Cross-Linking Nitroxide-Mediated Radical Copolymerization from a Bayesian Experimental Design Angle

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Summary: In an attempt to collect "meaningful" experimental data in cross-linking nitroxide-mediated radical copolymerization of stryene and divinyl benzene, a Bayesian design approach was used to derive optimal experimental sequences to be carried out in the laboratory. Since a considerable amount of prior knowledge about this polymerization system was already available from previous experimental and modeling efforts, application of the Bayesian design of experiments seemed like a perfect approach. In addition, the implementation of the Bayesian approach would, in principle, result in running fewer experiments, hence saving considerable time and resources.

Keywords: Bayesian design of experiments; crosslinking; kinetics (polym); nitroxide-mediated radical polymerization; polystyrene (PS)

Introduction

Cross-linked polymers are very important in several areas, including medicine, biotechnology and agriculture, with applications such as super absorbent materials, chromatography packing, ion-exchange resins, dental restorative materials, and additives in surface coatings.[1] They are also used in cosmetics and pharmaceuticals, drug-delivery systems, artificial organs, sensors, optics and electronics. For most specialized applications (especially in pharmaceuticals, bioengineering or medicine), cross-linked polymers with uniform microstructures are needed for optimal performance.

Copolymerization of monovinyl monomers with divinyl cross-linkers via regular free radical polymerization (FRP) is one of the most popular routes for producing cross-linked polymers. However, due to the inherent features of FRP, including relatively slow initiation, fast chain propagation and high termination rates, the polymer network synthesized through this route is rather heterogeneous in structure.[2] That means that some sections may be very tightly cross-linked (high crosslink density), while other sections could exhibit a very loose network. This poses a problem, since a varying property distribution at the molecular level (i.e., heterogeneity) can lead to a polymer having inconsistent macroscopic properties. The non-uniformity of network morphology within cross-linked polymers makes consistent production challenging and limits their marketability. Therefore, it would be desirable to search for a synthetic route to produce polymer networks with homogenous structure (morphology).

Recently, the claim has been made that cross-linking under controlled radical polymerization (CRP) conditions might result in a more homogeneous network. Therefore, synthesis, characterization and

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modeling of polymer networks by CRP have received considerable attention in the last decade or so. For a comprehensive literature review and summary of previous work in CRP, see Hernandez-Ortiz et al.[3]

Although at first glance the cross-linking polymerization under CRP seems relatively well studied in the literature, with the production of a more homogeneous polymer network under CRP as an ''accepted'' concept, our observations after a comprehensive literature review are as follows: although the research conducted in the literature points to the direction that production of a more homogeneous polymer network is possible through CRP techniques, ''concrete'' evidence is only indirect and based on rather theoretical speculations of how polymer networks are produced (e.g., conversion of pendant double bonds in the initial stages of the reaction, theory of gelation, swelling ratios, etc.). Perhaps, a more detailed and comprehensive study is required to clarify many existing conflicting statements encountered in the literature, and also find a more formal, direct, and reliable way (if such a way exists) of characterizing the cross-linked polymer network with respect to homogeneity (and the closely related cross-link density distribution).

These observations motivated our work on cross-linking nitroxide-mediated radical polymerization (NMRP) of styrene (STY) in the presence of small amounts of a common cross-linker, divinyl benzene (DVB). The cross-linking copolymerization of STY/DVB is a system well studied under regular free radical polymerization conditions, hence an excellent system for the fundamental comparison between networks synthesized through CRP and FRP, and also for addressing the quest to identify a more formal indicator for network homogeneity. In addition, this copolymer has many applications, for example, it is used for chromatographic applications and as a precursor for ion-exchange resins.

An experimental study of the cross-linking NMRP of STY with DVB was first carried out in our group following a bimolecular NMRP approach, where a popular nitroxide controller, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), was added to the mixture of monomers and (a typical) initiator, such as benzoyl peroxide (BPO).[4] The results on monomer conversion, molecular weights, gel fraction, and swelling index were compared against a STY/DVB copolymer synthesized through FRP. No significant auto-acceleration effect was detected in the early and intermediate conversion ranges. It was observed that the gelation point was significantly delayed. However, based on the experimental data collected, it was not possible to offer any statements related to the homogeneity of the network synthesized through NMRP.

Later on, a detailed mechanistic model for cross-linking NMRP of STY with DVB was developed in our group.[3] Performance of the model was validated using the experimental data available from Tuinman et al.[4] The agreement between model predictions and experimental data for polymerization rate, molecular weights, gelation point and sol consumption was fairly good. However, the experimental data available were focused on only one nitroxide concentration, and molecular weight and gel content data were not collected over the whole conversion trajectory. Hence, supplementary experimental information was required in order to fully verify the validity of the trajectories predicted by the model, develop the ability of the model further to use nitroxides other than TEMPO, and to address our question of whether a network synthesized through NMRP is more homogeneous than the network produced through FRP. Since a considerable amount of prior knowledge related to cross-linking NMRP of STY/DVB was already available from previous experimental and modeling efforts, application of the Bayesian design of experiments seemed like a perfect approach.

A Bayesian approach to the design of experiments has the same objectives as standard experimental (full or fractional factorial) designs but with significant practical benefits over standard design methods.

The ability of the Bayesian approach to incorporate prior process knowledge (which is available in most of the cases but usually discarded) into the design (prior knowledge coming from a variety of sources) is a distinct advantage. Details about the Bayesian analysis steps have been highlighted in a series of publications in Nabifar et al.,[5–7] with examples drawn specifically from the NMRP of STY, under both bimolecular and unimolecular initiating options. The main advantages of this approach were the ability to incorporate prior process knowledge into the design, improvements with respect to information content retrieved from process data, relative ease in changing factor levels in the middle of the experimentation, flexibility with factor ranges and overall ''cost''-effectiveness (time and effort/resources) with respect to the number of experiments.

