

# Lessons Learned from Model Development that Seemed to Go Wrong

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# References and Acknowledgments

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- 1. Huang and Isoherranen, Development of a Dynamic Physiologically Based Mechanistic Kidney Model to Predict Renal Clearance. CPT:PSP 2018,7:593-602**
- 2. Huang and Isoherranen, Sampling Site Has a Critical Impact on PBPK Modeling. JPET 2019, doi: 10.1124**
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# The concept of fit-for-purpose modeling

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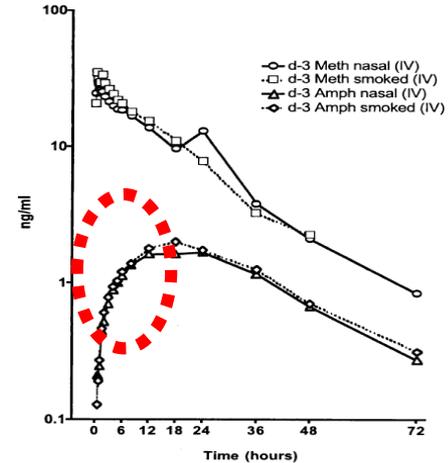
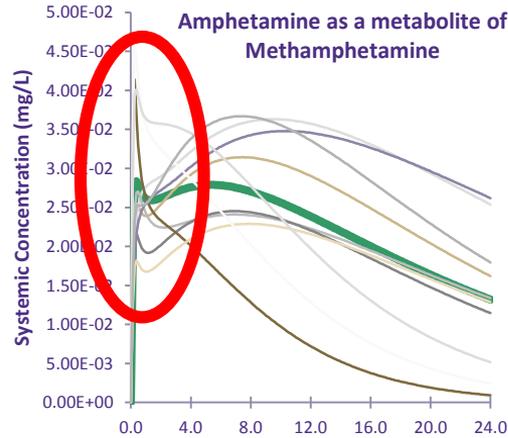
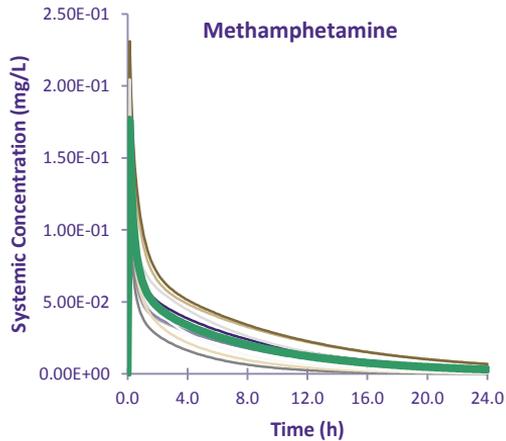
**To be useful, PBPK modeling should provide data that help with decision making at the appropriate stage of drug development**

**OR**

**Drive hypothesis generation of mechanisms or processes that can be tested in experiments- A model should help with understanding of the system**

**“Is the model used simply the “best available” at the present time, or is it truly adequate for the specific purpose of interest? How would adequacy for purpose be assessed, and what would it look like”? (Thompson and Smith, 2019)**

