Supplemental Material

A Bayesian Population Physiologically Based Pharmacokinetic Absorption Modeling Approach to Support Generic Drug Development: Application to Bupropion Hydrochloride Oral Dosage Forms

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1 Supplementary Data

The supplementary data include R code (**codes**) and datasets (**datasets**) that can reproduce the modeling and analyze result (in **outputs** folder) and visualize plots (in **plots** folder). All data will publicly release on GitLab after the paper published. The details and data pipelines are included in:

- **codes:** The R source code to reproduce the modeling and analyze result.
- **datasets:** The provided tidy data files.
- **MCSim:** The source fils of GNU MCSim software and the related modeling files that can conduct MCMC simulation and prediction.
- **outputs**: The files in the output folder are generated by the above R code and datasets.
- **plots:** All plots showed in the manuscript were saved with *fig{number}.jpeg* with solution of 300 dpi. The **suppl** folder includes the supplementary figures that showed below.

2 Physiologically Based Pharmacokinetic Absorption Model

2.1 Main differential equations

Two-compartment model was used to describe the quantity of drug in the central (plasma; $Q_{central}$) and peripheral (others tissues; Q_{periph}) compartments as:

$$\begin{aligned}\frac{\partial Q_{central}}{\partial t} =&(F_{portal} + F_{liver}) \cdot C_{blood,liver} - (F_{portal} + F_{liver}) \cdot C_{blood} \\ &+ \frac{V_{max,eff_{liver}} \cdot C_{u_{blood,liver}}}{K_{m,eff} + C_{u_{blood,liver}}} - \frac{V_{max,inf_{liver}} \cdot C_{u_{blood,liver}}}{K_{m,inf} + C_{u_{blood,liver}}} \\ &- K_{c2p} \cdot Q_{central} - K_{p2c} \cdot Q_{periph} - K_{elim} * Q_{central}\end{aligned} \tag{1}$$

$$\frac{\partial Q_{periph}}{\partial t} = K_{p2c} \cdot Q_{periph} - K_{c2p} \cdot Q_{central} \tag{2}$$

where F_{portal} and F_{liver} are the portal blood flow and direct arterial flow to the liver, respectively; C_{blood} is the input (arterial) blood drug concentration; $C_{blood,liver}$ is the blood concentration at the liver exit; $V_{max,inf_{liver}}$ is the Michaelis-Menten maximum rate of active drug transport from blood into liver tissue; $C_{u_{blood,liver}}$ is the concentration of unbound drug in blood at the liver exit; $K_{m,inf}$ is the Michaelis-Menten constant for active transport into tissues (influx) (assumed to be the same for all tissues); $V_{max,eff_{liver}}$ is the Michaelis-Menten maximum rate of active drug transport from liver tissue to blood; $C_{u_{liver}}$ is the concentration of unbound drug in liver tissue; $K_{m,eff}$ is the Michaelis-Menten constant for active transport out of tissues (efflux) (assumed to be the same for all tissues); K_{c2p} and K_{p2c} are the rate constants that control the exchange rate between central and peripheral compartments. K_{elim} is the elimniation rate of central compartment.

$C_{blood,liver}$ is given by:

$$C_{blood,liver} = \frac{C_{u_{blood,liver}}}{f_{u_{blood}}} \tag{3}$$

where $f_{u_{blood}}$ is the fraction of drug unbound in blood (computed as $f_{u_{plasma}}$, fraction unbound in blood plasma, divided by the blood over plasma concentration ratio r_{BP}).

$C_{u_{blood,liver}}$ is given by:

$$C_{u_{blood,liver}} = \frac{C_{u_{liver}}}{K_{puu_{liver}}} \tag{4}$$

where $K_{puu_{liver}}$ is the equilibrium ratio (partition coefficient) of unbound drug concentration in liver over unbound concentration in blood.

$C_{u_{liver}}$ is given by:

$$C_{u_{liver}} = f_{u_{liver}} \cdot C_{liver} \tag{5}$$

where $f_{u_{liver}}$ is the fraction of drug unbound in liver tissue, and C_{liver} is the total liver concentration (Q_{liver} divided by V_{liver}).

Note that the apparent liver over blood partition coefficient, PC_{liver}, is given by:

$$PC_{liver} = \frac{K_{puu_{liver}} \cdot f_{u_{blood}}}{f_{u_{liver}}} \tag{6}$$

Addition, the plasma concentration can further compute with volume of central compartment ($V_{central}$) and body weight (BW) as

$$C_{central} = \frac{Q_{central}}{V_{central} \cdot BW} \tag{7}$$

The differential equation for the quantity of drug in the liver is the sum of terms for blood transport, active transporter influx from blood, active transporter efflux from liver tissue and metabolism:

$$\begin{aligned}\frac{\partial Q_{liver}}{\partial t} =& R_{in} + F_{liver} \cdot C_{blood} - (F_{portal} + F_{liver}) \cdot C_{blood,liver} \\ &+ \frac{V_{max,inf_{liver}} \cdot C_{u_{blood,liver}}}{K_{m,inf} + C_{u_{blood,liver}}} - \frac{V_{max,eff_{liver}} \cdot C_{u_{blood,liver}}}{K_{m,eff} + C_{u_{blood,liver}}} \\ &- \frac{V_{max,met_{liver}} \cdot C_{u_{liver}}}{K_{m,met} \cdot f_{u_{liver,vitro}} + C_{u_{liver}}}\end{aligned} \tag{8}$$

where R_{in}, whose formula is given below, is the rate of input from the gut walls via the portal blood flow (F_{portal}); $V_{max,met_{liver}}$ is the Michaelis-Menten maximum rate of metabolism in liver; $K_{m,met}$ is the Michaelis-Menten constant for metabolism (assumed to be the same for all tissues); and $f_{u_{liver,vitro}}$ is the fraction of drug unbound in the in vitro system used to estimate liver metabolism and available for metabolism.

R_{in} is given by:

$$R_{in} = \sum_{i \in O} F_i \cdot C_{blood,wall_i} \tag{9}$$

where the summation is taken over the set O of gut segments (O = {stomach, duodenum, jejunum, ileum, cecum, colon}), F_i is the blood flow perfusing segment i, $C_{blood,wall_i}$ is the drug blood concentration at the exit of segment i wall. Note that the sum of the flows F_i is equal to F_{portal}.

Similarly to liver, $C_{blood,wall_i}$ is given by:

$$C_{blood,wall_i} = \frac{C_{u_{blood,wall_i}}}{f_{u_{blood}}} \tag{10}$$

$C_{u_{blood,wall_i}}$ is given by:

$$C_{u_{blood,wall_i}} = \frac{C_{u_{wall_i}}}{K_{puu_i}} \tag{11}$$

where K_{puu_i} is the equilibrium ratio (partition coefficient) of unbound drug concentration in segment i wall

over unbound concentration in blood.

