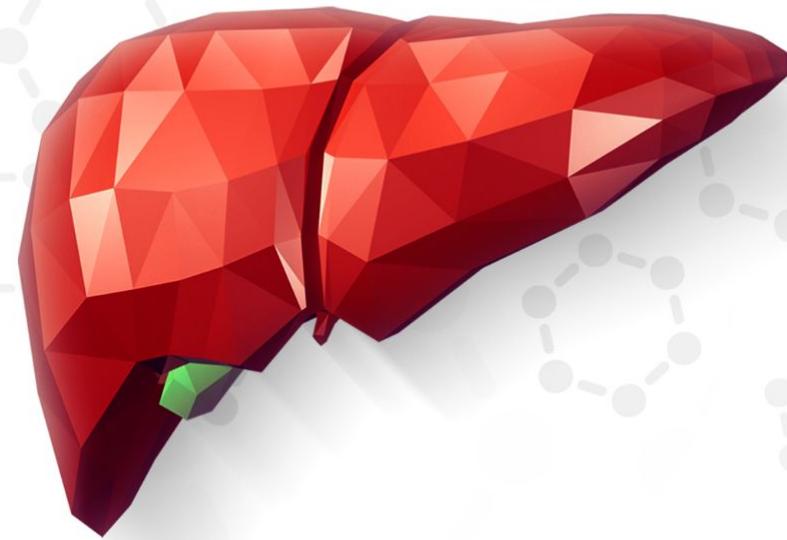


PK-DB: A Pharmacokinetics Database for Individualized and Stratified Computational Modelling

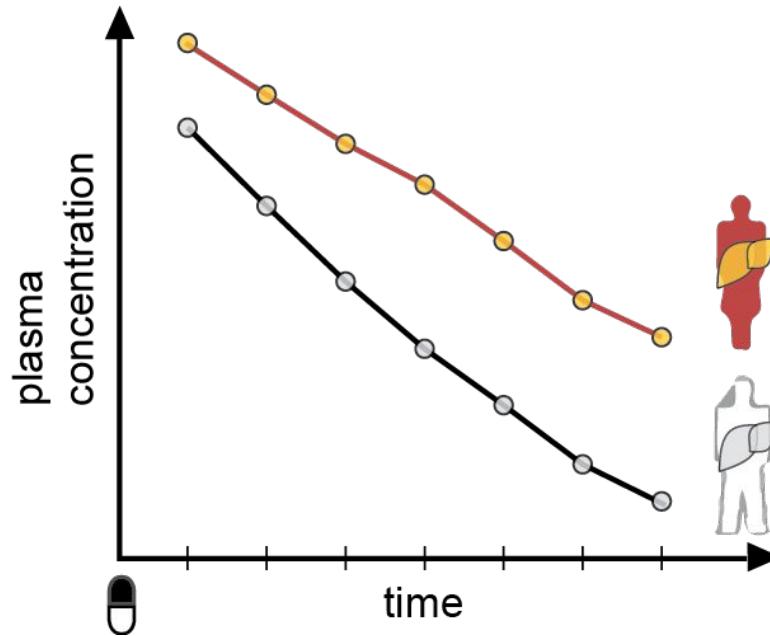
Jan Grzegorzewski



Bundesministerium
für Bildung
und Forschung

Motivation:

