

Combining DOE and First-Principles Science to Maximize Yield and Minimize Impurity with Fit Curve CDOE

JMP Discovery Summit - Americas

Brian Taylor, Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, *Macclesfield*, *UK*

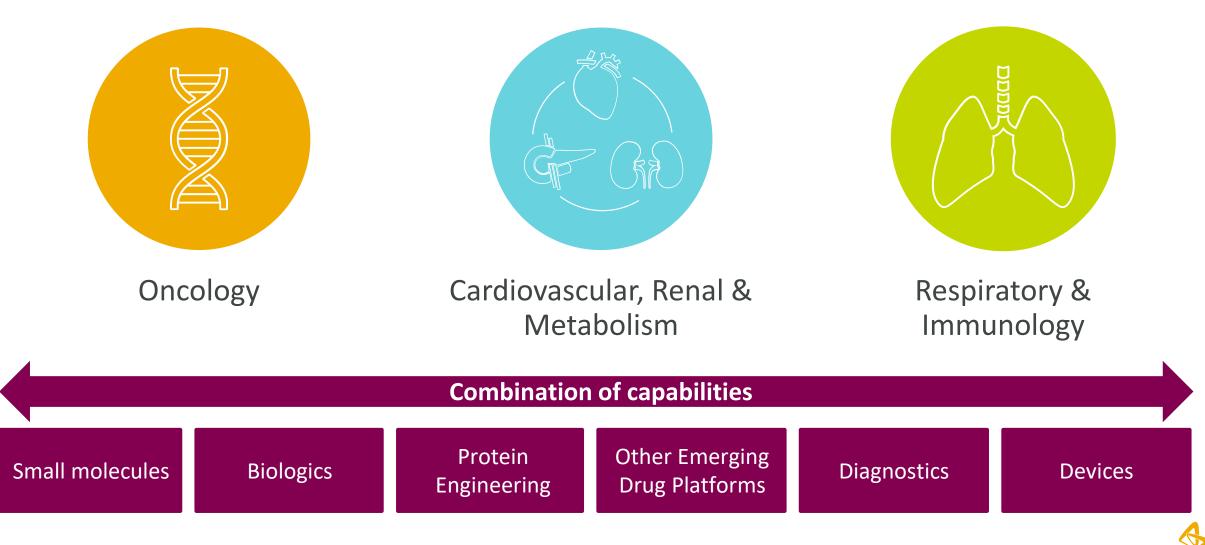
Chris Gotwalt, JMP

AstraZeneca 2

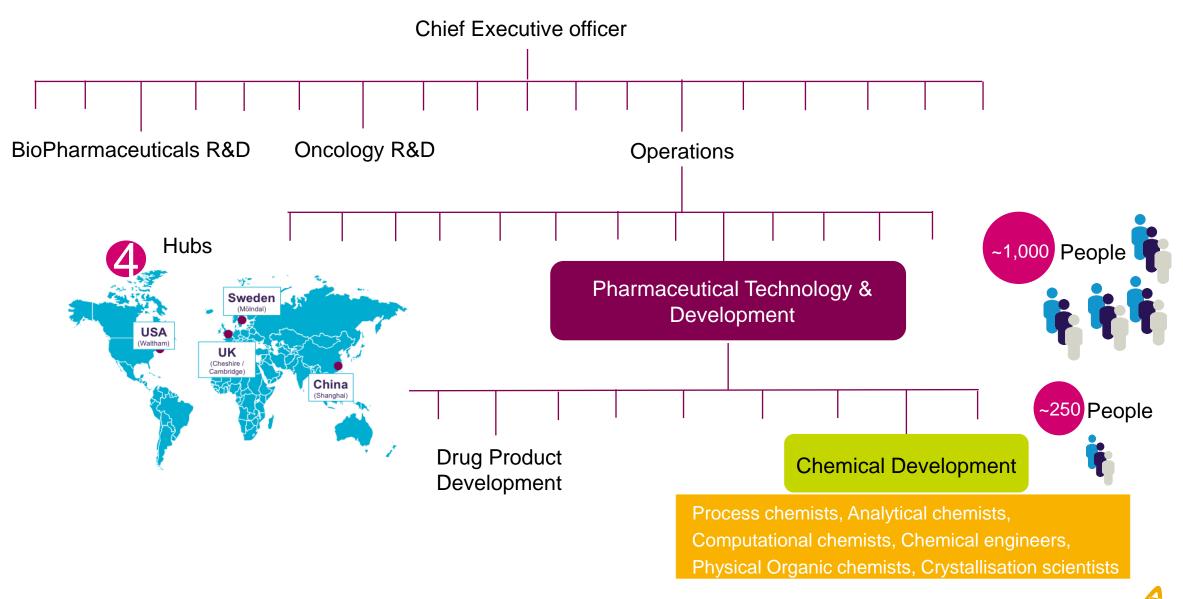
October 2021



Focus on three main therapy areas and across key platforms



PT&D in AstraZeneca



Lifecycle of Medicine



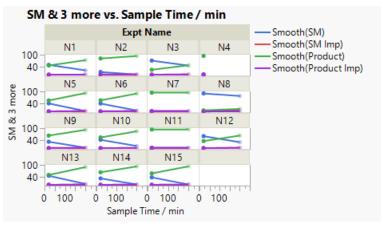
AstraZeneca spans the **entire life-cycle** of a medicine from research and development to manufacturing and supply, and the global commercialisation of primary care and speciality care medicines.

PT&D develops technologies to support products from **PhII clinical studies** through to **post product launch**

Chemical Development Design, develop and optimise synthetic routes, processes and analytical methods for the Active Pharmaceutical.

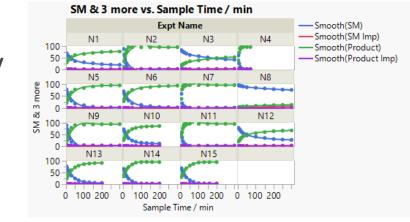
Lab Experimentation & DoE's Analysing Profiles

Early 2000s – 1or2 samples/Expt



More experiments are routinely sampled to produce a reaction profile or distribution

2020s – 12 Samples/Expt



- Analysing DoEs with reaction profiles from sampling experiments' over time
 - Strategies aim to reduce multiple response results into a single value
 - A common approach is to select a slice in time to analyse.
 - What process insight is lost from analysing a response in slices?
- What analysis approach can make use of all the time course reaction profile data?

What analysis approach can make use of all the time course reaction profile data?

Can we refine the analysis to consider subject matter knowledge?

Grand Presentation Title: Combining DOE and First-Principles Science to Maximize Yield and Minimize Impurity with Fit Curve CDOE

What we do in JMP: Analyse DoE Reaction Profiles with Fit Curve and CDOE



DoE Case Study Background

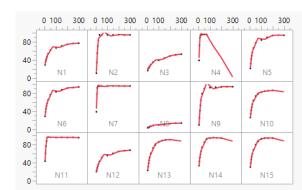
- 4 factor Definitive Screening Design (Conference Matrix Derived)
 - Solvent Volume 6.0 10.0 rel vols, Catalyst Charge 0.70 -1.30 mol%, Base Charge 4.50 -7.50 eq, Amine Starting Material 1.00 - 1.10 eq
- Sampling: 12 samples per experiment.
 - Time points selected to coincide every time 10% conversion expected to happen.
 - Each experiments samples time points can differ
- Process Response Target Criteria

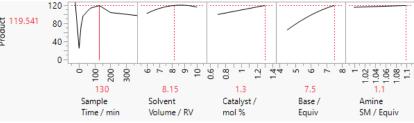
Responses	Target Criteria
-	
SM – Starting Material	Minimise
SM Imp – Starting Material Imp	Minimise
Prod – Product	>95 %
Prod Imp – Product Impurity	<2 %
Reaction Time	120 – 240 Mins

• Prod Imp priority to control

JMP Functional Data Explorer in combination with DoE to Chemical Reactions

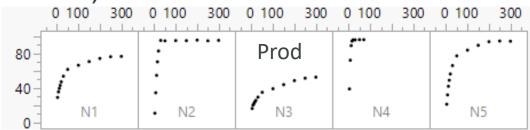
- FDE flexible Spline fitting approach can be a strength and a weakness for fitting smooth continuous time course data
 - Countless shapes can be approximated
 - Unrealistic shapes are approximated
 - when domain specific knowledge infers what shapes of profiles to expect
- Combining FDE and DoE has strengths and weakness
 - FDoE converts output to relate profiles to factors studied in the DoE
 - Unrealistic predictions estimated negative values, values greater than theoretical maximum. Eg Prod Max 100%, prediction 119%.

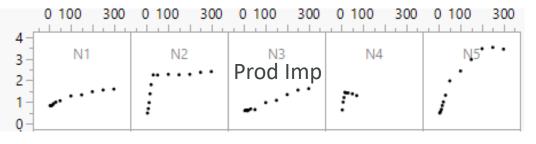




Chemical Reaction profile shape properties

- Natural Minimum and Maximum bound
 - Starting Materials and Products bounds: Minimum 0%, Maximum 100%.
- Profile Gradient
 - Montonic increasing or decreasing
 - Plateau travels to an optima and remains at optima over time
- Single Profile Peak/Trough
 - Product Peak (maxima) reached, reaction held longer, decay occurs for some reason
- End of Reaction (EOR) can occur over different time scales (SM or Prod plateaus)
 - 50mins, 300 mins or 1200mins.
- Sum of Response Area % results add up to 100%.
 - SM + SM Imp + Prod + Prod Imp = 100%

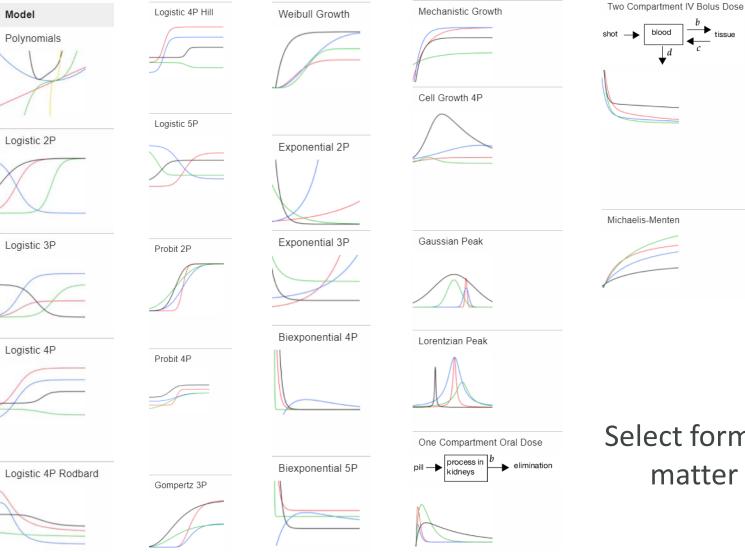




Functional DoE with Fit Curve

- Pre-loaded equations represent profiles more likely observed in Chemical Reactions
 - Some flexibility lost on fitting profile shapes
 - The profiles shapes fitted assumed to resemble more closely the underlying physical equations controlling chemical reaction profiles
 - Fitted curves compared to determine best fitted to use in DoE Modelling
 - Fit curve formula parameters used as responses in DoE Modelling

Fit Curve Pre-loaded Formulas



Michaelis-Menten

blood

tissue

Select formulas to try that match the subject matter domain profile characteristics.



Analysis Steps Analyse – Specialised Modelling – Fit Curve

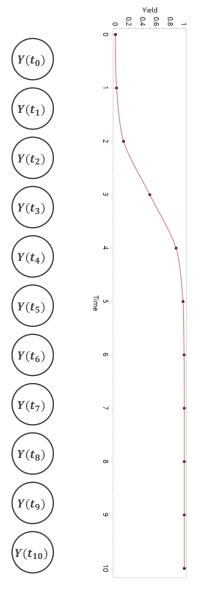
- Define the Data Structure for analysis
- Fit Multiple Curves to chemical reaction Response
 - Compare Curve fits and select preferred one
- Select Curve DoE on formula parameter Coefficients
 - Decide the DoE Analysis approach
 - Default is Forward Selection
 - Decide which Parameter Coefficients Distribution
 - Default is Gaussian
 - DoE Profiler for each chemical response
 - Compare multiple response profiles to understand reaction behaviour

Chris Gotwalt Fit Curve – CDoE Demonstration

Curve DOE Analysis Demo

	Expt Name	Sample Time / min	Solvent Volume / RV	Catalyst / mol %	Base / Equiv	Amine SM / Equiv	Product	Product Imp	SM	SM Imp
1	N1	3	8	1.3	4.5	1	29.375	0.8351	69.623	0.1674
2	N1	7	8	1.3	4.5	1	35.85	0.8283	63.027	0.2945
3	N1	11	8	1.3	4.5	1	39.816	0.8428	58.857	0.4844
4	N1	15	8	1.3	4.5	1	43.438	0.8693	55.102	0.5912
5	N1	20	8	1.3	4.5	1	47.531	0.9292	50.879	0.6609
6	N1	30	8	1.3	4.5	1	53.969	0.9954	44.227	0.809
7	N1	50	8	1.3	4.5	1	61.919	1.0611	36.096	0.9243
8	N1	100	8	1.3	4.5	1	66.736	1.282	31.091	0.8916
9	N1	150	8	1.3	4.5	1	70.972	1.3323	26.764	0.9308
10	N1	200	8	1.3	4.5	1	74.555	1.4797	22.934	1.0305
11	N1	250	8	1.3	4.5	1	76.611	1.56	20.675	1.1537
12	N1	300	8	1.3	4.5	1	77.024	1.6041	20.252	1.1202
13	N2	3	8	0.7	7.5	1.1	11.069	0.4895	88.197	0.2446
14	N2	7	8	0.7	7.5	1.1	34.798	0.6968	63.886	0.619
15	N2	11	8	0.7	7.5	1.1	54.966	0.9749	43.416	0.6434
16	N2	15	8	0.7	7.5	1.1	70.737	1.3847	27.302	0.5759
17	N2	20	8	0.7	7.5	1.1	83.222	1.8063	14.562	0.4093

How Curve DOE Works

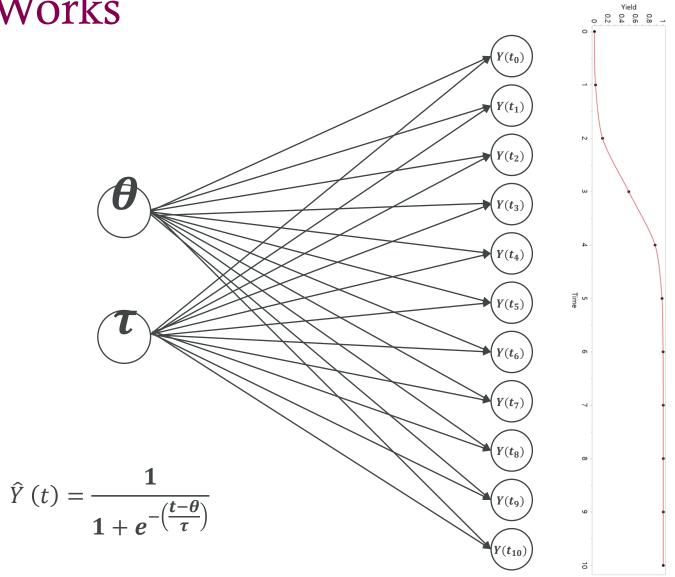


Responses

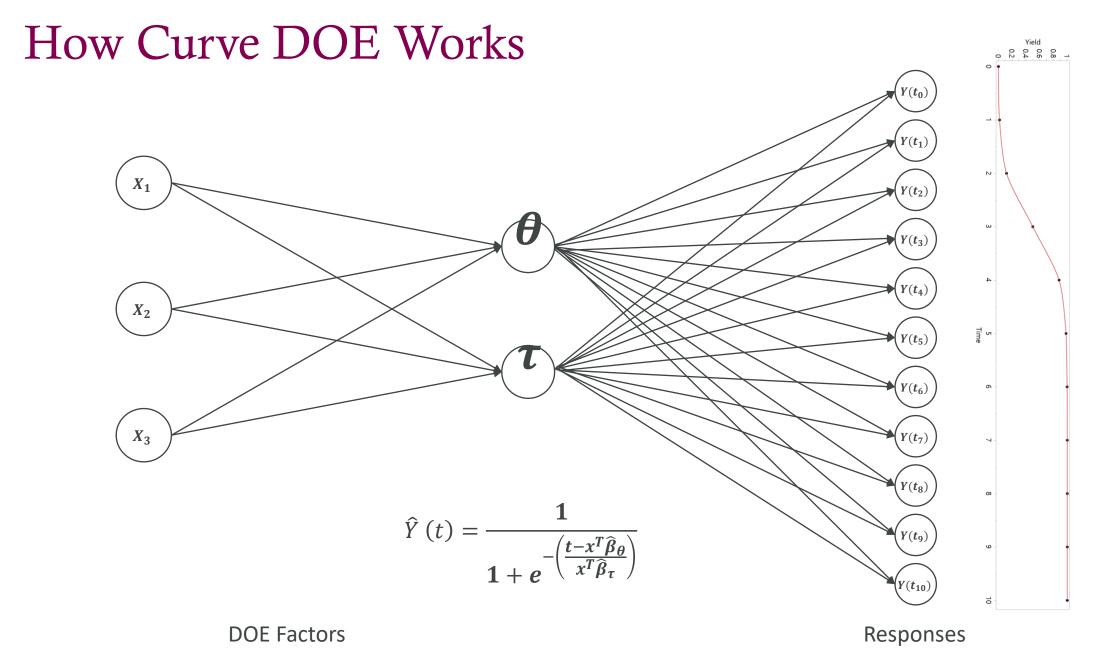


Statistical Discovery.™ From SAS.

