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Physiologically-based PK/PD modelling, mathematical model reduction and a mechanistic interpretation of simple empirical models

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NUI MAYNOOTH
Ollscoil na hÉireann Má Nuad

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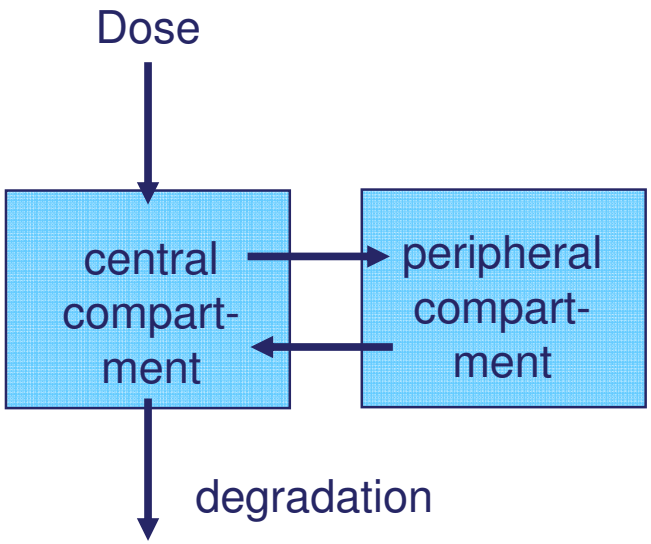
Different modeling approaches to analyze clinical data …

Classical compartment PK models



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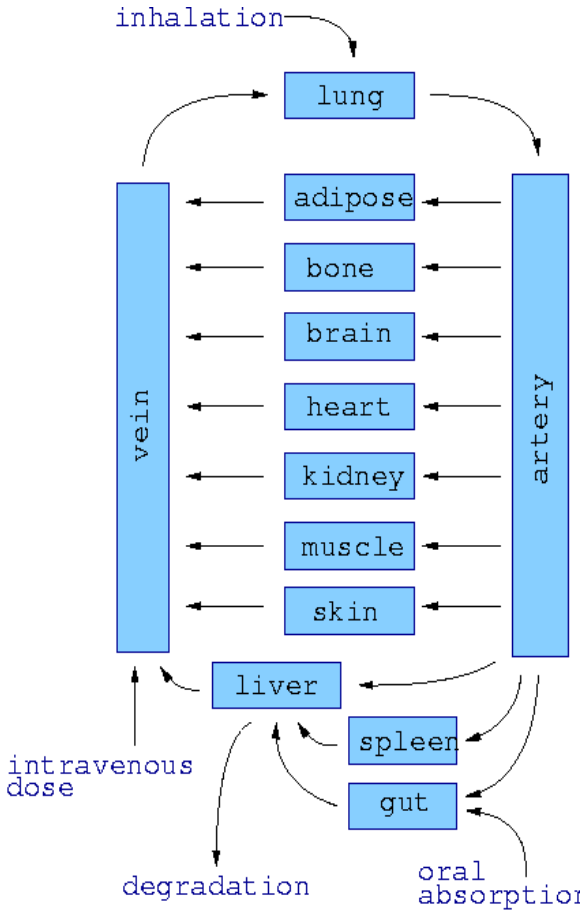
Physiologically-based PK models



The benefits

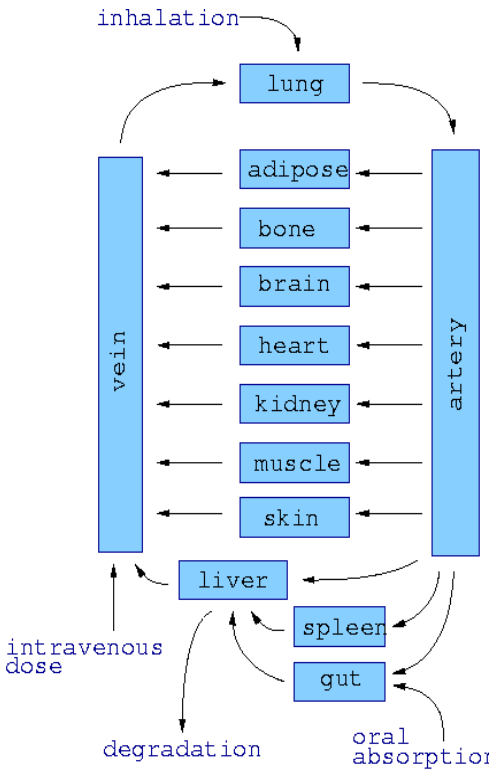
1. Physiologically based PK model are mechanistic by design.
   → Mechanistic interpretation of classical compartment models

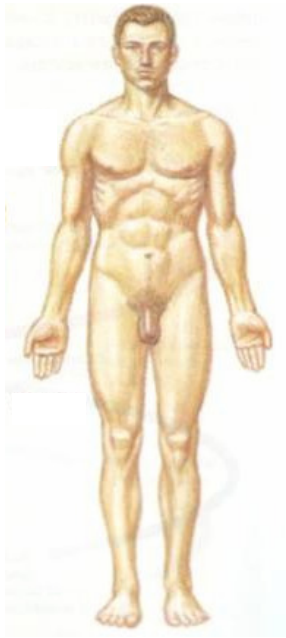
2. Properties of lumped models for a number diverse drugs.
   → design criteria for classical compartment models, examining e.g., the 'elimination at the point of observation' assumption

3. Physiologically based PK model allow to generate virtual populations, including critical sub-populations
   → important characteristic of the population will appear as covariates in the lumped model parameters (using 1.)

A very brief introduction to physiologically-based pharmacokinetic models

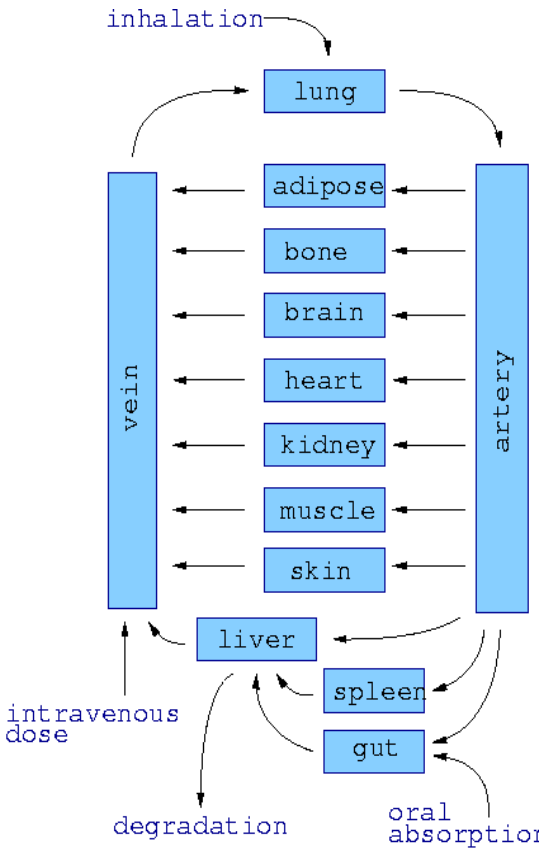
Whole-body compartmental model structure





E.g., Poulin /Theil, J Pharm Sci. (2002); Luepfert/Reichel, Chem Biodiv, (2005); Jones et al, AAPS J (2009)

Mass balance differential equations for each tissues/organ



Non-eliminating tissue:

$$V_{tis}\frac{d}{dt}C_{tis} = Q_{tis}\cdot\left(C_{in} - \frac{C_{tis}}{K_{tis}}\right)$$

inflowing blood conc.

out-flowing blood conc.

