Reproducible Digital Twins
for Personalized & Stratified Treatment

Prof. Dr. Matthias König

Systems Medicine, Digital Twins & AI
https://livermetabolism.com

Metabolic Inflammation and Carcinogenesis of the Liver
University Hospital Schleswig Holstein, Campus Lübeck, First Department of Medicine
Head of Systems Medicine of the Liver Lab
Humboldt-Universität zu Berlin, Institute of Biology

2026-08-25, EKF MSG Seminar Series

We build open, FAIR **digital twins** of human physiology —
AI-powered models that predict disease and therapy, patient by patient.

Digital Twins

Physiologically based models that mirror individual patients, from molecule to whole body.

AI

Mechanistic modeling meets machine learning for predictive, personalized medicine.

Digital Pathology

AI-driven analysis of whole-slide histology to quantify liver structure and disease at scale.

Pharmacometrics

Physiologically based pharmacokinetic/ pharmacodynamic models for precision dosing.

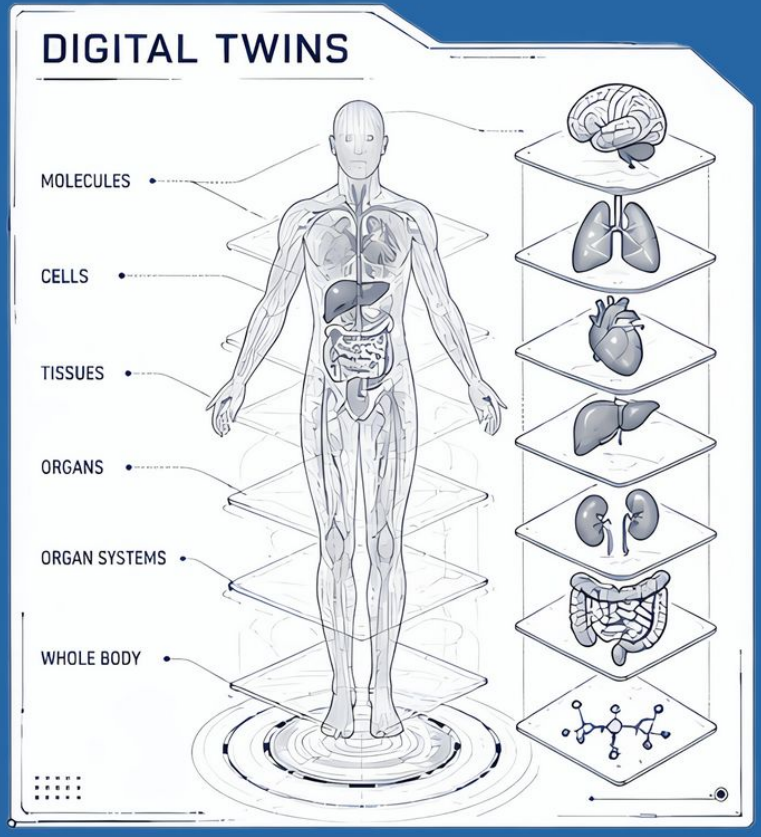
Open & FAIR

Reproducible, standardized models and data that the community can build on.

Digital Twins

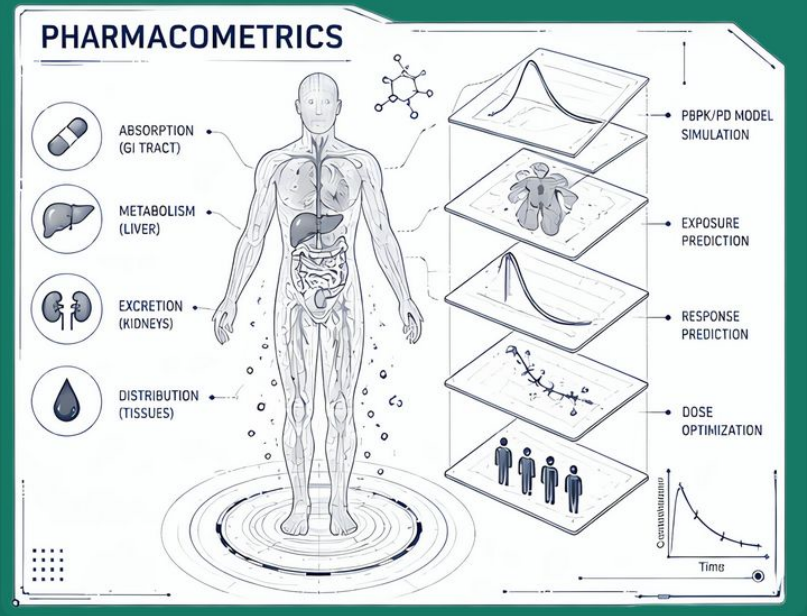
Physiologically based models that mirror individual patients, from molecule to whole body.

Every patient becomes a model. We build physiologically based digital twins — living simulations that mirror an individual from molecule to whole body — so care can be planned before it is given.



Digitaler Zwilling

- Eine **virtuelle Repräsentation eines Patienten**, die multidimensionale, patientenspezifische Informationen enthält.
- **Mechanistische Computermodelle**, die mit Patientendaten personalisierte Vorhersagen erlauben.
- Dient zur **Unterstützung medizinischer Entscheidungen**.

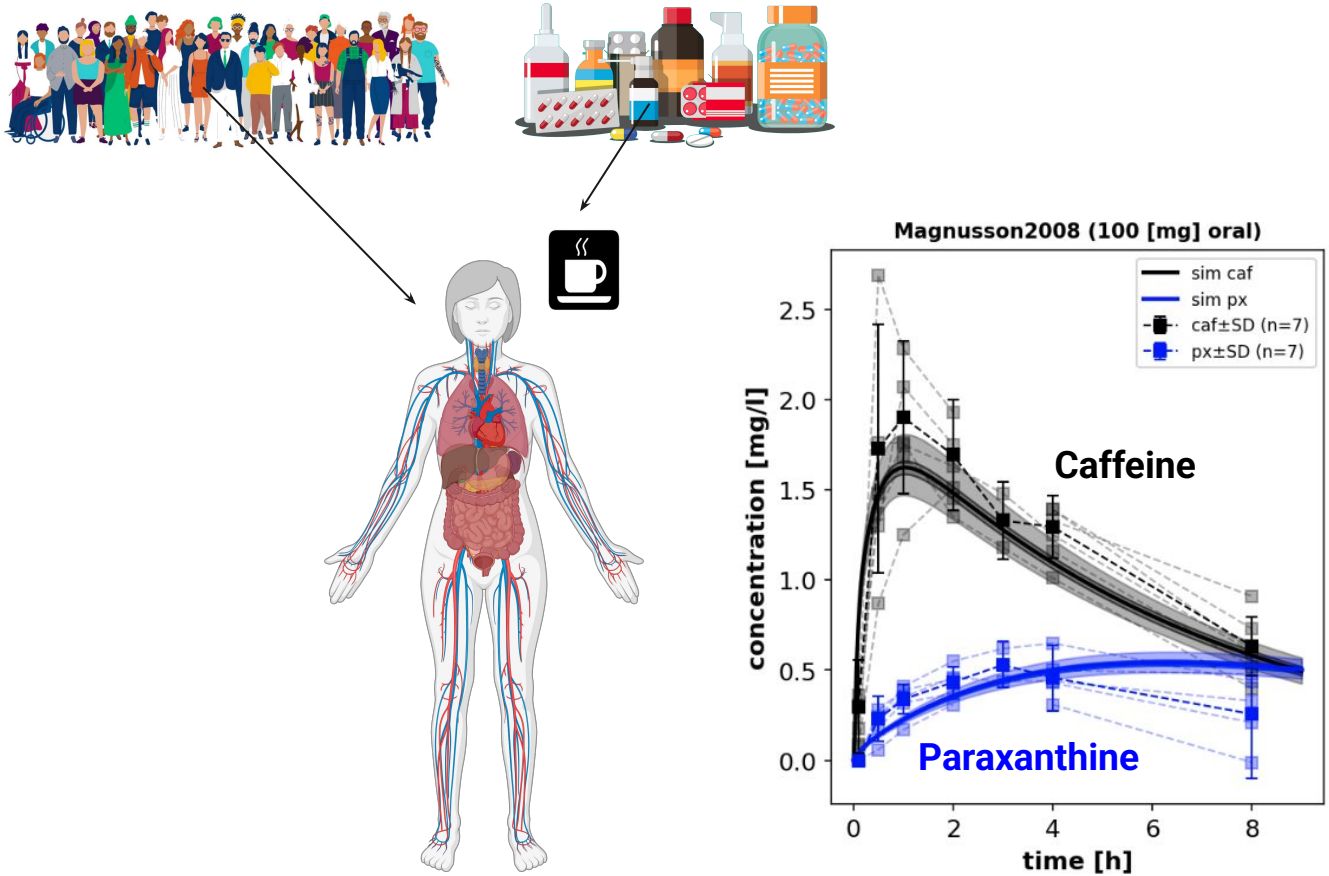


Pharmacometrics

Physiologically based pharmacokinetic/ pharmacodynamic models for precision dosing.

The right dose is never one-size-fits-all. Our PBPK/PD models simulate how each body absorbs, distributes, and clears a drug, turning population averages into individual precision.

