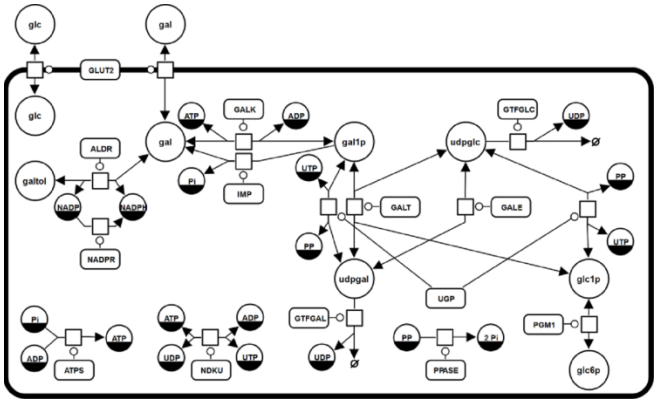
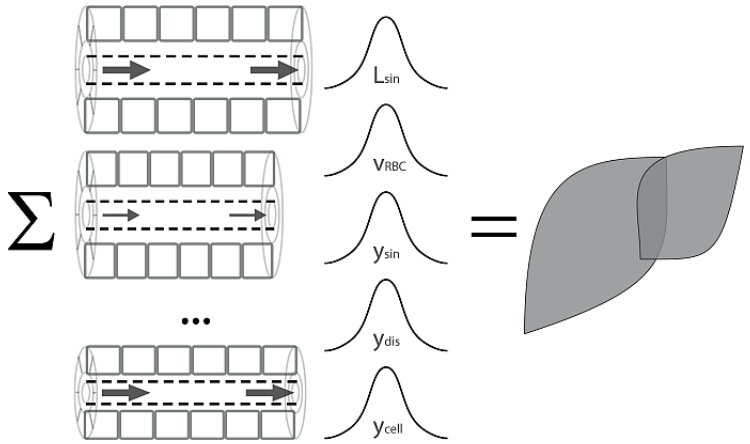
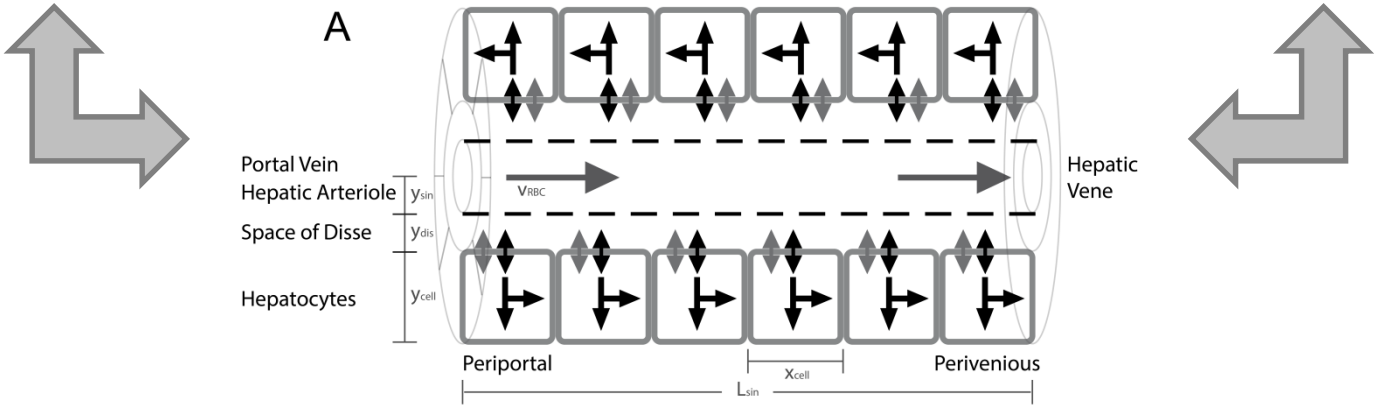
From Hepatocytes to Whole Liver Function: A Multi-scale Model of Human Galactose Metabolism - Sampling Parameter Distributions

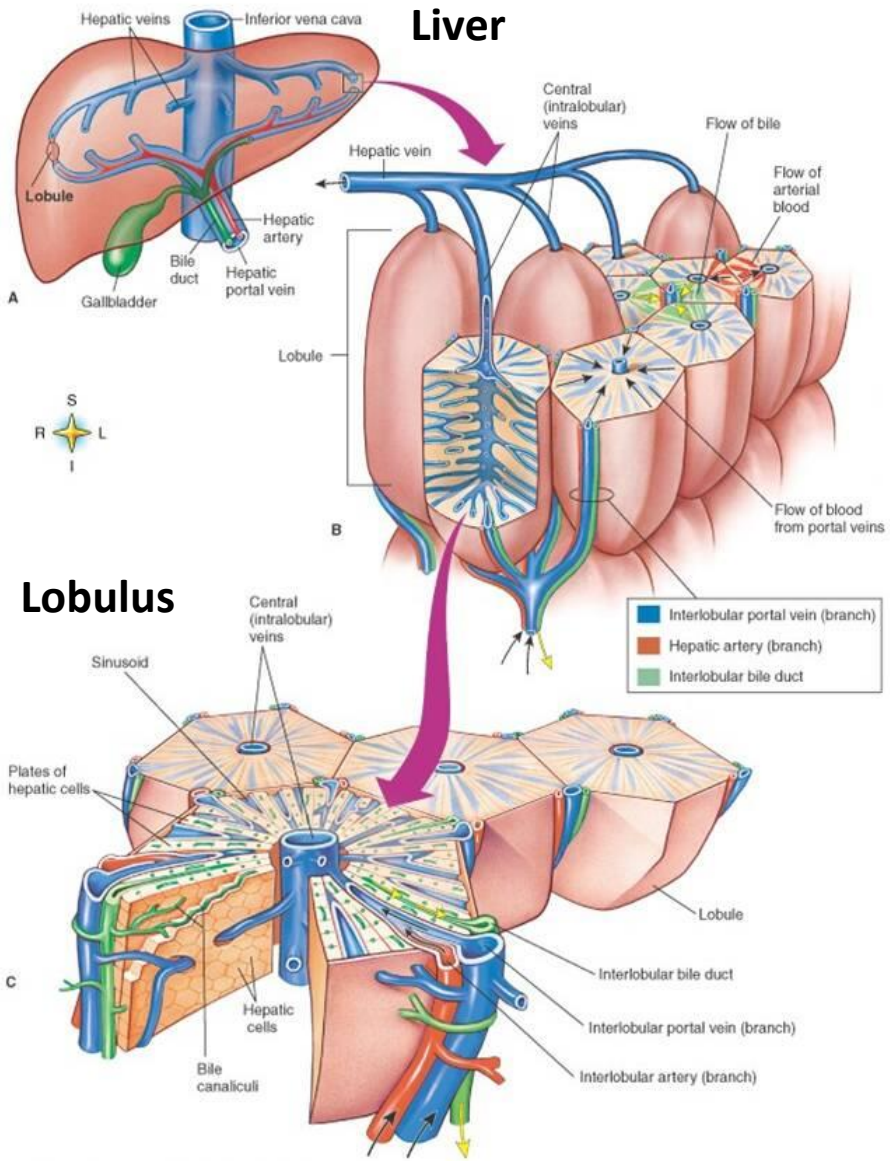
König M. & Holzhütter HG.



