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

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ABRREVIATIONS

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	**Facilitated glucose transporter member 2** D-glucose (disse) [**glc_dis**] ↔ D-glucose (cytosol) [**glc**] D-galactose (disse) [**gal_dis**] ↔ D-galactose (cytosol) [**gal**] **Mechanism** TCDB:2.A.1.1 (glucose transporter subfamily) **Protein/Structure** UniProt:P11168 (GTR2_HUMAN) **Gene** SLC2A2, GLUT2 **Disease** MIM:227810 (Fanconi-Bickel syndrome; FBS) Galactose and glucose transported via GLUT2 (competitive inhibition kinetics) (Brown, 2000; Colville, et al., 1993) 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).	**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) **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) Km(D-fru) = 66mM (Walmsley, et al., 1998) Km(D-fru)=212±32mM (rat? hepatocytes) (Elliott and Craik, 1982) **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 **v(D-glc)=220±19**mmol/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)
GALK	**Galactokinase** D-galactose [**gal**] + ATP [**atp**] ↔ D-galactose 1-phosphate [**gal1p**] + ADP [**adp**] **Reaction** EC:2.7.1.6 RHEA:13556 KEGG:R01092 **Protein**	**Two-substrate ordered, ternary complex reaction** (Timson and Reece, 2003) **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), (Sangiuolo, et al., 2004) **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

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

	UniProt:P51570 (GALK1_HUMAN) homodimer P51570*2 **Gene** GALK, GALK1 **Disease** MIM:230200 (GALCT2 Galactosemia II) Galactokinase being rate limiting for galactose clearance (Schirmer, et al., 1986) -> [27,28, 50]	(1mM gal1p caused 15% inhibition, 5mM gal1p 50% inhibition) **ki(gal1p) = 5.3mM (5.0-5.7mM)** (adult rat liver) (Cuatrecasas and Segal, 1965)
IMP	**Inositol monophosphatase** D-galactose 1-phosphate [**gal1p**] ↔ D-galactose [**gal**] + phosphate [**pi**] **Reaction** EC:3.1.3.25 **Protein** UniProt:P29218 (IMPA1_HUMAN) homodimer P29218*2 **Gene** IMPA1, IMPA Normal substrate inositol-1p (ino1p)	**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 (Slepak, et al., 2007) **km(ino1p) = 0.320±0.050mM** (Slepak, et al., 2007) **km(gal1p) = 0.35mM** (similar kinetics gal1p to ino1p in vitro) (Parthasarathy, et al., 1997)
GALT	**Galactose-1-phosphate uridyl transferase** UDP-D-glucose [**udpglc**] + D-galactose 1-phosphate [**gal1p**] ↔ D-glucose 1-phosphate [**glc1p**] + UDP-D-galactose [**udpgal**]. **Reaction** EC:2.7.7.12 RHEA:13992 KEGG:R00955 **Protein** UniProt:P07902 (GALT_HUMAN) homodimer P07902*2 **Gene** GALT **Disease** MIM:230400 (GALCT Galactosemia)	The catalytic mechanism of GALT is **ping-pong kinetics** with covalent intermediate UMP-enzyme (Facchiano and Marabotti, 2010). **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) **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) (?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**

		Potent linear competent inhibitors UTP and UDP of UDP-glucose (Segal and Rogers, 1971)**:** **Ki(UTP) = 0.13mM** (rat, liver) **Ki(UDP) = 0.35mM** (rat, liver) Ki(UMP) = 2.3mM (rat, liver) Ki(UDP-glucuronic acid)=0.40mM (rat, liver)
GALE	**UDP-glucose 4-epimerase** UDP-D-glucose [**udpglc**] ↔ UDP-D-galactose [**udpgal**] **Reaction** EC:5.1.3.2 RHEA:22171 KEGG:R00291 **Protein** UniProt:Q14376 (GALE_HUMAN) homodimer Q14376*2 **Gene** GALE **Disease** MIM:230350 (GALE deficiency) Alternative activity with GlcNAc: UDP-GalNAc ↔ UDP-GlcNAc "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) "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)". "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	**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**
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	**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)