By using the Bayesian design technique, valuable prior knowledge can be practically incorporated into the design. This helps identify optimal experimental settings in order to collect meaningful experimental data that could satisfy the needs mentioned above. In addition, using the Bayesian design would, in principle, result in running fewer experiments, hence saving considerable time and resources (since a typical polymerization trial, and especially a cross-linking polymerization one, may take more than a month, to plan, prepare, execute, and subsequently fully characterize the resulting polymer product).

Bayesian Design Preliminaries

As explained previously[5–7] and summarized in Figure 1, implementation of the

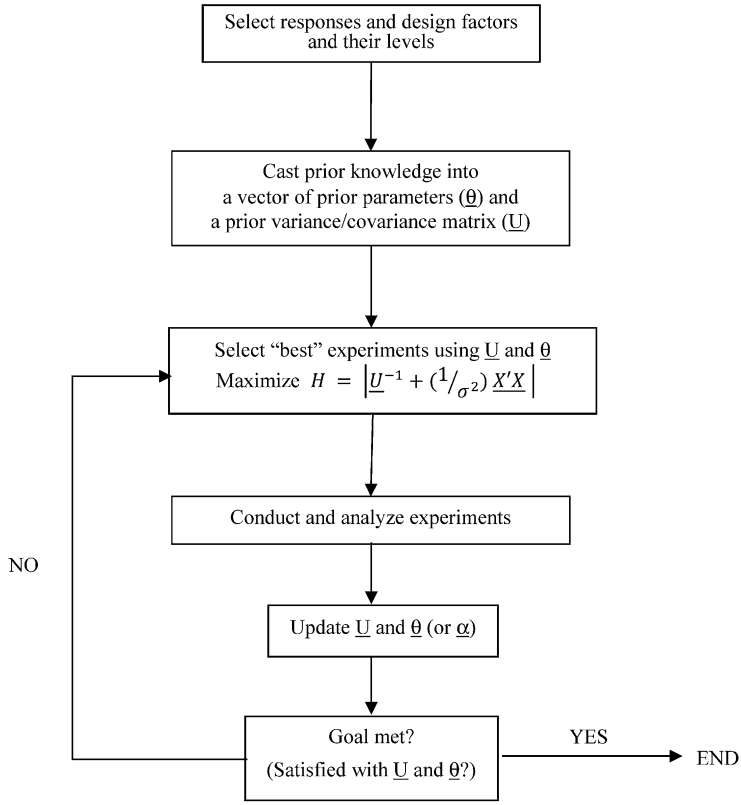

Figure 1.
Procedure for the Bayesian design of experiments.

Bayesian design of experiments requires several steps. A step by step discussion on the application of the Bayesian design methodology to cross-linking NMRP of STY/ DVB is presented herein.

Selection of Design Factors and Levels

As can be seen in Figure 1, the first step in the Bayesian procedure is selecting design factors and their levels. Three factors were chosen and are shown (with their initial levels) in Table 1. Selection of factors and their low and high level values were based on a detailed and critical analysis of the literature,[8–10] combined with some of our previous experience with cross-linking NMRP.[3,4] Based on our prior information, it was felt that temperature (T), concentration of alkoxyamine initiator ([N]) and concentration of the cross-linker ([DVB]) could be influential factors in the cross-linking copolymerization of STY/ DVB.

In the case of temperature, low and high levels chosen were 120 and 130 °C because these were common temperatures used in the NMRP polymerization of styrene and values of kinetic rate constants were readily available for these two temperatures. Divinyl benzene (DVB) was used as the cross-linker. The cross-linked copolymerization of STY/DVB is a system well studied under regular free radical polymerization conditions, and also some research has already been carried out on the NMRP of STY/DVB in our group[3,4] and in the literature.[8,11–13]

It was decided to use an alkoxyamine unimolecular initiator as opposed to using a nitroxide and a bimolecular approach. An alkoxyamine can act as both initiator and nitroxide upon decomposition. By using a unimolecular approach one can avoid the complications that occur because of the side reactions between nitroxide and the (peroxide) initiator in the bimolecular approach.[14–16] A unimolecular initiator based on TEMPO had been synthesized in our lab and a comprehensive kinetic study on the polymerization of styrene with this unimolecular initiator had been carried out.[10] Based on this experience, it was decided to use a commercially available alkoxyamine initiator, as it would eliminate the difficulties involved in making the unimolecular initiator consistently. After a complete survey of the commercially available alkoxyamine initiators, N-tert-butyl-N-(2-methyl-1-phenylpropyl)-O-(1-phenylethyl)hydroxylamine (TIPNO-based alkoxyamine) was chosen, since based on previous research, relatively faster rates could be achieved using this alkoxyamine.[9,17] When decomposing, this alkoxyamine produces 2,2,5-trimethyl-4-phenyl-3-azahexane-3-oxyle which is known as a TIPNO nitroxide.

1 wt% (with respect to monomer) was chosen for the low level values of both alkoxyamine initiator and cross-linker. For the high level value of the alkoxyamine initiator, 2 wt% was chosen; based on [9], polymerization of styrene with 2 wt% TIPNO-based alkoxyamine had the characteristics of controlled-radical polymerization and gave acceptable rates, without TIPNO slowing the reaction considerably or acting as an inhibitor. Based on our previous experience with cross-linking copolymerization of STY/ DVB,[4] it was noted that handling the polymerization mixture was very difficult with 3 wt% DVB, as the system gelled very quickly and the polymer mixture became very viscous; hence, 1.5 wt% was chosen as the high level for the cross-linker.

Table 1.
Selected factors and their levels (T = temperature, [N] = alkoxyamine concentration, [DVB] = cross-linker concentration).

