

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

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ABBREVIATIONS

IVM – in vivo microscopy
IPM – in plastic microscopy
OPS – orthogonal polarization spectral imaging
QSD – quantitative stereological description
SEM – scanning electron microscopy
SE – standard error (measurement)
SD – standard deviation
TEM – transmission electron microscopy

SUPPLEMENTARY TABLES

Supplementary Table 1 - Reactions and transporters in human galactose metabolism and kinetic parameters.

Id	Information	Kinetics
GLUT2	<p>Facilitated glucose transporter member 2</p> <p>D-glucose (disse) [glc_dis] ↔ D-glucose (cytosol) [glc] D-galactose (disse) [gal_dis] ↔ D-galactose (cytosol) [gal]</p> <p>Mechanism TCDB:2.A.1.1 (glucose transporter subfamily)</p> <p>Protein/Structure UniProt:P11168 (GTR2_HUMAN)</p> <p>Gene SLC2A2, GLUT2</p> <p>Disease MIM:227810 (Fanconi-Bickel syndrome; FBS)</p> <p>Galactose and glucose transported via GLUT2 (competitive inhibition kinetics) (Brown, 2000; Colville, et al., 1993)</p> <p>Deficient transport of galactose into hepatocytes in human patients with defective GLUT2 transporters (Fanconi-Bickel syndrome) resulting in galactose malabsorption/intolerance (Brown, 2000; Leslie, 2003).</p>	<p>km(D-glc)=21.7 ± 1.8mM (rat liver) (Ciaraldi, et al., 1986) km(D-glc)=66±14mM (rat? hepatocytes) (Elliott and Craik, 1982) km(3-O-MG)=42.3±4.1mM (human liver) (Gould, et al., 1991; Walmsley, et al., 1998) km(3-O-Methyl glc)=17.3 ± 4.3mM (rat liver) (Ciaraldi, et al., 1986)</p> <p>km(D-gal)=174±48mM (rat? hepatocytes) (Elliott and Craik, 1982) km(D-gal) > 50mM (GLUT2 enderocytes) (Walmsley, et al., 1998) km(D-gal) = 85.5 ± 10.7mM (human, liver-type GLUT2) (Colville, et al., 1993) km(D-gal) = 92 ± 8.4mM (human, liver-type GLUT2) (Arbuckle, et al., 1996)</p> <p>Km(D-fru) = 66mM (Walmsley, et al., 1998) Km(D-fru)=212±32mM (rat? hepatocytes) (Elliott and Craik, 1982)</p> <p>Accumulation rate (human GLUT2) v(deoxy-D-glc) = 4.33±0.15 pmol/min/oocyte v(D-gal) = 1.68±0.09 pmol/min/oocyte v(D-fru) = 0.78±0.09 pmol/min/oocyte</p> <p>v(D-glc)=220±19mmol/min/l of cell H2O (rat? hepatocytes) (Elliott and Craik, 1982) v(D-gal)=288±48 mmol/min/l of cell H2O (rat? hepatocytes) (Elliott and Craik, 1982) v(D-fru)=291±26 mmol/min/l of cell H2O (rat? hepatocytes) (Elliott and Craik, 1982)</p>
GALK	<p>Galactokinase</p> <p>D-galactose [gal] + ATP [atp] ↔ D-galactose 1-phosphate [gal1p] + ADP [adp]</p> <p>Reaction EC:2.7.1.6 RHEA:13556 KEGG:R01092</p> <p>Protein</p>	<p>Two-substrate ordered, ternary complex reaction (Timson and Reece, 2003)</p> <p>kcat(gal) = 8.7±5 1/s (SABIORK:14785)(Timson and Reece, 2003) km(atp) = 0.034±0.004mM (SABIORK:14792)(Timson and Reece, 2003) km(gal)=0.97±0.22 mM (SABIORK:14785) (Timson and Reece, 2003) km(gal) = 0.436mM (SABIORK:45367), (Sanguiuolo, et al., 2004)</p> <p>Uncompetitive product inhibition of GALK (adult rat liver) by gal1p with both 1mM and 5mM gal1p altering the Km for galactose from 0.150mM to 0.800mM</p>

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TODO: Update the SABIO-RK entries as soon as available in database
TODO: crosscheck the table with annotations in SBML

	<p><u>UniProt:P51570</u> (GALK1_HUMAN) homodimer P51570*2 Gene GALK, GALK1 Disease <u>MIM:230200</u> (GALCT2 Galactosemia II)</p> <p>Galactokinase being rate limiting for galactose clearance (Schirmer, et al., 1986) -> [27,28, 50]</p>	<p>(1mM gal1p caused 15% inhibition, 5mM gal1p 50% inhibition) ki(gal1p) = 5.3mM (5.0-5.7mM) (adult rat liver) (Cuatrecasas and Segal, 1965)</p>
IMP	<p>Inositol monophosphatase D-galactose 1-phosphate [gal1p] ↔ D-galactose [gal] + phosphate [pi]</p> <p>Reaction EC:3.1.3.25 Protein <u>UniProt:P29218</u> (IMPA1_HUMAN) homodimer P29218*2 Gene IMPA1, IMPA</p> <p>Normal substrate inositol-1p (ino1p)</p>	<p>Competitive inhibition model Kinetic analysis demonstrated that gal1p competitively inhibited human IMP1 by increasing Km for inositol-1p (ino1p) from 320±50µM to 980±70µM without changing the Vmax (Slepek, et al., 2007) km(ino1p) = 0.320±0.050mM (Slepek, et al., 2007) km(gal1p) = 0.35mM (similar kinetics gal1p to ino1p in vitro) (Parthasarathy, et al., 1997)</p>
GALT	<p>Galactose-1-phosphate uridyl transferase UDP-D-glucose [udpglc] + D-galactose 1-phosphate [gal1p] ↔ D-glucose 1-phosphate [glc1p] + UDP-D-galactose [udpgal].</p> <p>Reaction EC:2.7.7.12 <u>RHEA:13992</u> <u>KEGG:R00955</u> Protein <u>UniProt:P07902</u> (GALT_HUMAN) homodimer P07902*2 Gene GALT Disease <u>MIM:230400</u> (GALCT Galactosemia)</p>	<p>The catalytic mechanism of GALT is ping-pong kinetics with covalent intermediate UMP-enzyme (Facchiano and Marabotti, 2010).</p> <p>Mutation analysis (Quimby, et al., 1996) km(gal1p) = 0.57±0.14mM (human, wildtype) (Quimby, et al., 1996) km(udpglc) = 0.21±0.04mM (human, wildtype) (Quimby, et al., 1996)</p> <p>Mutation analysis (Tang, et al., 2012) km(gal1p) = 1.25±0.36mM (human, wildtype) (Tang, et al., 2012) km(udpglc) = 0.43±0.09mM (human, wildtype) (Tang, et al., 2012)</p> <p>(?species, 4°C) (Geeganage and Frey, 1998) km(udpglc) = 0.5±0.1mM v(glc1p) = 281± 18 1/s km(glc1p) = 0.37±0.18mM v(glc1p) = 226± 10 1/s km(gal1p) = 0.061±0.020mM v(glc1p) = 166± 13 1/s</p>

	<p>Potent linear competent inhibitors UTP and UDP of UDP-glucose (Segal and Rogers, 1971):</p> <p>Ki(UTP) = 0.13mM (rat, liver)</p> <p>Ki(UDP) = 0.35mM (rat, liver)</p> <p>Ki(UMP) = 2.3mM (rat, liver)</p> <p>Ki(UDP-glucuronic acid)=0.40mM (rat, liver)</p>
GALE	<p>UDP-glucose 4-epimerase</p> <p>UDP-D-glucose [udpglc] ↔ UDP-D-galactose [udpgal]</p> <p>Reaction</p> <p>EC:5.1.3.2</p> <p>RHEA:22171</p> <p>KEGG:R00291</p> <p>Protein</p> <p>UniProt:Q14376 (GALE_HUMAN)</p> <p>homodimer Q14376*2</p> <p>Gene</p> <p>GALE</p> <p>Disease</p> <p>MIM:230350 (GALE deficiency)</p> <p>Alternative activity with GlcNAc:</p> <p>UDP-GalNAc ↔ UDP-GlcNAc</p> <p>“Ethanol treatment increases the NADH/NAD ratio in liver (Keppler, et al., 1970) [2-4] and by this inhibits the GALE [3,5]. Under these conditions oxidation and elimination [6-8] of galactose are impaired. Combined galactose+ethanol treatment results in accumulation of gal1p and udpgal in rat liver. The formation of high amounts of udpgal leads to a change in the distribution of liver uracil nucleotides. A marked decrease of udpglc, utp, udp and ump is followed by an increase of the sum of uracil nucleotides.” (Keppler, et al., 1970)</p> <p>“The GALE reaction is indicated as the rate-limiting step of galactose metabolism in rat liver by the ratio of galactose metabolites (Keppler, et al., 1970)“.</p> <p>“The almost 4-fold increase of gal1p and updgal and the even stronger drop of the udpglc content in the ethanol treated liver after a galactose load demonstrates the ethanol-induced</p>

