Population Modeling

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Consider

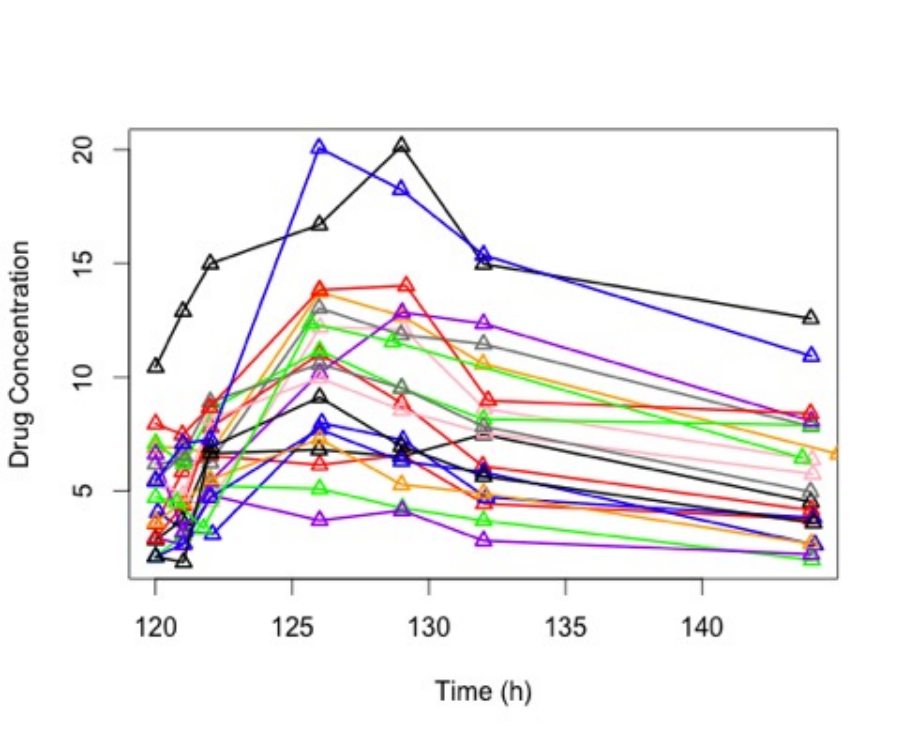
Question 1

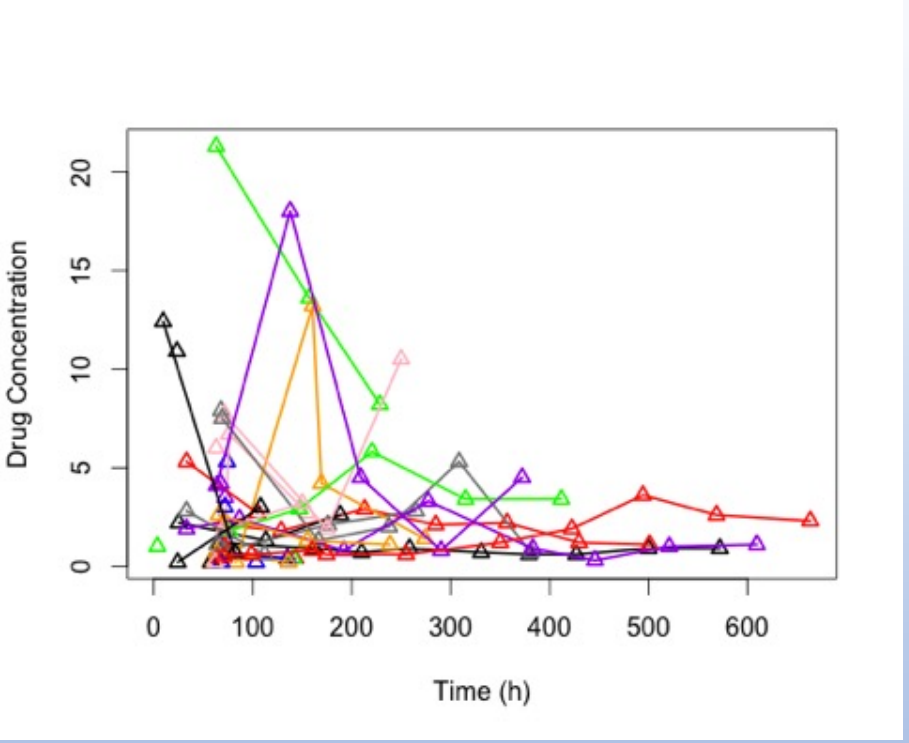
What is the initial drug dose most likely to achieve a safe and effective concentration in the maximum number of patients?

Question 2

What is the drug dose most likely to achieve a safe and effective concentration in an individual patient?

