Steps for Implementing a Bayesian Design Framework: Complex Polymerizations

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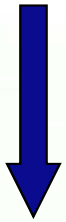
Introduction

- Complex Polymerizations:
  - Some sort of experimental information available from industrial or exploratory laboratory work
  - Mathematical models usually do exist, albeit with unreliable and/or highly correlated parameters



Ideas from model-based design of experiments applied as early as possible beneficial for clarification of polymerization kinetics

Standard Experimental Designs

- Elegant and efficient
- Commonly used in industrial research and development
- However…

Limitations encountered in standard designs
Available resources don't match number of trials
Handling of impractical treatment combinations
Handling of situations with missing observations
Factor levels change in the middle of experimentation
Factors with several (or combinations of) levels
Dropping/adding factors
Incorporation of prior knowledge

Solutions known to experts but practicing scientist or engineer cannot handle them and may give up on use of statistical designs altogether

Ignoring prior information = waste of time, material, and other experimental resources

Bayesian Design of Experiments

- Using a more efficient experimental design which can accommodate previous restrictions can lead to optimal performance in fewer trials, thus saving time and money

- Family of Bayesian design approaches
  - Accommodate practical limitations encountered in standard designs
  - Incorporate prior knowledge into the design to suggest a set of future experiments in an optimal, sequential and iterative fashion
  - Allow use of a nonlinear model along with experimental information (an optimal model-based design of experiments)

Bayesian Design of Experiments (Cont'd)

- Bayesian methodology well established, especially among statisticians
- Based on Bayes' theorem

$$P(\theta \mid y) \propto L(\theta \mid y) \times P(\theta)$$

posterior distribution of θ | likelihood function of θ | prior distribution of θ

- Classical applications: early 1960s
- Recent applications relevant to chemical and process engineering (primarily concerned with (multi)parameter estimation questions):
  - Catalytic systems; pharmaceutical kinetics; drug and cell transport
- Bayesian design of experiments has not been exploited in complex polymerization systems, which could benefit tremendously from its important traits

Research Objectives

- Apply ideas from design of experiments (applied statistical methodology) to :
  - Verify/clarify polymerization kinetics
  - Identify optimal operating conditions to achieve certain polymer properties
  - Refine values of key kinetic parameters of related process models
- To illustrate capabilities and benefits of Bayesian design approach case studies drawn from a representative complex polymerization process are presented

Controlled Radical Polymerization (CRP)

- Synthesis of polymers with controlled / well-defined structure for specialty applications

- Currently most popular approaches to CRP:
  - **N**itroxide-**M**ediated **R**adical **P**olymerization (NMRP)
  - **A**tom **T**ransfer **R**adical **P**olymerization (ATRP)
  - **R**eversible **A**ddition-**F**ragmentation **T**ransfer (RAFT)

Implementation of Bayesian Design in NMRP (Why?)

- Literature on NMRP extensive, but conflicting observations
- Many mechanistic claims, based on few data points over a typical 50 hr polymerization period; replication non-existent
- Modeling efforts sporadic and very "case-specific"
- Design of experiments and systematic, concerted efforts lacking

Bayesian Analysis

- As in any typical modeling scenario, process response(s) related to process settings via a set of parameters in the presence of error

$$\underline{y} = f(\underline{X}, \underline{\theta}^*) + \underline{\varepsilon}$$

- Distribution function for prior knowledge

$$\underline{\theta}^* : N[\underline{\alpha}; \underline{U}]$$

$\underline{y}$: n X 1 vector of observations
$\underline{X}$: n X p matrix of process information
n : number of trials
p : number of parameters
$\underline{\theta}^*$: p X 1 vector of parameters
$\underline{\varepsilon}$: n X 1 vector of errors; N (0, $I\sigma^2$)
$\underline{\alpha}$: p X 1 vector of parameter means
$\underline{U}$: p X p variance/covariance matrix of parameter means

Bayesian Analysis (Cont'd)

- Bayes' theorem gives the posterior (updated) distribution of $\underline{\theta}^*$:

$$\hat{\underline{\theta}} = [\underline{U}^{-1} + (1/\sigma^2)\underline{X}'\underline{X}]^{-1}[\underline{U}^{-1}\underline{\alpha} + (1/\sigma^2)\underline{X}'\underline{y}]$$

$$\underline{U} = [\underline{U}^{-1} + (1/\sigma^2)\underline{X}'\underline{X}]^{-1}$$

- Design problem: choose the "best" n-trial fraction of a full factorial experiment

- Design criterion: select experiments to maximize

$$H = \left|\underline{U}^{-1} + (1/\sigma^2)\underline{X}'\underline{X}\right|$$