# Simulations that seem to go horribly wrong

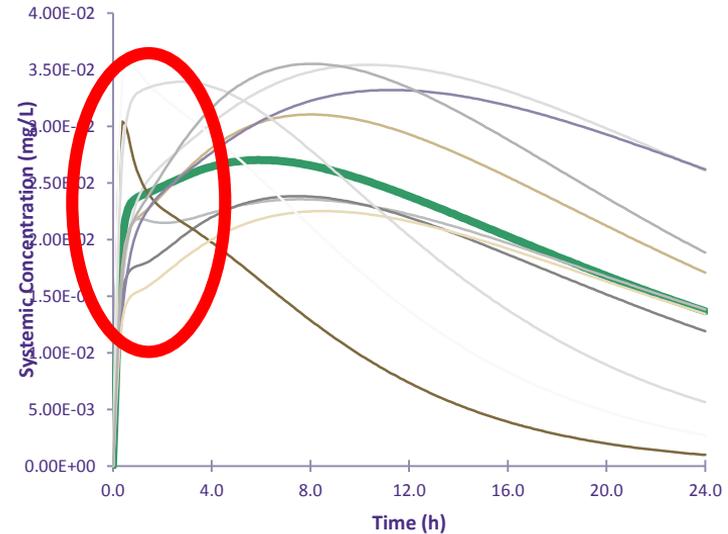
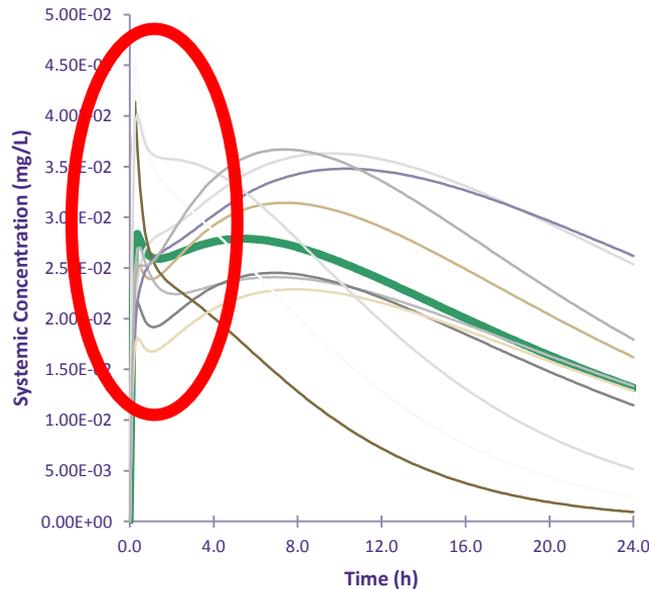


Several hypotheses what could be “wrong”

1. Something is not right with the solver/how the simulation is running
2. The structural model is not right
3. Drug model is somehow flawed

# By “optimizing” the $K_p$ values we can get a curve that overall agrees with observations

Increasing liver methamphetamine  $K_p$  value from predicted 3.3 to 13.3 starts to resolve the shape issue of the amphetamine concentration curve (CL fixed)

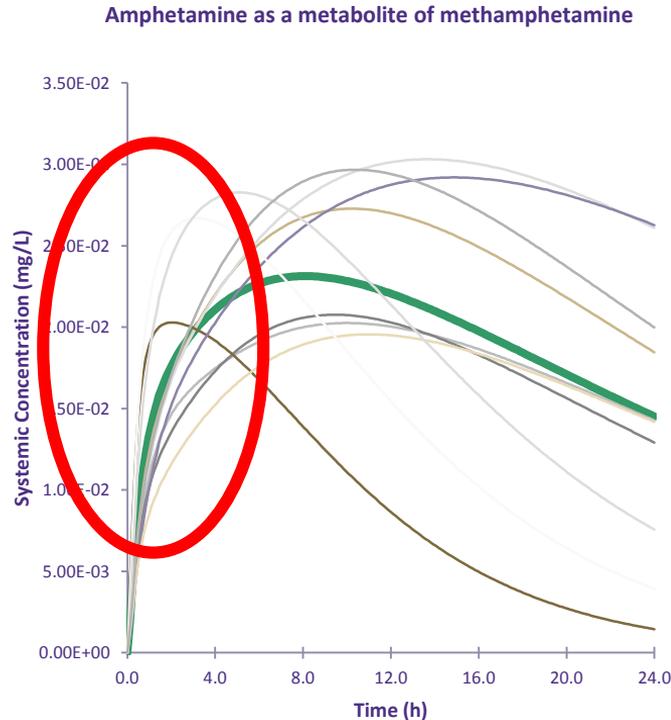


# The degrees of freedom and level of uncertainty in $K_p$ values

- >  $K_p$  values can be predicted (commonly done with Rodgers & Rowland method) but is this good enough?
- > “distinction between simulated variables and their real-world counterparts can become unclear” (Thompson and Smith, 2019)

Tissue	Predicted using R, L & R eq with rat-human hybrid	Predicted using commercial software	Observed from PET data (Volkow et al 2010)
Brain	1.85	1.82	9.67
Heart	2.28	1.44	5.21
Kidney	2.13	1.55	14.55
Liver	3.02	1.65	24.96
Lung	1.58	1.51	6.94