PK Data

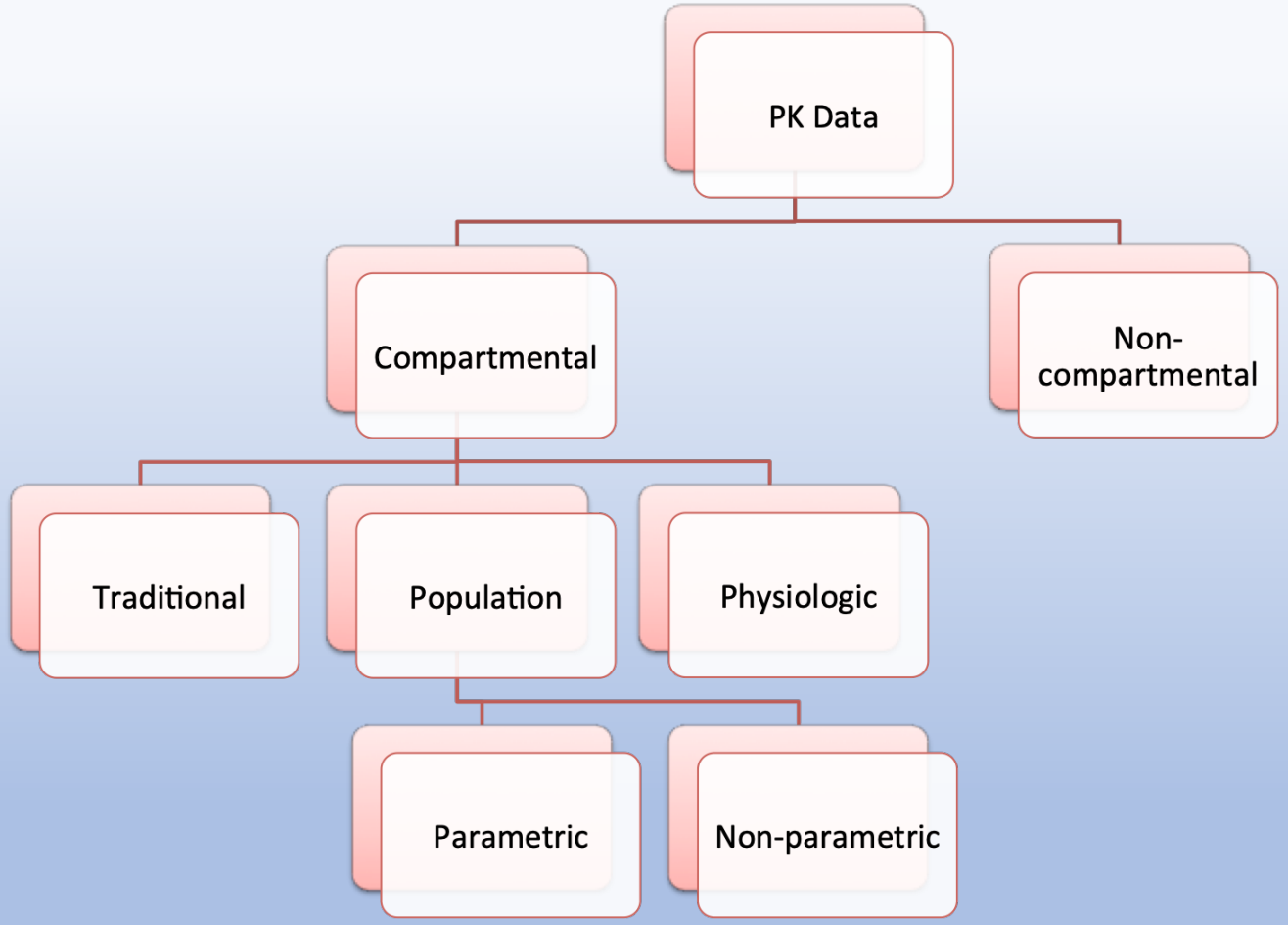

Drug Concentration
5
10
15
20
120
125
130
135
140
Time (h)


Drug Concentration
0
5
10
15
20
0
100
200
300
400
500
600
Time (h)

PK Modeling Objective

Describe and summarize drug exposure after a given dose or doses in individuals and populations

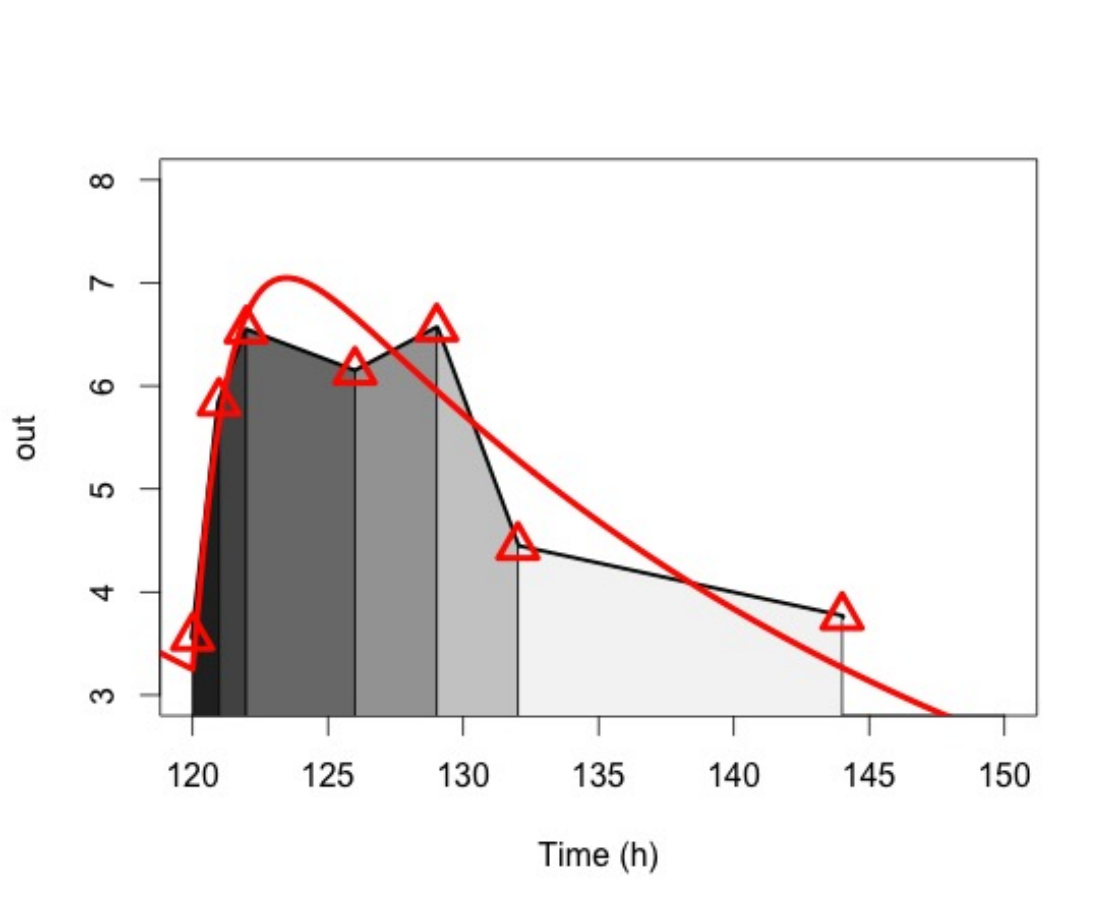
Modeling Approaches



Non-Compartmental

- Based on the shape of the time concentration curve
- Driven by estimation of AUC0-∞ and AUMC0-∞
- Typically used in bioequivalence, dose proportionality, and drug interaction studies (e.g. drug-food, drug-drug)

