Supplemental Material

The model contains venous, arterial and portal blood pools, as well as the following organs: kidney, heart, gonads, brain, muscle, adipose, bone, skin, lung, liver, spleen, pancreas, stomach, small intestine and large intestine. For all organs (subscript 'org'), differential mass balance equations exist for the sub-compartments of red blood cells (subscript 'rbc'), plasma and interstitial space (subscript 'int') and cellular space (subscript 'cell').

For non-eliminating organs:

Red blood cells

$$V_{rbc\_org} \cdot \frac{dC_{rbc\_org}}{dt} = Q_{org} \cdot HCT \cdot (C_{rbc\_art} - C_{rbc\_org}) + PS_{rbc\_org} \cdot f_u \cdot \left(C_{int\_org} - \frac{C_{rbc\_org}}{K_{rbc}} \right)$$

where $V_{rbc\_org} = f_{vas\_org} \cdot V_{org} \cdot HCT$ and $PS_{rbc\_org} = PS_{rbc\_ven} \cdot f_{vas\_org} \cdot V_{org} \cdot HCT$

Plasma + interstitial

$$V_{int\_org} \cdot \frac{dC_{int\_org}}{dt} = Q_{org} \cdot (1 - HCT) \cdot (C_{pls\_art} - C_{int\_org}) - PS_{rbc\_org} \cdot f_u \cdot \left(C_{int\_org} - \frac{C_{rbc\_org}}{K_{rbc}} \right) - PS_{cell\_org} \cdot f_u \cdot \left(C_{int\_org} - \frac{C_{cell\_org}}{K_{org}} \right)$$

where $V_{int\_org} = V_{org} \cdot \left[f_{int\_org} + f_{vas\_org} \cdot (1 - HCT) \right]$

Cellular

$$V_{cell\_org} \cdot \frac{dC_{cell\_org}}{dt} = PS_{cell\_org} \cdot f_u \cdot \left(C_{int\_org} - \frac{C_{cell\_org}}{K_{org}} \right)$$

where $V_{cell\_org} = f_{cell\_org} \cdot V_{org}$

For liver:

Red blood cells

$$V_{rbc\_liv} \cdot \frac{dC_{rbc\_liv}}{dt} = HCT \cdot (Q_{liv} \cdot C_{rbc\_art} + Q_{pv} \cdot C_{rbc\_pv}) - (Q_{liv} + Q_{pv}) \cdot HCT \cdot C_{rbc\_liv} + PS_{rbc\_liv} \cdot f_u \cdot \left(C_{int\_liv} - \frac{C_{rbc\_liv}}{K_{rbc}} \right)$$

Plasma + interstitial

$$V_{int\_liv} \cdot \frac{dC_{int\_liv}}{dt} = (1 - HCT) \cdot (Q_{liv} \cdot C_{pls\_art} + Q_{pv} \cdot C_{pls\_pv}) - (Q_{liv} + Q_{pv}) \cdot (1 - HCT) \cdot C_{int\_liv} - PS_{rbc\_liv} \cdot f_u \cdot \left(C_{int\_liv} - \frac{C_{rbc\_liv}}{K_{rbc}} \right) - PS_{cell\_liv} \cdot f_u \cdot \left(C_{int\_liv} - \frac{C_{cell\_liv}}{K_{liv}} \right)$$

Cellular

$$V_{cell\_liv} \cdot \frac{dC_{cell\_liv}}{dt} = PS_{cell\_liv} \cdot f_u \cdot \left(C_{int\_liv} - \frac{C_{cell\_liv}}{K_{liv}} \right) - \frac{CL_{BPA\_liv} \cdot C_{cell\_liv\_BPA} \cdot f_{u\_BPA}}{K_{liv\_BPA}}$$

where CL_{BPA_liv} is the intrinsic clearance of BPA and is calculated from the plasma clearance of BPA using the well stirred liver model. This clearance term is positive in the cellular compartment of the BPA-Glu sub-model and represents the only input function to the BPA-Glu sub-model.

For kidney in BPA_Glu submodel to incorporate renal plasma clearance (CL_{pls_kid}):

Plasma + interstitial

$$V_{int\_org} \cdot \frac{dC_{int\_kid}}{dt} = Q_{kid} \cdot (1 - HCT) \cdot (C_{pls\_art} - C_{int\_kid})$$

$$- PS_{rbc\_kid} \cdot f_u \cdot \left(C_{int\_kid} - \frac{C_{rbc\_kid}}{K_{rbc}} \right)$$
$$- PS_{cell\_kid} \cdot f_u \cdot \left(C_{int\_kid} - \frac{C_{cell\_kid}}{K_{kid}} \right)$$
$$- CL_{kid} \cdot C_{int\_kid} \cdot f_u$$

where $CL_{kid} = \frac{CL_{pls\_kid} \cdot Q_{kid} \cdot (1 - HCT)}{f_u \cdot \left[Q_{kid} \cdot (1 - HCT) - CL_{pls\_kid} \right]}$

For lung:

Red blood cells

$$V_{rbc\_lung} \cdot \frac{dC_{rbc\_lung}}{dt} = Q_{lung} \cdot HCT \cdot (C_{rbc\_ven} - C_{rbc\_lung}) + PS_{rbc\_lung} \cdot f_u \cdot \left(C_{int\_lung} - \frac{C_{rbc\_lung}}{K_{rbc}} \right)$$

Plasma + interstial

$$V_{int\_lung} \cdot \frac{dC_{int\_lung}}{dt} = Q_{lung} \cdot (1 - HCT) \cdot (C_{pls\_ven} - C_{int\_lung}) - PS_{rbc\_lung} \cdot f_u \cdot \left(C_{int\_lung} - \frac{C_{rbc\_lung}}{K_{rbc}} \right) - PS_{cell\_lung} \cdot f_u \cdot \left(C_{int\_lung} - \frac{C_{cell\_lung}}{K_{lung}} \right)$$

where Q_{lung} is the addition of all blood flows except Q_{pv} and equals cardiac output.

