Considerations for model application: VBE trials vs. single representative modeling, dealing with within and between subjects variability and parameter uncertainty

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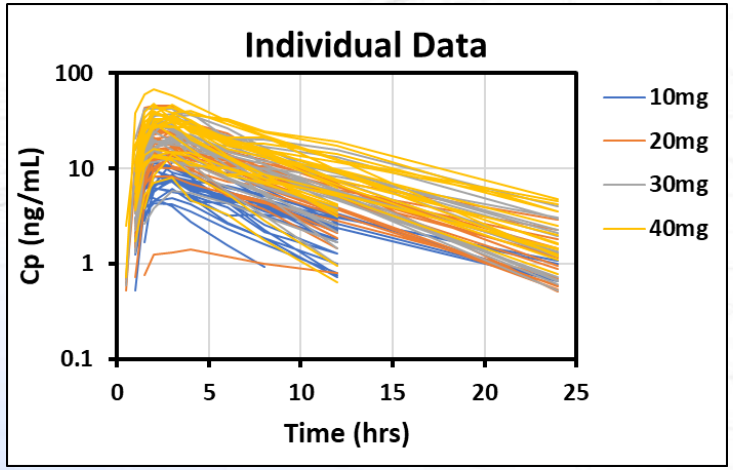
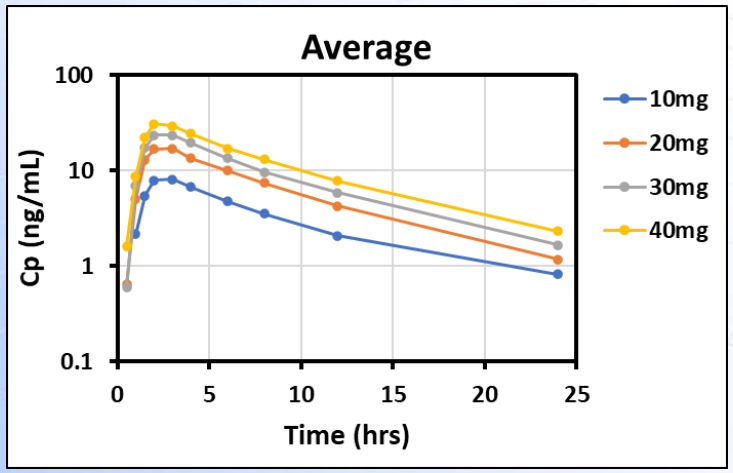
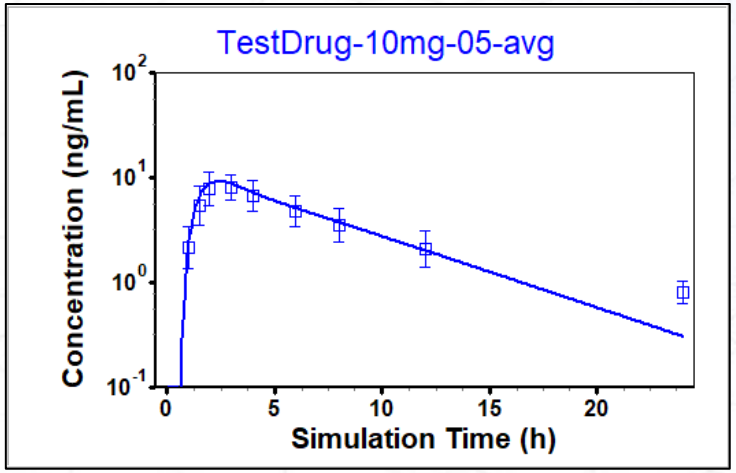
Baseline Model