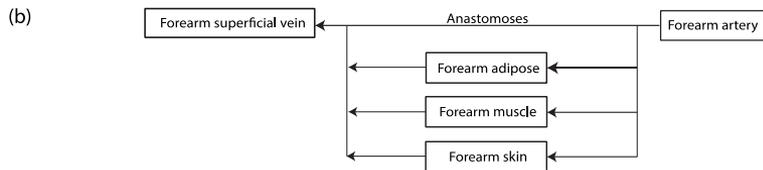
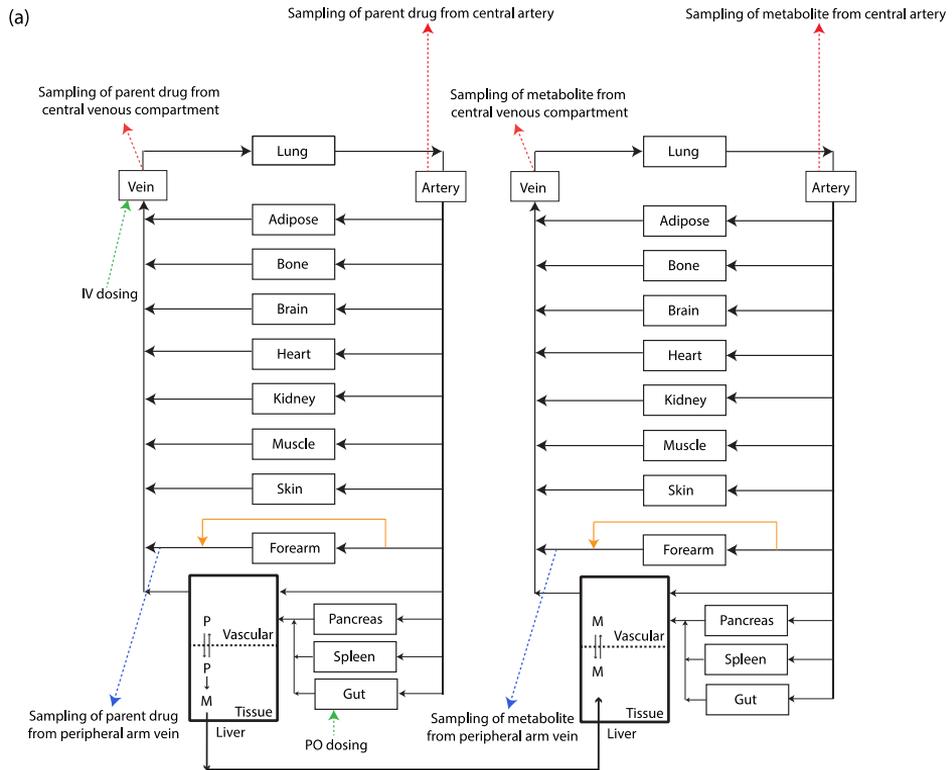
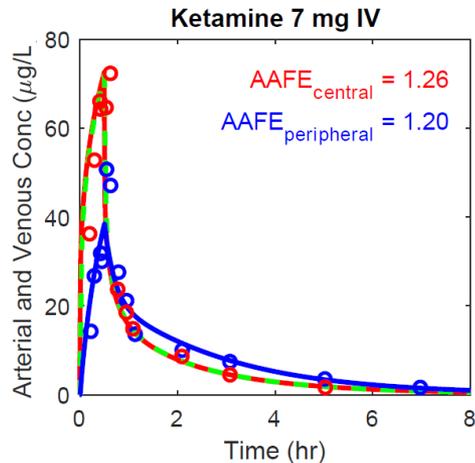
# Using PET-scan $K_p$ values metabolite curve looks acceptable



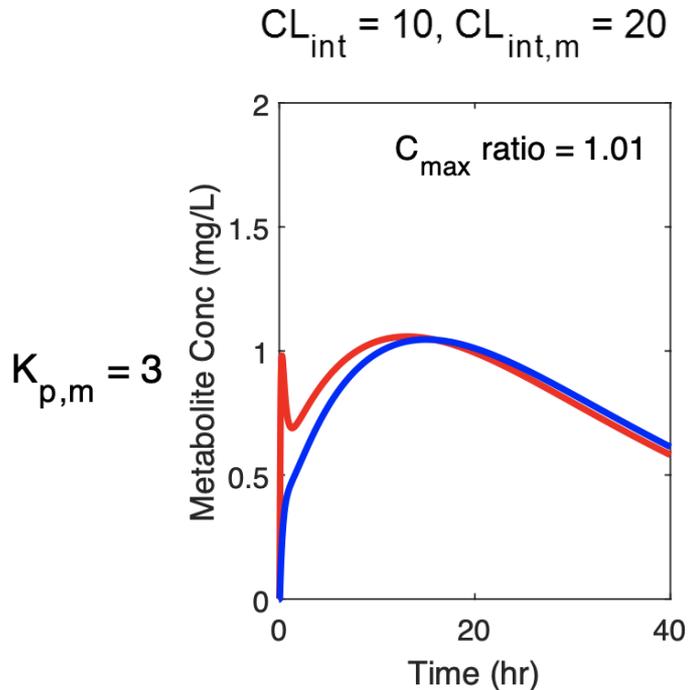
- Is this model good enough? Fit-for-purpose?
- Does it replicate observed data for the wrong reasons?
- Conclusion that the drug model was the cause for the unacceptable simulation?

