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Introduction

- **Physiologically-based pharmacokinetic (PBPK)** model are powerful tools for the estimation of first-pass metabolism [1,2].
- **Limitations of PBPK** models for estimating parameters is their high complexity and long run times [1].
- The extended well-stirred liver model, adequately characterized hepatic bioavailability (F_H) [3]. The **Q_{gut} model** is used to estimate gut wall bioavailability (F_G) [4]. However, it has limited generalizability to drugs with low permeability.

Aims

- **Characterize F_G and F_H** through the estimation of intestinal ($CL_{int,G}$) and hepatic ($CL_{int,H}$) intrinsic clearance using minimal PBPK models.
- **Generalized Q_{gut} (gQ_{gut}) model derivation** to be applied to drug with varied physicochemical properties.

Methods

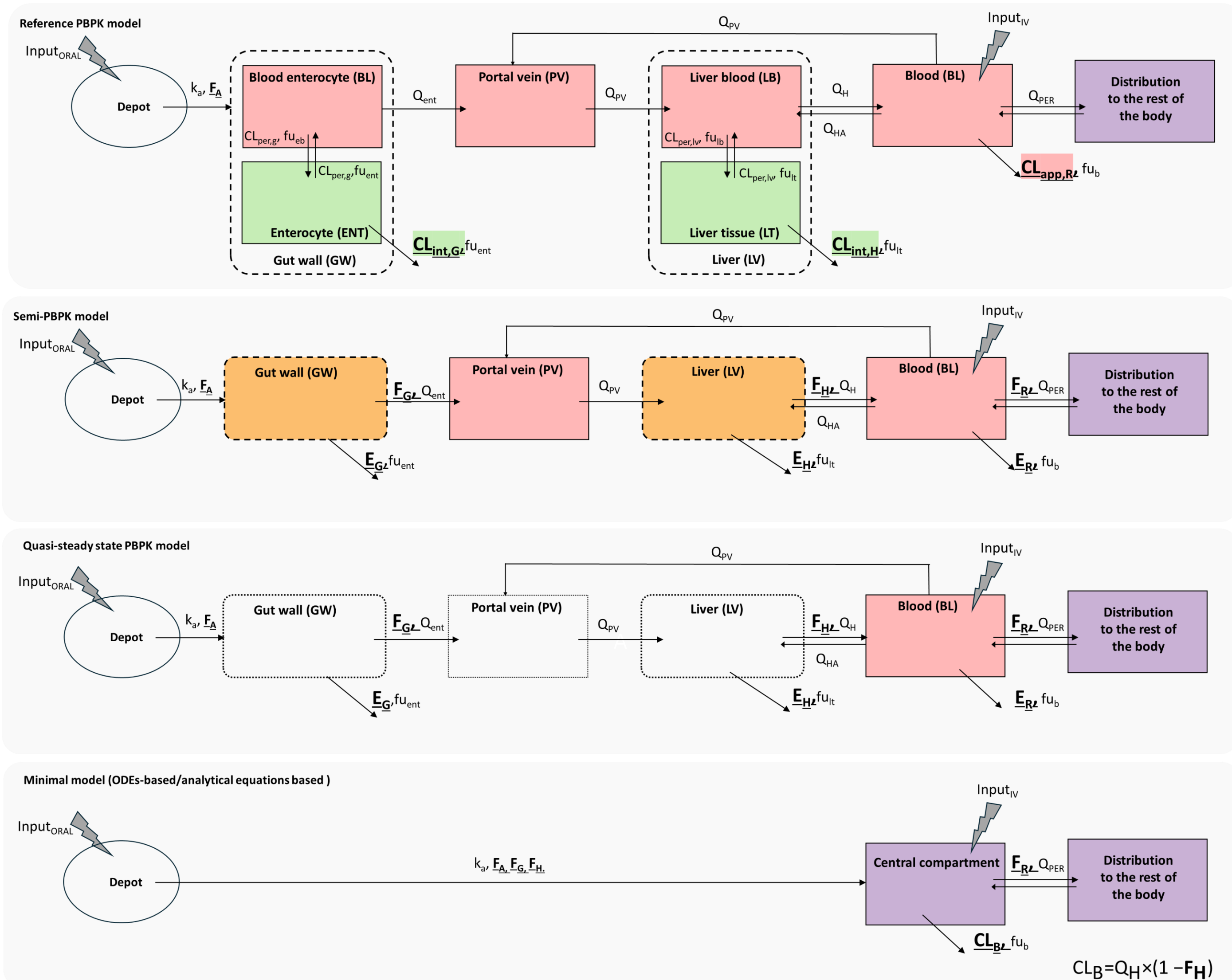


Figure 1. Schematic representation of reference PBPK models (references and model reductions) describing first-pass metabolism after oral and iv administration. F_G , E_G , F_H and E_H are defined as in equations 1-4. Highlighted parameters are estimated and non-highlighted parameters are fixed to their physiological value in adult population.

- The reference PBPK model was built on a previous framework [5,6] (Fig. 1)
- Physiological parameters are taken from the literature [5,6].
- Assumptions include: (i) no active drug transport mechanisms and (ii) unbound concentrations drive distribution and metabolism

Eq 1 (generalized F_G):
$$gF_G = \frac{gQ_{gut}}{CL_{int,G} \times fu_{eb} + gQ_{gut}}$$