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Ki(UDP-glucuronic acid)=0.40mM (rat, liver)

Mutation analysis(Timson, 2005)

km(udpgal)=0.069±0.012mM (human, wildtype) (Timson, 2005)

kcat(udpgal) = 36±1.4 1/s (human, wildtype) (Timson, 2005)

km(udpgal) = 0.15 ± 0.02mM (human, wildtype) (Wohlers and Fridovich-Keil, 2000)

km(udpgal, V94M) = 0.27 ± 0.01mM (human, V94M) (Wohlers and Fridovich-Keil, 2000)

km(udpgal)=0.140± 0.007mM (human, wildtype) (SABIORK:19823) (Winans and Bertozzi, 2002)

km(udpgal)=0.120± 0.04mM (human, wildtype) (SABIORK:46260) (Wasilenko, et al., 2005)

kcat= 33.8±11.2 (human, wildtype) (SABIORK:16222) (Thoden, et al., 2002)

km(udpgal) = 0.230±0.06mM (human, wildtype) (SABIORK:46263) (Quimby, et al., 1997)

inhibition of the GALE” (Keppler, et al., 1970).
“Galactose provokes pronounced alterations of the uracil nucleotide contents in the liver, which are intensified by an inhibition of the GALE” (Keppler, et al., 1970)

UGP	UDP-glucose pyrophosphorylase D-glucose 1-phosphate [glc1p] + UTP [utp] ↔ UDP-glucose [udglc]+ diphosphate [pp] Reaction EC:2.7.7.9 RHEA:19892 KEGG:R00289 Protein UniProt:Q16851 (UGPA_HUMAN) homooctamer Q16851*8 Gene UGP2, UGP1	Enzyme displays simple Michaelis-Menten kinetics in both directions (Chang, et al., 1996) MgUTP is a product inhibitor that shows competitive inhibition with respect to UDP-Glc (Chang, et al., 1996) (human, liver, wildtype) (Chang, et al., 1996) km(udpglc) = [0.031 - 0.051]mM km(pp) = [0.172 - 0.210] mM km(glc1p) = [0.172 - 0.174] mM km(utp) = [0.563 - 0.692] mM ki(utp) = 0.477± 41 mM (competitive inhibition with respect to UDP-glc) V_{fwd}/V_{rev} = 0.260 (human, liver, wildtype) (Duggleby, et al., 1996) km(udpglc) = 0.049±0.004mM km(pp) = 0.166±0.013 mM km(glc1p) = 0.172±0.010 mM km(utp) = 0.563±0.115 mM ki(utp) = 0.643± 0.047 mM (competitive inhibition with respect to UDP-glc) ki(udpglc) = 0.013± 4 mM (competitive inhibition with respect to UTP?) (human, liver, wildtype) (Knop and Hansen, 1970) keq([udpglc][pp]/([UTP][glc1p])) = 0.15 – 0.16 km(udpglc) = 50mM km(utp) = 48 mM km(glc1p) = 95±10 mM keq([UTP][glc1p]/([udpglc][pp])) = 4.55±0.1 (Guynn, et al., 1974) (0.22) The saturating concentration for UDP-galactose is 10 times that of UDP-glucose: km(udpgal) = 10*km(udpglc) ~ 0.5mM (human, liver, wildtype) (Knop and Hansen, 1970) km(udpgal) = 0.420mM (rabbit, liver, wildtype) (Turnquist, et al., 1974) udpgal was an adequate substrate at 10 times the concentration of udpglc, showing 14.3% of udpglc (Calf) and 12.0% (Human). activity with udpgal 2-12% of udpglc (12% with 3mM udpgal) (human liver) (Turnquist, et al., 1974)
UGALP	UDP-galactose pyrophosphorylase D-galactose-1-phosphate [gal1p] + UTP [utp] + ↔ UDP-D-galactose [udpgal] pyrophosphate [pp] Reaction EC:2.7.7.10 RHEA:14212 KEGG:R00502 Protein UniProt:Q16851 (UGPA_HUMAN) homooctamer Q16851*8 Gene UGP2, UGP1 The formation of UDP-glucose is the major physiological function of UGP, however at slow rates, the enzyme also catalyzes the phosphorylation of UDP-galactose (Knop and Hansen, 1970) [Segal1968]. Not significant in normal physiological conditions, but in galactosemic patients could circumvent GALT deficiency	

	<p>(Isselbacher ?).</p> <p>Stable transfection of human UGP (hUGP2) rescued galactose GALT deficient yeast from “galactose toxicity [Lai2002].</p>	<p>“The activity of UDPG:galactose-1-phosphate uridylyltransferase from rat liver under optimal conditions in vitro is less than 5% of the UDPG pyrophosphorylase activity” (Keppler, et al., 1970)[Keppler1970 ->39,40]</p> <p>gal1p as competitive inhibitor of glc1p</p> <p>“Previously, we showed that galactose-1-phosphate competitively inhibited UDP-glucose pyrophosphorylase, leading to 66% reduction in UDP-glucose/galactose contents in GALT-deficient cells under galactose challenge” [Slepek2007->Lai2002].</p>
ALDR	<p>Aldose reductase (galactitol NAD 1-oxidoreductase)</p> <p>D-galactose [gal] + NADPH [nadph] + H ↔ galactitol [galtol] + NADP [nadp]</p> <p>Reaction EC:1.1.1.21 RHEA:12792 -> RHEA:37967 KEGG:R01095</p> <p>Protein UniProt:P15121 (ALDR_HUMAN) monomer P15121*1</p> <p>Gene AKR1B1, ALDR1</p> <p>Aldolase reductase is specific for NADPH as cofactor (NADH ~10% of NADPH-dependent activity) (Wermuth and von Wartburg, 1982). “Aldolase reductase catalyzes the conversion of aldoses and a number of other aldehydes to the corresponding alcohol metabolites. It is one of several cytosolic, monomeric, NADPH-dependent aldehyde and ketone reductases of wide substrate specificity” (Wermuth, et al., 1982)”.</p>	<p>km(gal) = 40.0mM (human brain) (SABIORK:22893) (Wermuth, et al., 1982) kcat(gal) = 0.40 1/s (human brain) (SABIORK:22893) (Wermuth, et al., 1982)</p> <p>km(gal) = 110.0mM (human brain) (SABIORK:15695) (Wermuth and von Wartburg, 1982)</p>
PGM1	<p>Phosphoglucumutase-1</p> <p>D-glucose 1-phosphate [glc1p] ↔ D-glucose 6-phosphate [glc6p]</p> <p>Reaction EC:5.4.2.2 KEGG:R00959 RHEA:23539</p> <p>Protein (multiple isoforms PGM1, PGM2)</p>	<p>The equilibrium lies strongly toward glc6p and reaction proceeds through ping-pong mechanism (Guynn, et al., 1974) The kinetic properties of PGM1 and PGM2 are essentially the same. PGM1 is specific for mutation of glucose, whereas PGM2 also has phosphoribomutase activities. (human, RBC) (Accorsi, et al., 1989)</p> <p>[glc6p]/[glc1p] ~10-12 (Guynn, et al., 1974) DeltaG = -7.1 kJ/mol (König, et al., 2012)</p>