# Structural model may still need reassessment

- > PBPK models typically sample from merged venous compartment- analogous to right atrium
- > Observed PK is usually from an arm vein
- > Does the difference in sampling sites matter?



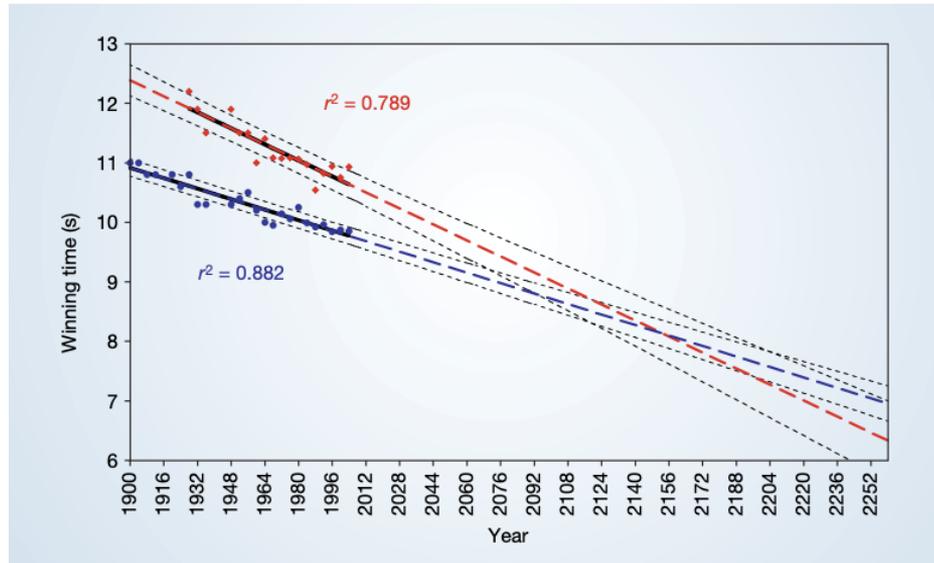
# The model structure and/or discrepant sampling site may be the reason for model rejection



- The metabolite profile is different from different sampling sites
- Optimizing a model to discrepant sampling site may lead to wrong parameters
- For different compounds/scenarios different parts of the model may be sensitive
- Does this impact extrapolation to unstudied scenarios

# Momentous sprint at the 2156 Olympics?

Women sprinters are closing the gap on men and may one day overtake them.

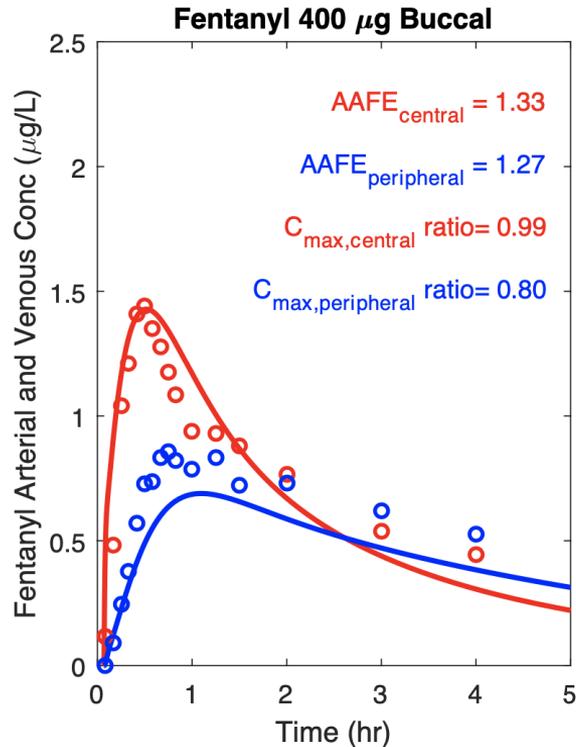


**Figure 1** The winning Olympic 100-metre sprint times for men (blue points) and women (red points), with superimposed best-fit linear regression lines (solid black lines) and coefficients of determination. The regression lines are extrapolated (broken blue and red lines for men and women, respectively) and 95% confidence intervals (dotted black lines) based on the available points are superimposed. The projections intersect just before the 2156 Olympics, when the winning women's 100-metre sprint time of 8.079 s will be faster than the men's at 8.098 s.

