Supplemental modeling information for paper (2013 in review):

"Modeling Serotonin Uptake in the Lung Shows Endothelial Transporters Dominate over Cleft Permeation"

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This section contains detailed listings of all parameters needed to reproduce the models used in the analysis. There are three sets of four tables, one set for each of three data sets analyzed. Each set contains the following tables: four region model parameters and variables, four region organ input function parameters, four region model heterogeneity flows and weights, and two region model parameters and variables.

Rickaby et al. 1981 data:

Table S1: (Four region model) List of parameters and variables used in four region kinetic models fit Rickaby 1981 data. If a value is listed, then it is used for all relevant simulations**. ***See Table 2 of paper and $^{+}$Tables S2, S3 for values used for model fit to each experiment.

Symbol	Definition	Value	Unit
V_{art}	Arteriole Volume	*	ml/g
V_{vein}	Venule Volume	*	ml/g
L	Mean length of a capillary	0.1	cm
L1	Mean length of a arteriole	0.1	cm
L2	Mean length of a venule	0.2	cm
V_p	Capillary Volume	*	ml/g
F_p	Mean Plasma flow	*	ml/(g*min)
V_{ec}	EC volume of distribution	*	ml/g
V_{isf}	ISF volume of distribution	*	ml/g
V_{pc}	PC volume of distribution	*	ml/g
D_p	Capillary axial dispersion	$1x10^{-4}$	cm^2/sec
D_{ec}	Endothelium axial dispersion	$1x10^{-6}$	cm^2/sec
D_{isf}	Interstitial axial dispersion	$1x10^{-6}$	cm^2/sec

D_{pc}	Parenchymal axial dispersion	$1x10^{-6}$	cm^2/sec
OrgW	Organ weight with blood.	*	g
Cin(t)	Organ input function	+	1/sec
CM_p	Plasma Serotonin (mother) concentration		nmol/ml
CT_p	Plasma Serotonin tracer concentration		pmol/ml
CR_p	Plasma vascular reference concentration		umol/ml
CM_{ec}	Endothelial Serotonin concentration		nmol/m
CT_{ec}	Endothelial Serotonin tracer concentration		pmol/ml
CM_{isf}	ISF Serotonin concentration		nmol/m
CM_{pc}	Parenchymal cell Serotonin concentration		nmol/m
CT_{pc}	Parenchymal cell Serotonin tracer concentration		pmol/ml
V_{max_ecl}	V_{max} for PS luminal side of endothelial cell		nmol/(g*min)
Km_{ecl}	K_m for PS luminal side of endothelial cell		nmol/ml
V_{max_eca}	V_{max} for PS anti-luminal side of endothelial cell	V_{max_ecl}	nmol/(g*min)
Km_{eca}	K_m for PS anti-luminal side of endothelial cell	Km_{ecl}	nmol/ml
PSg	Diffusive PS from capillary to ISF		ml/(g*min)
Gec_{max}	V_{max} for EC consumption		nmol/(g*min)
Km_{Gec}	K_m for EC consumption		nmol/ml
V_{max_pc}	V_{max} for PS ISF to PC	V_{max_ecl}	nmol/(g*min)
Km_{pc}	K_m for PS ISF to PC	Km_{ecl}	nmol/ml
Gpc_{max}	V_{max} for PC consumption	Gec_{max}	nmol/(g*min)
Km_{G_pc}	K_m for PC consumption	Km_{Gec}	nmol/ml
DoseT	Dose of labeled serotonin injected	0.1	pmol
DoseR	Dose of intravascular reference injected	0.1	umol
DoseM	Dose of serotonin injected.	10, 30, 100	nmol
CM_init	Initial conc. of serotonin in capillary	0	nmol/ml
PDF(f)	Flow probability density function	Random walk	unitless
PDF RD	PDF relative dispersion	0.55	unitless
	PDF skew	1.8	unitless
f_{min}	Minimum relative flow for PDF	+	unitless
f_{max}	Maximum relative flow for PDF	+	unitless

Table S2. Four region model organ input function for Rickaby 1981 data (Lag normal function with fitted exponential decay).