	<p>UniProt:P36871 (PGM1_HUMAN) monomer P36871*1 main isoform for glc1p ↔ glc6p reaction</p> <p>Gene PGM1</p> <p>Disease MIM:612934 (Glycogen storage disease 14) MIM:614921 (Congenital disorder of glycosylation 1T CDG1T)</p> <p>Protein UniProt:Q96G03 (PGM2_HUMAN)</p> <p>Gene PGM2</p> <p>CDG1T - A multisystem disorder caused by a defect in glycoprotein biosynthesis and characterized by under-glycosylated serum glycoproteins.</p>	<p>km(glc1p) = 0.049mM (human, RBC) (Quick, et al., 1974)</p> <p>km(glc1p) = 0.045mM (rat, heart) (Kashiwaya, et al., 1994) km(glc6p) = 0.67mM (rat, heart) (Kashiwaya, et al., 1994)</p> <p>km(glc1p) = 0.083mM (human, RBC, PGM1) (Accorsi, et al., 1989) ki(fru16bp) = 0.092mM (human, RBC, PGM1) (Accorsi, et al., 1989)</p>
PPASE	<p>Pyrophosphatase Pyrophosphate [pp] + H2O → 2 phosphate [pi]</p> <p>Reaction EC:3.6.1.1 RHEA:24579 KEGG:R00004</p> <p>Protein UniProt:Q15181 (IPYR_HUMAN) homodimer Q15181*2</p> <p>Gene PPA1, IOPPP, PP</p>	<p>km(pp) = 0.005mM (rat liver) (Yoshida, et al., 1982) km(pp) = 0.14mM (human erythrocyte) (Thuillier, 1978) km(pp) = 0.07mM (rat liver) (Irie, et al., 1970) Delta G0 = -23.56 kJ/mol (Thuillier, 1978) Delta G0 = -19.2 kJ/mol (Guynn, et al., 1974)</p>
NDKU	<p>Nucleoside diphosphokinase (ATP:UDP phosphotransferase) ATP [atp] + UDP [udp] ↔ ADP [adp] + UTP [udp]</p> <p>Reaction EC: 2.7.4.6 RHEA:25101 KEGG:R00156</p> <p>Multitude of isoforms</p>	<p>Compulsory-order substituted-enzyme (Ping Pong Bi Bi) mechanism (Lam and Packham, 1986)</p> <p>km(atp) = 0.38mM (human, platelets) (Lam and Packham, 1986) km(adp) = 0.024mM (human, platelets) (Lam and Packham, 1986) km(gtp) = 0.12mM (human, platelets) (Lam and Packham, 1986)</p> <p>km(atp) = 1.33mM (rat, liver) (Kimura and Shimada, 1988) km(adp) = 0.042mM (rat, liver) (Kimura and Shimada, 1988) km(udp) = 0.19mM(rat, liver) (Kimura and Shimada, 1988)</p>

		km(atp) = 1.80 mM (rat, liver) (Fukuchi, et al., 1994) km(adp) = 0.066 mM (rat, liver) (Fukuchi, et al., 1994) km(utp) = 27.00mM (rat, liver) (Fukuchi, et al., 1994) km(gtp) = 0.15mM (rat, liver) (Fukuchi, et al., 1994) km(gdp) = 0.049mM (rat, liver) (Fukuchi, et al., 1994)
NADPR	NADP reductase NADP [nadp] + H ₂ →NADPH [nadph] Modeled via glucose-6-phosphate dehydrogenase in pentose phosphate pathway D-glucose 6-phosphate [glc6p] + NADP [nadp] → 6-phospho-D-glucono-1,5-lactone + NADPH [nadph] + H Reaction EC: 1.1.1.49 RHEA:15844 KEGG:R00835 Protein UniProt:P11413 (G6PD_HUMAN) homotetramer (dimer of dimer) P11413*4 Gene G6PD	Delta G0 = -19.6 kJ/mol [Schuster1995] km(glc6p) = 0.040±0.008 mM (human, placenta) (Ozer, et al., 2001) km(nadp) = 0.020±0.010 mM (human, placenta) (Ozer, et al., 2001) ki(nadph) = 0.0171±0.0032 mM (human, placenta) (Ozer, et al., 2001) km(glc6p) = 0.072 mM (human, RBC) (Bautista, et al., 1992) km(glc6p) = 0.069±0.003 mM (human, recombinant) (Bautista, et al., 1992) km(nadp) = 0.013 mM (human, RBC) (Bautista, et al., 1992) km(nadp) = 0.012±0.002 mM (human, recombinant) (Bautista, et al., 1992) km(nadph) = 0.015±0.002 mM (human, RBC) (Bautista, et al., 1992) km(nadph) = 0.014±0.003 mM (human, recombinant) (Bautista, et al., 1992) km(glc6p) = 0.326mM (rat, liver) km(glc6p) = 0.157mM (rat, liver) (Corpas, et al., 1995; Corpas, et al., 1995) km(nadp) = 0.108 mM (rat, liver) km(nadp) = 0.258 mM (rat, liver) (Corpas, et al., 1995; Corpas, et al., 1995) ki(nadhp) = 0.010 mM (rat, liver) ki(nadhp) = 0.021 mM (rat, liver) (Corpas, et al., 1995; Corpas, et al., 1995)
ATPS	ATP synthesis ADP [adp] + phosphate [pi] → ATP [atp] Modeled via general ATP producing reaction representative for ATP production via glycolysis and oxidative phosphorylation	
GTF GTFGAL GTFGLC	Glycosyltransferase Acceptor [gac] + UDP-glucose [udpglc] -> Acceptor-glucose[gacglc] + UDP [udp] Acceptor [gac] + UDP-glucose [udpgal] -> Acceptor-glucose[gacgal] + UDP [udp] Enzymes that transfer mono- or oligosaccharides from donor molecules to growing oligosaccharide chains or proteins are called glycosyltransferases (Gtfs)	

GALDH	Galactose 1-dehydrogenase D-galactose + NAD ⁺ ↔ D-galactono-1,4-lactone + NADH + H ⁺ EC.1.1.1.48 (Brenda only bacteria) D-galactose -> galactonate (first enzyme in oxidative pathway) [Segal1968 -> Cuatrecasas1966,15] Alternative pathway to xylulose. D-Galactose + Oxygen + H2O <=> D-Galactonate + Hydrogen peroxide EC:1.1.3.9 <u>KEGG:R01098</u> (only bacteria)
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Supplementary Table 2 - Metabolites in hepatic galactose metabolism.

Id	Name (mass) Annotation	Initial Concentration	Comments
glc	D-glucose (M _w 180.2) <u>CHEBI:4167</u> <u>KEGG:C00031</u>	5.5mM (König, et al., 2012)	[glc] = 5.5mM (König, et al., 2012) 3-10mM (depending on physiological state)
gal	D-galactose (M _w 180.2) <u>CHEBI:4139</u> <u>KEGG:C00124</u>	0.00012mM (no galactose) 0.00144mM (GALT deficient) 0.0013-0.0027mM (GALE deficient)	plasma of post-absorptive humans (data considerable lower (3-18-fold) than conventional enzymatic assay) (Schadewaldt, et al., 2000) [gal] = 0.12±0.03μM (n=16) healthy subjects [gal] = 1.44±0.54μM (n=10) classical galactosemia (GALT deficiency) [gal] = 0.17±0.07μM (n=5) obligate heterozygous parents of classical galactosemia [gal] = 0.11±0.04μM (n=15) diabetic patients GALE deficient patients (blood) (Yamaguchi, et al., 1989) [gal]=24-29mg/L (0.013-0.016mM) [gal]= 48mg/L (0.027mM) Neonatal control (blood): [gal]=13±6 mg/L (0.0072±0.0033mM) (Yamaguchi, et al., 1989) normal values: [gal]= 0.015±0.009mM (range 0-0.044mM) (Orfanos, et al., 1986) Cut-off values for newborn screening blood for galactosemias: “If gal > 60mg/L (0.033mM) or gal1P > 150mg/L (0.058mM).” (Yamaguchi, et al., 1989)
glc1p	D-glucose 1-phosphate (M _w 258.1) <u>CHEBI:58601</u> <u>KEGG:C00103</u>	0.012mM (no galactose) 0.011mM (1h galactose) 0.012mM (1h galactose, GALE inhibition)	[glc1p] = 0.012mM (König, et al., 2012) (Keppler, et al., 1970) [glc1p] = 0.010 ±0.004μmol/g_{ww} (~0.011mM) (starved + galactose 1h, rat, liver) [glc1p] = 0.011 ±0.005μmol/g_{ww} (~0.012mM) (ethanol, starved + galactose 1h, rat, liver) (Guynn, et al., 1974) [glc1p] = 0.0075±0.0010 μmol/g_{ww} (~0.0083mM) (rat liver, starved) [glc1p] = 0.0115±0.008 μmol/g_{ww} (~0.0127mM) (rat liver, fed ad

