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

TABLE OF CONTENT

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 METHODS

Convection, Diffusion, Pore Theory

Diffusion and blood flow are modelled by discretizing the sinusoid and Disse space in small volumes with the transport between neighbouring volumes governed by one-dimensional diffusion and convection equations (analogue to (Konig, et al., 2013)). The periportal (pp) and perivenous (pv) blood compartment are located adjacent to the first and last sinusoidal volume, respectively. A single sinusoidal unit consists of N_c hepatocytes with each cell having a single associated sinusoid and Disse volume ($N_c = N_{\sin} = N_{dis}$). Concentrations of the modelled compounds $s \in \{gal, glu, rbc, alb, suc, h2o\}$ in pp and pv are denoted $\lfloor s_{pp} \rfloor$ and $\lfloor s_{pv} \rfloor$, the concentrations in the sinusoidal and Disse space $\left[s_{\sin}^k\right]$ and $\left[s_{dis}^k\right]$ ($k = 1,..., N_c$). The diffusion coefficients are denoted $D_{\sin}^s = D_{dis}^s$ within the sinusoid and space of Disse and $D_{\sin dis}^s$ between sinusoid and space of Disse (Supplementary Table 5). With the sinusoidal blood flow velocity v_{blood}, the sinusoidal radius $y_{\sin}$, the width of space of Disse y_{dis} and the discretization along the sinusoidal axis $x_{\sin}$ and the exchange areas $A_{\sin}$ between adjacent space sinusoidal volumes, A_{dis} between adjacent space of Disse volumes A_{dis} and $A_{\sin dis}$ between adjacent sinusoid and space of Disse volumes, the rates of transport are given by

Blood flow in sinusoid ($\left[\frac{mole}{\sec}\right]$)

$$v_{\sin,flow}^{pp \to k=1} = v_{blood} A_{\sin} \left[s_{pp}\right] \qquad \left(s_{pp} \to s_{\sin}^1\right)$$

$$v_{\sin,flow}^{k \to k+1} = v_{blood} A_{\sin} \left[s_{\sin}^k\right] \qquad \left(s_{\sin}^k \to s_{\sin}^{k+1}\right) \quad \forall k = 1,...N_{\sin} - 1$$

$$v_{\sin,flow}^{k=N_{\sin} \to pv} = v_{blood} A_{\sin} \left[s_{\sin}^{N_{\sin}}\right] \qquad \left(s_{\sin}^{N_{\sin}} \to s_{pv}\right)$$

$$v_{\sin,flow}^{pv \to} = v_{blood} A_{\sin} \left[s_{pv}\right] \qquad \left(s_{pv} \to\right)$$

Diffusion in sinusoid and space of Disse ($\left[\frac{mole}{\sec}\right]$)

$$v_{\sin,dif}^{pp \to k=1} = \frac{D_{\sin}^s A_{\sin}}{x_{\sin}} \left(\left[s_{pp}\right] - \left[s_{\sin}^1\right]\right) \qquad \left(s_{pp} \to s_{\sin}^1\right)$$

$$v_{\sin,dif}^{k\to k+1} = \frac{D_{\sin}^{s} A_{\sin}}{x_{\sin}} \left(\left[s_{\sin}^{k} \right] - \left[s_{\sin}^{k+1} \right] \right) \qquad \left(s_{\sin}^{k} \to s_{\sin}^{k+1} \right) \quad \forall k = 1,\ldots N_{\sin} - 1$$

$$v_{\sin,dif}^{k=N_{\sin}\to pv} = \frac{D_{\sin}^{s} A_{\sin}}{x_{\sin}} \left(\left[s_{pp} \right] - \left[s_{\sin}^{1} \right] \right) \qquad \left(s_{\sin}^{N_{\sin}} \to s_{pv} \right)$$

$$v_{dis,dif}^{k\to k+1} = \frac{D_{dis}^{s} A_{dis}}{x_{dis}} \left(\left[s_{dis}^{k} \right] - \left[s_{dis}^{k+1} \right] \right) \qquad \left(s_{\sin}^{k} \to s_{dis}^{k} \right) \quad \forall k = 1,\ldots N_{dis} - 1$$

$$v_{\sin dis,dif}^{k} = \frac{D_{\sin dis}^{s} f_{fen} A_{\sin dis}}{y_{dis}} \left(\left[s_{\sin}^{k} \right] - \left[s_{dis}^{k} \right] \right) \qquad \left(s_{\sin}^{k} \to s_{dis}^{k} \right) \quad \forall k = 1,\ldots N_{\sin} = N_{dis}$$

Analysis dilution curves

The area under the curve (AUC), mean transit time (MTT), and variance of the transit time (VTT) were calculated directly from the dilution curves using the following equations {Warren, 2008 #137}:

$$AUC = \int_{0}^{\infty} s_{pp}^{k}(t) \cdot dt$$

$$MTT = \frac{\int_{0}^{\infty} t \cdot s_{pp}^{k}(t) \cdot dt}{AUC}$$

$$VTT = \frac{\int_{0}^{\infty} t^{2} \cdot s_{pp}^{k}(t) \cdot dt}{AUC} - (MTT)^{2}$$

The catheter and nonexchangable vessel transit time (t_0) was estimated from the time of first appearance of radioactivity above background levels in the experimental dilution curves.

