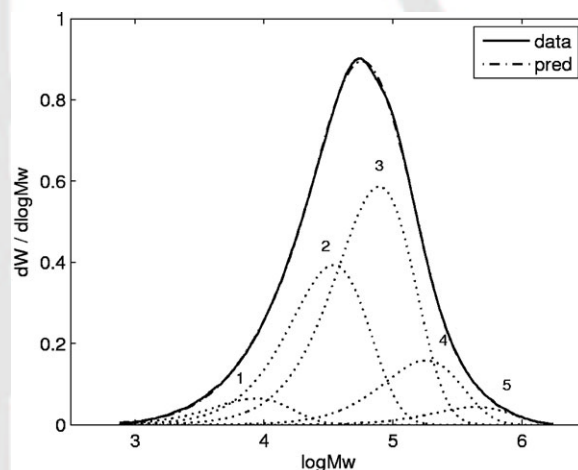


Design of Optimal Sequential Experiments to Improve Model Predictions from a Polyethylene Molecular Weight Distribution Model

Duncan E. Thompson, Kim B. McAuley,* P. James McLellan

Reliable model predictions require an appropriate model structure and also good parameter estimates. For good parameter estimates to be obtained, it is important that the data used in parameter estimation are informative. Alphabet-optimal experimental designs can be used to ensure that new experiments are as informative as possible. This work presents the development of D- and A-optimal sequential experimental designs for improving parameter precision in a molecular-weight-distribution model for Ziegler-Natta-catalyzed polyethylene. Novel V-optimal designs techniques are developed to improve the precision of model predictions, and anticipated benefits are quantified. Problems with local minima are discussed and comparisons between the optimality criteria are made.



Introduction

Owing to the multi-site nature of Ziegler-Natta catalysts, kinetic models of ethylene copolymerizations that use these catalysts tend to be very large with many parameters that need to be estimated.^[1–7] Experimental runs on industrial reactors are expensive, especially when the required setpoints lie outside of the normal pattern of process operating conditions. Because of the expense of obtaining custom experimental data and difficulties that can be associated with parameter estimation, it is important to design experiments and to use data as

effectively as possible when building mathematical models. It is also important to extract all of the available information from prior experiments that may have been performed for other purposes.

Many end-use and processing properties of polyethylene are influenced by molecular weight distribution (MWD) and comonomer incorporation.^[8] Industrial polyethylene producers desire mathematical models that can predict the MWD of ethylene/hexene and ethylene/butene copolymers produced in gas-phase reactors using Ziegler-Natta catalysts. If models that predict MWDs from reactor operating conditions are combined with models that predict end-use properties from MWDs,^[9] then end-use properties that are important to customers can be predicted directly from reactor conditions. To this end, our research group has used industrial data to develop simplified models to predict the MWD and comonomer incorporation in

D. E. Thompson, K. B. McAuley, P. J. McLellan
Department of Chemical Engineering, Queen's University,
Kingston, ON, K7L 3N6, Canada
Fax: +1 613 533 6637; E-mail: kim.mcauley@chee.queensu.ca

Ziegler-Natta-catalyzed polyethylene.^[10,11] The first step in developing the MWD models was to use deconvolution of MWD curves from industrial ethylene/hexene copolymers to gain insight into the kinetics of different types of catalyst sites.^[12] This insight was then used to develop a simplified reaction scheme and steady-state model to predict MWDs of ethylene/hexene copolymer produced at 90 °C.^[10] Finally, a more complete model was developed that accounts for the effects of the reactor temperature and for use of either butene or hexene comonomer.^[11] Estimability analysis and cross-validation were used to obtain parameter estimates from the available industrial data.^[11] The model equations are shown in Table 1, and the best parameter estimates that were obtained are shown in Table 2.

Equation (1) is the overall MWD curve produced by five types of active sites, assuming that each site produces a Flory distribution.^[13,14] The MWD of the copolymer component produced by the j th type of active site depends on τ_j and m_j defined in Equation (2) and (3), respectively, where τ_j is the ratio of the rates of chain-termination reactions to those of propagation reactions at the j th type of site, and m_j is the mass fraction of copolymer produced at the j th type of site, which is calculated using Equation (4) to (8). Detailed information about the derivation of the equations in Table 1 is provided in earlier articles.^[10,11] Note that the model in Table 1 contains 25 parameters, some of which are shared by multiple active sites. For example, the activation energy parameter ε_{K1low} in Equation (2) is shared by sites 1 and 2, which produce lower-molecular-weight copolymer, and ε_{K1high} is shared by sites 3, 4 and 5, which produce higher-molecular-weight polymer. The parameters in Table 2 can also be used to predict overall comonomer incorporation in the polymer. Equation (9a) and (9b) describe the mass fractions of butene and hexene, respectively, using the comonomer mole fractions for each site, as described in Equation (10a) and (10b).

Although advanced statistical techniques, including correlation analysis^[12] and estimability analysis,^[11] were used as aids in model simplification and parameter estimation, many of the parameter estimates in Table 2 are imprecise. Some parameter values are not significantly different from zero, and others were left at their initial guesses due to insufficient information in the industrial data set.^[11] To further improve the model predictions, additional data are required. An objective of the current work is to select a small number of experimental runs that, when combined with the existing data, can be used to improve parameter estimates and model predictions for this polyethylene MWD model. A review of the use of alphabet-optimal experimental designs is presented below, and the sequential experimental design problem is discussed. Sequential A- and D-optimal design methods

are used to select four new experimental runs aimed at improving parameter precision. Novel V-optimal designs techniques are developed to improve the precision of model predictions, and anticipated benefits are quantified. Difficulties with local optima are addressed and the A-, D-, and V-optimal experimental designs are compared.

Application of Optimal Experimental Designs

Well-designed experiments ensure that the data that are collected are useful for parameter estimation and for improving model predictions. One common way of selecting appropriate experiments for parameter estimation is with an alphabet-optimal design. Although a large number of these designs have been proposed (e.g., A, D, E, G, I, L, T, V)^[15–17] only a few are of interest in this work, where the goal is to improve parameter estimates and predictions from a simplified model. Note that considerable work has been done on selecting experimental runs for model discrimination,^[16,18–21] but this is beyond the focus of the current article.

