SUPPLEMENTAL DATA

Predictions of Hepatic Disposition Properties Using a Mechanistically Realistic, Physiologically Based Model

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Example Calculations. Application of the FCMA was automated. Nevertheless, below we walk through examples of predicting two ISL parameter values for prazosin and propranolol.

I. Predict a value of the parameter *B2CJumpProb* for prazosin and propranolol:
1. For prazosin:

Step 0. Selection of PCPs and creating the data set.

The data set contains $n = 4$ compounds: S = {atenolol, antipyrine, labetalol, diltiazem} for which the simulation parameters are known:

ISL Parameters	ATENOLOL	ANTIPYRINE	LABETALOL	DILTIAZEM
B2CJumpProb	0.3	0.35	0.5	0.5

B2CJumpProb is one of the four parameters in the ISL subgroup B, moving between spaces (Table 1). All four are calculated in the same way. Figure 4 specifies that for the three PCP properties in subgroups II (partitioning) and IV (topology related) are expected to be equally influential in determining the value of all ISL subgroup B parameters.

PCP Subgroups II & IV	Atenolol	Antipyrine	Labetalol	Diltiazem	Prazosin
RB count	8	1	8	7	4
TPSA	84.6	26.9	95.6	59.1	107.0
logP_{app}	0.14	0.33	2.69	3.53	1.88

Step 1. Let $q = 4$, and S_{new}= {atenolol, antipyrine, labetalol, diltiazem, prazosin}.

Step 2. If $q = 1$ go to step 4. Else, classify S_{new} into q clusters using Fuzzy c-Means algorithm.

Step 3. If prazosin is not in the same group with *at least* another member, then decrease q to $q - 1$. Repeat steps 2 and 3. (For the values above, prazosin is not in the same group with *at least* one other member. When we repeat for $q = 3$, we observe that prazosin is in the same group with *at least* one other member, so we stop.)

Else, let *G-value* be the number of group-mates of prazosin, (the clustering results show that prazosin has two group-mates, $G = 2$.) Go to step 4.

Step 4. The five compounds are clustered into three groups with the following membership degrees.

cluster	Atenolol	Antipyrine	Labetalol	Diltiazem	Prazosin
C 3	**0.987**	0.001	0.050	0.060	0.316
C 2	0.006	**0.998**	0.020	0.045	0.179
C 1	0.007	0.001	**0.930**	**0.895**	**0.506**

PRAZOSIN'S simulation parameter, *B2CJumpProb***,** is estimated as:

$B2CJumpProb_{\text{Prazosin}} = 0.506 \bullet P_{C1} + 0.179 \bullet P_{C2} + 0.316 \bullet P_{C3}$

where P_{Ci} is the average ISL parameter values of members of cluster *i*:

$P_{C1} = (B2CjumpProb_{\text{labetalol}} + B2CjumpProb_{\text{diltiazem}})/2 = 0.5$

$P_{C2} = B2CjumpProb_{\text{antipyrine}} = 0.35$

$P_{C3} = B2CjumpProb_{\text{atenolol}} = 0.3$

Consequently,

$B2CjumpProb_{\text{prazosin}} = 0.506 \times 0.5 + 0.179 \times 0.35 + 0.316 \times 0.3 = 0.4104$ (rounded to 0.41)

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2. For PROPRANOLOL:

PCP Subgroups II & IV	Atenolol	Antipyrine	Labetalol	Diltiazem	Propranolol
RB count	8	1	8	7	6
TPSA	84.6	26.9	95.6	59.1	41.5
$\log P_{app}$	0.14	0.33	2.69	3.53	3.10

Steps 1-3. Let $q = 4$, and S_{new}= {atenolol, antipyrine, labetalol, diltiazem, propranolol}.

For $q = 4$ and the values above, propranolol is in the same group with *at least* one other member, and $G = 1$.