Dynamical Liver Function Tests



Liver specific clearance of test substances

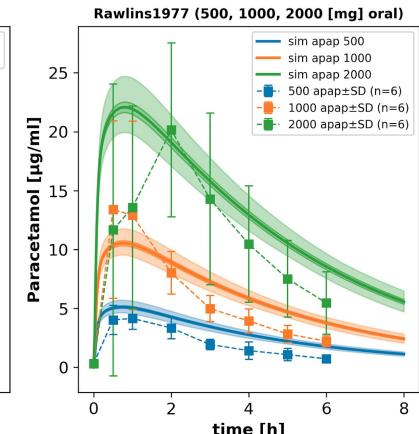
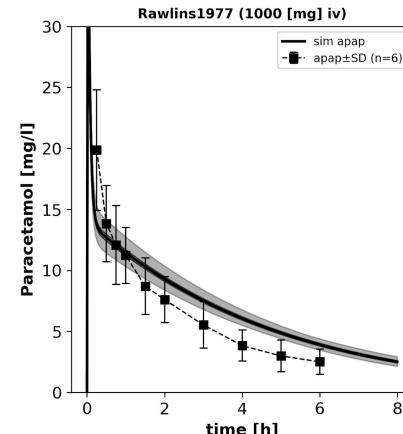
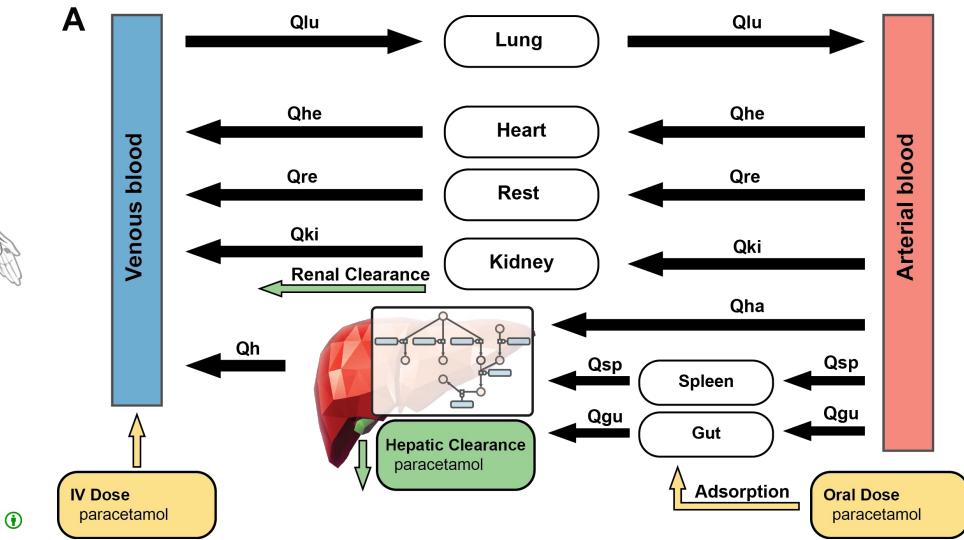
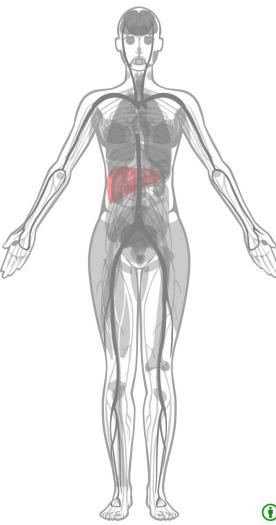
- Rate of (dis-) appearance as proxy for liver function
- e.g. caffeine, paracetamol, codeine

Challenges

- High interindividual variability
- Dose dependency

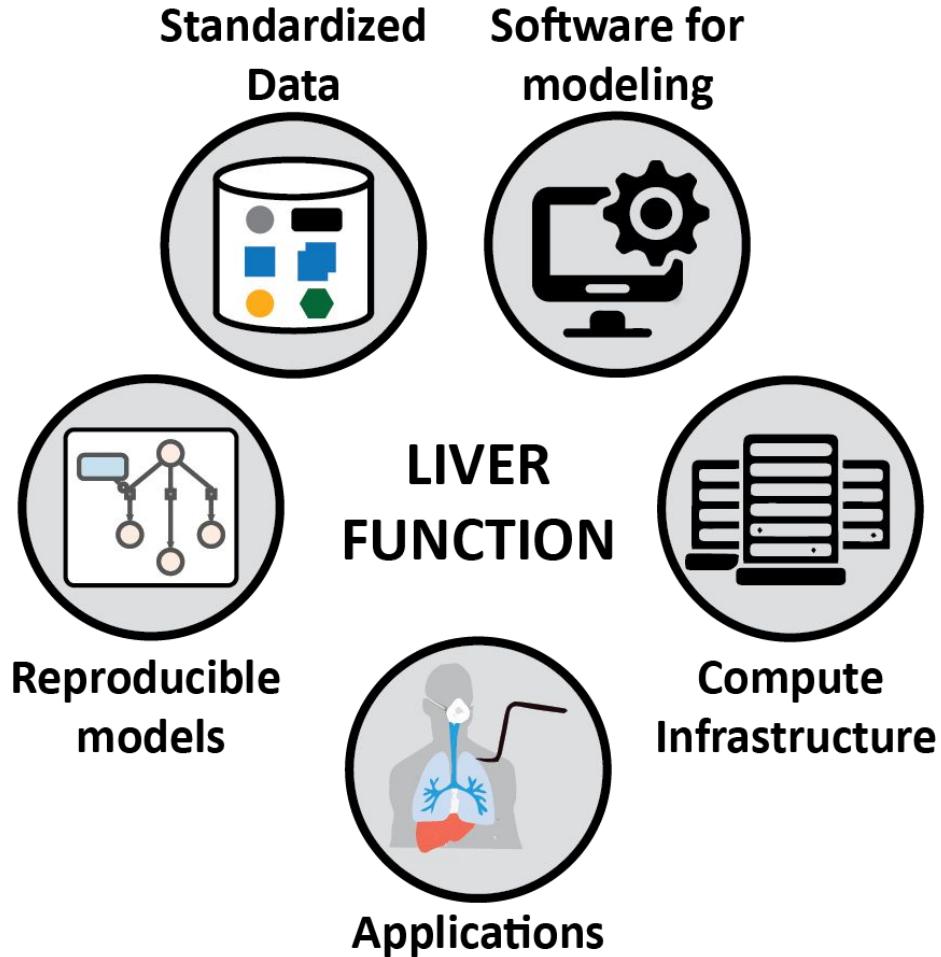
Motivation:

Physiologically Based Pharmacokinetics Models



Motivation:

Standardized Data



Our subjects were 13 normal males (age range 18 to 71 years; mean weight \pm S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight \pm S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight \pm S.D. 58.4 ± 9.6 kg) who had been on OCS for more than 6 months. Five of the 9 normal women not taking OCS were studied during the second half of their menstrual cycle and 4 during the first half. All subjects studied had a normal clinical history, physical examination, and sequential multiple analyzer of 12 vital determinations (SMA₁₂) profiles and, apart from oral contraceptives as indicated above, had taken no drugs or alcohol for at least 2 weeks prior to the study. Smokers were not included in this study.