Equation 2 (F_H):
$$F_H = \frac{Q_H \times (CL_{int,H} + CL_{per,H})}{CL_{int,H} \times CL_{per,H} \times fu_{lb} + Q_H \times (CL_{int,H} + CL_{per,H})}$$

Equation 3 (Gut wall extraction ratio (E_G)):
$$E_G = 1 - gF_G$$

Equation 4 (Hepatic extraction ratio (E_H)):
$$E_H = 1 - F_H$$

Midazolam case example

- Plasma concentrations of 12 healthy individuals following both oral and intravenous administration were available.
- $CL_{int,G}$, $CL_{int,H}$, V_{blood} , and K_a were estimated using population PK analysis in NONMEM with the five model structures presented in Figure 1.

Results

Equation 5 (gF_G with gQ_{gut}):
$$gF_G = \frac{Q_{ent} \times CL_{per,G}}{CL_{int,G} \times CL_{per,G} \times fu_{eb} + CL_{int,G} \times Q_{ent} + CL_{per,G} \times Q_{ent}}$$

- Contrast to previous results [3], fu_{eb} (fraction unbound in blood) remains a relevant parameter whereas fu_{ent} does not.

Midazolam case example

- Data is best described by a first-order absorption model coupled to a linear three-compartment model disposition model (Fig. 2).
- Across all models (Figure 1), estimated parameters, relative standard errors, and objective function values were similar (Table 1). Individual parameter estimates were consistent across models ($R^2 > 0.99$).
- Difference across model parameterization was computation efficiency (running times) (Table 1).

Figure 2. Goodness-of-fit plots: Observed versus population or individual predictions, conditional weighted residuals versus time and versus population predictions