Step 4. The classification results are:

cluster	Atenolol	Antipyrine	Labetalol	Diltiazem	Propranolol
C 4	**1**	0	0	0.014	0.014
C 3	0	**1**	0	0.010	0.014
C 2	0	0	**1**	0.067	0.036
C 1	0	0	0	**0.908**	**0.936**

$P_{C1} = B2CjumpProb_{\text{diltiazem}} = 0.5$

$P_{C2} = B2CjumpProb_{\text{labetalol}} = 0.5$

$P_{C3} = B2CjumpProb_{\text{antipyrine}} = 0.35$

$P_{C4} = B2CjumpProb_{\text{atenolol}} = 0.3$

Consequently,

$B2CJumpProb_{\text{propranolol}} = 0.936 \times 0.5 + 0.036 \times 0.535 + 0.014 \times 0.35 + 0.014 \times 0.3 = 0.4951$ (rounded to 0.50)

II. Predict parameter *SoluteBindingProb* for prazosin and propranolol

1. For prazosin:

Step 0. Selection of PCPs and creating the data set.

The data set contains $n = 4$ compounds: S = {atenolol, antipyrine, labetalol, diltiazem} for which the simulation parameters are known:

ISL Parameters	ATENOLOL	ANTIPYRINE	LABETALOL	DILTIAZEM
SoluteBindingProb	0.35	0.5	0.6	0.35

SoluteBindingProb is one of the four parameters in the ISL subgroup C, binding to LOBULAR components (Table 1). All four are calculated in the same way. Figure 4 specifies that for the three PCP properties in subgroups V (hydrogen bound related) are expected to be equally influential in determining the value of all ISL subgroup C parameters.

PCP Subgroups III & V	Atenolol	Antipyrine	Labetalol	Diltiazem		Prazosin
fuB	0.74	0.6	0.52	0.28		0.54
HBD count	3	0	4	0		1
HBA count	4	2	4	5		8
Tautomer count	2	0	7	0		3

Steps 1-3. Let $q = 4$, and S_{new}= {atenolol, antipyrine, labetalol, diltiazem, prazosin}.

For $q = 4$ and the values above, prazosin is in the same group with *at least* one other member, and $G = 1$.

Step 4. The classification results are:

Cluster	Atenolol	Antipyrine	Labetalol	Diltiazem	Prazosin
C4	**0.980**	0.001	0.001	0.010	0.320
C3	0.007	**0.994**	0.000	0.037	0.191
C2	0.007	0.000	**0.999**	0.003	0.118
C1	0.006	0.004	0.000	**0.950**	**0.371**

$P_{C1} = SoluteBindingProb_{\text{Antipyrine}} = 0.35$
$P_{C2} = SoluteBindingProb_{\text{Labetalol}} = 0.6$
$P_{C3} = SoluteBindingProb_{\text{Diltiazem}} = 0.5$
$P_{C4} = SoluteBindingProb_{\text{Atenolol}} = 0.35$

Consequently,

$SoluteBindingProb_{\text{Prazosin}} = 0.371\times0.35 + 0.118\times0.6 + 0.191\times0.5 + 0.320\times0.35 = 0.4082$ (rounded to 0.41)

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2. For propranolol:

PCP Subgroups III & V	Atenolol	Antipyrine	Labetalol	Diltiazem		Propranolol
fuB	0.74	0.6	0.52	0.28		2
HBD count	3	0	4	0		3
HBA count	4	2	4	5		0
Tautomer count	2	0	7	0		0.45

Steps 1-3. Let $q = 4$, and S_{new}= {atenolol, antipyrine, labetalol, diltiazem, propranolol}.

For $q = 4$ and the values above, propranolol is in the same group with *at least* one other member, and $G = 1$.