Tissue-to-blood partition coefficient:

$$K_{tis} = \frac{C_{tis,ss}}{C_{blood,ss}}$$

Parameterization of PBPK models

Species specific

- blood flows, organ volumes

Drug specific

- intrinsic clearance (CLint)
- tissue-to-blood partition coefficients
- Administration (dose, route, etc)

Non-eliminating tissue:

$$V_{tis}\frac{d}{dt}C_{tis} = Q_{tis}\cdot\left(C_{in} - \frac{C_{tis}}{K_{tis}}\right)$$

inflowing blood conc.

out-flowing blood conc.

Tissue-to-blood partition coefficient:

$$K_{tis} = \frac{C_{tis,ss}}{C_{blood,ss}}$$

Parameterization of PBPK models

Species specific

- blood flows, organ volumes
- tissue composition data

Drug specific

- intrinsic clearance CLint
- blood:plasma ratio B:P
- fraction unbound fuP
- octanol-water coeff Pow
- pKa value

- Administration (dose, route, etc)

Non-eliminating tissue:

$$V_{tis}\frac{d}{dt}C_{tis} = Q_{tis}\cdot\left(C_{in} - \frac{C_{tis}}{K_{tis}}\right)$$

inflowing blood conc.

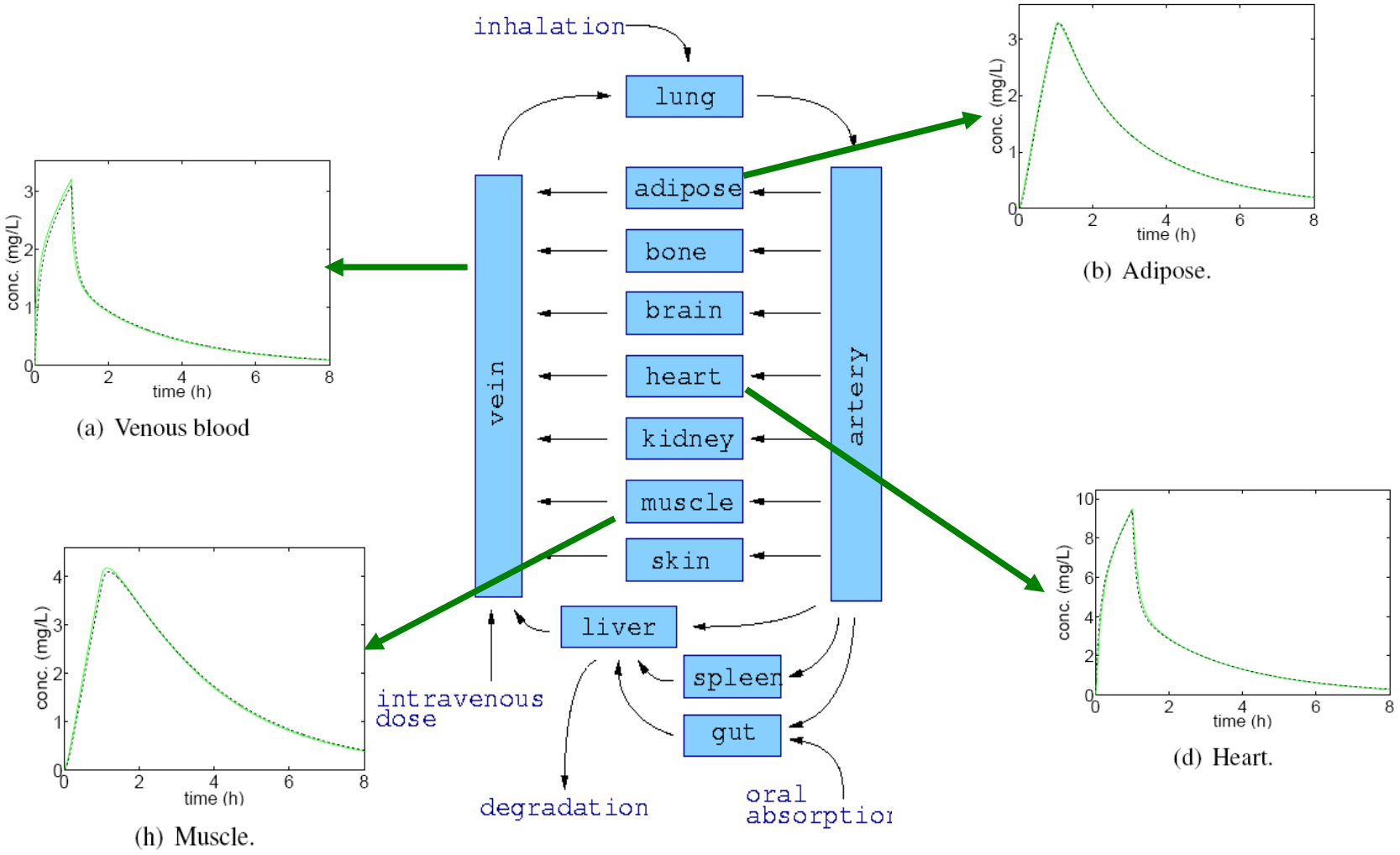
out-flowing blood conc.

Tissue-to-blood partition coefficient:

$$K_{tis} = \frac{C_{tis,ss}}{C_{blood,ss}}$$

Poulin/Theil (2000), Rodgers/Rowland (2005), Schmidt (2008)

Example: Lidocaine (60 min i.v. infusion in human)



→ different concentrations and profiles in different tissues/organs

Observation

In classical PK analysis, almost exclusive 1,2,or 3 compartment models are sufficient to describe *in vivo* blood/plasma data.