After an overnight fast the subjects received 250 mg of caffeine (approximately equivalent to 3 cups of coffee) in a capsule with 150 ml of water.

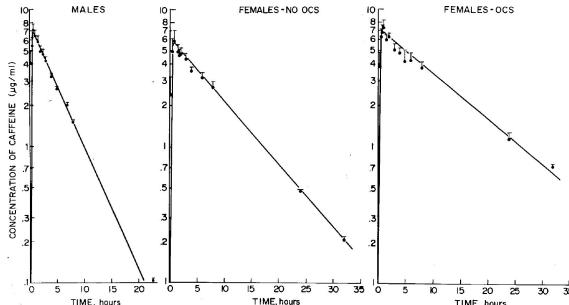


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean \pm S.E.).

Table I. Pharmacokinetic parameters of caffeine (250 mg) in males, females, and females on OCS

	Normal males (n = 13)	Normal females taking no OCS (n = 9)	Normal females on OCS (n = 9)
$t_{1/2}(\beta)$ (hr)	5.5 ± 2.6	6.2 ± 1.6	$10.7 \pm 3.0^\dagger$
$V_d(\beta)$ (L/kg)	0.54 ± 0.18	$0.69 \pm 0.16^*$	0.72 ± 0.24
$V_d(\text{extrap})$ (L/kg)	0.54 ± 0.13	$0.70 \pm 0.14^*$	0.75 ± 0.28
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	$0.79 \pm 0.21^\dagger$
Plasma binding (%)	31.4 ± 1.9	31.5 ± 4.5	29.35 ± 2.17
Plasma clearance of unbound drug (ml/min/kg)	1.8 ± 0.6	1.97 ± 0.57	$1.12 \pm 0.28^\dagger$

Values are mean \pm S.D.

* $p < 0.05$ for normal males vs females taking no OCS.

† $p < 0.001$ for females taking no OCS vs. females on OCS.

Groups



Individuals



Intervention



Our subjects were 13 normal males (age range 18 to 71 years; mean weight \pm S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight \pm S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight \pm S.D. 58.4 ± 9.6 kg) who had been on OCS for more than 6 months. Five of the 9 normal women not taking OCS were studied during the second half of their menstrual cycle and 4 during the first half. All subjects studied had a normal clinical history, physical examination, and sequential multiple analyzer of 12 vital determinations (SMA₁₂) profiles and, apart from oral contraceptives as indicated above, had taken no drugs or alcohol for at least 2 weeks prior to the study. Smokers were not included in this study.

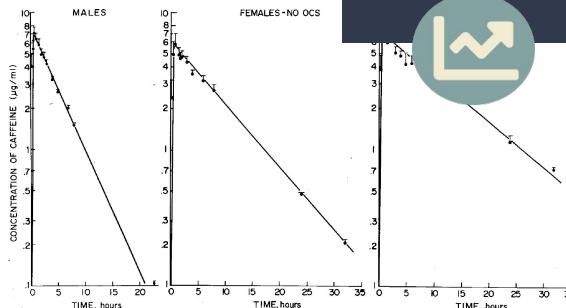


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean \pm S.E.).

After an overnight fast the subjects

received 250 mg of caffeine (approximately equivalent to 3 cups of coffee) in a capsule with 150 ml of water.

Time courses



Table I. Pharmacokinetic parameters of caffeine (250 mg) in males, females, and females on OCS

	Normal males (n = 13)	Normal females taking no OCS (n = 9)	Normal females on OCS (n = 9)
t ^{1/2} (β) (hr)	5.5 ± 2.6	6.2 ± 1.6	10.7 ± 3.0†
Vd(β) (L/kg)	0.54 ± 0.18	0.69 ± 0.16*	0.72 ± 0.24
Vd(extrap) (L/kg)	0.54 ± 0.13	0.70 ± 0.14*	0.75 ± 0.28
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Values are mean \pm S.D.

*p < 0.05 for normal males vs females taking no OCS.

†p < 0.001 for females taking no OCS vs. females on OCS.

