virtual liver network

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From Single Hepatocytes to Whole Liver Function: A Multi-Scale Model of Human Galactose Metabolism

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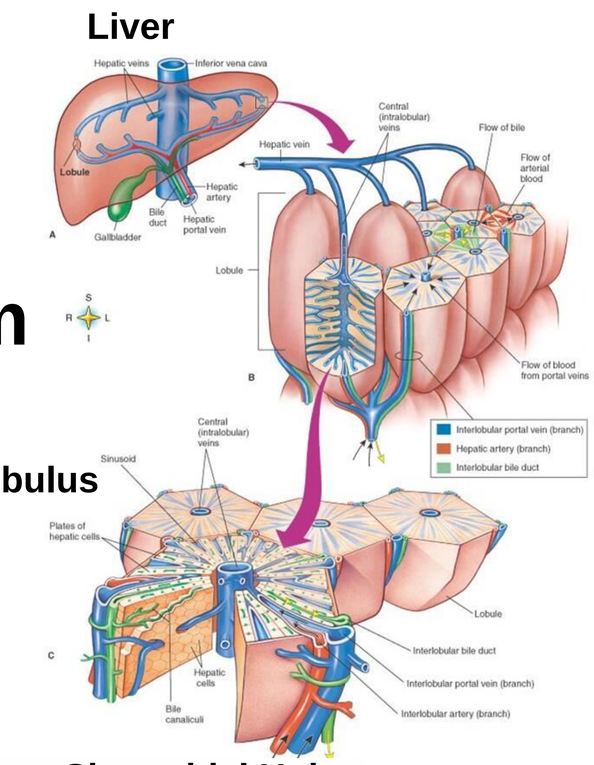
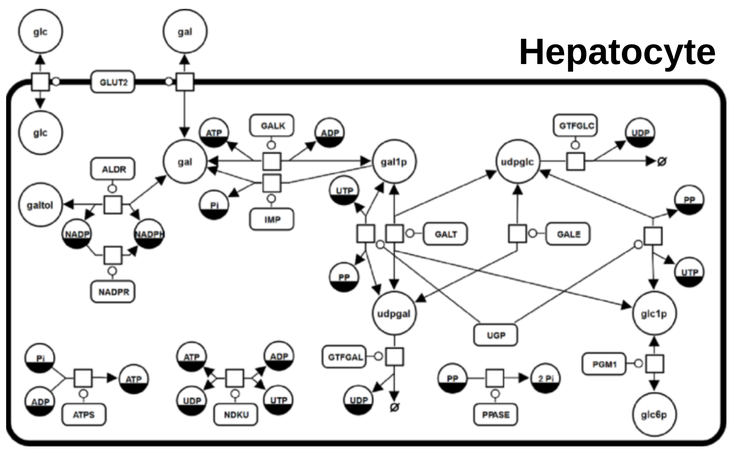
MODEL

Introduction

The liver plays a central role in maintaining the homeostasis of numerous plasma metabolites, clearance of substances and detoxification of xenobiotics. For galactose, the liver is the most important organ for the whole-body metabolism and clearance.

The liver architecture is unique within the body in that hepatic functionality is parallelized across a multitude of structural similar hexagonal subunits, the lobuli.





Reactions: (ALDR) Aldose reductase (galactitol NAD 1-oxidoreductase); (ATPS) ATP synthesis; (GALDH) Galactose 1-dehydrogenase; (GALE) UDP-glucose 4-epimerase; (GALK) Galactokinase; (GALT) Galactose-1-phosphate uridyl transferase; (GLUT2) Facilitated glucose transporter member 2; (GTFGAL) Glycosyltransferase galactose; (GTFGLC) Glycosyltransferase glucose; (NADPR) NADP reductase; (NDKU) Nucleoside diphosphokinase, ATP:UDP phosphotransferase; (IMP) Inositol monophosphatase; (PGM1) Phosphoglucomutase-1; (PPASE) Pyrophosphatase; (UGALP) UDP-galactose pyrophosphorylase; (UGP) UDP-glucose pyrophosphorylase;

Metabolites: (adp) ADP; (atp) ATP; (gal) D-galactose; (gal1p) D-galactose 1-phosphate; (galnat) D-galactonate; (galtol) D-galactitol; (glc) D-glucose; (glc1p) D-glucose 1-phosphate; (glc6p) D-glucose 6-phosphate; (nadp) NADP; (nadph) NADPH; (pi) phosphate; (pp) pyrophosphate; (udp) UDP; (udpgal) UDP-D-galactose; (udpglc) UDP-D-glucose; (utp) UTP;

Within a single lobulus a network of capillaries, the so-called liver sinusoids, which are surrounded by hepatocytes, form the smallest functional units.