Level	T (°C)	[N] (wt%)	[DVB] (wt%)
low	120	1	1
high	130	2	1.5

Selection of Responses

It was decided that three responses satisfied our objectives of controlling the polymer production rate and product quality. The responses chosen were: conversion at gel point, gel content at 85% conversion, and weight-average molecular weight at 45% conversion. Conversion at gel point gave

information on the extent of reaction at the gel point and how much the presence of the TIPNO-based alkoxyamine had affected the cross-linking reaction. Gel content and weight-average molecular weight were specified to be measured at particular conversion levels. Gel content was chosen to be measured at 85% conversion because of the interest in obtaining a well-developed polymer network for further characterization. From previous experience,[4] it was known that the presence of the controller (i.e., nitroxide) would delay gelation and a well-developed network was achieved only towards the end of the reaction, therefore, measuring gel content at 85% conversion seemed suitable. Weight-average molecular weight was selected to be measured at 45% conversion because again, based on Tuinman et al.,[4] the copolymer of STY/DVB would gel at higher conversion levels and therefore, it would be impossible to have reliable molecular weight measurements.

The prior variances for the responses, calculated from previous experience, are shown in Table 2. The error associated with conversion is usually considered around 3-5%.[18–20] However, since in cross-linking copolymerization of STY/DVB we are dealing with gels, which means that there might be higher error associated with the conversion measurement, 6% error was considered for conversion, resulting in a prior variance of 360×10^{-3}. The error in gel content was estimated from previous experimental data.[4] The variance of the molecular weight response was calculated from replicated molecular weight measurements available from prior experimental work, which gave a good idea about the variability in weight-average molecular weight. From replicated results, it was calculated that molecular weight values vary by ≈5000 g/mol in the current range of molecular weights, leading to a variance of 2.50×10^{7}.

Table 2.
Prior variances of the responses of interest.

Response	Prior Variance
Conversion at gel point	3.60×10^{-3}
Gel content	7.05×10^{-4}
Molecular weight (weight-average)	2.50×10^{-4}

Incorporation of Prior Knowledge

Having chosen the factors (and their levels) and the response(s) of interest, as illustrated in Figure 1, casting prior information into the vector $\underline{\alpha}$ and the matrix $\underline{U}$ was the next step. $\underline{\alpha}$, the vector of the parameter means, and $\underline{U}$, the variance/covariance matrix of the means, can be considered as the storehouse of prior knowledge. To generate the prior information about the parameters and their variances, a general mechanistic model developed for cross-linking NMRP of styrene was used to obtain the responses for a 2^3 standard factorial design (8 trials). For details about this mechanistic model and the related predicted profiles see Hernandez-Ortiz et al.[21] The computer simulations were run and the corresponding responses were recorded for each of the $2^3 = 8$ trials. $\underline{\alpha}$ (the vector of parameter means) was obtained by performing linear regression on the data and is shown in the second columns of Tables 3, 4 and 5, for the conversion, gel content and weight-average molecular weight responses, respectively. It was decided that the three-factor interaction ($T \times [N] \times [DVB]$)was not important; hence, it was not included in the results.

In order to determine the variances of the parameters, each parameter was examined separately and, based on the expert's prior knowledge of the process, an informed 'guess' of the maximum/minimum value of the parameter was made.

Table 3.
Elements of prior $\underline{\alpha}$ and $\underline{U}$ for conversion at gel point.

Effect	α_i	U_{ii}	Test 1
Mean	0.663	1.00E-04	66.30
T	0.004	4.00E-06	1.97
[N]	0.091	2.03E-03	2.03
[DVB]	−0.052	6.25E-04	−2.07
T × [N]	0.001	4.90E-07	0.79
T × [DVB]	0.001	8.10E-07	1.40
[N] × [DVB]	−0.005	6.25E-06	−2.06

Table 4.
Elements of prior $\underline{\alpha}$ and $\underline{U}$ for gel content at 85% conversion.

Effect	α_i	U_{ii}	Test 1
Mean	0.664	8.10E-05	73.73
T	−0.005	6.76E-06	−1.87
[N]	−0.227	4.00E-04	−11.33
[DVB]	0.139	4.00E-04	6.95
T × [N]	−0.006	9.00E-06	−1.86
T × [DVB]	0.003	9.00E-06	1.16
[N] × [DVB]	0.079	9.00E-04	2.62

Note that the parameter value is one half of the estimated effect (of the variable in question) on the process output. This stage was where most of the brainstorming took place and when the expert's opinion was used to make a calculated guess about the prior elements of the variance/covariance matrix. In the cases where the parameter was considered to be well known, a smaller interval of uncertainty was given, i.e., a smaller fluctuation about the mean was tolerated. The difference between the parameter mean and its maximum or minimum was taken to be 2σ on a normal distribution curve. Dividing this value by 2 and squaring it gives the variance of the parameter. The diagonal elements of the prior variance/covariance matrices ($\underline{U}$) for conversion, gel content and molecular weight responses were calculated in this manner and are shown in the third columns of Tables 3, 4 and 5, respectively. The off-diagonal elements were initially all set to zero.

Scrutinizing the 2nd columns of Tables 3, 4 and 5, one can observe that the values of prior parameters for the temperature effect (for all three responses) were the smallest among the parameter values of the main factors and were closer to the values for the two-factor interactions. Although it was expected that temperature would show a significant effect on our responses, it was decided to keep the related parameter values as they were first arrived at and also assign relatively smaller variances for the temperature effects at the same time. The reason was that the effect of temperature on our responses was considered to be well known. At the same time, we were interested in finding more information about the effects of the TIPNO-based alkoxyamine, the cross-linker and the interaction between them (if there were any present). Therefore, relatively higher initial variances were allocated to these parameters (see the 3rd columns in Tables 3, 4 and 5). The corresponding values for test 1 are shown in the last columns of Tables 3, 4 and 5. This test checked the null hypothesis that $\alpha_i = 0$ purely in the opinion of the ''expert'' (the person who assigned the values for the prior effects and variances). This was essentially a measure of the uncertainty of the ''expert''. A value greater than 2 or less than -2 was considered significant (this is equivalent to a 95.44% confidence interval). Test 1 was defined as the ratio of the prior mean (α_i) to the prior standard deviation (Std) of the mean $(U_{ii})^{1/2}$. As can be seen in Tables 3, 4 and 5, based on the expert's opinion, [N], [DVB] and [N] × [DVB] were considered important factors that would influece all three responses.

