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Modeling Sub-Visible Particle Data
Product Held at Accelerated Stability Conditions

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Outline

- Sub-Visible Particle (SbVP)
  - Poisson
  - Negative Binomial
- Stability Data Structure
- Simulated Drug Product SbVP Data @25°C
  - Random Coefficients Model
  - Random Intercepts Model
- Summary

Sub-Visible Particle (SbVP) Data

- Discrete counts measured over time for a given lot.
  - Number of particles of a given size
  - Bounded below by 0
  - Large counts possible
- Four sizes measured per lot per time
  - $\geq$ 2μm, $\geq$ 5μm, $\geq$ 10μm, $\geq$ 25μm
  - Repeated measures per lot $\rightarrow$ correlation
- Goal is to model particle counts as a function of *time* accounting for Lot-to-Lot variation including correlation.
  - Need to take into account the discrete nature of the data
  - Poisson or negative binomial distributions.

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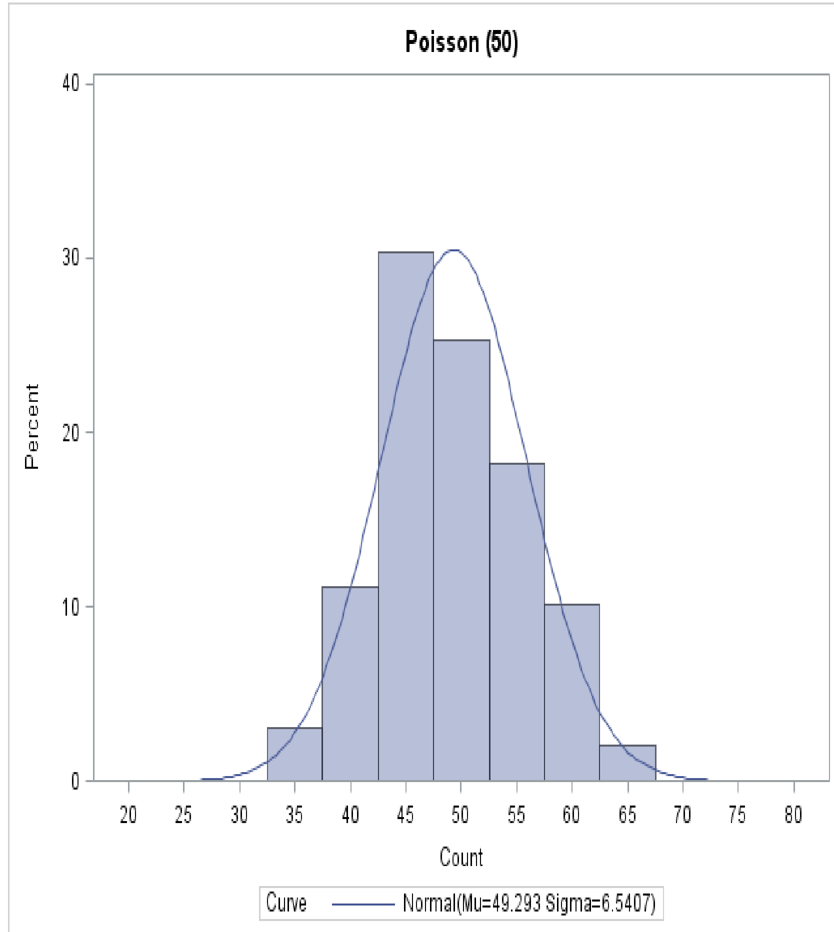
Sub-Visible Particle (SbVP) Data Poisson Distribution

- The Poisson distribution is a function of the average number of counts, λ .

$$\frac{e^{-\lambda}\lambda^{\text{count}}}{\text{count!}}$$

- For the Poisson distribution mean = variance
  - Mean = λ
  - Variance = λ
- What if variance > mean?