Design Four Optimal Experiments: Bimolecular NMRP

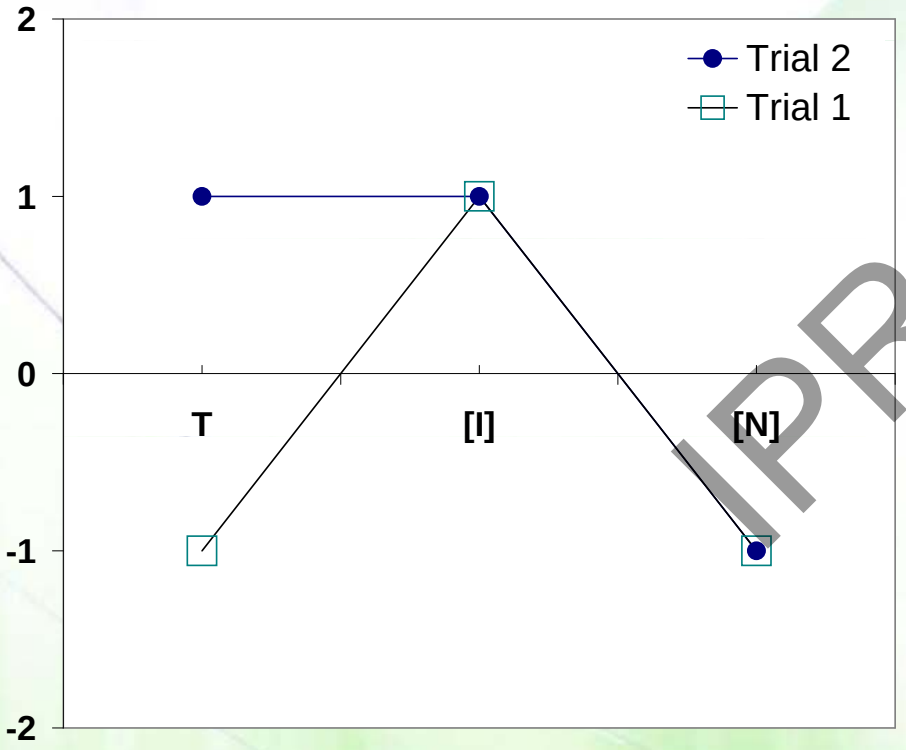
- Choose design factors and their levels

Factors	Level (Low)	Level (High)
T (°C)	120 °C	130 °C
$[I]_0$ (M)	0.036	0.072
$[N]_0$ (M)	0.058	0.082

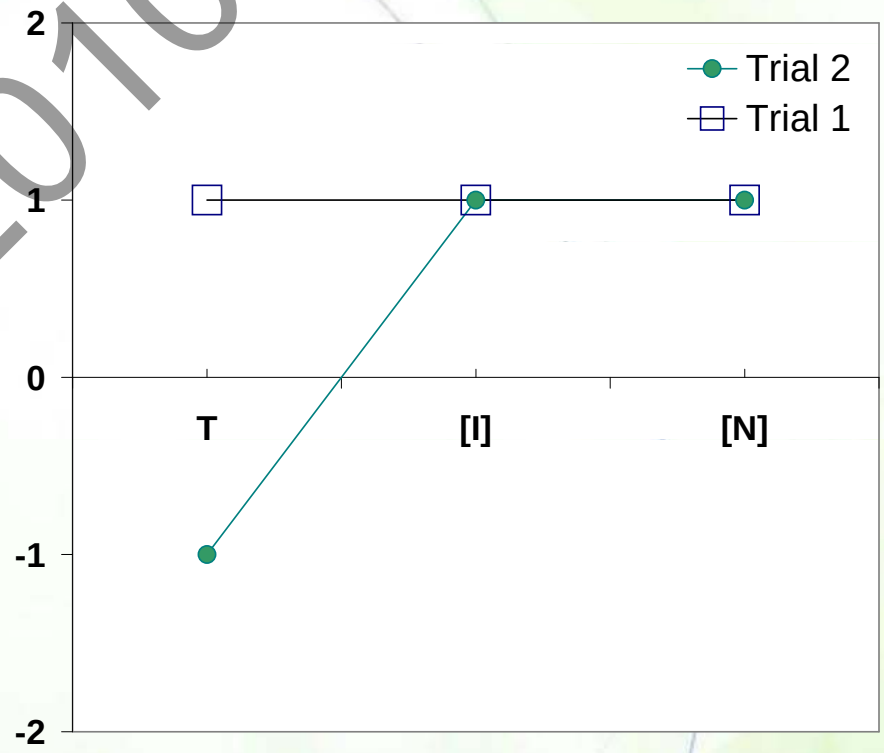
- Single response: batch time at 75% conversion
- Incorporation of prior knowledge
  - To generate the prior : 2^3 conventional factorial design was simulated with a general mechanistic model developed for bimolecular NMRP
  - For simplicity, linear regression on the data : vector of parameter means ($\underline{\alpha}$)
  - "Brainstorming" on the maximum/minimum value of the parameters: variance ($\underline{U}$)

