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Can pharmacokinetic modelling keep up with risk assessment in the 21st Century?

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Conflict of Interest Statement

I have no conflicts of interest to disclose

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Can pharmacokinetic modelling keep up with risk assessment in the 21st Century?

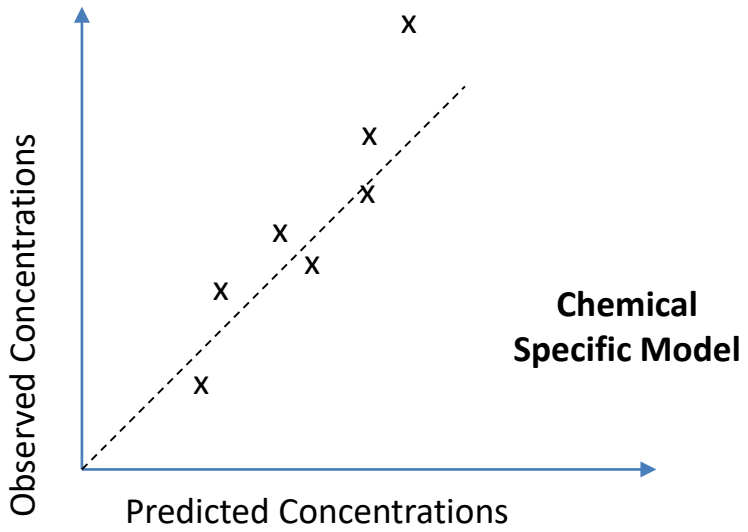
Yes, but…

- *In vitro* and *in silico* tools for toxicology require chemical-specific toxicokinetics (TK)
- High throughput TK (HTTK) methods work well enough but require analytical chemistry and that the chemical is amenable to *in vitro* testing
  - Too slow to keep up
- *In silico* HTTK methods offer path forward (see Sipes et al., (2017) Env. Sci. & Tech)
- Model reliability continues to be an issue, but generic models offer a path forward

Building Confidence in TK Models

- In order to evaluate a **chemical-specific TK model** for "chemical x" you can compare the predictions to *in vivo* measured data
  - Can estimate bias
  - Can estimate uncertainty
  - Can consider using model to extrapolate to other situations (dose, route, physiology) where you don't have data

- However, we do not typically have TK data



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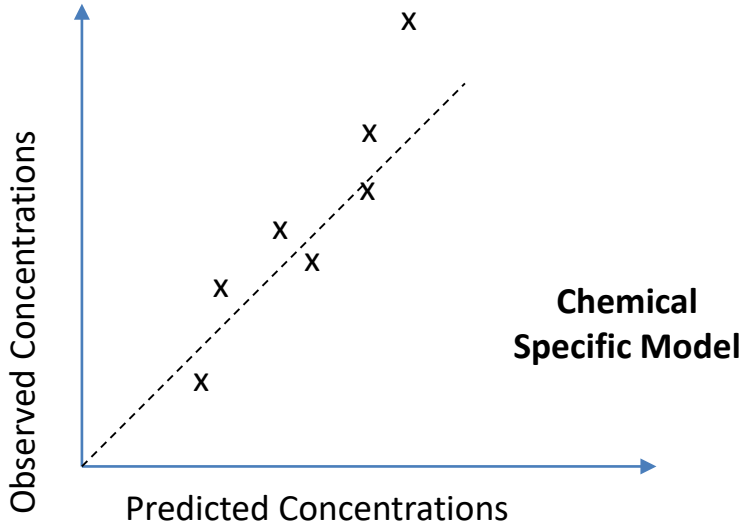
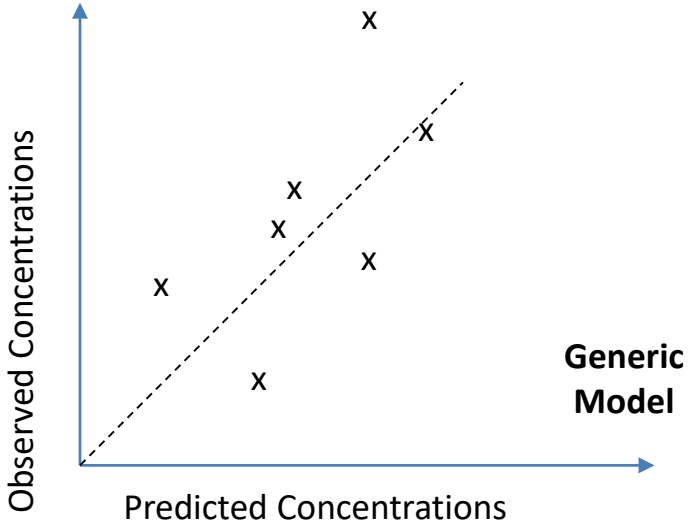
- We can parameterize a **generic TK model**, and evaluate that model for as many chemicals as we do have data
  - We do expect larger uncertainty, but also greater confidence in model implementation
  - Estimate bias and uncertainty, and try to correlate with chemical-specific properties
  - Can again consider using model to extrapolate to other situations (chemicals without *in vivo* data)