	(Isselbacher ?). Stable transfection of human UGP (hUGP2) rescued galactose GALT deficient yeast from "galactose toxicity [Lai2002].	"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] **gal1p as competitive inhibitor of glc1p** "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" [Slepak2007->Lai2002].
ALDR	**Aldose reductase (galactitol NAD 1-oxidoreductase)** D-galactose [**gal**] + NADPH [**nadph**] + H ↔ galactitol [**galtol**] + NADP [**nadp**] **Reaction** EC:1.1.1.21 RHEA:12792 -> RHEA:37967 KEGG:R01095 **Protein** UniProt:P15121 (ALDR_HUMAN) monomer P15121*1 **Gene** AKR1B1, ALDR1 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)".	**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) **km(gal) = 110.0mM** (human brain) (SABIORK:15695) (Wermuth and von Wartburg, 1982)
PGM1	**Phosphoglucomutase-1** D-glucose 1-phosphate [**glc1p**] ↔ D-glucose 6-phosphate [**glc6p**] **Reaction** EC:5.4.2.2 KEGG:R00959 RHEA:23539 **Protein (multiple isoforms PGM1, PGM2)**	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) **[glc6p]/[glc1p] ~10-12** (Guynn, et al., 1974) DeltaG =-7.1 kJ/mol (König, et al., 2012)

	UniProt:P36871 (PGM1_HUMAN) monomer P36871*1 main isoform for glc1p ↔ glc6p reaction **Gene** PGM1 **Disease** MIM:612934 (Glycogen storage disease 14) MIM:614921 (Congenital disorder of glycosylation 1T CDG1T) **Protein** UniProt:Q96G03 (PGM2_HUMAN) **Gene** PGM2 CDG1T - A multisystem disorder caused by a defect in glycoprotein biosynthesis and characterized by under-glycosylated serum glycoproteins.	**km(glc1p) = 0.049mM** (human, RBC) (Quick, et al., 1974) **km(glc1p) = 0.045mM** (rat, heart) (Kashiwaya, et al., 1994) **km(glc6p) = 0.67mM** (rat, heart) (Kashiwaya, et al., 1994) **km(glc1p) = 0.083mM** (human, RBC, PGM1) (Accorsi, et al., 1989) ki(fru16bp) = 0.092mM (human, RBC, PGM1) (Accorsi, et al., 1989)
PPASE	**Pyrophosphatase** Pyrophosphate [**pp**] + H2O → 2 phosphate [**pi**] **Reaction** EC:3.6.1.1 RHEA:24579 KEGG:R00004 **Protein** UniProt:Q15181 (IPYR_HUMAN) homodimer Q15181*2 **Gene** PPA1, IOPPP, PP	**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)
NDKU	**Nucleoside diphosphokinase (ATP:UDP phosphotransferase)** ATP [**atp**] + UDP [**udp**] ↔ ADP [**adp**] + UTP [**udp**] **Reaction** EC: 2.7.4.6 RHEA:25101 KEGG:R00156 **Multitude of isoforms**	Compulsory-order substituted-enzyme (**Ping Pong Bi Bi**) mechanism (Lam and Packham, 1986) **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) **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)

		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**] + H2→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** Aceptor [**gac**] + UDP-glucose [**udpglc**] -> Acceptor-glucose[**gacglc**] + UDP [**udp**] Aceptor [**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 KEGG:R01098 (only bacteria)