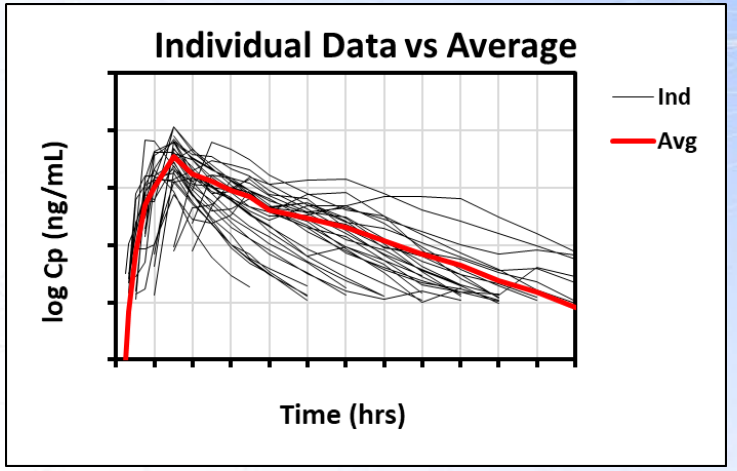
Use both individual data and average

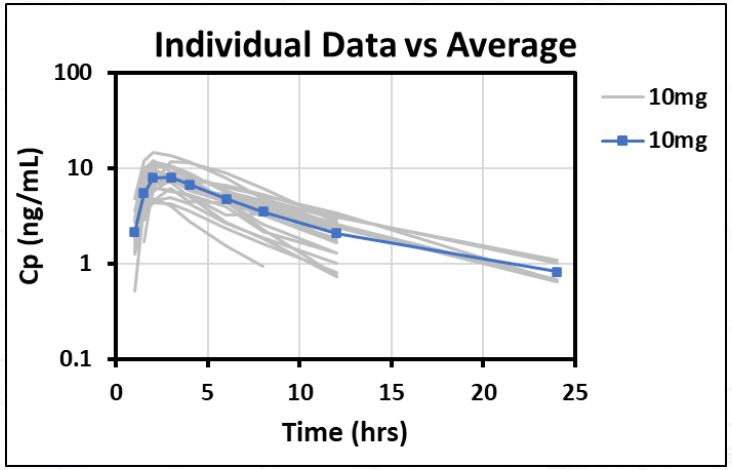


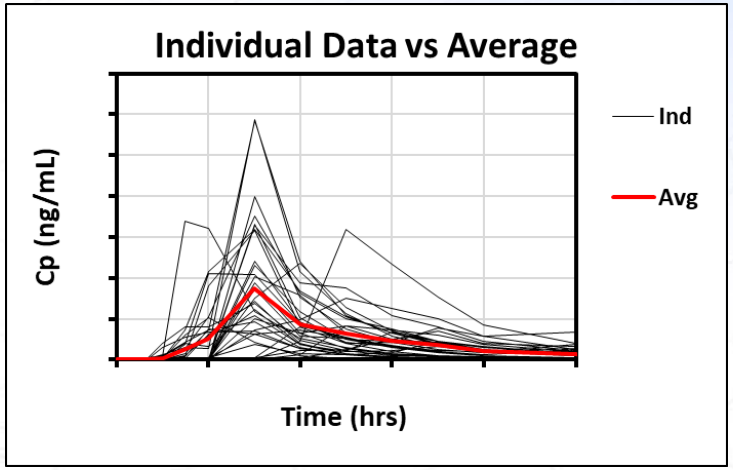


Make sure to understand the data
(know what the average represents)









Uncertainty & Variability

Uncertainty:

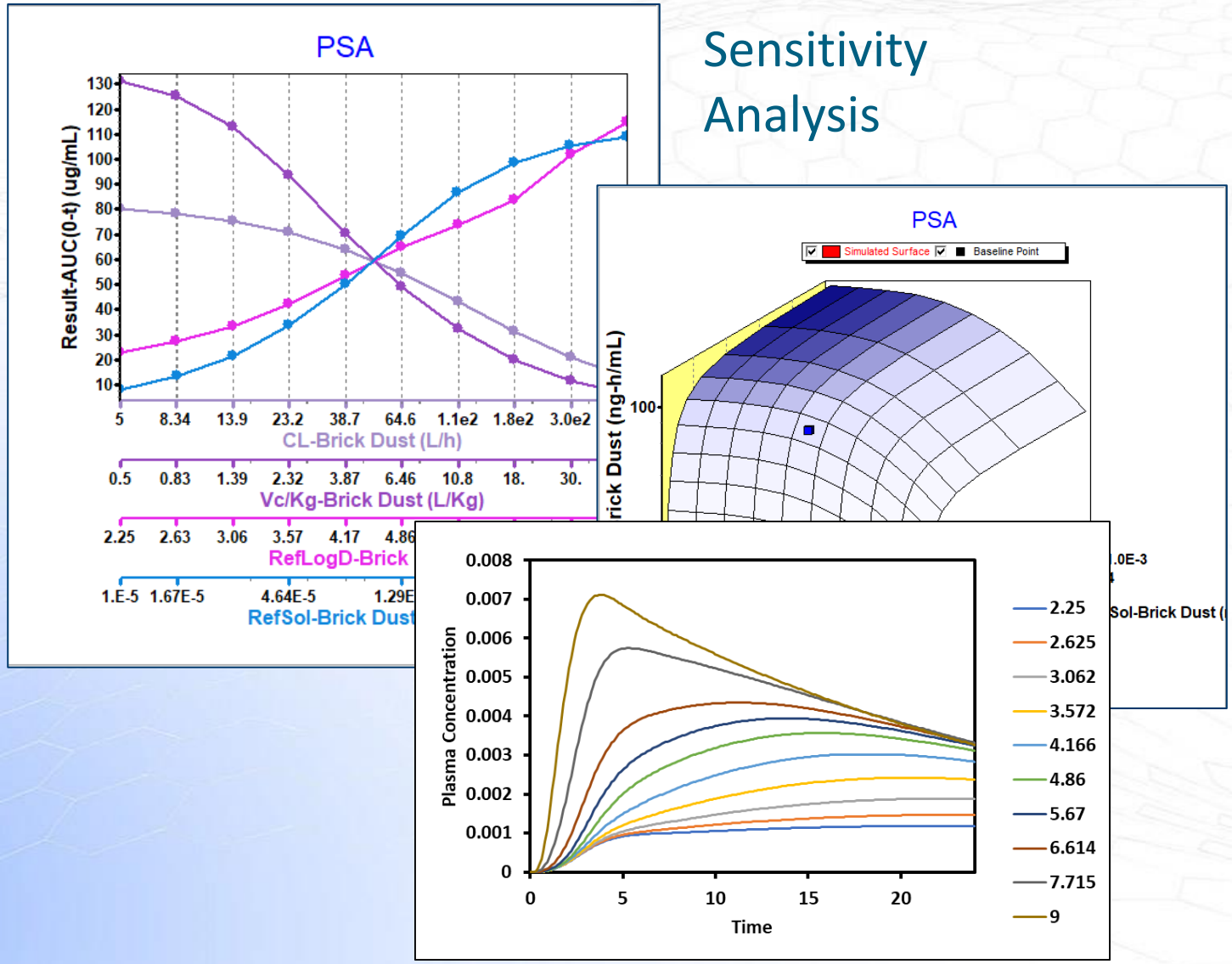
- Limited data
- Lack of mechanistic understanding
- Disconnect between in vitro and in vivo data
- Uncertainty in some physiological parameters

Physiological variability:

