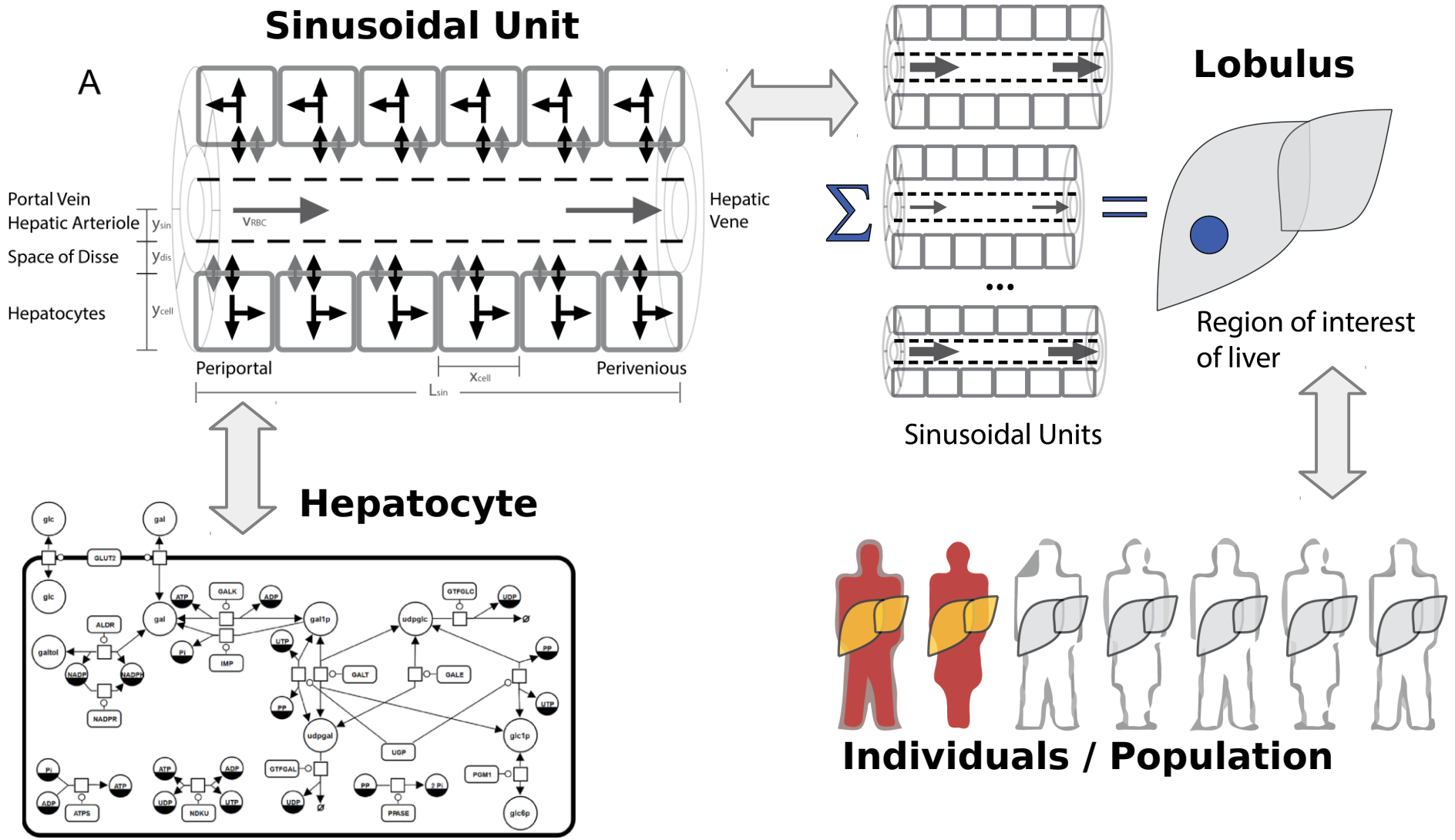
Population Variability in Liver Function

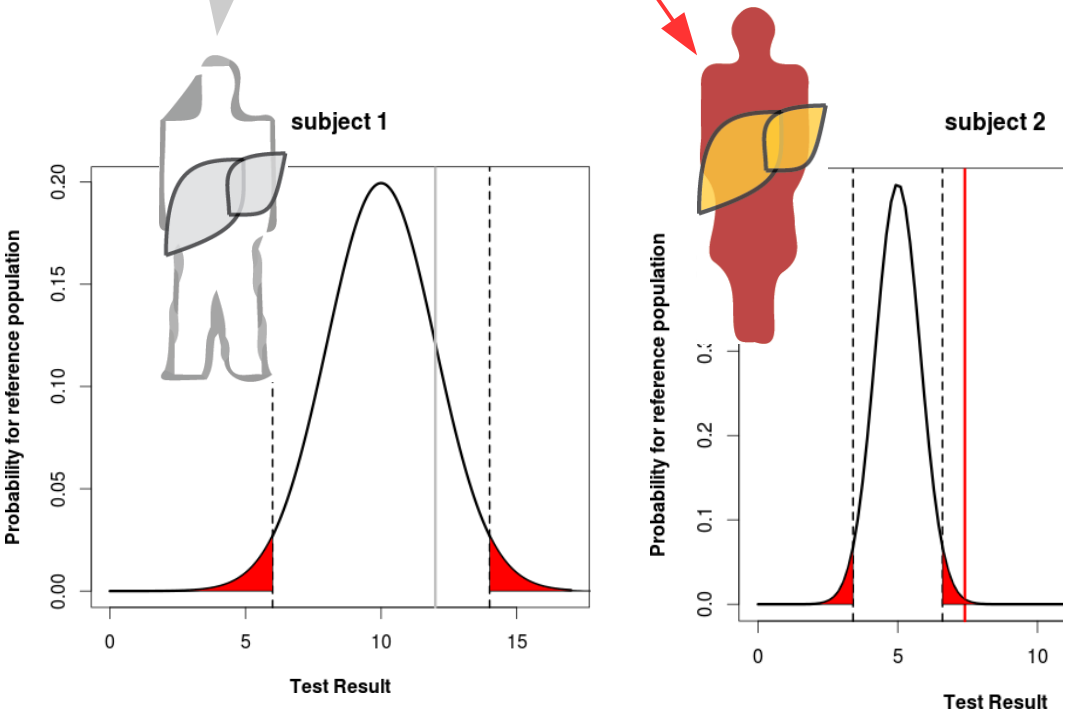
König M. & Holzhütter HG.




We are all different ...
… so why no individualized predictions?

Individualized Liver Function Tests

- Large population variability in liver volume & blood flow
  - Age, gender, bodyweight, height, ethnicity, …
- What are the effects of this variability on model prediction?
- Improved evaluation of liver function in given antropomorphic context
  - Individualized liver function test
  - Reference range for sample of comparable individuals
  - Values outside range → further investigation & treatment



