ***u-***

factor-design must be correctly set. Since the ***x-factor***-design does not "know" this restriction, this correct setting of these dependent factors must be achieved by using the slider mechanism as described in section 5. Since sliders are set independently for each row (or run) of the experimental design, the mechanism will work just as well for dependent multilvevel quantitative factors as for Scale-Up factors.

Case (c) is the most interesting and of course the hardest case to treat. It typically occurs when the qualitative factor is catalyst type, since this influences reaction rate via the activation energy and Arrhenius law. Hence by the relay mechanisms described in section 9 the exponent matrix $\mathbf{V}$ now depends on the setting of the qualitative factor — and consequently also the augmented $\mathbf{V}$, its left-inverse $\mathbf{W}$, **VRES**, **WRES** and **SLI** but not the ***x-factors*** and not the coefficients in the ***x-factor y-response*** model.

As in cases (a) and (b) the qualitative factor with assumed K settings is coded using the same $K-1$ contrast variables. Furthermore for each of the $k = (1, \ldots, K)$ settings there is a separate $\mathbf{V_k}$-matrix of exponents, a corresponding left inverse $\mathbf{W_k}$ and an associated residual vector matrix $\mathbf{RES_k}$.

We assume $\mathbf{Q_k}$ to be an $N \times N$-square matrix with 1s in those rows where in the design the k^{th} factor setting is to be used, otherwise 0s. $\mathbf{Q_k}$ is only known after the ***x-design*** has been decided upon, so that it is known which setting of the qualitative factor is to be used for which experimental run. This puts us in a position to adapt equation (2) and make it k-dependent:

$$\mathbf{U_{W,k}} := \boldsymbol{x\text{-}design} \cdot W_k. \tag{14}$$

The $\mathbf{U_W}$-design, which can be defined as the concatenation of the $\mathbf{U_{W,k}}$-designs, is not yet useful for application because the settings for the qualitative factors and the levels of corresponding dependent multilevel quantitative factors do not match. So the slider scenario has to be adapted again. In fact each $\mathbf{U_{W,k}}$ has to be modified by adding $\mathbf{SLI_k} \cdot \mathbf{RES_k^T}$ to satisfy

$$(\mathbf{U_{W,k}} + \mathbf{SLI_k} \cdot \mathbf{RES_k^T})_{\mathbf{red}} = \mathbf{u_{given}} \tag{15}$$

where $\mathbf{u_{given}}$ is appropriately chosen and the index $\cdot_{\mathbf{red}}$ indicates, that only the last $R_{const} - D$ columns are considered.

Table 1: Pendulum example: Relevent technical factors for a pendulum, with exponents of dimensionless factor $tan(\alpha)$ in the last column.

	roles	uu.low	uu.high	userunit	m	k	s	Kel	mol	amp	cand	tanA
mass	contr	210.00	450.00	g	0	1	0	0	0	0	0	0
len	scup	0.50	1.00	SI	1	0	0	0	0	0	0	-1
g	const	9.81	9.81	SI	1	0	-2	0	0	0	0	0
offset	contr	5.00	20.00	cm	1	0	0	0	0	0	0	1

11 Example: Pendulum

The first example is a trivial example to illustrate the functioning of dim-doe: The pendulum. The ***u-factors*** are in the rows and and the **V**-matrix for the ***x-factor***, $tanA$, is in the last column. Please note that units are in "user-units"; these are transferred into SI-units where necessary and transformed using log-tranformation.

The mass of the pendulum is to be varied from $210g$ to $450g$, the length of the pendulum is to be scaled up from $0.5m$ to $1m$. We vary the offset from $5cm$ to $20cm$. We assume gravity, g, to be constant at $9.8m/s^2$ — although we could also scale up to Saturn with its gravity of $10.44m/s^2$; we leave this as an exercise for the reader.

The dimension matrix **D** are the columns $m, k, s, Kel, mol, amp, cand$ in the table above — corresponding to the seven SI-units, and the exponent matrix **V** is the last column, $tanA$, in that table. It is easily verified that $\mathbf{D^T V} = \mathbf{0}$.