Outputs

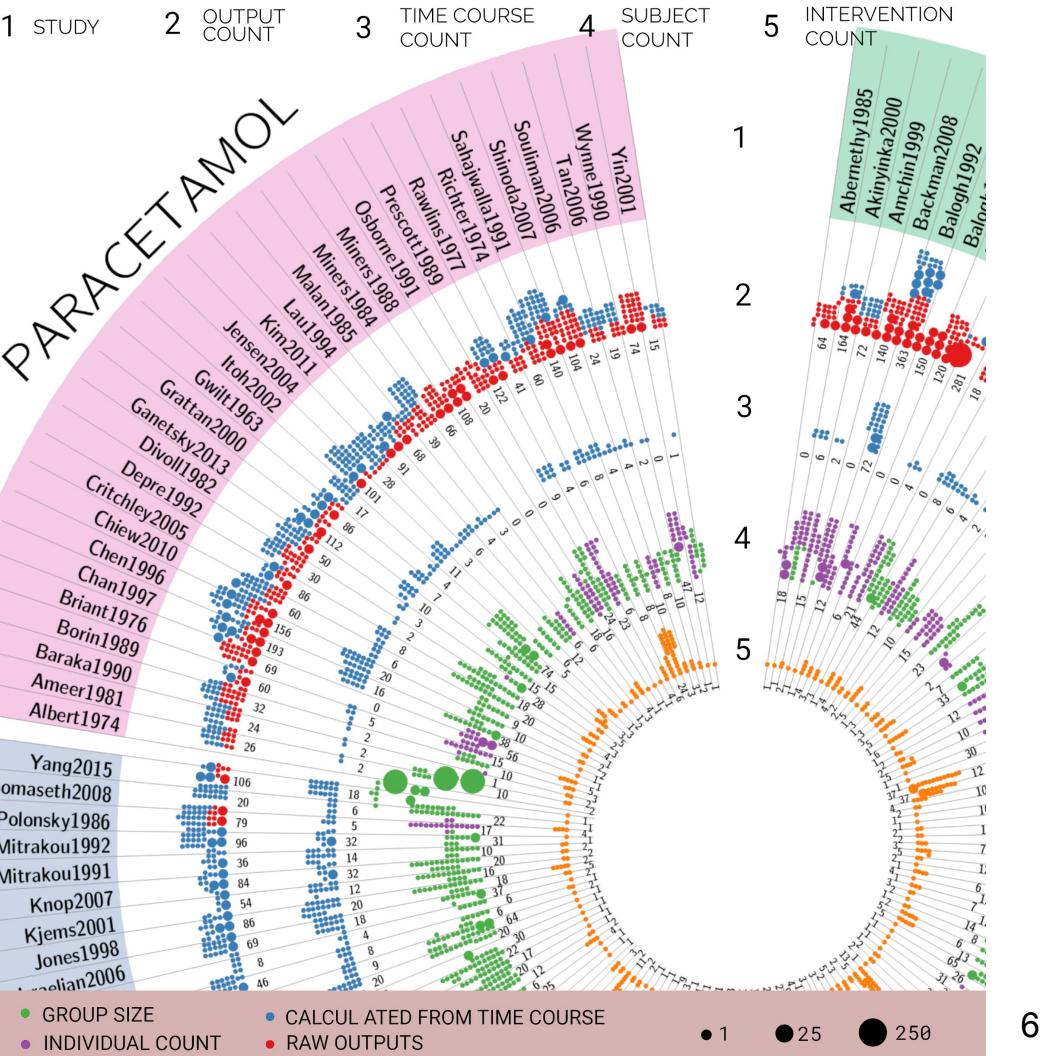


Live Demonstration

Overview:

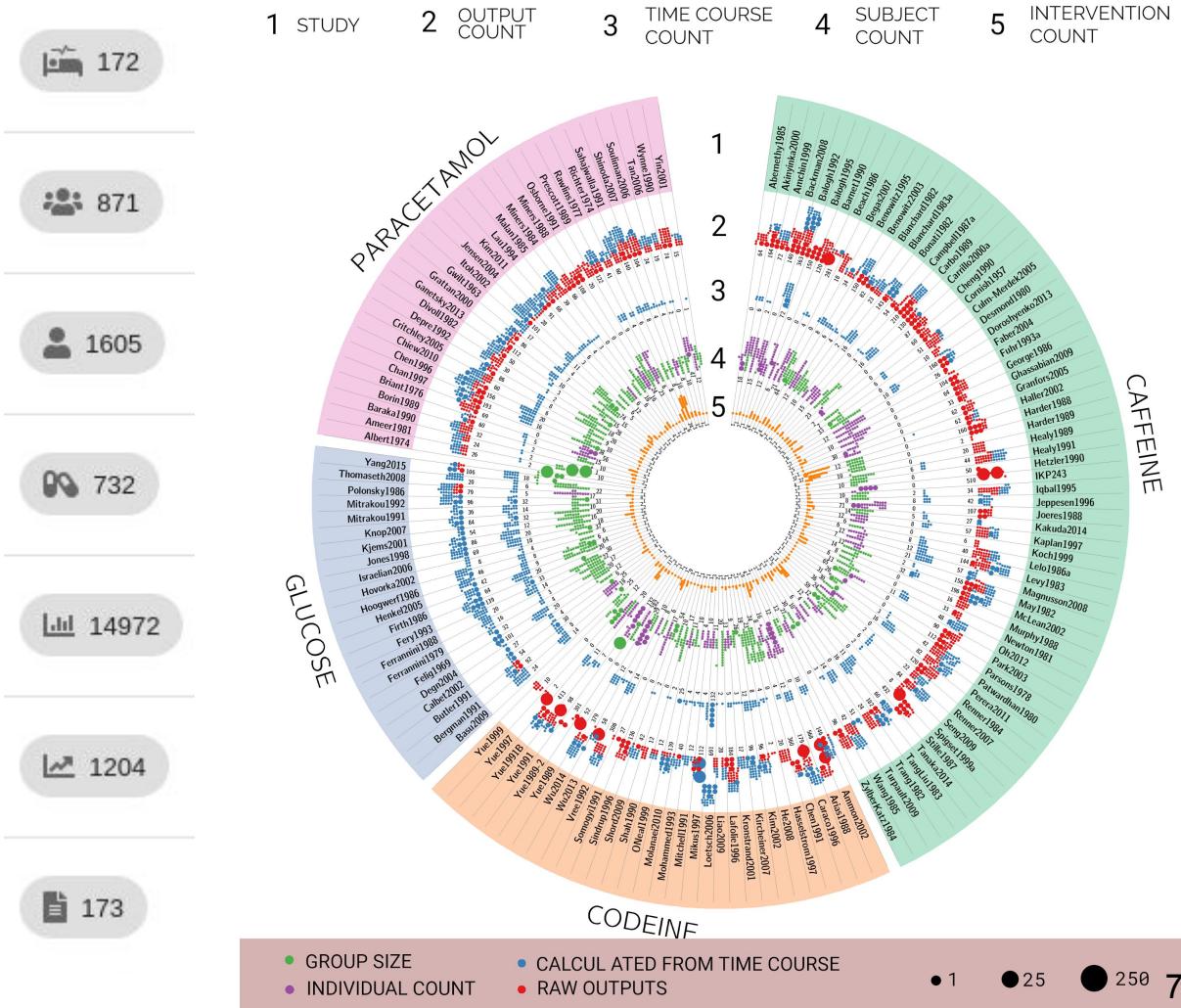
Studies

Jan Grzegorzewski & Matthias König. (2019, May).
matthiaskoenig/pkdb: PKDB
Zenodo. <http://doi.org/10.5281/zenodo.2670026>
Manuscript in preparation



Overview:

Studies



Meta-Analysis:

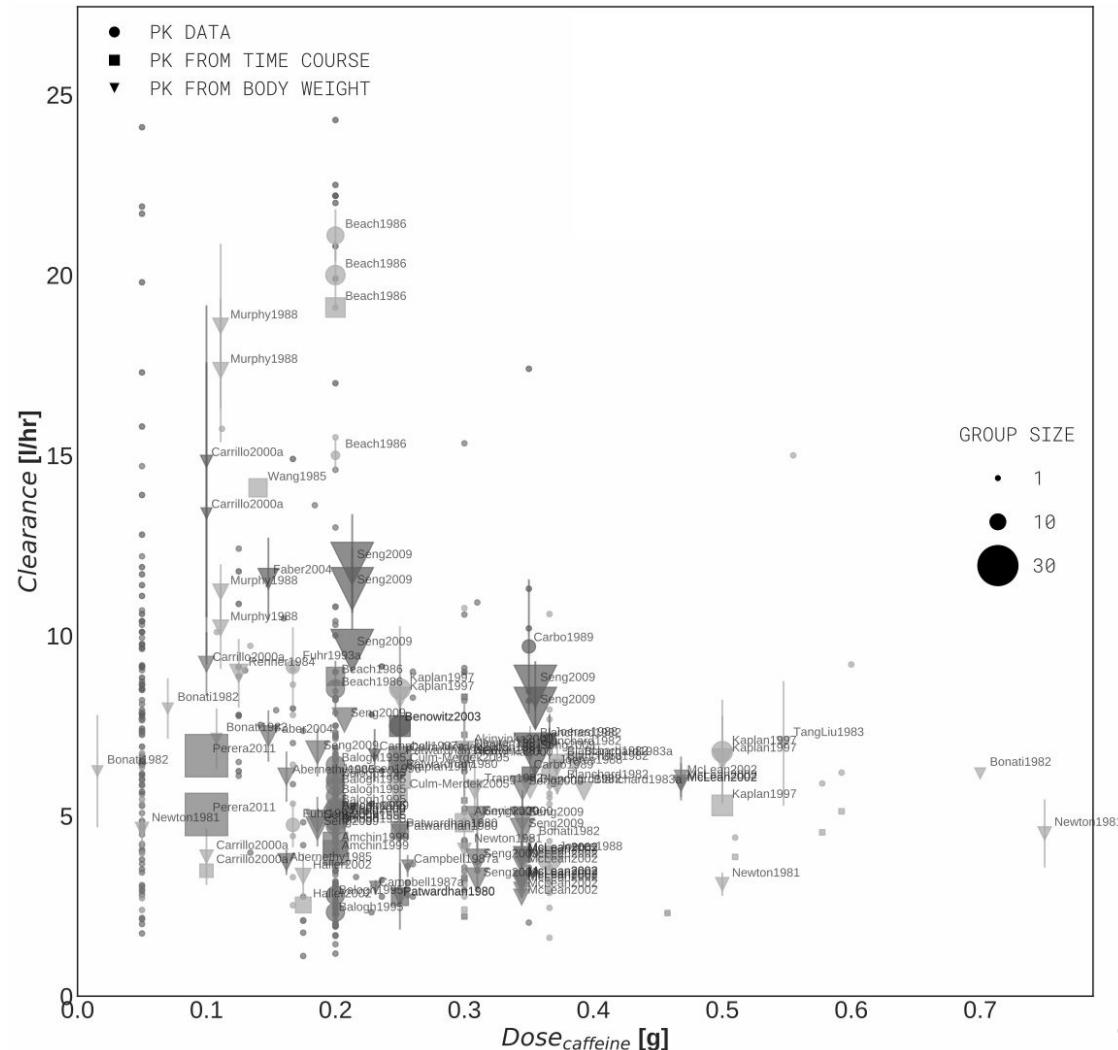
Caffeine Clearance

Open Challenges:

Large Inter-Individual variability of clearance

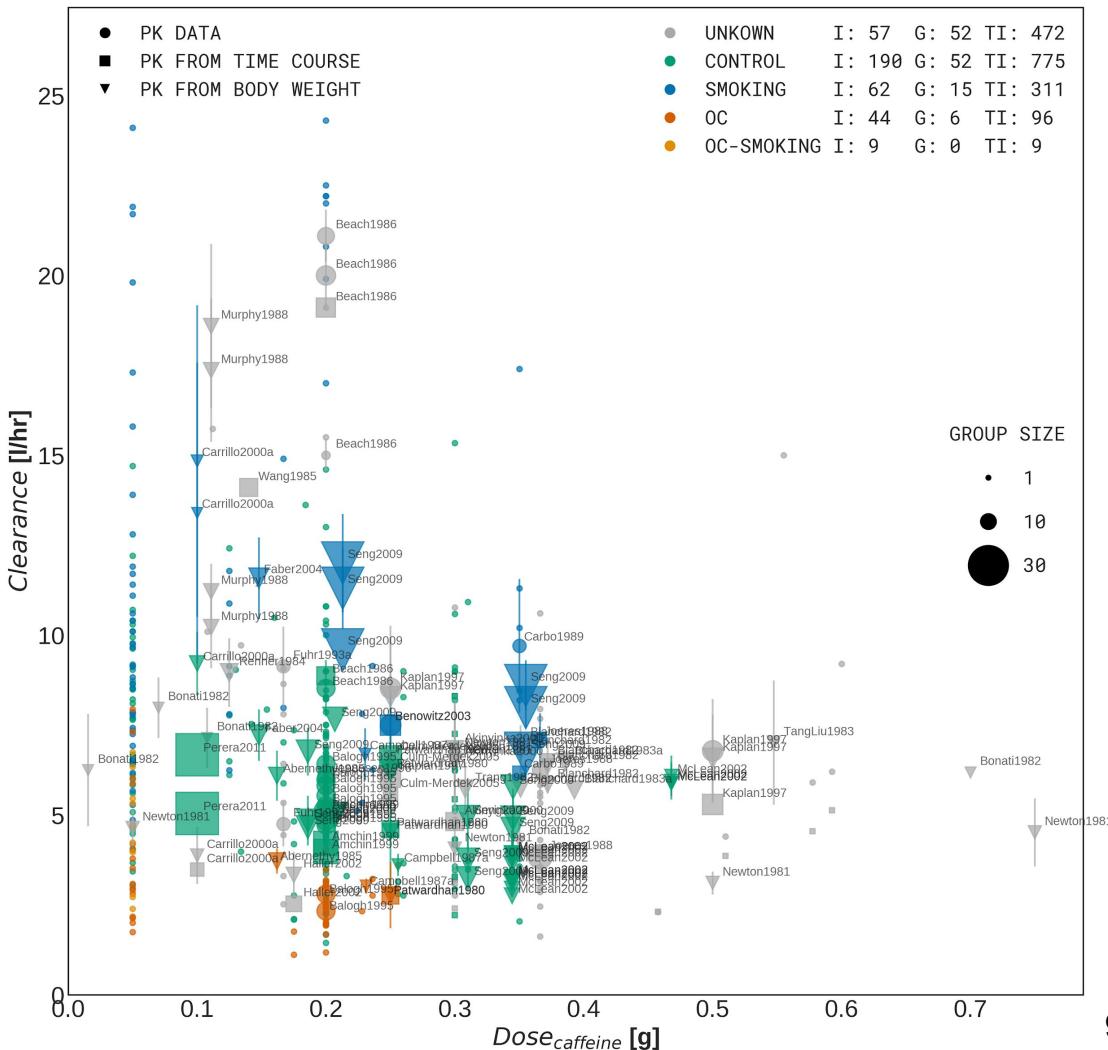
Dose dependency of clearance

Jan Grzegorzewski & Matthias König. (2019, May).
matthiaskoenig/pkdb: PKDB
Zenodo. <http://doi.org/10.5281/zenodo.2670026>
Manuscript in preparation



