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THE SEARCH FOR EXPERIMENTAL DESIGN WITH TENS OF VARIABLES: PRELIMINARY RESULTS

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ABSTRACT

Simulation models have importantly expanded the analysis capabilities in engineering designs. With larger computing power, more variables can be modeled to estimate their effect in ever-larger number of performance measures. Statistical experimental designs, however, are still somewhat focused on the variation of less than about a dozen variables. In this work, an effort to identify strategies to deal with tens of variables is undertaken. The aim is to be able to generate designs capable to estimate full-quadratic models. Several strategies are contrasted: (i) generate designs with random numbers, (ii) use designs already in the literature, and (iii) generate designs under a clustering strategy. The first strategy is an easy way to generate a design. The second strategy does focus on statistical properties, but the designs become somewhat inconvenient to generate when increasing the number of variables. The third strategy is currently being investigated as a possibility to provide a balance between (i) and (ii).

1 INTRODUCTION

Systems in Engineering and the Sciences are affected by multiple factors simultaneously. Understanding how these factors affect key performance indicators is important for design, control and optimization purposes. Moreover, achieving an appropriate understanding level must commonly be carried out while being mindful of resource consumption. Assessing the effects of multiple factors on multiple performance measures has been made a lot more convenient with the development of computer simulation.

A somewhat standard approach to understand variation through experimental means is the use of a regression model. Of special interest to this work is the situation in which curvature is suspected in the experimental response of interest, thus, a full quadratic regression model is sought. There seems to be an imbalance between the increasing capability of simulation models to relate large numbers of variables to similar numbers in performance measures and the restricted focus of statistical experimental designs in dealing with a low number of variables.

This work attempts to bring attention to this imbalance and foster the generation of designs to investigate dozens of variables at a time. A more effective use of simulation models is possible with developments in this area including a more powerful capability of simulation optimization.

This manuscript is organized as follows: first, an exploration of the literature in terms of number of variables and designs included in several studies is presented followed by a proposed strategy under development to approach the study of dozens of variables. Then, three strategies are compared for 10 and 20 variables on their ability to estimate a full quadratic model: (i) generate a random design; (ii) generate a design from techniques already established in the literature (Full Factorial Design, Central Composite Design, D-Optimal Design); and (iii) generate designs under a clustering strategy. Finally, the results of the comparison are discussed and future directions are outlined.

2 LITERATURE REVIEW

As the technology and the computational capacity increase, the possibility to analyze and simulate systems that are affected by multiple factors simultaneously is more attractive and feasible. For many experimental designs, the number of variables being investigated –however- is less than a dozen; in fact, in most cases it is only three or four factors (Alkhatib 2011, Anotai 2012, Christin 2008, Job 2010, Laferriere 2011, Larentis 2011, Marwa 2011, Rigas 2009, Sudheer 2010, Vishwantha 2010).

For many cases, the intention is to predict the parameters for the characterization of the system with a second order model (Anotai 2012, Cabrera-Ríos 2002, Larentis 2011, Laferriere 2011, Mahapatra 2009, Marwa 2011, Nobuyuki 2010, Rigas 2009, Sudhankar 2011, Vaithanomsat 2011). The experimental design used for these systems are usually the fractional factorial design, the central composite design or the Box-Behnken (Anotai 2012, Cabrera-Ríos 2002, Job 2010, Laferriere 2011, Marwa 2011, Nair 2008).

It is desirable to analyze dozens of factors that significantly affect a system simultaneously to be more realistic when trying to characterize and model it. In the literature, it is common to find works that analyze fewer than ten variables simultaneously. The number of variables tends to be smaller when the objective is to build a full quadratic model since a minimum of three levels per variable is necessary to estimate quadratic effects.(Cabrera-Ríos 2002, Christin 2008, Sudheer 2010).

There are different methods to generate experimental designs. In the literature, the full factorial is a highly popular one. This design enumerates all possible combinations of the levels of all variables involved. Needless to say, this strategy becomes impractical rapidly with a small number of variables. For example, for 10 variables at three levels, the full factorial requires 3^{10}= 59,049 runs. Due to this combinatorial explosion, a prevalent strategy is to run a fraction of the full factorial design, that is, to run a fractional factorial design. In contrast to two level fractional factorial designs, three-level fractional factorial designs have not been favored in the literature due to complex aliasing structures (Sanchez 2005).

One of the best-known practices when fitting a full quadratic model is to use a Central Composite Design which entails the use of either a two-level full factorial or fractional factorial design, plus 2 axial runs per variable involved, plus a defined number of center runs. This design capitalizes on the use of a fraction of the full factorial to keep the number of runs low while providing a stable and minimal variance in the coefficients. Because the fractions of the full factorial used to build the central composite design result from the expression 2^{k-p}, where k is the number of variables and p is the number of fraction generators, the resulting number of runs might be a lot more than those necessary for a full quadratic model (Alkhabit 2011, Montgomery 2009, Sayara 2010, Wass 2011, Zambare 2011, Zhou 2010).