$C_{u_{wall_i}}$ is given by:

$$C_{u_{wall_i}} = f_{u_i} \cdot C_{wall_i} \tag{12}$$

where f_{u_i} is the fraction of drug unbound in segment i tissues (same value assumed for wall and epithelium), and C_{wall_i} is the total segment i wall drug concentration (Q_{wall_i} divided by V_{wall_i}).

The differential equations governing drug quantity in gut walls for the various segments are:

$$\frac{\partial Q_{wall_i}}{\partial t} = F_i(C_{input} - C_{blood,wall_i}) + K_{a_i}(C_{u_{epith_i}} - K_{E/At} \cdot C_{u_{wall_i}}) \tag{13}$$

where C_{input} is the (arterial) blood concentration in input of segment i, K_{a_i} is the absorption flow in segment i, $C_{u_{epith_i}}$ is the free drug concentration in the epithelium of segment i, and $K_{E/At}$ is the wall to epithelium excretion over absorption ratio.

$C_{u_{epith_i}}$ is given by:

$$C_{u_{epith_i}} = f_{u_i} \cdot C_{epith_i} \tag{14}$$

where $C_{u_{epith_i}}$ is the total segment i epithelium drug concentration (Q_{epith_i} divided by V_{epith_i}).

For the drug quantities in epithelia, Q_{epith_i}, the differential equations are:

$$\begin{aligned}\frac{\partial Q_{epith_i}}{\partial t} =& K_{a_i}(C_{diss} - K_{E/Ae} \cdot C_{u_{epith_i}}) - K_{a_i}(C_{u_{epith_i}} - K_{E/At} \cdot C_{u_{wall_i}}) \\ &+ \frac{V_{max,inf_i} \cdot C_{diss_i}}{K_{m,inf} + C_{diss_i}} - \frac{V_{max,eff_i} \cdot C_{u_{epith_i}}}{K_{m,eff} + C_{u_{epith_i}}} \\ &- \frac{V_{max,met_i} \cdot C_{u_{epith_i}}}{K_{m,met} \cdot f_{u_{i,vitro}} + C_{u_{epith_i}}}\end{aligned} \tag{15}$$

where C_{diss_i} is the dissolved drug concentration in the lumen of segment i; $K_{E/Ae}$ is the epithelium to lumen excretion over absorption ratio in i; V_{max,inf_i} is the Michaelis-Menten maximum rate of active drug transport from lumen into epithelium in segment i; $K_{m,inf}$ is the Michaelis-Menten constant for active transport into tissues (influx) (assumed to be the same for all tissues); V_{max,eff_i} is the Michaelis-Menten maximum rate of active drug transport from epithelium tissue to lumen in segment i; $K_{m,eff}$ is the Michaelis-Menten constant for active transport out of tissues (efflux) (assumed to be the same for all tissues); V_{max,met_i} is the Michaelis-Menten maximum rate of metabolism in epithelium i; $K_{m,met}$ is the Michaelis-Menten constant for metabolism (assumed to be the same for all tissues); and $f_{u_{i,vitro}}$ is the fraction of drug unbound in the in vitro system used to estimate epithelium i metabolic parameters.

2.2 Drug dissolution equations

For the dissolved drug quantities in lumina, Q_{diss_i}, the differential equations are:

$$\begin{aligned}\frac{\partial Q_{diss_i}}{\partial t} =& R_X - K_t \cdot C_{diss_i} - K_{a_i}(C_{diss_i} - K_{E/Ae} \cdot C_{u_{epith_i}}) \\ &+ K_{diss_i}(t) \cdot Q_{undiss_i} - K_{precip} \cdot Q_{diss_i} \\ &+ \frac{V_{max,eff_i} \cdot C_{u_{epith_i}}}{K_{m,eff} + C_{u_{epith_i}}} - \frac{V_{max,inf_i} \cdot C_{diss_i}}{K_{m,inf} + C_{diss_i}}\end{aligned} \tag{16}$$

where R_X is the dissolved drug release rate in the stomach (see below), for the other gut segments R_X is zero; K_{t_i} is the intestinal transit rate in i; $K_{diss_i}(t)$ is the instantaneous drug dissolution rate in i (see next paragraph), and K_{precip} is the drug precipitation rate constant (assumed to be same in all gut segments).

The instantaneous dissolution rate constants, $K_{diss_i}(t)$ in 1/hours, are computed at any time as:

$$K_{diss_i}(t) = K_{diss}(C_{sat_i} - C_{diss_i}) \tag{17}$$

where K_{diss} is the drug baseline dissolution rate constant (in 1/microM/hours), and C_{sat_i} is the saturation concentration in segment i (see below).

For the undissolved drug quantities in lumina, Q_{undiss_i}, the differential equations are:

$$\frac{\partial Q_{undiss_i}}{\partial t} = R'_X - K_t \cdot C_{undiss_i} - K_{diss_i}(t) \cdot Q_{undiss_i} + K_{precip} \cdot Q_{diss} \tag{18}$$

In the stomach, $R'X$ is the undissolved drug release rate (see below). For the other g.i. tract segments, $R'X$ is zero. The dissolved and undissolved drug quantities excreted in the feces are given by:

$$\frac{\partial Q_{diss_{feces}}}{\partial t} = K_{t_{colon}} \cdot C_{diss_{colon}} \tag{19}$$

$$\frac{\partial Q_{undiss_{feces}}}{\partial t} = K_{t_{colon}} \cdot C_{undiss_{colon}} \tag{20}$$

2.3 Drug release models

Drug release in the stomach can take various forms. First, the drug can be released in a dissolved or undissolved form (which may then equilibrate according to equations 13 and 15). Next, the release can be immediate or delayed.

Immediate release: The rate R_X (dissolved) or R'_X (undissolved) is equal to the oral administration rate D_{rate} (a model input, in μM / hours). A bolus administration can be simulated by giving D_{rate} a high value for a short time, or by setting it to zero and setting the initial value of the state variable $Q_{diss_{stomach}}$ to the bolus dose prescribed.

Delayed release:

The delayed release form was set to Weibull-based function for release rate constant ($K_{release}$), which is given by:

$$K_{release} = \frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1} \tag{21}$$

where k is Weibull slope and λ is Weibull scale. When $k = 1$, the $K_{release}$ will be a constant and follow the first-order release. Also, in that case, we would have:

$$Rx = K_{release} \cdot Q_{remain} \tag{22}$$

which would require the following differential equation for the quantity Q_{remain} remaining to be released to the stomach at time t:

$$\frac{\partial Q_{remain}}{\partial t} = D_{rate} - R_x \tag{23}$$

2.4 Miscellaneous equations

Miscellaneous equations are used to compute various quantities of eventual interest. The quantities absorbed in each gut segment are computed by integration of the following differential:

$$\frac{\partial Q_{abs_i}}{\partial t} = K_{a_i}(C_{diss_i} - K_{E/Ae} \cdot C_{u_{epith_i}}) + \frac{V_{max,inf_i} \cdot C_{diss_i}}{K_{m,inf} + C_{diss_i}} - \frac{V_{max,eff_i} \cdot C_{u_{epith_i}}}{K_{m,eff} + C_{u_{epith_i}}} \tag{24}$$

The quantity metabolized in each gut segment is computed by integration of the following differential:

$$\frac{\partial Q_{met_i}}{\partial t} = \frac{V_{max,met_i} \cdot C_{u_{epith_i}}}{K_{m,met} \cdot f_{u_{i,vitro}} + C_{u_{epith_i}}} \tag{25}$$

The quantity reaching the portal vein at time t ($Q_{abs_{portal}}$) has the following differential:

$$\frac{\partial Q_{abs_{portal}}}{\partial t} = R_{in} \tag{26}$$

see equation 6 for the definition of R_{in}.