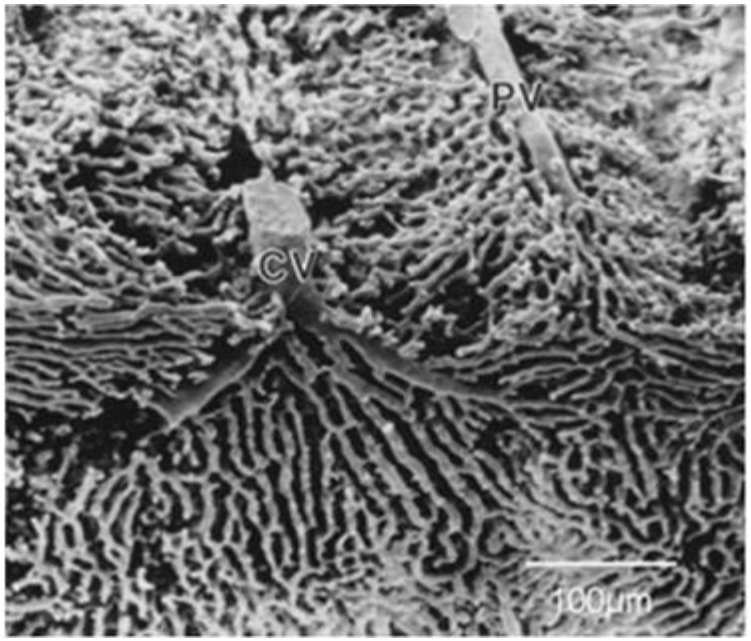




LIVER ARCHITECTURE



- liver structured in parallel subunits (**liver lobule**)
- liver lobulus consists of **network of sinusoids** connecting hepatic artery and portal vein with the **central vene (periportal → perivenous)**



MODELING PIPELINE

Tissue parameter distributions
- Fit distributions to experimental data

Sampling Sinusoidal Unit Architectures
- LHS
- Distribution
- Mixed

Algorithm
- Method (ODE, SS, MCA)
- Parameters (tolerances, stepsize,..)

Simulation
- C++

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- Fit Vmax to experimental data
- Initialization (i.e. Galactosemias)

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- Define changes in boundary conditions (peaks, parameters changes, …)

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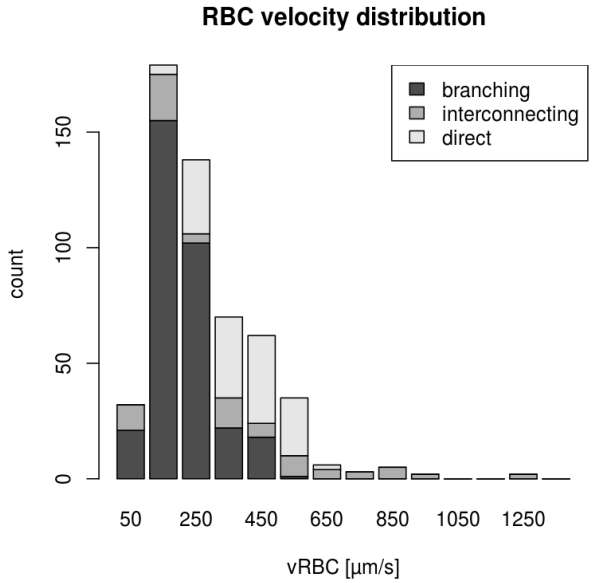
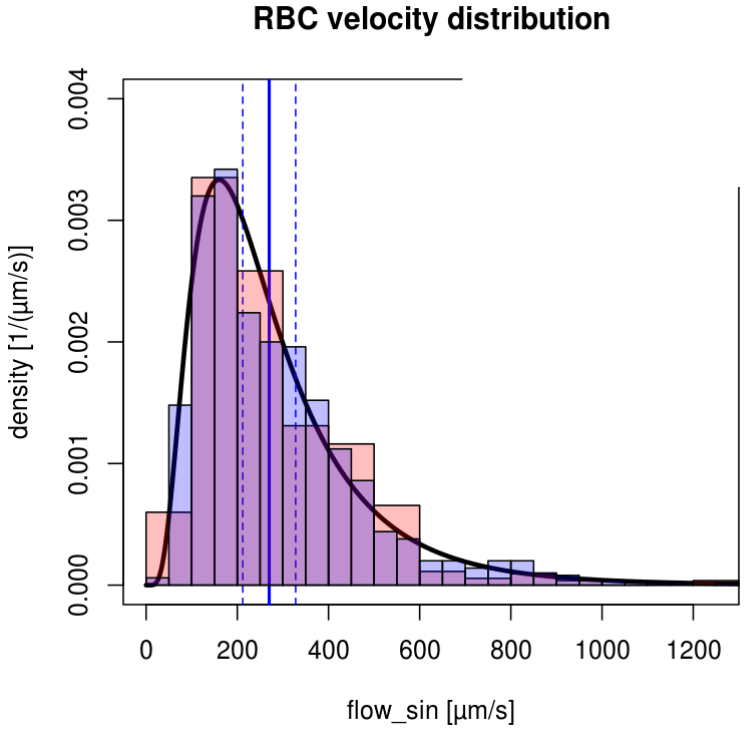
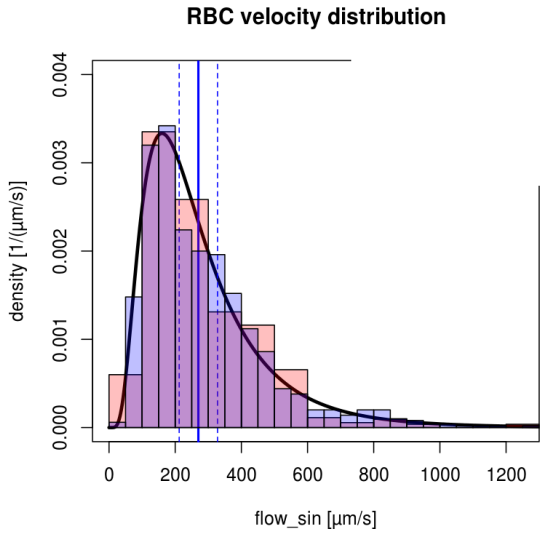
FITTING DISTRIBUTIONS