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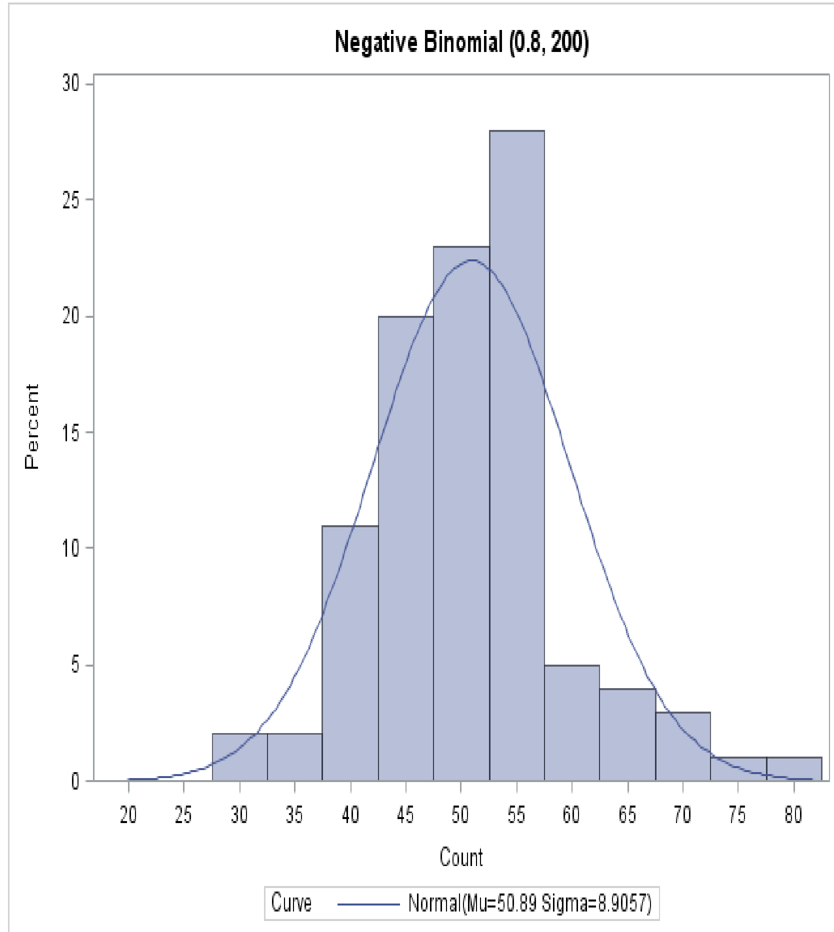
Sub-Visible Particle (SbVP) Data Negative Binomial (Gamma-Poisson)

- Negative Binomial has two parameters
  - Number of successes ϕ
  - Probability of success $\phi/(\phi + \lambda)$
- Mean $= \lambda$
- Variance $= \lambda + \lambda^2/\phi$
  - > Poisson variance
  - "over-dispersion".
- As ϕ gets large (λ fixed), the negative binomial $\rightarrow$ Poisson