Two sequences of 2-trials each

- First sequence of a 2-trial experiment



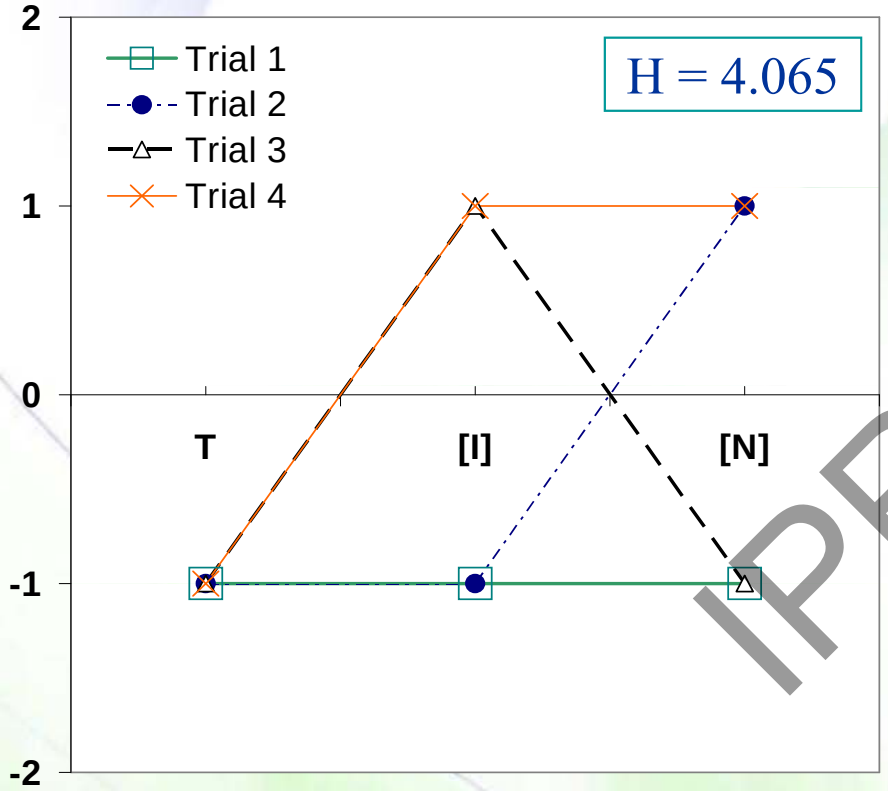
- Second sequence of 2-trials using updated U



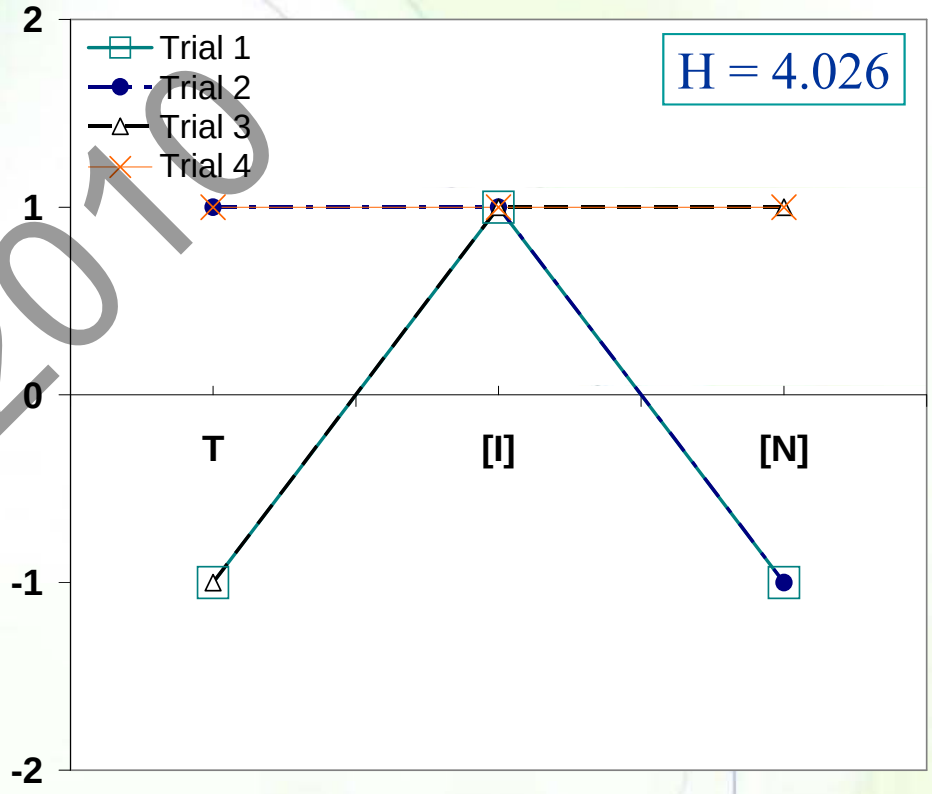
- Level of T is changing between trials in each sequence