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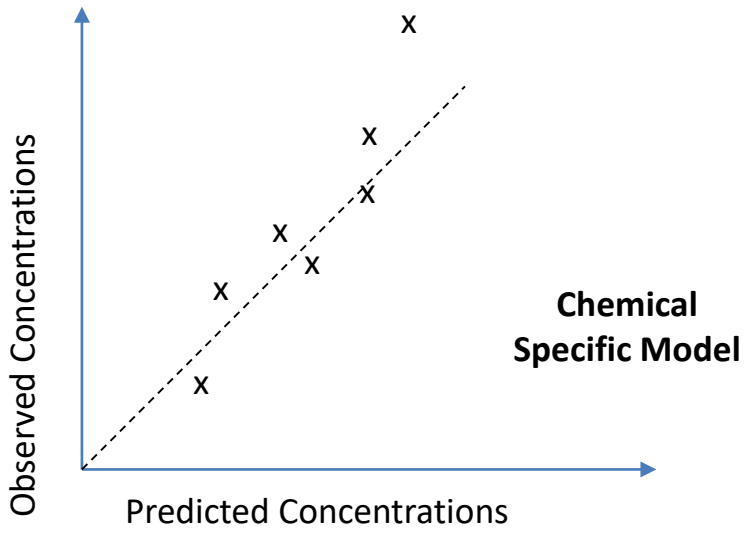

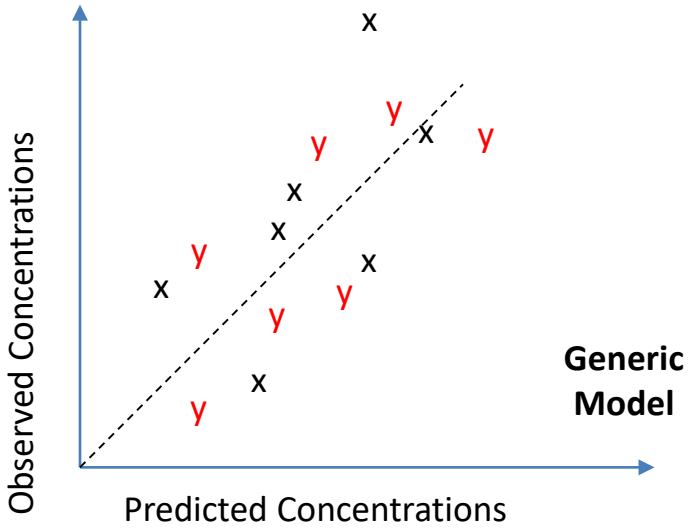

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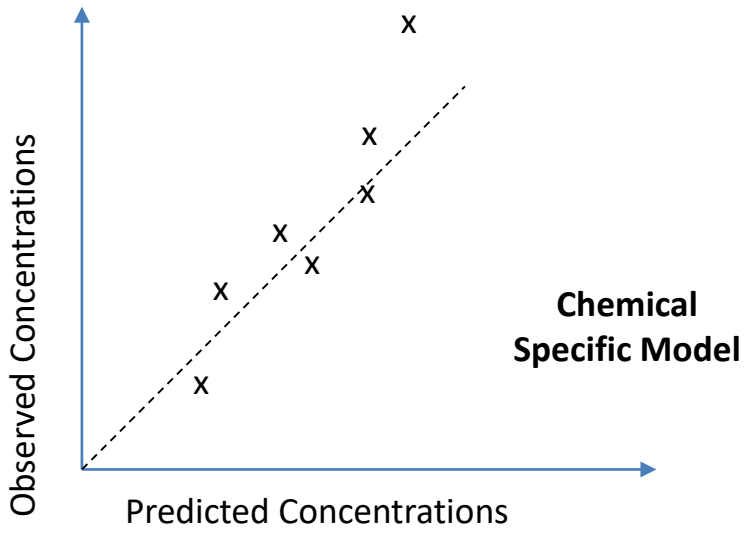

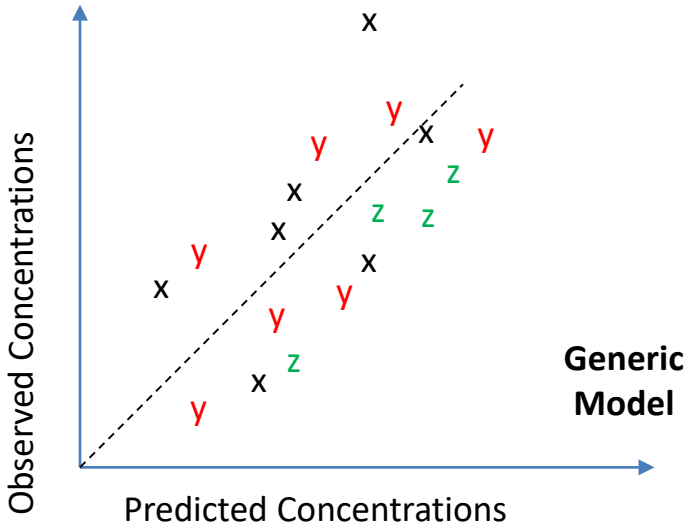

Generic TK enables *In Vitro-In Vivo* Extrapolation (IVIVE)

