Developing a Predictive Model for Chemical Excretion in Urine

Presented by Zachary Stanfield

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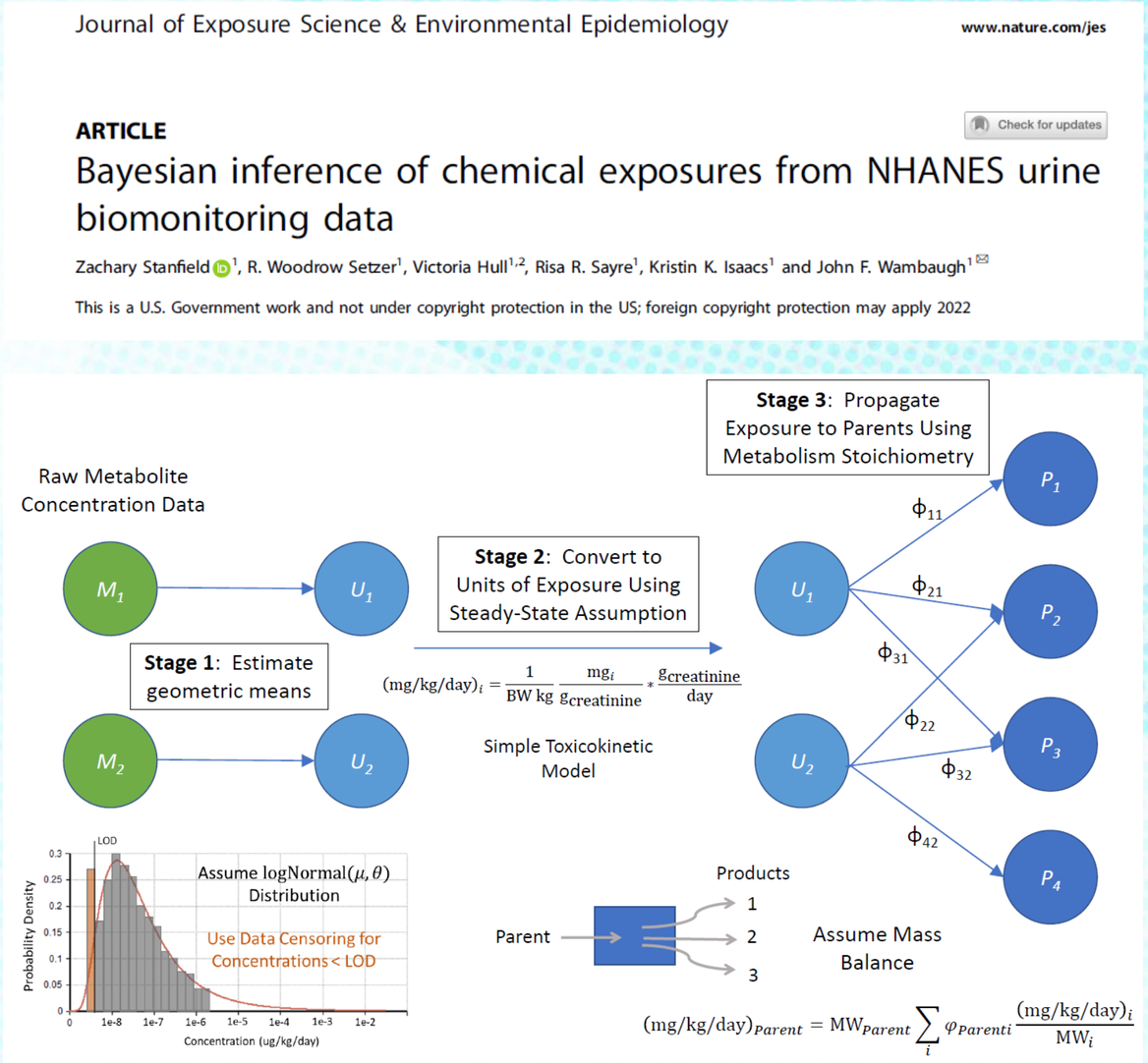
Motivation

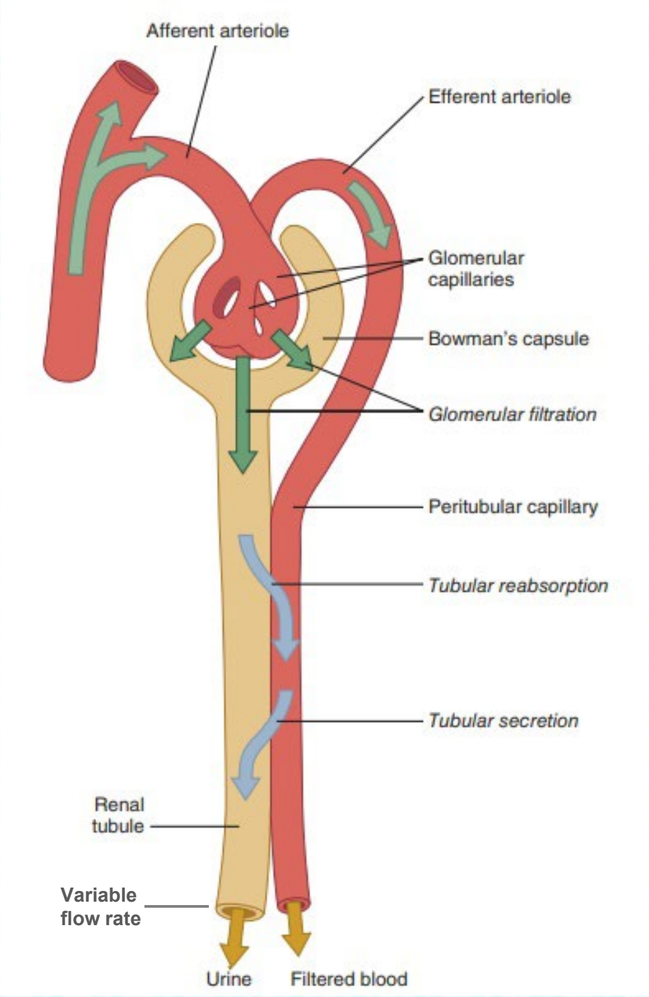
- Recently developed the R package “bayesmarker” (Stanfield et al, 2022; https://github.com/USEPA/CompTox-HumanExposure-bayesmarker)
- Employs Bayesian methodology to infer parent chemical exposures from biomonitoring data (concentrations of urinary metabolites)
- Urinary biomonitoring data plays an important role in exposure science (GAO, 2009; NRC 2006; NRC, 2007; NRC, 2009)
- Some research uses include:
  - Exposure reconstruction
  - PK/PBPK model evaluation
- During exposure calculation, we adjust all metabolite concentrations based on urine creatinine
- There is no general guidance on how to process urinary metabolite concentrations (Middleton et al, 2016; Aylward et al, 2012)
  - Many approaches apply creatinine correction for all chemicals by default (assumes same kidney elimination route)
  - However, the elimination pathway is more complex than this for some substances