Single 4-trial experiment

- Single 4-trial experiment



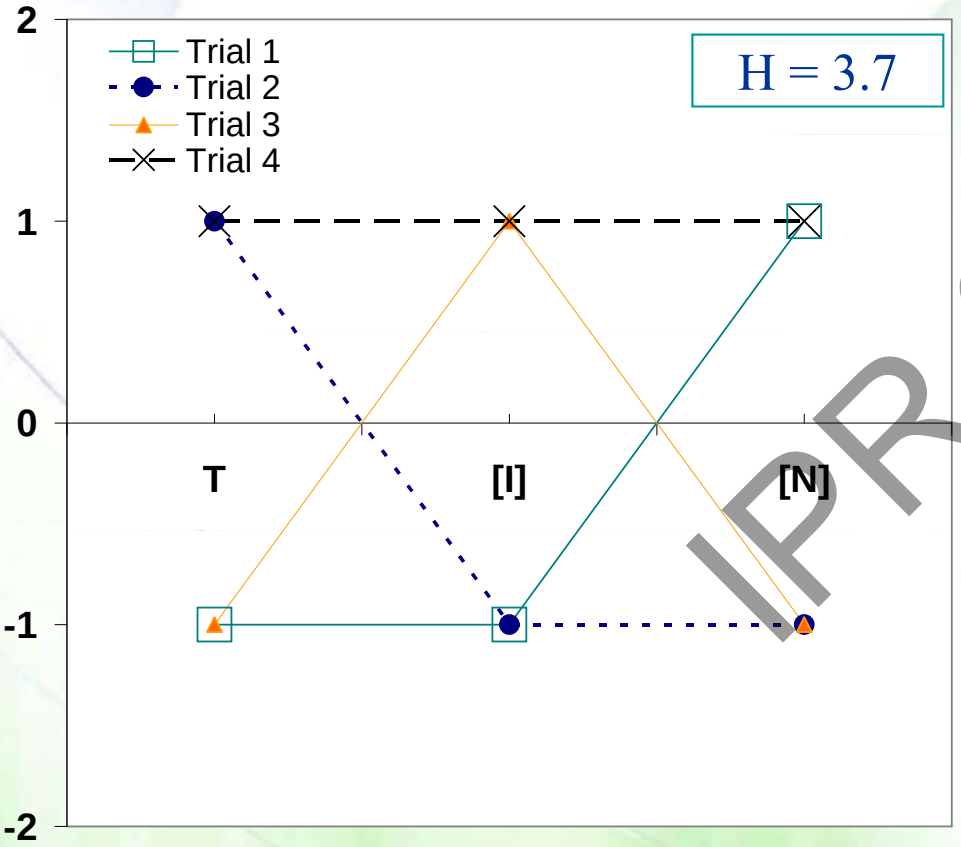
- Two sequences of 2-trials each



- Sequential approach offers more flexibility (e.g., changing the level of factors, adding/dropping factors, etc.)

Comparison with Fractional Factorial

- Half-fraction of 2^3 full factorial



- Comparing H-values, all experiments designed through Bayesian approach superior to ones designed through conventional fractional factorials
- If experimenter is more interested in effect of only a subset of factors, changing the level of all factors at the same time is superfluous
- Fractional factorial: resolution III