D-optimal designs are the most commonly used of the alphabet-optimal designs.^[15,22–30] A D-optimal design is one that minimizes the volume of the parameter joint confidence region, based on linearization of the model. Minimizing this volume is equivalent to minimizing the determinant of the variance-covariance matrix, or maximizing the determinant of the Fisher Information matrix. Thus, the D-optimality objective function for nonlinear regression problems is:^{Q2}

$$J_D = |Z^T Z| \quad (11)$$

where Z is a scaled parametric sensitivity matrix:

$$Z = \begin{bmatrix} \frac{\partial y_{11}}{\partial \theta_1} s_{y11} & \dots & \frac{\partial y_{11}}{\partial \theta_P} s_{y11} & \frac{s_{\theta P}}{s_{y11}} \\ \vdots & \ddots & \vdots & \vdots \\ \frac{\partial y_{Rn}}{\partial \theta_1} s_{yRn} & \dots & \frac{\partial y_{Rn}}{\partial \theta_P} s_{yRn} & \frac{s_{\theta P}}{s_{yRn}} \end{bmatrix} \quad (12)$$

Where y_{jk} is a predicted response at experimental condition j for variable k , θ_i is the i th parameter, and $s_{\theta i}$ and s_{yjk} are scaling factors related to the uncertainties in initial parameter guesses and in measured responses, respectively. Note that the Z matrix in Equation (12) is the same scaled sensitivity matrix used for estimability analysis.^[11]

D-optimal designs have found considerable use in biological and chemical kinetic studies.^[15,29,30] For example, Van Derlinden et al.^[28] used them to determine parameter values for models relating temperature to

Table 1. Model equations.

$$\frac{dW}{d \log_{10} M_w} = m_1 [r^2 \ln(10) \cdot \tau_1^2 \cdot \exp(-\tau_1 r)] + m_2 [r^2 \ln(10) \cdot \tau_2^2 \cdot \exp(-\tau_2 r)] \quad (1)$$

$$+ m_3 [r^2 \ln(10) \cdot \tau_3^2 \cdot \exp(-\tau_3 r)] + m_4 [r^2 \ln(10) \cdot \tau_4^2 \cdot \exp(-\tau_4 r)]$$

$$+ m_5 [r^2 \ln(10) \cdot \tau_5^2 \cdot \exp(-\tau_5 r)]$$

$$\tau_j = K_{1j} \exp\left(\varepsilon_{K1,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2]} + K_4 \frac{1}{[C_2]} \text{ for } j = 1, 2 \text{ OR}$$

$$\tau_j = K_{1j} \exp\left(\varepsilon_{K1,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2]} + K_4 \frac{1}{[C_2]} \text{ for } j = 3, 4, 5 \quad (2)$$

$$m_j = \frac{N_j}{\sum_{j=1}^5 N_j} \quad (3)$$

$$N_1 = \left(\alpha_{21} \exp\left(\varepsilon_{\alpha 21} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) + \alpha_{3B,low} \exp\left(\varepsilon_{\alpha 3B,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[C_4]}{[C_2]} + \alpha_{3H,low} \exp\left(\varepsilon_{\alpha 3H,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[C_6]}{[C_2]} \right)$$

$$\left(1 + \alpha_{1,low} K_{12} \exp\left(\varepsilon_{K,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2] + \alpha_{4B} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_4] + \alpha_{4H} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_6]} \right)$$

$$\prod_{j=3,4,5} \left(1 + \alpha_{1,high} K_{1j} \exp\left(\varepsilon_{K,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2]} \right) \quad (4)$$

$$N_2 = \left(1 + \alpha_{3B,low} \exp\left(\varepsilon_{\alpha 3B,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[C_4]}{[C_2]} + \alpha_{3H,low} \exp\left(\varepsilon_{\alpha 3H,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[C_6]}{[C_2]} \right)$$

$$\left(1 + \alpha_{1,low} K_{11} \exp\left(\varepsilon_{K,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2] + \alpha_{4B} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_4] + \alpha_{4H} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_6]} \right)$$

$$\prod_{j=3,4,5} \left(1 + \alpha_{1,high} K_{1j} \exp\left(\varepsilon_{K,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2]} \right) \quad (5)$$

$$N_3 = \left(\alpha_{23} \exp\left(\varepsilon_{\alpha 2,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) + \alpha_{3B,high} \frac{[C_4]}{[C_2]} + \alpha_{3H,high} \frac{[C_6]}{[C_2]} \right)$$

$$\prod_{j=1,2} \left(1 + \alpha_{1,low} K_{1j} \exp\left(\varepsilon_{K,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2] + \alpha_{4B} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_4] + \alpha_{4H} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_6]} \right)$$

$$\prod_{j=4,5} \left(1 + \alpha_{1,high} K_{1j} \exp\left(\varepsilon_{K,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2]} \right) \quad (6)$$

$$N_4 = \left(\alpha_{24} \exp\left(\varepsilon_{\alpha 2,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) + \alpha_{3B,high} \frac{[C_4]}{[C_2]} + \alpha_{3H,high} \frac{[C_6]}{[C_2]} \right)$$

$$\prod_{j=1,2} \left(1 + \alpha_{1,low} K_{1j} \exp\left(\varepsilon_{K,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2] + \alpha_{4B} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_4] + \alpha_{4H} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_6]} \right)$$

$$\prod_{j=3,5} \left(1 + \alpha_{1,high} K_{1j} \exp\left(\varepsilon_{K,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2]} \right) \quad (1.7)$$

$$N_5 = \left(\alpha_{25} \exp\left(\varepsilon_{\alpha 2,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) + \alpha_{3B,high} \frac{[C_4]}{[C_2]} + \alpha_{3H,high} \frac{[C_6]}{[C_2]} \right)$$

$$\prod_{j=1,2} \left(1 + \alpha_{1,low} K_{1j} \exp\left(\varepsilon_{K,low} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2] + \alpha_{4B} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_4] + \alpha_{4H} \exp\left(\varepsilon_{\alpha 4} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) [C_6]} \right)$$

