## Dilution-Indicator studies

The single-injection, multiple-indicator dilution approach provides a method to determine the composition of the liver and the rates of hepatic processes [[1](#_ENREF_1)]. Labeled red blood cells (RBC) are used as vascular reference. Larger materials are excluded from the space of Disse. The model of Goresky provides a realistic alternative to the too simple lumped compartmental descriptions of the liver classically utilized in pharmacokinetics. It provides a framework such that each curve can be directly compared with each other, the outflow concentration of each tracer is divided by the total injected, providing a normalized value, an outflow fraction per ml.

### Relationship vascular tree and sinusoid transit times ?

It is assumed that no displacement occurs between reference intravascular and diffusible tracers in the large vessels: all displacement occurs in the exchanging vessels (sinusoids). The interrelations between whole-organ outflow reference and diffusible tracer curves will depend not only on the phenomena occurring within each sinusoid but also on the way the transit times in larger vessels and sinusoids are interrelated. Various combinations are possible, depending on the structure of the network and the kind of flow coupling in the system. **The pattern corresponding to the liver was found to lie at a simple extreme in this possible spectrum [Rose1976, Goresky1970]**. The distribution of out-flow transit times was found to correspond to the distribution transit of sinusoidal times in large transit times; **the distribution of vessels was so compact that a single value could be assumed**. Thus it was possible to derive a test for the single-sinusoid modeling. If, after a common transit time in large vessels, the sinusoidal transit time for each diffusible label in the liver is increased by the ratio of its total-to-accessible sinusoidal vascular space, then it should be possible to reverse this flow-limited delay effect in the curve for each diffusible label.

Goresky et al.1 previously have considered two models representing the extreme cases, i.e., no heterogeneity, and maximum heterogeneity in capillary transit times. Multiple indicator-dilution data from the liver fit the latter model very well [Rose1976].