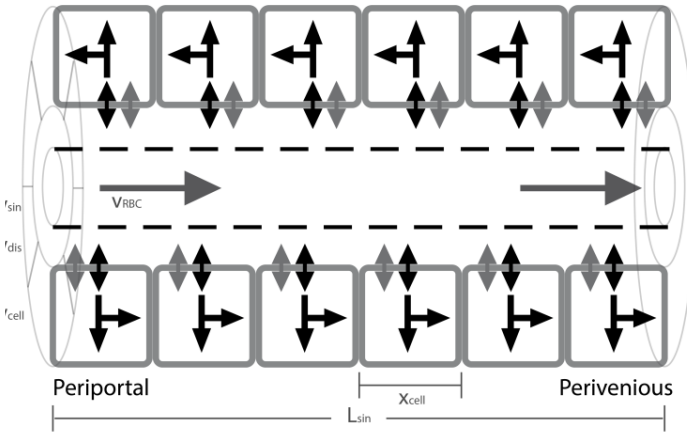
- maximum-likelihood method for univariate distributions (log-normal)

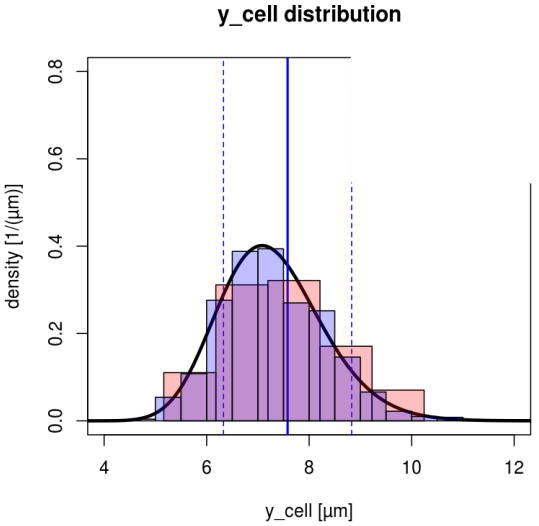


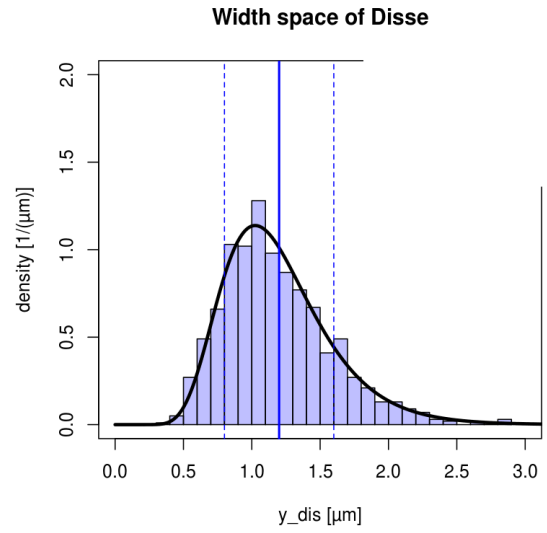


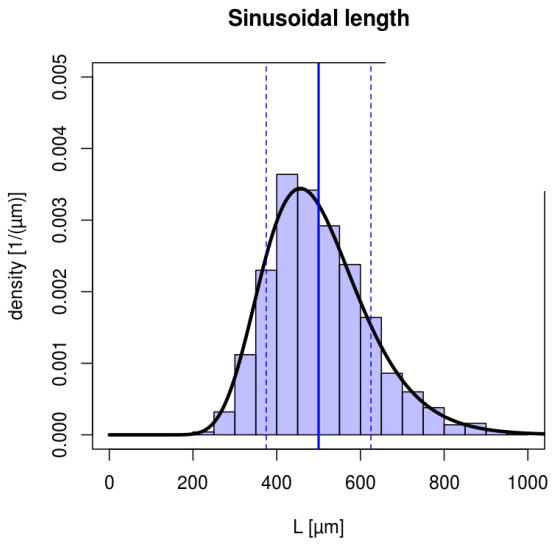
TISSUE-SCALE SINUSOIDAL UNIT

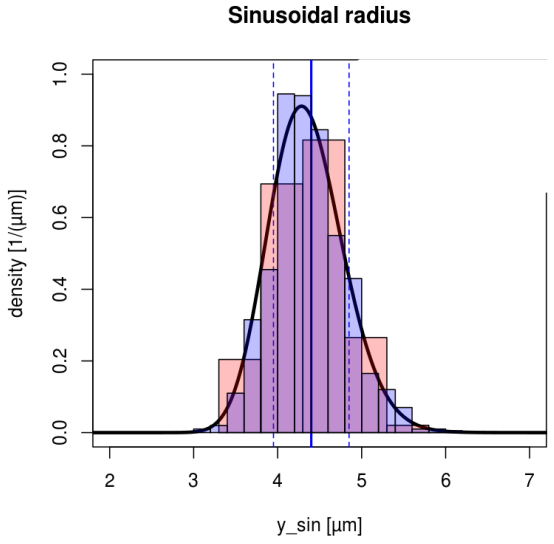






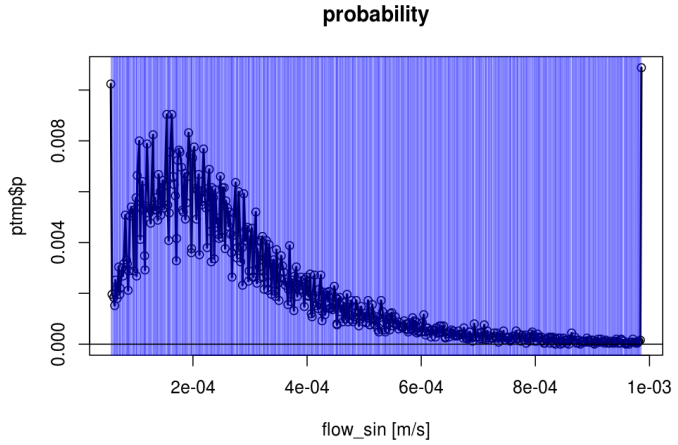


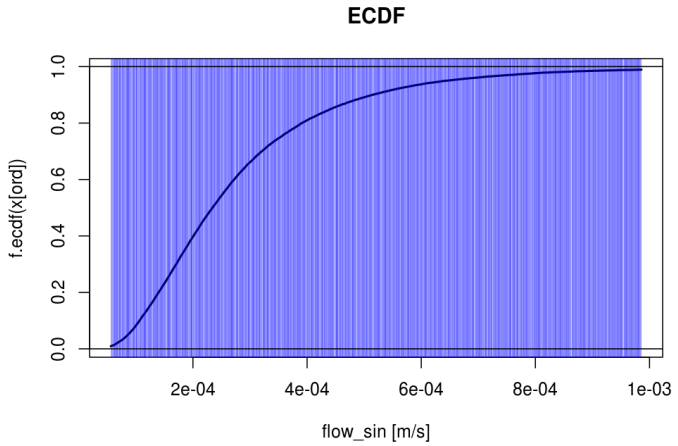