Table 5.
Elements of prior $\underline{\alpha}$ and $\underline{U}$ for molecular weight at 45%.

Effect	α_i	U_{ii}	Test 1
Mean	34,607	1.23E + 07	9.89
T	−3,898	4.00E + 06	−1.95
[N]	−22,643	4.90E + 07	−3.23
[DVB]	12,215	2.50E + 07	2.44
T × [N]	3,802	4.00E + 06	1.90
T × [DVB]	−3,656	4.00E + 06	−1.83
[N] × [DVB]	−11,173	9.00E + 06	−3.72

Results and Discussion

Selection of Experimental Designs

It was decided to run a total of 3 experiments in two sequences, 2-trials first followed by 1-trial. As illustrated in Figure 1, the next step is using the prior variances ($\underline{U}$) in the Bayesian design algorithm to choose the design conditions ($\underline{X}$), in order to satisfy the optimality criterion for each response. The optimality criterion is maximization of the determi-

nant H, as illustrated in Figure 1. This determinant is a function of $\underline{U}$, $\underline{X}$ and σ^2, where $\underline{X}$ is the matrix of factor settings (design matrix) and its elements have the values +1 and −1 which correspond to the high and low levels of the design factors, respectively; σ^2 is the variance of the responses (see Nabifar et al.[5–7] for more details on the algorithmic steps). There happened to be four optimal 2-trial designs detected for each response. The optimal experiments from the conversion response were the same as the ones for the molecular weight response. Since two out of the three responses were optimal with the experiments designed for conversion, one of the 2-trial designs from this response was chosen as the 'best' 2-trial for the first sequence.

Table 6 shows the four possible 'optimal' 2-trial experiments. It can be seen that all sets of 2-trial experiments chosen by the Bayesian design follow a similar pattern, and the only setting being changed from the first trial to the second one within the first sequence is the level of [N]. For example, if we look at set No. 1, the first trial is chosen with all the factors at the low level; the second is suggesting to keep the same settings but just change the [N] level from low to high. From our previous experience with the cross-linking NMRP of styrene,[4] we know that it is easier to handle samples at lower levels of cross-linker and temperature. Hence, set No. 1 was chosen as the first sequence of 2-trials. This is, once again, a good demonstration of one of the benefits of the Bayesian design, whereby combining our process knowledge with the Bayesian design approach, we could make a judicious choice of the appropriate experiment, which may be optimal in both statistical and process senses. In the next step of the procedure (see Figure 1), these experiments were run in the lab and the responses were collected, as shown in Table 7. The related experimental details and the profiles of conversion, molecular weights, and gel content versus time will be discussed in detail in another publication and are not shown here.

For all the responses, the posterior variance/covariance matrix was calculated using the prior vector of parameter means ($\underline{\alpha}$), and the prior $\underline{U}$ (shown in the second and third columns of Tables 3, 4 and 5, respecively), along with the $\underline{X}$ matrix (part of it shown in Table 7), and the responses collected via experimentation (reported in the last three columns of Table 7). The updated variance/covariance matrices were then used back into the Bayesian procedure to design (in an iterative sequential fashion) the next sequence of 1-trial that maximized the determinant H for all three responses. This time there was only one set of experimental conditions that maximized the determinant H for all responses. Hence, this was chosen as the second 1-trial sequence and was subsequently carried out in the laboratory.

The settings along with the corresponding responses collected from the single trial are shown in Table 8. As can be seen, the Bayesian design is suggesting to keep the temperature at the low level, while running the experiment at the high levels of [N] and [DVB]. The design suggested by the Bayesian approach made process sense. We ran both trials in the first sequence with low levels of [DVB], hence it made sense to run the experiment in the second sequence at the high level of [DVB], as we were

Table 6.
Four possible 2-trial experiments for the **first** sequence.

No.	T	[N]	[DVB]
1	−1	−1	−1
	−1	1	−1
2	1	−1	−1
	1	1	−1
3	−1	−1	1
	−1	1	1
4	1	−1	1
	1	1	1

Table 7.
Experimental responses for the **first** sequence.

T	[N]	[DVB]	Conversion @ gel point	Gel content @ x = 85%	Molecular weights @ x = 45%
−1	−1	−1	0.617	0.915	53,889
−1	1	−1	0.834	0.484	14,756

Table 8.
Experimental responses for the **second** sequence.

T	[N]	[DVB]	Conversion @ gel point	Gel content @ x = 85%	Molecular weight @ x = 45%
−1	1	1	0.723	0.774	23,682

interested in finding more information about [DVB] (by changing the level of this factor, we could gather more information). Although the temperature level was also kept constant at −1 in the first sequence, since we were relatively certain about T, it was more convenient experimentally to keep T at the low level, and that was also what was suggested by the Bayesian approach. The level suggested by the Bayesian design for [N] also made process sense. As we would be running the experiment at the high level of [DVB], having a higher level for [N] would make it easier to control gelation and avoid a very viscous polymerization mixture, which would be difficult to handle.