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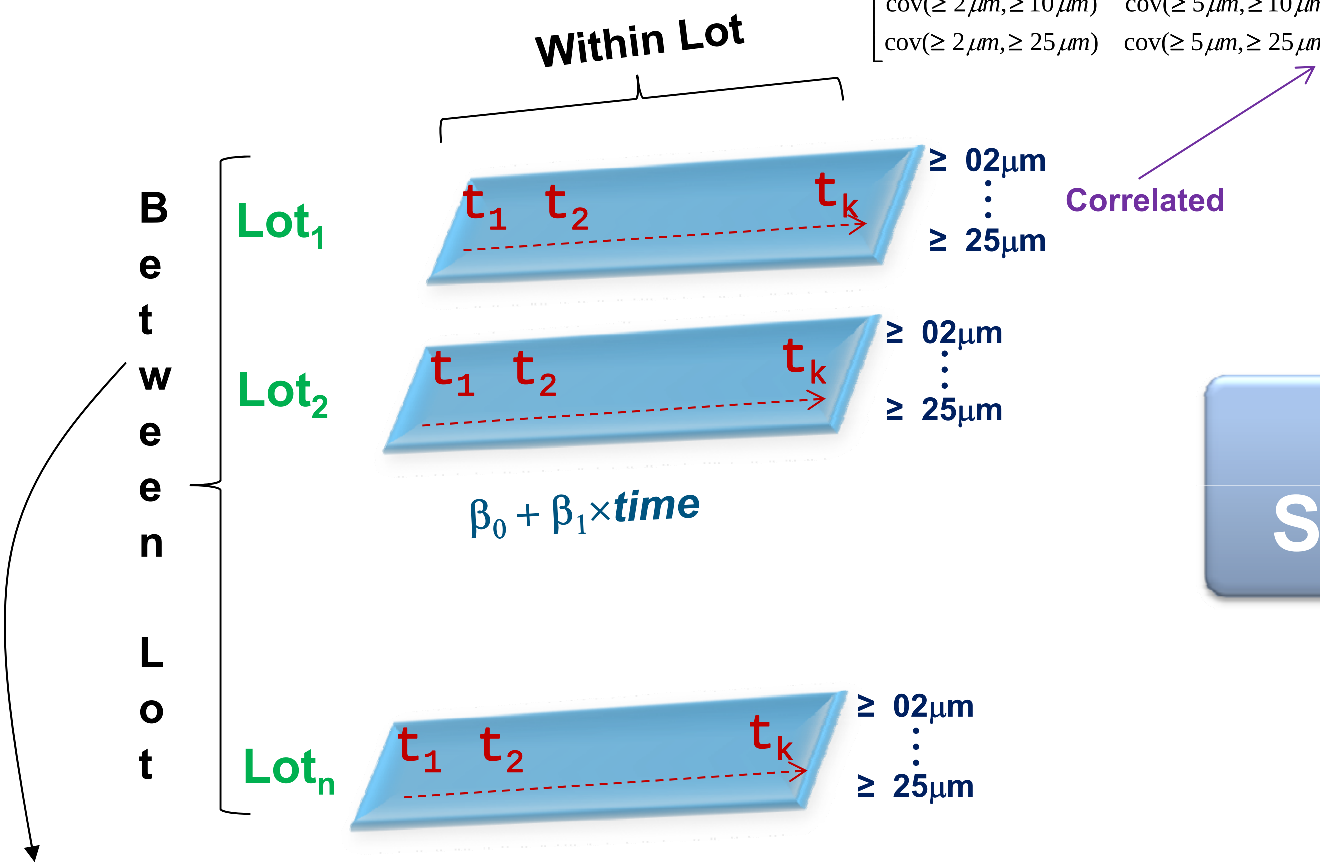
Outline

- Sub-Visible Particle (SbVP)
- Stability Data Structure

Stability Data Structure
Sub-Visible Particle (SbVP)

$$\begin{bmatrix} \sigma^2_{\geq 2\mu m} & \mathrm{cov}(\geq 2\mu m, \geq 5\mu m) & \mathrm{cov}(\geq 2\mu m, \geq 10\mu m) & \mathrm{cov}(\geq 2\mu m, \geq 25\mu m) \\ \mathrm{cov}(\geq 2\mu m, \geq 5\mu m) & \sigma^2_{\geq 5\mu m} & \mathrm{cov}(\geq 5\mu m, \geq 10\mu m) & \mathrm{cov}(\geq 5\mu m, \geq 25\mu m) \\ \mathrm{cov}(\geq 2\mu m, \geq 10\mu m) & \mathrm{cov}(\geq 5\mu m, \geq 10\mu m) & \sigma^2_{\geq 10\mu m} & \mathrm{cov}(\geq 10\mu m, \geq 25\mu m) \\ \mathrm{cov}(\geq 2\mu m, \geq 25\mu m) & \mathrm{cov}(\geq 5\mu m, \geq 25\mu m) & \mathrm{cov}(\geq 10\mu m, \geq 25\mu m) & \sigma^2_{\geq 25\mu m} \end{bmatrix}$$