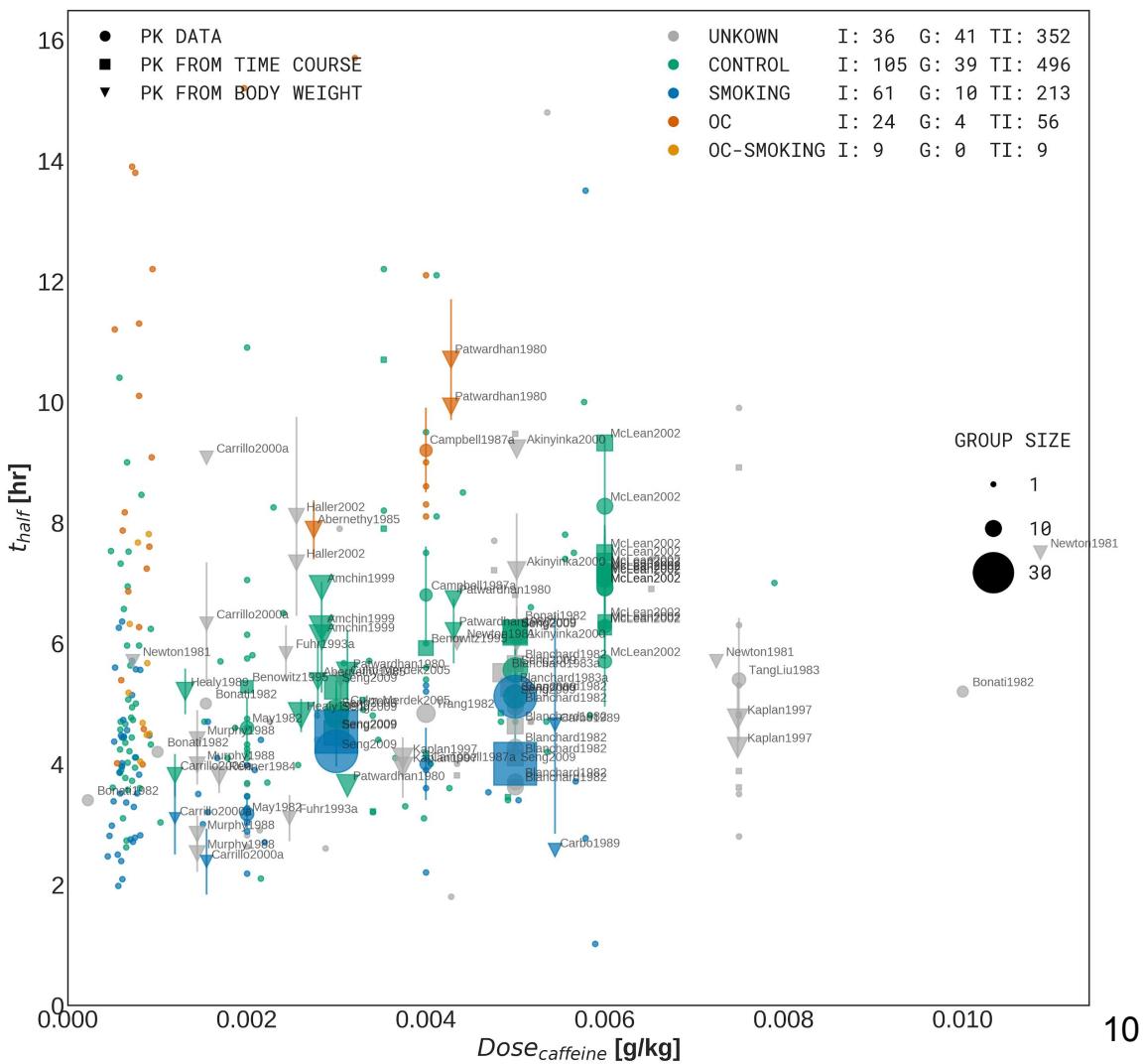
Meta-Analysis: Caffeine Clearance

Jan Grzegorzewski & Matthias König. (2019, May).
matthiaskoenig/pkdb: PKDB
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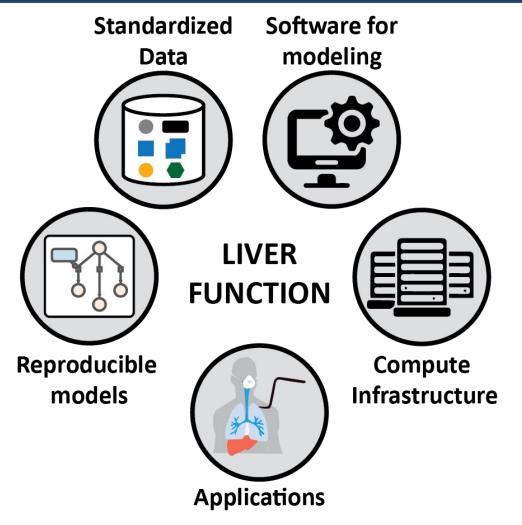


