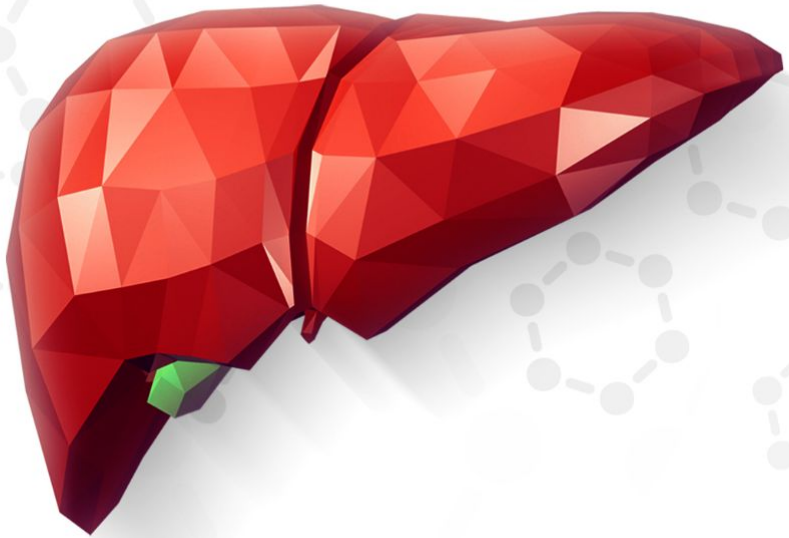
PK-DB: A Pharmacokinetics Database for Individualized and Stratified Computational Modelling

Jan Grzegorzewski

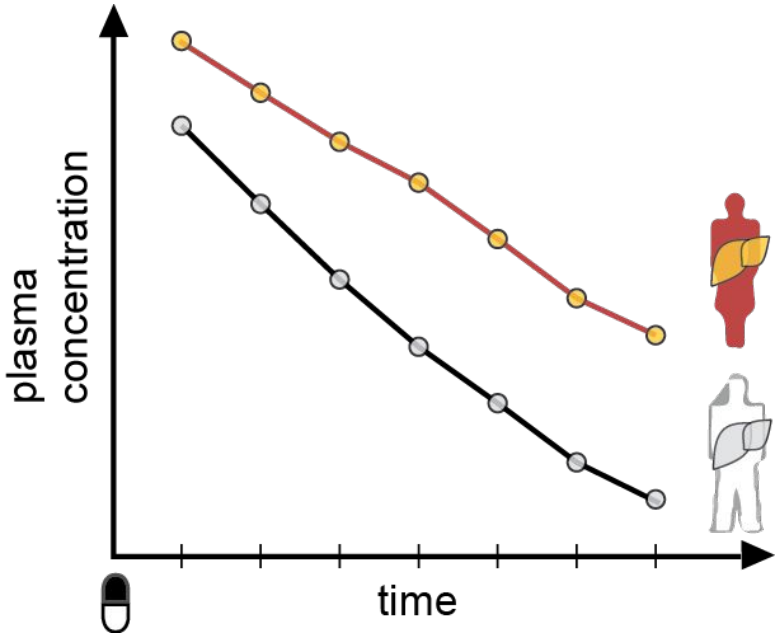


Bundesministerium
für Bildung
und Forschung

LiSyM
Liver Systems Medicine

Motivation:

Dynamical Liver Function Tests



Liver specific clearance of test substances

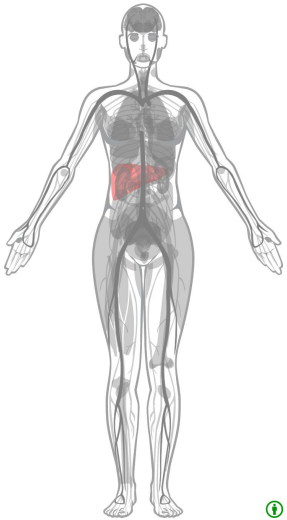
- Rate of (dis-) appearance as proxy for liver function
- e.g. caffeine, paracetamol, codeine

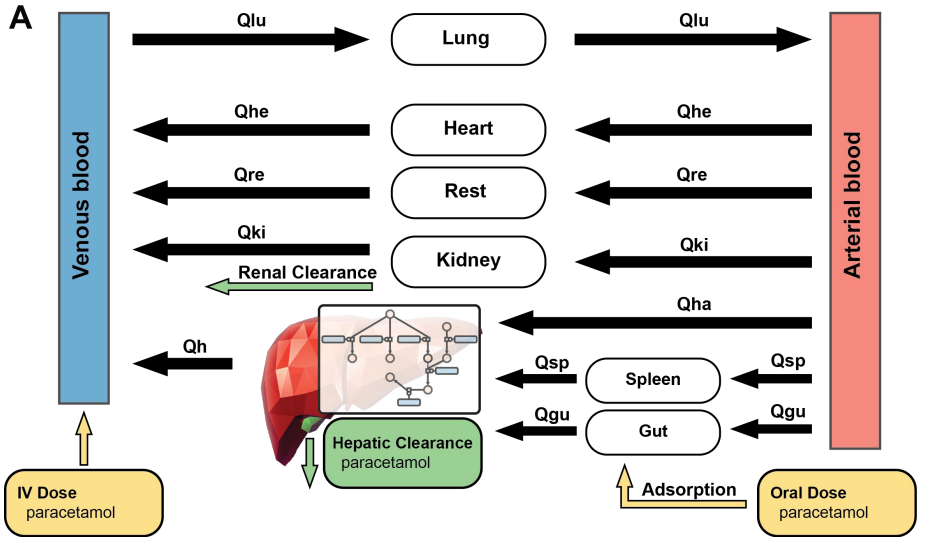
Challenges

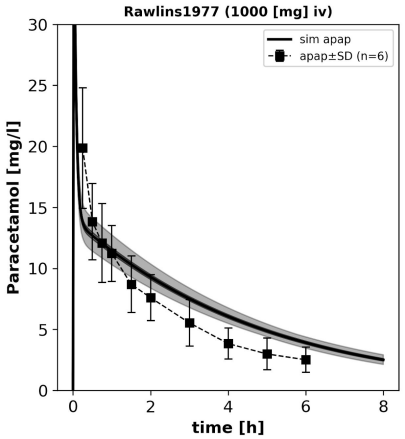
- High interindividual variability
- Dose dependency