## Tables

**Table** – Model parameters (OPS – orthogonal polarization spectral imaging; QSD – quantitative stereological description; IVM – in vivo microscopy)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **Symbol** | | **Value** | **Human** | **Dog** | **Rat** | **Mouse** |
| **Liver/lobule/sinusoid architecture** |  |  | |  |  |  |  |
| **number of hepatocytes along sinusoid** |  | **20** | | **15-25 hepatocytes** [[2](#_ENREF_2)] |  |  |  |
| **diameter hepatocytes** |  | **25µm** | | **20 – 40µm** [[2](#_ENREF_2)] |  | **20.8±0.2µm** (rat, periportal, QSD)  **20.8±0.3µm** (rat, midzonal, QSD)  **21.0±0.3µm** (rat, perivenious, QSD) [[3](#_ENREF_3)] |  |
| **sinusoid length** |  | (**500µm**) | | **350–500µm** [[2](#_ENREF_2)] (diameter of hepatic lobules 1.0 – 1.3mm [[2](#_ENREF_2)])  **1000µm** (diameter of acinus) [[4](#_ENREF_4)] | **500µm** [[5](#_ENREF_5)] |  | **~300µm** (estimated from microcorrosion cast mouse) [[6](#_ENREF_6)] |
| **sinusoidal diameter** |  | **8.8µm** | | **8.8±0.9µm** (human, OPS) [[7](#_ENREF_7)]  **4-15µm** (human) [[2](#_ENREF_2)] |  | **5.9**±0.17**µm** (rat, Zone 1), **7.1**±0.29**µm** (rat, Zone 3) [30?];  **6.4**±0.1**µm** (rat, Zone 1), **8.3**±0.2**µm** (rat, Zone 3) [15?] | **5.9±0.1µm** (mouse, periportal Zone 1, IVM), **7.3±0.1µm** (mouse, perivenious, Zone 3, IVM), [[8](#_ENREF_8)]  **6.2±0.1µm** (SD; n=48; mouse) [[6](#_ENREF_6)] |
| **intersinusoidal distance** |  | **22.6** | | **22.6±2.5µm** (human, OPS) [[7](#_ENREF_7)] |  |  |  |
| **hepatocyte sheet thickness** |  | (**11.3**) | |  |  | ~**10µm** (scanning electron microscopy, images)[Wisse1983] |  |
| **volume single cell layer surrounding sinusoid** |  |  | |  |  | ~5100(rat, single cell, QSD) [[3](#_ENREF_3)] |  |
| **total liver weight** |  | **1500g** (human) | | **1500-1800g** (man), **1300-1500g** (woman) [[2](#_ENREF_2)]  **1697±171g** (±SD, n=6)[[9](#_ENREF_9)] | **556g** (400 – 800g) (dog) [[5](#_ENREF_5)] | **17.1±2.2g** (**±**SD. N=13, in situ perfused rat livers)[[10](#_ENREF_10)] |  |
| **total liver volume** |  | 1.5 Liter | | 1.5L [?] [-> data Matrion] |  |  |  |
| **total number of hepatic lobules** |  |  | | **1.0E6–1.5E6** [[2](#_ENREF_2)] |  |  |  |
| **total number of hepatic acini** |  |  | | 100 000 [[4](#_ENREF_4)] |  |  |  |
| **Extrasinusoidal Spaces** |  |  | |  |  |  |  |
| **Sinusoidal blood volume, % liver weight** |  | **15%** | | **15–25%** (percent of liver volume) [[2](#_ENREF_2)]  **9-15%** ( n=6, isolated perfused human liver)[[9](#_ENREF_9)] | **15.2%** (indicator dilution dog) [[5](#_ENREF_5)] **15.0%** (dog) [[5](#_ENREF_5), [11](#_ENREF_11)] | **19.4%** (rat) [[5](#_ENREF_5), [12](#_ENREF_12)] **11.6%** (rat) [[5](#_ENREF_5), [13](#_ENREF_13)]  **10.6%** (morphological studies, % volume) [[4](#_ENREF_4), [14](#_ENREF_14)] ->Blouin1977? | Friedman (from Everett in mouse ?) |
| **Extravascular volumes, % liver weight** |  | **6**% | | **~5%** (percent of liver volume) [[2](#_ENREF_2)]  **5-8%**  (n=6, isolated perfused human liver)[[9](#_ENREF_9)] | **6.2%**(indicator dilution dog) [[5](#_ENREF_5)] **9.5±2.1%**(±SD, indicator dilution dog, sucrose volume) [[5](#_ENREF_5)]  **6.7%** (dog) [[5](#_ENREF_5), [11](#_ENREF_11)] | **7.3%** (rat) [[5](#_ENREF_5)] **6.0%** (rat) [[5](#_ENREF_5), [13](#_ENREF_13)]  **4.9%** (morphological studies, % volume) [[4](#_ENREF_4), [14](#_ENREF_14)] |  |