“a far more interesting race should occur in about 2636, when times of less than zero seconds will be recorded.” Rice K, Nature, 2004

“Since all models are wrong the scientist must be alert to what is importantly wrong” “we make tentative assumptions about the real world which we know are false but which we believe may be useful nonetheless” Box G, JASA, 1976

# Is peripheral sampling necessary in PBPK simulations? Buccal Fentanyl as an example



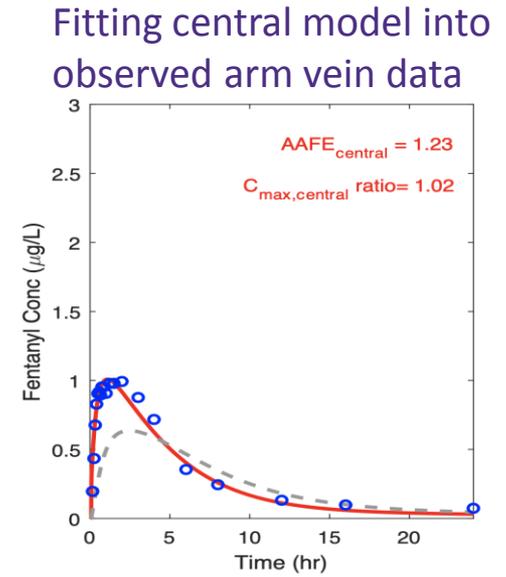
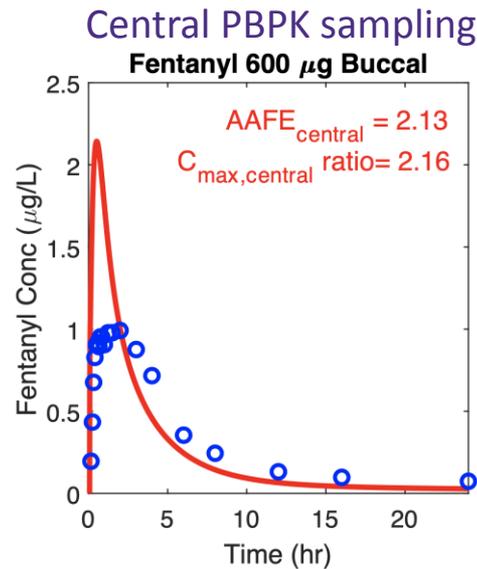
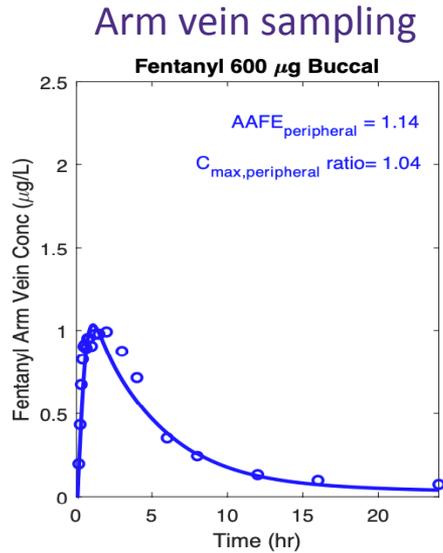
- > Observed arterial and venous concentrations are different
- > Arteriovenous difference can be captured by PBPK
- > Each site independently captures the corresponding plasma concentrations-time curves