SUPPLEMENTARY TABLES

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

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

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(D-glc)=17mM** (perfused rat liver, cited) (Elliott and Craik, 1982) **km(D-glc)=30mM** (rat hepatocytes, cited) (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) **V_{max}(D-glc)=220±19**mmol/min/l of cell H2O (rat hepatocytes) (Elliott and Craik, 1982) **V_{max}(D-glc)=345**mmol/min/l of cell H2O (perfused rat liver, cited) (Elliott and Craik, 1982) **V_{max}(D-glc)=70**mmol/min/l of cell H2O (rat hepatocytes, cited) (Elliott and Craik, 1982) **km(D-gal)=174±48mM** (rat hepatocytes) (Elliott and Craik, 1982) **km(D-gal)=100mM** (rat hepatocytes, cited) (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-gal)~27.7mM** (dog liver, multiple indicator dilution curves (Goresky, et al., 1973) **V_{max} (D-gal)=288±48** mmol/min/l of cell H2O (rat hepatocytes) (Elliott and Craik, 1982) **V_{max} (D-gal)=160**mmol/min/l of cell H2O (rat hepatocytes, cited) (Elliott and Craik, 1982) Km(D-fru)=66mM (Walmsley, et al., 1998) Km(D-fru)=67mM (perfused rat liver, cited) (Elliott and Craik, 1982) Km(D-fru)=>100mM (rat hepatocytes, cited) (Elliott and Craik, 1982) v(D-fru)=291±26 mmol/min/l of cell H2O (rat hepatocytes) (Elliott and Craik, 1982) V_{max} (D-fru)=50mmol/min/l of cell H2O (perfused rat liver, cited) (Elliott and Craik, 1982) V_{max} (D-fru)=>160mmol/min/l of cell H2O (rat hepatocytes, cited) (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
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** 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)	**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(atp) = 0.12mM** (adult, rat liver){Cuatrecasas1965} **km(gal)=0.97±0.22mM** (SABIORK:14785) (Timson and Reece, 2003) **km(gal) = 0.436mM** (SABIORK:45367), (Sangiuolo, et al., 2004) **km(gal) = 0.15mM** (adult, rat liver){Cuatrecasas1965} km(gal) = 0.65mM (newborn, rat liver){Cuatrecasas1965} km(gal) = 0.91mM (18 day fetal, rat liver){Cuatrecasas1965} **km(gal) = 0.14±0.01mM** (SEM, N=6, adult rat liver) {Walker1968} km(gal) = 0.15±0.01mM (SEM, N=4, neonatal rat liver) {Walker1968} km(gal) = 0.14±0.01mM (SEM, N=4, foetal rat liver) {Walker1968} **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 (1mM gal1p caused 15% inhibition, 5mM gal1p 50% inhibition) **ki(gal1p) = 5.3mM (5.0-5.7mM)** (adult rat liver) (Cuatrecasas and Segal, 1965) **km(gal)<0.83mM** (dog liver, multiple indicator dilution curves) (Goresky, et al., 1973)
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**	**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)

	IMPA1, IMPA Normal substrate inositol-1p (ino1p)	
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	**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)

	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 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)	**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)
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 (Isselbacher ?). Stable transfection of human UGP (hUGP2) rescued galactose GALT deficient yeast from "galactose toxicity [Lai2002].	**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) "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)	**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)

	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)".	
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)** 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.	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) **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**]	**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)
	Reaction EC:3.6.1.1 RHEA:24579 KEGG:R00004 **Protein** UniProt:Q15181 (IPYR_HUMAN) homodimer Q15181*2 **Gene** PPA1, IOPPP, PP	**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**]	Compulsory-order substituted-enzyme (**Ping Pong Bi Bi**) mechanism (Lam and Packham, 1986)
	Reaction EC: 2.7.4.6 RHEA:25101 KEGG:R00156 **Multitude of isoforms**	**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)	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)

	homotetramer (dimer of dimer) P11413*4 **Gene** G6PD	**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)	[**adp**] = **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)	**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)
endothelial thickness	y_{end}	**165nm**	Determined by transmission electron microscopy **165±17nm** (human, young) {Warren2005} **130±8nm** (baboon, young) {Warren2005}	Determined by transmission electron microscopy **230±5nm** (rat, young) {Warren2005} **154±4nm** (mouse, young) {Warren2005}
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}	$\pi(y_{\sin}+y_{end}+y_{dis})^2-\pi(y_{\sin}+y_{end})^2$			
Area between adjacent sinusoid and Disse compartments	$A_{\sin dis}$	$2\pi\cdot y_{\sin}\cdot x_{\sin}$			
Volume sinusoid compartment	$V_{\sin}$	$A_{\sin}\cdot x_{\sin}$			
Volume Disse compartment	V_{dis}	$A_{dis}\cdot x_{\sin}$			
Volume cell	V_{cell}	$\pi(y_{\sin}+y_{end}+y_{dis}+y_{cell})^2\cdot x_{cell}$ $-\pi(y_{\sin}+y_{end}+y_{dis})^2 x_{cell}$			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	$V_{\sin unit}$	$L_{\sin}\cdot\pi\cdot(y_{\sin}+y_{end}+y_{dis}+y_{cell})^2$ **272.9E3** μm^3 (calculated)			
Volume fraction sinusoidal blood volume, % liver	$f_{\sin}$	$\frac{V_{\sin}}{V_{\sin unit}}$ **11.1%** (calculated)	**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}	$\frac{V_{dis}}{V_{\sin unit}}$ **6.9%** (calculated)	**~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)

Commented [WU3]: Update with final calculated values

Volume fraction parenchymal cells, % liver	f_{cell}	$\frac{V_{cell}}{V_{\sin unit}}$ **81.9%** (calculated)			**78%** (morphological studies, % volume) (Blouin, et al., 1977; Lautt, 2009)
RBC velocity	v_{flow}	**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 mean transit time of RBC in multiple indicator dilution curves) (Goresky, 1963)	**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	$Q_{\sin unit}$	$\pi(y_{\sin})^2 v_{flow}$ **16.4E3** $\frac{\mu m^3}{s}$ (calculated)	flow through cylinder analogue to (Gross and Aroesty, 1972; Puhl, et al., 2003)		