Pharmakokinetik von Medikamenten



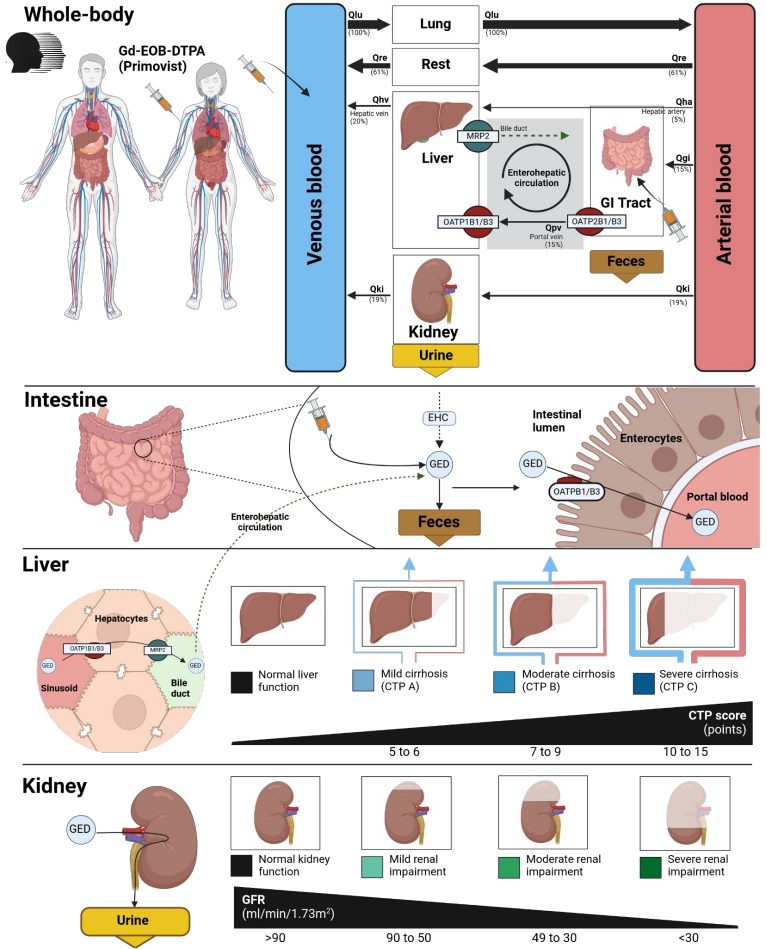
Physiologisch basierte Pharmakokinetik (PBPK)-Modelle

Digitaler Zwilling
- Menschliche Physiologie *in silico*

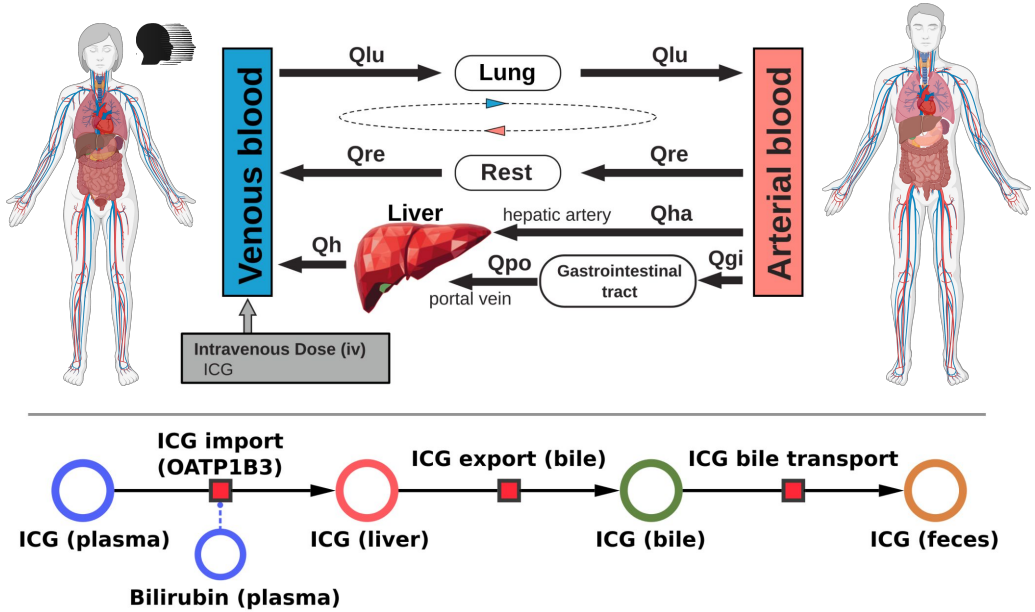
ADME
- Absorption
- Distribution
- Metabolismus
- Elimination

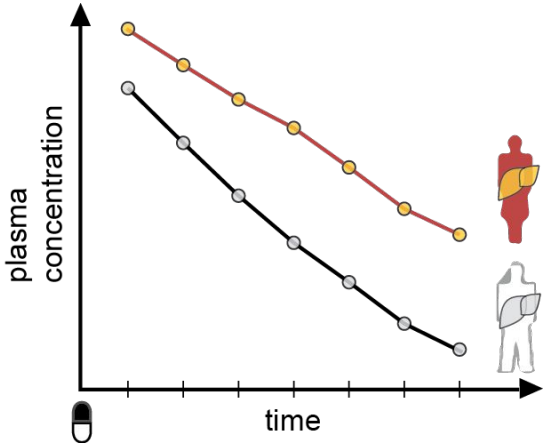
Multi-Skalen Modelle

Hohe klinische Relevanz
- Individualisierung & Stratifizierung
- Pathophysiologie



Leberfunktionstest: Indocyanine green (ICG)



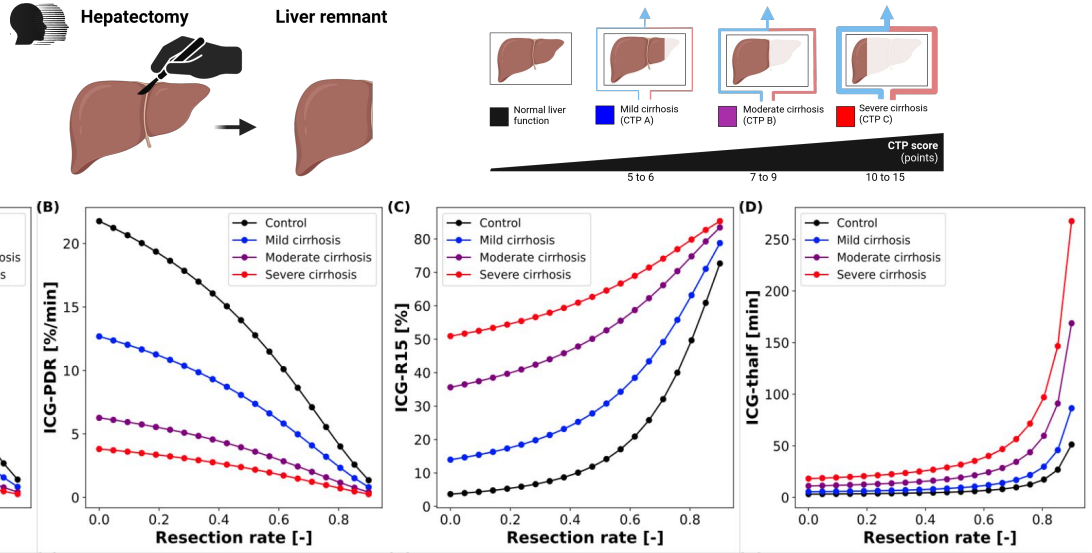


- **Anthropometrischen Faktoren** (Alter, Gewicht, Geschlecht)
- **Physiologischen Faktoren** (Blutfluss, Lebervolumen)
- **Lebererkrankung** (Zirrhose)
- **Operativen Eingriffen** (Hepatektomie)

Prediction of survival after hepatectomy using a physiologically based pharmacokinetic model of indocyanine green liver function tests. A Köller, J Grzegorzewski, MH Tautenhahn, **M König.** Front. Physiol., 22 November 2021; doi: 10.3389/fphys.2021.730418

Physiologically based modeling of the effect of physiological and anthropometric variability on indocyanine green based liver function tests. A Köller, J Grzegorzewski, **M König**. Front Physiol. 2021 Nov 22;12:757293. doi: 10.3389/fphys.2021.757293. eCollection 2021.

In silico Hepatektomie



A Köller, J Grzegorzewski, MH Tautenhahn, **M König**
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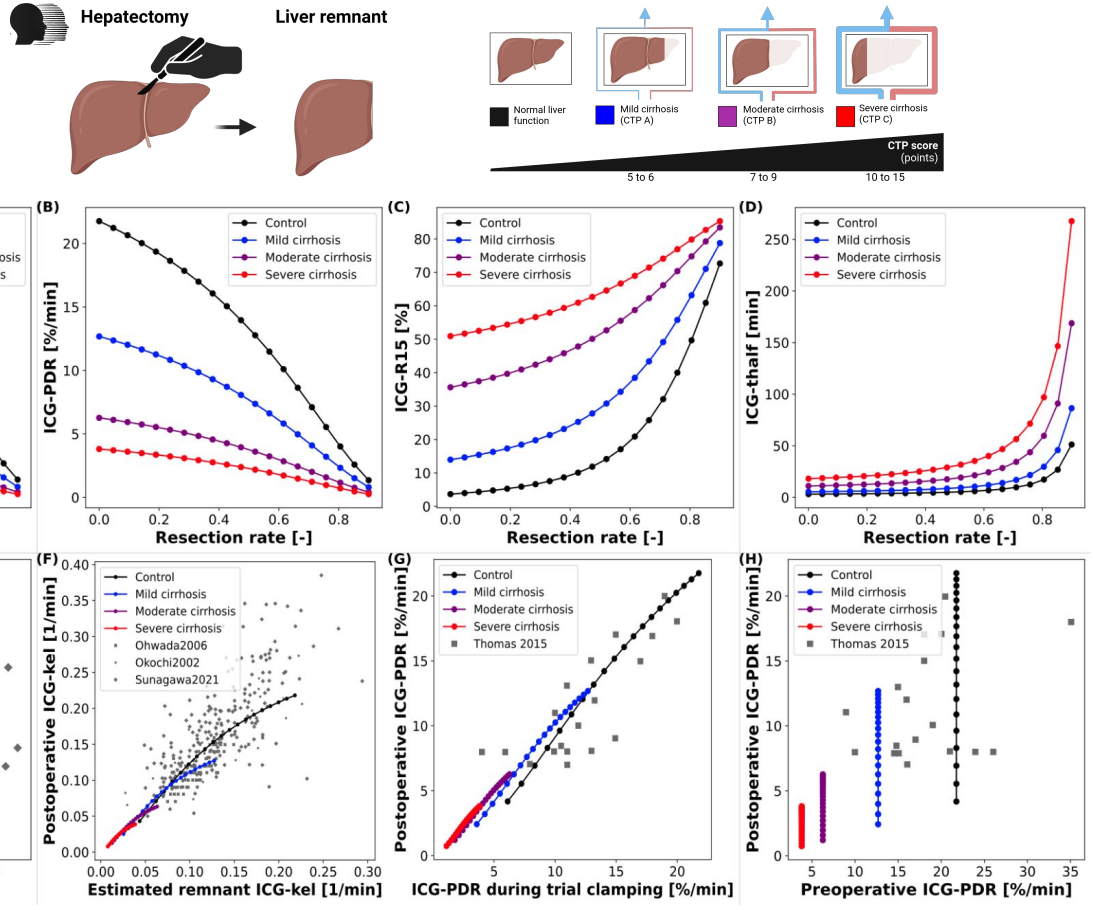
Front Physiol. 2021 Nov 22;12:757293. doi: 10.3389/fphys.2021.757293. eCollection 2021.