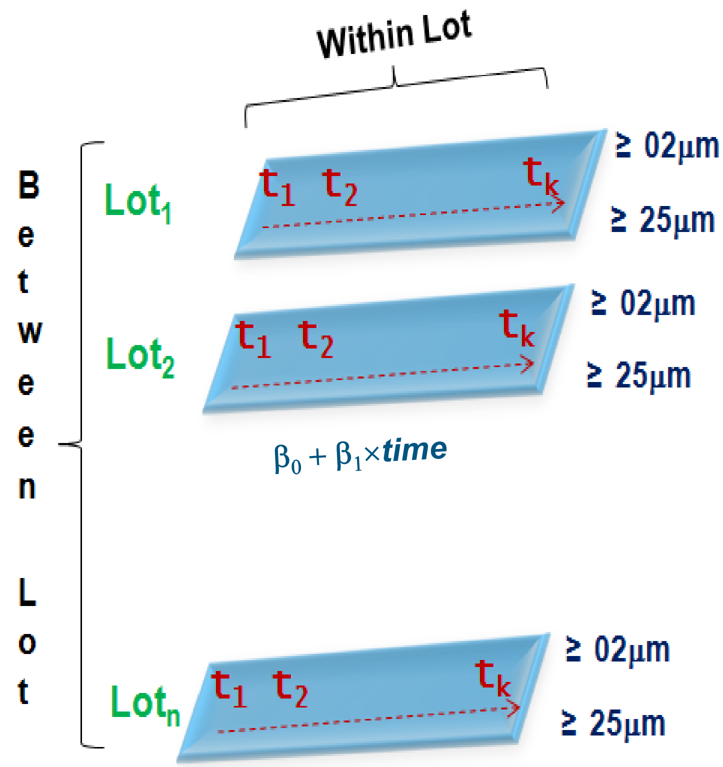


$$\begin{bmatrix} \sigma^2_{\mathrm{int}} & \mathrm{cov}(\mathrm{int}, \mathrm{slope}) \\ \mathrm{cov}(\mathrm{int}, \mathrm{slope}) & \sigma^2_{slope} \end{bmatrix}$$

Rich Structure

SbVP Stability Data Questions of Interest

- Do counts increase or decrease linearly with *time*?
  - $\beta_0 + \beta_1$ *time*
- Do we have Lot-to-Lot variation?
  - If we do, does it affect the linear *time* relationship?
    - Random coefficients β_0 & β_1
- What about repeated the measurements per Lot?
  - Are the 4 sizes correlated?
    - 4×4 covariance matrix
  - Autocorrelated time points



