

Scaling and systems biology for integrating multiple organs-on-a-chip

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Electronic Supplementary Information (ESI)

We provide in both PDF and Excel formats a Scaling Spreadsheet with ~250 physiological parameters describing brain, heart, kidney, liver, lung, and blood. In this section, we also discuss in more detail than in the manuscript the Shannon-Wiener Index as a measure of cellular heterogeneity.

Cellular Heterogeneity

The Shannon-Wiener Index (*SWI*)^{1,2} provides a useful measure of the effective heterogeneity of organs that can guide organ-on-chip (OoC) and human organ construct (HOC) design:

$$SWI = -\sum_i^N p_i \log_2 p_i ,$$

where there are *N* cell types and p_i is the probability that a cell is of type *i*. By using log base 2, we compute *SWI* in bits. The Diversity Index (*DI*)¹ is simply 2^{SWI} and indicates the effective

number of cell types in the tissue. If we have only one cell type in a tissue, then $SWI = -1 \log_2 1 = 0$, and $DI = 1$. If we have two cell types that are equally abundant (*i.e.*, $p_1 = p_2 = 0.5$), $SWI = -(0.5 \log_2(0.5) + 0.5 \log_2(0.5)) = -(0.5 \times -1 + 0.5 \times -1) = 1$. If we have two cell types with disparate abundances (*e.g.*, $p_1 = 0.1$ and $p_2 = 0.9$), then $SWI = -(0.1 \log_2(0.1) + 0.9 \log_2(0.9)) = -(0.1 \times -3.32 + 0.9 \times -1.52) = -(0.332 + -1.36) = 0.469$, and $DI = 2^{0.469} = 1.38$. So the more monodisperse (less heterogeneous) is a two-cell tissue, the closer the *SWI* is to 0 because one cell type dominates. The more heterogeneous the tissue, then the closer is *SWI* to 1, since each cell type is equally represented (*DI* = 2). If the abundance of the two cell types is imbalanced, then the *SI* is intermediate between 1 and 2. Table S1 lists *SWI* and *DI* for several organs, which we can use in designing and validating OoCs and HoCs. The sources of the brain data are listed in the Scaling Spreadsheet. We were unable to identify from the literature a self-consistent set of cell distributions for the kidney.

Table S1 Heterogeneity of cell types in different organs and the corresponding the Shannon-Wiener Index (*SWI*), in bits, and the effective number of cell types, known as the diversity index (*DI*= 2^{SWI})

Organ	# of cell types, <i>N</i>	Cell type	%	Shannon-Wiener Index, <i>SWI</i>	Diversity Index, <i>DI</i>	$P_i = 1/N$ for uniform distribution of <i>N</i> cell types	<i>SWI</i> for uniform cell-type distribution
Brain (Neocortex) ³	4	Glia	41%				
		Neurons	33%				
		Vascular	17%				
		Microglia	8%				
		Total	100%	1.8	3.4	0.25	2.0
Heart ^{4,5}	5	Cardiomyocytes	55%				
		Fibroblasts	25%				
		Vascular smooth muscle	10%				
		Endothelial	7%				
		Neuronal	3%				
		Total	100%	1.7	3.3	0.20	2.3
Liver ⁶	4	Hepatocyte	60%				
		Sinusoidal endothelial	20%				
		Kupffer	15%				
		Hepatic stellate	5%				
		Total	100%	1.5	2.9	0.25	2.0
Lung (Alveolar) ⁷	5	Endothelial	39%				
		Interstitial	29%				
		Type II epithelial	18%				
		Type I epithelial	11%				
		Alveolar macrophages	3%				
		Total	100%	2.0	4.0	0.20	2.3
Blood ⁸	6	Erythrocytes	99%				
		Neutrophils	0.50%				
		Lymphocytes	0.30%				
		Monocytes	0.050%				
		Eosinophils	0.025%				
		Basophils	0.007%				
		Total	99.9%	0.1	0.1	0.20	2.3

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Scaling Spreadsheet

The following pages contain a PDF of **Table S1. Structural and functional parameters to guide the scaling of organs-on-chips and human organ constructs based upon human and animal data.** This is in the form of a spread sheet, with ~250 parameters from brain, heart, kidney, liver, lung and blood that are useful in designing coupled organs on a chip. The user is urged to validate all numbers from the primary references therein and report any discrepancies to the authors. A live version of the spread sheet can be downloaded from <http://www.vanderbilt.edu/vibre/organs-on-a-chip.php>. There is a moderated section for comments on and additions to the table.

