

# Illustrative example (Midazolam)

Shan Pan  
Vittal Shivva  
Stephen Duffull

# Original midazolam PK model

Dosing: 5 mg intravenous bolus

Sample collection from central

Sampling time of interest: till 6 h

Literature reported parameter values:

$$CL = 0.36 \text{ L} \cdot \text{min}^{-1}$$

$$Q = 1.31 \text{ L} \cdot \text{min}^{-1}$$

$$Q_2 = 0.15 \text{ L} \cdot \text{min}^{-1}$$

$$V_1 = 36.4 \text{ L}$$

$$V_2 = 76.6 \text{ L}$$

$$V_3 = 76.6 \text{ L}$$

**Reparameterised**

$$k_{10} = 0.010 \text{ min}^{-1}$$

$$k_{12} = 0.036 \text{ min}^{-1}$$

$$k_{13} = 0.004 \text{ min}^{-1}$$

$$k_{21} = 0.017 \text{ min}^{-1}$$

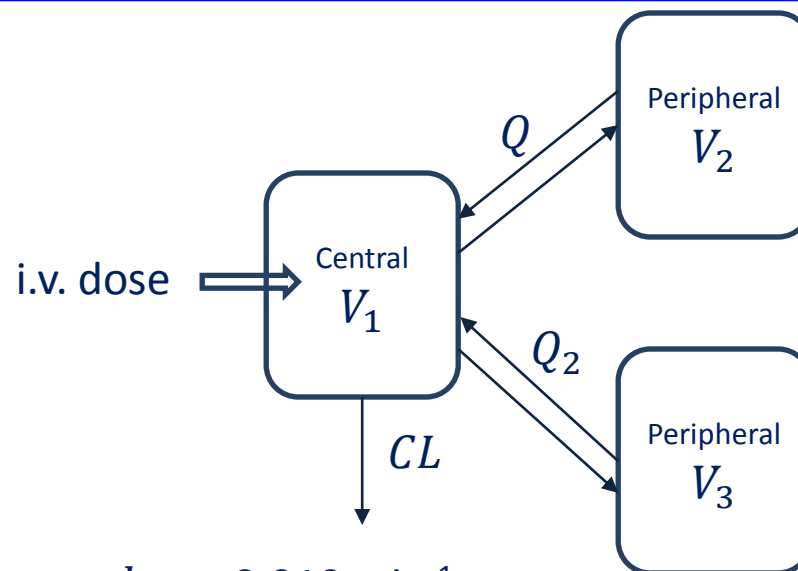
$$k_{31} = 0.002 \text{ min}^{-1}$$

$$V_1 = 36.4 \text{ L}$$

$$t_{1/2 \alpha} = 10.9 \text{ min}$$

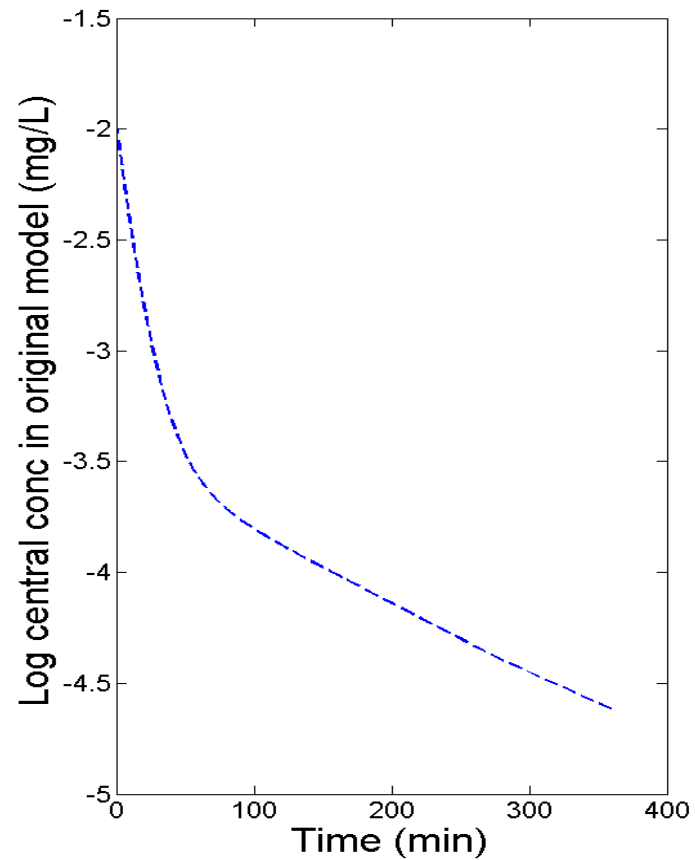
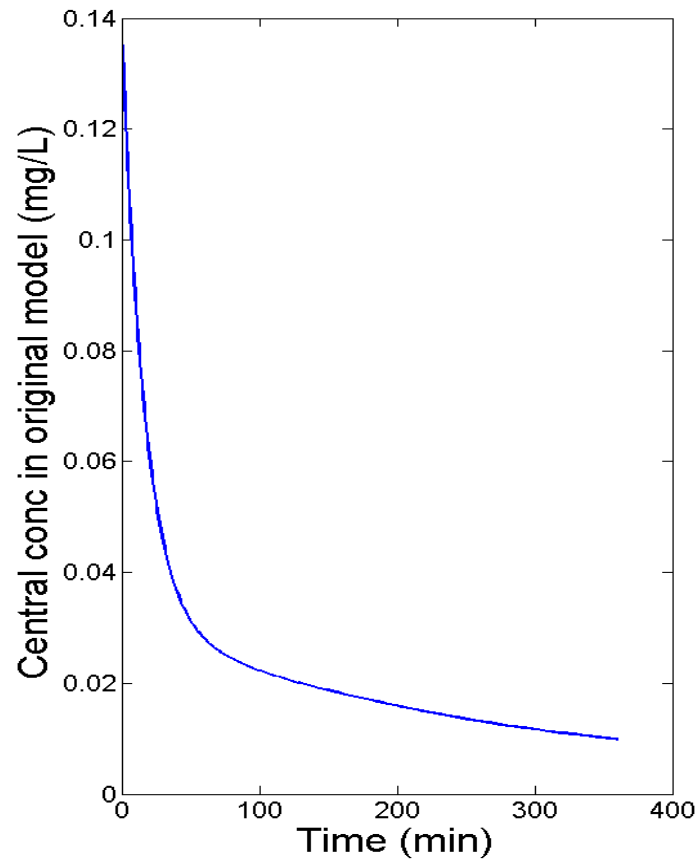
$$t_{1/2 \beta} = 153 \text{ min}$$