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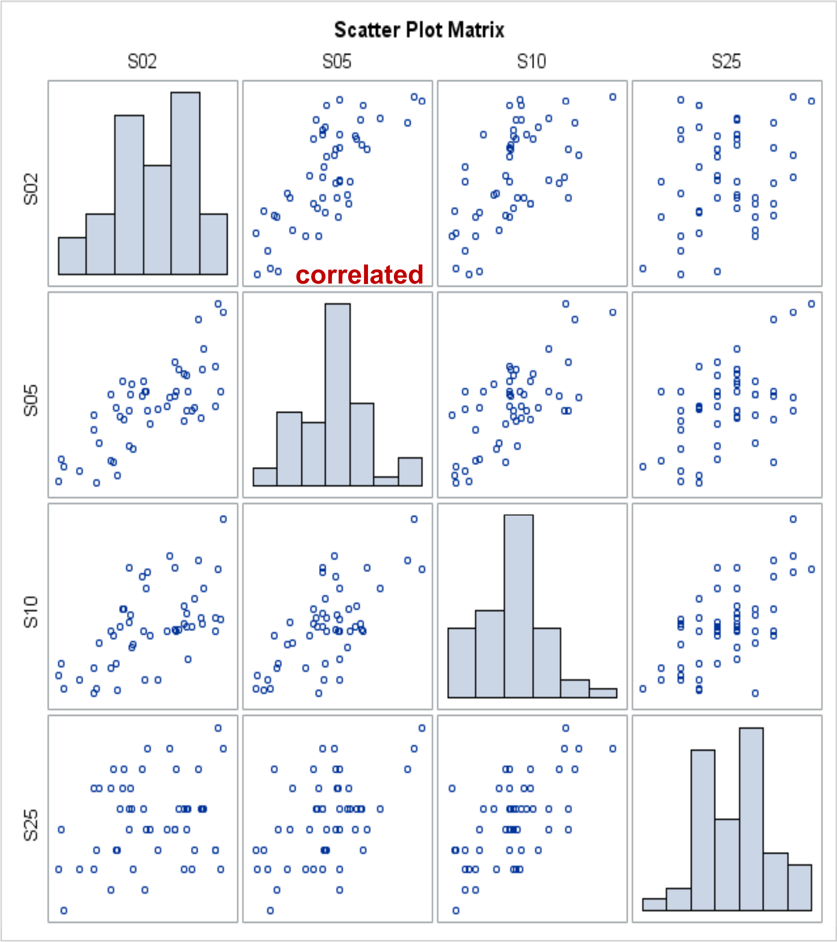
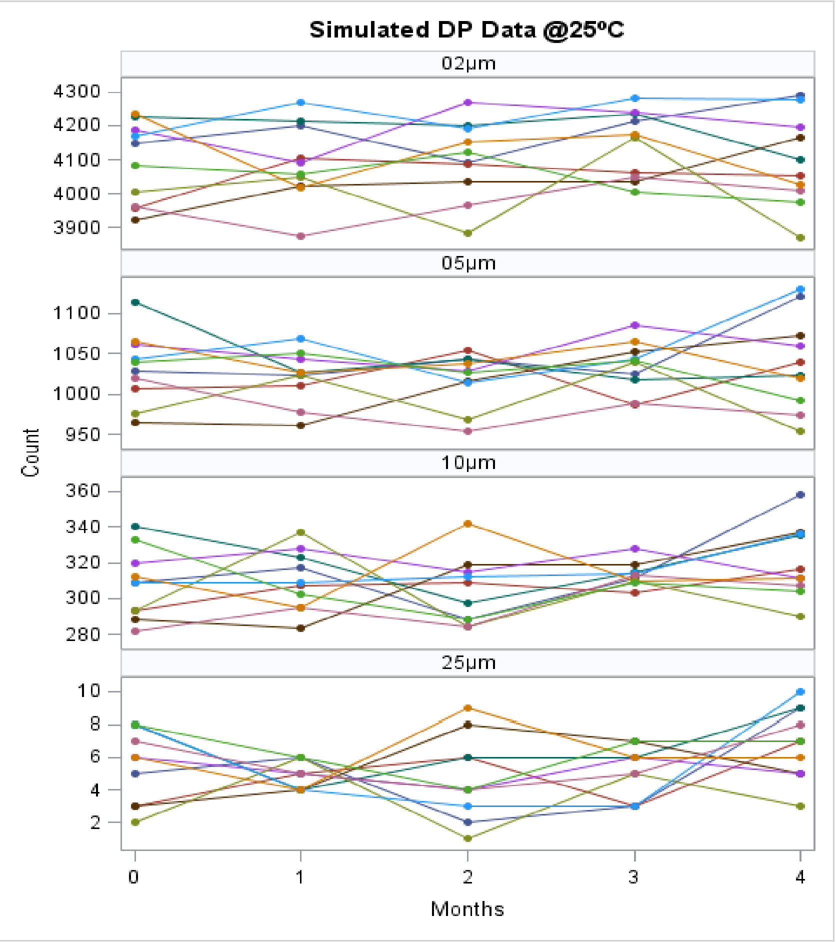
Simulated DP 25°C Stability SbVP Data

- Four particle sizes: 2µm, 5µm, 10µm, 25µm
- Counts follow a multivariate Poisson distribution
  - 2µm average number of particles ~ 4000
  - 5µm average number of particles ~ 1000
  - 10µm average number of particles ~ 300
  - 25µm average number of particles ~ 5
- Counts are correlated
  - 4x4 covariance matrix
- Ten lots: A, B, C, D, E, F, G, H, I, J
- Five time intervals per lot: 0, 1, 2, 3, 4 months

