

Monte Carlo for variability simulation and uncertainty

Caroline L. Ring



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Overview

- Uncertainty vs. Variability in HTK model parameters
- Characterizing key uncertainty in chemical-specific TK parameters
 - Fraction unbound in plasma protein (F_{up})
 - Intrinsic hepatic clearance rate (Cl_{int})
- Characterizing variability: HTK-Pop for human TK variability
- Relative contributions of uncertainty and variability to TK model predictions
- Simulating sensitive subpopulations

Uncertainty vs. variability in HTTK model parameters

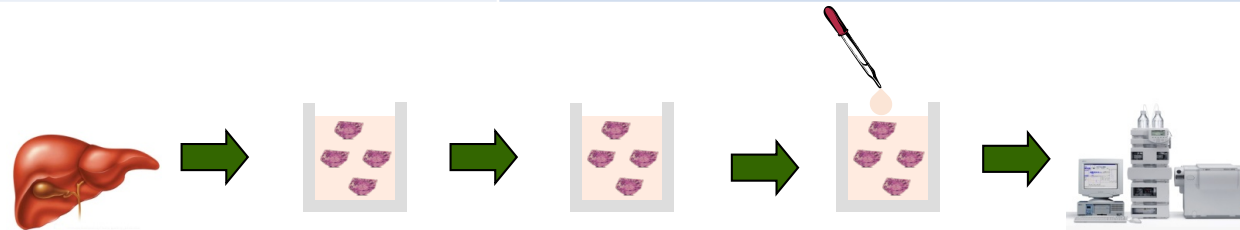
Review: HTK model parameters

Chemical-specific parameters	
Intrinsic hepatic clearance rate (CL _{int})	Measured in HT <i>in vitro</i> assays (Rotroff <i>et al.</i> 2010; Wetmore <i>et al.</i> 2012, 2014, 2015; Wambaugh <i>et al.</i> 2019) or predicted <i>in silico</i> (Sipes <i>et al.</i> 2017)
Fraction unbound to plasma protein (F _{up})	
Tissue:blood partition coefficients (for compartmental models)	Predict from phys-chem properties and tissue properties (Pearce <i>et al.</i> , 2017)
Physiological parameters	
Tissue masses (including body weight)	Gathered from data available in the published literature [Wambaugh <i>et al.</i> 2015; Pearce <i>et al.</i> 2017a]
Tissue blood flows	
Glomerular filtration rate (passive renal clearance)	
Hepatocellularity	

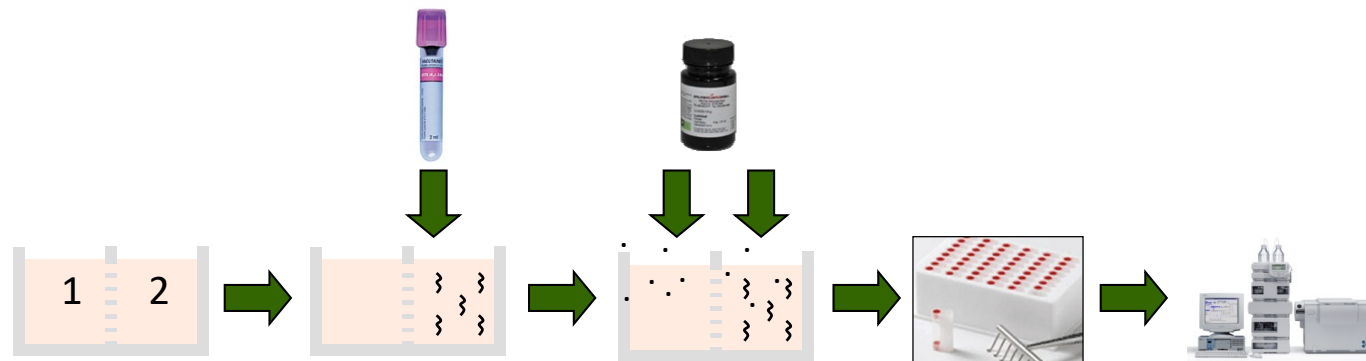
Chemical-specific parameters measured *in vitro* carry measurement uncertainty

Chemical-specific parameters	
Intrinsic hepatic clearance rate (CL _{int})	Measured in HT <i>in vitro</i> assays (Rotroff <i>et al.</i> 2010; Wetmore <i>et al.</i> 2012, 2014, 2015; Wambaugh <i>et al.</i> 2019)
Fraction unbound to plasma protein (F _{up})	

CL_{int}: Cryo-preserved
hepatocyte suspension
Shibata *et al.* (2002)



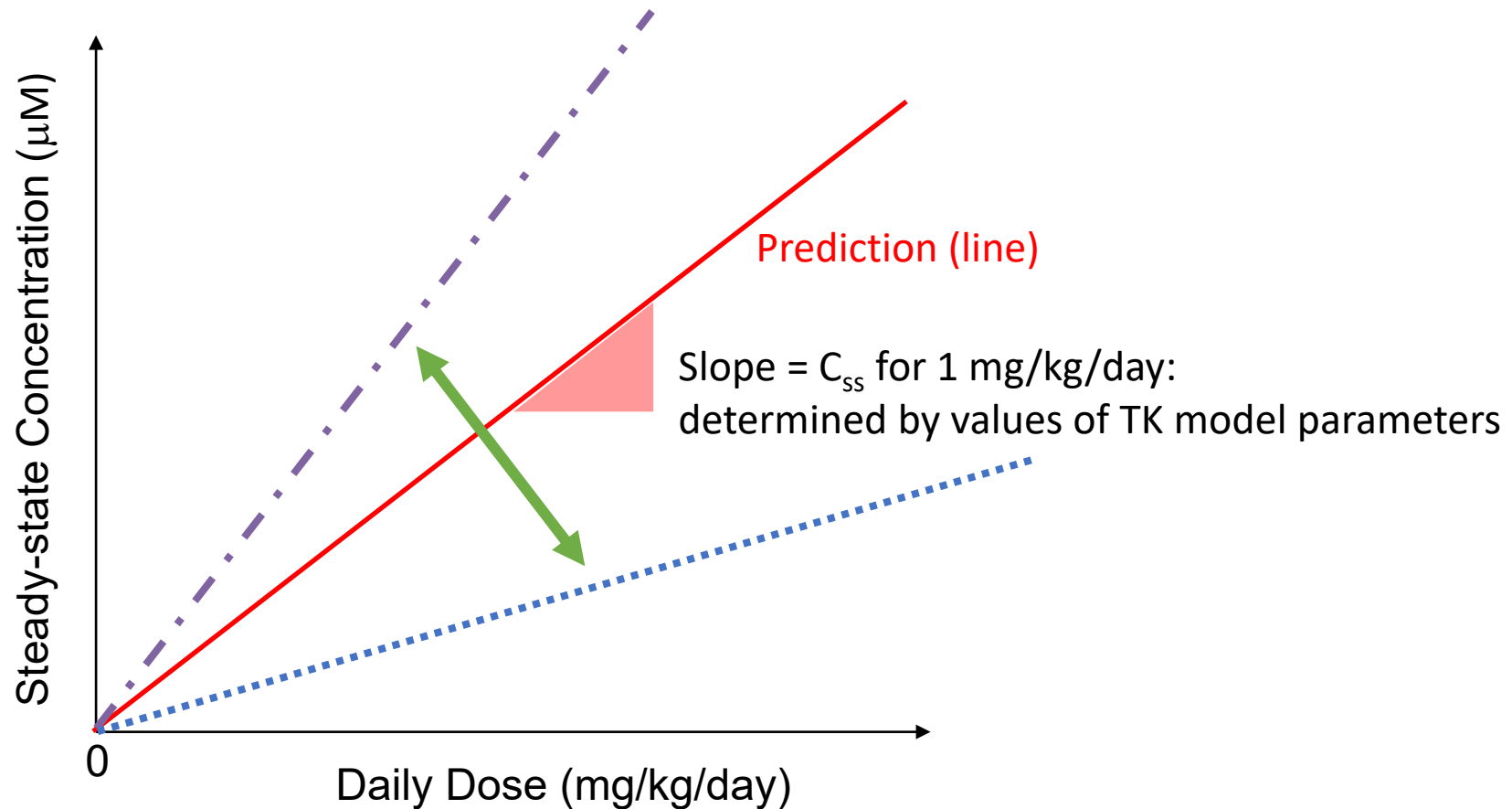
F_{up}: Rapid Equilibrium
Dialysis (RED)
Waters *et al.* (2008)



Parameters represent biology — so they have population variability

Chemical-specific parameters	
Intrinsic hepatic clearance rate (CL _{int})	Represent chemical-body interactions — vary with individual genetics, environmental factors, age, etc.
Fraction unbound to plasma protein (F _{up})	
Tissue:blood partition coefficients (for compartmental models)	
Physiological parameters	
Tissue masses (including body weight)	Represent physiology — vary with individual genetics, environmental factors, age, etc.
Tissue blood flows	
Glomerular filtration rate (passive renal clearance)	
Hepatocellularity	

HTTK model parameters determine the slope relating C_{ss} to daily dose –
need to propagate both uncertainty & variability



Approach to uncertainty & variability: Monte Carlo

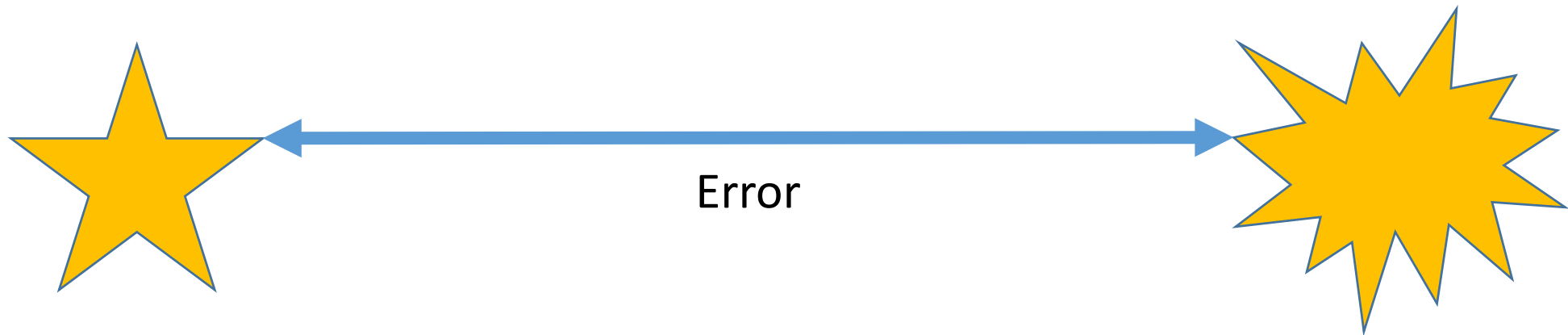
- Characterize uncertainty in chemical-specific parameters F_{up} and Cl_{int} in terms of probability distributions
- Characterize population variability in physiological parameters in terms of (correlated) probability distributions
- Draw samples from distributions: “simulated population”
- Evaluate HTTK model for each “simulated individual” in the “simulated population”
- Describe resulting distribution of HTTK model predictions