1. What is the relation between detailed PBPK models and much simpler compartmental PK models?

2. Can we predict the classical PK model from a detailed PBPK model?

3. Are their general properties that hold for certain drug types?

Lumping of PBPK model and its link to classical compartment models

—jointly with Sabine Pilari—

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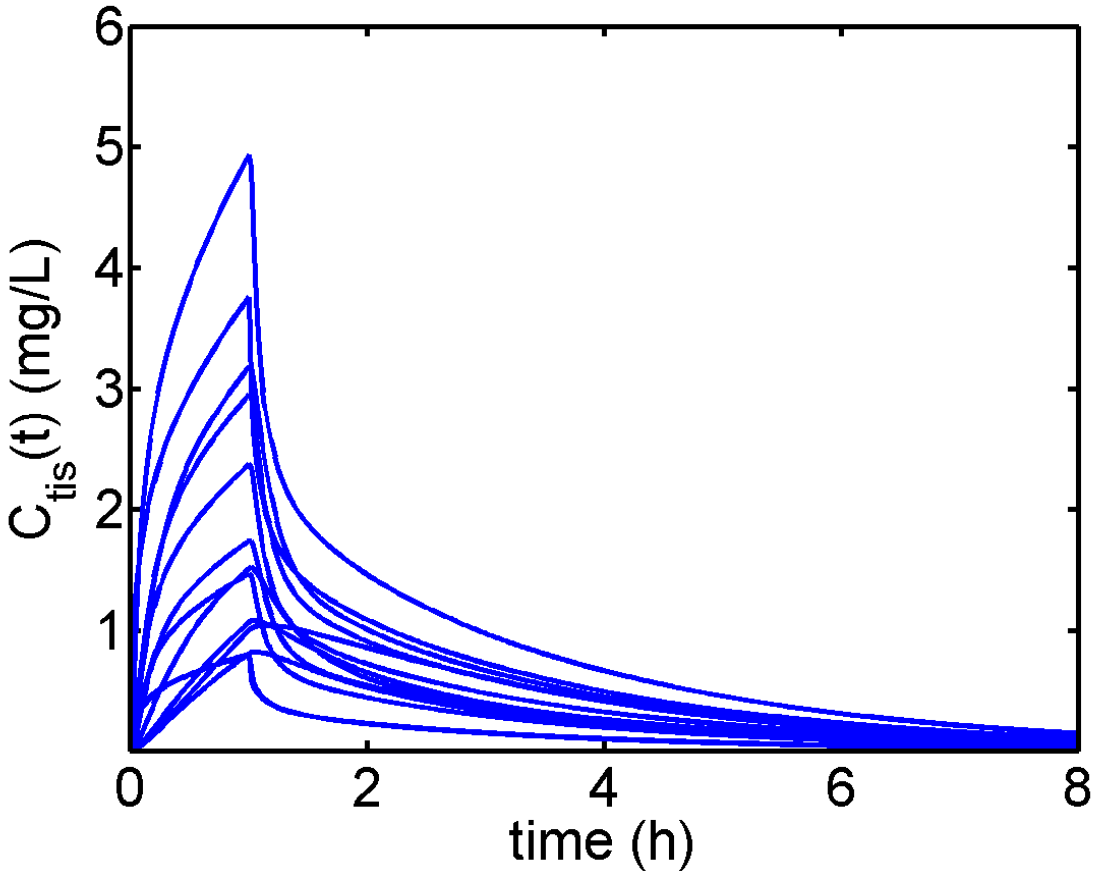
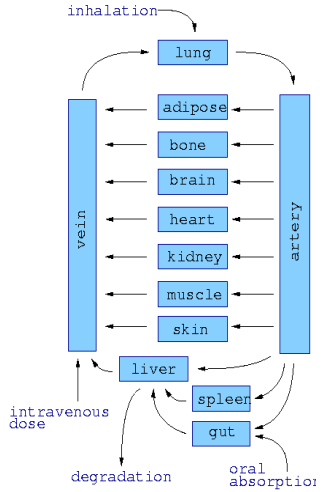
All 13 tissue/organ concentration time profiles

- Lidocaine (60 min i.v. infusion in human)





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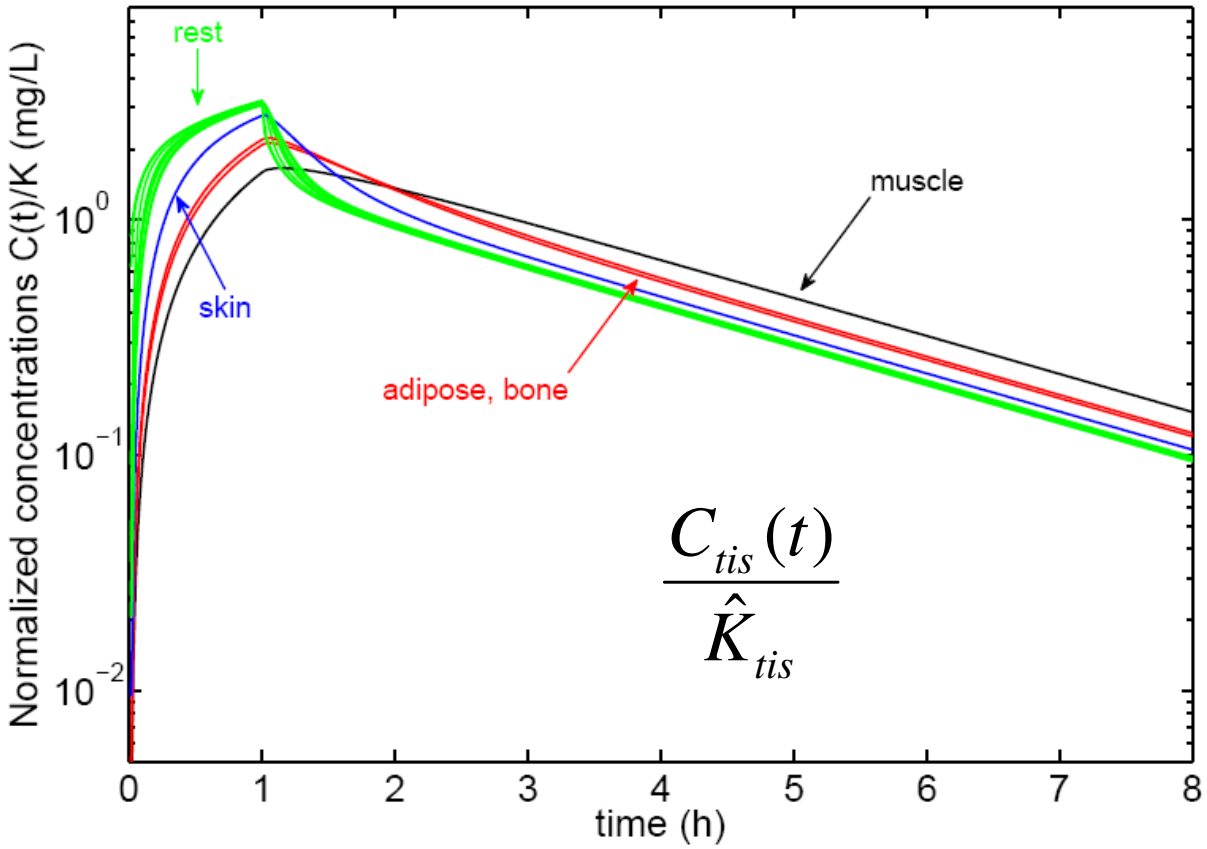
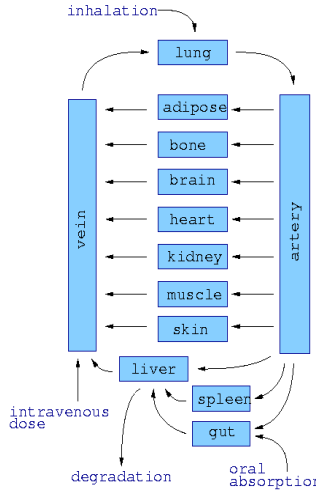
Normalized tissue concentration time profiles