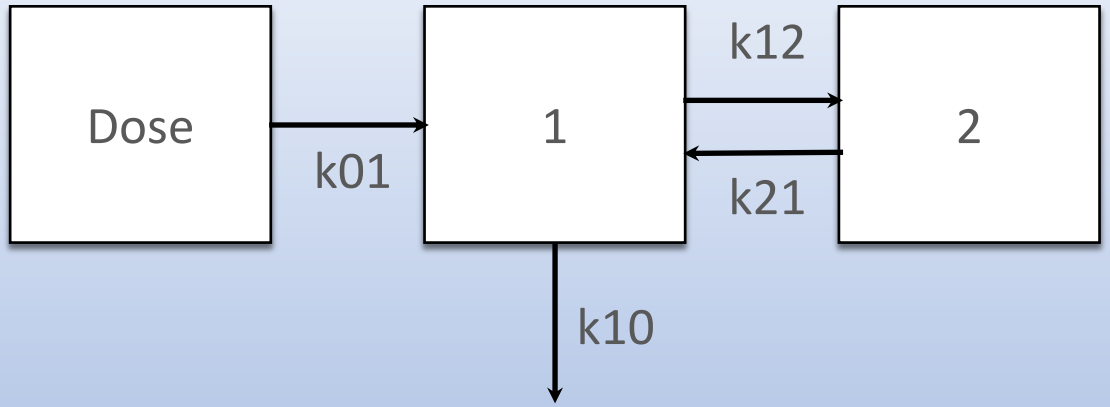
NCA AUC Estimation



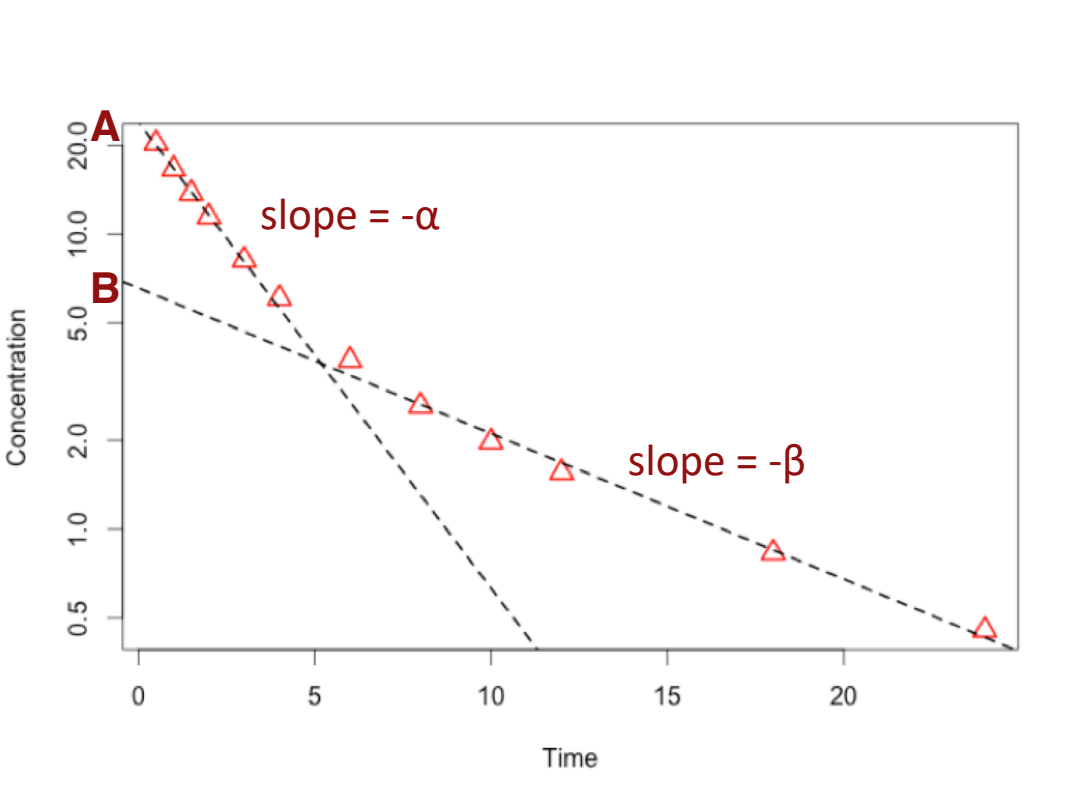
Challenges for NCA

- Analysis of sparse or unbalanced data
- Complex dosage regimens
- Non-linear PK
- Simulation of exposure from different regimens than those studied
- Elimination of drug other than from sampling pool

Compartmental Models



Traditional Compartmental



$$C_t = A*e^{-\alpha t} + B*e^{-\beta t}$$

Challenges

- Only uses information from one dosing interval
- Can be biased by sparse or unbalanced data
- Assumes parameters remain constant
- Neglects errors in observations (measurement or timing)
- Need at least one drug level per parameter in the model (eg. peak and trough to estimate volume and clearance)
- Does not distinguish sources of variability (e.g. interpatient from intrapatient)

Population Modeling

aka “Pharmacometrics”

Why Pop Model?

- **To understand and describe...**
  - the time course of drug concentrations in the body
  - relationships between drug concentration and effects, both desired and undesired
  - effects of covariates, e.g. renal function, on these relationships
  - sources of PK variability in the population

Why Pop Model?

- **To simulate new scenarios which is useful for...**
  - hypothesis generation, study design, dose finding
  - extrapolation to dosing in novel populations
- **To optimize and personalize therapy for individual patients**


My volume,
my clearance

The Best Population Model

- The correct structural PK/PD model, e.g. one-, two-compartment, inclusion of relevant covariates,...
- The collection of each subject's exactly known parameter values for that model, e.g. absorption, volume, clearance