How Curve DOE Works

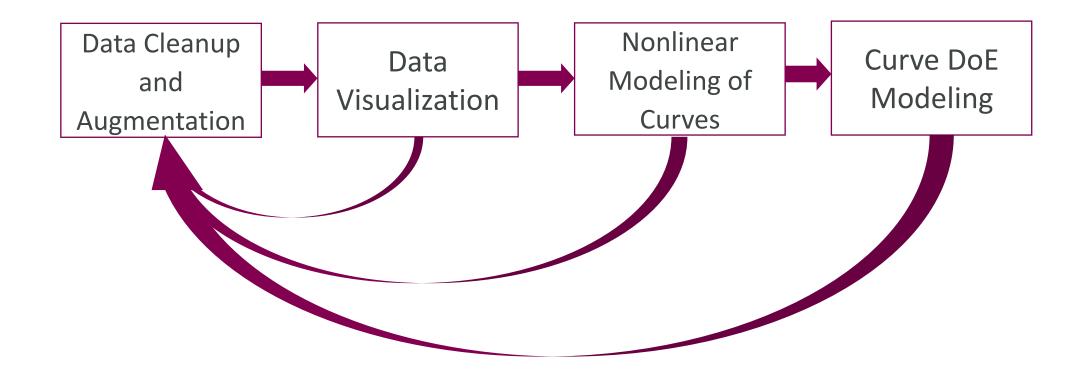


Responses

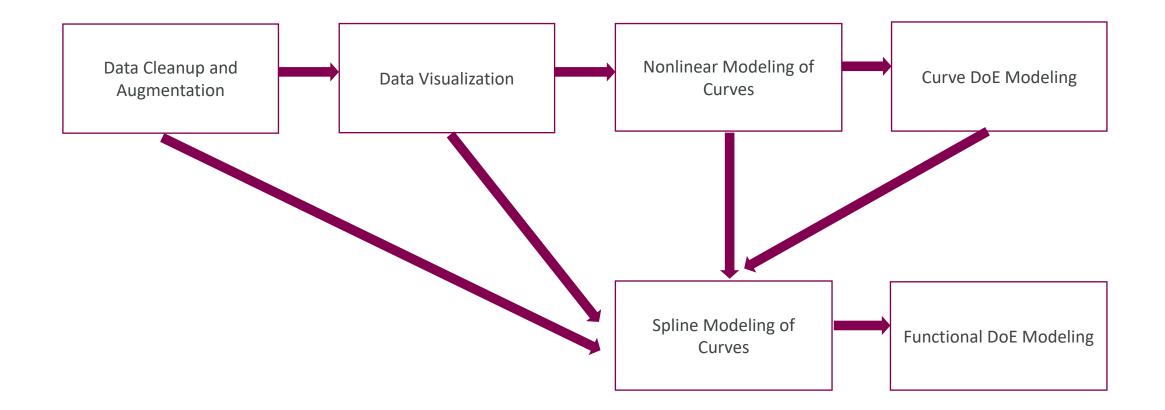


Statistical Discovery.™ From SAS.

Fit Curve Workflow



Fit Curve Workflow



Fit Curve or Functional Data Explorer?

• Is there scientific basis for a particular nonlinear function?

• Do the trajectories fall into one (and only one) of the supported shapes?

• Does there seem to be a time-translation effect that would be nicely modelled with a location parameter? • Is there little first principles theory to work from?

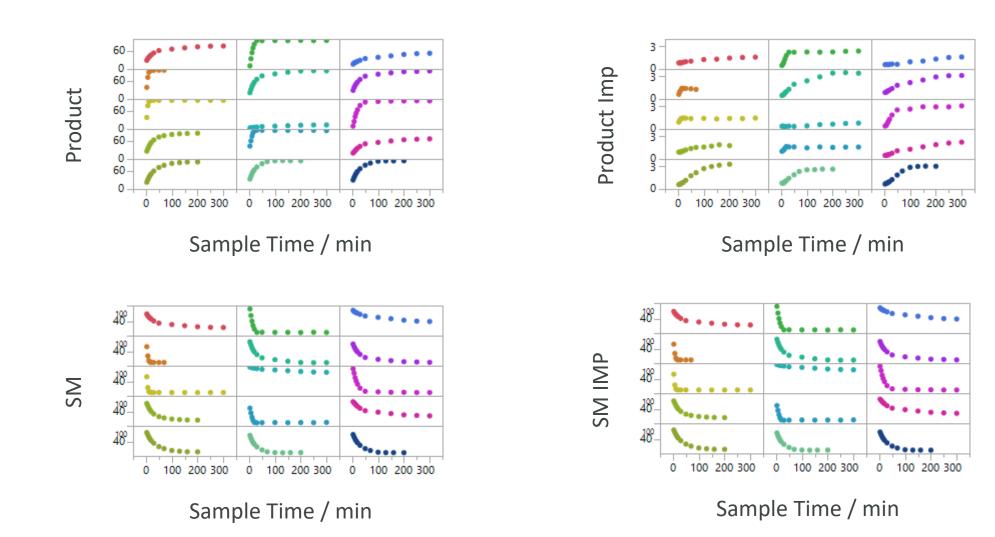
• Are the trajectories highly non-homogenous?

• Do the curves have three or more "features"?

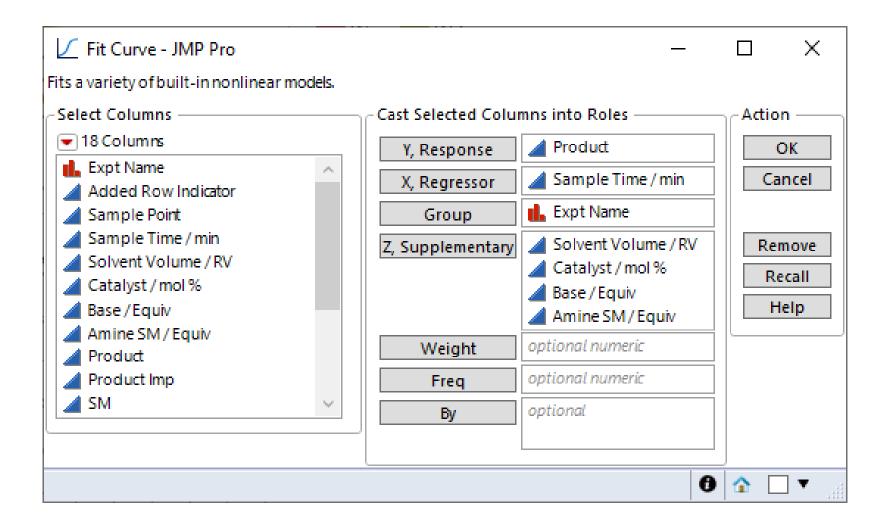
 $YES \Rightarrow$ Functional Data Explorer

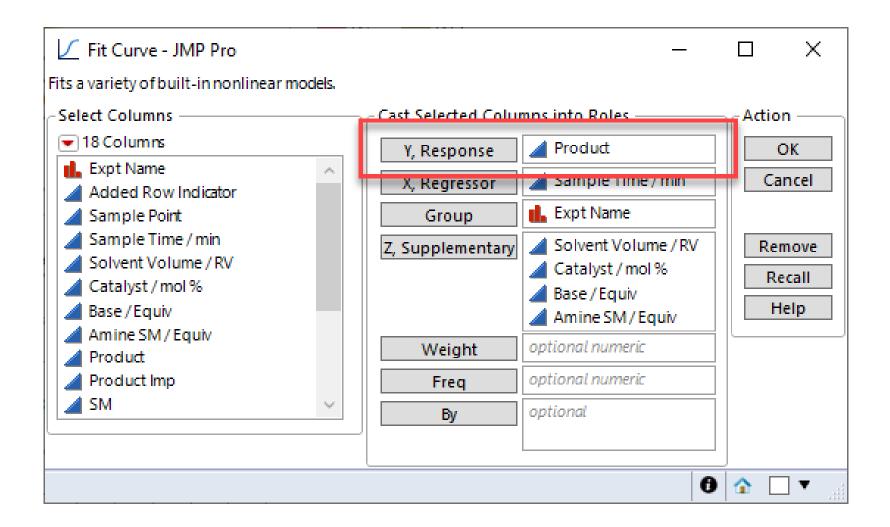


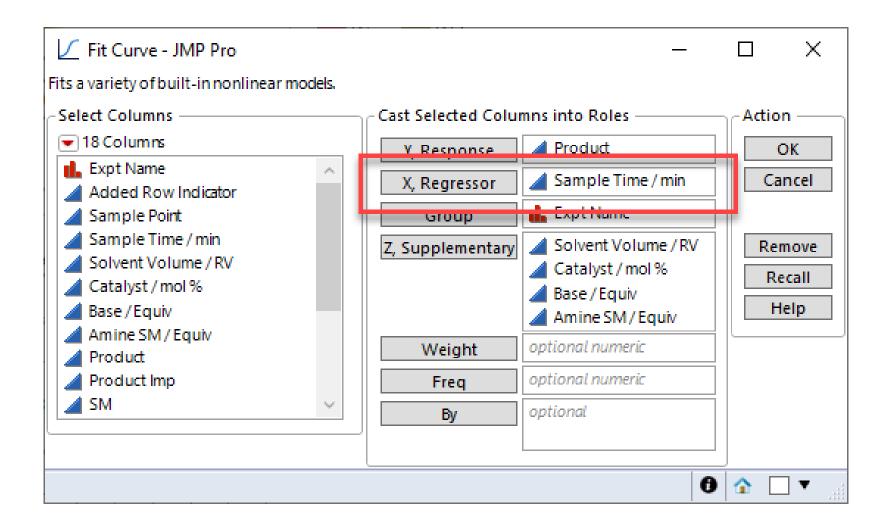
The Four Response Curves

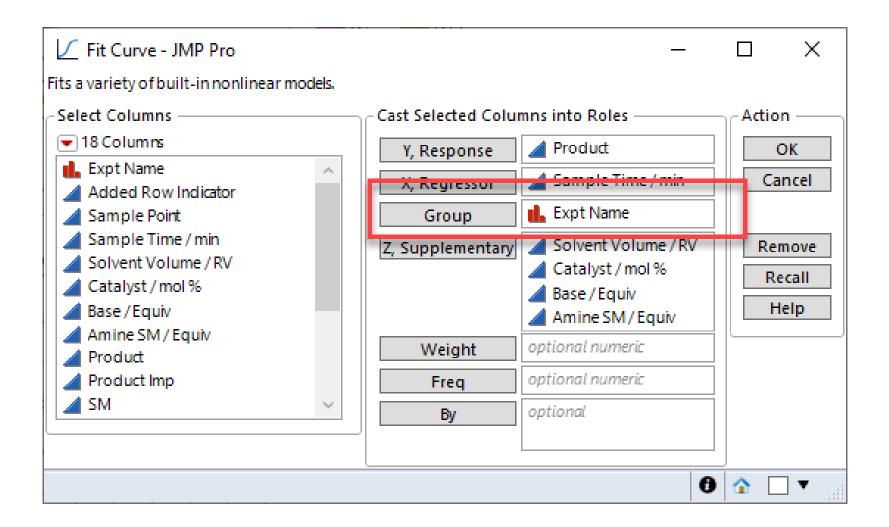


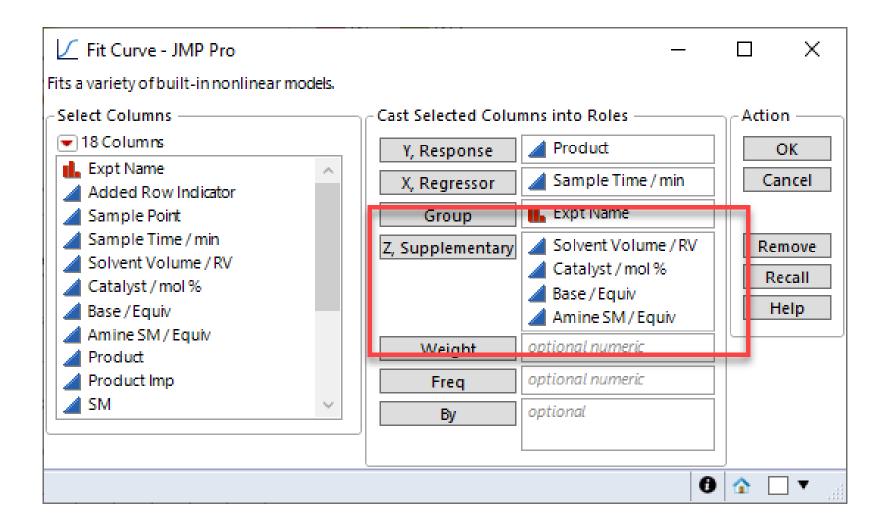
🕎 Fit Curve Example - JMP Pro									—		>
File Edit Tables Rows Col	s DOE	Analy	ze Graph Tools Add-Ins		/iew W	indow Help					
: 🛤 🎦 💕 🔚 🐰 🗈 🔍	56.		Distribution								
Fit Curve Example	· \	<u>у</u> х	Fit Y by X								
Design Definitive Screening Design Source			Tabulate								
Model DOE Dialog Crazy Curve DOE		-dat	Text Explorer		mol %	Base / Equiv	Amine SM / Equiv	Product	ProductImp	SM	1
Product CDOE Logistic3P	•	≥	Fit Model		1.3	4.5	1	29.37459756	0.835080239	69.622	9579
Product Imp CDOE Logistic3P	•	-			1.3	4.5	1	35.85010208	0.82834393	63.027	0626
 SM CDOE Expon3P SM Imp Fit Curve Overfit 	•		Predictive Modeling	•	1.3	4.5	1	39.81607367	0.84278963	58.856	7294
SM Imp FDOE P Spline	•		Specialized Modeling	•	🗹 F	it Curve	, 1	Fits a variety o	of built-in nonlir	near 101	6918
	•		Screening +	S. N	Nonlinear		models.		879	1406	
	•		Multivariate Methods		~ ["	ioninicai	1	53.96907749	0.995378004	44.226	5883
	•			1	🔅 F	unctional Data	Explorer 1	61.91892842	1.061143748	36.095	6525
Columna (11/0)	•		Clustering	*	. –		1	66.73583593	1.282049257	31.090	5086
💌 Columns (11/0)	•		Quality and Process		🤸 🛛 G	aussian Proces	s 1	70.97244996	1.332256616	26.764	4804
۹	•		-			ina Canina	1	74.5553563	1.479735172	22.934	4183
Expt Name	•		Reliability and Survival			Time Series		76.61089629	1.559971515	20.675	4739
Sample Point	•		Consumer Research		💥 т	ime Series Fore	cast 1	77.02376098	1.604085012	20.251	9814
Sample Time / min Solvent Volume / RV	•	1	3 8	-			1	11.06909695	0.489543727	88.196	7997
Catalyst / mol %			14 8		₩ N	Matched Pairs		34.79812829	0.696797357	63.886	0921