Characterizing key uncertainty in chemical-specific TK parameters

General approach to uncertainty quantification

Unknown true value

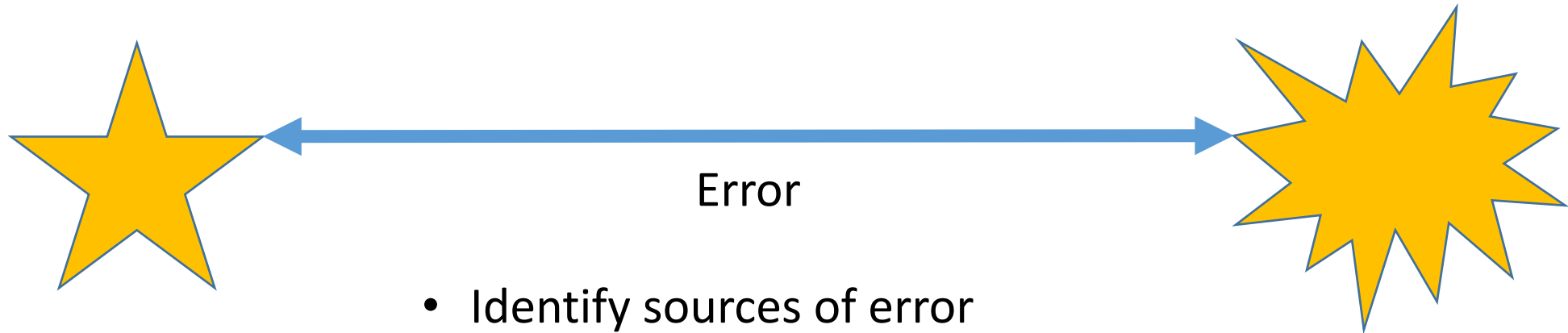
Observed (measured) value



General approach to uncertainty quantification

Unknown true value

Observed (measured) value

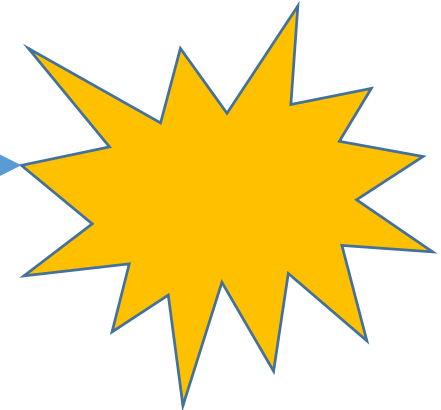


- Identify sources of error
- Develop mathematical model of error

General approach to uncertainty quantification

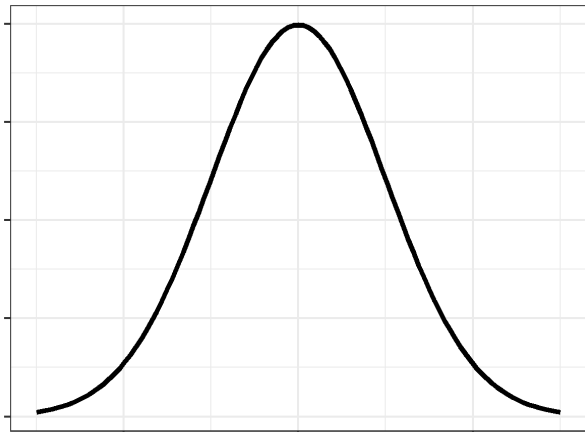
Unknown true value

Observed (measured) value



Error

- Identify sources of error
- Develop mathematical model of error

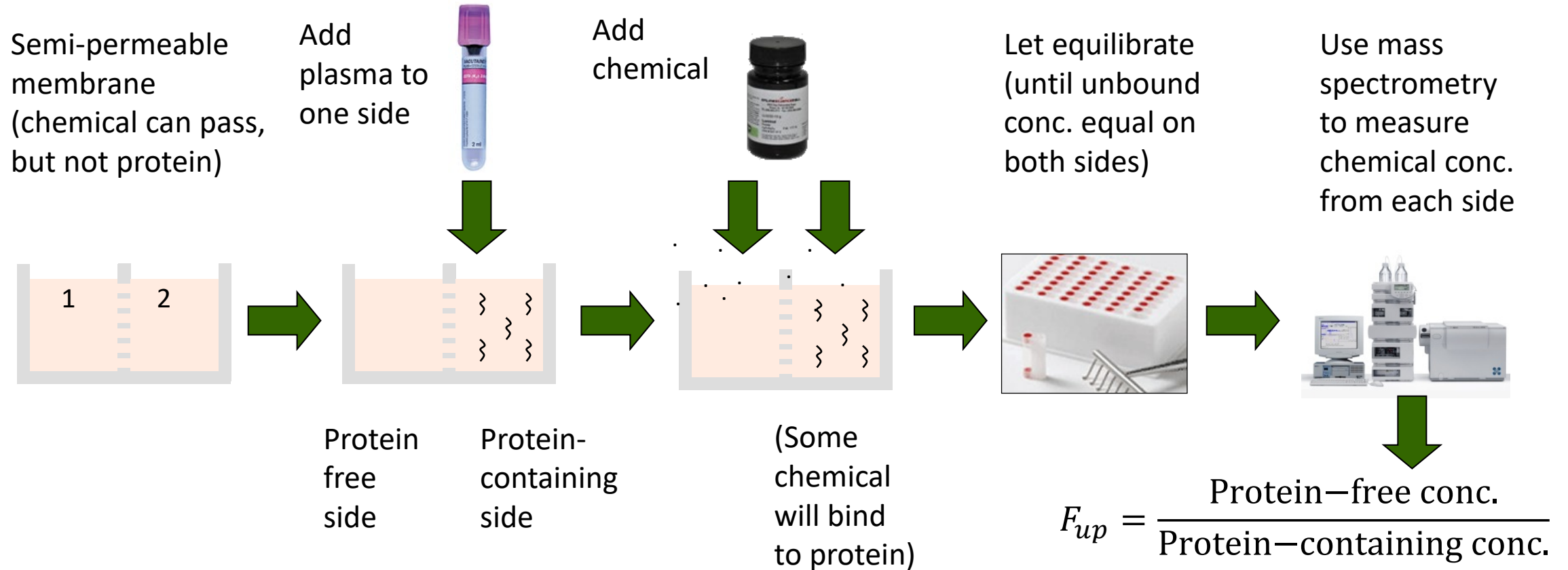


Bayesian inference:

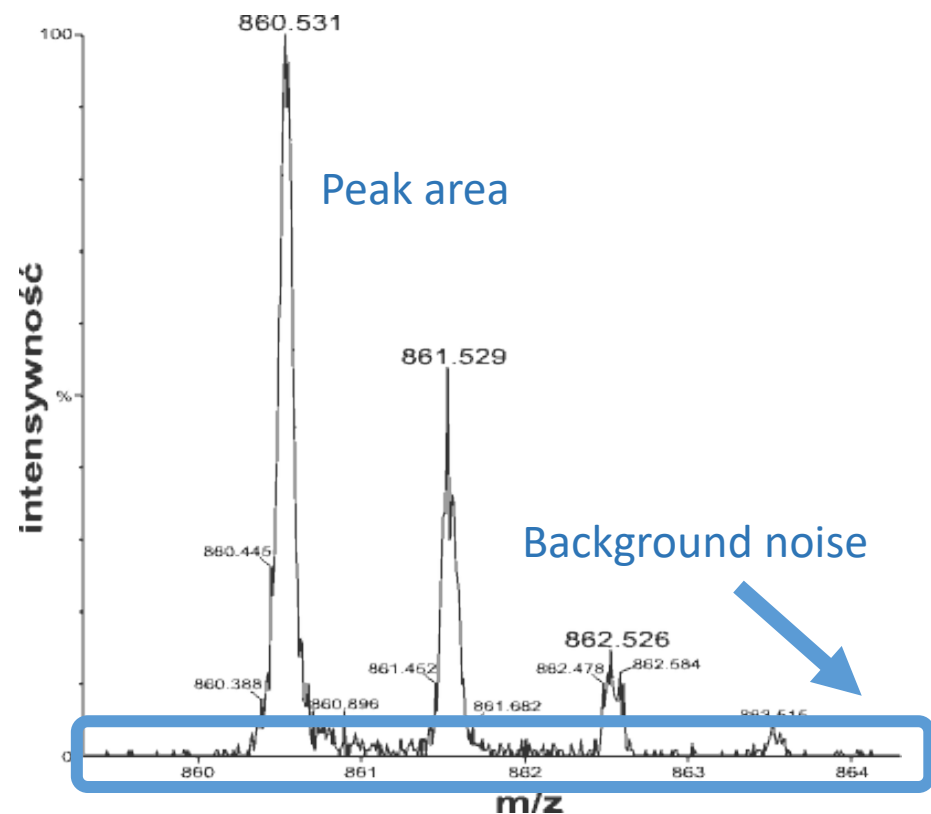
Find a *distribution* of possible true values compatible with the observed values, under this error model

Uncertainty in Fup

Fup: How to measure *in vitro* using Rapid Equilibrium Dialysis (RED)