#ISES2022LIBSON

Understanding Urinary Excretion

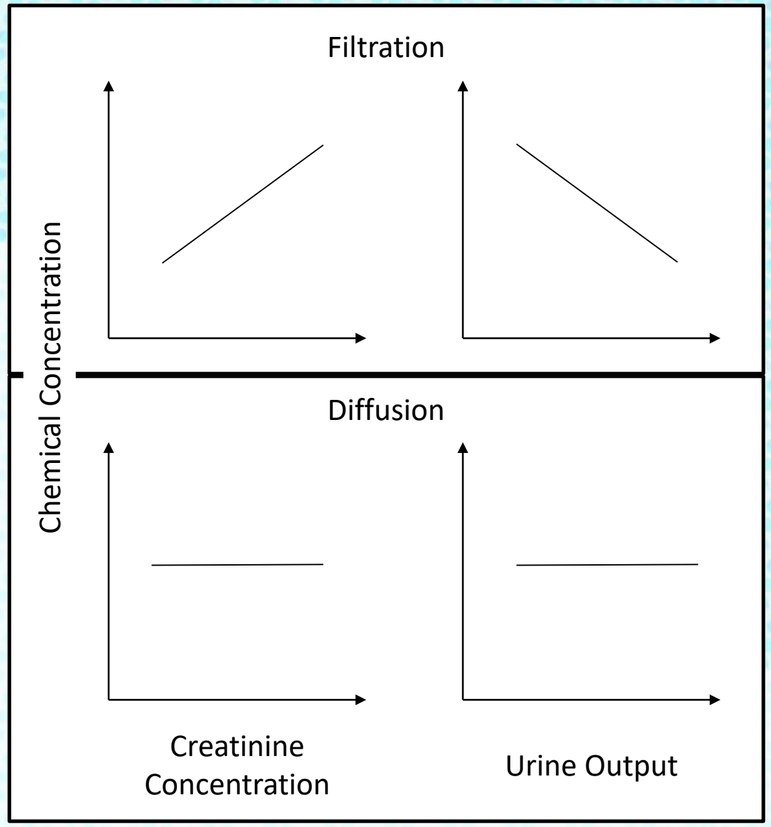
- There are 3 main steps in the process of urine elimination (Boeniger et al, 1993)
  1. Glomerular filtration: substances are filtered in the glomerulus capsule into the renal tubule
  2. Active transport: substances are actively transported between the blood and the filtrate in the renal tubule (sometimes called secretion when leaving the blood)
  3. Passive transport: substances diffuse between the blood and the filtrate in the renal tubule (sometimes called reabsorption when leaving the filtrate)



https://www.pharmacy180.com/article/tubular-secretion-3673/

Understanding Urinary Excretion (Cont.)

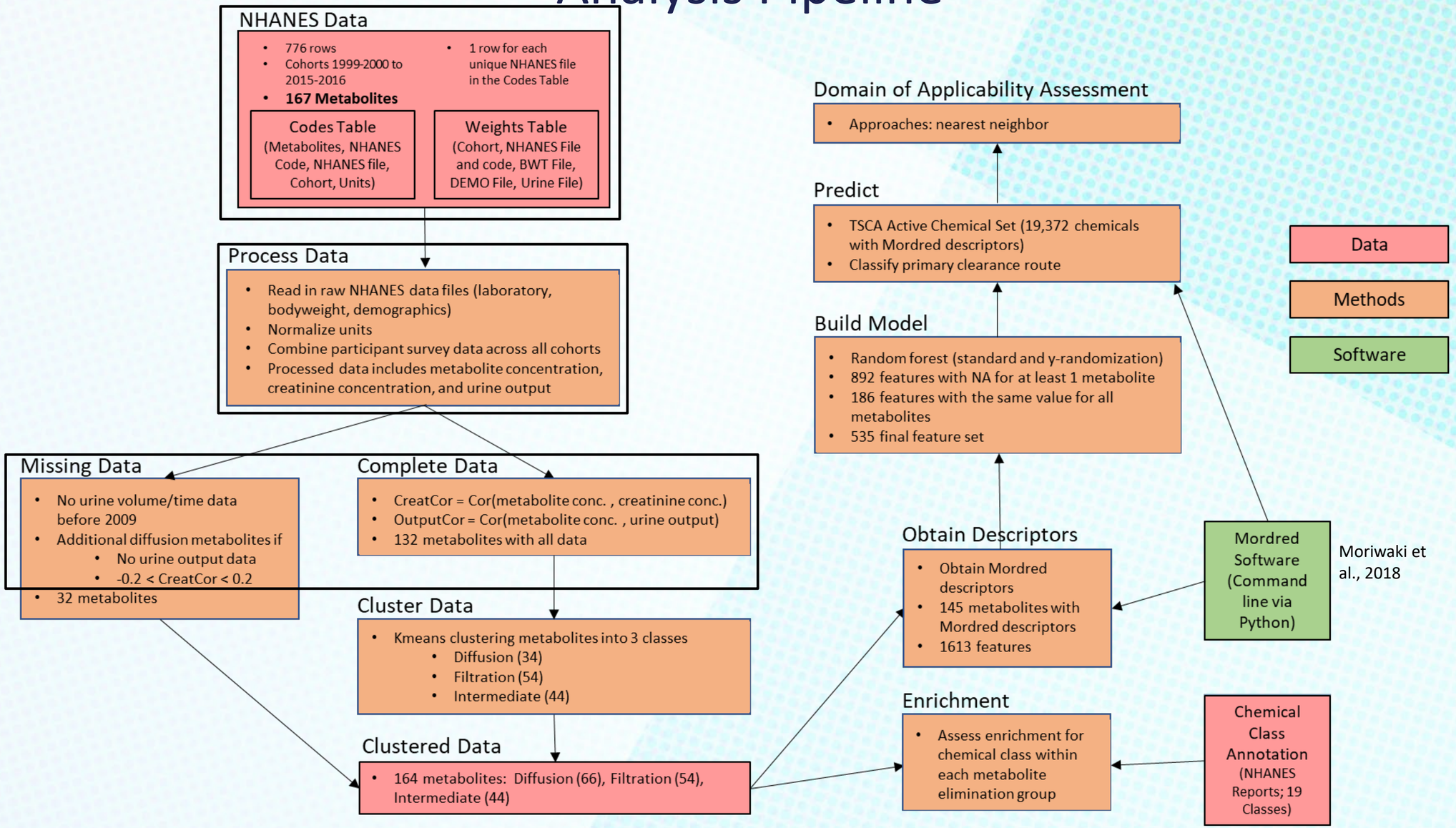
- There are 3 main steps in the process of urine elimination (Boeniger et al, 1993)
  1. Glomerular filtration: substances are filtered in the glomerulus capsule into the renal tubule
  2. Active transport: substances are actively transported between the blood and the filtrate in the renal tubule (sometimes called secretion when leaving the blood)
  3. Passive transport: substances diffuse between the blood and the filtrate in the renal tubule (sometimes called reabsorption when leaving the filtrate)
- Due to our knowledge about renal elimination, we hypothesize that:
  1. Substances undergoing glomerular filtration should follow creatinine concentration (directly) and urine output (indirectly)
  2. Substances undergoing passive diffusion should be independent of creatinine concentration and urine output
- A number of studies (Boeniger et al, 1993; Watanabe et al, 2019) have suggested that some portion of substances belong to an “intermediate” class, which isn’t as well defined as the filtration and diffusion groups