Supplementary Table 2 *- Metabolites in hepatic galactose metabolism.*

Id	Name (mass) Annotation	Initial Concentration	Comments
glc	**D-glucose** (M_w 180.2) CHEBI:4167 KEGG:C00031	**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) CHEBI:4139 KEGG:C00124	**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) CHEBI:58601 KEGG:C00103	**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) CHEBI:58885 KEGG:C00029	**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) CHEBI:66914 KEGG:C00052	**0.11mM** (no galactose) **0.36mM** (1h galactose) **1.39mM** (1h galactose, GALE	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)	**[udpgal] =0.32 ±0.07µmol/g_{ww} (~0.36mM**) (starved + galactose 1h, rat, liver) **[udpgal] =1.25 ±0.16µmol/g_{ww} (~1.39mM**) (ethanol, starved + galactose 1h, rat, liver) (Keppler, et al., 1970) **[udpgal]/[udpglc] =3.4 ±0.3 (**fed, rat, liver) **[udpgal]/[udpglc] =3.3 ±0.3 (**starved, rat, liver) **[udpgal]/[udpglc] =0.78 ±0.39 (**starved + galactose 1h, rat, liver) **[udpgal]/[udpglc] =0.11 ±0.02 (**ethanol, starved + galactose 1h, rat, liver) **[udpgal]/[gal1p] =1.94 ±0.35 (**starved + galactose 1h, rat, liver) **[udpgal]/[gal1p] =1.85 ±0.27 (**ethanol, starved + galactose 1h, rat, liver) (Lai, et al., 2003) (human cells, in µmol/100g(cell protein)) [udpgal] = 82±10 (Control glucose medium) [udpgal] = 46±4 (**56% glucose**) (Control galactose medium 24h) (Lai, et al., 2003) (human cells, in µmol/100g(cell protein)) [udpgal] = 25±5 (GALT-deficient glucose medium) [udpgal] = 17±3 (**68% glucose**) (GALT-deficient galactose medium 24h)
galtol	**D-galactitol** (M_w 182.2) CHEBI:16813 KEGG:C01697	**0.001mM** (no galactose) **~8mM** (GALT deficiency)	**[galtol]**=4.8-40µmol/g (**~5.3-44mM**) (occupational gray matter, human) [**galtol]**=17.6µmol/g (~)(basal ganglia, human) (Wang, et al., 2001) **[galtol]=12.9µmol/g (~14.3mM)** (Wang, et al., 2001) (Wells, et al., 1965) **[galtol]=22.18µmol/g (~24.6mM)** (Wang, et al., 2001) (Quan-Ma, et al., 1966) 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)
atp	**ATP** (M_w 503.2) CHEBI:30616 KEGG:C00002	**2.7mM** (no galactose) **2.9mM** (1h galactose) **2.9mM** (1h galactose, GALE inhibition)	[**atp**] = **2.8mM** (König, et al., 2012) (Guynn, et al., 1974) **[atp] = 2.49±0.12 µmol/g_{ww} (~2.77mM**) (rat liver, starved) **[atp] = 2.56±0.09 µmol/g_{ww} (~2.84mM**) (rat liver, fed ad libitum) **[atp] = 2.32±0.07 µmol/g_{ww} (~2.58mM**) (rat liver, meal fed) **[atp] = 2.42±0.50 µmol/g_{ww} (~2.69mM**) (rat liver) (Keppler, et al.,

			1969) (Keppler, et al., 1970) **[atp] =2.60 ±0.16µmol/g_{ww} (~2.89mM)** (starved + galactose 1h, rat, liver) **[atp] =2.81 ±0.15µmol/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±0.08µmol/g_{ww} (~1.53mM)** (rat liver, starved) **[adp] = 1.06±0.03µmol/g_{ww} (~1.18mM)** (rat liver, fed ad libitum) **[adp] = 1.24±0.04µmol/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 ±0.17µmol/g_{ww} (~0.98mM)** (starved + galactose 1h, rat, liver) **[adp] =0.97 ±0.19µmol/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 ±0.05µmol/g_{ww} (~0.38mM)** (fed, rat, liver) **[utp+udp] =0.23 ±0.05µmol/g_{ww} (~0.26mM)** (starved, rat, liver) **[utp+udp] =0.15 ±0.03µmol/g_{ww} (~0.17mM)** (starved + galactose 1h, rat, liver) **[utp+udp] =0.11 ±0.02µmol/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*