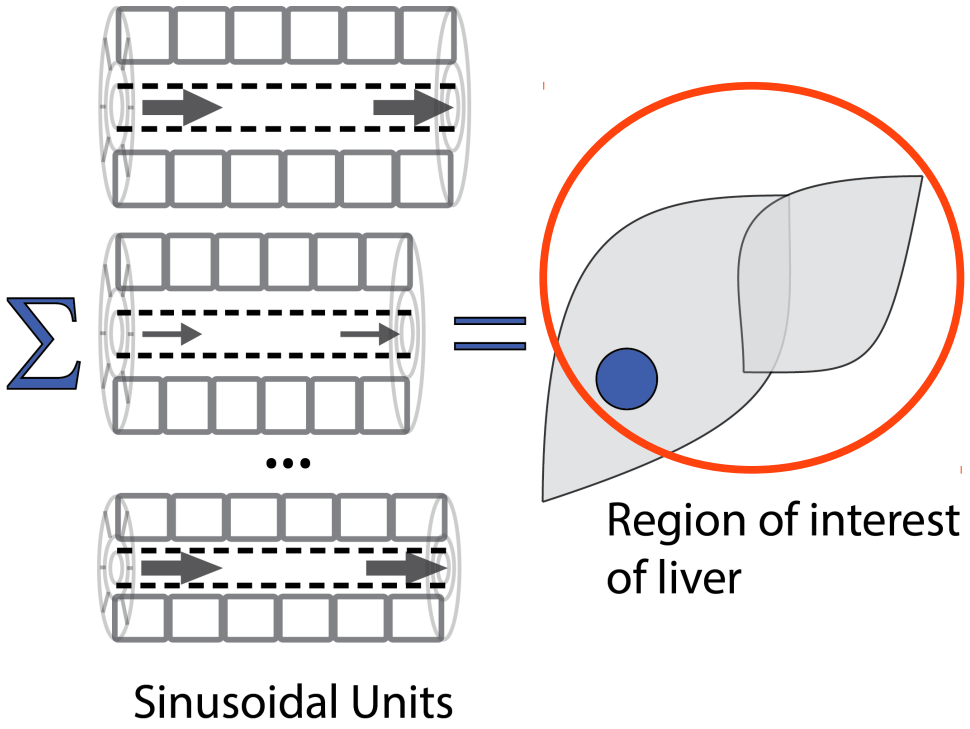
Variability & Sensitivity

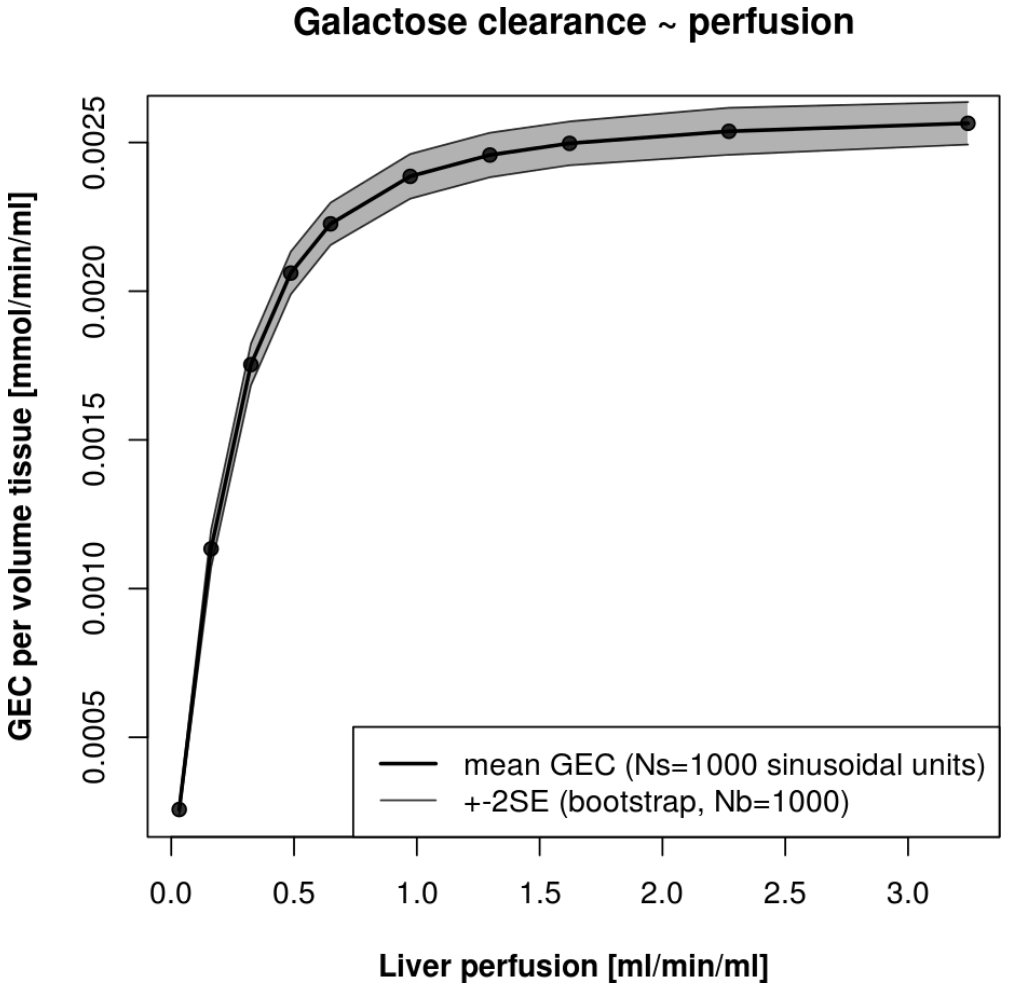
- **Variability**
  - The focus of variability analysis is to evaluate the range of values that a parameter expected to be present in individuals may have in a population and the impact of that variability on the simulation prediction.

- **Sensitivity**
  - Sensitivity analysis provides a quantitative evaluation of how parameters influence the simulation prediction of a model. Sensitivity analysis compares the magnitude in change in output for a defined change in each input parameter.

GEC - Liver Function Test

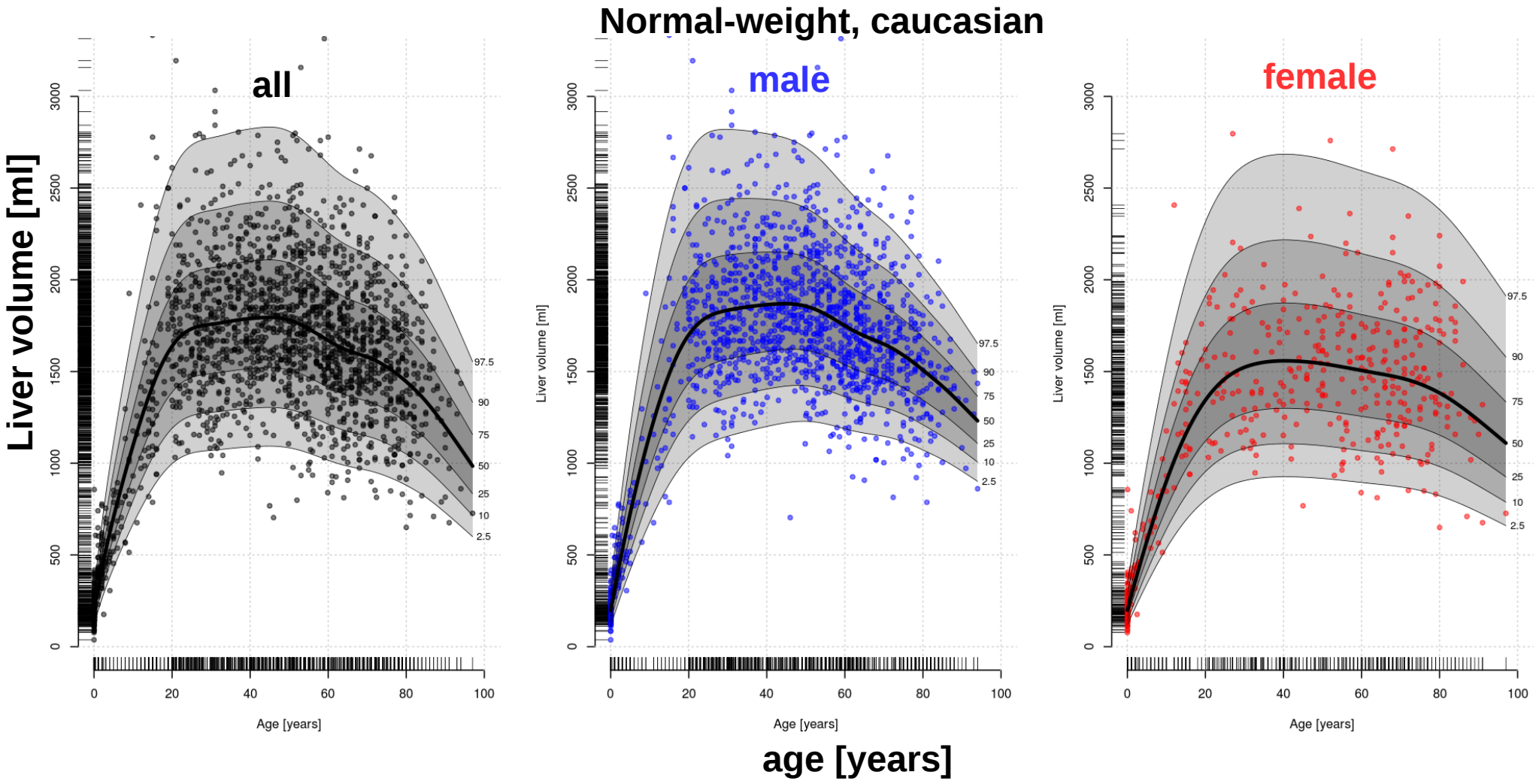
- Evaluation of liver function via galactose clearance capacity (GEC)
- Model prediction for galactose clearance per tissue volume for given perfusion in the region (**regional GEC**)
- Use individual **liver volume and perfusion** for scaling (**total GEC**)
- Evaluation of individual & population variability in GEC