Figure 2 shows the visual illustration of all three runs suggested by the Bayesian design for cross-linking NMRP of STY/DVB. As can be seen in trial 1, the suggestion was to run an experiment at 120 °C, with 1 wt% alkoxyamine and 1 wt% cross-linker. The temperature and the cross-linker concentration for trial 2 were the same as in trial 1 (120 °C and 1 wt%, respectively), but the suggestion was to change the alkoxyamine concentration to 2 wt%. Finally, trial 3 was suggested to be run at low temperature (120 °C) and high levels of both alkoxyamine and cross-linker (2 wt% and 1.5 wt%, respectively).

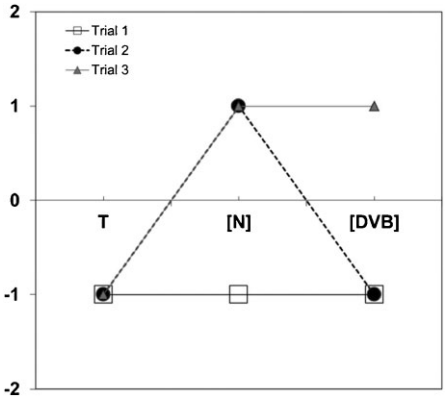

Figure 2.
Visual illustration of the three runs suggested by the Bayesian design for cross-linking NMRP of STY/DVB.

The smallest number of experiments that could be designed through a standard fractional factorial design was four experiments, which is the $\frac{1}{2}(2^3)$. The 4-trial experiment chosen by the fractional factorial design would be completely balanced with respect to all the factors (the levels of all the factors would be changing). Altering the levels of all the factors would be desirable if there were no knowledge available a priori, and the experimenter was equally interested in finding more information about all three factors. However, in our case, since the interest was more focused on finding more information about the effects of the alkoxyamine and the cross-linker on the three responses, changing the level of all factors at the same time would be superfluous. Once again, some of the advantages of the Bayesian design approach were illustrated. There were no restrictions in the number of experiments that could be performed in the Bayesian design method (3 in the Bayesian vs. 4 in the standard fractional factorial). In addition, runs could be 'tailored' to the experimenter's interest with the Bayesian design, where more emphasis could be given to one or two factors only.

Diagnostic Tests

In addition to the analysis presented above, a series of diagnostic tests can be carried out. A detailed discussion about these tests was presented previously,[7] however, whenever necessary, explanations are repeated here as a reminder for the reader. These diagnostic tests serve to quantify the relative importance of the parameters (i.e., factor effects) and their interactions, as well as the quality of prior knowledge (in other words, the adequacy of the model used to generate the ''prior knowledge).

Table 9.
Summary results of diagnostic tests for conversion at gel point response.

Parameter	Prior α_i	$\theta_i^{(2)}$	Prior Std	Std (after 2st seq.)	Test 1	Test 2 (after 2nd seq.)
Mean	0.663	0.664	1.00E-02	9.66E-03	66.30	68.80
T	0.004	0.004	2.00E-03	2.00E-03	1.97	1.95
[N]	0.091	0.102	4.50E-02	2.79E-02	2.03	3.65
[DVB]	−0.052	−0.052	2.50E-02	2.06E-02	−2.07	−2.52
T × [N]	0.001	0.001	7.00E-04	7.00E-04	0.79	0.78
T × [DVB]	0.001	0.001	9.00E-04	9.00E-04	1.40	1.40
[N] × [DVB]	−0.005	−0.005	2.50E-03	2.49E-03	−2.06	−2.04

Results from these statistical diagnostic tests are shown in Tables 9, 10 and 11 for conversion, gel content, and molecular weight responses, respectively. The 2nd columns in all the tables present the initial values of the parameter means ($\underline{\alpha}$), while the 3rd columns contain the updated estimates of the parameter means after the second sequence. The prior standard deviations assigned to each parameter are shown in column 4, while column 5 exhibits the updated values for the standard deviations (Std) after the second sequence. Test 1 is shown in the 6th columns of these tables. As mentioned before, this test is a measure of the uncertainty of the ''expert'' and is defined as the ratio of the prior mean to the prior standard deviation of the mean $[\alpha_i/(U_{ii})^{1/2}]$. A value greater than 2 or less than -2 is considered significant. Results for test 2 after the second sequence are shown in the 7th column. Test 2 is a measure of the actual significance of an effect and can be calculated after each sequence. It is equal to the last updated estimate of the effect, $\underline{\theta}$, divided by the square root of the diagonal element of the posterior variance/covariance matrix (which is equal to the (posterior) standard deviation of the mean value of the parameter; $\left[\theta_i^{(2)}/(U_{post(ii)})^{1/2}\right]$). Once again, a value greater than 2 or less than −2 implies significance.

Results of the diagnostic tests for the conversion response, shown in Table 9, indicate that the TIPNO-based alkoxyamine ([N]) had the highest positive effect on this response. This trend was expected; as [N] was increased, the gel point was

Table 10.
Summary results of diagnostic tests for gel content at 85% conversion response.

Parameter	Prior α_i	$\theta_i^{(2)}$	Prior Std	Std (after 2st seq.)	Test 1	Test 2 (after 2nd seq.)
Mean	0.664	0.690	9.00E-03	8.23E-03	73.73	83.80
T	−0.005	−0.007	2.60E-03	2.58E-03	−1.87	−2.72
[N]	−0.227	−0.160	2.00E-02	1.36E-02	**−11.33**	−11.82
[DVB]	0.139	0.083	2.00E-02	1.36E-02	**6.95**	6.12
T × [N]	−0.006	−0.007	3.00E-03	2.98E-03	−1.86	−2.37
T × [DVB]	0.003	0.005	3.00E-03	2.98E-03	1.16	1.59
[N] × [DVB]	0.079	0.092	3.00E-02	1.53E-02	**2.62**	6.04

Table 11.
Summary results of diagnostic tests for molecular weight at 45% conversion response.