Meta-Analysis: Caffeine Half-lives

Jan Grzegorzewski & Matthias König. (2019, May).
 matthiaskoenig/pkdb: PKDB
 Zenodo. <http://doi.org/10.5281/zenodo.2670026>
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Summary



First open database for pharmacokinetic data

integrates meta information for individualization & stratification
(*e.g. smoking status, body weight, medication*)

automatic normalization of data
(*e.g. unit conversion, calculation of pharmacokinetic parameters from time courses*)

validation rules to ensure high quality data and comparability

simple interactive and collaborative curation workflow

Work in Progress

Automatic integration with computational models
(*parameter fitting, model calibration, model validation*)

Acknowledgement



Humboldt University Berlin
Dr. Matthias König



Humboldt University Berlin
Janosch Brandhorst



Dimitra Eleftheriadou



Kathleen Green

Dr. Wünsch & Prof. Stockmann (LiSym, Pillar IV)

Charite Berlin, Department of General, Visceral and Transplantation Surgery

Dr. Hofmann & Orif. Schwab (LiSym, Pillar I)

Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology,
Stuttgart

Daniel Lill & Prof. Timmer (LiSym, Pillar II)

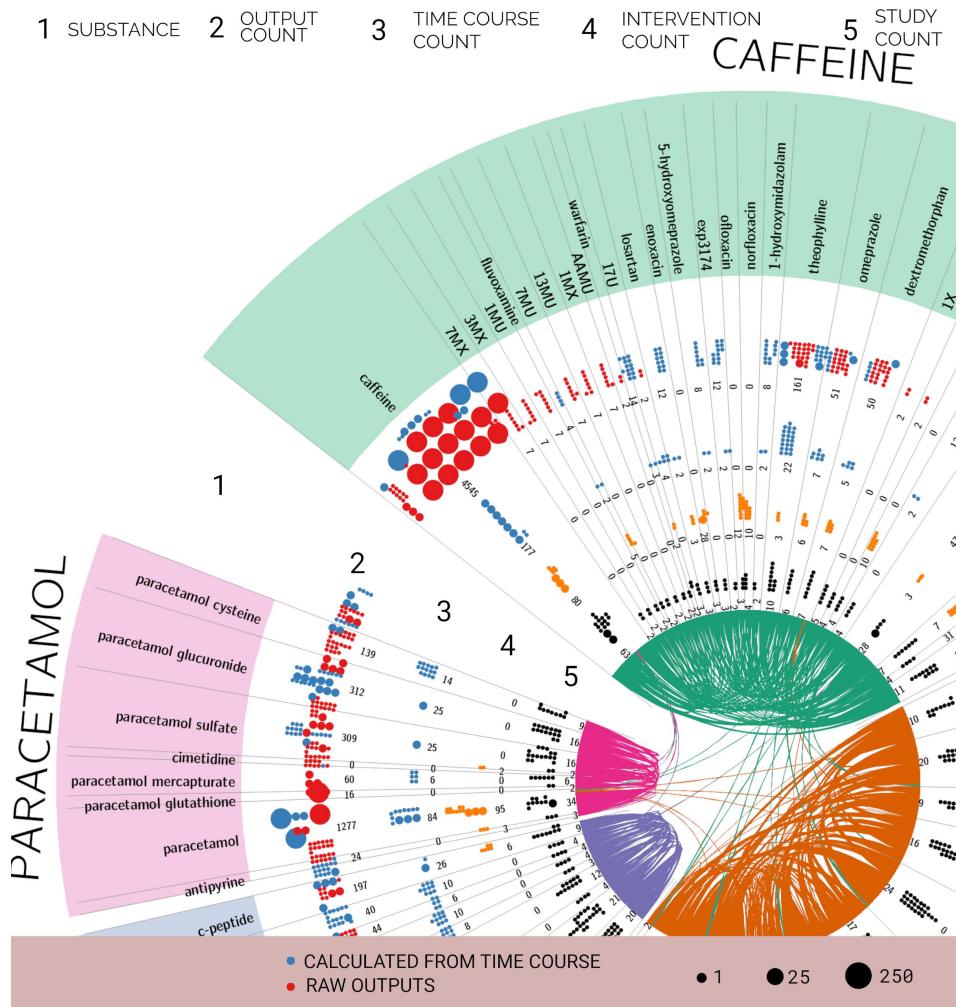
University of Freiburg, Institute of Mathematics

Thank You For
Your Attention



Federal Ministry
of Education
and Research

Overview: **Substances**



Jan Grzegorzewski & Matthias König. (2019, May).
matthiaskoenig/pkdb: PKDB
Zenodo. <http://doi.org/10.5281/zenodo.2670026>
Manuscript in preparation