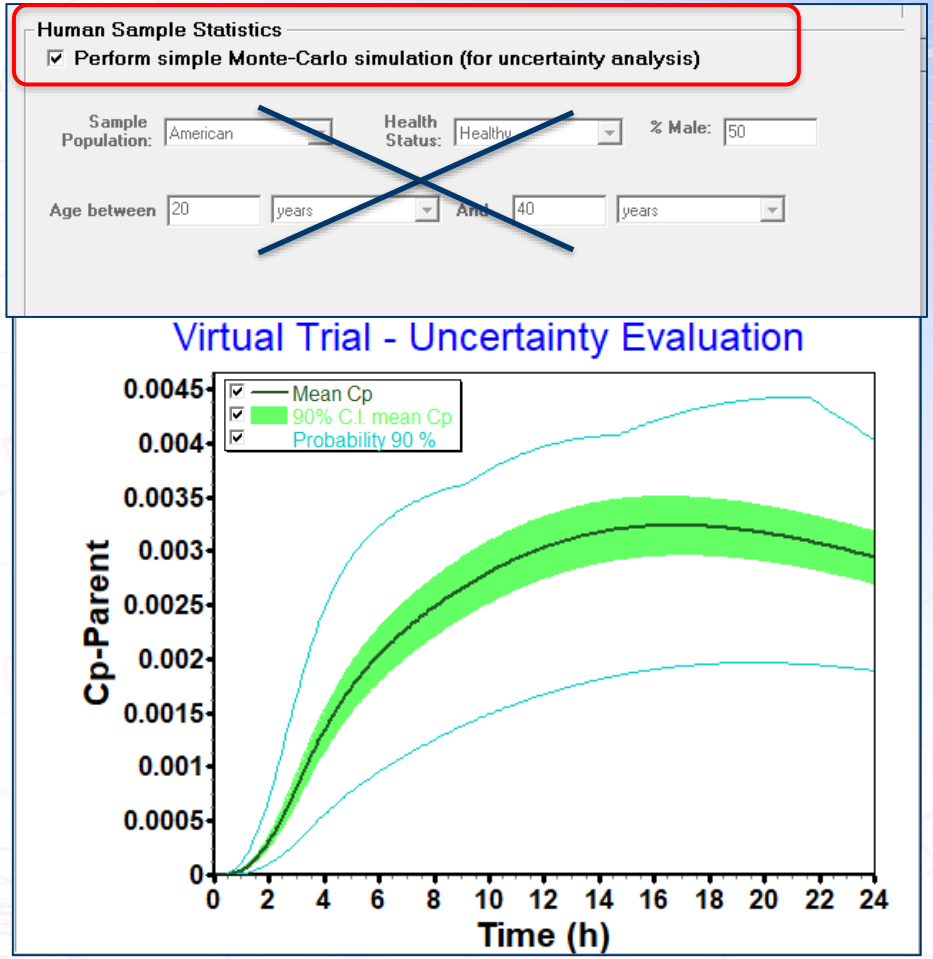
- Different strategies are used to create virtual subject population
- Intrasubject (within subject, inter-occasion)
- Intersubject (between subject)
  - Combines intersubject and intrasubject variability
- Quantitatively characterized for some physiological parameters
  - Smaller numbers for intrasubject variability than intersubject variability
  - Usually larger numbers of samples/subjects than for intrasubject variability, more studies available in literature
  - Information still missing for some physiological parameters