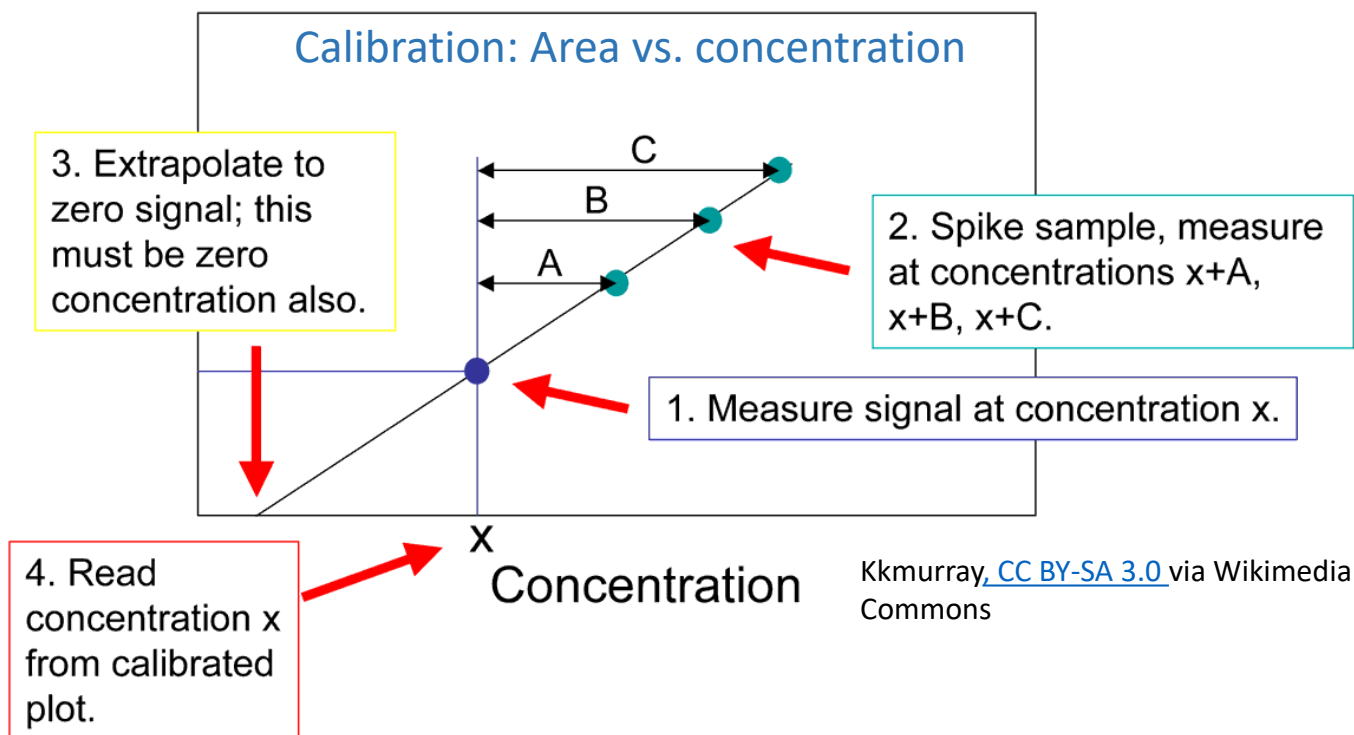
Sources of measurement uncertainty: Mass spectrometry



<https://commons.wikimedia.org/wiki/File:ObwiedniaPeptydu.gif>
(GPL)

Wambaugh et al. (2019)

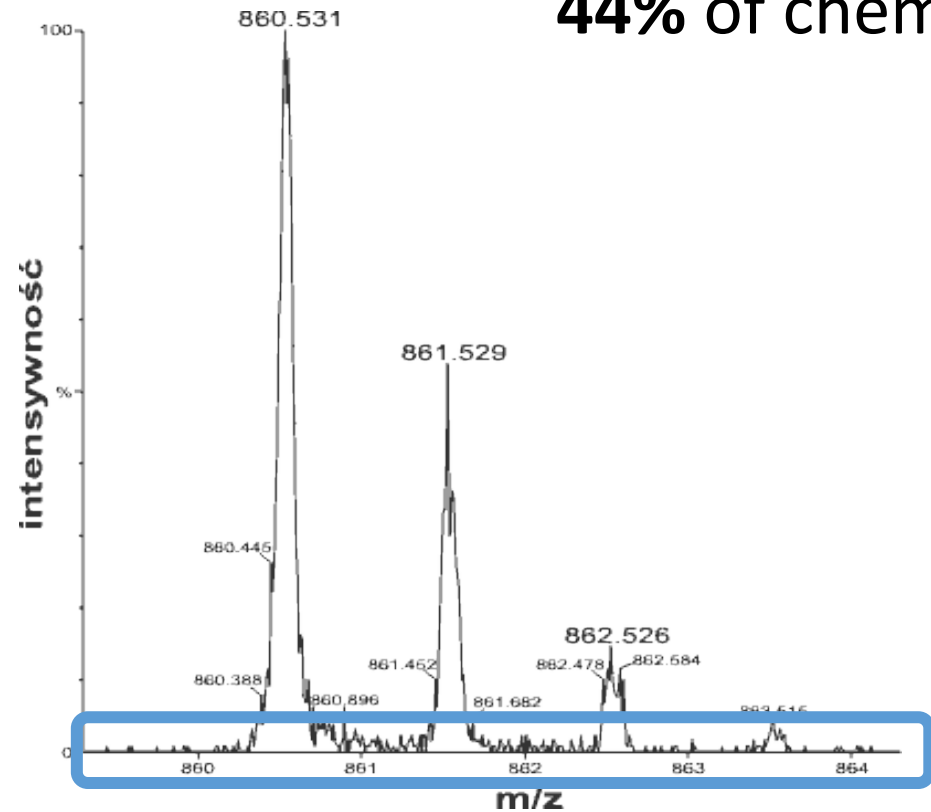
- Instrument noise
- Limit of quantification (LOQ)
- Instrument calibration



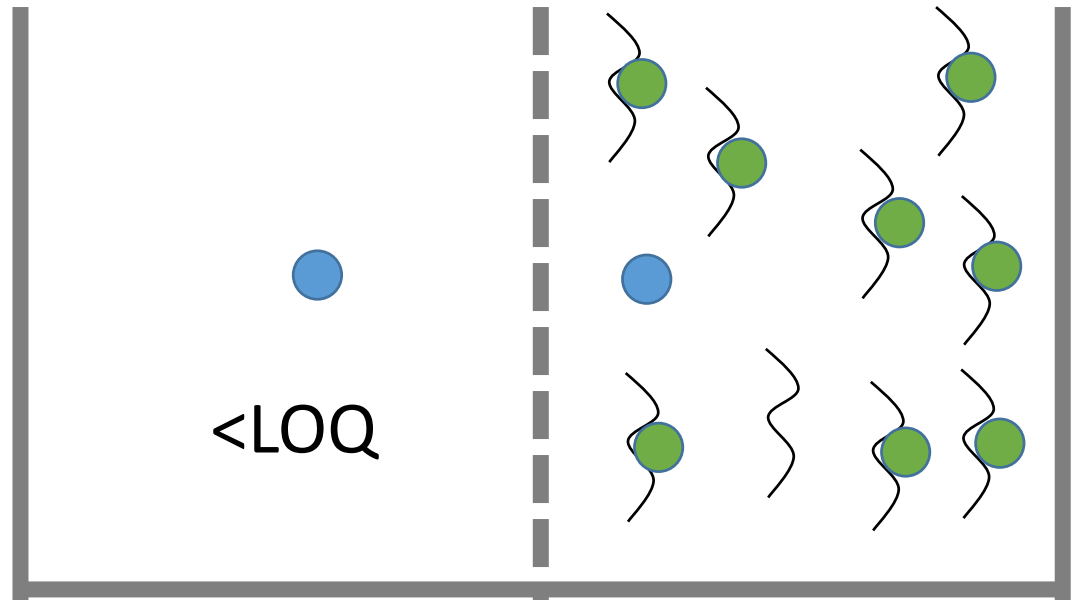
Kkmurray, [CC BY-SA 3.0](https://commons.wikimedia.org/wiki/File:ObwiedniaPeptydu.gif) via Wikimedia Commons

LOQ is a problem in the RED assay for highly-bound chemicals

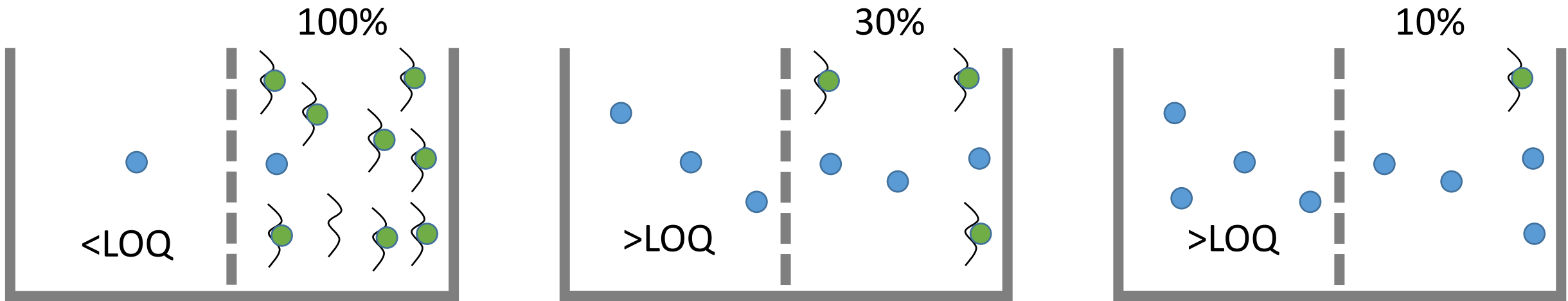
44% of chemicals in Wambaugh et al. (2019)



<https://commons.wikimedia.org/wiki/File:ObwiedniaPeptydu.gif>
(GPL)

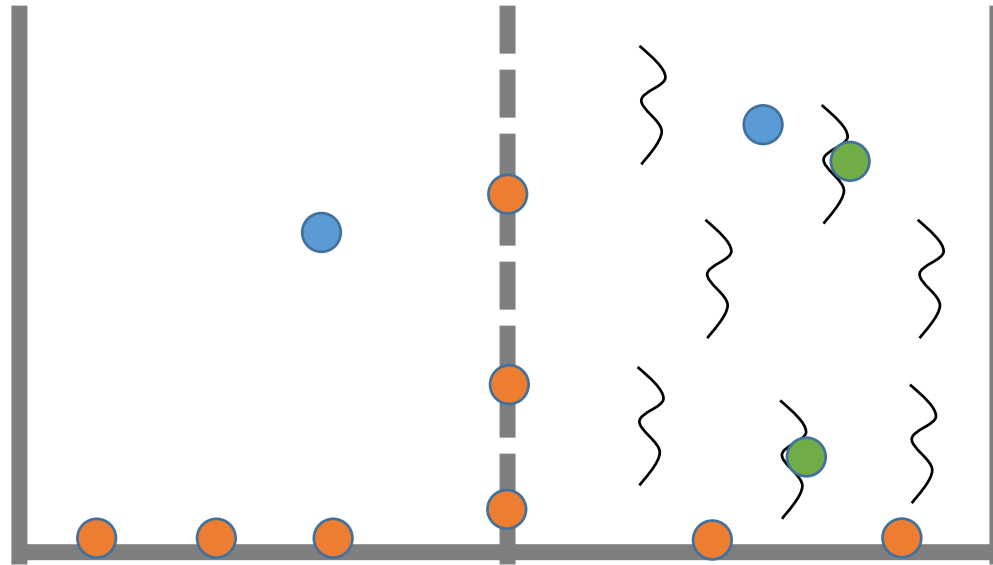


Approach to <LOQ problem:
Repeat RED assay with varying amounts of protein



Estimate dissociation constant K_d
(strength of binding affinity between chemical and protein)