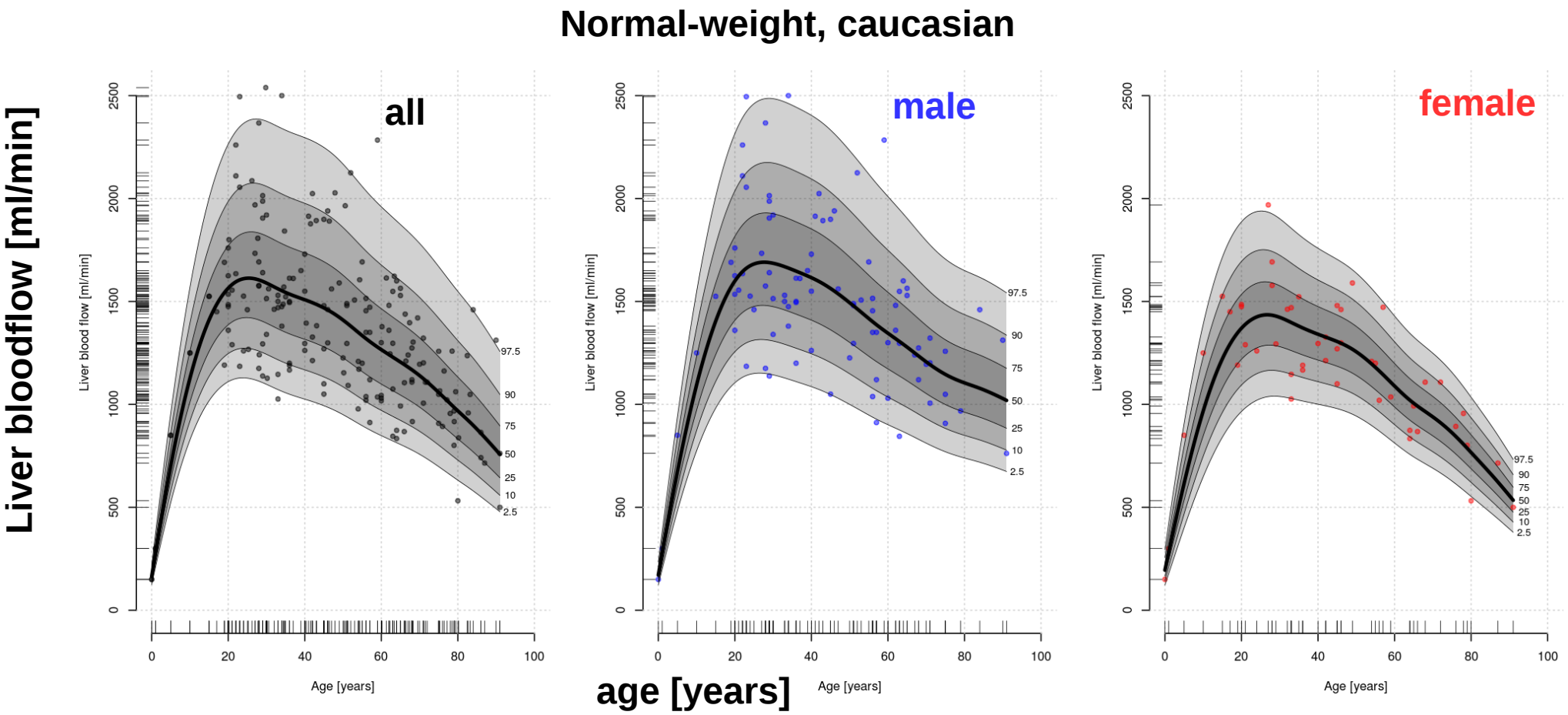
Liver volume = f(sex, age, ...)

- Density estimation via generalized additive models (GAM) combined with centile estimation
- Combined dataset from multiple sources & experimental methods
- Analog volLiver ~ bodyweight, volLiver~height, volLiver~BSA, ...

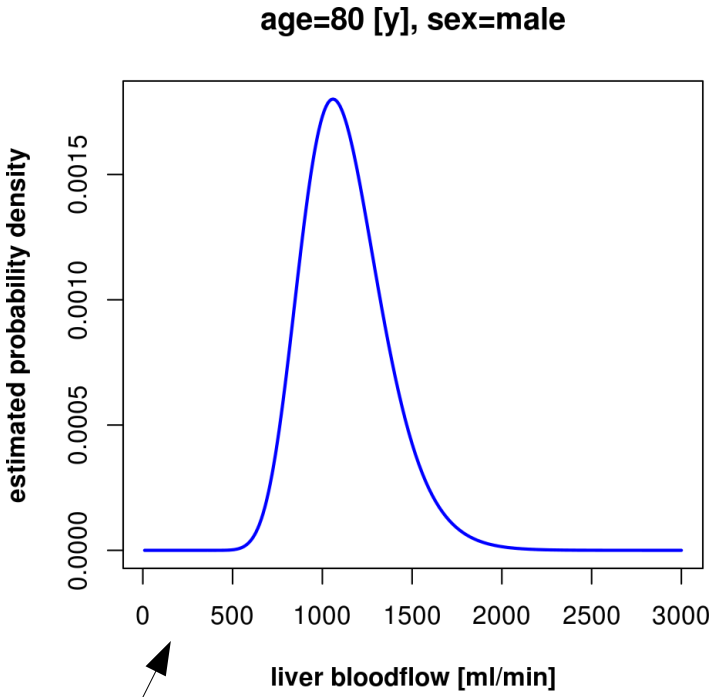


Age & gender dependence blood flow

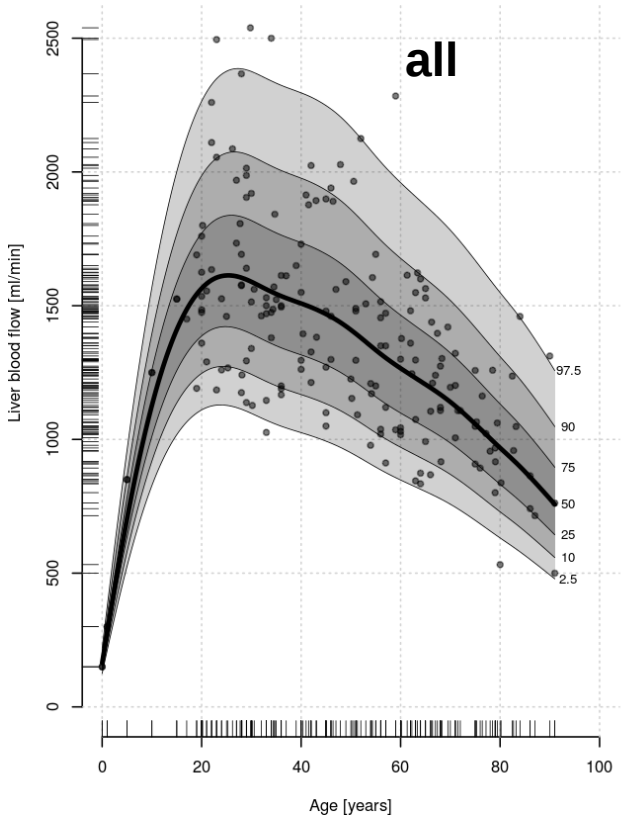
- Analog for bloodflow with additional flowLiver~volLiver correlation
- **Results**: probability densities for liver volume & liver bloodflow

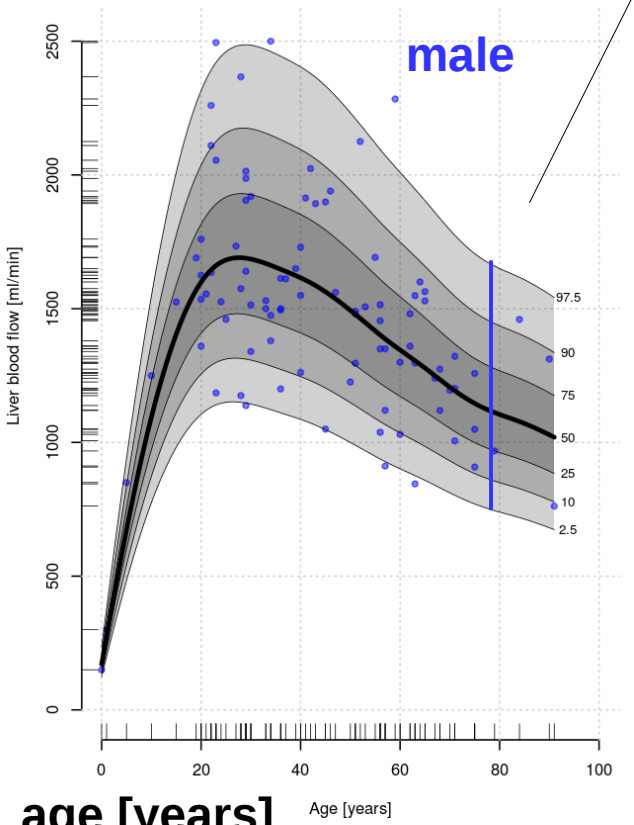


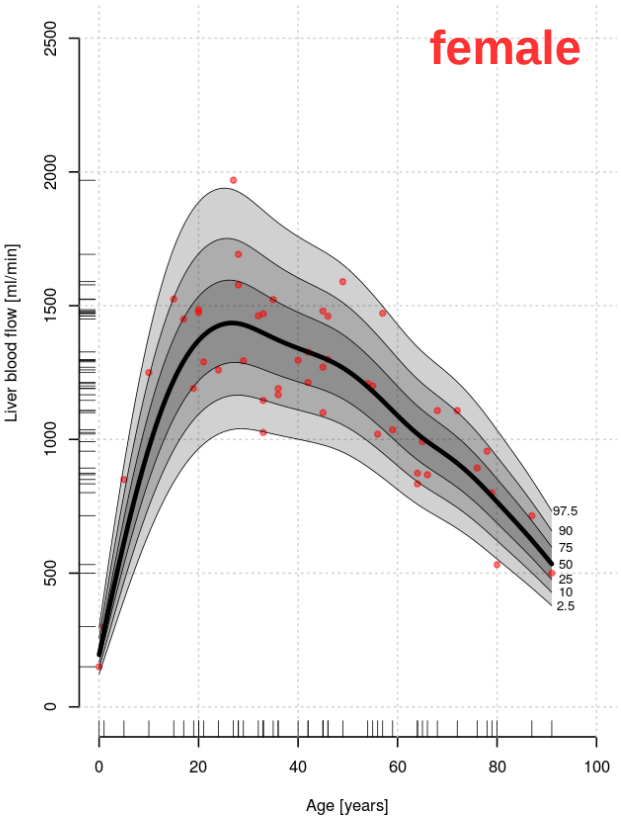
Probability distribution of liver blood flow
- normal-weight (BMI<24.9)
- caucasian
- male
- 80 years old