$$t_{1/2 \gamma} = 588 \text{ min}$$

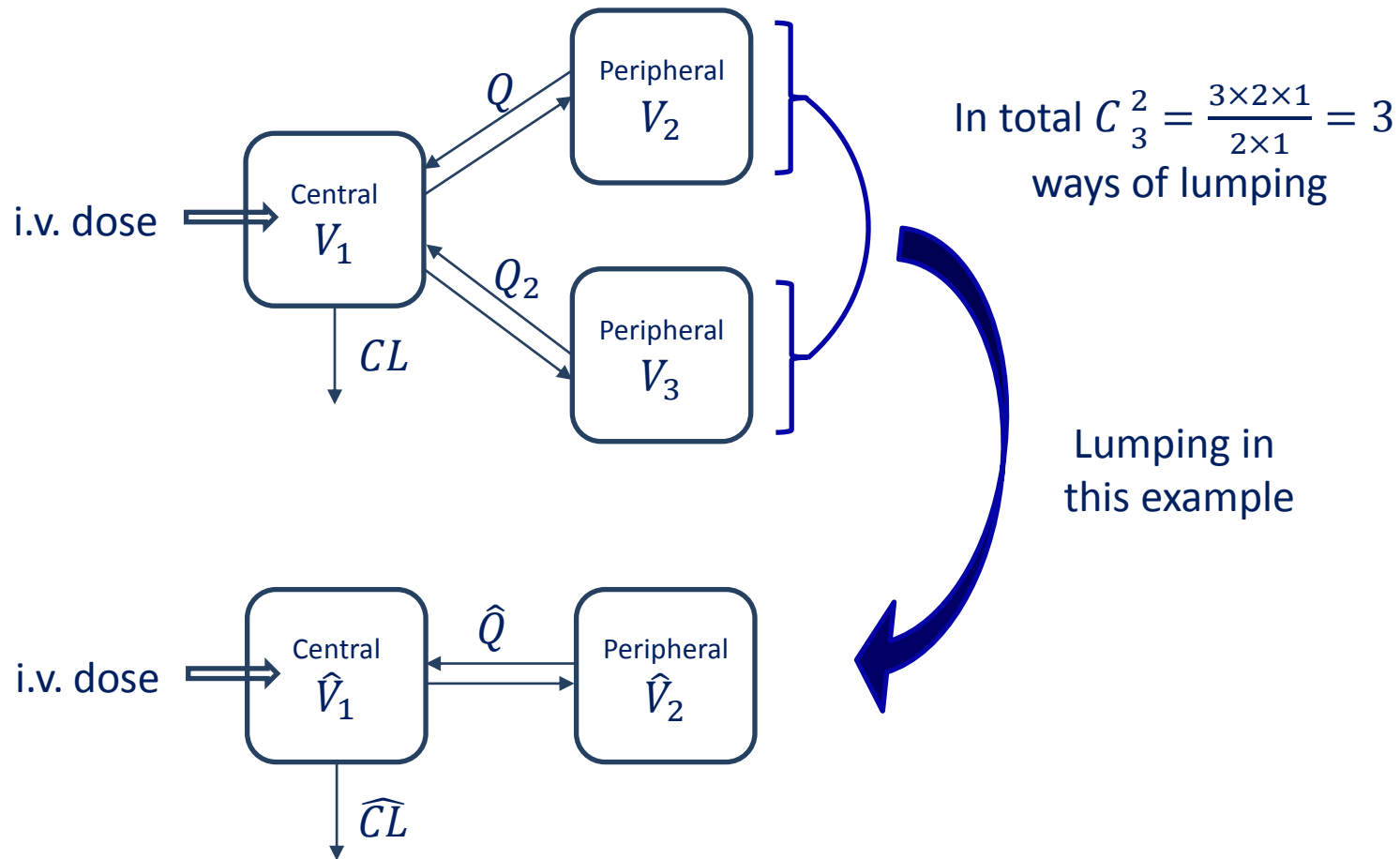


Brill et al, Clin Pharmacokinet 2014 (doi:10.1007/s40262-014-0166-x)

# Simulated profile in original PK model (3cpt)



# Simplification of midazolam PK model



# Parameter comparison in original & simplified PK models

$$\begin{aligned}CL &= 0.36 \text{ L}\cdot\text{min}^{-1} \\ Q &= 1.31 \text{ L}\cdot\text{min}^{-1} \\ Q_2 &= 0.15 \text{ L}\cdot\text{min}^{-1} \\ V_1 &= 36.4 \text{ L} \\ V_2 &= 76.6 \text{ L} \\ V_3 &= 76.6 \text{ L}\end{aligned}$$

Reparameterised

$$\begin{aligned}k_{10} &= 0.010 \text{ min}^{-1} \\ k_{12} &= 0.036 \text{ min}^{-1} \\ k_{13} &= 0.004 \text{ min}^{-1} \\ k_{21} &= 0.017 \text{ min}^{-1} \\ k_{31} &= 0.002 \text{ min}^{-1} \\ V_1 &= 36.4 \text{ L}\end{aligned}$$

Lumped

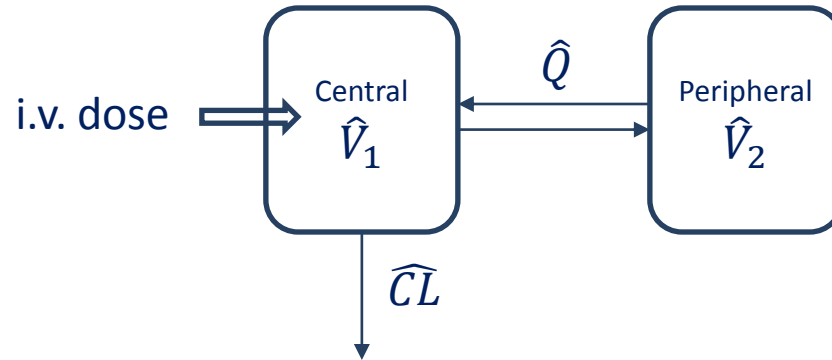
$$\begin{aligned}\hat{k}_{10} &= k_{10} \\ \hat{k}_{12} &= k_{12} + k_{13} \\ \hat{k}_{21} &= (k_{21} + k_{31})/2\end{aligned}$$

$$\begin{aligned}\hat{CL} &= 0.36 \text{ L}\cdot\text{min}^{-1} \\ \hat{Q} &= 1.46 \text{ L}\cdot\text{min}^{-1} \\ \hat{V}_1 &= 36.4 \text{ L} \\ \hat{V}_2 &= 154 \text{ L}\end{aligned}$$