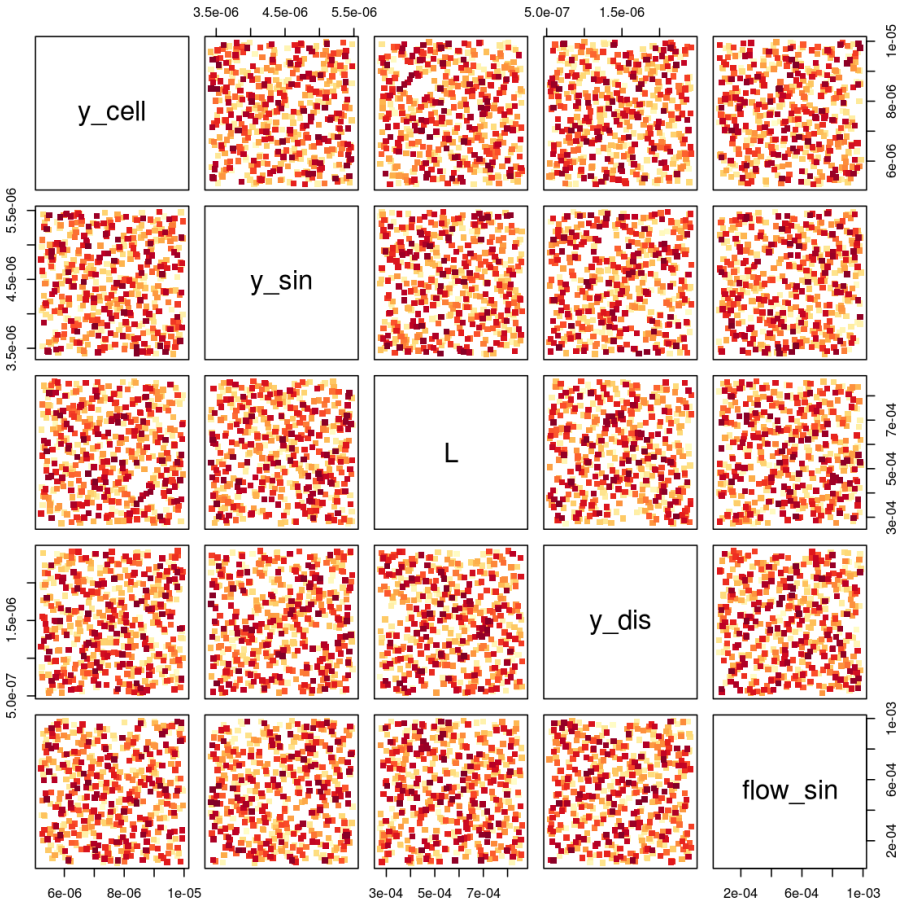


LHS SAMPLING

- Latin hypercube sampling (LHS) & Methods from MonteCarlo sampling

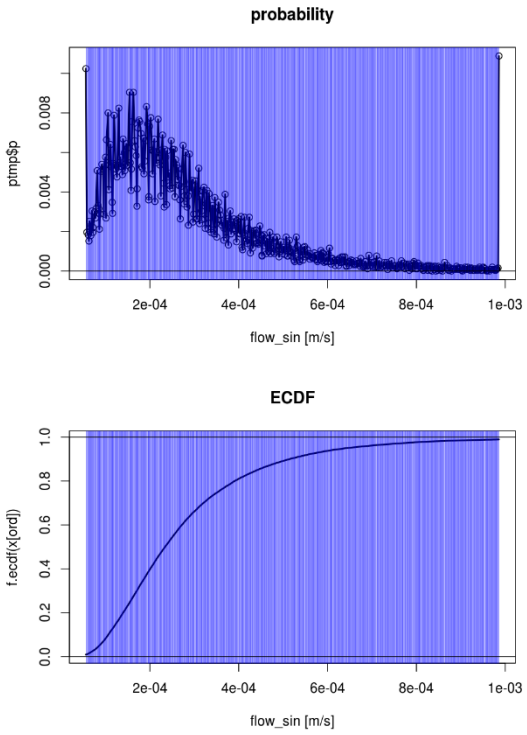


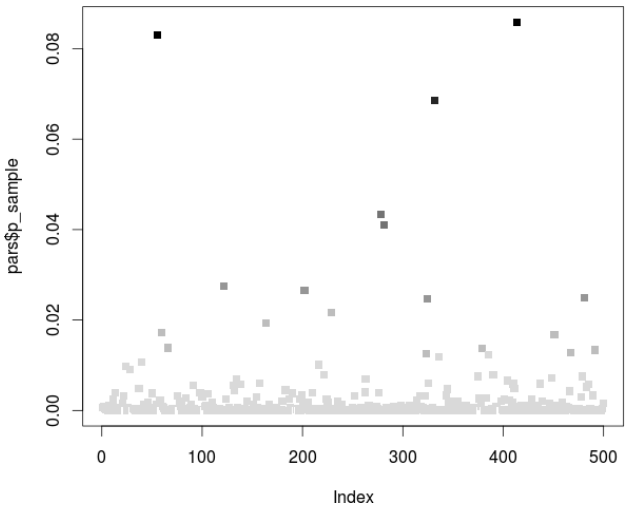


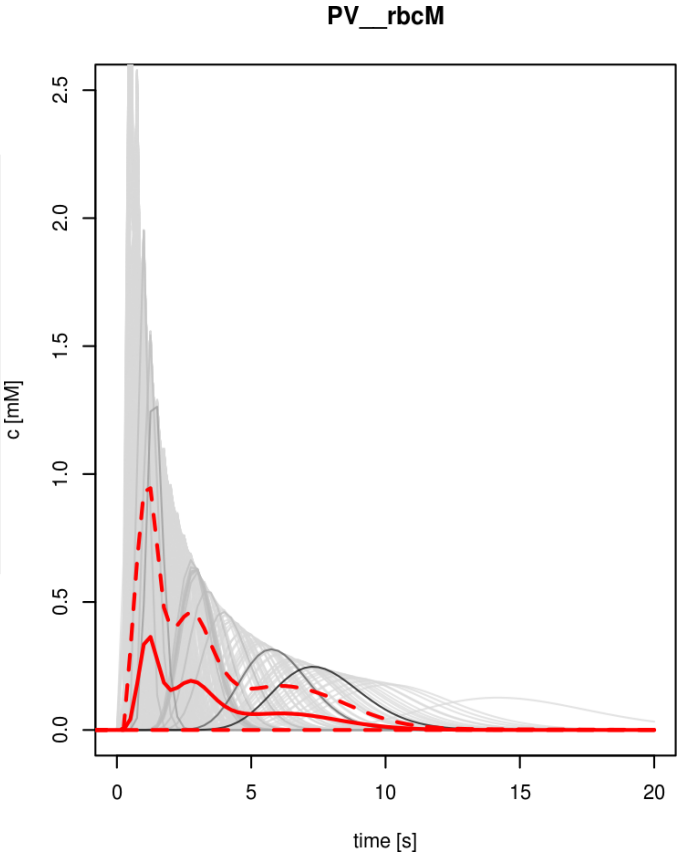


CONVERGENCE

- Challenge:
  - High-dimensional parameter space (5-10 dimensions in tissue & metabolic parameters)
  - Many „clever“ samples necessary to cover space properly