Approximating the best

- observed = f(pred,error)
  - For example, obs = pred + error

Approximating the Best

$$y_{ij} = f(x_j, \beta_j) + \varepsilon_{ij}$$

Parametric

$\beta_j = h(\theta,\eta)$

$h = \theta+\eta,\ \theta^*e^{\eta},\ or\ \theta^*(1+\eta)$

$\eta \sim N(0,\omega)$

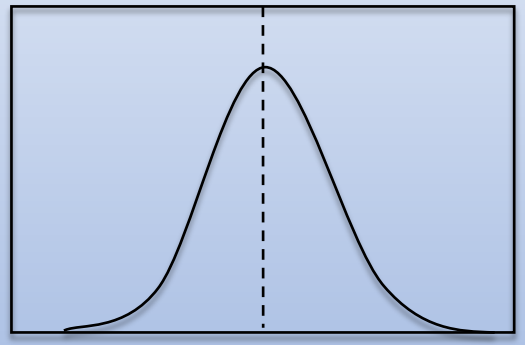
Non-Parametric

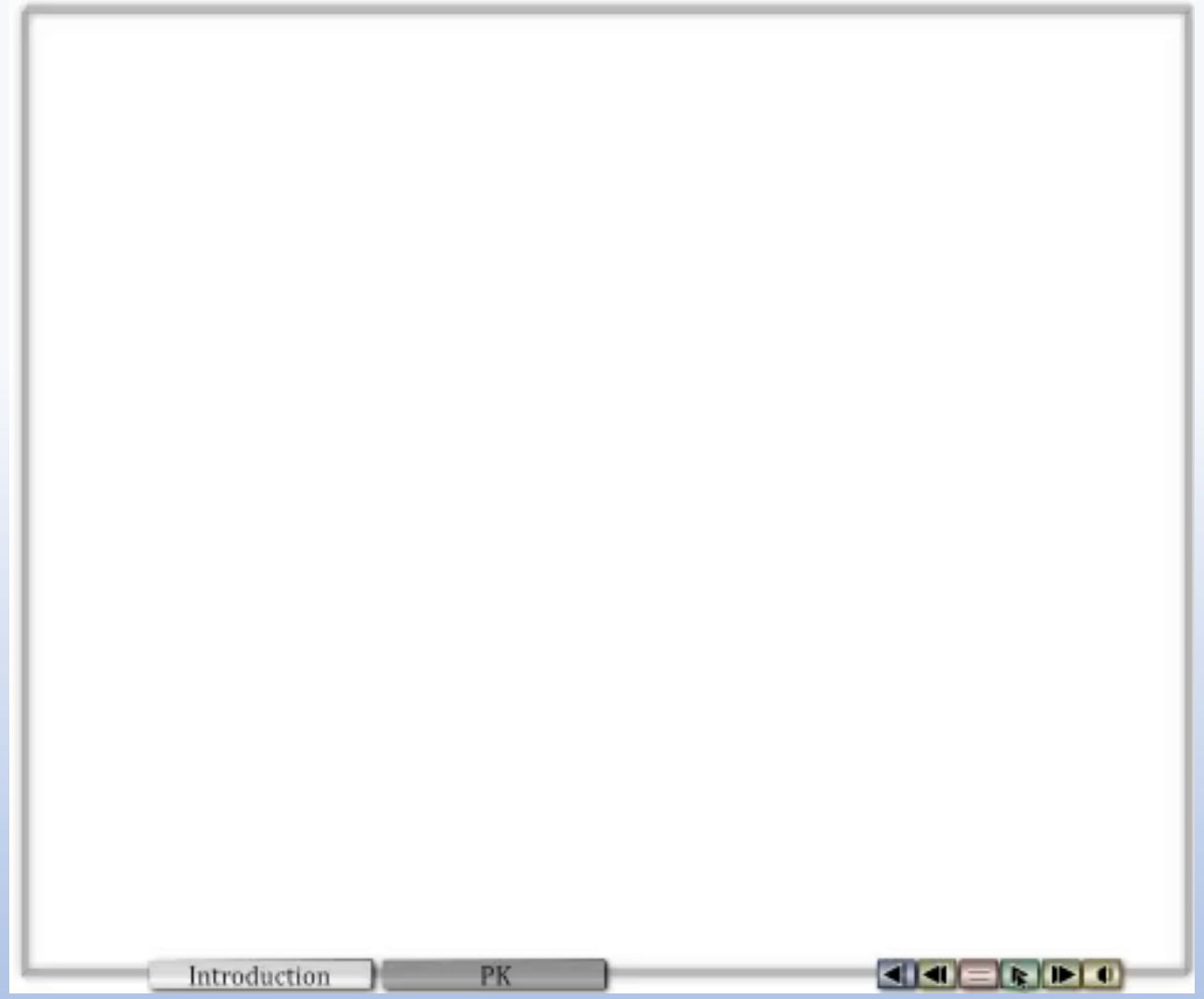
$FML(\beta) = p_1\delta_1(\beta_1) + \ldots + p_K\delta_K(\beta_K),\ K \leq N$

$\varepsilon \sim N(0,\sigma)$

Parametric

- Familiar, easy to summarize
  - e.g. Clearance = 0.7 +/- 0.3 L/min

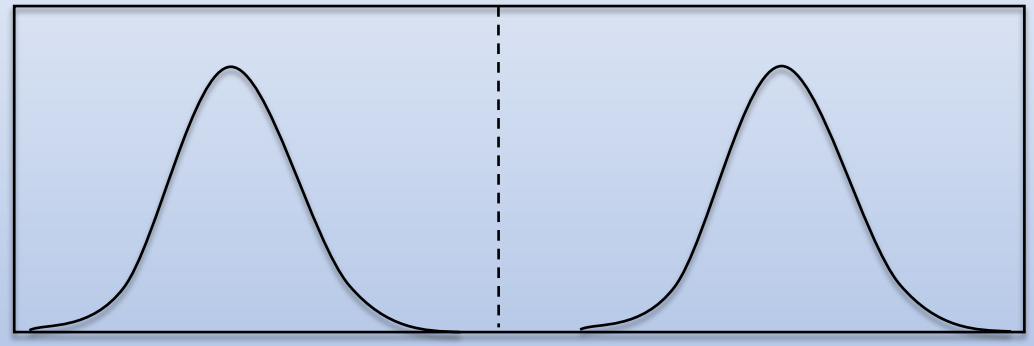




Video courtesy of Marc Lavielle, Ph.D.
Institut national de recherche en informatique et en automatique (INRIA), Paris, France, available at https://team.inria.fr/popix/files/2011/11/PopulationApproach.swf

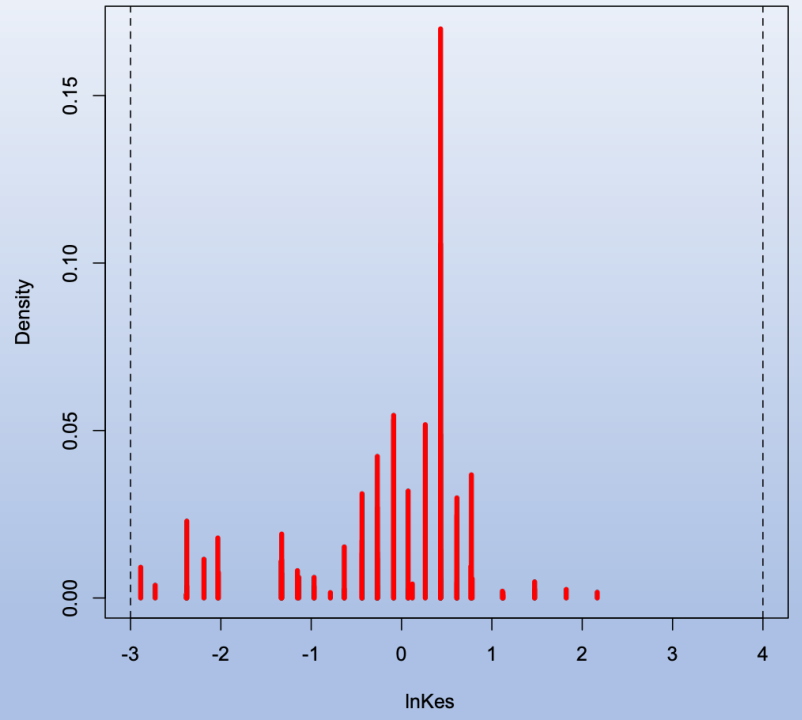
Non-Parametric

But what if the population distribution of clearance is this?



Non-Parametric

Or this?



Non-Parametric

- We don’t need to look at the infinity of all continuous distributions.
- The most likely distribution, given a set of data, can be found in a discrete collection of points, up to one per subject.
- Each (support) point is a vector of estimates for each parameter value, and of the probability of those values.

