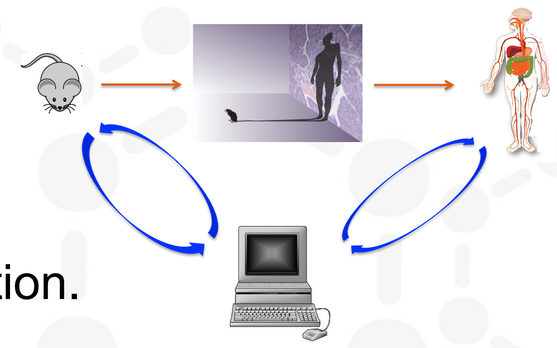
Poster 17: LiSyM Midterm Evaluation 2018
Drasdo Group (Dortmund)



Facts & Figures:

Area of Expertise: Modelling
Methodes: Computational Multi-Cellular Agent-Based Modeling, Flow Simulation.
Scientific Involvement: Pillar II, III
LiSyM Resources: ~ 600 000 € / 3yrs, ~1 Mio €/ 5yrs

LiSyM Scientists: PhD Student: Noémie Boissier; PostDocs: Jieling Zhao, Ayham Zaza, Paul van Liedekerke; Research Engineer: Tim Johann
Collaboration (main): Groups Hengstler (Dortmund), Höhme (Leipzig), Dooley (Mannheim), Klingmüller, Kauczor (Heidelb), Timmer (Freiburg); Junior group Ghallab(Do)

Objectives: general

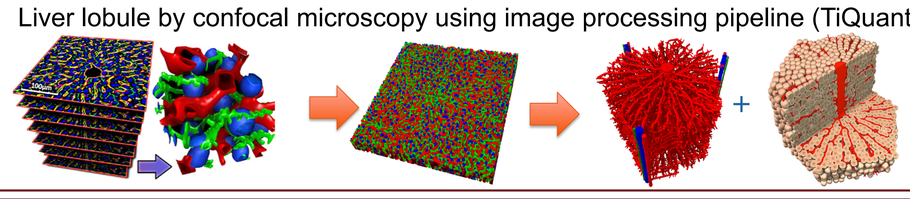
- Development of mathematical models to guide experimental designs & clinical decisions
- Long-term prospective: virtual twin of a patient

Objectives: specific

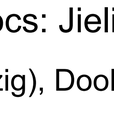
- Fibrosis: disease progression
- Fibrosis: functional consequences
- ACLF: acute damage in advanced fibrosis = acute on chronic

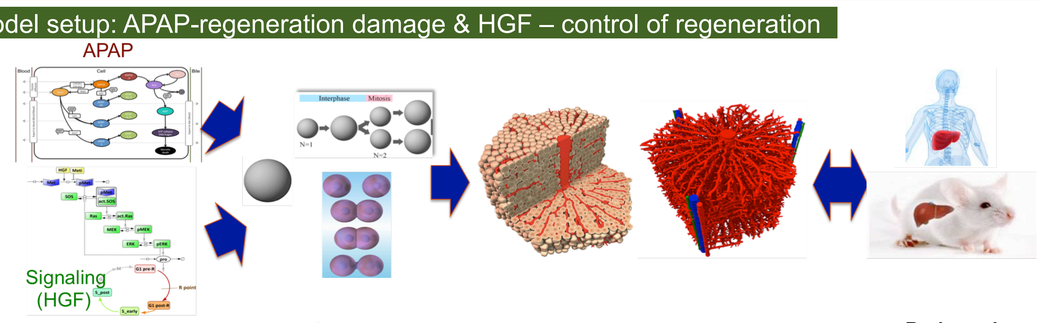
Acute damage: reference model for ACLF & chronic damage

Liver lobule by confocal microscopy using image processing pipeline (TiQuant -> Poster 3)