			libitum) [glc1p] = 0.0132±0.0007 µmol/g _{ww} (~0.0146mM) (rat liver, meal fed) [glc6p]/[glc1p] ~10-12
glc6p	D-glucose 6-phosphate (M _w 258.1) CHEBI:58225 KEGG:C00668	0.12mM (no galactose) 0.29mM (1h galactose) 0.30mM (1h galactose, GALE inhibition)	[glc6p] = 0.12mM (König, et al., 2012) (Guynn, et al., 1974) [glc6p] = 0.078±0.011 µmol/g _{ww} (~0.086mM) (rat liver, starved) [glc6p] = 0.147±0.012 µmol/g _{ww} (~0.163mM) (rat liver, fed ad libitum) [glc6p] = 0.157±0.007 µmol/g _{ww} (~0.174mM) (rat liver, meal fed) [glc6p]/[glc1p] ~10-12 (Keppler, et al., 1970) [glc6p] = 0.26 ±0.06µmol/g _{ww} (~0.29mM) (starved + galactose 1h, rat, liver) [glc6p] = 0.30 ±0.13µmol/g _{ww} (~0.33mM) (ethanol, starved + galactose 1h, rat, liver) [glc6p]/[glc1p] = 22.2 ±5.9 (starved + galactose 1h, rat, liver) [glc6p]/[glc1p] = 22.8 ±5.9 (ethanol, starved + galactose 1h, rat, liver)
gal1p	D-galactose 1-phosphate (M _w 258.1) CHEBI:58336 KEGG:C00446	0.001mM (no galactose) 0.20mM (1h galactose) 0.77mM (1h galactose, GALE inhibition) 1.2mM (GALT deficient, glucose) 5.2mM (GALT deficient, galactose)	(Lai, et al., 2003) (human cells) [gal1p] = ND (not detectable) (Control glucose medium) [gal1p] = 0.2±0.01mM (Control galactose medium) (Keppler, et al., 1970) [gal1p] = 0.18 ±0.04µmol/g _{ww} (~0.2mM)(starved + galactose 1h, rat, liver) [gal1p] = 0.69 ±0.11µmol/g _{ww} (~0.77mM) (ethanol, starved + galactose 1h, rat, liver) (Lai, et al., 2003) (human cells) [gal1p] = 1.2±0.4mM (GALT-deficient glucose medium) [gal1p] = 5.2±0.02mM (GALT-deficient galactose medium) GALT deficiency detected (blood) [gal1p] > 3.0mM (human cells) (Diepenbrock, et al., 1992) GALE deficient patients (blood) (Yamaguchi, et al., 1989) [gal1p]=330-360mg/L (1.28-1.39mM) [gal1p]=474 mg/L (1.84mM) (Yamaguchi, et al., 1989) Neonatal control (blood):

			gal1P=15±11 mg/L (0.058±0.042mM) (Yamaguchi, et al., 1989) normal values: gal1P = 0.038±0.027 mM (range 0-0.096µM) (Orfanos, et al., 1986) Mean concentration of gal1p (blood) was 0.15mM in cases below the cut-off of 0.74mM (Diepenbrock, et al., 1992)
udpglc	UDP-D-glucose (M _w 564.3) <u>CHEBI:58885</u> <u>KEGG:C00029</u>	0.34mM (no galactose) 0.27mM (1h galactose) 0.17mM (1h galactose, GALE inhibition)	[udpglc] = 0.38mM (König, et al., 2012) [udpglc] = 0.32±0.05 µmol/g_{ww} (~ 0.36mM) (rat liver)(Keppler and Decker, 1969) [udpglc] = 0.26±0.07 µmol/g_{ww} (~ 0.29mM) (rat liver)(Keppler, et al., 1969) (Keppler, et al., 1970) [udpglc] = 0.32 ±0.04µmol/g_{ww} (~ 0.36mM) (fed, rat, liver) [udpglc] = 0.29 ±0.05µmol/g_{ww} (~ 0.32mM) (starved, rat, liver) [udpglc] = 0.24 ±0.09µmol/g_{ww} (~ 0.27mM) (starved + galactose 1h, rat, liver) [udpglc] = 0.15 ±0.03µmol/g_{ww} (~ 0.17mM) (ethanol, starved + galactose 1h, rat, liver) (Guynn, et al., 1974) [udpglc] = 0.342±0.024 µmol/g_{ww} (~ 0.38mM) (rat liver, starved) [udpglc] = 0.433±0.023 µmol/g_{ww} (~ 0.48mM) (rat liver, fed ad libitum) [udpglc] = 0.347±0.027 µmol/g_{ww} (~ 0.39mM) (rat liver, meal fed) (Lai, et al., 2003) (human cells, in µmol/100g(cell protein)) [udpglc] = 236±25 (Control glucose medium) [udpglc] = 179±24 (76% glucose) (Control galactose medium) (Lai, et al., 2003) (human cells, in µmol/100g(cell protein)) [udpglc] = 157±10 (GALT-deficient glucose medium) [udpglc] = 110±10 (70% glucose) (GALT-deficient galactose medium)
udpgal	UDP-D-galactose (M _w 564.3) <u>CHEBI:66914</u> <u>KEGG:C00052</u>	0.11mM (no galactose) 0.36mM (1h galactose) 1.39mM (1h galactose, GALE inhibition)	Both the levels and approximate ratio of 1:3 of udpgal and udpglc are very tightly controlled in normal human cells. (Fridovich-Keil, 2006; Segal, 1995) (1:3 rule udpglc) (Keppler, et al., 1970) [udpgal] = 0.09 ±0.01µmol/g_{ww} (~ 0.10mM) (fed, rat, liver) [udpgal] = 0.09 ±0.01µmol/g_{ww} (~ 0.10mM) (starved, rat, liver)

	inhibition)		<p>[udpgal] = 0.32 ± 0.07 μmol/g_{ww} (~0.36mM) (starved + galactose 1h, rat, liver)</p> <p>[udpgal] = 1.25 ± 0.16 μmol/g_{ww} (~1.39mM) (ethanol, starved + galactose 1h, rat, liver)</p> <p>(Keppler, et al., 1970)</p> <p>[udpgal]/[udpglc] = 3.4 ± 0.3 (fed, rat, liver)</p> <p>[udpgal]/[udpglc] = 3.3 ± 0.3 (starved, rat, liver)</p> <p>[udpgal]/[udpglc] = 0.78 ± 0.39 (starved + galactose 1h, rat, liver)</p> <p>[udpgal]/[udpglc] = 0.11 ± 0.02 (ethanol, starved + galactose 1h, rat, liver)</p> <p>[udpgal]/[gal1p] = 1.94 ± 0.35 (starved + galactose 1h, rat, liver)</p> <p>[udpgal]/[gal1p] = 1.85 ± 0.27 (ethanol, starved + galactose 1h, rat, liver)</p> <p>(Lai, et al., 2003) (human cells, in μmol/100g(cell protein))</p> <p>[udpgal] = 82±10 (Control glucose medium)</p> <p>[udpgal] = 46±4 (56% glucose) (Control galactose medium 24h)</p> <p>(Lai, et al., 2003) (human cells, in μmol/100g(cell protein))</p> <p>[udpgal] = 25±5 (GALT-deficient glucose medium)</p> <p>[udpgal] = 17±3 (68% glucose) (GALT-deficient galactose medium 24h)</p>
galtol	D-galactitol (M _w 182.2) <u>CHEBI:16813</u> <u>KEGG:C01697</u>	0.001mM (no galactose) ~8mM (GALT deficiency)	<p>[galtol] = 4.8-40 μmol/g (~5.3-44mM) (occupational gray matter, human)</p> <p>[galtol] = 17.6 μmol/g (~) (basal ganglia, human) (Wang, et al., 2001)</p> <p>[galtol] = 12.9 μmol/g (~14.3mM) (Wang, et al., 2001) (Wells, et al., 1965)</p> <p>[galtol] = 22.18 μmol/g (~24.6mM) (Wang, et al., 2001) (Quan-Ma, et al., 1966)</p> <p>Galactitol measured directly in GALT-deficient mice are lower (2mM) than levels detected by MRS in human subjects (8mM) (Leslie, 2003; Wang, et al., 2001)</p>
atp	ATP (M _w 503.2) <u>CHEBI:30616</u> <u>KEGG:C00002</u>	2.7mM (no galactose) 2.9mM (1h galactose) 2.9mM (1h galactose, GALE inhibition)	<p>[atp] = 2.8mM (König, et al., 2012)</p> <p>(Guynn, et al., 1974)</p> <p>[atp] = 2.49±0.12 μmol/g_{ww} (~2.77mM) (rat liver, starved)</p> <p>[atp] = 2.56±0.09 μmol/g_{ww} (~2.84mM) (rat liver, fed ad libitum)</p> <p>[atp] = 2.32±0.07 μmol/g_{ww} (~2.58mM) (rat liver, meal fed)</p> <p>[atp] = 2.42±0.50 μmol/g_{ww} (~2.69mM) (rat liver) (Keppler, et al.,</p>