Non-Parametric

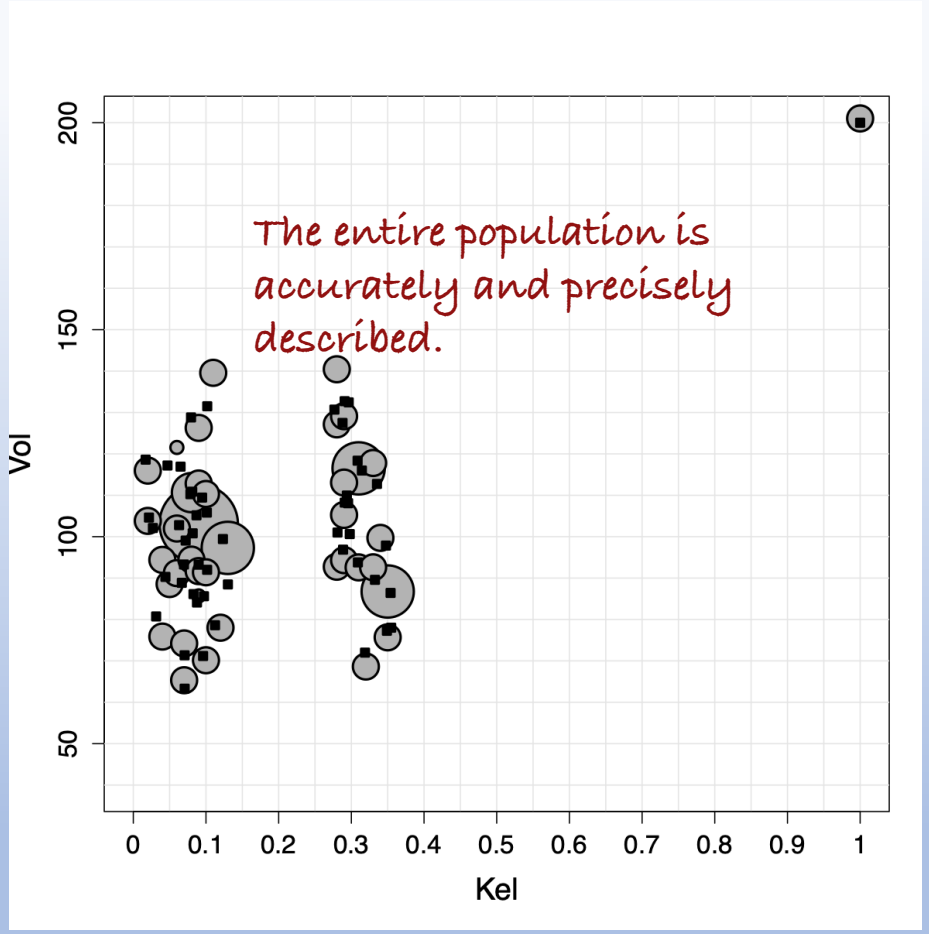
- The shape of this distribution is determined only by the data itself, not by an equation.
- This forms a natural basis for optimal control of dosage regimen with estimates of precision.

Non-Parametric

- Nonparametric – unfamiliar, harder to conceptualize
- Makes no assumptions about underlying parameter distributions
- Assigns a probability to each parameter value in the population based on the frequency of occurrence
- Can detect unexpectedly different subpopulations

Non-Normal Populations

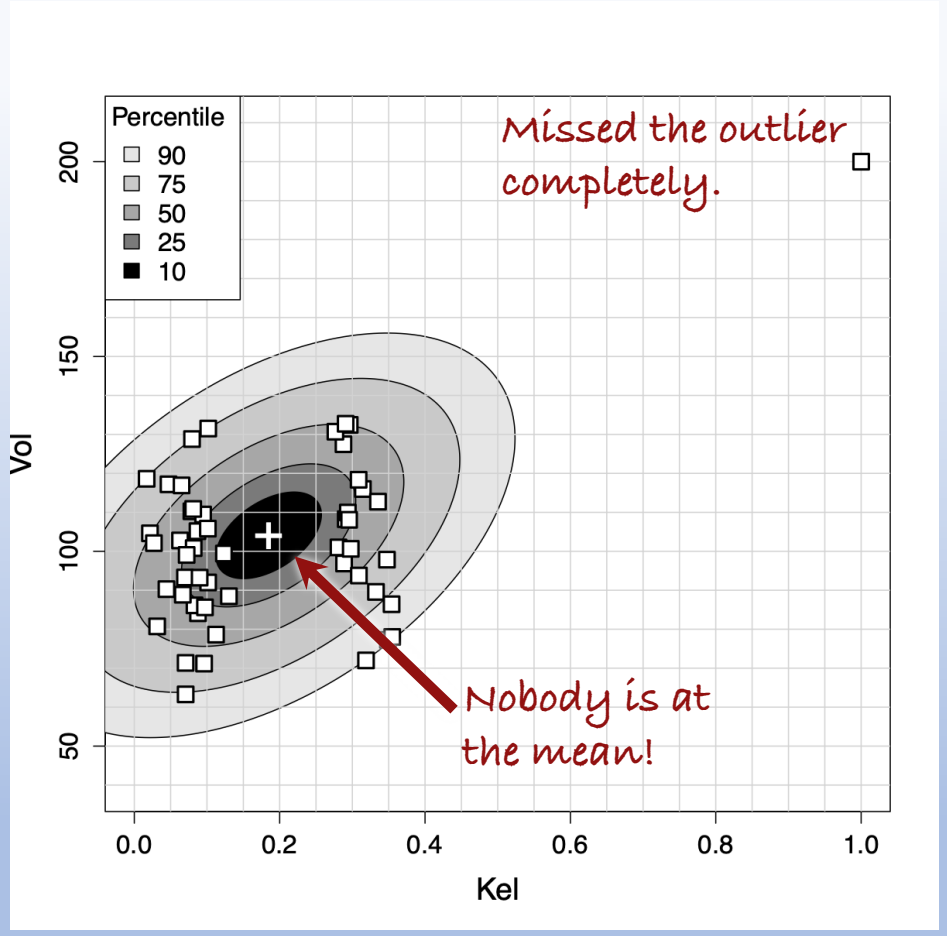
- Simulated population (■)
- Non-parametric estimation of population values (●)
  - Size proportional to probability