Validierung



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Front. Physiol., 22 November 2021; doi: 10.3389/fphys.2021.730418

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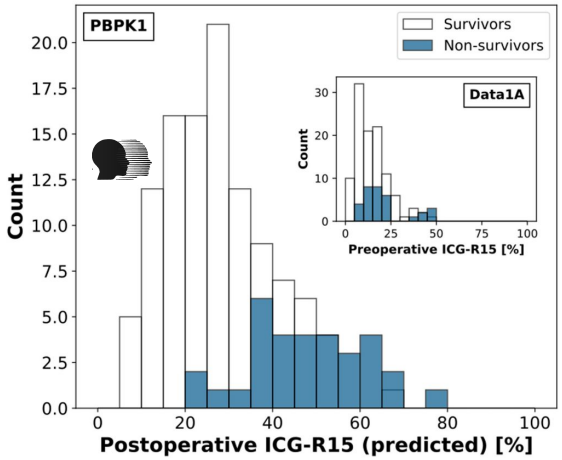
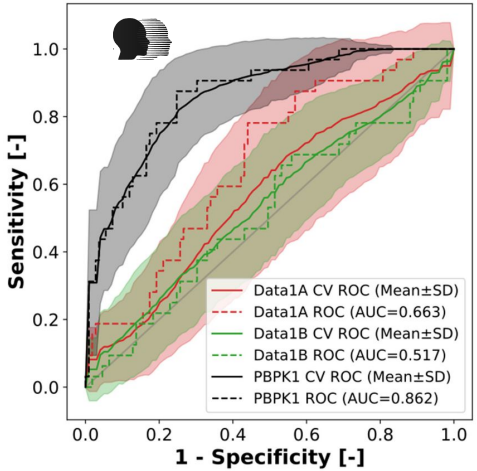
Front Physiol. 2021 Nov 22;12:757293. doi: 10.3389/fphys.2021.757293. eCollection 2021.

Risikovorhersage nach Hepatektomie





Vorhersage mit Digitalem Zwilling (PBPK) ist besser als nur Daten.

TABLE | Evaluation metrics for classification models of survival after hepatectomy.

Classification model	Data1A	Data1B	PBPK1
Features	Preoperative ICG-R15	Postoperative ICG-R15 (calculated)	Postoperative ICG-R15 (predicted)
ROC AUC	0.663 (0.555 ± 0.072)	0.517 (0.481 ± 0.052)	0.862 (0.753 ± 0.090)
Balanced accuracy	0.562 (0.555 ± 0.072)	0.515 (0.481 ± 0.052)	0.761 (0.753 ± 0.090)
F1-score	0.267 (0.243 ± 0.152)	0.143 (0.118 ± 0.126)	0.611 (0.587 ± 0.136)
Precision (PPV)	0.462 (0.443 ± 0.295)	0.300 (0.192 ± 0.227)	0.550 (0.538 ± 0.152)
Recall	0.188 (0.182 ± 0.133)	0.094 (0.170 ± 0.273)	0.688 (0.681 ± 0.172)
NPV	0.797 (0.792 ± 0.067)	0.779 (0.745 ± 0.133)	0.901 (0.898 ± 0.057)

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Front. Physiol., 22 November 2021; doi: 10.3389/fphys.2021.730418

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Front Physiol. 2021 Nov 22;12:757293. doi: 10.3389/fphys.2021.757293. eCollection 2021.

Digitale Zwillinge für viele Medikamente

Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan. J.Grzegorzewski, J.Brandhorst, **M.König**. Front Pharmacol. 2022 Oct 24;13:1029073. doi:10.3389/fphar.2022.1029073.

Prediction of survival after hepatectomy using a physiologically based pharmacokinetic model of indocyanine green liver function tests. A Köller, J Grzegorzewski, MH Tautenhahn, **M König**. Front. Physiol., 22 November 2021; doi: 10.3389/fphys.2021.730418

Physiologically based modeling of the effect of physiological and anthropometric variability on indocyanine green based liver function tests. A Köller, J Grzegorzewski, **M König**. Front Physiol. 2021 Nov 22;12:757293. doi: 10.3389/fphys.2021.757293.

A physiologically based pharmacokinetic model for CYP2E1 phenotyping via chlorzoxazone. J. Küttner, J. Grzegorzewski, HM. Tautenhahn, **M. König.** bioRxiv 2023.04.12.536571 (preprint). doi:10.1101/2023.04.12.536571

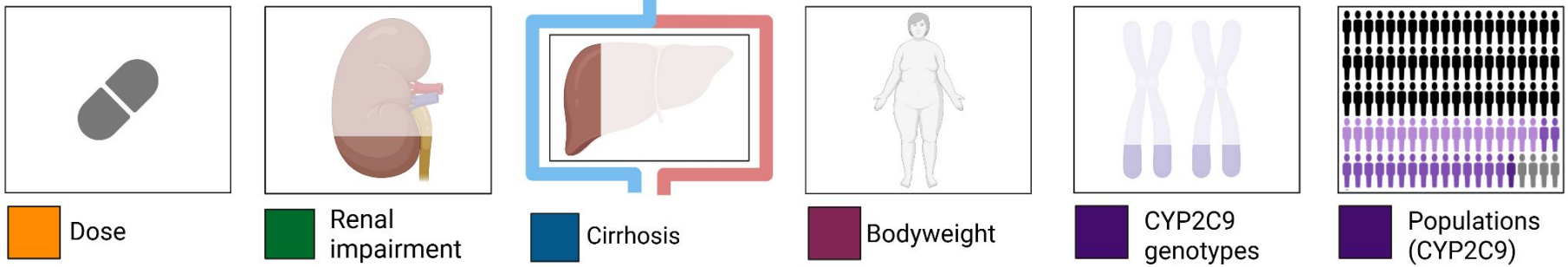
Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing. J.Grzegorzewski, F.Bartsch, A.Köller, and **M.König**. Frontiers in Pharmacology 2022, Vol12; doi: 10.3389/fphar.2021.752826

A physiologically based pharmacokinetic (PBPK) model of pravastatin: Impact of hepatorenal impairment and genetic polymorphisms of OATP1B1, OATP2B1 and MRP2. HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn, **M.König**. *[submitted]*

A Physiologically-Based Pharmacokinetic Model of Tirzepatide, Internship Report Abhinav Mishra (supervisor: Matthias König), Internship Report, Mar 2025