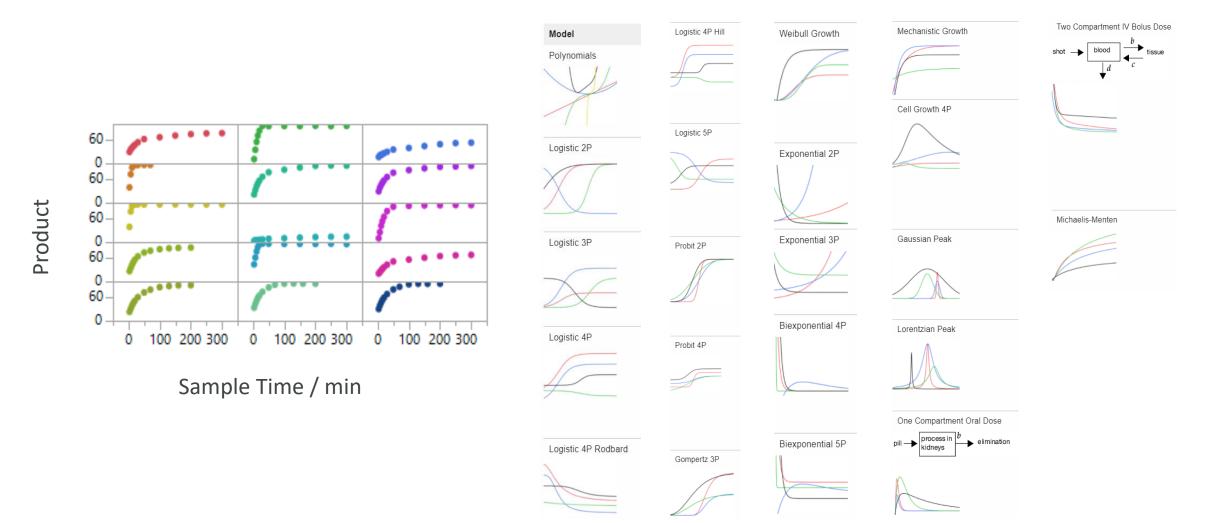






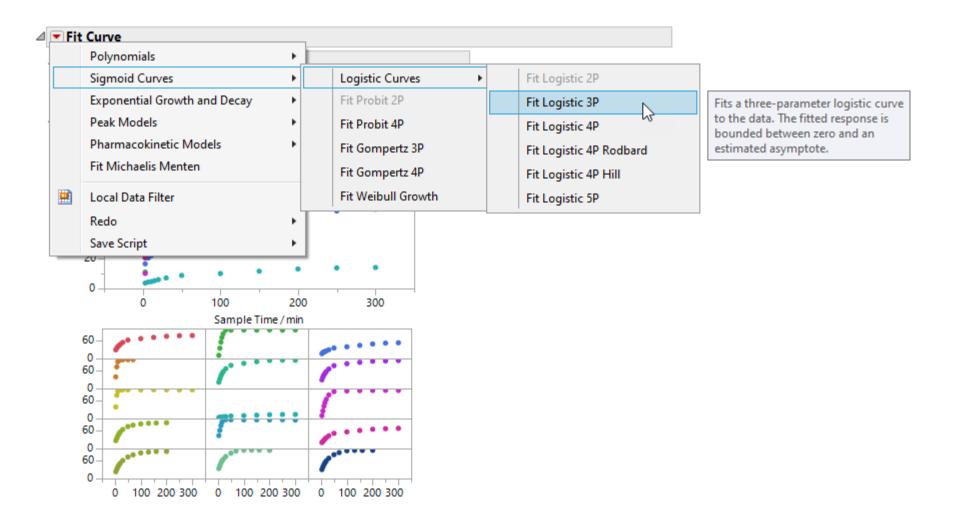


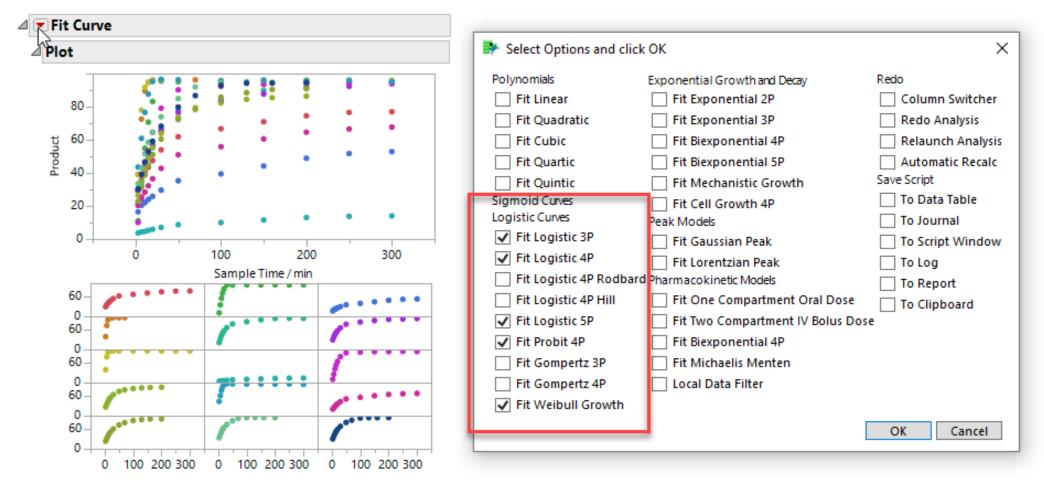
Data Visualization and the Nonlinear Model Key



S

Fitting Nonlinear Models To the Data





Alt+Right Click on red triangle to select multiple options

🛛 💌 Fit Curve

Model Comparison .2 .4 .6 .8 BIC SSE Model AICc ~ AICc Weight MSE RMSE R-Square Logistic 4P 2,4788613 1.57444 774.21661 901.26526 287.54791 0.9980418 1 Logistic 3P 925,40129 1.481e-33 970.09161 0.9933937 1037.7242 7.4052794 2.7212643 1132.045 Weibull Growth 1.989e-78 1244.3679 3138,5071 23,958069 0.9786268 4.8946981 Logistic 5P 1.19e-127 5000.6892 49.511775 7.0364604 0.9659454 1358,7337 1481.4682 Probit 4P 1463.7303 1.88e-150 1590.7789 14459.122 124.64761 11.164569 0.9015335

🖉 💌 Fit Curve

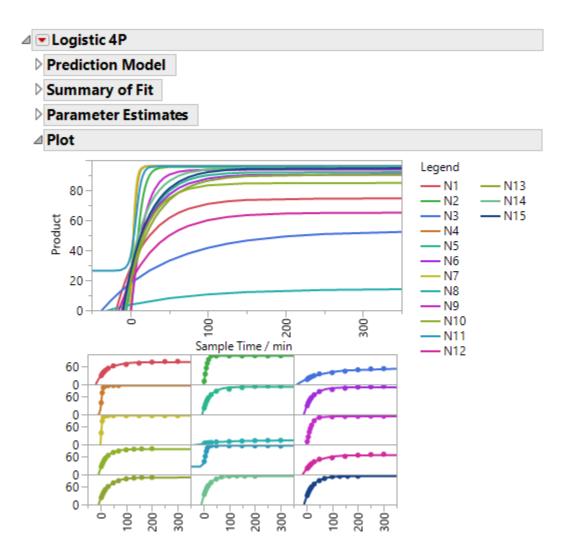
Δ	Model Comparison											
	Model	AICc ^	AICc Weight	.2	.4	.6	.8	BIC	SSE	MSE	RMSE	R-Square
	Logistic 4P	774.21661	1					901.26526	287.54791	2.4788613	1.57444	0.9980418
	Logistic 3P	925.40129	1.481e-33					1037.7242	970.09161	7,4052794	2.7212643	0.9933937
	Weibull Growth	1132.045	1.989e-78					1244.3679	3138.5071	23.958069	4.8946981	0.9786268
	Logistic 5P	1358.7337	1.19e-127					1481.4682	5000.6892	49.511775	7.0364604	0.9659454
	Probit 4P	1463.7303	1.88e-150					1590.7789	14459.122	124.64761	11.164569	0.9015335

🖉 💌 Fit Curve

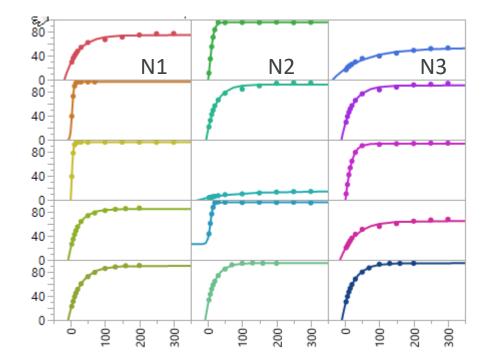
⊿ Model Comparison										
	Model	AICc ^	AICc Weight	.2 .4 .6 .8	BIC	SSE	MSE	RMSE	R-Square	
	Logistic 4P	774.21661	1		901.26526	287.54791	2.4788613	1.57444	0.9980418	
	Logistic 3P	925.40129	1.481e-33		1037.7242	970.09161	7.4052794	2.7212643	0.9933937	
	Weibull Growth	1132.045	1.989e-78		1244.3679	3138.5071	23.958069	4.8946981	0.9786268	
	Logistic 5P	1358.7337	1.19e-127		1481.4682	5000.6892	49.511775	7.0364604	0.9659454	
	Probit 4P	1463.7303	1.88e-150		1590.7789	14459.122	124.64761	11.164569	0.9015335	



Logistic 4P Model



Logistic 4P Model



🛛 💌 Logistic 4P

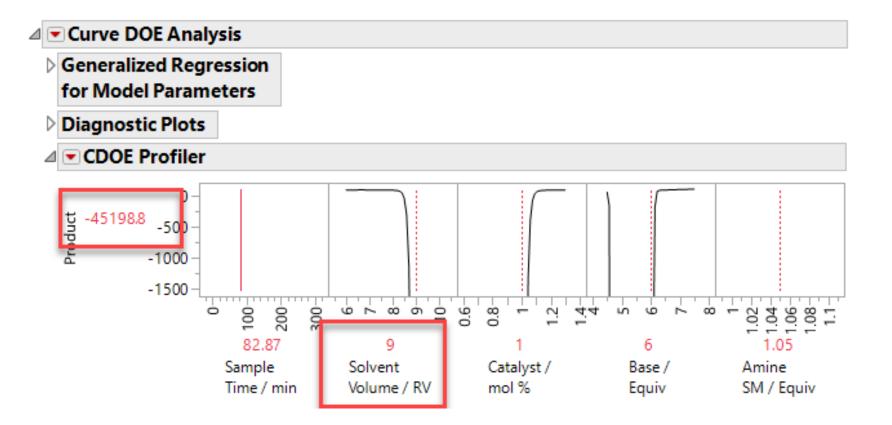
Prediction Model

Summary of Fit

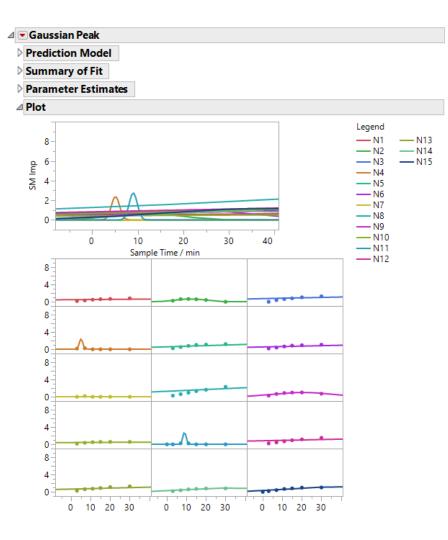
Parameter Estimates

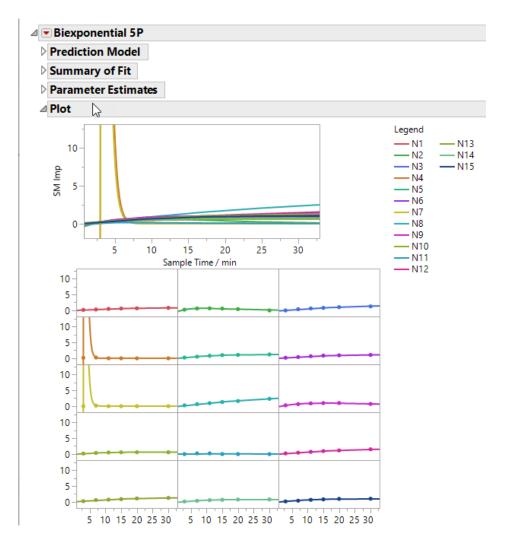
Parameter	Group	Estimate	Std Error
Growth Rate	N1	0.0254486	0.0080311
Inflection Point	N1	-431.7105	1141239
Lower Asymptote	N1	-2751999	7.992e+10
Upper Asymptote	N1	/4.50802/	0.9428258
Growth Rate	N2	0.1636571	0.0169077
Inflection Point	N2	5.4759384	1.9387716
Lower Asymptote	N2	-44.86278	21.420603
Upper Asymptote	N2	95.642648	0.6257901
Growth Rate	N3	0.0112444	0.0071275
Inflection Point	N3	-1159.956	33420084
Lower Asymptote	N3	-16149627	6.069e+12
Upper Asymptote	N3	52.970350	2.8297727
Growth Rate	N4	0.3668455	0.0869127
Inflection Point	N4	3.8772156	2.1243712
Lower Asymptote	N4	-2.131121	35.994322
Upper Asymptote	N4	96.311589	0.7976433

Logistic 4P Model

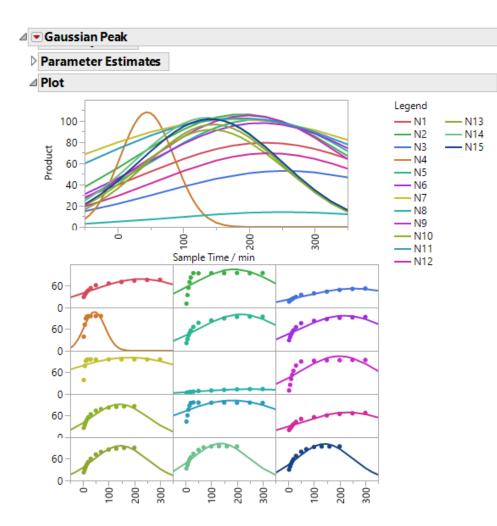


Checking the Nonlinear Model

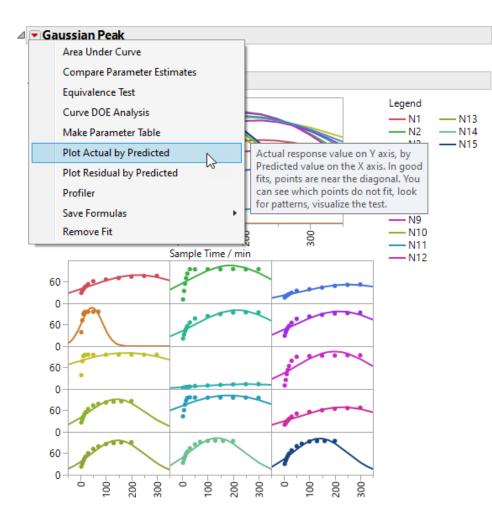


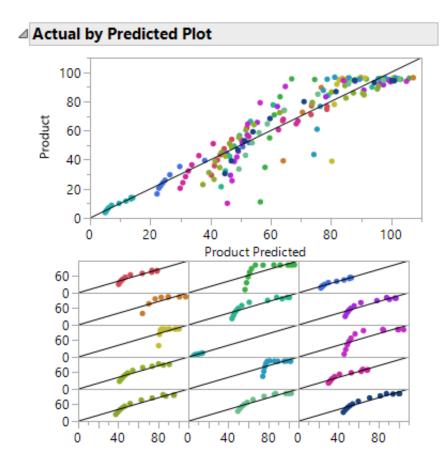


Checking the Nonlinear Model



Checking the Nonlinear Model



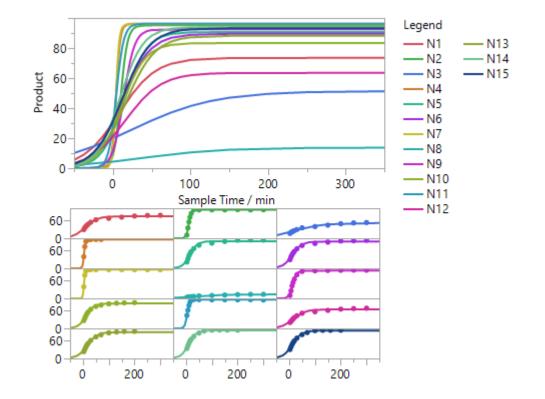


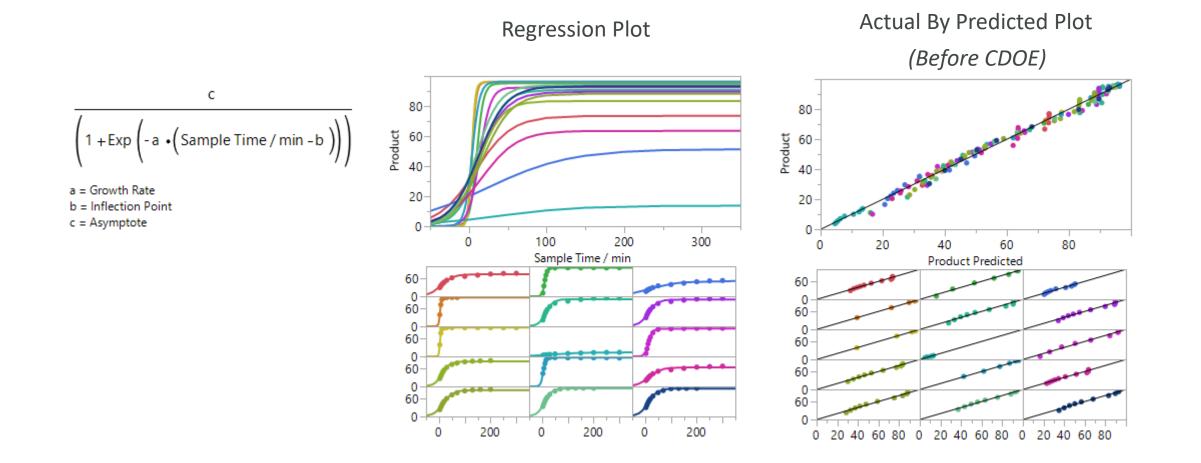
⊿ 💌 Logistic 3P

Prediction Model

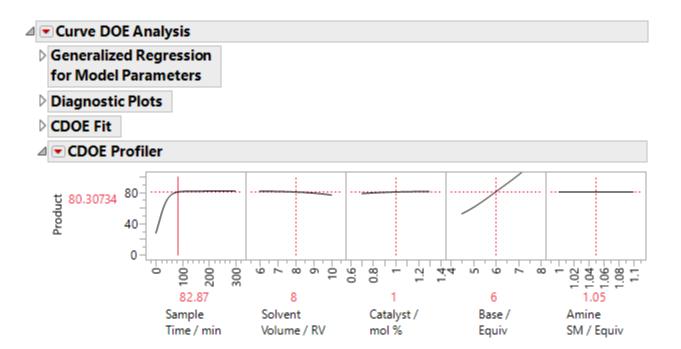
$\frac{c}{\left(1 + Exp\left(-a \cdot \left(Sample Time / min - b\right)\right)\right)}$

