MODEL DISCRIMINATION AND ESTIMABILITY ANALYSIS IN EARLY PROCESS DEVELOPMENT

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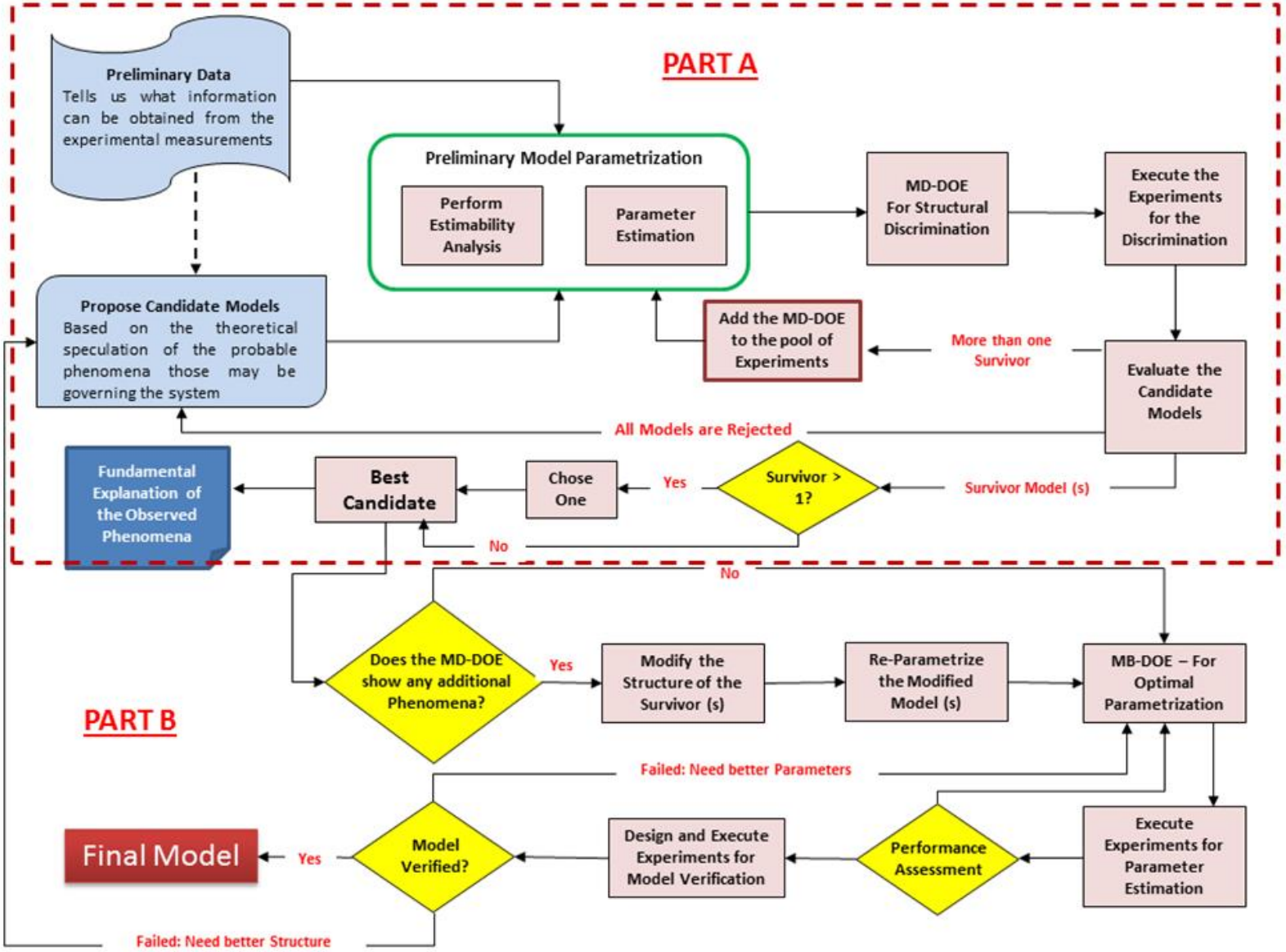
Model Development Scheme



Introduction

At the development of any modeling exercise, the modeler needs to identify the best mathematical structure to represent the system and at times that implies the need to choose among various candidate models.

Examples:

In chemical kinetic identification, the observed measurements could be explained by various candidate reaction pathways, which one is better?

Model Discrimination Design of Experiments (MD-DOE) is a model based technique that uses optimization technology to determine the best experiment to assist in the decision of what model is more appropriate to represent the system. Calculated conditions are intended to maximize the difference in the predictions among the candidate models.

Introduction

Steps of performing Model Discrimination:

1. Develop the different candidate models.
2. Perform a preliminary parameter estimation of the estimable parameters.
3. Identify the measurable variables and the manipulated variables and their corresponding uncertainty.
4. Perform the MD-DOE (Model Discrimination- Design of Experiment) calculation ➔ Experimental conditions
5. Perform the Experiment at the calculated conditions.
6. Contrast results against predictions from each candidate model
7. Model whose prediction is closer to result is the better candidate!

Case Study 1: Mechanism comparison

*Each letter represents a chemical species
AH is the starting material. D and M are the reacting reagents

Tom's Mechansim

- R1: $AH + D \xrightarrow{k1} Ra1^*$
- R2: $Ra1^* \xrightarrow{k-1} AH + D$
- R3: $D + M \xrightarrow{k2} Ra2^*$
- R4: $Ra2^* \xrightarrow{k-2} D + M$
- R5: $Ra2^* + Ra1^* \xrightarrow{k3} D + H + Ra3^*$
- R6: $Ra3^* \xrightarrow{k4} Product + D + C$

Ra1* , Ra2* and Ra3* are intermediates

Stan's Mechanism

- R1: $D + M \xrightarrow{k1} Ra1^* + C$
- R2: $Ra1^* + AH \xrightarrow{k2} Ra2^* + H$
- R3: $Ra2^* + H \xrightarrow{k-2} Ra1^* + AH$
- R4: $Ra2^* \xrightarrow{k3} Product + D$
- R5: $Ra1^* \xrightarrow{k4} D + O$

Ra1* and Ra2* are intermediates

Parameter estimation

Reaction rate constants are the unknown parameters

Tom's Model: k_1, k_{-1}, k_2, k_{-2}, k_3 and k_4

Arrhenius Equation

$k_1 = A_1 e^{(-E_1/RT)} \rightarrow k_1 = f(A_1, E_1)$

$k_{-1} = f(A_{-1}, E_{-1})$, $k_2 = f(A_2, E_2)$, $k_{-2} = f(A_{-2}, E_{-2})$, $k_3 = f(A_3, E_3)$, $k_4 = f(A_4, E_4)$

Frequency factor: A_1, A_{-1}, A_2, A_{-2}, A_3 and A_4

Activation energy: E_1, E_{-1}, E_2, E_{-2}, E_3 and E_4

Stan's Model: k_1, k_2, k_{-2}, k_3 and k_4

Arrhenius Equation

Frequency factor: A_1, A_2, A_{-2}, A_3 and A_4

Activation energy: E_1, E_2, E_{-2}, E_3 and E_4

Tom's Model: 12 unknown parameters

Stan's Model: 10 unknown parameters

Experiments (for parameter estimation)

	AH (Initial mass) (mg)	D (Initial Volume) (µL)	M (Initial Volume) (µL)	Temperature (C)	Volume of reaction (mL)
Experiment 1	35	85	750	75	0.87
Experiment 2	72	170	760	55	1.002
Experiment 3	72	170	760	75	1.002

Measures Variables:

1) Concentration of AH vs time
2) Concentration of D vs time
3) Concentration of Product vs time
4) Concentration of Impurity vs time

Discrepancy in structure of the impurity, so not included for parameter estimation

Estimability Analysis

- Ranking exercise seeking to aid the modeler in the selection of the parameters to estimate.
  - And the parameters to fix and forget.

MATHEMATICAL MODELLING OF CHEMICAL PROCESSES—OBTAINING THE BEST MODEL PREDICTIONS AND PARAMETER ESTIMATES USING IDENTIFIABILITY AND ESTIMABILITY PROCEDURES

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Estimability analysis

1. Perform a parameter estimation ModelBuilder

2. Use those initial values to perform the parameter estimability MATLAB™ (MathWorks) and gO:MATLAB was used.

3. Fix the non estimable (or least estimable) parameters and estimate the top ranked ones.

- Kevin A. P. McLean and Kim B. McAuley, 2012, The Canadian Journal of Chemical Engineering 90 351-366

Rank of the remaining parameters

Rank	Stan's Model	Tom's Model
1	E_1	E_2
2	E_3	E_1
3	E_2	E_{-2}
4	E_4	E_4
5	A_1	A_2
6	A_3	A_1
7	E_{-2}	A_{-2}
8	A_2	E_3
9	A_4	E_{-1}
10	A_{-2}	A_3
11	--	A_4
12	--	A_{-1}

Stan's Model: Parameter Values (Set 1)

Model Parameter	Final Value
A_1	2.07864×10^{8}
A_2	3.45822×10^{10}
A_{-2}	3.92475×10^{6}
A_3	2.0225×10^{10}
A_4	2.37114×10^{8}
E_1	92815.1
E_2	41924.7
E_{-2}	2761.25
E_3	84495.1
E_4	199601

Final Objective Function (Maximum Likelihood) : 684.602

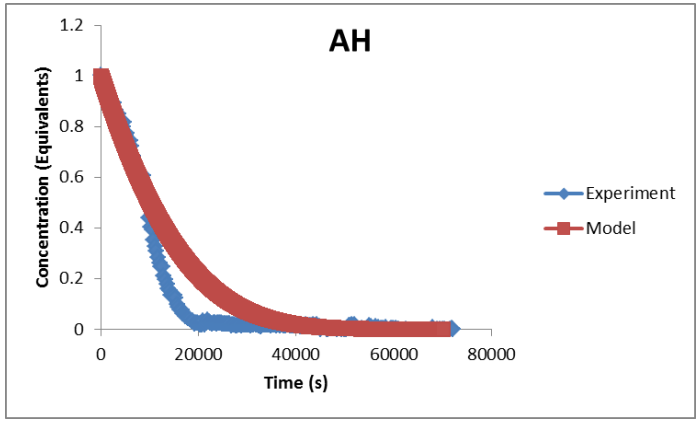
- The fit obtained from the model using this set of parameters is not satisfactory
- There is a possibility of further improvement