Liver bloodflow [ml/min]



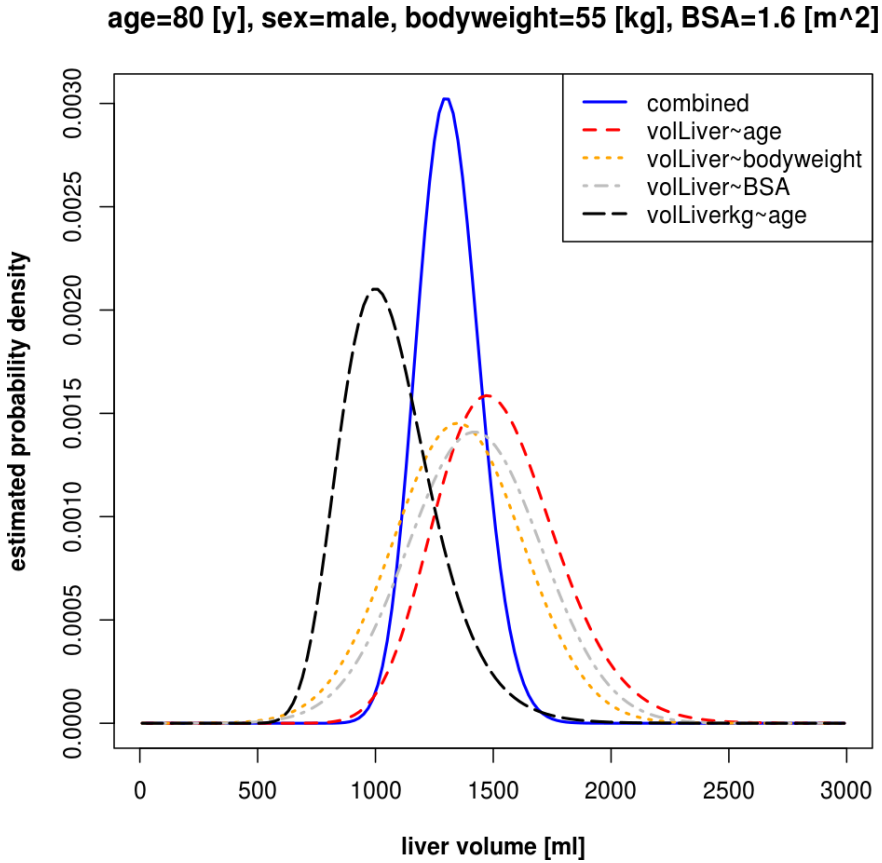


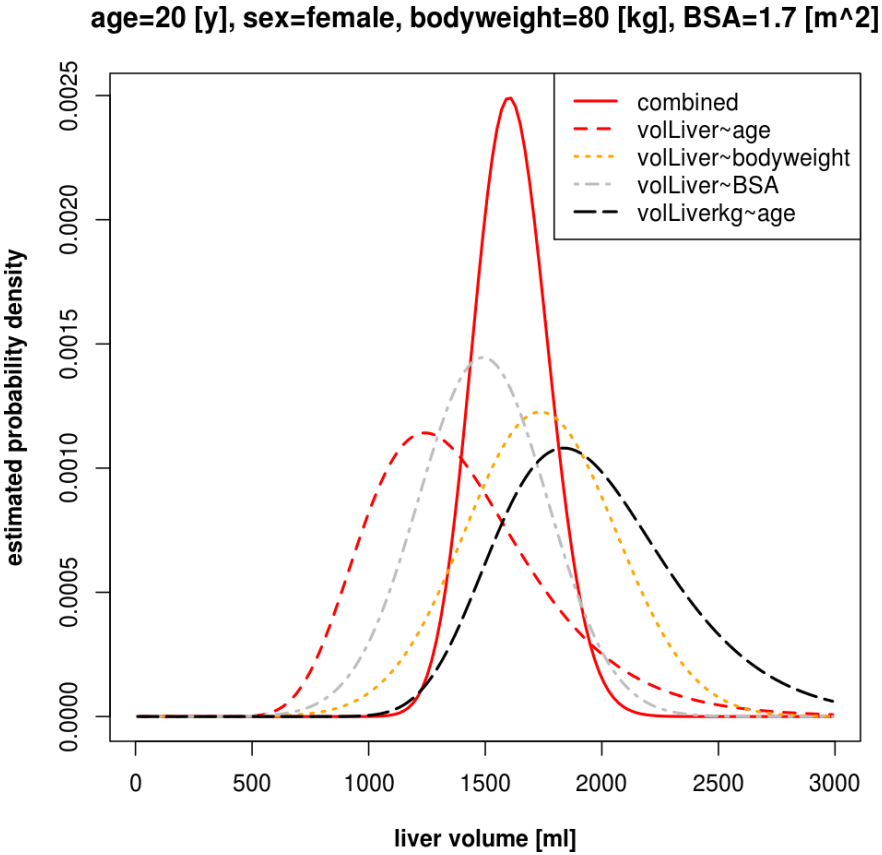


age [years]

Combining the information

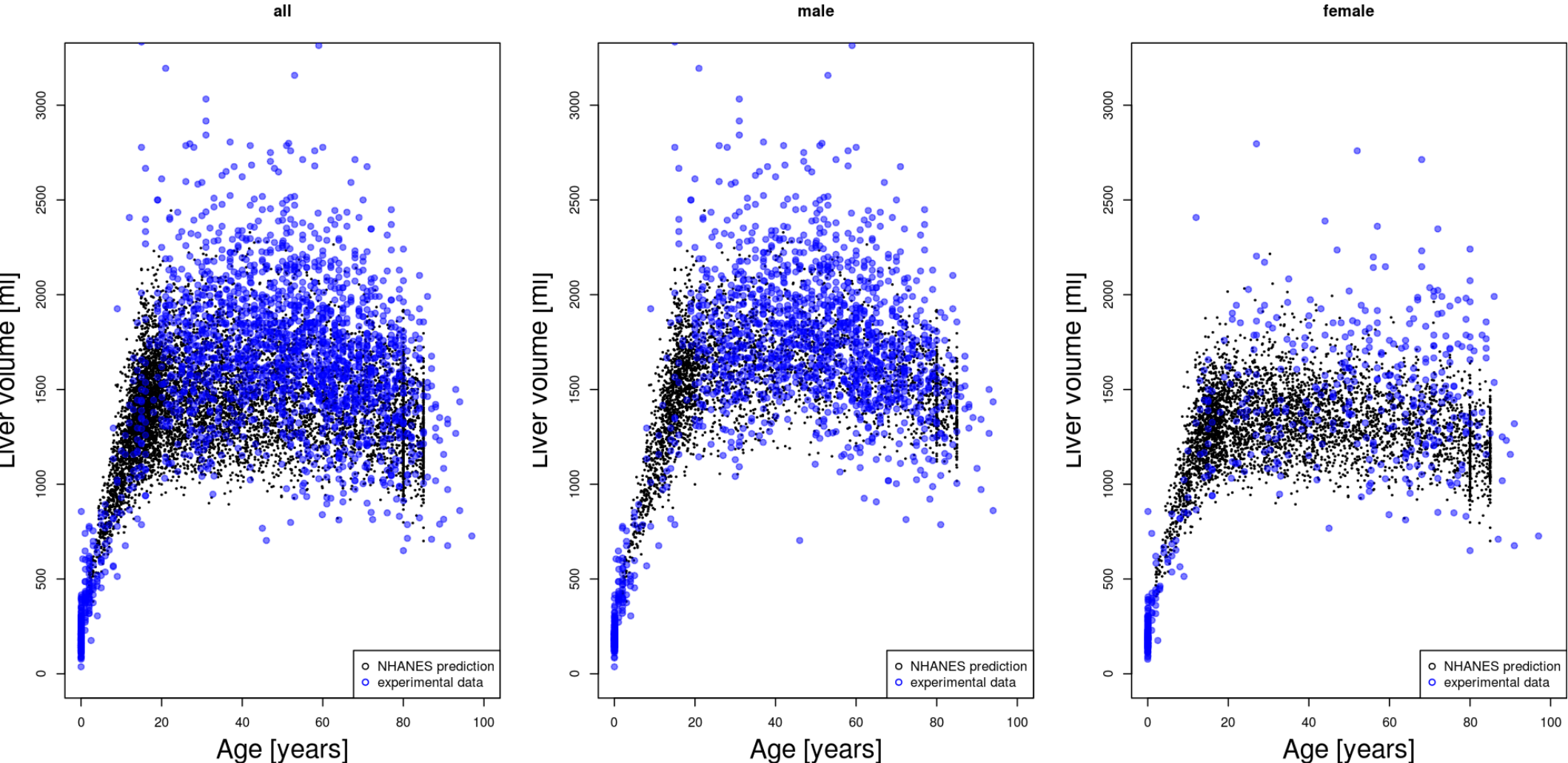
- Set of probabilty distributions for pair-wise correlations
- Important to keep the correlation structure between different data pairs
- Combination of individual probability distributions for best estimate (**use all the available knowledge**)
- **Result: individual probability distributions** for liver volume and bloodflow based on normal reference population