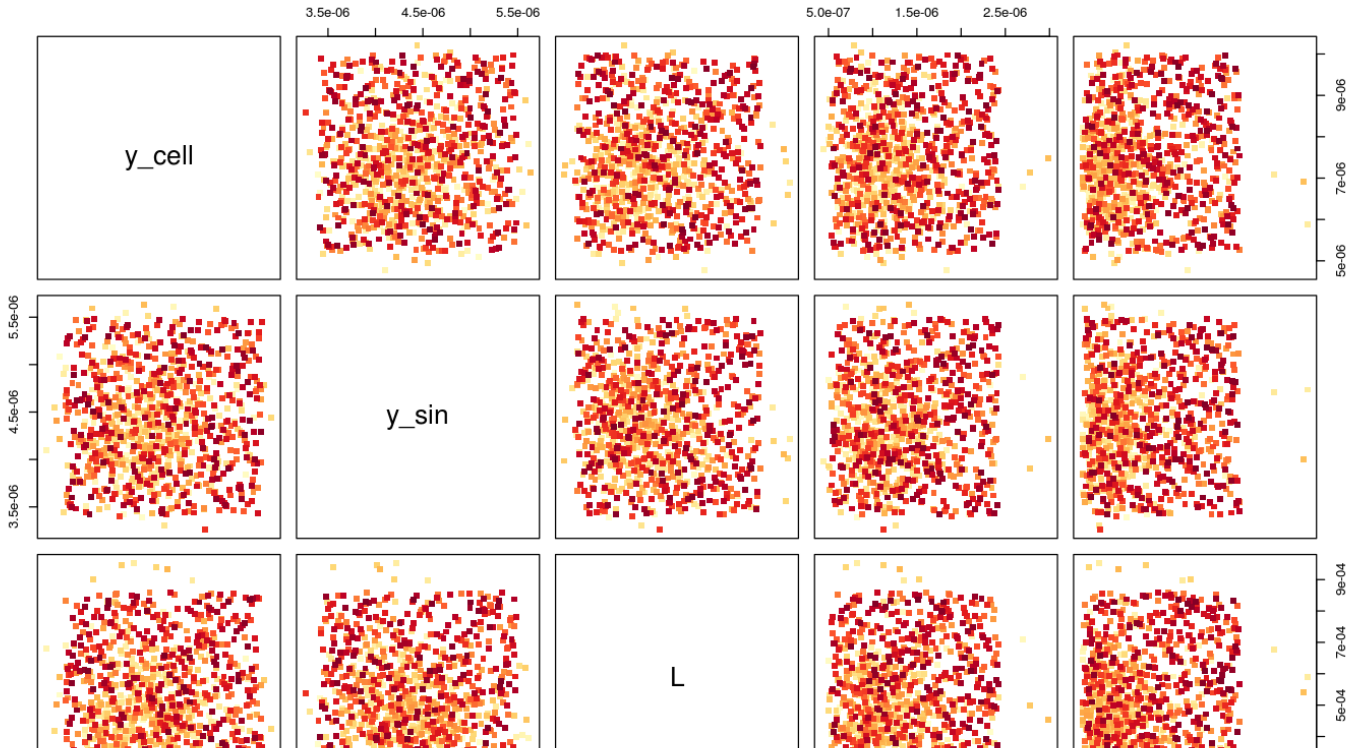




RBC
albumin
sucrose
water

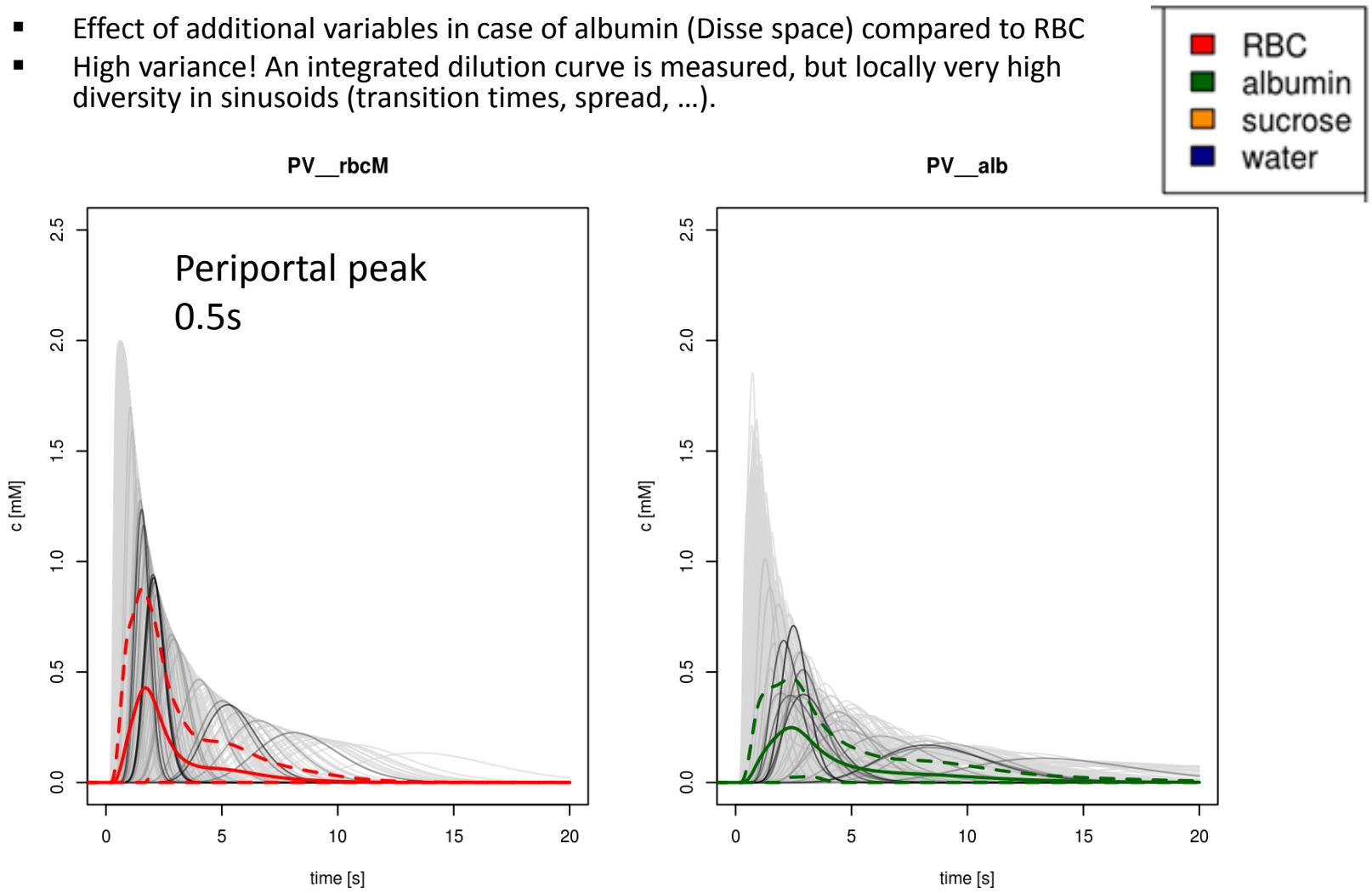
COMBINATION STRATEGY

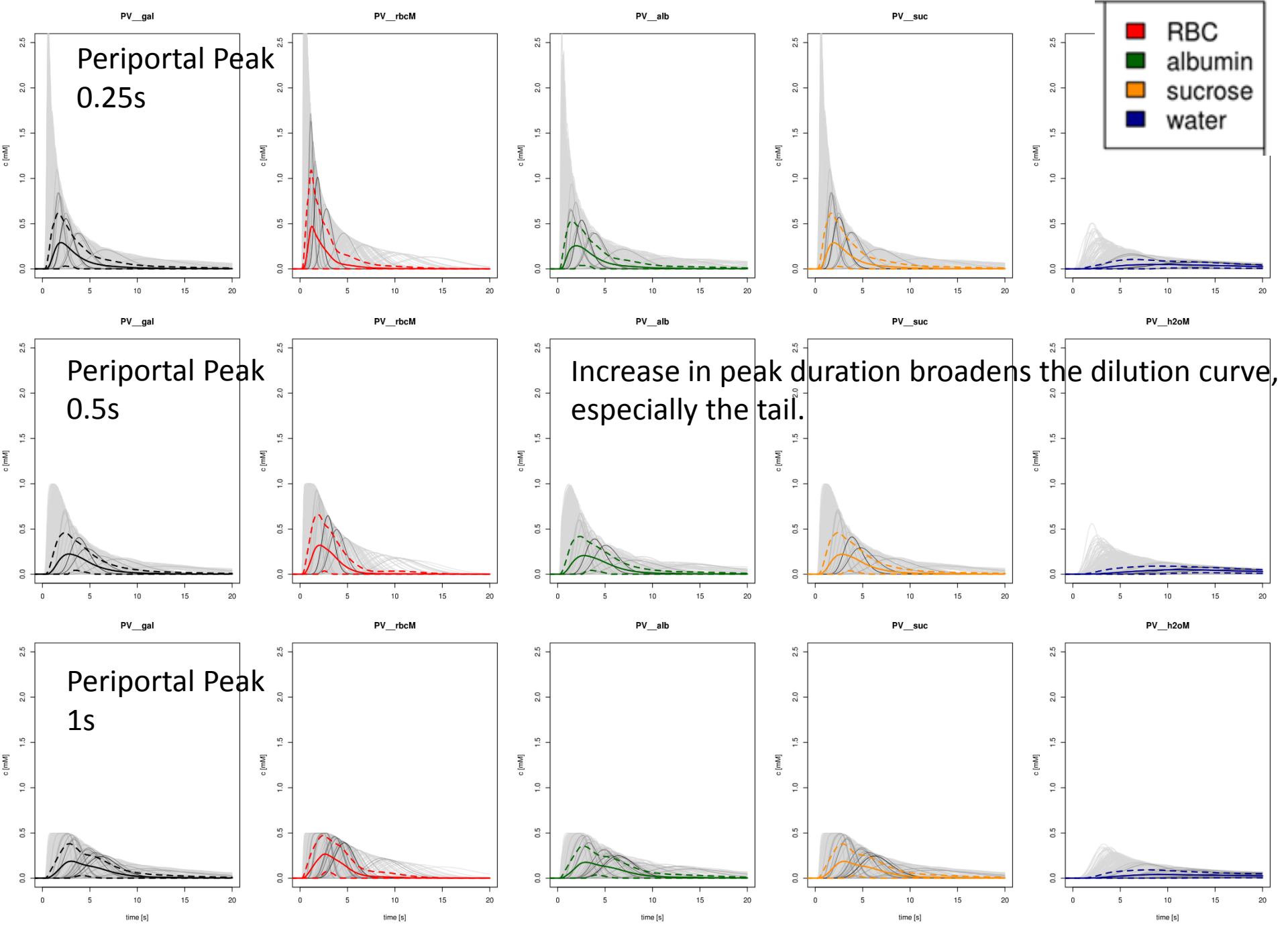
- **50% LHS** (cover full range from 0.01-0.99 quantiles)
- **50% distribution sampling** (account for highly probable events)