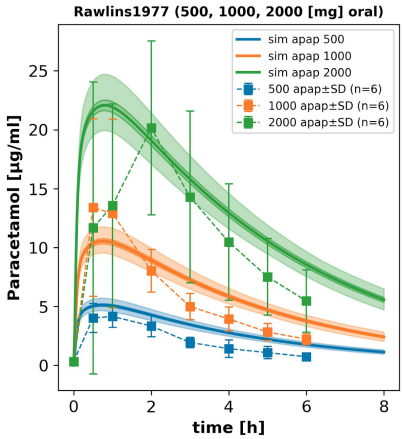
Motivation:

Physiologically Based Pharmacokinetics Models



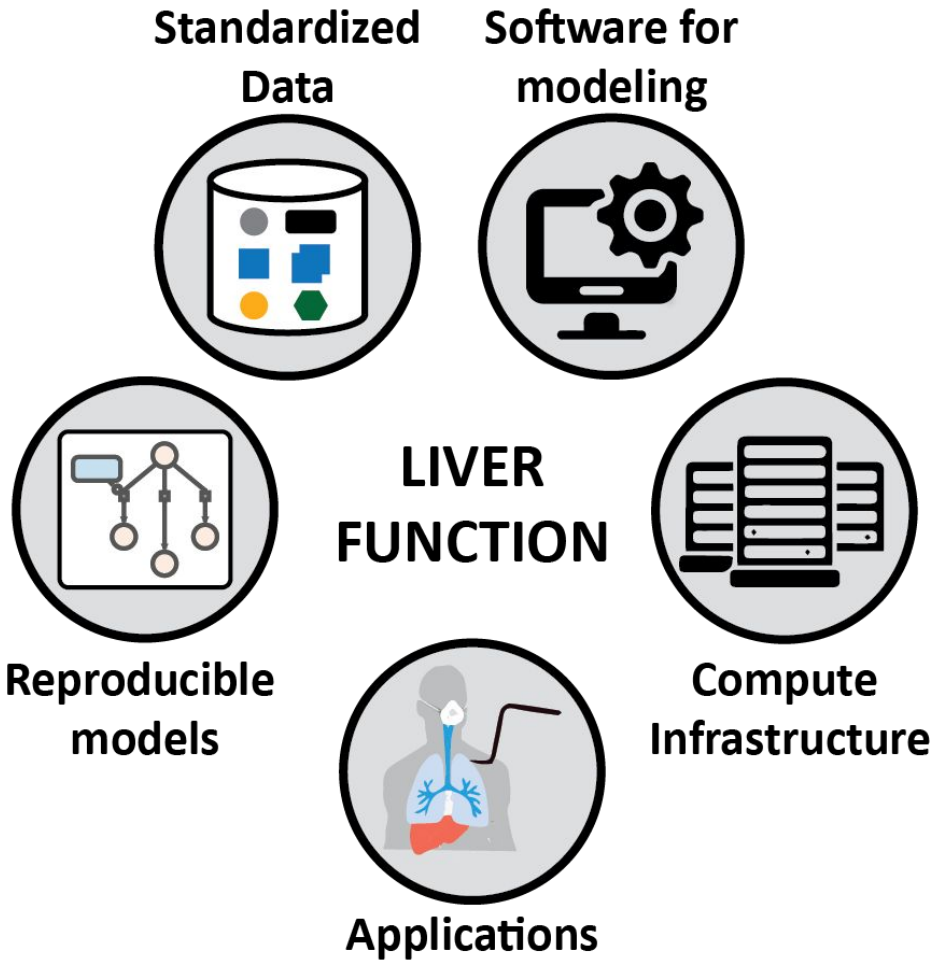






Motivation:

Standardized Data



Our subjects were 13 normal males (age range 18 to 71 years; mean weight ± S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight ± S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight ± 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 (SMA_{12}) 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.

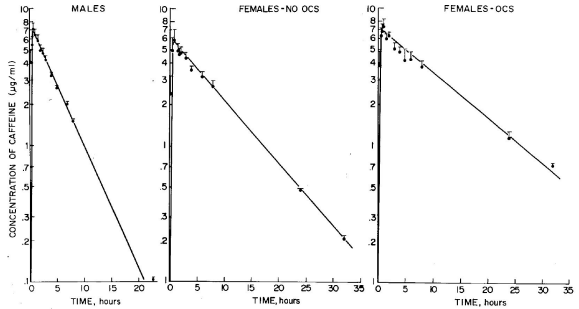


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

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)
$t½_{(\beta)}$ (hr)	5.5 ± 2.6	6.2 ± 1.6	10.7 ± 3.0†
$Vd_{(\beta)}$ (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
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	0.79 ± 0.21†
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 ± 0.28†

Values are mean ± 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 ± S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight ± S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight ± 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 (SMA_{12}) 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.

Time courses

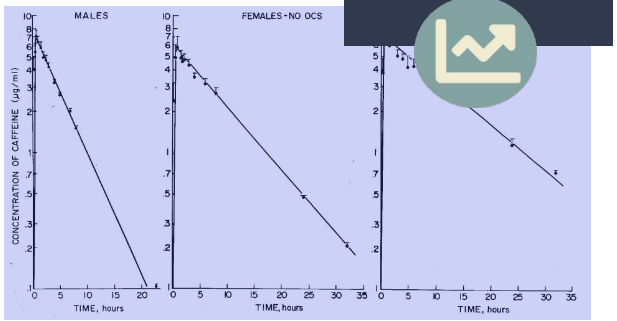


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

Outputs

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)
$t½_{(\beta)}$ (hr)	5.5 ± 2.6	6.2 ± 1.6	10.7 ± 3.0†
$Vd_{(\beta)}$ (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
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	0.79 ± 0.21†
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 ± 0.28†

Values are mean ± 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.