Squared correlations (*cosines*) of all ***u-factors*** with $tanA$ are calculated to see which ones are suited for upscaling. In this example all factors are ok since the *cosines* are small. *mass* and g being orthogonal would be best suited, followed by *length* and *offset* with squared cosines of 0.5. The augmented **V**-matrix consists of the columns for $tanA$ and and the constant g, the **VRES**-matrix contains the additional columns for the orthogonalized *mass* (which is unchanged as it does not load into $tanA$) and *len* (see table 2).

The inverse of **VRES** is **WRES** and can be seen in table 3.

Low and high levels for ***x-factors*** are shown in table 4. The extreme left and right

Table 2: Pendulum example: Relevent technical factors and their cosines that determine whether Scale-Up is possible

	cosines	roles	tanA	g	len	mass
mass	0.0	contr	0	0	0.0	1
len	0.5	scup	-1	0	0.5	0
g	0.0	const	0	1	0.0	0
offset	0.5	contr	1	0	0.5	0

Table 3: Pendulum example: Inverse **WRES** of the exponent extended exponent matrix **VRES**

	mass	len	g	offset
tanA	0	-0.5	0	0.5
g	0	0.0	1	0.0
len	0	1.0	0	1.0
mass	1	0.0	0	0.0

Table 4: Pendulum example: Factor settings for the dimensionless variables

	DL.calc.low	DL.des.low	DL.des.high	DL.calc.high
tanA	0.050	0.100	0.400	0.400
g	9.810	9.810	9.810	9.810
len	0.158	0.158	0.447	0.447
mass	0.210	0.210	0.450	0.450

columns are low and high as calculated from low and high of the ***u-factors***, the two columns in the middle give low and high values, as the user has entered, then, i.e. 0.1 and 0.4 for $tanA$. Note that values in the len-column are those of the orthogonolized r_j version of len, i.e. the slider values of the corresponding RES-vector not those of the original ***u-factor*** length of the pendulum. Since for $mass$, r_j and s_j are the same, the values of low and high correspond to the original values (although in SI-units and not user-units).

If the Similarity Principle is to be checked, the ***x-design*** will be a 2^2-*factorial* for $tanA$ and $mass$, otherwise just a 2^1-*factorial* for $tanA$ (see table 5).

The corresponding ***u-design*** in user units with an additional column where the results of the experiments for the response *period* in *sec* have already been entered (of course it is no surprise that with all experients having been done at the same length, the period is also the same - see table 6).

The next step is to calculate ***y-response***-values from the ***z-response***-values using $St\_P = period \cdot \sqrt{g/len}$ (see table 7), then to fit the model
$y \sim tanA + mass + tanA : mass$ to get predictions first for the ***y-response*** and subsequently for the ***z-response***. Of course the model in this example is particularly uninteresting. It is just constant, because the *period* just does not depend on $tanA$ or $mass$ as long as *length* is kept constant. So St_P, the ***y-response***, is also constant.

Of course, the interesting part is to use the model for Scale-Up. The new ***u-factor***-settings are first converted to ***x-factor***-settings, then the model can be used to

Table 5: Pendulum example: ***x-design*** for the pendulum example. The actual design is a $2^2 - factorial$ for $tanA$ and $mass$ — $mass$ is varied in order to check the Similarity Principle. g is a constant — constants always appear in both ***x-design*** and ***u-design*** — $length$ is the Scale-Up factor here, but the values shown are those of the SLI-vector that was calculated so that $length$ is at its low value. Thus the values are not to be immediately interpreted, they are a calculational base, so that in the ***u-design*** $length$ will be constant at $0.5m$. Please remark that the actual ***x-design*** is the log-tranformed version of what is shown here (which is also why the center point is the geometrical mean)

tanA	g	len	mass
0.050	9.81	0.112	0.210
0.400	9.81	0.316	0.210
0.050	9.81	0.112	0.450
0.400	9.81	0.316	0.450
0.141	9.81	0.188	0.307

Table 6: Pendulum example: ***u-design*** in user units, together with one column for the ***u-response***, *period*.