Reparameterised

$$\begin{aligned}\hat{k}_{10} &= 0.010 \text{ min}^{-1} \\ \hat{k}_{12} &= 0.040 \text{ min}^{-1} \\ \hat{k}_{21} &= 0.0095 \text{ min}^{-1} \\ \hat{V}_1 &= 36.4 \text{ L}\end{aligned}$$

# Simplified midazolam PK model



Parameters in the simplified model following proper lumping technique:

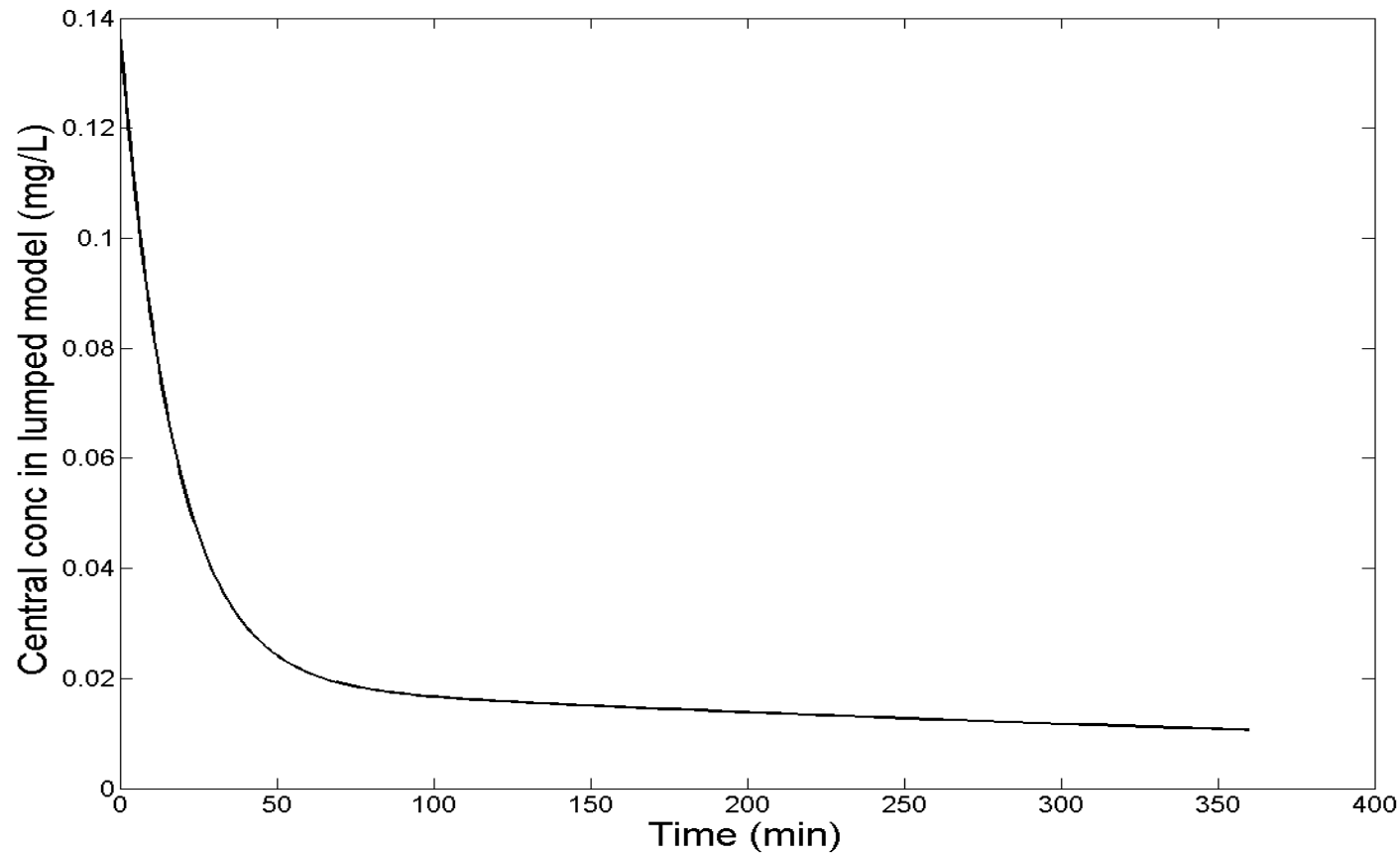
$$\hat{CL} = 0.36 \text{ L} \cdot \text{min}^{-1}$$