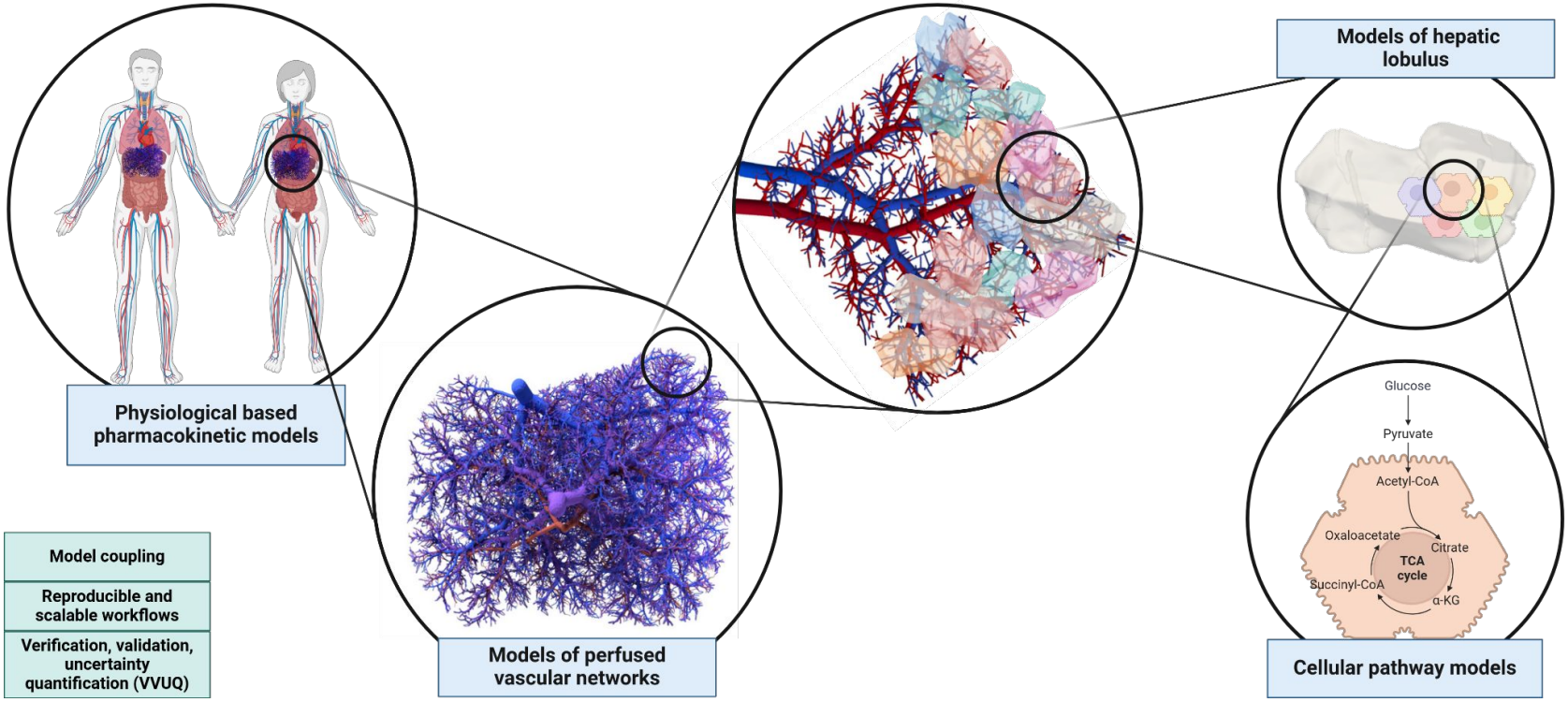
- Gd-EOB-DTPA
- Indocyanine green (OATP1B3)
- Caffeine (CYP1A2)
- LIMAX (CYP1A2)
- Creatine, creatinine, inulin
- Omeprazol (CYP2C19)
- Pravastatin (OATP1B1)
- Metacetin (LiMAx, CYP1A2)
- Talinolol (P-Glycoprotein)
- Chlorzoxazone (CYP2E1)
- Paracetamol
- Metoprolol (CYP2D6)
- Simvastatin (OATP1B1)
- Midazolam (CYP3A4)
- Galactose
- Codeine/Morphine
- Ramipril, lisinopril, enalapril, captopril
- Sorafenib
- Losartan
- Semaglutide, tirzapetide,
  Glucose, Insulin, C-Peptide, Glucagon, FFA

Anwendungsbeispiele



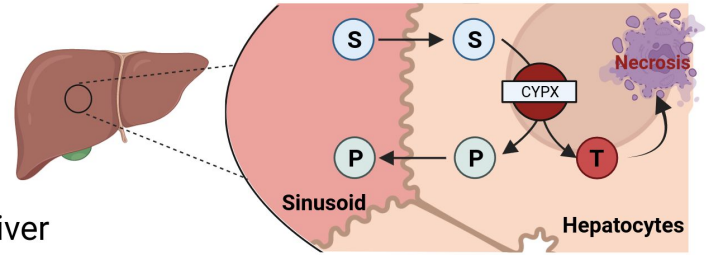
M Elias, **M König.*A Digital Twin of Glimepiride for Personalized and Stratified Diabetes Treatment***
Preprints 2025, 2025061264. (preprint). doi:10.20944/preprints202506.1264.v1

Multiskalen Modell der Leber



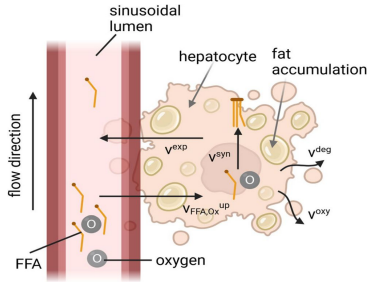
Lebermetabolismus

Medikamentenstoffwechsel

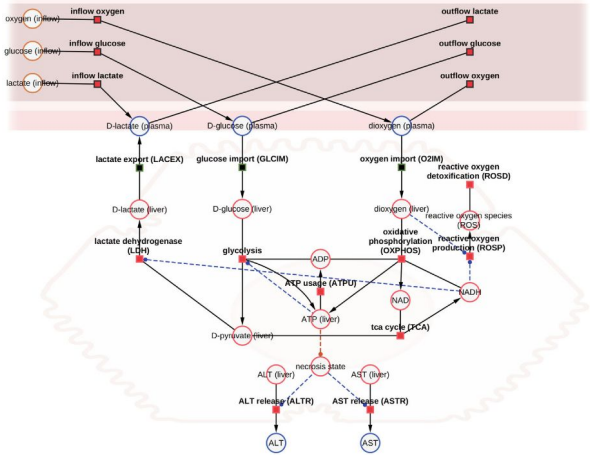


Liver

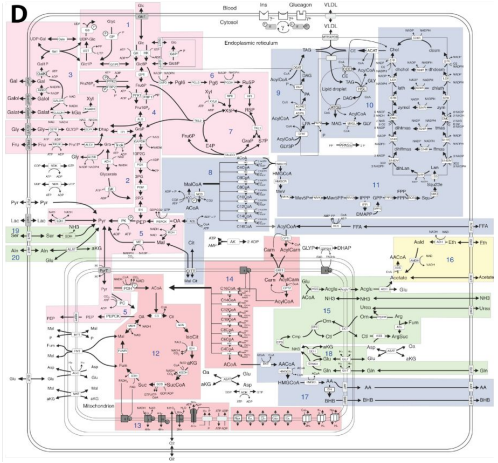
Steatose



Energiestoffwechsel & Schädigung



Zentralstoffwechsel



L Lambers, N Waschinsky, J Schleicher, **M König**, HM Tautenhahn, M Albadry, U Dahmen, T Ricken. ***Quantifying fat zonation in liver lobules: an integrated multiscale in silico model combining disturbed microperfusion and fat metabolism via a continuum biomechanical bi-scale, tri-phasic approach.*** Biomech Model Mechanobiol. 2024 Feb 25.. doi: 10.1007/s10237-023-01797-0.

S Gerhäusser, L Lambers, L Mandl, J Franquinet, U Dahmen, T Ricken, **M König. *Simulation of zonation-function relationships in the liver using coupled multiscale models: Application to drug-induced liver injury.*** bioRxiv 2024.03.26.586870; doi:10.1101/2024.03.26.586870

Maheshvare MD., Raha S., König M.Δ, and Pal D.Δ (Δ equal contribution). ***A pathway model of glucose-stimulated insulin secretion in the pancreatic β-cell.*** Front. Endocrinol. 14:1185656 (publication). doi:10.3389/fendo.2023.1185656

Berndt N., Bulik S., Wallach I., Wünsch T., **König M.**, Stockmann M., Meierhofer M., Holzhütter HG. ***HEPATOKIN1: A Biochemistry-Based Model of Liver Metabolism Suited for Applications in Medicine and Pharmacology***. Nat Commun. 2018 Jun 19;9(1):2386. doi:10.1038/s41467-018-04720-9.

Gille C, Bölling C, Hoppe A, Bulik S, Hoffmann S, Hübner K, Karlstädt A, Ganeshan R, **König M**, Rother K, Weidlich M, Behre J, Holzhütter HG. ***HepatoNet1: a comprehensive metabolic reconstruction of the human hepatocyte for the analysis of liver physiology.*** Mol Syst Biol. 2010 Sep 7;6:411 doi:10.1038/msb.2010.62.

König M., Holzhütter HG., Berndt N. ***Metabolic Gradients as Key Regulators in Zonation of Tumor Energy Metabolism: A Tissue-scale Model Based Study.*** Biotechnol J. 2013 Sep;8(9):1058-69. (publication). doi:10.1002/biot.201200393.

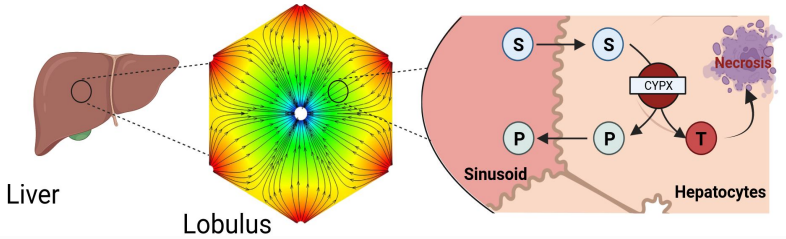
König M. and Holzhütter HG. ***Kinetic Modeling of Human Hepatic Glucose Metabolism in T2DM Predicts Higher Risk of Hypoglycemic Events in Rigorous Insulin Therapy*** J Biol Chem. 2012 Oct 26;287(44):36978-89. doi:10.1074/jbc.M112.382069.

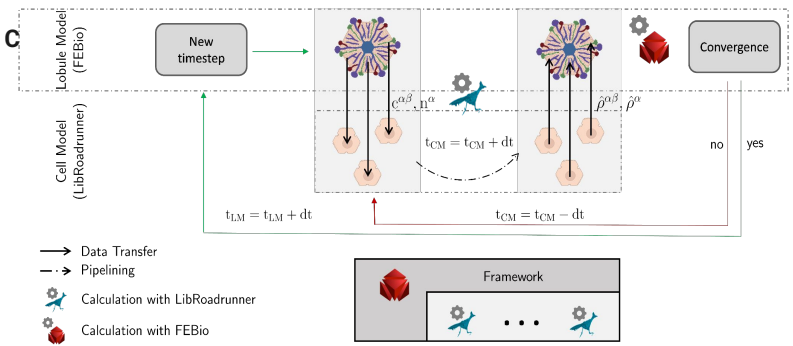
König M., Bulik S. and Holzhütter HG. ***Quantifying the Contribution of the Liver to the Homeostasis of Plasma Glucose: A Detailed Kinetic Model of Hepatic Glucose Metabolism Integrated with the Hormonal Control by Insulin, Glucagon and Epinephrine.*** PLoS Comput Biol. 2012 Jun;8(6):e1002577. Epub 2012 Jun 21. doi:10.1371/journal.pcbi.1002577

König M, Bulik S, Holzhütter HG. ***Enzymatic Features of the Glucose Metabolism in Tumor Cells.*** Herling A, FEBS J. 2011 Jul;278(14):2436-59. doi:10.1111/j.1742-4658.2011.08174.x.