Parameter	Prior α_i	$\theta_i^{(2)}$	Prior Std	Std (after 2st seq.)	Test 1	Test 2 (after 2nd seq.)
Mean	34,607	39,349	3.50E + 03	2.77E + 03	9.89	14.20
T	−3,898	−5,446	2.00E + 03	1.87E + 03	−1.95	**−2.91**
[N]	−22,643	−23,925	7.00E + 03	3.65E + 03	**−3.23**	**−6.56**
[DVB]	12,215	10,102	5.00E + 03	3.29E + 03	**2.44**	**3.07**
T × [N]	3,802	3,906	2.00E + 03	1.94E + 03	1.90	**2.01**
T × [DVB]	−3,656	−3,318	2.00E + 03	1.91E + 03	−1.83	−1.74
[N] × [DVB]	−11,173	−8,214	3.00E + 03	2.52E + 03	**−3.72**	**−3.26**

delayed to a higher conversion. For example, in the first sequence of our experiments (see Table 7), conversion at gel point was shifted from 62% to 83%, when [N] was increased from low to high (i.e., from 1 wt% to 2 wt%). The cross-linker concentration had the second highest effect on conversion; however, this effect was negative, meaning that by increasing [DVB], conversion at gel point was lower. Again, this trend was anticipated; as we increased the amount of cross-linker, the polymer mixture would become more viscous and therefore, would gel sooner (at lower conversions). For example, if the conversion at gel point for the second run in the first sequence (see last row in Table 7) were compared with this response in the second sequence (see Table 8), it could be seen that while keeping T and [N] at the same levels, going from low to high [DVB], would shift (decrease) the conversion at gel point from 83% to 72%.

Our results show that the interaction between [N] and [DVB] was also among the factors influencing the conversion at gel point. (For confirmation purposes, a fourth run was carried out in the laboratory with low level of [N] and high level of [DVB] (complementing the run in the second sequence; see the first settings in run No. 3 of Table 6)). The corresponding interaction plot for [N] and [DVB], based on our experimental data, is shown in Figure 3. As can be seen, at both levels of [N], the cross-linker concentration ([DVB]) had a strong negative effect on conversion at gel point. However, the effect of [DVB] at the low level of [N] (open circles) was not as strong as this effect at the high level of [N] (black squares). Figure 3 illustrates that there was interaction present between [N] and [DVB] (revealed by the nonparallel lines) and this confirmed that our result from test 2 about the [N] × [DVB] parameter was indeed valid (see Table 9), hence the Bayesian design spotted this interaction correctly. It can also be seen that results from test 1 and test 2 were in good agreement, therefore the expert's opinion was valid, and the model used gave reliable trends for the conversion at gel point response.

Table 10 summarizes the diagnostic tests for the gel content response (at 85% conversion). As can be seen, concentration of the TIPNO-based alkoxyamine ([N]) had the highest effect on gel content as well; however, this factor had a negative effect

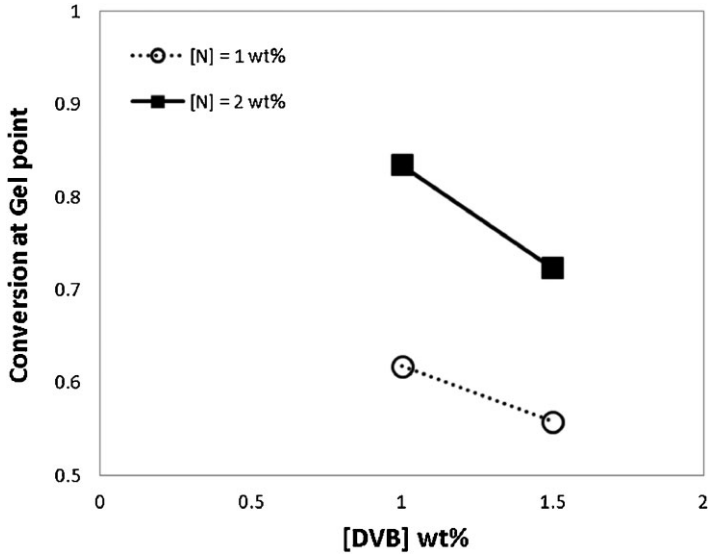

Figure 3.
Interaction plot for [DVB] and [N]: conversion at gel point response.

on the response. This trend made sense; the presence of the alkoxyamine controller ([N]) slows down the reaction and delays the gelation in NMRP, hence, the amount of gel (gel content) produced at 85% conversion will be lower for the run with higher concentration of the alkoxyamine. This trend was observed in our experiments; in the first sequence of our experiments (see Table 7), gel content changed from 0.91 to 0.48 when [N] was increased from the low to the high level (i.e., from 1 wt% to 2 wt%).

On the other hand, [DVB] had a significant positive effect on the gel content, as would have been expected. When the concentration of the cross-linker increases, there will be more gel produced, resulting in higher gel content at 85% conversion. For example, if the gel content at 85% for the second run in the first sequence (see last row in Table 7) is compared with the gel content of the second sequence (see Table 8), it can be seen that while keeping T and [N] at the same level, going from low to high [DVB], shifts (increases) the gel content from 0.48 to 0.77. Again, the interaction between [N] and [DVB] appeared as significant for the gel content response in Table 10. The same as for the conversion response, the interaction plot is shown in Figure 4. Once more, the interaction between [N] and [DVB] was obvious in the nonparallel lines (see open circles and black squares in Figure 4). At both levels of [N], the cross-linker concentration ([DVB]) had a strong positive effect on gel content. However, the effect of [DVB] at the low level of [N] (open circles) was not as strong as this effect at the high level of [N] (black squares). This confirmed that the test 2 result about the [N] × [DVB] parameter (shown in Table 10) was indeed valid, and once more the Bayesian design had correctly spotted this interaction.