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mass	len	g	offset	period
210.00	0.5	9.81	2.50	15.10
210.00	0.5	9.81	20.00	15.00
450.00	0.5	9.81	2.50	14.90
450.00	0.5	9.81	20.00	15.05
307.41	0.5	9.81	7.07	14.95

Table 7: Pendulum example: Experimental results for the ***x-*** and ***u-design*** in table 6: first ***y-response*** *St_P*, then its predictions and in the third column the preditions for the relevent technical ***z-response*** *period*.

St_P	St_P_pred	period_pred
1.825	1.825	15.087
1.822	1.822	14.988
1.820	1.819	14.888
1.824	1.824	15.037
1.821	1.822	15.000

predict ***y-response***-values, which are in turn converted into the desired ***z-response***-values. This is shown in table 8.

12 Example: Defoamer

The second example is much more interesting. It is concerned with the modelling of a mechanical foam breaker used for instance in a bioreactor. No knowledge of the physical properties of the foam are presupposed The ***u-*** and ***x-factors*** are shown in table 9 (a more detailed discussion can be found in [5]).
The diameter of the centrifugal foam breaker was varied from $0.2m$ to $0.4m$, tenside concentration was varied from $0.05ml/l$ to $0.1ml/l$ $50ppm$ to $100ppm$, so it acts as both a ***u-*** and ***x-factors***. Gas throughput varied from $1.12ccm/sec$ to $5.5ccm/sec$. Material Constants of the foam and of the tensides were unknown but assumed to be constant. They appear just as a 1. Gravity plays a role, hence it is taken up as a constant.

The ***z-response*** is a critical rotation speed n_{crit} for which foam formation can still be controlled. This reponse will be called n_{crit}, which in turn loads into the ***z-response*** Q^{-1} given by $Q^{-1} = n_{crit}d^3/q$.
We would like to perform a minimalistic Design of Experiments to (a) check the

Table 8: Pendulum example: Predictions for the dimensionless ***y-response***, *St_p*, and for the relevent technical ***z-response***, *period*, for the upscaled length. Note that although *length* is far away from the values in the experimental runs, *tanA* and *mass* are both well within the experimental ***x-domain*** so that predictions for the ***y-response***, *St_p* are reliable. These reliable predictions for ***y*** are then used to calculate the new values for the ***z-response***, *period*.

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mass	len	offset	tanA	g	len.1	mass.1	St_P_upscale	period_upscale
0.3	1	0.05	0.05	9.81	0.224	0.3	1.822	21.204
0.3	1	0.10	0.10	9.81	0.316	0.3	1.822	21.212
0.3	1	0.20	0.20	9.81	0.447	0.3	1.823	21.220

Table 9: Defoamer example: ***u-factors*** in this example are diameter, tenside concentration, which is already dimensionless, so it acts as both a ***u-*** and ***x-factor***, and gas throughput. Material Constants of the foam and of the tensides were unknown but assumed to be constant. Gravity plays a role, hence it is taken up as a constant. It plays a role in defining *Froude*-number, which is the second dimensionless variable.

	roles	uu.low	uu.high	userunit	m	k	s	Kel	mol	amp	cand	Fr	cT
d	scup	0.20	0.4	SI	1	0	0	0	0	0	0	-5	0
q	contr	1.12	5.5	ccm/s	3	0	-1	0	0	0	0	2	0
cT	contr	0.05	0.1	ml/l	0	0	0	0	0	0	0	0	1
MC	const	1.00	1.0	SI	0	0	0	0	0	0	0	0	0
g	const	9.80	9.8	SI	1	0	-2	0	0	0	0	-1	0

Table 10: Defoamer example: n_{crit} is a critical rotation speed for which foam formation can still be controlled. n_{crit} is made dimensionless using $Q^{-1} = n_{crit}d^3/q$.

	m	k	s	Kel	mol	amp	cand	Q_1
d	1	0	0	0	0	0	0	3
q	3	0	-1	0	0	0	0	-1
cT	0	0	0	0	0	0	0	0
MC	0	0	0	0	0	0	0	0
g	1	0	-2	0	0	0	0	0
ncr	0	0	-1	0	0	0	0	1

Equivalence Principle and (b) realize the Scale-Up from diameter, $d = 0.2m$, to diameter, $d = 0.4m$.
The response information for this problem is shown in table 10.