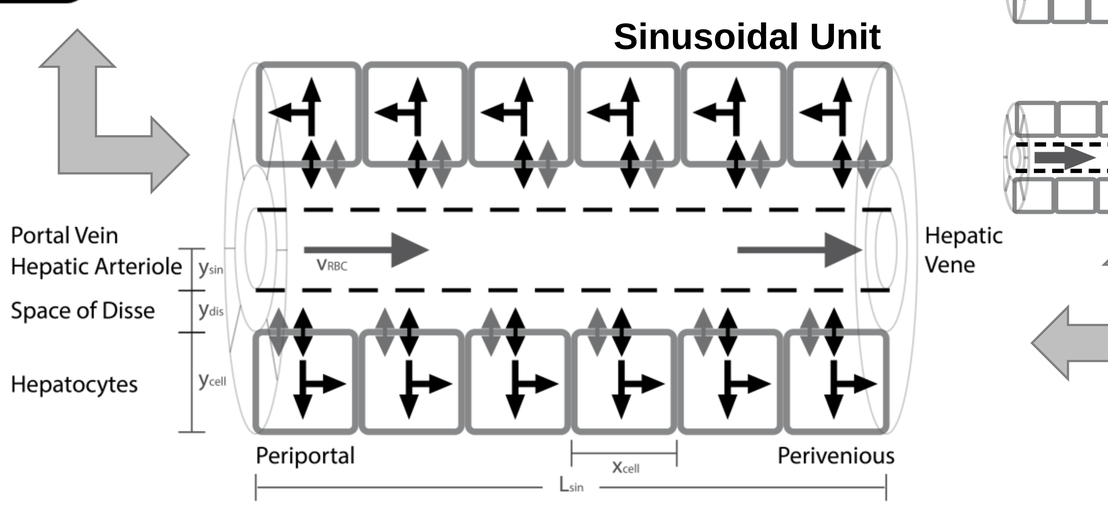
Model Overview

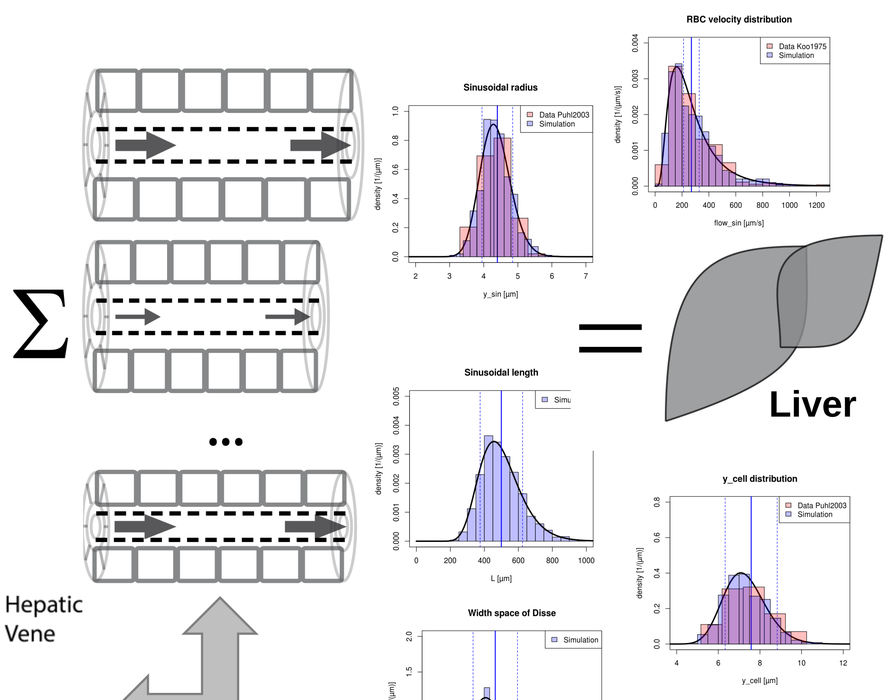
We present a multi-scale model of liver galactose metabolism bridging the scales from single-cell metabolism over the tissue level to the whole-organ. The model combines a detailed kinetic model of the cellular galactose metabolism with a tissue-scale perfusion model of the sinusoid. The metabolic capacity of the whole liver is modelled by integrating the heterogeneous contribution of sinusoids differing in blood-flow rates and tissue-architecture and metabolism.

[<] Fig.1A Schema of the metabolic network in system in Systems Biology Graphical Notation (SBGN). The kinetic model of hepatic galactose metabolism is implemented in SBML.