Model setup: APAP-regeneration damage & HGF – control of regeneration

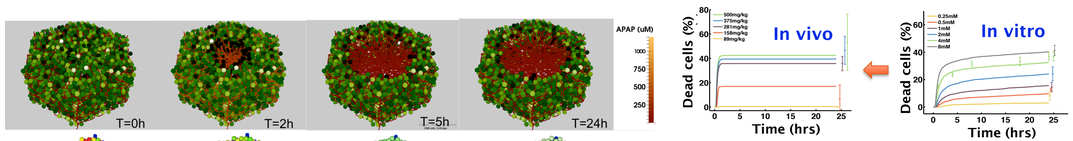




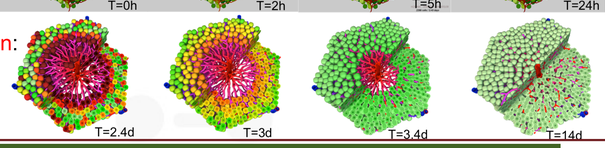
- Multi-scale model, executing APAP & HGF-pathway in each hepatocyte
- Each cell represented within “center-based”-model that mimics forces between cells as forces between cell centers
- Cells move due to an equation of motion (one per cell) as consequence of active and passive forces
- Cell division controlled by HGF-controlled cell cycle progression
- Cell death below ATP threshold concentration triggered by APAP
- Blood flow and molecular transport modeled as for ammonia detoxification (see below)
- Coupling to extra-hepatic body model for HGF clearance and APAP pharmacokinetics by population PK or PBPK model

Results:

APAP: simulation scenario

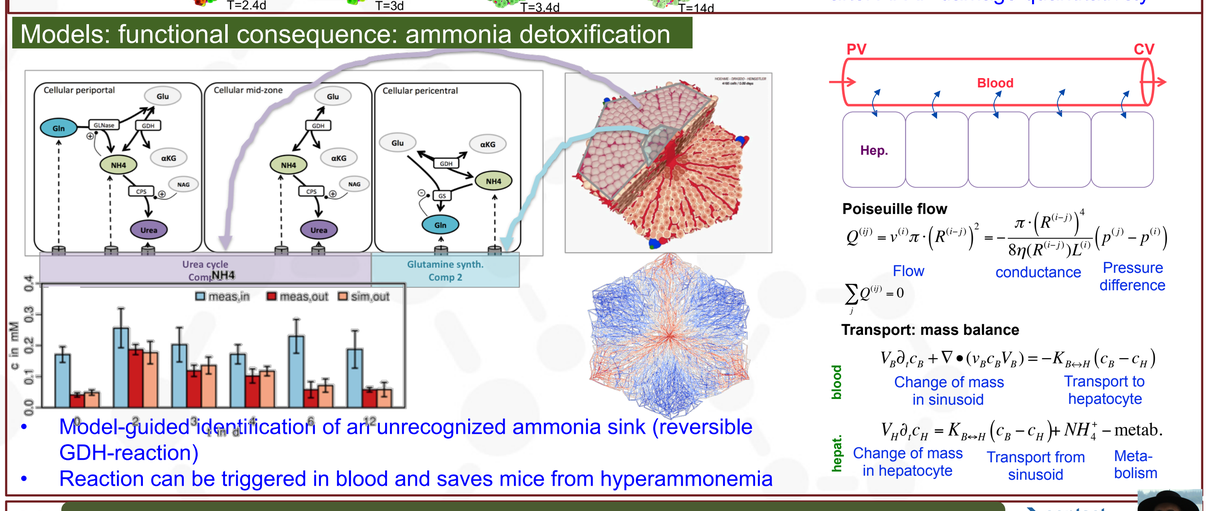


Regeneration: simulation scenario



- Model permits extrapolation from in-vitro -> in-vivo for APAP
- Model explains data on regeneration after APAP damage quantitatively