The original **V**-matrix is augmented by two columns for the constants for g and MC. Subsequently a residual column is added for d. These together form **VRES** (first five columns in table 11). In addition we see the squared cosines for the controlled and Scale-Up ***u-factors*** and deduce that Scale-Up will be difficult because d is heavily involved in the dimensionless Froude-Number.

In this example we now import a ***u-design***, namely those 10 out of 31 experiments reported by Zlokarnik in [5], that were done at $d = 0.2m$. The other 21 were done at $d = 0.3m$ and $d = 0.4m$; we shall use them later to test validity of the Similarity Prinicple. In table 12 you see the (non-standard) design for q and cT that was actually performed at the time, as well as – already – the corresponding measured response values for n_{crit}.

This translates into the dimensionless ***x-design*** (in logarithms — also non-standard) shown in table 13, together with the ***y-response*** Q^{-1}. Remember the d column contains the *slider*-values for the low diameter values $d = 0.2m$, not the d-values or their *logs* themselves).

Table 11: Defoamer example: **VRES** – *matrix* and *cosines*, showing that Scale-Up will be difficult.

	Fr	cT	MC	g	d	cosines
d	-5	0	0	0	0.138	0.862
q	2	0	0	0	0.345	0.138
cT	0	1	0	0	0.000	1.000
MC	0	0	1	0	0.000	NA
g	-1	0	0	1	0.000	NA

Table 12: Defoamer example: ***u-design*** as reported by Zlokarnnik in [5].

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d	q	cT	MC	g	ncr
0.2	1.12e-06	5e-05	1	9.8	0.0462
0.2	1.63e-06	5e-05	1	9.8	0.0525
0.2	2.23e-06	5e-05	1	9.8	0.0571
0.2	2.79e-06	5e-05	1	9.8	0.0596
0.2	3.33e-06	5e-05	1	9.8	0.0627
0.2	1.66e-06	1e-04	1	9.8	0.0624
0.2	2.23e-06	1e-04	1	9.8	0.0687
0.2	2.78e-06	1e-04	1	9.8	0.0745
0.2	3.37e-06	1e-04	1	9.8	0.0796
0.2	4.43e-06	1e-04	1	9.8	0.0918

Table 13: Defoamer example: ***x-design*** generated from the ***u-design*** in table 12

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Fr	cT	MC	g	d	Q_1
-9.398	-4.3	0	0.991	-2.148	2.519
-9.072	-4.3	0	0.991	-2.092	2.411
-8.800	-4.3	0	0.991	-2.045	2.311
-8.605	-4.3	0	0.991	-2.012	2.233
-8.451	-4.3	0	0.991	-1.985	2.178
-9.056	-4.0	0	0.991	-2.089	2.478
-8.800	-4.0	0	0.991	-2.045	2.392
-8.608	-4.0	0	0.991	-2.012	2.331
-8.441	-4.0	0	0.991	-1.983	2.276
-8.204	-4.0	0	0.991	-1.942	2.219

The model used is a two factor interaction model to describe dependency of Q^{-1} on Fr and c_T (first coefficient is intercept, the second is gradient w.r.t. Fr and the third gradient w.r.t. c_T and the forth the interaction term, $Fr : c_T$).
The coefficients shown below are centred but not scaled coefficients, i.e. for a model in which the factors Fr and c_T have been centred. This allows easier interpretation and better comparison to the original work, [5].

This seems to be in reasonably good agreement with the original work by [5], where, using all 31 experiments, $Y = Q^{-1}$ was modelled as $Y = X^{-0.40} \cdot c_T^{0.36}$ with the variable X being $q^2/(d^5 \cdot S)$, where $S = 55ms^{-2}$, which was used instead of our $g = 9.8ms^{-2}$.
At least the fit of the model to the ***y-response*** data is very good and transferring it to the ***z-response*** also gives very good fit as can be seen in figure 1.
The interesting question is how the model performs for Scale-Up. Just using the ***u-design***, in which $d = 0.2m$ for all 10 experiments, it seems unreasonable to expect to be able to make predictions of n_{crit} for $d = 0.3m$ and $d = 0.4m$.