The instantaneous apparent rate of gut absorption is:

$$K_a = \frac{Q_{abs_{portal}}}{\sum_{i \in O} Q_{diss_i}} \tag{27}$$

The major mass balance checking equations are:

$$Q_{diss} = \sum_{i \in O} Q_{diss_i} \tag{28}$$

$$Q_{epith} = \sum_{i \in O} Q_{epith_i} \tag{29}$$

$$Q_{wall} = \sum_{i \in O} Q_{wall_i} \tag{30}$$

$$Q_{abs} = \sum_{i \in O} Q_{abs_i} \tag{31}$$

$$Q_{elim_{gut}} = \sum_{i \in O} Q_{met_i} + Q_{diss_{feces}} + Q_{undiss_{feces}} \tag{32}$$

Finally, epithelial permeability in gut segment i is given by:

$$K_{a_i} = P_{eff} \cdot SA_i \tag{33}$$

where P_{eff} is the effective permeability of gut epithelia, and SA_i the epithelial surface area of i (calculated from the lengths and radii).

3 Supplementary Tables

Table S1. Summary of distributions of the physiologically-specific parameters.

Parameter	Description	Default	Minimum	Maximum	Reference
BDM	Body mass, kg	NA	NA	NA	Observed
sc_F_total	Cardic output scaling coeficient, $L \cdot kg^{-0.75}$	15.0000	10.50000	19.50000	Perdaems et al. [2010]
f_Flow_stom	Fraction of cardiac output going to stomach, -	0.0240	0.01900	0.02900	Perdaems et al. [2010]
f_Flow_duod	Fraction of cardiac output going to duodenum, -	0.0160	0.01100	0.02100	Perdaems et al. [2010]
f_Flow_jeju	Fraction of cardiac output going to jejunum, -	0.0560	0.05100	0.06100	Perdaems et al. [2010]
f_Flow_ileum	Fraction of cardiac output going to ileum, -	0.0330	0.02800	0.03800	Perdaems et al. [2010]
f_Flow_cecum	Fraction of cardiac output going to cecum, -	0.0060	0.00100	0.01100	Perdaems et al. [2010]
f_Flow_colon	Fraction of cardiac output going to colon, -	0.0380	0.03300	0.04300	Perdaems et al. [2010]
f_Flow_liver	Fraction of cardiac output going to liver, -	0.2500	0.20000	0.30000	Perdaems et al. [2010]
f_BDM_stom	Body mass fraction of stomach, -	0.0021	0.00160	0.00260	Perdaems et al. [2010]
f_BDM_duod	Body mass fraction of duodenum, -	0.0003	0.00010	0.00050	Perdaems et al. [2010]
f_BDM_jeju	Body mass fraction of jejunum, -	0.0009	0.00040	0.00140	Perdaems et al. [2010]
f_BDM_ileum	Body mass fraction of ileum, -	0.0006	0.00010	0.00110	Perdaems et al. [2010]
f_BDM_cecum	Body mass fraction of cecum, -	0.0005	0.00010	0.00090	Perdaems et al. [2010]
f_BDM_colon	Body mass fraction of colon, -	0.0048	0.00430	0.00530	Perdaems et al. [2010]
f_BDM_liver	Body mass fraction of liver, -	0.0243	0.01390	0.02930	Perdaems et al. [2010]
f_BDM_stom_lu	Lumina as fraction of body mass in stomach, -	0.0036	0.03100	0.04100	Perdaems et al. [2010]
f_BDM_duod_lu	Lumina as fraction of body mass in duodenum, -	0.0003	0.00010	0.00100	Perdaems et al. [2010]
f_BDM_jeju_lu	Lumina as fraction of body mass in jejunum, -	0.0023	0.00180	0.00280	Perdaems et al. [2010]
f_BDM_ileum_lu	Lumina as fraction of body mass in ileum, -	0.0032	0.00270	0.00370	Perdaems et al. [2010]
f_BDM_cecum_lu	Lumina as fraction of body mass in cecum, -	0.0001	0.00010	0.00100	Perdaems et al. [2010]
f_BDM_colon_lu	Lumina as fraction of body mass in colon, -	0.0051	0.00460	0.00560	Perdaems et al. [2010]
Length_stom	Lengths of stomach, dm	2.8300	1.98100	3.67900	Ando et al. [2015]
Length_duod	Lengths of duodenum, dm	1.4100	0.98700	1.83300	Ando et al. [2015]
Length_jeju	Lengths of jejunum, dm	11.6800	8.17600	15.18400	Ando et al. [2015]
Length_ileum	Lengths of ileum, dm	17.5200	12.26400	22.77600	Ando et al. [2015]
Length_cecum	Lengths of cecum, dm	1.7000	1.19000	2.21000	Perdaems et al. [2010]

Table S1. Summary of distributions of the physiologically-specific parameters. *(continued)*