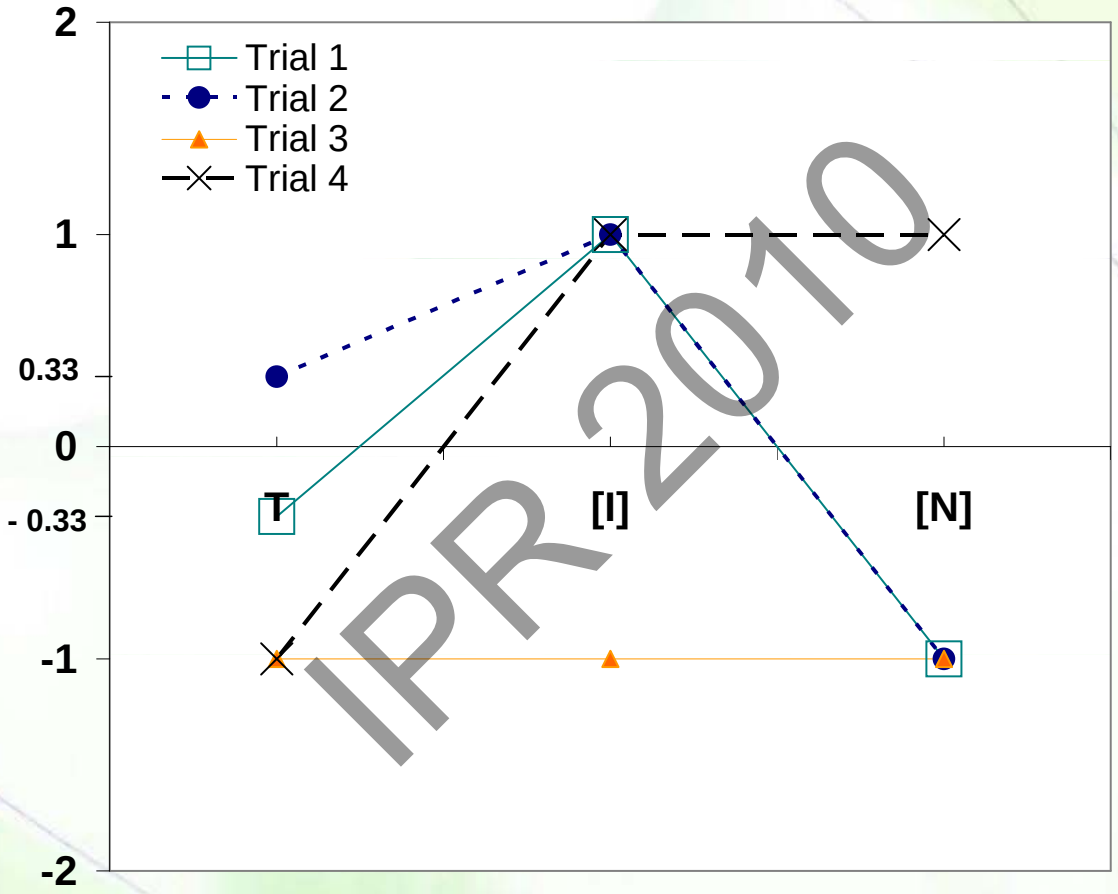
Bayesian approach: no confounding

Expand Factor Range

- Not permitted in conventional factorial designs
- Example: change temperature levels to 110 (-) and 140 °C (+) in the second sequence in order to expand the factor range
  - Demonstrate another advantage of the Bayesian design: flexibility to change factor levels in the middle of experimentation
- Coding for the first sequence revised

T	[I]	[N]
-0.33	1	-1
0.33	1	-1

Expand Factor Range (Cont'd)



- Change in coding of the temperature levels after the first sequence, resulted in temperature attaining more than two levels ("exposed" more process information; leads naturally to studying nonlinearities!)

Design Three Optimal Runs: Unimolecular NMRP

- Choose design factors and their levels

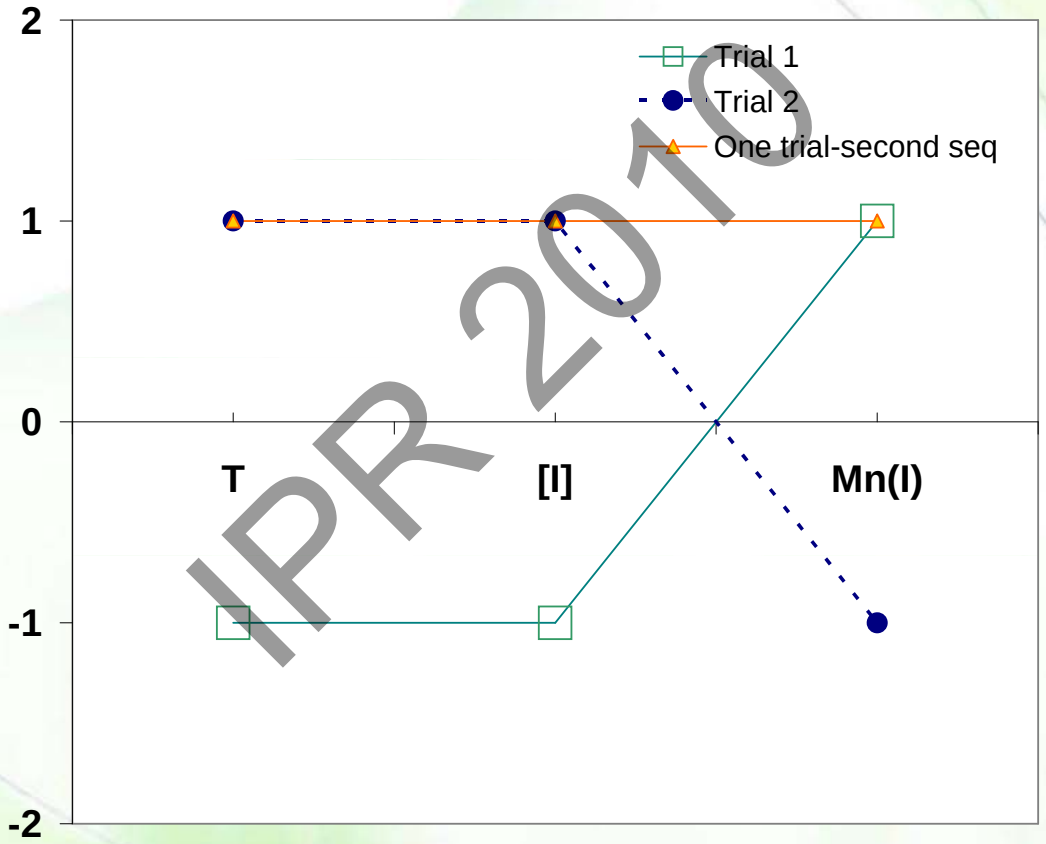
Factors	Level (Low)	Level (High)
T (°C)	120 °C	140 °C
[I] (M)	0.03	0.05
M_n[I] * (g/mol)	2200	6200