Porosity, fenestrae frequency and diameter The presence of fenestrae reduces the surface available for free transport, whereas the parenchymal surface available for uptake is 6.0 times enlarged by microvilli (Schaff and Lapis, 1990; Wisse, et al., 1985)	f_{fen} N_{fen} r_{fen}	$N_{fen}\pi \cdot (r_{fen})^2$ **0.09** (calculated) **10 [1/µm^2]** **53.5 nm** (diameter 107nm)	**diameter fenestrae** **107**±1.5**nm** (SE, human) (Wisse, et al., 2008) **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)	(Wisse, et al., 1985) demonstrated presence of fenestrae in dog liver with preliminary measurements indicating that the size distribution was almost equal to rat liver fenestrae.	**diameter fenestrae** **175nm** (Wisse, et al., 1996) **161**±2.7**nm** (Spraque-Dawley rats) (Wisse, et al., 2008) **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)
fenestration in aging	$\frac{r_{fen}^{old}}{r_{fen}^{young}}$ $\frac{f_{fen}^{old}}{f_{fen}^{young}}$	**1.0** old (60 years)/young (20 years) **0.25** old (60 years)/young (20 years)	**diameter** **58**±1**nm** (young, baboon), **70**±2**nm** (old, baboon), old/young **1.21** {Warren2005} **porosity** determined by scanning electron microscopy **4.2**±0.5**%** (young, baboon),		**diameter** **73**±1**nm** (young, rat), **60**±1**nm** (old,rat), old/young **0.82** {Warren2005} **74**±4**nm** (young, mouse), **58**±12**nm** (old,mouse), old/young **0.78** {Warren2005} **porosity** determined by scanning electron microscopy **4.1**±2.3**%** (young, rat), **2.5**±1.2**%** (old, rat), old/young

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			2.4±0.4**%** (old, baboon), old/young **0.61 {**Warren2005} **frequency** determined by transmission electron microscopy **7.7**±0.7 **[1/µm]** (young, human), **1.5**±0.4 **[1/µm]** (old, human), old/young **0.19 {**Warren2005} **9.4**±0.9 **[1/µm]** (young, baboon), **5.5**±0.7 **[1/µm]** (old, baboon), old/young **0.58 {**Warren2005}	**0.61 {**Warren2005} **4.1**±2.2**%** (young, mouse), **2.2**±3.5**%** (old mouse), old/young **0.54 {**Warren2005} **frequency** determined by transmission electron microscopy **2.7**±1.1 **[1/µm]** (young, rat), **0.9**±0.8 **[1/µm]** (old, rat), old/young **0.33 {**Warren2005}
	$\frac{N_{fen}^{old}}{N_{fen}^{young}}$	**0.25** old (60 years)/young (20 years) (calculated from changes in r and f)		
endothelial thickness in aging	$\frac{y_{end}^{old}}{y_{end}^{young}}$	**1.75** old (60 years)/young (20 years)	Determined by transmission electron microscopy **165±17nm** (human, young), **289±9nm** (human, old), old/young **1.75** {Warren2005} **130±8nm** (baboon, young), **186±9nm** (baboon, old) , old/young **1.43** {Warren2005}	Determined by transmission electron microscopy **230±50nm** (rat, young), **320±80nm** (rat, old) , old/young **1.39**{Warren2005} **154±4nm** (mouse, young), **245±8nm** (mouse, old), old/young **1.59** {Warren2005}

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

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Calculated fit table to make sure the values are correct

Supplementary Table 5 *– Diffusion parameters*

Id	**Molecular weight Mw [Da]**	**Diffusion constant [µm²/s]**	**Effective radius (sphere of equivalent diffusion coefficient) [nm]** $r = \frac{RT}{6\pi\eta DN}$	**References [µm²/s]**
h2o water	18	2300	0.15	**D=2300** (water in water) Bionumbers id=104087, ver=3)(Milo, et al., 2010) **D=2100** (water in water) Bionumbers id=104087, ver=7)(Milo, et al., 2010) D=2360 **(**D25) {Renkin1954}
urea urea	60	1750	0.19	**D=1750 (**D37, measurements in hindlimbs of cats) {Pappenheimer1951} D=1450 **(**D25) {Renkin1954}
glc D-glucose	180	910	0.36	**D=910** (D37, hexose, free diffusion coefficient in water at 37°C)(Renkin, 1977) (Casciari, et al., 1988; Groebe, et al., 1994) **D=900 (**D37, measurements in hindlimbs of cats) {Pappenheimer1951} D=680 **(**D25) {Renkin1954} D=600 (glucose in water) (Bionumbers id=104089, ver=6)(Milo, et al., 2010) D=673 (glucose in water) (Bionumbers id=109504, ver=1)(Milo, et al., 2010) Dimensions from xray: 0.45 x 0.35 x 0.25 {Pappenheimer1951}
gal D-galactose	180	910	0.36	**D=910** (D37, hexose, free diffusion coefficient in water at 37°C)(Renkin, 1977)
suc sucrose	342	720	0.44	**D=720** (D37, free diffusion coefficient in water at 37°C)(Renkin, 1977) **D=750 (**D37, measurements in hindlimbs of cats) {Pappenheimer1951} D=550 **(**D25) {Renkin1954} D=520 (sucrose in water) (Bionumbers id=100614, ver=7)(Milo, et al., 2010) Dimensions from xray: 0.58 x 0.53 x 0.40 {Pappenheimer1951}
inu inulin	3400	210	1.52	**D=210 (**D37, measurements in hindlimbs of cats) {Pappenheimer1951} (inulin polymer, values depend on n)
alb albumin	66500	90	3.64	**D=90** (D37, free diffusion coefficient in water at 37°C)(Renkin, 1977)
rbc red blood cells	-	0	3000	