Another possibility to obtain full quadratic model is the use of D-Optimal design, with which one can decide upon the number of experimental runs a priori. This strategy, as coded in many commercial and open-source software packages, uses a full factorial enumeration from which the predefined number of runs is chosen with the objective to provide a minimum variance across all regression coefficients (Langner, 2003).

Finally, if simplicity is important, a naïve way to generate a design is by using a probability mass function to prescribe a desired number of experimental combinations. This strategy is considered here due to its feasibility to explore several tens of variables simultaneously, although no control over variance or any other statistical properties can be exercised in this instance.

3 CLUSTER DESIGN METHOD

3.1 Initial Version

The Cluster Design Method is currently under development in our group and it was as follows in its initial form: (i) generate a full factorial design as an initial enumeration; (ii) add a column with uniformly distributed random numbers to the full factorial design; (iii) generate k clusters with the k-means algorithm, with k being the number of necessary regression coefficients plus one;(iv) retrieve the k-medoids associated to the k clusters; (v) delete the values associated to the column with the random numbers, and (vi) present the experimental design.

The rationale behind step (i) is to provide orthogonal design points. A random dummy variable is introduced as a means to add a controlled perturbation in step (ii). This is necessary because clustering equally spaced orthogonal points results in very similar clusters, and thus to very similar centroids in the next step.

The k-means algorithm is the most basic of the clustering techniques. It iteratively forms a user-defined number k of exclusive clusters with each cluster organized around its average location or centroid. As proposed here, k is set to the number of necessary regression coefficients to fit a full quadratic model plus one in step (iii). The number of coefficients for v variables of interest can be calculated as:

$$1 + 2v + \binom{v}{2}. \tag{1}$$

From step (iii), then, k clusters result. In step (iv) the medoid of each cluster is obtained. The medoids, which are data points in the center of a cluster, are intended as the k runs in the resulting cluster design. In this work, an approximate medoid is computed for each cluster by using the median of each of the values of the v variables of interest within the cluster under analysis. Steps (v) and (vi) of the method are self-explanatory.

Equation (1) is useful also to show the growth of the intended method when increasing the number of variables, as shown in Figure 1, where this growth is contrasted with that of the full factorial design. Looking at Figure 1, it is clear that –if feasible- the cluster design would be convenient to explore tens of variables. However, a limitation also becomes apparent. The first step of the initial version of the method requires a full factorial enumeration, thus it would become computationally inconvenient at some point. This observation, corroborated by a series of tests, lead to the following modified version of the method.

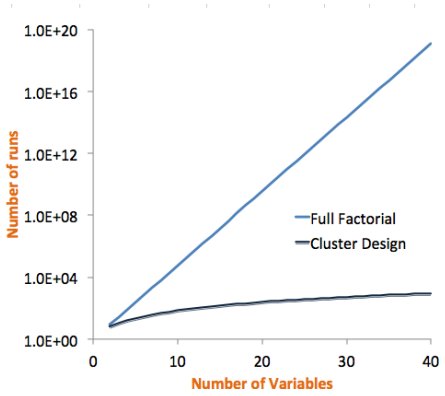

Figure 1: Growth in the number of runs as a function of the number of variables for the cluster design and the full factorial design.

3.2 Modified Version

The first step of the original method required the generation of a full factorial enumeration, which would become computationally inconvenient at some point as shown previously. A slower growing enumeration would help alleviate this situation. The following modification was then introduced:

1) Generate a cluster design D1 of moderate size, say one to explore v=10 variables, using the original version of the method. D1 will have n runs.
2) Generate a second cluster design D2 as in the previous step. This second design will be different due to the random realization in step (ii). D2 will also have n runs.
3) Concatenate every run in D1 together with every run in D2. The resulting enumeration contains n^2 runs with $2v$ variables.

With this new enumeration in place, steps (ii) through (vi) can then be applied to generate a design for up to $2v$ variables. Figure 2 shows the enumeration growth compared to the cluster design and the full factorial design.

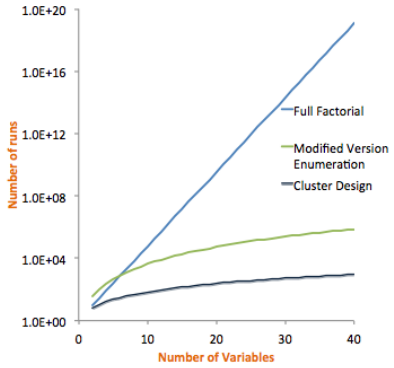

Figure 2: Growth on number of runs of the modified version enumeration compared to the full factorial enumeration.