$$\hat{Q} = 1.46 \text{ L} \cdot \text{min}^{-1}$$

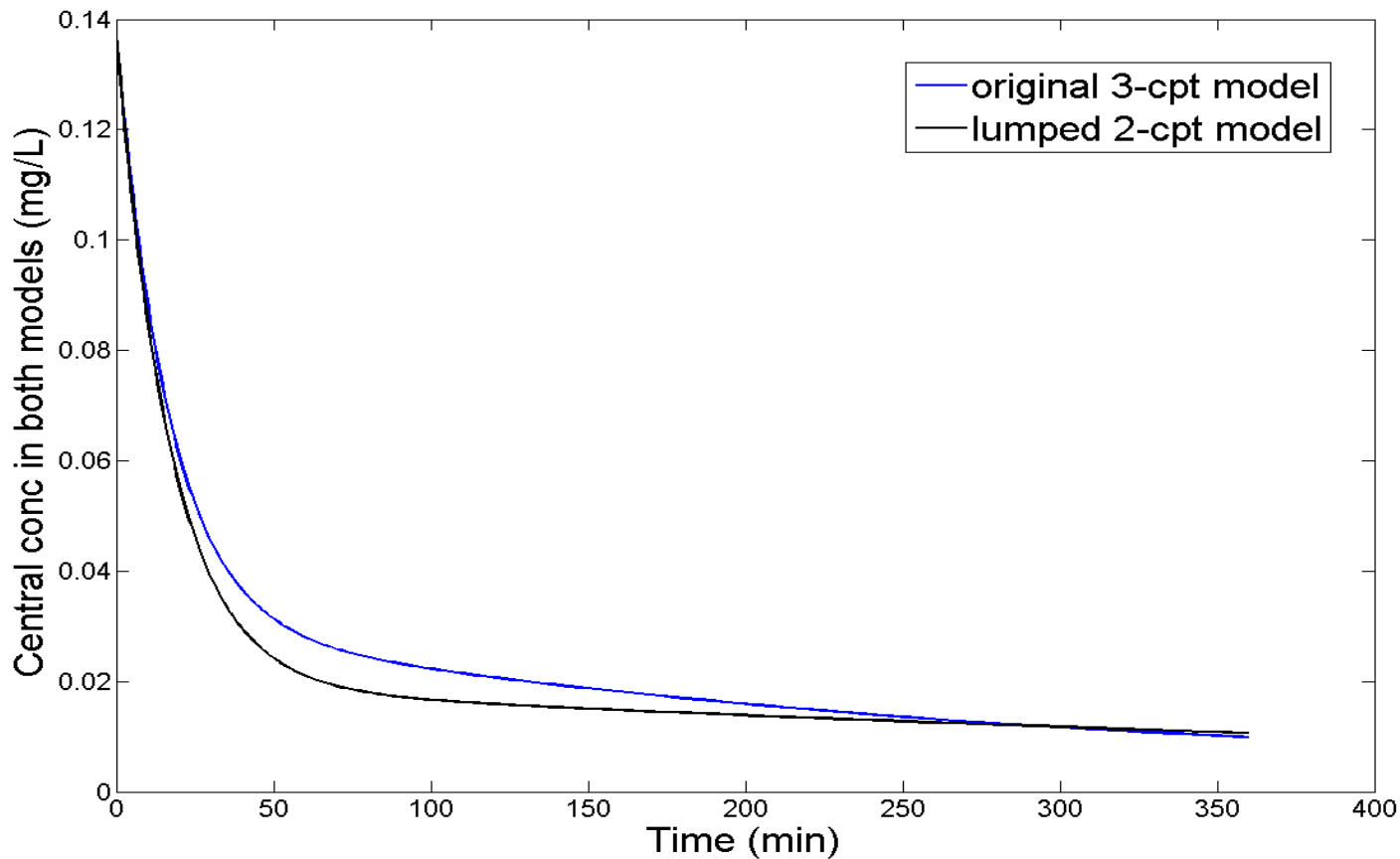
$$\hat{V}_1 = 36.4 \text{ L}$$

$$\hat{V}_2 = 154 \text{ L}$$

# Simulated profiles from simplified PK model (2cpt)



# Simulated profiles from original & simplified PK models





# Simulated profiles from original & simplified PK models