Parameter	Description	Default	Minimum	Maximum	Reference
Length_colon	Lengths of colon, dm	11.0000	7.70000	14.30000	Valentin [2002]
Radius_stom	Radius of stomach, dm	0.9670	0.67690	1.25710	Ando et al. [2015]
Radius_duod	Radius of duodenum, dm	0.1530	0.10710	0.19890	Ando et al. [2015]
Radius_jeju	Radius of jejunum, dm	0.1370	0.09590	0.17810	Ando et al. [2015]
Radius_ileum	Radius of ileum, dm	0.0980	0.06860	0.12740	Ando et al. [2015]
Radius_cecum	Radius of cecum, dm	0.3500	0.24500	0.45500	Perdaems et al. [2010]
Radius_colon	Radius of colon, dm	0.2500	0.17500	0.32500	Perdaems et al. [2010]
T12_stom_lu	Transit half-lives in stomach lumina, h	0.2500	0.10000	0.40000	Perdaems et al. [2010]
T12_duod_lu	Transit half-lives in duodenum lumina, h	0.2500	0.10000	0.40000	Perdaems et al. [2010]
T12_jeju_lu	Transit half-lives in jejunum lumina, h	1.0200	0.40800	1.63200	Perdaems et al. [2010]
T12_ileum_lu	Transit half-lives in ileum lumina, h	2.0400	0.81600	3.26400	Perdaems et al. [2010]
T12_cecum_lu	Transit half-lives in cecum lumina, h	4.5500	1.82000	7.28000	Perdaems et al. [2010]
T12_colon_lu	Transit half-lives in colon lumina, h	13.5000	5.40000	21.60000	Perdaems et al. [2010]
pH_stom	pH of stomach, -	1.7000	1.20000	2.20000	Perdaems et al. [2010]
pH_duod	pH of duodenum, -	6.0000	5.50000	6.50000	Perdaems et al. [2010]
pH_jeju	pH of jejunum, -	6.5000	6.00000	7.00000	Perdaems et al. [2010]
pH_ileum	pH of ileum, -	7.4000	6.90000	7.90000	Perdaems et al. [2010]
pH_cecum	Radius of cecum, -	5.9000	5.40000	6.40000	Perdaems et al. [2010]
pH_colon	Radius of colon, -	7.0000	6.50000	7.50000	Perdaems et al. [2010]
MicroProt_stom	Microsomal proteins of stomach, mg/g of tissue	0.0000	0.00000	10.00000	
MicroProt_duod	Microsomal proteinsof duodenum, mg/g of tissue	18.0000	13.00000	23.00000	Paine et al. [1997]
MicroProt_jeju	Microsomal proteins of jejunum, mg/g of tissue	25.0000	20.00000	30.00000	Paine et al. [1997]
MicroProt_ileum	Microsomal proteins of ileum, mg/g of tissue	4.0000	0.00000	10.00000	Paine et al. [1997]
MicroProt_cecum	Microsomal proteins of cecum, mg/g of tissue	0.0000	0.00000	10.00000	
MicroProt_colon	Microsomal proteins of colon, mg/g of tissue	0.0000	0.00000	10.00000	
MicroProt_liver	Microsomal proteins of liver, mg/g of tissue	45.0000	40.00000	50.00000	Houston et al. [2012]
H_ep	Gut epithelium thickness, dm	0.0003	0.00021	0.00039	Ando et al. [2015]

Table S2. Summary of distributions of the drug-specific parameters for bupropion hydrochloride.

Parameter	Description	Default	Minimum	Maximum	Reference
MM	Molecular mass, g/mol	2.3974e+02	NA	NA	Williams et al. [2017]
Mol_vol	Solute molar volume, ml/mole	2.2500e+02	NA	NA	Williams et al. [2017]
AB_type	Acido-basic type, -	2.0000e+00	NA	NA	Williams et al. [2017]
pKa	Acid dissociation constant	8.7500e+00	8.0e+00	9.0e+00	Takayanagi et al. [2016]
pKb	Basic dissociation constant	0.0000e+00	NA	NA	
G_immediate_d	Dosage form switches / immediate dissolved release	0.0000e+00	NA	NA	
G_immediate_u	Dosage form switches / immediate undissolved release	0.0000e+00	NA	NA	
G_delayed_d	Dosage form switches / delayed dissolved release	0.0000e+00	NA	NA	
G_delayed_u	Dosage form switches / delayed undissolved release	1.0000e+00	NA	NA	
R_type	Released type	1.0000e+00	NA	NA	
Weibull_scale	Weibull scale coefficient	1.0000e+00	1.0e-01	4.0e+00	
Weibull_slope	Weibull slope coefficient	1.0000e+00	1.0e+00	3.0e+00	
G_Radius	Galenic radius, microm	2.5000e+01	1.0e+01	1.0e+02	
G_Density	Powder density, g/ml	1.4000e+00	1.0e+00	1.8e+00	Melillo et al. [2019]
Solubility	Intrinsic water solubility, microg/L	1.0000e+05	1.0e+04	1.0e+05	Assumed
K_precip	Precipitation rate, 1/h	4.0000e+00	4.0e-01	4.0e+01	Assumed
f_Abs_stom	Absorption switches of stomach	0.0000e+00	NA	NA	Assumed
f_Abs_duod	Absorption switches of duodenum	1.0000e+00	NA	NA	Assumed
f_Abs_jeju	Absorption switches of jejunum	1.0000e+00	NA	NA	Assumed

Table S2. Summary of distributions of the drug-specific parameters for bupropion hydrochloride. *(continued)*

Parameter	Description	Default	Minimum	Maximum	Reference
f_Abs_ileum	Absorption switches of ileum	1.0000e+00	NA	NA	Assumed
f_Abs_cecum	Absorption switches of cecum	1.0000e+00	NA	NA	Assumed
f_Abs_colon	Absorption switches of colon	1.0000e+00	NA	NA	Assumed
Peff	Effective permeability of gut epithelia, dm/h	1.4500e-01	5.0e-02	3.1e-01	Melillo et al. [2019]
Ke_over_a_epit	Excretion over absorption rate constant ratios between lumen and epithelium, -	0.0000e+00	NA	NA	Assumed
Ke_over_a_tiss	Excretion over absorption rate constant ratios between epithelium and tissue, -	0.0000e+00	NA	NA	Assumed
Vmax_eff_stom	Maxumun rate of efflux from stomach, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_eff_duod	Maxumun rate of efflux from duodenum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_eff_jeju	Maxumun rate of efflux from jejunum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_eff_ileum	Maxumun rate of efflux from ileum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_eff_cecum	Maxumun rate of efflux from cecum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_eff_colon	Maxumun rate of efflux from colon, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_eff_liver	Maxumun rate of efflux from liver, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_inf_stom	Maxumun rate of active influx to stomach, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_inf_duod	Maxumun rate of active influx to duodenum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_inf_jeju	Maxumun rate of active influx to jejunum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_inf_ileum	Maxumun rate of active influx to ileum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_inf_cecum	Maxumun rate of active influx to cecum, micromole/h	0.0000e+00	NA	NA	Assumed
Vmax_inf_colon	Maxumun rate of active influx to colon, micromole/h	0.0000e+00	NA	NA	Assumed

Table S2. Summary of distributions of the drug-specific parameters for bupropion hydrochloride. *(continued)*

Parameter	Description	Default	Minimum	Maximum	Reference
Vmax_inf_liver	Maxumun rate of active influx to liver, micromole/h	0.0000e+00	NA	NA	Assumed
Km_eff	Active efflux Km, microM	1.0000e+00	NA	NA	Assumed
Km_inf	Active influx Km, microM	1.0000e+00	NA	NA	Assumed
Ratio_BP	Blood over plasma concentration ratio, -	8.2000e-01	7.2e-01	9.2e-01	Xue et al. [2018]
Fu_plasma	Fraction unbound in plasma, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_stom	Fraction unbound in stomach, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_duod	Fraction unbound in duodenum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_jeju	Fraction unbound in jejunum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_ileum	Fraction unbound in ileum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_cecum	Fraction unbound in cecum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_colon	Fraction unbound in colon, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_liver	Fraction unbound in liver, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_vitro_plasma	Fraction unbound in in-vito metabolic assay in stomach, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_vitro_stom	Fraction unbound in in-vitro metabolic assay in stomach, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_vitro_duod	Fraction unbound in in-vitro metabolic assay in duodenum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_vitro_jeju	Fraction unbound in in-vitro metabolic assay in jejunum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_vitro_ileum	Fraction unbound in in-vitro metabolic assay in ileum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_vitro_cecum	Fraction unbound in in-vitro metabolic assay in cecum, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Fu_vitro_colon	Fraction unbound in in-vitro metabolic assay in colon, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]