- Lidocaine (60 min i.v. infusion in human)





$$\hat{K}_{tis} = K_{tis}(1 - E_{tis})$$

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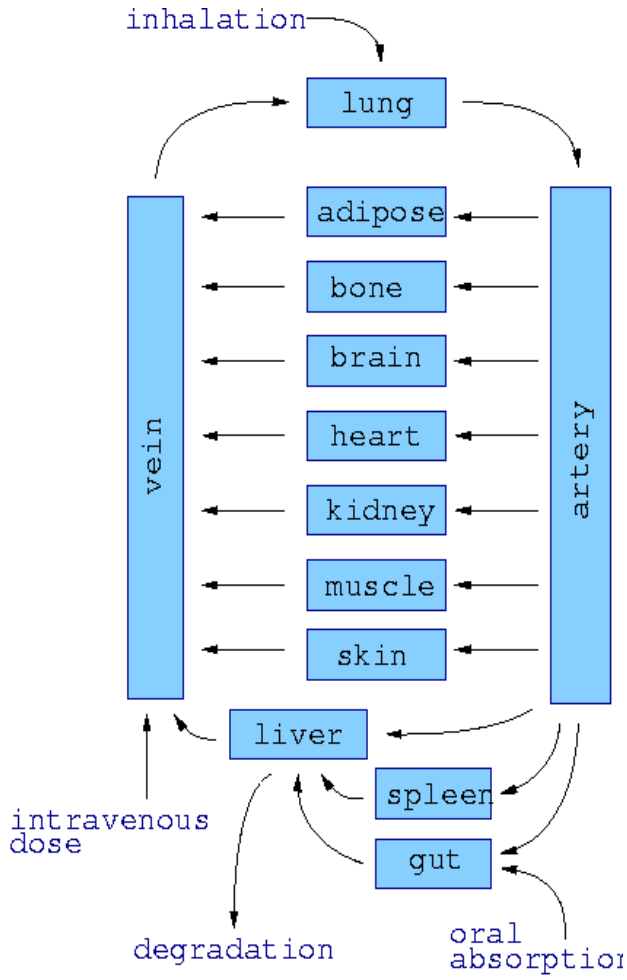
Two step approach to lumping

1. Mechanistically lumped model
   - Aims to approximate all 13 tissues/organs with high accuracy

2. Minimal lumped model
   - Aims to approximate only the venous blood compartment



Idea: Simplify PBPK model based on kinetic homogeneity

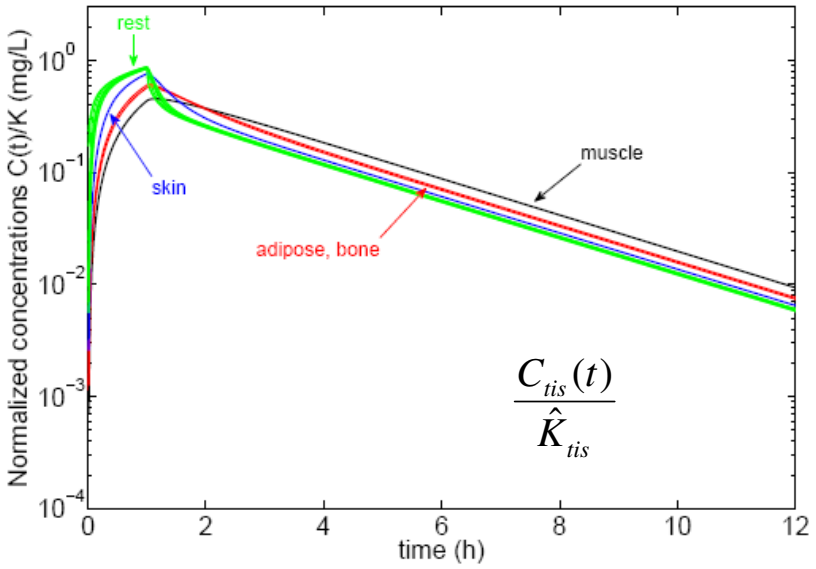
- Lumping condition

$$\frac{C_1(t)}{\hat{K}_1} = \frac{C_2(t)}{\hat{K}_2} = \ldots$$

- Define lumped concentration + parameters

$$C_L = \frac{1}{V_L}\left(V_1 C_1 + \ldots + V_m C_m\right)$$

$$V_L = V_1 + \ldots + V_m$$



Groups of similar profiles

- {muscle}
- {adipose, bone}
- {skin}
- {vein + rest}

Pilari/Huisinga (2010)

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Idea: Simplify PBPK model based on kinetic homogeneity

- Lumping condition

$$\frac{C_1(t)}{\hat{K}_1} = \frac{C_2(t)}{\hat{K}_2} = \ldots = \frac{C_L(t)}{K_L}$$

- Define lumped concentration + parameters

$$C_L = \frac{1}{V_L}\left(V_1 C_1 + \ldots + V_m C_m\right)$$

$$V_L = V_1 + \ldots + V_m$$

$$Q_L = Q_1 + \ldots + Q_m$$

$$K_L = \frac{1}{V_L}\left(V_1 \hat{K}_1 + \ldots + V_m \hat{K}_m\right)$$

Lumped differential equations:

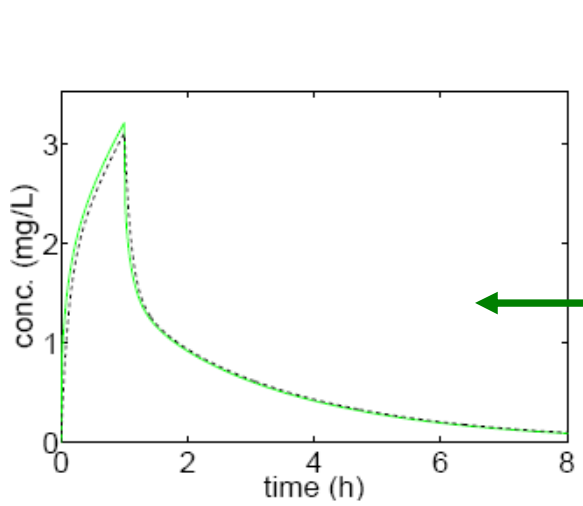
$$V_L \frac{d}{dt} C_L = Q_L \cdot \left(\frac{C_{cen}}{K_{cen}} - \frac{C_L}{K_L}\right)$$