			1969) (Keppler, et al., 1970) [atp] = 2.60 ± 0.16 μmol/g_{ww} (~2.89mM) (starved + galactose 1h, rat, liver) [atp] = 2.81 ± 0.15 μmol/g_{ww} (~3.12mM) (ethanol, starved + galactose 1h, rat, liver) [atp]/[adp] = 3.14 ± 0.52 (starved + galactose 1h, rat, liver) [atp]/[adp] = 3.10 ± 0.53 (ethanol, starved + galactose 1h, rat, liver)
adp	ADP (M _w 424.2) CHEBI:456216 KEGG:C00008	1.2mM (no galactose) 1.0mM (1h galactose) 1.0mM (1h galactose, GALE inhibition)	[atp] = 0.8mM (König, et al., 2012) (Guynn, et al., 1974) [adp] = 1.38 ± 0.08 μmol/g_{ww} (~1.53mM) (rat liver, starved) [adp] = 1.06 ± 0.03 μmol/g_{ww} (~1.18mM) (rat liver, fed ad libitum) [adp] = 1.24 ± 0.04 μmol/g_{ww} (~1.38mM) (rat liver, meal fed) [adp] = 1.08 ± 0.12 μmol/g_{ww} (~1.20mM) (rat liver) (Keppler, et al., 1969) (Keppler, et al., 1970) [adp] = 0.88 ± 0.17 μmol/g_{ww} (~0.98mM) (starved + galactose 1h, rat, liver) [adp] = 0.97 ± 0.19 μmol/g_{ww} (~1.08mM) (ethanol, starved + galactose 1h, rat, liver)
utp	UTP (M _w 480.1) CHEBI:46398 KEGG:C00075	0.27mM (no galactose)	[utp] = 0.27mM (König, et al., 2012) (Guynn, et al., 1974) [utp] = 0.362 ± 0.014 μmol/g_{ww} (~0.40mM) (rat liver, starved) [utp] = 0.494 ± 0.038 μmol/g_{ww} (~0.55mM) (rat liver, fed ad libitum) [utp] = 0.443 ± 0.039 μmol/g_{ww} (~0.49mM) (rat liver, meal fed)
udp	UDP (M _w 401.1) CHEBI:58223 KEGG:C00015	0.09mM (no galactose)	[udp] = 0.09mM (König, et al., 2012) [utp+udp] = 0.35 ± 0.07 μmol/g_{ww} (~0.39mM) (rat liver) (Keppler, et al., 1969) [utp+udp] = 0.35 ± 0.05 μmol/g_{ww} (~0.39mM) (rat liver) (Keppler and Decker, 1969) (Keppler, et al., 1970) [utp+udp] = 0.34 ± 0.05 μmol/g_{ww} (~0.38mM) (fed, rat, liver) [utp+udp] = 0.23 ± 0.05 μmol/g_{ww} (~0.26mM) (starved, rat, liver) [utp+udp] = 0.15 ± 0.03 μmol/g_{ww} (~0.17mM) (starved + galactose 1h, rat, liver) [utp+udp] = 0.11 ± 0.02 μmol/g_{ww} (~0.39mM) (ethanol, starved + galactose 1h, rat, liver)

			Marked decrease in [utp+udp] under galactose challenge.
phos	Phosphate (M _w 96.0) CHEBI:43474 KEGG:C00009	5.0mM (König, et al., 2012)	[pi] = 5.0mM (König, et al., 2012) (Guynn, et al., 1974) [pi] = 4.37±0.16 μmol/g_{ww} (~4.86mM) (rat liver, starved) [pi] = 3.64±0.32 μmol/g_{ww} (~4.04mM) (rat liver, fed ad libitum) [pi] = 4.41±0.10 μmol/g_{ww} (~4.90mM) (rat liver, meal fed) [pi] = 3.18±0.56 μmol/g_{ww} (~3.53mM) (rat liver)(Keppler and Decker, 1969)
ppi	Pyrophosphate (M _w 175.0) CHEBI:33019 KEGG:C00013	0.008mM(König, et al., 2012)	[pp] = 0.008mM (König, et al., 2012) (Guynn, et al., 1974) [pp] = 0.0023±0.0003 μmol/g_{ww} (~0.0026mM) (rat liver, starved) [pp] = 0.0038±0.0004 μmol/g_{ww} (~0.0042mM) (rat liver, fed ad libitum) [pp] = 0.0049±0.0006 μmol/g_{ww} (~0.0054mM) (rat liver, meal fed) [pp] = 0.0065±0.00086 μmol/g_{ww} (~0.0072mM) (rat total liver)
nadp	NADP (M _w 740.4) CHEBI:58349 KEGG:C00006	0.1mM	
nadph	NADPH (M _w 741.4) CHEBI:57783 KEGG:C00005	0.1mM	
suc	Sucrose (M _w 342.3) CHEBI:17992 KEGG:C00089		
h2oM	H2O M CHEBI:15377 KEGG:C00001		
alb	albumin PR:000003918		
rbc	red blood cell BTO:0000424		
galnat	D-galactonate (M _w 195.1) CHEBI:12931		

KEGG:C00880		
galn	galactosamine	Uptake of galactosamine by rat liver is a~0.4μmol/g(liver)/min as measured by the disappearance of galactosamine from the medium (Keppler, et al., 1969) Time-dependent decrease in uridine nucleotides in isolated perfused rat livers after galactosamine addition. (Keppler, et al., 1969)
amp	AMP	[amp] = 0.28±0.06 μmol/g _{ww} (~0.31mM) (rat liver) (Keppler, et al., 1969) (Keppler, et al., 1970) [amp] =0.15 ±0.09μmol/g _{ww} (~0.167mM) (starved + galactose 1h, rat, liver) [amp] =0.19 ±0.07μmol/g _{ww} (~0.21mM) (ethanol, starved + galactose 1h, rat, liver)
ump	UMP	[ump] = 0.04 μmol/g _{ww} (~0.044mM) (rat liver) (Segal and Rogers, 1971)

Supplementary Table 3 - Tissue-and organ parameters

Parameter	Symbol	Model value	Human	Dog	Rat
number of hepatocytes along sinusoid	N_c	20	15-25 (human) (Kuntz and Kuntz, 2006)		12-20 (rat, from image) (Burkel and Low, 1966)
sinusoid length	L_{sin}	500μm (\pm125μm)	500-650μm diameter of hepatic lobules 1.0–1.3mm (Kuntz and Kuntz, 2006)) 500μm (distance between central veins 1000 μ m) (Lautt, 2009) 350–500μm (Kuntz and Kuntz, 2006)	500μm (Goresky, 1963)	400-450μm distance between central veins 809\pm199μm (SD, n=79, young rat, SEM of corrosion cast)(Warren, et al., 2008) 891\pm190μm (n=78, old rat, SEM of corrosion cast)(Warren, et al., 2008)
Diameter hepatocyte in sinusoidal direction	x_{cell}	L_{sin} / N_c 25μm (calculated from geometry)	20 – 40μm (Kuntz and Kuntz, 2006)		No significant difference could be shown in the average size of parenchymal cells among the lobular zones of rat liver. 20.8\pm0.2μm (SD, n=50, rat, periportal, QSD) (Loud, 1968) 20.8\pm0.3μm (SD, n=50, rat, midzonal, QSD) (Loud, 1968) 21.0\pm0.3μm (SD, n=50, rat, perivenious, QSD) (Loud, 1968) Parenchymal cells of normal rat liver are at least 80% homogeneous with respect to the structural parameters measured. 20.1μm (rat, QSD) (Wiener, et al., 1968)
sinusoidal radius	y_{sin}	4.4μm (8.8 μ m sinusoidal diameter)	Sinusoidal diameter 8.8\pm0.9μm (human, OPS) (Puhl, et al., 2003) 4-15μm (human) (Kuntz and Kuntz, 2006) 13.23\pm2.36μm (human, n=100, SEM) (Debbaut, et al., 2014)		Sinusoidal diameter 5.9\pm0.17μm (SE, n=545, rat, periportal, IVM) (Wisse, et al., 1985) 7.1\pm0.29μm (SE, n=498, rat, central, IVM) (Wisse, et al., 1985) 6.42\pm0.12μm (SE, n=696, rat, periportal, IPM) (Wisse, et al., 1985) 7.62\pmNDμm (SE, n=696, rat, central, IPM) (Wisse, et al., 1985) 5.9\pm0.17μm (rat, Zone 1), 7.1\pm0.29μm (rat, Zone 3) (MacPhee, et al., 1995) 6.4\pm0.1μm (rat, Zone 1), 8.3\pm0.2μm (rat, Zone 3) (MacPhee, et al., 1995) 6.6\pm0.09μm (SEM, n=139, rat, direct sinusoids)(Koo,