Project Goals

- Test hypotheses of relationships between chemical concentration, creatinine concentration, and urine output for different kidney elimination routes
  - Apply to the CDC's National Health and Nutrition Examination Survey (NHANES)
    - https://www.cdc.gov/nchs/nhanes/index.htm
    - Combine data from the NHANES continuous survey (9 two-year cohorts spanning 1999-2016)
  - Cluster metabolites based on correlation between these 3 measures
  - Characterize these clusters by some criteria
- Build a high-throughput model to predict the primary kidney route of elimination for thousands of chemicals
  - Use clustering of NHANES chemicals as the training data in a classification model
  - Use structural or molecular features that are easily obtained or calculated for most chemicals
- Apply model to a large set of chemicals of interest to provide recommendations on how to handle chemicals for various approaches in exposure reconstruction and/or PBPK model evaluation
  - Assess applicability of model to this large chemical set

Analysis Pipeline



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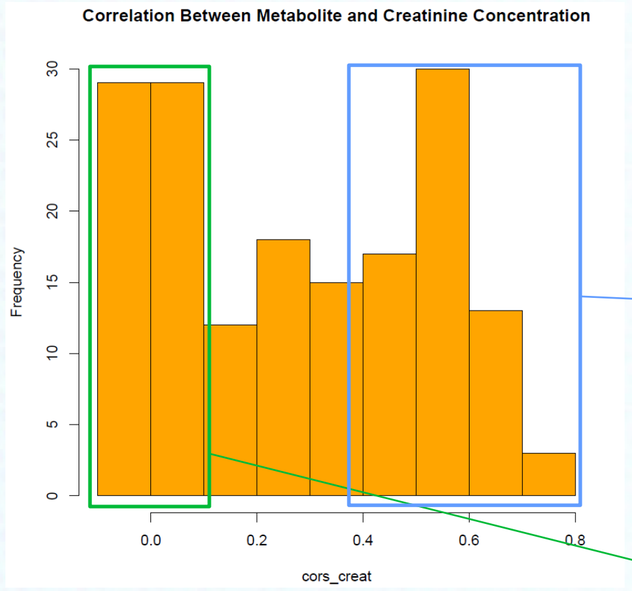
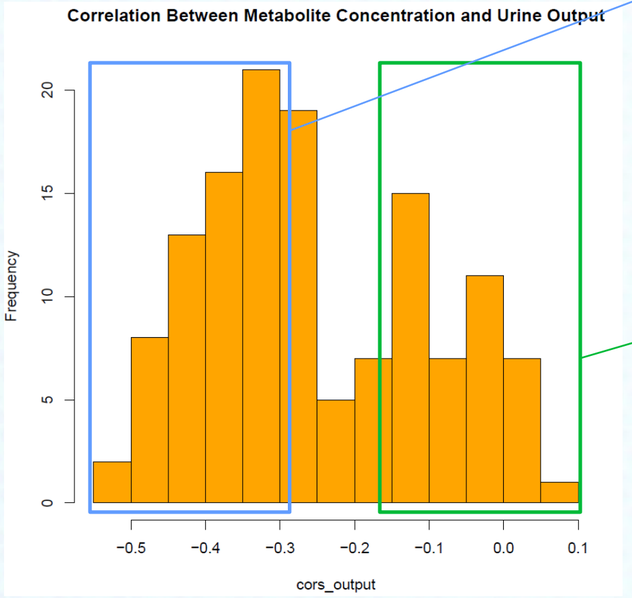
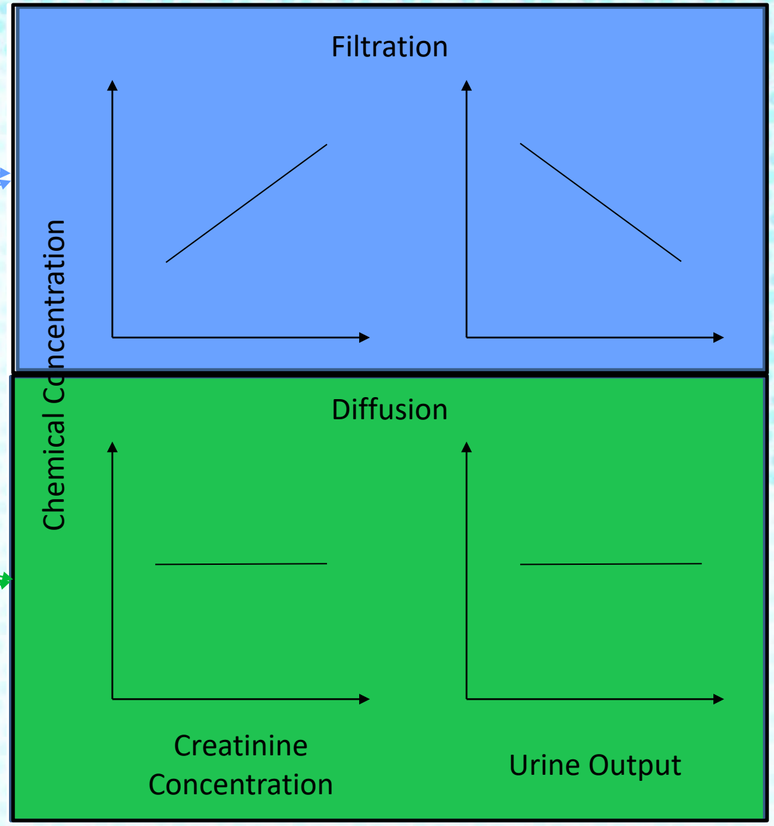
Observing Correlations