Step 4. The classification results are:

Cluster	Atenolol	Antipyrine	Labetalol	Diltiazem	Propranolol
C4	**0.989**	0.006	0.000	0.002	0.325
C1	0.004	**0.977**	0.000	0.004	**0.376**
C2	0.003	0.002	**1**	0.000	0.045
C3	0.003	0.014	0.000	**0.993**	0.254

$P_{C1} = SoluteBindingProb_{\text{Antipyrine}} = 0.5$
$P_{C2} = SoluteBindingProb_{\text{Labetalol}} = 0.6$
$P_{C3} = SoluteBindingProb_{\text{Diltiazem}} = 0.35$
$P_{C4} = SoluteBindingProb_{\text{Atenolol}} = 0.35$

Consequently,

$SoluteBindingProb_{\text{Propranolol}} = 0.376\times0.5 + 0.045\times0.6 + 0.254\times0.35 + 0.325\times0.35 = 0.4176$ (rounded to 0.42)

TABLE S1

Description of ISL parameters and their values for the simulations in Figs. 5-7 and S3, except where noted otherwise

ISL Parameters[a]	Description	Values[b]	Ranges[c]
	Device Framework Parameters		
cycleLimit	(B)[d] Provides the simulation with an artificial stopping criterion so that it will not run forever	200	200
monteCarloRuns	(I)[d] The number of runs in a Monte-Carlo set. Aggregate measures for the whole system are calculated at the end of all Monte-Carlo runs	48	[2, 50]
similarityMeasure	Specifies which similarity measure to use.	global_sd	global_sd
nominalProfile	(S)[d] Specifies which model to use as the nominal for use in calculating similarity between the experimental and nominal models		
experimentalProfile	(S) Specifies which model to use as the experimental for use in calculating similarity between the experimental and nominal models		
	In Silico Liver Parameters		
StepsPerCycle	(I) Parameterizes the granularity of time for the Research model (the ISL). The data has a "sampling rate" that provides a default time scale for it. Finer granularity requires interpolation between the data points. The Reference (PK) model[a] is a time-reversible, continuous function, which allows sampling at any frequency	2	2
GraphInputFile	(S) Specifies the file to read if the SS graph is to be specified by an explicit graph (file format is GML)	null	
GraphSpecFile	(S) Provides the lobule graphical specification, and specifies the base file name (*extension.ls*) to be used if the graph is to be specified according to the Lobule Specification		
	Nodes in Zone I	45	[20, 50]
	Nodes in Zone II	21	[10, 35]