Table S2. Summary of distributions of the drug-specific parameters for bupropion hydrochloride. *(continued)*

Parameter	Description	Default	Minimum	Maximum	Reference
Fu_vitro_liver	Fraction unbound in in-vitro metabolic assay in liver, -	1.6000e-01	6.0e-02	2.6e-01	Xue et al. [2018]
Kpuu_stom	Partition coefficient of stomach, -	1.0000e+00	5.0e-01	5.0e+00	Assume
Kpuu_duod	Partition coefficient of duodenum, -	1.0000e+00	5.0e-01	5.0e+00	Assume
Kpuu_jeju	Partition coefficient of jejunum, -	1.0000e+00	5.0e-01	5.0e+00	Assume
Kpuu_ileum	Partition coefficient of ileum, -	1.0000e+00	5.0e-01	5.0e+00	Assume
Kpuu_cecum	Partition coefficient of cecum, -	1.0000e+00	5.0e-01	5.0e+00	Assume
Kpuu_colon	Partition coefficient of colon, -	1.0000e+00	5.0e-01	5.0e+00	Assume
Kpuu_liver	Partition coefficient of liver, -	1.0000e+00	5.0e-01	5.0e+00	Assume
V_central	Volume of central compartment, L/Kg	1.5000e+01	6.0e+00	2.4e+01	Connarn et al. [2017]
V_periph	Volume of peripheral compartment, L/Kg	3.5000e+01	1.4e+01	5.6e+01	Connarn et al. [2017]
Kc2p	Transfer rate constants from central to peripheral compartment, 1/h	1.0000e-01	1.0e-02	1.9e-01	Connarn et al. [2017]
Kp2c	Transfer rate constants from peripheral to central compartment, 1/h	4.0000e-02	4.0e-03	7.6e-02	Connarn et al. [2017]
Kelim	Elimination rate constant from central compartment, 1/h	0.0000e+00	NA	NA	Assumed
Vmax_met_vitro_intestine	Metabolism Vmax in intestine, micromole/min/mg microsomal proteins	2.6000e-05	1.0e-03	1.0e-05	Connarn et al. [2015]
Vmax_met_vitro_liver	Metabolism Vmax in liver, micromole/min/mg microsomal proteins	1.0000e-04	1.0e-03	1.0e-05	Connarn et al. [2015]
Km_met_vitro_intestine	Metabolism Km in intestine, micromole/min/mg microsomal proteins	5.7340e+02	NA	NA	Connarn et al. [2015]
Km_met_vitro_liver	Metabolism Km in liver, micromole/min/mg microsomal proteins	2.6570e+02	NA	NA	Connarn et al. [2015]

Table S3. Summary of stage I Weibull parameters posteriors, calibrated by MCMC simulations.

Parameter	Q5	Q50	Q95	Mean	SD	n_eff	Rhat
Weibull_scale_IR75	0.1408	0.1651	0.1912	0.1654	0.0152	1903	1.0045
Weibull_scale_IR100	0.1486	0.1719	0.1955	0.1719	0.0144	1969	1.0019
Weibull_scale_SR100	2.4004	2.7565	3.1307	2.7565	0.2228	1934	1.0018
Weibull_scale_SR150	2.6947	3.0675	3.4599	3.0693	0.2361	2349	1.0011
Weibull_scale_ER150	2.4570	2.8115	3.2456	2.8288	0.2329	331	1.0057
Weibull_slope_ER150	1.4709	1.7419	2.0707	1.7540	0.1811	340	1.0054
Weibull_scale_ER300	2.6432	3.0440	3.5052	3.0546	0.2633	263	1.0249
Weibull_slope_ER300	1.5000	1.7580	2.0639	1.7689	0.1793	268	1.0244

Table S4. Stage II prior parameter distributions used.

Parameter	Distribution	Mean	SD	Lower.bound	Upper.bound	Notes
G_Radius	Uniform	NA	NA	10.00000	100.000	Vague prior
Peff	Uniform	NA	NA	0.05000	0.310	Melillo et al. [2019]
Fu_plasma	Truncated Normal	0.1600	0.032	0.06400	0.256	20% CV with truncation 3 SD
Fu_vitro_liver	Truncated Normal	0.1600	0.032	0.06400	0.256	20% CV with truncation 3 SD
Kpuu_liver	LogUniform	NA	NA	0.50000	5.000	Vague prior
Vmax_met_vitro_liver	Truncated LogNormal	0.0001	2.000	0.00001	0.001	Connarn et al. [2015]
V_central_LKg	Truncated Normal	15.0000	4.500	1.50000	28.500	Connarn et al. [2015]
Kc2p	Truncated Normal	0.1000	0.030	0.01000	0.190	Connarn et al. [2015]
Kp2c	Truncated Normal	0.0400	0.120	0.00400	0.076	Connarn et al. [2015]
Weibull_scale_IR	Truncated Normal	0.1700	0.034	0.06800	0.272	Posterior of stage I
Weibull_scale_SR	Truncated Normal	3.0000	0.600	1.20000	4.800	Posterior of stage I
Weibull_scale_ER	Truncated Normal	3.0000	0.600	1.20000	4.800	Posterior of stage I
Weibull_slope_ER	Truncated Normal	1.8000	0.180	1.26000	2.340	Posterior of stage I

Table S5. Summary of stage II parameters posteriors, calibrated by MCMC simulations.