4 COMPARISON

The comparison was carried out by artificially building a response through the addition of a known function and a random error. The known function was a full quadratic model, in the first case for 10 variables and an extension in a second case for 20 variables, with all regression coefficients arbitrarily set equal to 10. The random error came from a normal distribution with 0 mean and standard deviation of 1.5 units. The idea behind having an artificial response is to provide a controllable expected value and a random noise around it. The idea is focused in verification: if true experimental data can be effectively modeled with a full quadratic regression model, it will look very similar to our artificial response. If we control the artificial response, then we can measure the performance of our method when approaching it.

Experimental design from each strategy (i) random design, ii) Full Factorial, Central Composite Design and D Optimal Design, and (iii) the proposed Clustering Design were used to sample and then to estimate the artificial response described previously. The following were measured: (M1) Number of runs, (M2) Mean Square Error, (M3) Number of regression coefficients estimated, (M4) Adjusted coefficient of determination, R^2, (M5) The trace of $(\mathbf{X}'\mathbf{X})^{-1}$, that is, the trace of the inverse of the so-called design information matrix, which is proportional to the covariance of the regression coefficients, and (M6) The determinant of $(\mathbf{X}'\mathbf{X})^{-1}$ (Montgomery, D. C., 2009).

Residual analysis was also considered in this comparison to assess the assumptions of normality, independence and constant variance. This is carried out mostly through hypothesis testing. The residual is

computed for the ith data point in n data points as $e_i=Y_i-\tilde{Y}_i$; i=[1, 2.....n], where Y_i is an actual observation and $\tilde{Y}_i$ is the corresponding fitted value from the regression model (Montgomery 2009).

A design with the lowest possible number of runs, the lowest MSE, capable to estimate all regression coefficients, with the highest adjusted R^2 value, the lowest value of the trace and determinant of $(\mathbf{X'X})^{-1}$, and which complies with the residuals assumptions, would clearly dominate any other option.

Furthermore, it was important to assess how easy was to generate a design under each strategy. This last was done qualitatively by necessity. Finally, it was decided to tabulate the frequency of the coefficients by their percentual deviation from the target value. The results of the comparison are shown next for both cases set forth.

5 RESULTS WITH THE INITIAL VERSION OF THE CLUSTER DESIGN METHOD (10 VARIABLES)

Table 1 summarizes the comparative results for M1-M6. The D-Optimal design seems to be an overall robust and sensitive alternative according to these results, with a minimum number of runs, the lowest MSE, the capability to estimate all coefficients, and performing well in goodness-of-fit. Its coefficient variance is only larger than the full factorial and the central composite design. The full factorial and the central composite designs, even at 10 variables, start to seem impractical in terms of number of runs. This behavior is expected to be more drastic with larger numbers of variables.

Qualitatively speaking, the easiest option to generate is the Random Design, although the cost seems to come in terms of coefficient variance, where it performs worst. At a competitive number of runs and an adequate performance in coefficient variance, the proposed clustering design could be improved to become a competitive option for larger numbers of variables. From running this comparison, it was experienced that both solving for the D-Optimal design as well as carrying out the clustering procedure can be consuming in terms of computing resources. Devising a way to use a more efficient clustering procedure as well as to reduce the dependency on a complete enumeration as a starting point should help importantly improve the proposed strategy.

Table 1: Comparative results for different experimental design for 10 variables.

	Full Factorial	**Central Composite**	**D Optimal Design**	**Random Design**	**Clustering Design**
Experimental runs	59,049	158	71	71	71
MSE	2.2558	1.2351	0.0774	0.0902	0.0944
Estimated coefficients	66/66	66/66	66/66	66/66	66/66
R-Sq(adjusted)	100%	100%	100%	100%	100%
Trace of $(X'X)^{-1}$	0.065	86.24	140.56	2854.7	670.1
Determinant of $(X'X)^{-1}$	0.00	6.33E-124	1.495E-96	3.65E-89	5.39E-66

Table 2 shows the results of the residual analysis and Figure 3, show residual plots for all designs under comparison. Normality was assessed with the Kolmogorov-Smirnov test, and independence with the Signs test. Variance homogeneity was assessed through plot analysis and by measuring the percentage of residuals falling within a distance of two standard deviations of the estimated mean. Regarding residuals normality test, only the random design showed some deviation, while independence did not seem a concern for any design. The results in standard deviation are somewhat similar across all design and, together with Figure 3, nothing too concerning was found in terms of unequal variance.

Table 2: Comparative results of the residual analysis for different experimental design for 10 variables.