Uncertainty Evaluation

Sensitivity Analysis

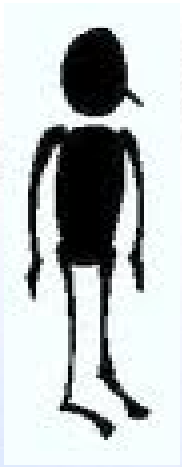


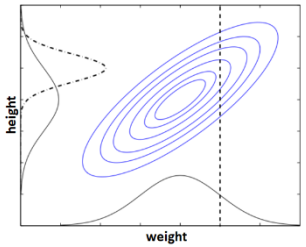
Virtual Trial

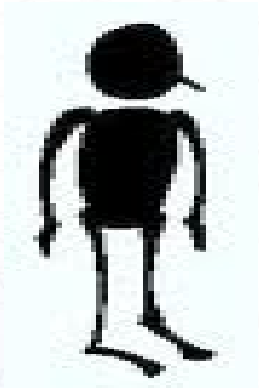


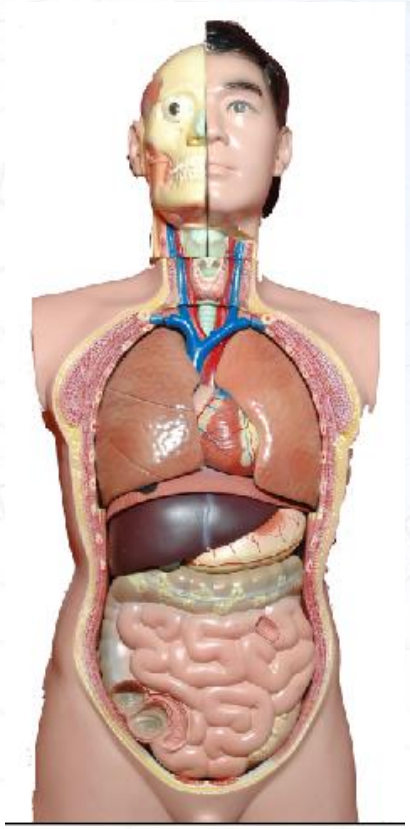
SimulationsPlus

Generating Virtual Population: GastroPlus®









Randomly select age and gender from defined population

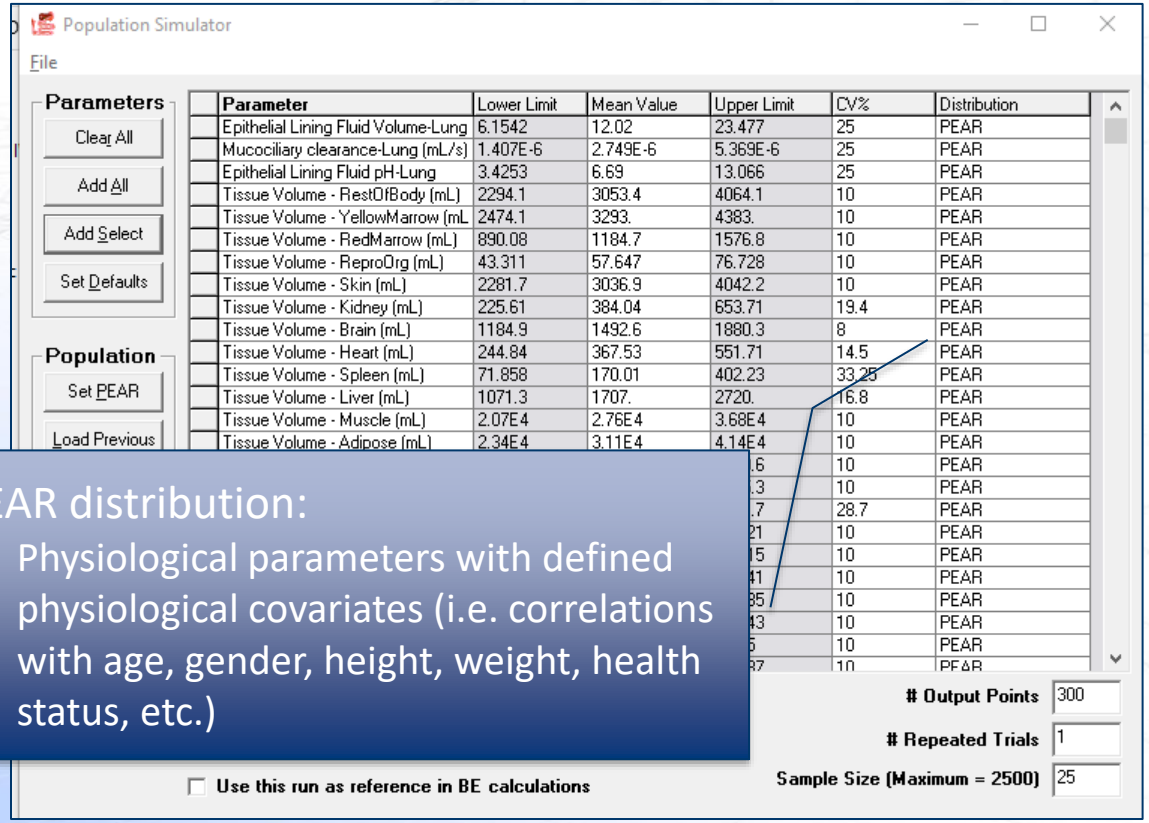
Select body weight and height for the subject based on bivariate distribution for given age and gender

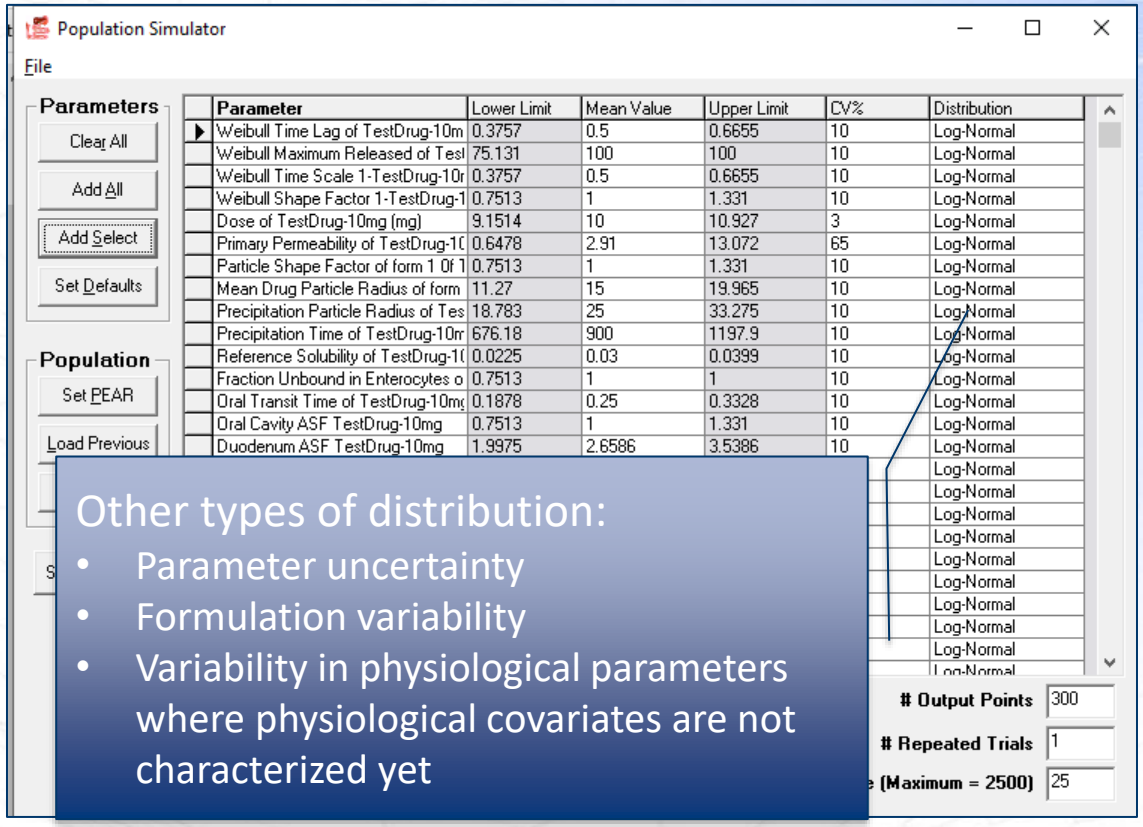
Generate the physiology with the tissue sizes corresponding to the selected age, gender, height and weight

*There is an option to add the additional random variability on tissue sizes as in the previous algorithm

Contributions to Variability In PK

GastroPlus® Population Simulator





PEAR distribution:

- Physiological parameters with defined physiological covariates (i.e. correlations with age, gender, height, weight, health status, etc.)