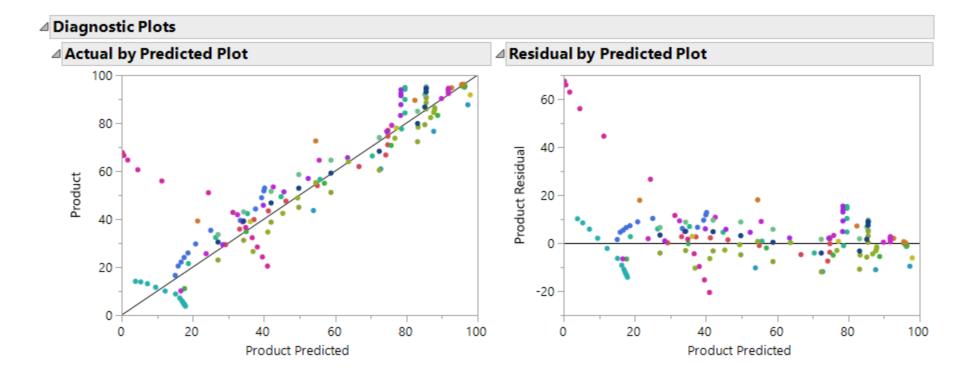
a = Growth Rate b = Inflection Point c = Asymptote

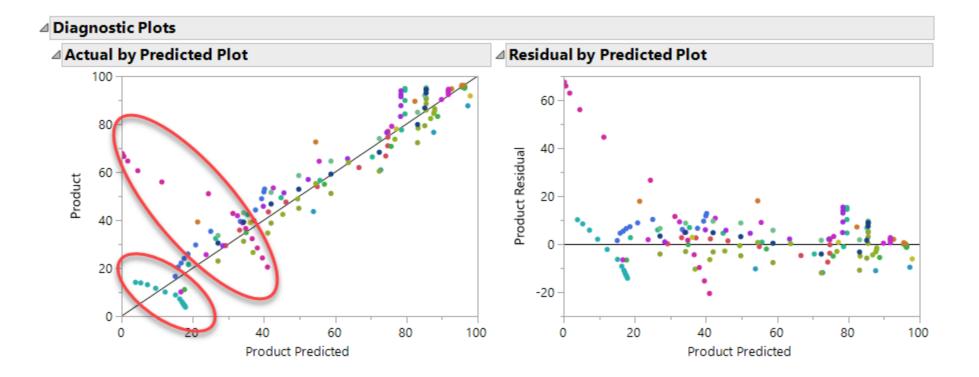


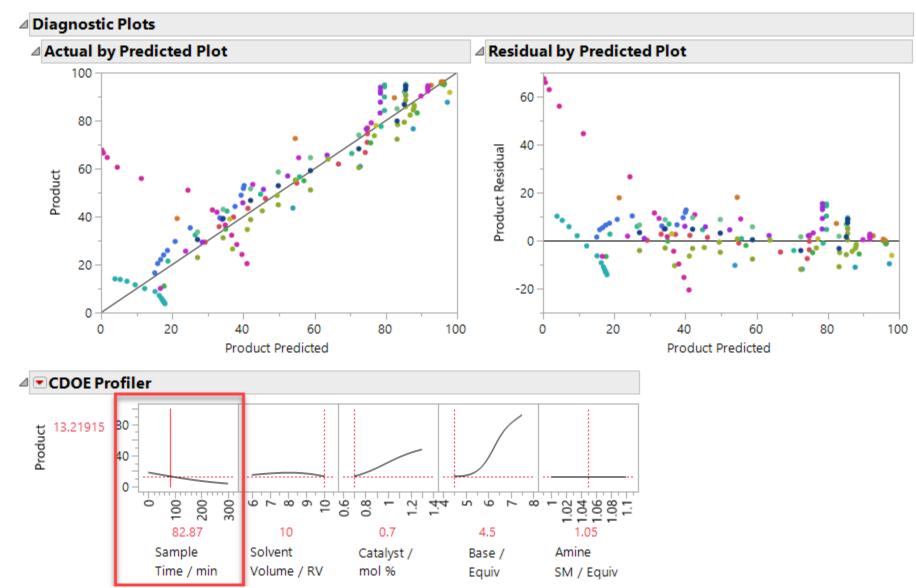


✓ Fit Curve	
⊿ 🔽 Loaistic 3P	
Test Parallelism	
Compare Parameter Estimates	
Equivalence Test	
Curve DOE Analysis	
Make Parameter Table	Legend N1 N13
✓ Plot Actual by Predicted —	— N2 — N14
Plot Residual by Predicted	——————————————————————————————————————
Profiler	N5
Save Formulas	N6 N7
Custom Inverse Prediction	N8 N9
Remove Fit	300 — N10
Sample Time / min	— N11 — N12
60-	NIL .
0	
60-	
60 -	
0	
	200









⊿ ⊂ Curve DOE Analysis

Generalized Regression for Model Parameters

Generalized Regression

for Growth Rate

Generalized Regression

for Inflection Point

⊿ ⊂ Curve DOE Analysis

Generalized Regression for Model Parameters

Generalized Regression

for Growth Rate

Generalized Regression

for Inflection Point

⊿ ⊂ Curve DOE Analysis

Generalized Regression for Model Parameters

Generalized Regression

for Growth Rate

Generalized Regression

for Inflection Point

⊿ ⊂ Curve DOE Analysis

Generalized Regression for Model Parameters

Generalized Regression

for Growth Rate

Generalized Regression

for Inflection Point

⊿ ⊂ Curve DOE Analysis

⊿	Generalized	Regression	for Model	Parameters
---	-------------	------------	-----------	------------

⊿ Generalized Regression for Growth Rate

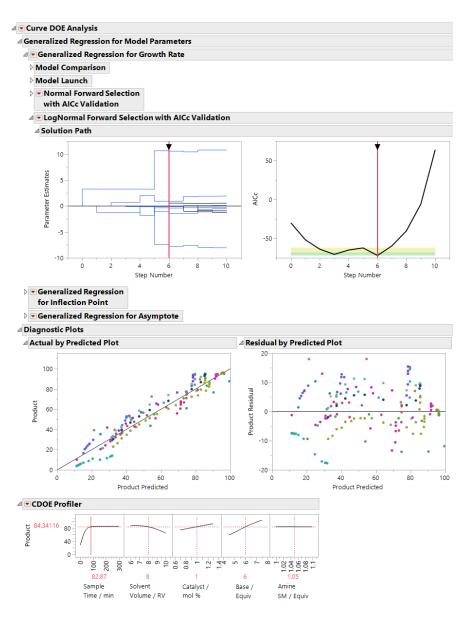
Model Comparison

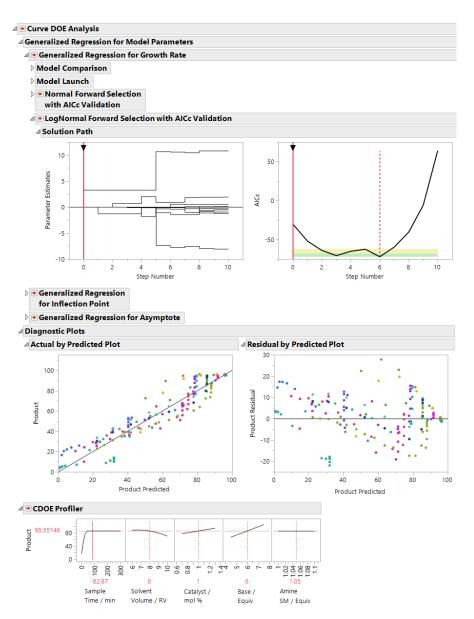
Normal Forward Selection AICc 6 -39.33529 -45.58699 odel Launch ingularity Details sponse Distribution Iormal Iormal auchy 5) xponential iamma /eibull		•					
odel Launch ingularity Details sponse Distribution lormal auchy 5) xponential aamma /eibull ogNormal	Show					AICc	BIC
ingularity Details sponse Distribution lormal auchy 5) xponential amma /eibull ogNormal]	Normal	Forward Selection	AICc	6	-39.33529	-45.58699
sponse Distribution lormal auchy 5) xponential amma /eibull ogNormal	Aode	el Launch					
lormal lormal auchy 5) xponential amma /eibull ogNormal	Sing	gularity Deta	ails				
Iormal auchy 5) ~ xponential amma /eibull ogNormal	espo	onse Distribution	ı ———				
auchy 5) ~ xponential amma /eibull ogNormal	Nor	mal	~				
5) v xponential amma /eibull ogNormal	Nor	mal					
xponential amma /eibull ogNormal	Cau	chy					
amma /eibull ogNormal	t(5)		~				
/eibull ogNormal	Expo	onential					
ogNormal	Gam	ima					
	Weik	oull					
	Logi	Normal					
eta	Beta						
Quantile Regression	Cox	Proportional Ha	azards				
ox Proportional Hazards	I ——		I				

⊿ ⊂ Curve DOE Analysis

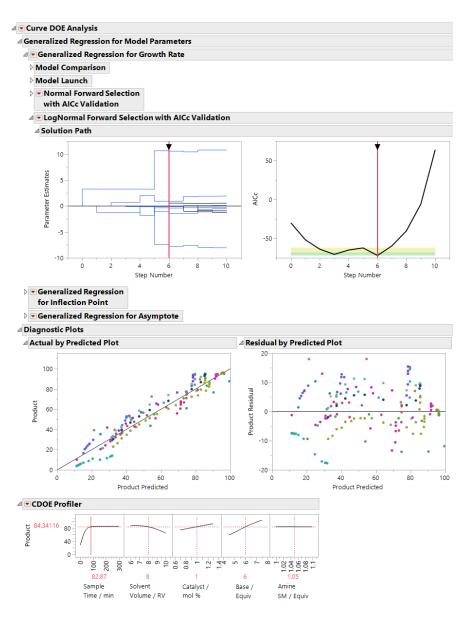
- ⊿ Generalized Regression for Model Parameters
 - ⊿ Generalized Regression for Growth Rate
 - Model Comparison
 - ⊿ Model Launch

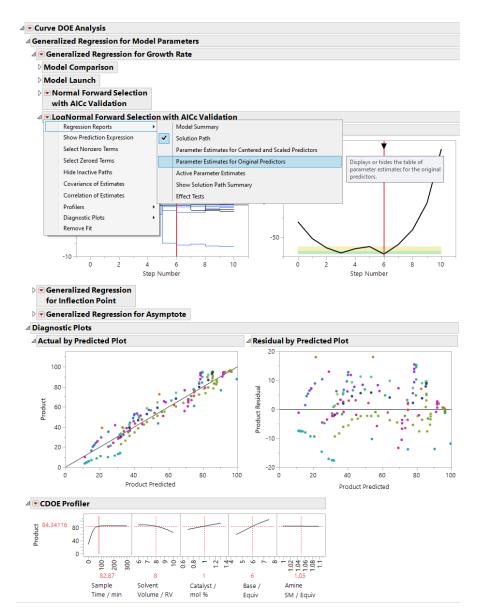
Singularity Details
Response Distribution
Normal
Estimation Method
Forward Selection ~
Advanced Controls
Enforce Effect Heredity
Initial Displayed Solution Best Fit
Force Terms
Validation Method —
AlCc ×