| **mean functional sinusoidal density** |  | **391** | | **391±30** (human, OPS) [[7](#_ENREF_7)] |  |  |  |
| **width space of Disse** |  | **0.81µm** (calculated from geometry & volume relations) | | **0.2–1µm [?imagages]** |  |  |  |
| **fenestraetion diameter** |  | **100nm** | | **~100nm** [[2](#_ENREF_2)]  **50– 300** [Wisse1983 -> Ref28) |  | **98.0±**13.0 [Wisse1983 -> Ref25) | **99.0±**18.0 [Wisse1983 -> Ref26) |
| **fenestraetion number** |  | **20** | | **15–25** [Wisse1983 -> Ref28) |  | **20.0±**6.3 [Wisse1983 -> Ref25) | **14.0±**5.0 [Wisse1983 -> Ref26) |
| **Blood flow parameters** |  |  | |  |  |  |  |
| **red blood cell velocity** |  | **60** | | **970**±430 (±SD; human, OPS) [[7](#_ENREF_7)] | **93**(dog, calculated from transit time of RBC, analog **53**15) [[5](#_ENREF_5)] | **180±20**(±SE, rat) [[6](#_ENREF_6)]  **250±3**(±SE, rat, IVM) [[15](#_ENREF_15)]  **150**±6(±SE, rat, stated in [[6](#_ENREF_6)]) | **69.2±30.6** (±SD; N=40-60; mouse, IVM) [[6](#_ENREF_6)] |
| **volumetric blood flow within the sinusoids assuming cylindrical geometry** |  |  | | analog to [[7](#_ENREF_7), [16](#_ENREF_16)] |  |  |  |
| **total hepatic blood flow (~75-80% portal vein partially deoxygenated, 20-25% hepatic artery well-oxygenated)**  **look Jakab 1995 PMID:**  **7782028**  **interaction between hepatic arterial and portal venous blood flows; simultaneous measurement by transit time ultrasonic volume flowmetry.** |  | **1.0** | | **1800**(man)[[2](#_ENREF_2)]  **1200**(woman)[[2](#_ENREF_2)]  **1067±160**(±SD, n=6, isolated perfused human liver)[[9](#_ENREF_9)]  **992±276**(n=14)[[17](#_ENREF_17)]  ~**1**[[2](#_ENREF_2)]  **1.0-1.3**[[4](#_ENREF_4)]  **17.0±2.72**(±SD, n=10 women, Doppler ultrasound)[[18](#_ENREF_18)] **30**[[4](#_ENREF_4)] | **869**(dog) [[5](#_ENREF_5)]  **1.83±0.55**(±SD, g liver weight, dog) | **20.9±**1.3 (**±**SD. N=13, in situ perfused rat livers, perfusate blood flow)[[10](#_ENREF_10)] |  |
| **hepatic artery flow** |  |  | | **20–33%** (total flow from HA) [[4](#_ENREF_4)]  **283±114**(±SD, n=6, isolated perfused human liver)[[9](#_ENREF_9)]  **377±**214[[17](#_ENREF_17)]  **3.5±**1.6 (±SD, n=10 women, Doppler ultrasound)[[18](#_ENREF_18)] |  |  |  |
| **portal vein flow** |  |  | | **66%** (total flow from PV)[[4](#_ENREF_4)]  **783±**90(±SD, n=6, isolated perfused human liver)[[9](#_ENREF_9)]  **614±**214[[17](#_ENREF_17)]  **13.5±**2.8 (±SD, n=10 women, Doppler ultrasound)[[18](#_ENREF_18)] |  |  |  |
| **hepatic artery pressure** |  |  | | **49±17 mmHg** (±SD, n=6, isolated perfused human liver)[[9](#_ENREF_9)]  mean pressure similar to aorta [[19](#_ENREF_19)] |  | **123±**4 mmHg (±SE, dogs), **125±**5 mmHg (±SE, cats) [[20](#_ENREF_20)] |  |
| **portal vein pressure** |  |  | | **6.5±1.8mmHg** (±SD, n=6, isolated perfused human liver)[[9](#_ENREF_9)]  **6-10mmHg** (humans direct cannulation or splenic puncture)[[19](#_ENREF_19)] | **7.0** mmHg [[21](#_ENREF_21)] |  |  |
| **interstitial pressure** |  |  | |  | **5.8** mmHg [[21](#_ENREF_21)] |  |  |
| **Vena cava pressure** |  |  | |  | **2.0** mmHg [[21](#_ENREF_21)] |  |  |
| **total hepatic lymph flow** |  |  | | **0.4-0.6**(estimated )[[4](#_ENREF_4)] -> Brauer Ref30 | **0.06** [[4](#_ENREF_4), [21](#_ENREF_21)] |  |  |