[V] Fig.1B Schema of the tissue-scale model of hepatic metabolism consisting of diffusion and convection based transport of substances in the blood, diffusion-based transport of substances in the space of Disse and detailed kinetic models of metabolism on the cellular level. Galactose metabolism was included in the sinusoid-scale model with exchangeable metabolites between the cells and the space of Disse.

[>] Fig.1C Modeling the liver via integration of heterogenous tissue-models. A multitude of sinusoidal units is sampled from the distribution of tissue parameters and integration over the whole liver volume is performed.





RESULTS

The model was validated with data from multiple scales and the effects of local & global metabolic & structural parameters were analysed

Simulations

- Multiple Indicator Dilution Curves
- Galactose elimination capacity (GEC) and galactose clearance
- Effect of metabolic deficiencies (galactosemias)

Work in progress

- Effect of alterations in global liver volume and blood flow (aging)
- Effect of structural alterations of the liver (cirrhosis)

Galactose Elimination

$$GE = (c_a^{gal} - c_v^{gal})$$

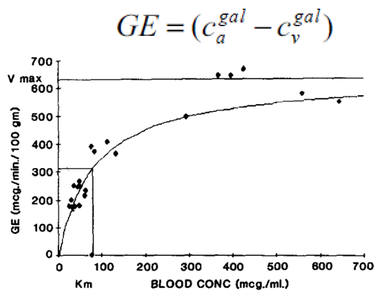
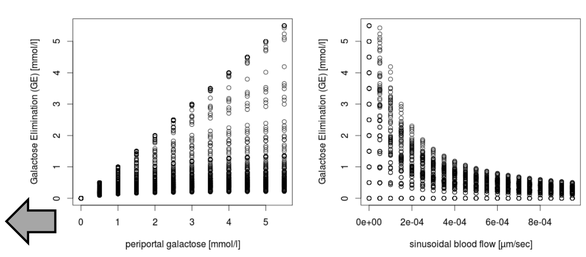
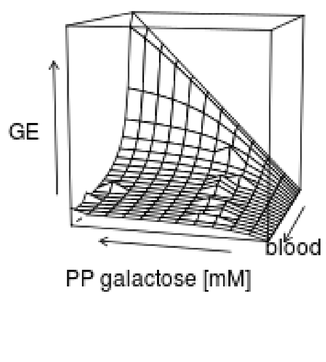


FIG. 1. Galactose elimination kinetics. Points represent individual animals. Superimposed line as determined by the Michaelis–Menten equation using the elimination constants, V_{max} and K_m, from Fig. 2.



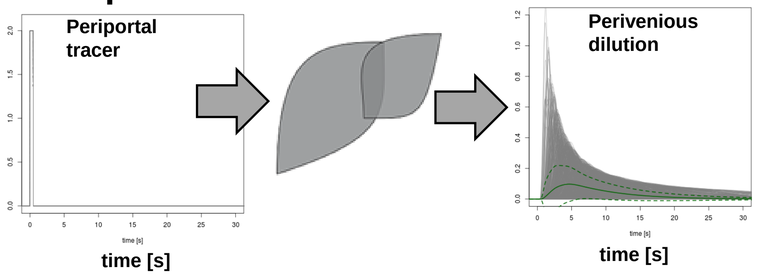


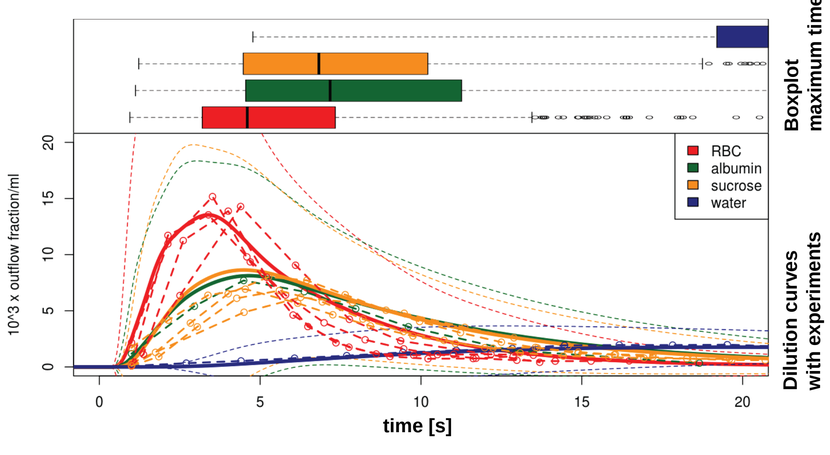
Galactosemias

Table 4 - Kinetic parameters in GALK, GALT and GALE deficiencies.