Variable name	Value	Units
Input function Area	0.72	unitless
tMean	2.11	sec
RD	0.0361	unitless
Skewn	1.88	unitless
frPeak	$1\ e^{-6}$	unitless
upslope	Regular	unitless
Time or fractional join	Time	unitless
Time join	2.35	sec
Exponential tail		
# of Exponentials	4	
Weight 1	1.001	Weight assigned to first

		exponential
Weight 2	2.974	
Weight 3	3.216	
Weight 4	0.541	
k1	1.0850	Relative magnitude of first exponential
k2	0.01996	
k3	0.3415	
k4	0.0500	

Table S3: Four region model heterogeneity flows and weights for fit to Rickaby 1981 data.

Rel flows:	0.94	1.03	1.11	1.20	1.29	1.37	1.46
Weights:	1.87	1.77	1.68	1.59	1.52	1.45	1.39

Table S4: (Two region model) List of parameters used in Two region kinetic models. If a value is listed, then it is used for all relevant simulations. *Also see Table 2 of paper for values specific to Linehan et al, 1998 analysis of Rickaby 1981 data.

Symbol	Definition	Value	Unit
L	Maximum length of a capillary	0.5	cm
Lmean	Mean relative length of capillary	1	dimensionless
$\bar{t}$	Mean organ plasma transit time	*	cm
V_p	Capillary Volume	*	ml/g
F_p	Mean Plasma flow	*	ml/(g*min)
V_{xv}	Extravasxular volume of distribution	0.4	ml/g
D_p	Capillary axial dispersion	0	cm^2/sec
D_{xv}	Extravascular axial dispersion	0	cm^2/sec
OrgW	Organ weight with blood.	*	g
Cin(t)	Organ input function	Lag Normal	1/sec
CM_p	Plasma Serotonin (mother) concentration		nmol/ml
CT_p	Plasma Serotonin tracer concentration		pmol/ml
CR_p	Plasma Intravascular reference concentration		umol/ml
CM_{ec}	Extravascularl concentration		nmol/m
CT_{ec}	Extravascularl tracer concentration		pmol/ml
V_{max_xv}	V_{max} for PS luminal side of EV space		nmol/(g*min)
Km_{xv}	K_m for PS luminal side of EV space		nmol/ml
PSev	Diffusive PS from EV to capillary		ml/(g*min)
G_{xv}	Extravascular consumption		ml/(g*min)
DoseT	Dose of labeled serotonin injected	0.1	pmol
DoseR	Dose of intravascular reference injected	0.1	umol
DoseM	Dose of serotonin injected.	10,30,100	nmol
CM_init	Initial conc. of serotonin in capillary	0	nmol/ml
CTTDF(f)	Cap transit time probability density function	Random Walk	unitless
CTTD RD	CTTD Relative Dispersion	0.75	unitless
	CTTD skewn	1.8	unitless
rtMax	Maximum relative transit time	3	unitless

Malcorps et al. 1984 data

Table S5: (Four region model) Malcorp 1984 Data fit. List of parameters and variables used in four region kinetic model. *****See Table 2 of paper, [+]Table S6, and Table S7 for heterogeneity flows and weights.