Simulated DP 25°C Stability SbVP Data





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Simulated DP 25°C Stability SbVP Data Random Coefficients Model

- Model Counts as a function of Size and Months.
  - Counts = Size + Months + Size*Months
- Model Counts using an appropriate distribution.
  - Poisson
- Account for Lot-to-Lot variation.
  - Independent random intercepts and slopes.
- Include correlation between particle sizes
  - General 4x4 covariance structure.
- Rich structure: many parameters to estimate
- PROC GLIMMIX (SAS)
  - Can fit mixed models with the Poisson or negative binomial
  - Handles repeated measures
  - Computes appropriate tests for covariance parameters

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Simulated DP 25°C Stability SbVP Data Random Coefficients Model (GLIMMIX)

- Covariance estimates
  - Random slopes variation ~0
  - Estimated correlations reflect the correlation structure between particle sizes.
    - Corr(2µm, 5µm) = 0.5725
    - Corr(10µm,25µm) = 0.6524

Covariance Parameter Estimates			
Cov Parm	Subject	Estimate	Standard Error
Intercept	Lot	0.000514	0.000298
Months	Lot	0.000018	.
Var(1)	Subj	1.3110	0.3386
Var(2)	Subj	0.9990	0.2261
Var(3)	Subj	0.7619	0.1605
Var(4)	Subj	0.7654	0.1563
Corr(2,1)	Subj	0.5725	0.1127
Corr(3,1)	Subj	0.4280	0.1311
Corr(3,2)	Subj	0.5975	0.09664
Corr(4,1)	Subj	0.2341	0.1522
Corr(4,2)	Subj	0.5086	0.1113
Corr(4,3)	Subj	0.6524	0.08533

- Random coefficients tests
  - Significant random intercepts
    - Lot-to-Lot variation
  - No need for random slopes

Tests of Covariance Parameters Based on the Residual Pseudo-Likelihood					
Label	DF	-2 Res Log P-Like	ChiSq	Pr > ChiSq	Note
No Random Intercepts	1	-556.55	12.96	0.0002	MI
No Random Slopes	1	-568.00	1.52	0.1088	MI

- Fixed effects tests
  - No Months*Size interaction
  - No overall slope
  - Significant size effect

Type III Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
Size	3	46.02	27673.4	<.0001
Months	1	49.25	2.59	0.1138
Months*Size	3	46.07	0.86	0.4689

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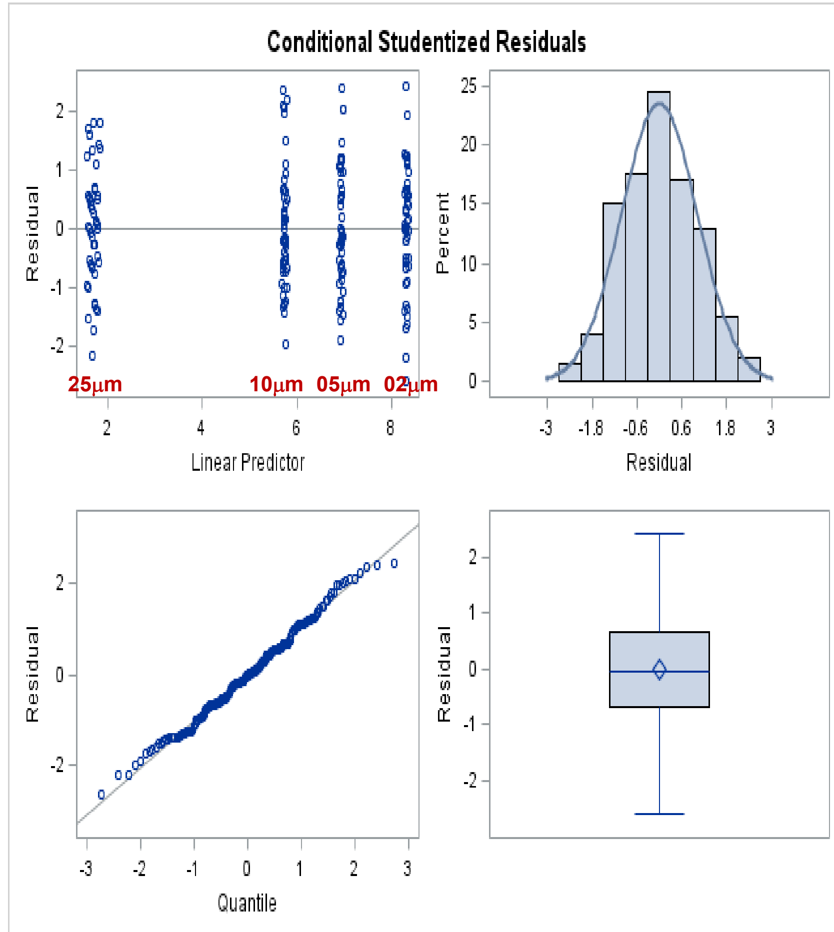
Simulated DP 25°C Stability SbVP Data Conditional Residuals Plots (GLIMMIX)