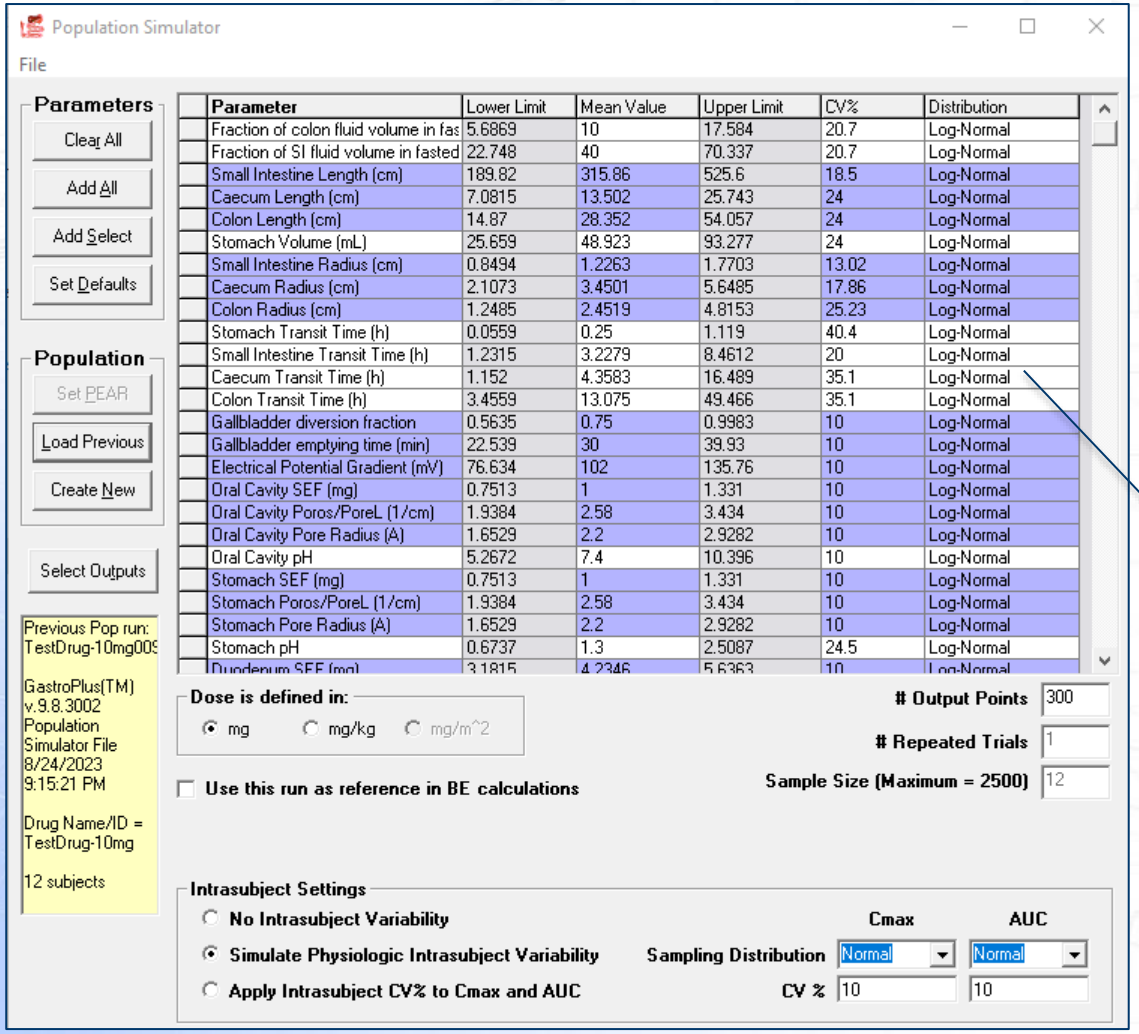
Other types of distribution:

- Parameter uncertainty
- Formulation variability
- Variability in physiological parameters where physiological covariates are not characterized yet

Model Type/Setting may lump together uncertainty and physiological variability

Contributions to Variability In PK

GastroPlus® Population Simulator



Intrasubject Variability with Crossover Trials:

- Additional variability will be added to parameters with known intrasubject variability (intestinal transit times, fluid volumes, pH, bile salts, etc.)

*blue rows represent parameters that will be fixed for each subject

Intrasubject and Intersubject Variability

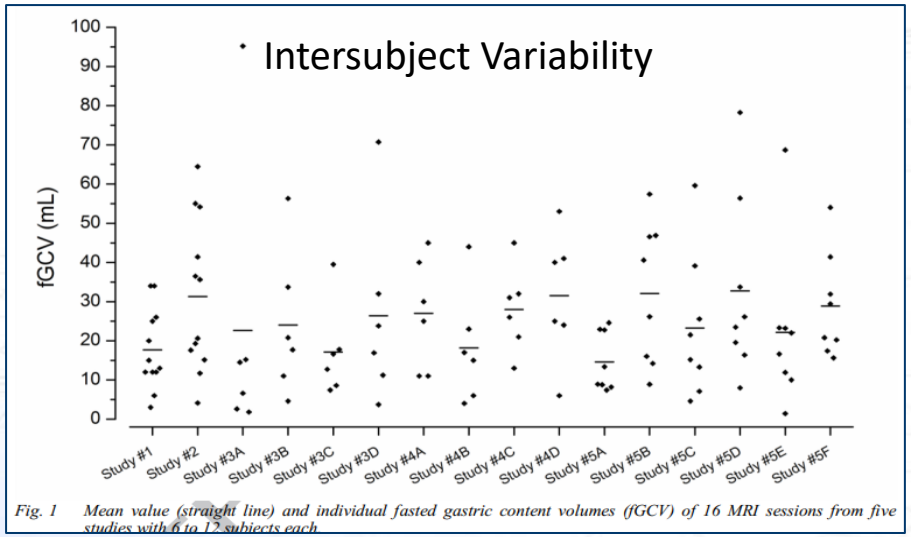


Fig. 1 Mean value (straight line) and individual fasted gastric content volumes (fGCV) of 16 MRI sessions from five studies with 6 to 12 subjects each