$$\prod_{j=3,4} \left(1 + \alpha_{1,high} K_{1j} \exp\left(\varepsilon_{K,high} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[H_2]}{[C_2]} \right) \quad (8)$$

$$m_B = \sum_{j=1-5} m_j \left(\frac{3f_{Bj}}{1 + 2f_{Bj}} \right) \quad (9a)$$

$$m_H = \sum_{j=1-5} m_j \left(\frac{3f_{Hj}}{1 + 2f_{Hj}} \right) \quad (9b)$$

$$f_{Bj} = \frac{1}{1 + \frac{\alpha_{2j} \exp\left(\varepsilon_{\alpha 2j} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right)}{\alpha_{3Bj} \exp\left(\varepsilon_{\alpha 3Bj} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[C_4]}{[C_2]}}} \quad (10a)$$

$$f_{Hj} = \frac{1}{1 + \frac{\alpha_{2j} \exp\left(\varepsilon_{\alpha 2j} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right)}{\alpha_{3Hj} \exp\left(\varepsilon_{\alpha 3Hj} \left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \frac{[C_6]}{[C_2]}}} \quad (10b)$$

Table 2. Parameter estimates.

Parameter	Estimate
K_{11}	0.0149
K_{12}	0.0030
K_{13}	0.0011
K_{14}	0.0003
K_{15}	4.0×10^{-13}
K_4	7.9×10^{-4}
$\alpha_{1, \text{low}}$	2 431.6
$\alpha_{1, \text{high}}$	390.7
α_{21}	0.4755
α_{23}	0.3419
α_{24}	0.0671
α_{25}	0.0154
$\alpha_{3B, \text{low}}$	0.0378
$\alpha_{3B, \text{high}}$	0.0154
$\alpha_{3H, \text{low}}$	0.3065
$\alpha_{3H, \text{high}}$	4.44×10^{-9}
α_{4B}	10.63
α_{4H}	28.84
$\varepsilon_{K, \text{low}}$	-3 095
$\varepsilon_{K, \text{high}}$	-4 070
$\varepsilon_{\alpha 21}$	-2 476
$\varepsilon_{\alpha 2, \text{high}}$	-259.5
$\varepsilon_{\alpha 3B, \text{low}}$	-4 377
$\varepsilon_{\alpha 3H, \text{low}}$	495.6
$\varepsilon_{\alpha 4}$	0

microbial growth rates, Balsa-Canto et al.^[31] to estimate kinetic parameters for thermal degradation of nutrients in food, Gueorguieva et al.^[32] to improve parameter estimates in pharmacokinetic models, Atkinson et al.^[16] for estimation of kinetic parameters for reversible chemical reactions, and Polic et al.^[33] for parameter estimation in a styrene/methyl methacrylate copolymerization model.

The D-optimality criterion is often used for sequential experimental designs. Sequential designs are appealing because they offer the chance to change strategy after a first round of experiments has been completed,^[24] when better information is available than at the start of the experimental program. New experimental runs are selected after some runs have been completed. Sequential designs also help modelers to build effectively on previously existing data within their organization. In sequential experimental design, the sensitivity coefficients for the prior experiments are included in the Z matrix, along with new rows

corresponding to the new experimental run conditions that are selected.^[34] The Z matrix for the sequential design therefore takes the form:

$$Z = \begin{bmatrix} Z_{\text{old}} \\ Z_{\text{new}} \end{bmatrix} \quad (13)$$

Where Z_{old} is the scaled sensitivity matrix for the pre-existing runs, and Z_{new} contains rows of scaled sensitivity coefficients corresponding to the new runs being selected. Given a set of initial parameter guesses, the coefficients in Z_{old} are fixed numerical values, and the coefficients in Z_{new} depend on the experimental settings for the proposed new runs. Many strategies have been developed for generation of D-optimal designs by sequentially adding runs to an existing design.^[27,34-39]

Criticisms of alphabet-optimal designs in general, and of D-optimal designs in particular, center mostly around sensitivity to model mis-specification and poor initial parameter guesses.^[24,35,40] Imperfect model structure and poor initial parameter guesses introduce bias into the design. In non-linear models, such as the ethylene copolymerization model in this work, the elements of Z used in the design depend on the initial parameter guesses. As a result of these problems, some effort has focused on methods of experimental design that are more robust to model mis-specification.

One approach taken to ensure model robustness is the use of Bayesian D-optimal designs. A Bayesian design allows the modeler to investigate additional parameters and effects that are believed to be unimportant for obtaining good model predictions.^[41] These unimportant factors, which were likely not included in the initial model, make the experimental design more robust to model mis-specification because the design can help to uncover poor initial assumptions. Ruggoo and Vandebroek^[35] simulated a Bayesian D-optimal design, followed sequentially by a classical D-optimal design, for an empirical linear regression model. They concluded that this combined approach produces superior results to either a Bayesian D-optimal design or a classical D-optimal design. Bayesian designs are more computationally intensive than standard optimal designs because they require numerical integration of probability density functions.^[36] To our knowledge, the sequential Bayesian approach developed by Ruggoo and Vandebroek^[35] has not been used for mechanistic non-linear models. Myers^[24,36] provides a good review of approaches to ensure robustness in optimal experimental designs. In addition to the Bayesian approach, Myers also advocates sequential design. Sequential designs offer improved robustness against errors in initial guesses by allowing for parameter values to be corrected and for model structure adjustments to be made after an initial round of experiments.