Live Demonstration

Overview:

Studies

329

869

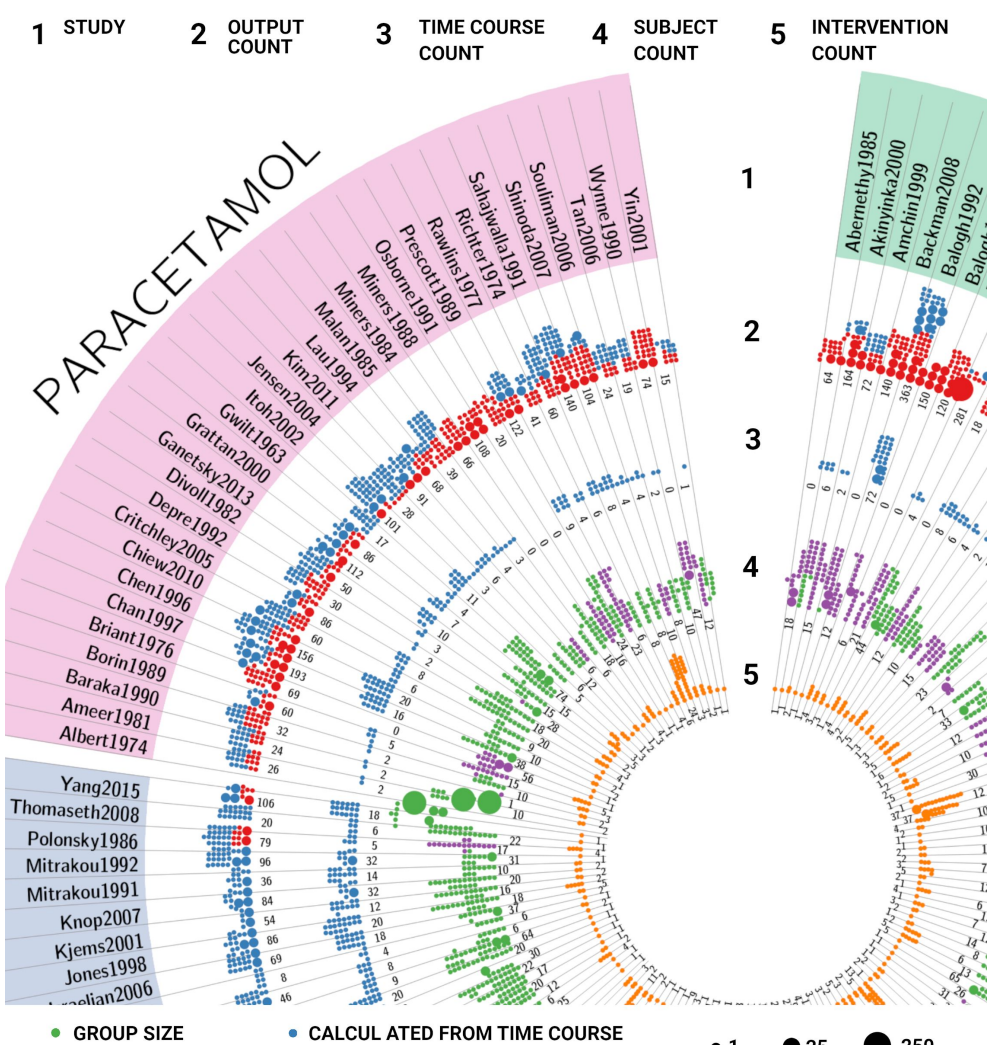
3785

992

28293

2186

330



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

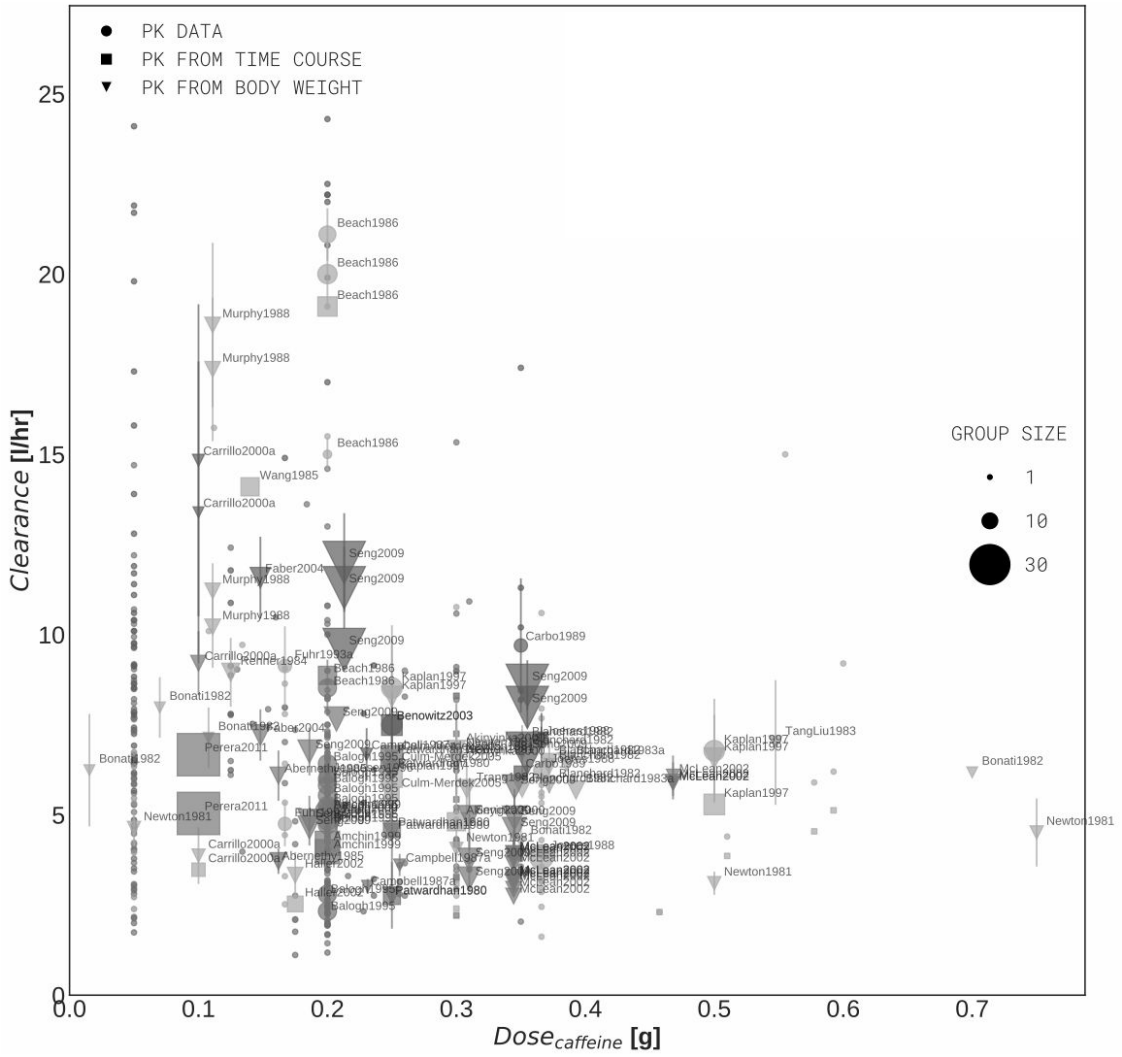
Meta-Analysis:

Caffeine Clearance

Open Challenges:

Large Inter-Individual variability of clearance

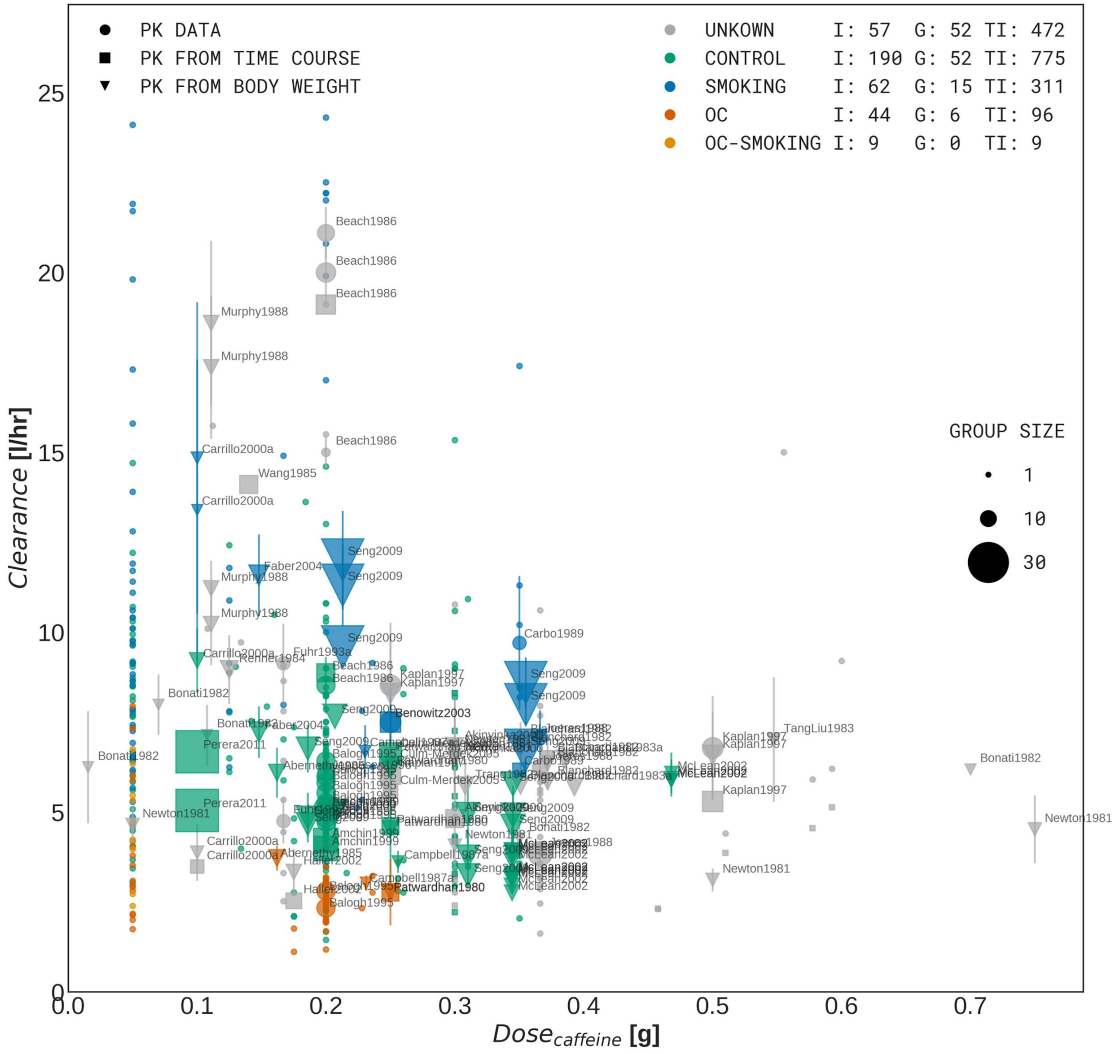
Dose dependency of clearance



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

Meta-Analysis:

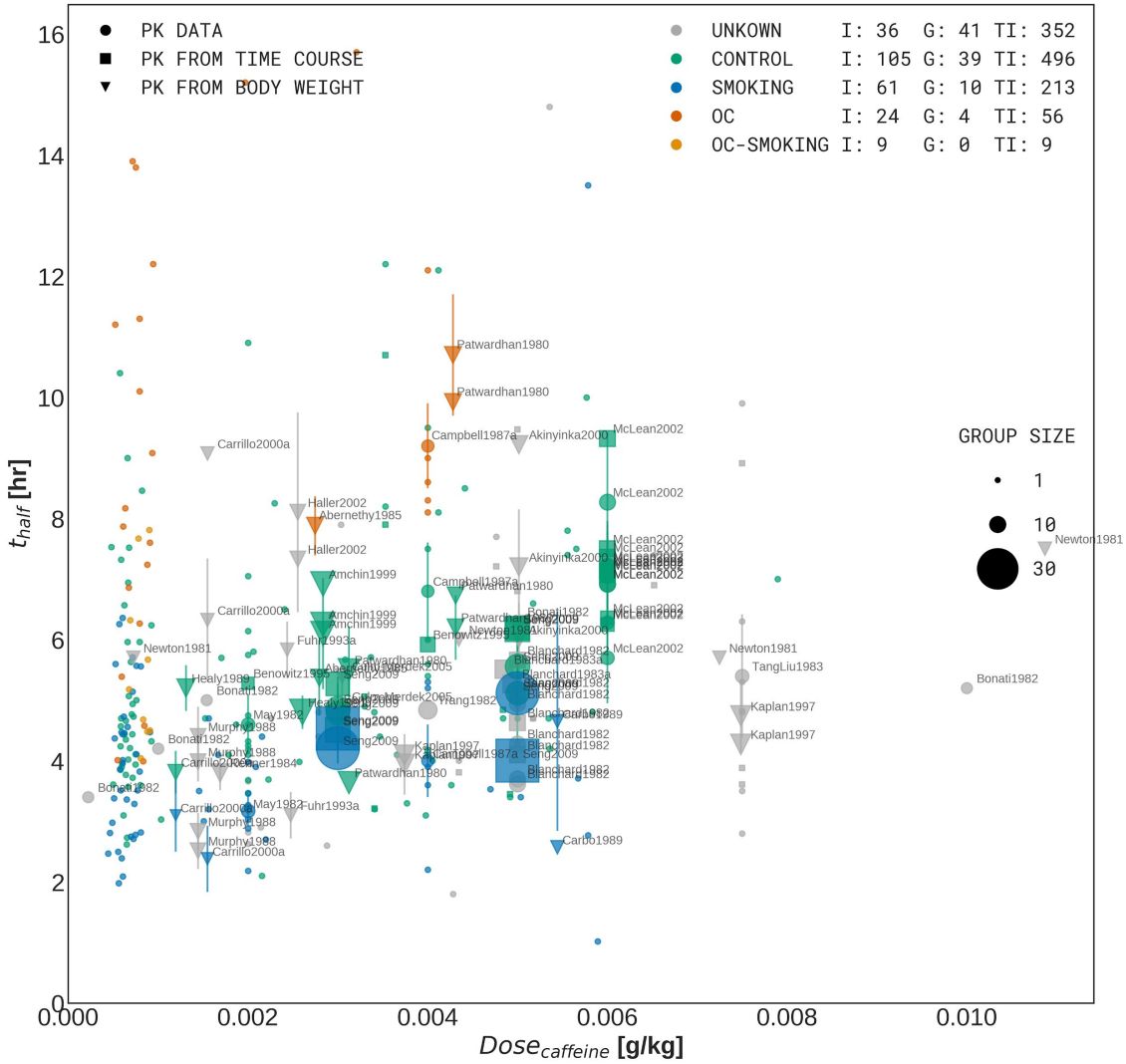
Caffeine Clearance



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

Meta-Analysis:

Caffeine Half-lives



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

Model Integration:

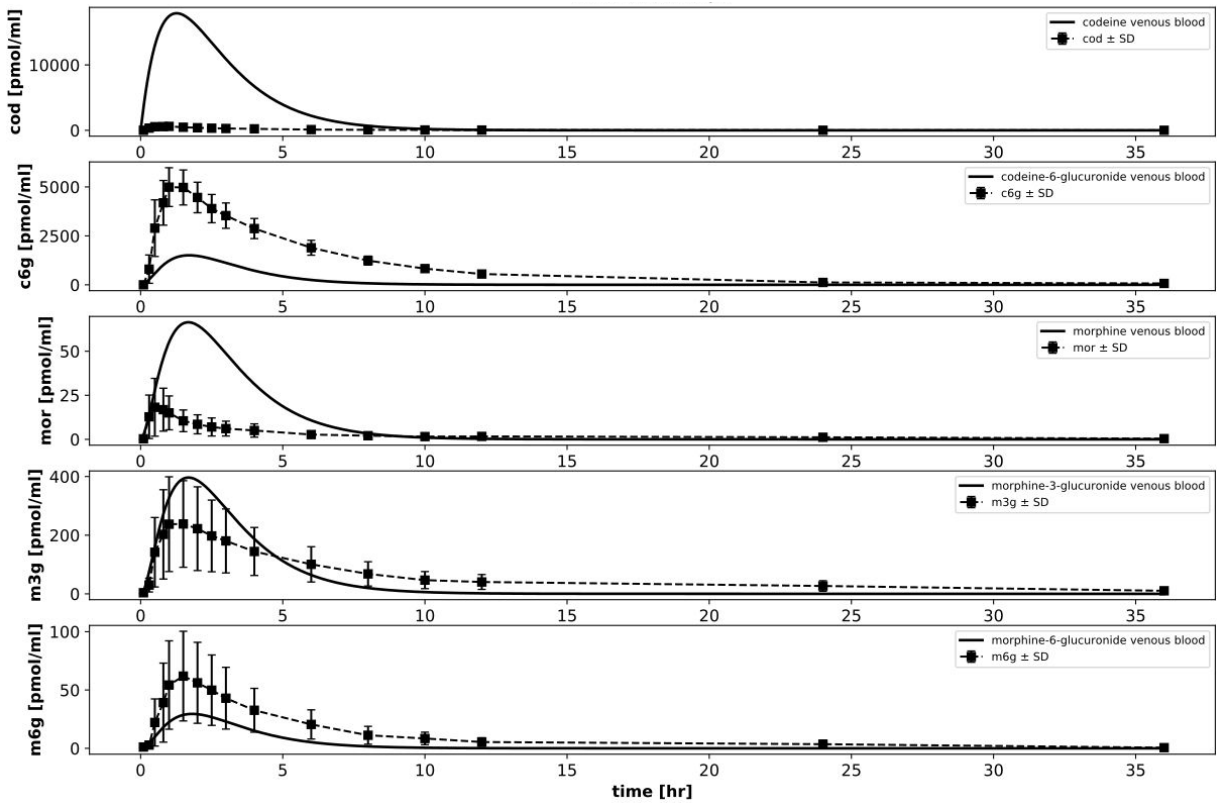
Codeine Simulation Experiment

Description:

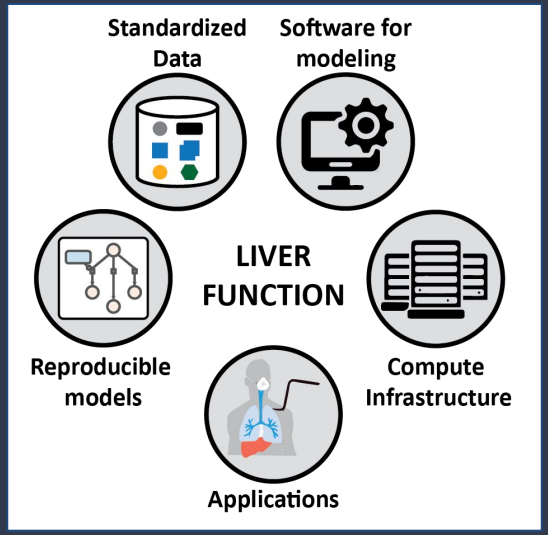
12 healthy volunteers received a single oral dose of 100 mg codeine phosphate as a tablet.