Additional source of uncertainty: Non-specific chemical binding to membrane or walls

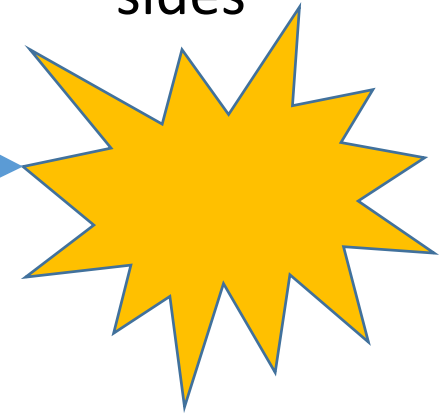


Bayesian inference model for Fup uncertainty

Unknown true value:
Fup for a chemical

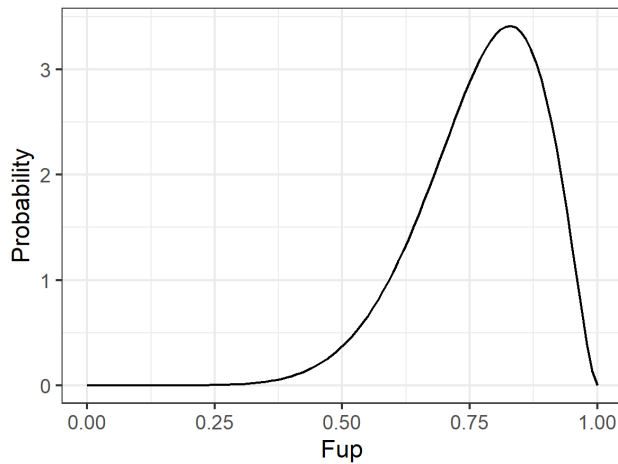


Observed (measured) value:
MS peak areas for protein-
free and protein-containing
sides



Error

- MS noise
- MS calibration
- LOQ
- Non-specific binding

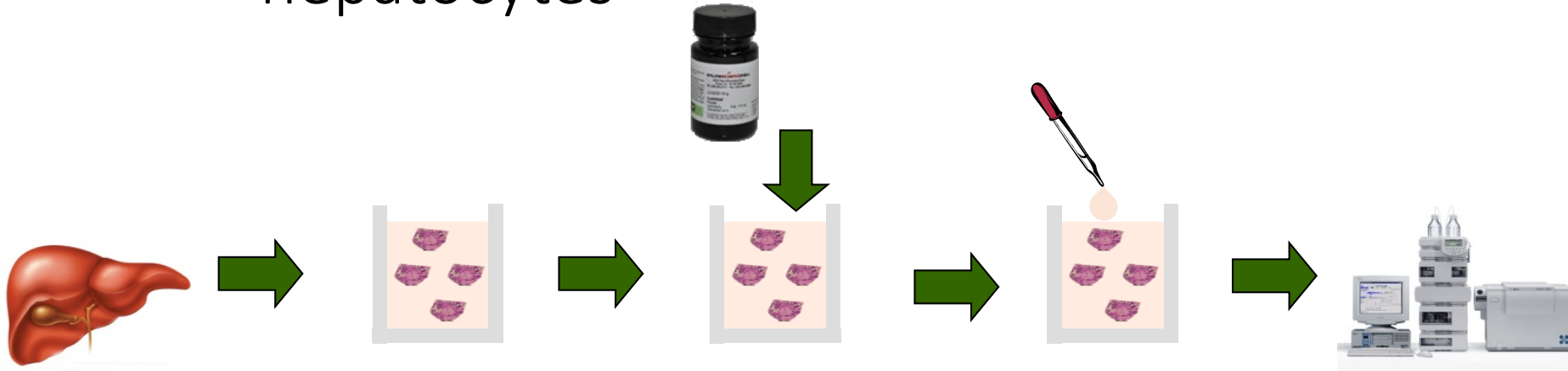


Wambaugh et al. (2019)

Result: *Distribution* of Fup values for a
chemical

Uncertainty in CLint

CLint: How to measure *in vitro* using pooled human hepatocytes

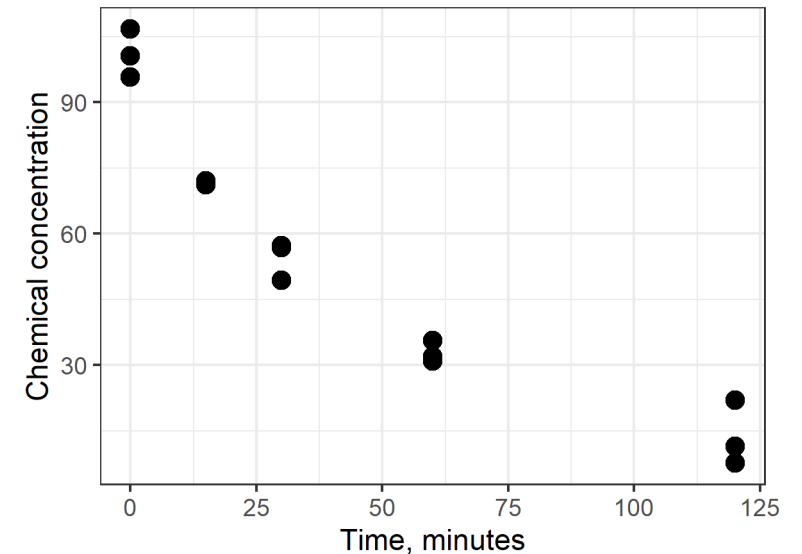


Culture donated human hepatocytes from 10 adult volunteers

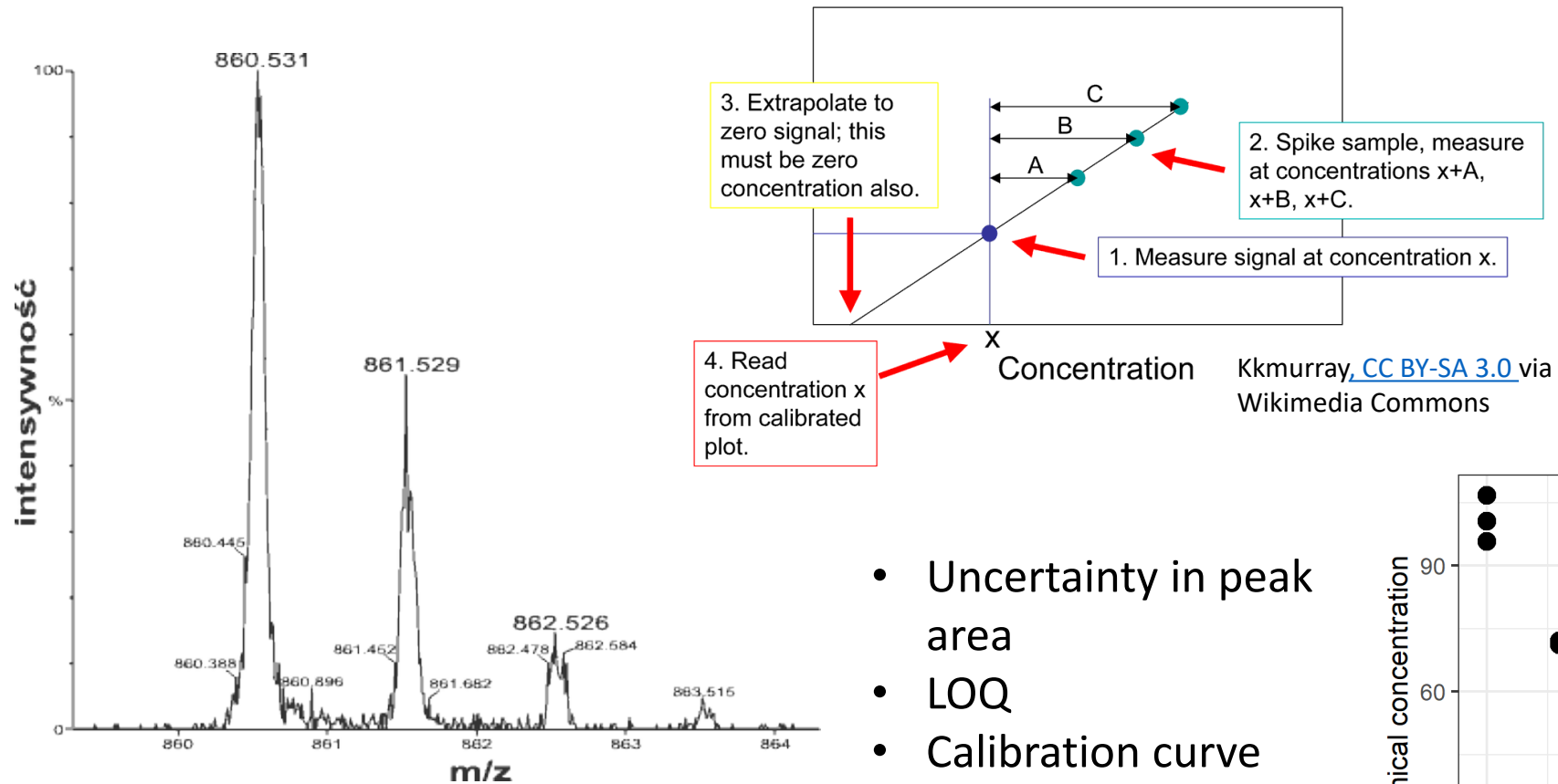
Add known amount of chemical

Measure chemical concentration remaining at 0, 15, 30, 60, and 120 minutes

CLint can be estimated from fitting a decaying exponential



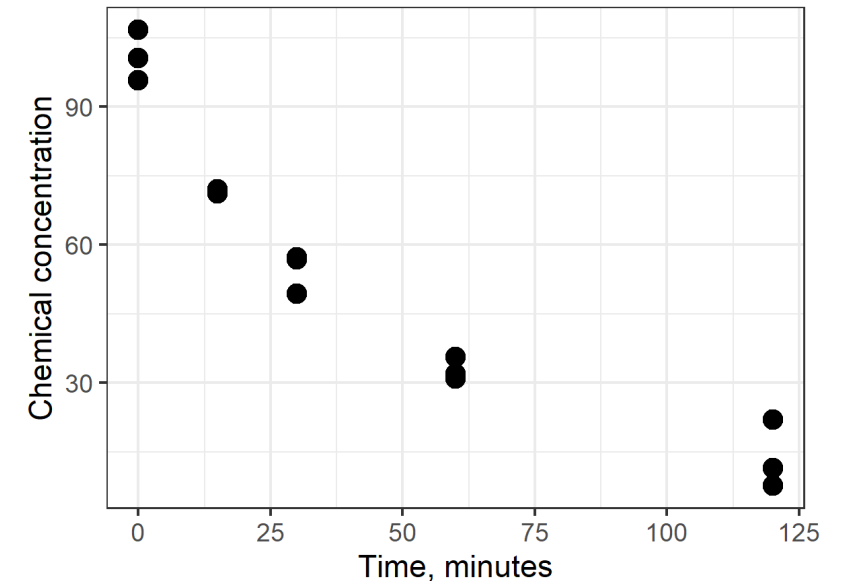
Mass spec uncertainties also apply to CLint