Models: functional consequence: ammonia detoxification

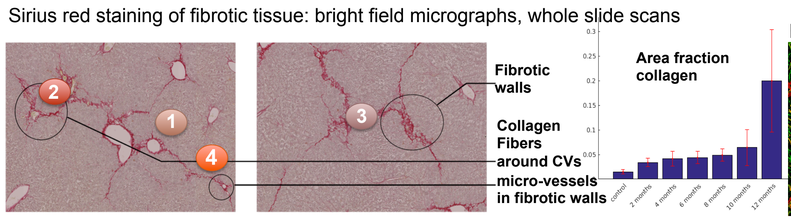


- Model-guided identification of an unrecognized ammonia sink (reversible GDH-reaction)
- Reaction can be triggered in blood and saves mice from hyperammonemia

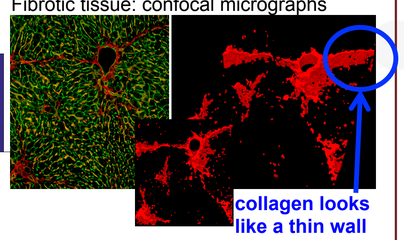
All simulations base on implementation in own software TiSim & TiQuant → contact Tim Johann

Fibrosis after CCl4: impact of architectural distortion on ammonia detoxification

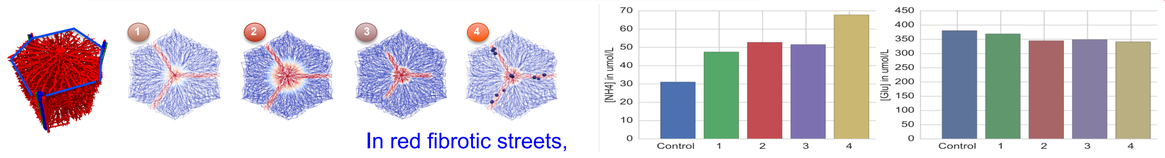
Sirius red staining of fibrotic tissue: bright field micrographs, whole slide scans



Fibrotic tissue: confocal micrographs

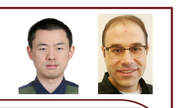


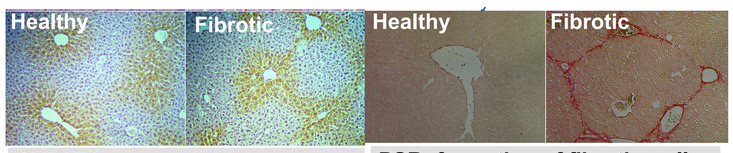
Models: functional consequence: ammonia detoxification



- Reduced permeability of sinusoids in fibrotic walls alone leads to reduced capacity of liver to detoxify blood from ammonia.
- For chosen geometries, no impact on flow.

Fibrosis: Chronic CCl_4 model: disease progression: CYP & ECM

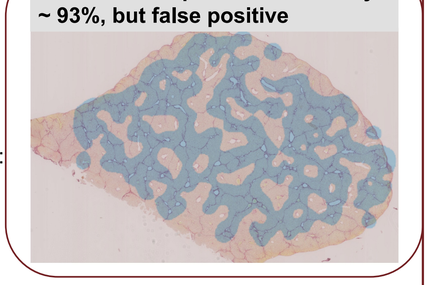




CYP2E1 pattern: bridging after repetitive CCl4 exposure

PSR: formation of fibrotic walls along CYP-positive pattern

Modeled CYP pattern. Sensitivity ~ 93%, but false positive



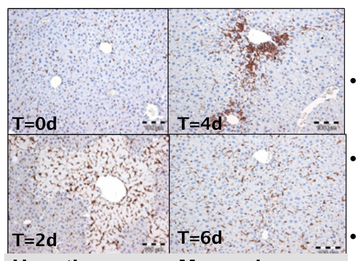
CYP-pattern: Activator-inhibitor system reproduces bridging in whole-slide scan:

Source for a (e.g. Rspondin3) : CV;
Source for b: PV
CYP positive if a > a_{th}

$$\frac{da}{dt} = s_{a;cv} - D_a \Delta a - d_a a - kab$$

$$\frac{db}{dt} = s_{b;pv} - D_b \Delta b - d_b b - gab$$

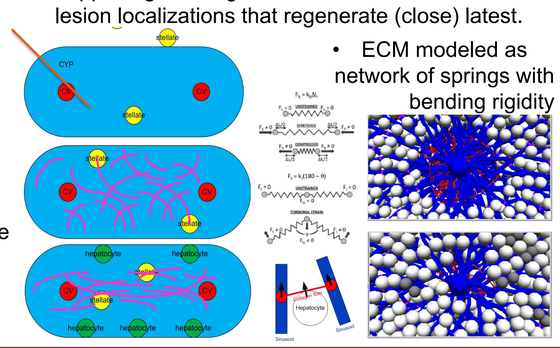
Towards a model of fibrotic wall formation



After single APAP-dose:

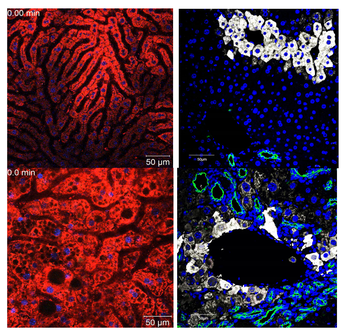
- Hepatic stellate cells in CYP-pos region at loc. of max. damage
- Macrophages peak close to CV at 4d, disappearing after closure
- Suggests HCSs produce ECM, later removed by macrophages

- Hypothesis: ***After multiple doses***, removal not happening, leading to accumulation of ECM at lesion localizations that regenerate (close) latest.



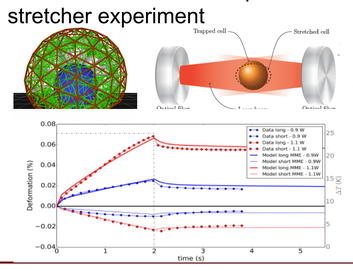
- ECM modeled as network of springs with bending rigidity

Architectural distortion after Western diet and repetitive CCl4-doses: call for new model

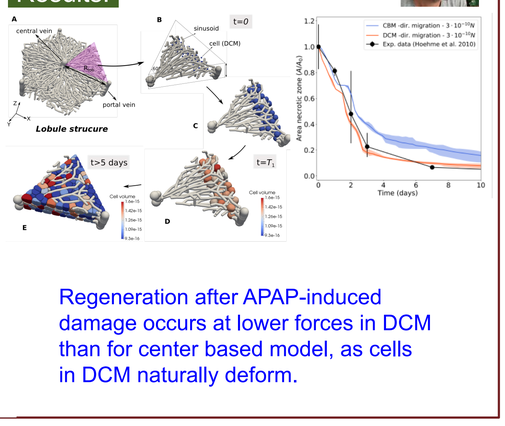


After WD (Left) or CCL4 (right) distortion of architecture;
Cell shape inhomogenous.

Center-based model cannot capture correctly architecture distortion & biomechanics after WD or CCl4-induced fibrosis
-> Deformable Cell Model (DCM), triangulating cell shape.
-> DCM calibrated with optical stretcher experiment



Results:



Regeneration after APAP-induced damage occurs at lower forces in DCM than for center based model, as cells in DCM naturally deform.

Publications (only those appeared): Ghallab, Celliere, ..., Drasdo*, Gebhardt*, Hengstler* 2016. Journal of Hepatology 64(4): 860 (*shared senior authors); Hoehme*, Bertaux*, ... Hengstler, Drasdo*, 2018 (*shared first authors). Bull. Math. Biol. Volume 80, Issue 5; Leist et. al. Arch Toxicol. 2017 Nov;91(11); Peters et. al. J Anat. 2017 Mar;230(3):471-483; Hoehme, …, Drasdo, Hengstler, Methods Mol Biol. 2017;1506:319-362

funded by Federal Ministry of Education and Research