	Nodes in Zone III	6	[3, 15]
	Intra-Zone I edges	18	[10, 30]
	Intra-Zone II edges	10	[5, 25]
	Intra-Zone III edges	0	0
	Zone I → Zone II edges	15	[2, 45]
	Zone I → Zone III edges	0	[0, 20]
	Zone II → Zone III edges	8	[5, 25]
GraphSpecIterates	(I) Tells the framework to modify LOBULE specification and run a Monte-Carlo set (consisting of *N* runs) for each different LOBULE specification. Set to 1, it runs 1 set and provides 1 set of outputs. Set to 5, the first run uses the current contents of *lobule.ls*; it then runs 4 more sets, slightly modifying the LOBULE specification each time, resulting in 5 sets.	1	[1, 10]
DirSinRatio	(F)[d] Specifies the percentage of SS that are type $\boldsymbol{S}_A$ ("direct")	0.75	[0, 1]
TortSinRatio	(F) Specifies the percentage of SS that are $\boldsymbol{S}_B$ ("tortuous")	0.25	[0, 1]
DirSinCircMin	(I) Sets the upper and lower bounds for a pseudo-RNG (random number generator) using the uniform distribution to choose a circumference for each SS	50	[1, 50]
DirSinCircMax		50	[1, 100]
TortSinCircMin		4	[1, 8]
TortSinCircMax		4	[1, 20]
DirSinLenAlpha	(F) Sets the parameters for a pseudo-RNG using a modified form of the Gamma distribution; The modification consists of a left-right shift of the distribution, allowing the user to clip off the front	3.0	[0.5, 5.0]
DirSinLenBeta		0.215	[0.1, 0.325]
DirSinLenShift		0.0	0.0
TortSinLenAlpha		10.0	[4, 18]
TortSinLenBeta		0.125	[0.03, 0.15]
TortSinLenShift		-40	[40.0, 40.0]
SinusoidTurbo	(F) The complement of the amount of turbulence allowed in any given SS. Lower turbo means more tendency of any one COMPOUND to wander sideways or backwards. Higher Turbo means a stronger flow from the input to the output of the SS	0.3	[0.05, 0.95]
ECDensity	(F) Specifies the relative ENDOTHELIAL CELL density, given that the number of grid points in Grid B is set by the geometry parameters of the SS; it specifies the percentage of Grid B points that index an ENDOTHELIAL CELL	0.8	[0.05, 1.0]
HepDensity	(F) Specifies the relative HEPATOCYTES density within Grid C, given that the number of grid points in Grid C is set by the geometry parameters of the SS, it specifies the percentage of Grid C points that index a HEPATOCYTE	0.6	[0.05, 1]
CoreFlowRate	(I) The number of slots solute in the SS core moves forward during each step	2	[1, 8]
A2BJumpProb	(F) Specifies the probability that, when given the option, SOLUTE will jump from Grid A to Grid B	0.1	[0.05, 1.0]
B2AJumpProb	(F) Specifies the probability that, when given the option, SOLUTE will jump from Grid B to Grid A	0.6	[0.05, 1.0]
B2CJumpProb	(F) Specifies the probability that, when given the option, SOLUTE will jump from Grid B to Grid C	0.35	[0.05, 1.0]
C2BJumpProb	(F) Specifies the probability that, when given the option, SOLUTE will jump from Grid C to Grid B	0.65	[0.05, 1.0]

BindersPerCellMin	(I) Max and min for a uniform pseudo-random draw for the number of binding agents inside each CELL. Simple binders for ECs and ENZYMES for HEPATOCYTES	5	[1, 30]
BindersPerCellMax		10	[10, 100]
MetabolizeProb	(F) Probability that an ENZYME will metabolize a SOLUTE before it releases it	0.4	[0, 1]
SoluteBindingProb	(F) Probability that, when a BINDER and SOLUTE make contact, the SOLUTE will be bound	0.5	[0, 1]
SoluteBindingCycles	(I) Number of cycles a binder holds a SOLUTE.	25	[5, 100]
isMembraneCrossing	(S) Specifies whether the SOLUTE can cross membrane or not	SUCROSE:NO DRUG: YES	YES NO
ISL2WetLabScaling	(F) Provides the precise validation mapping from ISL output to the wet-lab (IPRL) output fraction	7.0	[1.0, 8.0]
BolusStartTime	(I) Dictates when to let SOLUTES flow into the LOBULE	5	[2, 9]
DosageParamA [e]	(F) Parameter (A) of the dosage function: $D(t) = A(B^C t^{(C-1)} e^{-Bt})/(C-1)!$, where t = current cycle; Parameter (A) simply raises the amplitude of the function	2000	[1000, 7000]
DosageParamB	(F) Parameter (B) of the dosage function	1	[1, 2]
DosageParamC	(F) Parameter (C) of the dosage function	2	[2, 3]
	Actual dose for Figs. 5-7 and S3.	3,682	

[a] There are four classes of parameters: Device Framework, Research Model, Reference Model, and Data Model. Here, the Research Model is the ISL. Only a subset of the Device Framework parameters is listed here. The Data Model includes all the data against which the SM is being applied, and uses a parameter that specifies whether to interpolate between observations of the in silico data. The Reference Model is a traditional PK model previously fit to the in silico experimental data; it is run concurrently with the Research Model.

[b] Parameter values when SUCROSE and ANTIPYRINE were dosed in combination.

[c] Ranges from which values were drawn during searches of model and parameter space.

[d] B: Boolean; F: floating; I: integer; S: string

[e] The total dose is the area under the dosage function curve.