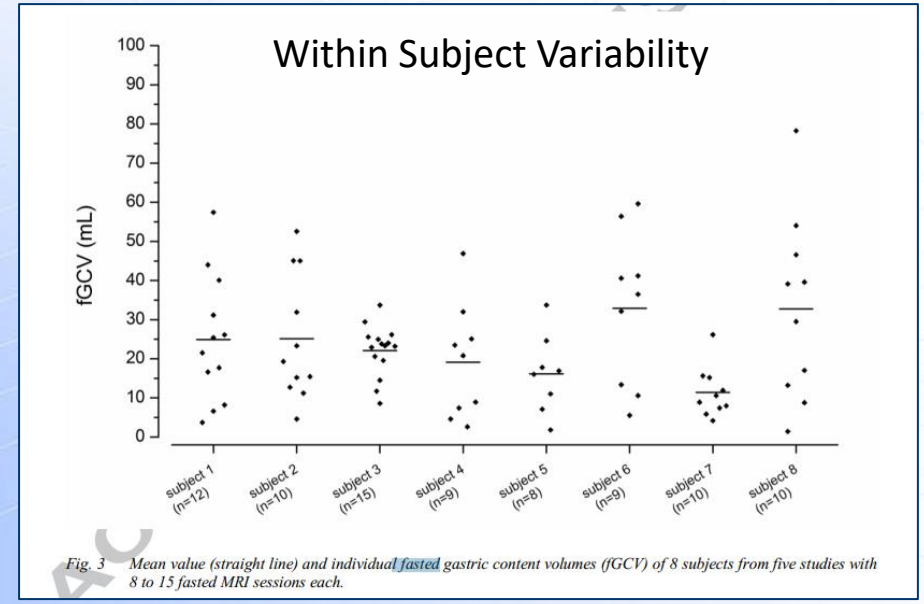


Fig. 3 Mean value (straight line) and individual fasted gastric content volumes (fGCV) of 8 subjects from five studies with 8 to 15 fasted MRI sessions each.