- Conditional residuals indicate how well the model fits given the random structure.
  - Observed – Fixed – Random
- Useful for
  - Diagnostics
  - Normality check
  - Constant variance
- Conditional studentized residual plots look good!



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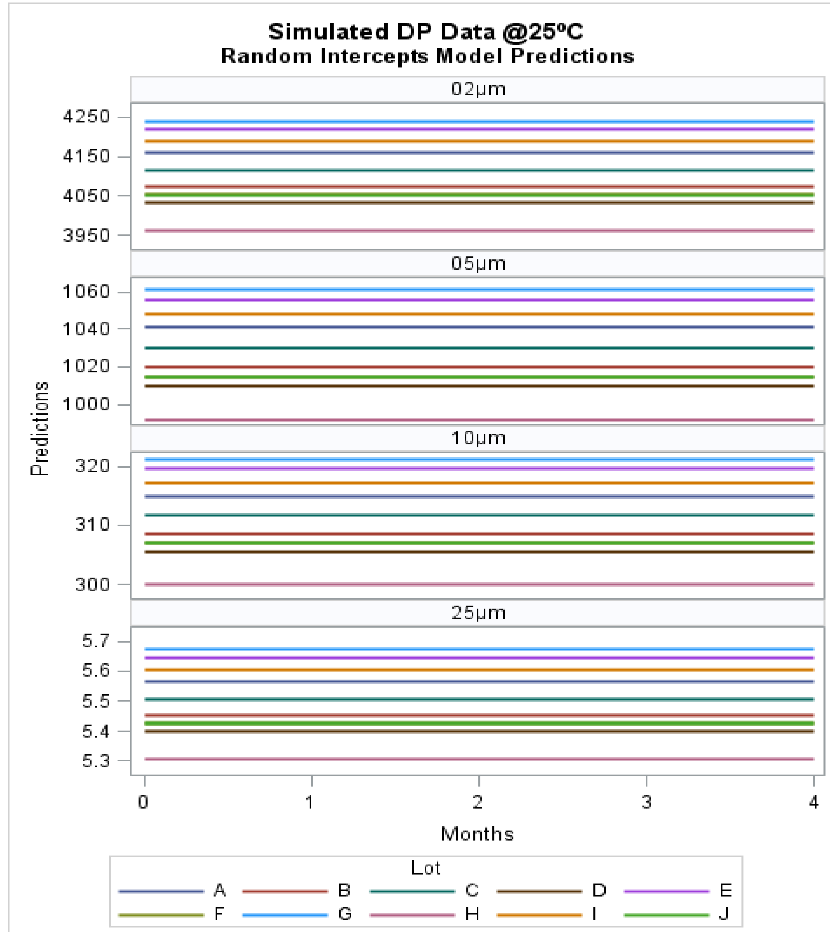
Simulated DP 25°C Stability Data Random Intercepts Model Predictions

- Parameter estimates predicted the average count for each size.