Commented [WU2]: TODO: Update table with final calculated values for model, i.e relative Volumes, and the number of sinusoids (scaling flow and volume)

			et al., 1975) 6.3±0.07µm (n=304, rat, branching sinusoids, SEM) (Koo, et al., 1975) 6.3±0.12µm (n=72, rat, direct sinusoids, SEM) (Koo, et al., 1975) 9.4±3.6µm (SD, n=977, young rat, SEM of corrosion cast)(Warren, et al., 2008) 9.7±3.5µm (n=1225, old rat, SEM of corrosion cast)(Warren, et al., 2008)
width space of Disse	y_{dis}	1.2±0.4µm	0.4-1.5µm (human, SEM, estimated from imaged) (Muto, et al., 1977) The sinusoidal lining of human liver appeared remarkably similar to that of the rat by both TEM and SEM. (Burwen, et al., 1982) 0.5-1.7µm (human, SEM, estimated from image) (Burwen, et al., 1982) 0.3-1.5µm (rat, SEM micrograph, estimated from image) (Burkel and Low, 1966) 0.2-1µm (rat, SEM micrograph, estimated from image) (Wisse, et al., 1985) 0.3-1.2µm (rat, TEM, estimated from image (Braet and Wisse, 2002)
cell sheet thickness	y_{cell}	7.58±1.25µm (calculated from FSD with geometry)	7.58µm Calculated from functional sinusoidal density FSD FSD 391±30 [1/cm] (SD, n=88, human, OPS) (Puhl, et al., 2003) $y_{cell} = \frac{1}{2 \cdot FSD} - (y_{sin} + y_{dis})$ 6.1±1.25µm Calculated from intersinusoidal distance ISD $y_{cell} = \frac{ISD}{2} - (y_{sin} + y_{dis})$ ISD 22.6±2.5µm (SD, n=88, human, OPS) (Puhl, et al., 2003) intersinusoidal distance ~ 15-30µm (SEM, estimated from image)(Wisse, et al., 1985) 16.1±3.9µm (SD, n=567, young rat, SEM of corrosion cast)(Warren, et al., 2008) 15.5±3.8µm (SD, n=558, old rat, SEM of corrosion cast)(Warren, et al., 2008)
Area between adjacent sinusoid compartments	A_{sin}	$\pi(y_{sin})^2$	
Area between adjacent Disse compartments	A_{dis}	$\pi(y_{sin} + y_{dis})^2 - A_{sin}$	
Area between adjacent sinusoid and Disse	$A_{sin\ dis}$	$2\pi \cdot y_{sin} \cdot x_{sin}$	

compartments				
Volume sinusoid compartment	V_{sin}	$A_{sin} \cdot x_{sin}$		
Volume Disse compartment	V_{dis}	$A_{dis} \cdot x_{sin}$		
Volume cell	V_{cell}	$\pi(y_{sin} + y_{dis} + y_{cell})^2 \cdot x_{cell}$ $-\pi(y_{sin} + y_{dis})^2 x_{cell}$		Volumes cytosol calculated per average cell, i.e. per nucleus 5100μm^3 (peripheral, rat, QSD) (Loud, 1968) 5100μm^3 (midzonal, rat, QSD) (Loud, 1968) 5100μm^3 (perivenousl, rat, QSD) (Loud, 1968) No significant difference could be shown in the average size of parenchymal cells among the lobular zones of rat liver. 5100μm^3 (all zones, rat, QSD) (Wiener, et al., 1968) Cell Volumes ~1.4*5100 μm^3 = 7140 μm^3
Volume sinusoidal unit	$V_{sinunit}$	$L_{sin} \cdot \pi \cdot (y_{sin} + y_{dis} + y_{cell})^2$ 272.9E3 μm^3 (calculated from geometry)		
Volume fraction sinusoidal blood volume, % liver	f_{sin}	$\frac{V_{sin}}{V_{sin} + V_{dis} + V_{cell}}$ 11.1% (calculated from geometry)	15–25% (percent of liver volume) (Kuntz and Kuntz, 2006) 9-15% (n=6, isolated perfused human liver)(Villeneuve, et al., 1996)	15.2% (indicator dilution dog) (Goresky, 1963) 15.0% (dog) (Allen and Reeve, 1953; Goresky, 1963) 19.4% (rat) (Everett, et al., 1956; Goresky, 1963) 11.6% (rat) (Brauer, et al., 1959; Goresky, 1963) 10.6% (morphological studies, % volume) (Blouin, et al., 1977; Lutt, 2009)
Volume fraction extravascular volumes, % liver	f_{dis}	$\frac{V_{dis}}{V_{sin} + V_{dis} + V_{cell}}$ 6.9% (calculated from geometry)	~ 5% (percent of liver volume) (Kuntz and Kuntz, 2006) 5-8% (n=6, isolated perfused human liver)(Villeneuve, et al., 1996)	6.2% (indicator dilution dog) (Goresky, 1963) 9.5±2.1% (±SD, indicator dilution dog, sucrose volume) (Goresky, 1963) 6.7% (dog) (Allen and Reeve, 1953; Goresky, 1963) 7.3% (rat) (Goresky, 1963) 6.0% (rat) (Brauer, et al., 1959; Goresky, 1963) 4.9% (morphological studies, % volume) (Blouin, et al., 1977; Lutt, 2009)
Volume fraction parenchymal cells, % liver	f_{hep}	$\frac{V_{hep}}{V_{sin} + V_{dis} + V_{cell}}$ 81.9% (calculated from geometry)		78% (morphological studies, % volume) (Blouin, et al., 1977; Lutt, 2009)

RBC velocity	v_{RBC}	270μm/s\pm58μm/s (mode 180μm/s)	<p>970\pm430μm/s (SD; human, OPS) (Puhl, et al., 2003) Values probably too high due to larger arterial contribution with high flow on organ surface. [TODO: Ref & discussion] 259μm/s (boundary condition, calculated from scaling to tissue sample, human) (Debbaut, et al., 2012) The mean flow velocities of simulations in model of human liver microcirculation based on a 3D image-based geometry were for the r, phi and z directions 100μm/s, 73μm/s and 77μm/s, respectively. (Debbaut, et al., 2012) The sinusoidal circulation is clearly anisotropic. Modeling in human corrosion cast showed that pressure drops significantly through certain sinusoids and stays almost constant through others. This corresponds to the typical presence of preferential pathways in the sinusoidal geometry along tracks with relevant pressure drops (streamlines). (Debbaut, et al., 2012)</p>	<p>93μm/s (dog, calculated from transit time of RBC) (Goresky, 1963) [CHECK, depends on injection time]</p>	<p>180\pm20μm/s (SE, rat) (MacPhee, et al., 1988) 250\pm3μm/s (SE, rat, IVM) (Koo and Liang, 1979) 150\pm6μm/s (SE, rat, stated in (MacPhee, et al., 1988), video flying spot method) 69.2\pm30.6μm/s (\pmSD, mice, IVM) (MacPhee, et al., 1988) 410\pm39μm/s (SEM, n=139, rat, direct sinusoids)(Koo, et al., 1975) 270\pm58μm/s (SEM, n=304, rat, branching sinusoids)(Koo, et al., 1975) 370\pm25μm/s (SEM, n=72, rat, direct sinusoids)(Koo, et al., 1975) Analysis of the blood cell velocity data of Koo as a cumulative distribution showed that the data is fitted better by a log-normal than a normal distribution (Roberts and Rowland, 1985).</p>
volumetric blood flow sinusoidal unit	$Q_{sinunit}$	$\pi(y_{sin})^2 v_{RBC}$ 16.4E3 $\frac{\mu m^3}{s}$ (calculated from geometry)	flow through cylinder analogue to (Gross and Aroesty, 1972; Puhl, et al., 2003)		
fenestraction parameter The presence of fenestrae reduces the surface available for free	f_{fen}	0.09	<p>107\pm1.5nm (SE, human) (Wisse, et al., 2008) diameter fenestrae</p>	<p>(Wisse, et al., 1985) demonstrated presence of</p>	<p>diameter fenestrae 175nm (Wisse, et al., 1996) 161\pm2.7nm (Sprague-Dawley rats) (Wisse, et al., 2008)</p>