Parameter	Q5	Q50	Q95	Mean	SD	n_eff	Rhat
G_Radius	11.0467	21.9547	66.0922	27.9249	17.7630	889	1.0064
Peff	0.2493	0.2926	0.3087	0.2877	0.0192	798	1.0104
Fu_plasma	0.1672	0.2018	0.2389	0.2021	0.0217	1122	1.0036
Fu_vitro_liver	0.0645	0.0692	0.0837	0.0711	0.0069	1159	1.0037
Kpuu_liver	3.8220	4.6248	4.9695	4.5388	0.3663	2228	1.0009
Vmax_met_vitro_liver	0.0008	0.0009	0.0010	0.0009	0.0001	2532	1.0030
V_central_LKg	3.9710	4.6953	5.4976	4.7076	0.4684	1381	1.0033
Kc2p	0.1539	0.1770	0.1886	0.1748	0.0108	636	1.0095
Kp2c	0.0222	0.0375	0.0548	0.0379	0.0100	183	1.0196
Weibull_scale_IR	0.1247	0.1736	0.2246	0.1741	0.0303	10783	1.0008
Weibull_scale_SR	1.2020	1.2271	1.3168	1.2392	0.0407	1668	1.0117
Weibull_scale_ER	1.4522	2.0442	2.9828	2.1054	0.4619	7587	1.0013
Weibull_slope_ER	1.4930	1.7779	2.0774	1.7802	0.1767	10851	1.0000
Vr_G_Radius	0.0158	0.2064	0.6001	0.2437	0.1836	1636	1.0059
Vr_Peff	0.0190	0.2062	0.5873	0.2425	0.1826	2612	1.0050
Vr_Fu_plasma	0.0049	0.0606	0.2485	0.0841	0.0834	968	1.0029
Vr_Fu_vitro_liver	0.0015	0.0211	0.1488	0.0421	0.0591	611	1.0093
Vr_Kpuu_liver	0.0034	0.0319	0.1626	0.0513	0.0572	966	1.0028
Vr_Vmax_met_vitro_liver	0.0132	0.2002	0.5866	0.2382	0.1831	1928	1.0087
Vr_V_central_LKg	0.0213	0.2050	0.5961	0.2438	0.1834	3062	1.0004
Vr_Kc2p	0.0230	0.2063	0.5958	0.2441	0.1815	3103	1.0010
Vr_Kp2c	0.0202	0.1980	0.5843	0.2366	0.1804	2852	1.0083
Vr_Weibull_scale_IR	0.1770	0.3877	0.7254	0.4118	0.1705	11851	0.9998
Vr_Weibull_scale_SR	0.0001	0.0025	0.0284	0.0067	0.0120	1117	1.0318
Vr_Weibull_scale_ER	0.0922	0.2782	0.6557	0.3137	0.1756	7664	1.0007
Vr_Weibull_slope_ER	0.0562	0.2528	0.6190	0.2827	0.1775	12292	1.0001
Va_Peff	0.0019	0.0333	0.1645	0.0531	0.0549	219	1.0487
Va_Vmax_met_vitro_liver	0.0436	0.0995	0.1743	0.1029	0.0400	1446	1.0071

Table S5. Summary of stage II parameters posteriors, calibrated by MCMC simulations. *(continued)*

Parameter	Q5	Q50	Q95	Mean	SD	n_eff	Rhat
Va_V_central_LKg	0.2570	0.3309	0.4233	0.3344	0.0509	8066	1.0003
Va_Kc2p	0.0007	0.0093	0.0531	0.0160	0.0194	321	1.0070
Va_Kp2c	0.0110	0.0688	0.1967	0.0818	0.0592	698	1.0176
Ve_C_central	18.6373	19.5281	20.4864	19.5412	0.5633	8991	1.0002

Table S6. Comparison of PK parameters from calibration, validation and simulation groups

Formulation	Calibation	Validation	Simulation
IR 75			
Cmax	94.5 [35.5]	83.0 [43.0]	52.0 [66.9]
Tmax	1.00 [0.750, 6.00]	1.00 [0.500, 4.00]	1.50 [1.00, 1.50]
AUC	439 [42.6]	405 [34.4]	438 [41.3]
IR 100			
Cmax	113 [61.2]	130 [34.6]	70.2 [67.0]
Tmax	1.00 [0.500, 3.00]	1.00 [1.00, 4.00]	1.50 [1.00, 1.50]
AUC	612 [66.2]	540 [26.9]	591 [41.3]
SR 100			
Cmax	64.0 [36.9]	48.6 [53.1]	49.0 [62.3]
Tmax	1.50 [0.500, 4.00]	1.50 [0.500, 3.00]	2.00 [2.00, 3.00]
AUC	366 [50.2]	252 [40.9]	581 [41.2]
SR 100			
Cmax	68.5 [61.7]	72.0 [47.1]	74.4 [62.5]
Tmax	1.50 [0.500, 6.00]	1.50 [0.500, 6.00]	2.00 [2.00, 3.00]
AUC	456 [73.1]	406 [53.2]	881 [41.3]
ER 150			
Cmax	53.3 [69.0]	52.7 [46.2]	67.8 [64.0]
Tmax	3.00 [1.50, 6.00]	2.00 [1.50, 6.00]	4.00 [2.00, 6.00]
AUC	648 [65.0]	527 [49.6]	883 [41.3]
ER 300			
Cmax	96.1 [62.5]	108 [37.2]	139 [64.7]
Tmax	3.00 [1.50, 8.00]	2.00 [1.00, 4.00]	4.00 [2.00, 6.00]
AUC	1090 [57.2]	1170 [37.9]	1810 [41.5]

Note:
The Cmax and AUC are represented by geometric mean and geometric coefficient of variation. The Tmax is represented by median and range