Work in Progress

Ammon2002



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

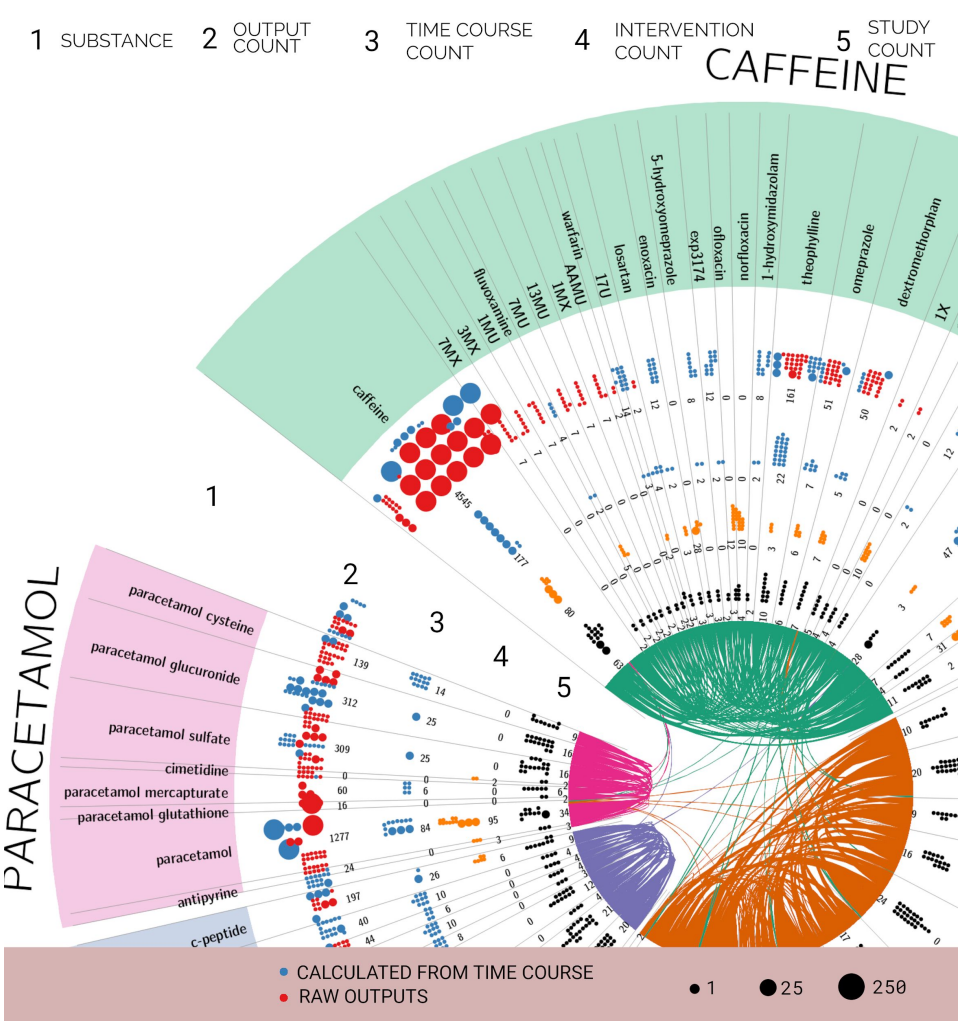
Thank You For
Your Attention

LiSyM
Liver Systems Medicine

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

Data Representation:

Interactive Data Curation

```
(pkdb_data) mkoenig@prime1:~/git/pkdb_data$ watch_study -s ./studies/acetaminophen/Renner2007/
INFO ------------------------------------------------------------------------------
INFO Watching [Renner2007]
INFO     /home/mkoenig/git/pkdb_data/studies/acetaminophen/Renner2007
INFO ------------------------------------------------------------------------------
INFO - 0.11 [s] : Upload references
INFO - 0.13 [s] : Upload files
INFO - 0.08 [s] : Upload core study
INFO - 0.05 [s] : Upload groups
INFO - 0.00 [s] : Upload individuals
INFO - 0.00 [s] : Upload study
INFO - 0.05 [s] : Index study
INFO ------------------------------------------------------------------------------
INFO http://0.0.0.0:8000/api/v1/studies/17442681/
INFO UPLOAD SUCCESSFUL ( http://0.0.0.0:8080/#/studies/17442681 )
INFO ------------------------------------------------------------------------------
```

```
INFO ------------------------------------------------------------------------------
INFO Updating [Renner2007]
INFO ------------------------------------------------------------------------------
INFO - 0.13 [s] : Upload references
INFO - 0.26 [s] : Upload files
INFO - 0.12 [s] : Upload core study
WARNING
{
  "groupset": {
    "group_exs": [
      {},
      {},
      {
        "groups": [
          {
            "characteristica": [
              {},
              {
                "non_field_errors": [
                  "{'unit': 'For measurement type 'weight' the unit [mol] with dimension [substance] is not allowed.', 'Only units with the following dimensions are allowed:': ['[mass]'], 'Units are allowed which can be converted to the following normalized units:': <QuerySet ['kg']>}"
                ]
              }
            ]
          }
        ]
      }
    ]
  }
}
INFO - 0.16 [s] : Upload groups
INFO - 0.08 [s] : Upload individuals
INFO - 0.08 [s] : Upload study
INFO - 0.10 [s] : Index study
INFO ------------------------------------------------------------------------------
ERROR UPLOAD ERROR (check error and warnings above)
INFO ------------------------------------------------------------------------------
```