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

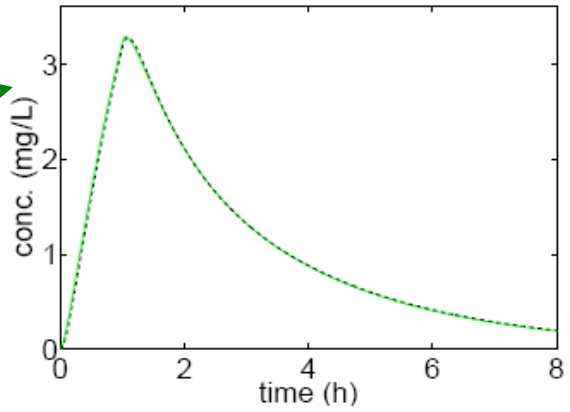
From lumped to original tissue concentration:

$$C_{tis} = \hat{K}_{tis} \cdot \frac{C_L}{K_L}$$

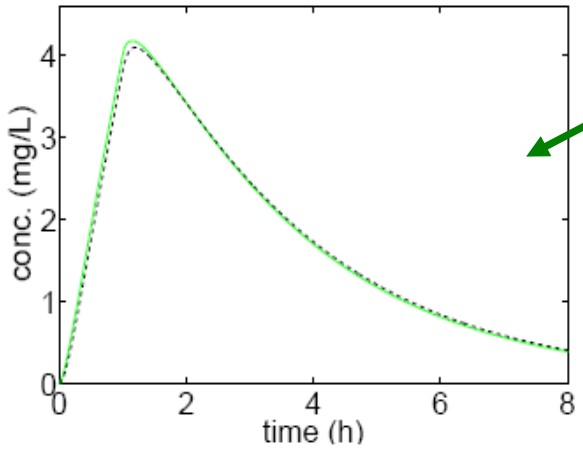
Comparison: 13 compartment PBPK vs. 4 compartment lumped model



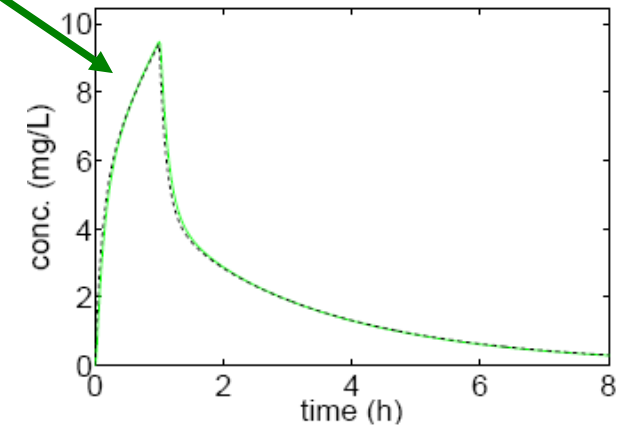
(a) Venous blood



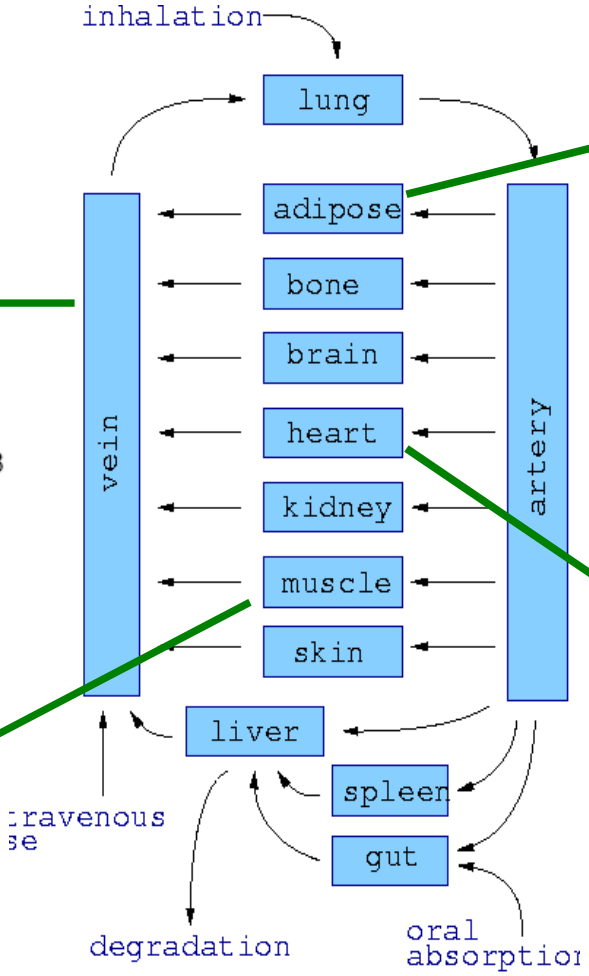
(b) Adipose.



(h) Muscle.



(d) Heart.



Comments on existing lumping approaches

- Nestorov/Aarons/Arundel/Rowland (1998)
  - First systematic lumping approach
  - Lumping based on tissue time constants (more restrictive)
  - No lumping of permeability rate limited compartments
  - Not possible to predict original tissue concentrations

$$T_{tis} = \frac{V_{tis} K_{tis}}{Q_{tis}}$$

- Brochot/Toth/Bois (2005)
  - Same underlying lumping approach
  - Constraint based lumping

- Gueorguieva/Nestorov/Rowland (2006)
  - Same underlying lumping approach
  - Global sensitivity analysis approach (FAST)
  - Considering variability and uncertainty

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Mechanistically lumped PK models for 25 diverse drugs