*Mn[I]: number average molecular weight for the unimolecular initiator

- Different response now: number average molecular weight at 50% conversion
- To generate the prior : 2^3 conventional factorial design with the following model: $Mn = \frac{[M]_o - [M]_t}{[I]_0} \times MWsty$
- Scenario: 2 trials were designed; can afford extra run

Analysis of Results

- Illustration of 3 runs suggested by Bayesian design



- Statistical diagnostic tests to quantify relative importance of parameters and quality of prior knowledge

Analysis of Results (Cont'd)

Effect	αi	θi	Test 1	Test 2	Test 3
Mean	9213	10576	**3.68**	**18. 96**	0.0044
T	-98	-112	-0.87	-1.01	-0.0011
[I]	-2686	-2909	**-5. 97**	**-8.00**	-0.0017
M_n[I]	-730	-222	-1.46	-0.58	0.0034
T*[I]	30	30	**2.02**	**2.02**	0.0002
T * M_n[I]	11	22	0.09	0.18	0.0007
[I] *Mn[I]	-3	13	-0.02	0.09	0.0007
T * [I]* M_n[I]	-0.25	11.17	-0.003	0.15	0.0020

- **Test 1**: Initiator concentration, [I], and interaction between temperature and initiator (T*[I]) are influential factors on molecular weight
- **Test 2** verifies the actual significance of an effect; in agreement with expert's opinion
- **Test 3** implies that expert's opinion is valid; the model used seems reliable
- 12 runs (literature) vs. **ONLY** 3 (Bayesian)!!

Concluding Remarks

- Bayesian approach
  - Improvement in *information content* retrieved from data compared to conventional designs (case study 1)
  - *Flexibility to change levels of factors* with relative ease (case study 2)
  - Flexible and "cost"- effective with respect to the *number of experiments* (case study 3)
  - *Incorporation of prior knowledge* into the design (all case studies)
  - Inherent *sequential nature* of the design method with any number of runs (case studies 1 and 3)

Concluding Remarks (Cont'd)

Overview of Issues handled in my research
Sources of prior knowledge (screening experiments vs. models)
Effect of informative vs. non-informative priors
Accommodating factor level and range changes and/or extra trial(s) mid-way through experimentation
Designing n-trial experiments vs. sequences of fewer trials
Diagnostic criteria for the quality of prior knowledge and significance of estimated effects
Single vs. multi-response scenarios
Handling process constraints and impractical treatment combinations
Reduction in overall number of experiments
Increase of information content, flexibility and cost effectiveness

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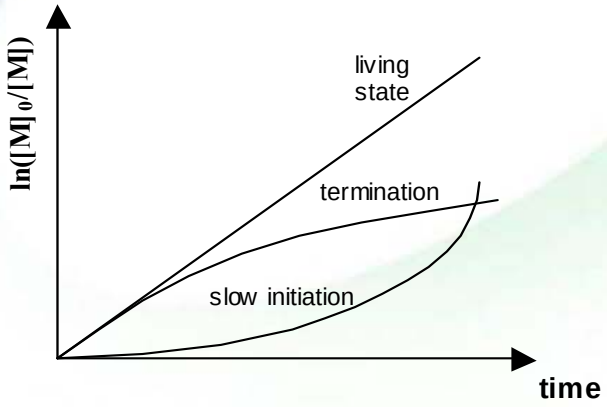
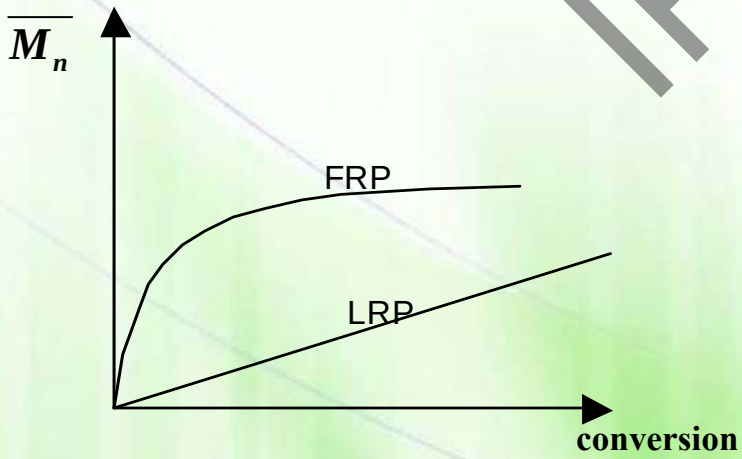
Typical Features