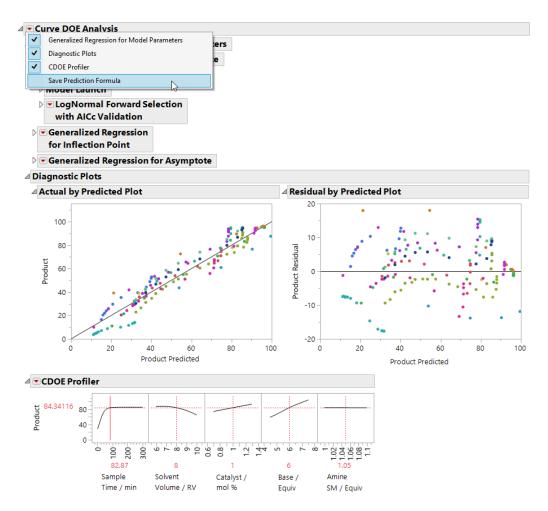




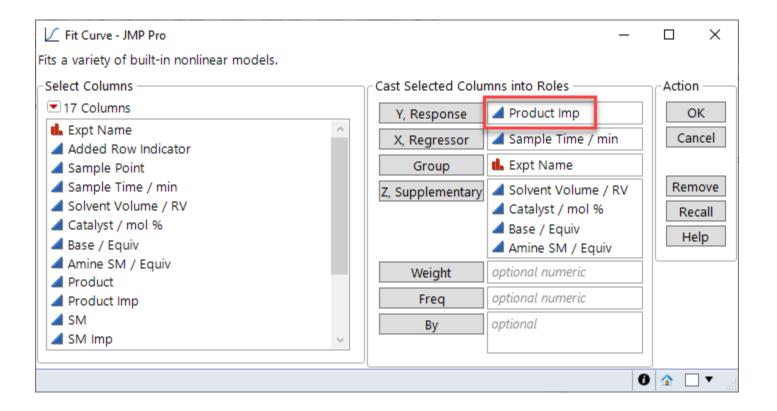


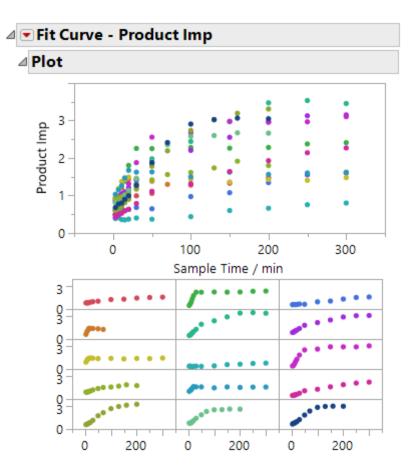


eneralized Regression for	or Model Pa	arameters						
- Generalized Regressio	on for Grow	/th Rate						
Model Comparison								
Model Launch								
Normal Forward Sel								
with AICc Validation								
🛛 💌 LogNormal Forward	Selection	with AICc V	alidation					
		+			1		+	
10 -	ſ		/				Ĭ	1
				50 -				
Parameter Estimates								/
								/
E -				0 AIC				/
0 6				_				
e j								/
								/
-5 -								/
- 1								
				-50 -			_ /	
_			·	-50 -				
-10 0 2	4	6	8 10	-50 -		2 4		8 10
-10	4 Step Nu		 8 10	-50 -	0		6 Number	8 10
-10 0 2	Step Nu	umber		-50 -	0			8 10
-10	Step Nu	umber				Step		8 10
-10 0 2	Step Nu	umber		Wald	Prob > ChiSquare	Step	Number	
-10 0 2	Step Nu	umber al Predictor	s Std Error	Wald	Prob > _	Step	Number Upper 95%	Singularity Detai
-10 - 0 2	Step Nu	al Predictor Estimate	Std Error 0.0224568	Wald ChiSquare	Prob > ChiSquare	Step	Number Upper 95%	Singularity Detai =17.111*Intercept
-10 0 2 Parameter Estimates Term Base / Equiv [®] Base / Equiv	Step Nu	umber al Predictor Estimate 0.1866392	S Std Error 0.0224568 0.0291016	Wald ChiSquare 69.073488	Prob > ChiSquare <.0001*	Step Lower 95% 0.1426248	Number Upper 95% 0.2306537	Singularity Detai =17.111*Intercept
-10-02 Parameter Estimates Term Base / Equiv/Base / Equiv Solvent Volume / RV	Step Nu	umber al Predictor Estimate 0.1866392 -0.168498	Std Error 0.0224568 0.0291016 0.2715392	Wald ChiSquare 69.073488 33.524041	Prob > ^ ChiSquare <.0001* <.0001*	Step Lower 95% 0.1426248 -0.225536	Number Upper 95% 0.2306537 -0.11146	Singularity Detai =17.111*Intercept
-10 0 2 Parameter Estimates Term Base / Equiv [®] Base / Equiv Solvent Volume / RV Base / Equiv	Step Nu	umber al Predictor Estimate 0.1866392 -0.168498 -1.564481	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395	Wald ChiSquare 69.073488 33.524041 33.195207	Prob > ChiSquare <.0001* <.0001* <.0001*	Step Lower 95% 0.1426248 -0.225536 -2.096688	Number Upper 95% 0.2306537 -0.11146 -1.032274	Singularity Deta =17.111*Intercept
-10 0 2 ■ Parameter Estimates Term Base / Equiv*Base / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %*Catalyst /	Step Nu	al Predictor Estimate 0.1866392 -0.168498 -1.564481 0.4771401	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052	Wald ChiSquare 69.073488 33.524041 33.195207 11.444846	Prob > ChiSquare <.0001* <.0001* <.0001* 0.0007*	Step Lower 95% 0.1426248 -0.225536 -2.096688 0.2007076	Number Upper 95% 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022	Singularity Deta = 17.111*Intercept
-10 - 0 2 Parameter Estimates Term Base / Equiv"Base / Equiv Solvent Volume / RV Base / Equiv Catalyst / imil %°Catalyst / intercept	Step Nu s for Origina	Al Predictor Estimate 0.1866392 -0.168498 -1.564481 0.4771401 1.5977317	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215	Wald ChiSquare 69.073488 33.524041 33.195207 11.444846 4.3301771	Prob > ChiSquare <.0001* <.0001* 0.0007* 0.0374*	Step Lower 95% 0.1426248 -0.225536 -2.096688 0.2007076 0.0928613	Number Upper 95% 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022	Singularity Detai = 17.111*Intercept = 0.6796*Intercept
Parameter Estimates Term Base / Equiv*Base / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %°Catalyst / Intercept Amine SM / Equiv	s for Origina mol % yst / mol %	al Predictor Estimate 0.1866392 -0.168498 -1.56481 0.4771401 1.5977317 -0.59341 -0.033073	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215 0.0329536	Wald ChiSquare 69.073488 33.524041 33.195207 11.444846 4.3301771 2.2692895	Prob > ChiSquare <.0001* <.0001* 0.0007* 0.0374* 0.1320	Step Lower 95% 0.1426248 -0.225536 -2.096688 0.2007076 0.0928613 -1.365481	Number Upper 95% 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022 0.1786622	Singularity Detai = 17.111*Intercept = 0.6796*Intercept
Parameter Estimates Term Base / Equiv*Base / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %*Catalyst / Intercept Amine SM / Equiv Solvent Volume / RV*Cataly Solvent Volume / RV*Solve Solvent Volume / RV*Solve	Step Nu s for Origina ' mol % yst / mol % int Volume / R' / Equiv	Al Predictor Estimate 0.1866392 -0.168498 -1.564481 0.4771401 1.5977317 -0.59341 -0.033073 V 0 0	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215 0.0329536 0 0 0 0 0 0 0	Wald ChiSquare 69.073488 33.524041 33.195207 11.444846 4.3301771 2.2692895 1.0072704	Prob > ChiSquare <.0001* <.0001* 0.0007* 0.0374* 0.1320 0.3156 1.0000	Step Lower 95% 0.1426248 -2.096688 0.207076 0.0928613 -1.365481 -0.097661 0 0 0 0	Number Upper 95% 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022 0.1786622 0.0315147	Singularity Detai = 17.111*Intercept = 0.6796*Intercept
10 10 0 2 Parameter Estimates Term Base / Equiv*Base / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %*Catalyst / Intercept Amine SM / Equiv Solvent Volume / RV*Cataly Solvent Volume / RV*Cataly	Step Nu s for Origina ' mol % yst / mol % int Volume / R' / Equiv	Al Predictor Estimate 0.1866392 -0.188498 -1.56481 0.4771401 1.5977317 -0.59341 -0.033073 V 00 0 0 0 0 0 0 0 0 0 0 0 0	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0	Wald ChiSquare 69.073488 33.524041 33.195207 11.444846 4.3301771 2.2692895 1.0072704 0	Prob > ChiSquare <.0001* <.0001* 0.0007* 0.0374* 0.1320 0.3156 1.0000	Step 0.1426248 -0.225536 -2.096688 0.2007076 0.0928613 -1.365481 -0.097661 0 0 0 0 0 0	Number Upper 95% 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022 0.1786622 0.0315147 0	Singularity Detai =17.111"Intercept =0.6796"Intercept
10 10 0 2 Parameter Estimates Term Base / Equiv*Base / Equiv Solvent Volume / RV* Solvent Volume / RV*Catalyst Intercept Amine SM / Equiv Solvent Volume / RV*Cataly Solvent / RV*Cataly Solven	Step Nu s for Origina mol % yst / mol % nt Volume / R ¹ / Equiv e SM / Equiv	Al Predictor Estimate 0.1866392 -0.186481 0.4771401 1.5977317 -0.59341 -0.033073 V 00 0 0 0 0 0 0 0 0 0 0 0 0	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215 0.3939215 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0	Wald Chi5quare 69.073488 33.524041 33.195207 11.444846 4.3301771 2.2692895 1.0072704 0 0 0 0 0	Prob > ChiSquare <.0001* <.0001* 0.007* 0.1320 0.3156 1.0000 1.0000 1.0000	Step Lower 95% 0.1426248 -0.225536 0.2096688 0.2007076 0.0928613 -1.365481 -0.097661 0 0 0 0 0 0 0 0 0 0 0 0 0	Number Upper 95% 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022 0.1786622 0.0315147 0 0 0 0 0 0 0 0 0 0 0	Singularity Detai =17.111"Intercept =0.6796"Intercept
Parameter Estimates Term Base / Equiv"Base / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %"Catalyst / Intercept Amine SM / Equiv Solvent Volume / RV"Salve Solvent	Step Nu s for Origina " mol % yst / mol % int Volume / R ¹ / Equiv e SM / Equiv uiv	Al Predictor Estimate 0.186392 -0.168498 -1.564481 0.4771401 1.5977317 -0.59341 -0.033073 V 0 0 0 0 0 0 0 0 0 0 0 0 0	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.33939215 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0	Wald ChiSquare 69.07348 33.524041 33.195207 11.444846 4.3301771 2.2692895 1.0072704 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Prob > ChiSquare <.0001* <.0001* 0.007* 0.3556 1.0000 1.0000 1.0000 1.0000	Step 0.1426248 -0.225536 -2.096688 0.2027076 0.0928613 -1.365481 -0.097661 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Number 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022 0.1786622 0.0315147 0 0 0 0 0 0 0 0 0 0 0 0	Singularity Detai =17.111"Intercept =0.6796"Intercept
10 10 0 2 Parameter Estimates Term Base / Equiv*Base / Equiv Solvent Volume / RV* Solvent Volume / RV*Catalyst Intercept Amine SM / Equiv Solvent Volume / RV*Cataly Solvent / RV*Cataly Solven	Step Nu s for Origina " mol % yst / mol % int Volume / R ¹ / Equiv e SM / Equiv uiv	Imper Impertation Estimate 0.1866392 0.1866392 0.186481 0.4771401 1.5977317 0.033073 0.03073 0 0.00 0 0 0	S Std Error 0.0224560 0.0291016 0.2715392 0.1410395 0.7676052 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0	Wald ChiSquare 69.073488 33.195207 11.44484 11.44484 4.3301771 2.2692895 1.0072704 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Prob > ChiSquare <.0001* <.0001* <.0001* 0.03756 0.03756 1.0000 1.0000 1.0000 1.0000	Step Lower 95% 0.1426248 -0.225536 -2.096688 0.2007076 0.0926613 -1.365481 -0.097661 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Number Upper 95% 0.2306537 -0.11146 -1.032274 0.7535725 3.1026022 0.01786622 0.0315147 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Singularity Detai =17.111"Intercept =0.6796"Intercept
Parameter Estimates Term Base / EquivBase / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %"Catalyst / Intercept Amine SM / Equiv Solvent Volume / RV"Solve Solvent Volume / RV"Sate, Solvent / RV"Sate, Solvent / RV"Sate, Solvent / RV Solvent / RV	Step Nu stor Origina mol % mol % mt Volume / R1 / Equiv e SM / Equiv uiv 4 / Equiv quiv	Al Predictor Estimate 0.1866322 -0.168498 -1.554481 0.4771401 1.5977317 -0.59341 -0.033073 V 0 0 0 0 0 0 0 0 0 0 0 0 0	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3399215 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0	Wald ChiSquare 69.073488 33.524041 33.15207 11.444846 4.3301771 2.2692895 1.0072704 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Prob > Chi5quare <.0001* <.0001* 0.0007* 0.0374* 0.1320 0.3156 1.0000 1.0000 1.0000 1.0000 1.0000	Step Lower 95% 0.1426248 -0.225536 -2.096688 0.0097661 -0.097661 0 0 0 0 0 0 0 0 0 0 0 0 0	Number	Singularity Detai =17.111*Intercept =0.6796*Intercept =-1.3037*Intercept
Parameter Estimates Term Base / Equiv"Base / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %"Catalyst / Intercept Amine SM / Equiv Solvent Volume / RV"Solve Solvent Volume / RV"Solve Solvent Volume / RV"Solve Solvent Volume / RV"Salve Solvent Volume / RV"Salve Solvent Volume / RV"Salve Solvent Volume / RV"Salve Solvent Volume / RV"Base / Eq Catalyst / mol %"Base / Eq Catalyst / mol %"Base / Equiv"Amine SM Base / Equiv"Amine SM / Equiv"Amine SM Base / Equiv"Amine SM / Equiv"Amine SM	Step Nu stor Origina mol % mol % mt Volume / R1 / Equiv e SM / Equiv uiv 4 / Equiv quiv	Imper Impertation Estimate 0.1866392 0.1866392 0.186481 0.4771401 1.5977317 0.033073 0.03073 0 0.00 0 0 0	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Wald ChiSquare 69.073488 33.524041 33.52507 11.444846 4.3301771 2.2692895 1.0072704 0	Prob > ChiSquare <.0001* <.0001* <.0001* 0.03756 0.03756 1.0000 1.0000 1.0000 1.0000	Step Lower 95% 0.1426248 -0.225536 -2.096688 0.2007076 0.0926613 -1.365481 -0.097661 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Number	Singularity Detai =17.111"Intercept =0.6796"Intercept
Parameter Estimates Term Base / EquivBase / Equiv Solvent Volume / RV Base / Equiv Catalyst / mol %"Catalyst / Intercept Amine SM / Equiv Solvent Volume / RV"Solve Solvent Volume / RV"Sate, Solvent / RV"Sate, Solvent / RV"Sate, Solvent / RV Solvent / RV	Step Nu stor Origina mol % mol % mt Volume / R1 / Equiv e SM / Equiv uiv 4 / Equiv quiv	Imperiation al Predictor Estimate 0.186392 0.186392 0.186392 0.186392 0.186392 0.186392 0.186392 0.186392 0.186392 0.186392 0.186392 0.186392 0.03073 0 <td>S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0</td> <td>Wald ChiSquare 69.073488 33.524041 33.15207 11.444846 4.3301771 2.2692895 1.0072704 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0</td> <td>Prob > ChiSquare <.0001* <.0001* 0.0007* 0.3156 1.00000 1.0000 1.00000 1.00000 1.00000 1.00000 1.00000</td> <td>Step</td> <td>Number</td> <td>Singularity Deta =17.111"Intercept =0.6796"Intercept =-1.3037"Intercept</td>	S Std Error 0.0224568 0.0291016 0.2715392 0.1410395 0.7678052 0.3939215 0.0329536 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Wald ChiSquare 69.073488 33.524041 33.15207 11.444846 4.3301771 2.2692895 1.0072704 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Prob > ChiSquare <.0001* <.0001* 0.0007* 0.3156 1.00000 1.0000 1.00000 1.00000 1.00000 1.00000 1.00000	Step	Number	Singularity Deta =17.111"Intercept =0.6796"Intercept =-1.3037"Intercept



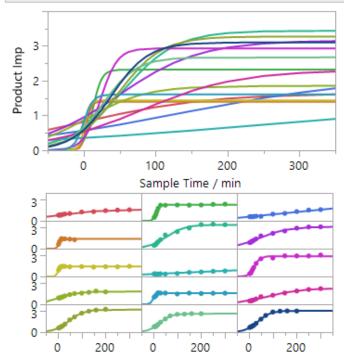
S





- Fit Curve Product Imp
 Model Comparison
 Plot
 Logistic 3P
 - Prediction Model
 - Summary of Fit
 - Parameter Estimates





Curve DOE Analysis Generalized Regression for Model Parameters ✓ Generalized Regression for Growth Rate Model Comparison Model Launch LogNormal Forward Selection with AICc Validation Generalized Regression for Inflection Point Generalized Regression for Asymptote ⊿ Diagnostic Plots Residual by Predicted Plot ⊿ Actual by Predicted Plot 1.5 1.0 3 Product Imp Residual 0.5 Product Imp 2. -0.5 -1.0 0 -0.5 1.5 2 2.5 0 0.5 1.5 0 Product Imp Predicted Product Imp Predicted CDOE Profiler Product Imp 1.966362 3 ò 100 200 300 ú r ò Ó ò Ó. 55 - ún Ó 26621 82.87 6 1.05