	Enzyme	Variant	k_{cat} [1/s] (%wt)	K_m(gal) [mM] (%wt)	K_m(atp) [mM] (%wt)	Reference
	GALK	Wild Type	8.7±0.5 (100)	0.97±0.22 (100)	0.034±0.004 (100)	[51]
1	GALK	H44Y	2.0±0.1 (23)	7.70±4.40 (794)	0.130±0.009 (382)	[51]
2	GALK	R68C	3.9±0.8 (45)	0.43±0.15 (44)	0.110±0.035 (324)	[51]
3	GALK	A198V	5.9±0.1 (68)	0.66±0.22 (68)	0.026±0.001 (76)	[51]
4	GALK	G346S	0.4±0.04 (5)	1.10±0.16 (113)	0.005±0.002 (15)	[51]
5	GALK	G347S	1.1±0.2 (13)	13.0±2.0 (1340)	0.089±0.034 (262)	[51]
6	GALK	G349S	1.8±0.1 (21)	1.70±0.48 (175)	0.039±0.004 (115)	[51]
7	GALK	E43A	6.7±0.02 (77)	1.90±0.50 (196)	0.035±0.0003 (103)	[100]
8	GALK	E43G	0.9±0.02 (10)	0.14±0.01 (14)	0.0039±0.0006 (11)	[100]
	Enzyme	**Variant**	**V_{max} [nmol/mg/s] (% wt)**	**K_m(gal1p) [mM] (%wt)**	**K_m(udpglc) [mM] (%wt)**	**Reference**
	GALT	Wild Type	804±65 (100)	1.25±0.36 (100)	0.43±0.09 (100)	[22]
9	GALT	R201C	396±59 (49)	1.89±0.62 (151)	0.58±0.13 (135)	[22]
10	GALT	E220K	253±53 (31)	2.34±0.42 (187)	0.69±0.16 (160)	[22]
11	GALT	R223S	297±25 (37)	1.12±0.31 (90)	0.76±0.09 (177)	[22]
12	GALT	I278N	45±3 (6)	1.98±0.35 (158)	1.23±0.28 (286)	[22]
13	GALT	L289F	306±23 (38)	2.14±0.21 (171)	0.48±0.13 (112)	[22]
14	GALT	E291V	385±18 (48)	2.68±0.16 (214)	0.95±0.43 (221)	[22]
	Enzyme	**Variant**	**k_{cat} [1/s] (%wt)**	**K_m(udpglc) [mM] (%wt)**		**Reference**
	GALE	Wild Type	36±1.4 (100)	0.069±0.012 (100)		[59]
15	GALE	N34S	32±1.3 (89)	0.082±0.015 (119)		[59]
16	GALE	G90E	0.046±0.0028 (0)	0.093±0.024 (135)		[59]
17	GALE	V94M	1.1±0.088 (3)	0.160±0.038 (232)		[59]
18	GALE	D103G	5.0±0.23 (14)	0.140±0.021 (203)		[59]
19	GALE	L183P	11±1.2 (31)	0.097±0.040 (141)		[59]
20	GALE	K257R	5.1±0.29 (14)	0.066±0.015 (96)		[59]
21	GALE	L313M	5.8±0.36 (16)	0.035±0.011 (51)		[59]
22	GALE	G319E	30±1.3 (83)	0.078±0.013 (113)		[59]
23	GALE	R335H	15±0.48 (42)	0.099±0.012 (143)		[59]

Multiple Indicator Dilution Curves





Galactose Clearance & Extraction

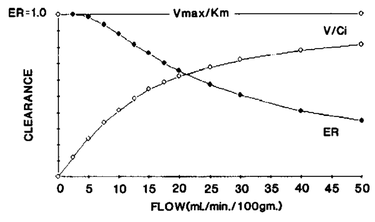
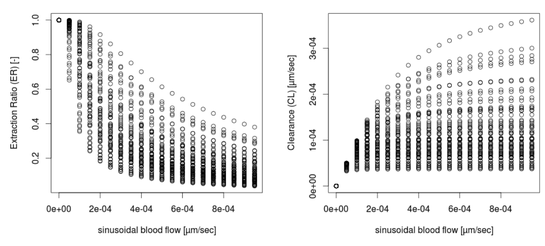


FIG. 6. Clearance and extraction ratio vs flow. Extraction ratio decreases as flow increases. Clearance increases with flow to a maximum of V_{max}/K_m.



$$GE = (c_a^{gal} - c_v^{gal})$$

$$R = F \cdot (c_a^{gal} - c_v^{gal})$$

$$ER = \frac{(c_a^{gal} - c_v^{gal})}{c_a^{gal}}$$

$$Cl = \frac{R}{c_a^{gal}} = Q_{tot} \cdot \frac{(c_a^{gal} - c_v^{gal})}{c_a^{gal}}$$