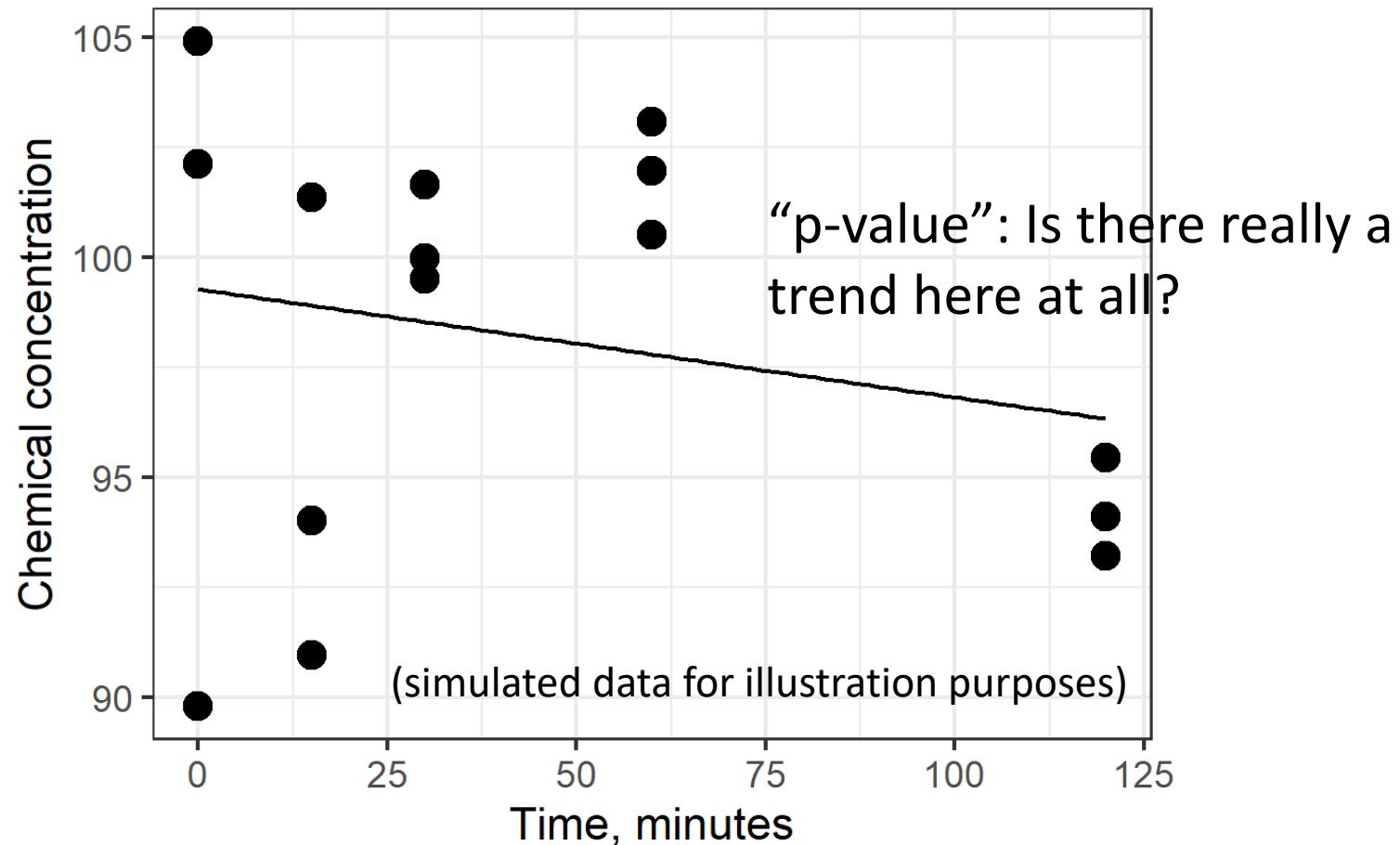
Kkmurray, [CC BY-SA 3.0](https://commons.wikimedia.org/wiki/File:ObwiedniaPeptydu.gif) via
Wikimedia Commons

- Uncertainty in peak area
- LOQ
- Calibration curve

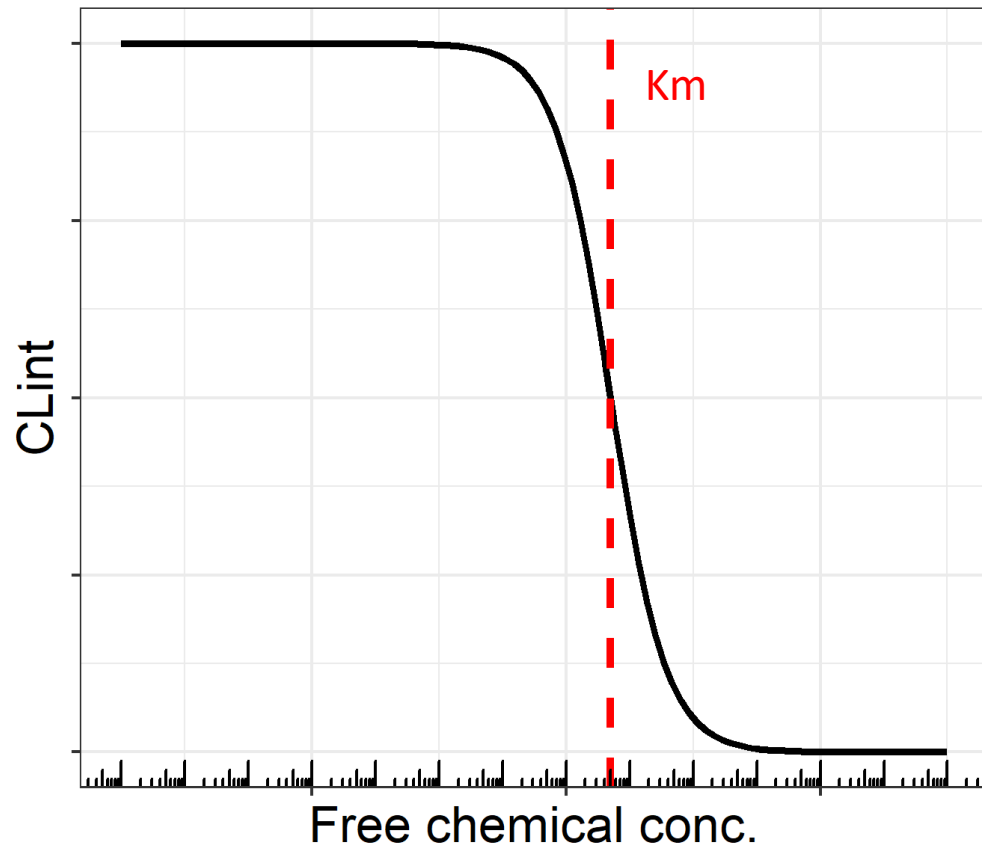
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(GPL)



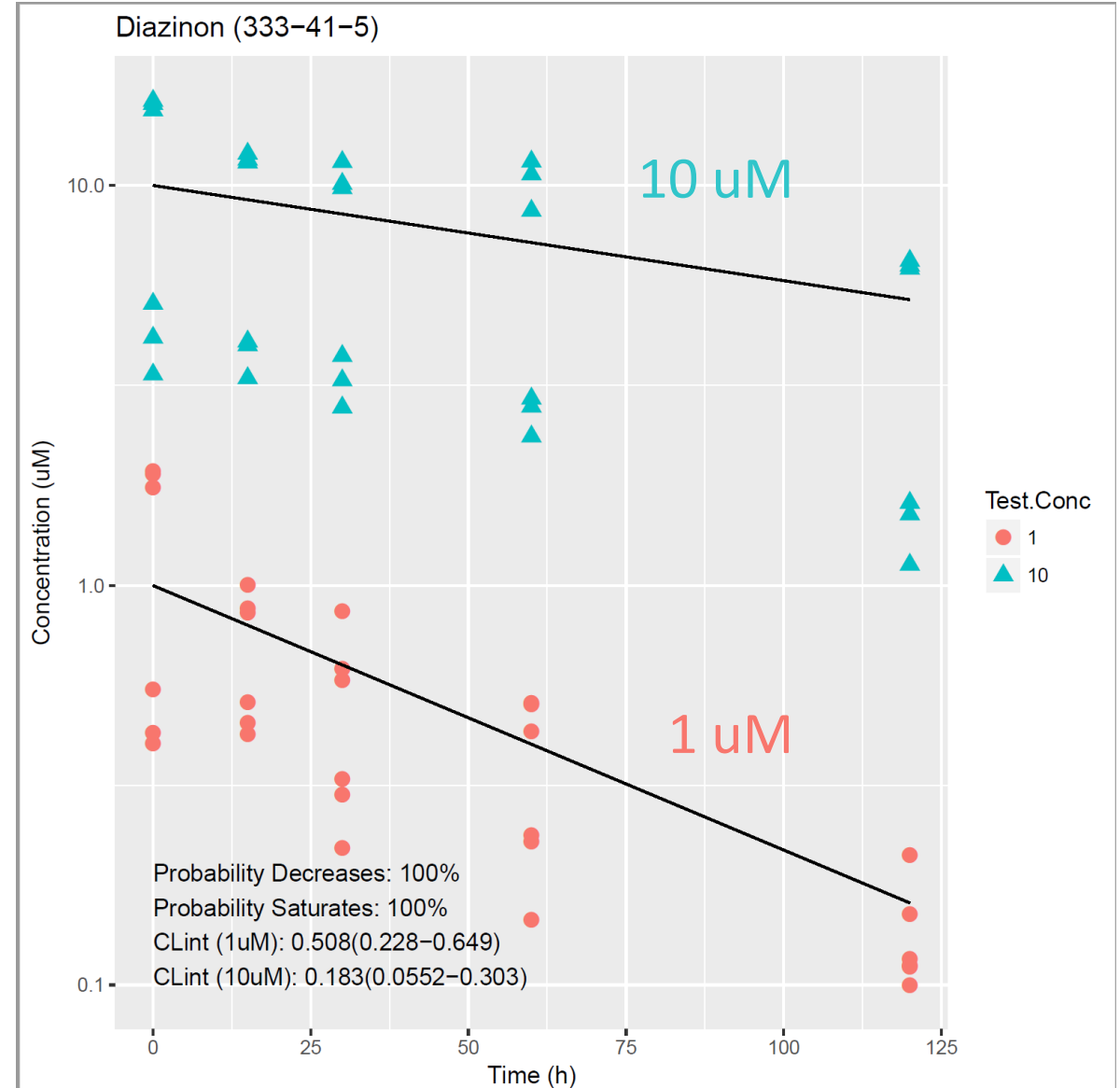
Additional uncertainty source: Is chemical really metabolized at all?