Supplementary Table 6 *– Organ/Liver parameters*

Parameter	Symbol	Model value	Human	Dog	Rat
body weight					**~200g** (80-308g)(Female Wistar) {Keiding1973}
liver weight	m_{liv}	$\rho_{liv} \cdot V_{liv}$ (**1650g** calculated)	**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) **~6.5g** (Female Wistar, from regression) {Keiding1973}
density liver tissue	ρ_{liv}	**1.08** $\frac{g}{ml}$	**1.1g/ml** (Debbaut, et al., 2012) Total cell density is ~1.1**g/mL** (BNID 103875, 102239, 106439) {Heinemann1999}		
total liver volume	V_{liv}	**1450ml**	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 $\frac{m_{liv}}{\rho_{liv}}$)	**17.1ml** (calculated $\frac{m_{liv}}{\rho_{liv}}$)
total hepatic blood flow per liver weight (~75-80% portal vein partially deoxygenated, 20-25% hepatic artery well-oxygenated)	q_{liv}	$\frac{Q_{liv}}{m_{liv}} = \frac{Q_{liv}}{\rho_{liv} \cdot V_{liv}}$ (**1.06**	**~1.0-1.3** $\frac{ml}{\min \cdot g_{LW}}$ (Lautt, 2009) **~1** $\frac{ml}{\min \cdot g_{LW}}$ (Vollmar and Menger, 2009) (Kuntz	**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)

		$\frac{ml}{\min \cdot g_{LW}}$ calculated)	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)		**1.54**±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}	**1700** $\frac{ml}{\min}$	**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.,	**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)

			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)
total number of hepatic sinusoids	$N_{\sin}$		Calculate based on flow $N_Q = \frac{Q_{liv}}{Q_{\sin unit}} = \frac{Q_{liv}}{A_{\sin} \cdot v_{flow}} = \frac{Q_{liv}}{\pi (y_{\sin})^2 \cdot v_{flow}}$ $N_Q = 2472E6$ (calculated) 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
parenchymal tissue fraction of liver ()	f_{tissue}	**0.8** (calculated)	Due to large vessel, connective tissue, lymphs system, only part of whole liver volume is parenchymal tissue. The number of sinusoidal units based on tissue volume $N_{vol} = \frac{V_{tissue}}{V_{\sin unit}} = \frac{f_{tissue} \cdot V_{liv}}{\pi \cdot (y_{\sin} + y_{dis} + y_{cell})^2 \cdot L_{\sin}}$ and $N_{vol} = N_Q$ result in $f_{tissue} = \frac{1}{N_Q} \frac{V_{liv}}{V_{\sin unit}}$ Literature (25 % large vessels, …)

Supplementary Table 7 *–Galactose elimination in normal state and disease*

	Human	Animals
Hepatic galactose elimination (HGE)	**Saturation of hepatic galactose elimination** The HGE rate falls at concentration below **500mg/l (=2.78mM**) (Tygstrup, 1963; Tygstrup and Winkler, 1958) Single injection galactose elimination capacity GEC=**341–609 mg(galactose)/min (1.89-3.38mmol/min)** Continuous infusion GEC=**295-509mg(galactose/min) (1.63-2.83mmol/min**) Single injection and infusion experiments will give different figures for the hepatic galactose elimination capacity and volume of distribution, depending on the degree of displacement of the arterial curve. (Tygstrup, 1963) Galactose elimination capacity progressively decreased from **GEC=3.05±0.58 (SD)mmol/min** in younger subjects to **GEC=1.83±0.24 (SD)mmol/min** in subjects over 81. (Marchesini, et al., 1988)". **GECliv** ~ 3.05mmol/min/1500g = **2.03µmol/min/glw** **GEC 1.89- 3.58mmol/min** (n=17, healthy, single injection method) **{Tygstrup, 1963 #78}** **GE 0.8- 2.2mmol/min** (n=20) **{Tygstrup, 1977 #148}** In healthy people plasma galactose clearance **CL=1366±172 ml/min** and hepatic extraction 95%, **ER=0.95** (during continuous infusion of 5% D-galactose at a rate of 50mg/min) {Henderson, 1983 #86} **GECkg** 7.48±0.94mg/min/kgbw (SD, n=70, <40 years, normal) {Schnegg, 1986 #145} **~2.91±0.37mmole/min GEC** (with 70kgbw) **GECkg** 7.08±0.68mg/min/kgbw (SD, n=11, 40-70 years, normal) {Schnegg, 1986 #145} **~2.75±0.26mmole/min GEC** (with 70kgbw) **GECkg** 6.08±1.30mg/min/kgbw (SD, n=13, >70years, normal) {Schnegg, 1986 #145} **~2.36±0.51mmole/min GEC** (with 70kgbw) **3.18±0.64mmole/min** [2.26-4.07] **GEC** (SD, n=9, **normal subjects**) {Tygstrup, 1961 #98} **1.98±0.25mmole/min** [1.69-2.53] **GEC** (SD, n=11, **cirrhotics**, total elimination rate >300mg/min) {Tygstrup, 1961 #98} **1.37±0.16mmole/min** [1.19-1.66] **GEC** (SD, n=10, **cirrhotics**, total elimination rate >210 & <300mg/min) {Tygstrup, 1961 #98} **0.61±0.11mmole/min** [0.87-1.16] **GEC** (SD, n=11, **cirrhotics**, total elimination rate <210) {Tygstrup, 1961 #98} **GECkg=6.94±0.88mg/min/kg** (SD, n=20 healthy controls) [Wernze1973] **GEC ~2.70±0.34mmole/min GEC** (with 70kgbw) **GECkg=5.17±0.83mg/min/kg** (SD, n=14, patients with renal insufficiency) [Wernze1973] **GEC~2.01±0.32mmole/min** (with 70kgbw) **Galactose uptake liver slices:** The galactose utilization rate of **human liver slices is twice as great as that of rat liver slices**. {Tygstrup, 1971 #159}. 60 min incubation at galactose of 1.7mM **5.64±0.41µmol/g** (SD, n=11, human liver tissue slices, medium 1.7mM galactose) **1.25±0.14µmol/g** (SD, n=11, human liver tissue slices, medium 1.7mM galactose + ethanol 10mM)	**Rat** The elimination of galactose infused in rats (female Wistar) was found to follow saturation kinetics with estimated maximal elimination rate **GEC(rat)=61µmol/h/100gbw** and estimated half saturation concentration of **Km=0.4mmol/l** {Keiding1973} **GEC(rat)=131±1(SE of estimate)µmol/h** and **Km(rat)=0.37mmol/l** Neither fasting nor nephrectomy has any effect on the GEC **GEC(rat)=118±30 (SD)µmol/h** in rats weighing about 200g (N=56) {Keiding1973} **GECliv(rat) ~** 122µmol/h/6.5glw = **0.31µmol/min/glw** GEC per g liver is considerably higher than that of liver slices (0.04µmol/min/glw) {Tygstrup1971} **GEC(rat)=73µmol/h/100gbw** {Salaspuro1968} **Galactokinase activity** **0.85±0.09µmol/min/glw (**N=10, adult male rats) {Walker1968} **0.80±0.02µmol/min/glw (**N=6, adult female rats) {Walker1968} **Pig** **GECliv(pig)=0.34-0.57µmol/min/glw** (0.34-0.57mmol/min/kglw) {Keiding1976} **Km(pig) = 0.12-0.30mM** {Keiding1976} (female, Danish country bred pigs 31-48kg) **Dog** **GEC(dog)=0.55mmol/min** (100mg/min) (N=8, adult, male mongrel dogs, 20-30kg, estimated liver weight 600-800g) **GECliv(dog)~0.8µmol/min/glw** {Madsen1979}