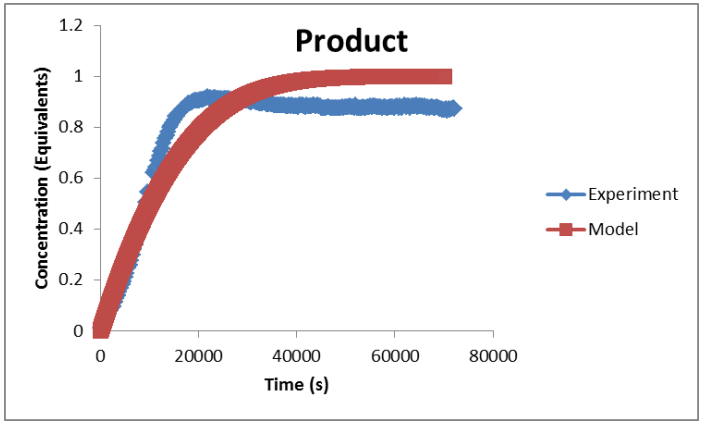
Model Fit Results

Experimental vs Model predicted result for Experiment 1

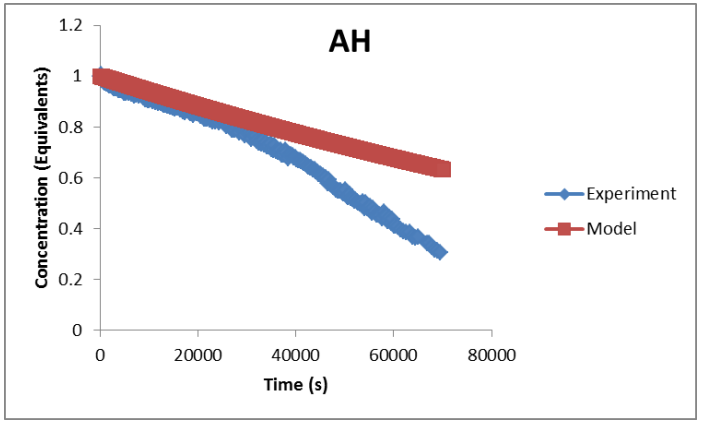
Parameter Values (Set 1)

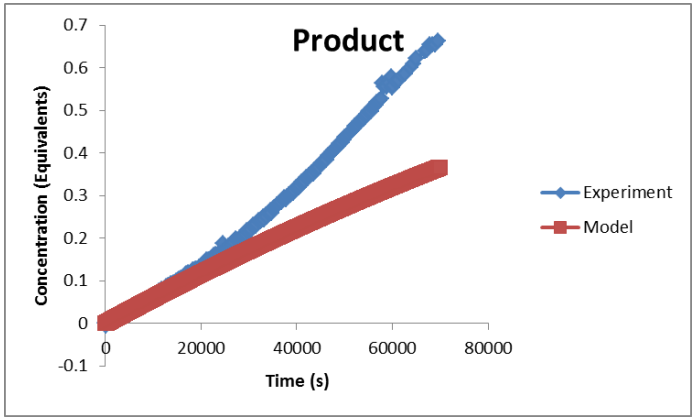
Experiment 1





Experiment 2





- There is scope to improve the fit of the model.
- The fit of the model prediction for Experiment 2 (55 C) is not satisfactory

Rank of the remaining parameters

Rank	Stan's Model
1	E_1
2	E_3
3	E_2
4	E_4
5	A_1
6	A_3
7	$\mathbf{E_{-2}}$
8	A_2
9	$\mathbf{A_4}$
10	$\mathbf{A_{-2}}$
11	--
12	--

Parameter Values

Model Parameter	Final Value	Standard Deviation
A_1	4.87665×10^{7}	2.049×10^{7}
A_2	4.04754×10^{11}	5.128×10^{11}
A_{-2} (Fixed)	3.92475×10^{6}	
A_3	2.96637×10^{10}	6.695×10^{11}
A_4 (Fixed)	2.37114×10^{8}	
E_1	88497.5	1208
E_2	95946.7	3560
E_{-2} (Fixed)	62805.2	
E_3	83140.5	6.316×10^{4}
E_4	93212.7	312.4
Reference t-value (95%):		1.646

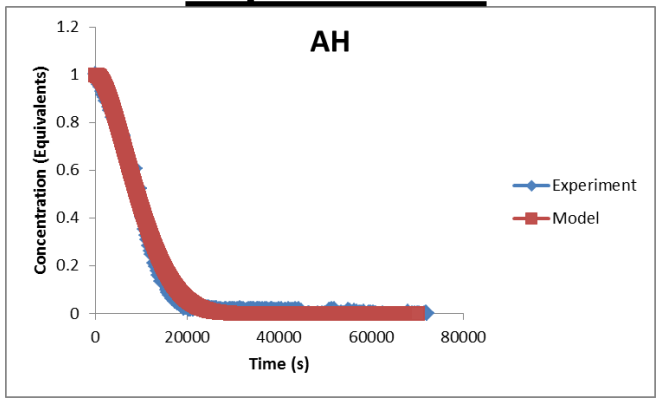
Final Objective Function (Max. Likelihood): -2819.35

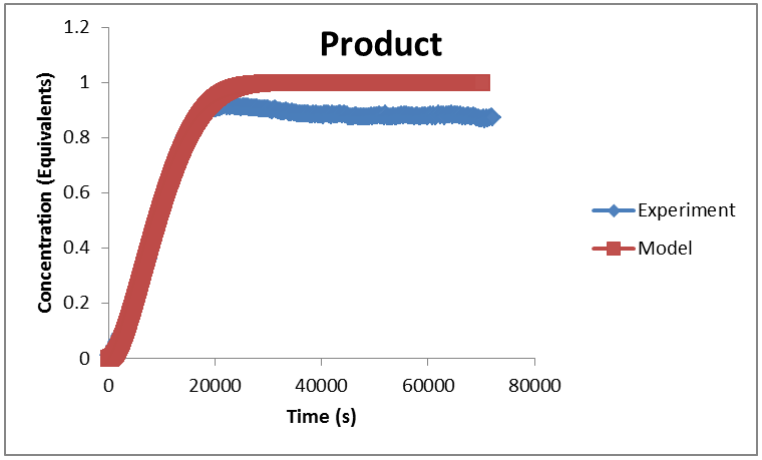
- The statistics of the estimated parameters improves further

Parameter Estimation Results

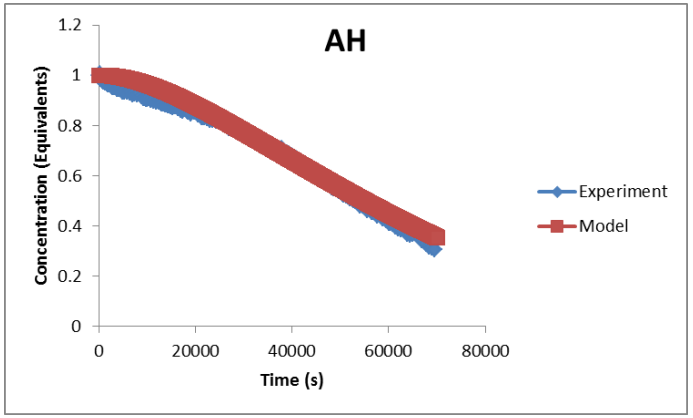
Model fit obtained after parameter estimation incorporating estimability analysis

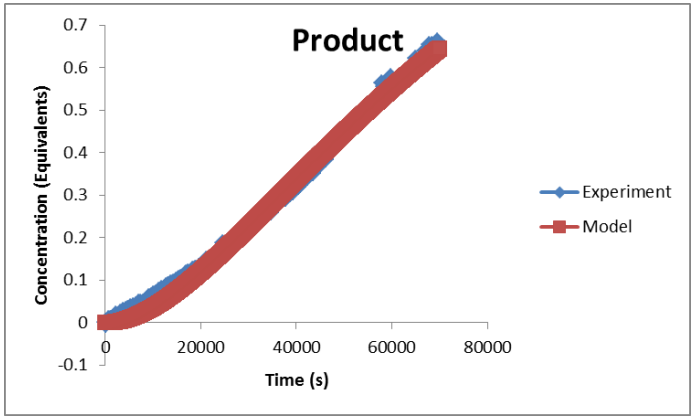
Experiment 1





Experiment 2





Tom's Model: Parameter Values

Model Parameter	Final Value
A_1	1×10^{11}
A_{-1}	1.88835×10^{9}
A_2	8.91386×10^{9}
A_{-2}	7.892×10^{9}
A_3	5.99256×10^{7}
A_4	7.83085×10^{10}
E_1	100073
E_{-1}	583314
E_2	588963
E_{-2}	80838.6
E_3	545723
E_4	67914.7

Final Objective Function (Maximum Likelihood): 640.064

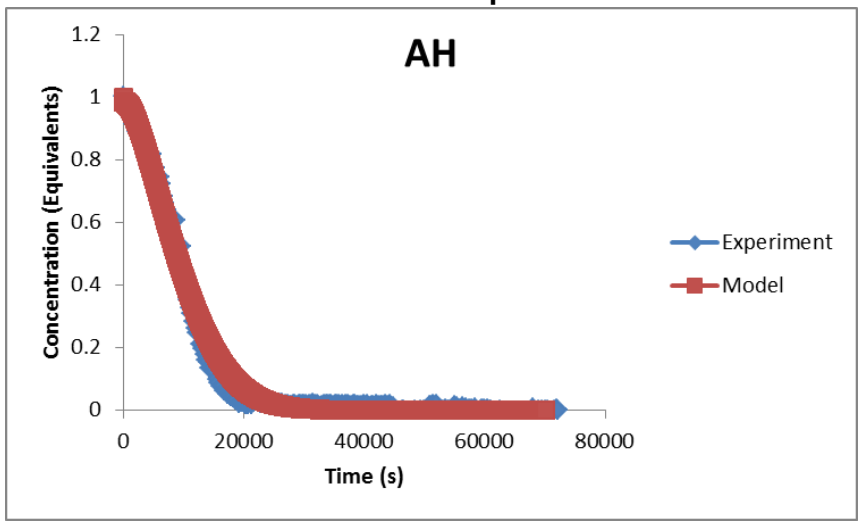
Parameter Values post Estimability

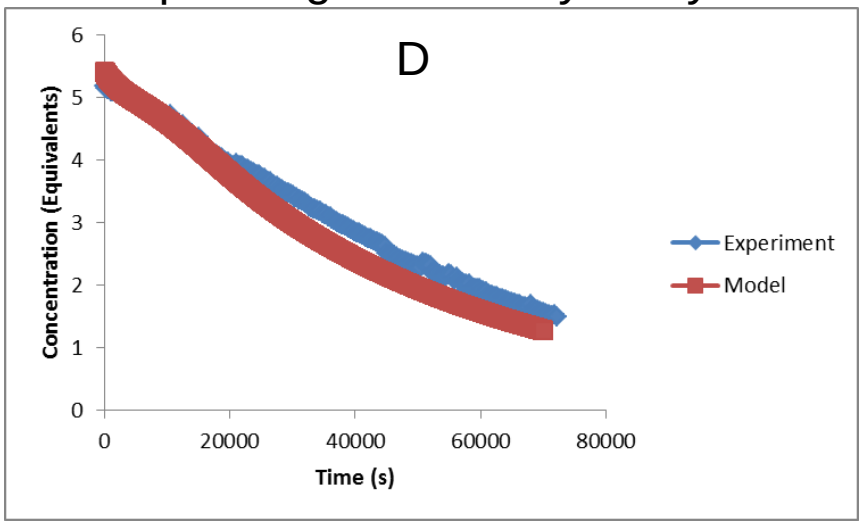
Model Parameter	Final Value	Standard Deviation
A_1	2.19037×10^{13}	6.52×10^{13}
A_{-1} (Fixed)	1.04458×10^{6}	
A_2	1.05307×10^{6}	2.427×10^{6}
A_{-2}	2.01167×10^{8}	1.558×10^{11}
A_3 (Fixed)	2.4808×10^{7}	
A_4 (Fixed)	5.2834×10^{8}	
E_1	115053	8092
E_{-1}	186834	7.808×10^{21}
E_2	77745.9	6648
E_{-2}	94246	2.242×10^{6}
E_3	59698.1	613.5
E_4	12944.5	2.22×10^{8}
Reference t-value (95%):		1.646