Catalyst /

mol %

Base /

Equiv

Amine

SM / Equiv

Sample

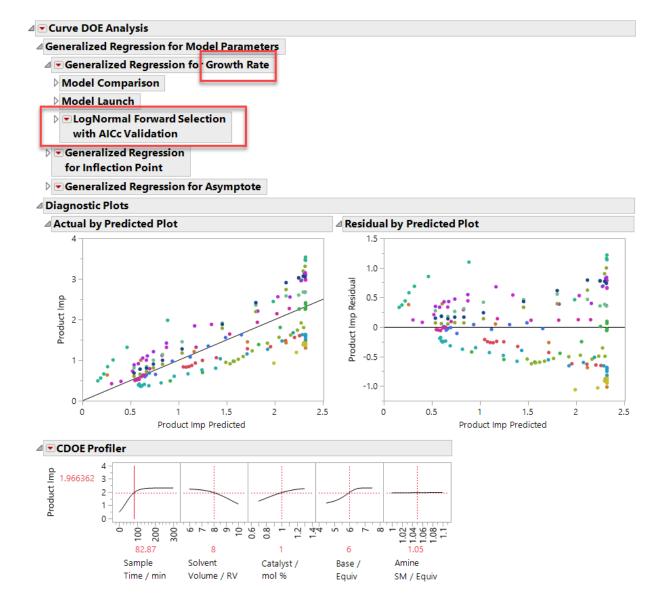
Time / min

Solvent

Volume / RV

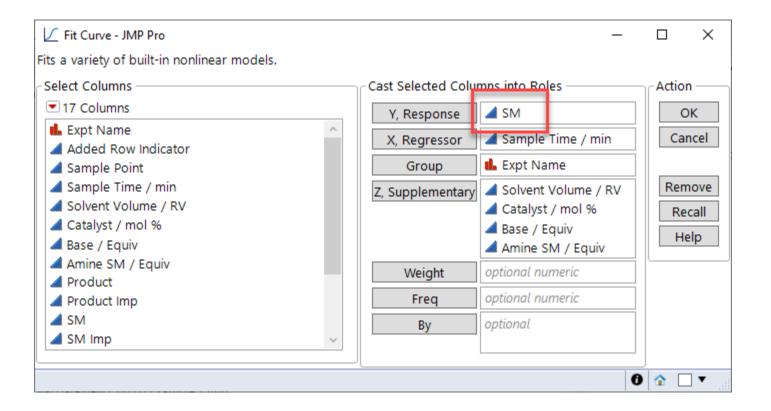
2

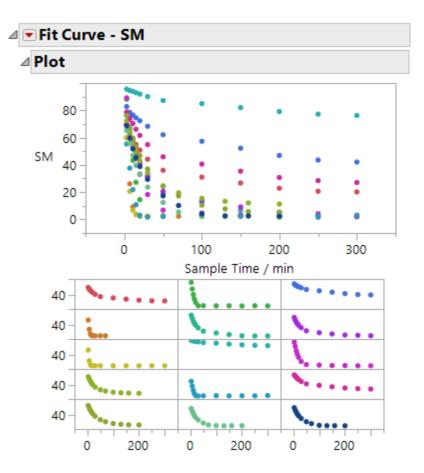
2.5



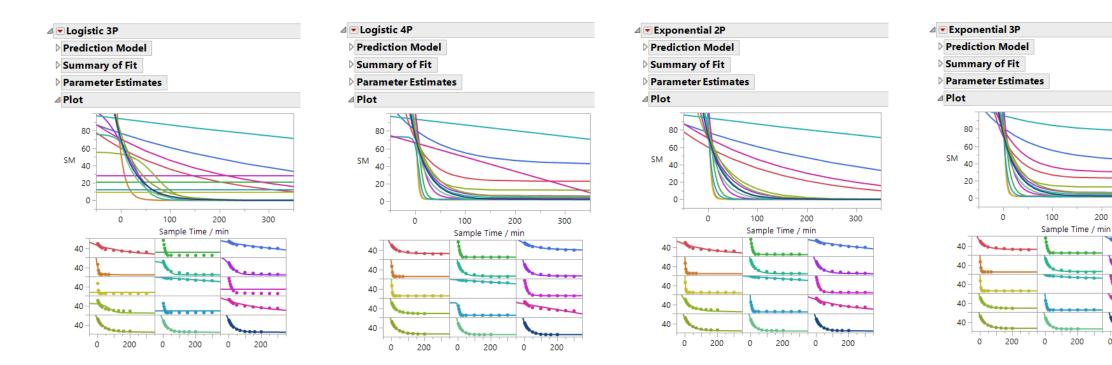


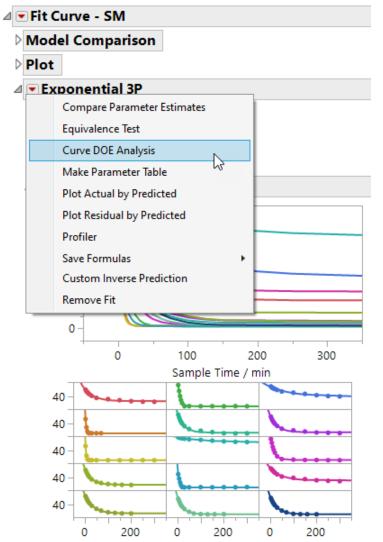
64

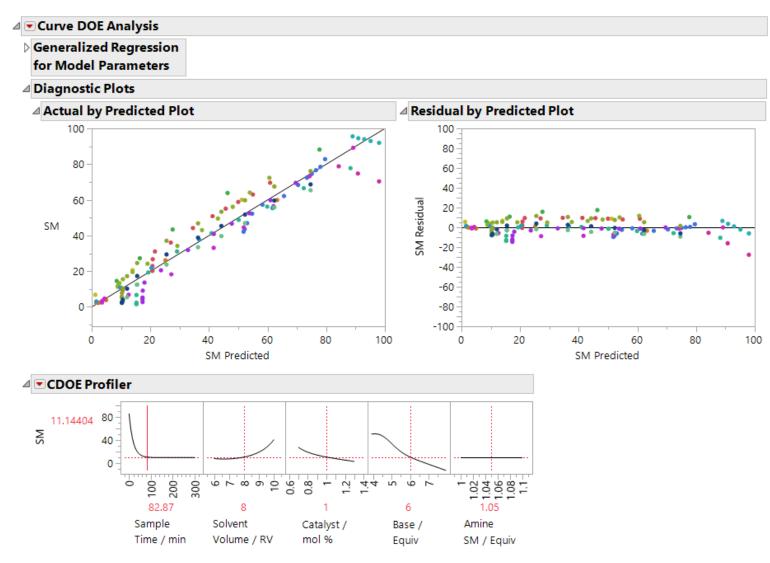


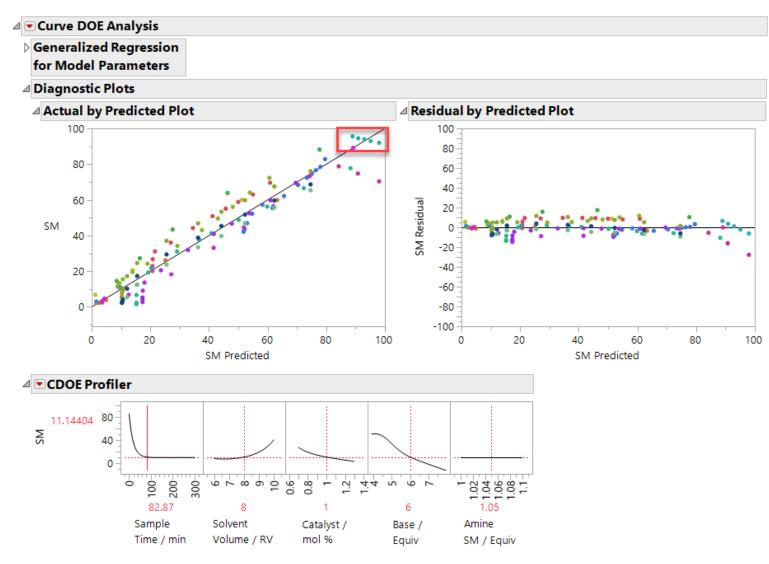


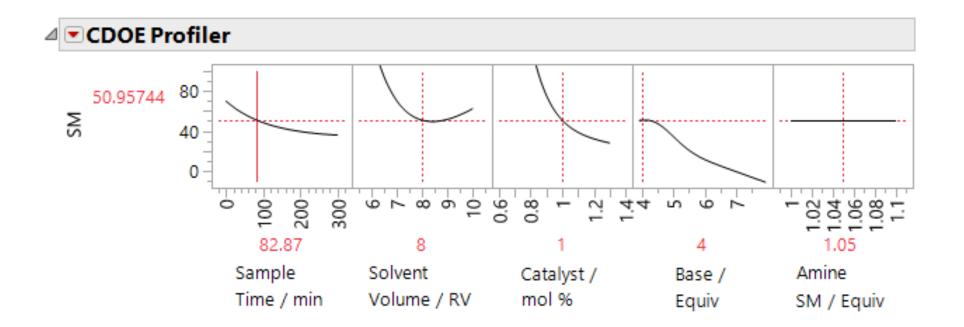
Fit Curve - SM										
Model Comparison										
Model	AICc ^	AICc Weight	.2 .4 .6 .8	BIC	SSE	MSE	RMSE	R-Square		
Exponential 3P	781.18844	1		893.51132	427.51924	3.2635056	1.8065175	0.9971092		
Logistic 4P	998.38685	6.854e-48		1125.4355	1027.7056	8.8595311	2.9764965	0.9930508		
Exponential 2P	1012.3501	6.366e-51		1096.8573	2109.1502	14.446235	3.8008203	0.9857383		
Logistic 3P	1532.4875	7.2e-164		1644.8104	30538.513	233.11842	15.268216	0.793503		



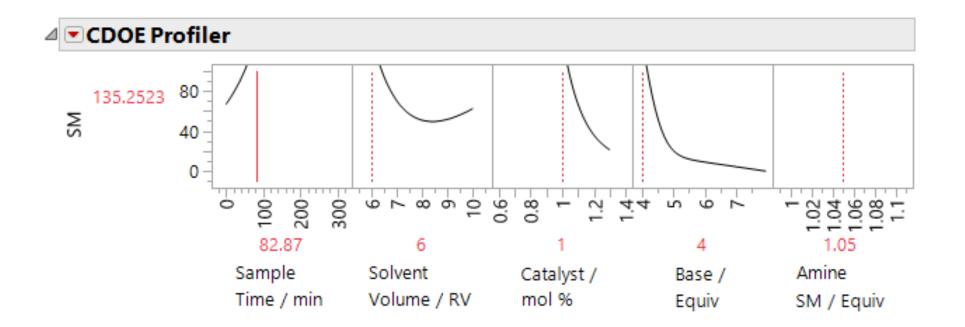














Exponential 3P

Prediction Model

a = Asymptote

b = Scale

/	Group	Asymptote	Growth Rate		Scale
1	N1	22.867857654	-0.025230049	48	146326097
2	N2	1.4481425305	-0.101923433	12	.96878526
3	N3	41.996217734	-0.010872558	39	131356511
4	N4	1.7514216034	-0.236676633	11	.17315056
5	N5	4.5055740659	-0.036396107	79	418733351
6	N6	6.1012035335	-0.031638593	67	319873264
7	N7	2.4152494821	-0.29774875	1.	1.1796014
8	N8	74.594130571	-0.007720537	20	725202973
9	N9	2.9957492718	-0.062309523	10	5.65985095
10	N10	12.860706683	-0.036963998	65	615700289
11	N11	1.8686494638	-0.135956892	83	181872531
12	N12	30.116992898	-0.021342944	50	610337466
13	N13	5.8948190062	-0.028967266	75	115805735
14	N14	2.2783260949	-0.04095745	70	945997632
15	N15	2.2343745293	-0.03296952	72	208209911

Curve DOE Analysis

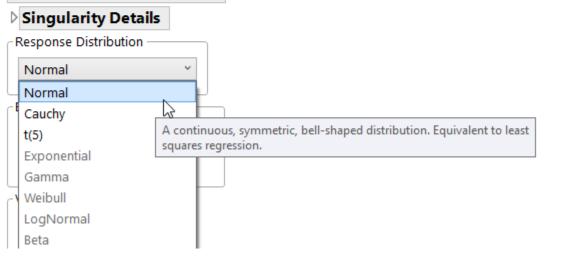
Generalized Regression for Model Parameters

- **Generalized Regression for Asymptote**
- Generalized Regression for Scale
- Generalized Regression for Growth Rate

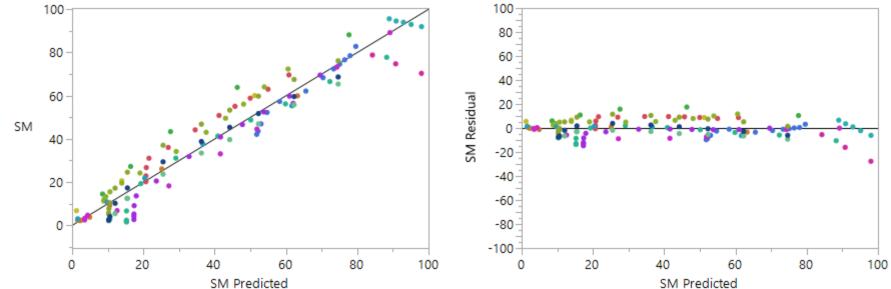
Model Comparison

Show	Response Distribution	Estimation Method	Validation Method	Nonzero Parameters	AICc	BIC	Generalized RSquare
\checkmark	Normal	Forward Selection	AICc	6	-49.06564	-55.31734	0.9285941

⊿ Model Launch







4.8054227983

- + Solvent Volume / RV (Solvent Volume / RV 1.5113228449
- + Solvent Volume / RV (Base / Equiv -3.380524086
- + -22.51564084 Catalyst / mol %
- + 15.580413139 Base / Equiv

34.1	65675219										
+ So	+ Solvent Volume / RV • (Solvent Volume / RV • -0.437773887)										
+ Ba	se / Equiv • (Base / Equiv • 1.9283370001)										
• Exp	(0.3868444112 + -0.067025251 • Solvent Volume / RV + Solvent Volume / RV • (Base / Equiv • 0.0143427946) + -0.099281912 • Catalyst / mol % + Base / Equiv • (Base / Equiv • -0.013697589)	, Sample Time / min									

Model Specification					
Select Columns	Pick Role	riables	Personality:	Generalized Regression	
7 Columns	Y	 Growth Rate 	Distribution		
L Expt Name		optional	Company Conde	LogNormal	
Solvent Volume / RV			Censor Code:		
🔺 Catalyst / mol % 🔺 Base / Equiv	Freq	optional numeric	Help	Run	
Amine SM / Equiv	Validation	optional numeric	Recall		
A Growth Rate	Censor	optional] Keep dialog open	
🥼 -Growth Rate			Remove		
	Ву	optional			
	Construct N	Iodel Effects			
	Add	Solvent Volume /	RV & RS	^	
	Cross	Catalyst / mol %			
	Nest	Base / Equiv & RS			
		Amine SM / Equiv	/ & KS RV*Solvent Volume / R	v	
	Macros	Solvent Volume /	RV*Catalyst / mol %	*	
	Degree	2 Catalyst / mol %*			
	Attributes				
	Transform	Catalyst / mol %*	Base / Equiv		
	🗌 No Inte	rcept Base / Equiv*Base	e / Equiv	\sim	

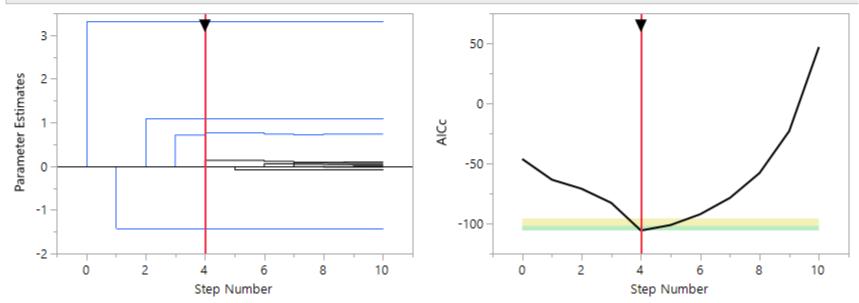
Generalized Regression for -Growth Rate

Model Comparison Response Estimation Validation Nonzero Show Distribution Method Method **Parameters** AICc ✓ LogNormal Forward Selection AICc 6 -105.8128 -112.0645

~ Normal Forward Selection AICc Model Launch

LogNormal Forward Selection with AICc Validation

- Model Summary
- ⊿ Solution Path



Generalized

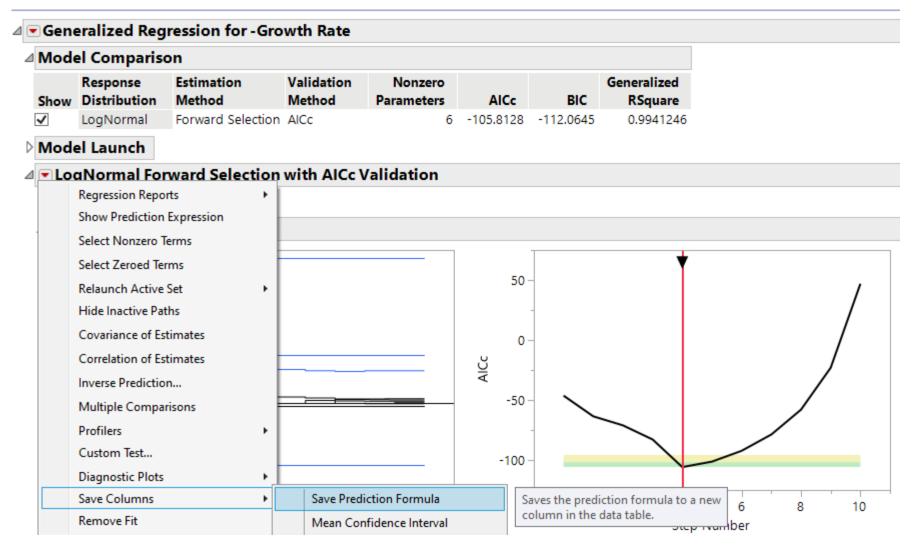
RSquare

0.9941246

0.9914435

BIC

8 -63.39106 -81.72666



Parameter	Estima	tes							
					Wald	Prob >			
Parameter	Group	Estimate	Std I	Error	ChiSquare	ChiSquare	Lov	ver 95%	Upper 95%
Asymptote	N1	22.867858	0.94	29534	588.12622	<.0001*	2	21.019703	24.716012
Scale	N1	48.146326	1.6		Table Chile		•	4.966198	51.326454
Growth Rate	N1	-0.02523	0.0		Table Style			0.029876	-0.020584
Asymptote	N2	1.4481425	0.7		Columns		•	.0294338	2.8668512
Scale	N2	120.96879	3.2		Sort by Column.			14.67599	127.26158
Growth Rate	N2	-0.101923	0.0		Make into Data 1	Table		Creates a	a new data table
Asymptote	N3	41.996218	1.8		Make Combined	Data Table		8 the value	es in the [[TableB
Scale	N3	39.131357	1.7					5.737057	42.525656
Growth Rate	N3	-0.010873	0.0		Make Into Matrix	C		0.014141	-0.007604
Asymptote	N4	1.7514216	0.9		Format Column.			0.033233	3.5360763
Scale	N4	119.17315	8.0		Show Properties			03.45358	134.89272
Growth Rate	N4	-0.236677	0.0					0.273948	-0.199405
Asymptote	N5	4.5055741	0.8		Copy Column			.8453776	6.1657706
Scale	N5	79.418733	1.8		Copy Table			5.741327	83.09614
Growth Rate	N5	-0.036396	0.0		-			0.040312	-0.03248
Asymptote	N6	6.1012035	0.8		Simulate			.3845257	7.8178814
Scale	N6	67.319873	1.		Bootstrap			63.84646	70.793286
Growth Rate	N6	-0.031639	0.00	20688	233.87727	<.0001*		-0.035693	-0.027584

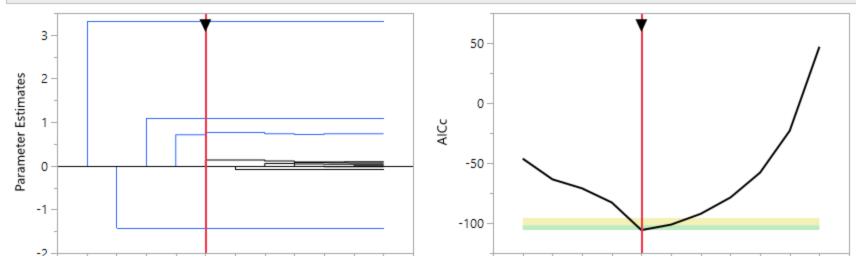
	Expt Name	Solvent Volume / RV	Catalyst / mol %	Base / Equiv	Amine SM / Equiv	Growth Rate	-Growth Rate	
1	N1	8	1.3	4.5	1	-0.025230049	0.0252300488	
2	N2	8	0.7	7.5	1.1	-0.101923433	0.1019234335	
3	N3	10	1	4.5	1.1	-0.010872558	0.010872558	
4	N4	6	1	7.5	1	-0.236676633	0.2366766326	
5	N5	6	0.7	6	1.1	-0.036396107	0.0363961067	
6	N6	10	1.3	6	1	-0.031638593	0.0316385934	
7	N7	6	1.3	7.5	1.05	-0.29774875	0.2977487499	
8	N8	10	0.7	4.5	1.05	-0.007720537	0.0077205372	
9	N9	10	0.7	7.5	1	-0.062309523	0.0623095232	
10	N10	6	1.3	4.5	1.1	-0.036963998	0.0369639976	
11	N11	10	1.3	7.5	1.1	-0.135956892	0.1359568915	
12	N12	6	0.7	4.5	1	-0.021342944	0.0213429442	
13	N13	8	1	6	1.05	-0.028967266	0.0289672656	
14	N14	8	1	6	1.05	-0.04095745	0.0409574504	
15	N15	8	1	6	1.05	-0.03296952	0.0329695197	

🍽 Fit Model - JMP Pro				- 🗆 ×
Model Specification				
Select Columns	Pick Role	riables	Personality:	Generalized Regression
7 Columns	Y	Growth Rate	Distribution	LogNormal ×
🔥 Expt Name		optional		Logivorniai
Solvent Volume / RV			Censor Code:	
Catalyst / mol % Base / Equiv	Freq	optional numeric	Help	Run
Amine SM / Equiv	Validation	optional numeric	Recall	T Kaan dialan anan
d Growth Rate	Censor	optional] Keep dialog open
🚄 -Growth Rate			Remove	
	Ву	optional		
	Construct M	odel Effects		
	Add	Solvent Volume / RV		^
	Cross	Catalyst / mol % & R	lS	
	Nest	Base / Equiv & RS Amine SM / Equiv &	RS	
	Macros			v
		2 Solvent Volume / RV	*Catalyst / mol %	
		Catalyst / mol %*Cat	•	
	Attributes			
	Transform			
	L No Inter	cept Base / Equiv*Base / E	-quiv	×