	2.47±0.16µmol/g (SD, n=16, rat liver tissue slices, medium 1.7mM galactose, Wistar rats ~200g bw) **0.82±0.11µmol/g** (SD, n=16, rat liver tissue slices, medium 1.7mM galactose + ethanol 10mM, Wistar rats ~200g bw)	
Endogeneous galactose production	**Rate of endogenous D-galactose appearance in plasma** **R = 0.17 µmol/kg$_{BW}$/h** (Schadewaldt, et al., 2000) **R = 2.9-5.4µmol/kg$_{BW}$/h** (Berry, et al., 1995)	
Renal galactose extraction / Kidney Clearance	"An **exponential component** might be attributed to renal extraction, which is known to be **proportional to concentration** [Gammeltoft, Kjerluf-Jensen1943, Dominguez1944]. The total renal extraction averages **8.8% of the amount given.**" {Tygstrup, 1954 #85}. Urinary excretion of galactose is **unimportant in relation to hepatic elimination at plasma concentrations below about 500mg/l=2.78mM (~3% of total elimination){Tygstrup, 1961 #98}** **11.7±1.7% (range 9.2 – 15.2)** of dose urinary excretion (SD, n=9, human, normal subjects) {Tygstrup, 1961 #98} The data agree with the concept of reabsorption of galactose in the renal tubulus with a low and incomplete threshold at a concentration in the body of 100 -200 mg/l. The relatively slow rise in clearance at higher concentrations indicates that Tm of the process is very high, unless the reabsorption of these high concentrations is mainly passive, i.e. by diffusion {Tygstrup, 1961 #98}.	In human subjects only small amounts are excreted by the kidneys. In rats, however, the urinary excretion of galactose rises to from 60 to 80% percent {Salaspuro, 1968 #70}

REFERENCES

Accorsi, A., *et al.* (1989) Isoenzymes of phosphoglucomutase from human red blood cells: isolation and kinetic properties, *Preparative biochemistry*, **19**, 251-271.

Allen, T.H. and Reeve, E.B. (1953) Distribution of extra plasma in the blood of some tissues in the dog of measured with P32 and T-1824, *The American journal of physiology*, **175**, 218-223.

Arbuckle, M.I., *et al.* (1996) Structure-function analysis of liver-type (GLUT2) and brain-type (GLUT3) glucose transporters: expression of chimeric transporters in Xenopus oocytes suggests an important role for putative transmembrane helix 7 in determining substrate selectivity, *Biochemistry*, **35**, 16519-16527.

Bautista, J.M., Mason, P.J. and Luzzatto, L. (1992) Purification and properties of human glucose-6-phosphate dehydrogenase made in E. coli, *Biochimica et biophysica acta*, **1119**, 74-80.

Blouin, A., Bolender, R.P. and Weibel, E.R. (1977) Distribution of organelles and membranes between hepatocytes and nonhepatocytes in the rat liver parenchyma. A stereological study, *The Journal of cell biology*, **72**, 441-455.

Braet, F. and Wisse, E. (2002) Structural and functional aspects of liver sinusoidal endothelial cell fenestrae: a review, *Comp Hepatol*, **1**, 1.

Brauer, R.W., Holloway, R.J. and Leong, G.F. (1959) Changes in liver function and structure due to experimental passive congestion under controlled hepatic vein pressures, *The American journal of physiology*, **197**, 681-692.

Brown, G.K. (2000) Glucose transporters: structure, function and consequences of deficiency, *Journal of inherited metabolic disease*, **23**, 237-246.

Burkel, W.E. and Low, F.N. (1966) The fine structure of rat liver sinusoids, space of Disse and associated tissue space, *Am J Anat*, **118**, 769-783.

Burwen, S.J., *et al.* (1982) The perfused human liver wedge biopsy: a new in vitro model for morphological and functional studies, *Hepatology*, **2**, 426-432.

Carlisle, K.M., *et al.* (1992) Estimation of total hepatic blood flow by duplex ultrasound, *Gut*, **33**, 92-97.