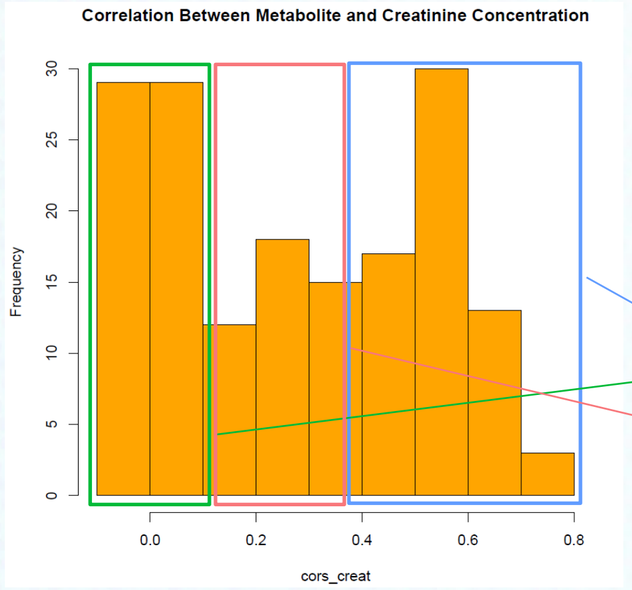


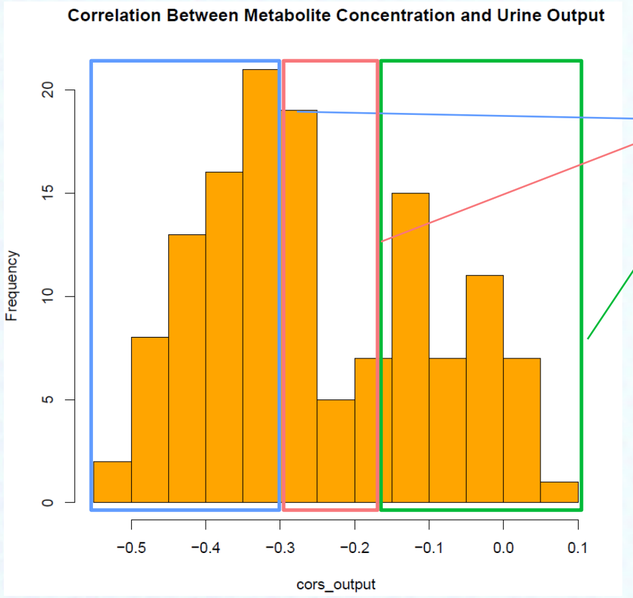
Filtration: follow creatinine concentration (directly) and urine output (indirectly)

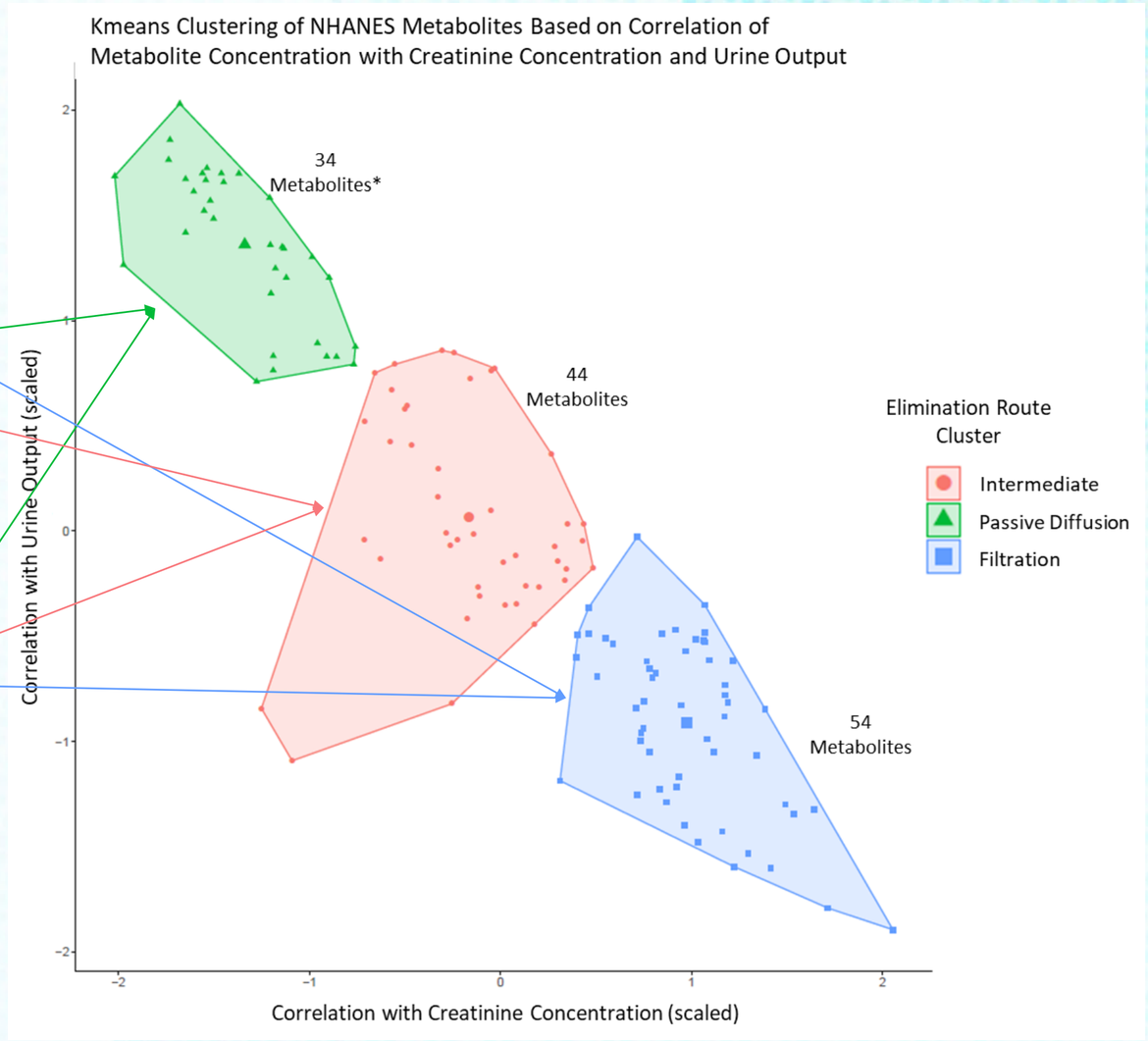
Passive diffusion: independent of creatinine concentration and urine output



Clustering Metabolites by Kidney Elimination Route







*32 additional metabolites added to the diffusion group. Missing urine output data but had very small correlation with creatinine concentration.