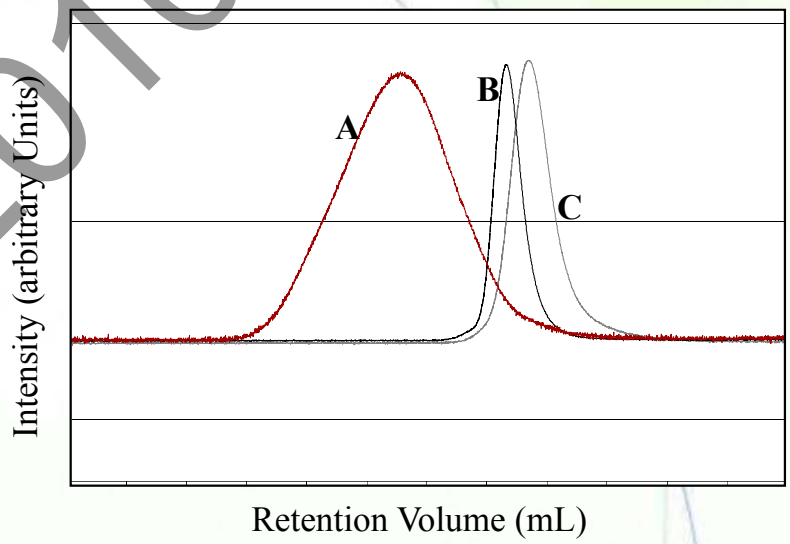
- First order kinetic plot



- Linear increase of MW with x



- Narrow molecular weight distribution; low polydispersity



A: regular radical polymerization
B: Anionic polymerization
C: Controlled radical polymerization

Kinetic Mechanism (Bonilla et al., 2002)

Description	Step
Chemical initiation	$I \xrightarrow{k_d} 2R_{in}\bullet$
Nitroxyl ether decomposition	$NO_E \underset{k_{d2}}{\overset{k_{a2}}{\rightleftarrows}} R_{in}\bullet + NO_x\bullet$
Mayo dimerization	$M + M \xrightarrow{k_{dim}} D$
Thermal initiation	$M + D \xrightarrow{k_{ia}} D\bullet + M\bullet$
First propagation (primary radicals)	$R_{in}\bullet + M \xrightarrow{k_p} R_1\bullet$
First propagation (monomeric radicals)	$M\bullet + M \xrightarrow{k_p} R_1\bullet$
First propagation (dimeric radicals)	$D\bullet + M \xrightarrow{k_p} R_1\bullet$
Propagation	$R_r\bullet + M \xrightarrow{k_p} R_{r+1}\bullet$
Dormant living exchange (monomeric alkoxyamine)	$M\bullet + NO_x\bullet \underset{k_{da}}{\overset{k_a}{\rightleftarrows}} MNO_x$
Dormant living exchange (polymeric alkoxyamine)	$R_r\bullet + NO_x\bullet \underset{k_{da}}{\overset{k_a}{\rightleftarrows}} R_rNO_x$
Alkoxyamine decomposition	$MNO_x \xrightarrow{k_{decomp}} M + HNO_x$
Rate enhancement reaction	$D + NO_x\bullet \xrightarrow{k_{h3}} D\bullet + HNO_x$
Termination by combination	$R_r\bullet + R_s\bullet \xrightarrow{k_{tc}} P_{r+s}$
Termination by disproportionation	$R_r\bullet + R_s\bullet \xrightarrow{k_{td}} P_r + P_s$
Transfer to monomer	$R_r\bullet + M \xrightarrow{k_{fM}} P_r + M\bullet$
Transfer to dimer	$R_r\bullet + D \xrightarrow{k_{fD}} P_r + D\bullet$

U Matrix for Case Study 1

$$U = \begin{pmatrix} 0.01 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0.25 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0.0625 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0.04431 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0.003906 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0.005625 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.0625 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.015625 \end{pmatrix}$$

Choosing the Optimal Design

- Two approaches have been used:
  - Monte Carlo approach: design a large number of different locally optimal experiments
  - Exhaustive search based on using Wegner's theorem (provides an upper bound on the determinant of a matrix)

Procedure for the Bayesian Design

Steps
1. Select the design factors and their levels; select responses
2. Cast the prior knowledge into a vector of prior parameter estimates and a prior variance/covariance matrix
3. Select the "best" experiments using a search algorithm
4. Analyze the experiments
5. Update the prior variance/covariance matrix (U) and vector of parameter estimates (θ)
6. Given the new variance/covariance matrix, select the next sequence of experiments. Analyze the experiments and update θ and U, accordingly
7. Repeat step 6 until the final sequence; select the last sequence of "optimal" experiments; after the analysis of the experiments, update the vector of the parameters, for the last time

Statistical Tests

- **Test 1**: measures uncertainty of the "expert"; ratio of prior means to prior standard deviations of the means [$\alpha i/(Ui)^{1/2}$] and tests the null hypothesis that $\alpha i = 0$ purely in the opinion of the ''expert''

- **Test 2**: measures the actual significance of an effect; the last updated estimate of effect divided by square root of diagonal element of the last posterior variance/covariance matrix