4 Supplementary Figures

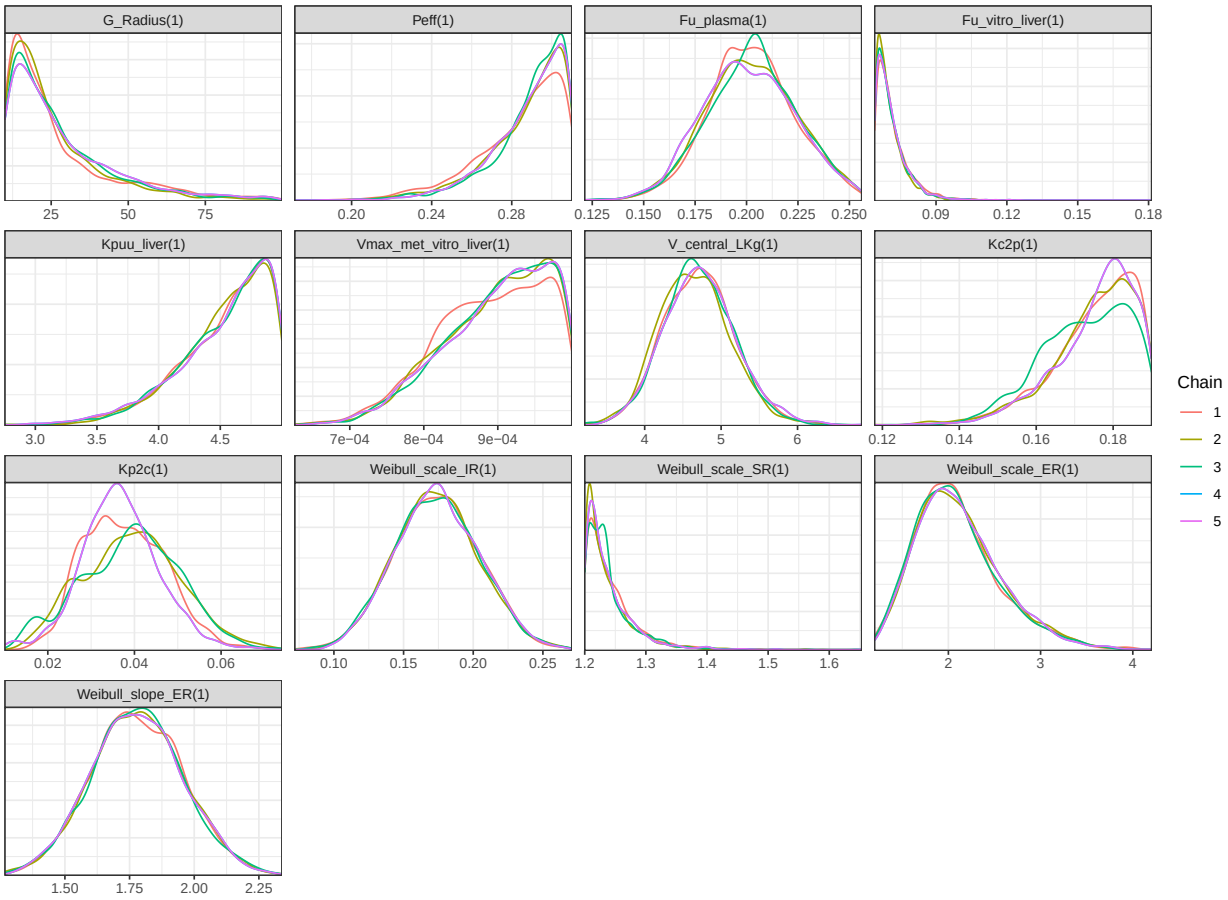

Figure S1. Marginal posterior distributions of the population mean from each simulation.

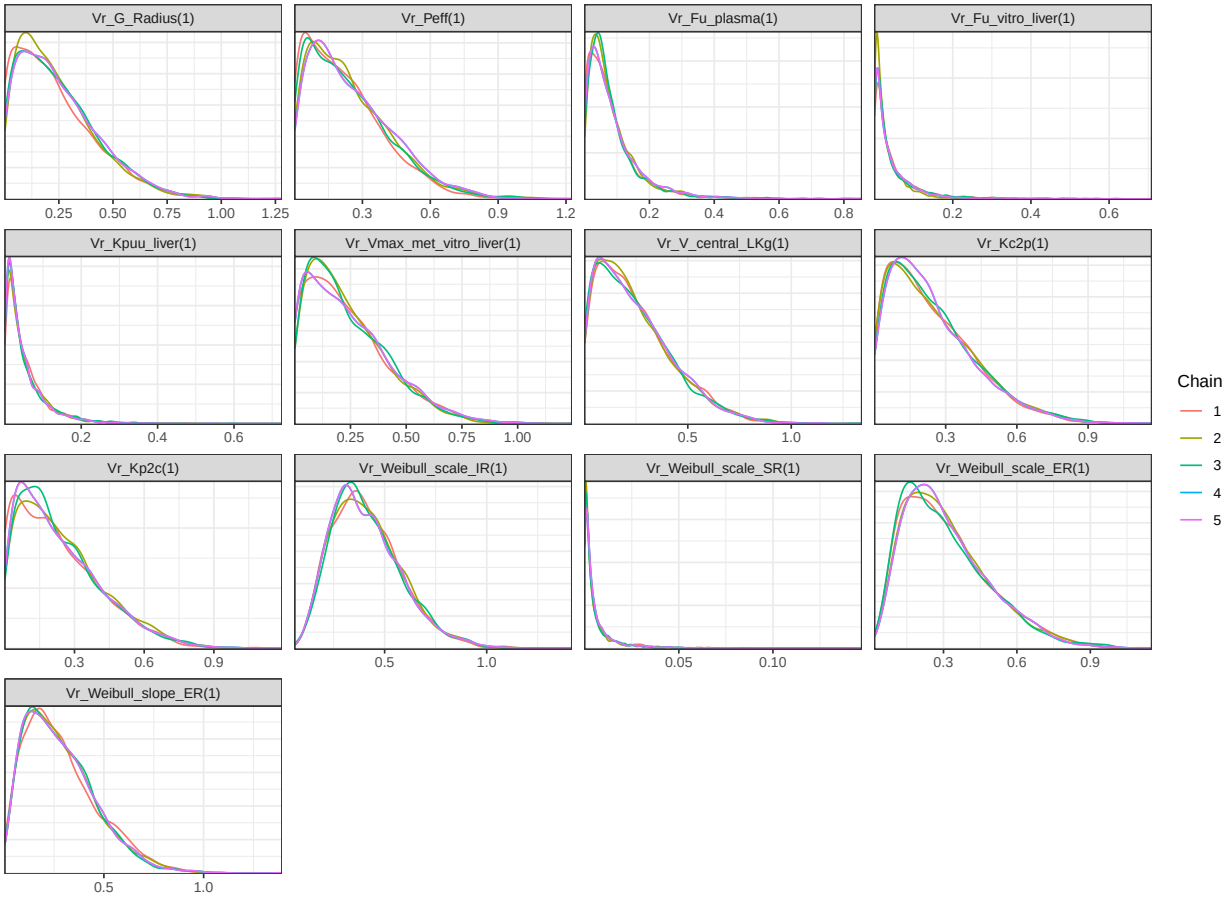

Figure S2. Marginal posterior distributions of the population inter-variance from each simulation.

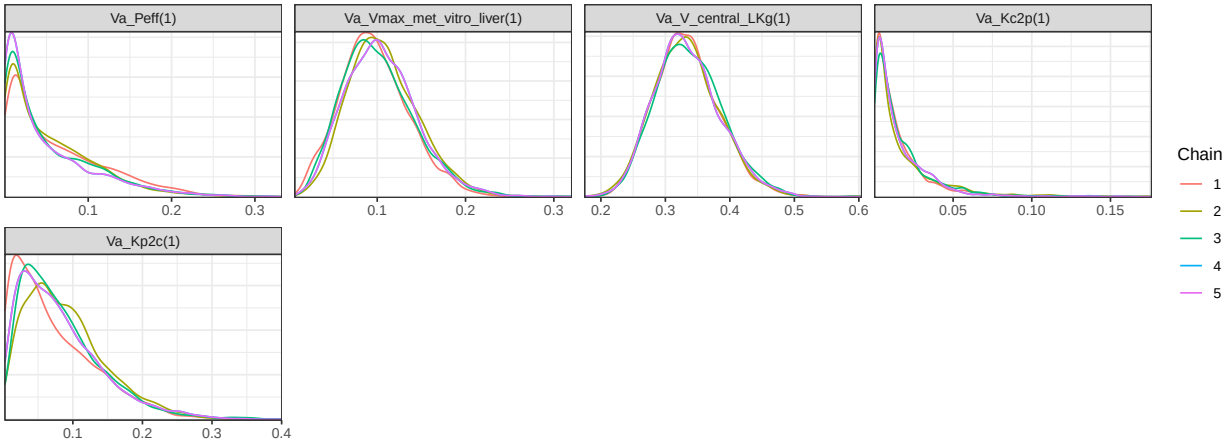

Figure S3. Marginal posterior distributions of the population intra-variance from each simulation.