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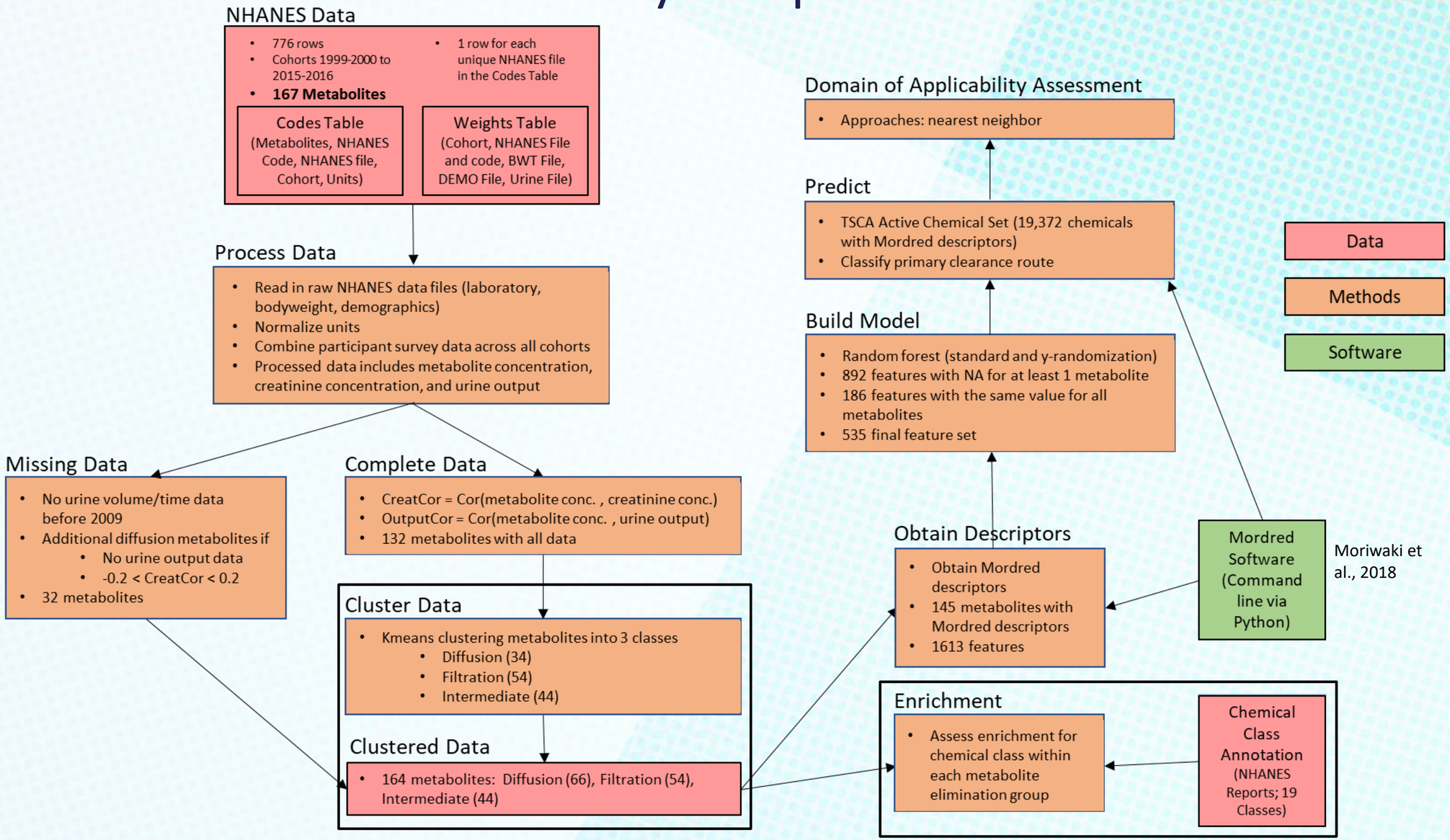
Analysis Pipeline



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Chemical Class Enrichment in Kidney Elimination Route Clusters

Enrichment determined by the hypergeometric test using the phyper() function of the stats R package (R Core Team, 2013).

Diffusion

Chemical Class	# in Route	# in Class Total	# in Class in Route	P-value
Herbicides	66	7	6	0.0174
Sulfonyl Urea Herbicides	66	17	17	4.702e-08
Fungicides	66	3	3	0.0634