Another type of alphabet-optimal design is the A-optimal design, which minimizes the total parameter variance. The total parameter variance is obtained from the sum of the diagonal elements of the variance covariance matrix. Therefore, A-optimal designs minimize:

$$J_A = \text{trace}\left((Z^T Z)^{-1}\right) \quad (14)$$

Although D-optimal designs are more commonly used, A-optimal designs are more computationally appealing^[42] since they only use the diagonal elements of the covariance matrix. Schittkowski used A-optimal designs for multi-response ordinary-differential-equation and differential-algebraic-equation models that describe the dynamic behavior of chemical processes.^[42]

Model users often care more about the quality of the model predictions than about how well the parameters in the model are estimated. D-optimal and A-optimal designs focus primarily on improving the quality of parameter estimates, rather than on improving the quality of the model predictions. Although better parameter estimates will generally lead to better predictions, it is possible to obtain good model predictions when some of the less-important parameters are poorly estimated. V-optimal designs (also known as Q-optimal designs) have been used to a limited extent to select experiments aimed specifically at improving model predictions.^[43] Thus, the information gained from a V-optimal design improves the estimates of the most important parameters more than the estimates of the less-important parameters, whereas D- or A-optimal designs treat all parameters equally. A V-optimal design is one that minimizes the average prediction variance over an operating region of interest. Thus a V-optimal design minimizes:

$$J_V = \text{trace}\left(Z_{\text{int}}(Z^T Z)^{-1} Z_{\text{int}}^T\right) \quad (15)$$

where Z_{int} is a matrix of scaled sensitivity coefficients corresponding to a particular set of operating conditions of interest (i.e., conditions where precise model predictions are desired by the model user). G-optimal designs, which also focus on model-prediction variance, minimize the maximum prediction variance over a domain of interest, which is equivalent to minimizing the *maximum* of $(Z_{\text{int}}(Z^T Z)^{-1} Z_{\text{int}}^T)$. G-optimal designs are more computationally intensive than V-optimal designs.

Box and Draper^[37,41] provide 14 criteria for what constitutes a good experimental design. Of particular interest to the current work is the criterion that a design should “ensure that the fitted value at $\hat{y}(X)$ be as close as possible to the true value”.^[40,p.19] In other words, the experimental design should ensure good model predictions.

Box outlined his concerns about the suitability of alphabet optimal designs.^[40] Of particular interest in the current work are his concerns about i) regions of experimental feasibility and modeling interest, and ii) acknowledging bias in experimental designs. When describing his first concern, Box asserts that the region of interest for making model predictions is usually much smaller than the region of feasible operation. He therefore reasons that designs that artificially constrain the design variables to the region of interest would not necessarily lead to the best predictions, since they do not take advantage of potential information that may be obtained by experimenting over a larger region. G- and V-optimal designs seem to address this concern very well; however, Box^[40] indicates that G-optimality may not be practically desirable because of its minimax nature. He does not discuss V-optimality, perhaps because the V-optimal criterion was not used in 1982, but it would seem that V-optimality does not suffer from the same problems as G-optimality and so may be better suited for designing effective and practical experiments. It is not clear when V-optimality was first invented; however, it appears to have evolved out of Box and Draper’s idea of integrated variance.^[17,45–48] Welch^[17] included V-optimality in a set of algorithms for computer-generated design of experiments. Liu and Neudecker^[48] used V-optimal designs in experiments involving mixtures of several components. François et al.^[49] used V-optimal designs for selecting experiments to develop univariate nonlinear calibration models. A recent review^[30] of the experimental design literature for chemical and biological models describes many instances of D- and A-optimal designs, but only one article that considers V-optimal design, which is used to select measurement times in a dynamic model for epidermal-growth-factor receptor signaling.^[50] A more recent review of the systems biology experimental design literature does not mention V-optimal designs at all.^[29] We are not aware of any applications of V-optimal design to polymerization or other chemical process models.

The second issue, bias in experimental design, is of concern in the current work because of the simplifying assumptions used in the formulation of the model in Table 1. More complete and complex models reduce the bias, but this comes at the cost of increasing prediction variance^[51,52] because uncertainty in the model parameters propagates into uncertainty in predictions. Thus there is a trade-off between minimizing prediction variance and reducing bias. Traditional alphabet optimal designs, which assume that the model structure is correct, do not address this concern. Some work has been done to include model imperfections and bias in the optimality criteria. Box and Draper^[45] proposed a method that accounts for both variance and bias. In a polynomial model, they minimized the expected mean square error, which is the combination of the variance error and the bias error. Box and Draper

noted that, in their example, the optimal design was very close to one that minimizes bias alone and ignores variance. Karson et al.^[46] have done work with minimum-bias designs. After they minimized the bias, they then minimized the variance while ensuring the minimum bias. Evans and Manson^[47] have also done work with minimum-bias estimation using the criterion outlined by Karson et al.^[46] Evans and Manson^[47] were able to select A-, D- and V-optimal designs from within the set of experiments that minimized the bias in a two-factor system. Draper and Sanders^[53] have also used this approach to select rotatable designs for simple models. This minimum-bias approach is appealing, but it is difficult to apply to nonlinear mechanistic models where the bias cannot readily be assumed to be some function of higher-order terms.

Experimental Designs for the Simplified Polyethylene MWD Model

Because of the multi-site nature of Ziegler-Natta catalysts, the associated olefin polymerization models tend to be very large and to have many parameters. In this work, an attempt is made to select new experimental runs to improve the predictions of the polyethylene copolymer MWD model. An existing industrial data set was used to obtain the parameter estimates presented in an earlier work.^[11] Many of these parameter estimates have wide confidence intervals, and not all of the parameter estimates are statistically different from zero. Some less-important model parameters were never estimated and were left at their initial guesses.

It is important to account for information from the 31 prior experimental runs that have been obtained (15 with butene comonomer and 16 with hexene) when planning additional experiments. For each of these 31 experimental runs, a MWD curve and a comonomer incorporation measurement are available. The MWD curves can be discretized to give twenty equally-spaced (on a log scale) points per curve (as shown in Figure 1) with each of these points leading to a row in the sensitivity matrix, Z . Twenty points are sufficient to provide a reliable picture of the MWD curve from each run, without causing an undue computational load during sequential optimal-design calculations. Additional rows in the Z matrix correspond to predictions of comonomer incorporation measurements (one row for each of the 31 experiments). As a result, Z_{old} , the sensitivity matrix from the prior experiments has $31 \times (20 + 1) = 651$ rows [see Equation (13)]. Since the simplified model has 25 parameters, the overall sensitivity matrix Z has 25 columns, each containing derivatives with respect to a particular parameter. Note that each element in the sensitivity matrix is scaled appropriately, as shown in Equation (12).^[11] In the analysis that follows, assume that