transport, whereas the parenchymal surface available for uptake is 6.0 times enlarged by microvilli (Schaff and Lapis, 1990; Wisse, et al., 1985)	<p>50-300nm (SEM, human)(Braet and Wisse, 2002; Horn, et al., 1987)</p> <p>No difference in ultrastructural morphology was seen between Zones 3 and 1 (Horn, et al., 1987)</p> <p>frequency (SEM, human) (Braet and Wisse, 2002; Horn, et al., 1987) 23.5 [15 – 25] [1/μm²] (n=13, SEM, human, Zone3) (Horn, et al., 1987) 19 [10-24] [1/μm²] (n=10, SEM, human, Zone1) (Horn, et al., 1987)</p> <p>porosity 9.3% [4.8-16.2] (n=13, Zone3, SEM, human) (Horn, et al., 1987) 7.6% [3.8-12.3] (n=10, Zone1, SEM, human) (Horn, et al., 1987)</p>	fenestrae in dog liver with preliminary measurements indicating that the size distribution was almost equal to rat liver fenestrae.	<p>174.6±1.0nm (SE, rat, periportal, TEM) (Wisse, et al., 1985) 147.2±0.9nm (SE, rat, pericentral, TEM) (Wisse, et al., 1985) SEM preparation causes significant shrinkage at the level of fenestrae (approximately 30%)!</p> <p>110.7±0.25nm (SE, rat, periportal, SEM) (Wisse, et al., 1985) 104.8±0.22nm (SE, rat, pericentral, SEM) (Wisse, et al., 1985) 98.0±13.0nm (SD, n=3, SEM, rat) (Fraser, et al., 1988)</p> <p>frequency 9 per μm (SE, rat, periportal, SEM) (Wisse, et al., 1985) 13 [1/μm²] (SE, rat, pericentral, SEM) (Wisse, et al., 1985) 9.08 – 13.3 [1/μm²] (SE, rat) (Wisse, et al., 1985) 20.0±6.3[1/μm²] (SD, n=3, SEM, rat) (Fraser, et al., 1988)</p> <p>porosity 6-8% (Wisse, et al., 1996) A lobular gradient of decreasing fenestrae diameter is compensated by an inverse gradient of fenestrae number. (Wisse, et al., 1996) Only a limited surface of the lining is available for free exchange (~10%) (Wisse, et al., 1996) 17.6±6.9 (SD, n=3, SEM, rat) (Fraser, et al., 1988)</p>
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Supplementary Table 4 – Parameters for the log-normal distributions

Parameter		meanlog	stdlog	mean μ (reported)	standard deviation (reported)	SD references
Sinusoidal length	L_{sin}	6.184	0.2462	500 μ m	125 μ m	based on distance between central veins 809\pm199μm (SD, n=79, young rat, SEM of corrosion cast) (Warren, et al., 2008) scaled to human sinusoidal length Based on distribution of sinusoidal diameter 8.8\pm0.9μm (SD, n=440 in N=11 human, OPS) (Puhl, et al., 2003)
Sinusoidal radius	y_{sin}	1.465 (\pm 0.010)	0.1017 (\pm 0.0073)	4.4 μ m	0.45 μ m	0.4-1.5μm (human, SEM, estimated from imaged) (Muto, et al., 1977)
Width of Disse space	y_{dis}	0.1296	0.3246	1.2 μ m	0.4 μ m	0.5-1.2μm (human, SEM, estimated from image) (Burwen, et al., 1982)
Hepatocyte sheet thickness	y_{cell}	1.977 (\pm 0.014)	0.1390 (\pm 0.0099)	7.58 μ m	1.25 μ m	7.58μm Calculated from functional sinusoidal density FSD FSD 391\pm30 [1/cm] (SD, n=88, human, OPS) (Puhl, et al., 2003) $y_{cell} = \frac{1}{2 \cdot FSD} - (y_{sin} + y_{dis})$ 6.1\pm1.25μm Calculated from intersinusoidal distance ISD $y_{cell} = \frac{ISD}{2} - (y_{sin} + y_{dis})$ ISD 22.6\pm2.5μm (SD, n=88, human, OPS) (Puhl, et al., 2003)
RBC flow velocity	v_{RBC}	5.457 (0.0267)	0.6178 (0.0189)	270 μ m/s	58 μ m/s	270\pm58μm/s (SEM, n=304, rat, branching sinusoids)(Koo, et al., 1975)

Model fit

	name	mean	std	unit	meanlog	meanlog_error	sdlog	sdlog_error	scale_fac	scale_unit
L	L	0.0005	0.000125	m	6.1842957875	NA	0.2462206771	NA	1000000	μ m
y_sin	y_sin	0.0000044	0.00000045	m	1.4652733102	0.0102747149	0.1017144881	0.0072653206	1000000	μ m
y_dis	y_dis	0.0000012	0.00000004	m	0.129641299	NA	0.324592846	NA	1000000	μ m
y_cell	y_cell	0.00000758	0.00000125	m	1.9769003149	0.0140416505	0.1390052478	0.0099289463	1000000	μ m
flow_sin	flow_sin	0.00027	0.000058	m/s	5.4572075437	0.0267357281	0.6178209697	0.0189050147	1000000	μ m/s

Commented [WU3]: TODO: remove
Calculated fit table to make sure the values are correct

Supplementary Table 5 – Diffusion coefficients

Diffusion coefficients	Symbol	Model value [$\mu\text{m}^2/\text{s}$]	References [$\mu\text{m}^2/\text{s}$]
water	D^{h2o}	2200	2100 (water in water) Bionumbers id=104087, ver=7)(Milo, et al., 2010) 2300 (water in water) Bionumbers id=104087, ver=3)(Milo, et al., 2010)
sucrose	D^{suc}	720	720 (D37, free diffusion coefficient in water at 37°C)(Renkin, 1977) 520 (sucrose in water) (Bionumbers id=100614, ver=7)(Milo, et al., 2010)
glucose	D^{glc}	910	910 (D37, hexose, free diffusion coefficient in water at 37°C)(Renkin, 1977) (Casciari, et al., 1988; Groebe, et al., 1994) 600 (glucose in water) (Bionumbers id=104089, ver=6)(Milo, et al., 2010) 673 (glucose in water) (Bionumbers id=109504, ver=1)(Milo, et al., 2010)
galactose	D^{gal}	910	910 (D37, hexose, free diffusion coefficient in water at 37°C)(Renkin, 1977)
albumin	D^{alb}	90	90 (D37, free diffusion coefficient in water at 37°C)(Renkin, 1977)

Supplementary Table 6 – Organ/Liver parameters

Parameter	Symbol	Model value	Human	Dog	Rat
total liver weight	m_{liv}	1500g	1500-1800g (man), 1300-1500g (woman) (Kuntz and Kuntz, 2006) 1697±171g (±SD, n=6)(Villeneuve, et al., 1996) 2.5% of body weight (Vollmar and Menger, 2009)	556g (400 – 800g) (dog) (Goresky, 1963)	17.1±2.2g (±SD. N=13, in situ perfused rat livers)(Garipey, et al., 1993)
density liver tissue	ρ_{liv}	$1 \frac{g}{ml}$	$1 \frac{g}{ml}$ (Debbaut, et al., 2012) Literature (data from metabolite conversions ~1.2g/ml)		
total liver volume	V_{liv}	1500ml	1500ml (calculated by $\frac{m_{liv}}{\rho_{liv}}$) measured by ultrasonography 1524ml (man, 24 years) (Wynne, et al., 1989) 1102ml (man, 91 years, -28%) (Wynne, et al., 1989) 1415ml (woman, 24 years) (Wynne, et al., 1989) 789ml (woman, 91 years, -44%) (Wynne, et al., 1989) 1474ml (all, 24 years) (Wynne, et al., 1989) 934ml (all, 91 years, -37%) (Wynne, et al., 1989) volumes per bodyweight (ultrasonography) 20.7 ml/kgbw (man, 24 years) (Wynne, et al., 1989) 14.5 ml/kgbw (man, 91 years, -30%) (Wynne, et al., 1989) 23 ml/kgbw (woman, 24 years) (Wynne, et al., 1989) 13.6 ml/kgbw (woman, 91 years, -43%) (Wynne, et al., 1989) 23.6ml/kgbw (all, 24 years) (Wynne, et al., 1989) 14.0 ml/kgbw (all, 91 years, -41%) (Wynne, et al., 1989)	556ml (calculated)	17.1ml (calculated)
parenchymal tissue fraction of liver (due to large vessel, connective tissue, lymphs system,	f_{tissue}	0.5	Tissue volume of liver is calculated by $V_{tissue} = f_{tissue} \cdot V_{liv}$ Literature (25 % large vessels, ...)		