	Central Composite Design	D-Optimal Design	Random Design	Clustering Design
P-value of Kolmogorov-Smirnov test	> 0.15	> 0.15	0.046	0.138
P-value of Signs test	0.3010	0.4764	0.6350	0.8124
Standard deviation	1.1149	0.2802	0.3024	0.3094
$\mu - 2\sigma < \varepsilon < \mu + 2\sigma$	149/158; 94%	69/71; 97%	66/71, 93%	67/71; 94%

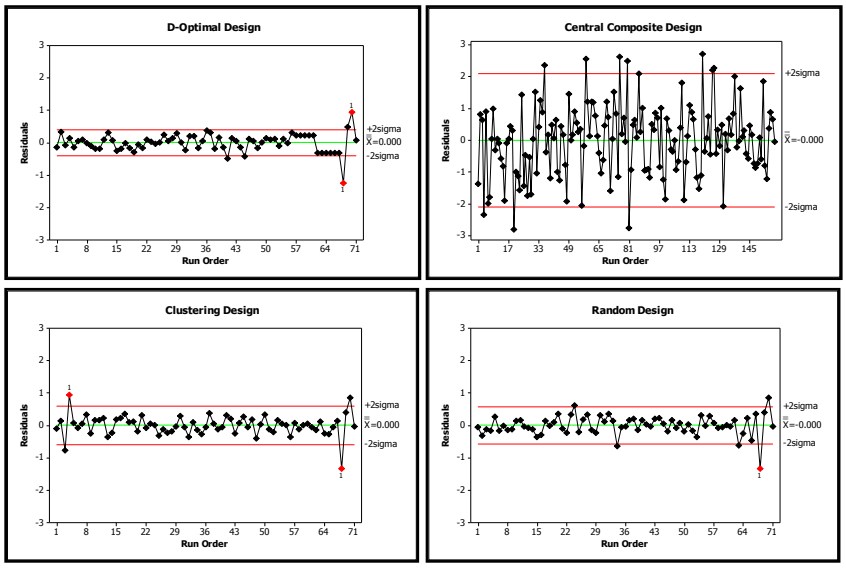

Figure 3: Plot of residuals in time sequence for 10 variables for the D-Optimal Design, Central Composite Design, Clustering Design and Random Design.

6 RESULTS WITH THE MODIFIED VERSION OF THE CLUSTER DESIGN METHOD AND A SHORTENED ENUMERATION FOR THE D-OPTIMAL DESIGN (20 VARIABLES)

In this second set of results, the treatment of 20 variables was attempted. Table 3 summarizes the comparative results for M1-M6. It is important to note that the D-Optimal Design was generated based on the shortened enumeration describe in Section 3.2. In this case, the Random Design presented the lowest MSE and has the capability to estimate all coefficients, but the precision for the estimates of the coefficient is lower than the D-Optimal Design (Table 3). The Clustering Design has an intermediate value of MSE, and has the capability to estimate all coefficients, but the precision for the estimates of the coefficient is less than the obtained by the Random Design and the D-Optimal Design. Of the three designs under comparison, the D-Optimal Design has the best accuracy to estimate the model coefficients and has the lowest trace of $(X'X)^{-1}$.

The full factorial and the central composite designs were not used in this comparison since at 20 variables, they are not practical. The Full Factorial Design, for 20 variables at three levels each, requires 3^{20}=3,486,784,401 runs. The Central Composite Design requires 1,048,617 experimental runs in its worst case. An important result is that of the D-Optimal paired with the shortened initial enumeration as proposed in this work, becomes feasible and is a competitive alternative for larger number of variables.

Table 3: Comparative results for different experimental design of 20 variables.

	D-Optimal Design	Random Design	Clustering Design
Experimental runs	232	232	232
MSE	0.0453	0.0036	0.0142
Estimates coefficients	231/231	231/231	231/231
Trace of$(X'X)^{-1}$	5100.65	15867.87	50480.98
Determinant of $(X'X)^{-1}$	0	9.843E-299	0

As in the previous case, a residual analysis was carried out. Table 4 shows the results of the hypothesis tests and the assessment of the variance and Figure 4 presents selected residual plots. All designs seemed to do well in terms of normality. The clustering design was the only one that showed a deviation from independence. This is, indeed something to be considered in the next steps in development of the clustering design.

Table 4: Comparative results of the residual analysis for different experimental design for 20 variables.