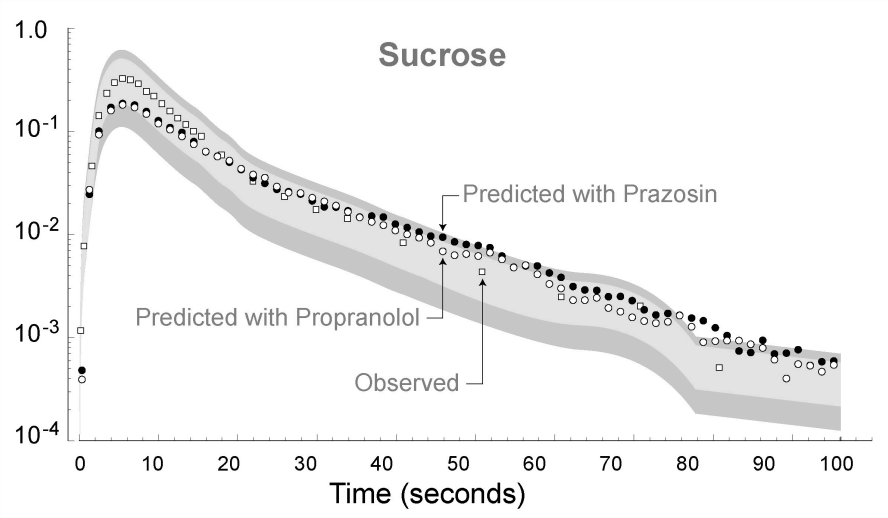

Figure S1. Expected outflow profiles for sucrose co-administrated with prazosin and propranolol using predicted parameter values. These semilog plots show results of simulation experiments for which the PCP-sensitive, PVs were predicted using the Method 2 values listed in Table 5. Black circles: SUCROSE co-administrated with PRAZOSIN; open circles: SUCROSE co-administrated with PROPRANOLOL. Otherwise, the graph components are same as for Fig. 5.

TABLE S2

Two sets of predicted ISL parameter values for prazosin and propranolol calculated using the two, different, FCMA-generated, drug-specific prediction strategies illustrated in Fig. S2.

The listed parameter values (as for Table 5) were combined with the PCP-insensitive parameter values. The resulting ISLs were used, as for Figs. 5-7, to generate the expected outflow profiles in Fig. S3

	FCMA Drug-specific Prediction Strategies			
ISL parameter values	Prazosin1	Prazosin2	Propranolol1	Propranolol2
ISL2WetLabScaling	3.0	3.0	7.0	7.0
A2BJumpProb	0.37	0.54	0.86	0.86
B2AJumpProb	0.21	0.32	0.21	0.21
B2CJumpProb	0.50	0.44	0.50	0.50
C2BJumpProb	0.49	0.39	0.22	0.22
MetabolizeProb	0.23	0.23	0.12	0.12
BindersPerCellMin	6	6	5	6
BindersPerCellMax	11	11	10	13
SoluteBindingProb	0.40	0.40	0.56	0.46
SoluteBindingCycles	24	24	24	24
SM values (±1 SD)	0.76	0.73	0.85	0.70
SM values (±1.5 SD)	0.97	0.97	0.88	0.85