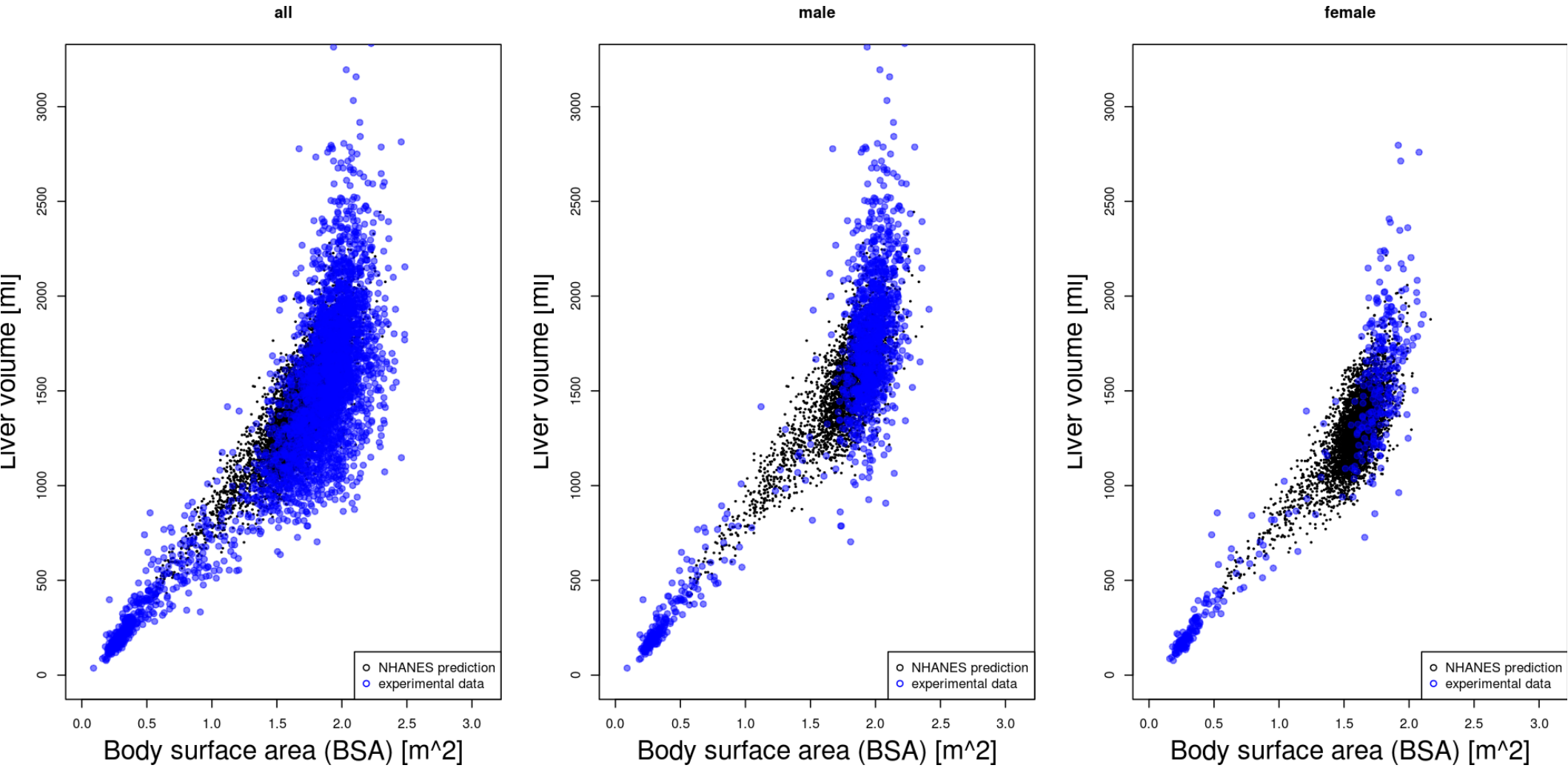


Prediction of population variability

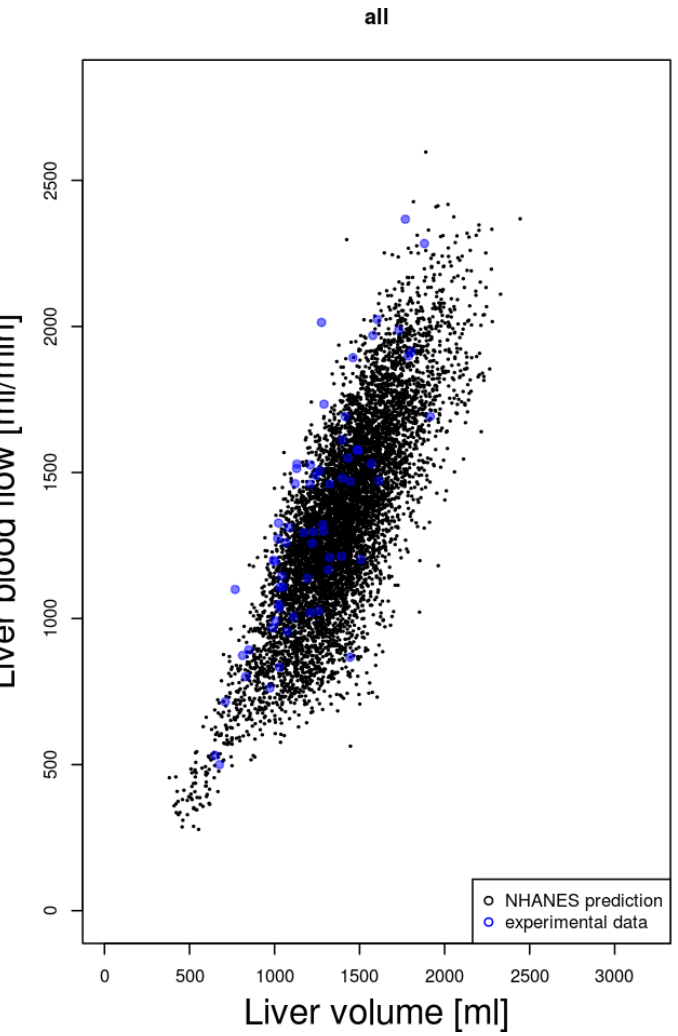
- NHANES prediction (~8000 normal-weight, caucasian)
  - Correlation structure of sex, age, bodyweight, height of US population
- Liver volume ~ age