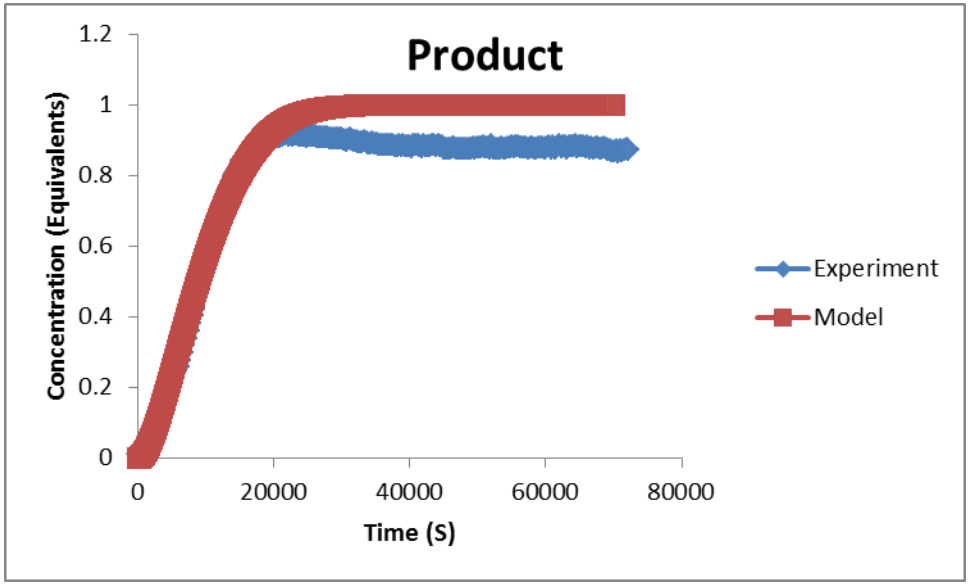
Final Objective Function (Maximum Likelihood): -2054.51

Experimental vs Model Predicted Result for Experiment 1

Model fit obtained after parameter estimation incorporating estimability analysis







Model Discrimination

Assumed Experimental Capabilities

Measured Variables:

- AH (Starting Material) concentration as a function of time
- Concentration of D as a function of time
- Product concentration as a function of time

Manipulating Variables (Experimental conditions)

- Temperature
- Initial loading of AH
- Initial loading of D
- Initial loading of M

Constraints

$V_{AH}+V_D+V_M=V_R$

V_R: Volume of reaction

V_{AH} , V_D , V_M: Volume of AH, D and M (calculated from the initial mass charged and the respective densities of the species)

Model Discrimination Objective

- 1 system
  - 1 set of manipulated variables (**u**)
- Multiple models
  - Multiple Predictions (**y**)
- Calculate the conditions **u** under which the models result in maximally different **y**
  - **Potentially suggest other y's than those available**
  - **Potentially suggest other u's than those available**

Mathematical Formulation of the Model Discrimination

Objective function: $\underset{\mathbf{u}}{\text{Max}} \left(\sum_{j=1}^{n_{species}} \sum_{t=1}^{T} (\hat{y}_m{}^{tom}(j,t) - \widehat{y_m}^{stan}(j,t))^2\right)$

Where

- Measured variables
  - Concentration profiles of of AH,

- Manipulated Variables.

Temperature	0<T<90 C (Safety constraint)
Initial charge of AH (C_{AH})	0<C_{AH}<10g (Material quantity constraint)
Initial charge of D (C_D)	0<C_D<10g (Material quantity constraint)
Volume of reaction (V_R)	0< V_R <50 mL (Vessel size constraint

Subject to:

$V_M = V_R - (V_{AH} + V_D)$

V_{AH} , V_D , V_M: Volume of AH, D and M

$C_M = \varrho_M V_M$

Initial charge of M (C_M) has been bounded by an “interior constraint”

$0 < C_M < 10$ (gram) (Material quantity constraint)

Objective function Values

The optimizer has a tendency to take the temperature at the maximum bound.

Measured Variables	Final Value	Initial guess	Lower Bound	Upper Bound
C_{AH} (g)	6.2268×10^{-2}	0.2	1×10^{-5}	10
C_{D} (g)	2.3532×10^{-2}	0.2	1×10^{-5}	10
Temperature (C)	90	60	0	90
V_R (L)	8.5975×10^{-3}	8.7×10^{-4}	1×10^{-5}	0.05

Objective Function: 1.6578×10^{4}

Different set of initial guess

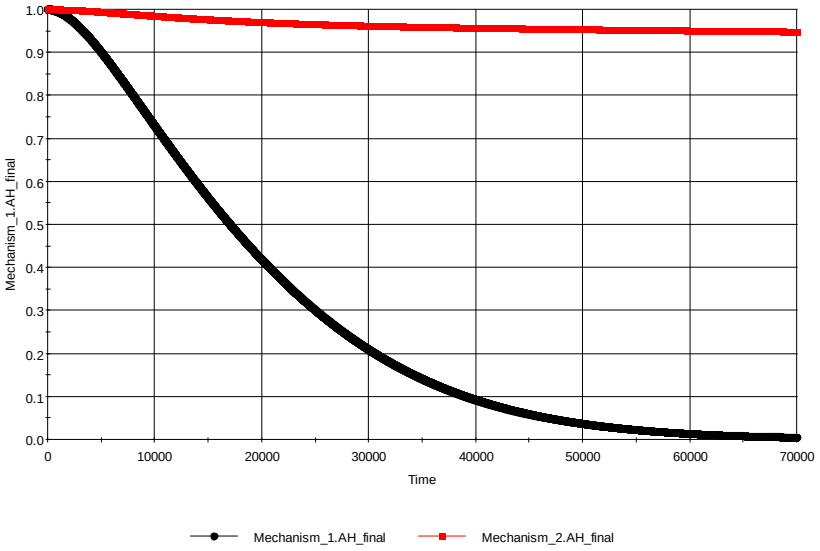
Measured Variables	Final Value	Initial guess	Lower Bound	Upper Bound
C_{AH} (g)	6.0746×10^{-2}	0.02	1×10^{-5}	10
C_{D} (g)	2.2960×10^{-2}	0.02	1×10^{-5}	10
Temperature (C)	90	60	0	90
V_R (L)	8.3877×10^{-3}	8.7×10^{-5}	1×10^{-5}	0.05

Objective Function: 1.6578×10^{4}

Results

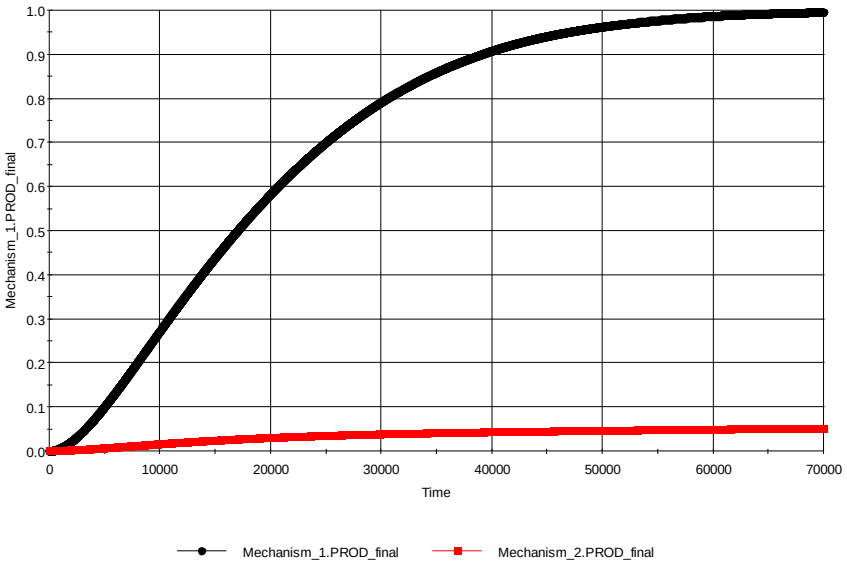
Stan's Model: (Black line)
Tom's Model: (Red line)

AH



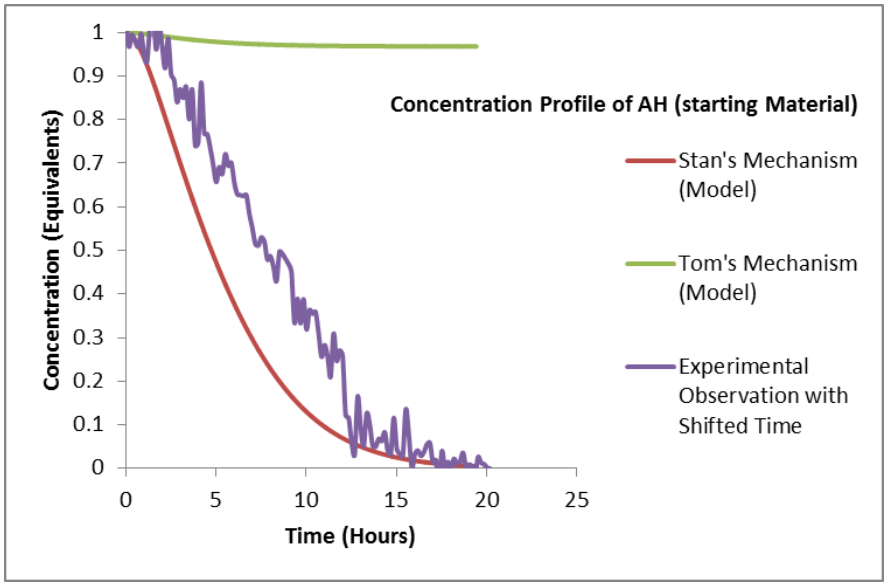
Optimal values:
AH initial loading: 62.3 mg
D initial loading: 23.5 µL
M initial loading: 8.5 mL
Temperature: 90 degree C