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Kidney	Metabolic	Mitochondrial Membrane SA (m^2) per cm^3 Tissue	m^2/cm^3	2.17E+01	-0.22		1.87E+00	8.53E+00	1.12E+01	3.90E+01	1.78E+02	64	
Kidney	Metabolic	Vol Mitochondria/mTAL Cell Vol %	%	5.62E+01	-0.06		4.43E+01	6.53E+01	7.00E+01	9.61E+01	1.41E+02	63	
Kidney	Metabolic	Inner Mitochondrial Membrane Area/Vol mTAL Mito	um^1	4.90E+01	-0.03		4.24E+01	5.36E+01	5.59E+01	6.78E+01	8.58E+01	63	
Kidney	Metabolic	Inner Mitochondrial Membrane Area/mTAL Cell Vol	um^1	2.75E+01	-0.09		1.86E+01	3.52E+01	3.95E+01	6.64E+01	1.25E+02	63	
Kidney	Metabolic	Basolateral Membrane Area/mTAL Cell Vol	um^1	5.50E+00	-0.08		4.00E+00	6.71E+00	7.38E+00	1.13E+01	1.89E+01	63	
Liver													
Liver	Structural	Organ Weight	g	3.70E-02	0.85		1.52E+03	1.36E+00	1.52E+00	1.50E+00	3.87E-03	1.52E-03	
Liver	Structural	Organ Volume	mL				1.69E+03	1.69E+00	1.30E+00		1.10E-05	1.52E-06	
Liver	Metabolic	Oxygen Consumption	mL/min	3.50E-02	0.69		2.07E+03	6.56E-01	2.07E+00		5.59E-03	4.76E-05	
Liver	Functional	Blood Flow	mL/min	9.40E-02	0.75		1.45E+03	2.27E+00	1.45E+00		1.28E-02	1.45E-03	
Liver	Structural	Resident Blood Volume	mL	2.50E-02	0.86			9.65E-01			7.19E-05	1.45E-06	
Liver	Functional	Bile Flow	mL/day				3.50E+02	3.50E-01	2.00E+00		3.50E-04	3.50E-07	
Liver	Structural	Hepatocyte Cells	cells	9.10E+06	0.89		3.00E+11	3.92E+08	3.00E+08		8.63E+05	3.00E+05	
Liver	Structural	Hepatocyte Cell Density	cells/g liver				1.39E+08 ± 2.50E+07	1.39E+05	1.35E+02 ± 1.00E+01		1.90E+03	3.00E+02	
Liver	Functional	Protein Concentration	mg/g liver				9.00E+01 ± 1.70E+01	9.00E-02	1.15E+02 ± 7.00E+00		9.00E-05	9.00E-08	
Liver	Structural	Liver Density	g liver/mL				1.03E+00		1.03E-03		1.03E-06	1.03E-09	
Liver	Functional	Potassium Uptake Rate	μmol K+/g wet * min	1.20E+00	-0.14			6.62E-01			1.74E+00	4.58E+00	
Liver	Metabolic	Tissue Metabolic Rate (Oxygen)	μmol O2/g wet * min	3.60E+00	-0.21			1.48E+00			6.29E+00	2.68E+01	
Liver	Functional	Shear Stress	MPa			Liver sinusoid	5.00E+01		5.00E-02		5.00E-05	5.00E-08	
Liver	Functional	Cl, intrinsic											
Liver	Functional	Antipyrine	mL/min	5.00E-02	1.84		Corrected with brain weight	3.43E+02	3.75E-04	3.43E-01		1.13E-09	3.43E-07
Liver	Functional	Caffeine	mL/min	7.00E-02	1.53		Corrected with brain weight	1.40E+02	1.20E-03	1.40E-01		3.08E-08	1.40E-07
Liver	Functional	Mibepradil	mL/min	3.63E+01	1.31		Corrected with brain weight	4.90E+02	1.11E+00	4.90E-01		1.31E-04	4.90E-04
Liver	Functional	Motorotene	mL/min	1.00E+02	1.64		Corrected with brain weight	7.70E+02	1.28E+00	7.70E-01		1.53E-05	7.70E-04
Liver	Functional	Theophylline	mL/min	3.00E-02	1.71		Corrected with brain weight	4.27E+01	3.18E-04	4.27E-02		2.36E-09	4.27E-05
Liver	Functional	Tolcapone	mL/min	1.03E+02	1.51		Corrected with brain weight	1.89E+02	1.86E+00	1.89E-01		5.48E-05	1.89E-04
Liver	Functional	Bromazepam	mL/min				Adjusted from reference weight to 70kg human	6.78E+01					61
Liver	Functional	Clonazepam	mL/min				Adjusted from reference weight to 70kg human	4.28E+02					61
Liver	Functional	Chlordiazepoxide	mL/min				Adjusted from reference weight to 70kg human	4.46E+02					61
Liver	Functional	Antipyrine	mL/min	8.16E+00	0.89			7.76E-01			1.32E-02	2.91E-05	66
Liver	Functional	Phenytoin	mL/min	4.71E+01	0.92			4.13E+00			4.13E+00	7.44E-03	66
Lung													
Lung	Structural	*averaged values - Reported									*averaged		
Lung	Structural	Total Lung Capacity (TLC)	mL	5.35E+01	1.06	70 kg human .25 kg rat		5.50E+03 ± 5.00E+02	3.19E+00	5.50E+00	9.50E+00	2.11E-03	5.50E-03
Lung	Structural	Functional Residual Capacity (FRC)	mL	2.41E+01	1.13	human .25 kg rat		3.05E+03 ± 6.50E+02	1.19E+00	3.05E+00	1.50E+00	4.86E-04	3.05E-03
Lung	Structural	Tidal Volume	mL	7.69E+00	1.04	human .25 kg rat		4.50E+02 ± 5.00E+01	4.84E-01	4.50E-01	1.65E+00	3.67E-04	4.50E-04
Lung	Structural	Dead Space	mL	2.76E+00	0.96	human .25 kg rat		1.50E+02 ± 0.00E+00	2.15E-01	1.50E-01	7.90E-01	2.83E-04	1.50E-04
Lung	Functional	Frequency of Respiration	min-1	5.35E+01	-0.26	human .25 kg rat		1.65E+01 ± 5.50E+00	1.07E+02	1.65E-02	1.06E+02	6.44E+02	1.65E-05
Lung	Functional	Minute Volume (ml/min)	mL/min	3.79E+02	0.80	human .25 kg rat		6.50E+03 ± 5.00E+02	4.52E+01	6.50E+00	2.00E-01	1.80E-01	6.50E-03
Lung	Functional	Lung Compliance	mL/cm H2O	2.10E+00	1.08	human .25 kg rat		1.63E+02 ± 3.75E+01	1.19E-01	1.63E-01	4.50E-01	6.84E-05	1.63E-04
Lung	Functional	Flow Resistance	cm H2O/(L/sec)	2.44E+01	-0.70	human .25 kg rat		1.40E+00 ± 5.00E-01	1.57E+02	1.40E-03	9.50E+01	1.98E+04	1.40E-06
Lung	Functional	Diffusion Capacity CO	mL/mmHg/min	2.20E-01	1.14	human .25 kg rat		3.35E+01 ± 1.65E+01	1.06E-02	3.35E-02	4.50E-02	4.03E-06	3.35E-05
Lung	Functional	Power of Breathing	g*cm/min	9.62E+02	0.78	human .25 kg rat		4.00E+04 ± 1.00E+04	1.21E+02	4.00E+01	6.25E+02	5.53E-01	4.00E-02
Lung	Structural	Organ Weight	g	1.13E+01	0.99	human .25 kg rat		1.00E+03	8.12E-01		1.50E+00	8.70E-04	1.00E-03
Lung	Structural	Acinar Diameter	cm	4.20E-02	0.17	human .25 kg rat		2.86E-01	2.66E-02	2.86E-04	7.40E-02	8.10E-03	2.86E-07
Lung	Structural	Terminal Bronchiole Diameter	cm	5.20E-03	0.21	human .25 kg rat		4.40E-02	2.97E-03	4.40E-05	4.10E-03	6.97E-04	4.40E-08