- **ECDF based weighting** (empirical cumulative distribution function) of sample contribution under assumption of statistical independence of parameters



PERIVENIOUS DILUTION CURVES

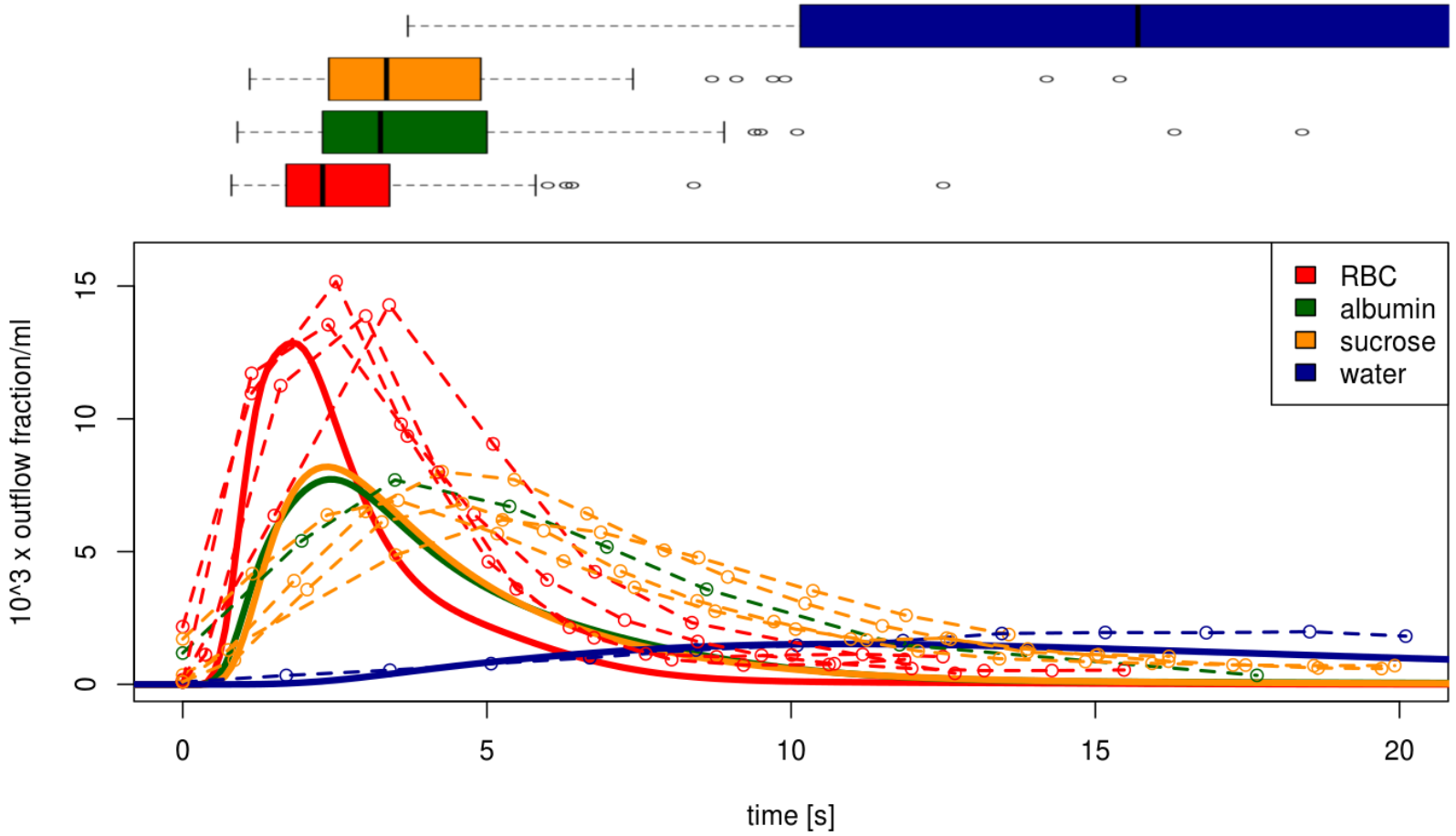
- Better, but still not optimal
  - N=1000 mixed (500 LHS & 500 distribution) + probability weighting
  - TODO: Drop the statistical independence & construct a multidimensional ECDF
- Note:
  - Effect of additional variables in case of albumin (Disse space) compared to RBC
  - High variance! An integrated dilution curve is measured, but locally very high diversity in sinusoids (transition times, spread, …).