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

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 (±125µm)**	**500-650µm** diameter of hepatic lobules 1.0–1.3mm (Kuntz and Kuntz, 2006)) **500µm** (distance between central veins 1000µm) (Lautt, 2009) **350–500µm** (Kuntz and Kuntz, 2006)	**500µm** (Goresky, 1963)	**400-450µm** distance between central veins **809**±199**µm** (SD, n=79, young rat, SEM of corrosion cast)(Warren, et al., 2008) **891**±190**µm** (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±0.2µm** (SD, n=50, rat, periportal, QSD) (Loud, 1968) **20.8±0.3µm** (SD, n=50, rat, midzonal, QSD) (Loud, 1968) **21.0±0.3µm** (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** (8.8µm sinusoidal diameter)	**Sinusoidal diameter** **8.8**±0.9µm (human, OPS) (Puhl, et al., 2003) **4-15µm** (human) (Kuntz and Kuntz, 2006) **13.23**±2.36**µm** (human, n=100, SEM) (Debbaut, et al., 2014)		**Sinusoidal diameter** **5.9**±0.17**µm** (SE, n=545, rat, periportal, IVM) (Wisse, et al., 1985) **7.1**±0.29**µm** (SE, n=498, rat, central, IVM) (Wisse, et al., 1985) **6.42**±0.12**µm** (SE, n=696, rat, periportal, IPM) (Wisse, et al., 1985) **7.62**±ND**µm** (SE, n=696, rat, central, IPM) (Wisse, et al., 1985) **5.9**±0.17**µm** (rat, Zone 1), **7.1**±0.29**µm** (rat, Zone 3) (MacPhee, et al., 1995) **6.4**±0.1**µm** (rat, Zone 1), **8.3**±0.2**µm** (rat, Zone 3) (MacPhee, et al., 1995) **6.6**±0.09**µm** (SEM, n=139, rat, direct sinusoids)(Koo,

				et al., 1975) **6.3**±0.07**µm** (n=304, rat, branching sinusoids, SEM) (Koo, et al., 1975) **6.3**±0.12**µm** (n=72, rat, direct sinusoids, SEM) (Koo, et al., 1975) **9.4**±3.6**µm** (SD, n=977, young rat, SEM of corrosion cast)(Warren, et al., 2008) **9.7**±3.5**µm** (n=1225, old rat, SEM of corrosion cast)(Warren, et al., 2008)
width space of Disse	y_{dis}	**1.2**±0.4**µm**	**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±**1.25**µm** (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**±1.25**µm** Calculated from intersinusoidal distance ISD $y_{cell} = \frac{ISD}{2} - (y_{\sin} + y_{dis})$ ISD **22.6**±2.5**µm** (SD, n=88, human, OPS) (Puhl, et al., 2003)	**intersinusoidal distance** ~**15-30µm** (SEM, estimated from image)(Wisse, et al., 1985) **16.1**±3.9**µm** (SD, n=567, young rat, SEM of corrosion cast)(Warren, et al., 2008) **15.5**±3.8**µm** (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** (periveniousl, 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*5100µm^3**=7140 µm^3**
Volume sinusoidal unit	$V_{\sin unit}$	$L_{\sin} \cdot \pi \cdot (y_{\sin} + y_{dis} + y_{cell})^2$ **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; Lautt, 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; Lautt, 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; Lautt, 2009)

RBC velocity	v_{RBC}	**270µm/s**±58**µm/s** (mode **180µm/s**)	**970**±430**µm/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)	**93µm/s** (dog, calculated from transit time of RBC) (Goresky, 1963) [CHECK, depends on injection time]	**180**±20**µm/s** (SE, rat) (MacPhee, et al., 1988) **250**±3**µm/s** (SE, rat, IVM) (Koo and Liang, 1979) **150**±6**µm/s** (SE, rat, stated in (MacPhee, et al., 1988), video flying spot method) **69.2**±30.6**µm/s** (±SD, mice, IVM) (MacPhee, et al., 1988) **410**±39**µm/s** (SEM, n=139, rat, direct sinusoids)(Koo, et al., 1975) **270**±58**µm/s** (SEM, n=304, rat, branching sinusoids)(Koo, et al., 1975) **370**±25**µm/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).
volumetric blood flow sinusoidal unit	$Q_{\sin unit}$	$\pi(y_{\sin})^2 v_{RBC}$ **16.4E3** $\frac{\mu m^3}{s}$ (calculated from geometry)	flow through cylinder analogue to (Gross and Aroesty, 1972; Puhl, et al., 2003)		
fenestraetion parameter The presence of fenestrae reduces the surface available for free	f_{fen}	**0.09**	**107**±1.5**nm** (SE, human) (Wisse, et al., 2008) **diameter fenestrae**	(Wisse, et al., 1985) demonstrated presence of	**diameter fenestrae** **175nm** (Wisse, et al., 1996) **161**±2.7**nm** (Spraque-Dawley rats) (Wisse, et al., 2008)