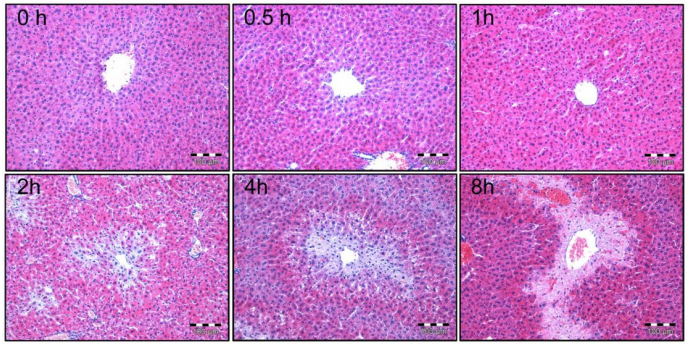
Digitaler Zwilling - Lobulus

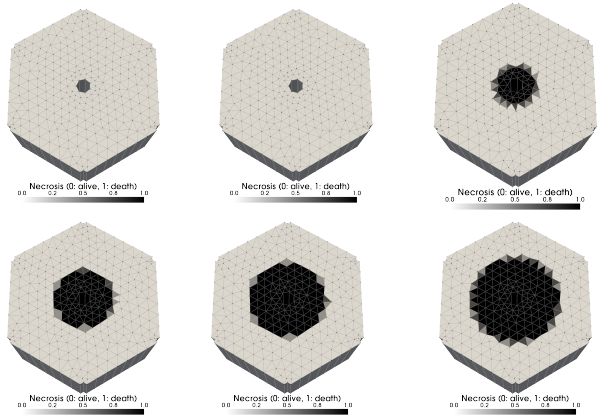
Cytochrome P450 & Nekrose





Necrosis





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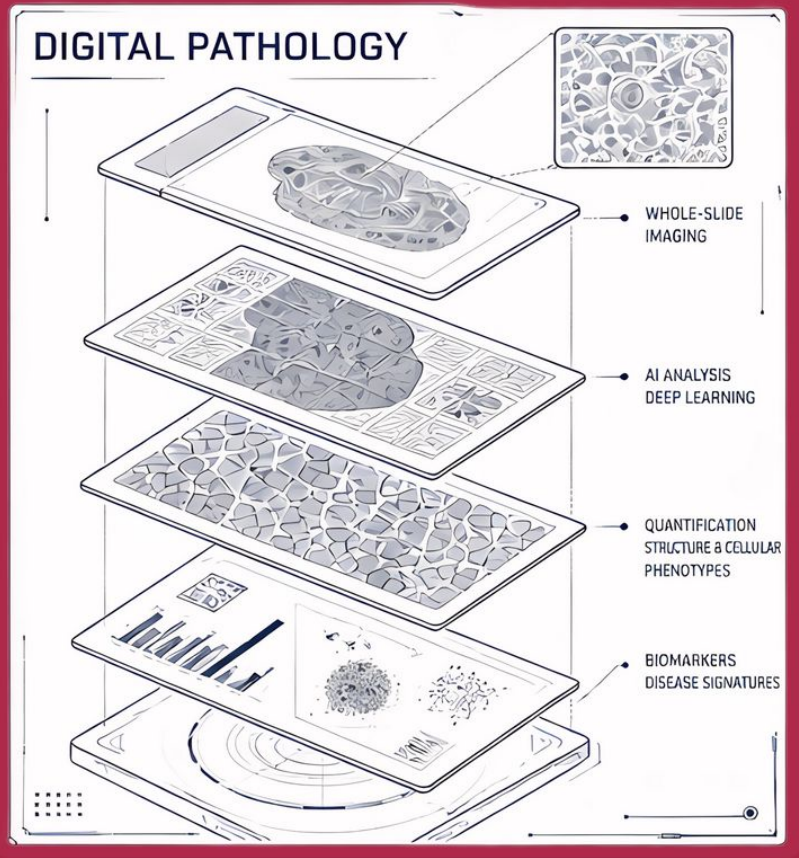
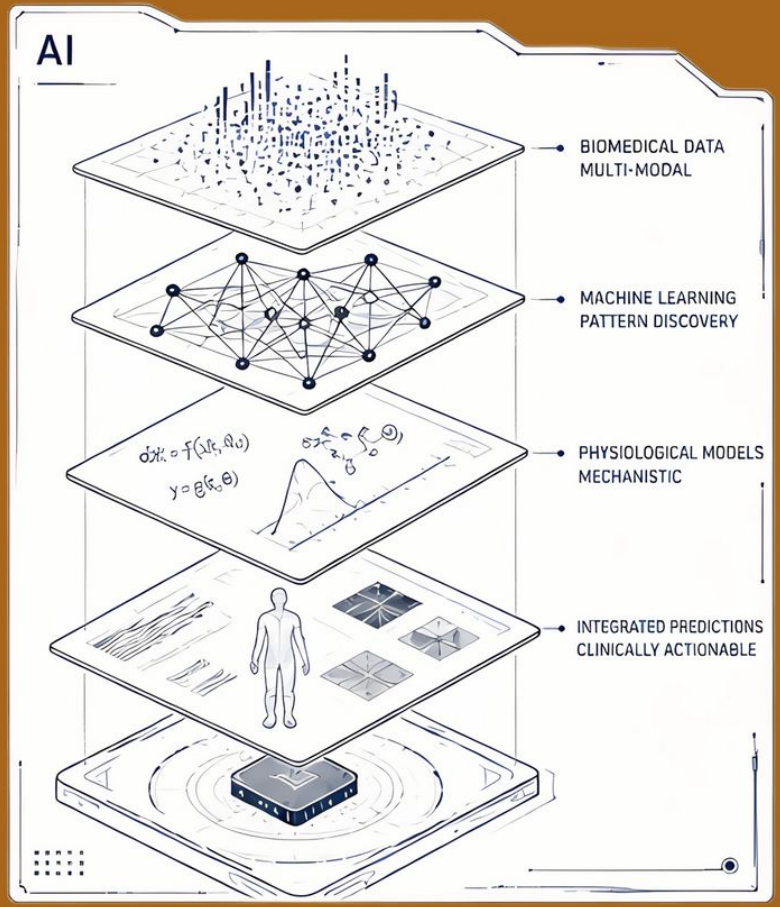
Digital Pathology

AI-driven analysis of whole-slide histology to quantify liver structure and disease at scale.

A biopsy holds a whole organ's story. We use AI to read whole-slide histology at scale, quantifying liver structure and disease with a precision no eye can match.



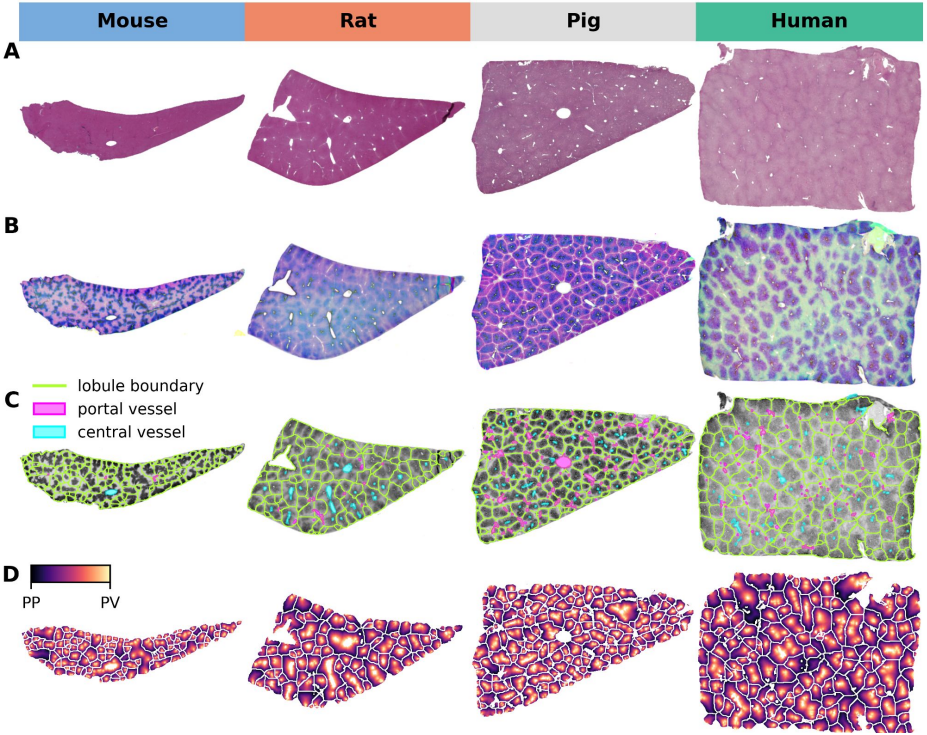


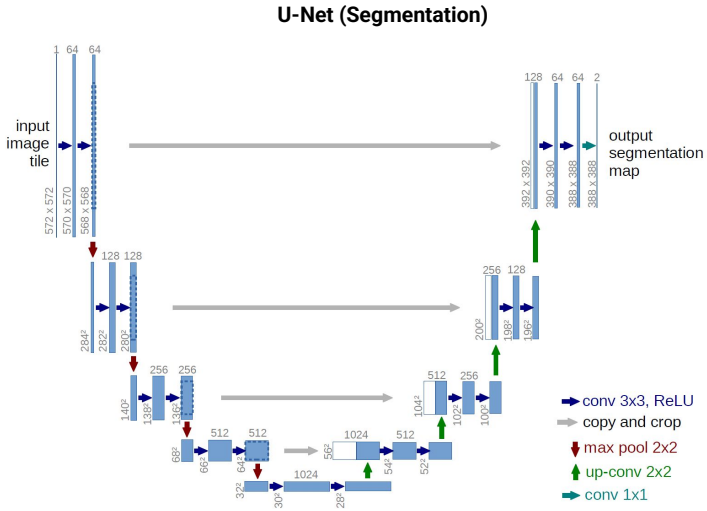
AI

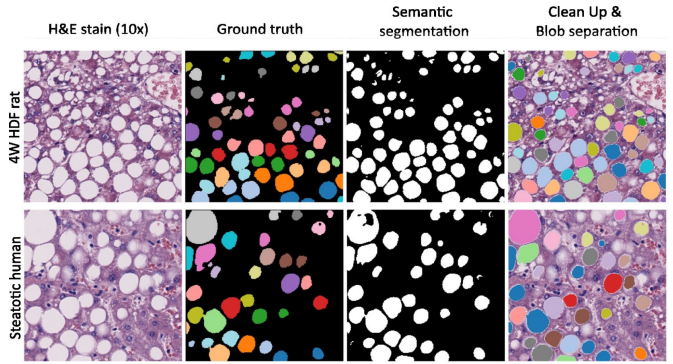
Mechanistic modeling meets machine learning for predictive, personalized medicine.