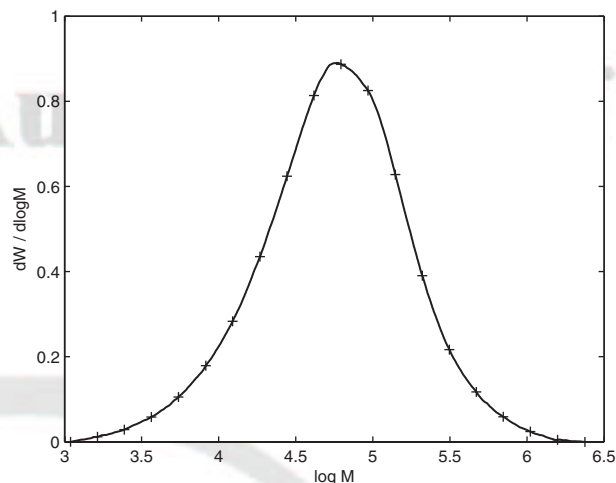


Figure 1. A measured HDPE MWD curve characterized by 20 discrete points.

four additional runs can be selected. Each proposed experiment will provide 20 new values from the associated MWD curve (equally spaced between 2.7 and 6.6 on the log scale), along with a comonomer incorporation measurement. Thus, the proposed experiments will add 84 new rows to the Z matrix. Since D-optimal designs are the most commonly used type of experimental design, a sensible starting point is to determine the D-optimal designs that arise from this sequential design problem. A D-optimal design is one that maximizes the determinant of the Fisher information matrix (i.e., that maximizes $|Z^T Z|$). The decision variables for this optimization problem are the following four reactor settings for each of the four proposed runs: reactor temperature (T), gas-phase hydrogen-to-ethylene ratio (H_2/C_2), the hexene-to-ethylene ratio (C_6/C_2), and the butene-to-ethylene ratio (C_4/C_2). The desired values of these reactor settings can be achieved and maintained using the available automatic control system of the pilot-plant reactor. The gas-phase polyethylene reactor of interest can operate over a wide range of temperatures below the melting point of the ethylene copolymers.^[54] High temperatures are desirable because they lead to high reaction rates and to higher yields per unit mass of catalyst. In this optimization problem, the temperature is constrained to be between 80 and 120 °C. Note that temperatures as low as 80 °C would not be desirable for industrial polymer production, but Box's advice^[40] that the region of operation for designed experiments should be larger than the region of commercial interest where good predictions are desired has been heeded. The hydrogen-to-ethylene mole ratio is constrained between 0.1 and 0.6 to ensure that accurate MWD measurements can be obtained, and the comonomer mole ratios are constrained between 0 and 0.3. It is assumed that only one comonomer (either butene or hexene) can be used at a time. The

1 following complementarity constraints are used to meet
2 this requirement:^[55]

$$\begin{aligned} (C_4/C_2)(C_6/C_2) &= 0 \\ (C_4/C_2) + (C_6/C_2) &\geq 0 \end{aligned} \quad (16)$$

3
4
5 Finally, to ensure that the reactor operating temperature
6 remains safely below the melting point of the polymer, the
7 following inequality constraint is used:

$$T \leq 122 - 81(C_x/C_2) \quad (17)$$

8
9
10 where T is the temperature (in °C) and C_x/C_2 is the
11 comonomer (butene or hexene)-to-ethylene ratio. A mini-
12 mum spacing constraint was also introduced to keep
13 multiple experiments from being stacked at the same
14 operating point:

$$\sqrt{\frac{(T_i - T_j)^2}{(T_{\max} - T_{\min})^2} + \frac{((H_2/C_2)_i - (H_2/C_2)_j)^2}{((H_2/C_2)_{\max} - (H_2/C_2)_{\min})^2} + \frac{((C_4/C_2)_i - (C_4/C_2)_j)^2}{((C_4/C_2)_{\max} - (C_4/C_2)_{\min})^2} + \frac{((C_6/C_2)_i - (C_6/C_2)_j)^2}{((C_6/C_2)_{\max} - (C_6/C_2)_{\min})^2}} \geq 0.5 \quad (18)$$

15 The optimization was performed using the *fmincon*
16 routine in MatlabTM, which can accommodate the required
17 equality and inequality constraints. The algorithm in
18 *fmincon* uses a sequential quadratic programming method.
19 Expressions for analytical partial derivatives of the model
20 equations with respect to the parameters (i.e., the elements
21 of Z) were developed using MapleTM. These partial
22 derivatives are complicated expressions, because the model
23 equations are complex. Note that Equation (1) [with
24 Equation (2) to (8) substituted] is used to predict MWD
25 and Equation (10a) and (10b) [with Equation (3) to (9)
26 substituted] are used to compute comonomer incorpora-
27 tion. Numerical values of the parameters in Table 2 were
28 substituted into the partial derivative expressions, produ-
29 cing numerical values for the elements of Z_{old} . The elements
30 of Z_{new} are analytical functions of the decision variables for
31 the four proposed experimental runs $[(H_2/C_2), (C_4/C_2), (C_6/C_2), T]$. The *fmincon* routine used these analytical expres-
32 sions to calculate numerical derivatives of the various
33 objective functions [Equation (5.6) to (5.8)] **to author –**
34 **please check/correct equation numbers here** with
35 respect to the decision variables. Using *fmincon*, each
36 optimization took between 15 and 40 min to solve.

37 Six different sets of initial guesses were used for the
38 decision variables. Unfortunately, several different local
39 optima for the D-optimal design were obtained from the
40 different initial guesses, as shown in Table 3. The value of
41 the objective function $I_D = |Z^T Z|$ is reported for each of these
42 local optima. The first set of initial guesses includes points
43 where good model predictions are desired. The resulting

locally optimal runs, which are all at constraints, are
reasonable since data collected over a wide operating
range are often the most informative.^[40] The second set of
initial conditions is only slightly different from first the set,
with each of the decision variables perturbed randomly up
or down by a small amount. As expected, the resulting local
optimum is the same as that obtained starting from the first
initial guess. The third set of initial guesses contains run
conditions at extremes of the operating range. In this case,
the resulting locally optimal design points have not moved
very far from the corresponding initial guesses. The fourth
set of initial guesses has runs that are tightly grouped near
the center of the operating range. The resulting converged
design points, which fall on constraints, have the highest
objective function value among those obtained from the six
attempts.