transport, whereas the parenchymal surface available for uptake is 6.0 times enlarged by microvilli (Schaff and Lapis, 1990; Wisse, et al., 1985)	**50-300nm** (SEM, human)(Braet and Wisse, 2002; Horn, et al., 1987) No difference in ultrastructural morphology was seen between Zones 3 and 1 (Horn, et al., 1987) **frequency** (SEM, human) (Braet and Wisse, 2002; Horn, et al., 1987) **23.5 [15 – 25] [1/µm^2]** (n=13, SEM, human, Zone3) (Horn, et al., 1987) **19 [10-24] [1/µm^2]** (n=10, SEM, human, Zone1) (Horn, et al., 1987) **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)	fenestrae in dog liver with preliminary measurements indicating that the size distribution was almost equal to rat liver fenestrae.	**174.6**±1.0**nm** (SE, rat, periportal, TEM) (Wisse, et al., 1985) **147.2**±0.9**nm** (SE, rat, pericentral, TEM) (Wisse, et al., 1985) SEM preparation causes significant shrinkage at the level of fenestrae (approximately 30%)! **110.7**±0.25**nm** (SE, rat, periportal, SEM) (Wisse, et al., 1985) **104.8**±0.22**nm** (SE, rat, pericentral, SEM) (Wisse, et al., 1985) **98.0**±13.0**nm** (SD, n=3, SEM, rat) (Fraser, et al., 1988) **frequency** **9 per µm** (SE, rat, periportal, SEM) (Wisse, et al., 1985) **13 [1/µm^2]** (SE, rat, pericentral, SEM) (Wisse, et al., 1985) **9.08 – 13.3 [1/µm^2]** (SE, rat) (Wisse, et al., 1985) **20.0**±6.3**[1/µm^2]** (SD, n=3, SEM, rat) (Fraser, et al., 1988) **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)