Comparing the results of test 1 and test 2 in Table 10, it can be seen that although based on the expert's opinion it was decided to consider temperature and its interactions not important (see Test 1 in Table 10), results from test 2 (which is an indicator of the actual significance of an effect) in Table 10 indicated that T and T × [N] could also be important factors influencing gel content. This result may be pointing to the direction that the mechanistic model's predictions of the gel content response with respect to T might need some correction.

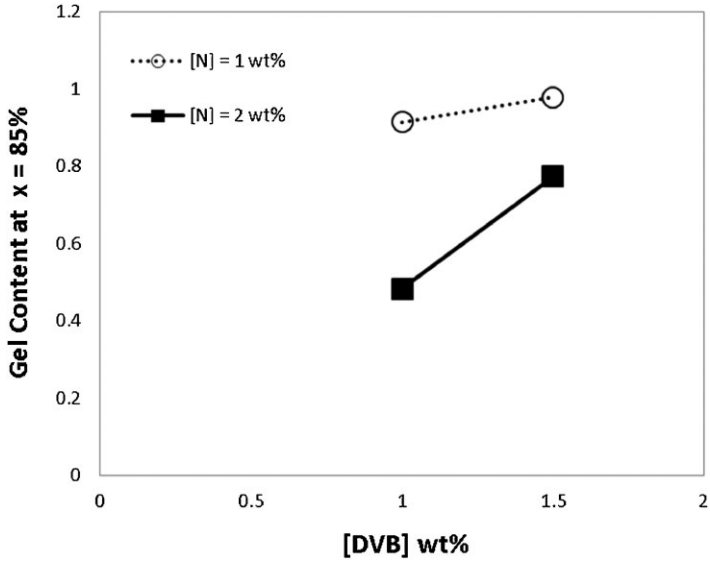

Figure 4.
Interaction plot for [DVB] and [N]: gel content at 85% conversion response.

However, this could as well be an artifact;[18,22] caution should be exercised in the interpretation of the results of the diagnostic tests, as correlation and nonlinearity in the model equations could also cause the results of these tests to become significant. At this point, since we do not have any experimental clarification of the trend recognized by the Bayesian design, we cannot make any comments. Hence, one of the future recommendations will be to run an experiment at the high temperature level (130 °C), and contrast the results obtained for the gel content response with the results from the trial with the low T level.

Finally, Table 11 illustrates the corresponding diagnostic tests for the molecular weight response (at 45% conversion). Again, [N] had the highest negative effect. As [N] increased, the weight average molecular weight at 45% conversion decreased. This is as expected; the inverse relationship between molecular weight and concentration of alkoxyamine initiator has been noted previously and is one of the characteristics of an ideal controlled radical polymerization.[23] On the other hand, [DVB] had a positive effect, meaning that by increasing the cross-linker concentration, molecular weight also increased, which was also expected. Based on the results of test 2 in Table 11, the [N] × [DVB] parameter was also spotted as a significant factor influencing the weight average molecular weight. The interaction plot of [DVB] and [N] for the molecular weight response, shown in Figure 5, offers a visual illustration of this interaction. Although at both levels of [N], the cross-linker concentration ([DVB]) had a strong positive effect on the molecular weight response, the effect of [DVB] at the high level of [N] (black squares) was slightly more significant than this effect at the low level of [N] (open circles).

Again, although based on the expert's opinion (test 1), temperature and its interactions were considered insignificant factors for the molecular weight response, test 2, which demonstrates the actual significance of an effect, was again significant for T and (borderline significant) for [T] × [N] (see Table 11). Temperature was expected to have a relatively significant

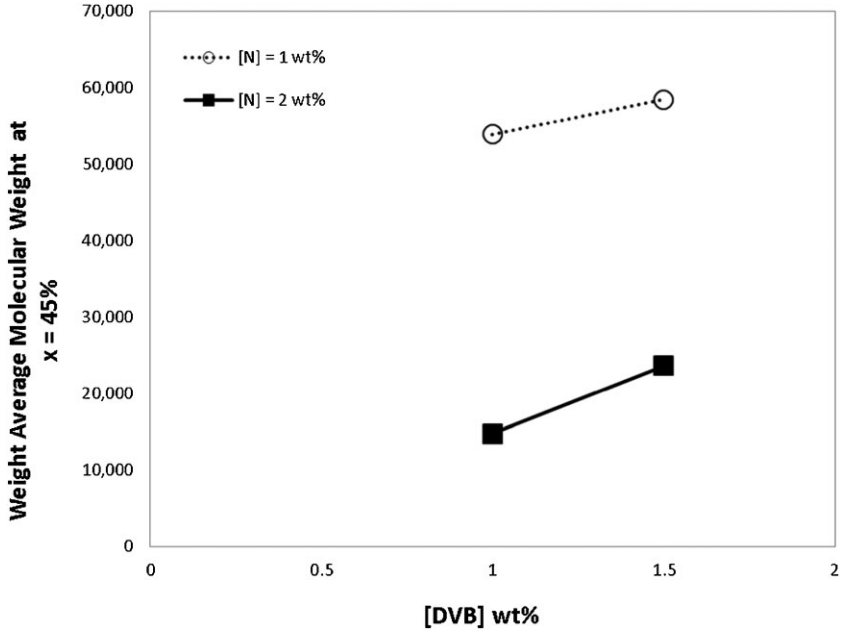

Figure 5.
Interaction plot for [DVB] and [N]: molecular weight at 45% conversion response.

effect on molecular weight, however, the T parameter calculated from the linear (regression) model based on the molecular weight response, as predicted by the non-linear mechanistic model, was smaller compared to the [N] and [DVB] parameters (see α_i for T in Tables 5 and 11). It is interesting to see that the Bayesian design, in fact, had picked this up and the analysis showed that indeed temperature could be an important effect on the molecular weight response. Therefore, either the mechanistic model's predictions of the molecular weight response might need some correction, or there could be some nonlinearities or correlations present that might have caused the test 2 results to be simply an artifact[18,22] (see earlier discussion on Table 10).