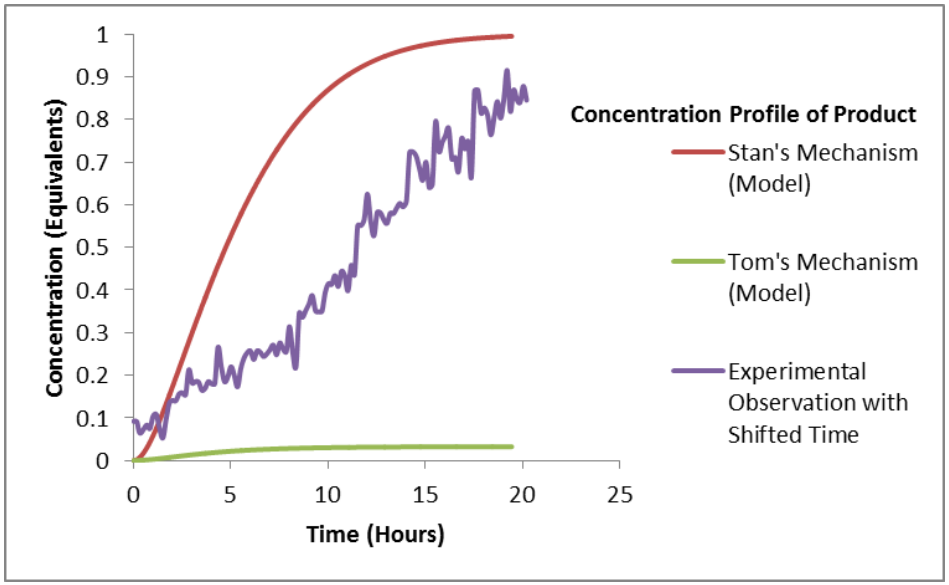
Product



Comparison of Experimental Observations with Model Predictions

Compare the MD-Experiment Results with Model Prediction



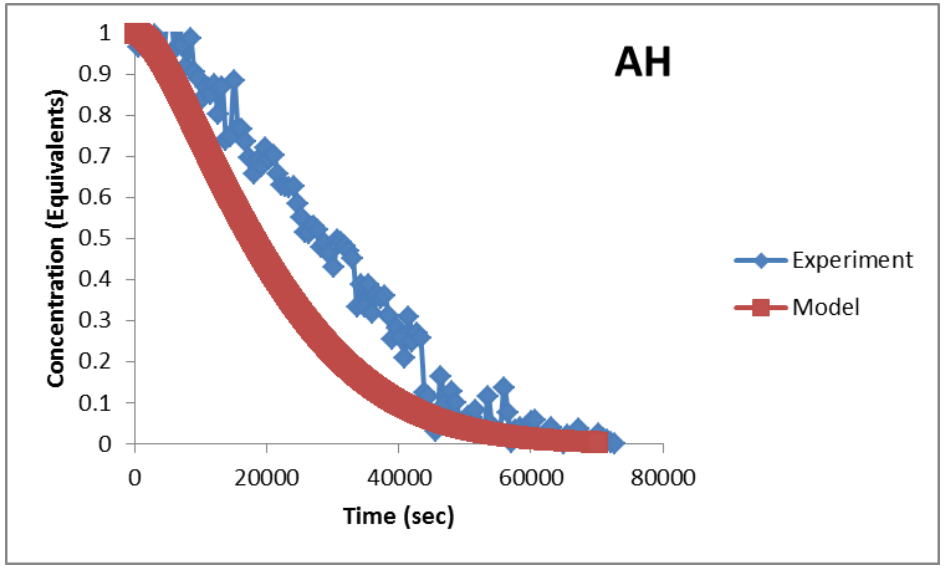


- It can be seen from the plots that Stan's mechanism model is the closest to the experimental observation when compared with Tom's Mechanism
- Stan's model predicts a full conversion of AH within 20 hours
  - Same observation is made in the experimental results
- Tom's mechanism model predicts less that 10% conversion of AH in 20 hours
- The prediction of Tom's model is drastically different from the experimental observation

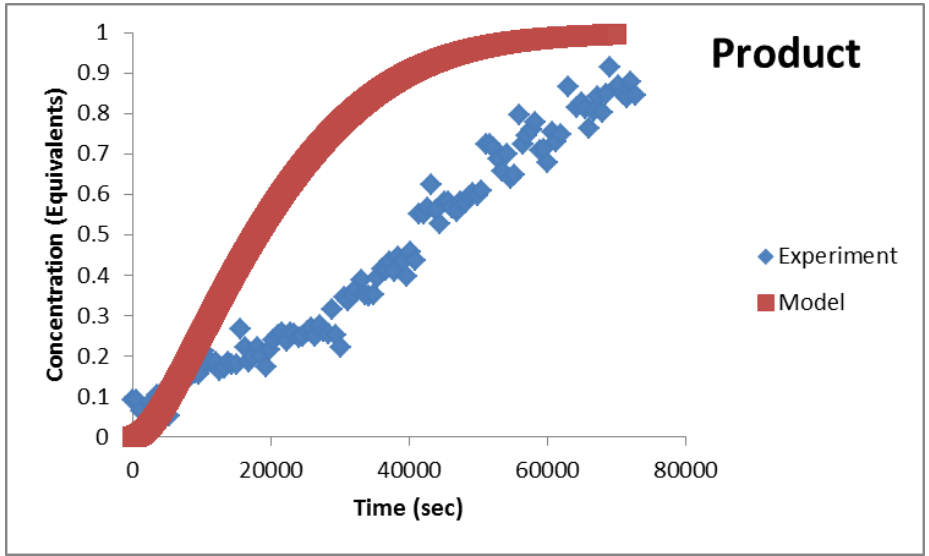
Model Discrimination Experiment

Compare the MD-Experiment Results with Model Prediction

Stan's Model



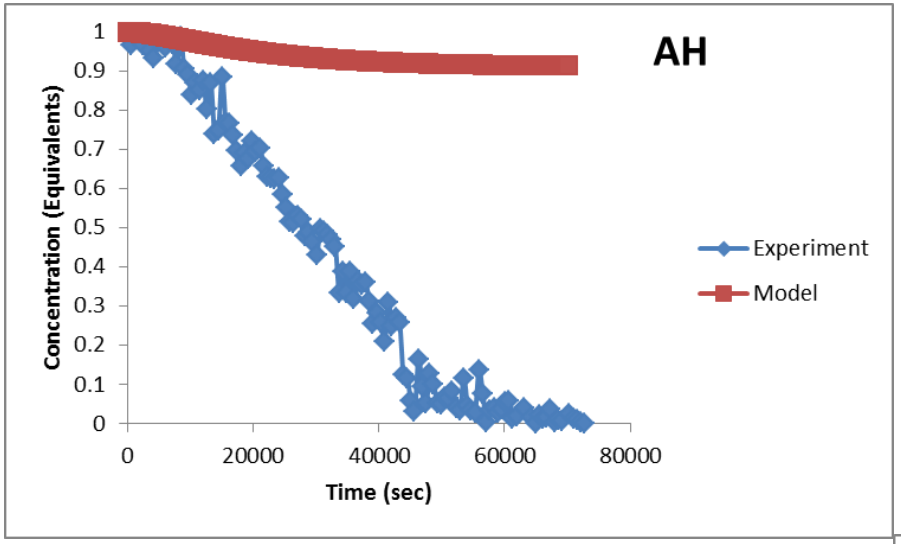
As seen from the plots, Stan's mechanism model is able to fit the experimental data from the model discrimination expt.



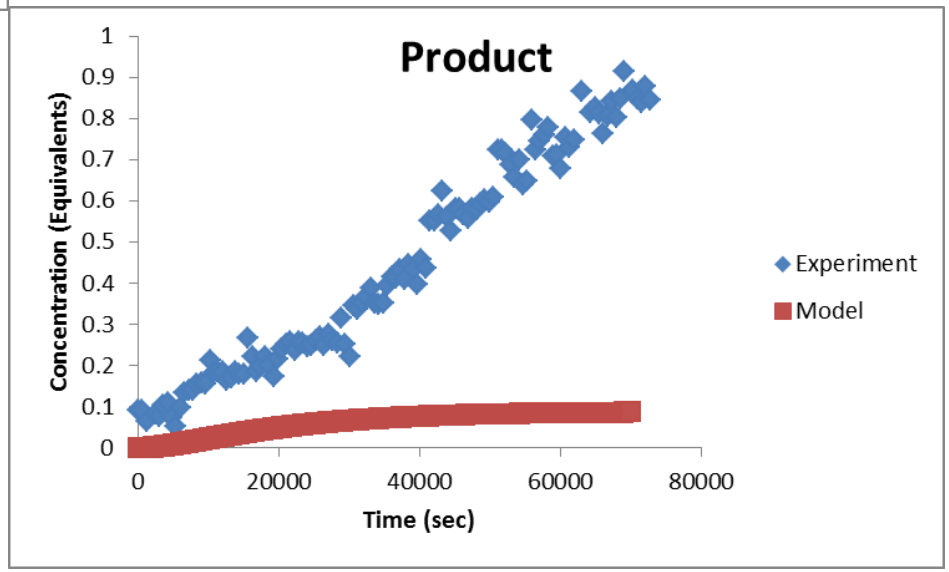
Model Discrimination Experiment

Compare the MD-Experiment Results with Model Prediction

Tom's Model

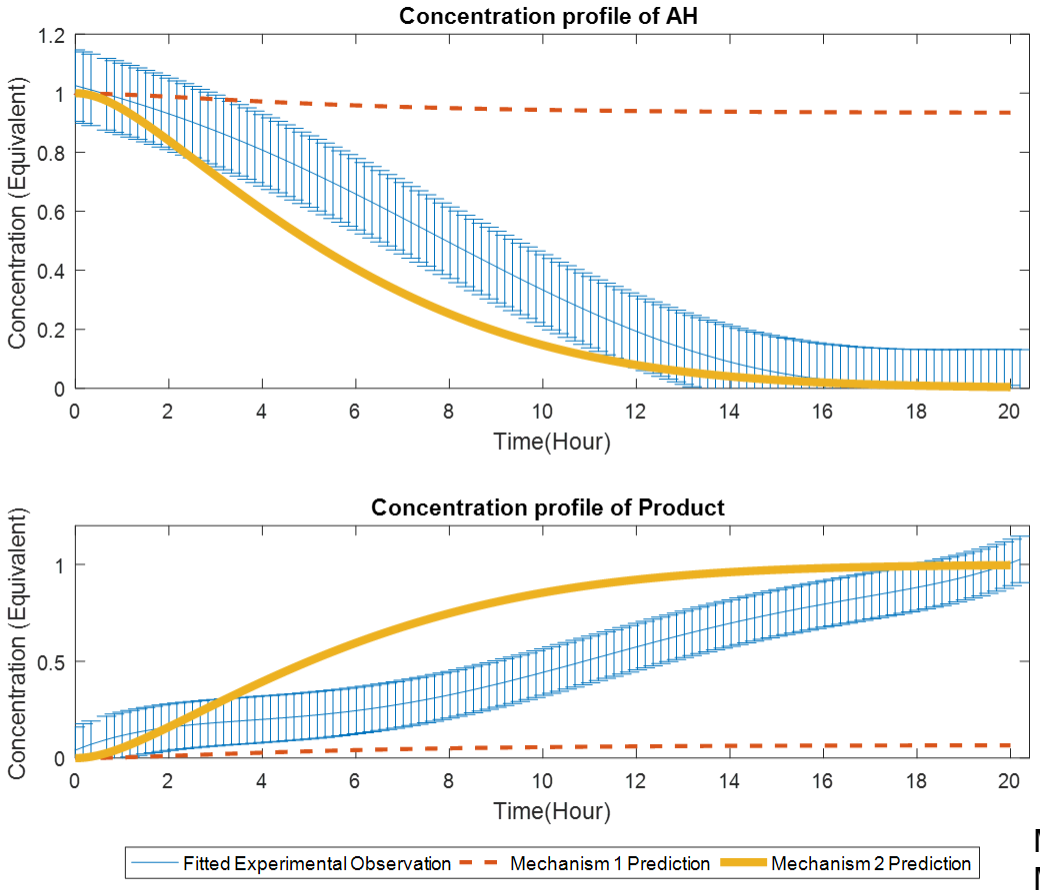


Tom's mechanism model is not able to fit the experimental data for the model discrimination experiment.
However, it is able to fit the other three (1-3) previous experiments