Symbol	Definition	Value	Unit
V_{art}	Arteriole Volume	*	ml/g
V_{vein}	Venule Volume	*	ml/g
L	Mean length of a capillary	0.2	cm
L1	Mean length of a arteriole	0.1	cm
L2	Mean length of a venule	0.2	cm
V_p	Capillary Volume	*	ml/g
F_p	Mean Plasma flow	*	ml/(g*min)
V_{ec}	EC volume of distribution	*	ml/g
V_{isf}	ISF volume of distribution	*	ml/g
V_{pc}	PC volume of distribution	*	ml/g
D_p	Capillary axial dispersion	$1x10^{-4}$	cm^2/sec
D_{ec}	Endothelium axial dispersion	$1x10^{-6}$	cm^2/sec
D_{isf}	Interstitial axial dispersion	$1x10^{-6}$	cm^2/sec
D_{pc}	Parenchymal axial dispersion	$1x10^{-6}$	cm^2/sec
OrgW	Organ weight with blood.	*	g
Cin(t)	Organ input function	+	1/sec
CM_p	Plasma Serotonin (mother) concentration		nmol/ml
CT_p	Plasma Serotonin tracer concentration		pmol/ml
CR_p	Plasma vascular reference concentration		umol/ml
CM_{ec}	Endothelial Serotonin concentration		nmol/m
CT_{ec}	Endothelial Serotonin tracer concentration		pmol/ml
CM_{isf}	ISF Serotonin concentration		nmol/m
CM_{pc}	Parenchymal cell Serotonin concentration		nmol/m
CT_{pc}	Parenchymal cell Serotonin tracer concentration		pmol/ml
V_{max_ecl}	V_{max} for PS luminal side of endothelial cell		nmol/(g*min)
Km_{ecl}	K_m for PS luminal side of endothelial cell		nmol/ml
V_{max_eca}	V_{max} for PS anti-luminal side of endothelial cell	V_{max_ecl}	nmol/(g*min)
Km_{eca}	K_m for PS anti-luminal side of endothelial cell	Km_{ecl}	nmol/ml
PSg	Diffusive PS from capillary to ISF		ml/(g*min)
Gec_{max}	V_{max} for EC consumption		nmol/(g*min)
Km_{G_ec}	K_m for EC consumption		nmol/ml
V_{max_pc}	V_{max} for PS ISF to PC	V_{max_ecl}	nmol/(g*min)
Km_{pc}	K_m for PS ISF to PC	Km_{ecl}	nmol/ml
Gpc_{max}	V_{max} for PC consumption	Gec_{max}	nmol/(g*min)
Km_{G_pc}	K_m for PC consumption	Km_{G_ec}	nmol/ml
DoseT	Dose of labeled serotonin injected	1	pmol
DoseR	Dose of intravascular reference injected	0.7	umol
DoseM	Dose of serotonin injected.		nmol
CM_init	Initial conc. of serotonin in capillary		nmol/ml
PDF(f)	Flow probability density function	Random walk	unitless
PDF RD	PDF relative dispersion	0.4	unitless
	PDF skew	1.6	unitless
f_{min}	Minimum relative flow for PDF	0.52	unitless
f_{max}	Maximum relative flow for PDF	1.45	unitless

Table S6. Organ input function for Four region model fit to Malcorps data (Pulse input).

Variable name	Value	Units
Start time	0.15	sec
Duration	0.1	sec
Amplitude	10	unitless
Offset	0	sec
Time to repeat	0	sec

Table S7: Four region model heterogeneity flows and weights for fit to Malcorps 1984 data.

Rel flows:	0.59	0.72	0.85	0.98	1.12	1.25	1.38
Weights:	1.19	1.54	1.46	1.22	0.96	0.75	0.59