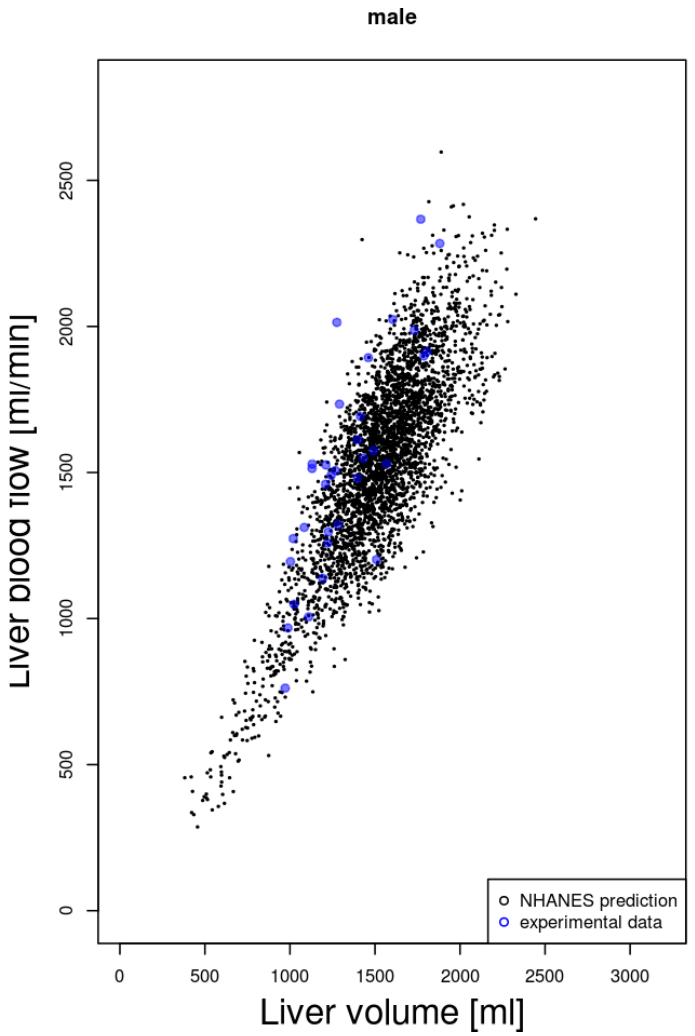


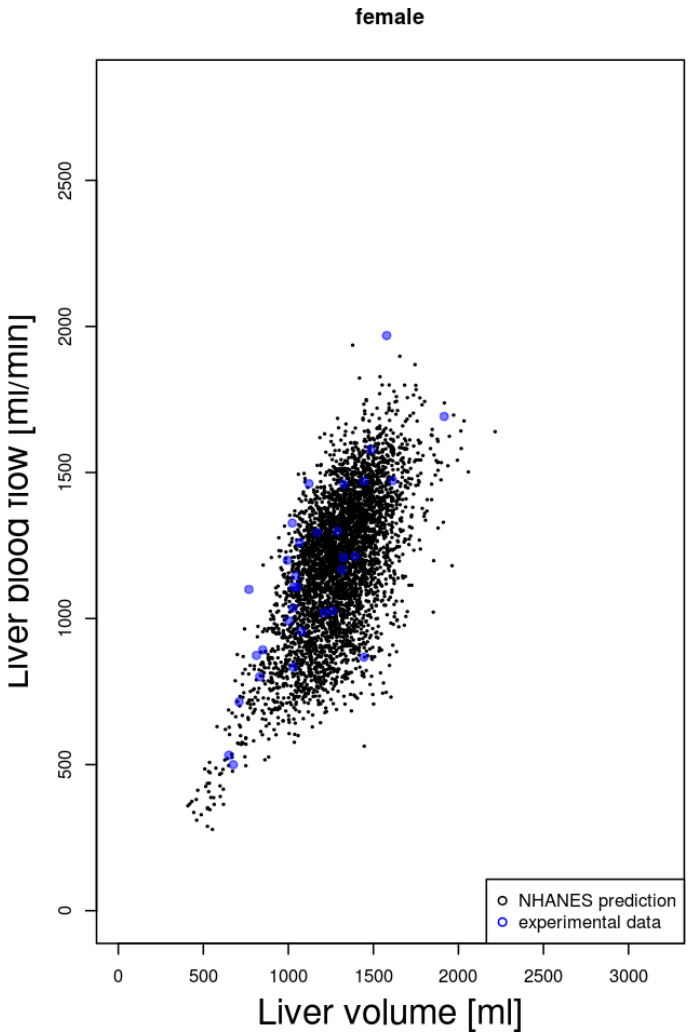
Liver volume ~ BSA (body surface area)