Model Comparison Response Estimation Validation Nonzero Generalized Show Distribution Method Method Parameters AICc BIC RSquare ✓ LogNormal Forward Selection AICc -105.8128 -112.0645 0.9941246 6 ~ Normal Forward Selection AICc 8 -63.39106 -81.72666 0.9914435

Model Launch

- LogNormal Forward Selection with AICc Validation
 - Model Summary
- ⊿ Solution Path

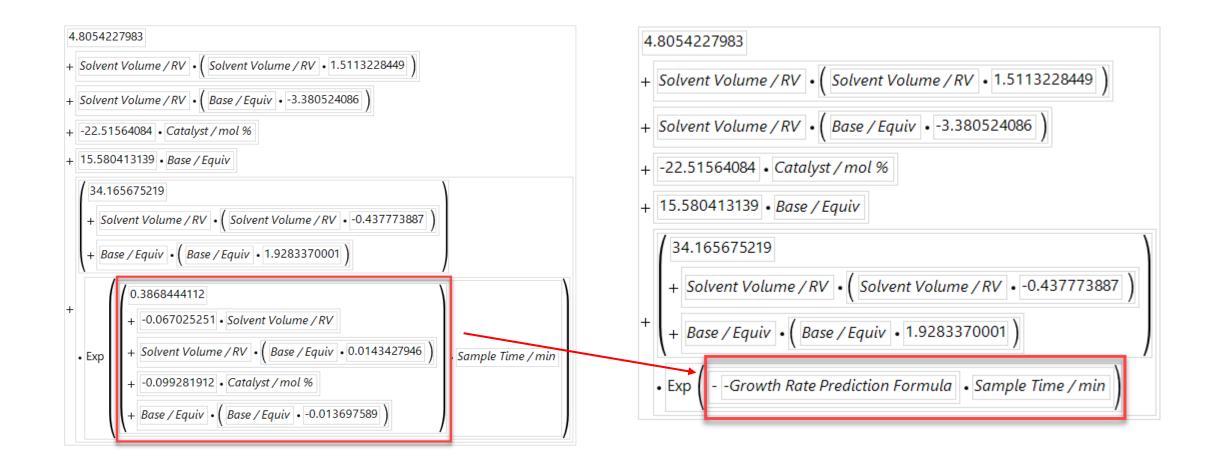


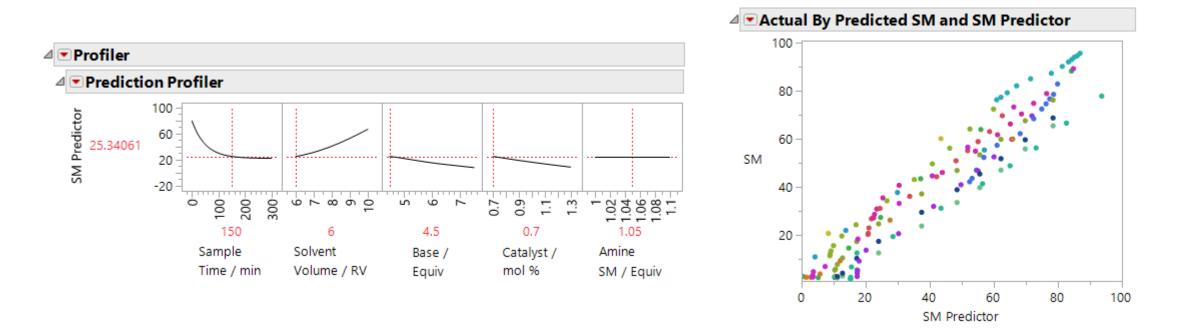
Generalized Regression for -Growth Rate Model Comparison Response Estimation Validation Generalized Nonzero Show Distribution Method Method AICc BIC Parameters RSquare ✓ LogNormal Forward Selection AICc 6 -105.8128 -112.0645 0.9941246 Model Launch LogNormal Forward Selection with AICc Validation Regression Reports ٠ Show Prediction Expression Select Nonzero Terms Select Zeroed Terms 50 Relaunch Active Set . Hide Inactive Paths Covariance of Estimates 0 Correlation of Estimates AICc Inverse Prediction... -50 Multiple Comparisons Profilers Custom Test... -100 **Diagnostic Plots** ۲ Save Columns Save Prediction Formula Saves the prediction formula to a new ٠ 6 10 8 column in the data table. Remove Fit Mean Confidence Interval occo readber

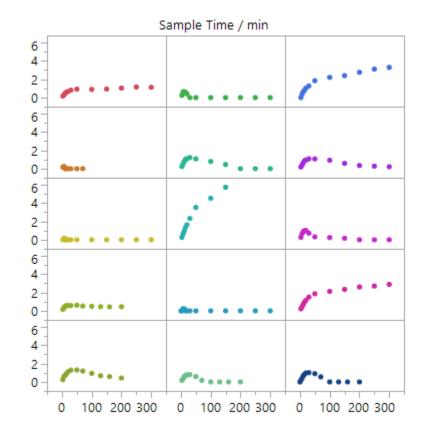
$\overline{)}$	Expt	Solvent Volume	Catalyst	Base /	Amine SM	Growth	-Growth		rth Rate liction		
	Name	/ RV	/ mol %	Equiv	/ Equiv	Rate	Rate		Column In	fo	
1	N1	8	1.3	4.5	1	-0.025	0.0252		Chandradia	e Attributes	
2	N2	8	0.7	7.5	1.1	-0.101	0.1019				
3	N3	10	1	4.5	1.1	-0.010	0.0108		Column P	roperties	•
4	N4	6	1	7.5	1	-0.236	0.2366	순	Formula		
5	N5	6	0.7	6	1.1	-0.036	0.0363		Recode		
6	N6	10	1.3	6	1	-0.031	0.0316		New Form	ula Column	,
7	N7	6	1.3	7.5	1.05	-0.297	0.2977		Insert Colu		,
8	N8	10	0.7	4.5	1.05	-0.007	0.0077				
9	N9	10	0.7	7.5	1	-0.062	0.0623		Delete Col	umns	
10	N10	6	1.3	4.5	1.1	-0.036	0.0369	0	Label/Unla	abel	
11	N11	10	1.3	7.5	1.1	-0.135	0.1359	0	L'al-ID		
12	N12	6	0.7	4.5	1	-0.021	0.0213	1	Link ID		
13	N13	8	1	6	1.05	-0.028	0.0289		Sort		
14	N14	8	1	6	1.05	-0.040	0.0409		Conv Colu	imn Properties	
15	N15	8	1	6	1.05	-0.032	0.0329			•	
									Copy Colu	imns	

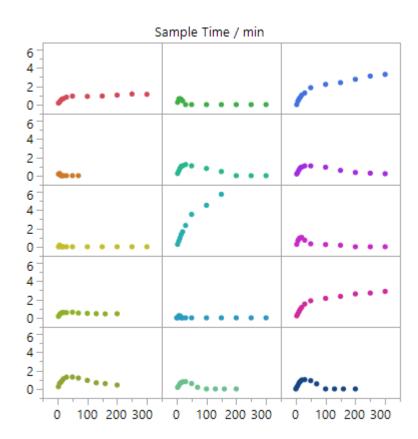
	Expt	Sample Time /	Solvent Volume /	Catalyst /	Base /	Amine SM /		Product		Product	Product Imp		-Growth Rate Prediction
	Name	min	RV	mol %	Equiv	Equiv	Product	Imp	SM	Predictor	Predictor	SM Predictor	Formula
1	N1	3	8	1.3	4.5	1	29.37459	0.835080	69.6229	29.5252	0.78054	60.823894854	0.0248591549
2	N1	7	8	1.3	4.5	1	35.85010	0.828343	63.0270	32.5001	0.80048	54.961328808	0.0248591549
3	N1	11	8	1.3	4.5	1	39.81607	0.842789	58.8567	35.5291	0.82043	49.954770117	0.0248591549
4	N1	15	8	1.3	4.5	1	43.43785	0.869276	55.1016	38.5707	0.84035	45.679231092	0.0248591549
5	N1	20	8	1.3	4.5	1	47.53072	0.929187	50.8791	42.3264	0.86518	41.201713038	0.0248591549
6	N1	30	8	1.3	4.5	1	53.96907	0.995378	44.2265	49.3969	0.91445	34.50828182	0.0248591549
7	N1	50	8	1.3	4.5	1	61.91892	1.061143	36.0956	60.4207	1.01012	26.956999806	0.0248591549
8	N1	100	8	1.3	4.5	1	66.73583	1.282049	31.0905	71.0601	1.21940	21.546516392	0.0248591549
9	N1	150	8	1.3	4.5	1	70.97244	1.332256	26.7644	72.6443	1.37219	20.794234497	0.0248591549
10	N1	200	8	1.3	4.5	1	74.55535	1.479735	22.9344	72.8455	1.47125	20.689636071	0.0248591549
11	N1	250	8	1.3	4.5	1	76.61089	1.559971	20.6754	72.8704	1.53063	20.675092546	0.0248591549
12	N1	300	8	1.3	4.5	1	77.02376	1.604085	20.2519	72.8735	1.56456	20.673070392	0.0248591549

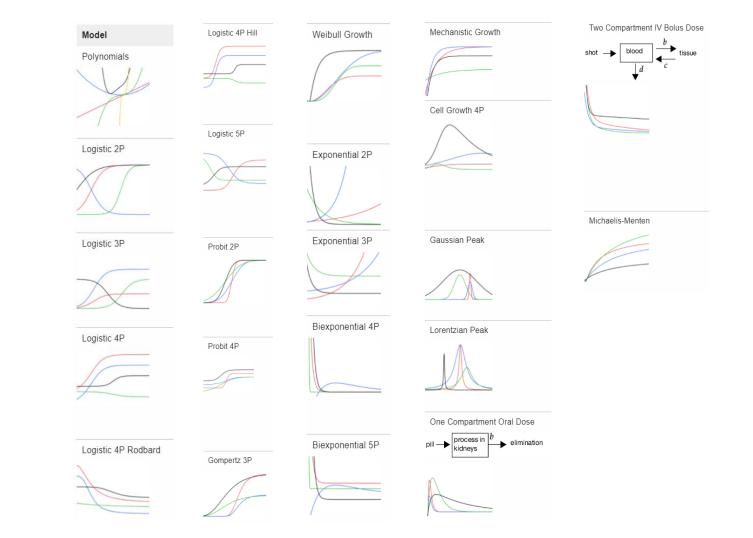
	Expt	Sample Time /	Solvent Volume /	Catalyst /	Base /	Amine SM /		Product		Product	Product Imp		-Growth Rate Prediction
	Name	min	RV	mol %	Equiv	Equiv	Product	Imp	SM	Predictor	Predictor	SM Predictor	Formula
1	N1	3	8	1.3	4.5	1	29.37459	0.835080	69.6229	29.5252	0.78054	60.823894854	0.0248591549
2	N1	7	8	1.3	4.5	1	35.85010	0.828343	63.0270	32.5001	0.80048	54.961328808	0.0248591549
3	N1	11	8	1.3	4.5	1	39.81607	0.842789	58.8567	35.5291	0.82043	49.954770117	0.0248591549
4	N1	15	8	1.3	4.5	1	43.43785	0.869276	55.1016	38.5707	0.84035	45.679231092	0.0248591549
5	N1	20	8	1.3	4.5	1	47.53072	0.929187	50.8791	42.3264	0.86518	41.201713038	0.0248591549
6	N1	30	8	1.3	4.5	1	53.96907	0.995378	44.2265	49.3969	0.91445	34.50828182	0.0248591549
7	N1	50	8	1.3	4.5	1	61.91892	1.061143	36.0956	60.4207	1.01012	26.956999806	0.0248591549
8	N1	100	8	1.3	4.5	1	66.73583	1.282049	31.0905	71.0601	1.21940	21.546516392	0.0248591549
9	N1	150	8	1.3	4.5	1	70.97244	1.332256	26.7644	72.6443	1.37219	20.794234497	0.0248591549
10	N1	200	8	1.3	4.5	1	74.55535	1.479735	22.9344	72.8455	1.47125	20.689636071	0.0248591549
11	N1	250	8	1.3	4.5	1	76.61089	1.559971	20.6754	72.8704	1.53063	20.675092546	0.0248591549
12	N1	300	8	1.3	4.5	1	77.02376	1.604085	20.2519	72.8735	1.56456	20.673070392	0.0248591549



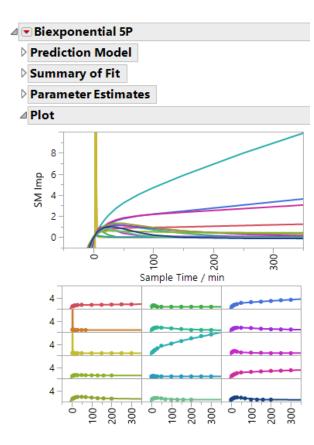


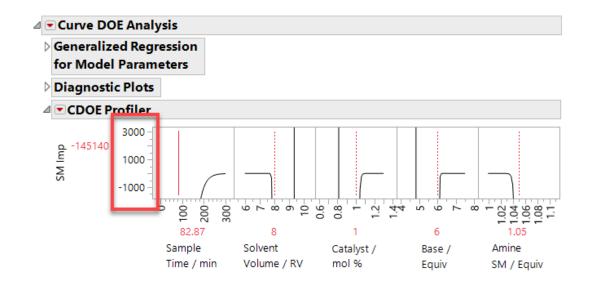


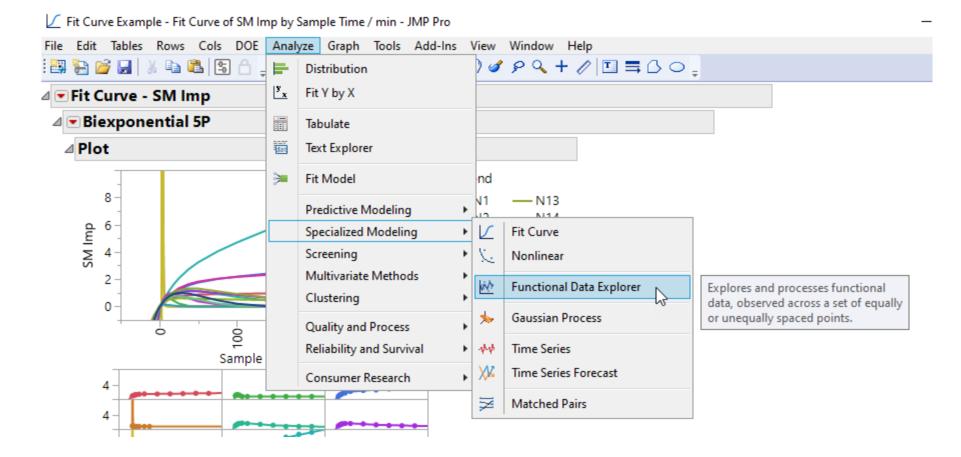




▼ Fit Curve - SM Imp											
✓ Model Comparison											
Model	AICc ^	AICc Weight	.2 .4 .6 .8	BIC	SSE	MSE	RMSE	R-Square			
Biexponential 5P	-248.5568	1		-122.6224	0.5726787	0.00556	0.0745653	0.9980244			
Biexponential 4P	-211.1367	7.4874e-9		-82.2548	1.1118453	0.0094224	0.0970691	0.9961644			







👾 Functional Data Expl	👬 Functional Data Explorer - JMP Pro 🦰											
 Functional Data Expl Stacked Data Format Stacked data format. Select Columns 17 Columns Expt Name Added Row Indica Sample Point Sample Time / mi Solvent Volume / Catalyst / mol % Base / Equiv Amine SM / Equiv Product 	Rows as Functions ator n RV	Columns as		tput put ction	mns into Roles SM Imp optional numeric Sample Time / min Expt Name Solvent Volume / RV Catalyst / mol % Base / Equiv		Car Rem Re	× K ncel nove call				
 Product Imp SM SM Imp 		~	Fre Valida By	ition	Amine SM / Equiv optional numeric optional numeric optional							
						8	☆ [