PV__gal
PV__rbcM
PV__alb
PV__suc
PV__h2oM
c [mM]
time [s]
RBC
albumin
sucrose
water
Periportal Peak
0.25s
Periportal Peak
0.5s
Periportal Peak
1s
Increase in peak duration broadens the dilution curve, especially the tail.

MULTIPLE INDICATOR DILUTION

Mean dilution curves with experimental data from 4 independent experiments
Periportal Peak (rectangular, duration 0.5s)
No fitting (only free parameter is peak duration).



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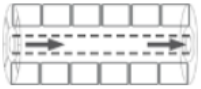
Multiscale-Galactose

- Models
- Tasks
- Integrations
- Cores
- Simulations
- Timecourses
- Plots

Admin



Tasks

pk	model	integration	simulations	status	info
25	MultipleIndicator_P04_v14_Nc20_Nf1	[0.0,100.0] 4000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
24	MultipleIndicator_P03_v14_Nc20_Nf1	[0.0,100.0] 4000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
23	MultipleIndicator_P02_v14_Nc20_Nf1	[0.0,100.0] 4000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
22	MultipleIndicator_P01_v14_Nc20_Nf1	[0.0,100.0] 4000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
21	MultipleIndicator_P00_v14_Nc20_Nf1	[0.0,100.0] 4000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
20	MultipleIndicator_P04_v14_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
19	MultipleIndicator_P03_v14_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
18	MultipleIndicator_P02_v14_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
17	MultipleIndicator_P01_v14_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
16	MultipleIndicator_P00_v14_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of multiple-indicator dilution curves (tracer peak periportal)
15	MultipleIndicator_P04_v13_Nc20_Nf1	[0.0,500.0] 2000	500	500 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
14	MultipleIndicator_P03_v13_Nc20_Nf1	[0.0,500.0] 2000	500	500 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
13	MultipleIndicator_P02_v13_Nc20_Nf1	[0.0,500.0] 2000	500	500 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
12	MultipleIndicator_P01_v13_Nc20_Nf1	[0.0,500.0] 2000	500	500 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
11	MultipleIndicator_P00_v13_Nc20_Nf1	[0.0,500.0] 2000	500	500 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
10	MultipleIndicator_P04_v11_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
9	MultipleIndicator_P03_v11_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
8	MultipleIndicator_P02_v11_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
7	MultipleIndicator_P01_v11_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
6	MultipleIndicator_P00_v11_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
5	MultipleIndicator_P04_v10_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
4	MultipleIndicator_P03_v10_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
3	MultipleIndicator_P02_v10_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
2	MultipleIndicator_P01_v10_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.
1	MultipleIndicator_P00_v10_Nc20_Nf1	[0.0,500.0] 2000	1000	1000 | 0 | 0	Simulation of tracer peak periportal with resulting dilution curves.

	A	B	C	D	E	F	G	H	I
1	status	core	y_cell	y_sin	L	y_dis	flow_sin	duration	sim
2	UNASSIGNED		6.64640464768893E-006	4.51517526406004E-006	0.0004561854	1.32136941126338E-006	0.000211178		18777
3	UNASSIGNED		8.65649669544174E-006	4.20931615364485E-006	0.0003531316	1.2242684723271E-006	9.00117286863366E-005		18776
4	ASSIGNED	10.39.34.27-cpu-7	0.000009368	4.21789594644714E-006	0.000303369	0.000001333	0.0002640036		18771
5	UNASSIGNED		7.806510890555E-006	3.7518369501097E-006	0.0004087027	7.44808383741511E-007	0.0001856388		18775
6	UNASSIGNED		6.56829981417262E-006	4.66838593564891E-006	0.0004450632	2.18105301284341E-006	0.0005594039		18774
7	UNASSIGNED		0.000007654	0.000004767	0.0004678695	1.28922128018918E-006	0.0006329357		18773
8	UNASSIGNED		6.16586931252047E-006	4.00557810337901E-006	0.0003860545	0.000002106	0.0003230328		18772
9	ASSIGNED	10.39.32.106-cpu-6	0.000006985	4.79876060470051E-006	0.0003815726	1.35365610180616E-006	0.0003462197		18770
10	ASSIGNED	10.39.32.106-cpu-2	7.64105547110986E-006	3.68658262867564E-006	0.0007089434	7.28091402600155E-007	0.0003975799		18769
11	ASSIGNED	10.39.32.106-cpu-3	5.48665402151281E-006	3.94156223503503E-006	0.0007403251	9.94301691554614E-007	0.0002118681		18768
12	DONE	10.39.32.106-cpu-3	7.51433734943539E-006	4.11137911122231E-006	0.0004835724	1.24009474604172E-006	0.0001130779	0:00:16.452447	18659
13	ASSIGNED	10.39.32.106-cpu-4	5.85964337540257E-006	4.98019213658844E-006	0.0005390215	1.10575700208949E-006	0.0004644926		18767
14	DONE	10.39.32.106-cpu-4	7.9036707368155E-006	3.8512395197718E-006	0.0004908441	9.42578939441774E-007	0.0001496508	0:00:19.849417	18654
15	UNASSIGNED		0.00000727	4.39158492126421E-006	0.0004649256	1.16989698017536E-006	0.0002237426		18766
16	UNASSIGNED		6.95890891772681E-006	4.89525231602892E-006	0.0005050888	0.000000766	0.0002073985		18765
17	UNASSIGNED		7.31786542779174E-006	4.33173985805061E-006	0.0004992128	9.06754602912661E-007	0.0001574594		18764
18	UNASSIGNED		6.95367709886474E-006	4.60523088829777E-006	0.0004184891	1.25009968194451E-006	9.28409181927323E-005		18763