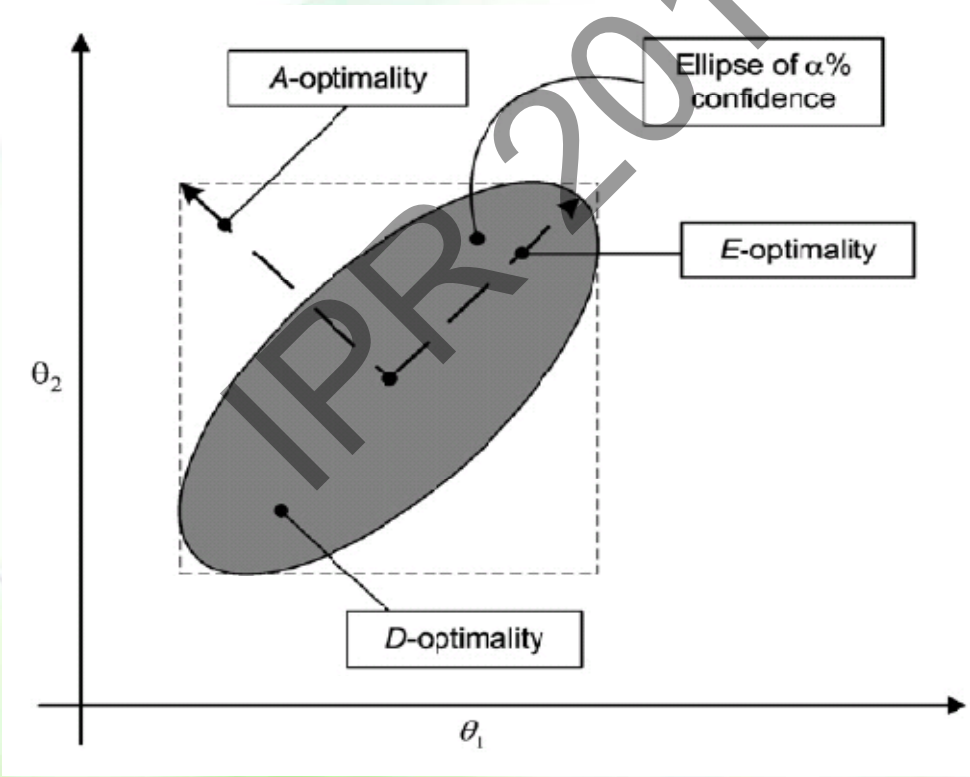
- **Test 3**: measures the quality of expert's opinion; equal to ($\underline{\theta}_i$ - αi) divided by the square root of the diagonal element of the last posterior variance/covariance matrix

Future Steps

- Use fully non-linear models in Bayesian design
- Combine Bayesian methodology with statistical criteria to reduce parameter correlation (**focus** on parameter values)
- Apply full Bayesian scheme to other polymerization processes with uncertain models/parameters, especially in industrial settings (examples: Emulsion copolymerization of NBR/SBR rubber; NMRP in supercritical carbon dioxide, etc.)

Most Common Criteria

- D-optimality: minimizes the determinant of the variance–covariance matrix
- E-optimality: minimizes the largest eigenvalue of the variance–covariance matrix
- A-optimality: minimizes the trace of the variance–covariance matrix



Criteria for Correlation Reduction

Criterion	Objective
A	Reduce the correlation between the parameters by minimizing all or some of the correlation coefficients
B	Reducing the correlation between the parameters as in criterion A, **subject to** an acceptable level of information content for the experiments (measured through one or more of the eigenvalues of the variance/covariance matrix; as in E-optimal design)
C	Maximize the information content of the experiment (as in E-optimal design), **subject to** an acceptable value of correlation between individual parameter pairs
D	Reduce the correlation between the parameters as in criterion A, **subject to** acceptable values of the variances of specified parameters (targeted experiments)

Emulsion Copolymerization of NBR/SBR

- Both complicated and largely unstudied
- Parameter uncertainties and conflicting statements in the limited literature with respect to factor effects
- Detailed model in our group (Washington) : good starting point for the Bayesian scheme
- Due to a long-term contract, access to industrial (pilot-plant and plant) data
- What are we planning to do?
  - Conduct the initial very important brain-storming phase
  - Guide a design of experiments to take place at the company site (pilot-plant scale), in order to generate further experimental data

Multi-Component Polymerization with Depropagation at Elevated Temperature

- All the equilibrium constants unknown
- Industrial interest; running experiments at high temperatures including acrylates and methacrylates: depropagation important
- Mathematical model developed in our group with depropagation : Leamen and Jung
- Data available from Leamen that can be used as “prior knowledge” in the Bayesian design

NMRP in Supercritical CO_2

- Emerging technology; green solvent; heterogeneous system
- Luxury of interacting with a group from UNAM University (Prof. Vivaldo-Lima) which has been working on using supercritical carbon dioxide in CRP systems
  - Waterloo providing the suggestion of new experimental regions
  - UNAM conducting the experiments and corroborating with model predictions
- Additional data: Prof. Tzoganakis's group in our department

NMRP in the Presence of Cross-linking

- Having both controlled behaviour and cross-linking characterization; potential for producing homogeneous networks
- Detailed mathematical model for NMRP copolymerization of styrene and divynyl benzene being developed by Ortiz et al. (UNAM, Mexico)
- Preliminary experimental results are available from Tuinman et al. and Ximenes