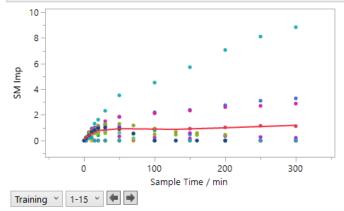


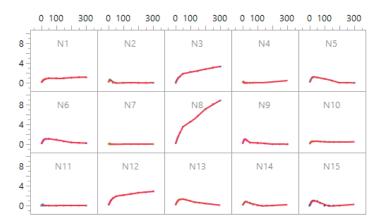
⊿ 💌 Functional Data Explorer - SM Imp

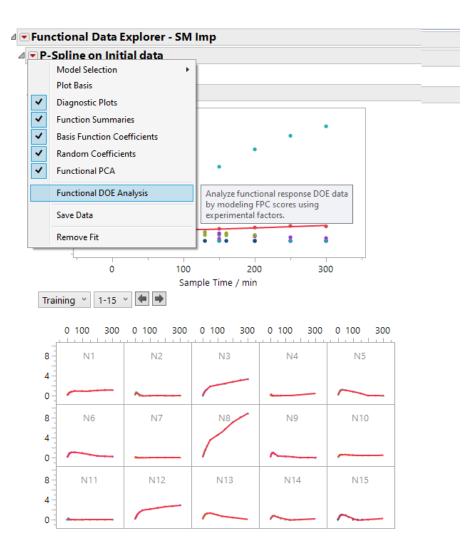
⊿ 💌 P-Spline on Initial data

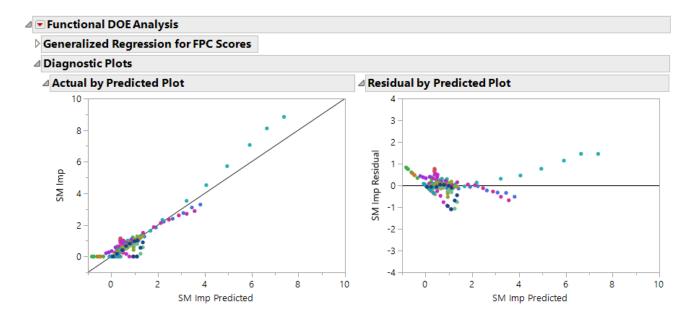
Model Controls

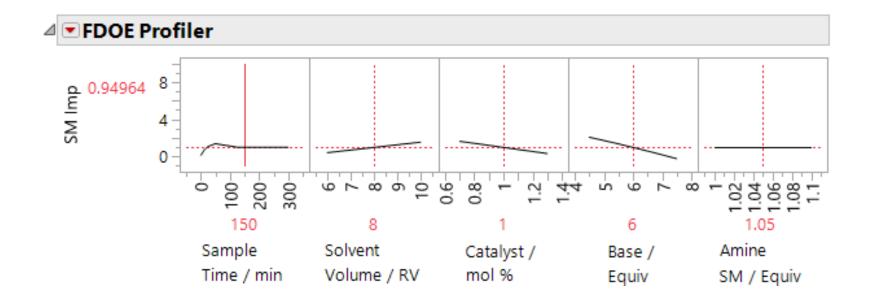
Model Selection

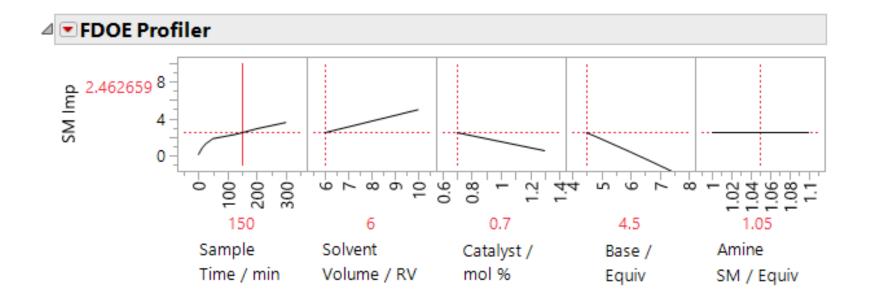










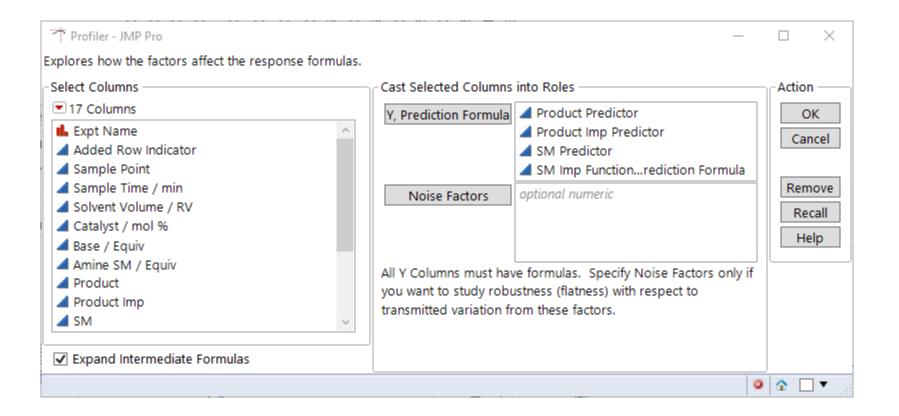


Profiler For All Four Responses

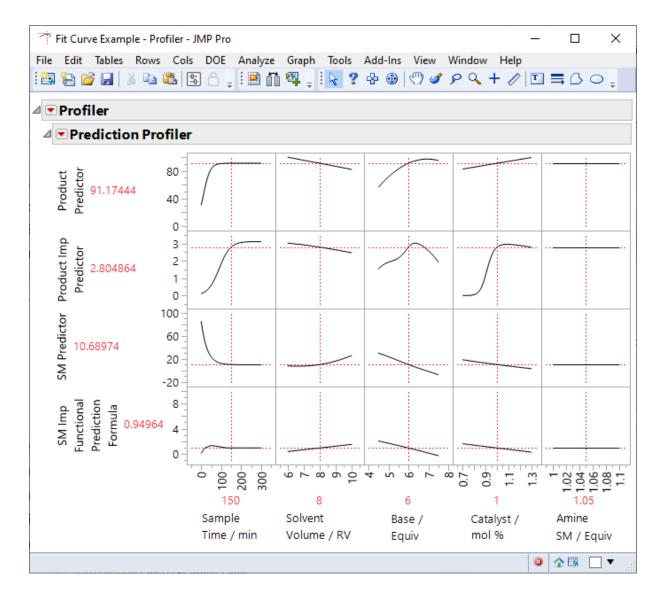
📴 Fit Curve Example - JMP Pro

File Edit Tables Rows Cols DO	E	Analyze	Grap	h Tools	Add-Ins	View	Window	Help	р	
i 🛤 😜 🎽 🖬 🐰 ங 🛝 🗊 A	Ŧ	:		Graph Bu	uilder					
Fit Curve Example	Þ	۹ 🔪	₽.	Bubble P	lot					
Design Definitive Screening Design Source	^	$ \rangle$	이 지지 지지다	Scatterpl	lot Matrix					
Model				Parallel P	Plot					
 DOE Dialog Product CDOE Logistic3P 				Cell Plot						
 Product CDOE LogisticsP Product Imp CDOE Logistic3P 			渓	Scatterpl	lot 3D		Sam	nle	Sample	Solvent Volume /
SM CDOE Expon3P			3	Contour	Plot		Poi	-	Time / min	RV
 SM Imp Fit Curve Overfit SM Imp FDOE P Spline 		•	Δ	Ternary F	Plot			1	3	ę
Profiler - All 4 Responses		•	4		21-1			2	7	8
Profiler with Target Ranges	\sim	•	**	Surface F	Plot			3		}
Columns (17/0)		•	*	Profiler	G				interactive grap to explore how	
۹		•	2	Contour	Profiler		_ predic	ted res	sponse changes	
🔥 Expt Name	\sim	•		Mixture	Profiler		chang	e facto	or settings.	{
Added Row Indicator		•	X	Custom	Profiler		<u> </u>	7	50	{
🚄 Sample Point		•	*	Excel Pro	ofiler			8	100	{
🚄 Sample Time / min		•						9	150	8
Solvent Volume / RV		•		Legacy		•	•	10	200	8
🚄 Catalyst / mol %		-	-	4 814		,			250	,

Profiler For All Four Responses



Profiler For All Four Responses





Fit Multiple Curves to Chemical Reaction Response Compare Model

- Fit Curve Choose multiple curves to fit.
 - Review Model Comparison and Model Diagnostics to select a Model.

▼ Fit Curve										
⊿ Model Comparison										
Model	AICc ^	AICc Weight	.2 .4 .6 .8	BIC	SSE	MSE	RMSE	R-Square		
Logistic 4P	774.21661	1		901.26526	287.54791	2.4788613	1.57444	0.9980418		
Logistic 3P	925,40129	1.481e-33		1037.7242	970.09161	7.4052794	2.7212643	0.9933937		
Weibull Growth	1132.045	1.989e-78		1244.3679	3138.5071	23.958069	4.8946981	0.9786268		
Logistic 5P	1358.7337	1.19e-127		1481.4682	5000.6892	49.511775	7.0364604	0.9659454		
Probit 4P	1463.7303	1.88e-150		1590.7789	14459.122	124.64761	11.164569	0.9015335		

- What diagnostic to assess to determine one model better than another?
- Response Fit Curve selections
 - Prod, Prod Imp Logistic 3P, SM Exponential 3P, SM Imp FDE P Spline

Subject Matter Expert Guided Selection - Product

• May not always choose pre-loaded formula with best "Statistical" diagnostic results

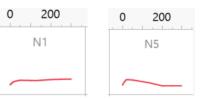
Model Comparison									
Model		AICc Weight	.2.4.6.8	BIC	SSE	MSE	RMSE	R-Square	
Exponential 3P	766.00441	1		878.32729	392.18215	2.9937568	1.7302476	0.9973292	
Logistic 3P	925.40129	2.44e-35		1037.7242	970.09161	7.4052794	2.7212643	0.9933937	

- For Product, Exponential 3P diagnostics better so why choose Logistic 3P
 - In this instance both very good. Subject matter proposal:
- The Exponential 3p is the same curve as kinetic reaction first order with fitted limits Kinetic: $A = A_f + (A_0 - A_f)e^{-kt}$ Exponential $a+b\cdot Exp(c\cdot Sample Time / min)$
- Looking at the curves, the shape is more sigmoidal, suggesting more complex kinetics than first order so Exponential 3P lacks shape flexibility.
- Logistic 3P, lacks similarity to kinetic equations, more effective at describing sigmoidal curves.
- Taking more samples near time point 0 may have helped discriminate between formulas.

Subject Matter Expert Guided Selection – SM Imp

- SM imp can be formed and consumed (to form Product Imp). The pathways could occur at different rates to the extreme where one pathways is switched off.
 - N3, N8, N12 SM Imp increases.
 - Pathways: Formation On, Consumption Off.
 - Other Expts SM Imp rate plateaus or peaks and reduces.
 - Pathways: Formation On, Consumption On.
- None of the pre-loaded formulas could adequately fit the variety of profiles shapes created by the combined pathway effect.
- FDE P spline fitted making use of greater curve shape fitting flexibility.
- Ambitions is for First principle fitting approximation but in case ambition scaled back to empirical fitting approximation.



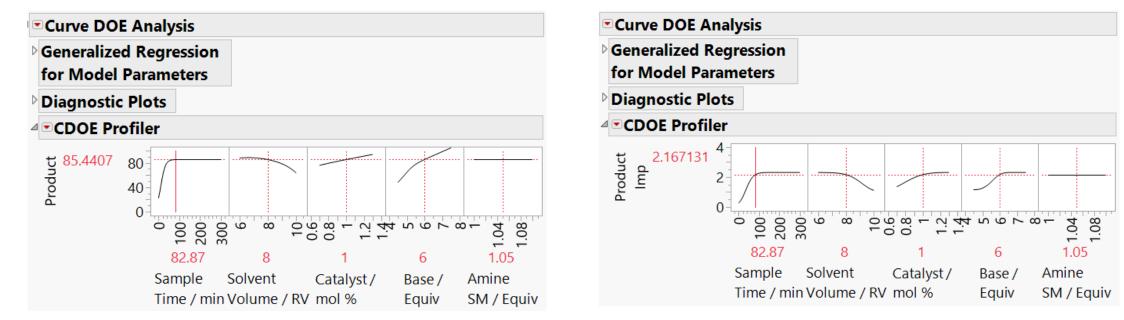


Select Curve DoE on formula parameter coefficients Compare Response Distributions

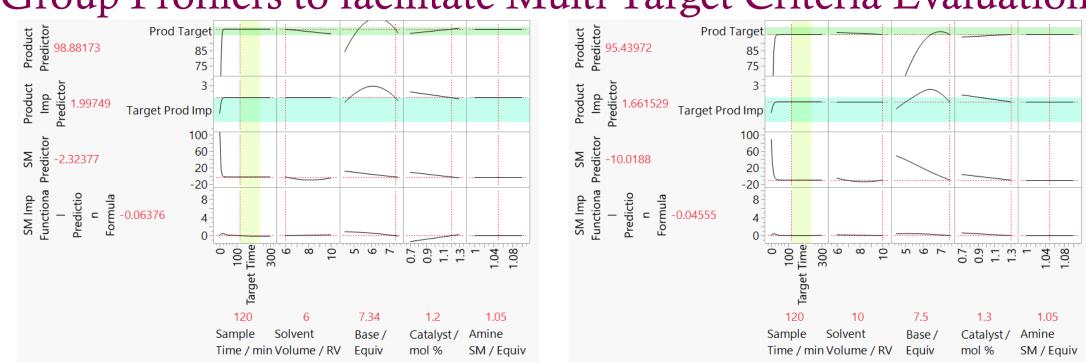
urve DOE Analysis eneralized Regression for Model Parameters											
Generalized Regression for Growth Rate											
Mode	el Compariso	n									
	Response	Estimation	Validation	Nonzero			Generalized				
Show	Distribution	Method	Method	Parameters	AICc	BIC	RSquare				
✓	Normal	Forward Selection	AICc	6	-39.33529	-45.58699	0.942605				
✓	Normal	Forward Selection	AICc	8	-38.70316	-57.03876	0.981357				
✓	Gamma	Forward Selection	AICc	6	-91.45945	-97.71115	0.995610				
✓	Weibull	Forward Selection	AICc	7	-80.04912	-91.09276	0.994417				
		Forward Selection		G	-88.25012	04 50100	0.994819				

• What diagnostic to assess to determine one model better than another?

DoE Profiler for each reaction response



- Review profiles to understand factor influence on reaction response behaviour.
- Assess which factor settings have potential to comply with all response target criteria.



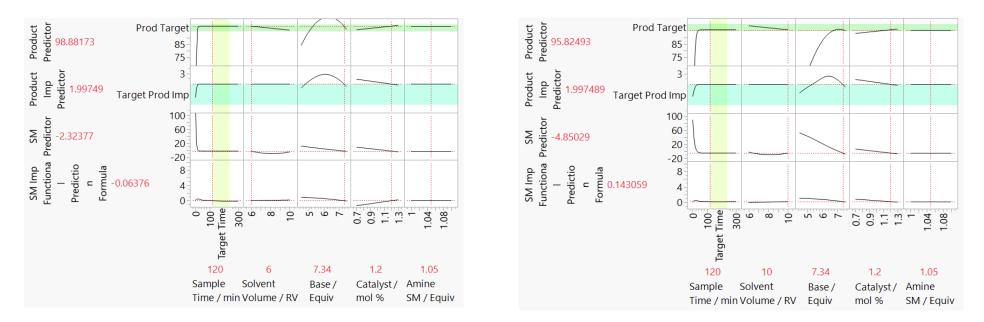
Group Profilers to facilitate Multi Target Criteria Evaluation

Response Target Criteria

Product, 95.0% or more (horizontal green) Product Imp, 2.0% or less (horizontal green/blue) Reaction Time, 120 – 240 mins (vertical green) Interested in the Group Profiler top 2 rows

Relating Group Profiler to Process Insight

- Key Responses: Prod and Prod Imp Group Profiler top 2 rows
- Visualises impact over timeline of changing factor levels on key responses
- Factor combinations exist predicting Responses achieving target criteria
 - SM Amine not influential (Flat line), High Base minimise solvent influence (Flatter line)
 - Factor combinations limited due to sensitivity in Base and Catalyst acceptable levels
 - 12–240 mins, 6–10 vols, Base 7.34–7.5 eq, Catalyst 1.2–1.3 mol%, SM Amine 1.0–1.10 eq



Summary: Fit Curve Pre-loaded formula Improvements

Fit Curve Pre-loaded formulas

- User Specify lower and upper bounds to theoretical values
- User Specify lower and upper asymptotes to meet defined lower and Upper theoretical values
- Help with alerts to over-fitted pre-loaded equations
- Improved AICs performance to detect over fitting
 - Until then check Model Diagnostics observed vs predicted results
 - How good should formula fit be on each experiment?
 - Majority of formulae parameter coefficients, for every experiment, statistically significant?

Summary: Curve DoE Improvements

Curve DoE

- For DSDs, default to 2-stage analysis approach.
- Bound original Y response to theoretical possible results eg 0 100% product.
- Select appropriate distribution to apply to fit curve parameter coefficients.
 - Gradient lies within 0 -1, therefore Beta distribution a better descriptor than a Gaussian(Normal) distribution?
 - Expand possible distribution options to cover distribution which reflect better features and number ranges observed in parameter coefficients estimates eg values always negative.
- What Design choices are most suited for reaction profile experimentation modelling Factorials, Definitive Screening Designs, Response Surface Modelling, space filling?



- 2-step Analysis approach.
 - i) Fit Curve on each experiments Chemical responses.

ii) Curve DoE analysis on Fit Curve coefficients, converted back into Chemical responses and visualised in CDOE profiler.

- Tries to introduces subject matter knowledge into Analysis approach.
- Curve DoE gives insight into which factors influential on each response.
 - Solvent, Base, Catalyst factors at least influential on one response. Some factors interact, some are non-linear. The detail is available if needed.
 - SM Amine non-influential on responses.
 - The Group Profiler shows the factors combined net influence on responses.
- Unfinished approach, shows potential, we will continue to develop and refine approach.

Acknowledgements

AstraZeneca

• Rob Cox, Brendan Nixon

Confidentiality Notice

This file is private and may contain confidential and proprietary information. If you have received this file in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this file is not permitted and may be unlawful. AstraZeneca PLC, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA, UK, T: +44(0)203 749 5000, www.astrazeneca.com