Casciari, J.J., Sotirchos, S.V. and Sutherland, R.M. (1988) Glucose diffusivity in multicellular tumor spheroids, *Cancer Res*, **48**, 3905-3909.

Chang, H.Y., *et al.* (1996) The importance of conserved residues in human liver UDPglucose pyrophosphorylase, *European journal of biochemistry / FEBS*, **236**, 723-728.

Ciaraldi, T.P., Horuk, R. and Matthaei, S. (1986) Biochemical and functional characterization of the rat liver glucose-transport system. Comparisons with the adipocyte glucose-transport system, *The Biochemical journal*, **240**, 115-123.

Colville, C.A., *et al.* (1993) Kinetic analysis of the liver-type (GLUT2) and brain-type (GLUT3) glucose transporters in Xenopus oocytes: substrate specificities and effects of transport inhibitors, *The Biochemical journal*, **290 (Pt 3)**, 701-706.

Corpas, F.J., *et al.* (1995) Kinetic properties of hexose-monophosphate dehydrogenases. II. Isolation and partial purification of 6-phosphogluconate dehydrogenase from rat liver and kidney cortex, *Molecular and cellular biochemistry*, **144**, 97-104.

Corpas, F.J., *et al.* (1995) Kinetic properties of hexose-monophosphate dehydrogenases. I. Isolation and partial purification of glucose-6-phosphate dehydrogenase from rat liver and kidney cortex, *Life sciences*, **56**, 179-189.

Cuatrecasas, P. and Segal, S. (1965) Mammalian Galactokinase. Developmental and Adaptive Characteristics in the Rat Liver, *The Journal of biological chemistry*, **240**, 2382-2388.

Debbaut, C., *et al.* (2014) Analyzing the human liver vascular architecture by combining vascular corrosion casting and micro-CT

scanning: a feasibility study, *J Anat*, **224**, 509-517.
Debbaut, C., *et al.* (2012) Perfusion characteristics of the human hepatic microcirculation based on three-dimensional reconstructions and computational fluid dynamic analysis, *J Biomech Eng*, **134**, 011003.
Diepenbrock, F., *et al.* (1992) Colorimetric determination of galactose and galactose-1-phosphate from dried blood, *Clinical biochemistry*, **25**, 37-39.
Duggleby, R.G., *et al.* (1996) Sequence differences between human muscle and liver cDNAs for UDPglucose pyrophosphorylase and kinetic properties of the recombinant enzymes expressed in Escherichia coli, *European journal of biochemistry / FEBS*, **235**, 173-179.
Elliott, K.R. and Craik, J.D. (1982) Sugar transport across the hepatocyte plasma membrane, *Biochemical Society transactions*, **10**, 12-13.
Everett, N.B., Simmons, B. and Lasher, E.P. (1956) Distribution of blood (Fe 59) and plasma (I 131) volumes of rats determined by liquid nitrogen freezing, *Circulation research*, **4**, 419-424.
Facchiano, A. and Marabotti, A. (2010) Analysis of galactosemia-linked mutations of GALT enzyme using a computational biology approach, *Protein engineering, design & selection : PEDS*, **23**, 103-113.
Fraser, R., *et al.* (1988) Nicotine decreases the porosity of the rat liver sieve: a possible mechanism for hypercholesterolaemia, *Br J Exp Pathol*, **69**, 345-350.
Fridovich-Keil, J.L. (2006) Galactosemia: the good, the bad, and the unknown, *Journal of cellular physiology*, **209**, 701-705.
Fukuchi, T., *et al.* (1994) Recombinant rat nucleoside diphosphate kinase isoforms (alpha and beta): purification, properties and application to immunological detection of native isoforms in rat tissues, *Biochimica et biophysica acta*, **1205**, 113-122.
Gariepy, L., *et al.* (1993) Clearance by the liver in cirrhosis. II. Characterization of propranolol uptake with the multiple-indicator dilution technique, *Hepatology*, **18**, 823-831.
Geeganage, S. and Frey, P.A. (1998) Transient kinetics of formation and reaction of the uridylyl-enzyme form of galactose-1-P uridylyltransferase and its Q168R-variant: insight into the molecular basis of galactosemia, *Biochemistry*, **37**, 14500-14507.
Goresky, C.A. (1963) A linear method for determining liver sinusoidal and extravascular volumes, *Am J Physiol*, **204**, 626-640.
Goresky, C.A., Bach, G.G. and Nadeau, B.E. (1973) On the uptake of materials by the intact liver. The transport and net removal of galactose, *The Journal of clinical investigation*, **52**, 991-1009.
Gould, G.W., *et al.* (1991) Expression of human glucose transporters in Xenopus oocytes: kinetic characterization and substrate specificities of the erythrocyte, liver, and brain isoforms, *Biochemistry*, **30**, 5139-5145.
Groebe, K., Erz, S. and Mueller-Klieser, W. (1994) Glucose diffusion coefficients determined from concentration profiles in EMT6 tumor spheroids incubated in radioactively labeled L-glucose, *Advances in experimental medicine and biology*, **361**, 619-625.
Gross, J.F. and Aroesty, J. (1972) Mathematical models of capillary flow: a critical review, *Biorheology*, **9**, 225-264.
Guynn, R.W., *et al.* (1974) The concentration and control of cytoplasmic free inorganic pyrophosphate in rat liver in vivo, *The Biochemical journal*, **140**, 369-375.
Horn, T., Christoffersen, P. and Henriksen, J.H. (1987) Alcoholic liver injury: defenestration in noncirrhotic livers--a scanning electron microscopic study, *Hepatology*, **7**, 77-82.
Irie, M., *et al.* (1970) Distribution and properties of alkaline pyrophosphatases of rat liver, *Journal of biochemistry*, **67**, 47-58.
Jakab, F., *et al.* (1995) The interaction between hepatic arterial and portal venous blood flows; simultaneous measurement by transit time ultrasonic volume flowmetry, *Hepato-gastroenterology*, **42**, 18-21.
Kashiwaya, Y., *et al.* (1994) Control of glucose utilization in working perfused rat heart, *The Journal of biological chemistry*, **269**, 25502-25514.
Keppler, D. and Decker, K. (1969) Studies on the mechanism of galactosamine-1-phosphate and its inhibition of UDP-glucose pyrophosphorylase, *European journal of biochemistry / FEBS*, **10**, 219-225.
Keppler, D., *et al.* (1969) Changes in uridine nucleotides during liver perfusion with D-galactosamine, *FEBS letters*, **4**, 278-280.
Keppler, D., Rudigier, J. and Decker, K. (1970) Trapping of uridine phosphates by D-galactose in ethanol-treated liver, *FEBS letters*, **11**, 193-196.
Keppler, D.O., *et al.* (1970) The trapping of uridine phosphates by D-galactosamine. D-glucosamine, and 2-deoxy-D-galactose. A study on the mechanism of galactosamine hepatitis, *European journal of biochemistry / FEBS*, **17**, 246-253.
Kimura, N. and Shimada, N. (1988) Membrane-associated nucleoside diphosphate kinase from rat liver. Purification, characterization, and comparison with cytosolic enzyme, *The Journal of biological chemistry*, **263**, 4647-4653.
Knop, J.K. and Hansen, R.G. (1970) Uridine diphosphate glucose pyrophosphorylase. IV. Crystallization and properties of the enzyme from human liver, *The Journal of biological chemistry*, **245**, 2499-2504.
König, M., Bulik, S. and Holzhütter, H.G. (2012) Quantifying the contribution of the liver to glucose homeostasis: a detailed kinetic model of human hepatic glucose metabolism, *PLoS computational biology*, **8**, e1002577.
Koo, A. and Liang, I.Y. (1979) Microvascular filling pattern in rat liver sinusoids during vagal stimulation, *J Physiol*, **295**, 191-199.
Koo, A., Liang, I.Y. and Cheng, K.K. (1975) The terminal hepatic microcirculation in the rat, *Q J Exp Physiol Cogn Med Sci*, **60**, 261-266.
Kuntz, E. and Kuntz, H.D. (2006) Hepatology - Principles and Practice.
Lai, K., *et al.* (2003) GALT deficiency causes UDP-hexose deficit in human galactosemic cells, *Glycobiology*, **13**, 285-294.
Lam, S.C. and Packham, M.A. (1986) Isolation and kinetic studies of nucleoside diphosphokinase from human platelets and effects of cAMP phosphodiesterase inhibitors, *Biochemical pharmacology*, **35**, 4449-4455.
Lautt, W.W. (2009). In, *Hepatic Circulation: Physiology and Pathophysiology*. San Rafael (CA).
Leslie, N.D. (2003) Insights into the pathogenesis of galactosemia, *Annual review of nutrition*, **23**, 59-80.