# Fit for purpose re-examined: Buccal fentanyl model optimization

$$k_{a,buccal} = 1 \text{ hr}^{-1}$$
$$k_{a,gut} = 3 \text{ hr}^{-1}$$



$$k_{a,buccal} = 0.35 \text{ hr}^{-1}$$
$$k_{a,gut} = 0.7 \text{ hr}^{-1}$$



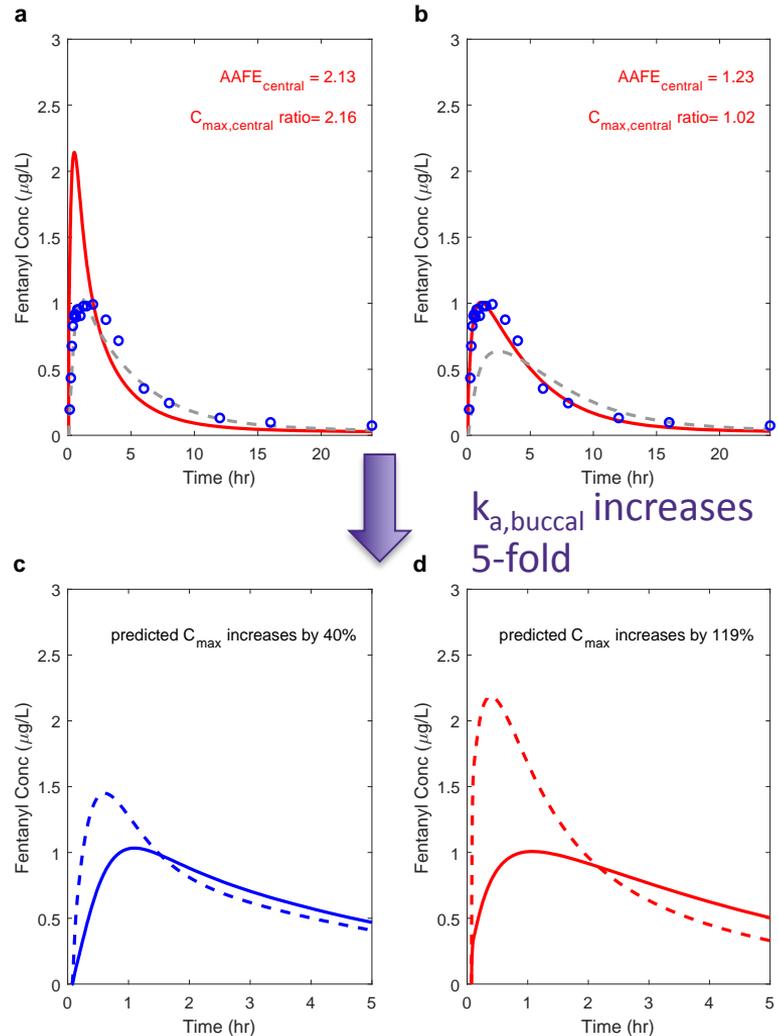
- > Is there a possibility that “best available” model, while providing accurate recapitulation of observed C data (for wrong reasons), results in inaccurate extrapolation

# Extrapolation built on wrong optimization could mislead decision making

- > Seemingly unimportant (minor) model optimizations can have a major impact on predictions of unstudied scenarios

“Lorenz’s butterfly effect”

- > "Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful." Box G, 1987

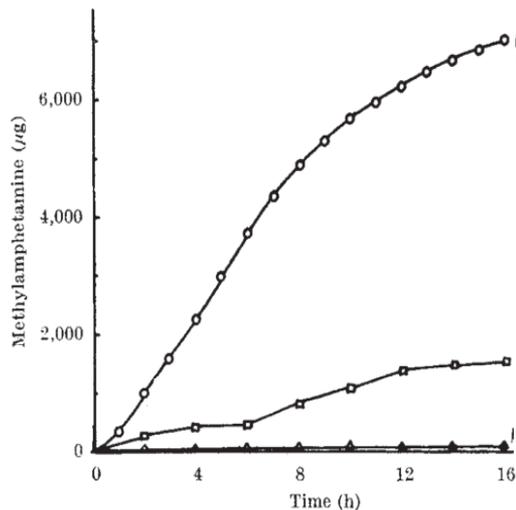


# The number of parameters and degrees of freedom - structural and drug models

- > PBPK models have multiple compartments, usually at least 14
- > Each compartment is associated with several parameters, for example: blood flow, organ volume,  $K_p$ ,  $CL_{\text{distribution}}$ ,  $CL_{\text{int}}$
- > At least 70 degrees of freedom ( $10^{70}$  simulations needed for global sensitivity analysis and 700 for local sensitivity analysis if testing 10 values per parameter): **identification of sensitive parameters and strategizing sensitivity analyses for particular model can be challenging**
- > Statistical dilemma; how many datapoints would be needed to differentiate one structural model from another?
- > In many cases, the optimization of multiple parameters is interdependent

# Models to predict renal clearance have several interdependent parameters

Methamphetamine and amphetamine have pH-dependent passive tubular reabsorption and active secretion transport