	D-Optimal Design	Random Design	Clustering Design
P-value of Kolmogorov-Smirnov test	0.133	> 0.15	> 0.15
P-value of Signs test	0.5546	0.7427	0.0105
Standard deviation	0.2130	0.0591	0.1195
$\mu - 2\sigma < \varepsilon < \mu + 2\sigma$	221/232; 95%	202/232; 87%	220/232; 95%

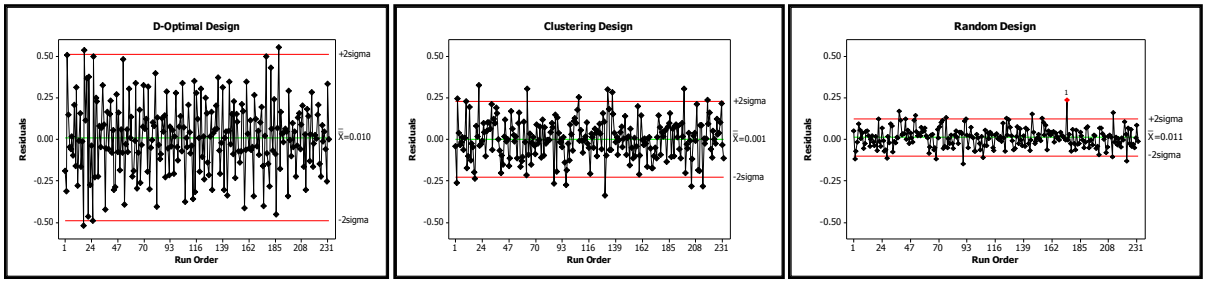

Figure 4: Plot of residuals in time sequence for 20 variables

7 ILLUSTRATIVE EXAMPLE: PRODUCTION LINE WITH 20 WORKSTATIONS

The capability of dealing with dozens of variables simultaneously opens important analysis possibilities ranging from statistical characterization to optimization. This section illustrates, for example, how a 20-variable simulation-optimization problem can be addressed aided by an experimental design with such capability.

Consider a production line with 20 workstations simulated with the software package Arena. The simulation is run for 8 hours per day with 10 replicates. The simulation parameters of interest were the mean process time on each of the workstations (WS_i). The process time in each workstation was assumed to follow a normal distribution with a mean that varied in three levels and a constant standard deviation of 0.25 minutes. It is further assumed that the nominal process time can be chosen by a particular user. The response of interest was the system time defined as the period of time elapsed since a raw part to be processed enters the system until it exits as a finished product.

A simulation optimization method based on design of experiments and metamodeling techniques was used(Villarreal-Marroquín, 2013). A summary of this method can be found in Appendix A. The method starts with an initial experimental design, which for twenty variables has 232 experimental runs using the modified version of the clustering design method. Figure 5 shows the ranges of values to be explored with the objective to minimize the system time per unit.

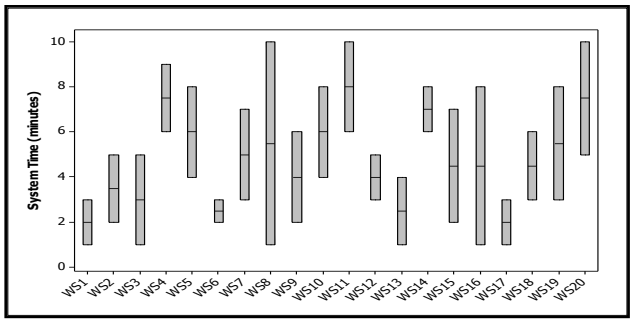

Figure 5: Range of values for the workstations' mean process time in simulation model.

The minimum value for the average cycle time in the experimental design was identified and selected as the first best solution (first incumbent solution) (I-1). I-1corresponded to a value of 2125 minutes (Table 5)**,** with parameters values as shown in Tables 6 and 7**.** With the initial experimental design, a full quadratic regression metamodel was built, and used as the objective function to be minimized to obtain a predicted competitive solution. A generalized reduced gradient optimization procedure along with a multi-start strategy was used for this purpose.

Table 5: System Time for the incumbent solution for the production line with 20 workstations.

Run	I-j	System Time (minutes)
82	I-1	2125
233	I-2	2089.9
234	I-3	2075.6
235	I-4	2029

Table 6: Results of the simulation optimization method for the example with 20 workstations (Workstations 1 thru 10).

I-j	Mean process time (minutes)									
	WS_1	WS_2	WS_3	WS_4	WS_5	WS_6	WS_7	WS_8	WS_9	WS_{10}
I-1	2.00	1.00	3.00	1.00	1.00	3.00	1.00	1.00	3.00	3.00
I-2	1.00	3.47	1.00	6.00	4.00	2.52	7.00	1.00	2.00	5.30
I-3	1.00	3.31	1.56	6.00	4.00	2.00	7.00	2.63	2.00	4.00
I-4	1.00	4.60	1.00	6.00	4.00	2.00	5.93	1.00	2.00	4.00

Table 7:Results of the simulation optimization method for the example with 20 workstations (Workstations 11 thru 20).