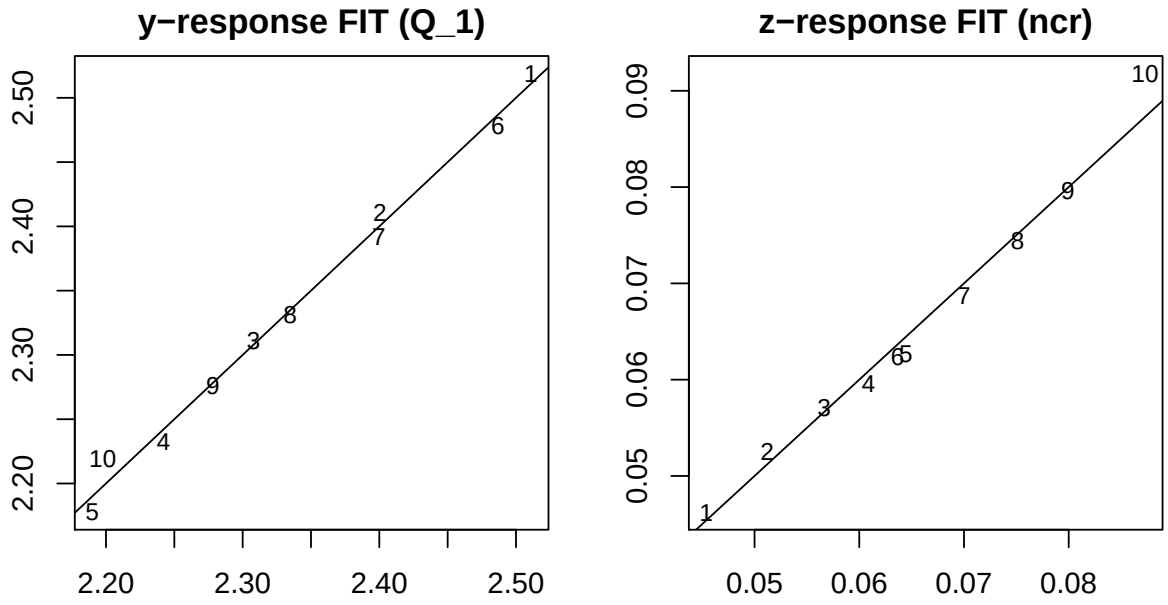

Figure 1: Defoamer example: Observed vs. Predicted for ***y-response*** (left) and ***z-response*** (right)

Table 14: Defoamer example: Summary of the linear model for the ***y-reponse*** fitted to the ***x-design***.

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	Estimate	Std. Error	t value	Pr(¿—t—)
(Intercept)	2.354	0.0039	596.14	0.0000e+00
Fr	-0.339	0.0123	-27.56	2.1200e-08
cT	0.305	0.0277	11.01	1.1309e-05

Using the ***x-design***, in which Fr and c_T were varied systematically, it may be possible to make reliable predictions also for $d = 0.3m$ and $d = 0.4m$, if the experiments, after being transferred to ***x-factor***-settings, are within — or at least not too far away from — the experimental domain. How good this works can be seen in figure 2.
Of course observed and predicted values fit better for the design points, with an $RMSEE$ of 0.0122885, than for the Scale-Up points, with an $RMSEP$ — or maybe better *RMSE-SCUP* — of 0.0504426, but the match is not bad at all!
Of course it is interesting to diagnose, if the *Scale-Up-residuals* are bigger due to a possible weakness in the Similarity Principle, or because making predictions for the higher values of d also means extrapolating beyond the experimental domain for the dimensionless $Froude$-number. It can be seen in the next figure, figure 3, that extrapolation causes more harm, because residual values far to the left, beyond the vertical line have the bigger residuals.