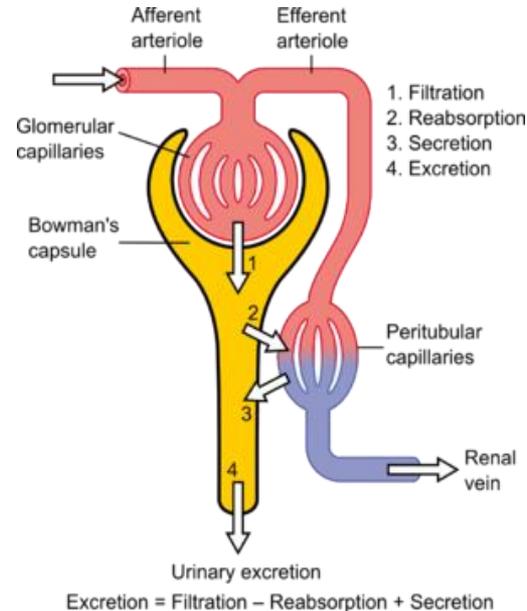


Acidic urine  
pH 4.9-5.3

Uncontrolled urine pH

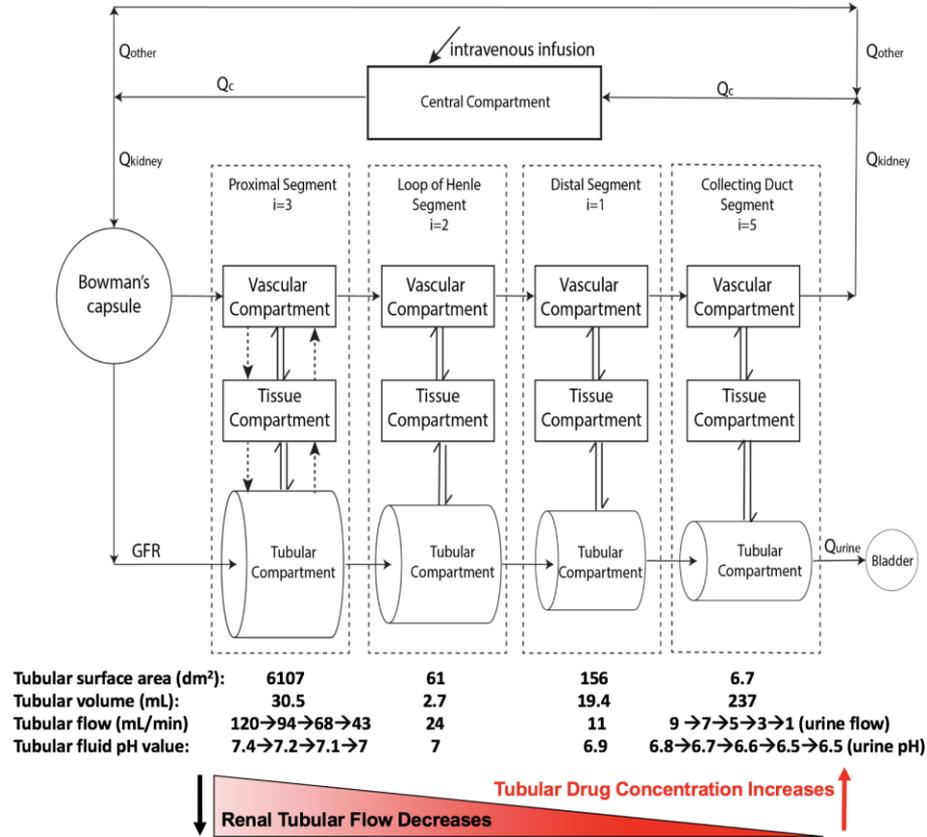
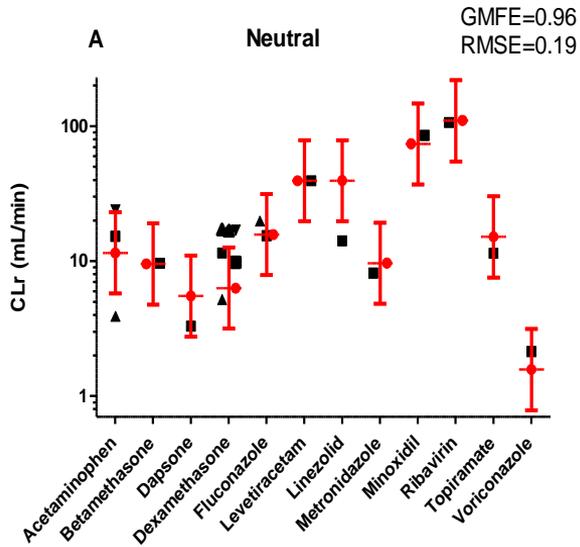
Alkaline urine pH 7.8-8.2

