Lumping of Physiologically Based Pharmacokinetic Models and a Mechanistic Derivation of Classical Compartmental Models

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Background/Objectives

Analysis and prediction of drug PK by:
- classical compartment models
- PBPK models

both approaches are used independently or in parallel, with little to no overlap

➡ classical modeling does not benefit from knowledge in PBPK models

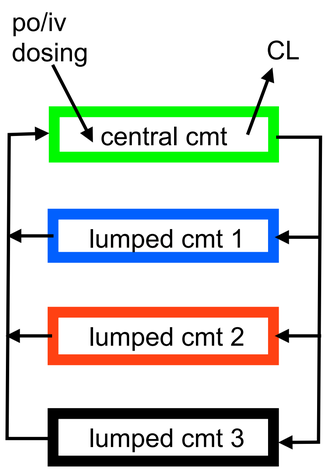
Linking classical PK compartment and PBPK modeling by:
- reducing the dimensionality of the PBPK model to derive mechanistically lumped compartment models
- interpreting parameters of the lumped model in terms of classical PK parameters
- lumped parameters as initial values for classical parameter estimation

Methods/Results

Lumping criteria

$$\frac{C_1(t)}{K_1} \approx \frac{C_2(t)}{K_2} \approx \frac{C_{el}(t)}{K_{el}(1-E_{el})} \approx \dots$$

Building up the lumped model



$$V_L = \sum_{tis} V_{tis}$$

$$Q_L = \sum_{tis} Q_{tis}$$

$$K_L = \sum_{tis} \frac{V_{tis} K_{tis}}{V_L}$$

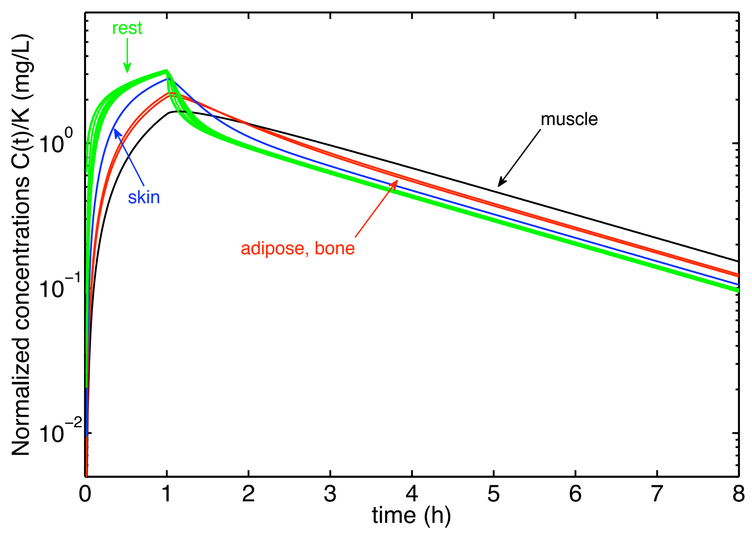
central compartment

$$V_{cen} \frac{d}{dt} C_{cen} = Q_L \left(C_{in} - \frac{C_{cen}}{K_{cen}} \right) - CL_{blood} \frac{C_{cen}}{K_{cen}}$$

lumped compartments

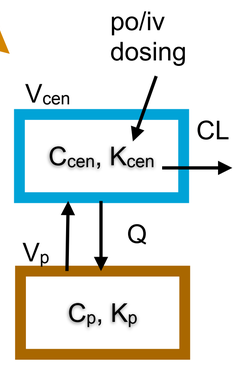
$$V_L \frac{d}{dt} C_L = Q_L \left(\frac{C_{cen}}{K_{cen}} - \frac{C_L}{K_L} \right)$$