13 Conclusion

The Dim-DoE framework exploits the advantages of Dimension Analysis (Dim-) and of Design of Experiments (-DoE) to gain a better understanding of experimentals setups and he working of industrial processes. Dimensionless variables (that were called ***x-factors*** in this paper) are defined as products and quotients of usual technical variables (the ***u-factors***). By logarithmic transformation these products are converted to sums and

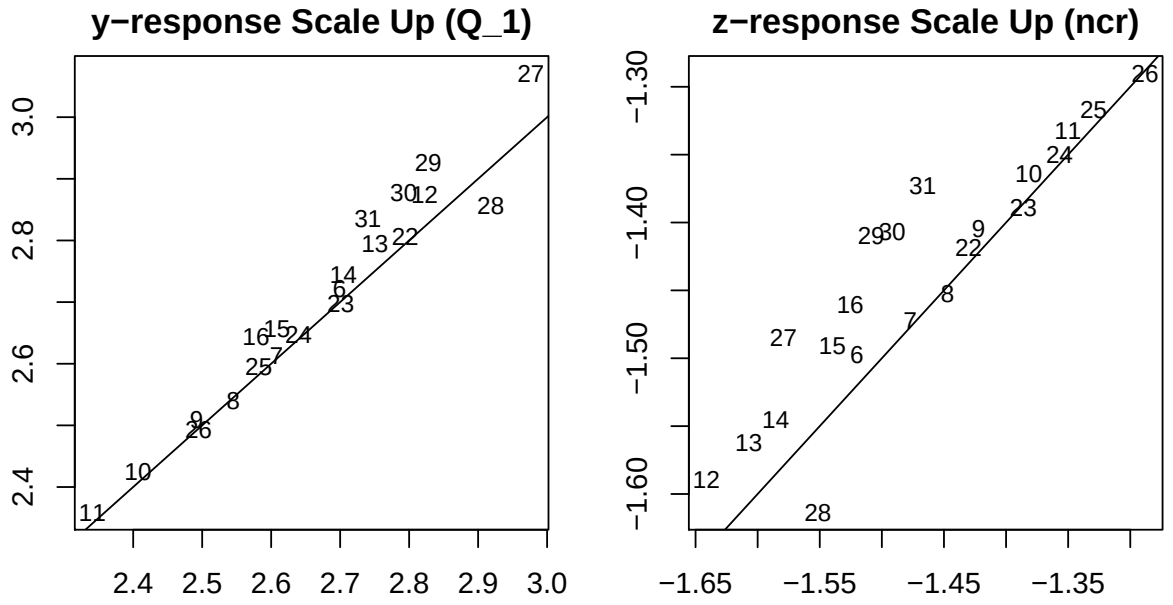

Figure 2: Defoamer example: Observed vs. Scaled-Up for ***y-response*** (left) and ***z-response*** (right)