Compare the MD-Experiment Results with Model Prediction

Statistical Comparison



Mechanism 1: Tom's model
Mechanism 2: Stan's Model

- The prediction from the fitted polynomial function has been plotted with error bars equal to ±3σ and then compared against the predictions of the two mechanism models
- It can be seen that the prediction of Stan's model (for both AH and product) match with the fitted experimental observation towards the end

Conclusions

- In early process development, the model structure is as uncertain as the data we collect.
- Need to make a decision to move on, this decision likely depends on early parametric estimates.
- Estimability analysis is a very useful tool for the model developer, especially when using non-designed data.
- Model discrimination is quite useful
  - Dependent on available measurements and degrees of freedom to manipulate the process

Conclusions

- This is not the end of the road, as of now we have:

a) A structure we believe

b) With the best parameters we could afford

But our *affordability power* was not very good at the time (data is not informative)

MBDOE for optimal parametrization follows

Thank you very much !

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Case Study 2: Model Structures

Three model structures were built using the proposed reaction mechanisms:

MODEL 1

$$A + B \xrightarrow{k\_1} C + D$$

$$D \xrightarrow{k\_2} H + I$$

$$E + H \underset{kr\_3}{\overset{k\_3}{\leftrightarrow}} F + N$$

$$F + B \xrightarrow{k\_4} P + D$$

MODEL 2

$$A + B \xrightarrow{k\_1} C + D$$

$$E + A \underset{kr\_2}{\overset{k\_2}{\leftrightarrow}} F + M$$

$$F + B \xrightarrow{k\_3} P + D$$

MODEL 3

$$A + B \xrightarrow{k\_1} C + D$$

$$D \xrightarrow{k\_2} H + I$$

$$E + A \underset{kr\_3}{\overset{k\_3}{\leftrightarrow}} F + M$$

$$E + H \underset{kr\_4}{\overset{k\_4}{\leftrightarrow}} F + N$$

$$F + B \xrightarrow{k\_5} P + D$$

Model 1

Batch reactor:

$$\frac{d(mol\_A)}{dt} = rate\_A * Volume$$

Rate Equations:

rate_E = - k_3* [E]* [H]+ kr_3* [F]* [N]
rate_B = -k_1* [B]* [A] – k_4* [B]* [F]
rate_A = -k_1* [B]* [A]
rate_P = k_4* [B]* [F]
rate_D = k_1* [B]* [A] – k_2*[D]+ k_4* [B]* [F]
rate_H = k_2* [D] - k_3* [E]* [H]+ kr_3* [F]* [N]
rate_I = k_2* [D]
rate_N = k_3* [E]* [H]- kr_3* [F]* [N]
rate_C = k_1* [B]* [A]
rate_F = k_3* [E]* [H]- kr_3* [F]*[N]-k_4* [F]* [B]

$$A + B \xrightarrow{k\_1} C + D$$

$$D \xrightarrow{k\_2} H + I$$

$$E + H \underset{kr\_3}{\overset{k\_3}{\leftrightarrow}} F + N$$

$$F + B \xrightarrow{k\_4} P + D$$

Temperature dependence of rate constants:

$$k = A * \exp(\frac{-Ea}{RT})$$

Model 2

Rate Equations: :

rate_E = - k_2* [E]* [A] + kr_2* [F]* [M]

rate_B = -k_1* [B]* [A] - k_3* [B]* [F]

rate_A = -k_1* [B]* [A] - k_2* [E]* [A] + kr_2*[F]* [M]

rate_P = k_3* [B]*[F]

rate_D= k_1* [B]* [A] + k_3* [B]* [F]

rate_C = k_1* [B]* [A]

rate_F = k_2* [E]* [A] - kr_2* [F]* [M] - k_3* [F]* [B]

rate_M= k_2* [E]* [A] - kr_2* [F]* [M]

$$A + B \xrightarrow{k\_1} C + D$$

$$E + A \overset{k\_2}{\leftrightarrow} F + M$$

$$F + B \xrightarrow{k\_3} P + D$$

Model 3

Rate Equations: :

rate_E = - k_3* [E]* [A] + kr_3* [F]* [M] - k_4* [E]* [H]+ kr_4* [F]* [N]

rate_B = -k_1* [B]* [A] - k_5* [B]* [F]

rate_A = -k_1* [B]* [A] - k_3* [E]* [A] + kr_3*[F]* [M]

rate_P = k_5* [B]*[F]

rate_D= k_1* [B]* [A] + k_5* [B]* [F] – k_2*[D]

rate_C = k_1* [B]* [A]

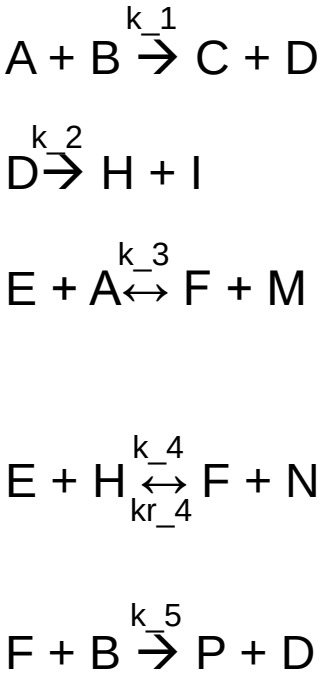
rate_F = k_3* [E]* [A] - kr_3* [F]* [M] k_4* [E]* [H]- kr_4* [F]*[N - k_5* [F]* [B]

rate_M= k_3* [E]* [A] - kr_3* [F]* [M]

rate_N = k_4* [E]* [H]- kr_4* [F]* [N]

rate_H = k_2* [D] - k_4* [E]* [H]+ kr_4* [F]* [N]

rate_I = k_2* [D]



Initial Parameter Estimation

Model1

Model Parameters	Model 1 Final Value
A1	1E20
A2	8.6564E12
A3	26044.8
Ar3	5.51292E13
A4	79230
E1	1688.14
E2	250
E3	459.965
Er3	480.263
E4	9.35852E-5

Model2

Model Parameters	Model 2 Final Value
A1	1E15
A2	2.95263E7
A3	4.96187E14
Ar2	9.99201E-11
E1	1360.18
E2	771.535
E3	86.9434
Er2	8877.89

Model3

Model Parameters	Model 3 Final Value
A1	1E25
A2	1.85E15
A3	1.66582E7
A4	6.41404E6
A5	3.19831E19
Ar3	1E-5
Ar4	6.41425E13
E1	2021.94
E2	2287.2
E3	753.831
E4	2091.95
E5	75
Er3	8877.89
Er4	1000

Estimability Ranking of Parameters

Sensitivity Rank	Parameters (MODEL1)	Parameters (MODEL2)	Parameters (MODEL3)
1st	E1	E1	E1
2nd	E3	E2	E3
3rd	Er3	A1	A1
4th	A1	A2	A3
5th	A3		E2
6th	A4		
7th	Ar3		
8th	E4		
Zero	Ar3, E2	A3, Ar2, E3, Er2	A2, A4, A5, Ar3, Ar4, E4, E5, Er3, Er4

Post-Estimability Parameter Estimation

Model1

Model Parameters	Model 1 Final Value
A1	1E20
A2	8.6564E12
A3	19734.9
Ar3	1.96318E14
A4	163268
E1	1688.14
E2	250
E3	452.676
Er3	507.886
E4	11.0885

Model2

Model Parameters	Model 2 Final Value
A1	1E17
A2	2.3026E7
A3	4.96187E14
Ar2	9.99201E-11
E1	1492.41
E2	764.181
E3	86.9434
Er2	8877.89

Model3

Model Parameters	Model 3 Final Value
A1	1E22
A2	1.85E15
A3	1.65171E7
A4	6.41404E6
A5	3.19831E19
Ar3	1E-5
Ar4	6.41425E13
E1	1823.3
E2	2287.2
E3	754.032
E4	2091.95
E5	75
Er3	8877.89
Er4	1000

Model Discrimination

Constraints: Amount of E added in solvent between 50-275 g/mL
Total reaction volume: 650 – 750 µL

Bounds: Amount of E: 0.036- 0.175 g
Volume_A : 80 – 750 µL
Volume_B :150 – 750 µL

Optimization Starting Point	OPT_1	OPT_2	OPT_3	OPT_4	OPT_5	OPT_6	OPT_7	OPT_8
E (g)	0.12	0.05	0.120	0.099	0.045	0.150	0.12	0.036
T (K)	353	340	345	340	338	338	335	335
V_A (L)	1.2E-4	3.3E-4	3.3E-4	1.8E-4	2.5E-4	2.5E-4	2.5E-4	2.5E-4
V_B (L)	3.3E-4	4.5E-4	4.5E-4	5.0E-4	4.5E-4	4.5E-4	1.5E-4	1.5E-4

Final Value	OPT_1	OPT_2	OPT_3	OPT_4	OPT_5	OPT_6	OPT_7	OPT_8
E (g)	0.18	0.038	0.175	0.175	0.038	0.18	0.18	0.18
T (K)	353	342	353	353	342	353	353	353
V_A (L)	8E-5	3.92E-4	8E-5	8E-5	3.92E-4	8E-5	2.14E-4	8E-5
V_B (L)	5.7E-4	3.55E-4	5.7E-4	5.7E-4	3.54E-4	5.7E-4	4.36E-4	5.7E-4