Additional uncertainty source: Saturable metabolism



Wambaugh et al. (2019)



Bayesian inference model for Clint uncertainty

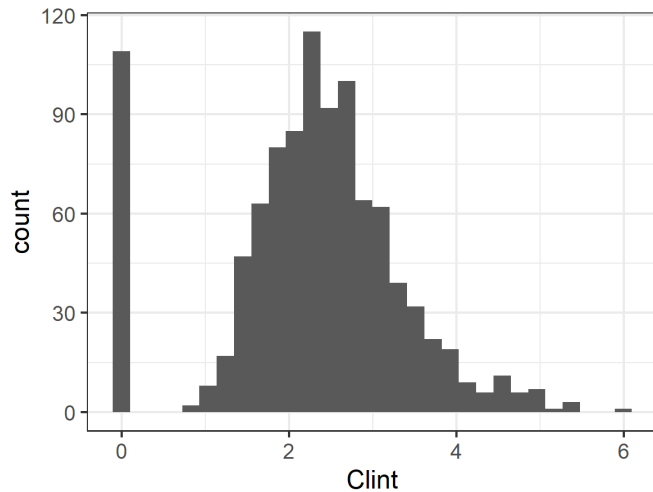
Unknown true value:
Clint for a chemical

Observed (measured) value:
MS peak areas at 5 time
points

Error

- MS noise
- MS calibration
- LOQ
- Probability of no metabolism
- Probability of saturation

Result: *Distribution* of Clint values for a chemical



Wambaugh et al. (2019)

Characterizing variability: HTTK- Pop for human TK variability

HTTK physiological parameters

Physiological parameters
Tissue masses (including body weight)
Tissue blood flows
Glomerular filtration rate (passive renal clearance)
Hepatocellularity

Data source for population physiology: CDC NHANES



CDC NHANES = Centers for Disease Control National Health and Nutrition Examination Survey

Large, representative, ongoing survey of US population: demographics, body measures, medical examination data....

NHANES does measure:

Sex
Age
Height
Weight
Serum creatinine



NHANES does not measure:

Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

Correlated Monte Carlo approach to simulating population variability in physiology: HTTK-Pop

Sample NHANES measured quantities for actual NHANES individuals (capturing covariance):

Sex
Age
Height
Weight
Serum creatinine



Regression equations from literature (McNally *et al.*, 2014) (+ residual marginal variability)

(Similar approach used in SimCYP [Jamei *et al.* 2009], GastroPlus, PopGen [McNally *et al.* 2014], P3M [Price *et al.* 2003], physB [Bosgra *et al.* 2012], etc.)

Predict physiological TK quantities (as used by generic TK model) for each individual:

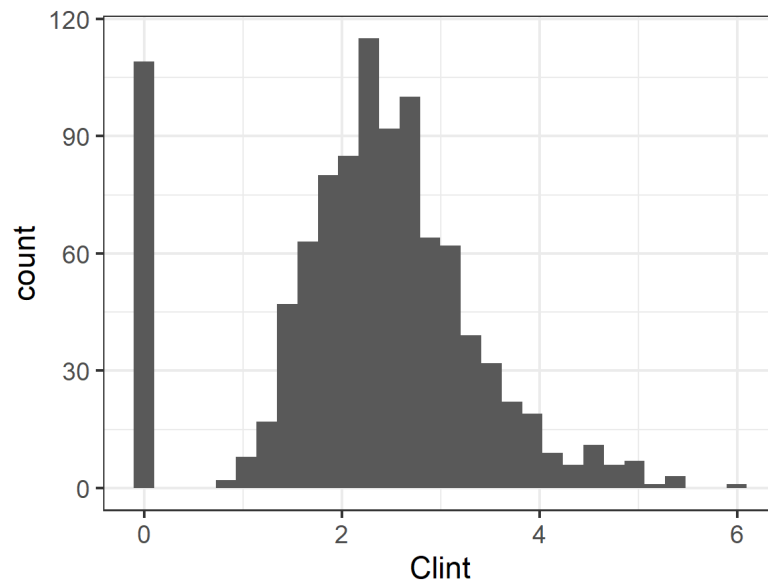
Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

Chemical-specific parameters have both uncertainty and variability

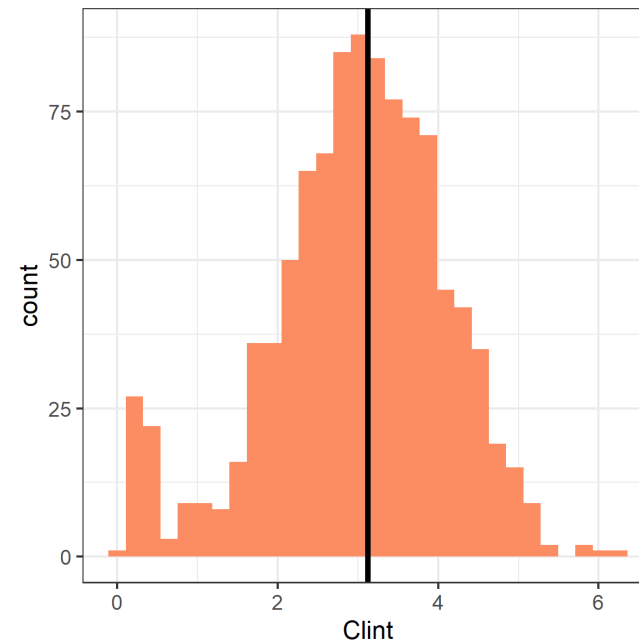
Chemical-specific parameters	
Intrinsic hepatic clearance rate (CL _{int})	Carry uncertainty from <i>in vitro</i> measurements Also have population variability: represent chemical-body interactions — vary with individual genetics, environmental factors, age, etc.
Fraction unbound to plasma protein (F _{up})	

Chemical-specific TK parameters: Two-stage Monte Carlo approach to modeling both *measurement uncertainty* and *population variability*

Step 1: Draw 1 sample from uncertainty distribution and treat as “population average” value

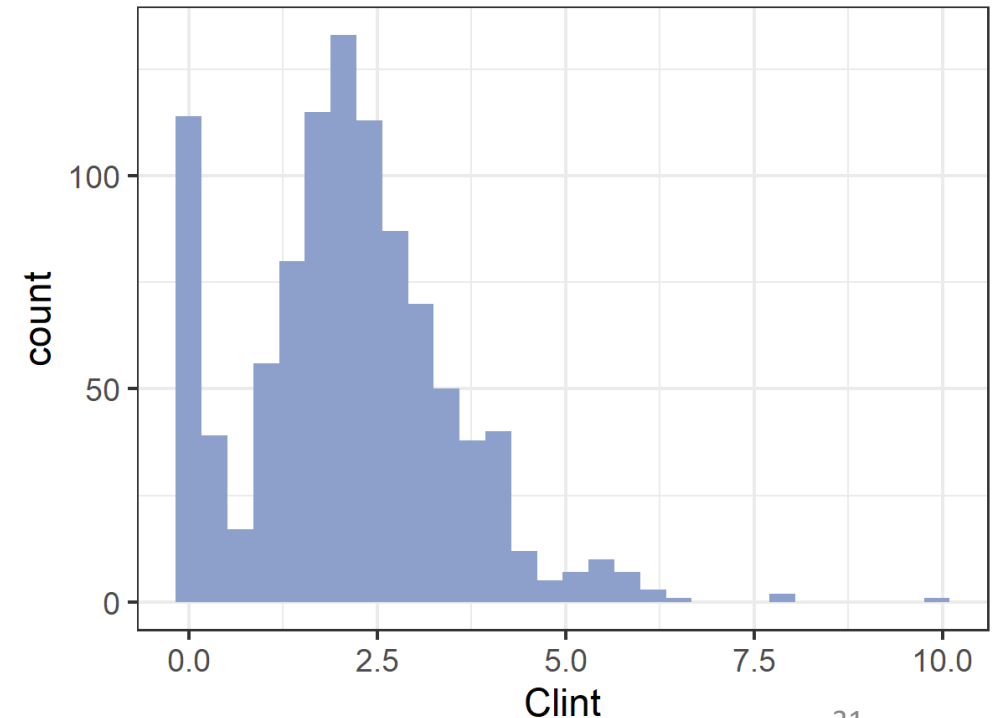


Step 2: Assume population variability (30% CV) around the sampled “population average” value from Step 1, and draw 1 sample



For CLint: Add 5% “poor metabolizers” (10% of original pop. average)

Repeat Steps 1 and 2 for each simulated individual to get sampled values that include both uncertainty & variability