Grimm - Eur J Pharm Biopharm - 2018

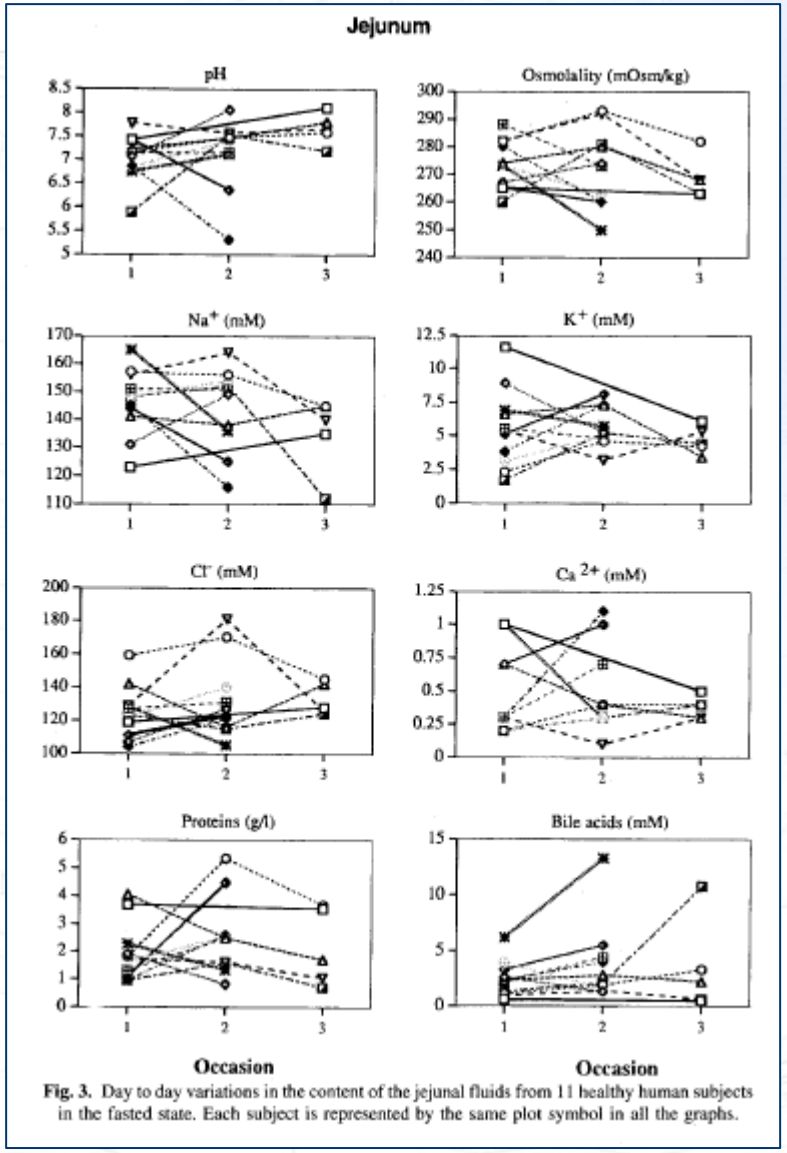
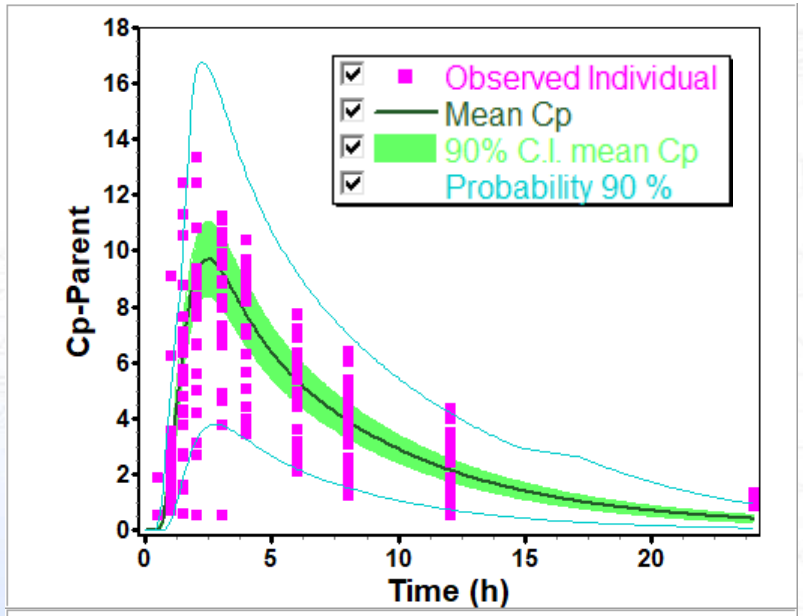
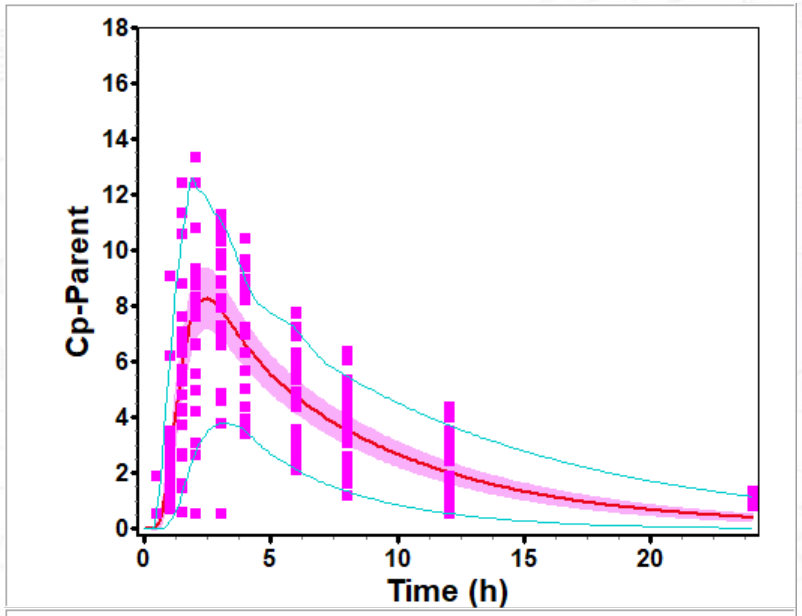


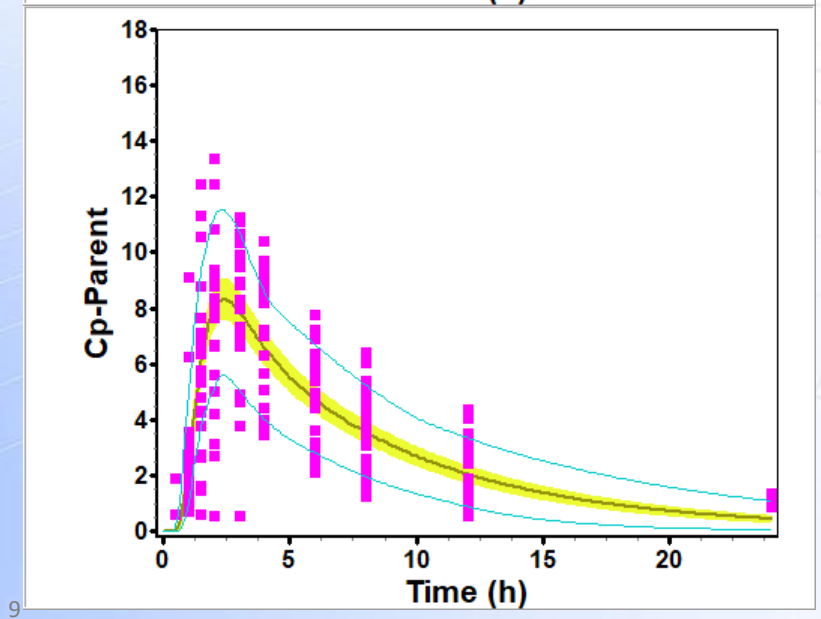
Fig. 3. Day to day variations in the content of the jejunal fluids from 11 healthy human subjects in the fasted state. Each subject is represented by the same plot symbol in all the graphs.