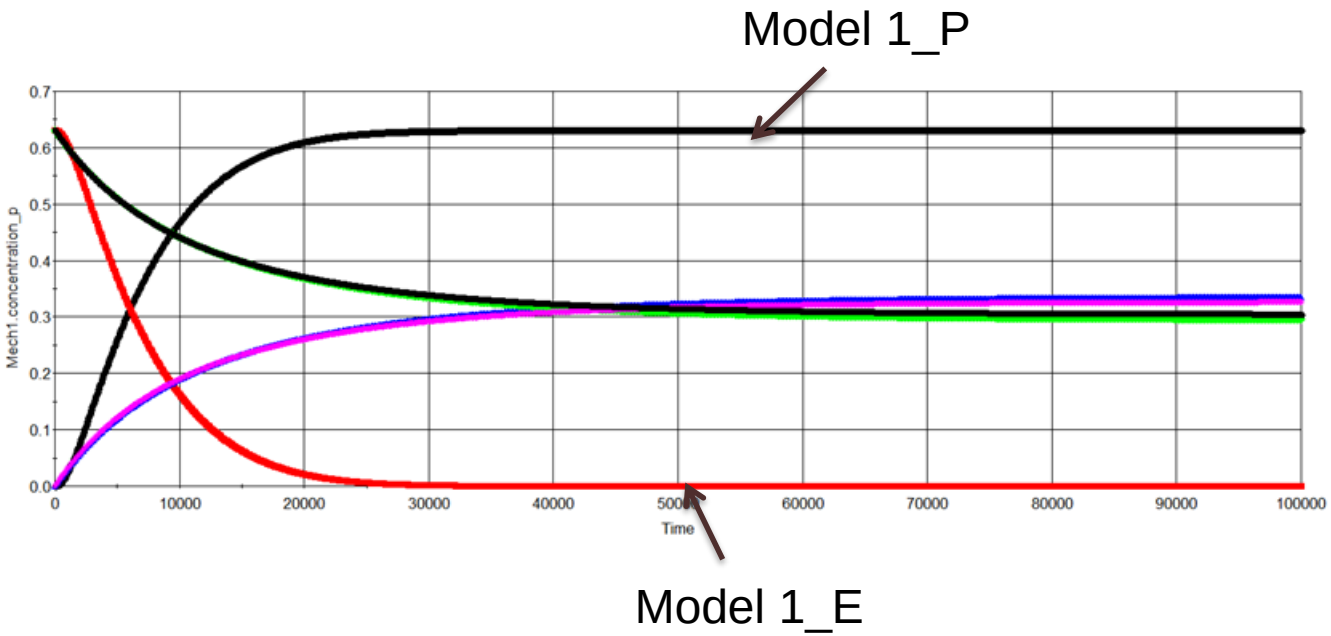
NMR Recipe
0.15
353
1.341E-4
4.5 E-4

Result: The optimizer found two optima.

Optimization 1

- Concentration profile of P and E in Model 1 predictions are very different from the ones in Model 2 and Model 3.
- Model 2 and Model 3 predicted similar concentration profiles for P and E.

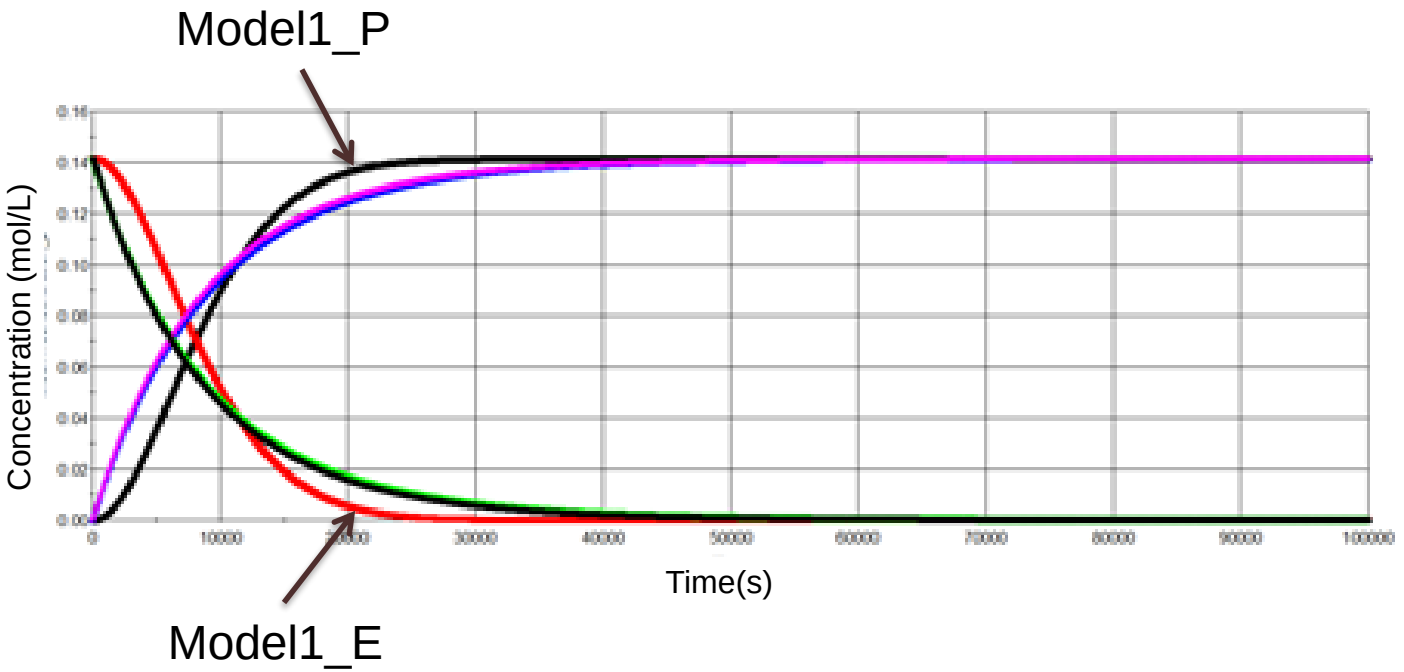
Final Value	OPT_1
E (g)	0.18
T (K)	353
V_A (µL)	80
V_B (µL)	570



Optimization 2

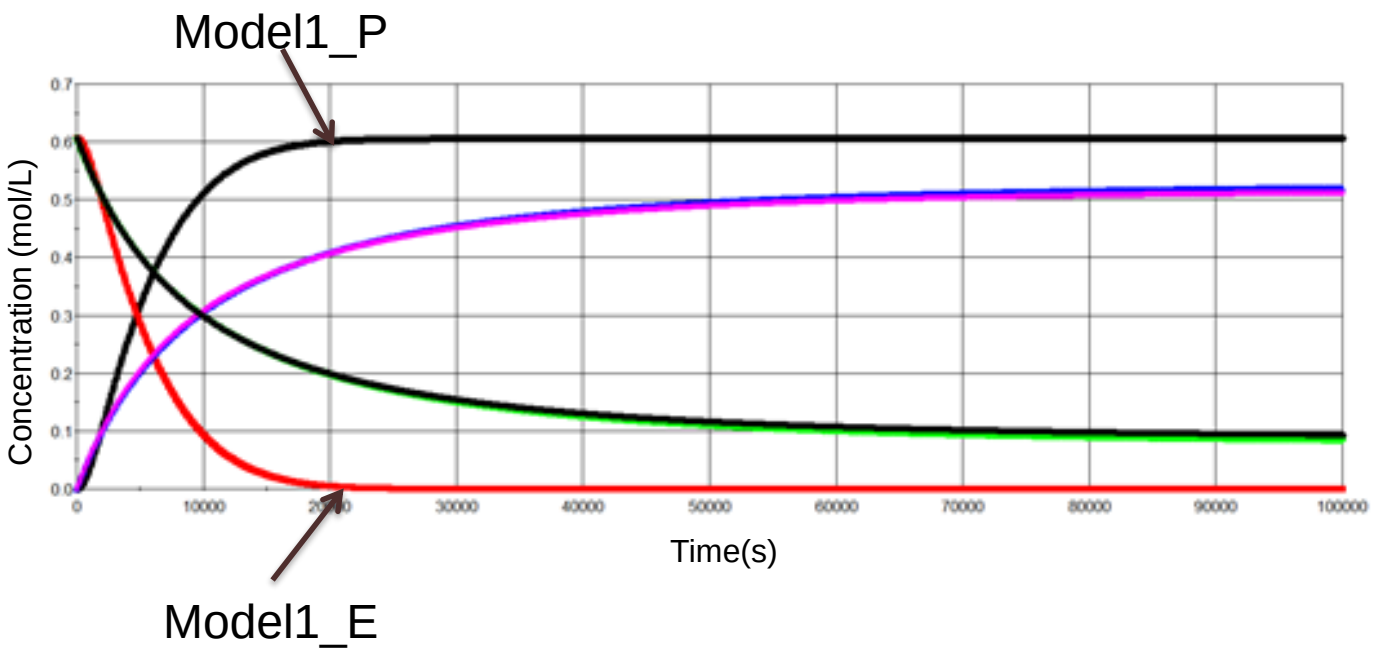
- Concentration profiles of P and E in all three models are similar.

Final Value	OPT_2
E (g)	0.038
T (K)	342
V_A (µL)	392
V_B (µL)	355



Experimental Recipe

Due to material limitations, the first approach was to use the most recent experimental recipe in the simulation.