Solutions for Fixed Effects						
Effect	**Size**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		1.6936	0.05380	50.47	31.48	<.0001
Size	02µm	6.6260	0.05270	49	125.74	<.0001
Size	05µm	5.2425	0.05093	49	102.94	<.0001
Size	10µm	4.0460	0.04891	49	82.73	<.0001
Size	25µm	0	.	.	.	.

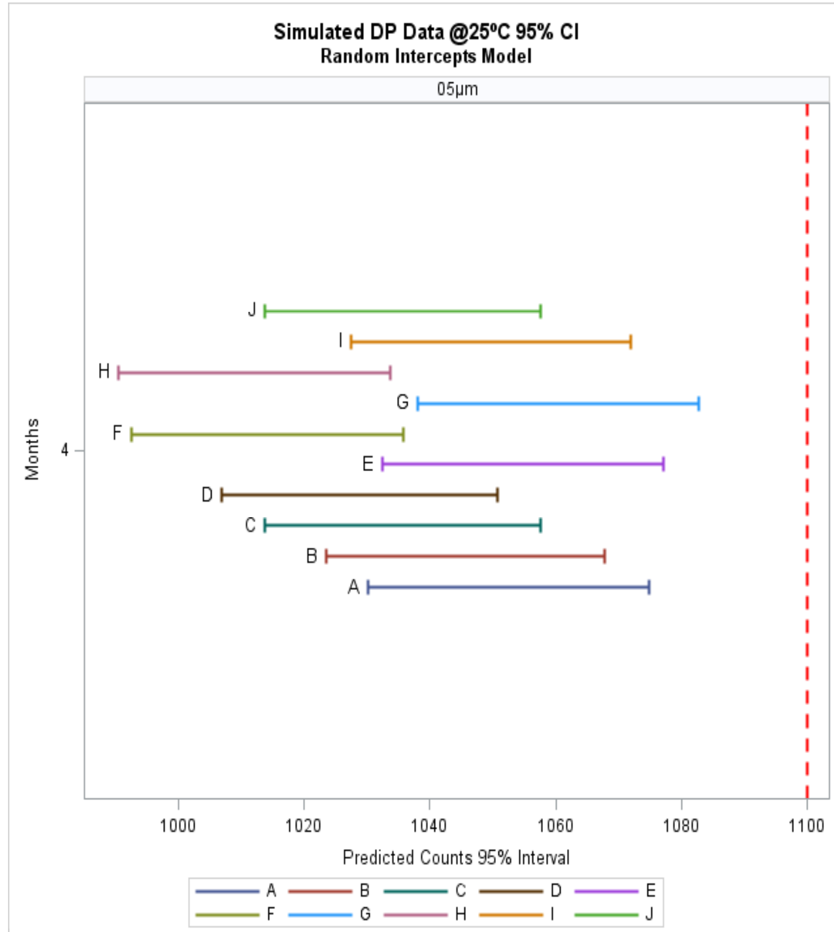
2µm : exp(1.6936 + 6.6260) ~ 4,103
5µm: exp(1.6936 + 5.2425) ~ 1,029
10µm: exp(1.6936 + 4.0460) ~ 311
25µm: exp(1.6936) ~ 5

- Random components modify the Size average for a given lot.
- Spread between the lines reflects the lot-to lot variation.



Simulated DP 25°C Stability Data 95% "Prediction" Intervals @4 Months

- Model allow us to calculate "prediction" intervals for each lot, at a given time point.
- We can compare the upper "prediction" bound with a given specification.
  - Upper bound should be less than given specification
  - Predicted counts will not be more than upper bound with 95% confidence.
- For example, for all lots the 5µm upper bounds < 1100



Summary

- Subvisible particle stability data has a rich structure that needs to be taken into account.
  - Discrete counts
  - Lot-to-Lot variation
  - Correlated responses (2μm, 5μm, 10μm, 25μm)
  - Time dependency
- Random coefficients models with correlated repeated measures using a Poisson or negative binomial distribution.
- PROC GLIMMIX makes it easy to fit these models.
  - Allows for different covariance structures
  - Appropriate covariance parameter tests
  - Conditional residuals for model evaluation

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