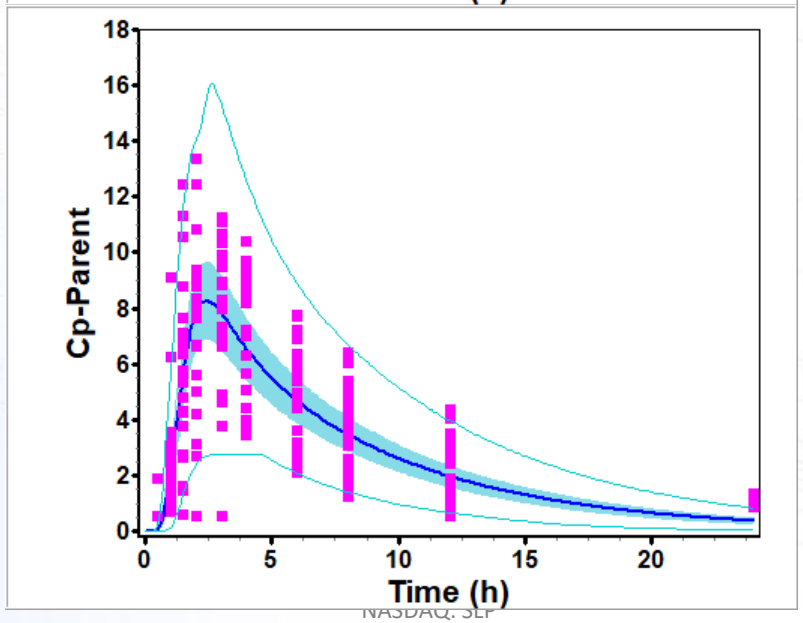
Lindahl – Pharm Res - 1997

Verify Variability Settings









- Does virtual trial reproduce clinical data?
- Repeat virtual trials will produce different results even with the same settings (CV%) especially with small numbers of subjects

How Many Subjects in VBE?

BE Summary **12 subjects**		(GeomMeanT/GeomMeanR)*100			90% CI (GeomMeanT/GeomMeanR)					
Trial #	PASS/FAIL	Cmax	AUC	AUCt	Cmax Geo Lower CI	Cmax Geo Upper CI	AUC Geo Lower CI	AUC Geo Upper CI	AUCt Geo Lower CI	AUCt Geo Upper CI
1	FAIL	103.4	101.4	101.5	84.006	127.2	82.478	124.6	83.049	124.08
2	FAIL	102.3	99.81	99.92	83.912	124.63	79.308	125.6	80.282	124.36
3	PASS	100.5	99.62	99.72	84.904	119.04	80.246	123.68	81.037	122.72
4	FAIL	96.3	97.58	97.54	77.217	120.11	80.974	117.59	81.126	117.28
5	PASS	96.42	102.4	102.3	80.723	115.18	86.761	120.88	86.829	120.48
6	FAIL	98.4	94.4							
7	FAIL	105.8	103							
8	PASS	104.1	101							
9	PASS	102.3	98.7							
10	PASS	100.5	98.5							

BE Summary **24 subjects**		(GeomMeanT/GeomMeanR)*100			90% CI (GeomMeanT/GeomMeanR)					
Trial #	PASS/FAIL	Cmax	AUC	AUCt	Cmax Geo Lower CI	Cmax Geo Upper CI	AUC Geo Lower CI	AUC Geo Upper CI	AUCt Geo Lower CI	AUCt Geo Upper CI
1	PASS	104.1	98.46	98.69	92.883	116.67	86.922	111.53	87.753	110.98
2	FAIL	102.9	102.3	102.3	77.755	136.12	76.717	136.4	76.959	136.05
3	PASS	98.68	100.2	100.2	84.865	114.75	84.977	118.08	85.293	117.61
4	PASS	102.1	101.3	101.4	89.229	116.77	88.068	116.57	88.644	116.1
5	PASS	98.32	97.92	97.91	88.536	109.19	86.224	111.21	86.663	110.63
6	PASS	100.4	99.71	99.7						
7	PASS	98.47	98.12	98.2						
8	FAIL	100.8	101.8	101						
9	FAIL	99.67	99.21	99.						
10	PASS	103	100.6	100						

BE Summary **48 subjects**		(GeomMeanT/GeomMeanR)*100			90% CI (GeomMeanT/GeomMeanR)					
Trial #	PASS/FAIL	Cmax	AUC	AUCt	Cmax Geo Lower CI	Cmax Geo Upper CI	AUC Geo Lower CI	AUC Geo Upper CI	AUCt Geo Lower CI	AUCt Geo Upper CI
1	PASS	99.29	100.4	100.4	88.011	112.03	88.471	113.89	88.7	113.55
2	PASS	99.12	98.06	98.08	88.737	110.72	86.604	111.02	86.886	110.72
3	PASS	100.2	99.89	99.89	90.544	110.91	90.002	110.87	90.241	110.56
4	PASS	100.5	99.54	99.58	90.635	111.53	89.701	110.45	89.816	110.4
5	PASS	98.78	99.19	99.23	90.291	108.07	89.316	110.16	89.771	109.69
6	PASS	101.9	99.48	99.67	92.986	111.64	89.514	110.57	90.175	110.17
7	PASS	97.67	98.02	98.02	85.038	112.19	84.651	113.51	84.877	113.2
8	PASS	98.46	99.13	99.12	91.129	106.39	89.017	110.38	89.513	109.76
9	PASS	99.74	100	99.97	91.091	109.21	90.43	110.62	90.719	110.16
10	PASS	102.2	101.1	101.1	92.108	113.39	90.634	112.71	90.949	112.36

- Testing the reference formulation against itself (including intrasubject variability) helps to define minimum number of subjects

Summary

- Both, uncertainty and physiological variability, are important
- For IR products or Class I drugs, virtual BE simulations can be (and has been) used to accurately simulate crossover trials
  - Our understanding today of inter (between) subject physiology differences allows for reasonable estimates
- Still room for improvements – especially in variability estimates and assumptions
  - Better methods for intra (within) subject variability estimates will lead to robust predictions
- What is the most appropriate strategy for performing virtual BE trials?
  - 1 large trial vs. ‘x’ smaller trials?

Questions and Contact Information

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