11/11/2019

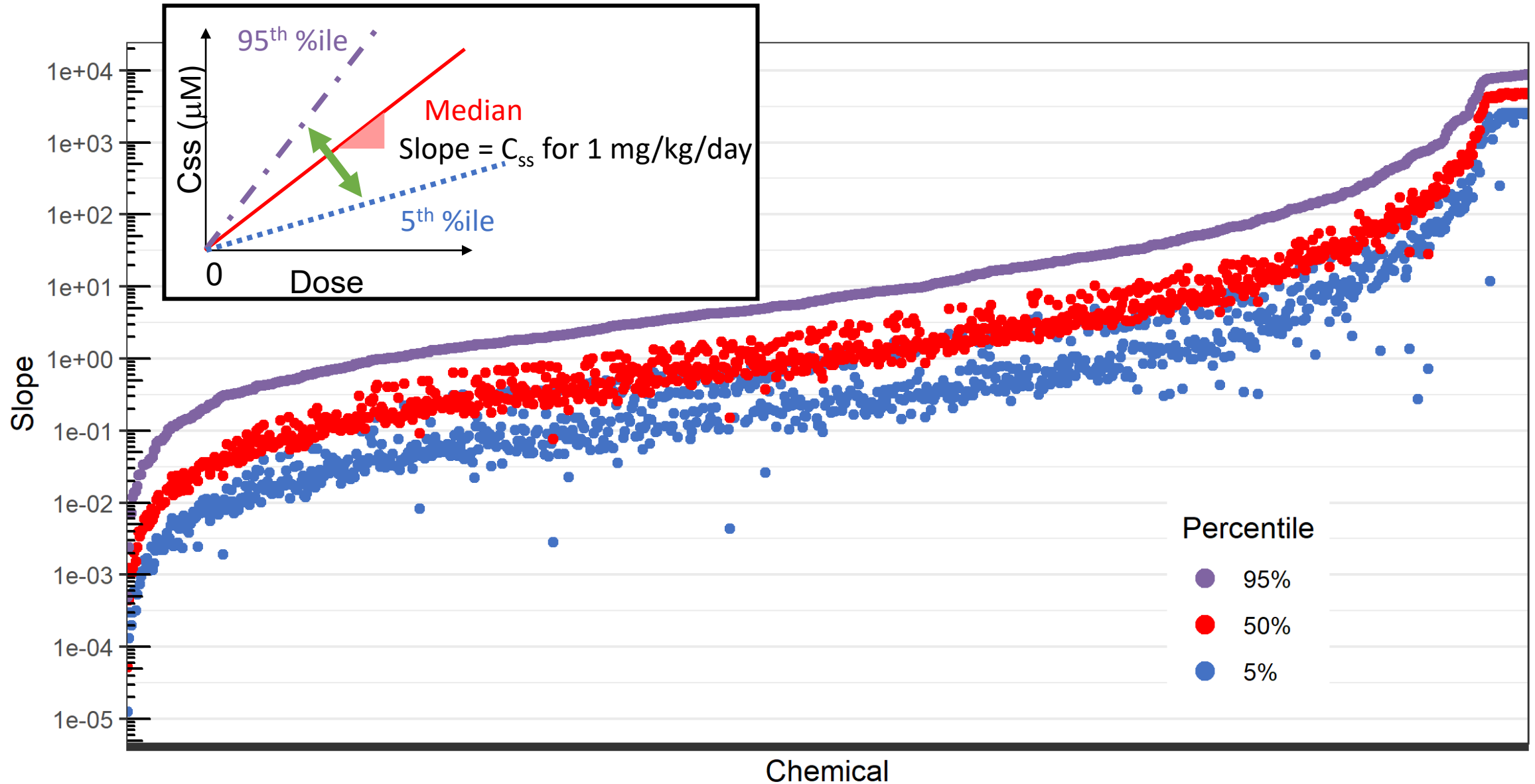
httk R package automates this Monte Carlo sampling & model evaluation process

```
> library(httk)
> set.seed(42)
> #Css for 1 mg/kg/day = slope
  calc_mc_css(chem.name="benzo(a)pyrene",
              which.quantile = c(0.95, 0.5, 0.05))
```

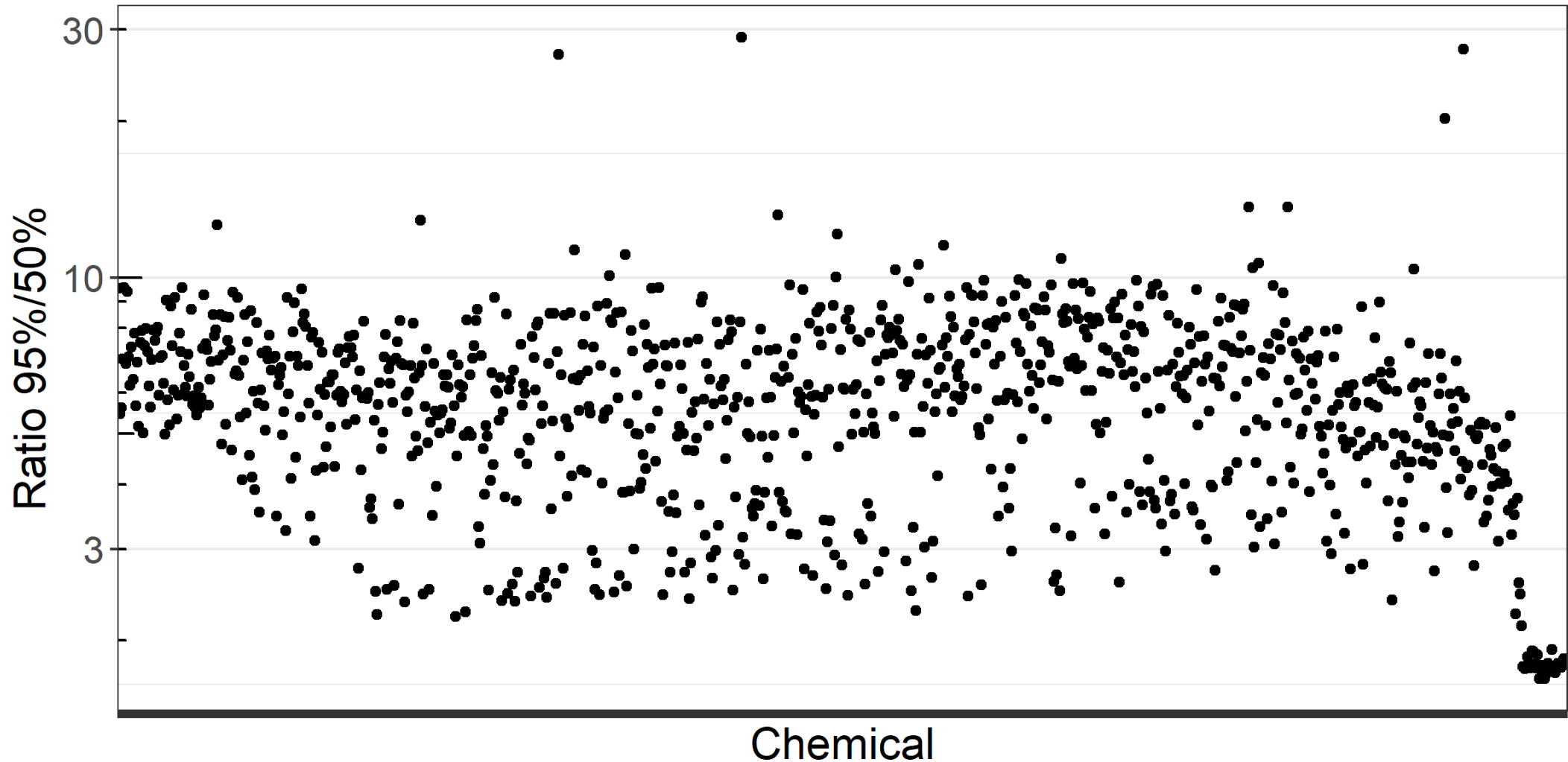
Human plasma concentration returned in mg/L units
for 0.95 0.5 0.05 quantile.

95%	50%	5%
68.510	13.070	3.742

Result: Percentiles of predicted C_{ss} vs. dose slope



Another way to visualize: ratio of 95th percentile to median
(roughly, how wide is the Css slope distribution?)