- Generic PBTK models based on HTTK seem to increase correlation between in vitro bioactivity and in vivo effects
- Histograms (at right) give number of correlated ToxCast assay and ToxRefDB *in vivo* effect pairs
- Using PBTK to predict tissue concentrations does better than using administered dose (or PBTK for random chemical)

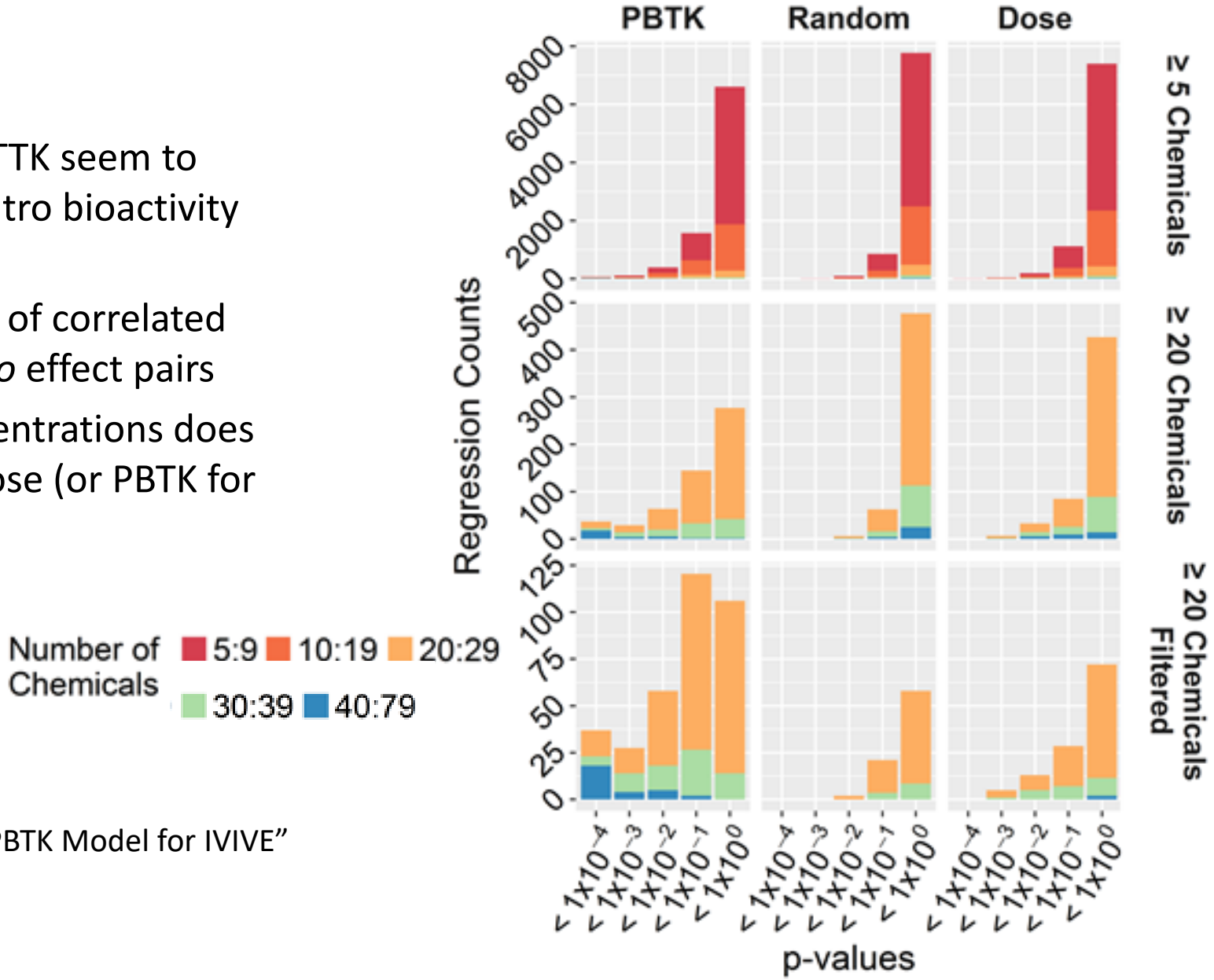

Figure from Greg Honda
See his poster P885 “Applying a High-Throughput PBTK Model for IVIVE” on Tuesday morning