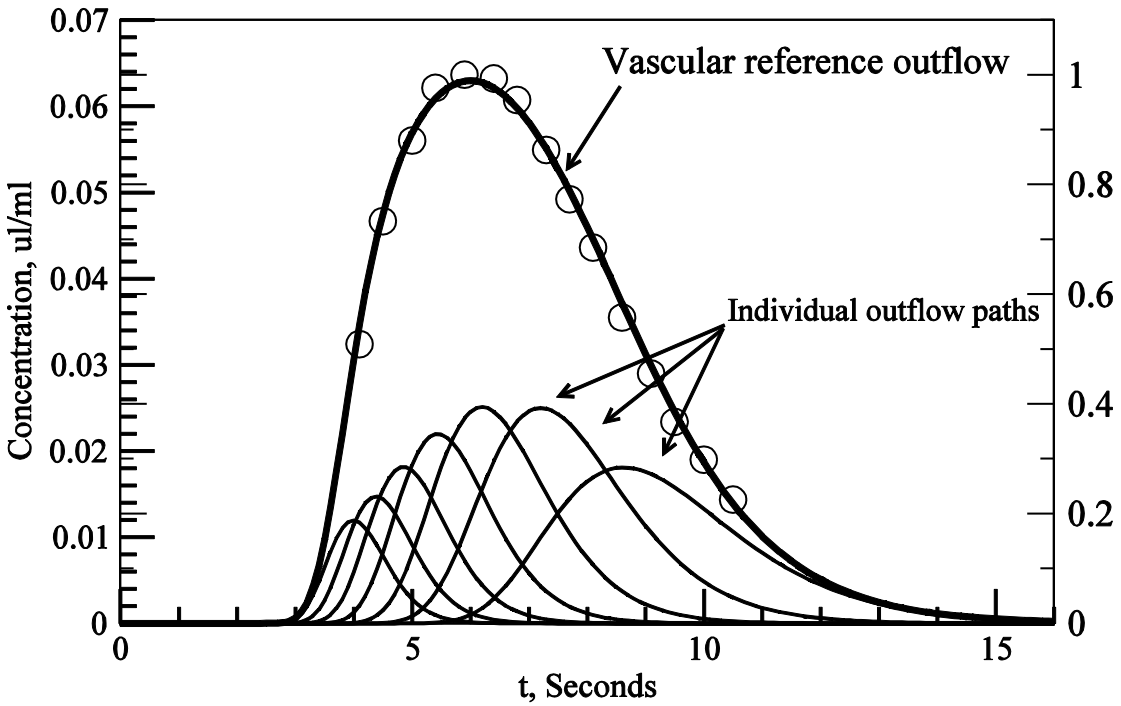

Figure S1. Vascular reference outflow heterogeneity. From four region model fit to Malcorps 1984 Method C data (normalized unitless, see Tables S5, S7, and paper for more details).

Table S8: (Two region model) List of parameters used in Two region kinetic model fit to Malcorps 1984 data. If a value is listed, then it is used for the simulation. *Also see Table 2 for values specific to Malcorps data fit.

Symbol	Definition	Value	Unit
L	Maximum length of a capillary	0.5	cm
Lmean	Mean relative length of capillary	1	dimensionless
$\bar{t}$	Mean organ plasma transit time	*	s
V_p	Capillary Volume	0.14	ml/g
F_p	Mean Plasma flow	*	ml/(g*min)
V_{xv}	Extravasxular volume of distribution	0.4	ml/g
D_p	Capillary axial dispersion	0	cm^2/sec
D_{xv}	Extravascular axial dispersion	0	cm^2/sec
OrgW	Organ weight with blood.	*	g
Cin(t)	Organ input function	Lag Normal	1/sec
CM_p	Plasma Serotonin (mother) concentration		nmol/ml
CT_p	Plasma Serotonin tracer concentration		pmol/ml
CR_p	Plasma Intravascular reference concentration		umol/ml
CM_{ec}	Extravascularl concentration		nmol/m
CT_{ec}	Extravascularl tracer concentration		pmol/ml

V_{max_xv}	V_{max} for PS luminal side of EV space		nmol/(g*min)
Km_{xv}	K_m for PS luminal side of EV space		nmol/ml
PSev	Diffusive PS from EV to capillary		ml/(g*min)
G_{xv}	Extravascular consumption		ml/(g*min)
DoseT	Dose of labeled serotonin injected	1.0	pmol
DoseR	Dose of intravascular reference injected	0.7	umol
DoseM	Dose of serotonin injected.		nmol
CM_init	Initial conc. of serotonin in capillary		nmol/ml
CTTDF(f)	Cap transit time probability density function	Random Walk	unitless
CTTD RD	CTTD Relative Dispersion	0.70	unitless
	CTTD skewn	1.6	unitless
rtMax	Maximum relative transit time	2.6	unitless

Rickaby et al. 1984 data

Table S9: **(Four region model)** Four region parameter values and variables used for fit to Rickaby 1984 data. * See Table 2 of paper. [+]See Tables S10 and S11 for values.