Relative contributions of variability & uncertainty

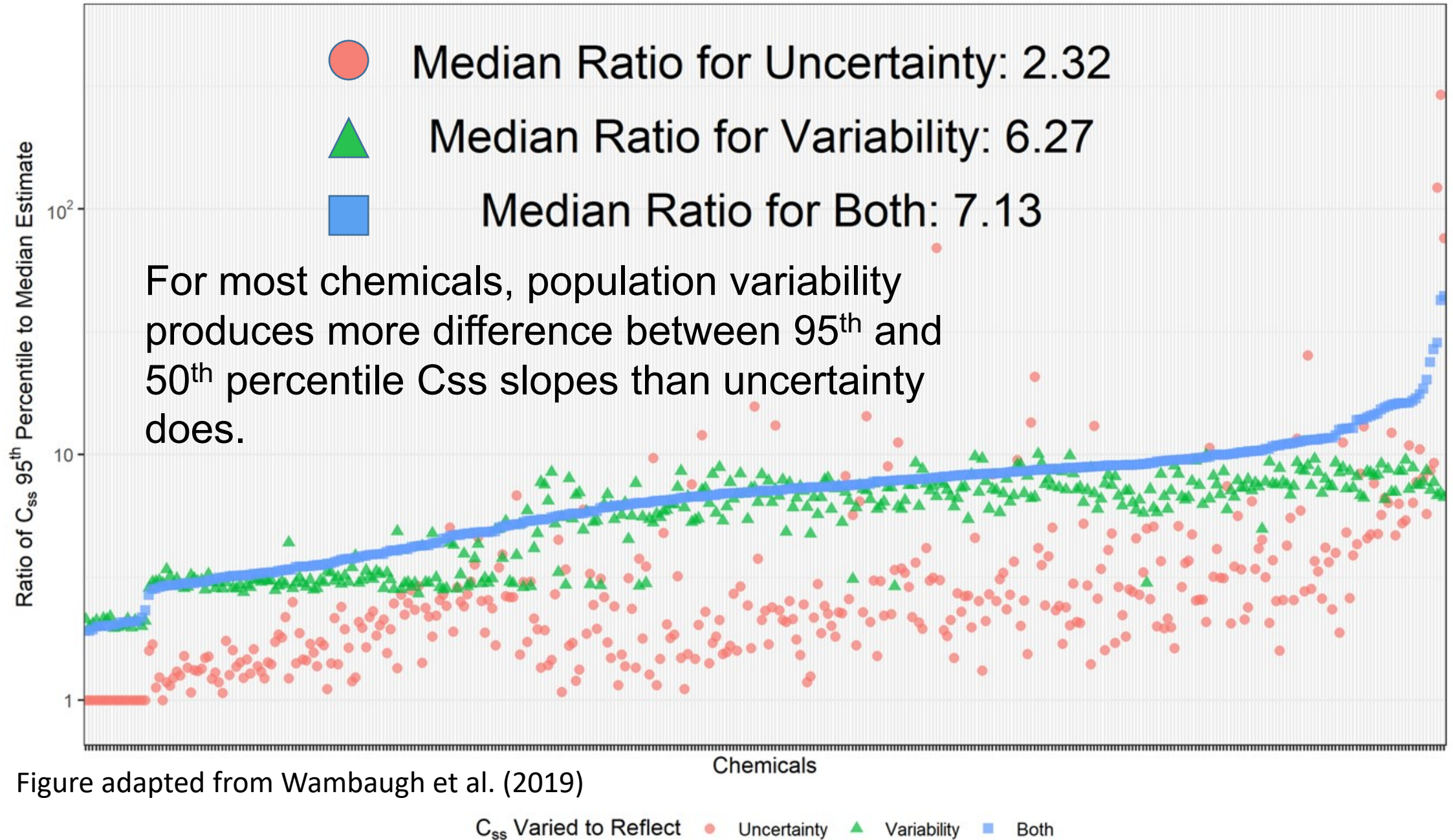
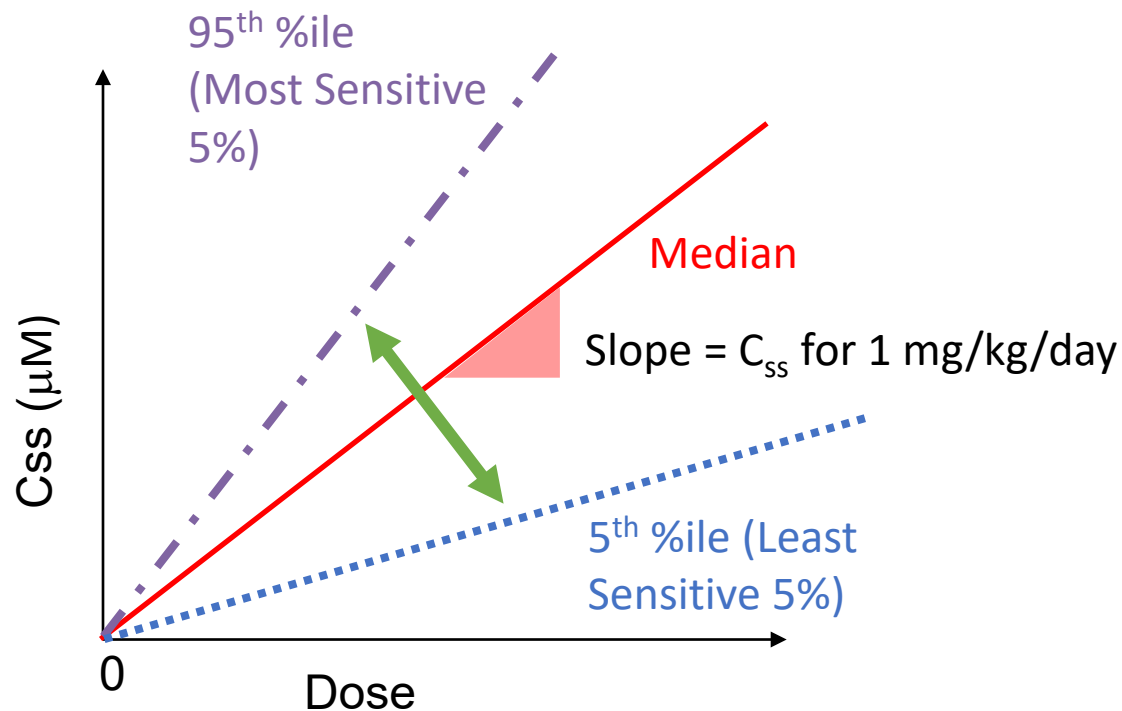


Figure adapted from Wambaugh et al. (2019)

Simulating sensitive subpopulations

Identifying potentially sensitive sub-populations



Who is in the most sensitive portion of the population?

What does this slope distribution look like for kids, for example?

Or people over 65?

To answer this question: Need to model TK variability for specified sub-populations

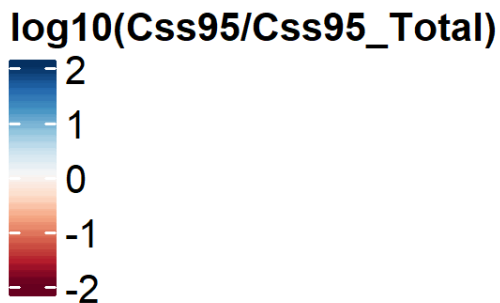
HTTK-Pop can generate simulated subpopulations with user-specified demographics

Use `httkpop.generate.args` argument to `calc_mc_css()` function: Takes a named list of arguments

Name of list element	User can specify...	Example		Default if not specified
<code>agelim_years</code>	Age limits in years	<code>c(6, 11)</code>	Ages 6-11 years	All NHANES (0-79 years)
<code>agelim_months</code>	Age limits in months	<code>c(0, 36)</code>	Ages 0-36 months	All NHANES (0-79 years)
<code>gendernum</code>	# of males and females	<code>list(Male = 1000, Female = 0)</code>	1000 males, 0 females	Randomly selected from NHANES
<code>weight_category</code>	BMI category	<code>c('Overweight', 'Obese')</code>	BMI > 25 (overweight & obese)	<code>c('Underweight', 'Normal', 'Overweight', 'Obese')</code>

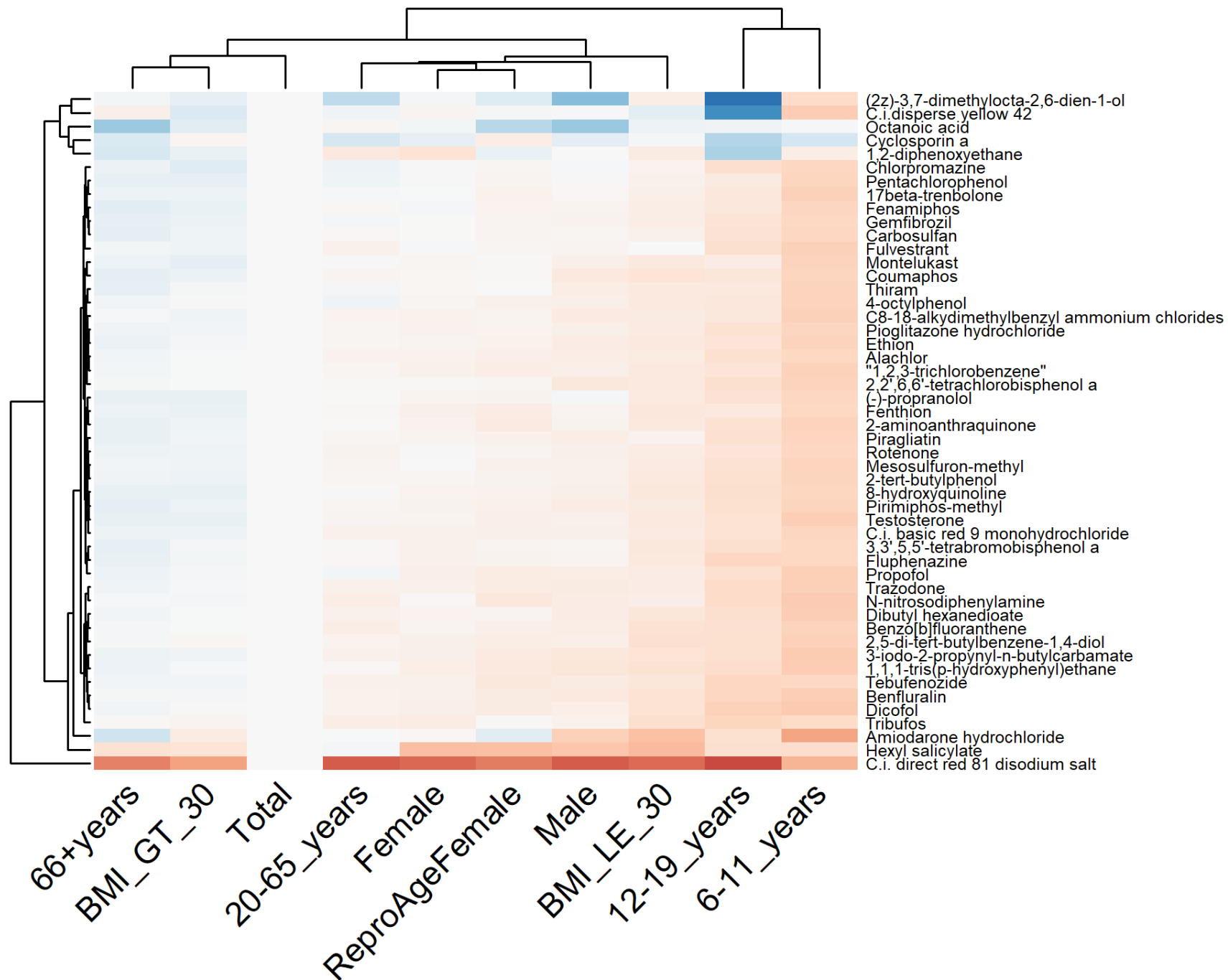
HTTK-Pop generates physiology based on NHANES respondents in the specified demographic groups

Example of C_{ss}95 differences by subpopulation



10 subgroups of interest

Heatmap: C_{ss}95 difference (subgroup vs. Total population) for 50 chemicals with largest C_{ss}95 difference in *any* subgroup



Conclusions

Conclusions

- Uncertainty vs. Variability in TK model parameters
 - Measurement uncertainty: Chemical-specific parameters measured *in vitro*
 - Population variability: Physiological & chemical-specific parameters
- Characterizing key uncertainty in chemical-specific TK parameters
 - Fraction unbound in plasma protein (Fup)
 - Intrinsic hepatic clearance rate (Clint)
- Characterizing variability: HTK-Pop for human TK variability
 - Correlated Monte Carlo approach based on CDC NHANES data
- Relative contributions of uncertainty and variability to TK model predictions
 - For most chemicals, population variability has larger effect
- Simulating sensitive subpopulations
 - HTK-Pop can simulate populations with user-specified demographics

Thank you!

Questions?



References

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