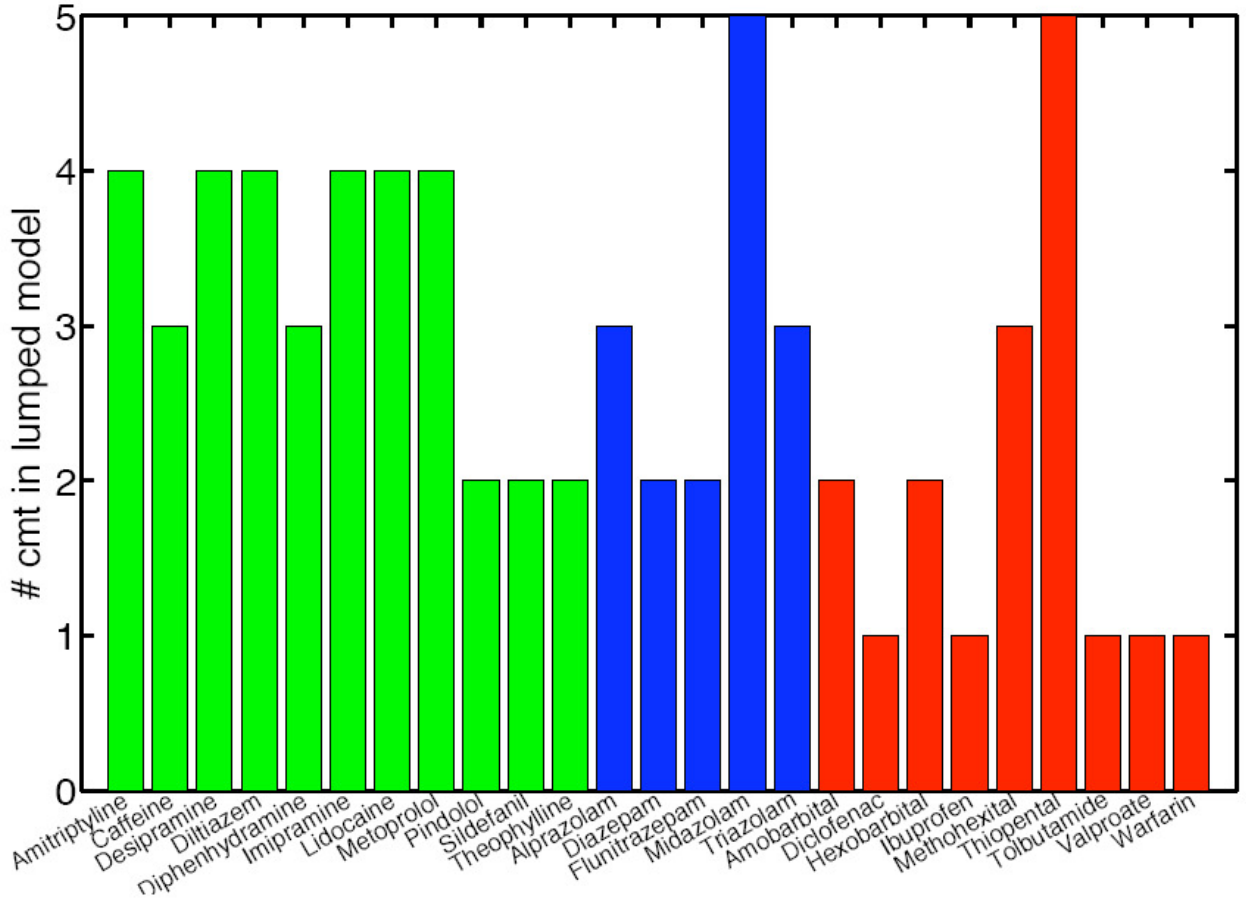
Moderate-to-strong bases

weak bases

acids

Drug	pK_a	$\log P_{ow}$	fu^p	B:P	CL_{blood} (ml/min/kg)
Moderate-to-strong bases					
Amitriptyline	9.40[1]	4.90[1]	0.056 [1]	0.86[1]	12.00[2]
Caffeine	10.40[1]	-0.09[1]	0.700[1]	1.04 [1]	1.40[3]
Desipramine	10.32[1]	4.90 [1]	0.190[1]	0.96[1]	12.00[2]
Diltiazem	7.70[1]	2.67 [1]	0.200[1]	1.03[1]	12.00[2]
Diphenhydramine	8.98[1]	3.31 [1]	0.089[1]	0.80[1]	9.50[2]
Imipramine	9.50[1]	4.80 [1]	0.130[1]	1.12[1]	12.00[2]
Lidocaine	8.01[1]	2.26 [1]	0.296[1]	0.84[1]	15.00[3]
Metoprolol	9.70[1]	2.15 [1]	0.900[1]	1.14[1]	12.15[3]
Pindolol	8.80[1]	1.75 [1]	0.410[1]	0.81[1]	4.20[3]
Sildefanil	7.60[1]	2.75 [1]	0.040[1]	0.62[1]	6.00[3]
Theophylline	8.71[1]	0.26 [1]	0.600[1]	0.83[1]	0.65[3]
Weak bases					
Alprazolam	2.40[4]	2.09 [4]	0.320[2]	0.78[2]	0.76 [2]
Diazepam	3.38[4]	2.84 [4]	0.013[2]	0.71[2]	0.60[2]
Flunitrazepam	1.80 [4]	2.06 [4]	0.250 [5]	1.20 [5]	9.8 (ml/min) [5]
Midazolam	6.01 [4]	3.15 [4]	0.050[2]	0.53[2]	8.70[2]
Triazolam	2.00 [4]	2.42 [4]	0.100[2]	0.62[2]	4.70[2]
Acids					
Amobarbital	7.90 [4]	1.89 [4]	0.390[2]	1.50[2]	0.35[2]
Diclofenac	4.15 [6]	3.90 [6]	0.005[2]	0.55[2]	7.60[2]
Hexobarbital	8.29 [4]	1.74 [4]	0.530[2]	1.00[2]	3.60[2]
Ibuprofen	4.70 [4]	4.06 [4]	0.010[2]	0.55[2]	1.50[2]
Methohexital	8.30 [4]	1.72 [4]	0.270[2]	0.70[2]	16.00[2]
Thiopental	7.53[4]	2.93 [4]	0.180 [4]	0.88[8]	2.02[9]
Tolbutamide	5.29 [4]	2.39 [4]	0.040[2]	0.55[2]	0.36[2]
Valproate	4.60 [4]	2.76 [4]	0.099 [4]	0.55[10]	0.11[10]
Warfarin	5.08 [4]	3.00 [4]	0.010[2]	0.55[2]	0.081[2]

Mechanistically lumped PK models for 25 diverse drugs



→ Only adi, mus, bon and ski lumped separately from central compartment

→ Liver and kidney were always part of the central compartment

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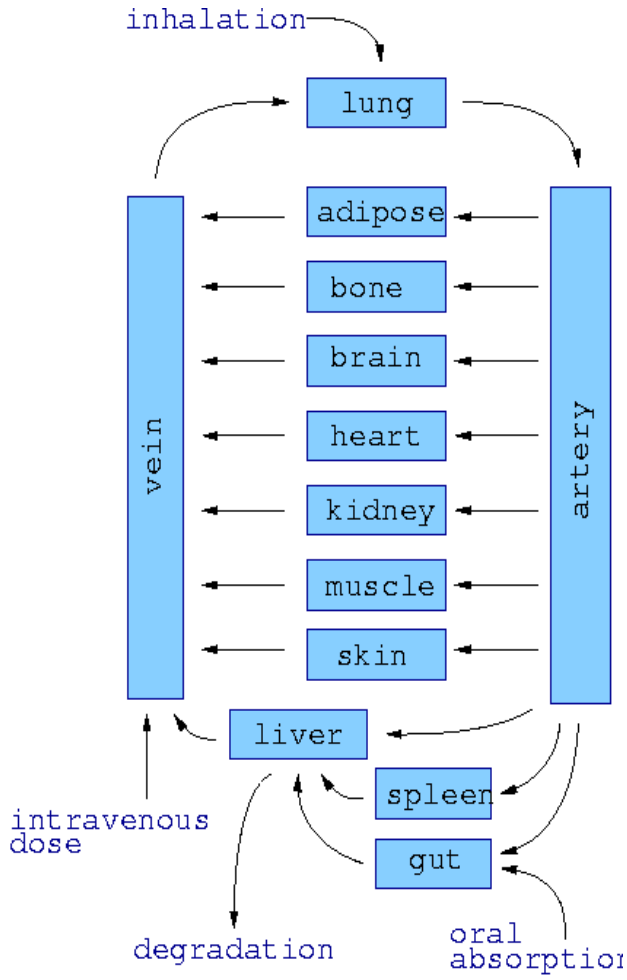
Two step approach to lumping