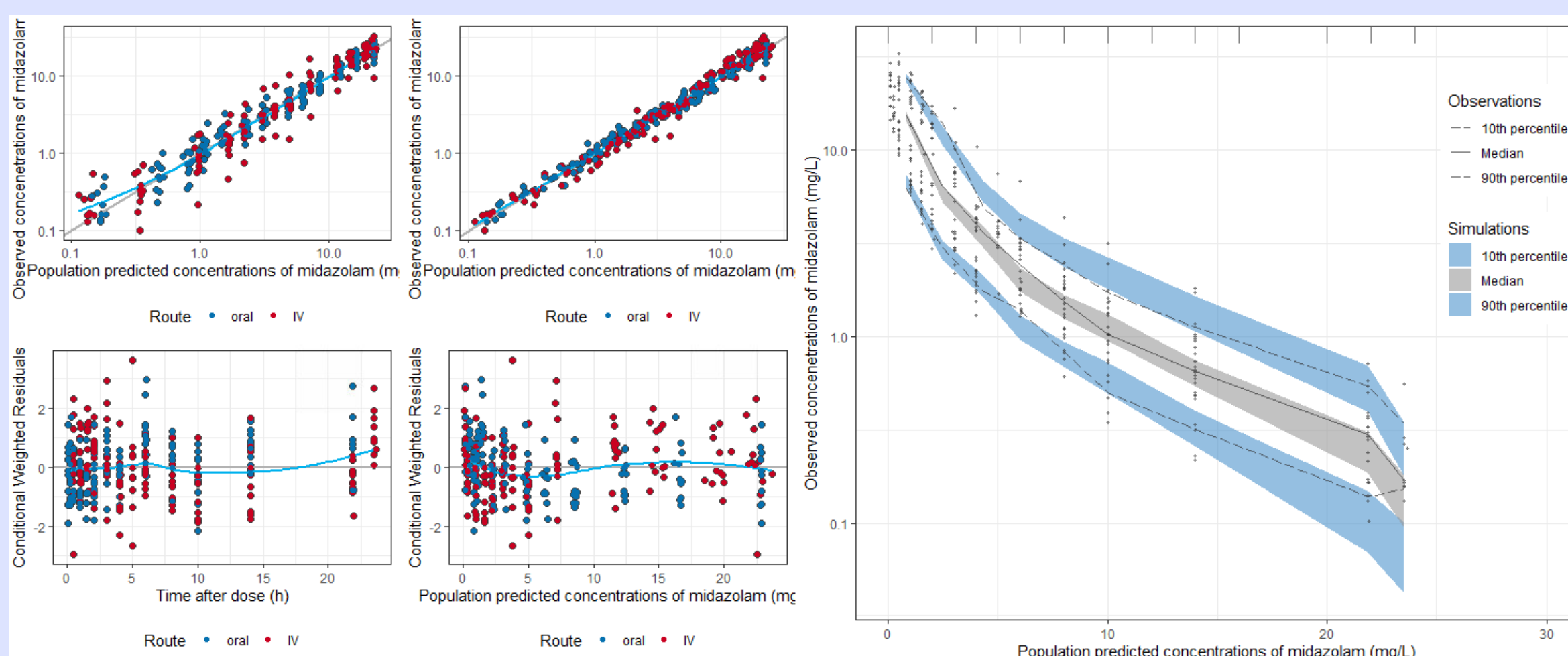


Table 1. Parameter estimates for the different PBPK models.

	Reference	Model A	Model B	Model C	Model D
OFV	104.31	103.23	108.57	109.25	109.25
Running times (s) for subproblem					
Estimation	6792.8	70.7	101.7	3.90	1.33
Covariance	9635.0	88.8	66.8	4.47	0.97
Population parameters (RSE%)					
$CL_{int,H}$ (L/h)	604 (8)	603 (8)	603 (8)	603 (8)	603 (8)
$CL_{int,G}$ (L/h)	11.2 (7)	11.3 (7)	10.9 (7)	10.9 (7)	10.9 (7)
Vc (L)	21.3 (8)	19.5 (9)	22.9 (8)	21.6 (8)	21.6 (8)
V2 (L)	39.7 (9)	39.6 (9)	39.6 (9)	39.6 (9)	39.6 (9)
V3 (L)	10.8 (18)	11.5 (17)	10.2 (20)	10.3 (20)	10.3 (20)
KA (1/h)	2.9 (6)	3.2 (7)	2.6 (6)	2.6 (6)	2.6 (6)
Q (L/h)	10.3 (9)	10.3 (9)	10.3 (9)	10.3 (9)	10.3 (9)
Q2 (L/h)	39.2 (29)	42.1 (27)	37.7 (34)	37.9 (35)	37.9 (35)
Inter-individual variability (IIV)					
IIV $CL_{int,H}$	0.24 (25)	0.24 (25)	0.24 (25)	0.24 (25)	0.24 (25)
IIV V2	0.22 (21)	0.22 (21)	0.22 (21)	0.22 (21)	0.22 (21)
Proportional error (%)	0.19 (7)	0.19 (7)	0.19 (7)	0.19 (7)	0.19 (7)

OFV: Objective function value; RSE: Relative Standard Error, IIV: Inter-individual variability

Conclusions

- PBPK models can be reduced to analytical PBPK without compromising physiological relevance
- The ODE-based approaches provide a mechanistic foundation, while the analytical form (applicable to linear kinetics) significantly reduce computation demand.
- The proposed gQ_{gut} enhances applicability to drugs with varied physicochemical properties.