Project

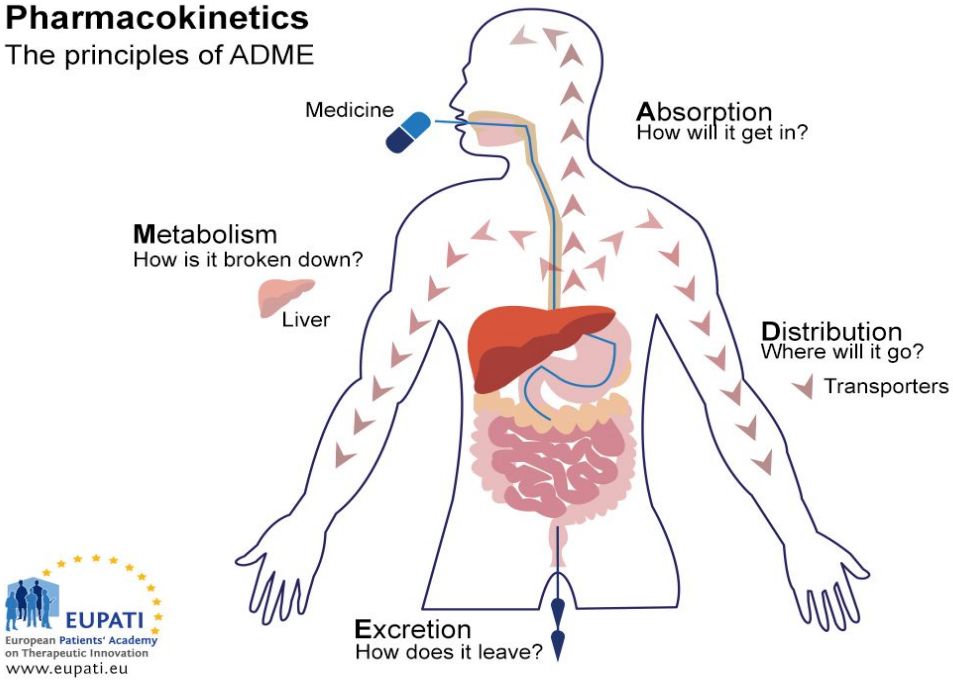
- Renner2007
  - reference.json
  - Renner2007_Fig4.png
  - Renner2007_Fig4.tsv
  - Renner2007_Tab1.png
  - Renner2007_Tab1.tsv
  - Renner2007.pdf
  - Renner2007.xlsx
  - study.json

study.json


```
            "max": 86,
            "median": 75,
            "unit": "kg"
          }
        ]
      },
      {
        "count": 12,
        "name": "women",
        "parent": "all",
        "characteristica": [
          {
            "measurement_type": "sex",
            "choice": "F"
          },
          {
            "measurement_type": "weight",
            "min": 51,
            "max": 66,
            "median": 57,
            "unit": "kg"
          }
        ]
      }
    ]
  },
  "individualset": {
    "descriptions": [],
    "comments": [],
    "individuals": []
  },
  "interventionset": {
    "descriptions": [
      "Each subject received a single dose of 1000 mg acetaminophen (Panadol), 130 mg caffeine, 1000 mg acetaminophen plus 130 mg caffeine (Panadol Extra), or placebo, taken with 150 mL of water, after fasting for 6 hours.",
      "Subjects remained fasted but were allowed to drink water during the study period. The washout periods between drug administrations were at least 6 days."
    ],
    "comments": [],
    "interventions": [
      {
        "name": "acetaminophen",
        "substance": "paracetamol",
        "route": "oral",
        "form": "tablet",
        "application": "single dose",
        "measurement_type": "dosing",
        "value": "1000",
        "unit": "mg",
        "time": "0",
        "time_unit": "hr"
      },
      {
        "name": "caffeine",
        "substance": "caffeine",
        "route": "oral",
        "form": "tablet",
        "application": "single dose",
        "measurement_type": "dosing",
        "value": "130",
        "unit": "mg",
        "time": "0",
        "time_unit": "hr"
      }
    ]
  },
  "outputset": {
    "descriptions": [
      "Peak plasma concentrations (Cmax) and time to peak concentration (tmax) were obtained from individual plasma data. Each AUC 0-t was calculated using the linear trapezoidal method for ascending concentrations and the log-trapezoidal method for descending concentrations.34
    ],
    "comments": [],
    "outputs": [
      {
        "group": "all",
        "groupby": "intervention & pktype",
        "interventions": "col==intervention",
        "source": "Renner2007_Tab1.tsv",
        "format": "TSV",
        "figure": "Renner2007_Tab1.png",
        "substance": "paracetamol",
        "tissue": "col==tissue",
        "measurement_type": "col==pktype",
        "time": "col==time",
```

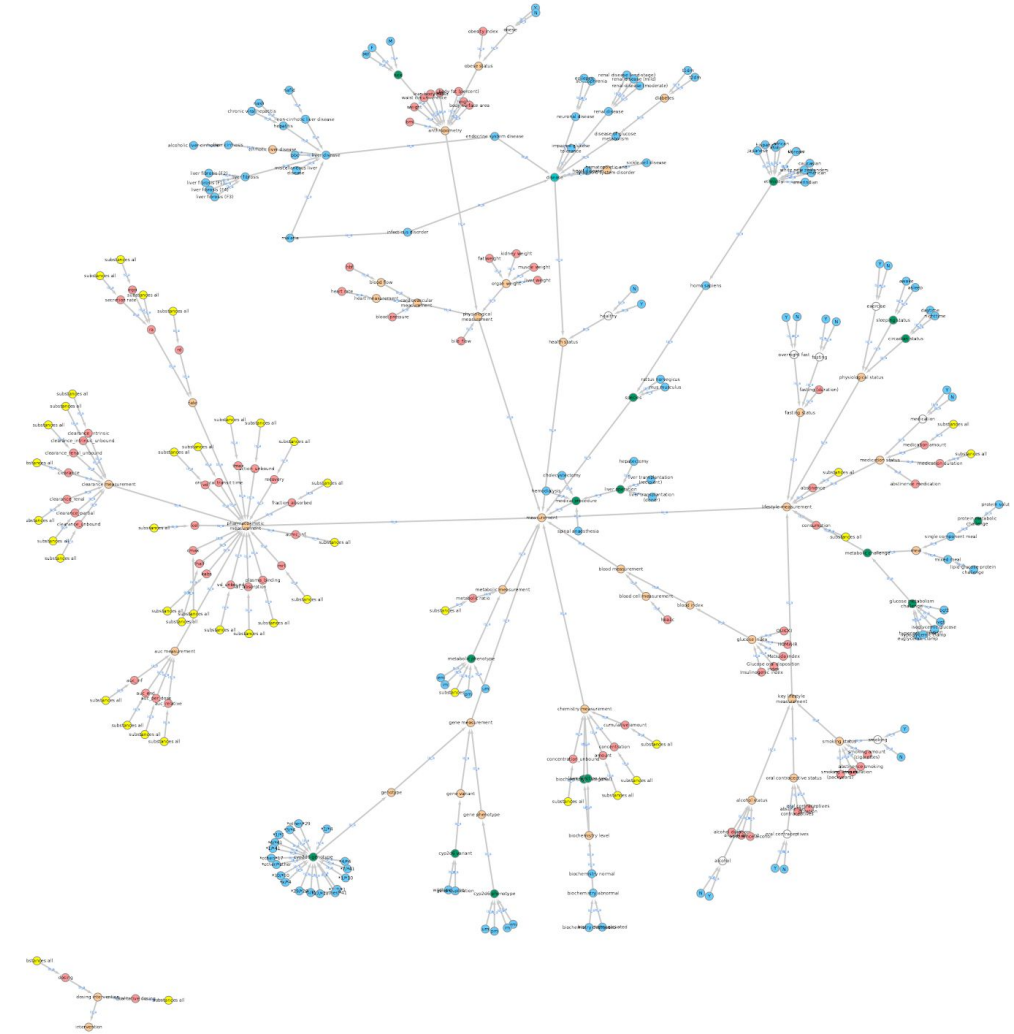
Motivation:

Pharmacokinetics



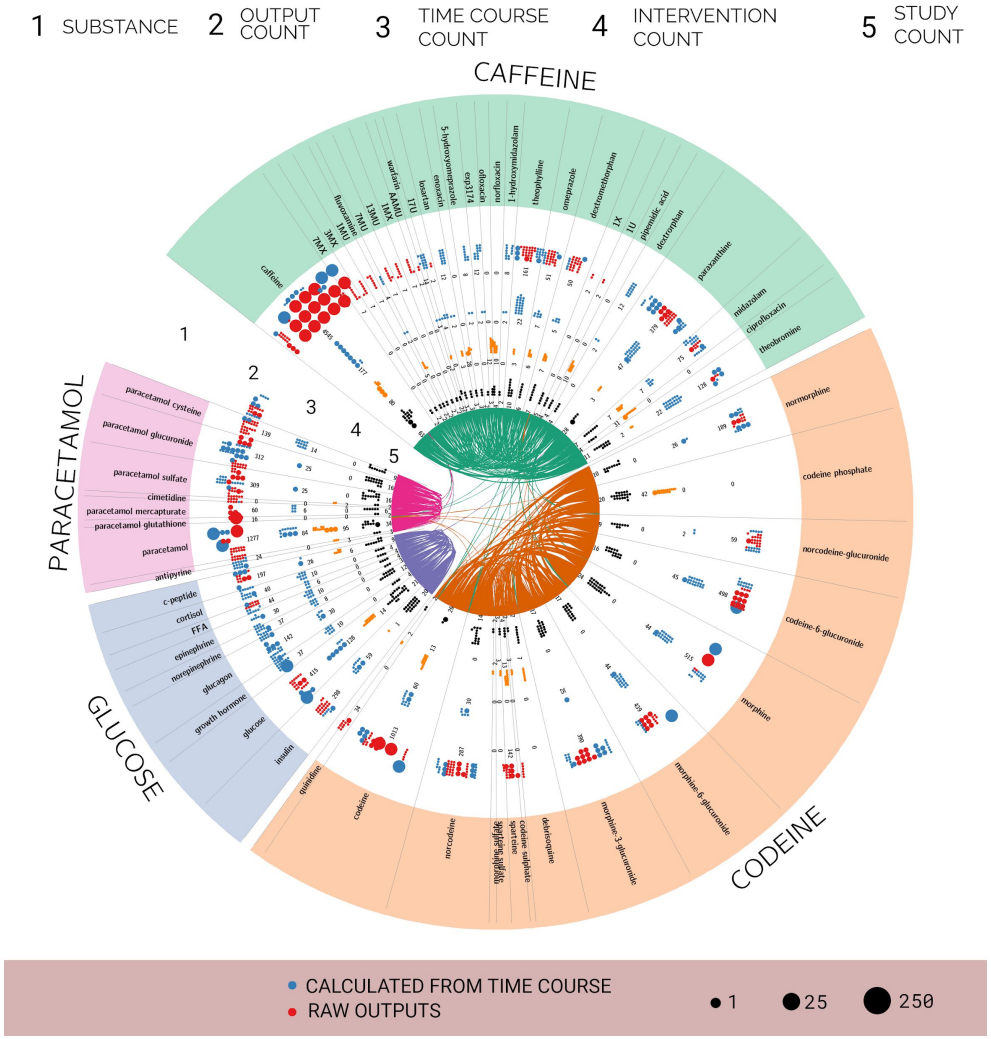
Supplement:

Overview of Measurement Types



Overview:

Substances



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

Data Representation:

Data Model

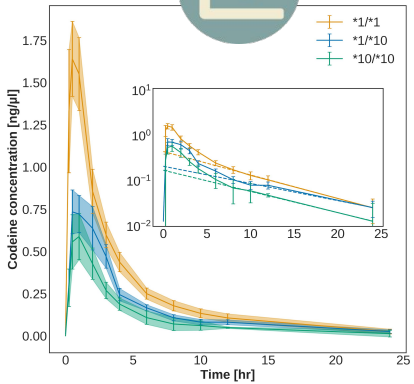
Live Demonstration

Groups

Individuals

Interventions

Time courses



Outputs

Paracetamol	
C_{max} (µg · ml^{-1})[a]	22.5 (20.3–28.5)
t_{max} (h)[a]	0.75 (0.5–1.5)
AUC_{∞} (µg · ml^{-1} · h)	85.0 (72.6–97.4)
$t_{1/2}$ (h)	2.31 (1.88–2.74)
CL_R (ml · min^{-1})[a]	12.8 (9.5–16.5)*
Actual conc. at 24 h	0.18 (0.10–0.27)
Extrapolated conc. at 24 h	0.04 (0.00–0.07)
Cysteine	
$t_{1/2}$ (h)[a]	11.3 (5.68–19.7)
AUC_{∞} (µg · ml^{-1} · h)[a]	4.54 (3.32–8.54)
C_{max} (µg · ml^{-1})[a]	0.30 (0.21–0.36)**
CL_R (ml · min^{-1})[a]	18.2 (9.1–20.4)**

Supplement:

Co-occurrence Clustering