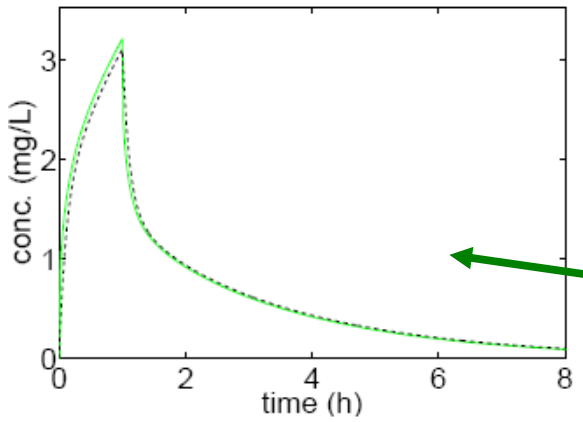
1. Mechanistically lumped model
   - Aims to approximate all 13 tissues/organs with high accuracy

2. Minimal lumped model
   - Aims to approximate only the venous blood compartment

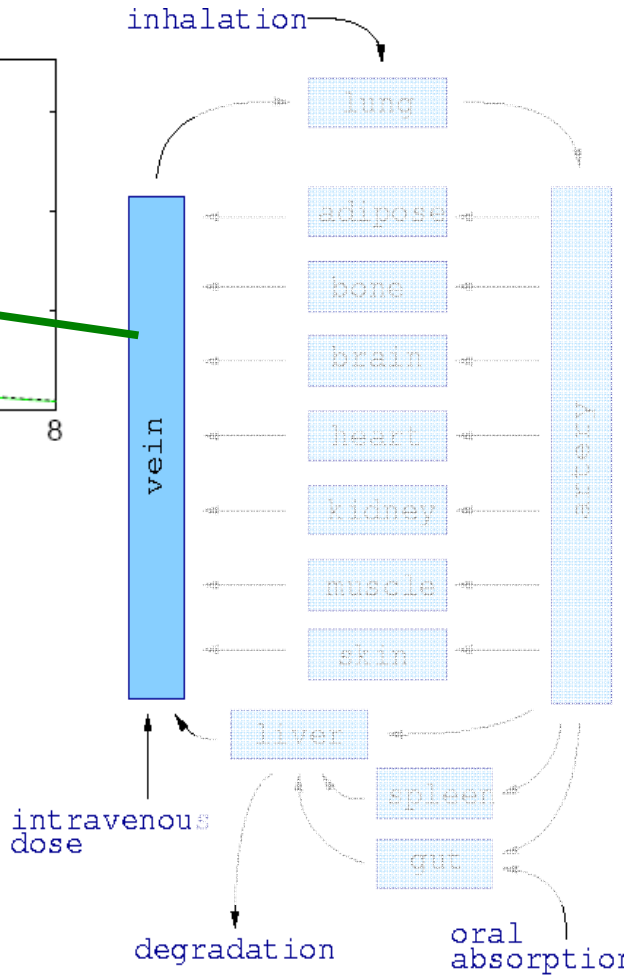


Minimal lumped models and the link to classical compartment models

- Often, only experimental blood data are available
- These data are used for development of classical compartment models
- Hence, what is the minimal lumped model that still predicts blood concentration?



(a) Venous blood



Minimal lumped models to predict venous blood concentration

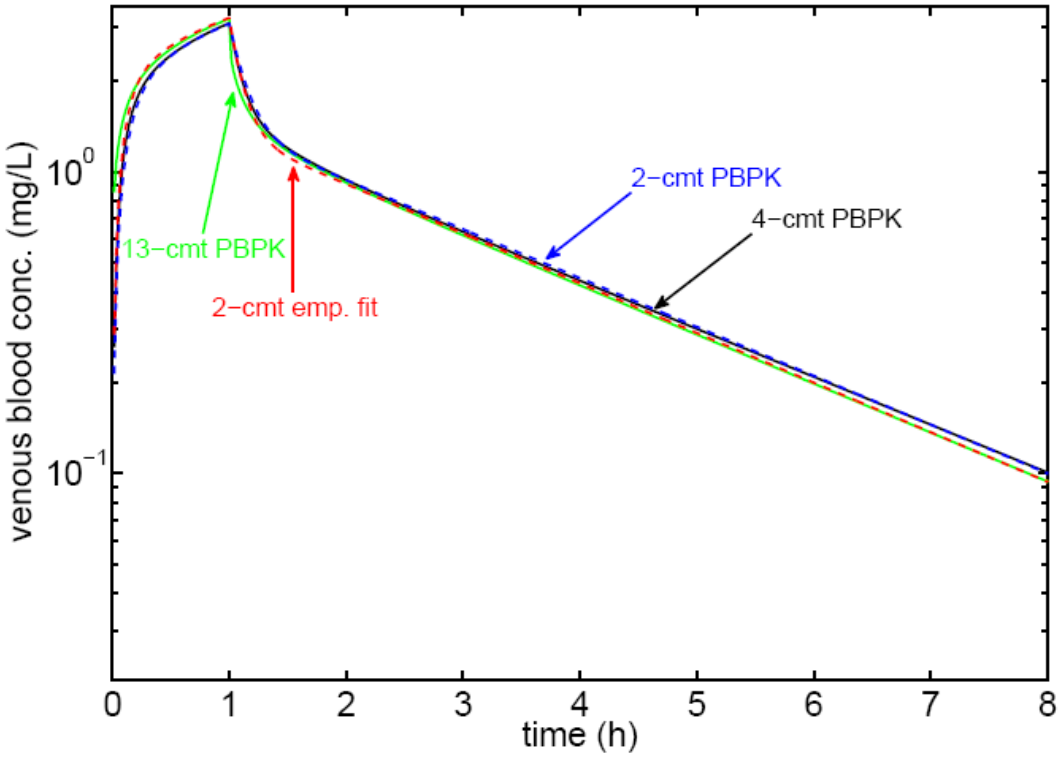
- Example: Lidocaine

Mechanistically lumped model:

- {muscle}
- {adipose, bone}
- {skin}
- {vein + rest}

Minimal lumped model:

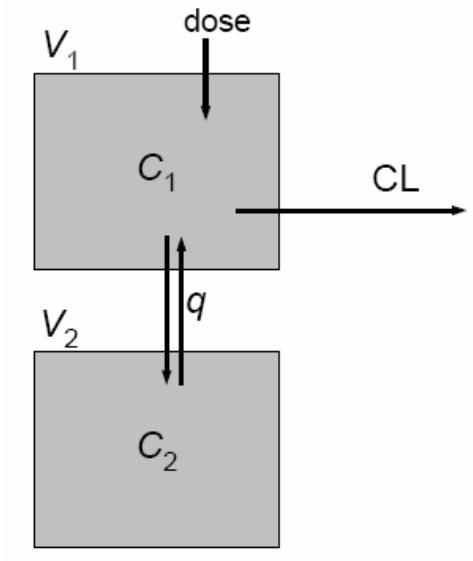
- {adipose, muscle, bone}
- {vein + rest}



Pilari/Huisinga (2010)

Minimal lumped model vs. empirical PK compartment model

- Empirical PK 2-compartment model:



minimal model		determination of empiric parameters based on:		
2-cmt model				
			min. param.	emp. fitting
V_{cen}	14.33	V_1	29.7	21.5
V_p	44.18	V_2	99.1	99.8
Q	1.91	q	1.91	1.85
K_{cen}	2.07	CL	1.10	1.09
K_p	2.24			

$$V_1 = V_{\text{cen}} \cdot K_{\text{cen}}$$
$$V_2 = V_{\text{p}} \cdot K_{\text{p}}$$
$$q = Q$$
$$\text{CL} = \text{CL}_{\text{blood}}$$

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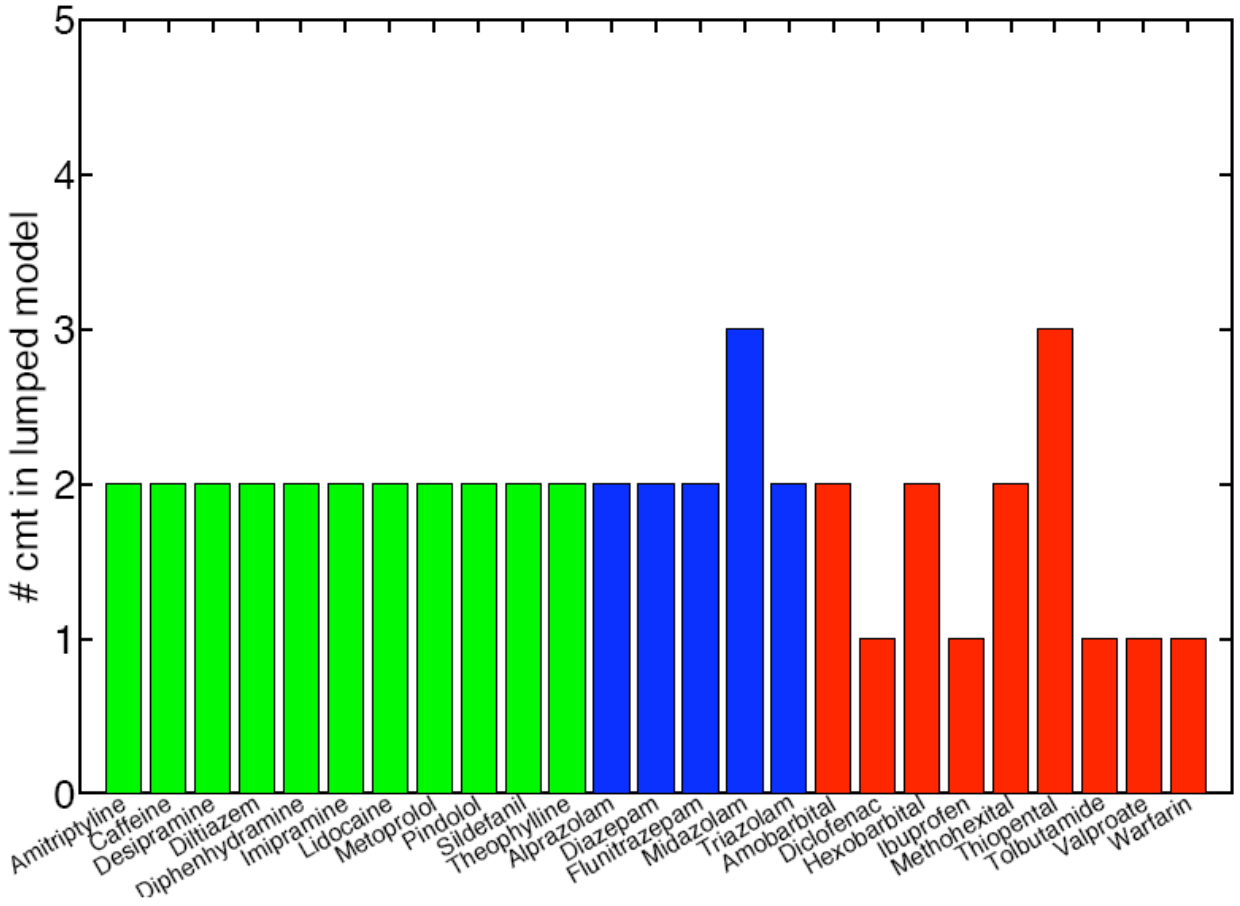
Minimal lumped models for 25 diverse drugs



→ almost always peripheral compartment = {adi,bon,mus}

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Comparison to literature data

	Predicted minimal lumped model	Classical compartment model (literature)
Midazolam	3 compartments	2-3 compartments
Thiopental	3 compartments	2-3 compartments
Valproate	1 compartments	1 compartments
Tolbutamide	1 compartments	2 compartments
Lidocaine	2 compartments	2-3 compartments

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Summary

- Minimal lumped models establish link between PBPK and classical PK models
- Mechanistic interpretation of classical compartment PK models

→ **Poster by Sabine Pilari**

Outlook

•Lumping in a population context: Combine lumping of PBPK models with methods to generate physiological parameters for entire populations

—Does the minimal lumped PK model differ for subpopulations?

—Important physiological parameters of the PBPK will appear as covariates in minimal lumped model

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Networking

Computational Physiology Group@Hamilton Institute (www.hamilton.ie/compphysiol):
Ludivine Fronton, Stephan Menz, Sabine Pilari, Alexander Solms

N. Beerenwinkel, Computational Biology @ D-BSSE/ETH Zürich
C. Kloft, Clinical Pharmacy @ MLU Halle-Wittenberg

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http://www.pharmacometrics.de