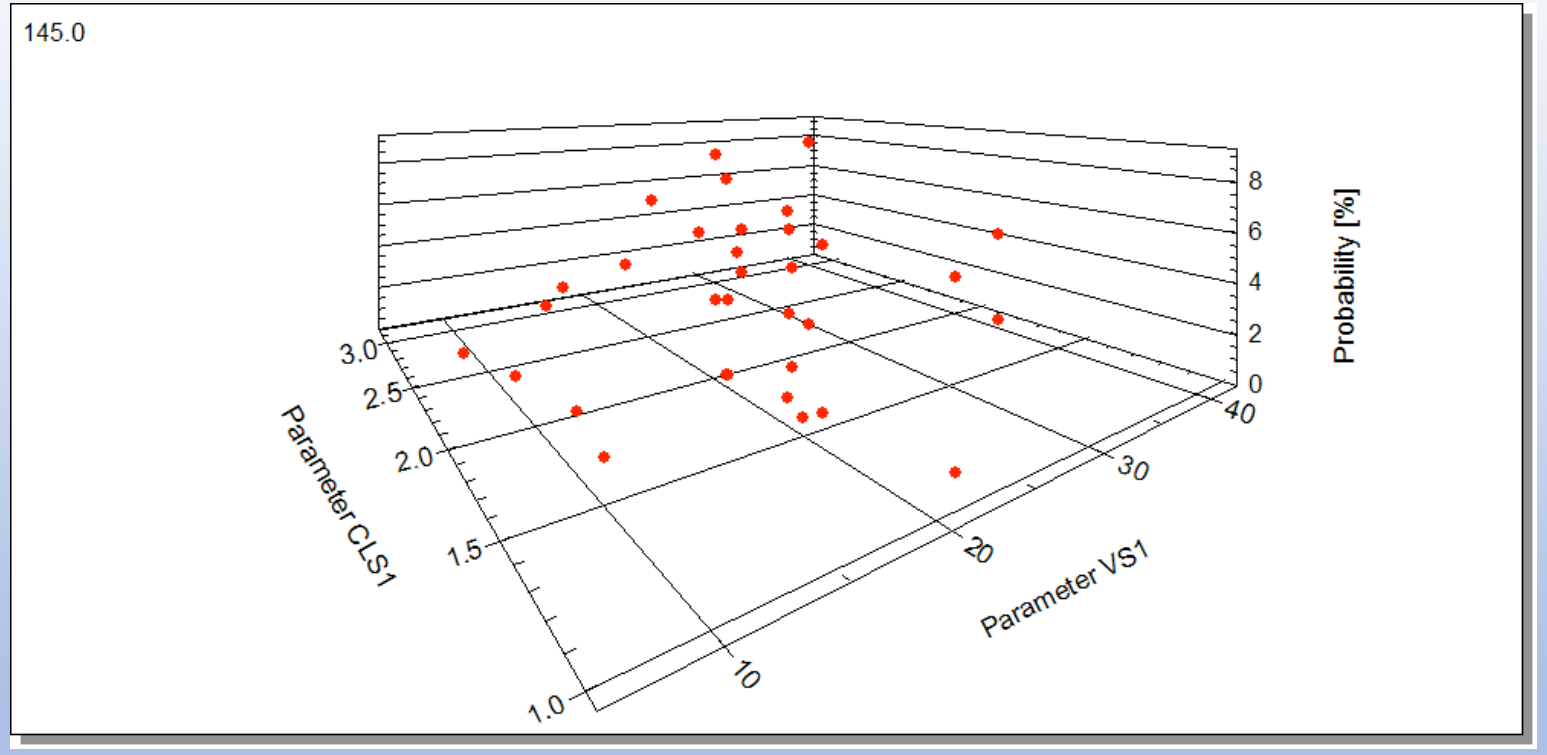
Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit. 2012;34(4):467–476.

Non-Normal Populations

- Simulated population (□)
- Mean (+) and percentile distributions of parametric population parameter estimates



Non-Parametric Model



Comparison

	Parametric	**Non-parametric**
Software	NONMEM, Monolix, ADAPT, S-Adapt, ITS, Phoenix	Pmetrics
Algorithms	FOCE, SAEM, MLEM, QRPEM, ITS	NPAG
Fixed effects	Population “typical” PK parameter values (TV)	Process and observation noise
Random effects	Inter-individual variability (IIV) and residual (intra-individual) variability (RV)	Population PK parameter values and residual variability
Assumptions	Normally distributed IIV and RV	Normally distributed RV

Software Tools

	Pmetrics	NONMEM	ADAPT	Phoenix	Monolix
Mode	NP, P	P, NP	P	P, NP	P
Cost	0	$$$/$[b]	$$$[a]	$$$/0[b]	$$$/0[b]
Simulate	Y	Y	Y	Y	Y
GUI	+	+	+	+++	+++
Platforms	W, U, L	W	W	W	W, L
All-in-one	+++	+	+	+++	++
Clinical	+++[c]	+	+	+	+

[a]Adapt is free, but it only uses the Intel Fortran compiler, which is $$$
[b]Academic license available
[c]With BestDose

Terminology

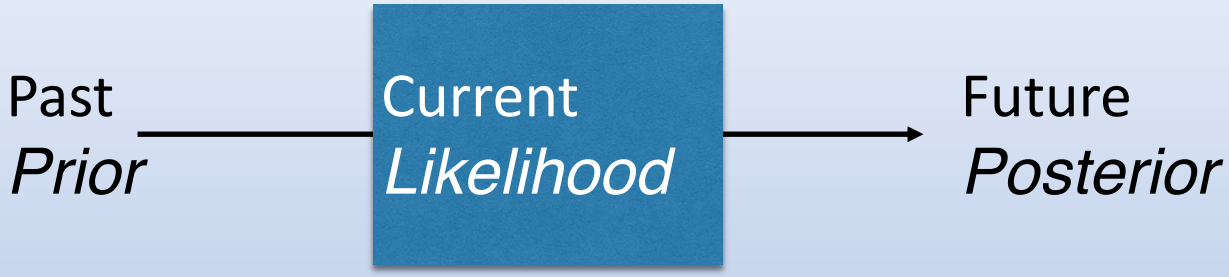
Model

- The collection of equations that relates the input to the output, AKA the “structural model”
- $C = Dose/V * e^{-ke*t}$
- Also can refer to the probability distribution of parameter values, which is more properly termed the joint probability density

Parameters

- Variables in the structural model equations
- e.g. $C = Dose/V * e^{-ke*t}$

Bayes' Theorem



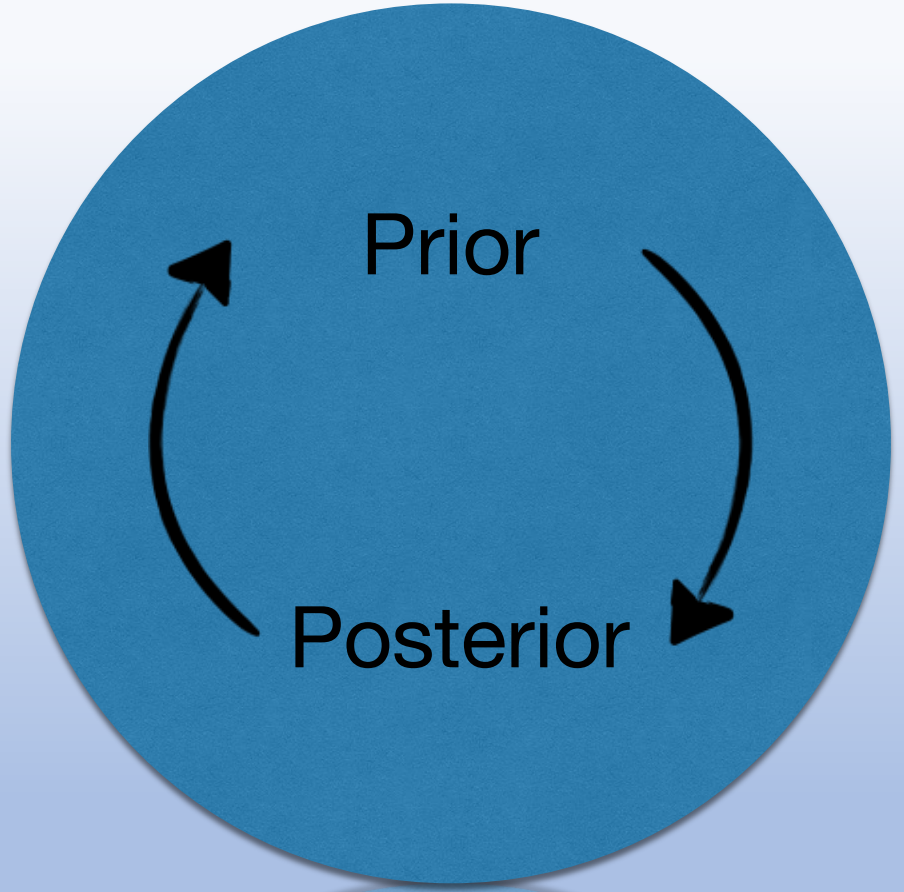
Bayesian Prior

- The probability distribution of parameter values without consideration of current data
- AKA “the model”, “the population prior”