Blood	Structural		Cl-	mmol/L	1.05E+02	-0.01	p value=0.299	1.03E+02 ± 7.50E+00	1.07E+02	1.03E+02	9.90E+01 ± 1.10E+01	1.13E+02	1.03E+02	1.19E+02	1.03E+02	77;78
Blood	Structural	Total Bilirubin	umol/L	4.20E+00	-0.09	p value=0.528	1.34E+01 ± 1.17E+01	5.32E+00	1.34E+01	7.70E+00 ± 7.70E+00	9.84E+00	1.34E+01	1.82E+01	1.34E+01	77;78;81	
Blood	Structural	Mg2+	mmol/L	9.00E-01	-0.03	p value=0.721	1.90E+00 ± 4.00E-01	9.64E-01	1.90E+00	2.35E+00 ± 1.55E+00	1.15E+00	1.90E+00	1.38E+00	1.90E+00	77;78;82	
Blood	Structural	Cholesterol	mmol/L	2.70E+00	-0.04	p value=0.774	4.75E+00 ± 1.75E+00	3.00E+00	4.75E+00	2.88E+00 ± 6.70E-01	3.96E+00	4.75E+00	5.22E+00	4.75E+00	77-79	
Blood	Functional	Wall Shear Stress Along the Infrarenal Aorta**	dyn/cm ²	2.60E+00	-0.38	p value<.05	4.80E+00 ± 3.00E-01	7.14E+00	4.80E+00	8.76E+01 ± 8.30E+00	9.86E+01	4.80E+00	1.36E+03	4.80E+00	83	
Blood	Functional	Oxygen Carriers	Relative oxygen capacity	α (mL O ₂ /mL B *atm) at 37 °C	Oxygen binding capacity (mL O ₂ /g)	Oxygen Diffusivity *10 ¹⁰ (m ² /s)										Blood O ₂ Carriers
Blood	Functional	Water	1	2.39E-02	-	2.89										84;85
Blood	Functional	Hemoglobin	70	3.30E-02	1.37	0.838										85
Blood	Functional	Perfluorocarbon	20	3.50E-01	-	8.29										86;87
Blood	Functional	Blood	70	2.23E-02	-	1.33										85

NOTES

1 In certain cases, the literature values for the allometric scaling laws were for body mass in units other than kg, and hence have been scaled for consistency

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