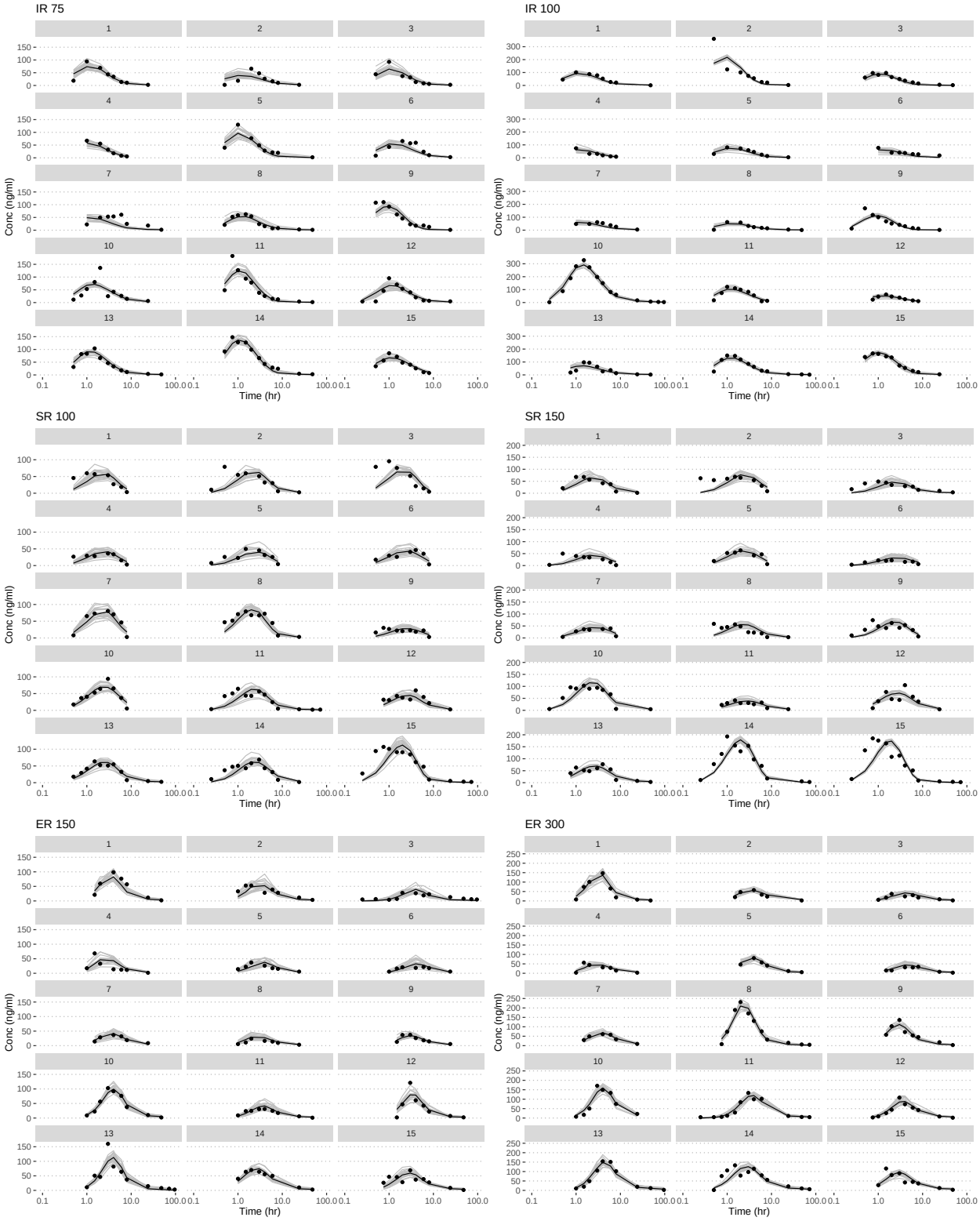

Figure S4. Posterior fits of the inter- and intra-individual variability data on plasma concentration in 15 subjects.

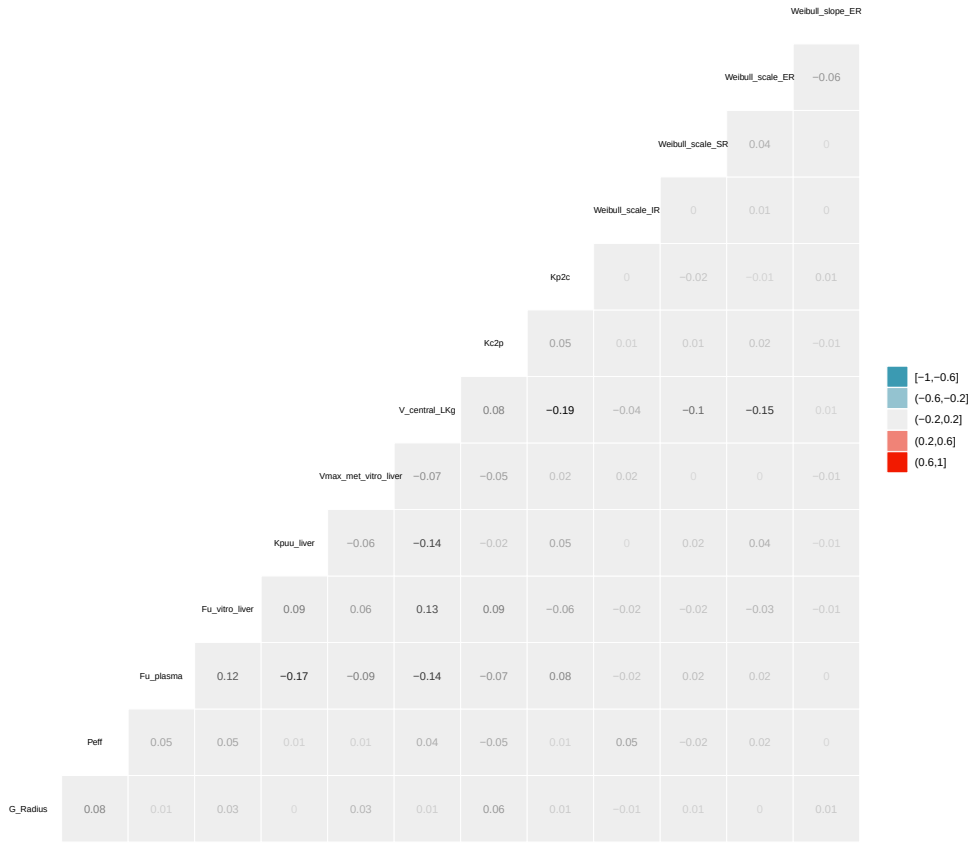

Figure S5. The correlation matrix between posterior parameter values.

Session Information

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R version 4.1.0 (2021-05-18)

Platform: x86_64-pc-linux-gnu (64-bit)

Running under: Ubuntu 20.04.2 LTS


Matrix products: default

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LAPACK: /usr/lib/x86_64-linux-gnu/atlas/liblapack.so.3.10.3


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attached base packages:

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[8] base


other attached packages:

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loaded via a namespace (and not attached):
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