Symbol	Definition	Value	Unit
V_{art}	Arteriole Volume	0.035	ml/g
V_{vein}	Venule Volume	0.05	ml/g
L	Mean length of a capillary	0.1	cm
L1	Mean length of a arteriole	0.2	cm
L2	Mean length of a venule	0.2	cm
V_p	Capillary Volume	0.16	ml/g
F_p	Mean Plasma flow	3.58	ml/(g*min)
V_{ec}	EC volume of distribution	0.03	ml/g
V_{isf}	ISF volume of distribution	0.06	ml/g
V_{pc}	PC volume of distribution	0.3	ml/g
D_p	Capillary axial dispersion	$1x10^{-4}$	cm^2/sec
D_{ec}	Endothelium axial dispersion	$1x10^{-6}$	cm^2/sec
D_{isf}	Interstitial axial dispersion	$1x10^{-6}$	cm^2/sec
D_{pc}	Parenchymal axial dispersion	$1x10^{-6}$	cm^2/sec
OrgW	Organ weight with blood.	81.8	g
Cin(t)	Organ input function	[+]Longtail	1/sec
CM_p	Plasma Serotonin (mother) concentration		nmol/ml
CT_p	Plasma Serotonin tracer concentration		pmol/ml
CR_p	Plasma vascular reference concentration		umol/ml
CM_{ec}	Endothelial Serotonin concentration		nmol/m
CT_{ec}	Endothelial Serotonin tracer concentration		pmol/ml
CM_{isf}	ISF Serotonin concentration		nmol/m
CM_{pc}	Parenchymal cell Serotonin concentration		nmol/m
CT_{pc}	Parenchymal cell Serotonin tracer concentration		pmol/ml
V_{max_ecl}	V_{max} for PS luminal side of endothelial cell		nmol/(g*min)
Km_{ecl}	K_m for PS luminal side of endothelial cell		nmol/ml
V_{max_eca}	V_{max} for PS anti-luminal side of endothelial cell	V_{max_ecl}	nmol/(g*min)
Km_{eca}	K_m for PS anti-luminal side of endothelial cell	Km_{ecl}	nmol/ml
PSg	Diffusive PS from capillary to ISF		ml/(g*min)
Gec_{max}	V_{max} for EC consumption		nmol/(g*min)
Km_{G_ec}	K_m for EC consumption		nmol/ml
V_{max_pc}	V_{max} for PS ISF to PC	V_{max_ecl}	nmol/(g*min)
Km_{pc}	K_m for PS ISF to PC	Km_{ecl}	nmol/ml

Gpc_{max}	V_{max} for PC consumption	Gec_{max}	nmol/(g*min)
Km_{G_pc}	K_m for PC consumption	Km_{G_ec}	nmol/ml
DoseT	Dose of labeled serotonin injected	0.1	pmol
DoseR	Dose of intravascular reference injected	0.1	umol
DoseM	Dose of serotonin injected.		nmol
CM_init	Initial conc. of serotonin in capillary		nmol/ml
K_{i_ecl}	Disassociation constant for serotonin inhibitor (Imipramine)	0.14	nmol/ml
CIaaa	Conc of serotonin transport inhibitor in curve A	3.5	nmol/min
CIbbb	Conc of serotonin transport inhibitor in curve B	3.5	nmol/min
CIccc	Conc of serotonin transport inhibitor in curve C	3.5	nmol/min
PDF(f)	Flow probability density function	Random walk	unitless
PDF RD	PDF relative dispersion	0.35	unitless
	PDF skew	1.8	unitless
f_{min}	Minimum relative flow for PDF	0.5	unitless
f_{max}	Maximum relative flow for PDF	2.0	unitless

Table S10: (Four region model) Long Tail input function parameters used for Four region fit to Rickaby 1984 data.

Parameter	**Value** (Control)	**Units**
Input function Area	1	unitless
tMean	0.086	sec
RD	0.5883	unitless
Skewn	1.98	unitless
frPeak	$1e^{-5}$	unitless
upslope	Regular	unitless
Time or fractional join	Time	unitless
Time join	0.27	sec
	Exponential tail	
# of Exponentials	4	
Weight 1	0.902	Weight assigned to first exponential
Weight 2	0.125	
Weight 3	0.001	
Weight 4	3.043	
k1	2.721	Relative magnitude of first exponential
k2	0.25	
k3	0.06	
k4	0.016	

Table S11: Four region model heterogeneity flows and weights for fit to Rickaby 1984 data.

Rel flows:	0.61	0.82	1.04	1.25	1.46	1.68	1.89
Weights:	0.89	1.64	1.05	0.57	0.3058	0.16	0.09

Table S12: (Two region model) List of parameters used in Two region kinetic model fit to Rickaby 1984 data. If a value is listed, then it is used for the simulation. * See Table 2 of paper.