only part of whole liver
volume is parenchymal
tissue)

total hepatic blood flow per liver weight (~75-80% portal vein partially deoxygenated, 20-25% hepatic artery well-oxygenated)	q_{liv}	$1.2 \frac{ml}{min \cdot g_{LW}}$	$\sim 1.0\text{--}1.3 \frac{ml}{min \cdot g_{LW}}$ (Lautt, 2009) $\sim 1 \frac{ml}{min \cdot g_{LW}}$ (Vollmar and Menger, 2009) (Kuntz and Kuntz, 2006) measured by ultrasonography 1.24 ml/min/gLW (man, 24 years) (Wynne, et al., 1989) 1.02 ml/min/gLW (man, 91 years, -18%) (Wynne, et al., 1989) 1.11 ml/min/gLW (woman, 24 years) (Wynne, et al., 1989) 0.88 ml/min/gLW (woman, 91 years, -21%) (Wynne, et al., 1989) 1.18 ml/min/gLW (all, 24 years) (Wynne, et al., 1989) 0.94 ml/min/gLW (all, 91 years, -20%) (Wynne, et al., 1989)	1.83±0.55 $\frac{ml}{min \cdot g_{LW}}$ (±SD, g liver weight, dog) (Goresky, 1963)	$1.30 \pm 0.13 \frac{ml}{min \cdot g_{LW}}$ (SD, rat 3 month, determined by clearance of albumin)(Warren, et al., 2008) $1.54 \pm 0.19 \frac{ml}{min \cdot g_{LW}}$ (SD, rat 6 month, determined by clearance of albumin)(Warren, et al., 2008) $1.33 \pm 0.28 \frac{ml}{min \cdot g_{LW}}$ (SD, rat 36 month, determined by clearance of albumin)(Warren, et al., 2008)
total hepatic blood flow per body weight			measured by ultrasonography 25.3 ml/min/kgBW (man, 24 years) (Wynne, et al., 1989) 14.5 ml/min/kgBW (man, 91 years, -43%) (Wynne, et al., 1989) 25.5 ml/min/kgBW (woman, 24 years) (Wynne, et al., 1989) 11.5 ml/min/kgBW (woman, 91 years, -55%) (Wynne, et al., 1989) 25.7 ml/min/kgBW (all, 24 years) (Wynne, et al., 1989) 13.5 ml/min/kgBW (all, 91 years, -47%) (Wynne, et al., 1989) $17.0 \pm 2.72 \frac{ml}{min \cdot kg_{BW}}$ (±SD, n=10 women, Doppler ultrasound)(Carlisle, et al., 1992) $30 \frac{ml}{min \cdot kg_{BW}}$ (Lautt, 2009)		

total hepatic blood flow	Q_{liv}	$q_{liv} \cdot m_{liv}$ $1800 \frac{ml}{min}$ (calculated)	<p>1800 ml/min (man) (Kuntz and Kuntz, 2006)</p> <p>1200 ml/min (woman) (Kuntz and Kuntz, 2006)</p> <p>measured by ultrasonography</p> <p>1864 ml/min (man, 24 years) (Wynne, et al., 1989)</p> <p>1126 ml/min (man, 91 years, -40%) (Wynne, et al., 1989)</p> <p>1546 ml/min (woman, 24 years) (Wynne, et al., 1989)</p> <p>645 ml/min (woman, 91 years, -58%) (Wynne, et al., 1989)</p> <p>1717 ml/min (all, 24 years) (Wynne, et al., 1989)</p> <p>807 ml/min (all, 91 years, -53%) (Wynne, et al., 1989)</p> <p>1067±160 ml/min(±SD, n=6, isolated perfused human liver)(Villeneuve, et al., 1996)</p> <p>992±276 ml/min (n=14)(Jakab, et al., 1995)</p>	869 ml/min (dog) (Goresky, 1963)	20.9±1.3 ml/min (±SD, N=13, in situ perfused rat livers, perfusate blood flow)(Garipey, et al., 1993)
total number of hepatic sinusoids	N_{sin}		<p>Calculate based on flow</p> $N_{sin} = \frac{Q_{liv}}{Q_{sin unit}} = \frac{Q_{liv}}{A_{sin} \cdot v_{RBC}} = \frac{Q_{liv}}{\pi (y_{sin})^2 \cdot v_{RBC}}$ <p>$N_{sin} = 2472E6$ (calculated) update</p> <p>Calculate based on volumes</p> $N_{sin} = \frac{V_{tissue}}{V_{sin unit}} = \frac{f_{tissue} \cdot V_{liv}}{\pi \cdot (y_{sin} + y_{dis} + y_{cell})^2 \cdot L_{sin}}$ <p>$N_{sin} = 3250E6$ (calculated) update</p> <p>With the number of hepatic lobuli:</p> <p>$N_{Lob} = 1.0E6-1.5E6$ (Kuntz and Kuntz, 2006)</p> <p>Comes this to an estimated number of sinusoids per lobules of ~2600 sinusoidal units per lobules</p>		
mean transit time RBC	MTT	~3-4s	Calculate from curves [Villeneuve1996]	Calculate from curves [Goresky1973, Goresky1983]	~6.3±0.5sec RBC ??(Garipey, et al., 1993) Calculate from curves
large vessel transit time	t_0	~5-10s	Calculate from curves [Villeneuve1996]	Calculate from curves [Goresky1973, Goresky1983]	Calculate from curves

Commented [WU4]: Check in Dilution curves what the real transit times are

SUPPLEMENTARY FIGURES

Supplementary Figure 1 – Validation of single cell model of galactose metabolism time courses in GALE inhibition via ethanol.

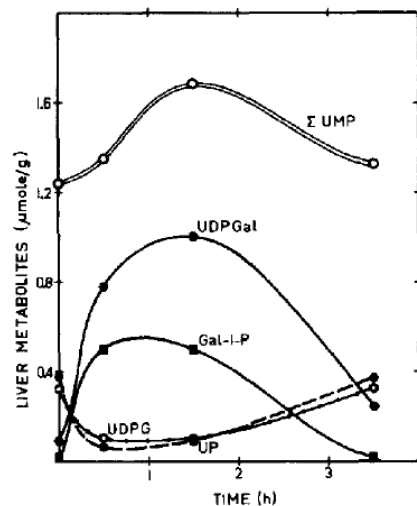


Fig. 1. Time-dependent changes of galactose metabolite and uracil nucleotide contents in livers of fed rats. D-galactose (2.7 mmole/kg) was injected at zero time, one hr after ethanol administration (130 mmole/kg). Uridine phosphates (UTP + UDP + UMP) are designated as UP, the sum of all acid soluble uracil 5'-nucleotides as ΣUMP. (Keppler, et al., 1970)

Typical effect of galactose challenge on the galactose metabolism of single cell model. Prediction of effects of GALE inhibition. GALE is inhibited by ethanol ingestion, due to altered NAD/NADH quotient resulting in altered GALE activity due to NAD cofactor. Ethanol ingestion was simulated by altering the NAD levels. Experimental data from (Keppler, et al., 1970)

Commented [WU5]: TODO: calculate the GALE inhibition, discuss in context of alcohol effects to the liver

Supplementary Figure 2 – Metabolic Control Analysis (MCA) - Role of the different parameters in controlling hepatic galactose metabolism on a single cell level

Supplementary Figure 2 – Multiple indicator dilution curves in galactosemias

Supplementary Figure 3 – Altered hepatic galactose clearance and dependency on flow in galactosemias analogue to Figure 4.

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