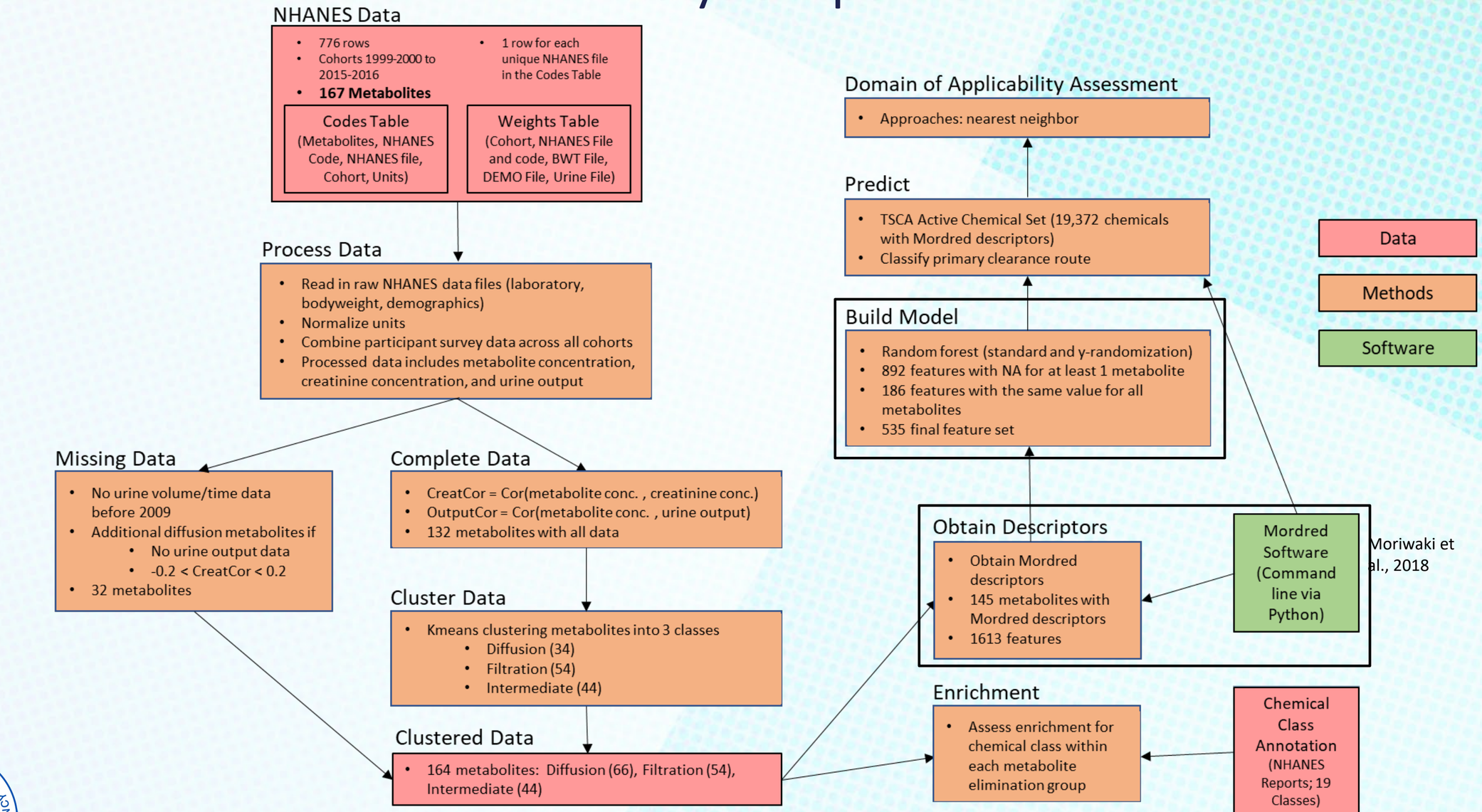
Intermediate

Chemical Class	# in Route	# in Class Total	# in Class in Route	P-value
Personal Care/Consumer Product	44	13	8	0.0066
Phytoestrogens	44	6	6	0.0003
Organochlorine Pesticides	44	2	2	0.0708

Filtration

Chemical Class	# in Route	# in Class Total	# in Class in Route	P-value
Phthalates	54	16	10	0.0106
Volatile Organic Compounds	54	22	13	0.0063
Polycyclic Aromatic Hydrocarbons	54	10	9	0.0002
Metals	54	20	11	0.0258

Analysis Pipeline



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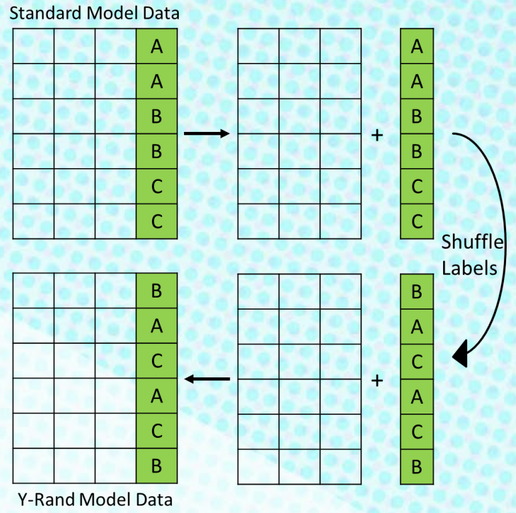
Build Model

- Trained a Random Forest model using the randomForest R package (RColorBrewer & Liaw, 2018)
- Mordred feature filtering:
  - Started with 1613 features
  - Dropped all features having a NA for any training chemical (892 descriptors)
  - Dropped all features having the same value for all training chemicals (186 descriptors)
  - Resulted in a final model of 535 features
- Balancing classes:
  - Sampled training instances from each route cluster where the sample size was set to the number of chemicals in the smallest cluster



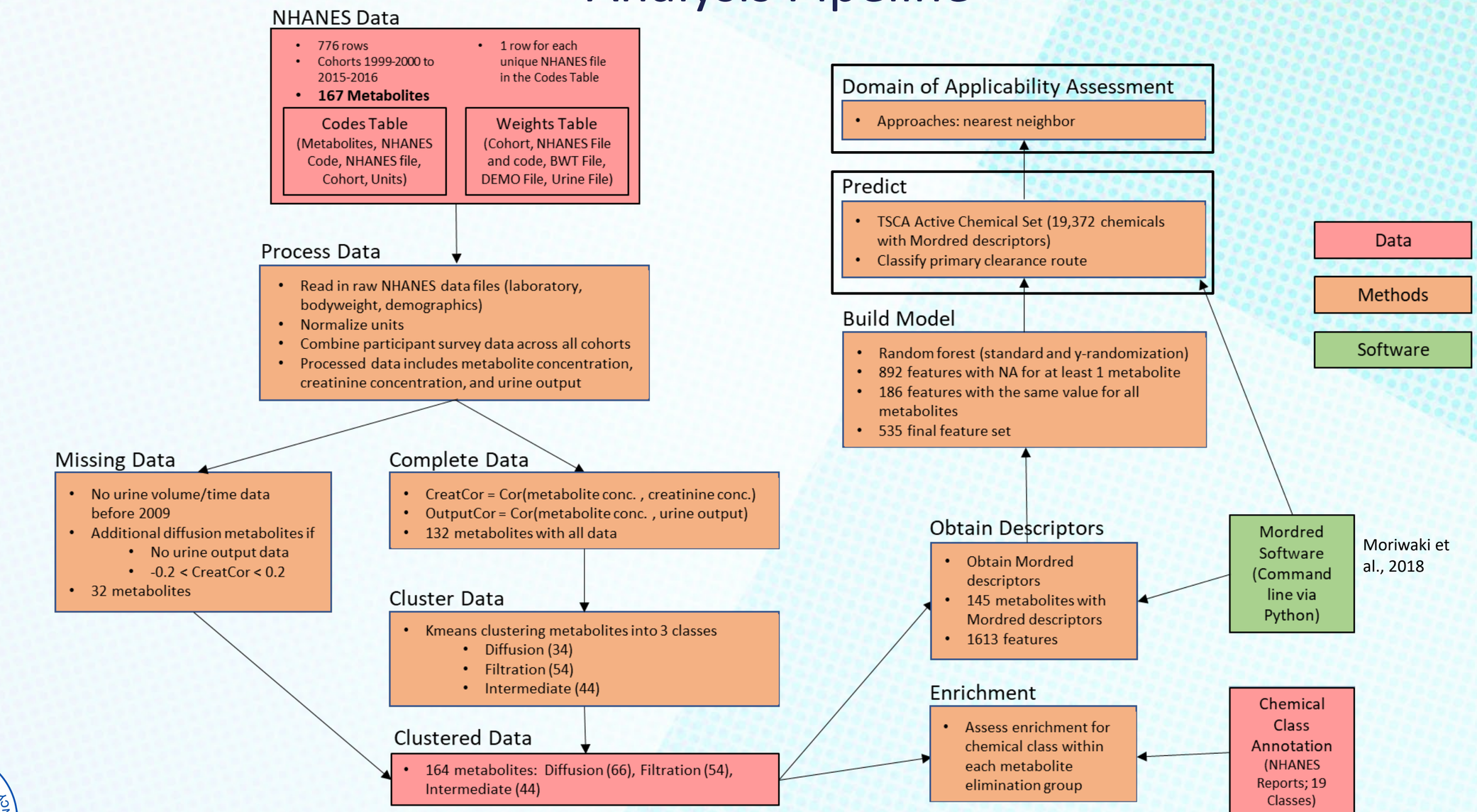
Standard Model Overall OOB Error = 34.48%