| **Average mean transit times total liver** |  | **10-15**s **(**correct for circular network) | |  | **8.36±2.66sec** RBC **15.11±4.82sec** sucrose  **42.22±12.96**sec urea  (±SD, dog) [[5](#_ENREF_5)] | **~6.3±0.5sec** RBC [[10](#_ENREF_10)]  **~12±1sec** sucrose [[10](#_ENREF_10)]  **~9±1sec** albumin[[10](#_ENREF_10)] |  |
| **hematocrit** |  | Accessible volume sinusoids? | | **40 – 45%** (human) (tissue haematocrit lower) |  | **36-37%** [[12](#_ENREF_12)]  **48%** [[12](#_ENREF_12)] -> Sharpe et al., rat)  **30%** (tissue haematocrit liver)[[12](#_ENREF_12)] |  |
| **Diffusion Parameters** |  |  | |  |  |  |  |
| **diffusion coefficient water** |  | **2100** | | 2100[http://bionumbers.hms.harvard.edu/bionumber.aspx?s=n&id=104087&ver=7] |  |  |  |
| **diffusion coefficient sucrose** |  | **520** | | 520 (sucrose in water)[http://bionumbers.hms.harvard.edu/bionumber.aspx?s=n&id=100614&ver=7] |  |  |  |
| **diffusion coefficient glucose** |  | **400** | | [[22](#_ENREF_22), [23](#_ENREF_23)]  600(glucose in water) [http://bionumbers.hms.harvard.edu/bionumber.aspx?s=n&id=104089&ver=5]  670(glucose in water 25°C) [Longsworth, L. G. 1955. Diffusion in liquids and the Stokes-Einstein relation, p. 225-247. In T. Shedlovsky (ed.), Electrochemistry in biology and medicine. John Wiley & Sons, Inc., New York, N.Y.] |  |  |  |
| **diffusion coefficient lactate (~70% glucose [**[**24**](#_ENREF_24)**])** |  | **230** | | [[25](#_ENREF_25), [26](#_ENREF_26)]  490(lactate in water 25°C) [Perry, R. H., and C. H. Chilton. 1973. Chemical engineers' handbook, 5th ed. McGraw-Hill Book Co., New York, N.Y.] |  |  |  |
| **diffusion coefficient** |  | **1500** | | [[27](#_ENREF_27), [28](#_ENREF_28)]  1800(oxygen in water)[http://bionumbers.hms.harvard.edu/bionumber.aspx?s=n&id=100615&ver=4]  2000(oxygen in water 25°C)[ J. Crank, "The Mathematics of Diffusion" (Oxford University Press, 1956; 2nd ed. 1976)] |  |  |  |
| **diffusion coefficient insulin** |  | **150** | | 150 (insulin in water)[http://bionumbers.hms.harvard.edu/bionumber.aspx?&id=100613&ver=6] |  |  |  |
| **diffusion coefficient glucagon** |  | **200** | | [?] |  |  |  |
| **Metabolic Parameters** |  |  | |  |  |  |  |
| **number of cellular concentrations per cell** |  | ~20 | |  |  |  |  |
| **number of extracellular concentrations (glc, lac, o2, ins, glu)** |  | 5 | |  |  |  |  |
| **number of blood and Dissé compartments per cell (discretization)** |  | 5 | |  |  |  |  |
| **total number of blood and Disse compartments ()** |  |  | |  |  |  |  |
| **Oxygen consumption** |  |  | | **0.758±**0.202 µmol/min/g liver (±SD, n=6, isolated perfused human liver)[[9](#_ENREF_9)] | **45±**3 (n=13, splenectomized cats)[[4](#_ENREF_4)]->Ref184, Laut1976 | **1.85±**0.32 µmol/min/g liver (**±**SD. N=13, in situ perfused rat livers, perfusate blood flow)[[10](#_ENREF_10)] |  |
| **Partial pressure oxygen** |  |  | | Oxygen saturation of the hepatic artery usally exceeds 95%;  Oxygen saturation of the portal blood during fasting state ranges up to 85%, however **it drops substantially after food ingestion**;[[19](#_ENREF_19)] |  | **65 mmHg** (periportal) **30-35 mmHg** (perivenious)[[4](#_ENREF_4), [29](#_ENREF_29)] |  |

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