I-j	Mean process time (minutes)									
	WS_{11}	WS_{12}	WS_{13}	WS_{14}	WS_{15}	WS_{16}	WS_{17}	WS_{18}	WS_{19}	W_{20}
I-1	6.00	3.00	1.00	6.00	2.00	1.00	1.00	4.32	3.00	5.00
I-2	6.00	3.00	1.00	6.00	2.00	1.00	1.00	4.22	3.00	5.00
I-3	6.00	3.00	1.00	6.00	2.00	1.00	1.00	4.19	4.11	5.00
I-4	6.00	3.00	1.00	6.00	2.00	1.00	1.00	4.32	3.00	5.00

Using the process times prescribed for each workstation by the first predicted competitive solution, a simulation was performed and the simulated values were compared with the incumbent solution (I-1) for updating purposes. Each iteration of the algorithm follows a similar structure (Appendix A) until either a solution that has already been visited is predicted, or a user-defined maximum number of iterations is met. For this example, a maximum of 20 iterations was used.

In Figure 6, the first 232 points represent the initial experimental design, and the following points are the simulation optimization method iterations. The first incumbent solution (I-1), is obtained in the 82th experimental run (Figure 6) of the initial DOE. The final solution (I-4) was obtained in the 3rd iteration of the method (Figure 6). The algorithm was stopped once it maxed out the allowed number of iterations. The best solution corresponded to a system time of 2029 minutes (I-4) (Table 5) with parameters' values as shown in Tables 6 and 7.

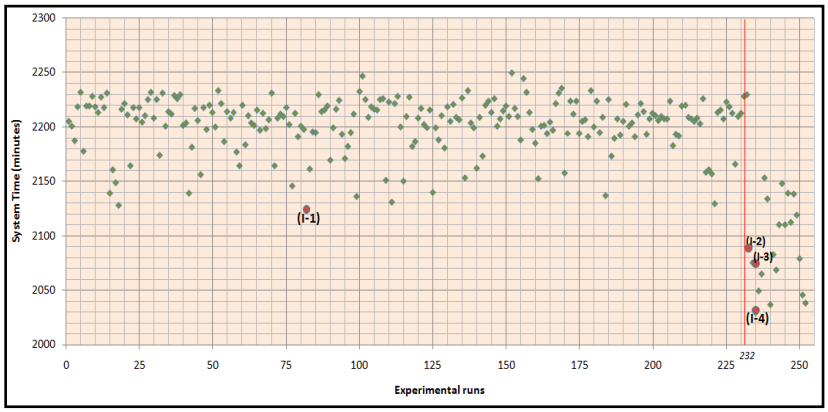

Figure 6: Results of to the simulation optimization method with the initial version of clustering experimental design.

When a comparison between the initial incumbent solution (I-1) with the final one (I-4) was performed, the result was that the system time decreased in 96 minutes. This represents a reduction of 4.52% in the system time per unit, in the simulated production system. Although many aspects are interesting in this example, it is important to emphasize that it was possible to run this simulation-optimization procedure because there existed an experimental design capable to build a full quadratic regression model for 20 variables with a low number of runs.

8 CONCLUSION

This study contrasts the performance of different strategies to generate experimental designs, aiming to devise feasible options to explore tens of variables simultaneously in the future. It was learnt that a more efficient initial enumeration would improve the generation of the D-Optimal Design. It was also learnt that the clustering design should be improved in terms of coefficient variance for it to be a competitor to the D-Optimal Design. Furthermore, at least the designs included in this preliminary comparison should be kept as benchmarks for future developments.

An illustrative example with simulation optimization was used to show how important analysis possibilities open when having an experimental design that can be used to obtain a full quadratic model with the least possible number of experimental runs for tens of variables. This encourages further research into the matter.

Future work includes exploring cases with larger number of variables as well as improving the clustering design to determine if it can be an option with the D-optimal strategy enhanced with the ideas of this work.

ACKNOWLEDGMENTS

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APPENDIX A

The illustrative example in this work follows a simulation-optimization algorithm developed in our research group and described in (Villarreal-Marroquín, 2013). This algorithm results in high quality solutions that can be achieved efficiently with a modest number of simulation runs. The algorithm starts with an initial design of experiments (DOE) from which an incumbent solution is obtained. In each iteration, a metamodel is obtained using the available set of points and is used to generate a new attractive point where a simulation is performed. The simulated value of the new point is compared against the incumbent for updating purposes. A series of stopping criteria are evaluated and, if none is met, the new point is added to the existing set of points and a new iteration begins. Otherwise, the iteration stops. A more detailed description is presented next.