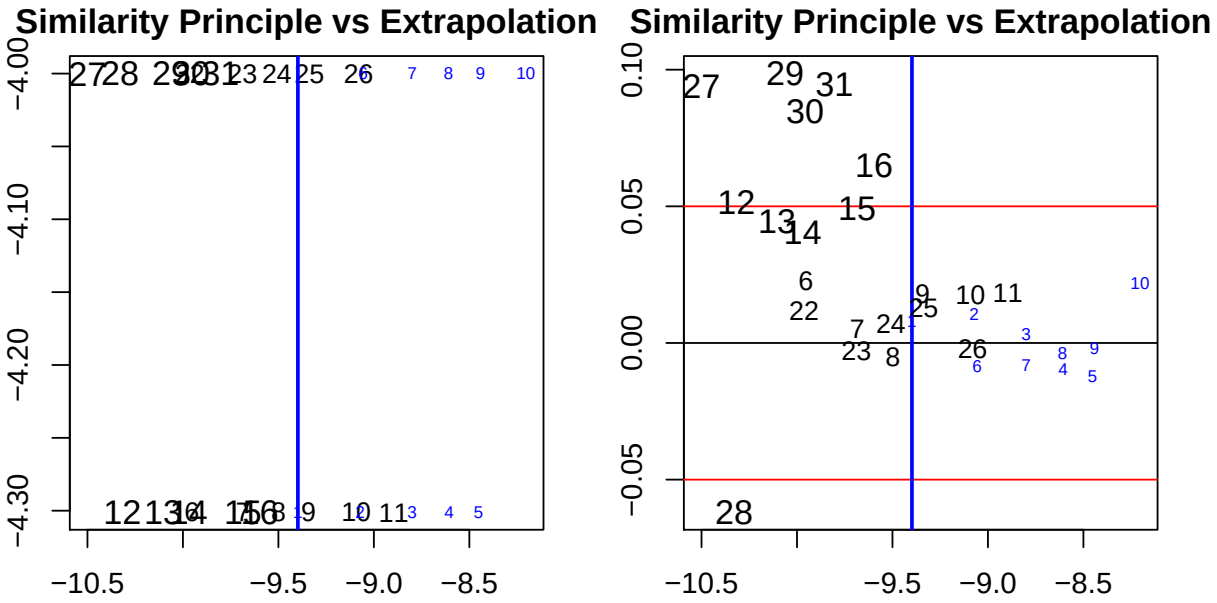

Figure 3: Defoamer example: ***x-design*** and ***x-scale-up-settings*** (at left), and ***y-residuals*** and ***y-scale-up-residuals*** (at right) with size indication the setting of d. The dimensionless factor $Froude$ is on the x-*axis* and a vertical line indicates where extrapolation w.r.t. $Froude$ begins

differences. A method is proposed to invert the resulting linear map, that maps real variables to dimensionless variables, that allows determing experimental settings for the technical factors, when a design has been chosen for the dimensionless variables.
It is argued that by contraposition of the Similarity Principle of Dimensional Analysis that if dimensionless variables are varied in a process, this will induce the greatest change in the process. Hence it is these variables that should be varied in a design whose aim is to maximize acquisition of information.
At the same time it is argued, that if it is possible to Scale-Up a design of experiments, then this should be done using designs for the dimensionless variables.
Applying the Similarity Principle to varying dimensionless variables creates a maybe unaccounted for difficulty in that it generates new – indirect – dependencies of the dimensionless variables upon real technical variables, that hitherto did not load into the former. This is the case if for example material properties depend on state variables like temperature or pressure, or reaction rates depend on temperatur and the material properties or reaction rate load into a dimensionless variable. A technique, named *exponent relaying*, is presented in order to cope with these dependencies.
The potential of the methods is illustrated using 2 examples, although not the technique of exponent relaying.

SUPPLEMENTARY MATERIAL

Scripts: How to used Dim-DoE, the R scripts used in this paper.

R-package: dimdoe-package for doing Design of Experiment for Dimensionless variables, analysing the designs and performingScale-Up.

Data sets: Data sets consist of directories of csv-files containing experimental data and meta-information for the two examples discussed in this paper.

References

[1] G.E.P. Box, W.G. Hunter, and Hunter J.S. *Statistics for Experimenters*. Ed. by John Wiley and New York Sons Inc. 1978.

[2] Expert Working Group ICH. *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological / Biological Entities) Q11. ICH Harmonised Tripartite Guideline*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, May 2012, pp. 1–26. URL: `https://database.ich.org/sites/default/files/Q11_Guideline.pdf` (visited on 01/03/2020).

[3] Expert Working Group ICH. *Pharmaceutical Development Q8(R2). ICH Harmonised Tripartite Guideline*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Aug. 2009, pp. 1–24. URL: `https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf` (visited on 01/03/2020).

[4] S. Soravia and A. Orth. "Design of Experiments". In: *Ullmann's Modelling and Simulation*. Wiley-VCH Verlag GmbH and Co. KGaA, 2007, pp. 363–400.

[5] M. Zlokarnik. "Auslegung und Dimensionierung eines mechanischen Schaumzerstoerers". In: *Chem.-Ing.-Tech.* 56.11 (1984). Ed. by Weinheim Verlag Chemie GmbH, pp. 839–844.

[6] M. Zlokarnik. *Scale-up in Chemical Engineering, 2nd, Completely Revised and Enlarged Edition*. Ed. by Wiley-VCH Verlag GmbH and Co. KGaA. 2006.