Bayesian Posterior

- The probability distribution of parameter values which has been updated based on new data
- AKA “individual distribution”

Iterative



Convergence

- In the eye of the beholder
- Iterate and search for new parameter value distributions
- Stop when likelihood changes less than a specified threshold

AIC

- Akaike Information Criterion
- AIC = -2*log likelihood + 2K
- Penalizes for the number of parameters in the model
- Useful for comparing any two models, selecting the one with the lowest AIC

BIC

- Bayesian or Schwartz Information Criterion
- Similar to AIC, but greater penalty on parameters

Covariates

- Subject/patient specific factors which are linked to PK/PD behavior
- E.g. volume of distribution linked to body weight or clearance linked to genotype

Covariates

- Typically included in a model if they improve the AIC or some other objective function

Assay Errors

The myth of quantification limits…

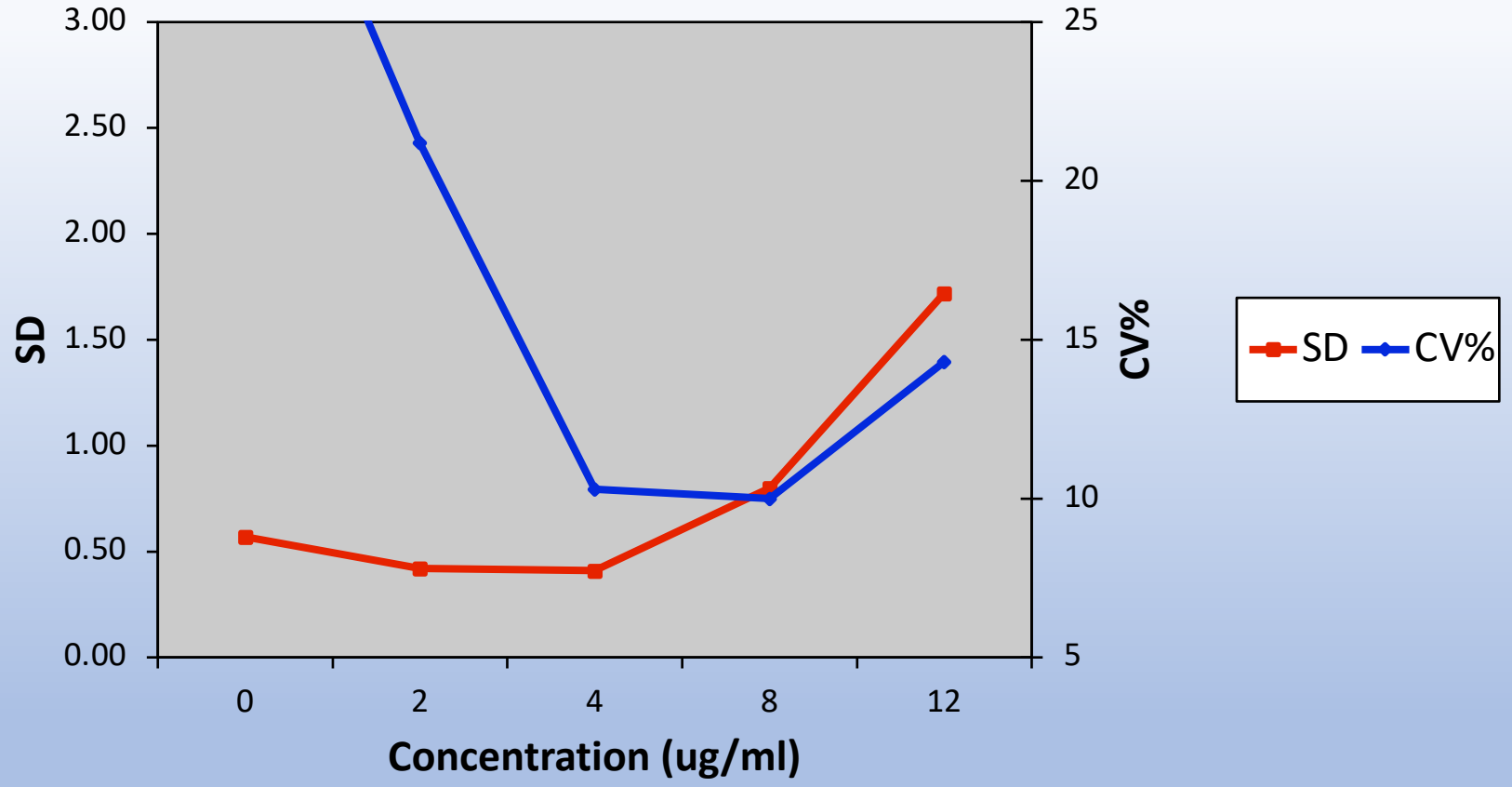
Assay Precision

- Estimate the SD of every measured observation
- Fisher Information = 1 / Variance = Weight
- Variance = SD^2
- Assay Error Polynomial (AEP): $SD = C_0[drug]^0 + C_1[drug]^1 + C_2[drug]^2 + C_3[drug]^3$

CV% vs Fisher

- Assume CV% = 10 when concentrations ≥10, and constant SD = 2 when concentrations <10.
  - If conc = 10, SD = 1, var = 1, weight = 1
  - If conc = 20, SD = 2, var = 4, weight = ¼
  - If conc = 0.1, SD = 2, var = 4, weight = ¼ but CV% = 2000%
- As concentration approaches zero, CV% approaches infinity