Initialization

1. Initial DOE: The initial DOE consists of n runs containing combinations of the v controllable variables of interest, $\mathbf{x}^i = (x_1, x_2, x_3, \ldots, x_v)^i$, as well as their evaluations $f(\mathbf{x}^i)$, where i=1,2,…,n. If a replicated DOE is used, the value of $f(\mathbf{x}^i)$ will be the average across the replicates.
2. Select incumbent*:* Considering a minimization instance, the DOE run with the minimum objective value is selected as the current best (incumbent) solution $[x_{k\text{-best}}, f(x_{k\text{-best}})]$. An iteration counter is initialized here at k= 0.

Main Iteration

3. Update counter: $k = k+1$
4. Obtain metamodel: Using the available points, build the k-th metamodel, $f(\cdot)_k$. In case of having only few variables, a saturated metamodel is preferred i.e. one that uses all available degrees of freedom, in this case a regression model with (n+k-1) coefficients.
5. Optimize metamodel: Using the metamodel as objective function in the optimization problem under analysis, a multiple-starting-points heuristic is used along with a local optimizer to obtain an attractive solution, $\mathbf{x}_k$.
6. Simulate the new point: Estimate, via simulation, the value of $f(\mathbf{x}_k)$ considering that if a replicated DOE was used, the same number of replicates is used for the new point and the mean value across them is reported.
7. Evaluate if the new point is better than the incumbent: In this case, evaluate if $\mathbf{x}_k$ has an objective value strictly lower than $\mathbf{x}_{(k\text{-}1)\text{-best}}$ i.e. if $f(\mathbf{x}_k) < f(\mathbf{x}_{(k\text{-}1)\text{-best}})$.
8. Update the incumbent: Update the incumbent according to the evaluation in the previous step. If $f(\mathbf{x}_k) < f(\mathbf{x}_{(k\text{-}1)\text{-best}})$, then the following is set $[\mathbf{x}_{k\text{-best}}, f(\mathbf{x}_{k\text{-best}})] := [\mathbf{x}_k, f(\mathbf{x}_k)]$, otherwise, the incumbent remains the same.
9. Evaluate the stopping criteria: Stop the algorithm if (i) $\mathbf{x}_k$ belongs to the initial DOE or is similar to any of the points generated on previous iterations; (ii) if the coefficient of determination, $R^2 \geq \varepsilon$ (where ε is defined by the user); or (iii) the maximum number of iterations has been reached. Both the ε and the maximum number of iterations are defined by the user.

If any of the stopping criteria is met, the method stops and the incumbent is reported as the final output.

Otherwise, $\mathbf{x}_k$ and its simulated objective function value are added to the set of points available to build a new metamodel, and the main iteration is repeated.

This algorithm has been empirically shown to converge in a moderate number of iterations even in the presence of several variables using global optimization test functions (Villarreal-Marroquín, 2013).

REFERENCES

Alkhatib, M. F., S. A. Muyibi, and J. O. Amode. 2011. "Optimization of Activated Carbon Production from Empty Fruit Bunch Fibers in One-Step Steam Pyrolysis for Cadmium Removal from Aqueous Solution." *Environmentalist Journal* 31:349-357.

Anotai, J., P. Thuptimdang, C. C. Su, and M. C. Lu. 2012. "Degradation of O-Toluidine by Fluidized-Bed Fenton Process: Statistical and Kinetic Study." *Environmental Science and Pollution Research* 19:169- 176.

Cabrera-Ríos, M. C., C. A. Mount-Campbell, and S. A. Irani. 2002. "An Approach to the Design of a Manufacturing Cell under Economic Considerations."*International Journal of Production Economics* 78:223-237.

Christin, C., A. K. Smilde, H. C. Hoeflsoot, F. Suits, R. Bischoff, and P. L. Horvatovich. 2008. "Optimized Time Aligment Algorithm for LC-MS Data: Correlation Optimitized Warping Using Component Detection Algorithm-Selected Mass Chromatograms." *Analytical Chemistry* 80:7012-7021.

Job, J., R. K. Sukumaran, and K. Jayachandranl. 2010. "Production of a Highly Glucose Tolerant B-Glucosidase by PaecilomycesvariotiiMG3: Optimization of Fermentation Conditions Using Plackett Burman and Box–Behnken Experimental Designs." *World Journal of Microbiology and Biotechnology* 26:1382-1391.

Laferriere, C., N. Ravenscroft, S. Wilson, J. Combrink, L. Gordon, and J. Petre. 2011. "Experimental Design to Optimize an Haemophilus Influenzae Type BConjugate Vaccine Made with Hydrazide-Derivatized Tetanus Toxoid." *Glycoconjugate Journal* 28:463-472.

Langner, H. W. 2003. "Genetic Algorithms for the Construction of D-Optimal Design." *Journal of Quality Technology* 35:28-46.