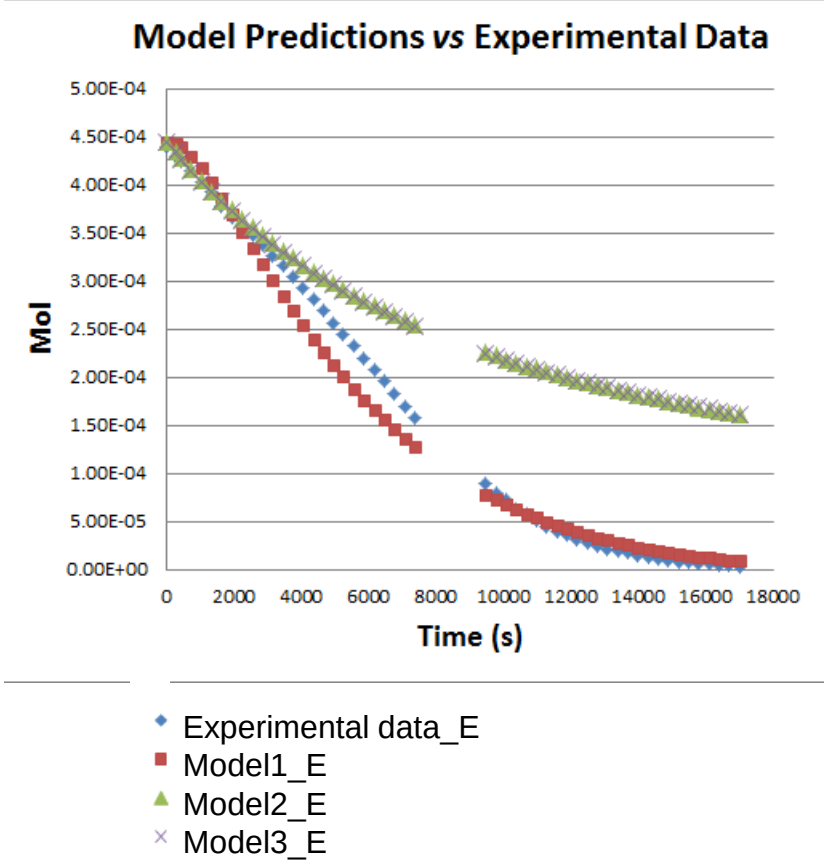


Material	Recipe
E (g)	0.15
T (K)	353
V_A (µL)	134.1
V_B (µL)	450

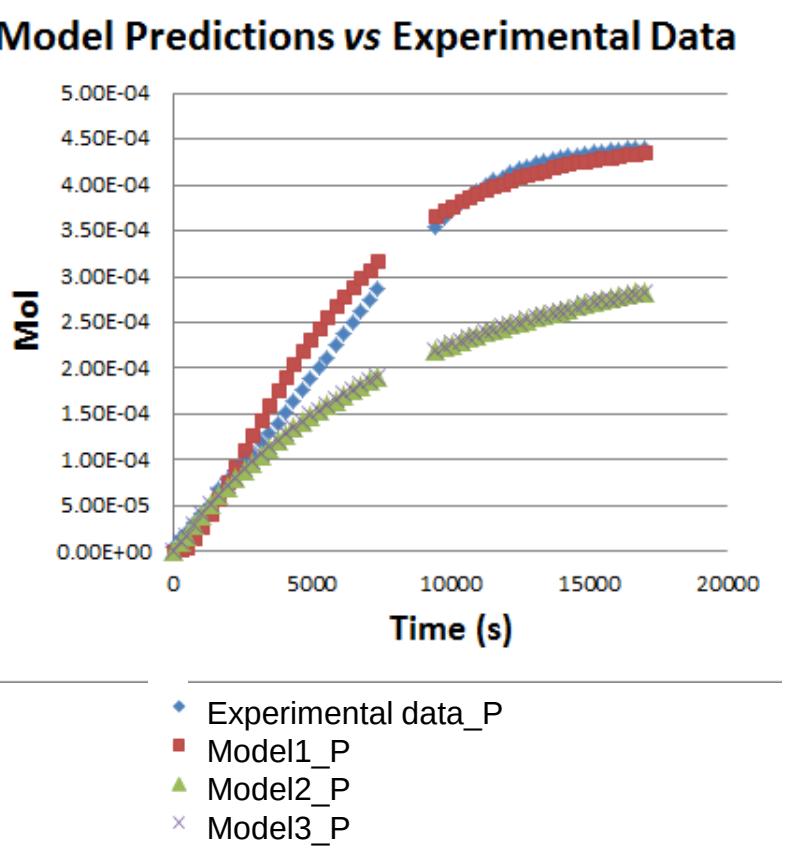
Result: Model predictions with experimental recipe led to similar model predictions obtained with Optimization1

Model Predictions vs Experimental Data

Compound E



Compound P



CONCLUSION: Model1 predictions explains the current reaction data better than Model 2 and Model 3 predictions.

Backup Slide: Another Case Study on Parameter Estimability

- There are four proposed mechanisms for the reaction step
- Data under only two experimental conditions are available
  - The concentration profile of the starting material and product has been observed for each set

Mechanism	Number of parameters to be Estimated
Mechanism 1	6
Mechanism 2	6
Mechanism 3	6
Mechanism 4	14

Parameter Ranking

Ranking	Mechanism 1	Mechanism 2	Mechanism 3	Mechanism 4
1	E_1	E_1	E_1	E_1
2	E_2	E_2	E_2	E_{-1}
3	E_{-1}	E_{-1}	A_1	E_2
4	A_1	A_1	A_2	A_1
5	A_2	A_2	E_{-1}	A_2
6	A_{-1}	A_{-1}	A_{-1}	A_{-1}

In Mechanism 4, the parameters A_3, A_4, E_3, E_4, A_{-2},A_{-3}, E_{-2} and E_{-3} are unranked

Parameter Estimates of Mechanism 1

Model Parameter	Final Value	Initial Guess	Lower Bound	Upper Bound	Confidence Interval			95% t-value	Standard Deviation
					90%	95%	99%		
A_1 (Fixed)	3.31776×10^6	3.31776×10^6	3.31776×10^6 *	3.31776×10^6 *					
A_2 (Fixed)	5.8944×10^6	5.8944×10^6	5.8944×10^6 *	5.8944×10^6 *					
A_{-1} (Fixed)	766634	766634	766634 *	766634 *					
E_1	57281.9	58000	1000	100000	392.8	470.8	627.2	121.7	234.6
E_2	56004.1	60000	1000	100000	452.1	541.9	722	103.3	270
E_{-1} (Fixed)	54033.9	54033.9	54033.9 *	54033.9 *					
Reference t-value (95%):								1.67432	

Parameter Estimates of Mechanism 2

Model Parameter	Final Value	Initial Guess	Lower Bound	Upper Bound	Confidence Interval			95% t-value	Standard Deviation
					90%	95%	99%		
A_1	6.19123×10^{6}	1×10^{6}	1000	1×10^{8}	2.895×10^{13}	3.471×10^{13}	4.629×10^{13}	1.783×10^{-7} **	1.727×10^{13}
A_2	5.54929×10^{6}	800180	1000	1×10^{7}	3.647×10^{13}	4.373×10^{13}	5.832×10^{13}	1.269×10^{-7} **	2.176×10^{13}
A_{-1} (Fixed)	991512	991512	991512 *	991512 *					
E_1	58151.8	58000	1000	100000	1.211×10^{10}	1.451×10^{10}	1.936×10^{10}	4.007×10^{-6} **	7.222×10^{9}
E_2	55956.5	60000	1000	100000	1.614×10^{10}	1.935×10^{10}	2.58×10^{10}	2.892×10^{-6} **	9.627×10^{9}
E_{-1}	49875.9	80000	1000	100000	5794	6947	9264	7.179	3457
Reference t-value (95%):								1.67627	

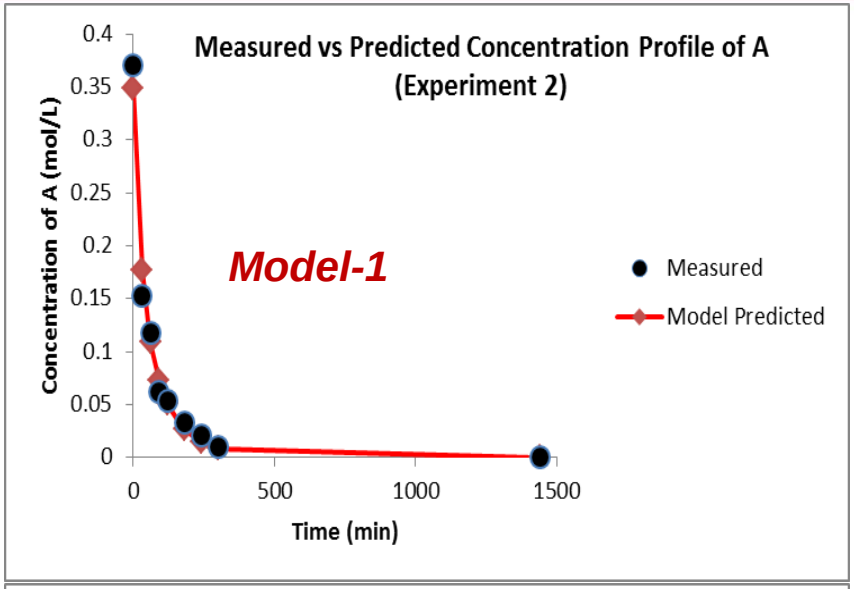
Parameter Estimates of Mechanism 3

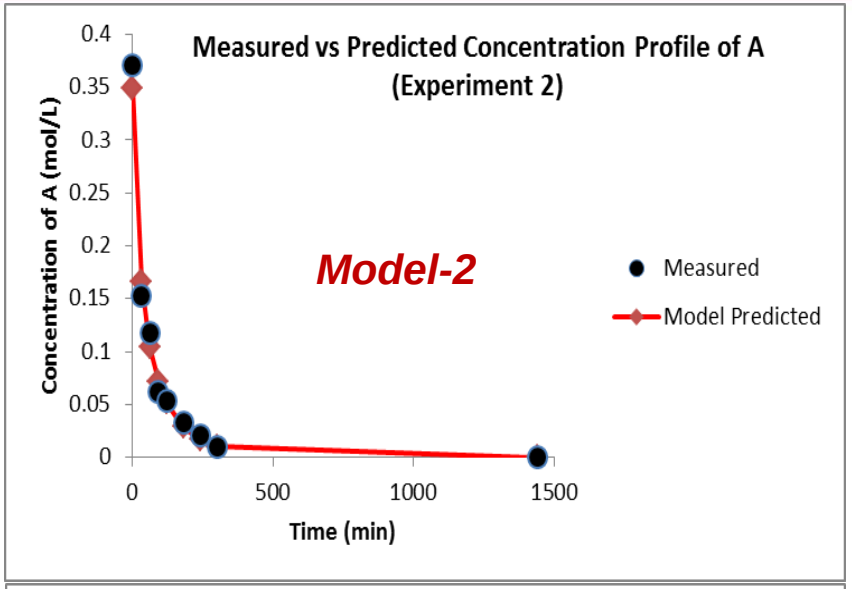
Model Parameter	Final Value	Initial Guess	Lower Bound	Upper Bound	Confidence Interval			95% t-value	Standard Deviation
					90%	95%	99%		
A_1 (Fixed)	2.73409×10^6	2.73409×10^6	2.73409×10^6 *	2.73409×10^6 *					
A_2 (Fixed)	1.89459×10^8	1.89459×10^8	1.89459×10^8 *	1.89459×10^8 *					
A_{-1} (Fixed)	2.19264×10^6	2.19264×10^6	2.19264×10^6 *	2.19264×10^6 *					
E_1	28480.3	58000	1000	100000	2237	2681	3572	10.62	1336
E_2	65775.1	60000	1000	100000	577.2	691.8	921.6	95.08	344.7
E_{-1} (Fixed)	25013.6	25013.6	25013.6 *	25013.6 *					
Reference t-value (95%):								1.67432	