It is disappointing, but not surprising, that numerous
local minima were obtained from different starting points

because of the nonlinearity of the system. Polic et al.^[33]
obtained a complex objective function surface with many
ridges and local optima when designing D-optimal experi-
ments for parameter estimation in a styrene/methyl
methacrylate copolymerization model. The best D-optimal
designs obtained for the MWD model (Sets 7 and 8 in
Table 3) consist of two hexene-comonomer runs, one
butene-comonomer run and one homopolymerization run.
Note that these optima were only obtained from a limited
set of starting points. The optimizer never switched from
the initial comonomer that was used in any of the runs as
the solution converged. Even when all-butene or all-hexene
designs (the fifth and sixth set of initial conditions) were
used as starting points, the optimizer did not change which
comonomer was used in any of the runs, suggesting that the
gradient-based optimizer in *fmincon* is not suitable for
solving this difficult optimal design problem, possibly due
to the complementarity constraints.

Several other optimization packages were considered,
including the gradient-based interior-point optimizer
IPOPTTM^[56] and the direct-search simplex optimizer
*simps*TM in MatlabTM. Using IPOPTTM proved to be
impossible because AMPLTM, which uses symbolic compu-
tation to provide analytical derivatives to IPOPTTM, has no
matrix algebra capabilities. Attempts were made to derive
symbolic expressions for the required objective functions in
MapleTM, but they were too large to compute and caused
memory overflow. Computation of the determinants and
matrix inverses required in the objective functions was
prohibitively difficult. Since *simps*TM uses MatlabTM, matrix

Table 3. D-optimal design of experiments. The most D-optimal design is shown in **bold**.

Set	J (*10 ⁻⁶⁰)	Run	Initial Conditions				D-optimal Runs			
			Temp (°C)	H ₂ /C ₂	C ₄ /C ₂	C ₆ /C ₂	Temp (°C)	H ₂ /C ₂	C ₄ /C ₂	C ₆ /C ₂
1	3.6	1	100	0.4	0	0.15	100	0.6	0	0.27
		2	105	0.4	0.1	0	120	0.6	0	0
		3	115	0.2	0	0.01	120	0.1	0	0
		4	90	0.6	0.25	0	80	0.6	0.3	0
2	3.6	1	101	0.41	0	0.16	100	0.6	0	0.27
		2	106	0.39	0.09	0	120	0.6	0	0
		3	114	0.21	0	0.009	120	0.1	0	0
		4	91	0.59	0.24	0	80	0.6	0.3	0
3	2.73	1	80	0.1	0	0.01	80	0.1	0	0
		2	80	0.6	0	0.3	80	0.1	0	0.3
		3	120	0.1	0.01	0	120	0.1	0	0
		4	120	0.6	0.02	0	120	0.6	0	0
4	9.01	1	105	0.4	0	0.1	112.3	0.6	0	0.118
		2	105	0.4	0	0.15	97.5	0.1	0	0.3
		3	105	0.4	0.1	0	120	0.6	0	0
		4	105	0.4	0.15	0	112.1	0.6	0.12	0
5	1.27	1	100	0.4	0.15	0	119.4	0.6	0.03	0
		2	105	0.4	0.1	0	120	0.6	0	0
		3	115	0.2	0.01	0	120	0.1	0	0
		4	90	0.6	0.25	0	80	0.6	0.3	0
6	2.19	1	100	0.4	0	0.15	97.5	0.1	0	0.3
		2	105	0.4	0	0.1	120	0.6	0	0.023
		3	115	0.2	0	0.01	120	0.1	0	0
		4	90	0.6	0	0.25	80	0.6	0	0.3
7	56.35	1	91.25	0.267	0.1	0	80	0.1	0.3	0
		2	97.07	0.4	0	0.2	120	0.6	0	0
		3	90	0.267	0	0.2	80	0.1	0	0.3
		4	90	0.4	0	0.2	105.2	0.1	0	0.205
8	51.44	1	80	0.1	0.3	0	80	0.1	0.3	0
		2	97.55	0.5	0.3	0	120	0.6	0	0
		3	100	0.1	0	0.182	97.5	0.1	0	0.3
		4	100	0.5	0	0.182	114.1	0.6	0	0.096

algebra is straightforward for this direct-search optimizer. However, *simps*TM does not readily accommodate some of the constraints [Equation (6) to (8)]. Perhaps the constraints could be reformulated using additional variables, but this option was not pursued. Instead, brute force optimization with *fmincon* was used, starting from a large number of initial guesses.

The existence of local optima makes it difficult to know whether the global optimum has been found. One way of addressing problems with local optima is to use a large

number of initial guesses spread over a range of values.^[33] By moving the optimization starting point to different places, there is a better chance that the optimization will converge to the global optimum at least once. Using this strategy, 112 different sets of initial guesses were selected at well-spaced points throughout the operating region. Local D-optimal designs were determined from each of these starting points. Once all of the optimizations had converged, the best locally D-optimal experimental design (among the results obtained) was determined and is

1 reported as the seventh case in Table 3. Although the solver
2 only converged on the optimal design once, there was
3 another point that had nearly as good an objective value
4 that was obtained 5 times and is reported as case 8 in
5 Table 3. The resulting design points are along constraints
6 and are far apart in the available operating region.

7 The A-optimality criterion was also used to design
8 experiments. Again, six different starting points, the same
9 as for the D-optimal designs, were used initially. The results
10 are shown in Table 4. When the optimization was started
11 from the well-spaced starting points, the “best” design was
12 selected with only butene comonomer and homopolymer-
13 ization runs included (set 9 in Table 4). The objective
14 function value for set 5 is nearly as good as for set 9, and
15 these experiments were obtained from 11 of the 118

different initial guesses. The optimizer showed the same
inability to switch between comonomers as was seen with
the D-optimality calculations. The best run selected using
the A-optimality criterion did not contain an experiment
with hexene. This A-optimal design has one homopolymer-
ization run and three runs with butene. Note that the best
D-optimal design (row 7 of Table 3) was very different from
the A-optimal design in that it consisted of a homopoly-
merization run along with two hexene runs and a butene
run.