Cellular

$$V_{cell\_lung} \cdot \frac{dC_{cell\_lung}}{dt} = PS_{cell\_lung} \cdot f_u \cdot \left(C_{int\_lung} - \frac{C_{cell\_lung}}{K_{lung}} \right)$$

For Portal Vein:

Red blood cells

$$\mathrm{HCT}\cdot V_{pv}\cdot\frac{dC_{rbc\_pv}}{dt}=\sum_{org}Q_{org}\cdot\mathrm{HCT}\cdot C_{rbc\_org}-Q_{pv}\cdot\mathrm{HCT}\cdot C_{rbc\_pv}+PS_{rbc\_pv}\cdot f_u\cdot\left(C_{pls\_pv}-\frac{C_{rbc\_pv}}{K_{rbc}}\right)$$

where $org\in\{sto, smint, lgint, spl, pan\}$

Plasma

$$(1-\mathrm{HCT})\cdot V_{pv}\cdot\frac{dC_{pls\_pv}}{dt}=\sum_{org}Q_{org}\cdot(1-\mathrm{HCT})\cdot C_{int\_org}-Q_{pv}\cdot(1-\mathrm{HCT})\cdot C_{pls\_pv}-PS_{rbc\_pv}\cdot f_u\cdot\left(C_{pls\_pv}-\frac{C_{rbc\_pv}}{K_{rbc}}\right)+\text{input function from gastrointestinal model}$$

where $org\in\{sto, smint, lgint, spl, pan\}$

For venous blood:

Blood cells

$$\mathrm{HCT}\cdot V_{ven}\cdot\frac{dC_{rbc\_ven}}{dt}=\sum_{org}Q_{org}\cdot\mathrm{HCT}\cdot C_{rbc\_org}+(Q_{liv}+Q_{pv})\cdot\mathrm{HCT}\cdot C_{rbc\_liv}+PS_{rbc\_ven}\cdot f_u\cdot\left(C_{pls\_ven}-\frac{C_{rbc\_ven}}{K_{rbc}}\right)-Q_{lung}\cdot\mathrm{HCT}\cdot C_{rbc\_ven}$$

where $org\in\{kid, hrt, gon, brn, mus, adi, bone, skin\}$

Plasma

$$(1-\mathrm{HCT})\cdot V_{ven}\cdot\frac{dC_{pls\_ven}}{dt}=\sum_{org}Q_{org}\cdot(1-\mathrm{HCT})\cdot C_{int\_org}+(Q_{liv}+Q_{pv})\cdot(1-\mathrm{HCT})\cdot C_{int\_liv}+PS_{rbc\_ven}\cdot f_u\cdot\left(C_{pls\_ven}-\frac{C_{rbc\_ven}}{K_{rbc}}\right)$$

$$- Q_{lung} \cdot (1 - HCT) \cdot C_{pls\_ven}$$

where $org \in \{kid, hrt, gon, brn, mus, adi, bone, skin\}$

For arterial blood:

Blood cells

$$HCT \cdot V_{art} \cdot \frac{dC_{rbc\_art}}{dt} = -\sum_{org} Q_{org} \cdot HCT \cdot C_{rbc\_art} + Q_{lung} \cdot HCT \cdot C_{rbc\_lung} + PS_{rbc\_art} \cdot f_u \cdot \left(C_{pls\_art} - \frac{C_{rbc\_art}}{K_{rbc}} \right)$$

where $org \in \{kid, hrt, gon, brn, mus, adi, bone, skin, liv, sto, smint, lgint, spl, pan\}$

Plasma

$$(1 - HCT) \cdot V_{art} \cdot \frac{dC_{pls\_art}}{dt} = -\sum_{org} Q_{org} \cdot (1 - HCT) \cdot C_{pls\_art} + Q_{lung} \cdot (1 - HCT) \cdot C_{int\_lung} - PS_{rbc\_art} \cdot f_u \cdot \left(C_{pls\_art} - \frac{C_{rbc\_art}}{K_{rbc}} \right)$$

where $org \in \{kid, hrt, gon, brn, mus, adi, bone, skin, liv, sto, smint, lgint, spl, pan\}$

Definitions:
Organs: kid=kidney, hrt=heart, gon=gonads, brn=brain, mus=muscle, adi=adipose, bone=bone, skin=skin, liv=liver, lung=lung, sto=stomach, smint=small intestine, lgint=large intestine, spl=spleen, pan=pancreas

Vasculature: ven=venous, art=arterial, pv=portal vein, pls=plasma

Physiology parameters: HCT=hematocrit, V=volume, Q=blood flow, C=concentration, K=partition coefficient, PS=permeability x surface area product, f_u=fraction unbound in plasma, f_{vas}=fraction vascular in organ, f_{int}=fraction interstitial in organ, f_{cell}=fraction cellular in organ