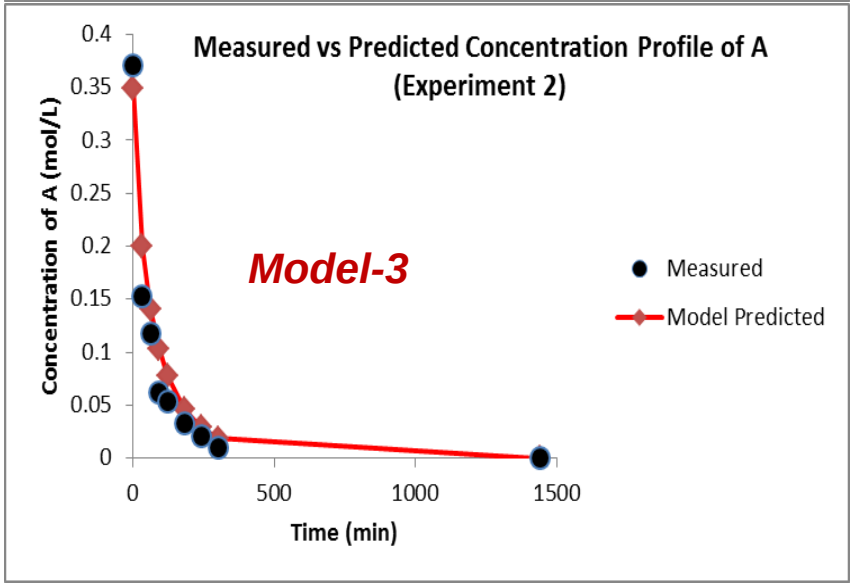
Parameter Estimates of Mechanism 4

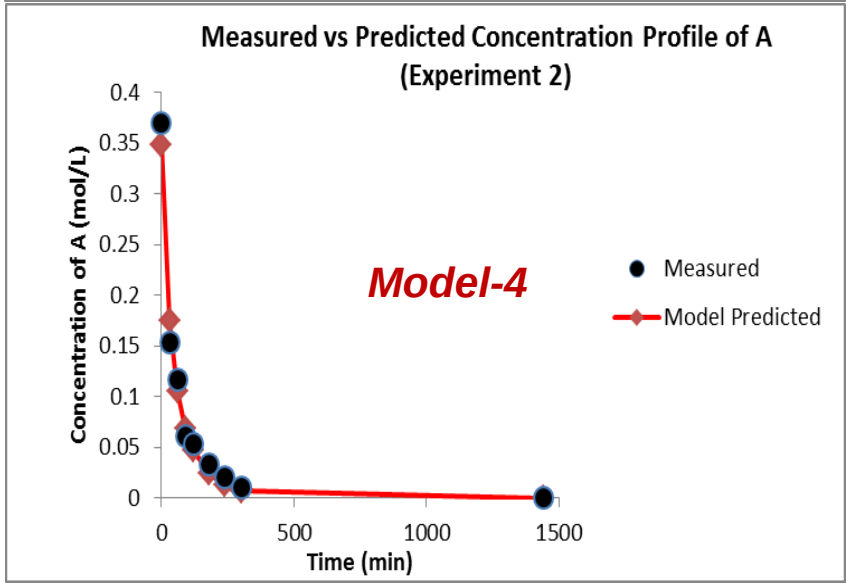
Model Parameter	Final Value	Initial Guess	Lower Bound	Upper Bound	Confidence Interval			95% t-value	Standard Deviation
					90%	95%	99%		
A_1	1.20253×10^{7}	9660	1000	1×10^{8}	6.821×10^{13}	8.201×10^{13}	1.103×10^{14}	1.466×10^{-7} **	4.027×10^{13}
A_2	582878	8001	1000	1×10^{7}	4.23×10^{12}	5.085×10^{12}	6.838×10^{12}	1.146×10^{-7} **	2.497×10^{12}
A_3 (Fixed)	91469.5	91469.5	91469.5 *	91469.5 *					
A_4 (Fixed)	14896.8	14896.8	14896.8 *	14896.8 *					
A_{-1} (Fixed)	2.25019×10^{7}	2.25019×10^{7}	2.25019×10^{7} *	2.25019×10^{7} *					
A_{-2} (Fixed)	16344.5	16344.5	16344.5 *	16344.5 *					
A_{-3} (Fixed)	67183	67183	67183 *	67183 *					
E_1	60683.4	80000	1000	90000	5.742×10^{9}	6.905×10^{9}	9.284×10^{9}	8.789×10^{-6} **	3.39×10^{9}
E_2	53630.1	82000	1000	90000	2.335×10^{10}	2.808×10^{10}	3.776×10^{10}	1.91×10^{-6} **	1.379×10^{10}
E_3 (Fixed)	9978.58	9978.58	9978.58 *	9978.58 *					
E_4 (Fixed)	15700.4	15700.4	15700.4 *	15700.4 *					
E_{-1}	90000	83000	1000	90000 *					
E_{-2} (Fixed)	76561.2	76561.2	76561.2 *	76561.2 *					
E_{-3} (Fixed)	81602.9	81602.9	81602.9 *	81602.9 *					
Reference t-value (95%):								1.69385	

Model Fitting Results (Starting Material)

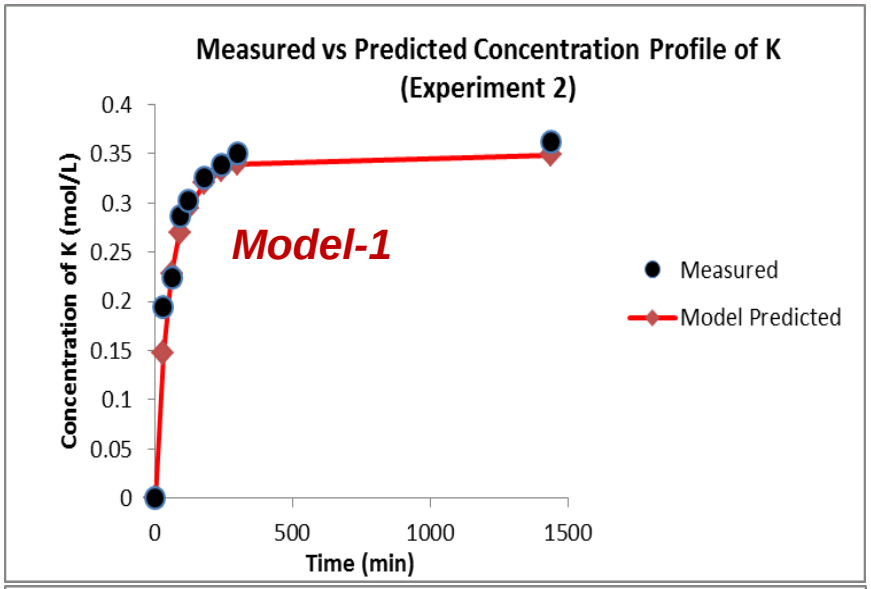


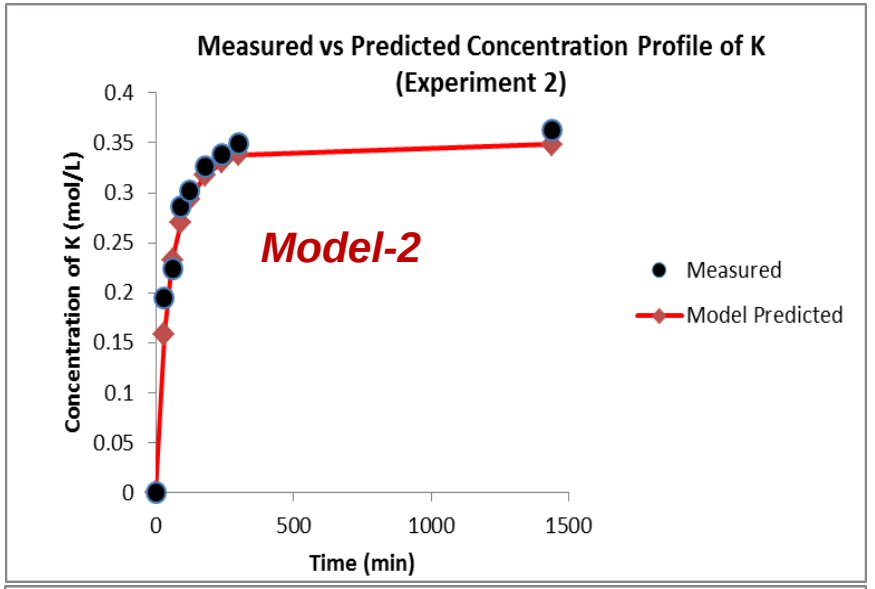


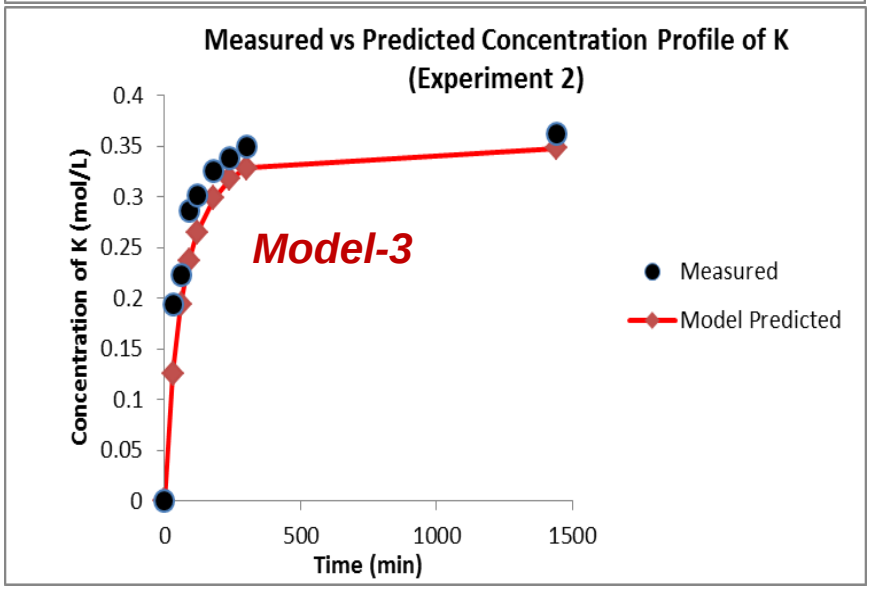


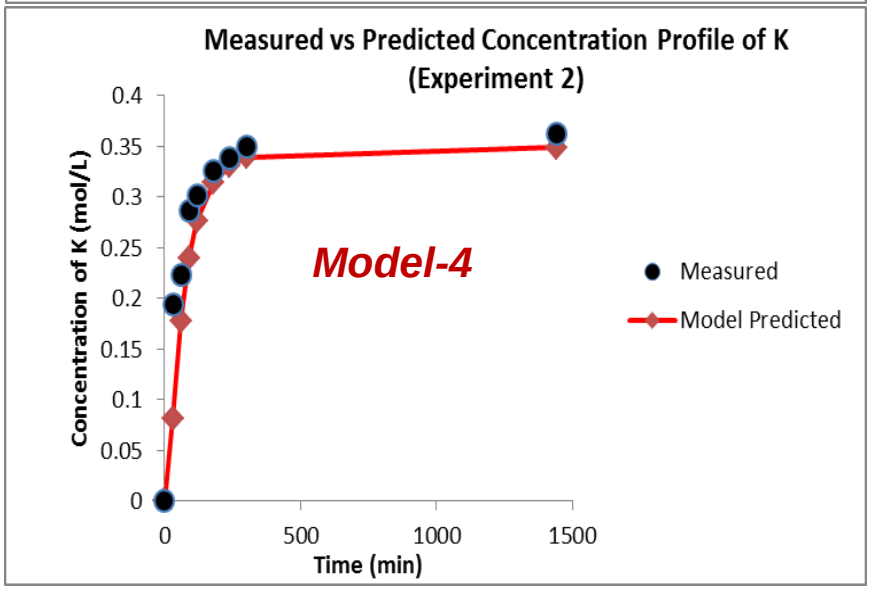


Model Fitting Results (Product)









Conclusion

The **parameter estimability** technique has proven to be useful when the information content of the measured data available is insufficient to obtain a good estimate of all the unknown model parameters.