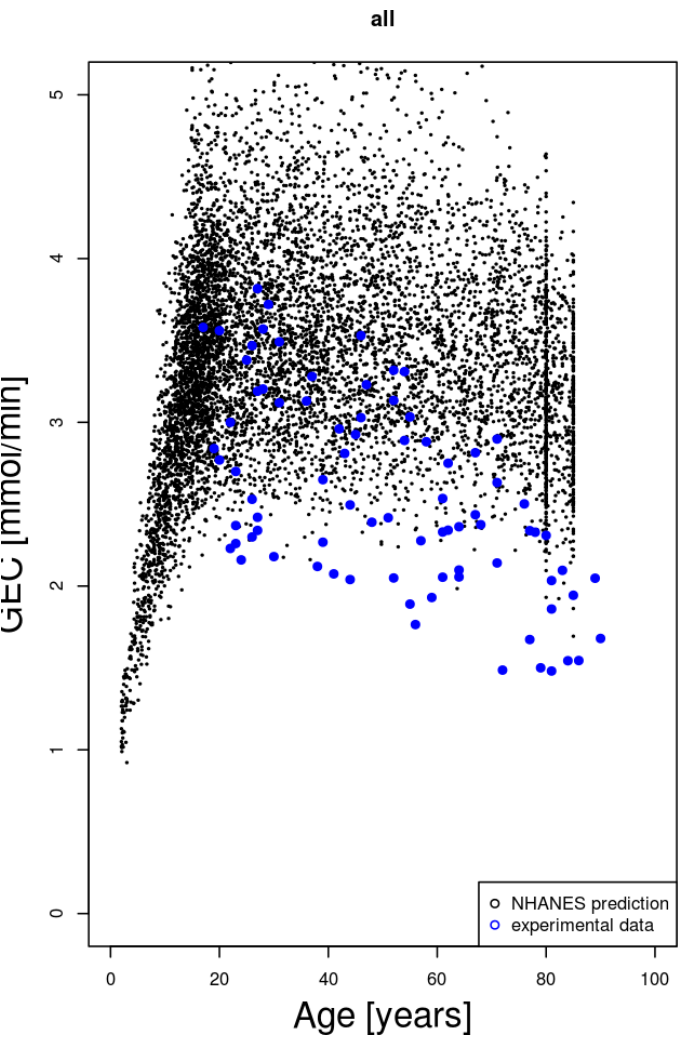
liver blood flow ~ liver volume

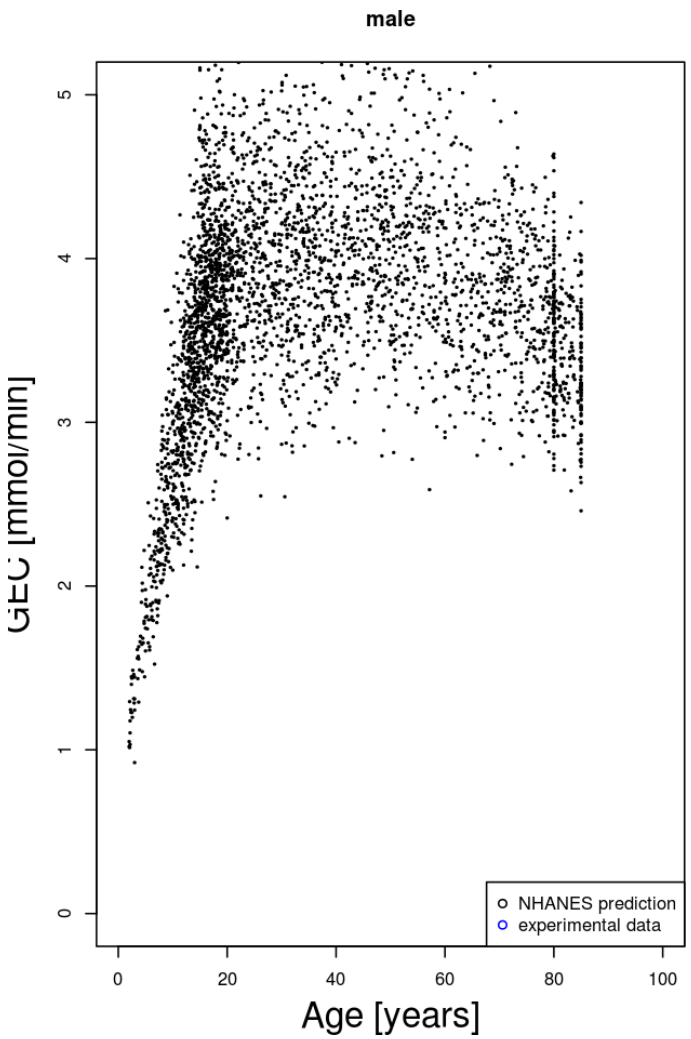


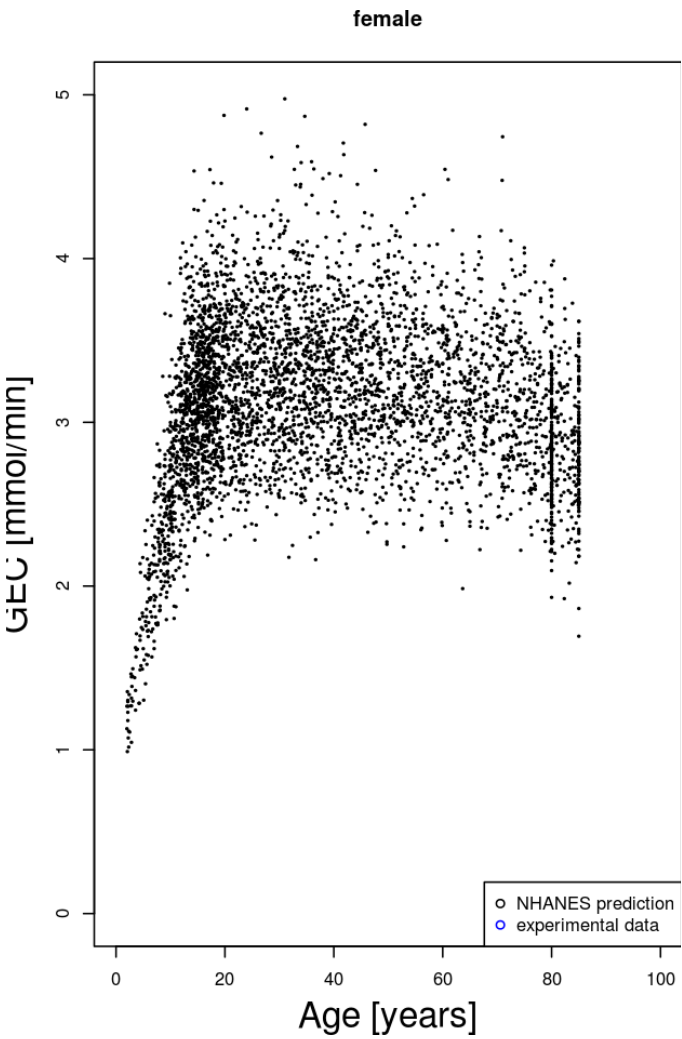




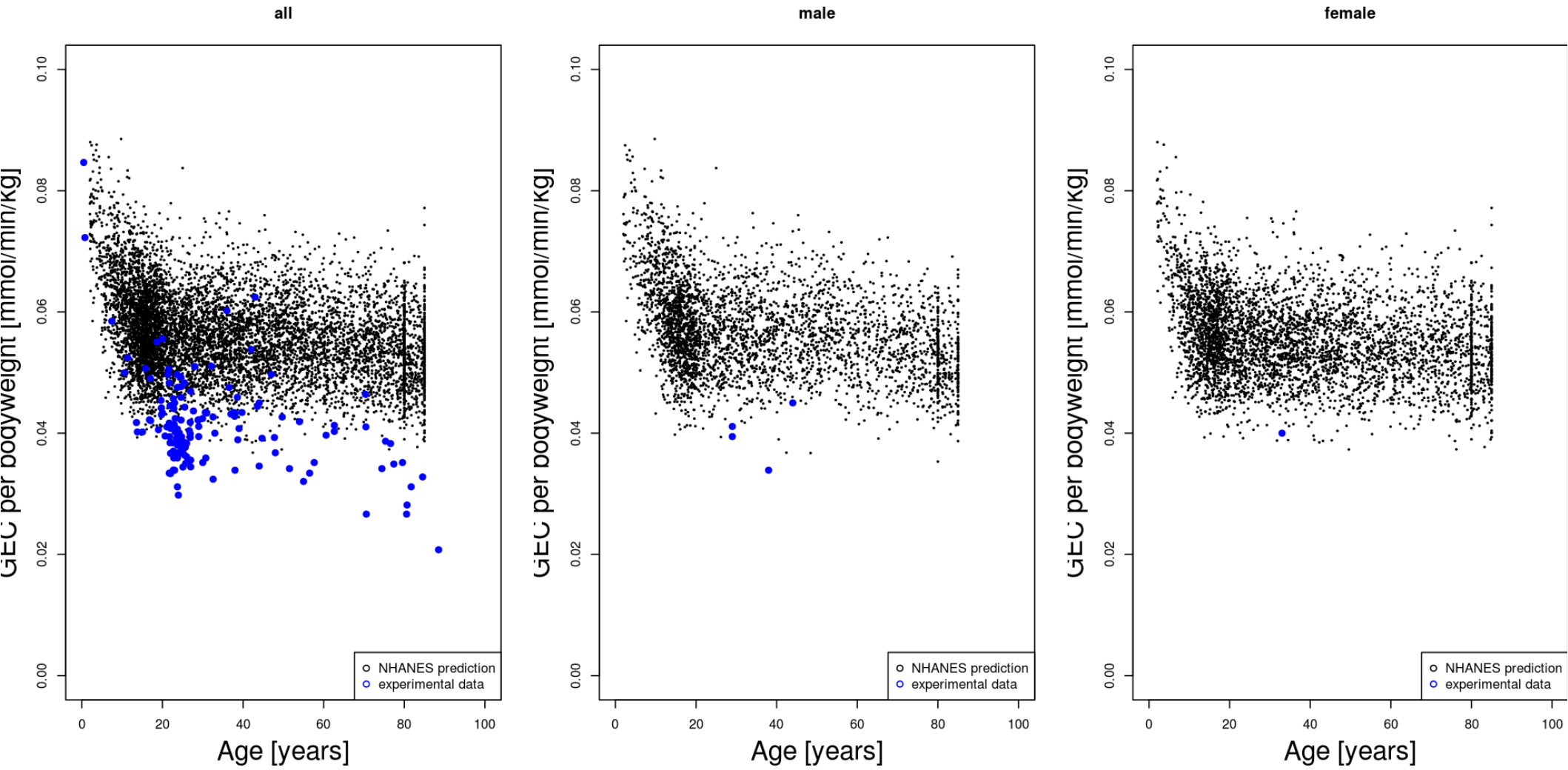
Prediction of GEC (galactose clearance capacity)