Organs with similar *normalized* concentration time profiles are lumped together

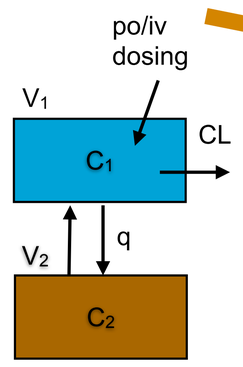


Minimal lumped model maintains predictive accuracy for venous blood

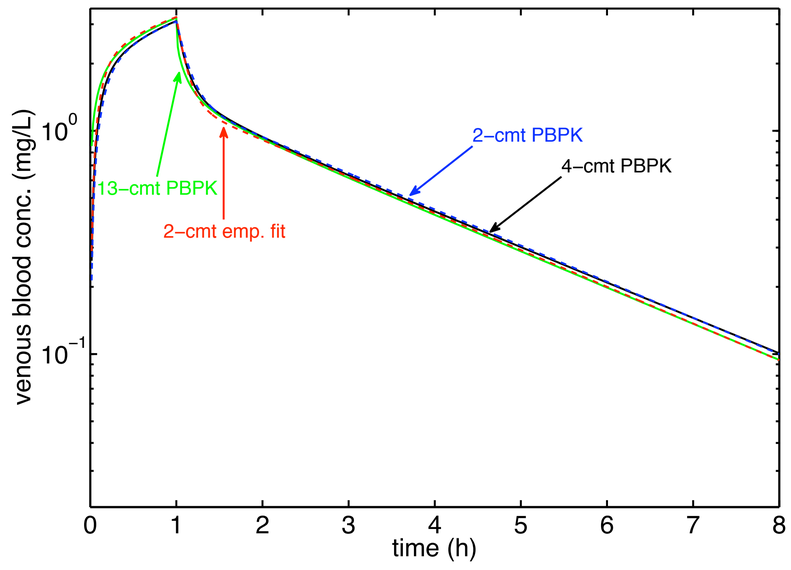
Mechanistic PK model



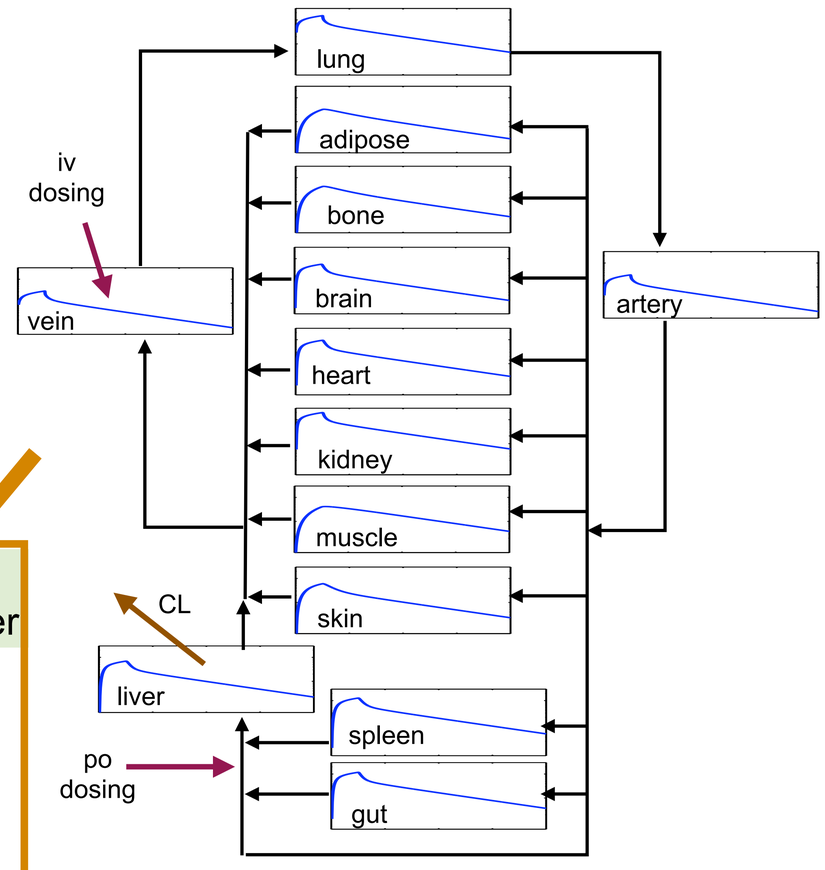
Classical PK model



$$C_1 = C_{cen} / K_{cen}$$
$$C_2 = C_p / K_p$$
$$V_1 = V_{cen} \cdot K_{cen}$$
$$V_2 = V_p \cdot K_p$$
$$Q = q$$



PBPK modeling results: Lidocaine, 60 min infusion



$$K = \frac{C_{tissue}}{C_{blood}}$$

non-eliminating tissue:

$$V \frac{d}{dt} C = Q \cdot \left(C_{in} - \frac{C}{K} \right)$$

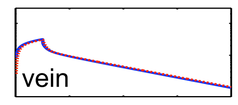
volume; blood flow; outflowing conc.; inflowing conc.

eliminating tissue (e.g. liver):

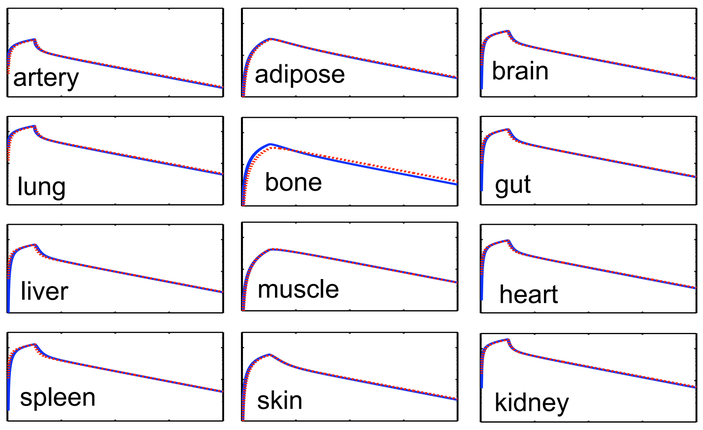
$$V_{liv} \frac{d}{dt} C_{liv} = Q_{liv} \cdot \left(C_{in} - \frac{C_{liv}}{K_{liv}} \right) - CL_{\text{int}} C_{liv}$$

Prediction of individual organ concentration from lumped model

$$C_{tis} = K_{tis} \frac{C_L}{K_L}$$



$$C_{el} = K_{el}(1-E_{el}) \frac{C_L}{K_L}$$



Advantages over existing lumping methods[1-4]

- lumping of perfusion rate limited as well as permeability rate limited PBPK models
- organs can be lumped together in any combination; no restrictions by PBPK model topology
- lumping to 1 or 2 compartments possible
- individual organ concentrations can be predicted based on concentration in lumped compartments
- lumping conditions have physiological interpretation and are easily visualized

Acknowledgement

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References

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