Loud, A.V. (1968) A quantitative stereological description of the ultrastructure of normal rat liver parenchymal cells, *The Journal of cell biology*, **37**, 27-46.
MacPhee, P.J., Schmidt, E.E. and Groom, A.C. (1995) Intermittence of blood flow in liver sinusoids, studied by high-resolution in vivo microscopy, *Am J Physiol*, **269**, G692-698.
MacPhee, P.J., *et al.* (1988) Microcirculatory changes in livers of mice infected with murine hepatitis virus. Evidence from microcorrosion casts and measurements of red cell velocity, *Microvasc Res*, **36**, 140-149.
Milo, R., *et al.* (2010) BioNumbers--the database of key numbers in molecular and cell biology, *Nucleic Acids Res*, **38**, D750-753.
Muto, M., Nishi, M. and Fujita, T. (1977) Scanning electron microscopy of human liver sinusoids, *Arch Histol Jpn*, **40**, 137-151.
Orfanos, A.P., Jinks, D.C. and Guthrie, R. (1986) Microassay for estimation of galactose and galactose-1-phosphate in dried blood specimens, *Clinical biochemistry*, **19**, 225-228.
Ozer, N., Aksoy, Y. and Ogus, I.H. (2001) Kinetic properties of human placental glucose-6-phosphate dehydrogenase, *The international journal of biochemistry & cell biology*, **33**, 221-226.
Parthasarathy, R., Parthasarathy, L. and Vadnal, R. (1997) Brain inositol monophosphatase identified as a galactose 1-phosphatase, *Brain research*, **778**, 99-106.
Puhl, G., *et al.* (2003) Noninvasive in vivo analysis of the human hepatic microcirculation using orthogonal polorization spectral imaging, *Transplantation*, **75**, 756-761.
Quan-Ma, R., *et al.* (1966) Galactitol in the tissues of a galactosemic child, *Am J Dis Child*, **112**, 477-478.
Quick, C.B., Fisher, R.A. and Harris, H. (1974) A kinetic study of the isozymes determined by the three human phosphoglucomutase loci PGM1, PGM2, and PGM3, *European journal of biochemistry / FEBS*, **42**, 511-517.
Quimby, B.B., *et al.* (1997) Characterization of two mutations associated with epimerase-deficiency galactosemia, by use of a yeast expression system for human UDP-galactose-4-epimerase, *American journal of human genetics*, **61**, 590-598.
Quimby, B.B., *et al.* (1996) Functional requirements of the active site position 185 in the human enzyme galactose-1-phosphate uridylyltransferase, *The Journal of biological chemistry*, **271**, 26835-26842.
Renkin, E.M. (1977) Multiple pathways of capillary permeability, *Circ Res*, **41**, 735-743.
Roberts, M.S. and Rowland, M. (1985) Hepatic elimination--dispersion model, *J Pharm Sci*, **74**, 585-587.
Sangiuolo, F., *et al.* (2004) Biochemical characterization of two GALK1 mutations in patients with galactokinase deficiency, *Human mutation*, **23**, 396.
Schadewaldt, P., *et al.* (2000) Analysis of concentration and (13)C enrichment of D-galactose in human plasma, *Clinical chemistry*, **46**, 612-619.
Schaff, Z. and Lapis, K. (1990) Fine structure of hepatocytes during the etiology of several common pathologies, *J Electron Microsc Tech*, **14**, 179-207.
Schirmer, W.J., *et al.* (1986) Galactose clearance as an estimate of effective hepatic blood flow: validation and limitations, *The Journal of surgical research*, **41**, 543-556.
Segal, S. (1995) Defective galactosylation in galactosemia: is low cell UDPgalactose an explanation?, *European journal of pediatrics*, **154**, S65-71.
Segal, S. and Rogers, S. (1971) Nucleotide inhibition of mammalian liver galactose-I-phosphate uridylyltransferase, *Biochimica et biophysica acta*, **250**, 351-360.
Slepak, T.I., *et al.* (2007) Involvement of endoplasmic reticulum stress in a novel Classic Galactosemia model, *Molecular genetics and metabolism*, **92**, 78-87.
Tang, M., *et al.* (2012) Correlation assessment among clinical phenotypes, expression analysis and molecular modeling of 14 novel variations in the human galactose-1-phosphate uridylyltransferase gene, *Human mutation*, **33**, 1107-1115.
Thoden, J.B., *et al.* (2002) Structural analysis of the Y299C mutant of Escherichia coli UDP-galactose 4-epimerase. Teaching an old dog new tricks, *The Journal of biological chemistry*, **277**, 27528-27534.
Thuillier, L. (1978) Purification and kinetic properties of human erythrocyte Mg2+-dependent inorganic pyrophosphatase, *Biochimica et biophysica acta*, **524**, 198-206.
Timson, D.J. (2005) Functional analysis of disease-causing mutations in human UDP-galactose 4-epimerase, *The FEBS journal*, **272**, 6170-6177.
Timson, D.J. and Reece, R.J. (2003) Functional analysis of disease-causing mutations in human galactokinase, *European journal of biochemistry / FEBS*, **270**, 1767-1774.
Turnquist, R.L., *et al.* (1974) Uridine diphosphate glucose pyrophosphorylase: differential heat inactivation and further characterization of human liver enzyme, *Biochimica et biophysica acta*, **364**, 59-67.
Villeneuve, J.P., *et al.* (1996) The hepatic microcirculation in the isolated perfused human liver, *Hepatology*, **23**, 24-31.
Vollmar, B. and Menger, M.D. (2009) The hepatic microcirculation: mechanistic contributions and therapeutic targets in liver injury and repair, *Physiol Rev*, **89**, 1269-1339.
Walmsley, A.R., *et al.* (1998) Sugar transporters from bacteria, parasites and mammals: structure-activity relationships, *Trends in biochemical sciences*, **23**, 476-481.
Wang, Z.J., *et al.* (2001) Proton magnetic resonance spectroscopy of brain metabolites in galactosemia, *Annals of neurology*, **50**, 266-269.
Warren, A., *et al.* (2008) Effects of old age on vascular complexity and dispersion of the hepatic sinusoidal network, *Microcirculation*, **15**, 191-202.
Wasilenko, J., *et al.* (2005) Functional characterization of the K257R and G319E-hGALE alleles found in patients with ostensibly peripheral epimerase deficiency galactosemia, *Molecular genetics and metabolism*, **84**, 32-38.
Wells, W.W., *et al.* (1965) The Isolation and Identification of Galactitol from the Brains of Galactosemia Patients, *The Journal of biological chemistry*, **240**, 1002-1004.