Finally, V-optimal designs were also determined, starting
from the same initial guesses used in selecting the D- and
A-optimal designs. Ten operating points that represent the
region where good predictions are required were selected
(see Table 5) to calculate the Z_{int} matrix in Equation (15).

Table 4. A-optimal design of experiments. The most A-optimal design is shown in bold.

Set	J	Run	Initial Conditions				A-optimal Runs			
			Temp (°C)	H ₂ /C ₂	C ₄ /C ₂	C ₆ /C ₂	Temp (°C)	H ₂ /C ₂	C ₄ /C ₂	C ₆ /C ₂
1	3.12	1	100	0.4	0	0.15	102.5	0.6	0	0.239
		2	105	0.4	0.1	0	110.8	0.1	0.136	0
		3	115	0.2	0	0.01	120	0.1	0	0
		4	90	0.6	0.25	0	80	0.1	0.3	0
2	3.12	1	101	0.41	0	0.16	102.5	0.6	0	0.239
		2	106	0.39	0.09	0	110.8	0.1	0.136	0
		3	114	0.21	0	0.009	120	0.1	0	0
		4	91	0.59	0.24	0	80	0.1	0.3	0
3	3	1	80	0.1	0	0.01	80	0.1	0	0
		2	80	0.6	0	0.3	80	0.1	0.3	0
		3	120	0.1	0.01	0	110.8	0.1	0.136	0
		4	120	0.6	0.02	0	120	0.6	0	0
4	4.72	1	105	0.4	0	0.1	119.2	0.6	0	0.032
		2	105	0.4	0	0.15	97.5	0.1	0	0.3
		3	105	0.4	0.1	0	112	0.6	0.122	0
		4	105	0.4	0.15	0	112.9	0.1	0.111	0
5	2.81	1	100	0.4	0.15	0	120	0.6	0	0
		2	105	0.4	0.1	0	110.8	0.1	0.136	0
		3	115	0.2	0.01	0	111.8	0.6	0.125	0
		4	90	0.6	0.25	0	80	0.1	0.3	0
6	10.54	1	100	0.4	0	0.15	105.7	0.6	0	0.2
		2	105	0.4	0	0.1	120	0.6	0	0
		3	115	0.2	0	0.01	120	0.1	0	0
		4	90	0.6	0	0.25	84.6	0.1	0	0.3
9	2.71	1	91.7	0.267	0.3	0	80	0.15	0.3	0
		2	85.85	0.4	0.3	0	80	0.1	0.3	0
		3	105	0.267	0	0	110	0.1	0.147	0
		4	105	0.4	0	0	120	0.6	0	0

Table 5. Points of interest used to determine the elements of Z_{int} .

Temperature °C	H ₂ / C ₂	C ₄ / C ₂	C ₆ / C ₂
100	0.4	0	0.15
105	0.4	0	0.1
110	0.4	0	0.05
90	0.6	0.25	0
90	0.6	0.15	0
100	0.6	0	0.05
100	0.6	0	0.1
115	0.2	0	0.01
90	0.6	0	0.25
110	0.2	0.1	0

Using these 10 operating points, Z_{int} has dimensions 210 by 25. Note that this approach for V-optimal design is different to that used by previous researchers. Instead of specifying discrete points of interest, Casey et al.^[50] and other advocates of V-optimal design express the objective function as an integral over a region of interest. We believe that selection of a set of discrete points in the operating space and incorporating the corresponding sensitivity information in Z_{int} is a more intuitive and less computationally intensive approach, which is better suited to modeling of polymerization reactors and other chemical processes. The V-optimal optimization had similar difficulties with local minima as the D- and A- optimization problems. The results for the V-optimal designs are summarized in Table 6. As expected, initial guesses 1 and

Table 6. V-optimal design of experiments. The most V-optimal design is in **bold**.

Set	J	Run	Initial Conditions				V-optimal Runs			
			Temp (°C)	H ₂ /C ₂	C ₄ /C ₂	C ₆ /C ₂	Temp (°C)	H ₂ /C ₂	C ₄ /C ₂	C ₆ /C ₂
1	8.15	1	100	0.4	0	0.15	100	0.6	0	0.28
		2	105	0.4	0.1	0	112	0.6	0.12	0
		3	115	0.2	0	0.01	114	0.6	0	0.1
		4	90	0.6	0.25	0	80	0.6	0.3	0
2	8.15	1	101	0.41	0	0.16	100	0.6	0	0.28
		2	106	0.39	0.09	0	112	0.6	0.12	0
		3	114	0.21	0	0.009	114	0.6	0	0.1
		4	91	0.59	0.24	0	80	0.6	0.3	0
3	12.07	1	80	0.1	0	0.01	80	0.1	0.3	0
		2	80	0.6	0	0.3	80	0.1	0	0.3
		3	120	0.1	0.01	0	120	0.1	0	0
		4	120	0.6	0.02	0	115	0.6	0.08	0
4	8.65	1	105	0.4	0	0.1	114	0.6	0	0.1
		2	105	0.4	0	0.15	99	0.6	0	0.28
		3	105	0.4	0.1	0	113	0.6	0.11	0
		4	105	0.4	0.15	0	111	0.6	0.13	0
5	12.32	1	100	0.4	0.15	0	113	0.6	0.11	0
		2	105	0.4	0.1	0	115	0.6	0.08	0
		3	115	0.2	0.01	0	111	0.1	0.13	0
		4	90	0.6	0.25	0	80	0.6	0.3	0
6	8.35	1	100	0.4	0	0.15	114	0.6	0	0.1
		2	105	0.4	0	0.1	116	0.6	0	0.08
		3	115	0.2	0	0.01	110	0.1	0	0.14
		4	90	0.6	0	0.25	98	0.6	0	0.3
10	7.72	1	102.5	0.1	0	0.1	98	0.6	0	0.3
		2	88.53	0.5	0.2	0	80	0.6	0.3	0
		3	105	0.1	0	0.069	113	0.6	0	0.11
		4	105	0.5	0	0.069	115	0.6	0	0.09

Table 7. Optimality over a large range of conditions. Freq. shows the number of times these experiments were selected out of the 118 different initial guesses. J_x is the objective function for the corresponding optimality criterion.