Symbol	Definition	Value	Unit
L	Maximum length of a capillary	0.5	cm
Lmean	Mean relative length of capillary	1	dimensionless
$\bar{t}$	Mean organ plasma transit time	*	s
V_p	Capillary Volume	0.16	ml/g
F_p	Mean Plasma flow	*	ml/(g*min)
V_{xv}	Extravasxular volume of distribution	0.4	ml/g
D_p	Capillary axial dispersion	0	cm^2/sec
D_{xv}	Extravascular axial dispersion	0	cm^2/sec
OrgW	Organ weight with blood.	*	g
Cin(t)	Organ input function	Lag Normal	1/sec
CM_p	Plasma Serotonin (mother) concentration		nmol/ml
CT_p	Plasma Serotonin tracer concentration		pmol/ml
CR_p	Plasma Intravascular reference concentration		umol/ml
CM_{ec}	Extravascular concentration		nmol/m
CT_{ec}	Extravascular tracer concentration		pmol/ml
V_{max_xv}	V_{max} for PS luminal side of EV space		nmol/(g*min)
Km_{xv}	K_m for PS luminal side of EV space		nmol/ml
PSev	Diffusive PS from EV to capillary		ml/(g*min)
G_{xv}	Extravascular consumption		ml/(g*min)
K_{i_ecl}	Disassociation constant for serotonin inhibitor (Imipramine)	0.14	nmol/ml
CIaaa	Conc. of serotonin transport inhibitor in curve A (imipramine data only)	3.5	nmol/min
CIbbb	Conc. of serotonin transport inhibitor in curve B (imipramine data only)	3.5	nmol/min
CIccc	Conc. of serotonin transport inhibitor in curve C (imipramine data only)	3.5	nmol/min
DoseT	Dose of labeled serotonin injected	1.0	pmol
DoseR	Dose of intravascular reference injected	0.7	umol
DoseM	Dose of serotonin injected.		nmol
CM_init	Initial conc. of serotonin in capillary	0	nmol/ml
CTTDF(f)	Cap transit time probability density function	Random Walk	unitless
CTTD RD	CTTD Relative Dispersion	0.75	unitless
	CTTD skewn	1.7	unitless
rtMax	Maximum relative transit time	3.0	unitless

2. Correlation matrix(s) for fits to Rickaby 1981 data

Table **S13** shows the correlation matrix (obtained through normalizing the covariance matrix) for the 4 PS_gfree model. The correlation for each parameter pair gives important information about their relationship. It gives an estimate of their negative or positive interdependence. Notice the relationship between Km_{ec} and V_{max_ecl} is positive, as V_{max_ecl} increases, Km_{ec} does as well, whereas PS_g will decrease as V_{max_ecl} increases. Pairs of parameters with correlation near ±1 are considered irresolvable and are not independent based on the model used and experimental data obtained. The correlation matrices show that model variants 4PSfree (Table S13) and $4PS_g$ (Not shown) give us two independent parameters: V_{max_ecl} and the ratio of Gec_{max} to Km_{g_ec}

(correlation between Gec_{max} and Km_{g_ec} is 1). Table S14 is the correlation matrix for the two region model fit to Rickaby 1981 data.

Note: The correlation matrixes can be generated for all fits through JSim. Just load the corresponding project file (either JardineSerotonin_FourRegion.proj or JardineSerotonin_TwoRegion.proj) and run a single run optimization (the 'Optimization' page in JSim).

Table S13: Correlation matrix for 4 region model **4PSgfree** fit to Rickaby 1981 data, PC transporter and consumption are the same as EC. Values are unitless. Bold values denote correlations greater than |0.8|.

	V_{max_ecl}	Km_{ec}	PS_g	Gec_{max}	Km_{g_ec}
V_{max_ecl}	1	**0.96**	**-0.93**	-0.48	-0.48
Km_{ec}	**0.96**	1	**-0.84**	-0.44	-0.47
PS_g	**-0.93**	**-0.84**	1	0.32	0.32
Gec_{max}	-0.48	-0.44	0.32	1	**0.99**
Km_{g_ec}	-0.48	-0.47	0.32	**0.99**	1

Table S14: The correlation matrix for 2 region fit to Rickaby 1981 data. Values are unitless. Bold values denote correlations greater than |0.8|.

	V_{max_xv}	Km_{xv}	PS_{ev}	G_{xv}
V_{max_xv}	1	0.46	**0.82**	0.74
Km_{xv}	0.46	1	-0.01	0.18
PS_{ev}	**0.82**	-0.01	1	**0.90**
G_{xv}	0.74	0.18	**0.90**	1

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