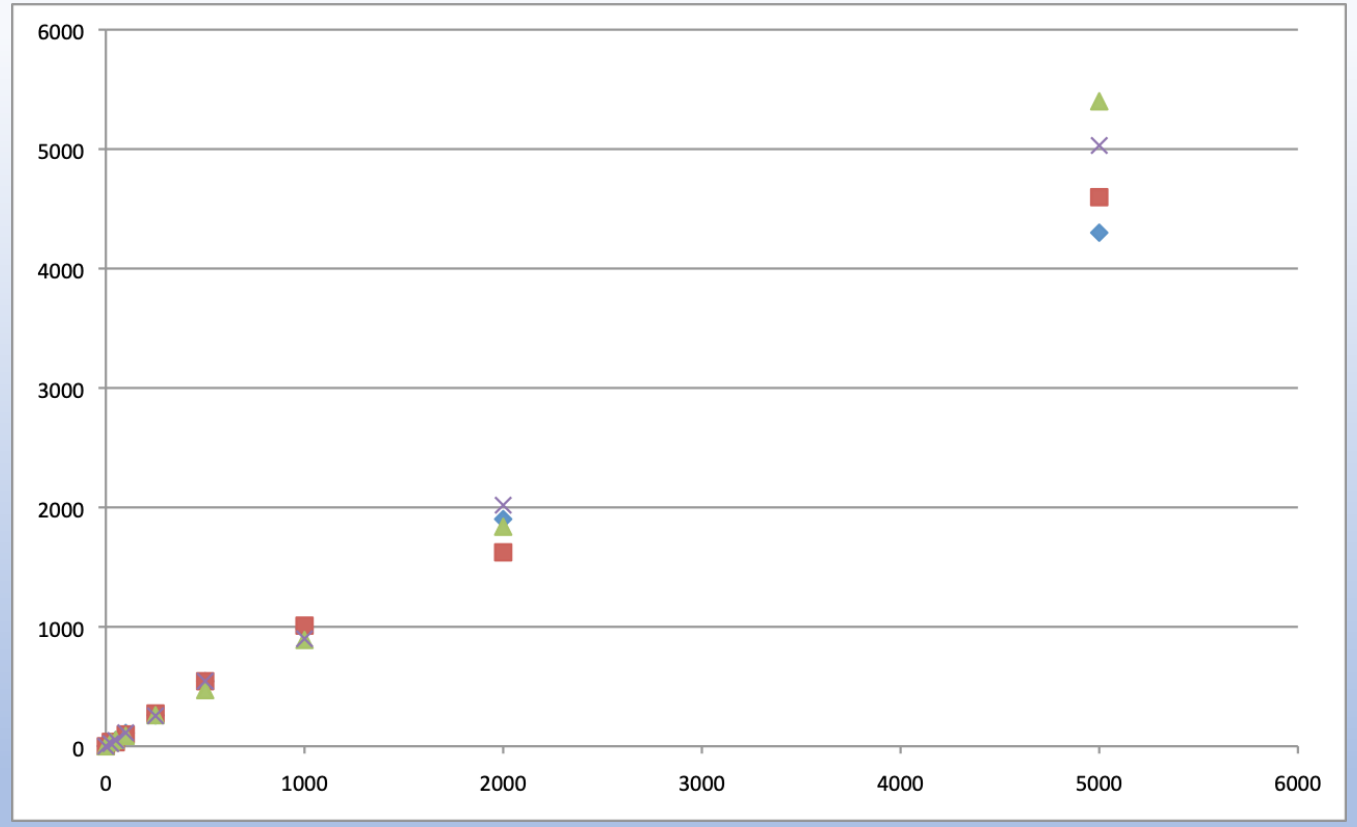
Assay error


3.00
2.50
2.00
1.50
1.00
0.50
0.00
SD
25
20
15
10
5
CV%
0
2
4
8
12
Concentration (ug/ml)
SD
CV%

CV% vs Fisher

- No LOQ with Fisher
- Assay SD, variance, and weight are always finite.

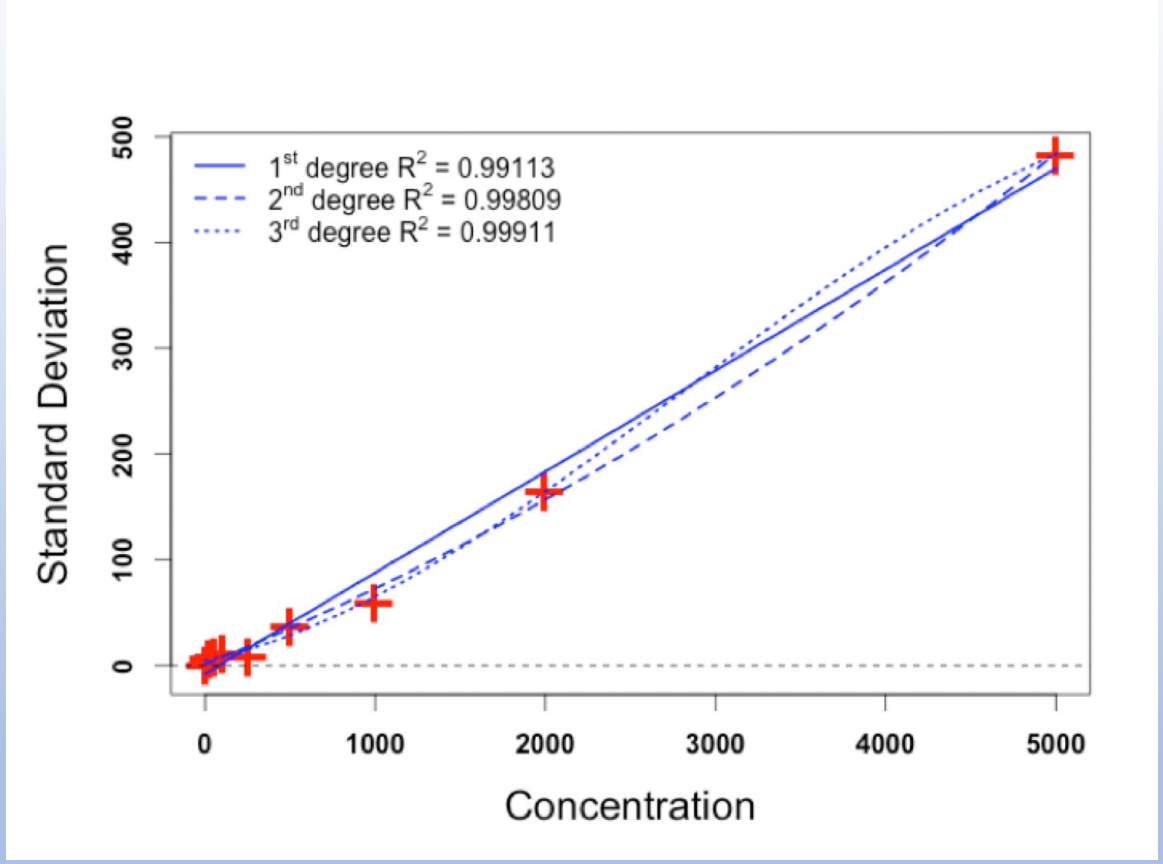
Fit assay error



Conc	SD	CV%	Wt
0	0.5	∞	4.000000
25	6.4	26%	0.024414
50	8.6	17%	0.013521
100	12	12%	0.006944
250	8.6	3%	0.013521
500	37.2	7%	0.000723
1000	60.1	6%	0.000277
2000	165.7	8%	0.000036
5000	483	10%	0.000004

Fit assay error

	C0	C1	C2	C3
First	-7.9	0.1		
Second	1.0	6.5E-02	6.2E-06	
Third	4.8	3.3E-02	3.1E-05	-3.6E-09



Additional error

- $SD = C_0[drug]^0 + C_1[drug]^1 + C_2[drug]^2 + C_3[drug]^3$
- Use additive (lambda) or multiplicative (gamma) model for weight:
  - $weight = 1/(\lambda + SD)^2$
  - $weight = 1/(\gamma \times SD)^2$

Modeling scheme