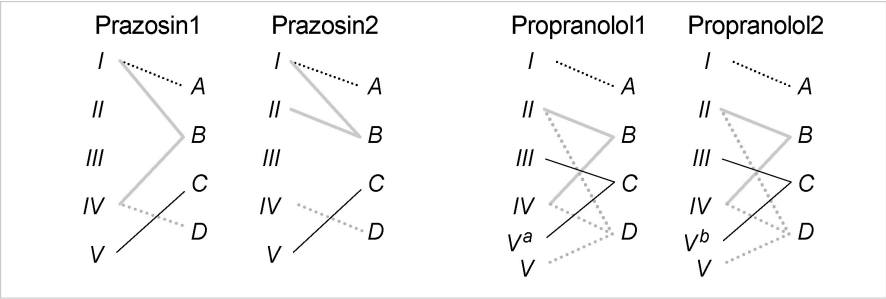

Figure S2. Mappings between PCP subgroups and ISL parameter subgroups (as in Fig.4). The four ISL subgroups are specified in Table 1; the five PCP subgroups are specified in Table 2. Each line represents a hypothesized strong influence. Except as follows, the identified PCP subgroups are the ones used by the FCMA to provide the membership degree values used in Eq. 1 to predict ISL parameter values for prazosin and propranolol in Table S2, exactly the same as done for Table 5. V^a: only HBA from group V was used; V^b: only Tautomer count from group V was used. The FCMA treats the identified PCPs as having equal influences. The influence of the other PCPs is neglected.

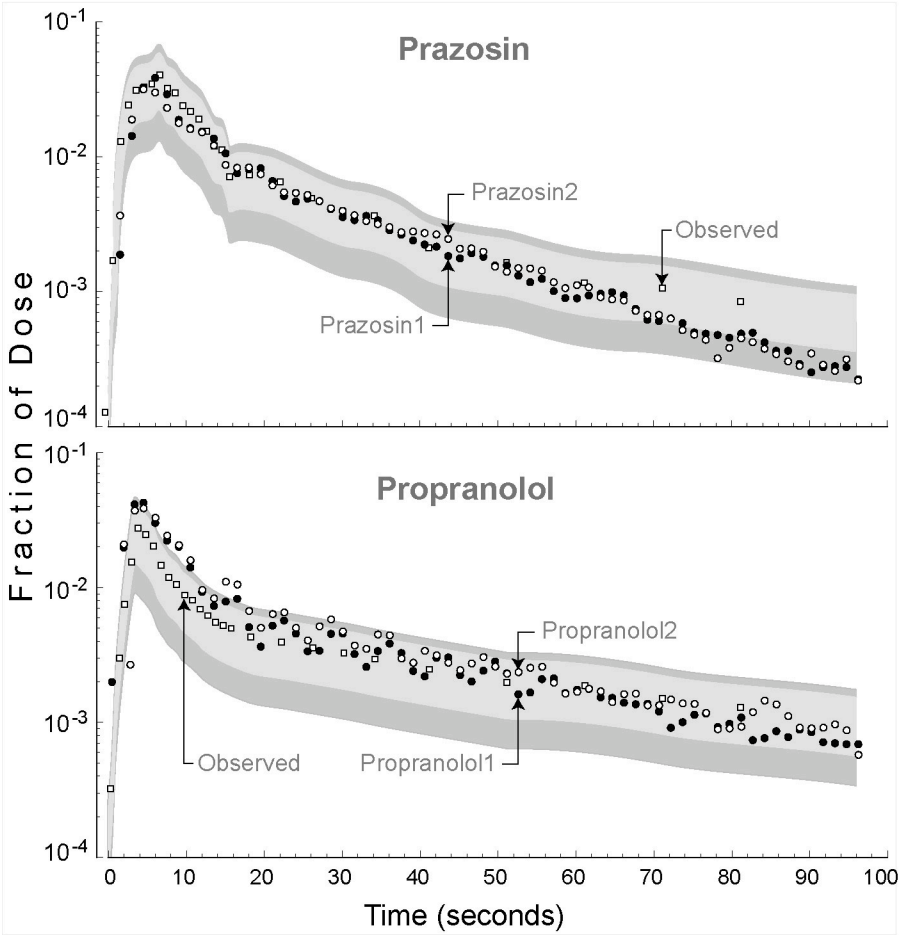

Figure S3. Expected outflow profiles for prazosin and propranolol using predicted parameter values. These semilog plots show results using the PCP-sensitive PVs in Table S2. Except as noted, the graph components are same as specified in Fig. 5.