Selection Criterion	Freq.	J_D	J_A	J_V	Run	Temp (°C)	H ₂ /C ₂	C ₄ /C ₂	C ₆ /C ₂
D	1	56.3×10^{60}	3.59	11.05	1	80	0.1	0.3	0
					2	120	0.6	0	0
					3	80	0.1	0	0.3
					4	105.2	0.1	0	0.205
A	1	5.84×10^{60}	2.71	13.75	1	80	0.15	0.3	0
					2	80	0.1	0.3	0
					3	110	0.1	0.147	0
					4	120	0.6	0	0
V	2	1.78×10^{60}	4.98	7.72	1	98	0.6	0	0.3
					2	80	0.6	0.3	0
					3	113	0.6	0	0.11
					4	115	0.6	0	0.09

1 2 resulted in the same local optimum. The best local
2 optimum obtained (from 2 out of 118 initial guesses) is set
3 10. This design has one butene run and three hexene runs.

4 Unlike the D- and A-optimal designs, the V-optimal
5 design does not contain any homopolymerization runs.
6 This result is not surprising because no homopolymeriza-
7 tion runs were specified in the points of interest in Table 5.
8 V-optimality focuses on improving model predictions at the
9 points of interest, and it seems that information from
10 homopolymerization runs is not crucial for obtaining good
11 predictions at the operating conditions specified in Table 5.
12 Of the three criteria considered, V-optimality best matches
13 the industrially-relevant objectives of this work, that is, to
14 produce a model that results in good predictions over the
15 operating region of interest. Table 7 compares the three
16 optimal designs obtained using the three different optim-
17 ality criteria. The objective function values J_D , J_A and J_V were
18 computed for each of three selected designs.

19 Comparing the J_D values for the three designs to the
20 locally-optimal objective function values shown in Table 3,
21 reveals that the A- and V-optimal designs are quite good in
22 the sense of D-optimality. Similarly, the D- and V-optimal

designs in Table 7 have good values of J_A (smaller is better),
when compared with the local optima in Table 4. Compar-
ison of the J_V values from Table 7 with the locally optimal
values in Table 6 shows that the D-optimal design is
reasonably good, but that the A-optimal design has worse
V-optimality than any of the local optima in Table 6.

As shown in Table 8, implementation of the D-, A- and V-
optimal designs results in a considerable reduction in the
variance of the model predictions (at operating points of
interest from Table 4). The average prediction variances in
Table 8 were computed using diagonal elements of
($Z_{\text{int}}(Z^T Z)^{-1} Z_{\text{int}}^T$) and variances for MWD and comonomer
incorporation responses. The entries in the first row were
computed using $Z = Z_{\text{old}}$, the scaled sensitivity matrix from
the original experiments without any additional runs.
Entries in subsequent rows of Table 8 were calculated by
augmenting this scaled sensitivity matrix with rows
corresponding to the best D-, A- and V-optimal designs.
The average variances in Table 8 indicate that the V-optimal
design will lead to a 35% reduction in the standard error for
prediction of points on the MWD curve and a 30% reduction
in the standard error for comonomer incorporation

Table 8. Influence of designed experiments on average variances of predictions for MWD responses and comonomer incorporation at the 10 points of interest shown in Table 5.

Design	Average prediction variance for points on MWD curves	Average prediction variance for comonomer incorporation
Original data only	1.98×10^{-5}	2.68×10^{-5}
D-optimal	1.22×10^{-5}	1.57×10^{-5}
A-optimal	1.56×10^{-5}	1.23×10^{-5}
V-optimal	0.84×10^{-5}	1.31×10^{-5}

1 predictions. Using the best D- and A-optimal designs,
2 instead, would be expected to improve the standard errors
3 for predicted MWD points by only 22 and 11%, respectively.
4 Standard errors for comonomer incorporation predictions
5 would be reduced by 24 and 32%, respectively. These results
6 help to confirm that the V-optimal experiments would be
7 more effective than the D- and A-optimal designs for
8 improving the predictive ability of the MWD model.

Conclusion

9 Optimizations were conducted to determine D-, A-, and
10 V-optimal sequential experimental designs for parameter
11 estimation in a simplified polyethylene MWD model. Many
12 local optima were observed because of the nonlinearity of
13 the system. The results of the optimizations were
14 dependent on the initial guesses for the experimental
15 conditions. To address this difficulty, 118 different well-
16 spaced sets of experimental runs were used as starting
17 points for the optimization. The best local optima obtained
18 are reported. It is possible that a different numerical
19 optimization algorithm would be less susceptible to local
20 optima. A more robust optimizer is desirable, and it
21 is recommended that other optimizers should be
22 investigated to solve the constrained optimization prob-
23 lems formulated in this article. The best four-run
24 D-optimal design obtained consisted of one butene run,
25 two hexene runs and a homopolymerization run. The best
26 A-optimal design consisted of three butene runs and a
27 homopolymerization run. The best V-optimal design
28 consisted of one butene run and three hexene runs. The
29 V-optimal objective function can be used to compute
30 average prediction variances for points where good
31 predictions are desired. Implementation of the four runs
32 from the best V-optimal design will reduce the average
33 standard error for predicted points along the MWD curves
34 by 35%, whereas implementing the D- and A- optimal
35 experiments will reduce the average standard error by only
36 22 and 11%, respectively. As a result, we advocate the use of
37 V-optimal design for obtaining the best possible predictions
38 from the current MWD model, and for application in other
39 polymer reactor modeling scenarios. Specification of
40 discrete points where good predictions are desired is
41 recommended as an intuitive and computationally simple
42 method for specifying sequential V-optimal objective
43 functions, and is recommended over specification of a
44 region of interest, which requires integration.

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