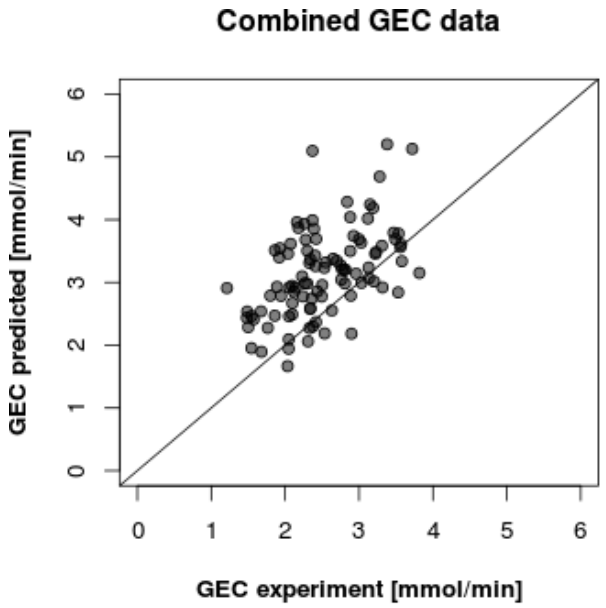


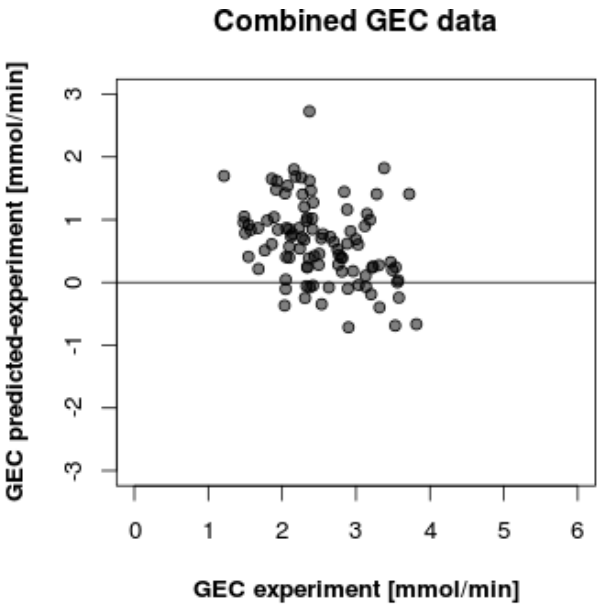


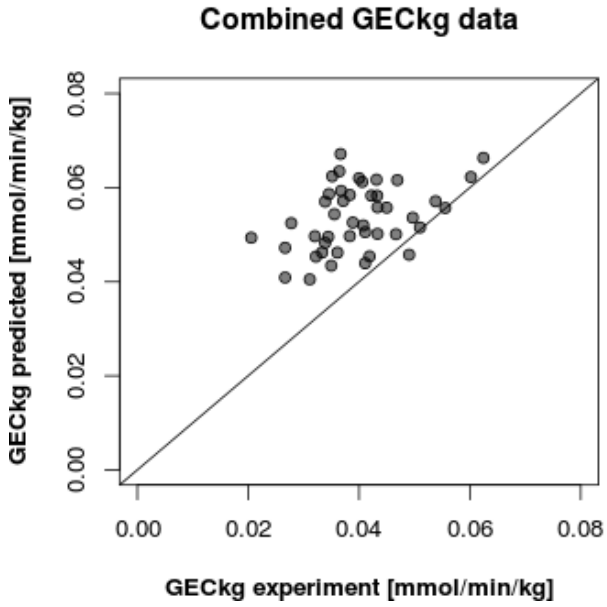
Prediction of GEC per bodyweight

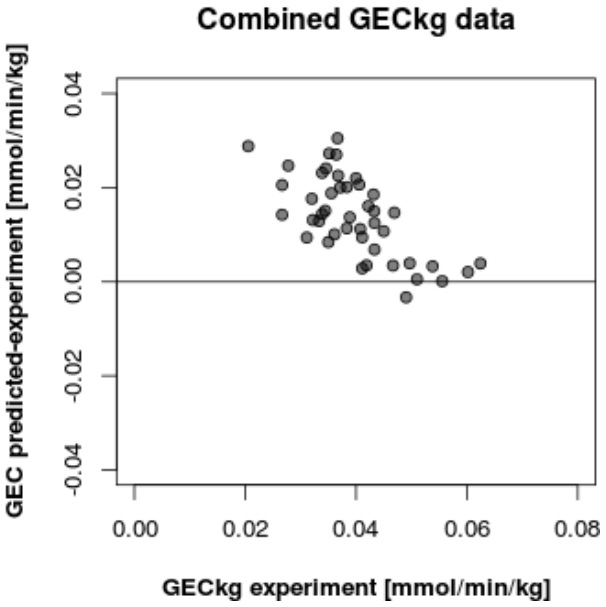


Individualized GEC prediction





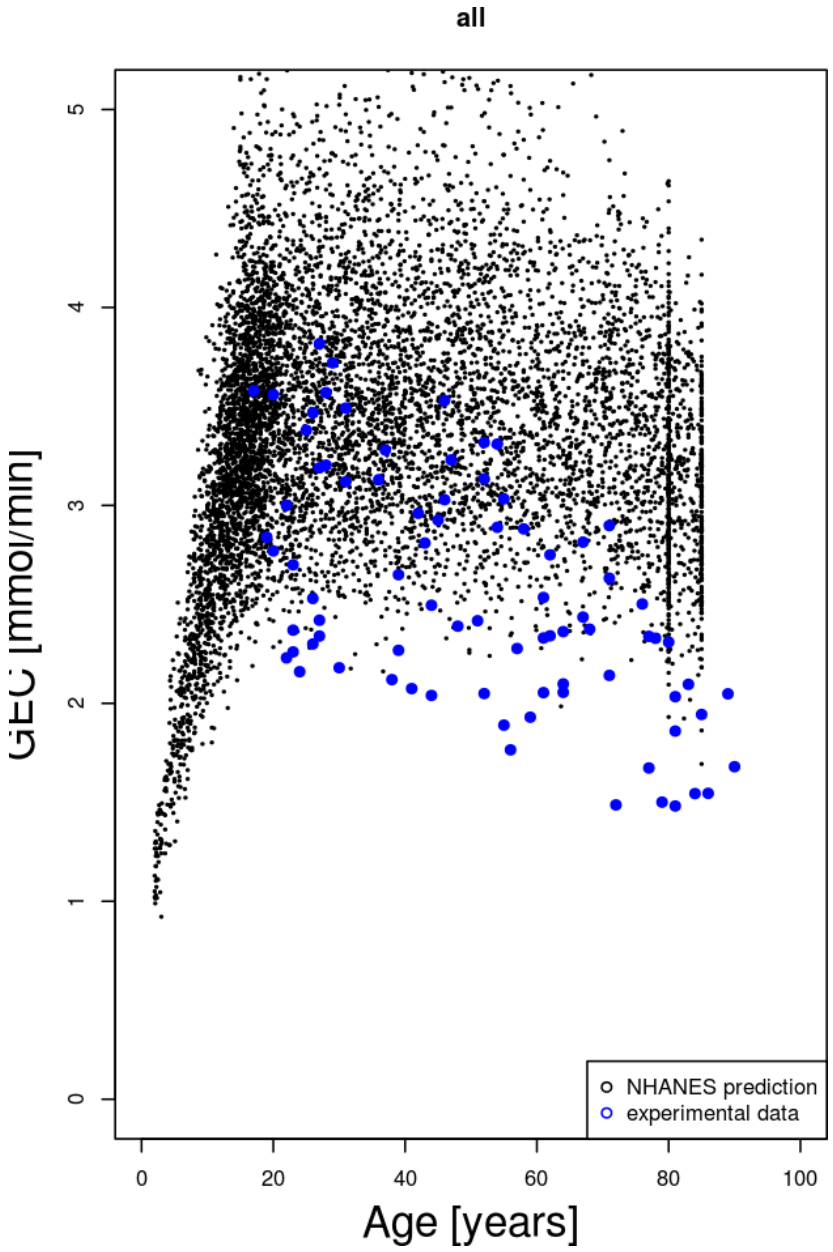




First draft predictions, no adaption of metabolic capacity

GEC variability

- Large part of GEC variability is explained by the population variability
  - Additional variability in metabolic (Vmax) & morphological components in population (→ sensitivity analysis)
  - For instance age changes in structure (pseudo-capillarization) & decrease in metabolic capacity (?)
- Next steps
  - Adaption of galactose clearance on cellular level
  - Prediction of additional GEC datasets



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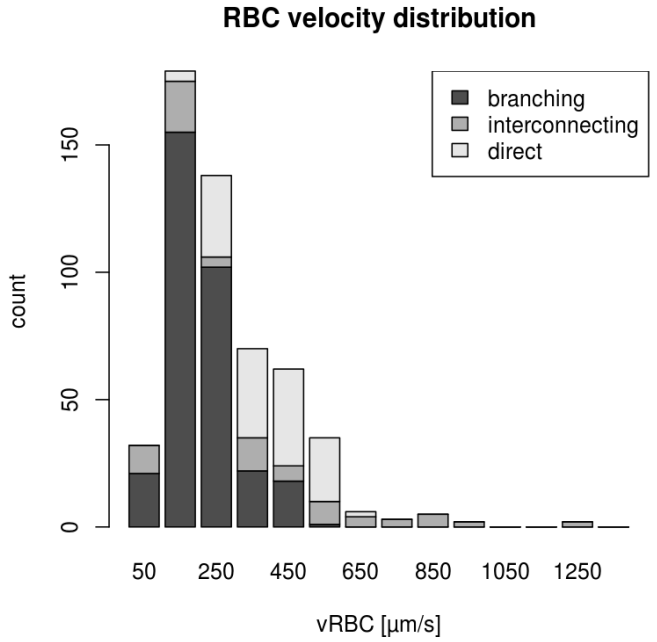
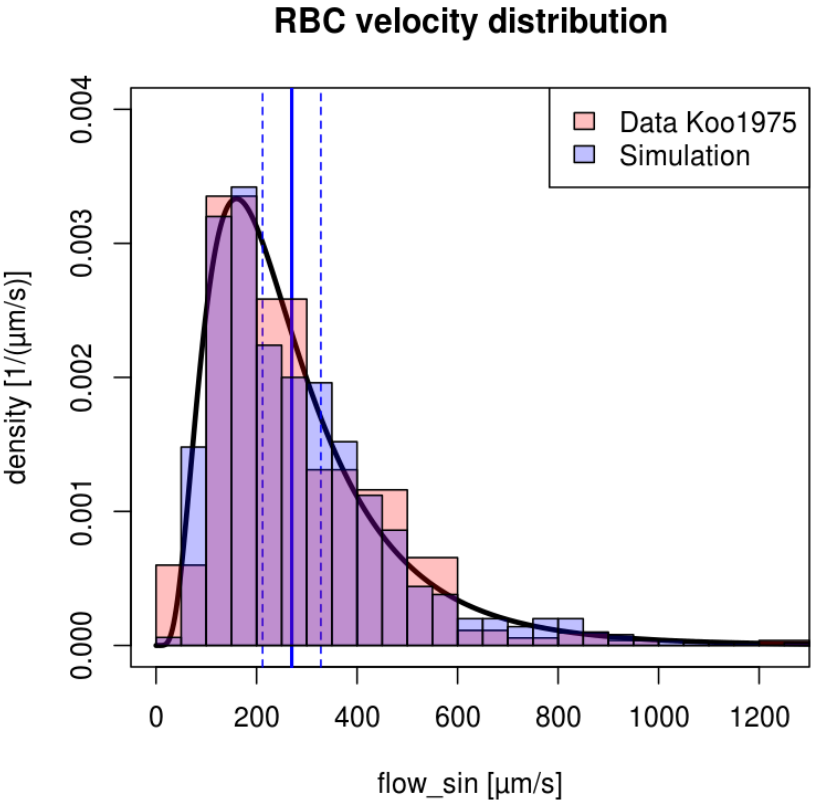
  - Charité
  - Virtual Liver Network

Fitting Distributions

- maximum-likelihood method for univariate distributions (log-norma'‘





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±199µm** (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)

Tissue-scale Sinusoidal Unit