Conclusion

The Bayesian design of experiments was successfully implemented to the cross-linking nitroxide-mediated radical copolymerization of styrene and divinyl benzene. The prior knowledge, generated from a mechanistic model already developed for cross-linking NMRP, was used in the Bayesian approach to design three 'optimal' experiments. After conducting these experiments in the laboratory and analyzing the results, we were able to determine the relative importance of the factors in the cross-linking nitroxide-mediated radical copolymerization of styrene and divinyl benzene. The combination of the mechanistic nature of the model used as the prior knowledge generator, the versatility of the Bayesian technique, and our process sense, allowed us to obtain valuable information about the effects of different factors via running a minimal number of experiments!

Our observations that both alkoxyamine concentration and cross-linker concentration were significant factors on the responses of conversion at gel point, gel content at 85% conversion and molecular weight at 45% conversion, were also confirmed via the diagnostic tests that are part of the Bayesian design approach. Results from our diagnostic checks also determined that there were interactions present between [N] and [DVB] for all three responses. Interaction plots corroborated the findings from our diagnostic tests and visually illustrated the interaction between [N] and [DVB]. However, when it came down to the temperature effect, the expert's opinion was not always in agreement with the actual significance of the effect picked up through the diagnostic checks. Hence, further investigations are needed in order to determine whether this discrepancy was indeed true (i.e., the mechanistic model needs improvement with respect to the temperature effect), or simply an artifact caused by nonlinearities and possible correlations induced by the model, which might have caused these slightly anomalous results. The trends observed here from the Bayesian analysis (diagnostic checks) have been experimentally verified and the detailed results will be discussed in a future publication.

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[1] C. S. Patrickios, *Macromolecular Symposia* **2010**, *291-292*, 1.
[2] H. Gao, K. Min, K. Matyjaszewski, *Macromolecules* **2007**, *40*, 7763.
[3] J. C. Hernandez-Ortiz, E. Vivaldo-Lima, L. M. F. Lona, N. T. McManus, A. Penlidis, *Macromol. React. Eng.* **2009**, *3*, 288.
[4] E. Tuinman, N. T. McManus, M. Roa-Luna, E. Vivaldo-Lima, L. M. F. Lona, A. Penlidis, *Macromol. Sci., A: Pure Appl. Chem* **2006**, *43*, 995.
[5] A. Nabifar, N. T. McManus, E. Vivaldo-Lima, P. M. Reilly, A. Penlidis, *Macromol. React. Eng.* **2010**, *4*, 387.
[6] A. Nabifar, N. T. McManus, E. Vivaldo-Lima, A. Penlidis, *Chem. Eng. Tech.* **2010**, *33*, 1814.
[7] A. Nabifar, N. T. McManus, E. Vivaldo-Lima, A. Penlidis, *Macromol. Symposia* **2011**, *302*, 90.
[8] N. Ide, T. Fukuda, *Macromolecules* **1999**, *32*, 95.
[9] M. Drache, K. Mandel, G. Schmidt-Naake, *Polymer* **2007**, *48*, 1875.

[10] M. X. Zhou, N. T. McManus, E. Vivaldo-Lima, L. M. F. Lona, A. Penlidis, *Macromol. Symposia* **2010**, *289*, 95.
[11] N. Ide, T. Fukuda, *Macromolecules* **1997**, *30*, 4268.
[12] P. B. Zetterlund, M. N. Alam, H. Minami, M. Okubo, *Macromol. Rapid Commun.* **2005**, *26*, 955.
[13] P. B. Zetterlund, M. N. Alam, M. Okubo, *Macromol. Chem. Phys.* **2006**, *207*, 1732.
[14] G. Moad, E. Rizzardo, D. H. Solomon, *Tetrahedron Letters* **1981**, *22*, 1165.
[15] M. K. Georges, G. Hamer, A. R. Szkurhan, A. Kazemedah, J. Li, *Abstracts of Papers of the American Chemical Society* **2002**, *224*, U464.
[16] Y. Fu, M. F. Cunningham, R. A. Hutchinson, *Macromol. React. Eng.* **2007**, *1*, 243.
[17] D. Benoit, V. Chaplinski, R. Braslau, C. J. Hawker, *J. American Chem. Society* **1999**, *121*, 3904.
[18] M. A. Dube, A. Penlidis, P. M. Reilly, *J. Macromol. Sci., A: Pure Appl. Chem* **1996**, *34*, 811.
[19] M. Roa-Luna, A. Nabifar, M. P. Diaz-Barber, N. T. McManus, E. Vivaldo-Lima, L. M. F. Lona, A. Penlidis, *J. Macromol. Sci., A: Pure Appl. Chem* **2007**, *44*, 337.
[20] A. Nabifar, N. T. McManus, E. Vivaldo-Lima, L. M. F. Lona, A. Penlidis, *Canadian J. Chem. Eng.* **2008**, *86*, 879.
[21] J. C. Hernandez-Ortiz, E. Vivaldo-Lima, A. Penlidis, *Macromol. Theo. Simul.* **2012**, DOI: 10.1002/mats.201100091.
[22] E. Vivaldo-Lima, A. Penlidis, P. E. Wood, A. E. Hamielec, *J. Appl. Polym. Sci.* **2006**, *102*, 5577.
[23] K. Matyjaszewski, **2002**, Fundamentals of Atom Transfer Radical Polymerization, K. Matyjaszewski,, T. P. Davis Eds. *Handbook of Radical Polymerization*, Hoboken John Wiley and Sons, Inc. (pp. 523–628).