Wermuth, B., *et al.* (1982) Purification and characterization of human-brain aldose reductase, *European journal of biochemistry / FEBS*, **127**, 279-284.
Wermuth, B. and von Wartburg, J.P. (1982) Aldose reductase from human tissues, *Methods in enzymology*, **89 Pt D**, 181-186.
Wiener, J., *et al.* (1968) A quantitative description of cortisone-induced alterations in the ultrastructure of rat liver parenchmal cells, *J Cell Biol*, **37**, 47-61.
Winans, K.A. and Bertozzi, C.R. (2002) An inhibitor of the human UDP-GlcNAc 4-epimerase identified from a uridine-based library: a strategy to inhibit O-linked glycosylation, *Chemistry & biology*, **9**, 113-129.
Wisse, E., *et al.* (1996) Structure and function of sinusoidal lining cells in the liver, *Toxicol Pathol*, **24**, 100-111.
Wisse, E., *et al.* (1985) The liver sieve: considerations concerning the structure and function of endothelial fenestrae, the sinusoidal wall and the space of Disse, *Hepatology*, **5**, 683-692.
Wisse, E., *et al.* (2008) The size of endothelial fenestrae in human liver sinusoids: implications for hepatocyte-directed gene transfer, *Gene Ther*, **15**, 1193-1199.
Wohlers, T.M. and Fridovich-Keil, J.L. (2000) Studies of the V94M-substituted human UDPgalactose-4-epimerase enzyme associated with generalized epimerase-deficiency galactosaemia, *Journal of inherited metabolic disease*, **23**, 713-729.
Wynne, H.A., *et al.* (1989) The effect of age upon liver volume and apparent liver blood flow in healthy man, *Hepatology*, **9**, 297-301.
Yamaguchi, A., *et al.* (1989) Microassay for screening newborns for galactosemia with use of a fluorometric microplate reader, *Clinical chemistry*, **35**, 1962-1964.
Yoshida, C., Shah, H. and Weinhouse, S. (1982) Purification and properties of inorganic pyrophosphatase of rat liver and hepatoma 3924A, *Cancer research*, **42**, 3526-3531.