- From observed data tubular secretion and passive reabsorption are interdependent processes

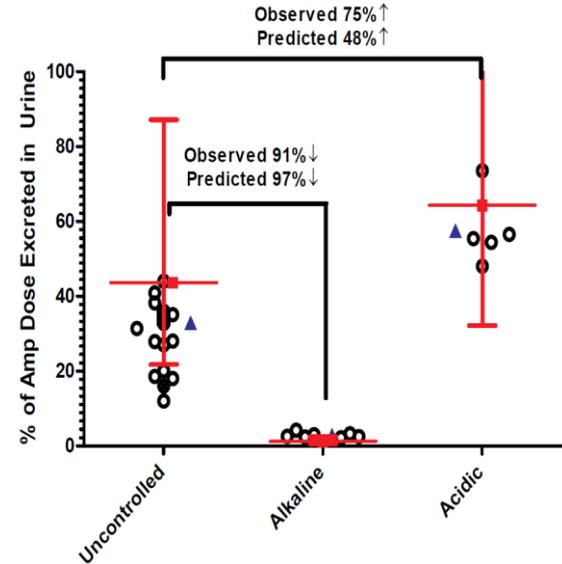
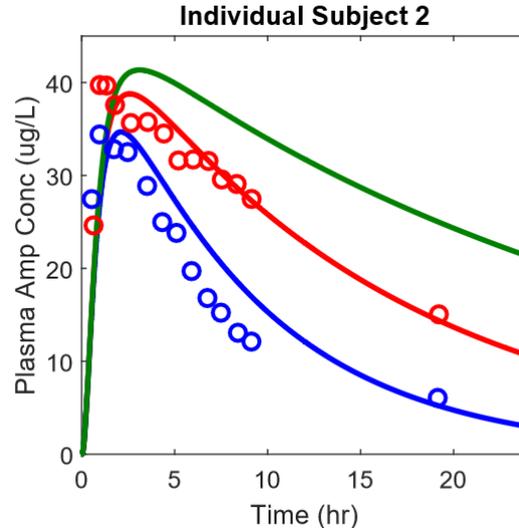
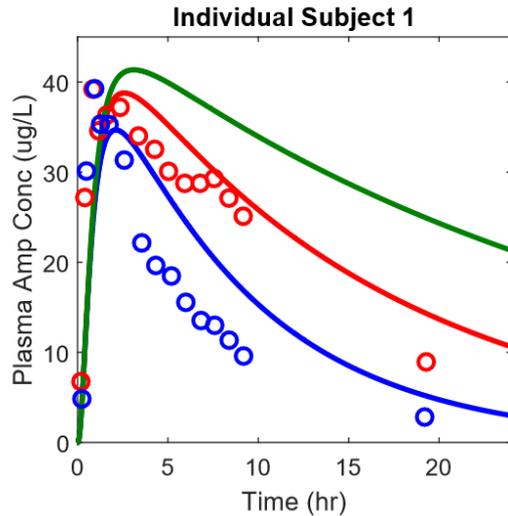


# Development of Mechanistic Kidney Model to Gain Confidence on Passive Reabsorption

- Model performance verified with number of drugs that do not have active secretion



# Application of Verified Mechanistic Kidney Model to Predict Urine pH effect on Amphetamine disposition



While different physiological scenarios can be simulated, their probability to be seen in a sample cannot be estimated without the knowledge of parameter distribution

# Conclusions

- >  **$K_p$  values should always be experimentally determined and  $V_{ss}$  confirmed with iv dosing data**
- > **The sampling site in PBPK simulations should be matched to the sampling site in experimental studies or vice versa**
- > **The level of complexity needed in PBPK models can vary. It is critical to determine the necessary complexity and aim for parsimony. This will allow identification of components in the model that are importantly wrong (ie make model not useful)**
- > **Statistical methods that account for increased degrees of freedom in “better fits” are needed to differentiate models**
- > **Extrapolation to unstudied scenarios makes an implicit assumption that the same mathematical relationships apply from interpolation through extrapolation**