Larentis, A. L., H. C. Cunha Sampaio, O. B. Martins, M. I. Rodriguez, and T. L. Moitinho Alves. 2011. "Influence of Induction Conditions on the Expression of Carbazoledioxyfenase Components (CarAa, CarAc and CarAd) from Pseudomonas Stutzeri in Recombinant Escherichia Coli Using Experimental Design." *Journal of Industrial Microbiology and Biotechnology* 38:1045-1054.

Mahapatra S. S. 2009. "Modelling and Analysis of Erosion Wear Behavior of Hybrid Composites Using Taguchi Experimental Design." *Journal of Engineering Tribology* 224:157-168.

Marwa, H. A., A. Sammour, A. El-ghamryHanaa, and M. El-nahasHanan. 2011. "Optimizing Proniosomes for Controlled Release of Ketoprofen Using Box-Behnken Experimental Design." *International Journal of Pharmaceutical Sciences and Research* 2:2195-2205.

Montgomery D. C., and G. C. Runger. 2007. *Applied Statistics and Probability for Engineers*. 4th ed.New York: John Wiley & Sons, Inc.

Montgomery, D. C. 2009. *Designs and Analysis of Experiments*. 8th ed. New York: John Wiley & Sons, Inc.

Nair, V., V. Strecher, A. Fagerlin, P. Ubel, K. Resnicow, S. Murphy, R. Little, B. Chakraborty, and A. Zhang. 2008. "Screening Experiments and the Use of Fractional Factorial Designs in Behavioral Intervention Research." *American Journal Public Health* 98:1354-1359.

Nobuyuki, R. M., P. S. Mello, L. M. Melo Santa Anna, and N. Pereira. 2010. "Nitrogen Source Optimization for Cellulase Production by Penicilliumfuniculosum, Using a Sequential Experimental Design Methodology and the Desirability Function." *Applied Biochemistry and Biotechnology* 161:411-422.

Rigas, F., K. Papadopoulou, A. Philippoussis, M. Papadopoulou, and J. Chatzipavlidis. 2009. "Bioremediation of Lindane Contaminated Soil by Pleurotusostreatus in Non Sterile Condition Using Multilevel Factorial Design." *Journal of Water Air and Soil Pollution* 197: 121-129.

Sanchez, S. M., and P. J. Sanchez. 2005. "Very Large Fractional Factorialand Central Composite Designs." *ACM Transactions on Modeling and Computer Simulation* 15:362-377.

Sayara, T., M. Sarra, and A. Sanchez. 2010. "Optimization and Enhancement of Soil Bioremediation by Composting Using the Experimental Design Technique."*Biodegradation Journal* 21:345-356.

Sudhankar, P., and P. Nagarajan. 2011. "Optimization of Chitinase Production Using Statistics Based Experimental Designs." *Journal of Chemical, Biological and Physical Sciences* 40:352-362.

Sudheer Kumar, Y., S. Varakumar, and O. V. Reddy. 2010. "Production and Optimization of Polygalacturonase from Mango (Mangiferaindica L.) Peel Using Fusariummoniliformein Solid State Fermentation." *World Journal of Microbiology and Biotechnology* 26:1973-1980.

Vaithanomsat, P., M. Songpim, T. Malapant, A. Kosugi, W. Thanapase, and Y. Mori. 2011. "Production of β-Glucosidase from a Newly Isolated Aspergillus Species Using Response Surface Methodology." *International Journal of Microbiology* 2011:1-9.

Villarreal-Marroquín, M. G., J. M. Castro, O. L. Chacón-Modragón, and M. Cabrera-Rios, 2013. "Optimisation Via Simulation: AMetamodelling-Based Method and a Case Study." *European J. Industrial Engineering* 7:275-294.

Vishwantha, K. S., A. G. AppuRao, and S. A. Singh. 2010. "Acid Protease Production by Solid-State Fermentation Using Aspergillusoryzae MTCC 5341: optimization of process parameters." *Journal of Industrial Microbiology and Biotechnology* 37:129-138.

Wass, J. A. 2011. "A Further Step in Experimental Design (III): The Response Surface." *Journal of Validation Technology* 17:54-62.

Zambare, V. 2011. "Optimization of Amylase Production from Bacillus Sp. Using Statistics Based Experimental Design." *Emirates Journal of Food and Agriculture* 23:37-47.

Zhou, W. W., Y. L. He, T. G. Niu, and J. J. Zhong. 2010. "Optimization of Fermentation Condition for Production of Anti-TMV Extracellular Ribonuclease by Bacillus Cereus Using Response Surface Methodology." *Bioprocess and Biosystems Engineering* 33:657-663.

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