	Diffusion	Filtration	Intermediate	Class Error
Diffusion	41	5	11	0.2807
Filtration	2	34	13	0.3061
Intermediate	9	10	20	0.4872

Y-Randomized Model Overall OOB Error = 75.86%

	Diffusion	Filtration	Intermediate	Class Error
Diffusion	20	27	10	0.6491
Filtration	27	10	12	0.7959
Intermediate	22	12	5	0.8718

Analysis Pipeline



High-Throughput Predictions

- List of Toxic Substances Control Act (TSCA) Active Chemicals obtained from the EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard)
- TSCA_ACTIVE_NCTI_0221 list with 33599 chemicals
- After obtaining SMILES and calculating Mordred descriptors, 19372 chemicals available for prediction
- Assess domain of applicability in the context of these predictions
  - Use a nearest neighbor approach with similarity threshold as first described in Tropsha & Golbraikh, 2007

Route	# Predicted (% of Total)	# In Domain (% of Route)	# Out Domain (% of Route)
Diffusion	13986 (72.20%)	10422 (74.52%)	3564 (25.48%)
Filtration	1682 (8.68%)	1339 (79.61%)	343 (20.39%)
Intermediate	3364 (19.91%)	2214 (60.43%)	1450 (39.57%)

Future Work

- Additional analyses:
  - Collect more NHANES data (most recent cohorts will have more metabolites all with complete urine metrics)
  - Incorporate additional features into the predictive model
- Model evaluation in the form of two case studies using chemicals clustered/predicted to undergo passive diffusion as primary route of urinary elimination:
  1. PBPK evaluation: run a PBTK model with GFR correction turned off and see if agreement with *in vivo* assay data improves
  2. Exposure reconstruction: estimate exposure intake rates based on urine metabolite concentrations; compare exposure ranges with GFR correction turned on and off

Future Work: Case Study 1

Journal of Statistical Software
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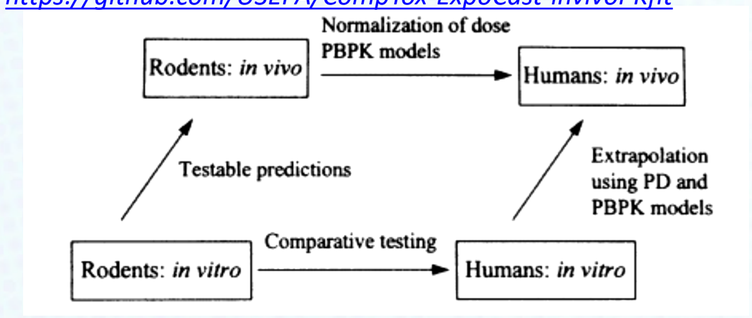
httk: R Package for High-Throughput Toxicokinetics

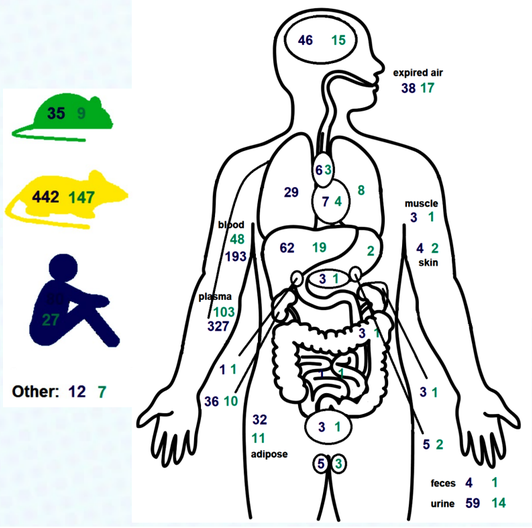
Robert G. Pearce, R. Woodrow Setzer, Cory L. Strope, Nisha S. Sipes, John F. Wambaugh

https://CRAN.R-project.org/package=httk

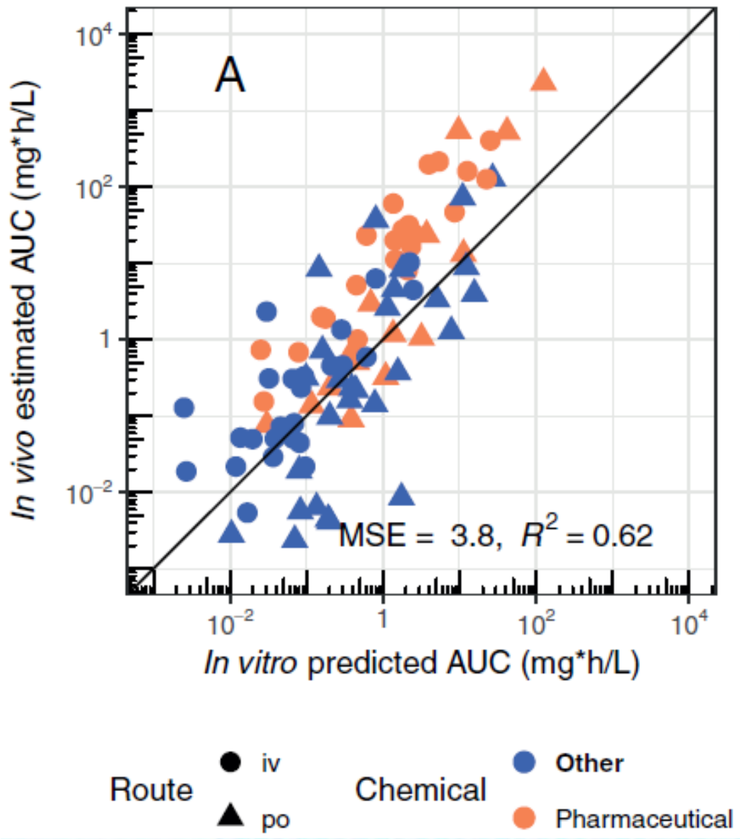
In Vitro-In Vivo Extrapolation (IVIVE)
https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit



Concentration vs Time Database (CvTdb)
http://github.com/USEPA/CompTox-PK-CvTdb

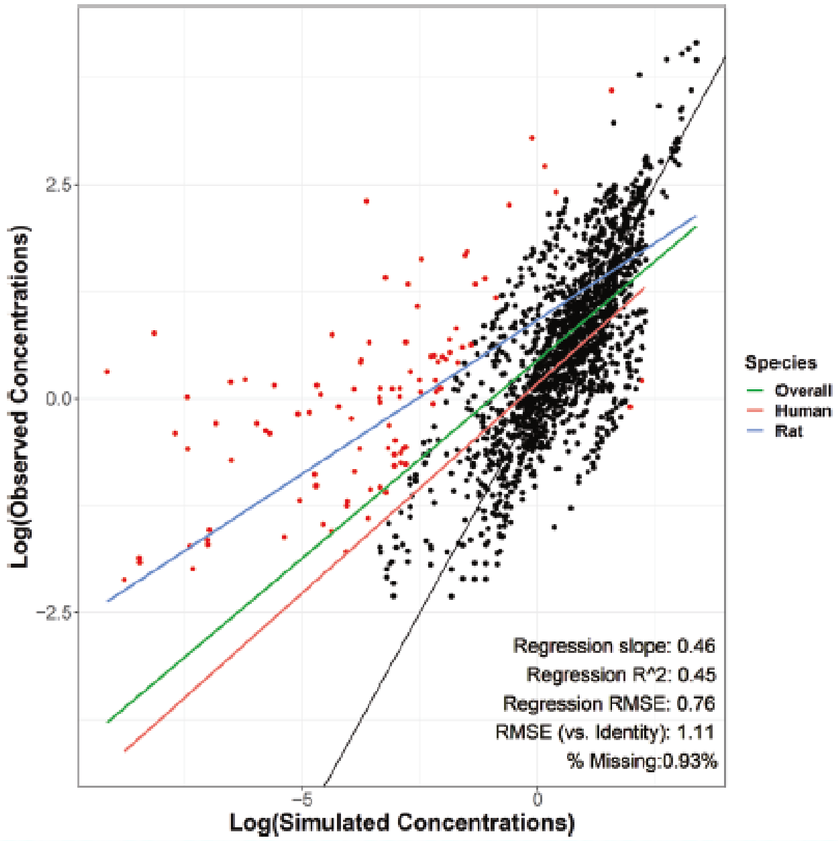


Comparison to *in vivo* rat data for 45 chemicals using httk and IVIVE methods



Wambaugh et al, 2018

Comparison to *in vivo* human and rat data for 41 volatile organic compounds under 142 exposure scenarios using a generic inhalation model (httk) and CvTdb



Linakis et al, 2018

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Future Work: Case Study 2

- Revisit our original motivation, the bayesmarker package for calculating parent chemical intake rates
- Analysis plan:
  - Rerun all metabolites clustered into the passive diffusion primary kidney elimination group through bayesmarker without creatinine correction
  - Compare exposure estimates for parent chemicals with and without correction

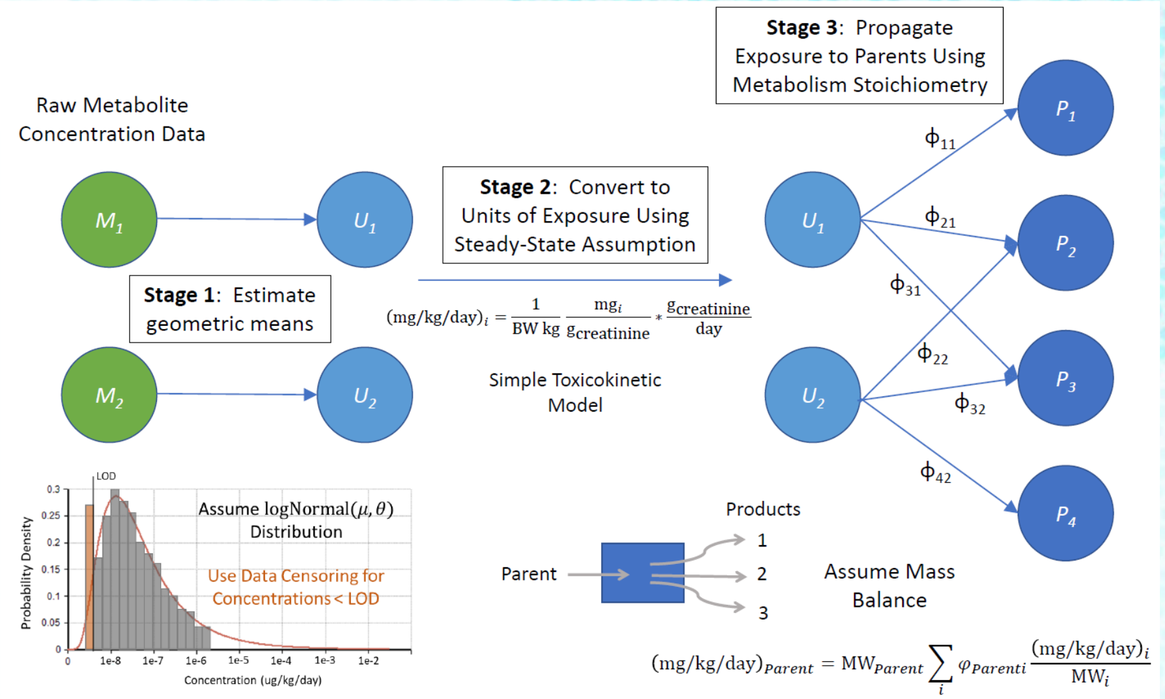
Journal of Exposure Science & Environmental Epidemiology www.nature.com/jes

ARTICLE

Check for updates

Bayesian inference of chemical exposures from NHANES urine biomonitoring data

Zachary Stanfield[1], R. Woodrow Setzer[1], Victoria Hull[1,2], Risa R. Sayre[1], Kristin K. Isaacs[1] and John F. Wambaugh[1]



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Thank You!

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