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	500µm	125µm	based on distance between central veins **809**±199**µm** (SD, n=79, young rat, SEM of corrosion cast) (Warren, et al., 2008) scaled to human sinusoidal length
Sinusoidal radius	$y_{\sin}$	1.465 (±0.010)	0.1017 (±0.0073)	4.4µm	0.45µm	Based on distribution of sinusoidal diameter **8.8**±0.9µm (SD, n=440 in N=11 human, OPS) (Puhl, et al., 2003)
Width of Disse space	y_{dis}	0.1296	0.3246	1.2µm	0.4µm	**0.4-1.5µm** (human, SEM, estimated from imaged) (Muto, et al., 1977) **0.5-1.2µm** (human, SEM, estimated from image) (Burwen, et al., 1982)
Hepatocyte sheet thickness	y_{cell}	1.977 (±0.014)	0.1390 (±0.0099)	7.58µm	1.25µm	**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**±1.25**µm** Calculated from intersinusoidal distance ISD $y_{cell} = \frac{ISD}{2} - (y_{\sin} + y_{dis})$ ISD **22.6**±2.5**µm** (SD, n=88, human, OPS) (Puhl, et al., 2003)
RBC flow velocity	v_{RBC}	5.457 (0.0267)	0.6178 (0.0189)	270µm/s	58µm/s	**270**±58**µm/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	µm
y_sin	y_sin	0.0000044	0.00000045	m	1.4652733102	0.0102747149	0.1017144881	0.0072653206	1000000	µm
y_dis	y_dis	0.0000012	0.0000004	m	0.129641299	NA	0.324592846	NA	1000000	µm
y_cell	y_cell	0.00000758	0.00000125	m	1.9769003149	0.0140416505	0.1390052478	0.0099289463	1000000	µm
flow_sin	flow_sin	0.00027	0.000058	m/s	5.4572075437	0.0267357281	0.6178209697	0.0189050147	1000000	µm/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 [µm²/s]	References [µm²/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)(Gariepy, 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** $\frac{ml}{\min \cdot g_{LW}}$	~**1.0-1.3** $\frac{ml}{\min \cdot g_{LW}}$ (Lautt, 2009) **~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**±0.13 $\frac{ml}{\min \cdot g_{LW}}$ (SD, rat 3 month, determined by clearance of albumin)(Warren, et al., 2008) **1.54**±0.19 $\frac{ml}{\min \cdot g_{LW}}$ (SD, rat 6 month, determined by clearance of albumin)(Warren, et al., 2008) **1.33**±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±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)	**1800 ml/min** (man) (Kuntz and Kuntz, 2006) **1200 ml/min** (woman) (Kuntz and Kuntz, 2006) measured by ultrasonography **1864 ml/min** (man, 24 years) (Wynne, et al., 1989) 1126 ml/min (man, 91 years, -40%) (Wynne, et al., 1989) **1546 ml/min** (woman, 24 years) (Wynne, et al., 1989) 645 ml/min (woman, 91 years, -58%) (Wynne, et al., 1989) **1717 ml/min** (all, 24 years) (Wynne, et al., 1989) 807 ml/min (all, 91 years, -53%) (Wynne, et al., 1989) **1067**±160 **ml/min**(±SD, n=6, isolated perfused human liver)(Villeneuve, et al., 1996) **992**±276 **ml/min** (n=14)(Jakab, et al., 1995)	**869 ml/min** (dog) (Goresky, 1963)	**20.9**±1.3 **ml/min** (±SD. N=13, in situ perfused rat livers, perfusate blood flow)(Gariepy, et al., 1993)
total number of hepatic sinusoids	$N_{\sin}$		Calculate based on flow $N_{\sin} = \frac{Q_{liv}}{Q_{\sin unit}} = \frac{Q_{liv}}{A_{\sin} \cdot v_{RBC}} = \frac{Q_{liv}}{\pi (y_{\sin})^2 \cdot v_{RBC}}$ $N_{\sin} = 2472E6$ (calculated) update Calculate based on volumes $N_{\sin} = \frac{V_{tissue}}{V_{\sin unit}} = \frac{f_{tissue} \cdot V_{liv}}{\pi \cdot (y_{\sin} + y_{dis} + y_{cell})^2 \cdot L_{\sin}}$ $N_{\sin} = 3250E6$ (calculated) update With the number of hepatic lobuli: N_{Lob} = **1.0E6–1.5E6** (Kuntz and Kuntz, 2006) Comes this to an estimated number of sinusoids per lobules of ~2600 sinusoidal units per lobules		
mean transit time RBC	MTT	**~3-4s**	Calculate from curves [Villeneuve1996]	Calculate from curves [Goresky1973, Goresky1983]	**~6.3±0.5sec** RBC ??(Gariepy, 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.*

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

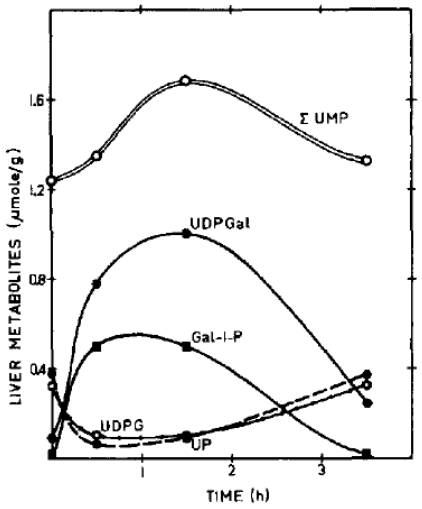

Fig. 1. Time-dependent changes of galactose metabolite and uracil nucleotide contents in livers of fed rats. D-galactose (2.7 mmole/kg) was injected at zero time, one hr after ethanol administration (130 mmole/kg). Uridine phosphates (UTP + UDP + UMP) are designated as UP, the sum of all acid soluble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

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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