Data alone cannot explain a patient — mechanism can. We fuse machine learning with physiological models to turn complex biomedical data into predictions clinicians can trust.

KI: Geometry & Steatose aus Whole-Slide Scans



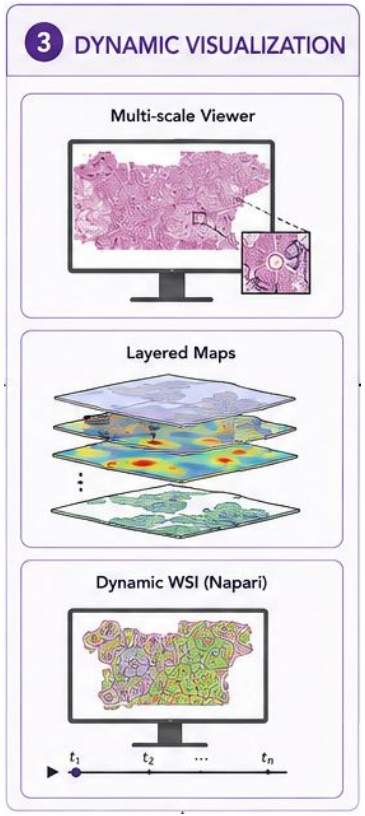


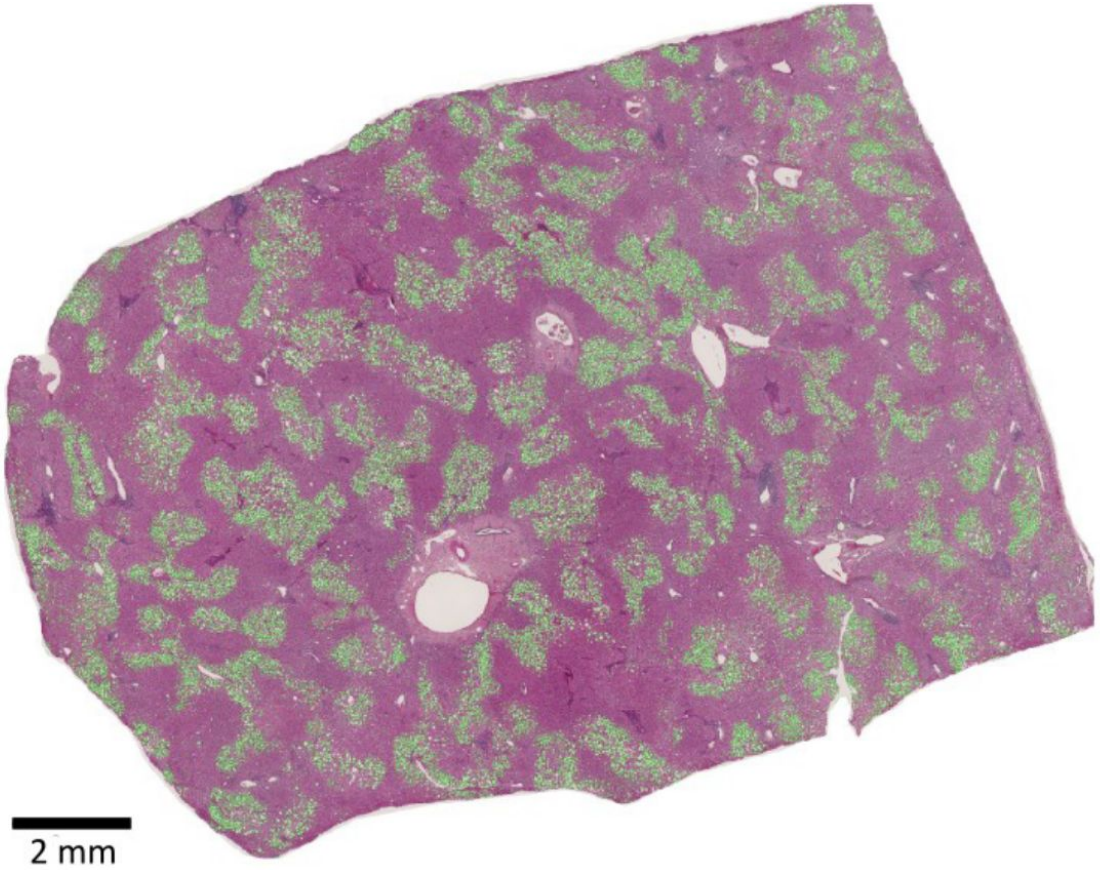


Cross-Species Variability in Lobular Geometry and Cytochrome P450 Hepatic Zonation: Insights into CYP1A2, CYP2E1, CYP2D6 and CYP3A4 Mohamed Albadry, Jonas Kuettner, Jan Grzegorzewski, Olaf Dirsch, Eva Kindler, Robert Klopfleisch, Vaclav Liska, Vladimira Moulisova, Sandra Nickel, Richard Palek, Jachym Rosendorf, Sylvia Saalfeld, Utz Settmacher, Hans-Michael Tautenhahn, **Matthias König***, Uta Dahmen* (* equal contribution).Front Pharmacol. 2024 May 16;15:1404938. doi:10.3389/fphar.2024.1404938

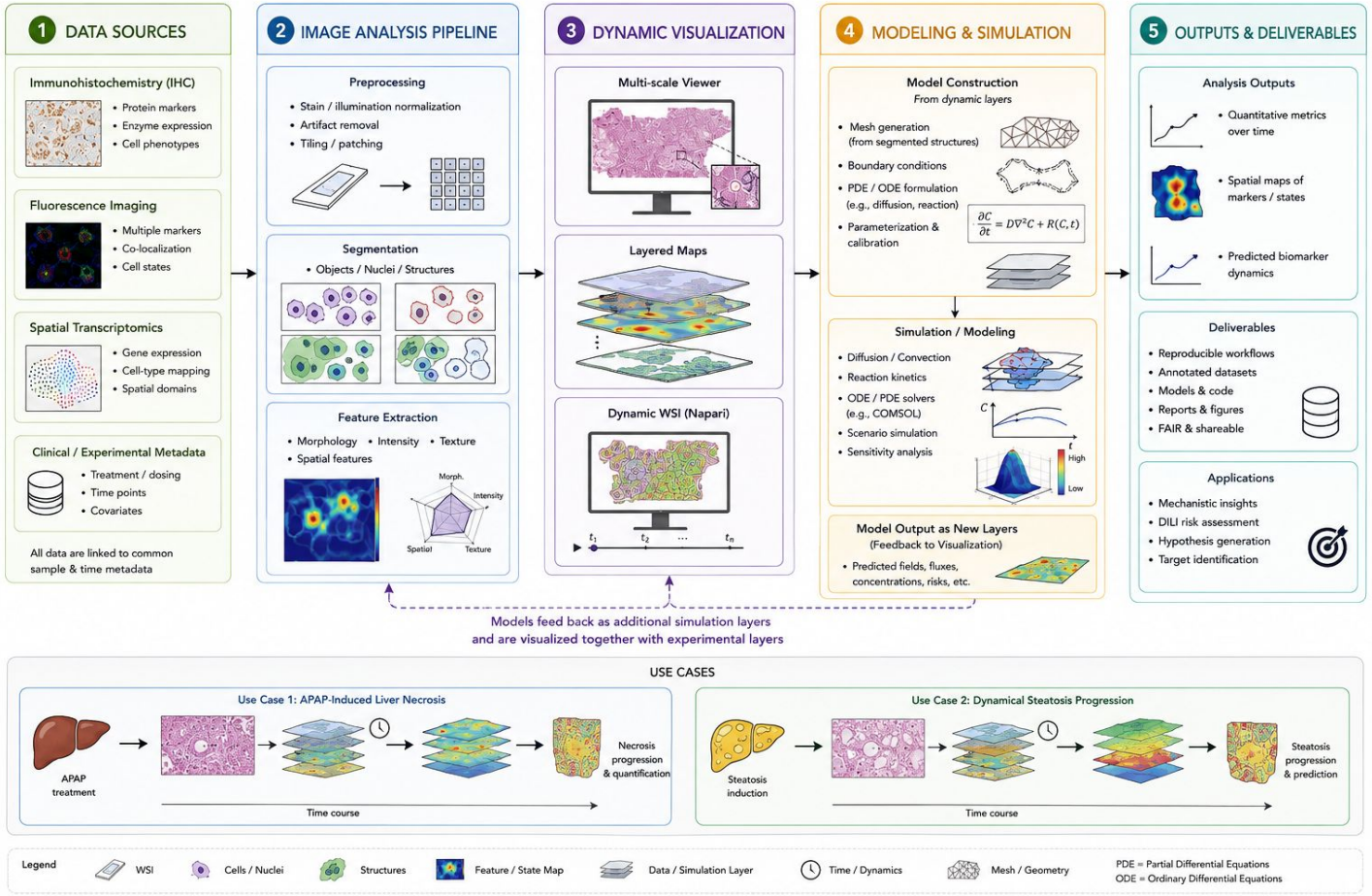
Quantitative Image Analysis of Hepatic Zonation in Cytochrome P450 and Steatosis Using Whole Slide Scans, Master Thesis J. Küttner (supervisor: **M. König**), August 2024

SlideViz


3 DYNAMIC VISUALIZATION
Multi-scale Viewer
Layered Maps
Dynamic WSI (Napari)
t_1
t_2
...
t_n

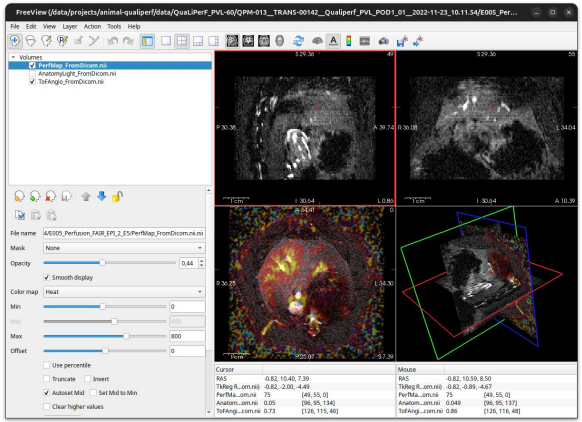

2 mm

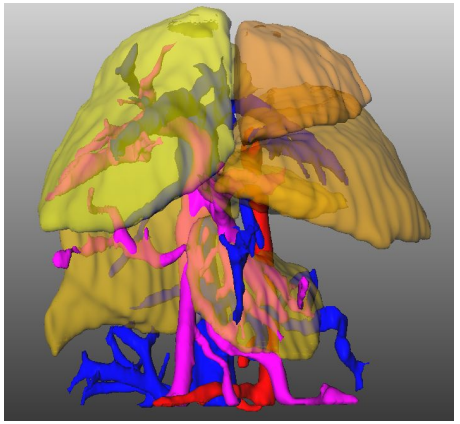
Spatial OMICS & Dynamical Functional Maps

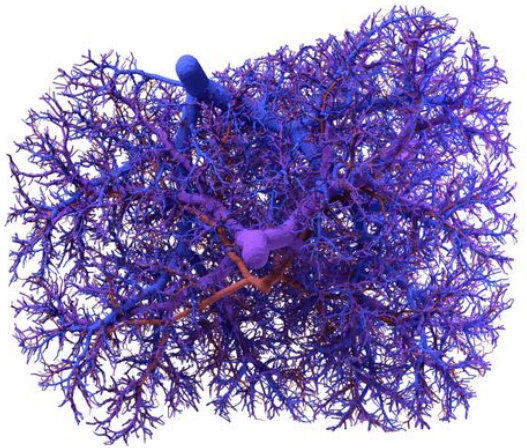


KI: Digitaler Zwilling - Organmodelle

- Effekt von Leber Geometrie und Vaskularisierung auf Perfusion und Funktion
- Rekonstruktion von Leber Geometrie und Gefäßbäumen
  - Perfusion MRI
  - Anatomisches MRI
  - Angiographie
  - Tumor
- Simulation von Perfusion und Metabolismus







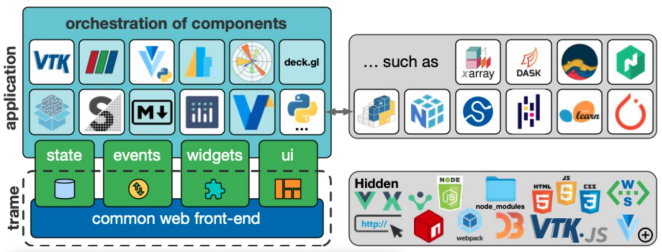
VisFEM

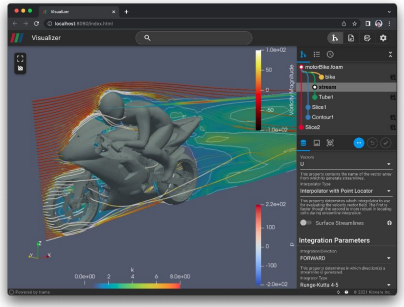
SPP FEMVis

T1 Project Setup & Requirement Analysis

T2 Development of Web Visualization Tool

T3 Integration with SPP2311 Projects

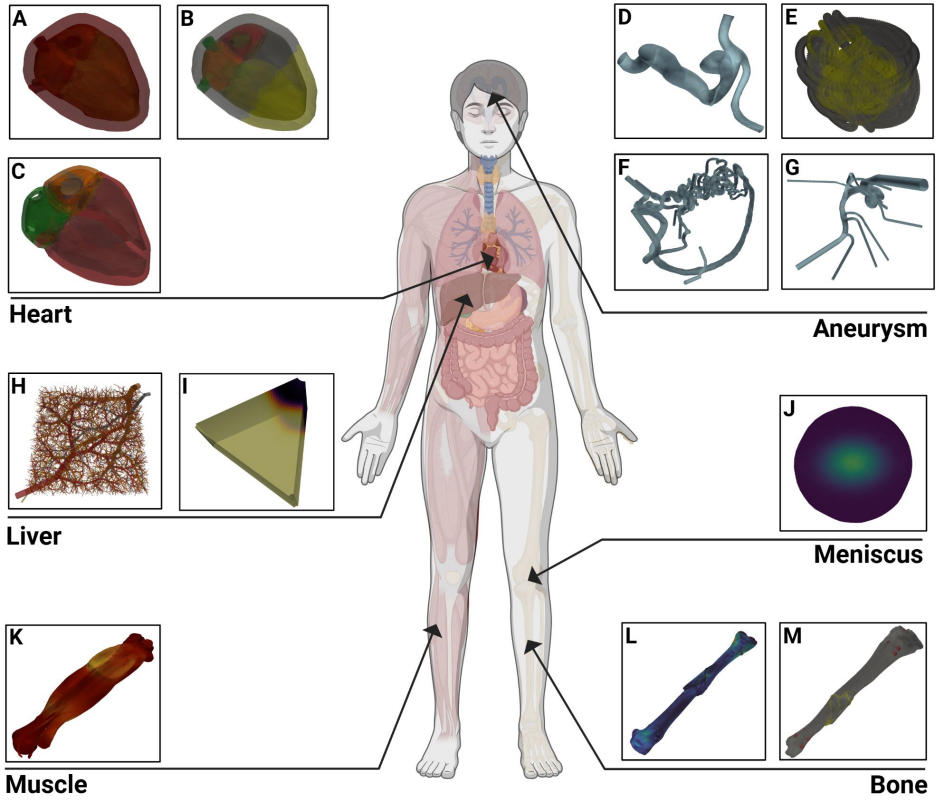




trame

PyVista

T4 Dissemination & Deployment



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Publications
Papers, reviews, and preprints on Open & FAIR.

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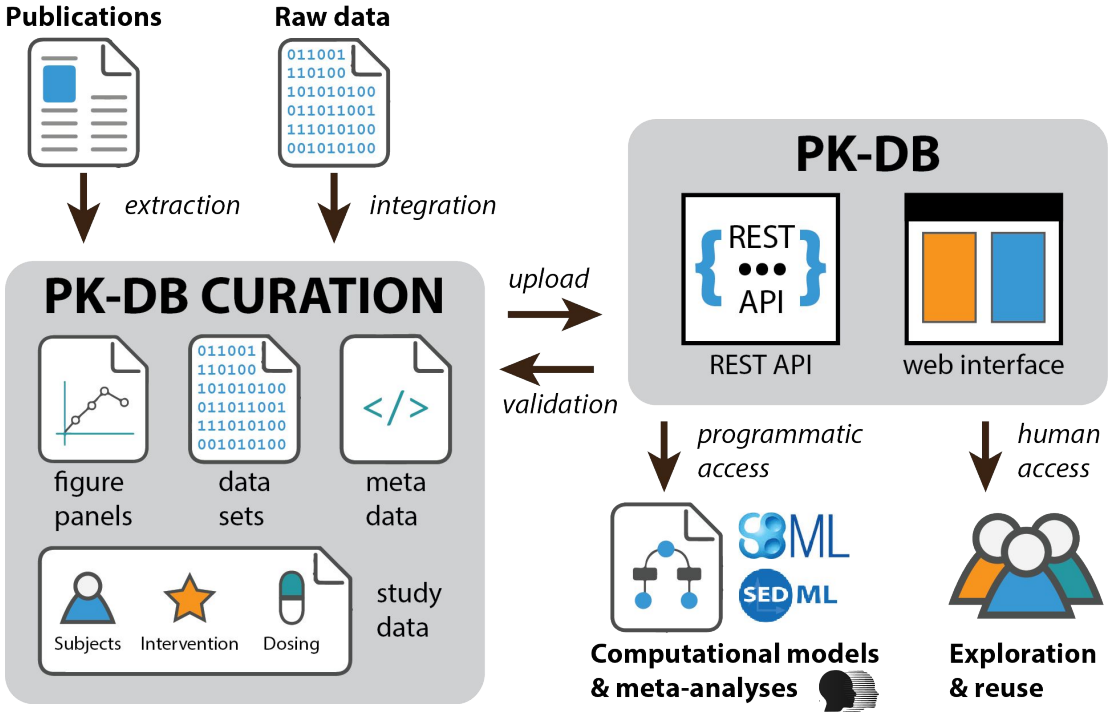
Pharmakokinetik Datenbank (PK-DB)



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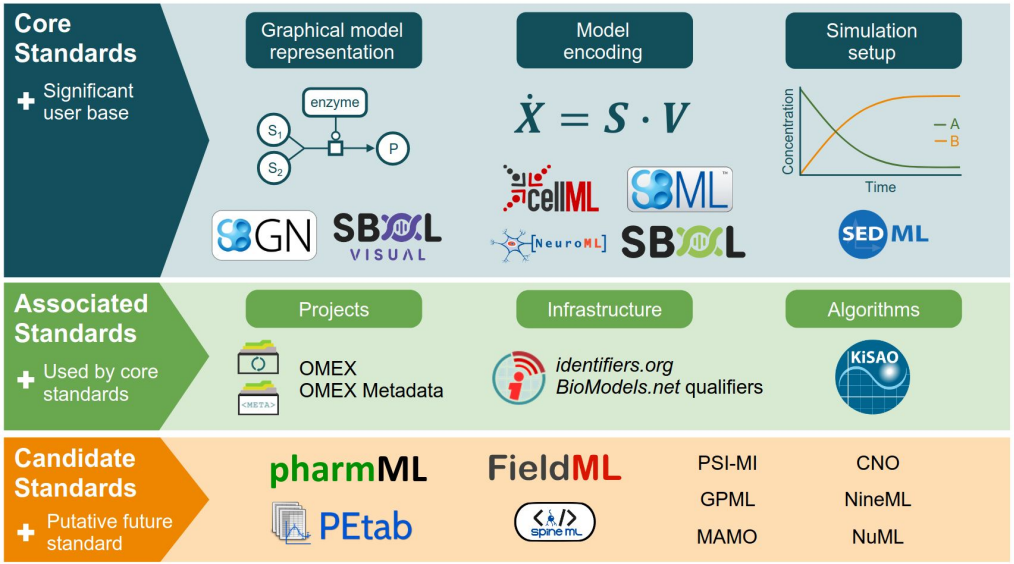
https://pk-db.com

Entwicklung von Standards



- Modelle (SBML)
- Simulationen (SED-ML)
- Visualisierung (SGBN)
- Parameter Optimierung (PETab)
- Metadaten (OMEX)

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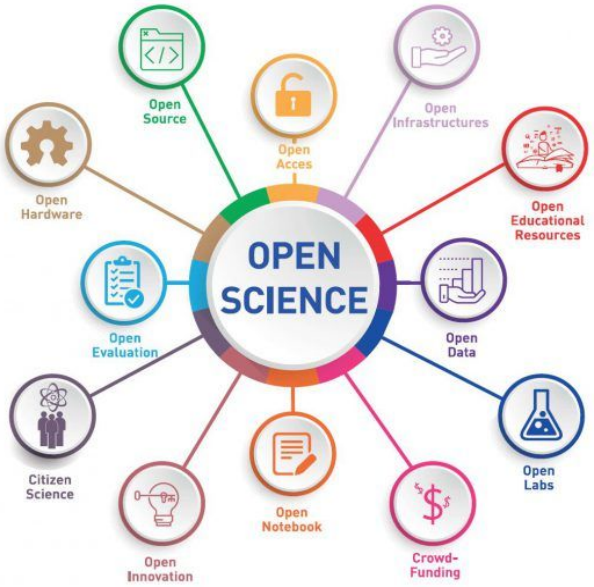
Open und FAIR Science



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Open Data in Repositories

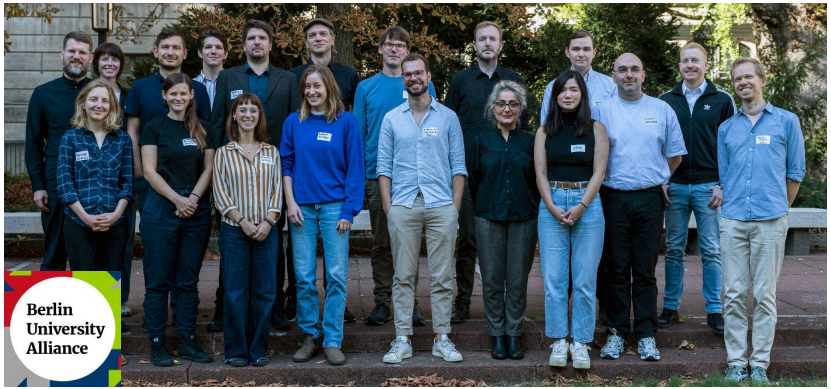
- BioModels DB, GitHub, Zenodo
- PK-DB

Open/FAIR models

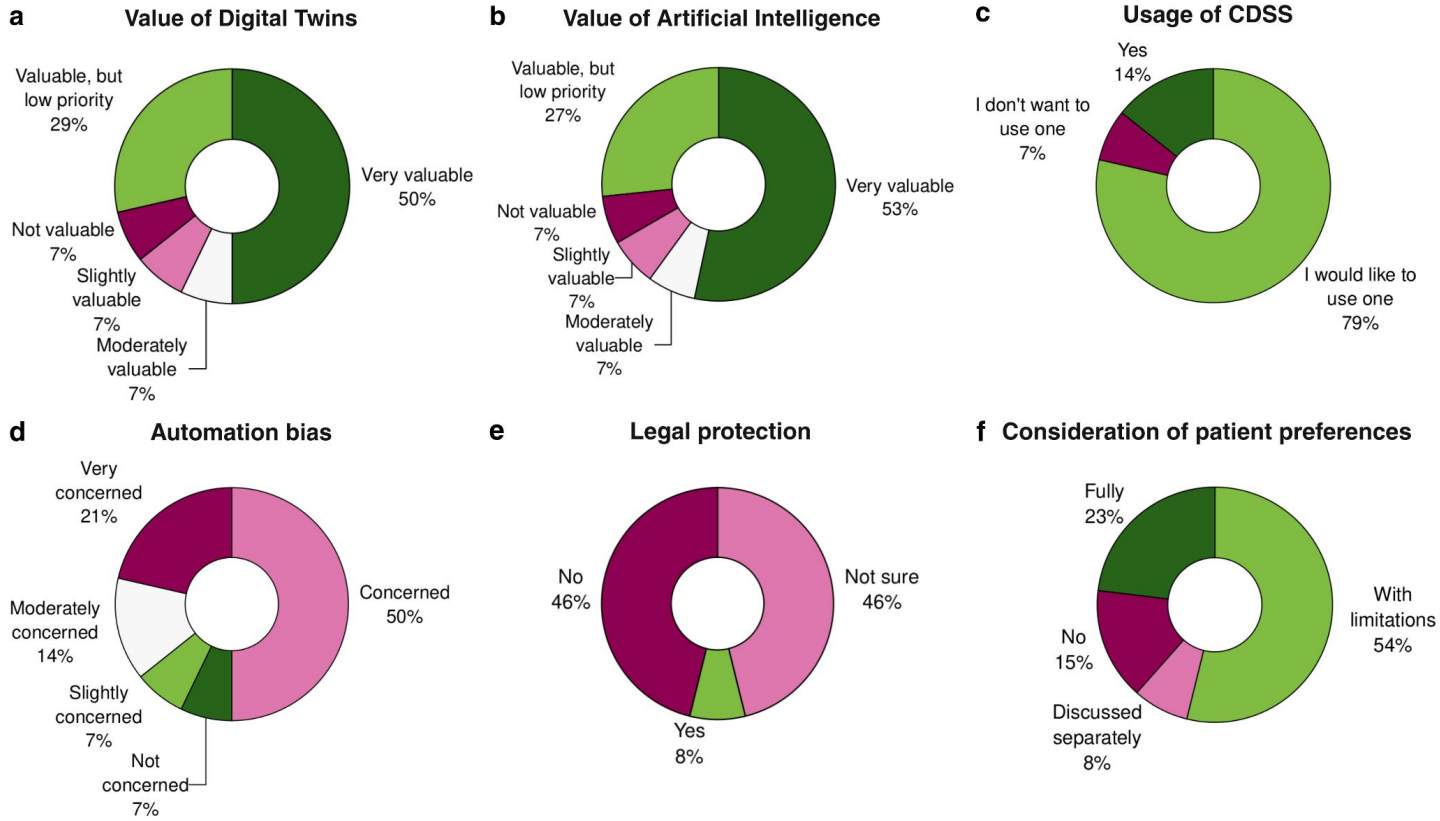
- CC-BY, Zenodo, GitHub, FAIR Indicators

Open Science Initiativen

- Strategieentwicklung (Open Science Training an Universitäten)
- Open Science Botschafter (2024-2025)



Impact of Digital Twins & AI



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Systems Medicine, Digital Twins & AI

Prof. Dr. rer. nat. Matthias König

Professor of Metabolic Inflammation and Carcinogenesis of the Liver

Digital Twins

Physiologically based models that mirror individual patients, from molecule to whole body.

AI

Mechanistic modeling meets machine learning for predictive, personalized medicine.

Digital Pathology

AI-driven analysis of whole-slide histology to quantify liver structure and disease at scale.

Pharmacometrics

Physiologically based pharmacokinetic/ pharmacodynamic models for precision dosing.

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Funding & Acknowledgement

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- **DFG**, Supported by BMBF-funded **de.NBI Cloud** within the German Network for Bioinformatics Infrastructure (de.NBI) (031A537B, 031A533A, 031A538A, 031A533B, 031A535A, 031A537C, 031A534A, 031A532B).
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- **EOSC-Life**, European Open Science Cloud, Reproducible simulation studies targeting COVID-19, H2020-INFRAEOSC-05-2018-2019
- **BMBF/excellence initiative**: **X-Student Research Group** - Physiologically based digital twins for the treatment of hypertension, 2022 & 2023
- **Google Summer of Code**, 2019-2025, student support
- **COMBINE**, travel grants